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Appendix A

The Modeling and Simulation of Feedback Control Systems

The purpose of this Appendix is to explain the basic vocabulary and principles of model development so that the reader may better grasp the description of the simulation models. Examples that describe the steps leading to the development of a computer algorithm of a model subsystem are provided, and the simulation techniques used to assess model behavior and accuracy will be discussed.

A.1 Definitions of Terms and Concepts

A.1.1 Parameters and Variables

Two general types of quantities are used in mathematical models: *parameters* and *variables*. The value of a *parameter* is generally constant with respect to time, whereas the value of a *variable* changes with time (i.e., is *time-varying*). Biological parameters often vary slowly with time but may be assumed to be constant in the mathematical model.

Parameters may be considered *independent* of system actions. Variables may also be considered independent if they influence the system from the outside, i.e., ambient temperature. Parameters and *independent variables* are also called *input functions*, or *forcing functions*. More often, variables are *dependent* (also called output functions), since they vary according to the relationships within the system. An objective of a systems analysis is to specify the state of the system; that is, to specify the values of all dependent variables at every instant of time.

A.1.2 Classification of Mathematical Model Systems

Mathematical models are classified according to the types of equations they employ [1].

A.1.2.1 Distributed and Lumped Parameter Systems.

In *distributed parameter systems*, the values of variables depend on time as well as space coordinates, and the system must be analyzed by solving *partial differential equations*. In a *lumped parameter system*, each element is treated as if it were concentrated (“lumped”) at one particular point, which is called a *node* or a *compartment*. The use of lumped parameters greatly simplifies the analysis because *ordinary differential equations* are used to describe the changes with time. To account for spatial changes that occur in such a system (e.g., the value of blood pressure is different in arteries, capillaries, and veins), compartments are added for each major space location until one reaches the level of compartmentalization (lumping) commensurate with the basic purpose of the model being designed.

Generally, as subdivisions are included in a model, the fidelity and accuracy of the model’s response increases. For example, in this project, two circulatory models were employed, one composed of 7 compartments and the other

of 28 compartments. The 7 compartment model can only simulate mean blood pressures in arteries and veins, whereas the 28 compartment model can simulate pulsatile flow and provide systolic and diastolic pressure for all anatomical portions of the vasculature (i.e., aorta, arteries, arterioles, capillaries, venules, veins, and vena cava).

All models described in this publication are lumped parameter systems. Whether the lumping of components and the simplifying of input–output relationships are appropriate depends entirely on the intended purpose of the model. Lumped, compartmental modeling is in keeping with a basic facet of the systems approach: to simplify the problem and define the essentials of its solution.

A.1.2.2 Linear and Nonlinear Systems. In modeling, systems generally consist of components with a known (or assumed) relationship. In a broad sense, a component of a system may be thought of as having the property to transform certain inputs into certain outputs. Such relationships are often (loosely) termed *transfer functions* (although transfer function has a rigorous meaning only in terms of Laplace transforms).

Mathematically, the components of a system may be represented by several operators, which transform one function into another. If all the operators for the system are linear, in the loose sense that their operation on two independent functions produces two independent results, then the system itself is said to be *linear*. Otherwise, the system is said to be *nonlinear*. Mathematically, much more is known about the behavior of linear systems.

Unfortunately, most biological systems—with their threshold and saturation behavior, sigmoidal dose-response relationship, and dead time—are nonlinear; analysis of such systems revolves around *numerical methods* and the use of *computers*. Obtaining rapid, accurate, numerical solutions of nonlinear system equations is absolutely essential in biological modeling and often represents a separate challenge. Solutions of nonlinear models are more likely to yield counter intuitive results than those of linear models. Most of the models used in this project can be classified as nonlinear.

A.1.2.3 Other Classifications and Nomenclature.

Models can be developed for either *predictive* or *descriptive* purposes. A predictive model must only produce accurate predictions of the output variables in the system. For example, a single equation may be used to predict the fractional saturation of hemoglobin with oxygen at different levels of oxygen partial pressure. In this case, the modeler is not concerned with a relative replication in the model of the interactions between the variables in the system. The relationships employed in the predictive model to

generate the predicted output need not conform to the mechanisms in the real system that lead to the same outputs. In contrast, descriptive models not only must generate predictions in agreement with real system output but *also* must employ intermediate relationships that are realistic representations of the true processes that generate the observed outputs.

The vast majority of biological systems are *continuous* systems, in which values are always changing with time, and they are best described by *differential equations*. These equations are typically solved with numerical procedures on digital computers by transforming them into *finite-difference equations*. In this process, the variables actually appear to be constant for the duration of the *integration step size* and, therefore, more properly belong to a *discrete* system. This approximation of continuous biological systems by discrete numerical systems can produce inaccuracies and instabilities in the solution, unless appropriate care is taken and the system is carefully verified.

The models described in this project can also be said to be *deterministic*, since the input-output relationships for each component are based on simple physical laws (i.e., flow-pressure, diffusion, mass action) and are therefore fixed, predictable, and reproducible. In reality, most biological systems are *stochastic*, in the sense they are subject to random noise, and their responses can be described by statistical laws and in terms of probabilities and expected values.

Riggs [1] makes the observation that “all naturally-occurring systems are, in the final analysis, time-varying distributed-parameter, quantized, stochastic, nonlinear systems. That we can sometimes obtain useful information by treating these wayward creatures as if they were fixed lumped-parameter, continuous, deterministic, linear systems is little short of miraculous.”

A.1.3 Biological Control Systems

It is difficult to conceive of any biological quantity that is not controlled or influenced by one or more factors. For example, blood pressure influences and controls the rate of baroreceptor neural firing. In this situation, baroreceptor neural firing is *controlled*, or *regulated*, within narrow limits at the expense of the other system quantities, the limits of which may vary widely. The relationship between blood pressure and baroreceptor neural firing would be construed as an *open-loop* system for controlling baroreceptor neural firing. Further examination of the process shows that the baroreceptor afferent signal is processed by the central nervous system (CNS) and results in an efferent neural signal that controls peripheral resistance. This relationship between baroreceptor firing and peripheral resistance is an open-loop system for controlling peripheral resistance. However, it is known that peripheral resistance directly regulates blood pressure. Once this control is added to the system, the complete loop of physical changes (blood pressure, peripheral resistance) and information transmission (afferent and efferent signals) forms a *closed-loop* control system. The difference between the closed-loop and open-loop systems is obviously the pres-

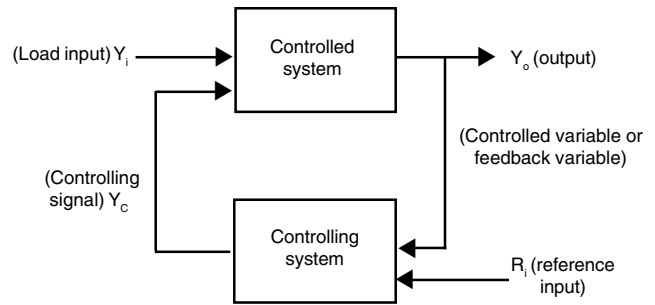


Figure A-1. A generalized feedback control system. Most biological homeostatic systems can be reduced to these basic components.

ence of the relationship of peripheral resistance to blood pressure. Blood pressure in the closed-loop system is called the *feedback variable*.

A feedback control system, as described previously, is composed of two major elements, or components: the *controlled* system and the *controlling* system or *controller*. Figure A-1 is a diagram illustrating the relationships of these elements. The purpose of the controlled system is to transform inputs from the outside (*load inputs*, *disturbances*, or *stress stimuli*) and inputs from the controller (*controlling signals*) into *responses* (*outputs*). The reference input of Fig. A-1 is also referred to as a *set-point*, and it represents a normal or desired value of a feedback variable. Differences between the set-point and the actual feedback variable result in corrective action by the controller; this correction permits the output to revert toward normal values in the face of the disturbance. Consequently, the presence of *feedback control* in biological systems allows important quantities to fluctuate within limits necessary for maintaining life in the face of many metabolic and environmental disturbances encountered by the organism.

In man-made technological control systems, the set-point is a physical quantity that can be varied at will (e.g., a thermostat setting for a home heating system). Biological systems, however, often have neither a reference input nor an error detector. The establishment of a set-point, or an *operating point*, in mathematical models of biological systems is often included for convenience, only because the real system behaves as if it were controlled by such a reference value [1,2].

In terms of the example described previously, blood pressure is the controlled feedback variable (Y_o) and peripheral resistance can be considered the controlling variable (Y_c). The controlled system consists of components that transform changes in blood pressure into changes in peripheral resistance (i.e., baroreceptor afferent signals, CNS processing, efferent signals, effect of autonomics on vasculature resistance). A typical blood pressure load disturbance (Y_i) might be an infusion of blood into the circulatory system (which implies that a description of the volume-pressure relationships of the circulation must be included in the controlled system) or the introduction of an upright tilt disturbance (which implies that a description of gravity effects on blood volume distribution must

be included in the controlled system). The set point (R_1) is the “normal” value for blood pressure.

A.2 Formulation of a Computer Model

It would be instructive to review the steps that lead from conceptualization of a model to digital computer implementation. Model systems can be graphically represented by some combination of boxes that represent the elements of the system. Such a representation is called a *block diagram*, which includes logic diagrams, schematics, flow diagrams, and system diagrams. An important step in constructing a model of any system is to draw a block diagram representing the blocks and their interconnections. This type of diagram, or series of block diagrams, becomes a “roadmap” or a “key” for taking a system apart and putting it back together. Some of the most common basic symbols used in a special form of block diagram, called an analog diagram, are shown in Fig. A-2. The analog diagram is an adaptation of the diagrammatic method so useful with linear systems. The mathematical operations are self-explanatory. As an example of the loosely termed “transfer function,” the graphical transfer function in the figure might represent the relationship between cardiac output x and right arterial pressure y . This transfer function can then represent a measured cardiac function curve.

As a specific example of the programming process, the subsystem of the circulatory, fluid, and electrolyte model that deals with angiotensin formation has been chosen. Figure A-3(a) can be construed as a hypothesis diagram for the open-loop control of renin-angiotensin. This diagram indicates the major factors that control angiotensin formation and the many effects of angiotensin on other subsystems. It is generally agreed that two of the major influences on renin release (a precursor to angiotensin formation) from the juxtaglomerular cells of the kidneys are renal perfusion pressure and the load of sodium filtered through the tubules (i.e., glomerular filtration times plasma sodium concentration). Renin enters the circulation and forms angiotensin, which has a slight negative feedback effect on renin formation (see dashed line in Fig. A-3(a)). The final effect of angiotensin is considered to be widespread, affecting vascular resistance, renal resistance, aldosterone secretion rate, thirst and drinking, and the rate of tubular fluid reabsorption.

To progress to a computer model of this system, each of the pathways connecting any two variables must be described in as much detail as necessary, commensurate with the objectives of the model design. Therefore, the next level of detail is shown in the block diagram of Fig. A-3(b), in which the relationships between variables are qualitatively organized. Functional relationships are identified wherever data describing hormonal secretion rates or hormonal effects are available. This diagram was developed from some very general algebraic relationships, and the mathematical operations of summation, division, multiplication, and integration are indicated.

Figure A-3(c) is the same diagram as Fig. A-3(d), reorganized to reflect the computer program names for each

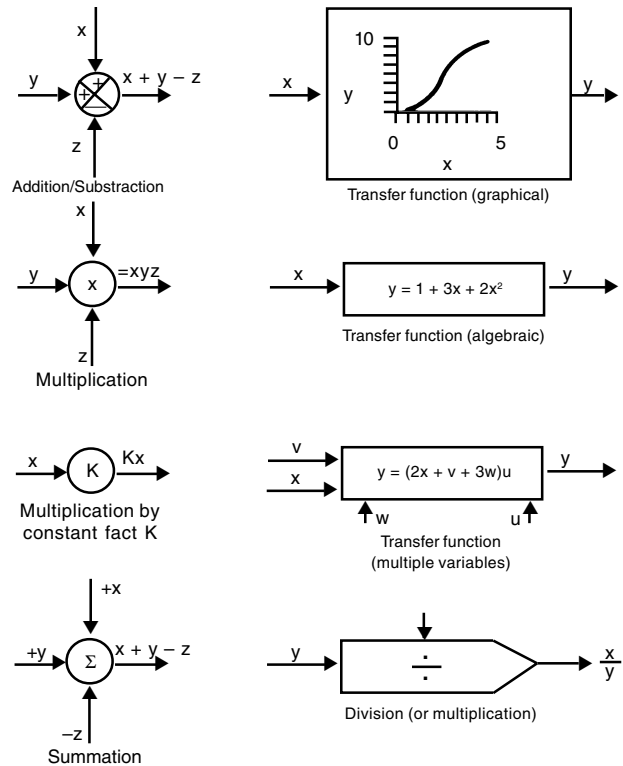
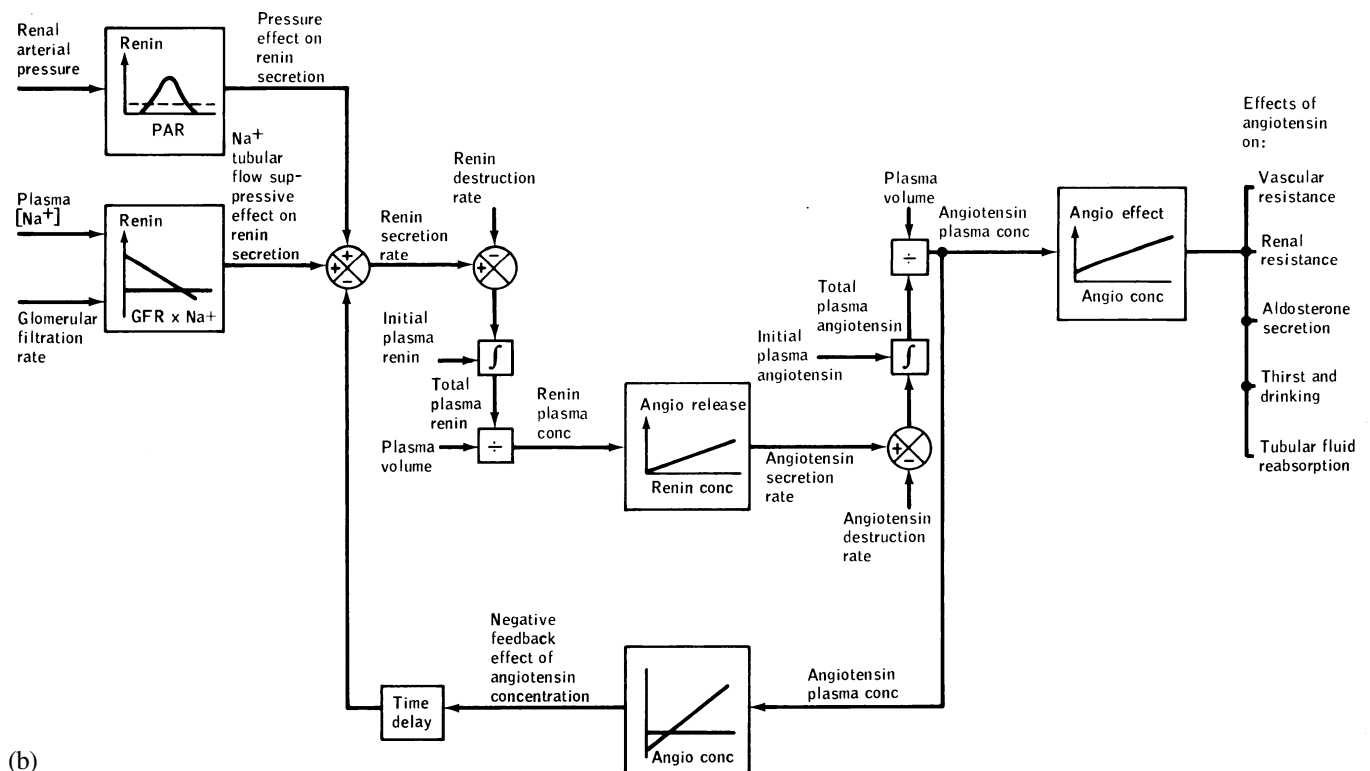
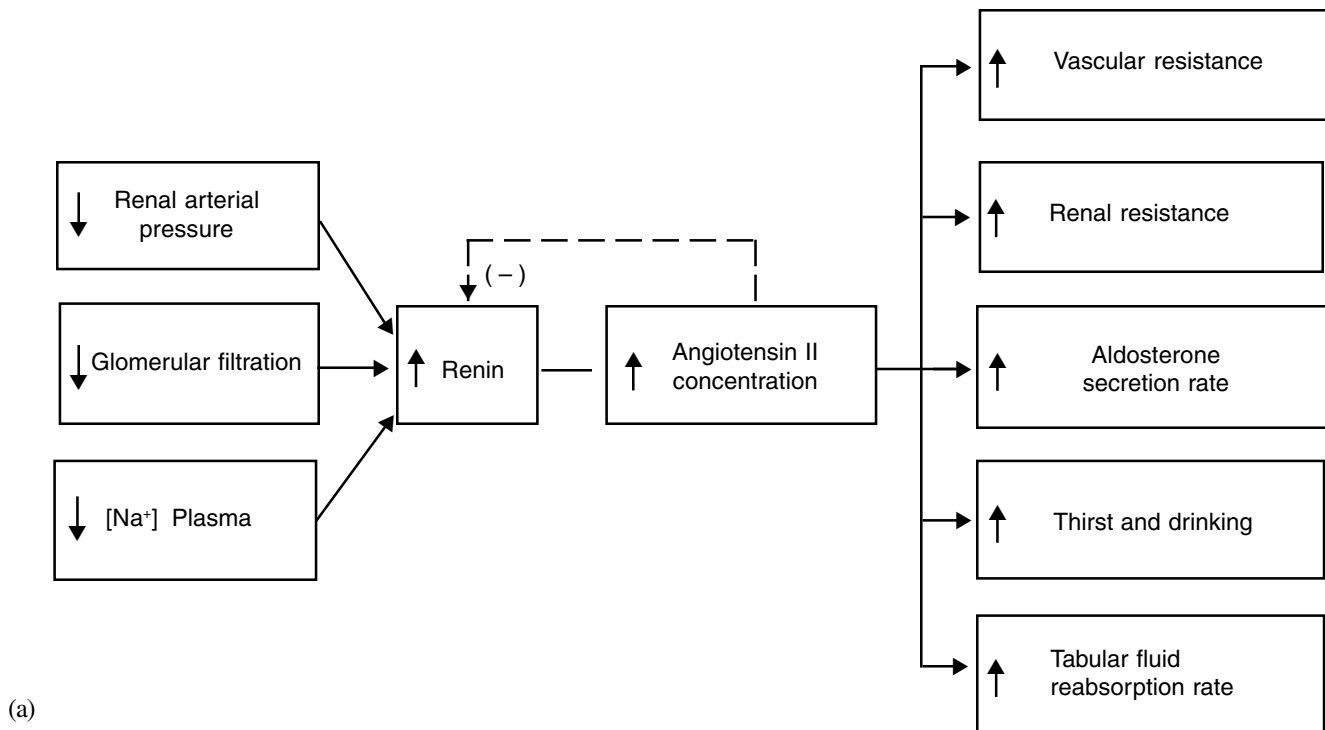


Figure A-2. Symbols used in block diagrams representing mathematical operations.

variable and the quantitative transfer functions for each element. It was common at one time to simulate models on analog computers, and Fig. A-3(c) is known as an analog diagram because it represents a circuit diagram for programming this segment of the model on an analog computer. However, a digital computer requires a different programming language, and Fig. A-3(d) is the Fortran version of the renin-angiotensin subsystem. The reader should be able to identify the meaning of the Fortran expressions from the previous diagrams. Note that the first statement represents a function relating renal pressure and renin secretion. In the analog computer, this function would be represented by a function generator; in the digital computer, it is represented by a table of x - y values (not shown) from which the desired operating points are interpolated. The exponential functions (e.g., $\text{EXP}(-I/\text{RNK})$) in Fig. A-3(d) are numerical approximations for integration, in which “I” is the integration step size.

It can be appreciated that the discipline of translating an ordinary physiological hypothesis diagram into a quantitative computer representation can lead to a better understanding of the biological system. Available data from diverse sources are integrated into a common framework; other data are excluded as being nonessential for the given level of detail (i.e., importance of data can be ranked), and missing information, which suggests the need for new experiments, is quickly identified.



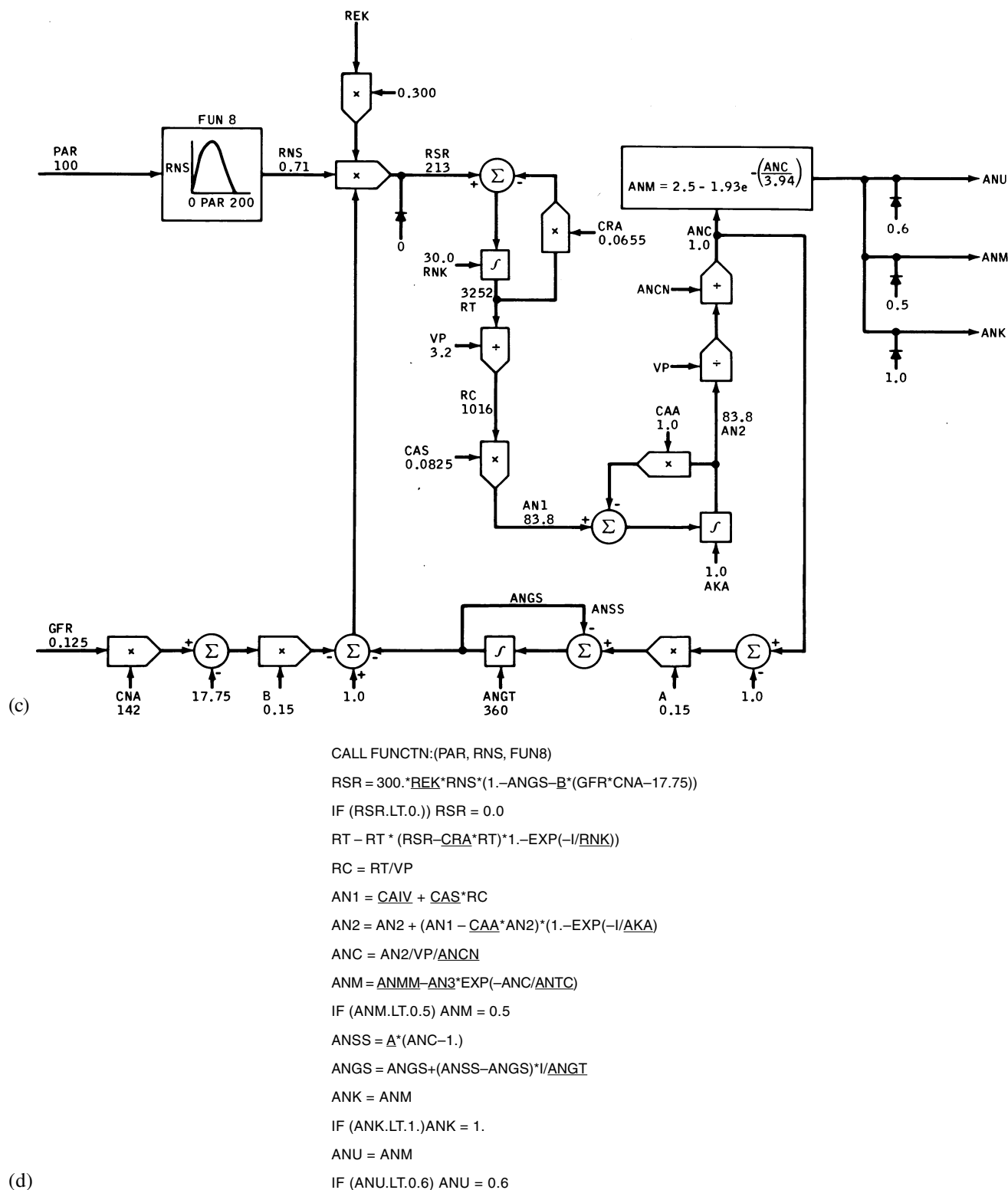


Figure A-3. Formulation of a control system algorithm (a) Hypothesis diagram showing factors which influence renin-angiotensin production and the quantities which they influence. These represent the assumptions for one of the hormonal subsystems in the Guyton model. (b) A more detailed block diagram of the hypothesis diagram of Fig. A-3(a) showing the mathematical operators relating each quantity. (c) An analog computer diagram of the renin-angiotensin system. This diagram contains sufficient information to wire a patch panel for programming an analog computer. (d) A Fortran algorithm for the renin-angiotensin control system as it appears in the Guyton model. The symbols can be interpreted from the preceding diagrams.

A.3 Simulation Techniques

Once a model is implemented on a computer and verification procedures ensure that it is operating appropriately, the model is ready to be tested for accuracy. A model that is deemed credible can be used to describe the behavior of the system in terms familiar to control engineers and can be used to predict system responses in terms that can be tested by biological experimentation. Some of the more important techniques used to produce model credibility and to predict system behavior are discussed below.

A.3.1 Dynamic Simulation

In the context of this study, obtaining the solution to a model means introducing some type of load disturbance (i.e., a parameter perturbation) and solving the model's differential equations iteratively, using numerical techniques. This process, known as dynamic simulation, is accomplished using high-speed digital computers and results in time-varying values of the dependent variables. These responses are examined in qualitative terms for their reasonableness by analysts who are familiar with the physiological system or, more often, they are compared quantitatively with experimental data. In this project, simulation responses were available from digital computers in tabular and graphical form and could be compared with previously stored data.

A.3.2 Sensitivity Analysis

Sensitivity analysis is a method for studying system responses due to variation in parameter value [3]. The conceptual basis of sensitivity analysis is simple; small variations are made in the values of the system parameters of a model, and the effects of these changes are observed individually in the solution (see Appendix E). Sensitivity functions that describe the observed effects may be computed, and these are interpreted to extract information about the dynamic system that could not be obtained from simply finding solutions with a particular set of input conditions. Sensitivity analysis provides the following.

1. A quantitative means of comparing the relative importance of individual parameters on any system variable;
2. A means of determining interactive effects of two or more parameters on model behavior;
3. A tool to help assess the validity of a particular model without the need to collect and use extensive measurements from the real system;
4. Information in a form that can be easily interpreted by those familiar with the subject matter of the model but not necessarily knowledgeable of simulation techniques;
5. A means of assigning relative importance to all parameters, a process that can be valuable both to the simulator in performing parameter estimation or stability analysis and to the experimenter in allocating resources for data collection;
6. A practical method of analyzing and comparing two different models designed to represent the same physical system.

A sensitivity analysis is very useful when performed early in model development, before model validation. This analysis is particularly important to the experimenter, who can help evaluate the model based on the relative sensitivities of the parameters without really knowing much about the model. The technique also is useful for involving the experimenter early in the modeling process, another important factor for eventual model acceptance [6]. The results of the sensitivity analysis must be evaluated in the light of other known information about the real system. For example, the fact that a parameter has a very significant effect on a particular variable of the model is of little importance if it is known that the parameter in the real system is relatively constant or that changes in other parameters are capable of canceling the original effects.

Although sensitivity analysis can be considered to be a special case of dynamic simulation, there are several important differences between these two procedures.

1. Sensitivity analyses are characterized by comparatively small perturbations.
2. Sensitivity analyses often are performed by varying one parameter at a time.
3. Sensitivity analyses often are performed to obtain sensitivity functions rather than solutions of the dependent variable.
4. Sensitivity analyses usually entail comparisons between two or more simulation runs rather than between model results and experimental data.

Examples of sensitivity analysis are provided in the descriptions of the erythropoietic model (Chapter 3.2.4.2) and of the thermoregulatory model (see Appendix E).

A.3.3 Variation of Parameters

Once a parameter has been identified as being particularly influential, either by sensitivity analysis or from direct knowledge of the real system, it is often desirable to determine the effect of different parameter values on specific variables. For example, the volume of blood is known to be important in the blood flow/pressure response to upright tilt from the supine position. It is reasonable to ask, "How does the response change as more and more blood is removed?" Another way to pose this question is, "What is the effect of hemorrhage on standing?" Documenting this effect with a simulation model of circulatory control is relatively straightforward; the parameter representing blood volume is assigned a series of values (i.e., a percentage of the control or normal value) and, at each level, a dynamic simulation is performed. The resulting time-varying responses (of, for example, heart rate, cardiac output, or blood pressure) can be plotted as overlays on the same graph. If steady-state responses are desired, the graph often is constructed with blood volume on the abscissa and the response variable on the ordinate (see Fig. 7-8).

A.3.4 Error Analysis

Parameters values are never known with 100% accuracy. If the standard deviation (SD) around the mean value can be estimated for each parameter, it is possible to place

statistical confidence limits on a model's behavior. For the example discussed previously, assume an experiment is performed in which blood volume reduction is measured as $-10\% \pm 1.5\%$ (SD). Dynamic simulations can be performed for three values of blood volume: -8.5% , -10% , and -11.5% , corresponding to the mean minus SD, the mean, and the mean plus SD, respectively. The response, for example, for heart rate could also be expressed in terms of a mean and a deviation. This expression would represent a prediction of the minimum error interval in the response variable, because of the inherent design of the system and the uncertainty in measuring blood volume, but would not include any experimental errors that could occur in measuring the response variables. Conversely, if a decrease in the confidence interval of a response variable to a given width was desired, it would be possible, using these techniques, to determine the minimum experimental accuracy required in measuring the independent parameter.

Error analysis becomes especially desirable in large-scale systems containing many parameters that promulgate errors through the model, and in certain nonlinear systems in which the interactive effects of different parameters lead to amplification of individual errors. Unfortunately, even though the techniques to accomplish this analysis are rather straightforward, there are few examples in the literature of physiological systems.

A related problem that has application to error and sensitivity analysis is the effect of noise on the behavior of the system. Noise can be described as a statistical disturbance of a particular variable, and it is characterized by statistical properties such as mean value, probability distribution, or spectral density. Model output variation which results from noise can be found by including a distribution function for each parameter or variable that exhibits noisy behavior. This problem becomes extremely relevant in parameter estimation analysis when model output is compared to data having a significant noise level [4].

A.3.5 Stability Analysis

At this point it is appropriate to mention stability analysis of dynamic systems because of the inverse relationship between sensitivity and stability in negative feedback systems. In general, sensitivity to disturbing factors can be reduced by an increase in feedback gain (in technological systems at least). However, instability occurs as a consequence of this gain increase. Thus, systems with high gain may have low sensitivity to external perturbations but may also be operating on the borderline of instability. Most biological systems are normally stable, and they do exhibit low sensitivity. Whether they are working somewhere near the stability limit by way of high gain factors is not known but should be studied on a case-by-case basis [5]. An analysis of stability can become an important measure of the competence of a model, in that if both model and actual system can be thrown into instability due to the same parametric changes, there is reason for having greater confidence in the mathematical representation.

Little practical work has been done on stability analysis of complex physiological systems. Formal techniques

for investigating stability in linear systems and in simple nonlinear systems have been reported [4,6]; but, for the most part, studying large-scale nonlinear models is a trial-and-error experience. Systems that exhibit oscillatory or periodic behavior in normal operation (e.g., eye movement, respiration) can often be made unstable more easily than systems that behave monotonically. Inherent instability is dependent on the properties of the system and is normally not a function of the specific disturbance. If the system is inherently stable, all transients will ultimately disappear regardless of the disturbance causing them. Conversely, any disturbance to an unstable system will initiate oscillations that increase in amplitude with time.

Stability can arise from either inherent features of the real system or from structural features of the mathematical model (such as a long integration interval). The techniques of sensitivity analysis can reveal both types, although it is not always possible to distinguish between the two. Like sensitivity, stability is a function of the operating point; therefore, all possible operating points must be tested for stability. A careful, systematic sensitivity analysis may often reveal not only points of instability but their causes as well.

A.3.6 Parameter Estimation

The object of parameter estimation (or identification) analysis is to determine the value of one or more parameters in a model. The parameters selected for estimation are usually impossible or difficult to measure directly in the real system. In practice, the technique involves repetitive adjustment of the parameter values until some objective judgment of acceptable correlation between model output and corresponding measurements in the system prototype has been satisfied (see Fig. A-4). The automatic optimization of parameters has been the object of considerable attention [7], consequently, there is a large body of literature on parameter estimation in physiological systems and algorithms.

The error criterion used in parameter estimation is usually a difference function of the form

$$e(t) = y(t) - y^*(t)$$

where y^* is a dependent variable that has been measured in the real system, y is the corresponding model variable, and t is time. The error criterion E is a function of e , usually $|e|$ or e^2 , integrated over a specified time interval; e.g.,

$$E = \int_0^T |e| dt$$

Since y is dependent on the system parameters q_i , e can be expressed as $e(t) = e(t, q_1, q_2, \dots, q_m)$. The criterion for the best fit between data and model is achieved when E reaches a minimum value.

Not every parameter can be estimated with the same degree of accuracy. Parameter estimation is used most effectively on parameters exerting a strong influence on a particular model variable that can be easily measured in

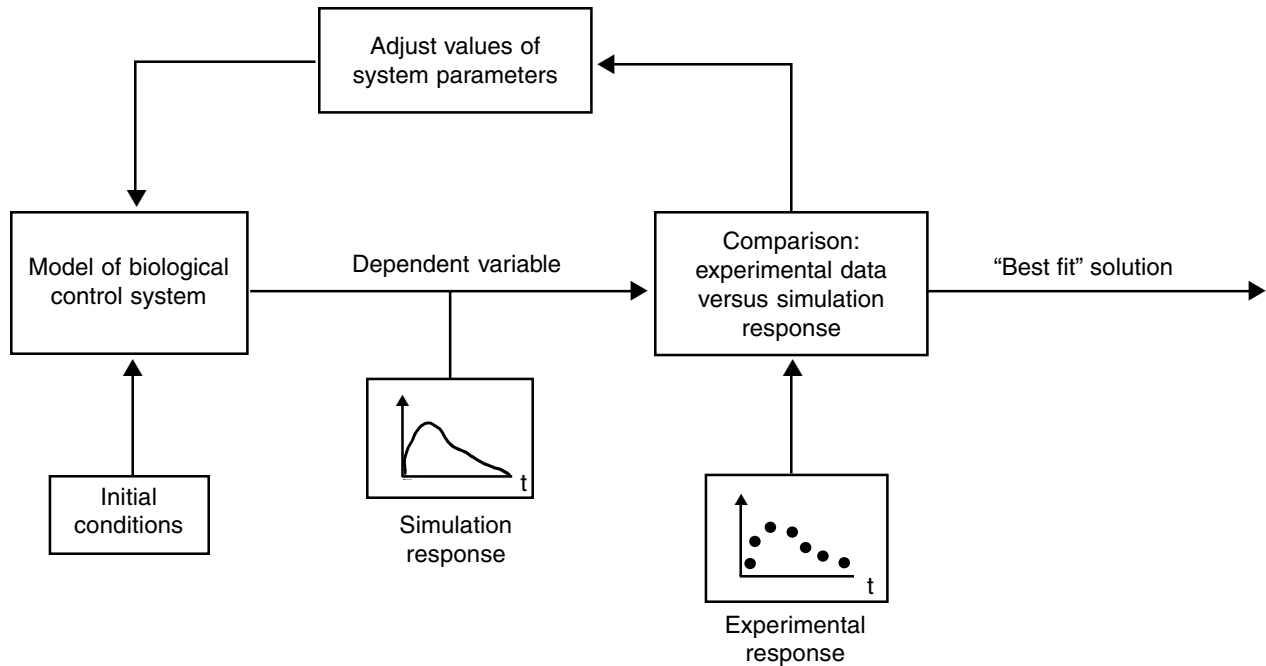


Figure A-4. Simulation procedure for parameter estimation. This method of fitting model output to experimental results can produce values for system parameters that are difficult to measure directly.

the real system. A useful technique for determining which parameters can be estimated with greatest precision is sensitivity analysis, discussed earlier in this Appendix. If sensitivity analysis is used before parameter estimation, it is possible to select those parameters with the highest sensitivity coefficients as the best candidates for parameter estimation analysis. When the parameter sensitivity is low, then that parameter value cannot be estimated with as much certainty. The low-sensitivity parameter should be set at a reasonable constant value determined from other sources.

If the problem of sensitivity analysis is expressed as determining the behavior of a model given all the parameter variations, then the inverse problem would be to determine (or identify) the parameter variations capable of producing a given behavior of the real system. Unlike sensitivity analysis, variation of parameters, error analysis, and stability analysis, parameter estimation requires data measurements from the real system. This inverse problem may not have a unique solution. Nevertheless, it would be valuable to know the various solutions possible, since this knowledge would be a great aid in hypothesis testing. If several different parameter perturbations could produce similar model results, it might be possible to accept the most reasonable, based on physiological plausibility; alternatively, this information could provide the basis for further experimental testing.

A.4 Model Validation

The validation process is primarily concerned with demonstrating the accuracy and the capability of simulation models. Two general criteria must be met before model

credibility can be established. First, a quantitative variable or parameter validity criterion must be met, and, second, a qualitative “plausibility” criterion must be met. The first condition refers to tests in which model output is compared directly to experimental data, whereas the second condition includes all other tests in which only the general behavior of the model is examined on a more subjective basis. In the first case, a high degree of fidelity in model response is expected, whereas in the second, the model responses need only be “reasonable.” No validation procedure is appropriate for all models. Rather, validation depends on the nature of the model and the goals and objectives of the modeling study.

A.4.1 Quantitative Tests

An important aspect of validation involves comparing the behavior of the model’s dependent variables with that of their experimental counterparts for the same stress. Differences between model behavior and experimental data can often be corrected or minimized either by introducing new, previously omitted elements into the model’s structure or by modifying the existing structure (i.e., adjusting the value parameters that are not well known).

The extent to which the validation process can be carried is often limited by data availability. Thus, if only steady-state data are available, validation in the dynamic, or transient, mode cannot be performed, even though the model has that capability. Similarly, if only a relatively small number of experimental variables have been measured during a particular stress, then it is possible to validate the model for the responses of only those measured variables; simulated values of all other variables can be

obtained but should be considered as predictions requiring experimental verification. The response of the body to a given stress is almost always related to the level or intensity of that stress, and more often than not, the relationship is nonlinear. Therefore, to validate the model properly, it is desirable to obtain data not merely for a given stress but for a range of intensities of that stress. If it is important to simulate more than one type of stress, the validation process will result in a more accurate model if the experimental response of the same variable is known for each of the desired stresses. Thus, an idealized set of experimental data suitable for complete validation of a complex model should include the following.

1. Steady-state data
2. Transient data
3. Data for a wide range of stress intensities
4. Data for all major dependent variables of interest or importance
5. Data for a variety of stresses

In addition, since experimental protocol, measurement techniques, and number and type of subjects may vary widely from one investigation to another, even when studying the same stress, it is desirable to obtain many of these data from the same experimental study.

The data used to validate the model should meet several conditions:

1. The data used for model validation should be different than that used in model development. The model must be capable of predicting beyond the data from which the model was generated.
2. The data must be of sufficient precision to make the test meaningful. The data should cover the range of interest and should have a minimum level of noise. The latter condition is best assured by including data representing a large subject population.
3. The data should be gathered under conditions similar to those represented in the model. Not all data are appropriate for use in validation. The assumptions about the biological system being studied are often reflected in the experimental protocol used to gather the data, and these are often not the same assumptions used in the model.

Obtaining good agreement between a simulation response and data is especially important when trying to simulate a diverse number of variables having constantly changing values. Agreement between simulation response and data is often improved by adjusting parameter values. This procedure is the same as that described under parameter estimation techniques. More than one combination of parameter values may lead to a good “fit.” In these cases, it is important that all changes be reasonable and consistent with known physiological processes.

A.4.2 Qualitative Tests

The purpose of modeling and simulation, in the context of the current study, is not necessarily to produce an

optimal fit between experimental data and model output, although this result would not be undesirable. Rather, the objectives are to help understand the behavior and interactions of the system and its components and to assist in new experimental approaches. Model credibility, in this case, can also be established by performing fewer quantitative tests.

Often, the model analyst is content to verify initially that the “shape” of the data and model output agree. This situation would occur if the modeler were primarily interested in the validation of model dynamics as contrasted to the exact fit of model output and data. In this case, it is not considered critical that the absolute magnitude of the response be without error; this type of discrepancy can often be remedied by the adjustment of a system parameter.

An important criterion for indicating whether a model is good enough to be used for forming conclusions about the real system is that a one-to-one correspondence and similarity of form must exist between model and real system. So-called “black box models” (i.e., models which represent overall behavior of systems without representing their underlying mechanisms) are not good models for making predictions regarding general system behavior; at best, they may be used as descriptions of data. Thus, there is always some model that can fit a particular set of experimental data (usually by adjusting one or more parameters), but only the biological plausibility of a particular model justifies preferring it to all others. Therefore, the inclusion of a greater number of adjustable parameters in a model, although perhaps providing a better agreement with the data, does not necessarily add insight into the physiological mechanisms.

The techniques described earlier in this Appendix—sensitivity analysis, error analysis, stability analysis, and variation of parameters—do not require extensive data sets. They can be very useful in establishing the plausibility of a model without necessitating excessive analysis of the mathematics of the model and all the explicit and implicit assumptions. Sensitivity analysis, in particular, can be important in this regard by quickly and systematically analyzing these component relationships without the need of actual subject data. This capability is particularly useful in comparing two different models.

For a model to contribute to a particular investigative field, it must ultimately be judged by scientists familiar with that area. When these scientists are not the people who developed and validated the model, it is important that lines of communication between them be established as early in the modeling process as possible. Model validation, ideally, should be an interdisciplinary process. During this project, the experience has been that general simulations, sensitivity analyses, or parameter variation studies performed without comparison to good experimental data appear to make less of an impact on experimenters not familiar with systems analysis than the same work supplemented with at least a single simulation showing reasonably good agreement with experimental data.

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Appendix B

Detailed Description of the Model for Regulation of Erythropoiesis

This Appendix contains the complete mathematical description of the erythropoiesis regulatory model. As this is the simplest of all models considered in this project, it provides a convenient example of how a physiological model is constructed. Reference should also be made to the overall description of the model provided in Chapter 3.2.4 and a diagrammatic view of the model in Fig. 6-10, as well as simulations of the model throughout Chapter 6.

The model developed for the spaceflight hematological program was designed to examine the relative influence of the controlling factors of erythropoiesis on total red blood cell (RBC) mass. The formulation was based on the generally accepted concept that the overall balance between oxygen supply and demand regulates the release of a hormone, erythropoietin, from renal tissues sensitive to oxygen tension levels and that this substance in turn controls bone marrow red cell production [1,2,3].

The amount of oxygen delivered to the tissue is accounted for in the model by the combined influence of several factors: hemoglobin concentration, lung oxygenation of hemoglobin, blood flow, and oxygen-hemoglobin affinity [4]. From this amount of oxygen, a certain fraction is extracted by the tissue depending on the oxygen demand parameter. Oxygen enters the cellular spaces by diffusion along an oxygen tension gradient between the venous capillaries and the cell [5]. Decreasing the oxygen supply in relation to the demand reduces tissue oxygen tension that is, in effect, monitored by a local oxygen detector [6] and results in increased rates of erythropoietin release [7]. Erythropoietin is released into the general circulation, and its final plasma concentration is determined by its rate of release, its volume of distribution, and the rate at which it is metabolized [8], the latter being represented in the model by the hormone plasma half-life. The target organ for erythropoietin is the bone marrow. The production rate and release of red cells in the model are determined by the plasma erythropoietin concentration [9]. A time delay exists between marrow stimulation and red cell release [10]. Destruction of cells is represented in the model by a lifespan parameter. Hemoglobin concentration in blood is based on the addition of new cells to existing cells and plasma.

It is known that red cell production is modulated by factors other than those considered in the model. These include iron levels [11], hormones other than erythropoietin [12], neural stimulation [13], as well as inhibitors and activators of erythropoietin [14]. Although it may be desirable to include these effects in future model applications, quantitative information regarding them is presently lacking or the need for their inclusion is not yet warranted.

Overall oxygen transport is under the control of homeostatic mechanisms in addition to the erythropoiesis system. Thus, some of the fixed parameters of the model such as blood flow, capillary diffusivity, arterial oxygen tension, plasma volume, and oxygen-hemoglobin affinity can be considered variable elements of circulatory, ventilatory, biochemical, and fluid regulatory feedback mechanisms that are beyond the scope of the current model's design objectives. Larger models that incorporate many of these features are available and these have been shown to be compatible with an erythropoiesis subsystem model [15]. Although these mechanisms are not included explicitly in the present erythropoiesis model, their influence can be tested, in most cases, by manual alteration of existing model parameters.

B.1 Mathematical Description of Model

B.1.1 Oxygenation of Blood

The oxygen concentration of arterial blood (neglecting oxygen dissolved in plasma) after passage through the lungs can be expressed as the product of the carrying capacity of a gram of hemoglobin ($CHbO$; i.e., 4 moles O_2 per mole Hb), times the hemoglobin concentration (Hb), times the fractional degree of oxygen-hemoglobin saturation (S_aO). It is convenient to use hematocrit rather than hemoglobin concentration as an index of red cell concentration in blood. These quantities are related by the mean corpuscular hemoglobin concentration, such that $MCHC = Hb/Hct$. Therefore, for arterial blood [1]

$$\begin{aligned} C_aO &= S_aO \times Hb \times CHbO \\ &= S_aO \times Hct \times MCHC \times CHbO \end{aligned} \quad (B1)$$

At full hemoglobin saturation, $S_aO = 1.0$, and Eq. (B1) then represents the maximum oxygen-carrying capacity of blood at a given hematocrit. In most instances, the parameters $MCHC$ and $CHbO$ will be invariant, so that the arterial oxygen concentration is influenced only by the hematocrit and hemoglobin saturation. In practice, the arterial oxygen tension (P_aO) is assigned a value,* and a corresponding value of S_aO is determined from the oxygen-hemoglobin equilibrium curve (OEC), an operation that can be expressed in functional form as

$$S_aO = OEC(P_aO) \quad (B2)$$

* See Table B-1 for symbol definitions, units, and normal values.

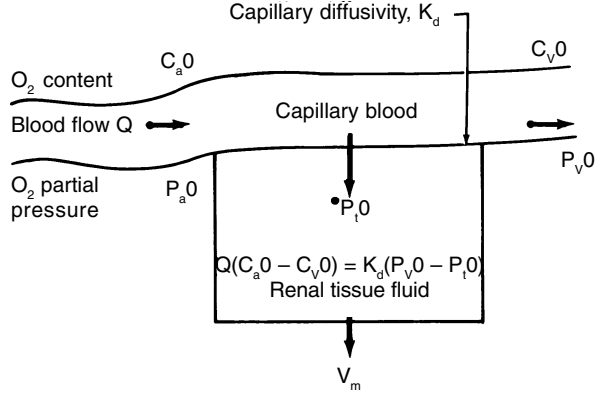


Figure B-1. Two-compartment steady-state model of renal tissue oxygenation.

B.1.2 Oxygen Delivery at Tissues

Oxygen transport at the tissue level is schematically represented in Fig. B-1. In the present model, the tissue of concern is taken to be the erythropoietin-producing cells known to be located primarily within the kidneys. It is assumed that the oxygen sensor as well as sites of erythropoietin production, is responsive to the mean oxygen tension of the kidneys. This assumption permits tissue oxygen tension to be derived from an oxygen balance using blood flows, arterio-venous oxygen concentrations, oxygen consumption, and transcapillary diffusion resistances common to the kidneys, which are considered to be a homogenous tissue.

The elements of tissue oxygenation were determined using a two-phase model consisting of capillary blood and tissue fluid [16]. It is assumed that the blood compartment is well mixed with an oxygen partial pressure (P_vO) equal to that in the venous outflow. Oxygen diffuses from blood to tissue along a gradient of oxygen partial pressure ($P_vO - P_tO$), where P_tO is the oxygen tension of the homogenous tissue. The amount of oxygen unloaded from the blood is given by the difference in oxygen concentration between arterial and venous blood ($C_aO - C_vO$). At equilibrium, the rate of oxygen transfer to the tissues is identical to the tissue oxygen consumption (V_m) and to the unloading of blood oxygen as determined by the arterio-venous oxygen concentration. In other words,

$$\underbrace{Q \times (C_aO - C_vO)}_{\text{Rate of oxygen unloading}} = \underbrace{K_d \times (P_vO - P_tO)}_{\text{Rate of oxygen diffusion}} = V_m \quad (\text{B3})$$

where Q is the rate of regional blood flow and K_d is the diffusive transfer coefficient between blood and tissue.

The venous partial pressure may be obtained by solving Eq. (B3) for C_vO

$$C_vO = C_aO - (V_m/Q) \quad (\text{B4})$$

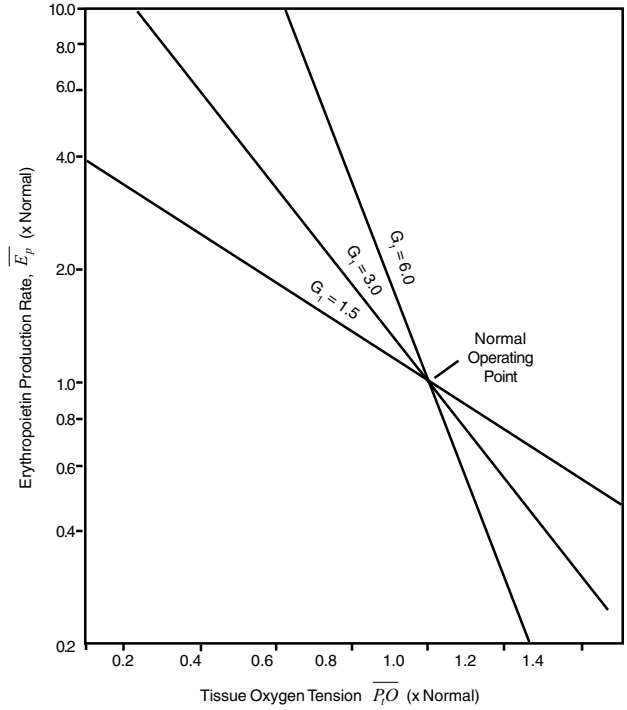


Figure B-2. Renal controller function for erythropoietin production rate showing effect of gain G_1 .

then computing venous hemoglobin saturation from a formulation analogous to Eq. (B1)

$$S_vO = C_vO / (Hct \times MCHC \times CHbO) \quad (\text{B5})$$

and determining P_vO from the OEC, expressed in functional form as

$$P_vO = OEC(S_vO) \quad (\text{B6})$$

Tissue oxygen tension can now be derived from Eq. (B3) as

$$P_tO = P_vO - V_m/k_d \quad (\text{B7})$$

The assumption of steady state in this formulation implies rapid equilibration of oxygen in the fluid phase and is not meant to suggest a constant tissue oxygen tension during the simulation of an erythropoietic disturbance. Since the erythropoietic process itself has been modeled dynamically, the hematocrit will be time-varying until red cell production achieves its own steady state. In this model, the hematocrit is a major influence on alterations in tissue oxygen tension. In addition, other quantities in this algorithm (P_aO , V_m , K_d , P_{50} , Q) are non-regulatory parameters and can also influence tissue oxygen tension if they are manually altered.

