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FINAL REPORT

ON

CONTRACT NAS9-12932

AUTOMATED SYSTEM FOR INTEGRATION AND DISPLAY OF PHYSIOLOGICAL RESPONSE DATA

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GENERAL ELECTRIC
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ABSTRACT

This final report documents the completion of work and summarizes the accomplishments of a three-year research project under contract NAS9-12932. This contract includes many tasks and work statement items with different completion dates which have been documented upon completion during the course of this contract and transmitted by Technical Information Release (TIR). There have been 69 TIR's (not including progress reports) and several published papers and new technology reports documenting and reporting the results of the work under this contract. This final report will, therefore, be a summary of this work, enumerate the individual task items and the corresponding reports which satisfy them.

The research performed under this contract has been dedicated to providing understanding of the physiological changes which occur during long duration exposure to the spaceflight environment. This work has provided the tools for analyzing the underlying processes based upon systems analysis. These tools, which are the deliverable end-items of this contract, include: (1) mathematical models of the major physiological subsystems of the body which are capable of simulating the response of that subsystem to the major medical experiments of the space program used to evaluate the physiological changes of the subsystem in the zero-g environment and return to 1-g; (2) a whole-body algorithm which combines these subsystem models into a dynamic simulation of the interaction between these subsystems and provides the capability to simulate the entire sequence of long term adaptation to zero-g, the short term experimental stresses, and the acute environmental stresses; (3) a data base and statistical analysis system which is capable of storing, retrieving, and analyzing experiment data; (4) an interactive retrieval and display system which is capable of automatically displaying data from the data base simultaneously with results from any of the simulation models including the whole-body algorithm on remote graphics terminals; and (5) an automated

reference retrieval system which is capable of handling the large file of literature from the environmental physiology branch which replaces a manual system created under a previous contract.

The documentation of the design specifications, design and development studies, and user's instructions (which include program listings) for these delivered end-items; the reports on the results of many research and feasibility studies; and many subcontract reports submitting results from consultant studies have generated such a volume of information that it is not feasible to present the technical findings and results of all the work under this contract in this final report. All the TIR's referenced herein must, therefore, be considered as a part of this final report and should be referred to for specific information concerning the results of any specific task items of interest. The work done under each major task item is briefly discussed in Section 2.0 and the conclusions derived from this research is summarized in Section 3.0. The major emphasis given in this report has been dedicated to presenting and discussing the recommendations for future activities which are indicated by the results of this work.

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1.0 INTRODUCTION

Early involvements with math models of human physiology at JSC was centered around thermoregulatory models because of their usefulness in evaluating space suits and associated life support systems under a variety of stresses and environmental conditions. The first major effort at JSC to develop physiological math models and to perform computer simulations started about 1970 with Contract NAS9-11657, Modeling and Integration of Physiological Control Systems, (General Electric Company). The objective of this initial effort was to provide information needed to make both technical and managerial decisions regarding the development or use of algorithms of the primary homeostatic regulatory mechanisms of man, and the integration of these algorithms into a total interactive simulation system. At this point in time, a number of investigators within the government, industry, and educational institutions had developed simulation models of biological processes in pursuit of specific lines of research, but had not applied them outside of those activities and the need for an integrated system simulation had not been addressed. The complexity and sophistication of physiological models are dependent upon their intended uses which were to be identified as a secondary objective.

The approach used to satisfy these objectives was to first identify possible end uses of biological subsystem models in order to establish the model requirements and level of detail needed. A thorough literature search, state-of-the-art survey, and personal contacts in government, university, and industry aided in identifying models that met these requirements. The following physiological subsystems were determined as being critical for meeting the simulation requirements of the aerospace medical program and for subsequent inclusion in an

integrated whole-body model; cardiovascular, respiratory, thermoregulatory, renal, endocrine, and body fluids. Candidate and alternate biological models were identified, selected, implemented, and evaluated for their application to simulating pre-, post-, and inflight physiological testing. This included identifying, developing, or modifying input/output transfer functions, assumptions, verification and validation concepts, limitations, success criteria, and missing model elements. This initial study was to provide a basic framework for evaluating models, defining objectives, developing software requirements for models and data base management, and developing a biomedical engineering literature retrieval system. Progress was so encouraging that a new contract NAS9-12932, Automated System for Integration and Display of Physiological Systems, was initiated to improve the models and to simulate the response to various medical experiments and space environments (such as bicycle ergometry, lower body negative pressure, changes in cabin environment, and zero gravity).

