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AN INTEGRATIVE APPROACH TO SPACE-FLIGHT PHYSIOLOGY USING SYSTEMS ANALYSIS AND MATHEMATICAL SIMULATION

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ABSTRACT

An approach has been developed to aid in the integration of many of the biomedical findings of space flight, using systems analysis. The mathematical tools used in accomplishing this task include an automated data base, a biostatistical and data analysis system, and a wide variety of mathematical simulation models of physiological systems. A keystone of this effort was the evaluation of physiological hypotheses using the simulation models and the prediction of the consequences of these hypotheses on many physiological quantities, some of which were not amenable to direct measurement. This approach led to improvements in the model, refinements of the hypotheses, a tentative integrated hypothesis for adaptation to weightlessness, and specific recommendations for new flight experiments.

INTRODUCTION

The most complete set of observations on man's adaptation to weightlessness collected by the U.S. to date was obtained during the 28-day, 59-day, and 84-day missions of the Skylab program (Reference 1). The primary goal of the Skylab medical experiments was to define the changes which took place in the human body and, thus, achieve an understanding of the physiological responses which occur during extended exposure to the space-flight environment. Achieving a unified theory of adaptation to weightlessness was difficult because it required integration of a voluminous quantity of data obtained by many scientists from various disciplines. This task was further confounded by the need to consider supplementary results from a diverse spectrum of ground-based studies which mimic the hypogravic environment of space flight. It was clear that proper interpretation of all these data would require the unraveling of a complex network of feedback regulators involving many individual physiological subsystems. Therefore, a program was developed, based on an interdisciplinary systems analysis approach, to address this task. It was hoped that the systems analysis approach would be particularly suitable here because it would allow us to analyze and assimilate vast quantities of information, to understand the behavior of complex homeostatic systems, and to test scientific hypotheses explicitly and in as unambiguous a manner as possible.

Of the various techniques developed to satisfy these requirements, the tool which has proven most useful is a set of mathematical models capable of simulating a number of physiological systems. The benefits of using mathematical models are well known among those physiologists who employ them in their research studies. Formulating the model, when based on experimental evidence and known concepts, provides insight into the organization of the system elements, the processes within the elements, and the multiple pathways

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connecting these elements. During simulation, the dynamic interaction between various subsystems and the relative importance of each element become more apparent through variation of the system's parameters. Once a model is validated, it is possible to predict quantitative responses of the human system that can be subjected to experimental verification. When experimental evidence is conflicting, difficult to interpret, or even difficult to obtain (as in the case of data obtained from space-flight studies), it is often possible to test the plausibility of an hypothesis by using an appropriate mathematical model. Also, models are an effective method of assembling knowledge about a physiological system. As this knowledge is organized, areas of missing information are revealed and the type of experiment needed to gather these missing data is suggested. In summary then, the simulation model can be considered a collection of integrated theories and empirical relationships against which a large portion of the space-flight data can be compared, evaluated, and tested for consistency.

Although mathematical modeling is now well established in the life sciences, this is the first time that a large array of models has been applied in a uniform manner to solve problems in space-flight physiology. This use of mathematical models was expected to complement the ongoing NASA program of employing ground-based experimental analogs of zero-g to provide additional insight into man's responses to weightlessness.

SYSTEMS ANALYSIS TECHNIQUES AND APPROACH

An important objective of the systems analysis project, at the outset, was to develop the mathematical and statistical techniques required to support an extensive integrative effort related to man's responses to weightlessness. It was apparent that data from all the major flight experiments of Skylab would need to be coupled with the appropriate analysis software in a single data base. Toward this end, a medical data analysis system was created which consisted of an automated data base, a software package of biostatistical and special purpose programs, and a set of simulation models of physiological systems (see Figure 1). Data from a wide variety of investigative areas were collected, including cardiopulmonary function, body fluids, biochemistry, nutrition and energy metabolism, musculoskeletal function, body composition, and hematology (see Table I). The total quantity of data contained in the data base is quite large in spite of the small number of astronaut subjects; information for approximately 900 man-days of space-flight study is provided by 80,000 measurement values representing over 900 independent parameters. Algorithms were provided to perform routine statistical tests, multivariate analysis, non-linear regression analysis, and autocorrelation analysis. Special purpose programs were prepared for rank correlations, factor analysis, and the integration of the metabolic balance data using models employing the conservation of mass, water, and energy. Figure 2 illustrates the data analysis system's for displaying data and visualizing computer generated model responses.