B.1.3 Erythropoietin Production and Distribution

Erythropoietin release is assumed to be governed by the tissue oxygen tension. A limited number of studies [5,17,18,19] suggest a relationship of the form[†]

$$\overline{E_p} = E_o \exp(-G_1 \overline{P_tO}) \quad (\text{B8})$$

where $\overline{E_p}$ is the rate of erythropoietin production, $\overline{P_tO}$ is the tissue oxygen partial pressure, G_1 is the gain or slope of the function plotted linearly as the natural log of $\overline{E_p}$ vs. $\overline{P_tO}$, and E_o is the $\overline{E_p}$ intercept at $\overline{P_tO} = 0$. Setting $E_o = \exp(G_1)$ ensures that Eq. (B8) will always pass through the normal operating point ($\overline{E_p} = 1.0$, $\overline{P_tO} = 1.0$) irrespective of values of G_1 . In certain cases, it may be desirable to postulate a shift in the normal operating point as well as gain, and in those cases, E_o and G_1 may be adjusted separately. Figure B-2 illustrates the semi-logarithmic relationship between tissue oxygen tension and erythropoietin production and shows the influence of G_1 .

The concentration of erythropoietin in the plasma (E) is a function of the rate of production (E_p), the rate of clearance or destruction (E_d), and the volume of distribution (V_e). If it is assumed that the rate of disappearance is proportional to the plasma concentration (i.e., $E_d = K_e \times V_e \times E$, where K_e = clearance constant = $\log_e 2$ /plasma half-life), then the following first-order differential equation can be written for the rate of change of erythropoietin concentration [8,17]:

$$\frac{dE}{dt} = \frac{E_p}{V_e} - K_e E \quad (\text{B9})$$

The steady-state concentration of E (at $dE/dt = 0$) is, therefore

$$E(o) = E_p(o) / K_e V_e \quad (\text{B10})$$

Eq. (B9) can be normalized by letting $\overline{E} = E/E(o)$ and $\overline{E_p} = E_p/E(o)$ and substituting Eq. (B1) into Eq. (B9):

$$\begin{aligned} \frac{d\overline{E}}{dt} &= K_e (\overline{E_p} - \overline{E}) \\ &= \frac{\log_e 2}{TE_{1/2}} (\overline{E_p} - \overline{E}) \end{aligned} \quad (\text{B11})$$

a form that has the advantage of being independent of distribution volume and, further, independent of erythropoietin half-life ($TE_{1/2}$) at steady state, since $\overline{E}(o) = \overline{E_p}(o)$. The value of $TE_{1/2} = 12$ hours was chosen for humans, but this does not appear to be well established for normal subjects [20].

[†] The bar over the symbols represents normalized values. Thus, $\overline{X} = X/X(o)$ where $X(o)$ is the control or pretreatment condition and X is a value during the post-control or treatment phase. The use of normalized values simplified comparison of model response with data from various laboratories.

B.1.4 Red Blood Cell Production

An equation expressing the semilogarithmic dose-response relationship between red cell production (RCP) and erythropoietin concentration (E) can be given as

$$\overline{RCP} = G_2 \log_e \overline{E} + P_1 \quad (\text{B12})$$

As has been the convention, RCP and E have been normalized with respect to their steady-state control values, G_2 is the gain or slope of the response curve, and P_1 is the value of RCP when $E = 1.0$ and is normally taken as unity.

The accuracy of Eq. (B12) may diminish considerably at very low and very high values of erythropoietin levels. For example, at decreasing values of E approaching zero, the production rate tends toward minus infinity rather than zero, whereas at high E values, the relationship does not exhibit a maximal production rate that is known to exist. Therefore, two additional equations were formulated and piecewise fitted to Eq. (B12) to account for suppressed and maximal erythropoiesis (see Fig. B-3). Their precise description is somewhat speculative, although this bone marrow function curve closely corresponds to the sigmoid shape of most biological dose-response relationships [21] and to those observed by others for the bone marrow [22,23,24].

In the present study, it was assumed that there is no basal production of red cells unless erythropoietin is present (i.e., $P_o = 0$). Maximal red cell production is assumed to be six times normal [17] ($P_m = 6$) and the upper limit of accuracy of Eq. (B12) was arbitrarily chosen at $RCP = 5$.

Iron uptake studies of red cells indicate a bone marrow transit time for red cell production of 3.5 to 4.5 days [10]. This effect was included in the model using a simple first-order time delay[‡] with a time constant T_{BM} . The inclusion of this transit delay clearly improved the realism of the dynamic response of the model, especially following sudden changes in tissue oxygen tension.

B.1.5 Red Cell Destruction and Red Cell Mass

The lifespan of the red cell dictates the destruction rate of cells. A model of red cell destruction was assumed in which cells are destroyed randomly and no cells survive past a given lifespan [25]. In that case, the rate of destruction (RCD) is simply proportional to the amount of cells present at any time. If that amount is given as RCM , then the rate of red blood cell destruction will be

$$\begin{aligned} RCD &= K_r \bullet RCM \\ &= \log_e 2 \bullet RCM / TRC_{1/2} \end{aligned} \quad (\text{B13})$$

where $TRC_{1/2}$ = red cell half-life and K_r = red cell clearance constant = $\log_e 2 / TRC_{1/2}$. At normal values used in the

[‡] If Y is the steady-state value predicted from a dose-response relationship, then the response delayed with a time constant T is obtained by the solution of the differential equation $T dy/dt + y = Y$. In finite difference form, suitable for iterative computer solution, this becomes $y_2 = y_1 + (Y - y_1) (H/T)$ where H = integration step size, y_1 = value of y at the i th iteration, and y_2 = value of y at the $i + 1$ th iteration.

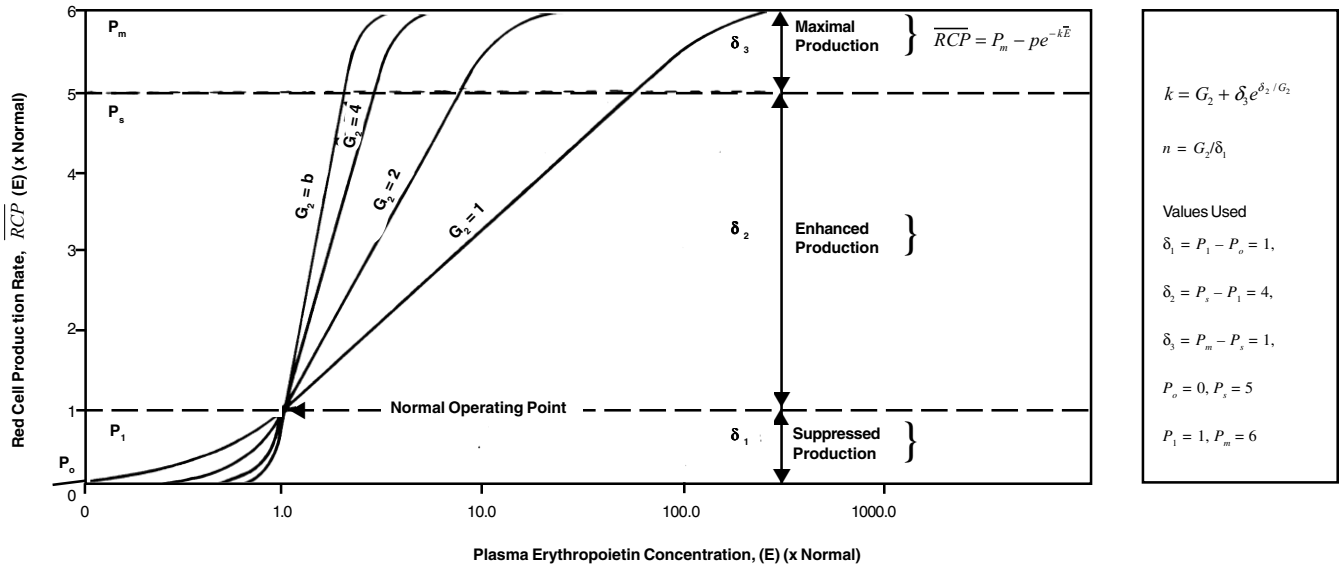


Figure B-3. Bone marrow controller function for red cell production rate showing equations used to piecewise fit the dose-response curve and demonstrating effect of gain G_2 (semi-log plot).

model, the rate of red cell destruction is 1.1% of the total amount present or 22 ml of packed cells/day.

The instantaneous change in total circulating red cell mass is the net difference between red cell production and red cell destruction rates:

$$\frac{d(RCM)}{dt} = RCP - RCD \quad (B14)$$

The quantity RCP is obtained from Eq. (B12) using the transformation $RCP = \overline{RCP} \times RCP(o)$, where $RCP(o) = RCD(o) = K_r \cdot RCM(o)$.

Finally, the current value of RCM , obtained by integration of Eq. (B14), is combined with the plasma volume to obtain the whole-body-hematocrit of the circulation:

$$Hct = \frac{RCM}{PV + RCM} \quad (B15)$$

and the feedback loop begun in Eq. (B1) is closed.

B.1.6 The Renal/Bone-Marrow Axis as a Proportional Controller

A more visual understanding of the relationships for renal and bone marrow function can be obtained by determining the overall dose-response curve of the combined kidney/bone marrow axis; that is, the relationship between tissue oxygen tension and red cell production. The results are shown here only for the midrange of erythropoietin production and were obtained by mathematically combining the renal function (Eq. (B9)) with the steady-state plasma distribution function of erythropoietin (Eq. (B11)); $E = \overline{Ep}$ and the bone marrow function (Eq. (B12)). In this way, erythropoietin is eliminated as an explicit variable; i.e.,

$$\overline{RCP} = G(1 - \overline{P_tO}) \quad (\text{for } \overline{P_tO} < 1) \quad (B16)$$

where $G = G_1 \times G_2$. This is a simple inverse linear relationship that has previously been used in the models of Guyton and co-workers [15] and Hodgson [5]. In this form, the gain of the renal/bonemarrow (open loop) system is seen to be the product of the two gain factors, G_1 and G_2 . Similar (although nonlinear) gain-product relationships were obtained for the extreme of hyperoxia and maximal hypoxia. The results of this analysis have been plotted in Fig. B-4 for a range of values of G . This function represents the entire controller circuit of the erythropoiesis model. In general, hypoxic tissue is predicted to have a greater effect on red cell production than hyperoxic tissue, as indicated by the relative slopes. However, at higher gain factors, the suppression of erythropoiesis can be considerable for relatively small increases in tissue oxygenation.

Equation (B16) is a typical controller function for a linear proportional control system in which the actuating error signal is the deviation of $\overline{P_tO}$ from its control value (unity) and G is the constant of proportionality or controller gain. The control value of $\overline{P_tO}$ is taken as an arbitrary reference standard and is not meant to imply that there is an internal set-point. It becomes clear from this control function that the primary controlled variable is tissue oxygen tension rather than red cell production, red cell mass, or hematocrit, which can be considered controller variables. The control system always adjusts the controller variables in a direction that returns the controlled variable toward normal after an initial load disturbance (see Fig. A-1 in Appendix A).

The controller gain is a major determinant of the final feedback compensation following a disturbance and, within limits, the speed at which a disturbance is corrected.

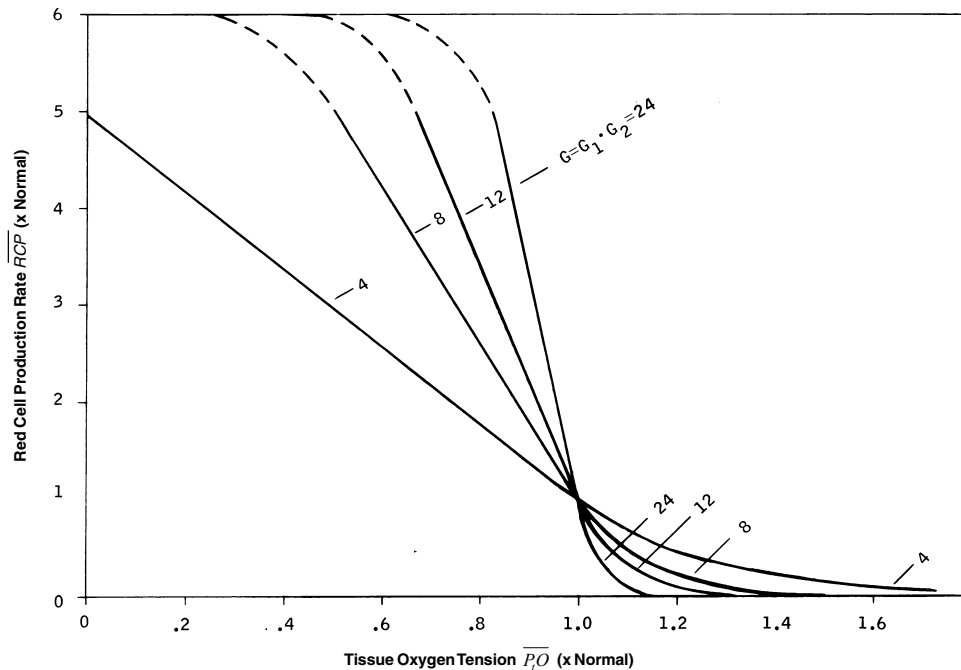


Figure B-4. Combined renal/bone-marrow controller function showing effect of tissue oxygen tension on erythropoiesis for various values of overall gain G .

Although increasing the gain increases the feedback effect, it may be at the sacrifice of an oscillatory approach to the steady state. Systems of higher order than this one will tend to become unstable as controller gain increases. Oscillations in the erythropoiesis system are known to occur in special cases, and analysis of these systems in terms of control system theory has proved to be rewarding [26,27].

B.1.7 Model Operation

The system of Eqs. (B1), (B2), (B4) through (B8), and (B11) through (B15) are solved by computer simulation using an iterative procedure. Equations (B11) and (B14) are integrated numerically using a simple Euler algorithm [28] and initial conditions $E(o)$ and $RCM(o)$, respectively. The program is currently implemented on a Univac 1110 and a PDP 11/40 using Fortran language. Remote terminals including graphic display of the simulation responses (and experimental data simultaneously, when desired) have greatly facilitated user interaction and have enhanced the convenience of model validation.

Perturbing the model away from its normal steady state (initial conditions) is accomplished by altering one of the model parameters.[§] These quantities are normally constant

in value but can be altered during a run to simulate either independent stress stimuli or long-term regulatory adjustments. Thus, hypoxia may be simulated by decreasing arterial oxygen partial pressure (P_{aO_2}), and hemolysis may be simulated by decreasing the red cell lifespan. In some cases, alteration of more than one parameter may be desired as in the simulation of altitude hypoxia that involves a primary change in arterial pO_2 and a compensatory shift in oxygen-hemoglobin affinity (P_{50}). Parameter values may be time-invariant with values fixed before a simulation run or they may be entered as a function that varies with time as the run progresses. Experimental data may be used to drive the model in this fashion. Thus, it is possible to simulate a wide variety of stresses and to test a large number of hypotheses regarding regulating mechanisms.

B.1.8 Parameter Estimation

Table B-1 lists the values of the system parameters, chosen as representative of the human system. Also shown are the steady-state control values (i.e., initial conditions) of the major dependent (output) variables. The precise values of most of the quantities shown in Table B-1 are not critical, however, to the general behavior of the model's response when expressed in percent deviation from control. An exception to this occurs for the highly nonlinear functions such as the oxygen equilibrium curves and the renal and bone marrow function curves. The location of the operating point on these curves can change the nature of the output response. Also, the shapes of these curves, as defined by the gains and threshold parameters, are critical to the magnitude of the response. These will be discussed next.

[§] The term "parameter" is used to denote time-invariant quantities that are not altered by the dynamic properties of the model as opposed to "dependent variables" that are time-varying and form the connecting links of the feedback circuit, i.e., P_{iO_2} , E , RCP , Hct , etc. (see Appendix A).

Table B-1. Parameters and Initial Conditions

Symbol	Definition	Value	Units
Parameters			
$CHbO$	Carrying capacity of hemoglobin	1.34	ml O ₂ /g Hb
E_o	Intercept of erythropoietin function	20.09	x normal
G_1	Gain of erythropoietin function	3	Nondimensional
G_2	Gain of red cell production function	2	Nondimensional
K_d	Capillary diffusivity	0.567	ml O ₂ min ⁻¹ mmHg ⁻¹
		4.25	ml O ₂ min ⁻¹ kPa ⁻¹
$MCHC$	Mean corpuscular hemoglobin concentration	0.375	g Hb/ml RBC
P_aO	Oxygen tension in arterial blood	95.0	mmHg
PV	Plasma volume	3.0	Liters
P_m	Maximum production rate of red cells	6	x normal
P_o	Minimum production rate of red cells	0	x normal
P_1	Normal production rate of red cells	1	x normal
$P50$	Oxygen tension of hemoglobin at 50% saturation	26.7	mmHg
Q	Renal blood flow	1.2	Liters/min
TBM	Bone marrow transit time	4	Days
$TE_{1/2}$	Plasma half-life of erythropoietin	12	Hours
$TRC_{1/2}$	Red cell half-life	63	Days
V_m	Oxygen uptake of kidneys	20	ml O ₂ /min
Initial Conditions			
C_aO	Oxygen content of arterial blood	19.6	ml O ₂ /100 ml blood
C_vO	Oxygen content of venous blood	17.9	ml O ₂ /100 ml blood
E	Erythropoietin concentration in plasma	1.0	x normal
	Erythropoietin production rate	1.0	x normal
Hct	Hematocrit	40	ml packed RBC/100 ml blood
P_tO	Oxygen tension in renal tissue fluid	20	mmHg
P_vO	Oxygen tension in venous blood	55.3	mmHg
RCM	Red cell mass	2.0	Liters
RCP	Production rate of new red blood cells	22	ml of packed cells/day
S_aO	Saturation of arterial hemoglobin with oxygen	97.6	Percent
S_vO	Saturation of venous hemoglobin with oxygen	89.3	Percent

An equation for the oxygen equilibrium curve was obtained from Aberman and co-workers [29]. Their study included a computer algorithm that converts oxygen tension to saturation and, with iteration, oxygen saturation to tension. The agreement between measured and computed values is claimed to be better than 0.2%. In addition, the algorithm includes the capability of altering $P50$ values (see Fig. B-5).

Analysis of Adamson's data [18] from which the erythropoietin release function was obtained, leads to an estimated value of $G_1 = 2.8$. In simulation studies of bedrest and hypoxia [30,31] values of G_2 were determined by parameter estimation to range from 2 to 5. No data exist to confirm these estimates directly. It is permissible to use the gain factors as adjustable parameters, within reasonable limits, in order to test hypotheses and possibly provide improved agreement between model and experiment

data. In addition to the gains or sensitivities, the other parameters of these functions (E_o , P_o , P_1) that can be thought of as threshold indices are also not well known and are available for parameter estimation during a simulation. Changing these latter quantities implies a shift of the normal rating points ($(E_p = 1, P_tO = 1)$ for Fig. B-2; $(RCP = 1, E = 1)$ for Fig. B-3). The value of K_d was obtained from Eq. (B7) by dividing the oxygen uptake by $P_vO - P_tO$. The value of P_tO was arbitrarily assumed to be 20 mmHg, and P_vO was computed from Eqs. (B1), (B2), and (B4) through (B6).

B.1.9 Steady-State Errors

It is an inherent property of most biological homeostatic mechanisms in general and proportional control systems in particular that there will be at least some residual steady-state deviation from the normal operating point

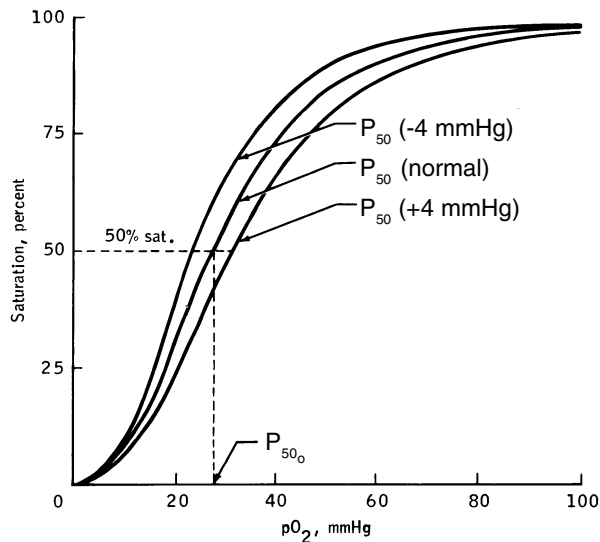


Figure B-5. Oxygen-hemoglobin equilibrium curves drawn directly from computer model output showing effect of changing the P_{50} parameter. The P_{50} value is the oxygen tension at which 50% of the hemoglobin is saturated and is, therefore, an index of oxyhemoglobin affinity. The position of the OEC may vary in accordance with known effects of hydrogen ion, CO_2 , temperature, or 2,3DPG (diphosphoglycerate). The effects of DPG are of interest because of its possible contribution to erythrokinetic changes during bedrest or weightlessness.

when the system is disturbed by a constant load. This “steady-state error” will vary in size depending on the gain of the system and the magnitude of the load disturbance. The sensitivity coefficients of Table 3-6, for example, indicate the steady-state errors of red cell production resulting from small changes in parameter disturbances.

A basis for understanding steady-state errors in the current model is as follows. At any equilibrium state, the term $dRCM/dt$ in Eq. (B14) must be identically zero. Therefore Eqs. (B13) and (B14) imply that, at steady state, daily red cell production and destruction rates are equal. Furthermore, if red cell lifespan is constant, a steady-state alteration in red cell mass implies a proportionate change in red cell production. Most load disturbances are accompanied by changes in circulating red cell mass (Fig. 6-13). This implies that red cell production and one or more of the factors that affect red cell production (including tissue oxygen tension, erythropoietin, hematocrit, controller gain, and set-point) must have incurred a steady-state error, however small. It can be appreciated from Fig. 6-13, that steady-state errors in tissue oxygen tension are reduced at the expense of larger errors in red cell mass and hematocrit.

Steady-state analysis may also provide insight into the independent determinants of the controlled variable [32]. Figure B-6(a) shows the effect of tissue oxygen tension on red cell production (the controller function of Fig. B-4) and the balance between red cell production and destruction. Feedback control ensures that the various elements of the model are adjusted until the rate of red cell mass change, $dRCM/dt$, becomes zero and that steady state

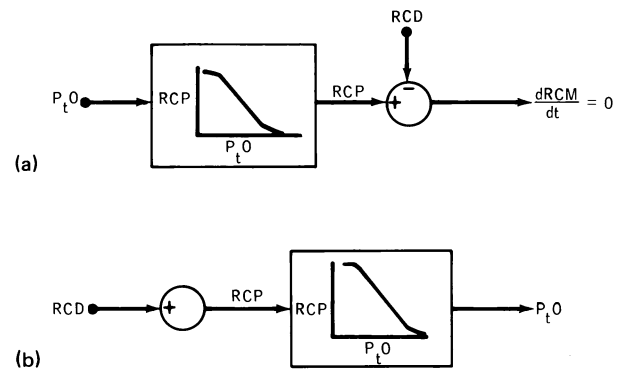


Figure B-6. Steady-state analysis of long-term determinants of tissue oxygen tension. (a) Segment of feedback circuit that results in the term $dRCM/dt$ becoming zero at steady state when destruction and production rates are equal. (b) Reversal of diagram in Fig. B-6(a) starting from the zero point and showing mathematically equivalent influences on tissue oxygen tension.

is defined by this condition. It is mathematically permissible to set $dRCM/dt$ to equal zero and work backward from this point to visualize those factors that determine tissue oxygen tension (Fig. B-6(b)). There are only two such factors in our model: red cell destruction (which determines production rate) and the relationship between tissue oxygen tension and red cell production. Only these factors and those quantities that affect these factors will ultimately determine tissue oxygen tension. Experimental evidence is severely lacking on the determinants of the shape of the controller function curve, although it appears that it may be under the influence of neural and biochemical factors (see Chapter B.2.2). The factors that are responsible for normal red cell destruction are also not apparent [10]. Except for overt pathology, rates of destruction are generally considered to be a constant fraction of total circulating red cell mass.

Aside from these experimental shortcomings, it is important to note that the factors usually agreed to play a role in acute changes of tissue oxygenation (i.e., blood flow, capillary diffusivity, oxygen uptake, P_{50} , hematocrit) are not represented between the zero point and the tissue oxygen point in Fig. B-6. Although they may be considered dependent variables in the system, none of them, from a mathematical point of view, are independent determinants of the final level at which the tissue oxygen tension will stabilize in the steady state. Although $dRCM/dt$ will always return to its initial zero value, the tissue oxygen tension may exhibit a steady-state error due to the inherent properties of the control system in the face of a constant disturbance. However, based on the preceding analysis, the authors believe that even tissue oxygen tension will return to its initial value (zero steady-state error) when both of the following conditions are satisfied: (1) a constant daily rate of red cell destruction and (2) a constant controller relationship between tissue oxygen tension and red cell production.

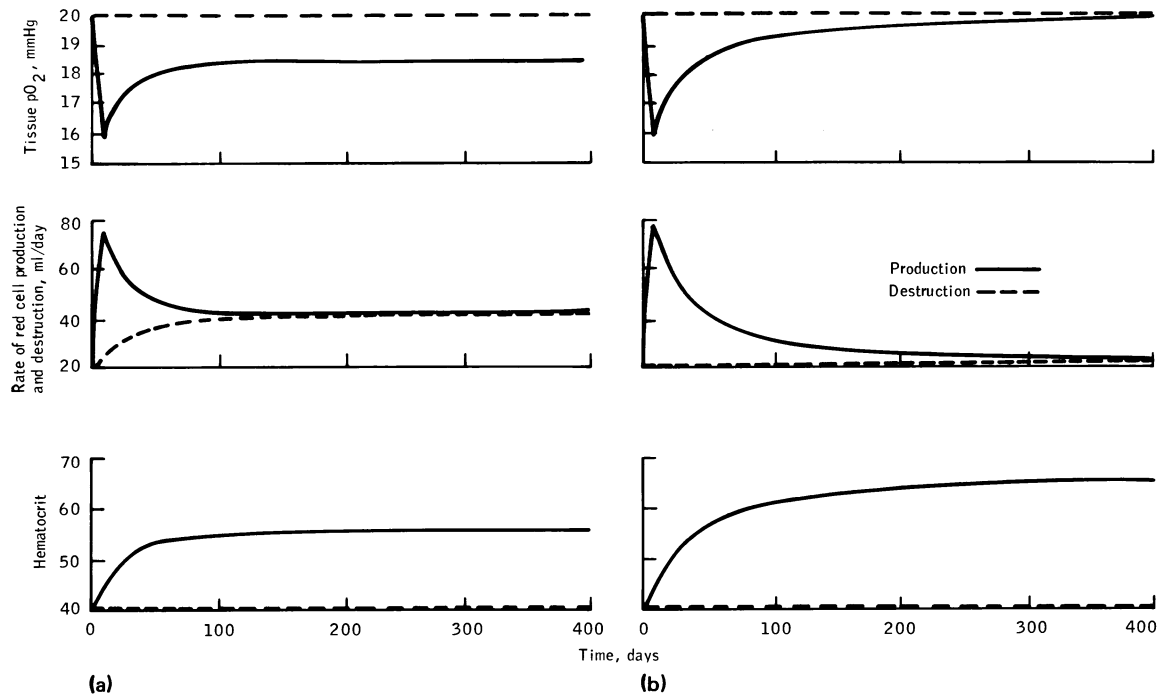


Figure B-7. Effect of destruction rate on long-term control of tissue oxygen tension. (a) Normal simulation response to hypoxic stress. (b) Hypoxic simulation with destruction rate clamped at control value and showing regulation of tissue pO_2 back to normal despite reduced P_{aO} .

As an example of the last point, a simulation of hypoxia was performed (Fig. B-7b) in which arterial oxygen tension (P_{aO}) was set at some low value for the entire run and red cell destruction was clamped at its control value of 22 ml of packed cells/day. Tissue oxygen tension decreased and then began to return toward normal as red cell production and hematocrit rose, similar to the simulations with the intact system shown in Fig. B-7(a). However, since the destruction rate was not permitted to increase, a greater net rate of red cells entered the circulation than would have occurred had destruction rate rose in accord with the mass action law of Eq. (B13). As a result, tissue oxygen tension continued to rise and red cell production rates declined. When the system reached its new steady state, red cell production and tissue oxygen tension returned exactly to the prehypoxic control conditions in accord with the concepts discussed in the previous paragraph. This was despite an arterial oxygen tension that was still significantly depressed and at the expense of hematocrit and circulating red cell mass that were considerably above normal.

It is perhaps easy to visualize that a primary change in destruction rate, as in hemolytic anemia, leads to secondary changes in tissue oxygen tension. It is more difficult to conceive of destruction rate being a determining factor of tissue oxygenation in a stress like hypoxia in which it appears, at first, that the decreased oxygen loading of arterial hemoglobin is the primary stimulus for hypoxia. However, it is important to distinguish between the initial stimulus of the acute phase, where blood pO_2 is controlling, and the ultimate stimulus of the steady-state condi-

tion, where destruction rate (and controller function) is controlling. These conclusions from a theoretical model may warrant further experimental examination. The simulation of hemolytic anemia presented in Chapter 6 (see Fig. 6-18) illustrates the capability of the control system to minimize steady-state errors.

B.2 Discussion

B.2.1 Renal pO_2 Sensor

A major assumption in the controlled system is the description of the renal oxygen detector. The evidence strongly indicates that the balance between oxygen supply and demand at intrarenal sites is the primary stimulus for erythropoietin release [33]. Furthermore, these detector sites must monitor venous or tissue pO_2 rather than arterial pO_2 since anemia or increased oxygen-hemoglobin affinity lead to increased erythropoietin production without significantly altering arterial blood oxygen tension [5,34,35]. The receptors sensitive to tissue pO_2 may be those cells that excrete erythropoietin or its precursor [13]. The present model is in accord with these concepts.

It has been suggested that the kidney has unique characteristics that enable it to function as a sensitive oxygen chemoreceptor and, in particular, be responsive to changing hemoglobin levels. The peculiar renal microcirculation and the uniquely low arteriovenous oxygen difference provide a gradient of tissue oxygen tension that amplifies changes in blood oxygen delivery [14,35]. In addition, the auto-regulatory features of the kidney ensure that

blood flow and oxygen uptake are effectively stable over a wide range of oxygen tensions and blood pressures [36,37]. Moreover, if blood flows should be altered, the kidney, in contrast to other organs, will exhibit proportionate changes in oxygen uptake [38]. This means that the ratio V_m/Q (the only term in which blood flow appears in the model (Eq. (B4))) may be relatively constant, and renal blood flow would not be expected to markedly influence tissue oxygenation.

The preceding discussion suggests that the powerful influence which oxygen uptake, per se, was found to have in the model (Fig. B-1 and Fig. 6-13) may be mitigated in the real system by concurrent changes in blood flow. Similarly, it is possible that an elevation of V_m , by whatever cause, promotes tissue hypoxia and results in local regulatory increases of K_d , the effective capillary diffusivity. This is now known to be true for skeletal muscle [39] but has not been confirmed for the kidney. Such regulation would, however, further dampen the effect of oxygen uptake because K_d appears only in the ratio V_m/K_d in Eq. (B7). It may be desirable to add these local regulatory effects—between oxygen uptake, blood flow, and capillary diffusivity—to the model. A current alternate approach is to assume they are constant and to examine their influence, if the data so suggest, in improving the accuracy of simulation. Under these circumstances, and in accord with Eqs. (B1) to (B7), tissue pO_2 would be a function of the hemoglobin concentration of the blood, the arterial oxygen saturation of hemoglobin, and the shape and position of the OEC [6].

It should be emphasized that the site of the intrarenal detector has not yet been confirmed and that the quantitative aspects of its oxygen supply-demand balance (including direct measurement of P_iO) remain unknown. Justification of this segment of the model is based on indirect evidence, gross characteristics of the kidney as a whole, and determinants of tissue oxygenation derived from other tissues.

The use of a steady-state formulation for tissue oxygenation (Eqs. (B1) to (B7)) in a dynamic model is justified because, in the well-perfused kidney, equilibrium of oxygen tension due to pure convection and diffusion may be achieved in the order of seconds to minutes following a load disturbance. This can be compared to the much slower changes of the erythropoietin distribution or bone marrow red cell production process. Estimates of true equilibration times were obtained from the non-steady-state version of this algorithm [16,40] that was originally employed in the NASA studies. The steady-state description permitted the use of a larger integration step size in the numerical algorithms and increased the solution speed significantly without decreasing the accuracy of the response for the long periods of time in which the investigators were interested.

B.2.2 Bone Marrow Controller System

An accurate description of the relationship governing erythropoietin release is not yet available, presumably because of the difficulty in measuring intrarenal oxygen levels and the uncertainty surrounding the specific location

of the receptor cells. The formulation used to relate tissue oxygen tension to erythropoietin release is in accord with the study of Adamson [18], who found a semilogarithmic inverse relationship between daily urinary erythropoietin excretion and hematocrit in humans. A parallel between urinary and plasma erythropoietin [7] as well as between hematocrit and tissue [41] pO_2 was assumed in deriving Eq. (B8). A similar relationship has been used by Hodgson [5], whereas Parer [42] has derived a linear relationship, and Mylrea and Abbrecht [17] have used arterial oxygen-hemoglobin concentration (i.e., $Hb \times S_aO$) rather than tissue oxygen tension as the independent variable. At the present time, sufficient data do not exist to reveal the precise shape of this function.

Measurement of plasma erythropoietin has, until recently, been restricted to levels above basal [1]. Therefore, no data are available to confirm the relationship to reduced release rates of erythropoietin. This region is of particular interest because of its application of simulation to bedrest, spaceflight, and related disturbances in which chronic elevation of hematocrit follows plasma volume shifts.

There is an abundance of information demonstrating that in experimental animals, a linear relationship exists between red cell production and the log of erythropoietin concentration (Eq. (B12)). This has been observed, for example, in bioassay animals in which doses of erythropoietin are injected either singularly with iron uptake used as the index of erythropoietic activity [2,24] or administered at frequent intervals for up to several weeks with production rate expressed in terms of increased red cell mass [9,23]. It is reasonable to assume that a similar dose response relationship exists for the human, although confirmatory evidence is lacking. In vivo estimates of the human function curve, especially for the suppressed erythropoiesis range, will be possible as erythropoietin becomes available in large quantities and as more sensitive assay methods for this hormone are developed.

The shape and position of the renal and bone marrow function curves have been found to be crucial elements in the control of erythropoiesis in general and in the long-term control of tissue oxygenation in particular. Model parameters have been incorporated to allow for shifts in sensitivities and thresholds away from the normal operating points. Values of controller sensitivities have not been well established in the human by direct methods and only to a limited extent in experimental animals [5]. Several studies suggest that alterations in these parameters occur during certain physiological stresses such as dehydration and hypoxia [43,44] and during pathological disturbances such as abnormal hemoglobin [34], erythrocytosis [18] and hemolytic anemia [45]. It appears that the rate of red cell production is determined not only by the concentration of erythropoietin but also by the size of the stem cell pool [46]. If the pool size increases, the bone marrow response to a given dose of erythropoietin should be greater than normal (i.e., an effective increase in G_1). The availability of iron to the erythron may also influence this function [11]. Certain hormones, such as androgens, as well as neural stimuli are assumed to exert their effect on erythro-

poiesis by their modification of erythropoietin release [12,13] (i.e., an effective change in G_1). It is possible, using the current model, to predict these parameters within narrow limits provided both the dynamic behavior of erythropoietin and red cell production rates are measured simultaneously during hematologic stress. Unfortunately, such data are seldom available, especially for humans.

B.2.3 General Comments

Feedback regulation of tissue oxygen tension is accomplished solely by adjustments of hemoglobin levels resulting from the output of a renal/bone-marrow controller. Other parameters that are known to effect acute changes in tissue oxygenation are incorporated explicitly in the model but are non-regulatory in nature and can be altered manually to test various hypotheses. Similarly, the characteristics of the controller can also be adjusted to test their effect on long-term control of tissue pO_2 and red cell mass. Such parameter adjustment (other than for the primary disturbance) has not been found to be essential, in most cases, to simulate the basic behavior of the dynamic and steady-state response. However, fine-tuning of param-

eters is required to scale the model output and achieve closer agreement with experimental values. In some cases, these studies indicate the need to propose additional regulatory elements to provide, for example, a more realistic simulation of the erythropoietin response to hypoxia. Other features of a general nature have also been identified that will increase the utility of the model even further, including (1) the effect of blood volume and viscosity on oxygen transport and (2) a description of stem cell kinetics and reticulocytosis [47,57].

B.3 Formulation of Mouse Model

B.3.1 System Parameters

The computer model for erythropoietic control was adapted to the mouse system by altering the system parameters originally given for the human, to those that more realistically represent the mouse [48]. Parameter values were obtained from a variety of literature sources as indicated in Table B-2. The immediate application of the mouse model was the study of the mouse as a potential experimental model for spaceflight. Data for the simula-

Table B-2. System Parameters for Erythropoiesis Control Model

Parameter	Model symbol	Parameter value		Reference	Units
		Human	Mouse		
Red cell mass*	<i>RCM</i>	2000	0.63	B-49	ml
Plasma volume*	<i>PV</i>	3000	0.77	B-49	ml
Blood volume	<i>BV</i>	5000	1.40	B-49	ml
Whole-body hematocrit	<i>Hct</i>	40.0	45.0	B-49	ml of packed RBC/100 ml blood
Mean corpuscular hemoglobin concentration*	<i>MCHC</i>	0.375	0.300	B-50	g Hb/ml RBC
Hemoglobin concentration	<i>Hb</i>	15.0	13.5	B-50, B-51	g Hb/100 ml blood
O ₂ capacity of blood*	<i>CaO</i>	20.1	19.0	B-51	ml O ₂ /100 ml blood
O ₂ capacity of hemoglobin	<i>CHbO</i>	1.34	1.41	B-50, B-51	ml O ₂ /g Hb
pO ₂ tension at one-half <i>Hb</i> saturation*	<i>P50</i>	27	39	B-52	MmHg
Arterial pO ₂ *	<i>P_aO</i>	95	78	B-53	mmHg
Arterial <i>Hb</i> saturation	<i>S_aO</i>	0.97	0.99	B-52	Percent
Renal metabolic rate*	<i>V_m</i>	20	0.04	B-54	ml O ₂ /min
Renal blood flow*	<i>Q</i>	1200	1.83	B-55	ml/min
Normal tissue pO ₂ *	<i>P_tO</i>	20	20		MmHg
Erythropoietin half-life*	<i>TE_{1/2}</i>	12	3.25	B-56	Hours
Red cell lifespan*	<i>TRC</i>	126	20	B-17	Days
Erythrocyte maturation time*	<i>TBM TE_{1/2}</i>	4	3.5		Days
Normal RBC production rate*	<i>RCP</i>	22	0.0437	B-49	ml RBC/day
RBC turnover rate	<i>RKC</i>	1.1	6.93	B-49	Percent/day

* Fundamental value from which other parameter values may be derived. Relationships used in deriving these other parameters are as follows:

Blood volume: $BV = RCM + PV = 0.63 + 0.77 = 1.4$ ml

Whole-body hematocrit: $Hct = RCM/BV = 0.63/1.4 = 0.45$ ml packed RBC/ml blood

Hemoglobin concentration: $Hb = Hct \times MCHC = 45 \times 0.3 = 13.5$ g Hb/100 ml blood

Capacity of hemoglobin: $CHbO = C_aO/Hb = 19.0/13.5 = 1.41$ ml O₂/g Hb

Arterial Hb saturation: $S_aO = \text{function}(P_aO)$ (See oxygen-hemoglobin dissociation curve (Fig. B-8).)

RBC turnover: $RKC = \text{turnover rate}/100 = 0.693/\text{RBC half-life } 0.693/20/2 = 0.0693$ per day = 6.93% per day

Steady-state destruction rate = $RCM \times RKC = 0.63 \times 0.0693 = 0.0437$ ml/day

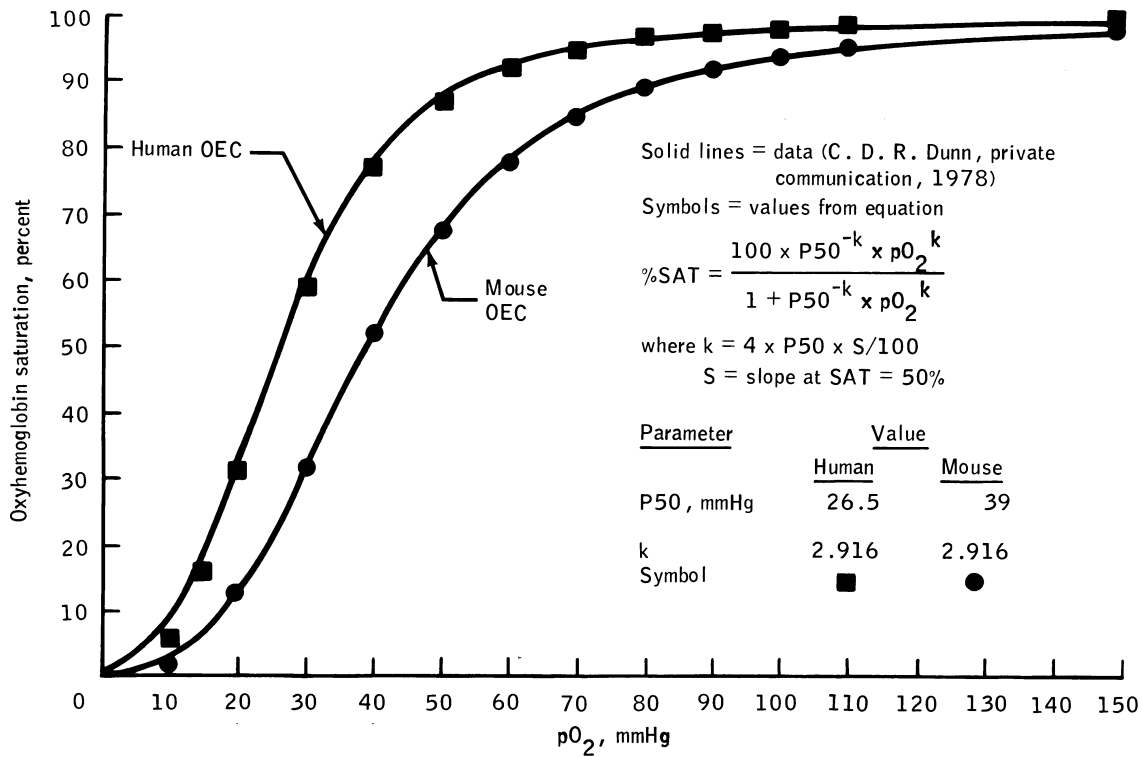


Figure B-8. Oxygen-hemoglobin equilibrium curves for human and mouse: experimental versus theoretical values.

Table B-3. Absolute Versus Specific Parameter Values

Parameter	Absolute units			Specific units*		
	Human	Mouse	Units	Human	Mouse	Units
Red cell mass	2000	0.63	ml	28.6	25.2	ml/kg body wt.
Plasma volume	3000	0.77	ml	42.9	30.8	ml/kg body wt.
Blood volume	5000	1.40	ml	71.4	56.0	ml/kg body wt.
Renal blood flow	1200	1.83	ml/min	4.28	6.10	ml/min ⁻¹ g ⁻¹ tissue
Renal O ₂ consumption	20	0.04	ml/min	0.73	0.133	ml/min ⁻¹ g ⁻¹ tissue
Body O ₂ consumption	250	0.51	ml/min	0.00357	0.0255	ml/min ⁻¹ g ⁻¹ tissue

*Based on

Body weight = 70 kg man and 25 g mouse

Renal mass = 280 g (0.4% body wt.) in man and 0.3 g (1.2% body wt.) in mouse

Table B-4. Oxygen Balance at Kidney

$ \begin{array}{c} \text{O}_2 \text{ supply equals} \\ \text{BF} \times \text{O}_2 \text{ concentration} \leftarrow \boxed{\text{Kidney}} \rightarrow \text{O}_2 \text{ venous} \\ \downarrow \\ \text{O}_2 \text{ demand} \end{array} $			
Parameter	Human	Mouse	Units
Oxygen demand	20.0	0.04	ml O ₂ /min
	0.073	0.153	ml O ₂ min ⁻¹ g ⁻¹
Oxygen supply			
P _a O ₂ , arterial	95.0	78	mmHG
S _a O ₂ , arterial	97.4	98.6	Percent saturation
O ₂ concentration	196.0	188	ml O ₂ /liter blood
BF, blood flow	1200	.0	1.83 ml
blood/min			
O ₂ supply	235.0	0.343	ml O ₂ /min
	0.839	1.143	ml O ₂ /min ⁻¹ g ⁻¹
Oxygen venous			
P _v O ₂ , venous	56.0	57	mmHG
S _v O ₂ , venous	89.0	86	Percent saturation
pO ₂ , tissue	20.0	20	mmHg
Percent oxygen extraction =	8.7	13.4	Percent
(O ₂ demand)/(O ₂ supply)			

tions were obtained from C. D. R. Dunn (University of Tennessee Memorial Research Center) and included studies of dehydration and hypoxia. The strain of mice used in these studies was C3H with an approximate weight of 25 grams. Parameter values were chosen for this strain where possible. In certain cases, the literature values were superseded by values obtained directly from Dunn's studies. In a few cases, mouse data were not available and data for the rat were substituted. A comparison of system parameters for the mouse and human models is shown in Table B-2. Aside from the obvious differences expected in fluid volumes, blood flows, and metabolic rates, large differences were observed in the following: erythrocyte lifespan (126 days vs. 20 days)** erythropoietin half-life (12 hours vs. 3.25 hours), and normal arterial pO₂ (95 mmHg vs. 78 mmHg). The shorter lifespan of the mouse red blood cells implies a turnover of erythrocytes that is six-fold faster. That is, the daily rates of red cell production and destruction (as well as reticulocyte index) are approximately six times higher in the C3H mouse than the human.** Other parameters that were found to be more similar between the two species were as follows: hematocrit (40 vs. 45), mean corpuscular hemoglobin concentration (0.375 vs. 0.30), and maximum oxygen-carrying capacity of hemoglobin (1.34 vs. 1.41).

** First and second numbers in parentheses refer to human and mouse, respectively.

†† Typical values for mice red cell lifespan found in the literature indicate only a threefold increase. Values used here were found by Dunn to be much different in the C3H strain.

Although the arterial pO₂ in the mouse is much lower than in the human, the oxygen saturation of hemoglobin of both species is nearly identical (97% vs. 99%). This is a result of the distinctly different oxygen-hemoglobin dissociation curves shown in Fig. B-8 and reflected in the different P_{50} values (26.5 mmHg vs. 39.0 mmHg). The P_{50} differences imply that, at the same level of tissue oxygen tension, oxygen is more easily unloaded in the mouse than in the human. It should be noted that the normal pO₂ of arterial blood assumed here (78 mmHg) was obtained from rat data [51,56] and has been used in a previous model validated for the mouse with reasonably good results [17]. No corresponding mouse data could be located. Values for renal blood flow of the mouse were not available, and data from rats were used (6 ml min⁻¹ g⁻¹ tissue).

B.3.2 Scaled Parameters

Some parameters of the mouse model differ considerably from the human model because of scaling factors alone. The values used in the model are given on an absolute basis for the whole animal rather than as a specific property in terms of "per gram of tissue." In terms of specific units, the differences between the mouse and human system are much smaller, as shown in Table B-3.

B.3.3 Oxygen Balance

The balance of oxygen supply versus oxygen demand is crucial to the feedback regulation of erythropoiesis. A parameter reflecting this complex balance is the tissue oxygen tension that is believed to govern the release of erythropoietin. The oxygen balances for the human and mouse systems as used in the model are given in Table B-4.

Oxygen consumption per gram of renal tissue in the mouse is approximately twice that for the human. (Overall total oxygen consumption per gram body weight is nearly seven times greater in the mouse.) This higher oxygen demand of the mouse is satisfied in two ways in the model. First, there is a 50% greater efficiency in oxygen extraction as indicated in Table B-4. (Note that, in both species, the amount of oxygen delivered at rest is more than sufficient; i.e., roughly 10 times that required by the tissues.) Second, there is a 30% higher blood oxygen supply per gram of tissue because of greater tissue blood flow in the mouse.

The normal tissue oxygen tension is arbitrarily assumed to be identical in both model systems; i.e., 20 mmHg. The equation describing oxygen diffusivity to the tissues from venous capillaries is given in the steady state as

$$\begin{aligned}
 \text{Net oxygen delivery} &= \text{tissue oxygen consumption} \\
 &= (pO_2 \text{ vein} - pO_2 \text{ tissue}) \times K \quad (\text{B17})
 \end{aligned}$$

where K = conductivity coefficient = O₂ diffusivity times the capillary surface area. The ratio $K_{\text{man}}/K_{\text{mouse}}$ would be expected to reflect the surface area ratio between species if diffusivity is assumed similar in mouse and man. Therefore, if S is capillary surface area, then

$$\begin{aligned}\frac{S_{\text{man}}}{S_{\text{mouse}}} &= \frac{K_{\text{man}}}{K_{\text{mouse}}} \\ &= \frac{(O_2 \text{ consumption})_{\text{man}}}{(O_2 \text{ consumption})_{\text{mouse}}} \times \frac{(pO_{2,\text{vein}} - pO_{2,\text{tissue}})_{\text{mouse}}}{(pO_{2,\text{vein}} - pO_{2,\text{tissue}})_{\text{man}}} \\ &= \frac{20 \text{ ml/min}}{0.04 \text{ ml/min}} \times \frac{(57.5 - 20) \text{ mmHg}}{(56.4 - 20) \text{ mmHg}} = 515\end{aligned}$$

This is in good agreement with the surface area ratio of 650 of the glomerulus derived from data in Ref. 54 (p. 174), lending support to the general representation of the kidney in the computer model.

B.3.4 Functional Relationships

Three functional relationships are included in the computer model: (1) oxygen-hemoglobin equilibrium curve (OEC), (2) erythropoietin release as a function of tissue pO_2 , and (3) erythrocyte production rate as a function of erythropoietin concentration. The first of these is shown in Fig. B-8 and will subsequently be described in detail. The form of the function curves for erythropoietin and red cell release will be assumed identical in the mouse and human models. There is no reason at the present time to take issue with this assumption, particularly since the bone marrow function was originally obtained from the mouse. These curves (as shown in Figs. B-2 and B-3 and as used in the models) are represented in normalized form (i.e., percent of control) so that any species may be represented. The gain factors G_1 and G_2 , representing the slope of the relationships, may be different between species. This is of little concern in the basic design of the model because these parameters will be adjusted during the simulation process and their actual values will be estimated by “fitting” the model output to the experimental data.