This three-year study, which is the subject of this final report, has the major objective of developing a whole-body algorithm which will be useful for evaluating hypotheses related to the physiological adaptation to space flight, developing new standards of remote medical care for advanced missions, and providing assistance to a real-time monitor during physiological testing. The identification and development of the necessary prototype software systems including data base systems, parameter identification systems, and automated CRT display systems are secondary benefits of this study.

The selected approach to develop the whole-body algorithm was to combine four complex subsystem models of major physiological systems that were previously identified as meeting the requirements of the program. The cardiovascular subsystem model was developed

by General Electric (Dr. R. C. Croston) under NASA sponsorship and provides a significant pulsatile circulatory model to simulate bicycle ergometer exercise responses. The other models have been developed previously by physiologists recognized as specialists in their fields: Thermoregulatory (Dr. J.A.J. Stolwijk); Respiratory (Dr. F. S. Grodins); Circulatory, Fluid and Electrolyte Control (Dr. A. C. Guyton). Another model was developed by General Electric under this contract (Dr. J. I. Leonard) in the absence of finding a suitable model in available literature; this model of erythropoiesis was developed in cooperation with NASA investigators. This model is expected to be useful in developing a coherent theory of depressed red cell formation during prolonged zero-g exposure. A new model was also developed under this contract, based on the cardiovascular exercise model, to simulate cardiovascular response to LBNP and tilt-table experiments. These two models were later combined into a single cardiovascular subsystem model and the ability to simulate tilt ergometry was added.

All of these models were modified to extend their usefulness and ability to simulate more realistically the systems they represent. Their utility was greatly increased in all cases by programming them for interactive use on remote terminals with graphical display capabilities. Validation of these models was accomplished by comparing their simulations with experimental data of stress responses similar to those encountered during preflight crew training programs.

The combining of these models into a multiple model system, called a whole-body algorithm, represents a significant step in the field of physiological systems modeling and simulation. All of the subsystem models are complex and sophisticated representations in their own right. Until now, however, little attention has been

directed at the functioning of these models together as a "whole-body" or total body system. One reason for this has been the unavailability of computation equipment and software capable of handling multiple interacting models of this magnitude and scope.

Independently operating subsystem simulations have important applications; but important interactions between subsystems, which are usually defined in an entirely artificial manner, are lost. The full power of the systems analysis approach is only utilized when the influence of all the major subsystems are fully accommodated in a dynamic sense. In addition, the whole-body algorithm is capable of responding to both long and short term stresses of various kinds. These stresses may act on any one or any collection of the subsystems of which the model is composed. The whole-body algorithm is capable of simulating the integrated physiological response to the following experimental and environmental stresses: a) CO_2 inhalation, b) Hypoxia, c) Thermal Stresses, d) Exercise (sitting and supine), e) LBNP (lower body negative pressure), and f) Tilt (changing body angles in gravity).

Extensive computer programming was required to initialize and execute the subroutines in a synchronous manner, since integration step sizes of the models were not the same. Other special computer software was designed and implemented which allows operation of the models through an "overlay" structure because they were far too large to all fit into core at the same time. This structure will allow the continued growth and development beyond the normal constraint of core size. The whole-body algorithm was designed to operate a long term model for a specified time which simulates the adaptation processes with characteristically long time constants (days). Then the short term models (cardiovascular, respiratory, and thermoregulatory) required to simulate the transient response of an experimental stress are employed with initialization data from the long term model.