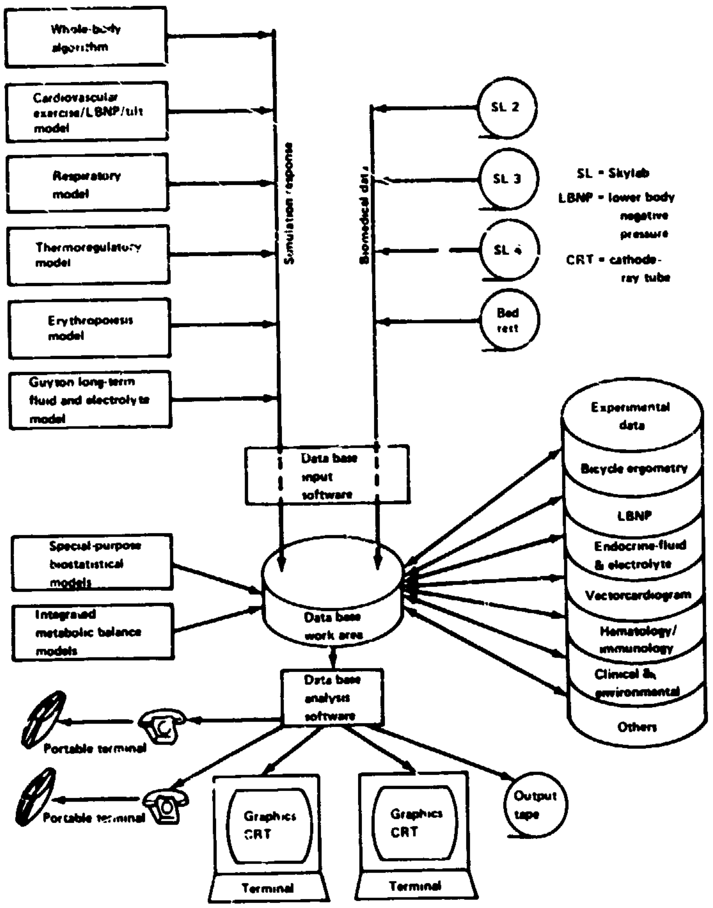


Figure 1: Skylab Integrated Medical Data Analysis System

TABLE 1

BIOMEDICAL EXPERIMENTS OF SKYLAB IN DATA BASE

Cardiovascular System

- o Lower body negative pressure
- o Submaximal exercise response
- o Resting flows, pressures, heart rate

Pulmonary Function

- o Respiratory function during rest and exercise
- o Mechanical and metabolic efficiences during exercise

Nutrition and Biochemical Metabolism

- o Metabolic balances of water, nutrients and electrolytes
- o Energy balance
- o Body mass measurements

Musculoskeletal Function

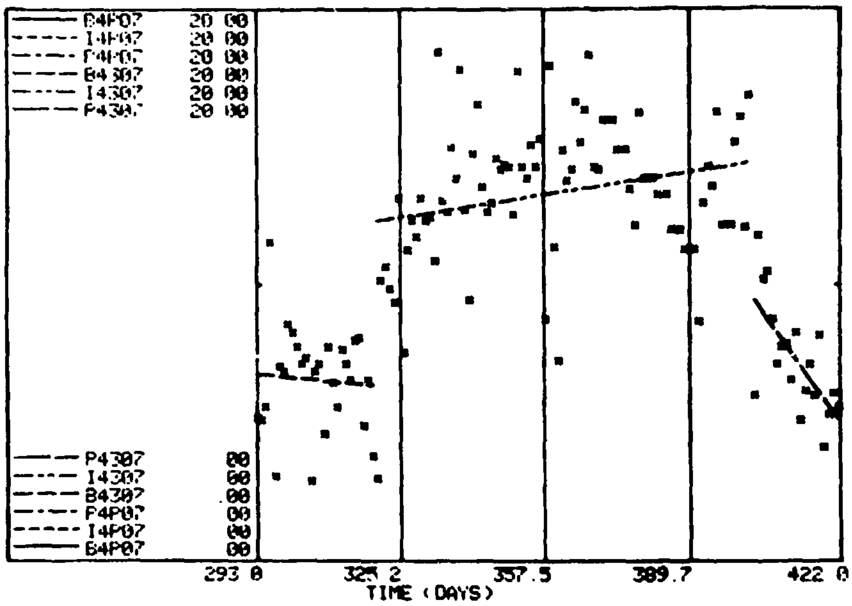
- o Bone densitometry
- o Calcium balance
- o Strength tests
- o Anthropometric measurements
- o Lean body mass measurements

Body Fluids and Composition

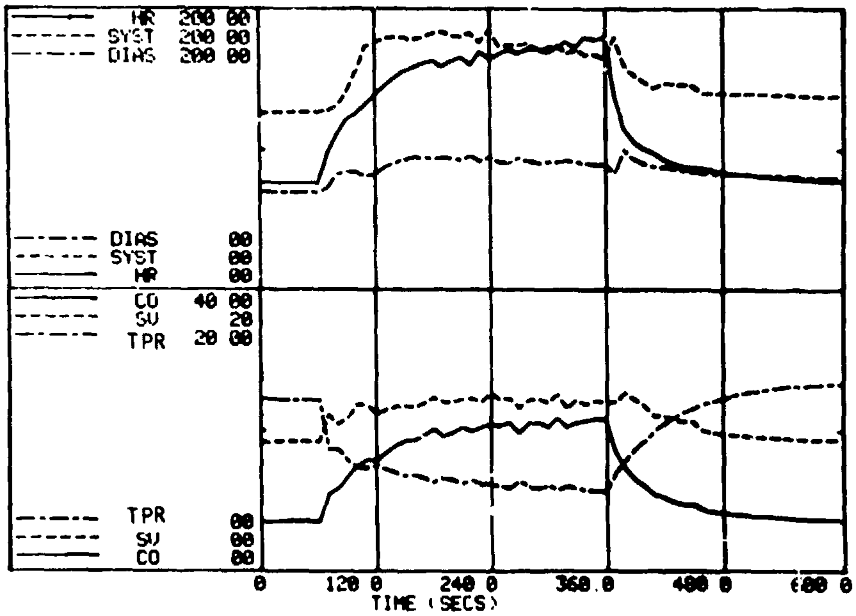
- o Body fluid volumes
- o Composition of plasma, urine, and feces
- o Hormones related to fluid-electrolyte balance and to stress