The equation describing the sigmoidal OEC is a form of the Hill equation and is shown in the insert of Fig. B-8. The two solid lines represent human and mouse blood, respectively, and were recently obtained from blood samples of the C3H mouse [49]. The value of P_{50} is explicitly stated in the equation so that shifts in oxygenhemoglobin affinity may be easily described. The value of the exponent k , found from the best fit of the mouse curve, also provides a good fit of the human curve as shown in Fig. B-8. Thus, the only difference between the equation describing the human and mouse OEC is the value of P_{50} .

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Appendix C

Guyton Model for Circulatory, Fluid, and Electrolyte Control: Modifications and Recommendations

The original version of the model developed by Arthur Guyton and used extensively as a basis for much of this work was built as a general-purpose model of overall circulatory regulation and was used by the authors to simulate a wide variety of real situations, including congestive heart failure, various types of hypertension, fistula, and hypoproteinemia [1,2]. Despite these successes, the model, as originally constructed, did not have the level of detail required to respond to the challenge of the microgravity environment. Modifications were made to the model to rectify this limitation and expand its capabilities. These modifications are available in report form [3,4], but they are presented and summarized here for the convenience of the interested reader.

The original version of the Guyton model is presented in Fig. C-1. A legend of symbols, definitions, and units is included. In addition, Fortran language versions of both the original and the modified model are obtainable [5,6].

There are two parts to this appendix. The first part summarizes the modifications that were concerned primarily with recompartmenting the circulatory subsystem to include leg volume and controller elements; adding gravity-dependent functions to the controlled and controller systems; and revising and updating the baroreceptor block, red blood cell block, and the angiotensin block. These modifications have extended the capability of the original model so that the effects of gravity and its removal on fluid distribution may be simulated more realistically. The second part is a set of recommendations for improving the capability of the model to simulate orthostatic (tilt and standing) maneuvers.

C.1 Modifications to the Guyton Model

C.1.1. Leg Circulatory Compartment

Two additional compartments have been added to the model of the circulatory system, one to represent the arteries in both legs and the other to represent the veins (see Fig. 3-36). Each compartment is characterized by a total blood volume, blood pressure, and compliance (see Table C-1). The values for volumes and compliances of the leg compartments were derived from the model of the 28-compartment pulsatile cardiovascular sub-system of the Whole-Body Algorithm. The blood volumes and compliances of the upper circulatory compartments were adjusted to keep the total volume and compliance of the arterial and venous vessels nearly identical to those in the original Guyton model.

C.1.2 Blood Flow Pathways and Metabolic Rates

The original Guyton model contained three blood flow pathways: renal, muscle, and the remainder of the circula-

tion. In the modified version, these three pathways remain intact; however, the muscle flow pathway represents the entire leg flow, and the non-muscle, non-renal pathway together with the renal flow represents total upper body flow. In this modified model, leg blood flow and total body muscle blood flow are identical. Muscle and non-muscle, non-renal flows were readjusted by changing their basic resistances so that cardiac output was similar to that of the unmodified version of the Guyton model and leg flow was similar to that of the leg blood flow of the short-term pulsatile cardiovascular model of the Whole-Body Algorithm. Metabolic demand in terms of oxygen consumption was also readjusted in proportion to the new blood flow rates.

C.1.3 Resistances of the Leg Blood Vessels

The single resistance in the muscle blood flow pathway of the original version was replaced by two variables in series to allow capillary filtration to occur in the muscles. These represent a precapillary arteriolar resistance and a postcapillary venular resistance, the values of each being dependent on autonomic and angiotensin effects. In addition, the venular resistance responds to passive distention due to hydrostatic pressure, whereas the arteriolar resistance includes autoregulatory and viscosity effects. These formulations for the leg muscle tissue are similar to that of the non-muscle, non-renal precapillary and postcapillary resistances in the original Guyton model with the following exceptions.

First, the passive distention effect resulting from hydrostatic pressure was not included as a determinant of the leg arteriolar resistance. This exclusion was based on the belief that, upon standing, a strong myogenic local reflex acts to constrict arteriolar vessels (as well as capillary sphincters) in response to the high hydrostatic load. The myogenic reflex opposes the passive distention effect. It was felt that the passive distention effect should be removed until the myogenic effect is included in the model. Otherwise, the effect of standing would create arteriolar distention great enough to overcome autonomic vasoconstriction, a condition that does not normally exist in the real physiological system.

Second, the veins are not known to participate in the myogenic response but, rather, should be highly responsive to passive distention under the high hydrostatic pressures of standing. Consequently, a passive distention effect was added to the leg venule resistance. This formulation permitted a 1 mmHg change in pressure to cause a 1% change in resistance in accordance with data reviewed by McDonald [7]. The net effect of excluding the passive distention effect in the leg arterioles and adding this effect to the leg venules is to favor a higher precapillary/postcapillary resistance ra-

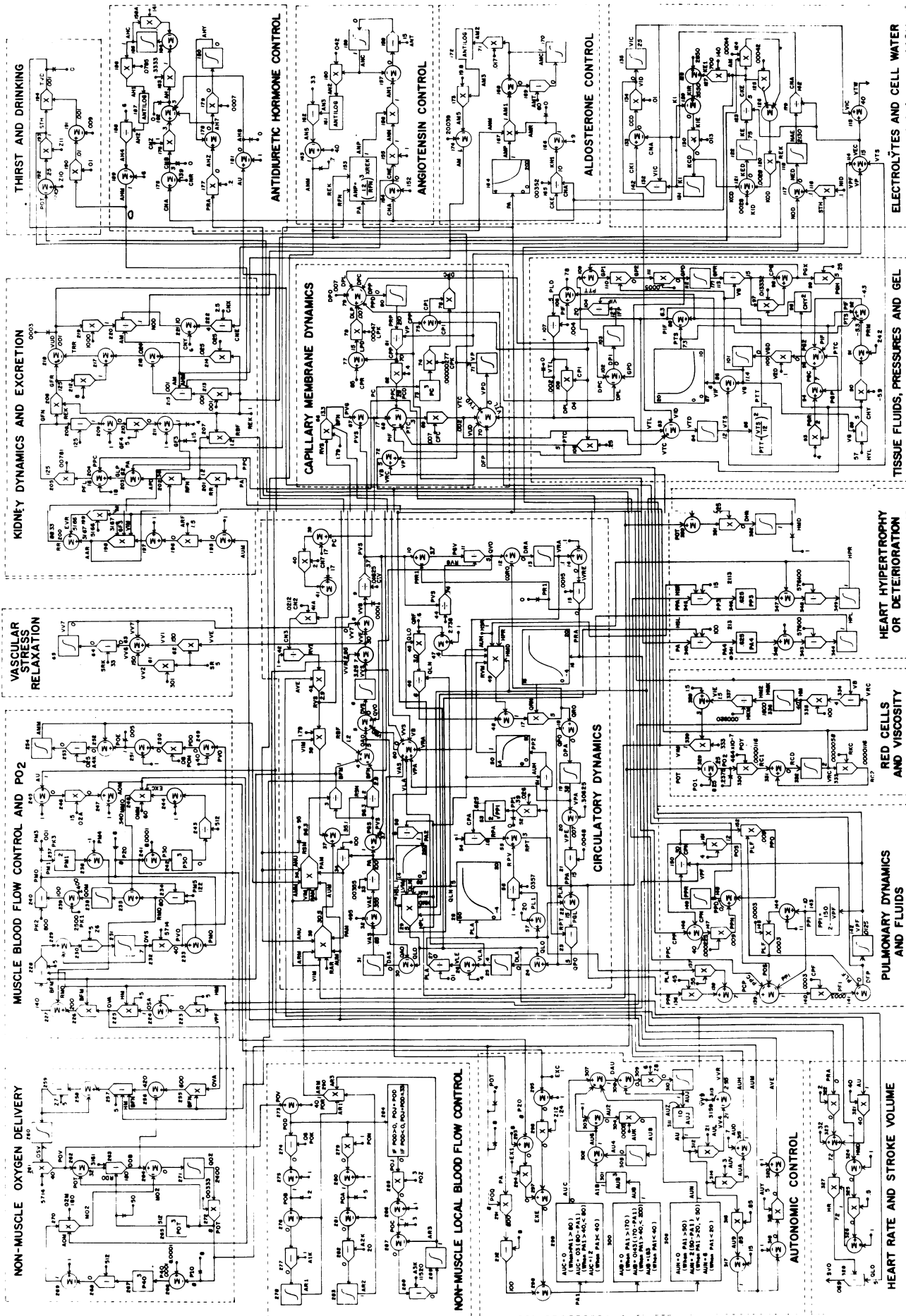


Figure C-1. Systems analysis diagram for regulation of the circulation according to Guyton and co-workers. Reprinted from Ref. [1] with permission of the publisher. Units are the following: volume in liters; mass in grams; time in minutes; chemical units in meq; pressure in millimeters of mercury; and control factors in arbitrary units but in most instances expressed as the ratio to normal—for instance, a value of 1 represents normal. Normal values are given on the lines that represent the respective variables. The important dependent and independent variables in the analysis are listed in the key. Additional variables are present for purposes of calculation but generally have no physiological significance.

Figure C-1 Key

AAR	afferent arteriolar resistance	PCD	net pressure gradient across capillary membrane
AHM	antidiuretic hormone multiplier, ratio of normal effect	PCP	pulmonary capillary pressure
AM	aldosterone multiplier, ratio of normal effect	PDO	difference between muscle venous oxygen pO_2 and normal venous oxygen pO_2
AMC	aldosterone concentration	PFI	rate of transfer of fluid across pulmonary capillaries
AMM	muscle vascular constriction caused by local tissue control, ratio to resting state	PFL	renal filtration pressure
AMP	effect of arterial pressure on rate of aldosterone secretion	PGC	colloid osmotic pressure of tissue gel
AMR	effect of sodium to potassium ratio on aldosterone secretion rate	PGH	absorbency effect of gel caused by recoil of gel reticulum
AMT	time constant of aldosterone accumulation and destruction	PGL	pressure gradient in lungs
ANC	angiotensin concentration	PGP	colloid osmotic pressure of tissue gel caused by entrapped protein
ANM	angiotensin multiplier effect on vascular resistance, ratio to normal	PGR	colloid osmotic pressure of interstitial gel caused by Donnan equilibrium
ANN	effect of sodium concentration on rate of angiotensin formation	PGV	pressure from veins to right atrium
ANP	effect of renal blood flow on angiotensin formation	PIF	interstitial fluid pressure
ANT	time constant of angiotensin accumulation and destruction	PLA	left atrial pressure
ANU	nonrenal effect of angiotensin	PLD	pressure gradient to cause lymphatic flow
AOM	autonomic effect on tissue oxygen utilization	PLF	pulmonary lymphatic flow
APD	afferent arteriolar pressure drop	PMO	muscle cell pO_2
ARF	intensity of sympathetic effects on renal function	POD	nonmuscle venous pO_2 minus normal value
ARM	vasoconstrictor effect of all types of autoregulation	POK	sensitivity of rapid system of autoregulation
ARI	vasoconstrictor effect of rapid autoregulation	PON	sensitivity of intermediate autoregulation
AR2	vasoconstrictor effects of intermediate autoregulation	POS	pulmonary interstitial fluid colloid osmotic pressure
AR3	vasoconstrictor effect of long-term autoregulation	POT	nonmuscle cell pO_2
AU	overall activity of autonomic system, ratio to normal	POV	nonmuscle venous pO_2
AUB	effect of baroreceptors on autoregulation	POY	sensitivity of red cell production
AUC	effect of chemoreceptors on autonomic stimulation	POZ	sensitivity of long-term autoregulation
AUH	autonomic stimulation of heart, ratio to normal	pO_2	oxygen deficit factor causing red cell production
AUK	time constant of baroreceptor adaptation	PPA	pulmonary arterial pressure
AUL	sensitivity of sympathetic control of vascular capacitance	PPC	plasma colloid osmotic pressure
AUM	sympathetic vasoconstrictor effect on arteries	PPD	rate of change of protein in pulmonary fluids
AUN	effect of CNS ischemic reflex on autoregulation	PPI	pulmonary interstitial fluid pressure
AUV	sensitivity control of autonomies on heart function	PPN	rate of pulmonary capillary protein loss
AUY	sensitivity of sympathetic control of veins	PPO	pulmonary lymph protein flow
AUZ	overall sensitivity of autonomic control	PPR	total protein in pulmonary fluids
AVE	sympathetic vasoconstrictor effect on veins	PRA	right atrial pressure
A1K	time constant of rapid autoregulation	PRM	pressure caused by compression of interstitial fluid gel reticulum
A2K	time constant of intermediate autoregulation	PRP	total plasma protein
A3K	time constant of long-term autoregulation	PTC	interstitial fluid colloid osmotic pressure
A4K	time constant for muscle local vascular response to metabolic activity	PTS	solid tissue pressure
BFM	muscle blood flow	PTT	total tissue pressure
BFN	blood flow in nonmuscle, nonrenal tissues	PVG	venous pressure gradient
CA	capacitance of systemic arteries	PVO	muscle venous pO_2
CCD	concentration gradient across cell membrane	PVS	average venous pressure
CHY	concentration of hyaluronic acid in tissue fluids	QAO	blood flow in the systemic arterial system
CKE	extracellular potassium concentration	QLN	basic left ventricular output
CKI	intracellular potassium concentration	QLO	output of left ventricle
CAN	extracellular sodium concentration	QOM	total volume of oxygen in muscle cells
CNE	sodium concentration abnormality causing third factor effect	QO2	nonmuscle total cellular oxygen
CPG	concentration of protein in tissue gel	QPO	rate of blood flow into pulmonary veins and left atrium
CPN	concentration of protein in free interstitial fluid	QRF	feedback effect of left ventricular function on right ventricular function
CPN	concentration of protein in pulmonary fluids	QRN	basic right ventricular output
CPP	plasma protein concentration	ORO	actual right ventricular output
CV	venous capacitance	QVO	rate of blood flow from veins into right atrium
DAS	rate of volume increase of systemic arteries	RAM	basic vascular resistance of muscles
DFP	rate of increase in pulmonary free fluid	RAR	basic resistance of nonmuscular and nonrenal arteries
DHM	rate of cardiac deterioration caused by hypoxia	RBF	renal blood flow
DLA	rate of volume increase in pulmonary veins and left atrium	RC1	red cell production rate
DLP	rate of formation of plasma protein by liver	RC2	red cell destruction rate
DOB	rate of oxygen delivery to nonmuscle cells	RCD	rate of change of red cell mass
DPA	rate of increase in pulmonary volume	REK	percent of normal renal function
DPC	rate of loss of plasma proteins through systemic capillaries	RFN	renal blood flow if kidney is not damaged
DPI	rate of change of protein in free interstitial fluid	RKC	rate factor for red cell destruction
DPL	rate of systemic lymphatic return of protein	RMO	rate of oxygen transport to muscle cells
DPO	rate of loss of plasma protein	RPA	pulmonary arterial resistance
DRA	rate of increase in right atrial volume	RPT	pulmonary vascular resistance
DVS	rate of increase in venous vascular volume	RPV	pulmonary venous resistance
EVR	postglomerular resistance	RR	renal resistance
EXC	exercise activity, ratio to activity at rest	RSM	vascular resistance in muscles
EXE	exercise effect on autonomic stimulation	RSN	vascular resistance in nonmuscle, nonrenal tissues
GFN	glomerular filtration rate of undamaged kidney	RVG	resistance from veins to right atrium
GFR	glomerular filtration rate	RVM	depressing effect on right ventricle of pulmonary arterial pressure
GLP	glomerular pressure	RVS	venous resistance
GPD	rate of increase of protein in gel	SR	intensity factor for stress relaxation
GPR	total protein in gel	SRK	time constant for stress relaxation
HM	hematocrit	STH	effect of tissue hypoxia on salt and water intake
HMD	cardiac depressant effect of hypoxia	SVO	stroke volume output
HPL	hypertrophy effect on left ventricle	TRR	tubular reabsorption rate
HPR	hypertrophy effect on heart, ratio to normal	TVD	rate of drinking
HR	heart rate	VAS	volume in systemic arteries
HSL	basic left ventricular strength	VB	blood volume
HSR	basic strength of right ventricle	VEC	extracellular fluid volume
HYL	quantity of hyaluronic acid in tissues	VG	volume of interstitial fluid gel
IFP	interstitial fluid protein	VGD	rate of change of tissue gel volumes
KCD	rate of change of potassium concentration	VIB	blood viscosity, ratio to that of water
KE	total extracellular fluid potassium	VIC	cell volume
KED	rate of change of extracellular fluid concentration	VID	rate of fluid transfer between interstitial fluid and cells
KI	total intracellular potassium concentration	VIE	portion of blood viscosity caused by red blood cells
KID	rate of potassium intake	VIF	volume of free interstitial fluid
KOD	rate of renal loss of potassium	VIM	blood viscosity, ratio to normal blood
LVM	effect of aortic pressure on left ventricular output	VLA	volume in left atrium
MMO	rate of oxygen utilization by muscle cells	VP	plasma volume
MO2	rate of oxygen utilization by nonmuscle cells	VPA	volume in pulmonary arteries
NAE	total extracellular sodium	VPD	rate of change of plasma volume
NED	rate of change of sodium in intracellular fluids	VPF	pulmonary free fluid volume
NID	rate of sodium intake	VRA	right atrial volume
NOD	rate of renal excretion of sodium	VRC	volume of red blood cells
OMM	muscle oxygen utilization at rest	VTC	rate of fluid transfer across systemic capillary membranes
OSA	aortic oxygen saturation	VTD	rate of volume change in total interstitial fluid
OSV	nonmuscle venous oxygen saturation	VTL	rate of systemic lymph flow
OVA	oxygen volume in aortic blood	VTS	total interstitial fluid volume
OVS	muscle venous oxygen saturation	VTW	total body water
O2M	basic oxygen utilization in nonmuscle body tissues	VUD	rate of urinary output
PA	aortic pressure	VV7	increased vascular volume caused by stress relaxation
PAM	effect of arterial pressure in distending arteries, ratio to normal	VVR	diminished vascular volume caused by sympathetic stimulation
PC	capillary pressure	VVS	venous vascular volume
		Z8	time constant of autonomic response

Table C-1. Steady-State Values of Major Physiological Parameters in Modified Guyton Model

Parameter	Value	Parameter	Value
Blood volume, liters		Flow Resistances, mmHg/liter/min	
Right heart	0.109	Total peripheral	15.60
Pulmonary	0.413	Renal	83.39
Left heart	0.431	Leg (muscle)	96.31
Total cardiopulmonary	0.953	Non-renal, non-muscle	22.20
Upper artery	0.714	Large veins	0.60
Leg artery	0.146	Leg arteries (fixed)	0.95
Total artery	0.860	Leg veins (fixed)	0.35
Upper veins	2.750	Pulmonary	2.76
Leg veins	0.440		
Total veins	3.190	Body fluid volume, liters	
Total stressed volume	0.877	Blood	5.003
Total unstressed volume	4.126	Plasma	3.007
Total upper body volume	4.417	Red cell	1.999
Total leg volume	0.586	Interstitial	12.013
Total blood volume	5.003	Free fluid	0.545
		Gel	11.467
Blood pressure, mmHg		Total body water	40.038
Upper arterial	100.1	Extracellular	15.042
Leg arterial	99.3	Intracellular	24.996
Upper venous	4.55		
Leg venous	4.89	Metabolic rate, ml O ₂ /min	
Right heart	0.63	Nonmuscle, nonrenal	252.0
Pulmonary	18.87	Leg (muscle)	58.0
Left heart	0.97	Total	310.0
Compliances, liter/mmHg		Concentration, meq/liter	
Upper arteries	0.00265	Plasma sodium	142.0
Leg arteries	0.00112	Plasma potassium	5.00
Upper viens	0.07905	Plasma protein	70.1
Leg veins	0.00772		
		Hematocrit, vol.%	39.95
Blood flow, liters/min			
Cardiac output	6.47	Stroke volume, liters	0.088
Renal	1.20		
Leg (muscle)	0.98	Heart rate, beats/min	73.3
Nonrenal, nonmuscle	4.30		

tio upon standing which tends to reduce leg capillary pressure towards leg venous pressure. According to Mellander [8], this is an appropriate response to limit outward filtration of plasma in the erect posture.

C.2 Effect of Gravity on Pressure Gradients

The average hydrostatic pressure gradient in the legs (PG_L) due to gravity has been expressed as

$$PG_L = H_L \times F \times \sin \phi \quad (C1)$$

where H_L is taken as the distance (in centimeters) from the heart to the knees. (The knee was used as a convenient

reference point to find the average hydrostatic effect in a lumped leg compartment.) The term F converts pressure from centimeters water to millimeters mercury, whereas ϕ is the angle (in radians) of body tilt measured from the horizontal. The pressure gradient PG_L is introduced into the formulation for leg flow at the input to the leg arterial compartment, where it aids flow, and at the output of the leg venous compartment, where it opposes flow.

The gravity effect on the carotid baroreceptors must also be included since the tilt angle changes the hydrostatic pressure at these important sensors. The hydrostatic gradient at the baroreceptors is given by an equation similar to Eq. (C1) except that the term H_L is taken to be the distance between the heart and the carotid receptor. The

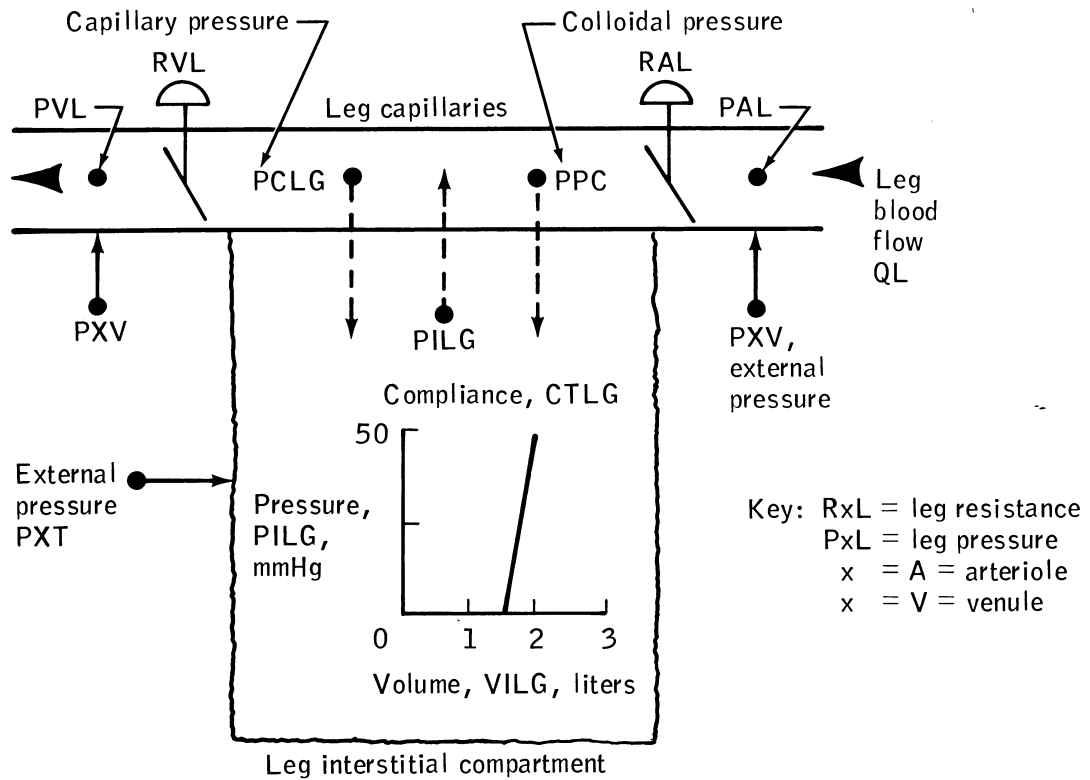


Figure C-2. Schematic diagram of leg filtration mechanisms.

pressure gradient so calculated is subtracted from the effective blood pressure sensed at the carotid body during a tilt simulation. Any angle of tilt may be simulated by adjusting ϕ , and other postures such as sitting may be studied by reducing the height H_L .

C.3 Venous Valves

The effect of venous valves has been added by permitting blood flow from the venous leg compartment to assume only positive values. Because this leg compartment can only be filled by arterial blood (rather than reverse venous flow from upper body veins), transient conditions can exist in which outflow to the veins is extremely low. This occurs, for example, during the onset of lower body negative pressure simulation. This situation was not possible in the original Guyton formulation.

C.4 Leg Plasma/Interstitial Filtration

A mechanism was added to permit plasma to filter into a new interstitial leg compartment. This mechanism is illustrated in Fig. C-2 in schematic form. Blood flow in the leg tissues is driven under an arterial-venous pressure gradient ($PAL - PVL$) across an arterial resistance RAL and a venous resistance RVL . The capillary pressure ($PCLG$) is computed as a function of upstream and downstream pressures and the precapillary/postcapillary resistance ratio,

in accordance with the Landis-Pappenheimer formulation:

$$PCLG = RCLG * PAL + (1 - RCLG) * PVL$$

where $RCLG = RVL / (RVL + RAL)$. Filtration rate into the leg interstitium ($QLEG$) is based on the transcapillary hydrostatic pressure and oncotic pressure gradients multiplied by a leg capillary filtration coefficient ($CFLG$).

$$QLEG = (PCLG - PILG - PPC) * CFLG$$

where $PILG$ is the leg interstitial pressure and PPC is the plasma colloid osmotic pressure. It is assumed that interstitial colloid osmotic pressure is negligible. The value of $PILG$ is determined from the leg interstitial volume ($VILG$) and the tissue compliance ($CTLG$).

Because of the lack of detailed information regarding the leg tissues and tissue pressure changes during standing, this represents a highly simplified model of leg filtration having the following major assumptions.

1. Leg tissue fluid volume is equal to 1.5 liters in supine steady state.
2. Linear compliance permits tissue pressures to rise by about 40 mmHg during standing when the fluid volume is increased by approximately 500 ml because of plasma filtration. This large pressure increase is necessary to oppose excessive filtration because of the equally high change in capillary pressure.

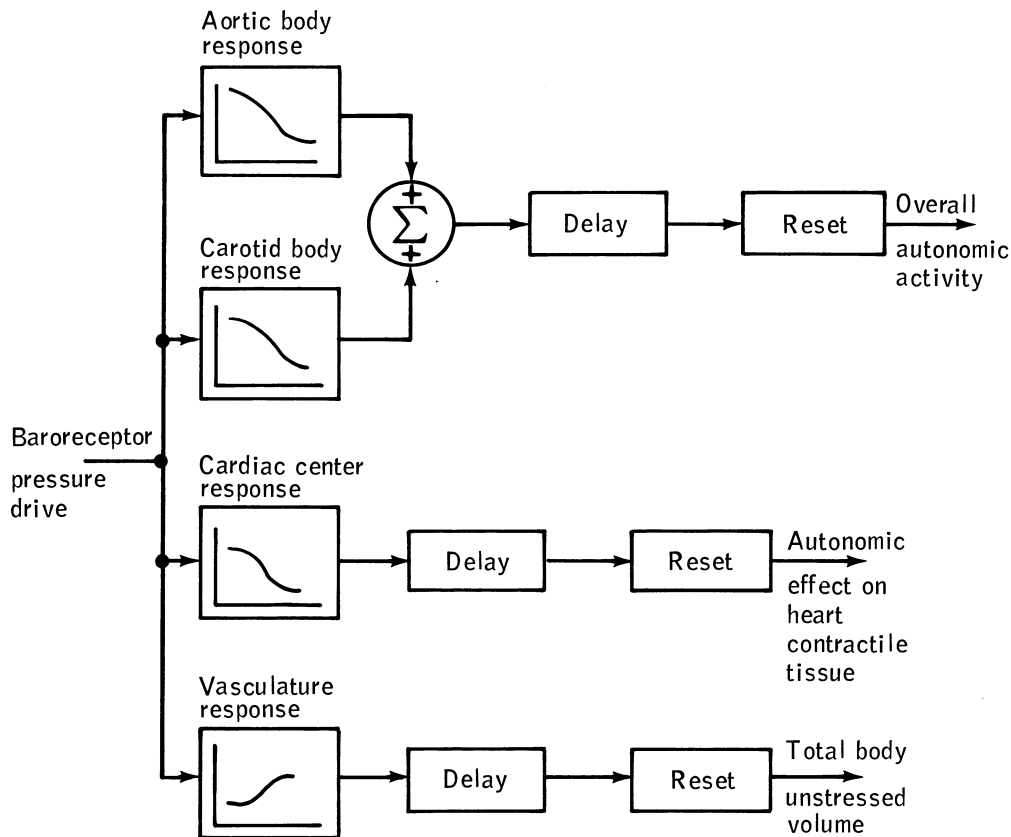


Figure C-3. Block diagram of baroreceptor system.

3. The effects of lymph flow, tissue colloidal concentration, and tissue gel have not been included.

The total resistance to blood flow through the leg muscle is given by the sum of the two variable resistances

$$RL = RAL + RVL$$

and the blood flow rate of the leg is taken to be the difference of pressure between the leg arteries (PAL) and veins (PVL) divided by the resistance

$$QL = (PAL - PVL)/RL.$$

C.5 External Leg Vascular Pressure

An external pressure term (PXV), shown in Fig. C-2, was included in the formulation for leg arterial and venous pressure, as was an external tissue pressure term (PXT). These terms are normally zero. By setting PXV and/or PXT to values less than zero, the effects of lower body negative pressure can be simulated. Values higher than zero will simulate various events such as positive pressure leg garments, water immersion, dehydration of the legs, and a muscle pump mechanism, all of which have the effect of

reducing venous leg blood volume and aiding in venous return during standing.

C.6 Vascular Stress Relaxation Effect

A term representing instantaneous stress relaxation was added to the stress relaxation block of the original model. This term appears as a constant factor (normally zero), which was found to be necessary to aid venous return during tilt simulation. In that case, reverse stress relaxation was used. Its physiological counterpart may be a combination of stress relaxation and the abdominal compression postural reflex, as well as a central venoconstrictor effect [9].

Stress relaxation of the vascular system was extended by the inclusion of new components with different time constants for action. These new components are associated with 6-hour and 14-day relaxation phenomena.

C.7 Baroreceptor System

The baroreceptor system in the original Guyton model was changed by direct inclusion of separate aortic and carotid effects and by separate inclusion of the autonomic influence on both contractility of the heart and whole-

body unstressed volume. Appropriate delays and resetting mechanisms were used. A flow chart for the modified system is given in Fig. C-3.

C.8 Modified Red Blood Cell Production Algorithm

A new algorithm for red cell regulation was also implemented in the recompartimentalized Guyton model. This new block was based on the erythropoiesis regulatory simulation model previously described in Chapter 3 and 6. This model has greater capability than the blood cell subroutine in the original Guyton model, especially with respect to the simulation of hemopoietic responses to hypoxia, red cell infusion, and bedrest. A detailed description of this algorithm, as it appears in the modified Guyton model, is presented in Ref. [3].

The new red blood cell algorithm was based on a kidney sensor of oxygen partial pressure located in tissue of constant metabolic rate and perfused with venous capillary blood, flowing at a constant rate. These restrictions permit erythropoiesis to be responsive primarily to changes in hematocrit and arterial oxygen partial pressure, shifts of oxyhemoglobin dissociation, and disturbances in oxygen-carrying capacity of hemoglobin.

C.9 Renin-Angiotensin System

The original version of the Guyton model did not possess a detailed representation of the renin-angiotensin system. In particular, renin secretion as such was not present, and the model did not respond correctly to low-level angiotensin II infusion. This original model contained what was essentially a black box, with angiotensin level dependent on tubular sodium flow. To extend the range of applicability of the model, the black box was replaced with a more physiologically oriented section. A flow chart of the added system is contained in Appendix A (Fig. A-3). The new system improved the mechanism for releasing angiotensin into the circulation and permitted thirst and salt intake as well as renal afferent and efferent arteriolar resistances to depend on angiotensin levels.

C.10 Recommendations for an Improved Orthostatic Model

The addition of gravity dependent elements to the Guyton model, discussed in Chapters 3.2.5 and 9.6, provided new capability to simulate changes in postural positions. The cardiovascular model of Croston is capable of even greater realism for short-term orthostatic tests. However, the Guyton model, with a circulatory system open to fluid transfer with adjoining compartments as well as with the external environment, and long-term controllers is theoretically capable of longer-term simulations. In the current project, the Guyton model failed to achieve the robust blood pressure control during standing that is seen in the human subject. It also did not achieve a longer term steady state during standing. Additional modifications are there-

fore required in the Guyton model for longer-term orthostatic capability. The object of these modifications would be to produce a model capable of maintaining normal, healthy ambulatory function. It is our hypothesis that understanding the hypogravic state is predicated on a better understanding of the orthostatic state. The recommendations below may serve as a start in this direction.

Table C-2 and the associated Fig. C-4 illustrate a number of mechanisms that are believed to aid in orthostatic protection. Orthostatic protection insures that blood pressure levels are preserved at close to a normal level during standing. Some of these mechanisms have already been included in the Guyton model and are discussed in Chapter 9 and the first part of this Appendix. These include:

- a) a leg tissue compartment that can normally receive about a half liter of plasma during standing;
- b) a muscle contracting effect that decreases transmural pressure and decreases leg fluid pooling;
- c) valves in the leg veins that allows blood flow to move only toward the central regions;
- d) a passive distention effect at the leg veins affecting postcapillary resistance and decreasing leg filtration;
- e) autonomic and angiotensin effects on leg arteriolar resistance which limits flow to the legs, raises arterial pressure, and decreases capillary filtration.

In addition, there are other suggested areas for model improvements as follows:

C.10.1 Factors Affecting Venous Capacitance

It is clear that a more faithful simulation of tilt requires a greater degree of compensatory venous return than was seen in the studies reported in Chapter 9. Venous return can be effectively enhanced in the model or in man by reducing capacitance of the central veins and perhaps leg veins. The mechanisms that are involved in these changes arise from centrally mediated high pressure and low-pressure baroreceptors in the upper body, from vasoconstriction hormones, and from local effects such as reverse stress relaxation and passive elastic recoil. Contraction of the leg and abdominal musculature, considered also to be important compensatory reflexes to orthostatic pooling, are probably mediated via central and local mechanoreceptors [10,11].

Observations on the behavior of the capacitance vessels in the human have been restricted to the limbs, but even here inconsistent results have been found during tilt studies [12]. It is not possible at present to determine whether changes in splanchnic blood volume are induced actively or passively, although this generally is considered to be an important fluid source during acute hypovolemia [13,14]. Boyers, *et al.* [15], using a model for tilt simulation, found it necessary to employ a low pressure autonomic input sensitive to central blood volume or pressure which acts, in part, on the veins to enhance venous return. Evidence for this effect is not yet strong [16]. The current version of the Guyton model does not include low pressure autonomic effects other than those used to influence ADH release. Perhaps a new autonomic reflex path-

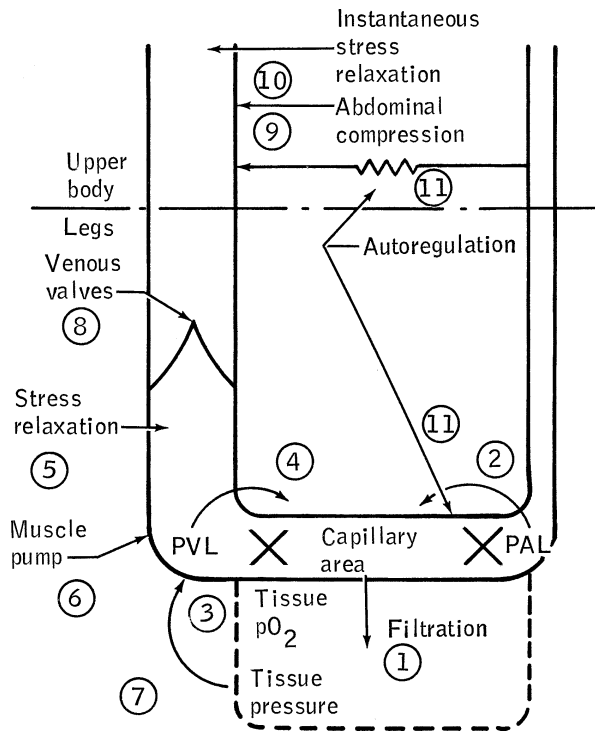


Figure C-4. Modifications for an improved tilt simulation. The numbers correspond to the elements in Table C-2. (PVL = Venous pressure in legs and PAL = arterial pressure in legs).

way, mediated by low-pressure receptors which influence venous resistance and capacitance, can be postulated and incorporated for future evaluation.

C.10.2 Stress Relaxation of Veins

In the erect position, reverse stress relaxation takes place in the large veins of the model following decrements of central blood volume. This may occur more rapidly and intensively than heretofore suspected according to recent evidence from Guyton's laboratory and others [17,18]. Such an effect greatly enhanced the present tilt responses reported in Chapter 9.6. Quantitative studies on the compensatory effects of stress relaxation and stress relaxation recovery following blood volume changes are meager [19]. It is important to ascertain where in the circulation it occurs. If stress relaxation has an influence on the smaller leg veins it would act in a direction to gradually increase blood pooling, as is known to occur during standing.

C.10.3 Pre- and Post-Capillary Resistance

Previous simulations with the Guyton model have led us to suggest that autoregulation effects (a mechanism which adjusts precapillary resistance to meet local oxygen demands) may be too strong and rapid in dampening peripheral resistance changes following intravascular fluid shifts either headward or feetward as occurs during postural changes. More recent studies on our part indicate that a more powerful influence on postcapillary resistance may be required rather than an attenuation of autoregulation.

Evidence for this hypothesis is only suggestive. Nevertheless, it is important to note that venous capacitance and venous resistance changes are theoretically independent in the model, but not necessarily in the human vasculature. Thus, any changes in the model that effect autonomic influence on capacitance, such as discussed above, should also be considered for their influence on postcapillary resistance. In addition, it is important to consider that under various conditions there may be a dissociation in the reflex changes of the (arterial) resistance and (venous) capacitance vessels due to competing control elements or perhaps redistribution of efferent autonomic signals [20,21]. The role of pre-/post capillary resistance takes on new importance in the Guyton model now that there are two distinct capillary beds. These elements have been implicated in the regulation of regional blood flow, number of patent capillaries, nutritional exchanges, plasma volume, and venous return.

C.10.4 Improved Leg Circulatory Elements

While the degree of fluid pooling in the legs appears to have been adequately simulated by the current model it should be realized that this is a preliminary study and that many factors which control fluid pooling, filtration and blood flow in the legs have not been included [22]. Fluid pooling in legs during standing is known to be reduced by the leg muscle pump, venous valves, autonomic vasoconstriction and humoral (angiotensin) mechanisms as well as by a buildup of fluid pressure in the interstitium [19]. All these effects have been included to some extent in the model. However, their mathematical representation was only estimated; quantitative data were mostly lacking. In addition, there is evidence for the presence of other major effects not presently included such as: a) catecholamine influence [23], b) postural sway [11], and c) myogenic vasoconstriction [21]. This latter effect acts in the face of high transmural pressures to increase precapillary resistance, induce sphincter closure and reduce filtration area. Several other effects are detrimental to orthostatic tolerance such as stress relaxation and passive distention of arteries and veins. These effects may be required for longer-term simulations. For example, it has been suggested that postural sway and the venous (muscle) pump are responsible for maintaining orthostatic tolerance during prolonged standing or minimal upright activity. An improvement in the leg muscle elements would do more than enhance the tilt response. Because of the large mass of the skeletal muscles, passive and active fluid mobilization, especially when reinforced by the mechanical effect of muscle contraction, provides the potential for large changes in capacity within the entire circulation during a wide variety of stress conditions.

C.10.5 Leg Interstitial Compartment

The leg interstitial compartment was modeled quite simply as a water reservoir with a linear compliance. For the present effort this appears to be adequate. However, absent from this formulation is a lymphatic system, a tissue gel, colloids and a nonlinear compliance, all of which

Table C-2. Mechanisms for Improving Fidelity of Tilt Simulations

Element Modification	Justification
1) Filtration of plasma between leg vasculature and interstitial fluid	Transfers about 300 – 500 ml plasma. The interstitial fluid volume increases during standing and decreases during supine.
2) Autoregulatory effect on leg capillary surface area	A local myogenic reflex that has been postulated to occur in response to increased leg hydrostatic pressures by decreasing effective capillary surface area. The effect is to limit the filtration of plasma.
3) Autoregulatory effect on leg venous resistance	Decreases venous resistance when standing and lowers capillary pressure. Although evidence is not strong for this effect, it appears to be necessary to prevent severe edema. The autoregulatory effect in the model with legs currently only affects arteriolar resistances.
4) Passive distention effect on leg veins	Decreases venous resistance proportional to the increase in hydrostatic pressure.
5) Stress relaxation of leg veins	Postulated mechanism similar to upper vein stress relaxation. It will not improve the short-term maintenance of blood pressure and venous return, but it will permit a more realistic gradual slow pooling of blood in legs and thereby improve bedrest and long-term standing simulations.
6) Muscle pump effect	Increases venous return from the legs and decreases leg pooling.
7) Effect of increasing leg tissue fluid pressure on transmural pressure of leg veins	Similar effect as the muscle pump, but is an automatic regulatory effect rather than a fixed parameter.
8) Venous valves	Slightly delays the rapid pooling of blood in legs by permitting leg blood flow in only headward direction.
9) Abdominal compression effect	Standing reflex that compresses splanchnic veins and releases a small quantity of stored blood. Effect is to restore venous pressure and enhance venous return.
10) Instantaneous stress relaxation (and reverse stress relaxation) in large veins	Allows rapid reverse stress relaxation in large veins during standing to enhance venous return. This effect was found to be necessary to simulate appropriate response to tilt, infusion and hemorrhage.
11) Short-term autoregulatory flow effect	Preliminary observations have shown that short-term autoregulation is too strong and too rapid. It does not allow flow resistances to decrease appropriately since it counteracts the central reflex vasoconstriction, so the effect was decreased.
12) O ₂ consumption	During standing O ₂ consumption increases by 10 to 20%. This increases autoregulatory flow and autonomic stimulation.
13) Renin-angiotensin response	Preliminary results showed that the renin response to the off transient to tilt was too slow. Angiotensin affects vessel constriction, urine flow, and aldosterone production. See text for recommendations.
14) ADH response	Preliminary results showed that the ADH response was not sustained as it is in the real system during tilt or zero-g
15) Cardiopulmonary autonomic response	Decreasing cardiopulmonary volumes are known to elicit autonomic responses during tilt, suggesting a low pressure receptor. The model currently has only high pressure receptors for volume and pressure control.

are important elements of the upper body tissue fluid compartment [24]. Data are not available to model a completely realistic distributed parameter interstitial compartment system.

C.10.6 Improvements in Endocrine Systems

This recommendation concerns improving the endocrine system of the Guyton model. The response to tilt of ADH, angiotensin, and aldosterone were in good agreement with available data. However, there are areas which can be immediately addressed that might improve responses to tilt and other stresses. First, it was noted that during the off transient to tilt, angiotensin did not fall as rapidly as it does in the tilt recovery of man [25]. This was believed to be due, in part, to the arterial pressure response which was unrealistically low for a short period and, in part perhaps, to an inadequate description of the renal pressoreceptor releasing site of renin. Several model descriptions have recently become available that would assist in improving this response [26,27]. Secondly, the aldosterone algorithm of the Guyton model has been recently revised [28], and it is suggested that if feasible, it be incorporated into the NASA/GE gravity dependent model. Finally, data has recently appeared which may allow a revision of the ADH algorithm. This concerns the ADH response to immersion and a quantitative description of the relative influence of blood volume and osmolarity on ADH concentration [29,30]. Unfortunately, there is still much conflict in the literature regarding the regulation and physiological role of ADH during postural changes both during short-term and prolonged studies [31].

C.11 Conclusion

A few other factors should be considered in an orthostatic model. Increasing the effects on cardiac contractility or heart rate on improving venous return have not been considered thus far in our studies. Also, in most individuals, orthostasis leads to syncope sooner or later during quiet standing. Some individuals are more prone to this, perhaps because of an inadequate sympathetic response. In the current project no attempt was made to model syncope, but it should be a future goal, especially in attempting to differentiate between individuals who are or who are not prone to syncope. Finally, it should be noted that many of the recommendations discussed above await more physiological studies (rather than mathematical definition) prior to developing algorithms for incorporating them into a model.

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Appendix D

Design, Development, and Validation of the Whole-Body Algorithm

This Appendix contains a detailed description of the design, development, and validation of a model that, for reasons revealed in the discussion, has been termed a Whole-Body Algorithm (WBA). This discussion is meant to supplement that of Chapter 3.

D.1 Summary of Subsystems

The individual subsystem models used in this project were carefully selected and modified to simulate the response of a human subject to the stresses under investigation in the Skylab medical experiments. These models are summarized in the following paragraphs.

D.1.1 Long-Term Fluid and Electrolyte Subsystem Model

The long-term model of circulatory, fluid, and electrolyte control, originally developed by Dr. A. C. Guyton, has been substantially modified to include the most current formulations for many of the regulatory functions and implemented in an interactive time-sharing mode. The systems analysis of overall circulatory regulation, as developed by Guyton, includes a large number of the physiological subsystems that affect the circulatory system. This model consists of 354 blocks. Each block represents at least one mathematical function that describes an important physiological facet of circulatory regulation, including autonomic, metabolic, renal, hormonal, and fluid transport function.

The circuit of blood flow in the Guyton model is divided into five volume segments: system arteries, system veins, right atrium, pulmonary arteries, and pulmonary veins-left atrium. Exchange of water, proteins, and electrolytes (sodium and potassium) is permitted between the plasma, interstitial, and intracellular fluid compartments by way of diffusion, active transport, transcapillary exchange, and lymph flow. Heart function is represented in a high degree of detail, which includes ventricular muscle strength, heart hypertrophy and deterioration, and autonomic and sympathetic stimulation. These characteristics of the model can be viewed as the controlled system, whereas the controlling system consists of three major components: local control, hormonal control, and autonomic control. The inclusion of such elements as hormonal control, autoregulation, baroreceptor adaptation, erythropoiesis control, protein formation and destruction, venous stress relaxation, and cardiac-conditioning factors clearly indicates that the Guyton model was originally developed to serve as a long-term model, i.e., simulate long-term adaptive events.

Many and varied experiments have been simulated with the Guyton model, including some involving infu-

sions of water, electrolyte, plasma, and angiotensin. Various pathologic conditions have also been simulated, including congestive heart failure, loss of kidney function, and nephritic proteinuria. The long-term simulation chosen as a test for the Whole-Body Algorithm was bedrest, because it appears to be a reasonable analog to zero-g. The addition of gravity-dependent stress factors and the inclusion of leg compartments in this subsystem greatly improved the subsystem's response to bedrest and weightlessness. Additional improvements were made by modifying the original algorithm for red blood cell control [1] (see Appendix C).

D.1.2 Cardiovascular Subsystem Model

A model of the human cardiovascular system capable of simulating bicycle-ergometry exercise was developed under this project by Dr. R. Croston. Subsequent modifications to this model were made to enable simulation of lower body negative pressure (LBNP) and tilt. The original model of the cardiovascular circulatory system was divided into 28 compartments, which described pulsatile blood flow, pressure, and volume. The model was modified to include gravity effects, muscle pumping, venous tone, venous valves, respiratory rate, and intrathoracic pressure. Heart-period control, peripheral resistance, venous tone, and other variables included in the new model were based on classical cardiovascular mechanisms. In addition, metabolic control mechanisms for oxygen uptake, for oxygen deficit, and for metabolite accumulation were included to enable simulation of metabolic changes. The feedback signals for the control algorithms in the model came from the chemoreceptors and from neurogenic response to muscular activity and to anticipatory stimuli. Exercise workload, work rate, gravity, resting oxygen consumption, and blood volume were required inputs. Typical outputs were oxygen uptake, oxygen deficit, total metabolites, heart rate, various blood flows, systolic pressure, mean arterial pressure, diastolic pressure, stroke volume, and venous pressure.

D.1.3 Respiratory Subsystem Model

The third major subsystem selected for inclusion in the Whole-Body Algorithm was the respiratory system. The model previously developed by Dr. F. Grodins was chosen as the best available (in 1975) representation. In this model, the controlled system is divided into three compartments (lung, brain, and tissue). The blood passes through the lungs, and, after a transport delay dependent on vascular volume and blood flow rate, the arterial blood arrives at the brain or the tissue compartment. In this model, carbon dioxide (CO₂) and oxygen (O₂) exchange rates are governed by metabolism. Venous blood leaving the brain combines, after a time delay, with venous blood from the

tissue to form mixed venous blood. After another delay, this mixed venous blood enters the lungs to complete the cycle of gas transport and exchange. The real system is composed of receptor elements that monitor chemical concentrations and of afferent nerves that transmit this information to the central nervous system, the neural centers, to motor nerves, and to the respiratory muscles that drive the thorax lung pump. In the model, conversely, this process is represented by chemical concentrations at receptor sites (which are inputs to the system) and by ventilation rate (which is the major controlled variable). Typical short-term stresses for which this model is suited include hypoxia, hypercapnia, and acid base disturbances. Modification of the original model provided the capability to simulate exercise.

D.1.4 Thermoregulatory Subsystem Model

A dynamic model of physiological regulation of body temperature, originally developed by Dr. J. Stolwijk and later modified slightly, basically accounts for the body's reaction to external temperature (environment) and for the effects of metabolic heat production (exercise). The controlled system consists of a representation of the thermal characteristics of the various body compartments. These compartments (or nodes) were designed to represent head, trunk, arms, hands, legs, and feet. These compartments were further divided into concentric layers designated as blood core, muscle, fat, and skin. Each node appropriately produces metabolic heat and also exchanges convective heat with adjacent compartments. The skin exchanges heat with the environment by way of radiation, convection, and evaporation. The thermoregulatory model receives temperature signals from all tissue compartments, and, after integration and processing, the control system sends commands to all appropriate compartments to change metabolic heat production, blood flow, or the rate of sweat secretion.

D.2 Design and Development

The Whole-Body Algorithm was designed to provide the capability of simulating long-term and short-term stresses with a single "master" model. The long-term simulation is accomplished by a circulatory, fluid, and electrolyte subsystem model, which may be used to provide initial operating conditions for a set of three short-term models representing the cardiovascular, respiratory, and thermoregulatory systems. These three short-term models, which are designed to simulate the response to acute changes both in the environment and in short-term experiment stresses, operate in parallel and interchange information as often as every 0.05 second of simulation time. Using this approach, a Whole-Body Algorithm evolved that could simulate with equal facility those adaptive changes occurring over a period of days, weeks, or even months and those experimental stresses in which significant changes might occur in a matter of seconds.