While the original contract did not anticipate direct application to actual Skylab inflight medical experiment data, the results were sufficiently promising that midway through this contract an additional task item (Modification 4S) was included to test the feasibility of using simulation models to suggest and evaluate hypotheses related to the medical experiments of the then current Skylab mission. The general approach for this zero gravity hypotheses testing study was to start with a model that had been validated with a crewman's preflight experimental data and compare this response for the same experimental stress over the course of the mission in the weightless environment. Any discrepancy between inflight data and simulation results would be assumed to be associated with the physiological response to weightlessness or perhaps other known environmental factors. With this in mind, a group of physiologically plausible hypotheses could be advanced which hopefully would account for the observed difference. These hypotheses can be generated by examination of the data base using its associated statistical analysis and display capabilities or by discussions with the Skylab medical team. This special data analysis system was also developed to facilitate the testing of model results with experimental data by direct comparison on graphic CRT plots. Model output results can be stored on mass storage devices at execution time and read by the data analysis system program for simultaneous display with data retrieved from Skylab experiments. This capability greatly decreases the time required to test the results of model modifications against experimental data and reduces the chance of human error in data transposition. The candidate hypotheses are reduced to mathematical expressions and incorporated into the model, and the resulting model behavior may then suggest the more significant of the hypotheses.

2.0 DISCUSSION OF RESULTS

The primary objective of this research project in the design, development, and validation of a whole-body algorithm. However, many supportive and secondary objectives, the development of the individual subsystem models which make up the whole-body algorithm, the development of a feasible design approach, the design and development of a data base and analysis system with graphic display capability, the development of an approach for testing physiological system hypotheses, and many other studies and investigations, preceded and paralleled the work on a whole-body algorithm. The results of all these activities must be considered as end items in themselves as well as being supportive to the development of the whole-body algorithm. Since these studies and developed systems were phased and scheduled to provide continuity for the orderly completion of the work under this contract, all of the completed tasks were documented with their respective results and conclusions by TIR as they were completed. These study reports, user's guides, research reports, subcontracted consultants' reports, etc., submitted by TIR under this contract constitute 69 individual reports, (not including quarterly progress reports), some of which have considerable volume. There are also many published articles and papers as well as new technology reports which are pertinent to this work. The results of this work presented in these reports are in many cases very intricate, detailed, and many faceted requiring individual handling and presentation in many different forms. Because of these reasons and the considerable volume of this material, even a compilation of the significant results would be impractical for a summary treatment in this final report and would certainly be a duplication of effort since these results have been transmitted by individual TIR. This section will, therefore, present

a brief discussion of the major task items of the contract with a reference to the individual TIR's which report the results of the work done under each respective task item.

Figure 1 presents the program task items and the corresponding TIR's which satisfy them. This figure does not reference all TIR's submitted under this contract because several were updated (particularly in the case of user's guides) as changes were made to improve simulation models or as other programs were improved. Other TIR's (such as quarterly progress reports) are not applicable to a particular task item and are therefore not referenced. All the TIR's and other publications pertinent to this contract are listed in Section 5.0.

A reviewer of this contract work or any aspect of this research project should, therefore, secure the particular TIR or other published article for the information and results of interest. For example, a reviewer interested specifically in only the whole-body algorithm results is referred to TIR 741-MED-5008. A potential user of the whole-body algorithm would also need TIR 741-MED-5009. A reviewer interested in the studies leading up to its design and development or other supportive programs (such as the data analysis and graphics display programs) would be referred to several other TIR's and published articles.

The following task descriptions provide a summary of the work done under each major task item and with Figure 1 provide a key to the particular TIR reporting the corresponding results.