Hematology

- o Red cell mass
- o Blood volume
- o Hemoglobin
- o Indices of erythropoiesis



EXAMPLE OF CRT DISPLAY OF SKYLAB DATA WITH REGRESSION ANALYSIS
SHOWING URINARY CALCIUM FOR PREFLIGHT, INFLIGHT & POSTFLIGHT PHASES



EXAMPLE OF CRT DISPLAY OF SIMULATION OUTPUT
SHOWING TRANSIENT RESPONSES TO EXERCISE (5 minutes @ 200 watts)

Figure 2: Examples of Graphic Displays of Data Base Analysis System

In order to simulate short-term and long-term events, five basic models were employed in this project: a pulsatile cardiovascular model; a respiratory model; a thermoregulatory model; a circulatory, fluid and electrolyte balance model; and an erythropoiesis regulatory model (Figures 3 and 4). A major objective that was achieved early in the project was the integration of these subsystem models into a common framework termed the "whole-body algorithm." In addition to these six models, a model of calcium regulation is currently under development. All of the subsystem models are characterized by an active controlling system which regulates a relatively passive controlled system, and, taken together, these two components function as a negative feedback control system. The feedback variables for these models include representations of many of the actual sensors present in the body, including temperature sensors, chemoreceptors, baroreceptors, oxygen sensors, and osmoreceptors. A majority of these models resulted from research directly associated with this project.

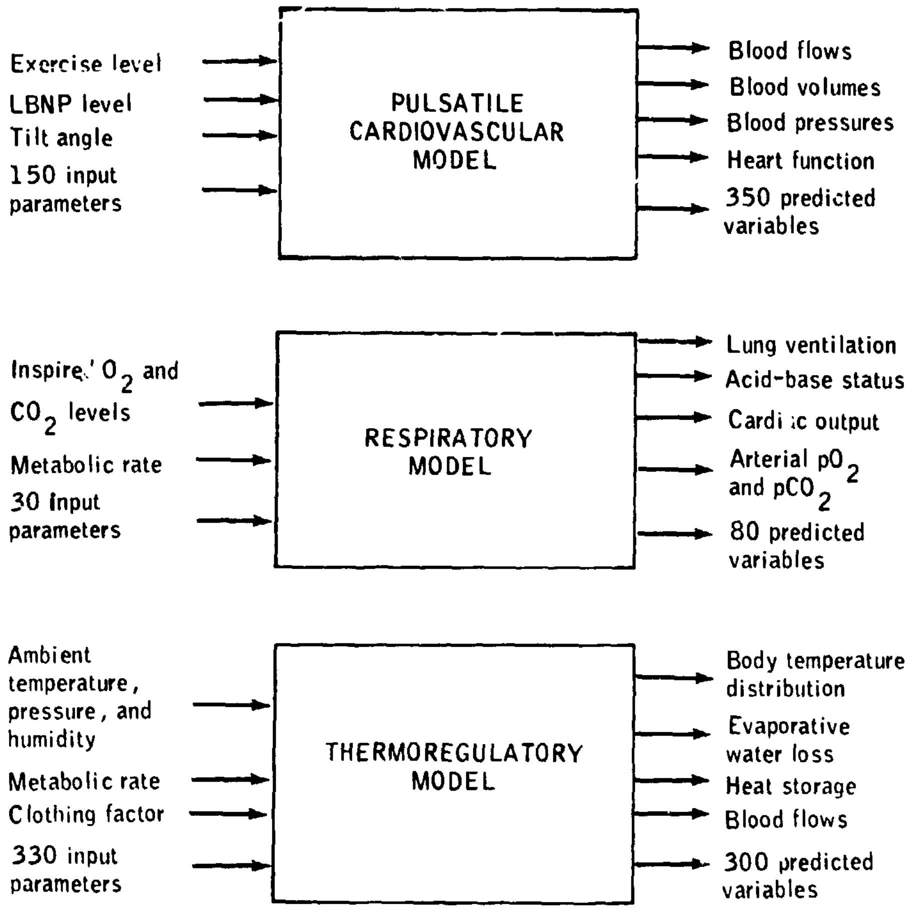


Figure 3: Models for Simulating Short-Term Events

Each of the models used in this project are deterministic and non-linear and are implemented using finite difference formulations. All models operate in an interactive time-sharing mode with the automated capability to display responses graphically and to compare data and model responses simultaneously. Most models were modified to include gravity dependent effects and to permit simulation of a human response to the stresses related to the space-flight program. In some instances, an alternative version of a model was developed to represent an animal species. Some of the experimental and clinical conditions for which the models were validated include hypogravic stresses, orthostatic stresses, metabolic stresses, environmental disturbances, and fluid shifts (Table II). Multiple stresses and sequential degrees of stress can be simulated just as in a real experimental protocol. Many hypotheses can be tested merely by adjusting the value of one or more of the fixed system parameters.