D.2.1 Approach to Whole-Body Algorithm

Since all subsystem models were designed as feedback control systems with identifiable controller elements,

they have a certain formal compatibility. The technical plan for integrating these subsystem models included verifying the subsystem modeling approach, verifying the compatibility of each subsystem model, providing for system expansion, and unifying the system software programs and languages and the subsystem computational approach. The plan also included identifying interfaces between subsystem models, providing uniform experimental checkout of each subsystem and of the assembled algorithm, examining all interfacing closed loops for stability, developing the executive program to control execution of the subsystems, and validating the Whole-Body Algorithm.

This plan led to development of a Whole-Body Algorithm that is limited only by the detail of the individual subsystem models, the lack of physiological experiment data to further refine the models, and the lack of knowledge regarding certain physiological phenomena. This model provides a basis for studying physiological phenomena and a basic model that can be refined as new parameters are recognized.

D.2.2 Subsystem Interfaces

The individual models have been described above in the form in which they were used in the Whole-Body Algorithm. In this section, the interfaces developed to represent the appropriate interaction between these subsystems are described. A diagram illustrating these interfaces is presented in Fig. D-1, where the interface variables are defined as shown.

The general philosophy of interfacing the subsystems was to combine the various models in a manner causing the least number of modifications to the basic model formulations, even at the cost of an occasional loss of computing efficiency. Since the units used in each model were substantially different, it was frequently necessary to convert the units of variables passed between models. The rule for the Whole-Body Algorithm was that conversion factors, where necessary, would be applied on the receiving end of the transfer. It is recommended that all future models be converted to a single set of consistent units.

D.2.2.1 Long-Term/Short-Term Interface. Although technically the least difficult to accomplish, the long-term/short-term interface (Fig. D-1) was one of the most important in the Whole-Body Algorithm. This interface provided the capability to simulate the spaceflight event sequence (see Fig. 2-2). From the modeling viewpoint, the basic plan was to use the long-term model to initialize the short-term models for simulating any short-term experiments or transient environmental conditions. After steady-state conditions were reached, the long-term model could be initialized for simulation of the subsequent long-term phase. Since the long-term/short-term interchange under this plan is sequential rather than simultaneous, the modeling problem consisted primarily of providing for the transfer of the interface variables through a common block and of modeling the mechanisms necessary to use these variables on either side of the interface in a physiologically representative manner.

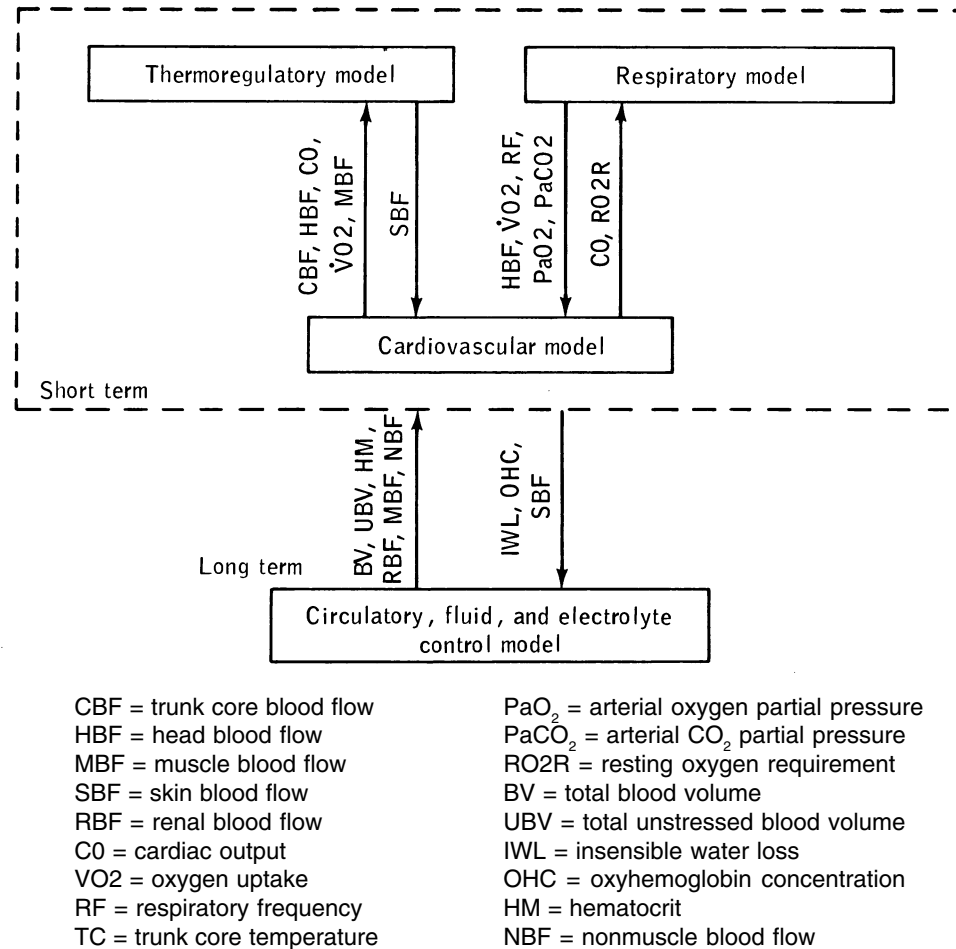


Figure D-1. Subsystem interfaces of Whole-Body Algorithm.

A major problem encountered was the transfer of state variables between models lacking identical initial conditions. This particular problem manifested itself as a drift from control steady-state conditions in the models at the time of transfer. A procedure to solve this interface problem involved choosing a supine resting (but not basal) state as the initial condition. This state was assumed to exist before any short-term stress was initiated and is closely related to the passive zero-g state. To properly represent this state, all subsystem models had to be initialized to this state at the time of transfer by matching metabolic rates (equivalent to the resting supine oxygen uptake), initial blood volumes, and major blood flows.

An additional problem was caused by the creation of new environmental conditions by the short-term models. The long-term/short-term interface had to include the capability to reinitialize the long-term model with the steady-state values of variables computed by the short-term loop (insensible water loss, oxyhemoglobin concentration, and skin blood flow) after simulation of the environmental stress. Including this capability provides the structure for

simulating the entire spaceflight sequence with environmental stresses performed throughout the interval. The next problem was to select, when simulating non-environmental stresses, the variables to exchange other than those required to represent transient environmental changes in the supine resting state. These variables should be direct functions of the long-term stresses being simulated and of the resultant hypotheses related to the level of physiological detail present in the models. By assumption, the short-term experimental stresses (other than environmental) would always include complete recovery to the state that existed before the stress. Hence, these stresses would not be allowed to perturb the long-term model.

The requirements for simulating bedrest made it necessary to identify important interfacing variables to more accurately simulate that condition. Bedrest is associated with the headward redistribution of blood and the resultant changes in blood volume, vasomotor conditions, hematocrit (due to plasma filtration), and blood flow through the major flow paths. Changes in total blood volume and total unstressed blood volume provide the necessary in-

formation to the short-term models for initializing blood volume and vasomotor changes (except tone changes, which were not considered in the initial bedrest hypothesis). Hematocrit was passed through the interface to provide the respiratory subsystem effect due to changes in red blood cell concentration. The blood flow changes in the renal, muscle, and non-muscle paths of the long-term model were passed through the interface to provide flow changes in the major flow paths of the short-term cardiovascular models. These flow changes are converted to a corresponding resistance changes and applied to the respective flow paths represented in the cardiovascular model. The renal blood flow changes was represented by a resistance change in the renal arterioles; the muscle blood flow changes was represented by a resistance change in the leg arterioles; and the non-muscle blood flow change was represented by a change in the resistance of the superior mesenteric artery. These hemodynamic changes were then reflected in the respiratory and thermoregulatory subsystems by way of the flow parameters in their respective interfaces with the cardiovascular subsystem during the simultaneous operation of these short-term models.

Model changes, other than those required to accommodate the variables passed through the interface as discussed previously, are associated with the specific hypotheses concerning the physiological changes that occur during bedrest. These modifications, as well as the requirements for additional variables to be passed through the interface to represent these specific hypotheses, will change as different hypotheses are considered. One value of the design approach selected for the Whole-Body Algorithm is the relative ease with which new interface pathways and hypotheses can be added and tested without total disruption of the system. These hypotheses and the required model changes are discussed in detail in Chapter 9. The hypotheses dealing with the occurrence of long-term rate changes and reverse stress relaxation during bedrest has been left in the Whole-Body Algorithm formulation. These points should be considered when repeating the simulation of bedrest with additional or different hypotheses.

It should be noted that all interfaces between the subsystems were designed for the simulation of the one-g response to the stresses of interest with the hypothesized physiological changes and responses as documented here. The assumption of different conditions, other stresses, other hypotheses, or other combinations of stresses and hypotheses would require the passing of additional or different variables through the interfaces. In most cases, additions to or improvements in the subsystem models would be required to accommodate the changes desired. The Whole-Body Algorithm was designed as a research tool to facilitate these structural changes.

D.2.2.2 Cardiovascular/Respiratory Interface. The interface between the cardiovascular and respiratory subsystems presented the most difficulty and, therefore, received the most attention. The difficulty was related to the physiological interaction and interdependence of these two short-term subsystems and to the fact that a larger

number of short-term stresses of interest to this project have responses manifested in these subsystems.

The initialized (resting) metabolic rate was different in each model, and this difference was the first problem encountered in the interacting of these two models. This problem was, in fact, encountered in all the model interfaces. The initial metabolic rate in the cardiovascular model was represented as a resting (non-exercising) oxygen uptake for an alert and ready subject. In the other models, the metabolic rate was initialized much closer to a basal rate. This problem was solved by using the resting oxygen requirement from the cardiovascular model to drive all subsystem models to a state of mutual equilibrium. Then the new state achieved was used as the initial conditions for subsystem models for all subsequent simulations.

The other interface elements of these two models were chosen to represent elements that changed significantly during the stresses of interest and that would significantly affect the subsystem model on the other side of the interface. The model having the better physiological representation of the variable of interest determined the direction in which these variables were passed. In most cases, this selection was made easily, since the counterpart variable of the interfaced subsystem model was generally represented non-physiologically or empirically in the other subsystem model. For example, respiration in the cardiovascular model was poorly represented by external pressure on the thoracic blood compartments. In some case, however, modifications in the receiving model were necessary to ensure proper model response to the passed variable, specifically when the receiving model had not been designed to respond to stresses generated in the sending model (e.g., the cardiovascular response to environmental stresses). For example, it was necessary to model changes in inspired gas concentrations where the model simulated the action of chemoreceptors, which are sensitive to changes in arterial partial pressures of oxygen and carbon dioxide. The chemoreceptor reflex was added to the cardiovascular subsystem model to ensure sensitivity to increases in carbon dioxide and decreases in oxygen in a manner similar to the baroreceptor response to changes in blood pressure. The premise for chemoreceptor control was derived from Scher [2] and is shown in Fig. D-2. The basic expression derived to produce the chemoreceptor autonomic reflex is

$$AUNC = 1.0 + (0.03448 \Delta pCO_2 - 0.016 \Delta pO_2)$$

where AUNC is the chemoreceptor autonomic effect and ΔpCO_2 and ΔpO_2 are changes in arterial carbon dioxide and oxygen partial pressures, respectively. Based on information from Duffin [3], it was necessary to limit the effect of the changes in arterial pCO_2 and arterial pO_2 . Results of this study showed that the response of the carotid chemoreceptor was very low or zero for arterial pO_2 greater than 80 mmHg and for arterial pCO_2 less than 30 mmHg. The resulting autonomic factor was then applied to the calculations of peripheral resistance, heart rate, and strength of heart contractions in the manner depicted in

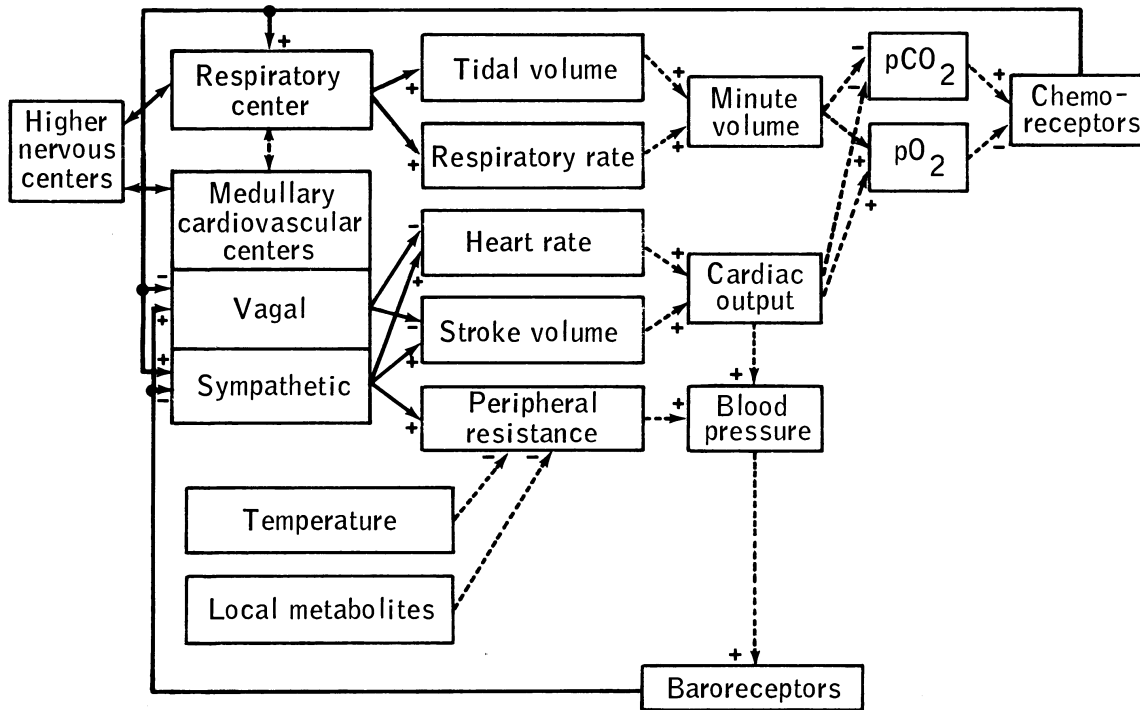


Figure D-2. Block diagram of autonomic control system. The major components of the cardiovascular and respiratory control systems are shown. A plus sign indicates that an increase in the input to a component increases its output; a minus sign indicates a decrease in output. When pressure rises at the baroreceptors, the sensory nerves will increase firing and there will be decreased firing in sympathetic fibers and increased firing in vagal fibers to produce vasodilation, decreased heart rate, decreased stroke volume, and decreased peripheral resistance. Decreases in heart rate and stroke volume will decrease cardiac output, which, combined with decreased peripheral resistance, will decrease blood pressure and, in turn, decrease pressure at the baroreceptors. An increase in arterial carbon dioxide partial pressure ($p\text{CO}_2$) or a decrease in arterial oxygen partial pressure ($p\text{O}_2$) at the chemoreceptors will increase the sensory discharge to cause decreased vagal and increased sympathetic activity, which will result in increased heart rate, increased stroke volume, and increased peripheral resistance. The heart rate and stroke volume increases produce an increase in cardiac output, which, combined with the increased peripheral resistance, increases the blood pressure. The combination of increased blood pressure and increased respiratory minute volume resulting from respiratory effects should produce increased transport of oxygen to the tissues.

Fig. D-2. These values in turn change blood pressure (which acts on the baroreceptors and closes a second feedback loop), as well as stroke volume and cardiac output. Cardiac output is passed to the respiratory subsystem model and thus completes the feedback loop across the interface.

The cardiovascular and respiratory subsystems, when initially exposed to exercise, responded in an unrealistic manner. It was noted, after all interface links were established, that a very good response from both subsystems was elicited for high exercise levels (150 to 200 watts) but that a poor response (worse than that for the stand-alone models) was elicited for the lower levels (100 watts and below). This problem was traced to a poor representation of the time-varying rate of oxygen uptake in the respiratory subsystem model. Since oxygen uptake is numerically integrated in the cardiovascular subsystem model (that is, the area to the left of the curve of oxygen uptake compared to time) to calculate oxygen deficit, a significantly different circulatory response resulted. An altered response would

be expected, in this case, because oxygen deficit affects many control functions in the cardiovascular model.

The studies of Whipp and Wasserman [4] indicate that variation of oxygen uptake with time for exercise levels greater than 100 watts cannot be represented accurately by the single exponential function used in the respiratory model (see Fig. D-3). Using this information, a new multiple exponential function for the higher exercise levels and an improved single exponential function for lower exercise levels were derived as shown in Fig. D-4 for 100 and 200 watts. Note that the curve for 200 watts, which is represented by multiple exponential function, breaks after approximately 2 minutes of exercise, as was indicated by the experimental data. This break corresponds to the anaerobic threshold, which is also indicated by the experimental data (Fig. D-3). When the exponential function (rate of change of oxygen uptake, or VO_2) is plotted on a semi-logarithmic scale, it becomes a straight line the slope of which is related to the time constant. Each exer-

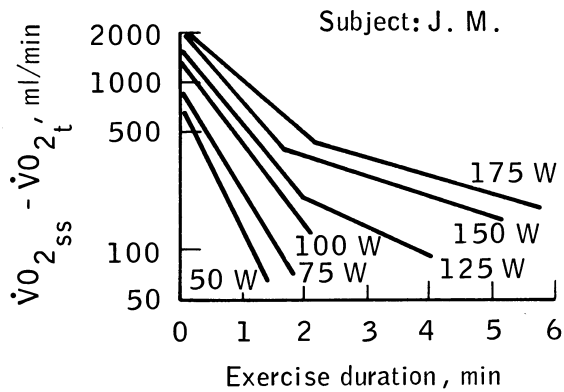


Figure D-3. Rate of change in oxygen uptake $\dot{V}O_2$ as a function of exercise duration for selected workloads. The subscript ss indicates steady state; t indicates transient (from Ref. 4).

cise level requires not only a different time constant but a minimum of two exponential functions to represent oxygen-uptake rates for exercise levels greater than 100 watts. The curves for this subject also show the anaerobic threshold to be very near the 2-minute mark of the exercise period for all levels above 100 watts. After these new oxygen-uptake functions were included in the respiratory subsystem model, the oxygen-deficit function in the cardiovascular model was tuned for these data and a good response from both subsystems was elicited for all levels of exercise (see Chapter 3).

D.2.2.3 Cardiovascular/Thermoregulatory Interface.

The principal functions of the thermoregulatory subsystem model are to simulate changes caused by variations in environmental parameters (for example, temperature, relative humidity, barometric pressure, cabin ventilation, clothing) and to simulate increases in metabolic production of heat (exercise). The function of the cardiovascular system, in the context of thermoregulation, is to provide a fluid medium for convective heat transfer away from tissues warmer than the blood and into tissues cooler than the blood.

The blood supply to the skin is of great significance to both cardiovascular and thermoregulatory subsystems. The skin exchanges heat with the environment through the pathways of radiation and convection. The amount of heat exchanged through these pathways is a function of the skin temperature and the various environmental factors mentioned previously. The temperature of the skin is determined through a heat balance of these environmental heat exchanges, through conduction to the adjacent fat compartment, and through convective heat exchange with the blood supply. The skin temperature acts in a feedback loop within the thermoregulatory subsystem, using the mechanisms of vasoconstriction and vasodilation to control the production of sweat and the skin blood flow. Therefore, since the skin blood flow is largely a function of the state of thermoregulation, the value for this parameter is

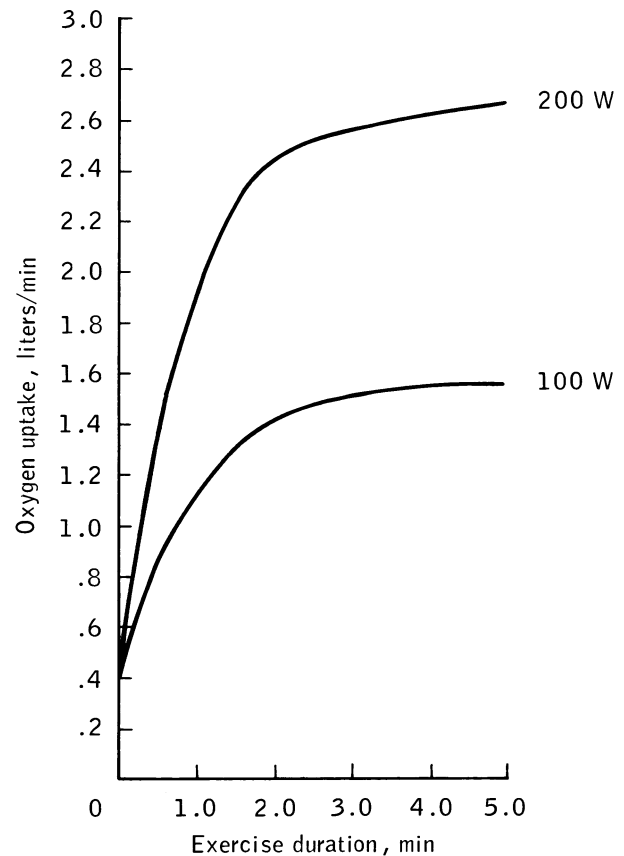


Figure D-4. New oxygen-uptake functions modeled in the respiratory subsystem.

computed and passed from the thermoregulatory subsystem to the cardiovascular subsystem. The other parameter passed from the thermoregulatory to the cardiovascular subsystem is the direct influence of temperature on heart rate. The temperature of pacemaker cells is known to influence heart rate. Since the thermoregulatory subsystem computes temperatures in the trunk core, this parameter is passed to the cardiovascular subsystem and is used to compute an additive term for the heart rate which is directly proportional to the change in temperature. Selkurt [5] indicates that the magnitude of this effect is approximately 13 to 20 beats/min $^{\circ}\text{C}$.

The remaining parameters of the cardiovascular/thermoregulatory interface are passed from the cardiovascular subsystem to the thermoregulatory subsystem (see Fig. D-1). The representation of the circulatory blood flow in the original thermoregulatory model was very crude and, therefore, caused significant inaccuracies in its response. These inaccuracies were expected to be relieved by interfacing the model with a fully developed cardiovascular model. This task was difficult, since the 28 blood-volume compartments of the cardiovascular subsystem had relatively little resemblance to the 40 geometrical body tissue compartments of the thermoregulatory subsystem. Correspond-

dence was found, however, between the two systems on a broader level. The blood flows that could be used directly from the cardiovascular model were the venous return from the brain and the sum of venous return flows from the heart, the kidney, and the liver. These two flow paths were used to replace the head core and trunk core blood flows, respectively, in the thermoregulatory model. The total muscle blood flow was passed from the cardiovascular to the thermoregulatory model as well. The muscle blood flow was distributed to various muscle tissues throughout the body, using the original distribution fractions in the thermoregulatory model as reported by Stolwijk [6] for rest and for bicycle-ergometry exercise. The remainder of the cardiac output was distributed to the remaining core and fat blood flows. This procedure provided a workable interface between the two models. However, in future studies, refinement of these blood flows using experimental data to acquire better representation of temperature distribution for the transient response to exercise is recommended.

A final variable passed from the cardiovascular to the thermoregulatory subsystem was the metabolic rate. This variable replaced an input parameter to the original thermoregulatory subsystem that had remained constant through an experiment. This refinement was required in the thermoregulatory model to improve the transient response to exercise. The arteriovenous oxygen difference computed in the cardiovascular subsystem included consideration of factors such as oxygen debt, oxygen deficit, and oxygen uptake in working muscle. These interface variables much more accurately represented the metabolic expenditures which resulted in the production of heat. The increase in metabolic rate from a basal to a resting state, as required by the design approach, was seen in the thermoregulatory model as mild exercise. Since metabolic heat generated during bicycle ergometry was distributed heavily to the leg muscles, adjustments had to be made to distribute the resting metabolic heat more equitably to other muscle compartments by using a distribution ratio proportional to the muscle mass fraction for each compartment.

An additional modification to the thermoregulatory subsystem was the addition of a countercurrent heat exchange formulation in the model's blood supply to improve performance in a cool environment. The new algorithm, as illustrated in Fig. D-5, represented the blood compartment as being in intimate thermal contact with the core compartments of the trunk, the arms, the legs, and the returning venous blood. These mechanisms are increasingly important in a cooler environment, where the venous return flows from muscle and skin are significantly cooler than the arterial blood supply.

In summary, the cardiovascular/thermoregulatory interface addressed the shortcomings of the cardiovascular model in the area of skin blood flow during exercise, the shortcomings of the thermoregulatory model in the area of blood flow rates, and the factors affecting metabolic use of oxygen. The principal result of an increase of skin blood flow in the cardiovascular subsystem was an increase in cardiac output, which, in turn, affected all other flows in the cardiovascular system. A primary benefit of this sub-

system interaction was that conditions of various levels of skin blood flow during exercise could be studied. With this combined model, the competitive effect of skin and muscle blood flow could be studied at various ambient temperatures for several levels of prolonged exercise and other conditions.

The chemoreceptor effect on the cardiovascular system and the respiratory system as well as the thermal-receptor effect on heart rate were bypassed during the exercise simulation. These effects, known to exist under abnormal conditions at rest, did not appear to be significant during exercise in normal environments. The reason for this apparent inconsistency during exercise and rest is not known. The importance of these receptors should be reevaluated if multiple stresses, such as exercise in hypoxic or hot environments, are to be considered.

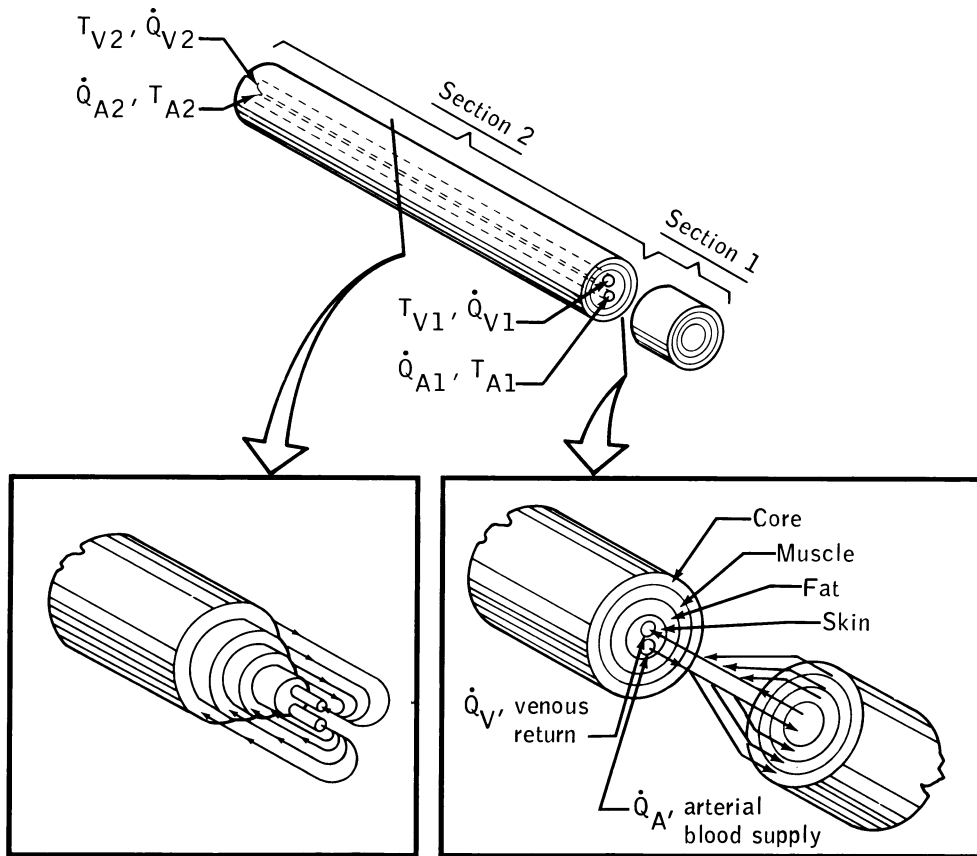
D.2.3 Computer Program Architecture

Extensive planning for a software structure for the Whole-Body Algorithm was required before it could be implemented. Design considerations required a model capable of simulating long-term adaptive changes as well as short-term acute experimental stresses. The approach taken was to run the long-term model for the desired amount of adaptation time and to initialize the short-term models with its results. Then, the short-term models were executed simultaneously and, on completion of the short-term experiment, significant effects of the short-term stresses were passed back to the long-term model to provide for further simulation of the adaptive process.

This procedure furnished the structure whereby entire spaceflights could be simulated using the Whole-Body Algorithm. The total amount of computer core required for the Whole-Body Algorithm was 29,200 decimal words. To operate within the limits of a 20,000-word core size (in the time-sharing mode), it was necessary to overlay the program. In the overlay process, which is commonly used in the programming of operating systems, parts of the program are stored on mass storage devices (disks) until a specified portion of the program (a segment) is required during the execution. At that time, the segment is brought into core and used until another segment of the program is required. Using this technique, programs such as the WBA may have a total size that is much larger than the available core size. Communication between programs through common blocks enables the updating of variables that are changed during execution.

The second advantage of this approach was that whenever the Whole-Body Algorithm completed a short-term experiment, control was returned to another segment brought into core. If the short-term models were called again, the programs were returned to core in their initialized state as updated by the long-term simulation. Therefore, a new short-term simulation could begin without memory of the past simulation. Such an approach assured that all computed variables were reset to their initial values without the need for additional computer programming.

To obtain synchronous operation of the short-term subsystems modes, an executive program was developed.



$$\dot{Q}_{V2} = \dot{Q}_{A2}$$

$$\dot{Q}_{V1} = \dot{Q}_{A1}$$

$$T_{V1} = \frac{\sum_{i=1}^4 (BF_{i1} * T_{i1})}{\dot{Q}_{A1}}$$

$$T_{V2} = \frac{\sum_{i=1}^4 (BF_{i2} * T_{i2})}{\dot{Q}_{A2} - \dot{Q}_{A1}}$$

$$CCH = (T_{V1} - T_{C1}) * \dot{Q}_{V1} + (T_{V2} - T_{C1}) * (\dot{Q}_{A2} - \dot{Q}_{A1}) + (T_{A2} - T_{C1}) * \dot{Q}_{A2}$$

$\dot{Q}_{V2}$ = blood flow rate (venous return, section 2)

T_{V1} = temperature of blood (venous return, section 1)

T_{C1} = temperature of core compartment, section 1

BF = blood flow

CCH = total countercurrent heat exchange

All variables are known except those on left-hand sides of the equations.

Figure D-5. Schematic diagram of countercurrent heat exchange.

The function of the executive program was to compare the value of time in the various subsystems and advance the time in the appropriate subsystem accordingly. The maximum difference in integration step sizes between the short-term subsystems occurred between the cardiovascular (0.002 second) and the thermoregulatory (3 second) models. It was possible for one subsystem to advance by several integration steps before another subsystem was advanced by even one step. Additional software details are contained in Ref. 7.

D.3 Validation Studies

From the outset, it was apparent that to obtain the idealized data set required to completely evaluate and validate the Whole-Body Algorithm would not be possible. A literature search revealed that very few transient data were available for any of the stresses, and responses to graded levels of stresses were not available for many of the cases considered; exceptions were a few easily measured variables such as heart rate and ventilation rates. Experimental studies documented in the literature were almost always concerned with only one major physiological system and entirely neglected other important systems. For example, investigators who reported cardiovascular responses to graded levels of environmental temperatures failed to measure body temperatures or ventilation rates. In many cases, it was impossible to obtain confirming data, and validation was based on a single source. The task of validating the Whole-Body Algorithm was more difficult than the validation of many other physiological models because it contains more subsystems, more parameters, and more dependent variables than other physiological models.

All the short-term stresses chosen for simulation were similar to those already used to validate at least one of the short-term subsystem models operated alone. A summary of the short-term models and the corresponding stresses for which they were tested on a stand-alone basis is shown in Table 3-8. If validation had been restricted to testing subsystems of the Whole-Body Algorithm that had been tested previously on a stand-alone basis, data collection and validation would have been simpler, since portions of the necessary data were available and documented. However, all the models were not previously capable of responding to all the stresses. The formulation of the Whole-Body Algorithm has increased the capability of each of these models and provided a basis, through the interfacing links and simultaneous operation of all the models, for simulating additional stresses in an integrative manner. For example, the thermoregulatory model has been previously validated for a thermal stress at rest; however, the respiratory and cardiovascular subsystem models had no capability until now, to simulate thermal stresses. Thus, it was necessary to attempt to locate a validation data set that included responses of these additional subsystems. Unfortunately, as previously discussed, physiological study of whole-body integrated responses to stresses is not usually undertaken and many of the desired data were unavailable. Nevertheless, a wide variety of re-

sponses have been tested and the overall capability and potential of the Whole-Body Algorithm is evident from the results presented in Chapter 3.

In a model as versatile and complex as the Whole-Body Algorithm, it is possible to test an endless variety and combination of situations, stresses, and parameter changes. To limit these tests to a reasonable number and still demonstrate the validity of the model, several restrictions were imposed. These restrictions are listed here.

1. Only one stress at a time would be imposed on the model; multiple-stress validation simulations, such as exercise in a hot environment, would not be performed.
2. A number of relevant short-term stresses would be used to validate all three subsystem models in the short-term section of the model.
3. The long-term portion of the model would be validated with only a single stress.
4. The emphasis on validation would be in the steady-state domain, although the capability to simulate dynamic changes would be demonstrated.
5. The model would be capable of performing experiments of short duration with the short-term subsystems and of passing changes representing new physiological steady state to the long-term subsystem, yet this capability would not be validated. Consequently, an attempt was made to determine long-term fluid-electrolyte changes or other adaptation effects which resulted from thermal stress, hypoxia, etc.
6. The reverse situation—automatically reinitializing the short-term subsystem models with changes resulting from a long-term stress—would be validated with a pre-and post-bedrest, exercise, and tilt stress following several simulated weeks of bedrest. This simulation would demonstrate the capability of the long-term subsystem to dynamically adapt through certain elements such as pressure-receptor resetting, autoregulation of blood flows, and stress relaxation.

Table 3-9 is a summary of information related to the validation tests performed under these guidelines. The bedrest validation of the Whole-Body Algorithm is presented in Chapter 9.2 and will not be discussed further here. The following discussion is meant to supplement the simulations described in Chapter 3.

D.3.1 Simulation of LBNP and Tilt

D.3.1.1 Physiological Response to Tilt and LBNP.

The physiological changes that occur when an individual assumes the erect position provide a hemodynamic stress on the entire circulatory system. The capability of the vasculature, the heart, and the nervous system to appropriately react to this stress formed the basis of the tilt-table test and the Lower Body Negative Pressure (LBNP) test.

Upon shifting from supine to erect position, changes occur in circulatory pressures and flows as well as in blood volume distribution. The arterial, capillary, and venous pressures become markedly elevated in the dependent ex-

limbs to cause a net capillary filtration into the tissues. This filtration can result in a loss of 5 to 10% of the supine blood volume [8]. An additional 10% of blood volume is shifted from the upper part of the body (mainly from the thoracic cavity) to the legs, where it is pooled primarily in the distensible venous segments [9]. Venous segments below the heart tend to distend, whereas those above the heart tend to collapse. In the absence of compensatory mechanisms, the effective central venous pressure would probably fall below that of the heart and result in insufficient cardiac pumping and orthostatic hypotension.

The defenses of the body against orthostatic hypotension consist of both passive and active elements [8,10,11]. Ultrafiltration into the tissues is minimized by increase of tissue fluid pressure and lymphatic flow, reduction of the pressure level in the veins by enhanced muscle pumping, and transient venoconstriction of the extremity venules. Systemic arterial pressure is maintained, and even elevated, by activation of intrathoracic and carotid blood pressure receptors. The reduction in effective central blood volume caused by a shift of blood from the upper to the lower part of the body is associated with a sustained increase in sympathetic activity to the resistance vessels in muscles and visceral organs and to the heart. This response maintains cardiac output and arterial blood pressure despite reduced cardiac filling pressure. The increase in leg vascular resistance also helps minimize venous pooling. Central venous pressure must be maintained to promote adequate right-ventricular filling.

The exact mechanisms controlling this adjustment have not yet been explained, but it is believed that three factors are important in preventing a debilitating fall in central venous blood volume and pressure: (1) contraction of large venous channels and venous reservoirs such as those in the visceral organs, (2) external compression of veins by skeletal muscles in the legs, and (3) an external pressure on the large abdominal veins exerted both by an increased hydrostatic pressure on abdominal organs and as an increase in abdominal muscular contraction. The net effects induced by standing or tilting and by the influence of the orthostatic defense mechanisms are a reduction in central blood volume, a decreased cardiac output due to reduced stroke volume (despite an increased heart rate), and an increase in peripheral resistance, which acts to elevate the mean systemic blood pressure [12]. Orthostatic hypotension develops when one or more of the compensatory mechanisms are not adequate.

Lower body negative pressure tests, in which an increased transmural pressure is created in the blood vessels below the waist, can also cause a considerable degree of venous pooling in the lower extremities, similar to that found in tilt-table experiments [13]. Other hemodynamic changes are also similar to the tilt response, such as decreases in cardiac output and stroke volume and increases in heart rate. However, investigators believe that there are certain fundamental differences between these two stresses [14,15]. The most important difference is that a hydrostatic gradient exists in tilt but not in LBNP. The tilt experiment causes a gravity gradient from the heart to the

extremities in every vascular segment, with varying amounts of blood pooling. The quantity of pooled blood depends on the length of the segment and its distance from the heart. The effect of these two different kinds of stresses on the cardiovascular system will be evident in the following results. Lower body negative pressure has been used in experimental studies as a means of creating an effective "hemorrhage" in the central portions of the vasculature [16] as well as of providing a hemodynamic stress for crewmen in weightless spaceflight.

D.3.1.2 Simulation of LBNP/Tilt with the Whole-Body Algorithm. The tilt experiment is simulated in the short-term subsystem model by applying the gravity pressure gradient terms to the vascular compartments. The overall effect is a decrease in blood volume above the heart and an increase in all segments below this region. In simulating LBNP, a negative pressure term applied externally to the leg vessels increases the transmural pressure and results in a calculated increase in blood volume of the leg compartments.

The cardiovascular subsystem model contains representation of many of the elements previously discussed that are involved in the physiological response to tilt and LBNP. The model has elements that simulate the shift in blood from upper to lower segments of the body, the baroreceptor reflex and the resulting sympathetic effects on heart and vasculature, the muscle leg pump, venous valves, collapsible and distensible veins, and stress relaxation. Extravascular compartments are not represented in the short-term model, and hence, transcapillary filtration and lymph flow are not simulated. Such a limitation is not as restrictive as it would first appear for the following reasons. First, filtration into the tissues on standing is not rapid; the process requires as long as 30 minutes to reach a steady state [12]. Second, the baroreceptor reflexes are fully developed within the first minute following postural changes [10]. Third, most measurements of hemodynamic variables during LBNP and tilt are usually completed within the first 5 minutes following the stress, well before the major effect of ultrafiltration is felt.

Furthermore, although tilting may result in extravasation of plasma, there is not conclusive evidence that the same is true during LBNP. Thus, the only real limitation that exists in simulating tilt is that the model's response should be compared to experimental measurements taken within several minutes after the stress is imposed.

Additional discussion of the physiology and simulation of postural change is presented in Chapter 9.6. Simulations of LBNP during spaceflight is discussed in Chapter 7.4.

D.3.2 Simulation of Respiratory Gas Disturbances: Hypoxia and Hypercapnia

D.3.2.1 Physiological Response to Hypoxia. An adequate supply of oxygen is essential to meet the varied metabolic requirements of every body cell. Oxygen transport from the inspired air to the individual cells involves many processes and organs, each with its own regulatory system. The essential components of the oxygen supply

system are ventilatory gas exchange, cardiovascular system function including cardiac pumping capability and blood flow distribution, hemoglobin affinity for oxygen, and hemoglobin concentration. All of these elements are present in the Whole-Body Algorithm in varying degrees of detail. In the normal subject, this complex system is adjusted to maintain an adequate tissue oxygen tension that meets the tissue requirements for the body as a whole. In the stressed individual in whom either metabolic requirements or oxygen supply are abnormal (as in exercise, hypoxia, or anemia), the system readjusts its oxygen supply capability to maintain adequate oxygen supply to the more critical organs such as the heart, the brain, and, in the case of exercise, the muscles tissue [17].

The most common experimental method to induce hypoxia consists of decreasing the oxygen content of the inspired gas. Since oxygen transport to the body cells is ultimately governed by diffusion, which is dependent on the partial pressure gradient, the critical indicator of oxygen level is its partial pressure (both in the inspired air and in the blood) rather than the absolute concentration (ml) O₂ per ml blood). Breathing air with less than normal oxygen will not cause noticeable effects either in pulmonary ventilation or in overall cardiovascular function until the inspired pO₂ level falls significantly from its normal value of 158 mmHg (corresponding to an inspired oxygen concentration of 21%). Thus, mild acute hypoxia is not considered a strong stimulus for physiological response [18]. Acute inhalation of 8 to 10% oxygen results in moderately severe hypoxia. Some of the more noticeable acute physiological effects are a sharp increase in pulmonary ventilation and a large rise in heart rate as well as in cardiac output [19]. The small changes in blood pressure that accompany this stress suggest that considerable vasodilation has occurred [20]. Little quantitative information is available for man regarding the redistribution of blood that results in overall peripheral vasodilation. In general, blood is believed to be shunted to tissues with high oxygen extraction (heart, muscle, and brain) at the expense of flow to tissue with low oxygen extraction (skin, viscera, and kidney). Severe hypoxia results in a reflex bradycardia and a significant and large vasoconstrictor effect. Because the WBA is not capable of simulating severe hypoxia, these extreme effects are not discussed herein.

The body has developed a complex of regulating systems that are integrated both at the central nervous system (CNS) level and at the local organ level. It is generally accepted that the hypoxia-induced increase in ventilation is a direct result of a decreased arterial pO₂, causing increased peripheral and central chemoreceptor activity [3]. Much less is known about the determinants of the accompanying cardiovascular changes. For many years, it was believed that the chemoreceptors were mainly responsible for stimulating most of the cardiovascular effects of hypoxia (or hypercapnia), but such a view is no longer tenable. The effects of chemoreceptors and other factors on the heart, the resistance vessels, and the capacitance vessels are shown in Fig. D-6 [2,19,21,24]. Figure D-7 is a schematic view of the integration of these factors during

the hypoxic or hypercapnic stress. It is obvious that the chemoreceptors provide only a part of the control necessary to withstand a decrease in oxygen supply. The actual degree and direction of cardiac and vasomotor behavior depend on the degree of hypoxia, the particular vascular bed, the animal species under investigation, and the relative influence of these competing local, autonomic, and hormonal factors. It is experimentally difficult to separate the various autonomic effects, and little quantitative information is available regarding the relative influence of these determinants in man.

A complicating factor that must be considered is that under the influence of low blood pO₂, the respiratory minute-volume output increases and, consequently, carbon dioxide is expired in greater than normal amounts. Thus, hypoxia is usually associated with hypocapnia, which is known to cause variation in central nervous activity, often in a direction that minimizes some of the cardiorespiratory effects of hypoxia [22,25].

D.3.2.2 Physiological Response to Hypercapnia. Carbon dioxide is a substance that is normally inspired in extremely small quantities (approximately 0.3 mmHg partial pressure). However, because large quantities of CO₂ are produced in the body by cell metabolism, the partial pressures in the blood are relatively high (approximately 40 and 46 mmHg) in arterial and venous blood, respectively). Blood carbon dioxide is one of several important chemicals used by the body to indicate local and overall rates of metabolism. These agents appear in various feedback pathways that adjust vascular resistance and blood flow to supply sufficient oxygen to meet the demand and to carry away toxic products of metabolism. During acute hypercapnic stress, the resting individual is confronted with an unfavorable environment for elimination of metabolic carbon dioxide and must therefore increase minute ventilation. The body responds to acute carbon dioxide inhalation in many ways. For example, it responds as if metabolism has suddenly increased, such as it would in exercise or as if an accumulation of metabolites has occurred by local occlusion of blood vessels. Besides the ventilatory response, other changes observed are an increase in blood pressure, heart rate, stroke volume, and cardiac output with a decrease in overall vascular resistance [26]. Except for the marked increase in blood pressure, the overall response to hypercapnia is similar to those previously described for hypoxia. Unlike oxygen, which does not appear to cause significant whole-body responses until its blood partial pressure has been reduced to about 40% of normal levels, the response to carbon dioxide is more linear and dramatic changes can be observed when blood pCO₂ changes only slightly from normal physiological values [3].

Although the *ventilatory* response to hypoxia and hypercapnia have been well studied and essentially understood (primarily a chemoreceptor-activated response), few studies of the *cardiovascular* effects of these disturbances, particularly for carbon dioxide inhalation, have been reported. Except for the brain (which is under local rather

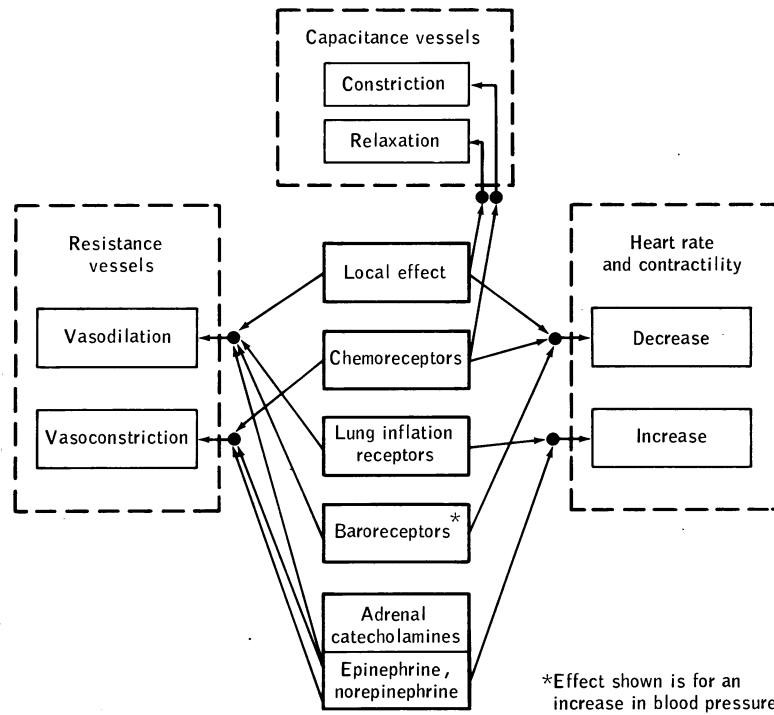


Figure D-6. Determinants of cardiovascular regulation during hypoxia and hypercapnia.

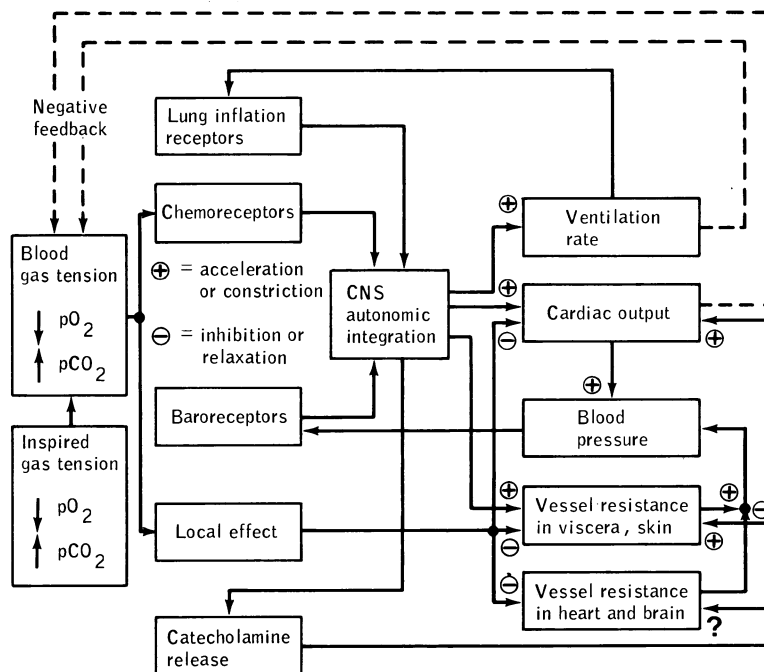


Figure D-7. Integrated cardiorespiratory regulation during hypoxia or hypercapnia.

than autonomic control), little attention has been paid to blood flow redistribution during hypercapnia.

It appears that the same mechanisms activated by breathing oxygen-poor mixtures are also activated by increase in carbon dioxide levels and act in very much the same way, but here, also, little quantitative information is available in man [22]. The scant attention paid to changes in the cardiovascular system during hypercapnia represents a severe challenge to modeling. For example, although peripheral blood flow resistance is known to decrease during hypercapnia, the mechanism is not clear. The few available studies in man have suggested that only the brain and heart are known to vasodilate [26].

D.3.2.3 Simulation of Hypoxia and Hypercapnia with the Whole-Body Algorithm. The respiratory model was capable of simulating reasonable ventilatory responses to hypoxia and hypercapnia before its incorporation into the Whole-Body Algorithm. The controlling mechanism was a chemoreceptor sensor responding to low levels of oxygen and high levels of carbon dioxide. However, the cardiovascular subsystem model was not capable of responding to change in blood gas tensions, and additional modeling was required to account for this effect. In attempting to cope with the lack of qualitative data regarding mechanisms controlling the cardiovascular system and with few previous modeling guidelines to follow, it was decided that only a gross approximation of the real system was justified.

The first major assumption was that the feedback systems (Figs. D-6 and D-7) responding to low levels of oxygen responded to increasing levels of carbon dioxide in the same qualitative manner. For example, it was assumed that both hypoxia and hypercapnia produce a local vasodilating effect and a depressant effect on the heart. Although all the evidence is not yet available to support this assumption in its entirety, there is little evidence to contradict it. The second major assumption was that, for the purposes of this preliminary study, it would be possible to lump many of these effects into an effective “chemoreceptor” feedback pathway. The sensor of this pathway would have a graded response to increasing arterial levels of carbon dioxide and decreasing levels of oxygen. This response is similar to the response of the ventilatory system chemoreceptors. The appropriate sensitivities of these new chemoreceptors to each of the gases would depend on available data regarding integrated effects in the intact animal. The actual level of oxygen and carbon dioxide tension in the blood at any moment would be obtained from the respiratory model that had previously been shown to provide good agreement with published studies. In terms of the elements shown in Fig. D-6, the cardiovascular “chemoreceptor” was used to represent a combination of local effects, chemoreceptor effects, lung inflation reflex, and adrenal catecholamine effects. The baroreceptor representation in the model was not changed and could function independently of the “chemoreceptor.” This configuration in the Whole-Body Algorithm is summarized in Fig. D-2.

To appropriately simulate the data available for hypoxia and hypercapnia in normal resting man, it was necessary to allow the chemoreceptors to affect heart rate, cardiac contractility, muscle flow resistance, renal flow resistance, and the resistance of flow through bone and fat in a manner generally seen in experimental animals. Since the sensitivities of the chemoreceptors to oxygen and to carbon dioxide were not the same, these feedback pathways were not expected to respond identically for both hypoxia and hypercapnia.