2.1 (TASK 1.0) CONTINUE AND COMPLETE DEVELOPMENT AND PRELIMINARY TESTING OF CARDIOVASCULAR, RESPIRATORY, THERMAL REGULATORY, FLUID BALANCE, AND RENAL/ENDOCRINE SUBSYSTEM MODELS

The major effort involved in this task was associated with the development of the individual subsystem models as individual analytical

FIGURE 1. PROGRAM TASK ITEMS AND TIR REFERENCES (NAS9-12932)
AUTOMATED SYSTEM FOR INTEGRATION AND DISPLAY OF PHYSIOLOGICAL RESPONSE DATA

SCHEDULE

	TASKS	FISCAL YEAR 1973 (1 2 3 4 5 6 7 8 9 10 11 12)	FISCAL YEAR 1974 (1 2 3 4 5 6 7 8 9 10 11 12)	FISCAL YEAR 1975 (1 2 3 4 5 6 7 8 9 10 11 12)
1.0	CONTINUE AND COMPLETE DEVELOPMENT AND PRELIMINARY TESTING OF CARDIOVASCULAR, RESPIRATORY, THERMAL REGULATORY, FLUID BALANCE, AND RENAL/ENDOCRINE SUBSYSTEM MODELS.			
1.1	Thermal Regulatory Subsystem Model			
1.1.1 1.1.2 -	Develop Color CRT Display Programs to Apply to Thermal Model Develop X-Y Plot Program Application for Thermal Model Outputs Combine these two tasks and implement in a conversational mode.		Completed-See TIR 741-MED-4011 TIR 741-MED-4015	
1.1.3 1.1.4	Add Remaining Program Operational Modes to Sigma 3 Library Checkout and Verify all Operational Modes	Completed-See TIR 741-MED-2011 TIR 741-MED-3011 TIR 741-MED-3013		
1.1.5	Institute Recommended Parameter Changes on Trial Basis and Compare Results to Laboratory and Other Available Data	Completed-See Thermoregulatory Subsystem in TIR 741-MED-2009 and TIR 741-MED-2004.		
1.1.6 1.1.7	Continue Development of an Improved Shivering Mechanism Hypothesis Verify Improved Shivering Mechanism		Completed-See TIR 741-MED-4011	
1.1.8 1.1.9 1.1.10 -	Complete Investigation & Finalize Respiratory Subsystem Model Interface Definition Complete Investigation & Finalize Fluid Subsystem Model Interface Definition Complete Investigation & Finalize Cardiovascular Subsystem Model Interface Definition Include above three tasks with whole-body subsystem integration analysis	Completed-See TIR 741-MED-3058		
1.1.11	Apply MINIQUASI to Thermal Program Boundary and Initial Value Problems Requiring Solution		Completed-See TIR 741-MED-4026	
1.1.12	Identify Other Classes of Identification Problems Requiring Solution in Support of Laboratory Objectives and Identify Techniques for Solving Those Problems		Completed-See TIR 741-MED-4028	
1.1.13	Identify Source of Differences Between Model Transient Response and Observed Responses of Test Subjects. Recommend Changes to Increase Model Fidelity and Improve Transient Response Characteristics. Develop and Test Algorithm Changes Designed to Improve Model Response.	Completed-See TIR 741-MED-2004 TIR 741-MED-3013		
1.2	CARDIOVASCULAR SUBSYSTEM MODEL			
1.2.1	Develop Color CRT Display Programs to Apply to CROS/C Cardiovascular Control System Model for Exercise.	Completed Demonstration reported in TIR 741-MED-3022		
1.2.2	Develop X-Y Plot Program Application for CROS/C Model Outputs	Completed-See TIR 741-MED-3044		
1.2.3	Define Guidelines and Test Procedures for Investigating Stability of Nonlinear Cardiovascular Control System Models		Completed-See TIR 741-MED-4029	
1.2.4	Continue Development of Croston Control System Model for Exercise and Perform Parametric Studies Using Pre- and Postflight Data to Verify Hypotheses	Completed-See TIR 741-MED-2010		
1.2.5	Program Croston Model for Sigma 3 Operations	Completed-See TIR 741-MED-3004		
1.2.6 1.2.7	Program M. D. Anderson Cardiovascular Model Refinements for Sigma 3 Operations Develop X-Y Plot Programs for M. D. Anderson Model	Completed-See TIR 741-MED-3007		
1.2.8	Conduct Comparative Study of M. D. Anderson Model Outputs Versus Available Flight Data, Test Data, and Data Available from Literature References and Other Sources	Completed-See TIR 741-MED-3054		