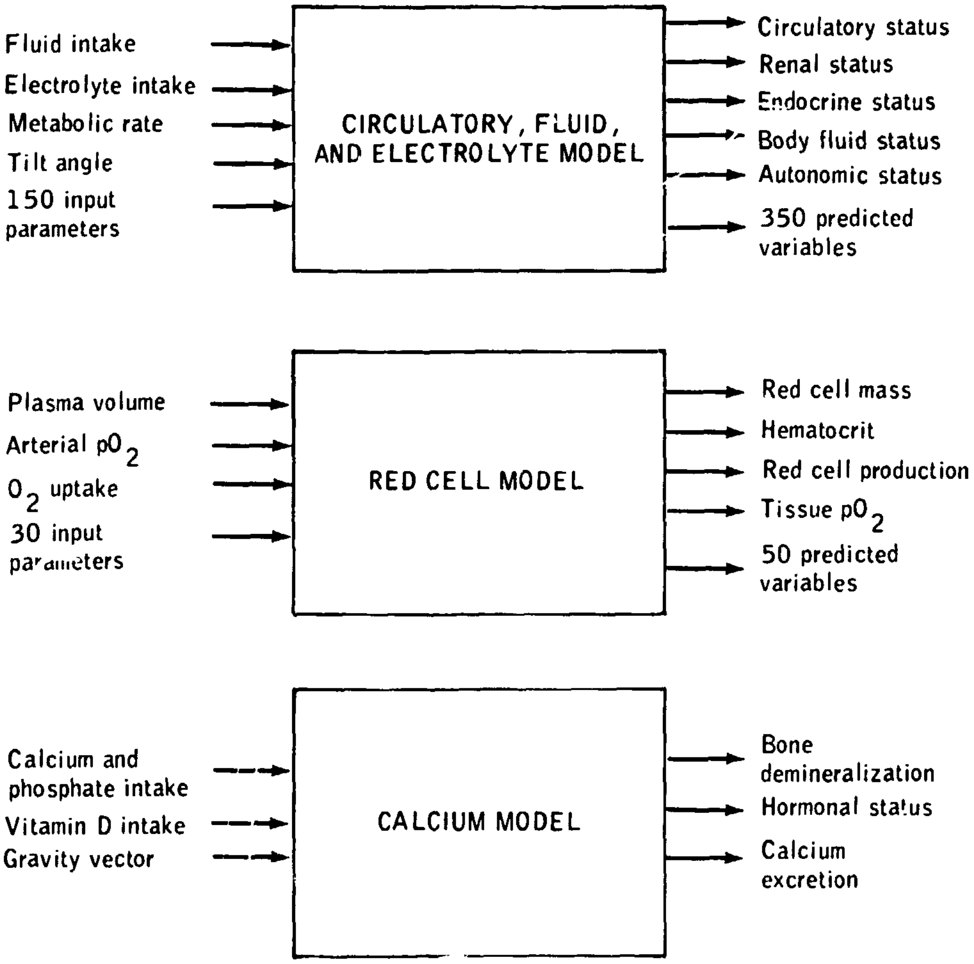


Figure 4: Models for Simulating Long-Term Events

The combinations of the data base analysis system with the group of simulation models formed the basis of the hypothesis testing approach that was used for integrating the Skylab findings (see Figure 5). The basic analysis systems permitted large arrays of space-flight data to be scanned rapidly, graphical visualization of correlations between variables, and statistical testing of hypotheses. This preliminary evaluation of space-flight data led naturally to qualitative examination of the mechanism involved in producing the observed responses. This procedure drew heavily upon the theory of physiological feedback regulating systems and often suggested hypotheses capable of being tested by using the predictive capabilities of the simulation models. The elements of the medical data analysis system (Figure 1) were designed to interact in either sequential or parallel fashion so that, for example, results from a data analysis could be employed as input forcing functions to a simulation model and the model's predicted responses could then be compared to additional data from the data base. While good agreement between model and data was desirable, it was not essential. The heuristic value of modeling is such that important objectives are often realized even when this agreement is poor. Such poor agreement often results in suggestions for additional data analysis, refinements of the mathematical models, changes in the hypothesis being considered, and suggestions for the design of new experiments to be performed either in space or on Earth. This is an interative process, as suggested by Figure 5, and is the heart of the systems analysis approach.

Table II

STRESSES RELATED TO SPACE FLIGHT THAT WERE STUDIED USING SIMULATION MODELS

o HYPOGRAVIC STRESS
  - Supine Bed Rest
  - Head-down Bed Rest
  - Water Immersion
  - Space Flight

o ENVIRONMENTAL DISTURBANCES
  - Hypoxia
  - Hypercapnia
  - Temperature
  - Ambient Pressure

o ORTHOSTATIC STRESS
  - LBNP
  - Tilt Table
  - Postural Change

o FLUID SHIFTS
  - Hemorrhage
  - Infusion
  - Water and Salt Loading
  - Dehydration