Brain blood flow was a variable already controlled by the respiratory subsystem model, and no changes were necessary in that section of the model. A chemoreceptor effect on coronary and skin blood flow was not included, despite data that demonstrated changes in these organs. Since their basal flow was small compared to cardiac output, it was felt that their effect on the overall system would be minimal.

Hypocapnia and hypoxia were simulated simply by changing the values of the parameters representing inspired air concentrations of oxygen, carbon dioxide and nitrogen.

D.3.3 Simulation of Thermal Stress

D.3.3.1 Physiological Responses to Thermal Stress in Resting Man.

If a resting man is exposed to a hot environment for short periods, changes are observed not only in the thermal regulating system but in other major physiological systems as well, notably the circulatory and ventilatory systems. Indeed, in a strict sense, all of these subsystems act as a functional unit to reduce the thermal stress on the body. Sweating, insensible heat loss from the lungs, redistribution of blood flows (notably to the skin tissues), and cardioacceleration all are manifestations of thermoregulation and require a multiple system of regulatory loops [27,28].

The effects of heat exposure are first manifested by an increase in skin temperature. As further heating takes place, the temperatures in all deep tissue masses tend to increase. In response, the body makes several adjustments (Fig. D-8) that act to remove this excess heat load and reduce its effects. These changes are discussed in the following paragraphs.

Blood flow through skin tissue increases as a result of both local and centrally mediated effects. Increased skin blood flow brings greater quantities of warm blood to the body surface, where its thermal energy can be transferred through the skin and, ultimately, by radiation and conduction to the environment. The normal skin blood flow of 150 to 200 ml/min can increase to 3500 ml/min and perhaps higher under maximum vasodilation [29]. The increase in skin blood flow tends to increase skin temperatures. If the environment is warmer than the body surface (that is, if ambient temperature is greater than 32° to 34°C, the body will gain heat by conduction and radiation; if cooler, it loses heat. Radiation is usually the more important route of heat exchange.

Because of the reduced or negative temperature gradient between skin and surroundings, circulatory adjustments alone are not adequate for dissipating heat by radiation at ambient temperatures above 32° to 34°C. At

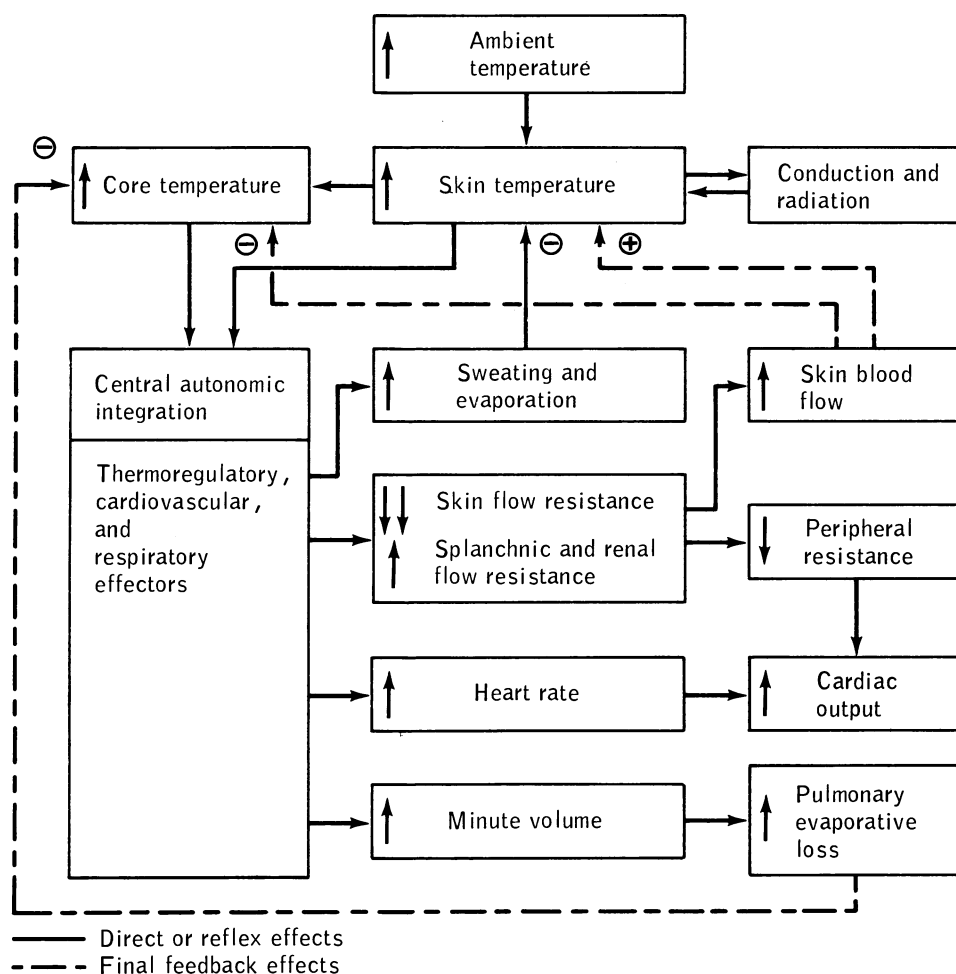


Figure D-8. Integrative physiological regulation of thermal stress at rest.

these temperatures, sweating is initiated; evaporation of the sweat removes heat from the body surface. Evaporative heat loss by sweating is a particularly effective cooling mechanism. Maximum sweating levels of nude resting man approach 400 ml/hr at ambient temperatures of 48°C. This maximum sweating level represents 270 watts of cooling power [30]. At these high temperatures, sweating and pulmonary water loss becomes the only avenues of heat loss. A humid environment and clothing decrease evaporation of sweat and increase the heat load, whereas an increase in free-air velocity on the skin decreases the heat load. The major circulatory change appears to be a shift of blood flow from central circulation to peripheral vasculature.

In resting man, renal, hepatic, and splanchnic flows have been observed to decrease (by some as yet unknown mechanism) when he is exposed to severe heat stresses, whereas skin blood flow increases [31]. This readjustment of arteriolar resistance elements results in a decreased peripheral resistance.

Heart rate has been observed to increase gradually with increasing body temperatures; this increase probably

results from autonomic stimulation from the thermoregulating centers. This effect on the heart, together with the decrease in peripheral resistance, results in an increase in cardiac output by as much as 80% [28,32]. No striking changes in stroke volume (or blood pressure) have been seen, despite a tendency for increased myocardial contractility [33].

The major response of the respiratory system to thermal stress is an increase in minute volume. Whether this effect is directly related to temperature is not known, but the effect is gradual and mild until deep body temperatures are increased from the normal value by more than 1° to 1.5°C, where marked increases in minute volume have been demonstrated [34]. The great effectiveness of the overall thermoregulatory system is such that, during rest, the core temperature is unlikely to rise more than 1°C even when ambient temperatures are increased by 30°C [35].

D.3.3.2 Simulation of Thermal Stress with the Whole-Body Algorithm.

The thermoregulatory subsystem model contained the major thermoregulatory elements, and it was capable of accurate and detailed simulation of thermal

stress in resting man even before it was integrated into the Whole-Body Algorithm. For example, it contained elements for conduction, radiation, sweating, skin blood flow regulation, shivering, and insensible pulmonary water loss. However, except for skin blood flow, the cardiovascular segments of the stand-alone model were only crudely developed and had no capability of simulating important cardiovascular parameters such as blood pressure, peripheral resistance, heart rate, and stroke volume. It was felt that the pulsatile cardiovascular model, when joined with the thermoregulatory model, would contribute this information as well as improve the cardiovascular portion of the thermoregulatory subsystem. Conversely, the thermoregulatory model's description of skin blood flow regulation during heat stress was markedly superior to the same formulation in the pulsatile cardiovascular model. As discussed previously, there are thermal effects on the cardiovascular system besides skin blood flow regulation. These effects concern resistance changes in visceral organs and thermal effects on heart rate. Compared to the available data relating heart rate to deep body temperature [30,32,34,36], little information was available concerning blood flow redistribution in response to changes in ambient temperatures. Consequently, only the former effect has been introduced in this version of the Whole-Body Algorithm. These and other changes have been described in detail earlier in this appendix. The effect of temperature on ventilation has been omitted from the model because this factor is not important for the ambient temperatures of interest in the preset studies [34].

The simulation of an environmental thermal stress was accomplished by changing values of the ambient dry-bulb input parameter. Wall temperatures, affecting the radiant elements of heat transfer, were also adjusted to be equal to the dry-bulb temperature, and wet-bulb temperature was set to correspond to a relative humidity of 35%.

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Appendix E

Sensitivity Analysis: A Simulation Technique with Application to the Human Thermoregulatory System Model

Analysis of the effects of parameter variation on the output (dependent) functions of a mathematical model can be important in predicting errors that may occur when designing technological control systems and in understanding the importance of specific parameters in biological systems. One of the simplest ways of understanding the response of a model system to parameter variation is called sensitivity analysis.

The conceptual basis of sensitivity analysis is straightforward. Small variations are made in the values of the system parameters of a model, and the effects of these changes are observed in the dependent variables during a simulation procedure. Following this step, sensitivity functions (described later) that describe the observed effects are computed. Such functions contain a considerable amount of information about the dynamic system under investigation. The most important use of sensitivity analysis is to determine the relative influence of different parameters on the system's response. This information is useful in assessing the validity of a model without the need for extensive model-to-data comparison studies and in guiding experimenters toward the investigation of the most important parameters in a real system.

The literature of physiological systems contains few examples that illustrate the formal application of sensitivity analysis, especially with regard to large-scale models [1,2]. The studies of ecological systems by Miller [3,4] provided the framework for the present study. Several texts are devoted exclusively to sensitivity analysis [5,6], but their sensitivity analysis is applied to nonbiological systems.

This appendix consists of a discussion of methods to compute sensitivity functions and contains examples of the manner in which these functions can be used to obtain meaningful information about a complex mathematical model of human thermoregulation. A more detailed study is available [7].

E.1 Theoretical Background

E.1.1 Definition of Sensitivity

Consider a model with an output (dependent) function y , which depends also on a (normally fixed) parameter q . Let y^o be the reference (or normal) value of y obtained when $q = q^o$, and let Δy represent the change in y that results from a change in q to $q^o + \Delta q$. The incremental sensitivity coefficient is defined as

$$\Delta S = \frac{\Delta y}{\Delta q} \quad (E1)$$

and the differential sensitivity coefficient is defined as

$$S(t, q) = \frac{\partial y(t, q)}{\partial q} = \lim_{\Delta q \rightarrow 0} \Delta S \quad (E2)$$

when this limit exists.

The term sensitivity function is often used instead of sensitivity coefficient to emphasize that S is not always constant but is dependent both on time t and on the value of q . In this appendix, S will be considered the mathematically rigorous definition of sensitivity, whereas ΔS will be an approximation. Values for S (or ΔS) may be obtained by several methods, both analytically and numerically, but the primary interest here will be on a numerical approach.

E.1.2 Supplementary Behavior

The simulation of any model usually involves determining the supplementary motion that results from a parametric disturbance. Sensitivity analysis can provide a convenient method for determining supplementary behavior. Supplementary behavior is defined as the difference between the varied behavior of the system $y = y(t, q + \Delta q)$ and the fundamental behavior (or reference solution) of the system $y^o = y(t, q)$. Thus,

$$\Delta y = y(t, q + \Delta q) - y^o \quad (E3)$$

Eq. (E3) can be expanded by a Taylor series. By neglecting higher order terms, it can be reduced to

$$\Delta y = S(t, q) \Delta q \quad (E4)$$

In the general case for a system with m parameters, the analogous form is

$$\Delta y(\Delta q_1, \dots, \Delta q_m) = \sum_{i=1}^m S_i \Delta q_i \quad (E5)$$

This important relationship allows one to predict the behavior of a system following a parametric variation using simple algebra and without the necessity of performing a simulation. However, knowledge of the sensitivity function, or sensitivity functions, is required. In many cases, this method of analyzing supplementary behavior is often more convenient than a direct simulation of the varied system.

E.1.3 Methods of Determining Sensitivity Functions

Assuming that the equations describing the dynamic system are known and are easily differentiable, sensitivity equations can be derived on the basis of the definition given by Eq. (E2). In practice, the system equations and the sensitivity equation are solved simultaneously on an analog or a digital computer. The solution to the sensitivity equations consists of the sensitivity coefficients. The sensitivity equations are generally linear even if the original system is nonlinear. For a system with n variables and m parameters, there are $n \times m$ sensitivity coefficients that may be obtained from a solution of the sensitivity equations. For large-scale systems, the derivation and the solution of the sensitivity equations become somewhat impractical; more straightforward numerical methods can be used to obtain the sensitivity functions.

In those cases where neither the analytic solution nor the explicit formulation of the sensitivity equations is readily obtainable, an empirical method is available. This technique involves varying a single parameter by a small increment about its normal value and performing a single computer simulation. The sensitivity coefficient is obtained by comparing the value of the output variable from this run with its value during a run in which none of the parameters are perturbed from their reference positions. For the general case having m parameters q_i (where $i = 1, \dots, j, \dots, m$) and q_j as the particular parameter of interest, the incremental sensitivity function that describes the change in y due to the variation Δq_j is given by

$$\Delta S_j(t, \Delta q_j) = \frac{y(t, q_j + \Delta q_j) - y(t, q_j)}{\Delta q_j} \quad (\text{E6})$$

If a parameter is perturbed by a small amount (for example, 1%) and the sensitivity function is sufficiently smooth, the value of ΔS_j determined from Eq. (E6) will be approximately equal to the true sensitivity coefficient defined by Eq. (E2). This method requires that each sensitivity function S_i ($i = 1, \dots, m$) be determined by a separate simulation during which only a single parameter is perturbed.

E.1.4 Logarithmic Sensitivity Coefficients

An alternative approach to sensitivity analysis is one that uses the function

$$\begin{aligned} \bar{S}_j &= \frac{\partial \ln y}{\partial \ln q_j} \\ &= \frac{q_j^\circ}{y^\circ} S_j \end{aligned} \quad (\text{E7})$$

where $\bar{S}_j$ is called the logarithmic sensitivity coefficient (function). Note that $\bar{S}_j$ may be approximated by the ratio of $\Delta y/y^\circ$ to $\Delta q_j/q_j^\circ$ in the same way that S_j is approximated by the ratio of Δy to Δq_j . If $\bar{S}_j$ is known, then the percent

change in the output variable y is given by $\bar{S}_j$ multiplied by the percent change in parameter q_j .

Once the sensitivity functions are determined for each parameter, it is possible to estimate the variation in y for any combination of parametric changes. Let U_i be defined as the fractional change of a parameter from its normal value

$$\begin{aligned} U_i &= \frac{\Delta q_i}{q_i^\circ} \\ &= \frac{q_i - q_i^\circ}{q_i^\circ} \end{aligned} \quad (\text{E8})$$

Equation (E5) can be rewritten using the definitions given in Eqs. (E7) and (E8) as follows.

$$\begin{aligned} \Delta y / y^\circ &= \sum_{i=1}^m \bar{S}_i (\Delta q_i / q_i^\circ) \\ &= \sum_{i=1}^m \bar{S}_i U_i \end{aligned} \quad (\text{E9})$$

Solving this expression for y yields fewer parameter disturbances.

$$y(t, \Delta q_1, \dots, \Delta q_m) = y^\circ \left(1 + \sum_{i=1}^m \bar{S}_i U_i \right) \quad (\text{E10})$$

This result allows the value of y to be computed easily for any number of single- and multiple-parameter changes, so long as these changes are small, in some sense. The agreement between the values of a response variable y as predicted by Eq. (E10) and those predicted by a complete model system has been found to be surprisingly good even when parameter values are changed by 100%, when highly complex models are used, or when highly nonlinear models are used [7]. The deviation becomes more pronounced as the operating point moves farther from the normal value because Eq. (E5) does not include the higher order terms of the Taylor expansion. These terms can become increasingly significant for larger perturbations.

The sensitivity coefficient defined by Eq. (E1) or (E6) depends on the total deviation of the parameter (Δq) from some normal value and the time or time period for which the sensitivity coefficient is computed. If the system is in a steady state, the sensitivity coefficient no longer depends on time. When the system under study is highly nonlinear or when the value of a parameter may vary within broad limits, sensitivity analysis can be difficult. When the dynamic system has many parameters ($q_1, q_2, \dots, q_m$) with values not known to a high degree of accuracy, the difficulty will be compounded, since sensitivity functions may depend on the particular values of all parameters. In the general case, the sensitivity coefficient $S(t, q_1, q_2, \dots, q_m)$ is a quantity associated with every point of parametric

space (i.e., every operating point) and changes with the position of the point. Thus, it is essential to carefully define and specify the times and parameter limits that are of primary interest.

E.2 The Performance Criterion

In many cases, when dealing with a model having many dependent variables, it is desirable to define a single measure of overall system performance. Such a measure, which can be called a *performance criterion*, could be extremely useful in performing sensitivity analysis and parameter estimation. Then, the effects of multiple-parameter variations can be related to changes in this single variable rather than in a large number of dependent variables. However, the definition of a performance criterion is not straightforward, since it depends on the purpose for which the simulation is performed and on subjective judgments.

If Y is the performance criterion selected, then the measure of deviance, as defined by Miller [3], is of the form

$$D = f(Y - Y^\circ)$$

where Y° is the normal value of Y . Note that Y itself may depend on one or all of the system parameters. The measure of deviance D can be subjected to sensitivity analysis in the same way as other system variables. The sensitivity coefficients are obtained by forming the partial derivatives $S_i = \partial D / \partial q_i$, where q_i ($i = 1, \dots, m$) are the m parameters of the system. Approximate values of S_i can be found by the method of parameter variation previously described following Eq. (E6). Thus,

$$\begin{aligned} \Delta S_i &= \frac{D(q_i + \Delta q_i) - D(q_i)}{\Delta q_i} \\ &= \frac{D(q_i + \Delta q_i)}{\Delta q_i} \end{aligned} \quad (E11)$$

Note that the value of $D(q_i)$ is zero by definition. The number of sensitivity coefficients of a large-scale system of n dependent variables and m parameters is reduced from $m \times n$ to m when a single performance criterion is used as a measure of overall system behavior since S_i is computed only for the variable D .

Although the choice of an overall performance criterion of a model is somewhat arbitrary, experience has provided certain guidelines in its formulation. These are discussed in the following paragraphs.

1. An overall performance criterion is a function of one or more of the systems dependent variables. This function is usually (but not necessarily) one of the following forms or a combination of them.

$$D = \sum_{j=1}^n |e_j| \quad (E12a)$$

$$D = \sum_{j=1}^n e_j^2 \quad (E12b)$$

$$D = \sum_{j=1}^n \left| \frac{e_j}{Y_j^\circ} \right| \quad (E12c)$$

$$D = \sum_{j=1}^n \left(\frac{e_j}{Y_j^\circ} \right)^2 \quad (E12d)$$

where Y_j° is the value of the performance criterion in the unperturbed case at some time t_j , Y_j is the corresponding value of the performance criterion in the simulation of interest, and $e_j = Y_j - Y_j^\circ$. The functions of Eqs. (E12a) through (E12d) are similar to the error criteria, or goodness of fit criteria, used in parameter estimation. In parameter estimation analysis, the parameter values of a simulation model are adjusted until model response agrees with the experimental data according to a specified criterion function. In these cases, the term $Y - Y^\circ$ is the difference between the model response and the experimental response. Because of these similarities, the techniques of sensitivity analysis can be used advantageously in parameter estimation [7].

2. The choice of variables used in forming the performance criterion should be related to the most important variables of the system or to a combination of variables that are representative of some index of overall behavior. This choice could, of course, change as the objectives of the simulation study change. For example, the Guyton model of circulatory regulation has been extremely valuable in elucidating the mechanisms that control long-term fluid volumes and blood pressure changes. Although the Guyton model contains more than 300 dependent variables, it is conceivable that a meaningful performance criterion can be formulated from only two variables, arterial blood pressure and extracellular fluid volume, since all the other variables are known to exert some influence on these two. It would be possible and is sometimes desirable to construct a performance criterion that gives more weight to one variable than another and also gives different weights to the transient and steady-state responses. Miller [3] has shown that a number of reasonable, but different, choices for the performance criterion all produce very similar results in a particular example. He states, "generally a balanced measure of all the output variables is more successful, and it is unwise to use one single output variable as a 'general indication of model behavior.'"
3. The value of D should be zero when there is no perturbation of parameters and should be positive otherwise.
4. The performance criterion chosen should correlate well with other possible performance measures and with intuitive estimates of model change.
5. The variables chosen to formulate D should be capable of easy and accurate measurement in the labora-

tory, even though these experimental measurements are not used in sensitivity analysis. The first reason for this requirement is that the results can be more easily interpreted and their validity judged if the behavior of these variables in the real system is known for certain situations. The second reason is that sensitivity analysis can be a very powerful tool for selecting those parameters for parameter estimation and this latter technique does depend very heavily on experimental measurements. The measure of deviance can be used in the same form in sensitivity analysis as the error criterion in parameter estimation analysis.

Although the discussion of performance criteria has been with regard to a mathematical model's behavior, these functions are useful from a clinical medicine viewpoint as well. For example, maximum oxygen uptake has long been used as a measure of a cardiopulmonary function under stress. It would be possible to use simulation models of various subsystems to examine other variables or combinations of variables as overall indices of subsystem behavior. The methods described in this appendix would provide preliminary criteria. The most promising of these could then be subjected to clinical trials.

In the next section, the usefulness of the performance criterion in sensitivity analysis will be developed by applying these techniques to a complex human thermoregulatory model.

E.3 An Example of Sensitivity Analysis

In this section, some of the techniques of sensitivity analysis will be applied to a complex model of the thermoregulatory system that has been described in Chapter 3 of this document. For simplicity, the steady-state version of the model will be used exclusively. This means that static sensitivity coefficients will be determined and parametric sensitivity during transient states will not be considered. The following presentation is not meant to be a complete sensitivity analysis but, rather, is suggestive of the type of analysis that might be performed.

E.3.1 Computing Sensitivity Coefficients

A traditional analysis of parametric variation is illustrated in Fig. E-1, in which the effects of metabolic rate RM (exercise) on certain important variables have been plotted. Table E-1 contains definitions of the symbols used in this model. Similar figures using other parameters for the abscissa such as TCAB, TW, PCAB, and VCAB could be prepared.

The sensitivity coefficients $S_i = \partial y / \partial RM$ (where y represents any variable) could be generated by computing the slope of the curves shown. Since the slopes are somewhat steeper at the lowest values of RM, the sensitivity coefficients are different at either end of the abscissa. For this reason, sensitivity coefficients are usually related to a perturbation from a specific operating point. Two operating points will be considered in this example, characterized by the input parameters shown in Table E-2. The first

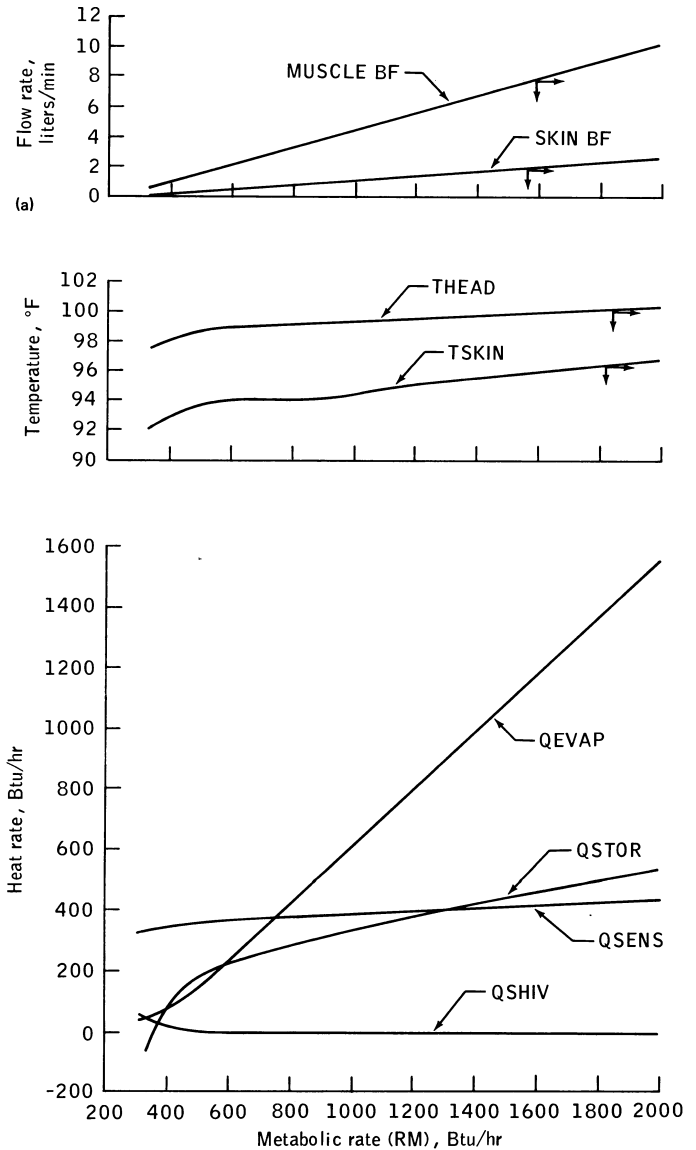


Figure E-1. Effect of changing metabolic rate on selected thermoregulatory variables. (a) MUSCLE BF and SKIN BF; (b) THEAD and TSKIN; and (c) QEVAP, QSTOR, QSENS, and QSHIV.

case represents a moderately relaxed, supine subject and the other an exercising, standing subject, both in comfortable environments.

The sensitivity coefficients have been computed for a selected variety of parameters and variables for each of the two operating points. As shown in Table E-3, each value has been computed by varying a single parameter, listed on the left, by +10% away from the operating point and determining the change in the particular variable shown across the top of the table using computer simulation of the model. The logarithmic sensitivity coefficients were determined from Eq. (E7).

There is a large variation of values among the coefficients shown in Table E-3; the higher the value, the greater

Table E-1. Thermoregulatory Model Glossary Terms

Symbol	Definition
Mathematical notation	
C	Heat capacity
D	Measure of deviance
D_{COMPUTE}	Computed deviance
D_{PREDICT}	Predicted deviance
e	Measure of error: difference between unperturbed and perturbed model output or between model output and corresponding experimental results
f	Function
i, j	Subscripts denoting iteration
m	Number of parameters
N	Number of variables
q	System parameter
S	Differential sensitivity coefficient
$\bar{S}$	Logarithmic sensitivity coefficient
T	Temperature
t	Time
U	Fractional perturbation of a parameter
Y	Performance criterion
y	Dependent variable
Δ	Change
ΔS	Incremental sensitivity coefficient
$^{\circ}$	Superscript denoting the unperturbed state of the model
Program notation	
CLOV	Clothing resistance
PCAB	Barometric pressure
MUSCLE BF	Muscle blood flow
QBASAL	Basal metabolic rate
QEVAP	Heat loss due to sweat evaporation
QSENS	Sensible heat loss
QSHIV	Heat generated due to shivering
QSTOR	Heat stored in body relative to a reference state
RM	Metabolic rate due to exercise
SKIN BF	Skin blood flow
TCAB	Ambient temperature
TDEWC	Ambient dewpoint temperature
THEAD	Head core temperature
TSET	Set-point temperature
TSKIN	Mean skin temperature
TW	Ambient wall temperature
UEFF	Efficiency of exercise
VCAB	Free-air velocity

the effect of a given parameter on the designated variable. The skin and head temperatures are relatively insensitive to any environmental parameter, which is expected, since negative feedback temperature regulation is an important feature of the model. Similarly, exercising muscle blood flow (case 2) is insensitive to all the parameters studied except for metabolic rate, whereas, perhaps surprisingly, the model predicts a generally higher sensitivity of the rest-

Table E-2. Input Parameters for Two Operating Points

Input parameter	Value	
	Case 1*	Case 2**
RM, W (BTU/hr)	330	1165
QBASAL, W (BTU/hr)	283	283
UEFF, percent	0	13.5
TCAB, (°F)	68	75
TW, (°F)	68	75
TDEWC, (°F)	50	55
PCAB, (lb/in ²)	14.7	14.7
CLOV, (clo)	0.35	0.5

* Moderately relaxed

** Medium exercise

ing muscle flow (case 1) to all the input parameters. Other differences in sensitivity between the two cases shown can be easily noted from this table (especially the effects on QSHIV, QEVAP, and QSTOR). This analysis enables one to easily determine the sections of the model that are most and least sensitive to a particular parameter. For example, both free-air velocity (VCAB) and clothing resistance (CLOV) are seen to have their greatest influence on shivering in the relaxed state and on sensible heat loss in the exercising state. Also, it appears that many of the variables studied are more sensitive to wall temperature than to air temperature. In general, it appears that RM, TCAB, and TW exert a more profound influence on the model than do TDEWC, VCAB, and CLOV. A determination of whether these sensitivities are physiologically appropriate is beyond the scope of this study. However, the ranking of parameter importance as shown here provides a rapid method, for someone familiar with the thermoregulatory system, to evaluate certain characteristics of the model.

E.3.2 Use of the Performance Criterion

As mentioned previously in this appendix, it is desirable to formulate a single performance criterion which represents overall model behavior. In the case of the thermoregulatory model, the variable QSTOR, representing the amount of heat stored in the body relative to the reference state, appears to satisfy the requirements previously mentioned for a performance criterion. In the 41-node model, QSTOR is defined as

$$QSTOR = \sum_{i=1}^{41} C_i (T_i - TSET_i) \quad (E13)$$

where T_i is the temperature of the i th body node, $TSET_i$ is the reference set-point (corresponding to the temperature in a neutral thermal environment), and C_i is the heat capacity (BTU per degree Fahrenheit) of the i th node. When the subject is in a neutral environment, $T_i = TSET_i$ and $QSTOR = 0$. Inasmuch as the individual body segment temperatures are the net result of all the thermal forces

Table E-3. Sensitivity Coefficients From 10% Change in Parameter Values

Parameter	Sensitivity coefficient for—							
	QSTOR	QEVAP	QSENS	QSHIV	SKIN BF	MUSCLE BF	THEAD	TSKIN
Case 1*								
RM	5.18	0.56	0.08	−6.77	0.10	0.37	0.00	0.02
TCAB	2.57	0.26	−1.16	−9.03	0.26	−3.15	0.00	0.05
TW	2.94	0.25	−1.23	−9.64	0.10	−3.36	0.00	0.05
TDEWC	−0.03	−0.81	−0.00	−0.70	0.09	−0.29	0.00	0.00
VCAB	0.49	0.04	0.15	0.66	0.06	0.18	0.00	−0.01
CLOV	0.69	−0.07	−0.18	−1.56	0.10	−0.59	0.00	0.01
Case 2**								
RM	0.62	1.51	0.11	0.00	1.35	1.28	0.01	0.01
TCAB	0.42	1.04	−1.62	0.00	1.04	0.01	0.01	0.04
TW	0.53	1.13	−1.77	0.00	1.11	0.01	0.01	0.04
TDEWC	−0.06	0.00	−0.01	0.00	0.18	0.01	0.01	0.00
VCAB	−0.03	−0.09	0.14	0.00	−0.03	0.01	0.00	0.00
CLOV	0.11	0.14	−0.21	0.00	0.21	0.01	0.02	0.01

* Rest

** Exercise

acting on the body, QSTOR is a good indicator of overall model performance. (A similar and related criterion might be mean body temperature.) The variable QSTOR has already been used successfully to define the limits of thermal comfort for manned spaceflight. The outside tolerance limits have been set at $QSTOR = \pm 300$ BTU. (These limits would be exceeded by slightly more than a 1°F) change in mean body temperature, an indication that QSTOR is very sensitive to changes in heat balance.)

The sensitivity coefficients for QSTOR relative to several input parameters have already been presented in Table E-3. As can be noted, QSTOR is many times more sensitive to the parameters studied near the resting operating point than in the exercising state. As a consequence, it can be argued that the absolute values of the input parameters should be known to a higher degree of accuracy during the resting state as opposed to the exercising state to enable achievement of the same degree of model accuracy.

The degree of linearity of QSTOR about the exercise operating point has been tested, and the results are summarized in Table E-4. The values in this table have been obtained in exactly the same manner as those already described in Table E-3, except that QSTOR is the only variable studied and each parameter has been varied over a $\pm 60\%$ range from the operating point. The results suggest that the sensitivities are extremely constant over a wide range.

The parameters studied thus far have been input (environmental) parameters to the model; the values of input parameters are usually known to a fairly high degree of accuracy. However, the model contains many other param-

eters, called system parameters, that are properties of the controlled or controlling systems and do not vary from run to run, as do the input parameters. These parameters represent various controller gains in the hypothalamic thermoregulatory centers of the model that control sweating, shivering, vasodilation, and vasoconstriction. The values of system parameters are not known with great certainty. Examples of these parameters are skin/air-interface heat-transfer coefficients, tissue thermal conductivities, basal blood flow rates, and thermoregulatory control mechanisms.

The sensitivity coefficients of the seven thermoregulatory control parameters have been investigated with respect to overall model performance as measured by QSTOR to illustrate several points. (See Table E-5.)

E.3.3 Prediction of QSTOR From a Sensitivity Model

It can be shown that the value of a particular variable in a complex model can be predicted from simple algebraic equations that are functions of the sensitivity coefficients without the need to perform simulations of the entire model on high-speed computers. Here, the attempt is to predict values of QSTOR for a wide range of simultaneous parameter variations.

Let D be a measure of deviance from some operating point,

$$D = \frac{QSTOR - QSTOR^\circ}{QSTOR^\circ} \quad (E14)$$

Table E-4. Values of the Overall Performance Sensitivity Coefficient* for Single-Parameter Changes About the Nominal Operating Point for Exercise**

QSTOR° = 97.2 W (332 BTU/hr)						
Parameter	Sensitivity coefficient for percent change, of —					
	0.5	1	10	20	40	60
Increase						
RM	0.626	0.627	0.619	0.738	0.696	0.668]***
TCAB	0.345	0.346	0.416	0.420]	0.276	0.169
TW	0.530	0.532	0.527	0.464]	0.291	0.242
TDEWC	−0.055	−0.054	−0.058	0.063]	0.059	0.019
VCAB	−0.028	−0.028	−0.026	−0.025	−0.024	−0.023]
CLOV	0.109	0.109	0.106	0.102	0.095	0.093]
UEFF	−0.065	−0.065	−0.064	−0.064	−0.064	−0.064]
Decrease						
RM	0.630	0.630	0.640	0.663	0.721	1.61]
TCAB	0.348	0.348	0.368	0.388]	0.450	0.653
TW	0.534	0.535	0.559	0.579]	0.632	0.744
TDEWC	−0.051	−0.051	−0.047	−0.043	−0.036]	−0.030
VCAB	−0.026	−0.027	−0.028	−0.029	−0.032	−0.028]
CLOV	0.113	0.111	0.115	0.120	0.131	0.045]
UEFF	−0.061	−0.063	−0.063	−0.063	−0.063	−0.063]

* Equation (E15)

** See Table E-2 for absolute values of parameters at operating point.

***See text for explanation of brackets

Table E-5. Sensitivity Coefficients for Thermoregulatory Control Parameters with Respect to Overall Performance

Each Parameter Varied Separately by 10%

System Parameter	Normal value	Sensitivity coefficient	
		Rest	Exercise
CSW, W/ (BTU/hr−°F)	705	0.040	0.407
SSW, W/ (BTU/hr−°F)	63.9	0.091	0.068
CDIL, * (lbm/hr−°F)	143	0.115	0.174
SDIL, * (lbm/hr−°F)	9.2	0.025	0.019
CCON, (°F ^{−1})	2.78	0.001	0.000
SCON, (°F ^{−1})	2.78	0.000	0.000
PCHIL, (BTU/hr−°F)	25.7	2.1	0.000

* Mass of blood

Table E-6. Values of Parameters and Sensitivity Coefficients Used for Predicting Changes in QSTOR

Parameter	Value			$\bar{S}_i$
	Nominal	Min.	Max.	
RM, W (BTU/hr)	1165	330	2000	0.627
UEFF, percent	13.5	5	22	-0.0647
TCAB, (°F)	75	55	75	0.346
TW, (°F)	75	55	75	0.532
TDEWC, (°F)	55	45	65	-0.0536
VCAB, (ft/min)	30	10	50	-0.028
CLOV, (clo)	0.5	0.1	0.9	0.109

The relative sensitivity coefficients S_i in Table E-4 have been determined by varying one parameter at a time

$$\bar{S}_i = \frac{\partial D}{\left(\frac{\partial q_i}{q_i} \right)} \approx \frac{[(QSTOR - QSTOR^\circ)]}{QSTOR^\circ} \left[\frac{(q_i - q_i^\circ)}{q_i^\circ} \right] \quad (E15)$$

where q_i is the value of any parameter, q_i° refers to the corresponding value at the operating point, and the symbol $\approx$ means “is approximately equal.” Rewriting Eq. (E9) for n parameters and substituting QSTOR for y results in a formula for predicting D

$$D_{\text{PREDICT}} = \sum_{i=1}^n \bar{S}_i U_i \quad (E16)$$

where U_i is defined by Eq. (E8). In this example, the concern is with varying only those parameters listed in Table E-4 and having those values for $\bar{S}_i$ listed in the $\pm 1\%$ columns. Furthermore, the parameter values about the operating point for case 2 (Table E-2) will be restricted to a range that has been shown to have reasonably constant sensitivity coefficients (see brackets in Table E-4). These ranges are shown in absolute values in Table E-6.

A series of 24 runs was simulated with the thermoregulatory model. Each run consisted of changing all seven parameters simultaneously. The actual parameter values for a given run were obtained by choosing values randomly within the limits given previously and assuming that all values have the same probability of being chosen. For each run, a value of D was computed (D_{COMPUTE}) from Eq. (E14) using the simulated values of QSTOR and compared to the value of D_{PREDICT} determined from Eq. (E16). The values of $\bar{S}_i$ used in Eq. (E16) are shown in Table E-6, whereas values for U_i were determined from the random perturbations for each parameter. It should be emphasized that the sensitivity coefficients in Eq. (E16) were obtained from simu-

lations performed by varying one parameter at a time by 1% to predict values for D , whereas computed values for D result from simulations in which all parameters are varied over a much wider range simultaneously.

The results of this study are shown in Fig. E-2. The dashed line represents perfect agreement between D_{PREDICT} and D_{COMPUTE} . The origin represents the operating point. Although the agreement becomes very poor for negative deviations from the operating point, it is encouraging to see a reasonable correlation of all runs that can be described by two straight lines intersecting the origin despite the very wide range of random parameter variations. Thus, D_{PREDICT} allows a good estimate of D (and therefore QSTOR) between the range of $-0.2 < D_{\text{PREDICT}} < +0.7$. For example, assume that it is desired to estimate the value of QSTOR for the following conditions: RM = 1300 BTU/hr; TCAB = TW = 80° F; and all other input parameters are identical to those given in Table E-2, case 2. Then, Eq. (E16) can be represented by only three terms which describe the perturbations of RM, TCAB, and TW from the operating point, so that

$$\begin{aligned} D_{\text{PREDICT}} &= 0.627 \frac{1300 - 1165}{1165} + 0.346 \frac{80 - 75}{75} \\ &\quad + 0.532 \frac{80 - 75}{75} \\ &= 0.131 \end{aligned} \quad (E17)$$

This value can be used to estimate, from Fig. E-2, $D_{\text{COMPUTE}} = 0.125$, which corresponds to QSTOR = 374 BTU. The value actually obtained during simulation of this particular condition is QSTOR = 379 BTU. Values of D outside the range mentioned previously can also be predicted once the correlation between D_{PREDICT} and D_{COMPUTE} has been established although the errors will be larger (Fig. E-2). The deviation from the theoretical line in Fig. E-2 probably results from two errors: first, the assumption that sensitivity is constant (especially for RM) over a range for which it is not really constant (Table E-4) and, second, the fact that higher order sensitivity coefficients were neglected.

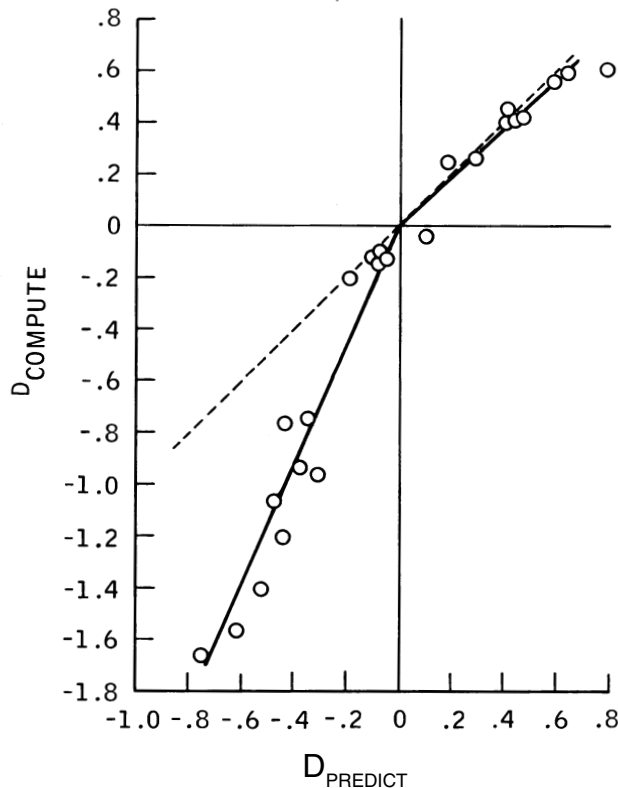


Figure E-2. Overall measure of deviance of thermoregulatory model due to variation of all input parameters simultaneously: comparison of computed and predicted results.

It would be possible to prepare a family of curves similar to those shown in Fig. E-2 for a series of important operating points. Once this has been done, QSTOR could be reasonably well predicted over a wide range in the manner just illustrated. Other variables besides QSTOR could be handled in the same way. Then, the relative values of each term in Eq. (E16) would also provide a quantitative measure of the importance of each parameter.

The usefulness of predicting model behavior with simple algebraic equations rather than by direct simulation of the original analog system (which involves solutions of differential equations or computer based numerical analysis) is, of course, obvious. Fundamentally, this procedure is not new, since it is based on linearization of a system using a Taylor series expansion. However, the coefficients of the Taylor series in this case are the sensitivity functions, which have intrinsic meaning by themselves. In addition, the results are expressed in terms of linear algebraic equations rather than linear differential equations. The technique illustrated in this example appears to be applicable to most nonlinear, multivariable, multi-parameter models. However, the following disadvantages have also become apparent: (1) all the sensitivity coefficients must be computed in the desired time period, (2) the degree of accuracy of the method around the operating point

should be established by some independent check, (3) in highly nonlinear systems, higher order sensitivity functions may have to be computed, or, alternatively, (4) a series of first-order sensitivity functions may have to be computed at closely spaced operating points. In addition, the equations for this procedure no longer describe a deterministic system, even though the coefficients were generated from one. There is a danger that persons not familiar with the use of this method may extend it beyond its limitations. Notwithstanding these restrictions, the method appears to be powerful enough to be suitable for certain types of application even with complex models, especially where high-speed, large-core computers are not available.

Another important application of sensitivity analysis is to investigate the interdependence of parameters. In Fig. E-3, the metabolic rate and ambient temperature have been varied simultaneously over a wide range and QSTOR contour lines were drawn. The convergence of contour lines toward the lower left shows that QSTOR becomes more sensitive to simultaneous changes of TCAB and RM as these parameters decrease in value. Also, there appears to be a region of very high sensitivity near 550 BTU/hr and 80°F, a commonly encountered environment. Further sensitivity analysis using these and other parameters would be suitable for obtaining human tolerance limits and may reveal minimum or maximum points of sensitivity. An analysis of second-order sensitivity coefficients of the type $\partial^2 y / \partial (q_1 \cdot q_2)$ would also help to reveal mutual interaction effects between parameters.

These results have been illustrated for the steady-state case. For models that are capable of predicting time-dependent behavior, the quantitative relationships of sensitivity coefficients are more complex than for the simpler steady-state relationships. For example, in the computation of sensitivity coefficients for studying transient behavior, it is important to define the time limits of interest, since sensitivity coefficients may be time-dependent.

E.4 Conclusions

Sensitivity analysis can be extremely useful early in the model development process. Identification of the relative importance of parameters can be made even in models that are somewhat inaccurate [4]. A person familiar with the subject matter of the model (but not necessarily familiar with simulation techniques) can make a judgment concerning the validity of the model, based on the reasonableness of the sensitivity relations. The possibility of identifying the most important parameters of a system and determining the accuracy needed in their measurement (using error analysis techniques) means that one could predict the effort required to produce a valid model before massive resources were committed. It can also suggest the relative priority in data collection because certain measurements will be more critical than others for understanding system behavior. One of the most important advantages of sensitivity analysis during these early stages of development is that it does not require extensive data collection to determine qualitative model validation.

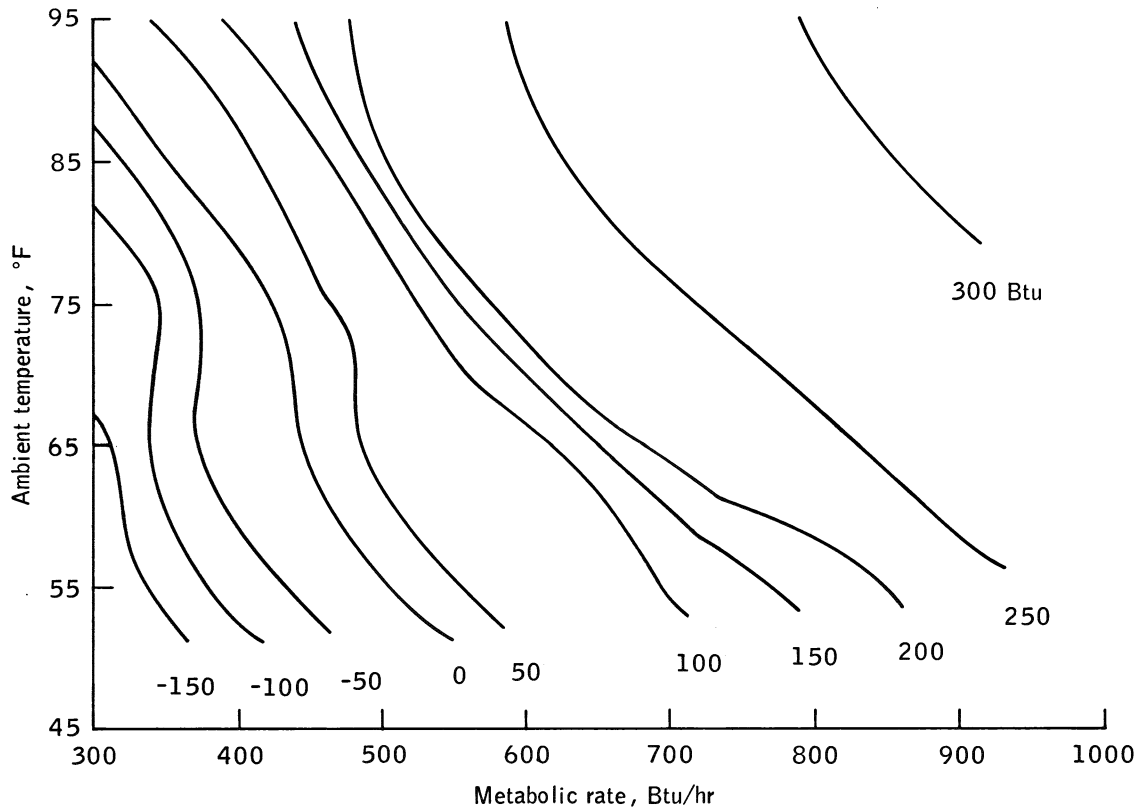


Figure E-3. QSTOR contour lines for simultaneous changes in ambient temperature and metabolic rate.

Once the model has been validated and its credibility ascertained, the techniques of sensitivity analysis can be used to perform advanced simulation studies such as noise analysis, parameter estimation, stability analysis, and inverse sensitivity, all of which are derived from sensitivity considerations. The examples discussed in this appendix demonstrate the capability of using sensitivity coefficients to form simple linear models of complex systems. The use of these algebraic models for making rapid, first-order calculations of system behavior should be explored further. In addition, certain aspects of the system may have to be modified more carefully by introducing new elements or by using improved parameter values. A sensitivity analysis performed on a validated model could provide the motivation, direction, and support for this effort. Finally, when a model is used for making inferences regarding untested situations, sensitivity analysis is useful for predicting uncertainty in model behavior, based on measurement errors in input data.

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Appendix F

Integrated Metabolic Balances: Details

This Appendix provides a more detailed discussion of the methods of computation and assumptions used to derive the results, tables, and figures in Chapter 4, the Integrated Metabolic Balance Analysis. Also included are descriptions of error analyses and supplementary data as they pertain to the specific studies. The Appendix is divided into subsections that generally correspond to the sections of Chapter 4.

F.1 Skylab Water Balance Analysis

The discussion of the Skylab Water Balance Analysis in Chapter 4.2 only presents and interprets the results of that analysis. This part of Appendix F contains details of the approach used in the analysis. Further details are also available [1,2].

F.1.1 Assumptions and Methods of Calculation

The daily change in total body water (i.e., daily water balance), ΔTBW , is given by the algebraic sum of all liquid quantities entering or excreted from the body according to the following relationship [3]:

$$\begin{aligned} \Delta TBW &= \text{water intake (food + drink) + metabolic H}_2\text{O} \\ &\quad - \text{water excreted (urine + feces)} \\ &\quad - \text{evaporative water loss (skin + respiratory)} \end{aligned} \quad (1)$$

Water intake and water excreted were measured on a daily basis during the Skylab missions and it was possible to estimate metabolic water from the known units of fat, protein, and carbohydrate consumed. However, it was not possible to compute a daily water balance using only this information since daily evaporative water loss, a significantly large quantity, was not measured. An alternative water balance equation can be derived which is independent of both evaporative water loss and any liquid quantity consumed or excreted by developing a complete gravimetric (mass) balance. The daily change in body mass, $\Delta BWGT$, can be found by summing up the total masses (liquids and solids) of all input (+) and (-) output quantities,

$$\begin{aligned} \Delta BWGT &= \text{dry weight of food + water intake (food + drink)} \\ &\quad - \text{dry weight of excreta (urine + feces)} \\ &\quad - \text{water excreted (urine + feces)} \\ &\quad - \text{evaporative water loss (skin + respiratory)} \\ &\quad - \text{weight of metabolic CO}_2 + \text{weight of} \\ &\quad \quad \text{metabolic O}_2 - \text{dry skin loss} \end{aligned} \quad (2)$$

Thus, combining Eq. (1) and (2),

$$\begin{aligned} \Delta TBW &= \Delta BWGT - \text{dry weight of food} \\ &\quad + \text{dry weight of excreta (urine + feces)} \\ &\quad + \text{metabolic H}_2\text{O} + \text{metabolic CO}_2 \\ &\quad - \text{metabolic O}_2 + \text{dry skin loss} \end{aligned} \quad (3)$$

The “dry skin loss” in these equations refer to sweat solids, sebaceous residues, desquamated epithelium, as well as nail and hair clippings. The metabolic H_2O , CO_2 , and O_2 refers to those insensible quantities produced or consumed by metabolism of food stuffs as well as the catabolism of body tissue (primarily body fat and protein).