SCHEDULE

TASKS (Continued)	FISCAL YEAR 1973 (1 2 3 4 5 6 7 8 9 10 11 12)	FISCAL YEAR 1974 (1 2 3 4 5 6 7 8 9 10 11 12)	FISCAL YEAR 1975 (1 2 3 4 5 6 7 8 9 10 11 12)
1.2.9 Identify Features of M. D. Anderson Model to be Incorporated Into Whole-Body Algorithm		Completed-See TIR 741-MED-3053	
1.2.10 Identify Improvements to M. D. Anderson Model to Increase Applicability to Skylab Experiments		Completed-See TIR 741-MED-3058	
1.2.11 Identify Model Features of Kuchar-Sittel Model to be Incorporated into Whole-Body Algorithm		Completed-See TIR 741-MED-3004	
1.2.12 Develop a Stand-Alone Cardiovascular Subsystem Model		Completed-See TIR-MED-3058	
1.2.13 Verify Cardiovascular Model Interface Compatibility with Other Subsystem Models		Completed-See TIR 741-MED-2010	
1.2.14 Identify Existing Cardiovascular Subsystem Transfer Functions and Control Mechanisms from Literature & Test Data 1.2.15 Define Splanchnic Circulation Control Mechanism		Completed-See TIR 741-MED-2010	
1.2.16 Define Vascular Bed Control Mechanism 1.2.17 Incorporate Vascular Bed and Splanchnic Circulation Control System into Cardiovascular Subsystem Model		Completed-See TIR 741-MED-3038 Completed-See TIR 741-MED-3041	
1.2.18 Program Cardiovascular Subsystem Model for Sigma 3 Operations 1.2.19 Verify Cardiovascular Subsystem Model for Normal and Stress States - Implement a high speed subsystem model		Completed-See TIR 741-MED-4024	
1.3 RESPIRATORY SUBSYSTEM MODEL 1.3.1 Develop Color CRT Display Programs to Apply to Respiratory Model		Completed-See TIR 741-MED-3045	
1.3.2 Develop X-Y Plot Program Application for Respiratory Model Outputs - Combine above two tasks and implement in a conversational mode.		Completed-See TIR 741-MED-3008 Completed-See TIR 741-MED-3009 Completed-See TIR 741-MED-3021	
1.3.3 Compare Respiratory Model Outputs to Environmental Physiology Branch and Other Available Data and Recommend and Implement Approved Model Changes to Improve Fidelity		Completed-See TIR 741-MED-3021	
1.3.4 Determine Requirements for Transient Response Outputs		Completed-See TIR 741-MED-3046	
1.3.5 Identify Model Changes Necessary to Implement Dynamic Response		Completed-See TIR 741-MED-3030	
1.3.6 Identify Parameters Necessary to Program Milhorn's Models 1.3.7 Program Milhorn's Models for Sigma 3 Operations		Completed-See TIR 741-MED-3058	
1.3.8 Compare Milhorn's Model Responses to Environmental Physiology Branch and Other Available Data 1.3.9 Compare Milhorn's Model Responses and Model Capabilities to Grodins Modified Model		Completed-See TIR 741-MED-3010 -See TIR 741-MED-3014	
1.3.10 Select/Design Model to be Used for Whole-Body Algorithm Study		Completed-See Fluid Subsystem report in TIR 741-MED-3020	
1.4 RENAL/ENDOCRINE AND BODY FLUID MODELS 1.4.1 Continue Study of Control Mechanisms and Their Relationship to Thermal Regulatory, Cardiovascular, and Respiratory Models			
1.4.2 Complete Preliminary Design of Models and Obtain Environmental Physiology Branch and Other Available Data 1.4.3 Finalize Models			