o METABOLIC STRESS
  - Exercise
  - Diet Restriction

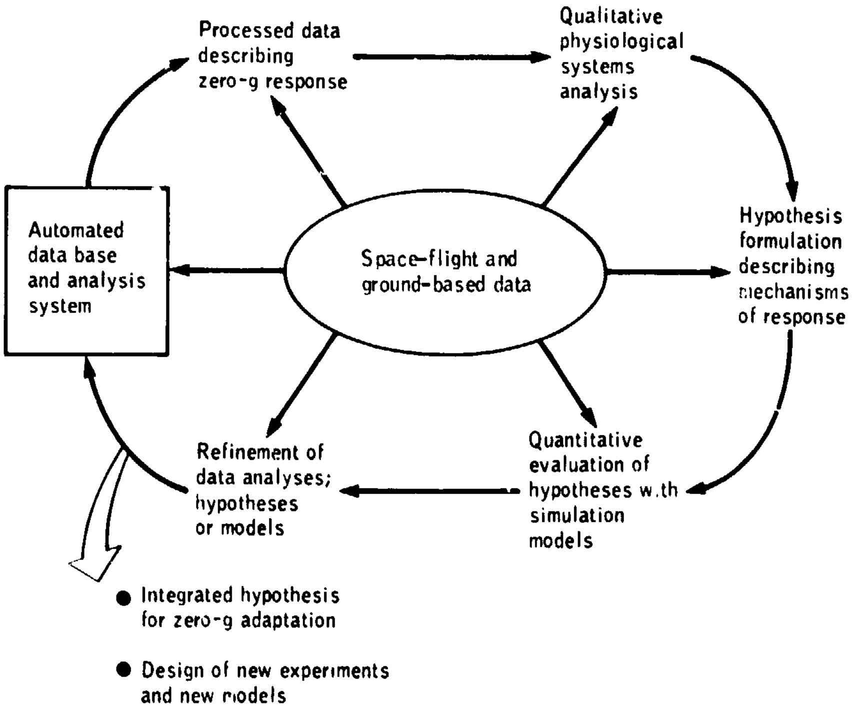


Figure 5: Systems Analysis Approach for Evaluation of Space-flight Data

Statistical and modeling techniques naturally complement each other for integrating and correlating results from many different investigative areas. Predicting the consequences of hypotheses on unmeasured variables from many subsystems is within the capability of models such as the whole-body algorithm, but is impossible if the testing of hypotheses is performed by traditional statistical approaches. As this simulation study progressed, it was possible to incorporate more and more diverse kinds of experimental results and hypotheses into a single model. While each hypothesis alone would not support a generalized theory, all of them taken together should converge toward a coherent picture of zero-g adaptation.

RESULTS AND DISCUSSION

This project encompasses a nine-year time period, and it has fostered many useful accomplishments. Several of these are discussed below.

Integrative Analysis

Systems analysis was valuable in performing various organization and integration functions that were not previously available to the space life sciences program on a systematic basis. These functions include:

a) integration of data from different investigative areas into a common data base to provide an interdisciplinary cross-correlation capability;

b) integration of physiological mechanisms relating to homeostatic control of a single functional system within the framework of a mathematical model;

c) integration of observed phenomena (experimental data) with simulated responses (theory) by simulating experimental conditions and comparing model and real-world behavior;

d) integration of diverse types of stresses acting on the same system to demonstrate common features of the regulatory processes;

e) integration of acute and long-term stress responses to hypogravity by systematic comparison of ground-based and space-flight studies;

f) integration of physiological subsystem models into a larger, more complex model to study theoretical interactive effects; and

g) integration of subsystem hypotheses related to zero-g adaptation into a unified theory showing overlapping and interactive effects between subsystems.

The last several items are of unusual importance and are therefore discussed in more detail below.

Whole-Body Algorithm

The physiological interaction of major body subsystems has been a subject of interest to researchers for some time. One objective in human system modeling is to produce not only reliable subsystem models but also an integrated model with each subsystem acting in concert with other subsystems to simulate the entire dynamic system of the body. However, efforts in this direction have been quite limited. A contribution to this area was made with the development of a "whole-body algorithm" (Figure 6), which is envisioned as a mathematical model that can simulate the response of several major body regulatory systems to diverse, but specified stresses related to the space-flight environment (Table II). The approach selected for the construction of this model combined existing subsystem models that describe short-term stress responses (cardiovascular, respiratory, thermoregulatory models) with a model which described appropriate long-term responses (circulatory, fluid-electrolyte, endocrine, erythropoiesis models). The whole-body algorithm was designed so that the entire sequence of major physiological events for long-duration space flight could be simulated. This sequence included preflight experiments, acute physiological responses to zero g, changes in cabin environment, inflight responses to the experiments of interest (lower body negative pressure and exercise), acute reentry to one g, long duration readaptation to one g, and postflight experiment simulation.