All of the quantities on the right side of Eq. (3) were measured directly except for the metabolic H_2O , CO_2 , and O_2 and the dry skin loss. The metabolic quantities can be estimated from the foodstuffs, while the dry skin loss can be estimated from the infrequent total body water measurements. The procedure used to compute these indirectly measured quantities is given below.

The term net insensible metabolic losses (IML) is defined as

$$\begin{aligned} \text{IML} &= \text{metabolic H}_2\text{O} + \text{metabolic CO}_2 - \text{metabolic O}_2 \\ &= \text{IML (foodstuff)} + \text{IML (body tissue)} \end{aligned} \quad (4)$$

The insensible metabolic losses associated with foodstuffs were determined indirectly from the daily amounts of carbohydrate (CHO), fat (FAT), and protein (PRO) in the ingested diet according to accepted stoichiometric relationships [3,4,5] for reduction of food to carbon dioxide, water, and urinary nitrogen:

$$\text{H}_2\text{O}(\text{met}) = \text{EFF}(0.555 \text{ CHO} + 1.071 \text{ FAT} + 0.413 \text{ PRO}) \quad (5)$$

$$\text{CO}_2(\text{met}) = \text{EFF}(0.829 \text{ CHO} + 1.427 \text{ FAT} + 0.775 \text{ PRO})p(\text{CO}_2) \quad (6)$$

$$\text{O}_2(\text{met}) = \text{EFF}(0.829 \text{ CHO} + 2.019 \text{ FAT} + 0.967 \text{ PRO})p(\text{O}_2) \quad (7)$$

The densities carbon dioxide and oxygen, $\rho(\text{CO}_2)$ and $\rho(\text{O}_2)$, were taken as 1.977 and 1.429 g/l, respectively. EFF is an efficiency factor to allow for incomplete digestion across the gastrointestinal tract. A value of EFF was obtained for *each* Skylab crewman based on a solids (mass) balance of food and feces according to the relationship:

$$\text{EFF} = \frac{\text{Total mission dry food} - \text{total mission dry feces}}{\text{Total mission dry food}} \quad (8)$$

An average value of EFF ($\pm$ SD) of $0.962 \pm .005$ was obtained; the individual crew values used in this study are given in Table F-1.

Table F-1. Digestive Efficiency Factor of Skylab Crews, EFF*

Mission	Man	Pre-flight	In flight	Post flight	Weighted Avg.**
28-day	1	0.967	0.966	0.968	0.967
	2	0.954	0.966	0.947	0.957
	3	0.961	0.965	0.972	0.965
59-day	1	0.967	0.965	0.982	0.968
	2	0.958	0.960	0.953	0.958
	3	0.959	0.959	0.967	0.960
84-day	1	0.950	0.955	0.948	0.953
	2	0.960	0.969	0.973	0.968
	3	0.963	0.961	0.959	0.961
Mean		0.960	0.963	0.963	0.962
SD		±.006	±.004	±.012	±.005

* EFF = $1 - \frac{\text{Fecal Solids}}{\text{Food Solids}}$

** The average values shown were weighted by the number of observations in each phase of the flight for each mission.

Substituting Eqs. (5) to (7) into Eq. (4) leads to the following relationship

$$\text{IML}(\text{foodstuff}) = \text{EFF} (1.009 \text{ CHO} + 1.007 \text{ FAT} + 0.563 \text{ PRO}). \quad (9)$$

Body protein ($\Delta\text{Protein Loss}$) and body fat ($\Delta\text{Fat Loss}$) catabolism occurred during the course of the Skylab mission. It would be expected that these quantities would contribute to the net insensible metabolic losses in a similar manner as equivalent amounts of foodstuffs; i.e.,

$$\text{IML}(\text{body tissue}) = 1.007 (\Delta\text{Fat Loss}) + 0.563 (\Delta\text{Protein Loss}) \quad (10)$$

It was not possible to estimate the metabolic losses associated with body tissue metabolism on a daily basis. However, this term was included numerically in the estimate for dry skin loss, which was averaged over the entire mission.

One of the purposes of this study was to obtain not only estimates of daily water balance, but also to sum these daily balances to compute the total body water changes over large time intervals (up to several months). Errors in the estimates of daily water balance would, therefore, be cumulative over time. It has been estimated previously that dry skin loss amount to at least 12-20 gm/day [6,7]. Exclusion of the difficult to measure insensible metabolic losses that are a result of body tissue catabolism potentially adds another 20 - 40 gm/day error in the water balance [8]. Summing these up, it can be seen from Eq. (3) that failure to take skin and body tissue losses into account could underestimate daily water balance by at least 30 - 60 gm/day and produce errors at the end of a one-month

period of 1 - 2 liters in total body water calculations. Thus, it was important to accurately estimate these quantities. This was achieved by rewriting Eq. (3) using Eq. (4).

$$\begin{aligned} \Delta\text{TBW} &= \Delta\text{BWGT} \\ &\quad - \text{dry weight of food} \\ &\quad + \text{dry weight of excreta} \\ &\quad + \text{IML}(\text{foodstuff}) + \text{IML}(\text{body tissue}) \\ &\quad + \text{dry skin loss} \end{aligned} \quad (11)$$

Define $\Delta\text{TBW}(\text{balance})$ as the right side of Eq. (11) excluding the last two terms, i.e.,

$$\Delta\text{TBW} = \Delta\text{TBW}(\text{balance}) + \text{IML}(\text{body tissue}) + \text{dry skin loss} \quad (12)$$

In other words $\Delta\text{TBW}(\text{balance})$ is the water balance typically obtained from directly measured quantities excluding corrections for skin and body tissue losses. The left side of Eq. (12) represents the true change in total body water as measured, in the case of the Skylab crew, by tritium dilution techniques before and after a period of several weeks or months. Let this direct measurement of total body water change be designated by TBW (direct), and let the non-measured quantities be termed a correction factor, CF. Then

$$\text{CF} = \text{IML}(\text{body tissue}) + \text{dry skin loss} \quad (13)$$

Use of Eq. (12) yields

$$\text{CF} = \overline{\Delta\text{TBW}(\text{direct})} - \overline{\Delta\text{TBW}(\text{balance})} \quad (14)$$

where

$$\begin{aligned} \overline{\Delta\text{TBW}(\text{balance})} &= \overline{\Delta\text{BWGT}} - \overline{\text{dry weight of food}} \\ &\quad + \overline{\text{dry weight of excreta}} + \overline{\text{IML}(\text{foodstuff})}. \end{aligned} \quad (15)$$

The bar above the terms in Eqs. (14) and (15) represent average daily quantities during the particular period between TBW measurements. During the Skylab experiments, total body water measurements were obtained at the beginning and end of each flight phase: preflight, inflight, and postflight. (In the case of the 59-day mission, the measurement at the start of inflight was not obtained). The value $\Delta\text{TBW}(\text{direct})$ was taken as the difference between any two consecutive tritium dilution measurements, and the value $\Delta\text{TBW}(\text{balance})$ was computed from the uncorrected balance, Eq. (15), using the total quantities consumed, excreted, or changed during this same time interval.

Thus, in the majority of cases, it was possible to compute a separate correction factor for each flight phase for each crewman. (Values for the terms in Eqs. (14) and (15) can be found in Tables 4-6 and F-4). These values, expressed in gm/day, are shown in Table F-2. It can be observed that the average CF value for preflight and inflight phases were similar, indicating that the sum of skin and tissue losses were similar during these phases. The low

Table F-2. Water Balance Correction Factor, CF [gm/day]

Mission	Man	Preflight	Inflight	Postflight
28-day	1	41.7	56.3	69.6
	2	100.0	126.5	32.1
	3	89.2	65.9	-11.2
59-day	1	66.6	66.6	-116.1
	2	97.7	97.7	-49.0
	3	63.6	63.6	14.7
84-day	1	24.9	26.0	74.1
	2	54.4	42.9	-7.8
	3	95.6	12.9	-27.9
Mean		70.2	61.8	3.6

Table F-3. Urinary Specific Gravity (s.g.)*

Mission	Man	Preflight	Inflight	Postflight
28-day	1	1.019	1.020	1.017
	2	1.028	1.027	1.020
	3	1.009	1.013	1.009
59-day	1	1.016	1.021	1.016
	2	1.021	1.021	1.019
	3	1.023	1.025	1.022
84-day	1	1.016	1.021	1.014
	2	1.020	1.021	1.017
	3	1.028	1.031	1.015
Mean		1.020	1.022	1.017
SD		±0.006	±0.005	±0.004

* Value shown are the averages of daily urine samples obtained during the designated period.

(and even negative) values for the postflight phase was possibly a result of a normal dry skin loss that was masked by a greater body tissue *gain* during the recovery period.

The final form of the water balance equation used in this study can be written by combining Eqs. (9), (11), and (13):

$$\begin{aligned} \Delta TBW = & \\ \Delta BWGT - \text{dry weight of food} + \text{dry weight of feces} & \\ + \text{urine volume} \times (\text{s.g.} - 1.0) + \text{EFF}(1.009 \text{ CHO} & \\ + 1.007 \text{ FAT} + 0.563 \text{ PRO}) + \text{CF} & \end{aligned} \quad (16)$$

where “s.g.” is the specific gravity of urine obtained for each sample and is given in Table F-3, and “urine volume $\times$ (s.g. - 1.0)” represents the dry urine weight. (See also Fig. 4-5 and 4-6 for a pictorial representation of Eqs. (16) and (18).

With the exception of s.g. and CF, each term in Eq. (16) was measured daily and continuously over the entire preflight, inflight, and postflight periods. The average values of these terms for each crewman are shown in Table F-4.

The change in total body water during a period of N consecutive days, $\Delta TBW(N)$ can be determined by algebraically summing (i.e., integrating) the daily water balance of each successive day, ΔTBW_i , over the interval. Thus,

$$\Delta TBW(N) = \sum_{i=1}^N \Delta TBW_i \quad (17)$$

In the water balance study $\Delta TBW(N)$ was computed for each day of the mission starting from either the day of launch or the day of recovery and summing backward and forward in time from these reference points. Thus, $\Delta TBW(N)$ had a value identically zero at the morning of launch or the morning of recovery. Mean values of $\Delta TBW(N)$ were used in this report by averaging the values for the three crewmembers on each flight ($n = 3$) or by pooling two ($n = 6$) or three ($n = 9$) flights. The method of obtaining variances of $\Delta TBW(N)$ is presented at the end of this Chapter. The effect that the correction factor has on estimating $\Delta TBW(N)$ is illustrated in Fig. F-1.

Evaporative water loss is a critical quantity in the whole-body water balance. Evaporative water losses (EWL) were estimated on a daily basis by rearranging the water balance Eq. (1),

$$\begin{aligned} \text{EWL} = & \\ = \text{water intake}(\text{food} + \text{drink}) & \\ + \text{metabolic H}_2\text{O} & \\ - \text{water excreted}(\text{urine} + \text{fecal}) - \Delta TBW & \end{aligned} \quad (18)$$

where ΔTBW is the quantity obtained from Eq. (16). (Another formulation for EWL is provided in Appendix F.2).

Average evaporative water loss for the entire Skylab crew is illustrated in Fig. F-2 for a 2 week period before and after launch and recovery. The changes in EWL during the mission are too small to easily discern in Fig. F-2 but can be noted in Table F-5.

Water balance graphs were prepared (see Chapter 4, Figs. 4-9 and 4-10) using the following definitions for intake and output:

$$\begin{aligned} \text{Total water intake} = & \\ = \text{water}(\text{drink}) + \text{water}(\text{food}) + \text{metabolic H}_2\text{O}, & \end{aligned} \quad (19)$$

$$\begin{aligned} \text{Total water output} = & \\ = \text{urine volume} + \text{fecal water} + & \\ + \text{evaporative water loss} & \end{aligned} \quad (20)$$

Equations (19) and (20) form the basis of a partitioned water balance that is provided in Table F-5. This table presents data for each of the 3 Skylab missions and serves as backup for Table 4-26 which is accompanied by a brief interpretation. The changes in body water cannot only be

Table F-4. Mean Values of Terms in Water Balance Equation for Skylab Crew [gm/day]**

Crewman:		1	2	3	4	5	6	7	8	9	Skylab Means**
No. of days Observed	Pre Inf.	30 28	30 28	30 28	20 59	20 59	20 59	26 84	26 84	26 84	
ΔBody Weight	Pre Inf.	-30.0 ± 68.8 -39.3 ± 68.0	-46.7 ± 65.5 -96.4 ± 91.4	-56.7 ± 60.4 -114.3 ± 77.8	+5.0 ± 83.2 -66.1 ± 45.1	-35.0 ± 118.8 -61.0 ± 45.2	+80.0 ± 122.6 -71.2 ± 69.0	30.8 ± 67.2 0.0 ± 34.4	-30.8 ± 79.8 -16.7 ± 45.9	0.0 ± 57.4 -16.7 ± 37.7	-9.16 ± 14.1 -53.5 ± 12.8
Food Solids	Pre Inf.	556 ± 8 578 ± 9	619 ± 7 610 ± 9	610 ± 13 585 ± 12	545 ± 6 596 ± 8	561 ± 8 572 ± 12	819 ± 10 822 ± 19	617 ± 9 639 ± 5	600 ± 11 621 ± 5	616 ± 6 646 ± 6	616 ± 27 630 ± 26
Insensible Metabolic Loss (food)	Pre Inf.	470 ± 7 498 ± 9	525 ± 18 522 ± 10	520 ± 13 506 ± 11	471 ± 5.4 527 ± 7.1	472 ± 8 487 ± 10	690 ± 10 701 ± 16	518 ± 8 541 ± 4	515 ± 10 536 ± 5	519 ± 6 548 ± 6	522 ± 22 541 ± 21
Urine Solids	Pre Inf.	25.5 ± 1.4 28.6 ± 1.3	23.8 ± 1.7 30.6 ± 1.7	24.6 ± 1.1 33.0 ± 1.9	22.3 ± 1.3 24.5 ± 0.8	23.3 ± 1.6 29.4 ± 0.8	34.5 ± 1.5 37.4 ± 0.8	27.8 ± 1.5 33.7 ± 0.9	27.0 ± 1.8 32.7 ± 1.3	53.0 ± 3.2 57.5 ± 1.6	29.1 ± 3.2 34.2 ± 3.2
Fecal Solids	Pre Inf.	18.4 ± 3.7 19.7 ± 4.3	28.4 ± 5.3 20.5 ± 5.6	23.7 ± 5.9 20.2 ± 3.0	18.1 ± 5.1 20.7 ± 3.4	23.8 ± 3 23.2 ± 3	33.6 ± 3.9 33.6 ± 2.8	31.2 ± 2.1 28.7 ± 2.4	24.1 ± 3.7 19.2 ± 2.7	22.8 ± 5.1 25.1 ± 3.2	24.9 ± 1.8 34.2 ± 1.6
Correction Factor	Pre Inf.	41.7 54.3	100.0 126.5	89.2 65.9	66.6 66.6	95.7 95.7	63.6 63.6	24.9 26.0	54.4 42.9	95.6 12.9	70.2 ± 6.9 61.8 ± 11.5
ΔTBW**	Pre Inf.	-30.1 ± 67.5 -14.5 ± 86.4	11.0 ± 83.9 -8.4 ± 9.4	-8.6 ± 58.4 -74.7 ± 78.0	38.3 ± 81.5 -23.1 ± 42.6	18.8 ± 116.4 2.1 ± 47.2	82.2 ± 122.6 -56.7 ± 67.8	15.1 ± 67.8 -9.2 ± 34.4	-10.0 ± 77.8 7.35 ± 45.7	74.2 ± 55.7 -19.0 ± 36.4	21.1 ± 12.6 -23.2 ± 25.6

* Values are mean ± SE, N = 9

** ΔTBW obtained from Eq. (16)

Table F-5. Partitional Water Balance for Each Skylab Mission (N = 3) [ml/day; mean ± SE]

Daily Water Balance Quantities	SL-2			SL-3			SL-4		
	Preflight	Inflight	Postflight	Preflight	Inflight	Postflight	Preflight	Inflight	Postflight
Input:									
Water Ingested (food & water)	2941±536	2932±533	3140±577	2678±295	2597±302	2794±371	3293±225	2937±227	3359±354
Metabolic Water	340±10	328±5	359±16	368±47	362±67	387±44	351±3	359±5	371±13
Output:									
Urine volume	1640±536	1702±428	1835±477	1333±116	1356±98	1374±73	1660±161	1672±93	1986±387
Fecal Water	79±8	67±5	18±5	90±25	77±18	64±22	77±26	61±8	70±20
Evaporative Water	1573±82	1522±133	1619±125	1576±272	1552±435	1653±534	1881±274	1574±160	1652±288
Net Water Balance:									
Mean	-9	-32	28	46	-26	90	26	-11	52
SE	±12	±22	±9	±19	±17	±53	±25	±4	±8
No. of Days Observed	30	28	14	20	59	17	26	84	18

Table F-6. Changes in Body Fluid Compartments for Each Skylab Mission (N = 3) [Liters ± (SE)]

Body Fluid Compartment	28-Day Mission	59-Day Mission	84-Day Mission	Skylab Mean
Total Body Water	-1.22±0.47	-0.60±0.64	-0.63±0.11	-0.82±0.25
Extracellular Fluid	-0.13±0.17	-0.87±0.41	0.00±0.52	-0.33±0.24
a) Plasma volume	-0.28±0.14	-0.43±0.10	-0.53±0.08	-0.41±0.06
b) Interstitial fluid *	+0.15±0.50	-0.44±0.46	+0.53±0.48	+0.08±0.76
Intracellular Fluid**	-1.08±0.64	+0.27±1.04	-0.63±0.63	-0.49±0.44

* Derived from extracellular fluid and plasma volume

** Derived from total body water and extracellular fluids

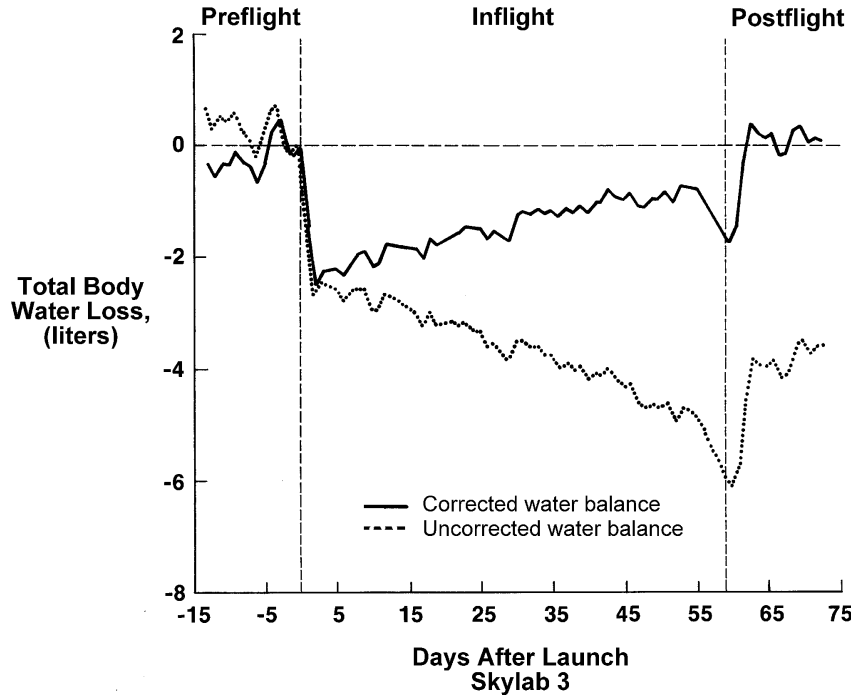


Figure F-1. Comparison of total body water for the Skylab crew on 59-day mission ($N = 3$) computed with and without correction factors (CF) in the daily water balance. (Values are shown as changes from morning of launch; (—) with correction factor and (---) without correction factor.

partitioned into rates of input and output but into fluid compartments of the body. Table F-6 presents the changes in the intracellular, extracellular and plasma compartments over the duration of each Skylab mission. The combination of data in Tables F-5 and F-6 provides the first complete gross assessment of fluid status in weightlessness.

The metabolic balance analysis accounts for changes in total dry body tissue (ΔTIS), protein (ΔPRO) and fat (ΔFAT) computed from the following assumed relationships:

$$\begin{aligned}\Delta BWGT &= \Delta TBW + \Delta TIS \\ &= \Delta TBW + \Delta PRO + \Delta FAT\end{aligned}\quad (21)$$

Thus, changes in total tissue weight can be found by subtracting ΔTBW from $\Delta BWGT$. Daily changes in total body protein were determined from the nitrogen balance:

$$\Delta PRO = 6.25 (N(\text{diet}) - N(\text{urine}) - N(\text{feces})) \quad (22)$$

Daily changes in body fat were computed from Eq. (21) as:

$$\Delta FAT = \Delta BWGT - \Delta TBW - \Delta PRO = \Delta TIS - \Delta PRO \quad (23)$$

Total body changes in these quantities over any interval of N days can be found by summing up (integrating) the daily balances analogously to Eq. (17) for total body water changes:

$$\text{Change in Total Body Tissue} = \Delta TIS(N) = \sum_{i=1}^N \Delta TIS_i \quad (24)$$

$$\text{Change in Total Body Protein} = \Delta PRO(N) = \sum_{i=1}^N \Delta PRO_i \quad (25)$$

$$\text{Change in Total Body Fat} = \Delta FAT(N) = \sum_{i=1}^N \Delta FAT_i \quad (26)$$

where N is the number of days of interest, usually a complete mission phase.

F.1.2 Water Balance Error Analysis

The use of an average constant value for CF in the daily water balance rests on the assumption that day-to-day skin and body tissue losses are similar (see Eq. (13)), and implies a linear rate of tissue change. Information indicating the variability of skin losses either on Earth or in space is unavailable. The assumption of a linear rate of fat loss was confirmed in the water balance study and body fat loss was believed to make the largest contribution to the correction factor in that study. Rates of protein losses or gains were also found to be nearly linear during the preflight and postflight periods. Protein loss inflight appeared to occur linearly over the first month before approaching a steady state. Thus, the assumption of linearity of the CF is reasonably correct for the entire preflight, inflight, and post-flight periods except for the later portions of the inflight phase. Thus, this assumption should not introduce significant error into daily water and cumulative balances.

The use of the correction factor insures that changes in total body water over each flight phase, as obtained from the corrected water balance, will be in absolute agreement with directly measured total body water. Estimates of the CF, therefore, were highly dependent on the accuracy of the direct tritium dilution method. These estimates have been shown to be realistic when compared to independent data of skin losses and body tissue losses. The use of direct total body measurements in conjunction with the balance method has been previously recommended as a technique to correct metabolic whole-body balances for otherwise unaccountable losses and to minimize accumulative error [9].

Random experimental error for this method includes sampling and instrumental errors associated with measuring the terms in Eq. (16); that is, body weight, dry food, urine volume and s.g., dry fecal mass and carbohydrate, fat and protein. Random errors associated with instrumentation were previously estimated to be less than ± 65 g/day [2].

Since the quantities defined in Eqs. (17), (24), (25), and (26) are sums of other random variables and if these random variables can be assumed to be independent, then errors (variances) associated with the summed quantities can be expressed as:

$$\sigma_{MN}^2(X) = \sum_i^N \sigma_M^2(\Delta X)_i \quad (27)$$

where

$$\sigma_{MN}^2(X)$$

represents the variance of the change in X (i.e., X = total body water, tissue, protein or fat) for the average of M subjects at the end of N days;

$$\sigma_M^2(\Delta X)_i$$

is the variance on the i th day of the average balance of X for M subjects. In this fashion, the errors are observed to be accumulative, starting from the reference day ($i = 1$, launch or recovery day). The cumulative error represented by Eq. (27) is probably an over-estimation of true error, since most of the variance in the balance on any particular day was due to random error. If the correction factor, CF, were deleted, it might be appropriate to use the above accumulative error in the calculation, since the daily water balance would always be underestimated by this quantity. For these reasons, both accumulative and non-accumulative errors were computed in this study. Accumulative errors were used in the 14-day analysis while non-accumulative errors have been plotted for the extended period (30-day and entire mission) analysis. The non-accumulative variances for M subjects on the N th day were computed in the following fashion:

$$\sigma_{MN}^2(X) = \sum_i^N \frac{[\Delta X_i - \Delta \bar{X}]^2}{M-1} \quad (28)$$

where ΔX_i is the water, tissue, fat, or protein balance for the i th crewmember on the N th day and $\Delta \bar{X}$ is the average

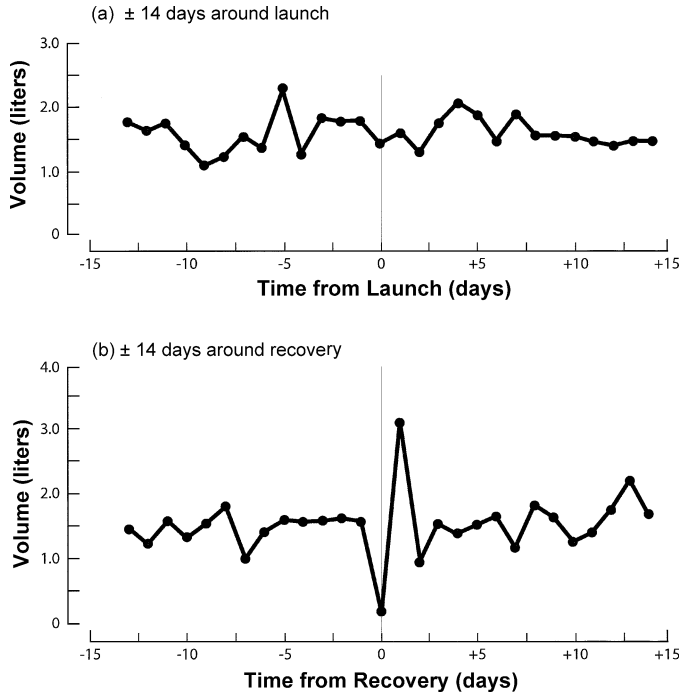


Figure F-2. Average evaporative water loss for the Skylab crew ($N=9$) at launch (a) and recovery (b).

balance of M crewmen on the N th day. Further details of the error analysis can be found in the literature [2].

Equation (28) is derived from the traditional formulation for standard deviation and standard error that is used throughout this book, specifically,

$$\text{Standard deviation (SD)} = \sqrt{\frac{\sum_i^n [X_i - \bar{X}]^2}{n-1}}$$

$$\text{Standard error (SE)} = \frac{SD}{\sqrt{n}}$$

where n is the number of samples, i is the iteration, X_i is the value of interest, and $\bar{X}$ is the mean value.

F.2 Skylab Evaporative Water Loss Analysis

The next part of this Appendix presents details of the Skylab Evaporative Water Loss Analysis not found in Chapter 4. Further details are available in the literature [10,11].

F.2.1 Assumptions, and Methods of Calculation

Two standard balance equations were combined to estimate evaporative water loss, EWL, from the input and output of fluids and solids for each crewman [3,12,13]. The first was the water balance equation, Eq. (1), and the second was the mass balance equation, Eq. (2). Solving Eq. (2) for EWL:

Table F-7. Measured and Derived Metabolic Data for Preflight and Inflight Phases; Average Daily Values for Each Mission

		28-Day Mission	59-Day Mission	84-Day Mission	Skylab Mean $\pm$ SE
No. of days observed	Pre	30	20	26	
	Inf.	23	54	79	
Total water Ingested	Pre	2941	2678	3293	2971 $\pm$ 208
	Inf.	2911	2670	2953	2845 $\pm$ 212
Food (Dry)	Pre	594.9	641.5	611.0	615.8 $\pm$ 27.2
	Inf.	598.5	686.4	638.2	641.0 $\pm$ 28.1
Urine	Pre	1610	1333	1660	1535 $\pm$ 172
	Inf.	1824	1386	1681	1630 $\pm$ 158
Fecal Water	Pre	78.4	90.0	77.2	81.8 $\pm$ 10.9
	Inf.	69.5	78.7	60.9	69.7 $\pm$ 6.9
Fecal Solids	Pre	23.5	25.2	26.0	24.9 $\pm$ 1.8
	Inf.	21.0	26.6	24.3	24.0 $\pm$ 1.7
Change in Body Weight	Pre	-44.5	16.7	0.0	-9.3 $\pm$ 14.5
	Inf.	-55.1	-25.9	3.8	-25.7 $\pm$ 12.5
Diet Protein	Pre	107.4	123.4	120.0	116.9 $\pm$ 6.5
	Inf.	102.3	117.9	120.0	113.4 $\pm$ 6.6
Diet Fat	Pre	105.0	113.3	110.5	109.6 $\pm$ 3.3
	Inf.	79.1	75.3	101.1	85.2 $\pm$ 4.5
Diet Carbohydrate	Pre	355.1	378.8	356.4	363.4 $\pm$ 17.5
	Inf.	394.4	468.3	393.5	418.7 $\pm$ 22.1
Metabolic Water	Pre	352	381	363	365 $\pm$ 15
		346	391	375	371 $\pm$ 15
Insensible Gas Loss (CO ₂ - O ₂)	Pre	164.4	176.7	166.6	169.2 $\pm$ 8.3
	Inf.	182.2	217.0	183.3	194.1 $\pm$ 10.4

*All liquid quantities are expressed in ml/day, all other quantities are in gm/day

**Data from the first 5 mission days were not included in determining these values

$$\begin{aligned}
 &\text{EWL} = \text{dry weight of food} \\
 &+ \text{total water ingested from food and liquids} \\
 &- (\text{urine volume} \times \text{urine s.g.}) - \text{wet weight of feces} \\
 &- \text{weight of CO}_2 \text{ expired} \\
 &+ \text{weight of O}_2 \text{ used} - \text{gain in body weight} \quad (29)
 \end{aligned}$$

Note that the term “dry skin loss”, used in the previous section, Appendix F.1, were neglected in this balance equation (primarily losses of sweat solids) and that this omission can be a source of systematic error. Because the differences in evaporative loss between flight phases were rather small, it was important to estimate the magnitude of these errors and locate their origins if possible. EWL estimated by these balance methods included *insensible* water losses from the respiratory tract and dermis, as well as *sensible* sweat losses. Metabolic water, CO₂, and O₂ were determined indirectly from the daily measured amounts of protein, fat, and carbohydrate in the ingested diet according to the relationships shown in Eqs. (5) to (7). Individual urinary specific gravity values were used in the computa-

tions (see Table F-3). Average measured and derived values for the terms in these balances are presented for each mission in Table F-7.

The evaporative water loss results presented in this study were obtained using the mass balance equation, Eq. (29). All terms in that relationship were measured either directly or indirectly on a continuous daily basis. Since total body water (TBW) was measured only several times for each subject, EWL as computed from the water balance equation (Eq. (1) or (18)), represented an average value for the period between the TBW measurements. A comparison between these two formulations (water balance and mass balance) served as a check on the accuracy of the experimental procedures (see Table 4-6). Other factors such as blood draws and sweat solids were estimated to be only 12-20 gm/day, a relatively insignificant amount relative to daily EWL [6,7]. Therefore, these factors were not considered in the analysis.

For the first few days of each flight, the crews experienced motion sickness, anorexia, temperature stresses, and

Table F-8. Propagation of Error Analysis of Mass Balance Equation in Determining Evaporative Water Loss*

<i>I</i>	Quantity	Inflight Mean $\overline{X}_i$	Total Error		Instrument Error	
			Standard Error $S_{\overline{X}_i}$	Total Error Contribution $S_{\overline{X}_i}^2 / S_{\overline{X}}^2 \times 100$	Instrument Error E_i	Instrument Error Contribution E_i^2 / E^2
1	Food (wet)	1063	± 50	4.2%	± 3	0.2%
2	Water (drink)	2389	± 190	60.6%	± 10	2.3%
3	Urine x s.g.	1612	± 140	34.7%	± 10	2.3%
4	Feces (wet)	92	± 8	0.1%	± 3	0.2%
5	(CO ₂ – O ₂)	192	± 9	0.1%	± 10	2.3%
6	Δ Daily Body Wgt	-53	± 13	0.3%	± 64	92.7%
		EWL = 1609	$S_{\overline{X}} = \pm 244$	100.0%	$E = \pm 66$	100.0%

$$\overline{X}(\text{EWL}) = \overline{X}_1 + \overline{X}_2 - \overline{X}_3 - \overline{X}_4 - \overline{X}_5 - \overline{X}_6 \quad (\text{Mass Balance Equation}) \quad (\text{a})$$

$$S_{\overline{X}}^2(\text{EWL}) = \sum_{i=1}^6 S_{\overline{X}_i}^2 \quad (\text{Propagation of Sampling Errors}) \quad (\text{b})$$

$$E^2(\text{EWL}) = \sum_{i=1}^6 E_i^2 \quad (\text{Propagation of Instrument Errors}) \quad (\text{c})$$

*Means and standard errors shown are pooled values for all inflight observations on all nine subjects; unless otherwise noted units are in grams

activities not typical of the remainder of the mission. Major readjustments in fluid and electrolytes also occurred during this period, and atypical, but appropriate changes in EWL were demonstrated. The atypical first five days of the inflight phase were omitted in the analysis. The experimental design provided that each subject serves as his own control; his inflight data were compared to data from his preflight control phase. Statistical analysis of the data included the paired t-test, correlation analysis, and analysis of variance with consideration for the unbalanced number of daily observations in each flight phase [14,15].

F.2.2 Error Analysis

Evaporative water loss is an indirect measurement and is subject to the random errors or variation in the directly measured components of the material balance equation. These random errors were mainly the result of two sources of variation: a) variation between daily observations and between subjects due primarily to biological variability

and environmental disturbances; and b) variation due to limited instrument resolution.

Table F-8 lists the sampling errors (S_{X_i} = instrument error + biological variability) and the instrument errors (E_i) for each term in the mass balance equation. Sampling errors were taken as the standard errors of the mean of each quantity for nine men during the inflight phase. Instrument errors were obtained by estimating the precision of each instrument from preflight and inflight studies [9,16]. The percent contribution of the errors associated with each term toward the total variance of sampling errors and instrument errors are also shown in Table F-8. (The data for the quantity $\overline{X}_i$ in Table F-8 are the mean values for only six of the crewmen corresponding to the subjects presented in Chapter 4, Table 4-6).

Since evaporative loss is given by a linear sum of terms (see Table F-8, Equation (a)) an estimate of the standard error in evaporative loss can be found by summing the square of the errors for each term as shown in Table F-8,

Equations (b) and (c). This is only true, if the errors in each term are statistically independent of one another (i.e., if the correlation coefficients are zero).

While the assumption of error independence is reasonable in computing total instrument error, this is not the case for total sampling error. For example, it is possible that the variation of water intake is highly correlated with the variation in urine output. For the case where high correlations exist, a more accurate estimate of $S_x(EWL)$ can be determined by taking into account the covariances, S_{ij} . The difference between the value of $S_x(EWL)$ in Table F-8 and the corresponding value in Chapter 4, Table 4-6 (244 vs. 89) may arise from the fact that in the former case the covariances were neglected. A more complete estimate of the propagation of errors in which the covariance terms were computed can be found in Ref. [10]. Nevertheless, the simplified analysis of errors presented in Table F-8 is very informative by demonstrating that the errors in computing evaporative water loss are almost entirely due to the total variation associated with measuring water intake and urine. One would expect a large correlation and covariance between water intake and urine since water intake physiologically drives urine excretion.

Random sampling errors can usually be reduced by increasing the number of samples. The large effect of water and urine variability and the high correlation between these quantities allow the precision of the evaporative loss estimates to be improved by measuring water intake with greater accuracy or, even better, by controlling water intake within smaller limits.

Total instrument error is due primarily to the body mass measuring device as shown in Table F-8. Also, it appears from this table that most of the error in the measurement of body weight is due to instrument error. Therefore, the instrument and overall sampling error of the body mass measurement can be reduced by improving the precision of this instrument rather than by increasing the sample size. However, this would not reduce the total error of the estimate of evaporative water loss, since the total instrument error was only a small component of the total sampling error and the average total error of the weight change measurements constituted only a small fraction of the final value of evaporative loss and its total error. The instrument error analysis also illustrates that the limiting resolution of the mass balance technique in measuring evaporative water loss on Skylab (in the absence of significant biological fluctuations) is about ± 70 gms, which represents approximately a 4% error.

Systematic errors in the present technique are associated with the neglect of less significant terms in the material balance equation. In particular, failure to account for sweat solids, sebaceous residues, and desquamated epithelium would systematically cause the calculated evaporative loss to be overestimated by about 12-22 gm./day [6,7]. This was a negligible fraction of the total evaporative loss, but could account for about 50% of the discrepancy found between the mass balance and water balance techniques (see Table 4-6). The water balance method does not require accounting for these solid residues. However,

uncertainties in other measured quantities may also account for this disagreement. Thus, it is not likely that serious systematic errors were present in the estimation of evaporative loss in the present study.

F.2.3 Supplementary Metabolic Balance Data

Tables F-9 and F-10 present the measured and derived data respectfully for each Skylab crew member that were used in the balance equations to obtain the presented calculations for evaporative water loss shown in Table 4-5. This is also the detailed backup data used to compute the mean mission values listed in Table F-7.

F.3 Skylab Sodium and Potassium Balance

The following section provides a more extensive discussion of the Skylab sodium and potassium balance analysis than that presented in Chapter 4. Further details of this analysis are available [17].

F.3.1 Assumptions and Methods of Calculations

Metabolic balances were performed for sodium and potassium using the following basic equations:

$$\text{Daily electrolyte balance} = \text{Dietary intake} - \text{Urine excretion} - \text{Fecal excretion} - \text{CF} \quad (30)$$

$$\text{Cumulative electrolyte balance over } N \text{ days} = \text{Change in total body electrolyte}$$

$$= \sum_{i=a}^N \text{Daily electrolyte balance} \quad (31)$$

where CF is a correction factor for sweat losses, unaccounted losses, and error terms; "a" is the day the balance begins (the first day of the mission phase); and "N" the day the balance ends (last day of the mission phase). These equations were added to the computer program that was used to compute the Skylab water balances. The output of the program allowed the visual display of the daily balance, the integrated or total balance, and the contribution of each term in the balance toward producing short-term and long-term changes in the balance. In the balance equations shown, the sweat losses, unaccounted losses, and error terms were combined since sweat losses were not measured during the Skylab program.

In order to obtain reasonable estimates of the time course and magnitudes of the daily balance and the changes in total body potassium and sodium, the balances were computed using correction factors based on matching the *measured* changes in the total body pools of sodium and potassium with the *cumulative balances* as computed from Eq. (31). For sodium, this correction factor was based on the product (plasma sodium concentration) x (extracellular fluid volumes). For potassium, whole-body values were measured directly.

The balance programs were run for a number of cases for both sodium and potassium. For each case, balances

Table F-9. Components of Metabolic Balance for Each Skylab Crewmember: Measured Variables Used in Balance Equations*

Mission	Crewman	Total Water Ingested, ml/d		Food Dry gm/d		Diet Protein gm/d		Diet Fat gm/d		Diet Carbohydrate gm/d		Urine gm/d		Fecal Water gm/d		Fecal Solids gm/d	
		Pre	In	Pre	In	Pre	In	Pre	In	Pre	In	Pre	In	Pre	In	Pre	In
28-Day	1	2500	2405	555.6	583.8	104.6	101.9	104.9	81.3	318.5	377.8	1340	1509	81.0	66.6	18.4	19.4
	2	2316	2239	619.3	619.1	107.9	105.9	101.2	82.2	382.3	408.9	849	1207	90.6	64.6	28.4	23.0
	3	4008	4089	609.8	592.6	109.8	99.0	109.0	73.9	364.4	369.5	2642	2757	63.5	77.2	23.7	20.5
Mean $\pm$ SE		2941 $\pm$ 536	2911 $\pm$ 591	549.9 $\pm$ 19.8	598.5 $\pm$ 10.6	107.4 $\pm$ 1.5	102.3 $\pm$ 2.0	105.0 $\pm$ 2.3	79.1 $\pm$ 2.6	355.1 $\pm$ 19.0	394.4 $\pm$ 9.0	1610 $\pm$ 535	1824 $\pm$ 474	78.4 $\pm$ 7.9	69.5 $\pm$ 3.9	23.5 $\pm$ 2.9	21.0 $\pm$ 1.1
59-Day	1	2214	2175	544.6	608.8	95.1	87.3	98.1	67.7	331.2	434.7	1392	1169	45.1	45.3	18.1	20.1
	2	2594	2554	560.7	593.1	112.4	111.6	110.1	78.7	315.4	381.0	1110	1453	91.5	74.8	23.8	24.6
	3	3227	3282	819.2	857.3	162.6	154.9	131.8	79.6	489.8	589.3	1498	1535	133.3	115.9	33.6	35.2
Mean $\pm$ SE		2678 $\pm$ 295	2670 $\pm$ 325	641.5 $\pm$ 89.0	686.4 $\pm$ 85.6	123.4 $\pm$ 20.2	117.9 $\pm$ 19.8	113.3 $\pm$ 9.9	75.3 $\pm$ 3.8	378.8 $\pm$ 55.7	468.3 $\pm$ 62.4	1333 $\pm$ 116	1386 $\pm$ 111	90.0 $\pm$ 25.5	78.7 $\pm$ 20.5	25.2 $\pm$ 4.5	26.6 $\pm$ 4.5
84-Day	1	2888	2630	617.3	641.5	120.7	118.5	108.2	100.6	363.1	398.6	1739	1635	128.6	75.8	31.2	28.4
	2	3325	2797	600.1	622.5	112.5	111.4	107.5	92.0	357.6	395.7	1350	1513	55.7	53.2	24.1	20.1
	3	3667	3433	615.6	650.7	126.9	130.0	115.8	110.6	348.4	386.1	1892	1896	47.2	53.6	22.8	24.3
Mean $\pm$ SE		3293 $\pm$ 225	2953 $\pm$ 245	611.0 $\pm$ 5.5	638.2 $\pm$ 8.3	120.0 $\pm$ 4.2	120.0 $\pm$ 5.4	110.5 $\pm$ 2.7	101.1 $\pm$ 5.4	356.4 $\pm$ 4.3	393.5 $\pm$ 3.8	1660 $\pm$ 161	1681 $\pm$ 113	77.2 $\pm$ 25.8	60.9 $\pm$ 7.5	26.0 $\pm$ 2.6	24.3 $\pm$ 2.4
Skylab Mean $\pm$ SE		2971 $\pm$ 208	2845 $\pm$ 212	615.8 $\pm$ 27.2	641.0 $\pm$ 28.1	116.9 $\pm$ 6.5	113.4 $\pm$ 6.6	109.6 $\pm$ 3.3	85.2 $\pm$ 4.5	363.4 $\pm$ 17.5	418.7 $\pm$ 22.1	1535 $\pm$ 172	1630 $\pm$ 158	81.8 $\pm$ 10.9	69.7 $\pm$ 6.9	24.9 $\pm$ 1.8	24.0 $\pm$ 1.7

* No. of days included in preflight is 30, 20, 26 and inflight is 23, 54, and 79 for the 28-day, 59-day and 84-day missions, respectively. The first 5 inflight days were excluded in Tables F-9 and F-10.

Table F-10. Components of Metabolic Balance for Each Skylab Crewmember: Derived Data Used in Balance Equations

Mission	Crewman	Days		Metabolic Water ml/d		Insensible Gas Loss (CO ₂ - O ₂), gm/d		Change in Body Weight, gm/d	
		Pre	In	Pre	In	Pre	In	Pre	In
28-Day	1	30	23	330	339	148.1	174.8	-30.0	-17.4
	2	30	23	364	359	176.5	188.9	-46.7	-30.4
	3	30	23	363	341	168.6	182.9	-56.7	-117.4
	Mean ± SE			352 ± 11	346 ± 6	164.4 ± 8.5	182.2 ± 4.1	-44.5 ± 7.8	-55.1 ± 31.4
59-Day	1	20	54	327	352	152.6	198.0	+5.0	-24.1
	2	20	54	337	342	147.7	177.9	-35.0	-24.1
	3	20	54	478	479	229.8	275.0	+80.0	-29.6
	Mean ± SE			381 ± 49	391 ± 44	176.7 ± 26.6	217.0 ± 29.6	16.7 ± 3.4	-25.9 ± 1.8
84-Day	1	26	79	365	377	169.8	185.3	+30.8	+10.1
	2	26	79	358	364	166.1	183.4	-30.8	-7.6
	3	26	79	367	385	163.9	181.1	0.000	+8.9
	Mean ± SE			363 ± 3	375 ± 6	166.6 ± 1.7	183.0 ± 1.2	0.0 ± 17.8	3.8 ± 5.7
	Skylab Mean ± SE			365 ± 15	371 ± 15	169.2 ± 8.3	194.1 ± 10.4	-9.3 ± 14.5	-25.7 ± 12.5

were obtained for the nine Skylab crewmen separately and in several combinations. Individual balances were run for a complete mission, while the average balances for groups of crewmen were run for a maximum of 28 consecutive days. The integrated balances were computed using the launch day as the day of reference. This allows a complete picture for preflight through the first 28 days for any individual crewman, mission, or combination of missions to be obtained. In addition, balances were performed for the 14-day recovery phase for each astronaut.

Average balances were computed for five mission combinations: each of the three missions separately, for all three missions combined, and for the 59-day and 84-day missions combined. Balances were computed for four intervals for each of these five mission combinations. The four intervals included:

- from 13 days before launch to mission day 14
- from the day of launch to mission day 28
- from 13 days before recovery to recovery day 14
- from 28 days before recovery to the day of recovery.

These balances, when presented graphically, provide a complete picture of the sodium and potassium balances

from 13 days before launch through 28 mission days followed by 14 days of recovery. This interval corresponds to all Skylab days for which data exists for all nine crewmen.

The correction factor, CF, in Eq. (30) was calculated as follows:

$$CF_i = \overline{Bal}_i - \frac{(\Delta TBX_i)}{N_i} \quad (32)$$

where $\overline{Bal}_i$ is the uncorrected average balance (i.e., diet - urine - fecal) for mission phase i (i = preflight, inflight, or postflight); ΔTBX_i represents the directly measured total body loss of electrolyte X (sodium or potassium) in phase i ; and N_i represents the number of days in phase i . While ΔTBX was measured directly for potassium, ΔTBX was not measured for sodium. Therefore, in order to calculate ΔTBX for sodium, the following assumptions were made:

- Subjects were in steady-state preflight,
- All changes in total body sodium and potassium come from the exchangeable pools,
- The exchangeable sodium pools can be represented as the extracellular fluid volume (ECF) multiplied by the plasma concentration of sodium $[Na^+]_{\text{plasma}}$,

Table F-11. Skylab Change in TBW, ECF, and Body Weight During Preflight*

Mission	Days of Measurement	Subject	ΔTBW(liters)	ΔECF(liters)	ΔBWGT(kg)
28-Day Mission	F-21**, F-1	CDR	-0.5		-0.1
		SPT	0.8		0.6
		PLT	-0.3		1.2
59-Day Mission	F-20, F-1	CDR			0.2
		SPT			-1.3
		PLT			1.5
84-Day Mission	F-15, F-1	CDR	0.1	-0.2	0.8
		SPT	0.2	-0.1	-0.4
		PLT	0.7	-0.5	-0.6

* Data from Leach and Rambaut [18]

**F-21 refers to 21-days prior to launch

d) Errors in ECF volume measurement, plasma, and sodium concentration are small.

Using these assumptions, the correction factor for sodium was calculated as follows:

$$CF_i = \overline{Na^+ Bal_i} - [\Delta ECNa^+_j / N_i] \quad (33)$$

where

CF_i = correction factor for phase i ,
 i = pre-, in-, or post-flight,

$\overline{Na^+ Bal_i}$ = average uncorrected sodium balance for phase i

N_i = number of days in phase i

$\Delta ECNa^+_j$ = change in extracellular sodium for period j

= $\Delta(ECF \times [Na^+]_{plasma})_j$

j = interval of time where change was measured as indicated below,

j assumes the following values:

for i = preflight; assume no change in TBNa, i.e., $\Delta ECNa^+ = 0$,

for i = inflight, $j = (R+0) - (Preflight\ Mean)$

for i = postflight, $j = (R+14) - (R+0)$

where R = day of recovery from orbit

The available data supports the hypothesis that the crewmen were in a preflight steady-state with respect to total body sodium and potassium. The measured preflight changes in total body water, body weight, and ECF volume were relatively small as shown in Table F-11. If one

considers a nine man average, the changes in TBW, ECF, and BWGT were 0.1667 ± 0.21 liters (mean $\pm$ SE), -0.27 ± 0.15 liters, and -0.056 ± 0.31 kg respectively and statistically are not significantly different from zero (t-test).

In addition to the assumptions described above, it was assumed that all changes in total body sodium occurred in the exchangeable pool, which is approximately 70% of the total body sodium [19]. Bone calcium is known to change during spaceflight [20], and some sodium loss might be expected to accompany the loss of bone calcium. If sodium leaves the body in proportion to the sodium and calcium ratio in bone, based on the calcium losses from the body, approximately 1 meq of bone sodium would be lost during the first month inflight. Estimates of exchangeable potassium on the other hand show that it represents from 85 to 96% of total body potassium [19]. Therefore the measurements are generally taken to accurately represent changes in total body potassium.

A further assumption made for sodium was that exchangeable sodium can be approximated by the ECF volume times the plasma sodium concentration, $[Na^+]_{plasma}$. The plasma compartment is in free communication with the interstitium and lymph and these compartments combined account for 57% of the total exchangeable sodium. Nichols [21] demonstrated that these compartments contribute 70% of the sodium loss during acute sodium loss in dogs.

A potential problem with this analysis concerns the errors associated with the measurements themselves. The inflight change in total body sodium was calculated using the following equation:

$$\Delta TBNa(inflight) = ECF_2 \times [Na^+]_2 - ECF_1 \times [Na^+]_1 \quad (34)$$

Table F-12. Preflight Total Body Potassium, TBK (meq)

Subject	F-20 & F-21	F-14 & F-16	F-7 & F-8	F-1 & F-2
1	3252	3309	3280	3301 3202
2	3876	3969	3937	3849 3952
3	3822	3839	3949	3920 3803
4	3333	3367	3314	3340
5	3094	3080	3034	3039
6	4536	4602	4687	4760
7	3228	3258		3197
8	3758	3698		3562
9	3612	3678		3551
Mean ±SE	3612 ±448	3644 ± 463		3607 ± 521

* F-20 represents the 20th day prior to launch

where 1 = measured just prior to launch
2 = measured at recovery

The error in computing ΔTBNa is about two times that of the error in the calculation of either preflight or postflight extracellular sodium alone, since each term above contributes to the change. If the error associated with the sodium concentration is nominally +1 meq and the error of the ECF volume measurement is 0.5 liter (3-4%), the error in $\Delta\text{TBNa}(\text{inflight})$ has a possible value of about 172 meq.