TASKS (Continued)	SCHEDULE: FISCAL YEAR 1973 (1 2 3 4 5 6 7 8 9 10 11 12) / FISCAL YEAR 1974 (1 2 3 4 5 6 7 8 9 10 11 12) / FISCAL YEAR 1975 (1 2 3 4 5 6 7 8 9 10 11 12)
1.4.4 Identify/Synthesize Transfer Functions - Implement a new hydrogen ion model.	Completed-See TIR 741-MED-4017
1.4.5 Program Models for Sigma 3 - Implement Guyton's and White's Versions.	Completed-See TIR 741-MED-3017
1.4.6 Compare Model Outputs with Life Sciences Directorate and Other Available Data 1.4.7 Improve Model Fidelity as Required	Completed-See TIR 741-MED-4021
1.4.8 Finalize Model Interfaces with Other Subsystems	Completed-See TIR 741-MED-3058
2.0 CONTINUE AND COMPLETE DEVELOPMENT AND TESTING OF ALGORITHMS TO IDENTIFY AND CLASSIFY SELECTED PHYSIOLOGICAL CHANGES OCCURRING AS A RESULT OF SPACEFLIGHT.	
2.1 Systems Identification and Application Systems Development 2.1.1 Identify Physiological Subsystems to be Analyzed	Completed - See TIR 741-MED-5012
2.1.2 Identify Physiological Parameters which Reflect the Status of the Chosen Subsystems	
2.1.3 Identify Data Required and Available to Define Symptom-Complexes for all Possible Physiological and Pathological States of Interest	
2.1.4 Identify Norms, Statistical Ranges, and Variations Caused by Environmental and Other Changes	
2.1.5 Develop and Implement a Pilot Program to Demonstrate Computerized Diagnostic Support and Fully Automated Interpretation of Physiological Signals, Both Real-Time and Post-Test	
2.1.6 Identify Methods of Classifying Data According to Biological Variables Which Affect Physiological Signals	
2.1.7 Define Methods of Using These Results to Assist in Refining Status Monitoring and Diagnosis	
2.1.8 Identify Statistical Programs to: a) Categorize, and,	
b) combine computer processed signals with anthropometric and physiologic data, history and laboratory test values for more complete diagnosis and to use this data as input to multivariate statistical discrimination and other programs,	
c) derive correlations between single or combination of parameters and physiological and disease states to assist in development of new or improved real-time status monitoring and diagnostic statements,	
d) develop approaches for establishment of probability figures for status and diagnostic statements.	

SCHEDULE

TASKS (Continued)	FISCAL YEAR 1973 (1 2 3 4 5 6 7 8 9 10 11 12)	FISCAL YEAR 1974 (1 2 3 4 5 6 7 8 9 10 11 12)	FISCAL YEAR 1975 (1 2 3 4 5 6 7 8 9 10 11 12)
2.1.9 Develop Improved Approaches, Algorithms and Computer Programs for Real-Time Crew Monitoring Under Stress Situations and for Analyzing Time Changes of Parametric Data as a Means of Developing Predictive Procedures			
2.1.10 Identify New Safety and Status Criteria Applicable to General Clinical Use			
2.1.11 Develop Improved Training Techniques for Personnel Involved in Real-Time Physiological Monitoring and Computer-Interactive Data Management and Display			
2.2 SIGMA 3 DATA INTEGRATION AND DISPLAY SYSTEM DEVELOPMENT			
2.2.1 Develop Data Integration and Display System (DIDS)			
- Prepare a design specification (DM-109T) for the Data Integration and Display System. This design specification will describe how each of the capabilities in the functional specification will be developed. The method of accomplishing each function will be described at the level necessary for programmer use. The design specification will contain flow charts of each program.	Completed-See TIR 741-MED-3016		
- Code and checkout the Data Integration and Display System. This activity will be accomplished in two phases: Phase 1 - Complete the coding and checkout of the Biomed Console Display Syst.	Demonstration Completed as reported in TIR 741-MED-3022		
Phase 2 - Add Computek CRT capabilities to DIDS.		Completed-See TIR 741-MED-3048	
- Prepare a User's Manual (DM-110T) for DIDS.			
2.2.2 Develop Statistical Evaluation System (SES)			
- Describe a conversational mode interactive communications philosophy.			
- Prepare the functional specification for the conversational mode executive software			
- Prepare the design specification for the conversational mode executive software.			
- Develop and checkout the conversational mode executive software		Completed-See TIR 741-MED-4019	
- Develop and checkout the statistical routines executive software.			
3.0 COMPLETE DESIGN AND IMPLEMENT A PLAN FOR COLLECTING, STORING, RETRIEVING AND COMPARING DATA COLLECTED WITHIN THE ENVIRONMENTAL PHYSIOLOGY BRANCH WITH GENERATED SUBSYSTEM ALGORITHM OUTPUT			Completed - See TIR 741-MED-5011
3.1.1 Continue the Determination of the Character of All Data Elements and Interrelationships, Including Maximum Character Length			
3.1.2 Lay Out a Master File for Consolidate Test Data and Associated Computational Elements			
3.1.3 Optimize Master File Layout and Define Retrieval Requirements Around Past Problems and Future Environmental Physiology Branch Goals			
3.1.4 Plan Requirements for Computer Programming and Production Based on Optimum Cost Effectiveness and Known Requirements to Other Life Sciences Directorate Interfaces Include Planning of Data Preparation Procedures and Automatic/Manual Test Data Recording			
3.1.5 Implement Requirements and Plans Above as Directed by the Technical Monitor			Completed - See TIR 741-MED-5010