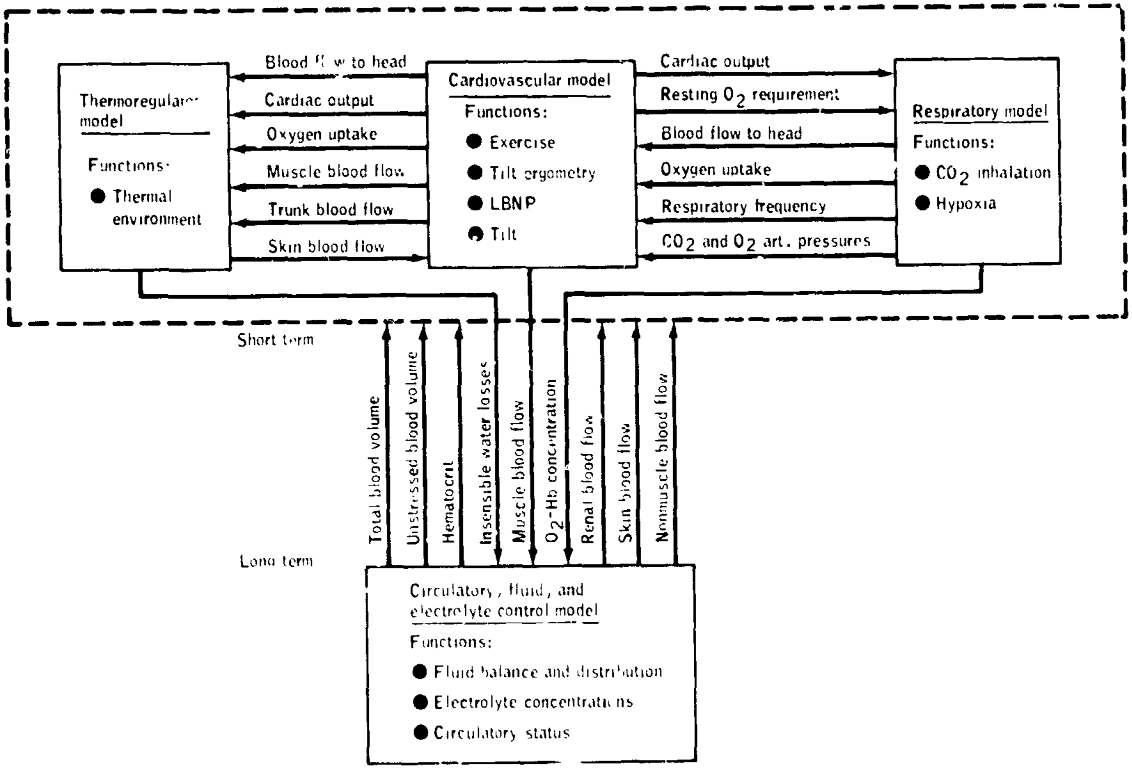


Figure 6: Whole-Body Algorithm

One advantage of using an approach which combines existing subsystem models is that each model considers various time lags, fast and slow controllers, and integration step sizes appropriate for its respective simulations. The model has a sufficiently flexible structure to permit changes to be made without totally disrupting the entire system. Such changes even include adding new subsystems or modifying existing subsystems. A model comprised of individual, well-defined subsystems also facilitates studying the interaction between the subsystems, and studying total system hypotheses, both important subjects in physiology today. An additional feature of the whole-body algorithm is its capability to simulate multiple and sequential stresses with little or no basic structural changes.

Sufficient testing was performed with the whole-body algorithm to demonstrate the basic capabilities of the model. Validations were performed for a number of single stresses as well as long-term bed rest accompanied by intermittent short-term stresses. Once model credibility was ascertained, it was possible to attempt simulations of entire space-flight missions. Figure 7 illustrates one such simulation of a composite Skylab flight and demonstrates

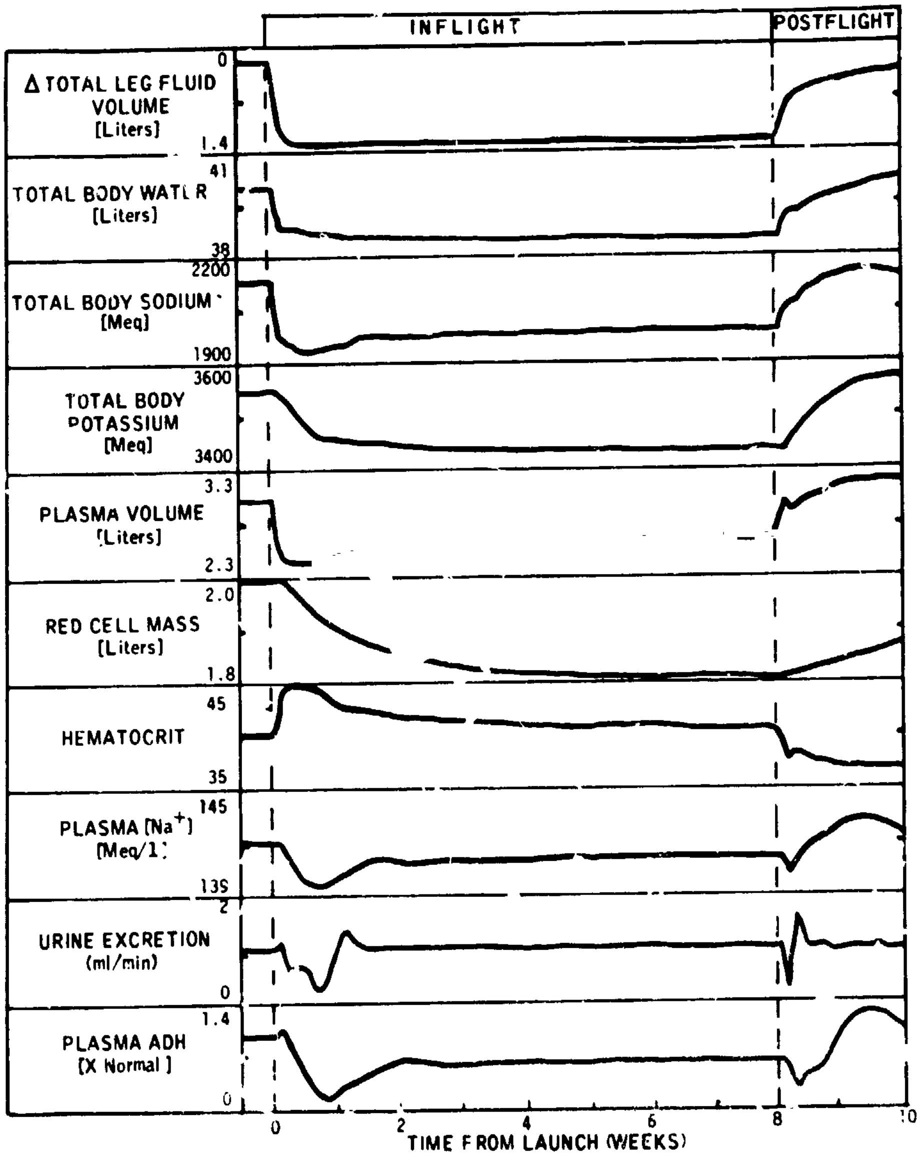


Figure 7: Simulation of Fluid-Electrolyte Regulatory Behavior During Composite Skylab Mission