Inasmuch as the calculated value of ΔTBNa inflight was approximately 100 meq, the error is greater than the quantity being calculated. The daily balance is still within acceptable accuracy since the error divided by the average mission length (e.g., 172/57) equals only 3.0 meq/day. Neither does it much affect the difference between flight phases. The error in the plasma Na^+ concentration may be less than 1 meq decreasing the potential error in ΔTBNa in proportion to the error of $[\text{Na}^+]_{\text{plasma}}$.

Total body potassium (TBK) was measured *directly* in Skylab using whole-body isotope counts and was not dependent on ECF volume measurements, which were a large potential source of error for computing body sodium. Therefore, the correction factor for potassium was calculated directly according to Eq. (32).

Table F-12 lists the individual preflight TBK measurements from which the mean values of ΔTBK (preflight) were computed and shown in Table F-13. Table F-14 shows the average values of potassium balance (KBal (uncor-

rected)). Table F-15 summarizes the calculations for preflight and inflight potassium skin losses.

Using the inflight values of $\overline{CF_K}$ in Table F-15, it is possible to obtain a corrected daily average for potassium balance:

$$\overline{KBal}(\text{corrected}) = \overline{KBal}(\text{uncorrected}) - \overline{CF_K}. \quad (35)$$

These results are presented in Table F-16. From these values, the monthly total cumulative losses of potassium at the end of each month of the mission can be obtained as follows:

$$\begin{aligned} \text{Total cumulative loss at the end of the inflight period } i \\ (i = \text{I, II, or III}) \\ = \overline{KBal}(\text{corrected})_i \times N_i \end{aligned} \quad (36)$$

where N the number of days in the inflight period i . These values are presented in Table F-17.

Absolute values of TBK were determined by subtracting the monthly losses from the directly measured TBK (preflight mean). The methods of calculating these absolute TBK values are presented below, along with a set of sample calculations.

F.3.2 Sample Calculation (Subject #5):

F.3.2.1 Preflight Skin Loss. From Table F-12, the changes in TBK during the preflight period are calculated as follows,

Table F-13. Changes in TBK from Preflight Average*

Subject	N	Preflight Mean $\pm$ SD	Postflight	Δ TBK
1	5	3269 $\pm$ 43	2998	-271
2	5	3917 $\pm$ 52	3678	-239
3	5	3867 $\pm$ 64	3528	-339
4	4	3339 $\pm$ 22	3151	-188
5	4	3062 $\pm$ 30	3029	-33
6	4	4647 $\pm$ 98	4485	-162
7	3	3228 $\pm$ 31	3108	-120
8	3	3673 $\pm$ 100	3348	-325
9	3	3614 $\pm$ 64	3169	-445
Mean SE$\pm$		3624 $\pm$ 484	3388 $\pm$ 471	-236 $\pm$ 125

* Preflight value is mean of *N* measurements; only one postflight measurement was made.

Table F-14. Crew Average for Uncorrected Potassium Balance (meq/day)

Mission	Subject	Periods			
		Preflight	Inflight I*	Inflight II	Inflight III
28-day	1	19.27	6.24		
	2	20.80	3.18		
	3	16.75	4.20		
59-day	4	14.66	0.79	9.35	
	5	16.17	0.92	13.17	
	6	20.20	5.16	21.77	
84-day	7	12.29	1.84	0.83	2.45
	8	14.94	4.95	8.08	9.42
	9	17.48	8.95	2.33	14.10
(Mean $\pm$ SE)	(1-9)	16.95 $\pm$ 2.80	4.03 $\pm$ 2.67	9.26 $\pm$ 7.65	8.66 $\pm$ 5.86
	(4-9)	15.96 $\pm$ 2.70			
	(7-9)	14.90 $\pm$ 2.60			

* inflight periods I, II, and III refer to the first, second, and third inflight months

Table F-15. Estimation of Preflight and Inflight Potassium Skin Losses*

Subject	Preflight**			Inflight			
	Direct ΔTBK (meq)	Uncorrected KBal (meq/day)	$\overline{CF_K}$ (meq/day)	Direct ΔTBK (meq)	Uncorrected KBal (meq/day)	N days	$\overline{CF_K}$ (meq/day)
1	0	19.27	19.27	-271	6.24	28	15.92
2	+25	20.80	19.55	-239	3.18	28	11.72
3	+40	16.75	14.75	-339	4.20	28	16.31
4	+7	14.66	14.31	-188	5.07	56	8.43
5	-55	16.17	18.92	-33	7.05	56	7.63
6	+224	20.20	9.00	-162	13.47	56	16.36
7	-31	12.29	13.84	-120	1.37	84	3.14
8	-196	14.94	24.74	-325	7.48	84	11.35
9	-61	17.48	20.53	-445	8.46	84	13.76
Mean	5	16.95	17.21	-236	6.28		11.62
$\pm SE$	± 111	± 2.80	± 4.67	± 125	± 3.50		± 4.55

$$\begin{aligned}\Delta TBK (\text{direct, preflight}) \\ &= TBK(F-1) - TBK(F-20) \\ &= 3039 - 3094 = -55 \text{ meq}\end{aligned}$$

From Table F-14, the uncorrected preflight potassium balance is,

$$\overline{KBal}(\text{uncorrected, preflight}) = 16.17 \text{ meq/day}$$

From Table F-15, the preflight potassium correction factor for skin losses is,

$$\begin{aligned}\overline{CF_K} &= \overline{KBal}(\text{uncorrected, preflight}) \\ &\quad - \Delta TBK (\text{direct, preflight}) / N \text{ days} \\ &= 16.17 - (-55/20 \text{ days}) = 18.92 \text{ meq/day}\end{aligned}$$

F.3.2.2 Inflight Skin Losses. From Table F-15, the inflight change in TBK measured directly is,

$$\Delta TBK (\text{direct, inflight}) = -33 \text{ meq}$$

From Table F-14 the uncorrected inflight potassium balance is

$$\begin{aligned}\overline{KBal}(\text{uncorrected, inflight}) \text{ for period I} &= 0.92 \text{ meq/day} \\ \text{for period II} &= 13.17 \text{ meq/day}\end{aligned}$$

From Table F-15, the inflight potassium correction factor for skin losses is,

$$\begin{aligned}\overline{CF_K} &= [(\overline{KBal}(\text{uncorr}) \times N)_I + (\overline{KBal}(\text{uncorr}) \times N)_{II} \\ &\quad - \Delta TBK(\text{direct})] / (N_I + N_{II}) \\ &= [0.92 \times 28 \text{ days} + 13.17 \times 28 \text{ days} - (-33)] / 56 \text{ days} \\ &= 7.63 \text{ meq/day}\end{aligned}$$

F.3.2.3 Corrected K⁺ Balances. The potassium balances can be corrected simply by subtracting the correction factor, $\overline{CF_K}$ from the uncorrected potassium balance:

$$\overline{KBal}(\text{corrected}) = \overline{KBal}(\text{uncorrected}) - \overline{CF_K}$$

So that from Tables F-14 and F-15:

$$\begin{aligned}\overline{KBal}(\text{corrected, preflight}) &= 16.17 - 18.92 = -2.75 \text{ meq/day} \\ \text{and}\end{aligned}$$

$$\begin{aligned}\overline{KBal} (\text{corrected, inflight}) \text{ for period I} &= 0.92 - 7.63 = -6.71 \\ \text{for period II} &= 13.17 - 7.63 = 5.54\end{aligned}$$

F.3.2.4 Monthly Inflight Losses (Gains), ΔTBK . The changes in TBK for each monthly inflight period is computed by summing the daily corrected balances over the 28 days in each period (see Table F-16 and F-17).

Table F-16. Crew Average for Potassium Balance (Corrected for Skin Losses), meq/day

Mission	Subject	Periods			
		Preflight	Inflight I*	Inflight II	Inflight III
28-day	1	0.00	-9.68		
	2	1.25	-8.54		
	3	2.0	-12.11		
59-day	4	0.35	-7.64	0.92	
	5	-2.75	-6.71	5.54	
	6	11.2	-11.20	5.41	
84-day	7	-1.55	-1.30	-2.31	-0.69
	8	-9.80	-6.40	-3.27	-1.93
	9	-3.05	-4.81	-11.43	0.34
Mean ± SE	1-9	0.35 ± 5.54	-7.60 ± 3.32	-0.86 ± 6.37	-0.76 ± 1.14
	4-9	-0.02 ± 6.9			
	7-9	-4.8 ± 4.39			

* Inflight periods I, II, and III refer to the first, second, and third inflight months

Table F-17. Crew Averages for Monthly TBK Changes* (meq)

Mission	Man	Periods			
		Preflight	Inflight I**	Inflight II	Inflight III
28-day	1	0	-271		
	2	+25	-239		
	3	+40	-339		
59-day	4	+7	-214	+26	
	5	-55	-188	+155	
	6	+224	-314	+152	
84-day	7	-31	-36	-65	-19
	8	-196	-179	-92	-54
	9	-61	-135	-320	+10
Mean ±SE		-5 ± 111	-213 ± 93	-24 ± 179	-21 ± 32
Cumulative Shift from Preflight			-208	-227	-243

* TBK changes = KBal (corrected) x N (days)

** Inflight periods I, II, and III refer to the first, second, and third inflight months

Inflight I Loss = $-6.71 \times 28 = -188$ meq
 Inflight II Gain = $+5.54 \times 28 = +155$ meq

F3.2.5 Total Body K⁺ During Mission. The value for TBK at the end of the several inflight periods is obtained as follows:

TBK(<i>preflight mean, direct</i>) =	3062
Inflight I Δ TBK =	- 188
TBK at end of Period I =	2874 meq
Inflight II Δ TBK =	+155
TBK at end of Period II =	3029 meq

F.3.3 Alternative Method for Computing Electrolyte Sweat Losses

During the evaluation of Hypothesis #5 (Chapter 5), another technique was discovered that could be useful for indirectly estimating sweat losses of sodium and potassium for the Skylab crew. Figure F-3 depicts a simplified fluid-electrolyte model of the body for the purpose of illustrating the exchange of fluid and electrolytes between intracellular and extracellular compartments including intake, sweat, and renal losses. The quantities that have been measured directly or derived are indicated with an asterisk. If only the water and sodium exchange across the extracellular compartment are considered (i.e., exclude potassium and water exchange with the intracellular compartment), the extracellular sodium concentration can be uniquely determined by knowing the initial concentration and any net changes which occur in the balance between intake and output from this compartment. This is similar to the problem of determining the concentration of a substance, X, in a holding tank after a certain quantity of water and X has been added. Conversely, if the change in

concentration of X is known, the amount of substance added can be derived. In this manner, it is possible to determine the sodium sweat component by using the experimental extracellular sodium concentration data and the other components of the metabolic balances. Similarly, potassium losses (from sweating and cell loss) can be estimated from the plasma potassium concentration.

All the elements shown were included in the Guyton model and the current version of the model can be used to evaluate this technique; alternatively, it may be desirable to formulate a much simpler model based on Fig. F-4. A suggested mode of operation is shown in that graphic. Known values of intake and renal losses are input into the model, and values for electrolyte losses are assumed. The normal mode of using the Guyton model does not include forcing renal excretion as required by this method; thus, the name "push-pull" has been adopted (i.e., fluids are both pushed and pulled from the model). Predicted sodium and potassium responses are then compared to the experimental response. Extracellular electrolyte concentrations and total body losses of electrolytes in a given time period can both be compared. Iteration to obtain the "best fit" between experimental and predicted results leads to an estimated value of the electrolyte losses.

Preliminary results using this method have been encouraging. They have suggested that potassium and particularly sodium sweat losses were actually higher than control during the first few days of flight, before being reduced below control as originally estimated in Fig. 9-18. This is in keeping with the results of evaporative water losses which show the same trend. This information was utilized in a simulation of combined hypotheses which are shown in Chapter 5 (Figs. 5-32 and 5-33).

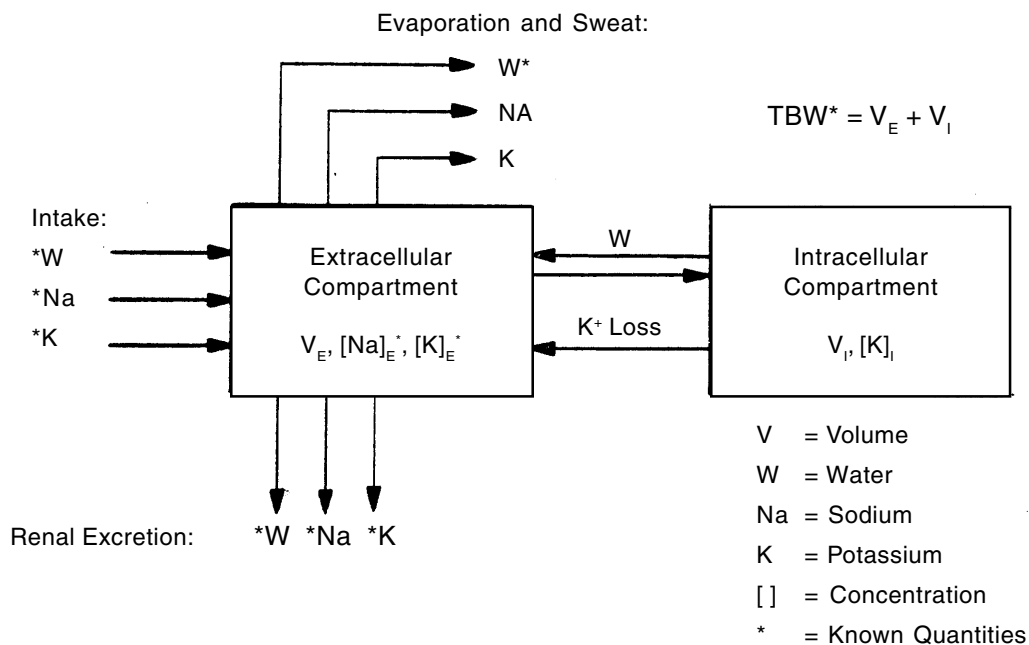


Figure F-3. Simplified fluid-electrolyte model.

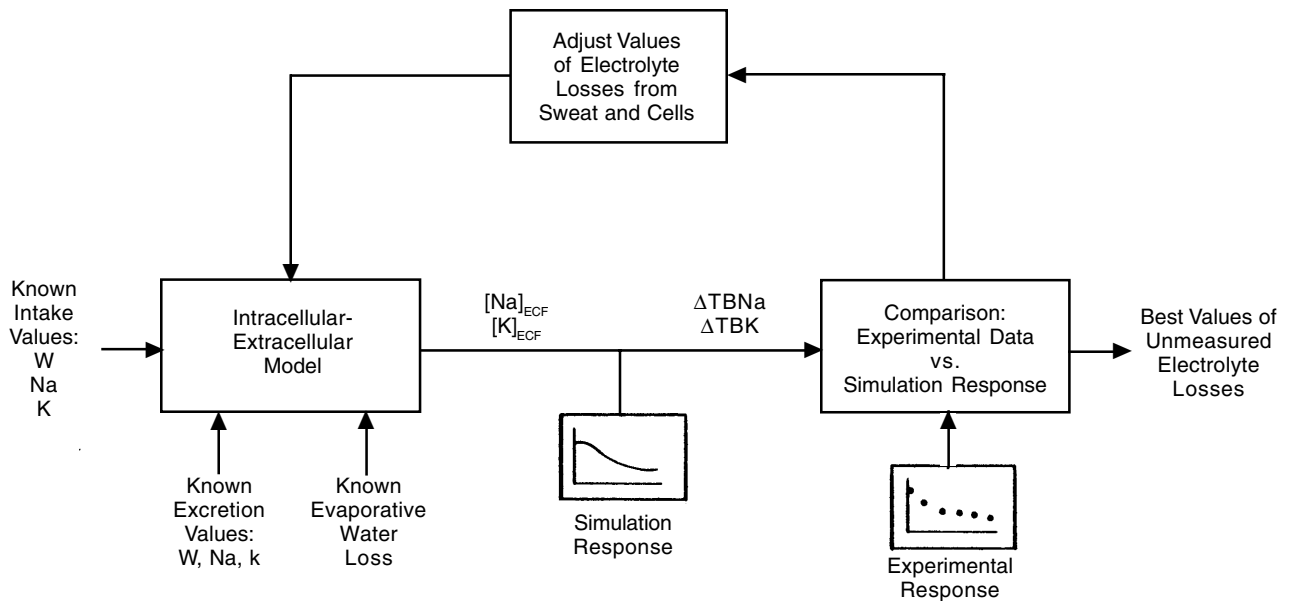


Figure F-4. Push-Pull simulation procedure for estimating unknown electrolyte loss rates.

F.4 Quantification of Tissue Loss Resulting From Prolonged Spaceflight

This section describes details of the Skylab lean body mass analysis that, for convenience, were not presented in Chapter 4.5. The reader is also referred to the original reports for a full discussion [22,23].

F.4.1 Methods of Calculation and Assumptions

Table F-18 summarizes alternative methods that were used in this study to quantify lean body mass (LBM)*. According to the references cited in Table F-18, the LBM [24] has a water content of about 73%, a potassium content of 60-70 meq/kg (in men), and a density of about 1.1 gm/cm³. In contrast, body fat contains less water (14%) and negligible potassium content, and has a lower density of about 0.9 gm/cm³. It is possible to estimate the relative proportions of fat and lean tissue in the body by measuring total body water (TBW), total body potassium (TBK), or body density (D), and assuming a simple two-compartment model (fat and fat-free). Body density is commonly derived from body mass or weight (BWGT) divided by body volume (BVOL). All of these measurements were available from the various Skylab experiments (see Table F-19). Empirical relationships have been suggested for predicting lean body mass from combinations of either TBW and TBK or TBW, TBK, BVOL and BWGT. Losses in lean body mass were obtained by using the relationships shown in

Table F-18 and by comparing the preflight period with the first postflight day of recovery. An inflight metabolic nitrogen balance provided an additional measure of lean tissue loss. The cumulative algebraic sum of nitrogen balances, obtained each day of the mission, indicates the net loss (or gain) of body nitrogen. Since protein contains an average of 16% nitrogen by weight, and lean body mass is composed of 19.4% protein, it is possible to quantify protein and lean body mass from the cumulative nitrogen balance [24,25].

Table F-20 presents individual subject results for inflight LBM changes derived from each method. This table is presented in summarized form in Chapter 4.5, Tables 4-16 and 4-20. The values in this table were used to perform correlation analyses between the various methods and these are discussed in Chapter 4.5. Further detailed calculation of each method can be found in the original report [22].

F.4.2 Experimental Approach

F.4.2.1 Measurements. Total body water (TBW) and total body potassium (TBK) were obtained by the isotopic dilution of isotopic hydrogen and potassium, respectively [18]. Body volume (BVOL) was computed from a stereophotogrammetric method involving four cameras to make two stereoscopic pairs of photographs from the front and back and using computer analysis to determine the volume of different body regions and of the body as whole [34]. Body mass (BWGT) was measured by conventional scales in terrestrial environment and by the principles of oscillating masses during spaceflight [16].

The nitrogen balance consisted of daily monitoring of dietary intake and daily collections and analysis of urine and fecal excreta [35]. Only preflight and postflight measurements were possible for TBW, TBK, and BVOL. Body mass and metabolic balances of nitrogen and potassium

* In this study, it was assumed that the difference between the lean body mass (body mass less storage fat) and fat-free mass (body mass less all other extractable fat); i.e., the essential body fat (about 2% of body weight), is negligible.

were determined daily throughout the preflight, inflight, and postflight period.

F.4.2.2 Pooling of Subjects. The periods of weightlessness associated with each of the three Skylab missions were 28 days, 59 days, and 84 days. Data presented in this and other reports [8] show that the largest losses in weight occurred during the first month and suggest that minimal changes were associated with the last two months, especially for body weight, body water, and lean body mass. For this reason, as well as the limited number of subjects available (three crewmembers on each flight), it was decided to pool the results of all nine subjects in summarizing changes in body composition. However, the data were also examined and discussed with respect to duration of flight. Paired t-tests were used to assess statistical significance of inflight changes.

F.4.3 Errors in the TBK Method

In Chapter 4.5, it was discussed that the method based on TBK did not at first provide reasonable results (labeled “uncorrected” in Table 4-16). A correction factor was successfully applied based on the assumption that a significant amount of potassium leaves the cellular compartment independently of other cell constituents due to osmotic considerations. The inflight changes of lean body mass calculated from the simple, *uncorrected* formula ($LBM = TBK/65$) was -3.63 ± 1.93 Kg while that calculated by applying a *correction* for an inflight osmotic effect was -1.55 ± 1.96 Kg. This latter value is in better agreement with the other methods studied. The following section discusses the possible errors in the TBK method and demonstrates precisely how the correction was applied.

F.4.3.1 Sources of Error. The unreasonably high values for LBM losses derived from the uncorrected TBK method were examined by considering the following factors:

- a) The factor of 65 meq K⁺/kg LBM used in the calculations (see Table F-18) may be inappropriate for the astronaut population. Values from the literature reveal that the potassium content of lean body mass is normally within the range of 60 - 70 meq K⁺/kg [28,36,37]. If the mean inflight LBM loss of 1.5 kg obtained by the average of the other methods is accepted, then the measured inflight loss of 235 meq K⁺ would require a concentration of $235/1.5 = 157$ meq K⁺/kg LBM, and this value is so far out of the normal range that other explanations must be sought, such as those described in (b) and (c) below,
- b) The possibility must be considered that the measured values of TBK were erroneous and that the potassium losses were overestimated due to systematic errors in the technique. The total accuracy of the isotope dilution method for ⁴⁰K may be several percent [38]. A systematic error of this magnitude could explain most of the discrepancy in the calculation of LBM loss. It had been noted that in certain pathological situations, this technique was subject to large errors in predicting LBM [39]. However,

preflight values were reasonable, and it was not clear how the inflight conditions or postflight measurements could challenge the suitability of this method.

- c) A significant fraction of the measured TBK loss may have been unaccompanied by other cellular components such as nitrogen and water (which together constitute about 90% of LBM). As discussed in Chapter 4.5 the ratios water:potassium:nitrogen in lost body mass are often greater than the normal cellular ratios of these components. Although it is not clear why this should happen, and the metabolic balance data for nitrogen and potassium do not support this conclusion, this phenomenon is still a possibility on Skylab.

In addition to the high values of lean body mass loss predicted by the uncorrected TBK method, the expected intracellular water loss also appears rather high. Using a value of 160 meq/liter for the intracellular potassium concentration [40], it would be expected that 1.5 liters of cell water would be lost with the observed decrement of 236 meq potassium assuming iso-osmotic loss and that potassium was the most significant osmotically active substance undergoing change. This was large compared to the total weight loss of 2.39 kg, the measured total body water change of 0.8 liters, or the derived intracellular water loss of 0.5 liters [18].

One explanation for these discrepancies could have been a mild, but persistent dilution of sodium concentration and osmolarity in extracellular fluid as measured from plasma samples obtained at regular intervals throughout the flight [18]. This was also noted in several bedrest studies [41,42], and while it has not yet been explained, osmotic balance requires that intracellular fluid be similarly dilute [19]. Also, it can be calculated that a lesser amount of water will be expected to accompany potassium osmotically from the cell if body fluids become hypotonic (see Fig. 5-28; [22]). Therefore, two components of potassium loss have been postulated: an *osmotic loss* which satisfies osmotic balance in the face of extracellular dilution and a *muscle atrophy loss* which was accompanied by nitrogen and other cellular constituents. This assumption has been translated into quantitative terms using the changes in plasma sodium concentration as correction factors. A sample calculation appears below.

F.4.3.2 Correction of the TBK Method. A mean change in plasma sodium concentration of -4.53 mEq/l was measured during the inflight phase over a three-month period (see Table F-21). Assume that a portion of the potassium leaving the cellular compartment unaccompanied by protein and water is equivalent to the amount necessary to dilute intracellular potassium to the same extent as sodium is diluted in the extracellular compartment (i.e., a mean decrease in sodium concentration of 4.53 meq/l measured throughout the inflight phase). Also assume that this is a generalized potassium loss throughout the intracellular compartment; i.e., 29.6 liters (measured preflight).

Therefore, this component of the potassium loss, to satisfy osmotic equilibrium, can be estimated to be

Table F-18. Mathematical Description of Methods Used in Determining Body Composition Changes*

Method	Concept	Equation
Total Body Water	Lean body mass is 73.2% water [26]	$LBM = TBW/0.732$
Total Body Potassium	Lean body mass contains 65 meq K ⁺ /kg [27,28]. This value is age dependent and has been adjusted to mean age of astronauts (40.7 years)	$LBM = TBK/65$
Total Body Water + Total Body Potassium	Lean body mass is estimated from sum of body water + cell solids + bone mineral. Cell solids estimated from TBK and bone mineral assumed to be a constant proportion of cell solids [28]. Assume inflight bone mineral loss does not contribute significantly to body weight change [29].	$LBM = TBW + \frac{TBK}{320.6} + \frac{0.334 TBK^*}{320.6}$ where TBK* = preflight value
Cumulative Nitrogen Balance	Cumulative inflight nitrogen balance assumes negligible loss of sweat component. Protein contains 16% nitrogen [30]; LBM contains 19.4% protein [24].	$N\ Bal = N(diet) - N(urine) - N(feces)$ $\Delta Protein =$ $N\ Bal \times Mission\ Length \times 6.25$ $\Delta LBM = \Delta Protein/0.194$
Body Density (Stereophotometric)	Body segmented into fat and essential body mass compartments, each having characteristic density. Densities determined from average of four different studies [26,31-33]: Fat (0.9168 gm/cm ³), LBM (1.0997 gm/cm ³).	$LBM = BW_{gt} \left(6.01 - \frac{5.51}{D} \right)$
“Combined” Method (Stereophotometric)	Lean body mass is the difference between body weight and fat mass. Body fat is estimated as the difference between measured volume of body and sum of the calculated volumes of body water and cell solids [28]. Method uses combination of all data shown in Table F-19. Results of this method reported here were taken directly from Whittle [29] and cannot be derived precisely from values given in Table F-19 because of the use of certain correction factors in the original calculations.	$LBM = BW_{GT}$ $- 0.901 \left(BodyVol - \frac{TBW}{0.994} - \frac{TBK}{448.6} - \frac{0.334 TBK^*}{847.8} \right)$ where TBK* = preflight value

Note 1. All quantities expressed as kg (LBM, FAT, BWGT, Protein) or milliequivalents (TBK).

Note 2. Assume essential body fat is negligible; i.e., fat free mass = lean body mass.

Note 3. Symbols: TBW=total body water; TBK=total body potassium; LBM=lean body mass; BWGT=body weight; D=body density; N=nitrogen

$$osmotic\ loss = 4.53\ meq/l \times 29.6\ liters = 134\ meq\ K^+$$

The actual loss of potassium that can be claimed to be a result of muscle atrophy (i.e., accompanied by nitrogen and water) is the difference between the measured inflight loss (Table F-19) and the osmotic loss:

$$muscle\ atrophy\ loss = 235 - 134 = 101\ meq\ K^+$$

The *lean body mass* (LBM) loss attributed to muscle atrophy is obtained from the relationship (Table F-18):

$$\Delta LBM = (\Delta TBK/65) = (101/65) = 1.57\ kg$$

The *protein loss* (PRO) is assumed to be 19.4% of the LBM loss:

$$\Delta PRO = 0.194 \times 1.57 = 0.30\ kg$$

Alternatively, the protein:potassium ratio of the LBM is known to be 3.06 gm/meq [36], so that

$$\Delta PRO = 3.06 \times 101 = 0.31\ kg.$$

The *fat loss* is:

$$\Delta FAT = \Delta BW_{GT} - \Delta LBM = 2.69 - 1.57 = 1.12\ kg.$$

The *intracellular water* loss accompanying 101 meq K⁺ can be estimated from the concentration of cell K⁺ [40]:

$$\Delta intracellular\ water = \left[\frac{101 meq}{160 meq / liter} \right] = 0.64 liters$$

These calculations are summarized below for both the uncorrected and corrected cases:

Table F-19. Body Composition Parameters Before and After Skylab Mission

Subject	Body Wgt (Kg) ¹			Body Volume (liters)			Total Body Water (liters)			Total Body Potassium (meq)		
	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ
1	62.2	60.2	-2.0	59.00	56.62	-2.38	41.55	40.8	-0.75	3270	3000	-270
2	77.9	74.3	-3.6	75.22	70.65	-4.57	48.80	48.0	-0.80	3915	3680	-240
3	80.2	76.0	-4.2	76.42	71.26	-5.16	52.15	50.0	-2.15	3865	3530	-340
4	68.6	64.6	-4.0	63.55	59.98	-3.57	42.50	41.9	-0.60	3340	3150	-190
5	61.8	58.7	-3.1	56.74	53.58	-3.16	39.10	39.6	+0.50	3060	3030	-35
6	88.0	84.1	-3.9	81.23	77.36	-3.87	53.60	51.9	-1.70	4645	4485	-160
7	67.8	67.8	+0.1	63.87	64.52	+0.65	41.85	41.0	-0.85	3230	3110	-120
8	71.5	68.6	-2.9	68.38	65.04	-3.34	45.40	44.9	-0.50	3675	3350	-325
9	67.6	66.1	-1.5	63.71	61.98	-1.73	45.65	45.1	-0.55	3615	3170	-445
Mean	71.7	68.9	-2.8*	67.57	64.55	-3.02*	45.62	44.8	-0.82*	3625	3390	-235*
SD	± 6.7	± 8.1	± 1.4	± 8.36	± 7.56	± 1.72	± 5.00	± 4.4	± 0.75	± 484	± 471	± 125

*p > 0.995 that postflight is different from preflight

Note 1. Preflight body weight is mean of daily measurements during 2-3 week period to launch. Postflight body weight value is the first shipboard measurement after reentry. Measurements of other parameters were made less frequently preflight and were made on either the 1st or 2nd day postflight.

Table F-20. Inflight Changes in Lean Body Mass for Each Skylab Subject using Various Methods*

Subject				Method	Body Density	Combined Method
	TBW	TBK	TBW + TBK	Cumulative Nitrogen Balance		
1	-1.02	-2.09	-1.17	-0.87	-2.43	-1.96
2	-1.10	-1.80	-1.16	-2.00	+2.21	-0.86
3	-2.93	-2.91	-2.74	-1.54	-4.20	-3.65
4	-0.82	-0.32	-0.67	-1.88	-7.47	-2.85
5	+0.69	-0.09	+0.48	-1.48	-4.61	-1.12
6	-2.32	+1.34	-1.43	-1.54	-2.07	-3.38
7	-1.16	-0.45	-0.94	-3.35	-4.49	-1.89
8	-0.68	-2.15	-0.94	-1.84	+3.31	-0.39
9	-0.75	-5.45	-1.65	-0.13	+4.06	-0.36
Mean	+1.12	-1.57	-1.14	-1.63	-1.74	-1.83
SD	±1.03	±1.96	±0.85	±0.87	±4.03	±1.25
Normalized to ΔBWGT = -2.72	-1.22	-1.58	-1.15	-1.85	-1.56	-1.64

*in kilogram

Body Composition Changes from TBK Loss

	Uncorrected	Corrected for Dilution	Other Estimates
ΔLean body mass (kg)	-3.63	-1.57	-(1.2 to 1.6)
ΔFat (kg)	+0.94	-1.12	-(1.0 to 1.5)
ΔProtein (kg)	-0.70	-0.31	-(0.2 to 0.4)
ΔIntracellular water (liter)	-1.50	-0.64	-0.5

While this is a speculative exercise, the predicted body composition variables (middle column) were in better agreement with other independent measurements discussed in Chapter 4.5 (last column) after the correction was applied. The computations for each crewman, based on the above method, are shown in Table F-21.

F.4.4 Errors in the Nitrogen Balance

Errors in the nitrogen balance technique have been reviewed by Hegsted [9], and discussed by Grande [24], Calloway [30], Forbes [43], Wallace [44], and Steffee [45]. The two major errors most often mentioned were: (a) the fact that certain losses are not measured in the usual balance study, especially fluid or nutrients lost through the skin, thereby making the balances falsely high, and (b) there is a consistent bias in most balance studies arising from an overestimation of intake (the subject may not eat all of the food offered, but cannot consume more than is offered) and an underestimation of output (it is difficult to collect all excreta and impossible to collect more excreta than was actually produced) thus making the balances falsely high. In the Skylab metabolic experiments, collection of excreta and measurement of food and water intake were carefully performed and corrections were included for food not eaten at each meal. However, it must be recognized that it was more the responsibility of the crewmen than the principal investigators to perform the actual collection and reporting tasks during the inflight phase. Nevertheless, the crewmembers were highly trained and well motivated subjects and it is unlikely that consistent errors were introduced.

With regard to other errors in the nitrogen balance, it has been estimated that dermal losses of nitrogen were found to be less than 0.5 g/day for sedentary men in a comfortable environment. Sweating due to heavy exercise may result in not more than another 0.5 g/liter of evaporative loss [9,30] (it has been estimated that sweat losses of the Skylab crew were less than one liter/day). The Skylab subjects exhibited such high net nitrogen retentions during the preflight phase of the study (3 gm/day) that it cannot be reversed by subtracting even 1 gm/day of unmeasured dermal losses. Further, it is important to note that the preflight Skylab nitrogen balances are in good agreement with the net retention found by other investigators for the particular dietary levels observed.

In attempting to explain the positive nitrogen balances that are normally seen in most normal subjects, Steffee [45] suggests that another route of unmeasured losses may be molecular nitrogen (gas). He says "there is now increasing evidence to indicate that this route, hith-

erto regarded as unlikely in mammalian organism, may be an important factor in nitrogen loss during generous intakes of protein in healthy subjects or during some pathological condition. The evidence, based on various approaches, has been reviewed and appears to provide a likely explanation for the positive balance values". It should be noted that a positive nitrogen retention, if real, argues as well for a positive total body potassium retention during the preflight phase. But TBK measurements do not suggest any change in this quantity, a discrepancy we cannot resolve.

The presence of these errors in the nitrogen balance should serve as a warning to interpret the balance results with some degree of caution. They do not, however, negate the fact that the Skylab crewmen's nitrogen balance changed direction upon launch and again upon recovery (see Fig. F-9). The positive nitrogen balances observed during the preflight phase could have been expected because of the following: a) the dietary nitrogen consumed in the calibrated preflight phase was probably higher than in the crew's daily life prior to flight and b) the increased activity of the crew as they exercised according to a rigid schedule may have had an anabolic effect on lean body mass. The dramatic shift in direction during the inflight phase to a negative balance is in keeping with the concept of atrophy of unused postural muscles in a microgravity environment. This concept would also argue for the observed postflight recovery of nitrogen when the subjects return to a world of gravity and must reactivate and rebuild the postural muscles. The leveling off of nitrogen loss after the first month during the last two flights suggests that there was a lower limit of protein loss reached irrespective of the level of exercise or time inflight.

F.5 Energy Balance and Body Composition of Weight Loss During Prolonged Spaceflight

This section of the Appendix presents the details of the approach, assumptions and methods of computation associated with Chapter 4.6. Further details can be found in Leonard [46,47].

F.5.1 Computational Procedures and Assumptions

The analysis for deriving body compositional changes were based on two formulations: a) an equation of body composition and b) an equation for energy balance. In the first of these equations, the change in body weight ($\Delta BWGT$) was assumed to result from changes in total body water (ΔTBW), body protein (ΔPRO), and body fat (ΔFAT). Thus,

$$\Delta BWGT = \Delta TBW + \Delta PRO + \Delta FAT \quad (37)$$

For the second equation which describes energy balance, net energy utilization (E_{util}), was computed as the sum of energy intake from diet (E_{diet}) minus energy excreted in urine (E_{urine}) and feces (E_{feces}) plus energy available from body tissue catabolism (energy from body fat, E_{fat} and body protein, E_{pro}). Thus,

Table F-21. Inflight Δ LBM from TBK Method (Corrected for Dilution Effect)

Subject	ICF (liters)	[ΔNa] (meq/l)	ΔTBK			ΔLBM (Kg)	ΔProtein (Kg)	ΔFat (Kg)	ΔBWGT (Kg)
			Estimated Osmotic Loss (meq)	Measured (meq)	Corrected (meq)				
1	25.4	-5.3	-135	-271	-136	-2.09	-0.406	+0.08	-2.01
2	33.3	-3.65	-122	-239	-117	-1.80	-0.349	-2.29	-4.09
3	36.6	-4.10	-150	-339	-189	-2.91	-0.565	-1.27	-4.18
4	24.6	+6.8	-167	-188	-21	-0.32	-0.62	-3.64	-3.96
5	24.4	-1.11	-27	-33	-6	-0.09	-0.018	-3.03	-3.12
6	34.7	-7.18	-249	-162	+87	+1.34	+0.260	-5.25	-3.91
7	28.0	-3.25	-91	-120	-29	-0.45	-0.087	+0.60	+0.15
8	29.0	-6.37	-185	-325	-140	-2.15	-0.417	+0.44	-1.71
9	30.3	-3.0	-91	-445	-354	-5.45	-1.06	+4.05	-1.40
Mean	29.6	-4.53	-135	-236	-101	-1.55	-0.30	-1.14	-2.69
SD	4.4	2.02	64	125	128	1.97	0.38	2.78	1.53
		(p < 0.001)	(p < 0.01)	(p < 0.01)	(p < 0.05)	(p < 0.05)	(p < 0.05)	NS	(p < 0.01)

Key: ICF – Intracellular fluid (measured preflight)
 $[\Delta\text{Na}]$ = Average change in sodium plasma concentration (inflight - preflight)
 ΔTBK (osmotic loss) = ICF x $[\Delta\text{Na}]$
 ΔTBK (corrected) = ΔTBK (measured) - ΔTBK (osmotic loss)
 ΔLBM = $\Delta\text{TBK}/65$
 $\Delta\text{Protein}$ = ΔLBM x 0.194

$$E_{util}^* = \text{Work (internal + external) + Heat lost} \\ = E_{diet} - E_{urine} - E_{feces} + E_{fat} + E_{pro} \quad (38)$$

As suggested by Eq. (38), the net energy available from food and tissue metabolism is assumed to be utilized entirely to perform work and produce heat. E_{util}^* is starred (*) to designate that it could not be measured directly or indirectly on a daily basis (i.e., by measuring work and heat lost or oxygen consumption) as were the other terms in Eq. (38). It was assumed that E_{util}^* , expressed as a daily average quantity for the preflight, inflight, or postflight phases, was constant throughout that phase for each crew member.

For convenience, the remainder of the computational procedures related to these equations are described in three parts: (F.5.1.1) determination of E_{util}^* , (F.5.1.2) determination of daily estimates of ΔTBW and ΔFAT and the latter's caloric equivalent, E_{fat} and (F.5.1.3) determining cumulative estimates of weight and tissue changes. In addition, (F.5.1.4) the computational procedures are provided for estimates of energy requirements that would prevent loss of body weight during spaceflight.

F.5.1.1 Determination of Mean Energy Utilization, E_{util}^* . E_{util}^* was determined from Eqs. (37) and (38) by assuming each term in these formulations represented overall mission quantities. For example, $\Delta BWGT$, which normally refers to daily changes in body mass would, in this part of the analysis, refer to change in net mass between the day of launch and day of recovery. When used in this way, the term is designated with a bar, thus $\Delta \overline{BWGT}$. Each term in Eq. (37), so designated, can be estimated except for $\Delta \overline{FAT}$. Body weight changes, $\Delta \overline{BWGT}$, were measured daily and directly, body water changes ($\Delta \overline{TBW}$) by isotope dilution techniques at launch and recovery, and protein losses ($\Delta \overline{PRO}$) estimated from cumulative daily nitrogen balance using a factor 6.25 to determine the protein equivalent of nitrogen [30]. Refer to Table F-22 for a summary of the methods used to compute each term in this analysis.

Overall mission fat losses for each subject were thereby calculated by solving Eq. (37) for $\Delta \overline{FAT}$. Using the caloric equivalent of this loss, E_{fat} , it was possible to derive the cumulative energy utilized, $\overline{E_{util}^*}$, from Eq. (38) in which $\overline{E_{diet}}$ was determined from the caloric equivalent of dietary content of protein, fat and carbohydrate [3,4], $\overline{E_{urine}}$ from urinary nitrogen (N_{urine}) and taken to be $8.32 \times N_{urine}$. $\overline{E_{feces}}$ was measured directly by bomb calorimetry, and $\overline{E_{pro}}$ was estimated from the caloric equivalent of the nitrogen balance losses (i.e., $\overline{E_{pro}} = 5.65 \times 6.25 \times N_{BAL}$). Each of these terms representing daily quantities was summed over the entire mission phase and used in Eqs. (37) and (38). The value of $\overline{E_{util}^*}$ obtained from this calculation was divided by the number of mission days to estimate E_{util}^* . Values of E_{util}^* so computed, are shown in Table F-23.

F.5.1.2 Daily Estimates of Body Water and Body Fat Changes. Daily changes in body fat were determined by solving Eq. (38) for E_{fat} , using the derived constant value

of E_{util}^* and daily measured values of the other components $\overline{E_{diet}}$, $\overline{E_{urine}}$, $\overline{E_{feces}}$, $\overline{E_{fat}}$, and $\overline{E_{pro}}$. Daily body fat changes were converted from energy (E_{fat}) to mass equivalents (ΔFAT) and used to compute ΔTBW from Eq. (37). Daily body mass changes ($\Delta BWGT$) and body protein changes (ΔPRO) used in this computation were estimated as previously described.

F.5.1.3 Cumulative Estimates of Weight, Water, and Tissue Changes. Cumulative changes in each of the quantities in Eq. (37) were calculated by summing the consecutive daily balances over any desired time interval. The interval of each day's balance period was taken to be from morning to morning. The experimental protocol specified that each day would begin after the last urine and fecal void prior to breakfast. Body mass measurements were made each day after overnight fasting. It was convenient to use the morning of the day of launch as the reference point from which cumulative balances were computed. Thus, the prelaunch period required a backward calculation from the point of reference (i.e., launch).

The calculation schema outlined above is shown in the idealized graph Fig. F-5. The average net dietary intake (i.e., $\overline{E_{diet}} - \overline{E_{urine}} - \overline{E_{feces}}$) is indicated by the lowest solid curve. The dashed horizontal line represents the average daily energy utilization, $\overline{E_{util}^*}$, for the inflight period. The difference between mean energy utilization and net dietary intake is the deficit between net calories derived from the diet and the energy actually required. This energy difference is assumed to be supplied by fat and protein tissue catabolism (carbohydrate stores in the body being assumed insignificant) as suggested by Eq. (38). The area bounded between the horizontal dashed and lower solid lines and any two time intervals is the energy equivalent of the cumulative tissue loss (protein + fat) during that interval. If daily protein changes can be assumed from the nitrogen balance (hatched area in Fig. F-5), it is possible to derive daily fat losses from this area of the graph as shown. The difference between total weight loss and the sum of fat and protein losses is then taken to be the daily change in body water, as indicated by Eq. (37).

The data corresponding to the idealized representation of Fig. F-5 is presented in Fig. 4-23. Figure F-6 show a similar analysis except that each mission is shown separately. Considering only the inflight period, the difference between the net caloric intake and the energy utilization curves is diminished for each longer mission. This was a result of increased caloric intake (per kg of BWGT). These differences, averaged over the inflight period are -448 kcal/day, -360 kcal/day, and +23 kcal/day for the 28-day, 59-day and 84-day missions respectively; (a negative sign indicates a dietary deficiency whereby tissue is catabolized, and a positive sign indicates a dietary excess whereby tissue is stored).

F.5.1.4 Estimates of Inflight Caloric and Exercise Requirements to Prevent Loss of Body Weight. After completing the above calculations it was possible to undertake regression analyses of the type described by Whittle [48] in attempts to estimate the caloric and exer-

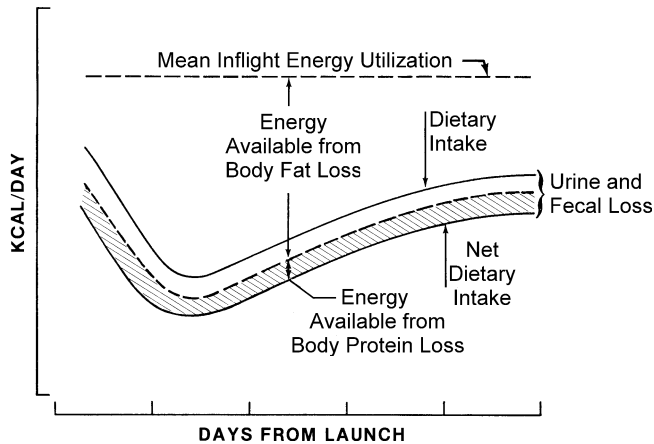


Figure F-5. Estimation of tissue loss from energy balance components. This figure is an idealized version of Fig. 4-23.

cise requirements that would maintain preflight body weight during the inflight phase. For these analyses a regression equation was derived and employed:

$$\Delta M / \Delta T = C \times (E_O - E_R) \quad (39)$$

where ΔM = change in body mass, body fat, or body protein (gm/kg BWGT) over an inflight time interval, ΔT

(days), E_O = observed energy intake from food (kcal/d/kg BWGT) or observed energy expenditures for exercise (kcal/d/kg BWGT), and E_R = energy required from food at which no change in body mass or body fat occurs (kcal/d/kg BWGT) or energy required for exercise at which no change in body mass or body protein occurs (kcal/d/kg BWGT).

Using Eq. (39) both caloric intake and exercise energy expenditures could be separately correlated with the average rate of body mass loss ($\Delta M / \Delta T$). In addition, caloric intake could be correlated with body fat assuming that an adequate diet would prevent loss of body fat. Similarly, exercise could be correlated with body protein on the assumption that an adequate exercise level would prevent the loss of body protein. The introduction of the term $\Delta M / \Delta T$ allows us to account for the effect of different mission lengths. Two sets of regression analysis were performed: a) using data for the entire mission, and b) using data for only the first month of each flight (see Table F-30).

F.5.2 Supplementary Data for Energy Balance Analysis

In Chapter 4.6 the results from the body composition and energy balance analysis are presented as mean values for each of the three Skylab missions. Tables F-24 to F-30 are referred to in Chapter 4.6, and show the corresponding results for each crewman. Figures F-7 to F-10 are an alternate method of viewing the daily estimated changes of body weight, body water, body protein, and body fat that are also illustrated in Fig. 4-28.

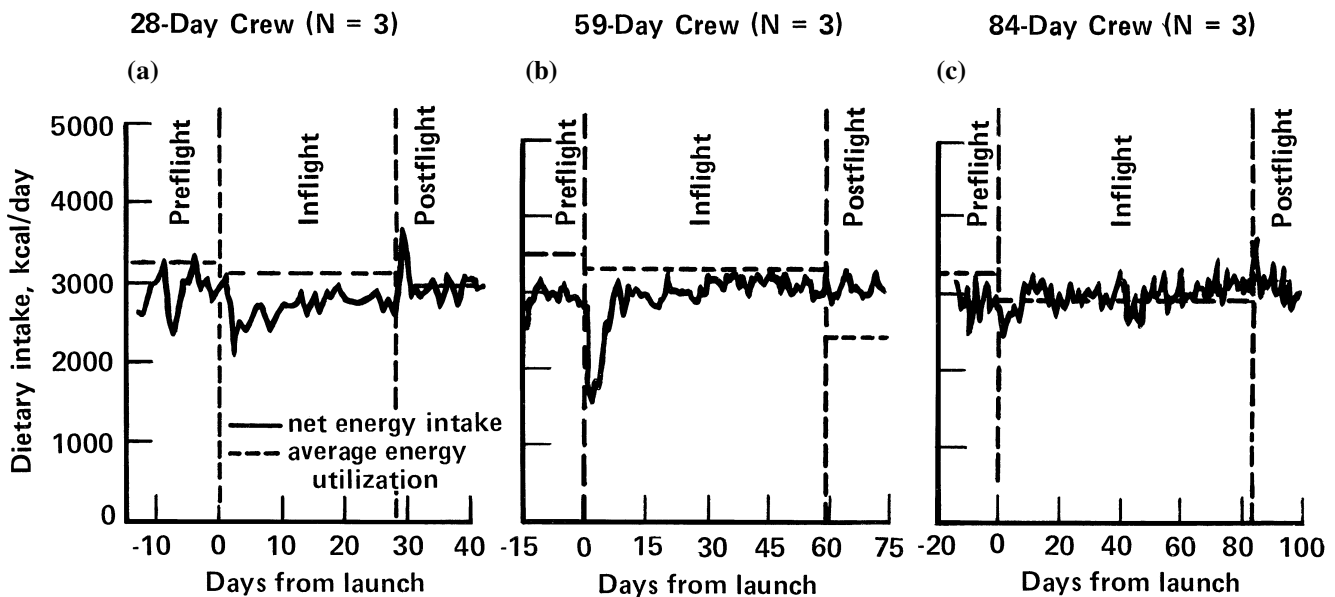


Figure F-6. Net food intake for each of the three Skylab missions ($N=3$). The difference between net energy intake (solid line) and average energy utilization (horizontal dashed line) represents the energy content of lost tissue, ΔTIS . Inflight values are: (a) 28-day mission $\Delta TIS = -448$ Kcal/day; (b) 59-day mission, $\Delta TIS = -360$ Kcal/day; (c) 84-day mission, $\Delta TIS = +23$ Kcal/day.

Table F-22. Methods for Computing Terms in Body Composition Equations

Quantity	Symbol	Method of Computation
Change in Body Mass, gm	$\Delta \overline{BWGT}$ and $\Delta BWGT$	Direct body mass/weight measurements
Change in Body Water, gm	$\Delta \overline{TBW}$ ΔTBW	Isotope dilution (tritium) method performed before and after flight Solve Equation (37) for ΔTBW
Change in Body Protein, gm	ΔPRO and $\Delta \overline{PRO}$	Nitrogen balance: $\Delta PRO = 6.25 \times N_{BAL} = 6.25 \times (N_{diet} - N_{urine} - N_{feces})$
Change in Body Fat, gm	$\Delta \overline{FAT}$ ΔFAT	Solve Equation (37) for $\Delta \overline{FAT}$ $\Delta FAT = -E_{fat} / 9.461$
Energy in Diet, kcal	E_{diet}	From stoichiometric relationships and known amounts of carbohydrate, fat, and protein in diet: $E_{diet} = 4.182 \times \text{diet carbohydrate (gm)}$ $+ 9.461 \times \text{diet fat (gm)}$ $+ 5.65 \times \text{diet protein (gm)}$
Energy in Urine, kcal	E_{urine}	From urine nitrogen: $E_{URINE} = 8.32 \times N_{urine} \text{ (gm)}$
Energy in Feces, kcal	E_{feces}	From bomb calorimetry
Energy in Catabolized Protein, kcal	E_{pro}	$E_{pro} = -5.65 \times PRO$
Energy in Catabolized Fat, kcal	$\overline{E}_{fat}$ E_{fat}	$E_{fat} = -9.461 \times \Delta \overline{FAT}$ Solve Equation (38) for E_{fat} using E_{util}^*
Net Energy Utilized, kcal	$\overline{E}_{util}^*$ E_{util}^*	From Equation (38) $E_{util}^* = \overline{E}_{util}^* / \text{days of mission phase}$

Note:

(1) Bar over symbol denotes overall mission phase mass losses or cumulative energy quantities summed over mission phase. Symbols without bars referred to daily values of that quantity. Δ = change in quantity, * denotes computed value.