reasonable predictions for a variety of fluid volume, electrolyte, endocrine, and renal responses. Nevertheless, many aspects and capabilities of the model have yet to be tested. One reason for this is that much of the data required to perform adequate validation of this large model have not yet been gathered. The whole-body algorithm has well over 1000 independent system variables, most of which correspond to physiological quantities. Unfortunately, in physiological research it is rare that more than a dozen parameters will be measured simultaneously during a single experiment. Therefore, data from multiple sources is required and, because identical biological conditions are not likely to be achieved, there is a risk in this approach. For these same reasons, the simulated responses to combined stresses have not been investigated. In a very real sense, this shortcoming is an opportunity to identify critical research areas related to measuring whole-body responses to combinations of environmental and metabolic disturbances. It should also be recognized that a model of this size is somewhat unwieldly and simulations take a relatively long time to perform. Therefore, most of the systems analysis performed in this program was accomplished with the individual subsystem models. The next phase of application will be to incorporate into the whole-body algorithm the candidate hypotheses for each subsystem that have shown promise in explaining the space-flight findings. When this is done, the whole-body algorithm will serve its main function as a central repository of a detailed integrated hypothesis of zero-g adaptation. In this way, the model should prove useful for supporting space-flight biomedical research programs, and for predicting indices of crew health.

Hypotheses of Zero-g Adaptation

The major application of these mathematical and data processing tools was directed toward achieving a better understanding of how humans adapt to long-term space flight. A detailed discussion of results in this area is out of the scope of this paper, but such a discussion will soon be available in book format (Reference 2). In terms of the several physiological systems studied, the following broad picture has emerged. Disturbances in the cardiovascular, fluid-electrolyte, erythropoietic, musculoskeletal, and metabolic systems, which are found during and after flights of various durations, appear to be attributed to two major effects of weightlessness (Figure 8). These are, first, the absence of hydrostatic forces, resulting in severe fluid shifts within the body, and second, the absence of deformation forces, resulting in disuse atrophy of normally load-bearing tissues. The first of these effects leads to a reduction in body fluids, most importantly, blood volume. The consequences of the second factor are reductions in bone and muscle mass. Whether disuse atrophy of musculoskeletal tissue can be prevented is still unresolved. In addition, a third factor, a long-term alteration of metabolic state, reflecting changes in dietary intake and exercise, was found to play an important role in aggravating the zero-g "deconditioning" processes of the space flight crews. However, it is doubtful at this time that these latter factors are beyond human intervention and correction on future missions. All of these events have both acute and long-term effects in the major physiological systems which lead to loss of weight and, upon return to a one-g environment, decreased tolerance for orthostasis and work.

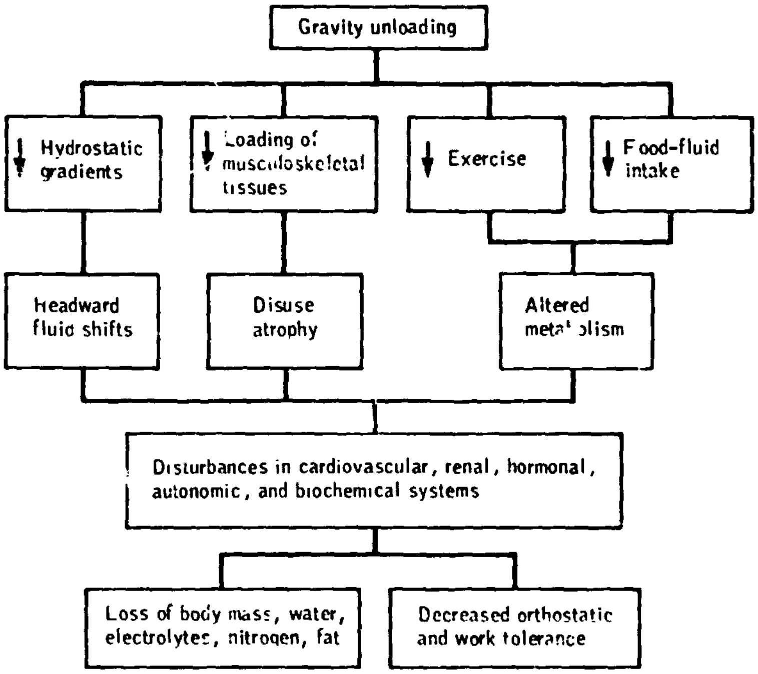


Figure 8: Physiological Effects of Exposure to Weightlessness

Our studies have been based on the belief that within the time span over which man has so far been studied in space, these responses to weightlessness are not pathological in nature; rather, they can be explained in terms of normal, although complex, feedback regulatory processes. Our simulation studies have supported this premise. Adaptation to weightlessness is said to occur when the body adjusts to these changes and reaches a new steady state (Figure 9). Each physiological system appears to have its own time course of adaptation. The rates of degradation and loss of such quantities as bone, muscle, fat, red cells, and water are all quite different, depending upon the nature of the disturbance and on the time constant of the correcting homeostatic system. In Figure 9, the return to baseline reflects the establishment of a new homeostatic level appropriate to weightlessness.