(2) $\overline{E}_{diet}$, $\overline{E}_{urine}$, $\overline{E}_{feces}$, $\overline{E}_{pro}$, and $\Delta \overline{PRO}$ are computed by summing the daily amounts of each quantity (as defined above) over each mission phase; (i.e. $\overline{E}_{diet} = \sum E_{diet}$)

(3) Units are in gm or gm/day and kcal or kcal/day depending on the period for which they are computed.

Table F-23. Net Utilization (E_{util}^*) [kcal/day]

Subject	Preflight	Inflight	Postflight
28-day mission			
1	2737	2861	3493
2	3522	3572	2729
3	3448	2969	2706
59-day mission			
4	3037	3049	1485
5	3354	3170	2248
6	3994	3678	3633
84-day mission			
7	2879	2842	3306
8	3130	2973	2833
9	3773	3031	3322
Mean ±SD	3319 +414	3127 +300	2862 +682

Table F-24. Tissue Components of Body Mass That Were Lost During the Inflight Phase [gm]

Mission	Crewmember	ΔBody Weight	ΔTotal Body Water	ΔTissue Solids	ΔProtein	ΔFat
28-day	1	-1100	-405	-695	-170	-52
	2	-2700	-180	-2520	-390	-231
	3	-3200	-2090	-1110	-300	-81
	Mean ±SD	-2330 ±1100	-890 ±1080	-1440 ±960	-290 ±110	-115 ±85
59-day	4	-3900	-1395	-2535	-365	-217
	5	-4200	+125	-3725	-285	-343
	6	-4200	-3345	-855	-295	-56
	Mean ±SD	-3900 ±300	-1530 ±1740	-2370 ±1440	-320 ±40	-205 ±144
84-day	7	0	-770	+770	-650	+142
	8	-1400	-615	-785	-355	-42
	9	-1400	-1600	+200	-30	+23
	Mean ±SD	-930 ±810	-995 ±530	+62 ±790	-350 ±310	+41 ±93
Skylab Mean ±SD		-2390 ±1460	-1140 ±1090	-1250 ±1425	-315 ±170	-93 ±144

*Time period considered is from morning of launch (one-g) to morning of recovery (zero-g)

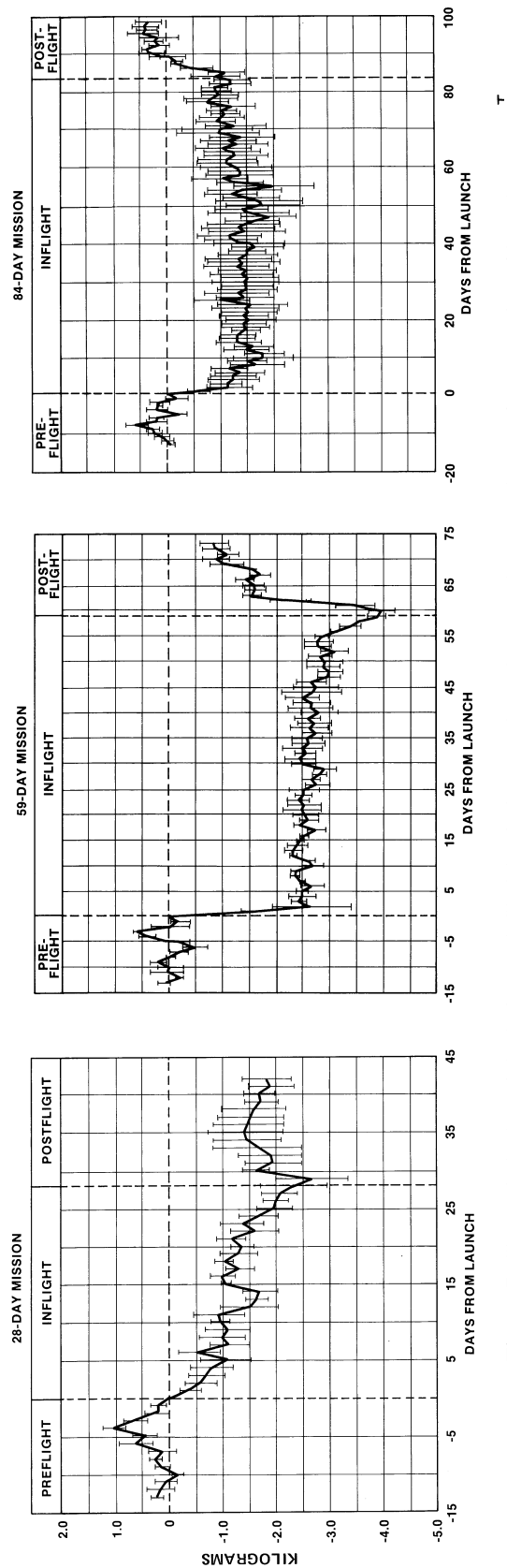


Figure 7. Change in body weight during each Skylab mission ($n = 3$). Values are shown as changes from morning of launch.

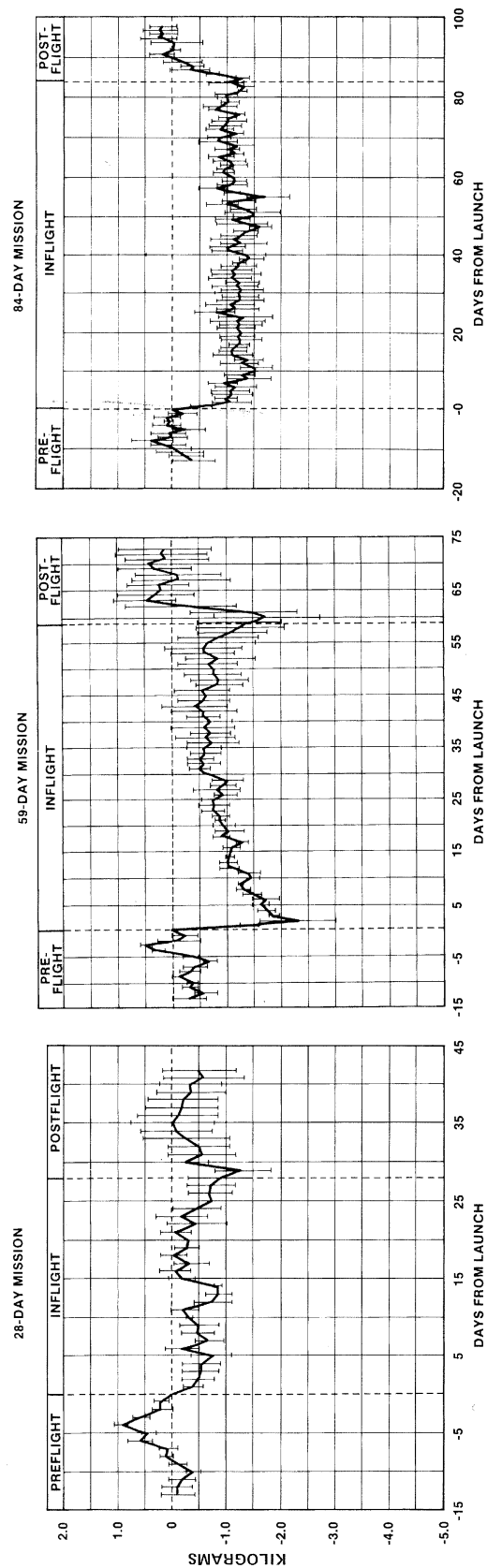


Figure 8. Change in body water during each Skylab mission ($n = 3$). Values are shown as changes from morning of launch.

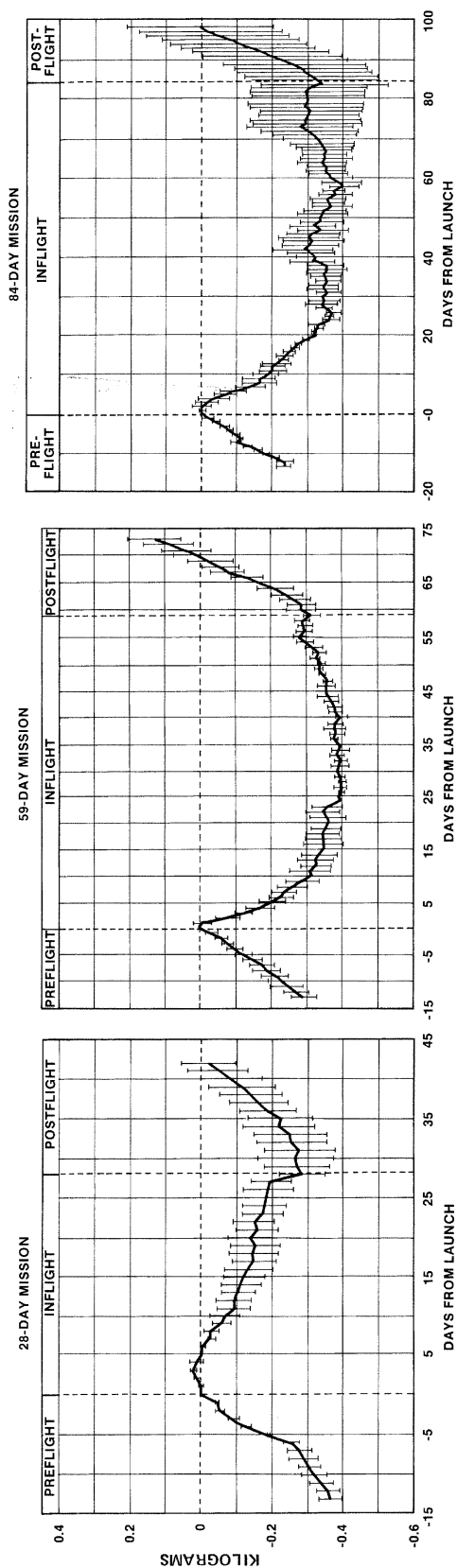


Figure 9. Change in body protein during each Skylab mission ($n = 3$). Values are shown as changes from morning of launch.

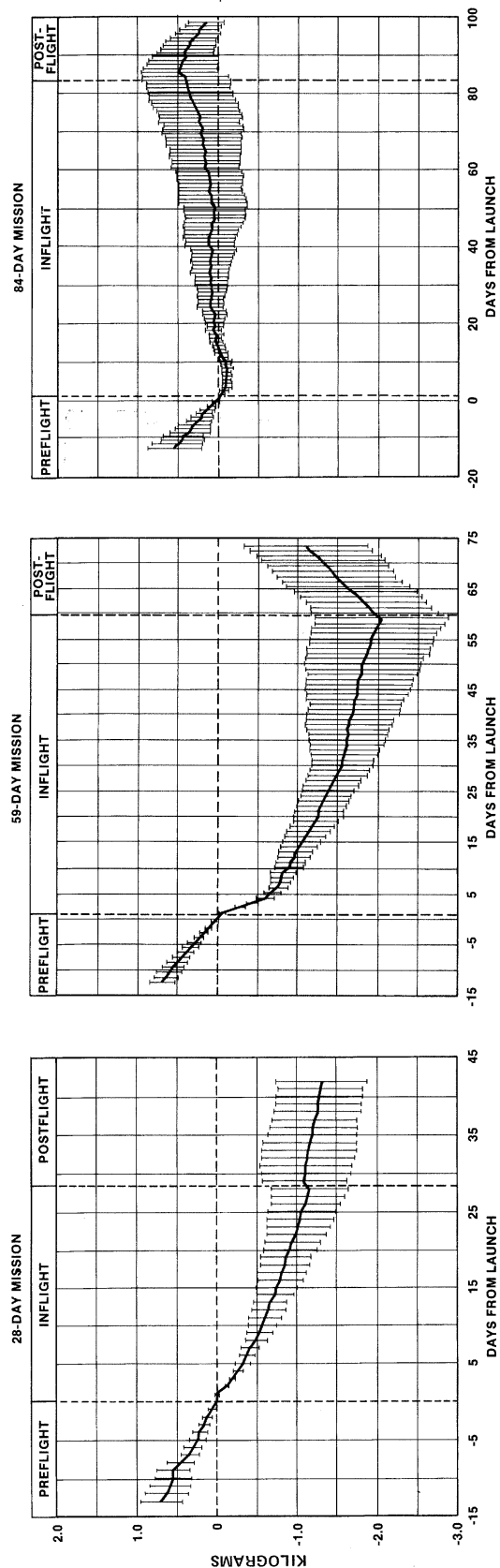


Figure 10. Change in body fat during each Skylab mission ($n = 3$). Values are shown as changes from morning of launch.

Table F-25. Changes of Body Weight/Mass and Body Water Before and After Skylab Missions [Kg]

Crewman	Body Weight			Total Body Water		
	Preflight Mean	$\Delta_1^{(a)}$	$\Delta_2^{(b)}$	Preflight Mean	Δ_1	Δ_2
1	62.21	-2.0	-1.1	41.55	-0.75	-0.41
2	77.89	-3.6	-2.7	48.80	-0.80	-0.18
3	80.18	-4.2	-3.2	52.15	-2.15	-2.09
4	68.56	-4.0	-3.9	42.50	-0.60	-1.37
5	61.82	-3.1	-3.6	39.10	+0.50	+0.12
6	88.01	-3.9	-4.2	53.60	-1.70	-3.34
7	67.75	+0.1	0	41.85	-0.85	-0.77
8	71.51	-2.9	-1.4	45.40	-0.50	-0.62
9	67.60	-1.5	-1.4	45.65	-0.55	-1.60
Mean	71.73	-2.8	-2.4	45.62	-0.82	-1.14
$\pm$SD	± 8.72	± 1.4	± 1.5	± 5.00	± 0.75	± 1.09

(a) Δ_1 = Change from preflight mean to first shipboard measurement at recovery. Body mass was measured within several hours of recovery. Body water was measured on first or second day of recovery.

(b) Δ_2 = Change from preflight mean to morning of day of recovery (a zero-g state). Total body water changes estimated by correcting for water intake and excretion between recovery a.m. and first shipboard measurement.

Table F-26. Components of Energy Balance During Skylab Preflight Phase [kcal/d]

Energy Balance Component	Crewman								
	1	2	3	4	5	6	7	8	9
Total Diet ^a	2916	3166	3175	2851	2996	4214	3224	3149	3269
Excreta:									
Urine ^b	106	105	110	93	108	166	116	121	135
Feces	142	158	143	110	125	171	160	146	129
Total Excreta	248	263	253	203	233	337	276	267	264
Body Tissue Loss:									
Protein ^{c,e}	-104	-110	-106	-108	-121	-143	-117	-78	-98
Fat ^d	173	730	632	497	712	260	47	326	866
Total Tissue ^e	69	620	526	389	591	117	-70	248	768
Net Energy Utilization ^f	2737	3523	3448	3037	3354	3994	2878	3130	3773

a) Diet (kcal/day) = 4.182 diet carbohydrates (gm/d) + 9.461 x diet fat (gm/d) + 5.65 x protein (gm/d)

b) Urine energy = 8.32 x urine nitrogen (gm/d)

c) Energy from protein tissue loss = 5.65 kcal/gm

d) Energy from fat tissue lost = 9.461 kcal/gm

e) Minus sign denotes a gain of body tissue

f) Net energy utilization = Diet Excreta + Energy from body tissue lost

Table F-27. Components of Energy Balance During Skylab Inflight Phase [kcal/d]

Energy Balance Component	Crewman								
	1	2	3	4	5	6	7	8	9
Total Diet ^a	2888	3031	2873	2888	2860	3927	3271	3149	3361
Excreta:									
Urine ^b	132	150	135	111	138	186	152	146	160
Feces	106	107	104	111	131	181	161	102	146
Total Excreta	238	257	239	222	269	367	313	247	306
Body Tissue Loss:									
Protein ^c	34	79	60	35	28	28	44	24	2
Fat ^{d,e}	178	720	274	348	551	90	-160	48	-26
Total Tissue ^e	212	798	334	383	579	118	-116	72	-24
Net Energy Utilization ^f	2861	3572	2968	3049	3170	3678	2842	2974	3031

(See footnotes for Table F-26)

Table F-28. Energy Balance Terms Related to Diet^{a,d}

Crewman	Days Observed		CHO (gm)		FAT (gm)		PRO (gm)		E _{diet} (kcal) ^b (calculated)		E _{diet} (kcal) ^c (bomb)	
	Pre	Inf	Pre	Inf	Pre	Inf	Pre	Inf	Pre	Inf	Pre	Inf
1	30	28	319	376	105	79	105	101	2916	2888	2632	2498
2	30	28	382	402	101	80	108	105	3166	3031	2901	2580
3	30	28	364	394	109	72	110	97	3175	2873	2881	2497
4	20	59	331	426	98	66	95	95	2851	2888	2561	2586
5	20	59	315	368	110	76	112	107	2996	2860	2688	2511
6	20	59	490	565	132	77	163	148	4214	3927	3716	3488
7	26	84	363	398	108	100	121	118	3224	3271	3152	3202
8	26	84	358	395	108	92	113	111	3149	3149	3088	3085
9	26	84	348	385	116	109	127	128	3269	3361	3194	3285
Skylab Mean ±SD			363 52	412 60	110 10	83 14	117 19	111 18	3218 400	3139 349	2979 358	2859 400

a) CHO = dietary carbohydrates; FAT = dietary fat; PRO = dietary protein

b) E_{DIET} (Calculated) = total energy derived from diet = (4.182)CHO + (9.461) FAT + (5.65) PRO

c) E_{DIET} (Bomb) = total of diet measured by bomb calorimetry. (The number of samples used to obtain E_{DIET} (Bomb) was somewhat less than that used to compute E_{DIET} (Calculated).

d) Regression coefficients for E_{DIET} (Calc) vs. E_{DIET} (Bomb): r = 0.93 (Preflight), r = 0.91 (Inflight); ratio Inflight/Preflight for E_{DIET} (Calc) = 0.975, for E_{DIET} (Bomb) = 0.96.

Table F-29. Energy Available versus Energy Utilized [kcal/day-kg BWGT]

Mission	Subject	Ediet		Ediet net		Eutil	
		Pre	Inf	Pre	Inf	Pre	Inf
28-day	1	46.9	46.4	42.9	42.6	44.0	46.0
	2	40.7	38.9	37.3	35.6	45.2	45.9
	3	39.6	35.8	36.4	32.9	43.0	37.0
	Mean	44.7	40.4	38.9	37.0	44.1	43.0
	±SD	±4.5	±5.5	±3.5	±5.0	±1.1	±5.2
59-day	4	41.6	42.1	38.6	38.9	44.3	44.5
	5	48.5	46.3	44.7	41.9	54.3	51.3
	6	47.9	44.6	44.1	40.5	45.4	41.8
	Mean	46.0	44.3	42.5	40.4	47.6	45.9
	±SD	3.8	±2.1	±3.4	±1.5	±5.4	±4.9
84-day	7	47.6	48.3	43.5	43.7	42.5	42.0
	8	44.0	44.0	40.3	40.6	43.8	41.6
	9	48.4	49.7	44.5	45.2	55.8	44.8
	Mean	46.7	47.3	44.7	43.2	47.3	42.8
	±SD	±2.3	±3.0	±2.9	±2.3	±7.3	±1.7
Skylab Mean		45.0	44.0	41.4	40.2	46.4	43.9
±SD		±3.6	±4.5	±3.3	±3.9	±4.9	±4.0

a) E_{diet} = total energy available from dietary carbohydrates, fats, proteins (calculated)

b) $E_{\text{diet net}}$ = E_{diet} – energy in urine and feces

c) E_{util} = energy utilized = $E_{\text{diet net}}$ + energy obtained from protein and fat catabolism.

Table F-30. Diet, Exercise and Tissue Weight Change Data Used for Regression Analysis*

Subject	Caloric Intake (kcal/d-kg)	Average Daily Exercise Work (kcal/d-kg)**	ΔBWGT	ΔFAT (gm/d-kg)	ΔPRO
1	46.4	2.35	-0.632	-0.302	-0.0966
2	38.9	1.35	-1.238	-0.977	-0.179
3	35.8	1.62	-1.426	-0.361	-0.133
4	42.1	3.68	-0.964	-0.537	-0.090
5	46.3	3.83	-0.987	-0.941	-0.0788
6	44.6	4.84	-0.809	-0.108	-0.0572
7	48.2	4.00	0	+0.249	-0.114
8	44.0	5.09	-0.233	-0.071	-0.0594
9	49.7	4.76	-0.247	+0.041	-0.0855

* These data used in regression analysis of Table 4-25

** Derived from Michel and co-workers [49] by dividing useful bicycle work by 22% efficiency. To compute total exercise performed over the mission in watt-minute (W-min), multiply value in table for average daily exercise work (kcal/d-dg) by BWGT x 70 W-min/kcal x 0.22 x N, where N is the number of inflight days in the Skylab Mission.

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Appendix G

Accomplishments and Recommendations

G.1 Accomplishments of the Systems Analysis Project

The investigative areas will be grouped, for purposes of summation, into four categories: (a) fluid, electrolyte, and renal function; (b) cardiovascular function; (c) hematology; and, (d) musculoskeletal function and body composition. The major systems analysis accomplishments for each area are summarized in Table G-1. The results from these studies have led to an interpretation of the spaceflight findings that are summarized in Chapter 10. In addition to the emphasis on interpreting physiological changes during spaceflight, this project has produced a number of accomplishments regarding the technological tools and information systems which have been indispensable to achieving its overall goals. These technology accomplishments are described in Chapter 3 and summarized in Table 10-1.

G.2 Recommendations for Model and Simulation Improvements

Throughout this book recommendations have been implicitly or explicitly made for improving the mathematical models or examining new model applications. For convenience, these recommendations have been assembled below. Although the recommendations, for the most part, are highly summarized, details can be found in the appropriate parts of the book.

G.2.1 Recommendations for Guyton Model

G.2.1.1 Areas Identified for Future Model Improvements

- a) Develop a capability for simulating acid-base balance. This would involve modification of the renal system, the buffering system, and the respiratory system.
- b) Formulation of upper body circulatory elements representing collapsed veins in modified Guyton model.
- c) Validate Guyton model for LBNP simulation.
- d) Develop an advanced renal subsystem model including peritubular capillary effects, third factor effects, factors influencing intrarenal blood flow, and the effect of calcium on electrolyte excretion.
- e) Hormonal regulation should be updated to reflect current knowledge, especially with regard to multiple and competitive influences, and identification of the different mechanisms which dominate short-term vs. long-term control.
- f) Experimental measurements of hormone levels are often obtained from urine samples. Existing models have the capability only of predicting plasma concentrations to hormones. It is recommended that a study be conducted to determine feasibility of adding hormone renal excretion capability to existing models.

- g) Develop a new upright reference position for the model in addition to its present supine reference.
- h) Test a more natural means of simulating weightlessness by starting with an upright reference control position and then removing the gravity effects from the reference model.

G.2.1.2 Recommendations for Additional Simulation Studies

- a) Now that a reasonable simulation of spaceflight has been accomplished, it is important to make a detailed analysis of the mechanisms that control specific responses. In most cases, redundant feedback pathways exist. Determine which pathways predominate.
- b) Determine the basic differences between simulations of bedrest, immersion, head-down tilt and spaceflight. What is the appropriate model stimulus for each of these conditions?
- c) Use models to create and evaluate circulatory indices of performance, both inflight and postflight. These algorithms should provide a simple measure of circulatory status.
- d) The new leg compartments of the modified Guyton model require additional validation studies, especially for characterization of resistance elements, capacitance elements and capillary exchange.

G.2.1.3 Recommendations for an Improved Simulation of Postural Studies. The ability to simulate postural maneuvers, both head-up and head-down, has proved to be a complex endeavor. Chapters 9.3.2, 9.6.3 and Appendix C.1 have described the model modifications that provided basic structural and mechanistic capabilities to respond to the gravitational vector. Appendix C.2 delineated a set of recommendations for an improved orthostatic model. Here we would like to mention several other recommendations for improving the head-down tilt simulation and, by extension, spaceflight simulation.

- a) **Addition of a Head Compartment.** The model at present does not contain a separate vascular compartment above the heart level and does not exhibit collapsed veins in the erect posture, nor refilling and fluid storage during hypogravity and anti-orthostasis. Reports from astronauts typically include symptoms of head fullness, head tissue puffiness and neck vein distention during prolonged hypogravity. Thus, the model may have to be altered in some manner to reproduce these effects. The most feasible approach is the addition of collapsible veins in a separate cephalic compartment.
- b) **Improved Resistance to Flow in Legs.** The leg resistance elements (both pre- and post-capillary) are

Table G-1. Accomplishments of Systems Analysis Study

Fluid-Electrolyte Regulation	
·	Modification of the Guyton model (circulatory, fluid and electrolyte regulation) to include gravity-dependent elements, leg compartments, and improvements in the erythropoietic, renal, autonomic and renin-angiotensin subsystems
·	Validation of the modified Guyton model for fluid-loading, hemorrhage, and postural-change studies
·	Simulation analysis of the fluid-electrolyte response to hypogravic studies including water immersion, head-down tilt, bedrest, and spaceflight
·	Analysis of evaporative water loss in the hypobaric, reduced-convective-flow environment of Skylab using metabolic balance analysis and the modified Stolwijk thermoregulatory model
·	Metabolic balance analysis of water, sodium, potassium, calcium, nitrogen, and magnesium including Skylab nine-man composite summaries of dietary intake, renal excretion, and sweat losses
·	Composite time profiles of the nine-man Skylab mean responses for plasma and urinary electrolytes, hormones, and total body changes in water, sodium, and potassium
·	Analysis of fluid-electrolyte regulatory feedback mechanisms involved in acute and long-term responses to weightlessness
·	Interpretation of all Skylab data related to disturbances in body fluid volumes and their composition including a description of the fluid-electrolyte status of the Skylab crewman and an integrated hypothesis to explain the behavior of renal-regulating hormones
·	Major support of bedrest and Spacelab flight experiment proposals
Cardiovascular Regulation	
·	Development of a new pulsatile cardiovascular system model
·	Validation of cardiovascular model for exercise, tilt, lower body negative pressure (LBNP) in one-g, and centrifugation.
·	Modification of the pulsatile model to include elements responsive to hypoxia and hypercapnia
·	Modification of the respiratory model of Grodins to include the capability to respond to exercise
·	Simulations of the exercise response using the combined thermoregulatory, respiratory, and cardiovascular subsystem models of the whole-body algorithm
·	Simulation analysis of spaceflight LBNP and postflight exercise (supine and sitting) using the pulsatile model
·	Simulation of disturbances in the circulatory system during short-term water immersion and head-down tilt and long-term bedrest and spaceflight using the modified Guyton model and the whole-body algorithm
·	Composite time profiles of the nine-man Skylab mean responses to LBNP
·	Sensitivity analyses for effects of blood loss and venous compliance changes on tilt and LBNP responses
·	Analysis to examine possible changes in inflight baroreceptor sensitivity
·	Analysis of mechanical and metabolic efficiencies and other performance indices during bicycle ergometry flight experiments
·	Modification of the pulsatile cardiovascular model to include physical training (conditioning) effects and evaluation of these hypotheses against Skylab exercise data
·	Formulation and evaluation of hypotheses to account for decreased orthostatic tolerance and decreased aerobic capacity during inflight and postflight phases
·	Analysis of cardiovascular response during the high-g of Shuttle reentry with reduced blood volume including identifying thresholds for visual grayout
·	Utilization of models to develop countermeasures for orthostatic intolerance during and after Shuttle reentry including fluid loading and leg pressure garments
·	Support of flight experiment proposal for advanced cardiopulmonary studies
Hematology	
·	Development of new models for control of erythropoiesis in the human and the mouse
·	Simulation analysis of hematological responses to altitude hypoxia and descent, red cell infusions, bedrest, water-restricted dehydration, and spaceflight
·	Collaboration in a research program that examined suppressed erythropoiesis in dehydrated mice
·	Analysis of all spaceflight and ground-based studies related to loss of red cell mass during hypogravity
·	Formulation and tentative evaluation of candidate hypotheses to explain the “anemia” of spaceflight with particular emphasis on explaining the differences in red cell loss among crewmen
·	Simulations of clinical syndromes (anemias, polycythemias, and Hb abnormalities) and partial development of a teaching model of erythropoiesis regulation
·	Support of a Shuttle Spacelab experiment by predicting expected results, critical measurements, frequency of measurements, and effect of blood sampling on the hematological response to microgravity.
Musculoskeletal System and Body Composition	
·	Metabolic mass, water and energy balance analyses including a new method for estimating cumulative total body changes (water, fat, protein, electrolytes) as a function of flight duration
·	Analysis of body composition changes (lean body mass and fat) based on body water, body potassium, nitrogen-potassium balance, and body density data
·	Analysis of inflight requirements for exercise and diet
·	Interpretation of components of body weight loss based on fluid and energy regulation and gravity unloading
·	Design and development of a new model for calcium regulation, including validation studies of bedrest and spaceflight
·	Support of a flight experiment proposal for advanced calcium regulation studies

presently modeled in a similar fashion as the upper body. They both account for passive distention and collapse, autonomic influence, angiotensin, vasoconstriction, and viscosity effects. However, there are undoubtedly some fundamental differences between the lower and upper body resistance capacitance and capillary elements. Mechanisms which are currently under consideration for inclusion in the lower extremity elements include those due to: a) locally produced vasoconstriction (myogenic), b) enhanced autonomic effects, and c) chemical effects (i.e., catecholemines).

- c) **Improved Model of Collapsible Veins.** Rather than model the veins according to the linearization of the compliance curve shown in Fig. 9-32, an alternative approach is to allow the veins to completely collapse at any point where transmural pressure approaches zero. This produces a “waterfall” effect where flow is independent of pressure drop. When pressure falls to zero, the resulting cessation of flow causes pressure to rise and the vessel reopens. This approach would likely resolve some current problems encountered with the model at the more extreme tilt angles and improve its stability.
- d) **Differentiation of Transcapillary Filtration.** Simulations that are more realistic can be achieved by improving the description of the differential behavior of upper and lower body capillary filtration and the factors which influence this process. We believe that capillary beds in the legs are especially suited to withstand elevated hydrostatic loads and the model should reflect this notion.

G.2.2 Erythropoiesis Regulatory Model

G.2.2.1 Improvements in Model Design. Many factors have been discussed that are known to affect erythropoiesis, but have not been included in the proposed model. This study has resulted in several specific recommendations for improvements in the model and suggestions for related models.

- a) The current model does not include a description of the kinetics of stem cell differentiation in the bone marrow. Such a description would represent the red cell proliferation and maturation cycle from multipotential cells to denucleated red cells. The model, thus modified, would be able to predict the reticulocyte index and have an improved characteristics of the bone marrow transit delay, among other benefits.
- b) The current model does not include extrarenal erythropoietin production or extramedullary erythropoiesis.
- c) The model should have an updated description of the renal sensor site(s), including the determination of oxygen tension and factors effecting erythropoietin production.
- d) The kinetics of erythropoietin formation should include descriptions of “pro-Ep-plasma factors” and “Ep inhibitors”.
- e) Account for the effect of certain factors on erythropoietin that are not included in the current model, such as iron levels, hormones other than erythropoi-

etin (i.e., growth hormone), and neural stimulation, as well as inhibitors and activators of erythropoietin.

- f) The effects of blood viscosity and blood volume changes on blood flow and tissue oxygenation should be added to the model.
- g) Other factors that control oxygen transport are only currently included as fixed parameters. They could be added as variable elements. These factors include blood flow, capillary diffusivity, arterial oxygen tension, plasma volume, and oxygen-hemoglobin affinity.
- h) Include an explicit representation of the DPG effect on oxyhemoglobin affinity; consider implementing a self-regulating mechanism perhaps based on levels of tissue oxygenation

G.2.2.2 Simulation Studies with Improved Model

- a) Sensitivity analysis with parametric variation study of improved model
- b) Characterization of bedrest response as a function of different plasma volume time profiles and red cell destruction rates
- c) Reexamination of spaceflight data in light of model improvements and bedrest validation study.

G.2.2.3 Design and Develop Related Models

- a) Teaching model for hematological abnormalities
- b) Species-specific animal models for predicting results and integrating data for ground-based and Shuttle animal experiments
- c) Ferrokinetic models for iron uptake studies

G.2.3 Cardiovascular Model (LBNP and Exercise)

A number of recommendations for improvements in the short-term cardiovascular model were suggested by the simulations of LBNP and exercise discussed in Chapter 7.

- a) If the model is to be used for real-time simulations longer than a half hour it needs a more adequate representation of longer-term mechanisms including tissue filtration, hormonal regulation, baroreceptors adaptation and delayed vessel compliance (stress relaxation and reverse stress relaxation).
- b) The current model has a neural component that uses a single autonomic signal for controlling flow resistances, compartmental compliances, and cardiac contractions. This signal combines the effects of sympathetic and parasympathetic neural control. A superior model can be achieved by developing a dual autonomic controller containing separate elements for these functions.
- c) The current model is limited to the submaximal range of exercise. To enable the capability for maximal oxygen uptake tests, suggestions have been raised to improve cardiac reserve or cardiac filling representations in the model. Other areas should be examined that control arterial pressure and heart rate at intense levels of exercise.
- d) The model should be adapted to differentiate between levels of physical conditioning; i.e., to individualize the model.

- e) A more specific type of individualization is the notion that male and females responses to orthostatic intolerance are thought to be quite different after spaceflight. The model should be individualized for these simulations based on gender.
- f) An explicit representation of chemoreceptor stimulation should be included to enable the model to respond to changes in the content of inspired gases during exercise.
- g) Representation of whole leg compliance (as opposed to leg venous compliance) should be included in the model for comparison with gross leg compliance measurements during LBNP. Also, there is a need for introducing non-linear compliances for the leg veins modeled after the upper body veins.

G.2.4 Calcium Regulatory Model

The model of calcium regulation did not reach the same level of maturity in development and application as the other math models in our repertoire. On the other hand in the years since Skylab, the problem of calcium demineralization in space has assumed a much higher research priority. The initial effort should be to reproduce the best model currently published (see Chapter 8) and then to validate the various sections.

- a) Update the current NASA model to include all the features of the most recent model by Jaros and co-workers [Jaros GG, Guyton AC, Coleman TG, Ann. Biomed. Eng., 8:103-141, 1980].
- b) Modify the renal and intestinal subsystems so that they are able to reproduce the excreta findings from prolonged bedrest and spaceflight.
- c) Modify the hormonal regulation subsystems so that the behavior of the calcitropic hormones are in agreement with published data for a variety of stresses including bedrest.
- d) Include in the model a description of bone regulatory forces that control mineralization such as piezoelectric and mechanical stresses.
- e) The model will eventually need to include a much improved skeletal subsystem that is representative of the osteoblastic and osteoclastic processes.
- f) Application of the model should be directed toward the identification, development and design of countermeasures for ameliorating bone demineralization in spaceflight.

G.2.5 Whole-Body Algorithm (WBA)

G.2.5.1 General Recommendations. Some important general recommendations include the following:

- a) **Top-Down Design Approach.** As discussed in Chapter 10, there was general agreement that an advanced version of the Whole-Body Algorithm should be designed as a single integrated system, using a top-down approach. Such an approach would have the following characteristics: a) a unified programming language, b) a standard set of input-output specifications, c) a standard set of acceptable numerical inte-

gration methods, d) a unified documentation method, e) a minimum of redundancy, g) the ability to develop the subsystems independently, knowing that the final products will be compatible, and h) a strongly coupled set of unique subsystems. This is a more logical, realistic and natural approach.

A top down approach would eliminate the deficiencies in the current model of having multiple autonomic nervous systems or circulatory systems. Another problem with the current version is the weakly linked artificial boundary between "short-term subsystems" and "long-term subsystems". Thus, it is not realistic at present to simulate exercise for more than 30 minutes because the hormonal changes, stress relaxation changes, and autoregulation functions are not present in the short-term models.

Figure 2-2 illustrates one approach that incorporates both horizontal integration (different subsystems linked in parallel fashion) and vertical integration (a hierarchy of biochemical, cellular, tissue, and organ function). The organism level is the top link in the hierarchy; organs are connected to each other wherein each organ is assigned 5 layers – organ system, organ, tissue, cellular, biochemical. New versions of modules can be designed and substituted with a minimum of interfacing difficulties.

- b) **Need for a Common Control Center.** The real physiological system is composed of many regulating systems with a common control center (the central autonomic nervous system) and with many commonalities in the basic controlled system (similar fluid compartments, blood pathways, etc.). In contrast, the integration of several self-contained models results in different control centers and different descriptions of the controlled system. An advanced top-down approach should lead to a model that is much more like the real system. Unfortunately, the experimental observations upon which an advanced neural and biochemical control system must be designed, are scarce and in many cases, non-existent. Thus, new experiments must be designed and additional information must be collected before there is a solid basis with which to pursue such a unified control center. Examples of the deficiencies in the current WBA include lack of discrimination between sympathetic and parasympathetic control, lack of a lung stretch receptor reflex; lack of connection between autonomics and catecholamine release.

- c) **Validation Database Required.** Validating a large-scale system model such as the Whole-Body Algorithm (or its advanced successor) requires a physiological database that is as equally detailed and integrated. However, it was found that much of the needed data was lacking. One of the limitations of developing this type of model was in finding data sets that stretched across disciplinary boundaries so that a number of model subsystems could be validated at the same time, for the same stress, using data obtained from the same laboratory. It is interesting to note that some of the

most valuable data for validating the Whole-Body Algorithm came from laboratories engaged in both physiological research and modeling. Thus, this project has provided additional support for advocating a continuing interdisciplinary research program concerned with measuring whole-body responses to combinations of environmental and metabolic disturbances. Once a large-scale model is validated it should be capable of integrating large quantities of data such as that available for Skylab. There are admittedly few scientific projects in which such grandiose multi-disciplinary data collection occurs, but for those occasions, large-scale models become a significant tool for data analysis and interpretation.

- d) **Central Repository Concept.** An advanced “digital human” would require the collaboration of researchers in many laboratories over a wide geographic area. A nationwide time-sharing system would allow contributors to affix their subsystem models into the larger model. A central committee of experts would administer the system, select the best models of each type for inclusion in the system, establish standards for programming language and interfaces, prepare documentation, and approve modifications. This approach would function as a central repository and communication system and could evolve into an important national resource contributing to the development and application of physiological modeling.
- e) **Test the Full Capability of the Existing Model.** The WBA, as developed in this project, is very versatile, capable of simulating many different conditions. Limited resources permitted the examination of only a few specific conditions, all related to spaceflight. Thus, we did not address the many possibilities for other important applications. Thus, even before developing a more advanced model, it may be useful to put the current model to more complete use. For example, the three short-term models of the WBA could operate independently of the long-term model. This short-term group was a significant accomplishment in itself especially for its ability to simulate such common conditions as the exercise response, or exercise combined with an environmental stress as hypoxia. Each of these three short-term subsystem models (thermoregulatory, circulatory, and respiratory) were originally designed to simulate exercise, but the capabilities for responding to combined stresses have never been thoroughly investigated.
- f) **Individualized Models.** The eventual goal of these systems analysis efforts is to provide a capability to predict normal responses for individual subjects in the spaceflight environment. Thus, the models, including the WBA, could be “tuned” for each individual crewmember.

G.2.5.2 Specific Recommendations for More Advanced Studies with the WBA

- a) Improve and integrate the autonomic control system for both the cardiovascular and respiratory subsystems.

This is particularly needed for central and local integrated autonomic control for all stresses with the same formulation or representation. Better discrimination between sympathetic and parasympathetic control, lung stretch receptor reflex, autonomic control affecting catecholamine release from the adrenal medulla, different representation of similar controllers in each subsystem, and resetting or sensitivity changes in receptors and control centers are other areas which need investigation.

- b) Improve definition of the long-term/short-term interface and improvements in the cardiovascular subsystem are needed to better simulate the gray area between short-term and long-term changes (particularly around one hour of simulated time). This is particularly needed to simulate the plasma filtration, stress relaxation changes, autoregulation, and many hormonal changes which do occur following many short term stresses (such as head-up tilt in 1-g).
- c) Improve representation and/or validation of long-term adaptation/acclimatization (particularly since this is an area of interest in spaceflight) to long-term stress. Examples of long-term stresses that could be examined with complex integrated models include the long-term effects of thermal stress, hypoxia, and exercise. Data from people living in hot and cold climates and at high altitudes may provide a starting place for such study. Very little modeling activity has been conducted for these purposes.
- d) Improve respiratory-thermoregulatory subsystem interface (other than through the cardiovascular subsystem) to improve simulation of respiratory heat losses and thermal influences on respiratory control.
- e) Improve the flexibility for simulating different population responses to stress such as the effect of training/conditioning, age, and gender.
- f) Continue validation, particularly in the areas of transient responses (both on and off) to exercise and thermal stress and multiple stresses for which data are available. Examples of some of the combined short-term stresses to which the WBA could be fruitfully applied includes: a) exercise + hypoxia, b) exercise + hypercapnia, c) exercise + thermal, d) exercise + dehydration, e) tilt + hypoxia, f) tilt + thermal stress, g) hypoxia + hypercapnia, h) exercise + hypoxia + thermal stress. Further testing of bedrest hypotheses is also needed.
- g) Changes in evaporative water loss have long-term effects on renal excretion. Validate the thermoregulatory model for spaceflight evaporative water loss and utilize Whole-Body Algorithm to pass this information to long-term model subsystem.
- h) The addition of vestibular and musculoskeletal subsystems to an advanced whole-body model should be considered. After a long-term spaceflight, stresses such as orthostatic intolerance is not only a result of circulatory problems, but muscular and vestibular activity as well. This would provide the capability, not present in the current version, of altering otolith/propriocep-

tor function or tissue loading functions.

- i) The degradation of hard tissues is not currently being considered in the WBA. The accompanying loss of calcium is a disturbing problem for long-term spaceflight. Excess calcium in the body fluids also produces alterations in hormone levels and renal function. These effects should be accounted for in more advanced models.

It appears from the foregoing that this development of a whole-body algorithm is not complete and probably never will be complete. It is, however, a very good beginning and this study has not only produced a very useful tool, but has pointed the way for future work in this area.

G.3 Recommendations for Experimental Studies

The ultimate value of a model lies in the degree to which understanding of the system under study is enhanced. However, any worthwhile scientific endeavor should not only answer questions, but to suggest new ones. Thus, a number of testable hypotheses were formulated during the modeling process. All these items are legitimate research issues suitable for experimental study. Some have been addressed by others in varying levels of detail. In many cases, the model has provided a scientific rationale for an alternative hypothesis.

G.3.1 Fluid-Electrolyte and Circulatory Regulation

- a) Regarding fluids shifted headward during hypogravic stress:
 - i. does excess fluid remain in the upper body throughout prolonged zero-g stress?;
 - ii. is this fluid stored primarily in circulatory compartments or do extravascular spaces accept a significant portion?;
 - iii. does cephalad fluid shifts merely fill previously collapsed veins in head and neck or does the volume increase beyond the zone of free distensibility?;
 - iv. how much storage volume does this represent?;
 - v. does central hypervolemia return to normal during prolonged periods of spaceflight as predicted by the model or does it persist as suggested by water immersion experiments.
- b) During one-g postural change, what is the extent of fluid movement between plasma and interstitium? Is there a significant amount of plasma refilling during standing due to reabsorption from the upper body's interstitial reservoir?
- c) What is the origin of fluids which disappear from legs during first several days after launch (i. e., blood, interstitial, intracellular). Also, why is the amount of fluid shifted from legs during weightlessness so much greater than that associated with postural changes in one-g?
- d) Recent experiments onboard Spacelab failed to reveal a diuresis. There may still be an issue regarding the voluntary withholding of fluids by astronauts the

first day of flight as well as confounding influences of reclining for long-wait periods on the launch pad. The model suggests that a zero-g diuresis and natriuresis cannot be entirely suppressed. A definitive test for a diuresis may have to await the availability of a human centrifuge aboard Space Station. This would allow a subject to adjust to 1-g and then suddenly be exposed to microgravity.

- e) Test the hypothesis, predicted by the model, that normally hydrated subjects in spaceflight will exhibit a normal diuresis when challenged by a fluid load. This study should be conducted well after the initial onset of weightlessness and with a statistically significant population.
- f) One explanation for the fall in plasma volume during the onset of hypogravity, in the absence of a diuresis, is that transcapillary filtration increases and causes an equivalent loss of plasma volume. The model supports this possibility but suggests that the effects are transitory, and that interstitial fluid will eventually return to normal. Lymph flow and plasma colloidal oncotic pressure are factors to consider in this normalization. Verify the details of transcapillary filtration during spaceflight, including the possibility of increased protein permeability, as suggested by the model. Also, one should attempt to differentiate between the transcapillary Starling forces in the legs and above the heart during hypogravity maneuvers.
- g) What is the etiology of hyponatremia and its effect on fluid-electrolyte regulating hormones. What is the contribution of natriuretic hormone in producing hyponatremia and in opposing aldosterone's effect on sodium excretion.
- h) Confirm the analysis which predicts reduced evaporative water and sweat electrolyte losses (hidromieosis) during prolonged spaceflight.
- i) Confirm the model predictions of the effect of potassium release from cells as a factor controlling aldosterone.
- j) What are the long-term adaptive mechanisms that are involved in circulatory and renal adaptation to prolonged spaceflight? That is, measurements are needed of central venous pressure, cardiac output, leg blood flow, renal flow, glomerular filtration rate, etc.
- k) Additional inflight data is necessary during the first several hours following launch. Particular data that is required includes: urine flow; hematocrit; plasma electrolytes; levels of aldosterone, ADH, and angiotensin; fluid and electrolyte intake; sweat components; and circulatory indices.
- l) Test the hypothesis, predicted by the model, that the renal-regulation hormones, angiotensin, aldosterone and ADH, are governed early in flight by pressure-volume regulating factors and later in flight by plasma electrolyte regulation.
- m) Conduct a meaningful assessment of renal function in microgravity using renal stress tests in humans (fluid loading, salt loading, dehydration) and animals (glomerular and tubular dynamics using micropunc-

ture techniques).

- n) Carefully controlled experiments are required to study metabolic rates, energy utilization, and thermoregulation (i.e., evaporative water loss), during prolonged spaceflight.

G.3.2 Cardiovascular

- a) There is currently an inadequate description of the circulatory mechanisms that accommodate redistributed blood volume over prolonged periods of weightlessness. These processes include venous stress relaxation and reverse stress relaxation, vascularization and devascularization, baroreceptors and volume receptor adaptation, and autoregulation of blood flow.
- b) The contribution of venous sympathetic activity to circulatory disturbances during spaceflight and recovery, at rest and during orthostasis, needs to be elucidated.
- c) No hypothesis for the resting tachycardia of spaceflight has been proposed and our studies have failed to provide additional insight into its etiology.
- d) The model has predicted a fall in venous pressure upon entering weightlessness is related to an increase in peripheral resistance. Determine the consequences of the known increases of angiotensin during bedrest and spaceflight on peripheral resistance. Is this a factor in the decline of venous pressure, or are there other causes?
- e) The effects of physical conditioning on orthostatic intolerance and exercise performance during and following spaceflight needs to be confirmed and documented.
- f) There does not appear to be adequate data describing how simple blood volume loss uncomplicated by weightlessness or similar conditions can modify the normal circulatory response to centrifugation. Such data would be highly useful to separate the effects of blood volume loss from other aspects of cardiovascular deconditioning.
- g) Several additional hypotheses remain to be tested in an effort to obtain a more complete picture of the LBNP response during spaceflight and recovery.
 - i. The influence of the slow adjustment of the circulatory capacity to a reduced blood volume (reverse stress relaxation). This hypothesis could help explain the increased stability of cardiovascular response to orthostatic testing.
 - ii. The influence of sympathetic tone which may be decreased early inflight and increased upon recovery.
 - iii. Postulated changes in baroreceptor activity which may occur in the immediate postflight period.
 - iv. The influence of fluid stored in the upper body (originally derived from leg fluid) during zero-g which may be available during LBNP stress.

G.3.3 Erythropoiesis Regulation

- a) Earth-based human studies showing the effects of exercise training on indices of erythropoiesis (i.e., red

cell production, erythropoietin, iron uptake, stem cell distribution, reticulocytosis) are needed to help interpret the red cell response on Skylab. Red cell mass appears to exhibit less of a decrement for crew who exercised the most.

- b) Earth based human studies showing the effects of negative caloric balance on the mechanisms of erythropoiesis are needed to help explain the effect of space motion sickness-induced anorexia on erythropoietin.
- c) Determine the acute decrease in red cell mass during the first few days of spaceflight. Is this decrement explicable from the reduction in red cell production or is there a destructive element involved (i.e., shortened life span)?
- d) Determine whether changes in P_{50} during bedrest and spaceflight has an effect on red cell production.
- e) Demonstrate whether or not changes in renal blood flow occur during bedrest or spaceflight and if it has an effect on red cell production.

G.3.4 Musculoskeletal Adaptation

- a) Demonstrate that the prevention of muscle atrophy will also lead to the prevention or retardation of bone losses.
- b) Characterize bone strains and loading patterns at clinically relevant sites in humans during specific types of movement and exercise in one-g. This information can be used to engineer the types of devices needed to provide representative one-g loads during spaceflight.

G.4 Data Utilization: Privacy Considerations

This project would have been nearly impossible to conduct if the data privacy policy that is currently in force was effective in the Skylab era. Federal guidelines, used by NASA's astronauts, prohibit the release of individual data to the general scientific community (even if coded without identifiers) if the data can be associated with a specific research subject. On a mission with only 3 astronauts (as was the case in Skylab) it would be impossible to shield the identity of the subject by merely using subject codes. Most of NASA's missions have few subjects, and thus, unless the individual data can be averaged with those from many missions (risking data degradation because each mission is different from another) the data cannot legally be used except by the principal investigator. NASA will not permit this data to be released. Average data is certainly not as powerful as the use of individual responses, as was demonstrated in the current project. There should be no need to remind the reader how expensive it is in time, resources and in human life, to collect space-based data. Thus, an extremely important recommendation is to modify the data sharing guidelines pertaining to human scientific astronaut-subjects to allow appropriate data analysis by third parties to occur and to permit the use of individual-subject data.