The contribution of the simulation models was significant in developing a group of zero-g hypotheses. The utility of the models, however, extended beyond their important predictive capabilities discussed earlier. A benefit of the modeling process was related to the ways in which models shaped the data analysis effort. Quantitative modeling often required a new look at data which had already been analyzed by more traditional methods. The simulation approach required certain patterns of data in very specific forms. Satisfying

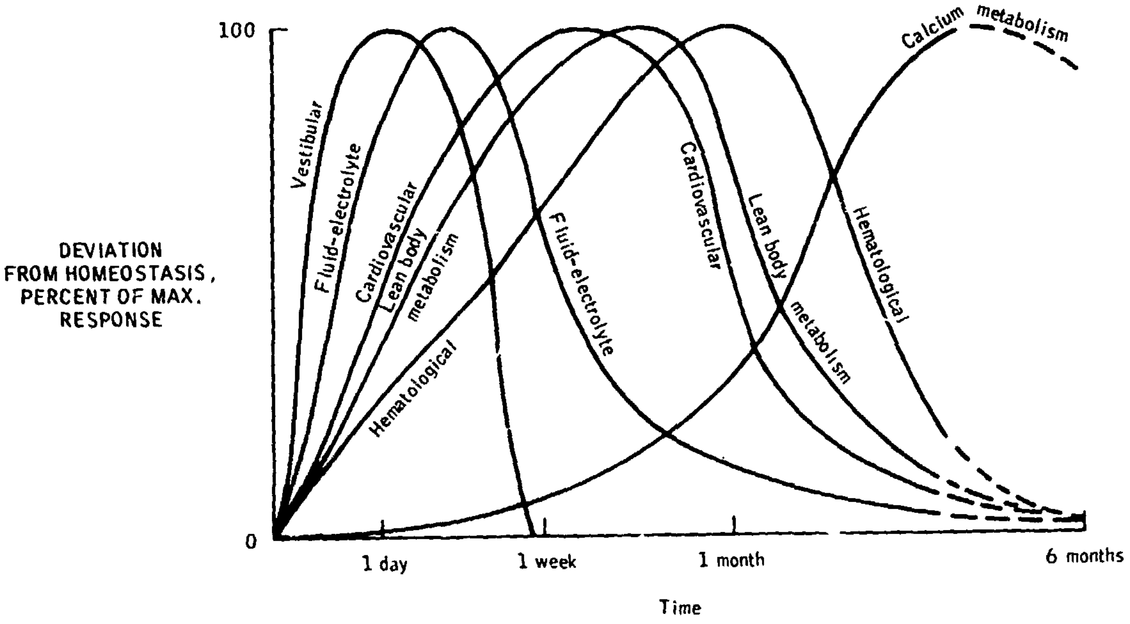


Figure 9: Approach Toward Homeostasis of Physiological Systems During Space Flight

these model requirements led, in one instance, to an extensive metabolic balance analysis for describing body composition changes during space flight. Another benefit of modeling, at this stage of its application to space physiology, was in forcing the analyst to think systematically, comprehensively, and quantitatively about the system of interest. The complexity of the models, reflecting the redundancy of the mechanisms in the body, helped resolve some paradoxical findings by suggesting the involvement of one or more competing pathways. Also, it was not always possible to explain the long-term adaptation phase of space flight in terms of regulatory feedback mechanisms more suited to corrective action of acute disturbances. This suggested a logical division of the space-flight period into acute and chronic segments for purposes of systems analysis. As a result, a comprehensive analysis of acute ground-based studies was undertaken to enhance our understanding of the immediate period following launch, an interval during which few space-flight observations were made.

CONCLUSION

The effort described here has resulted in a more advanced analysis of space-flight data than was previously available. The accomplishments associated with this project include the following:

a) Establishment of a more definitive data analysis based on a composite picture of the nine crewmen from all flights;

b) Allowing estimation of quantities which could not be measured directly but could be derived from simple metabolic balance models or advanced simulation models;

c) Integration of data across disciplinary lines;

d) Quantitative evaluation of hypotheses by computer simulation and interpretation of data in terms of feedback control theory;

e) Reevaluation and reinterpretation of previously published Skylab data in the light of more recent findings from ground-based studies and Soviet missions.

This is not to imply that a definitive theory of space-flight adaptation was formulated. Rather, the fundamental contribution of the systems analysis effort has been to organize many of the major biomedical findings from space flight and correlate these findings with the scientific concepts that describe the requisite organ systems. Out of this effort has come an array of methods, tools, and techniques that have been essential for the handling, processing, and interpretation of experimental data in general and space-flight data in particular. Another benefit arising from this systems analysis project was an improved understanding of the physiological events which occur during human adaptation to weightlessness and the concomitant identification of critical areas ripe for future study. Recommendations for new experimental approaches generated by the current program have already contributed to the design of ground-based and future Spacelab investigations. Full potential of the systems analysis method will be realized only by maintaining an interative cycle between model developments and experimental research.

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