	TASKS (Continued)	FISCAL YEAR 1973	FISCAL YEAR 1974	FISCAL YEAR 1975
		1 2 3 4 5 6 7 8 9 10 11 12	1 2 3 4 5 6 7 8 9 10 11 12	1 2 3 4 5 6 7 8 9 10 11 12
3.1.6	Monitor File Utilization and Incorporate Improvements as Required by User-Personnel			
4.0	DEVELOP HYPOTHESES REGARDING PHYSIOLOGICAL SUBSYSTEM RESPONSES TO SKYLAB ENVIRONMENTS AND STRESSES			
4.1	Perform bioengineering studies to assist NASA PI's & their assigned personnel in developing hypotheses of physiological responses to Skylab environments and stresses during postflight return to earth's gravity for potential application to advanced missions including ASTP and Shuttle. Study Skylab data relating to four Skylab experiments involving bicycle ergometer exercise, lower body negative pressure (LBNP) stress, hematology, and endocrinology. Participate in Skylab data analysis meetings & summarize proposed hypotheses to be tested under task 5.		Completed-See TIR 741-MED-4009	
4.2	Formulate mathematical model modifications to baseline physiological models to allow simulation of proposed hypotheses to be tested under task 5.		Completed-See TIR 741-MED-4009	
5.0	TEST PHYSIOLOGICAL SUBSYSTEM HYPOTHESES USING SKYLAB AND ENVIRONMENTAL PHYSIOLOGY BRANCH DATA			
5.1	Develop computer software systems to perform simulation tests of the proposed hypotheses developed under task 4. Implement in an interactive time-sharing mode, four existing subsystem models which include Guyton's circulatory model, a respiratory model, and an LBNP model. - Develop Guyton circulatory model for Univac 1106/1110 interactive and generate user's guide.		Completed-See TIR 741-MED-3049	
	- Develop Grodin's respiratory model for Univac 1106/1110 interactive mode operations - Develop exercise model for Univac 1106/1110 mode operations		Completed-See TIR 741-MED-3055 Completed-See TIR 741-MED-3041	
	- Develop LBNP model for Univac 1106/1110 operations and generate user's guide. - Design interfaces and develop combinations of these models where feasible and desirable to study combined hypotheses.		Completed-See TIR 741-MED-3053, TIR 741-MED-4003 and 4008 Completed-See TIR 741-MED-4009	
	- Develop alphanumeric and graphic display formats for output data from these models.		Completed-See TIR 741-MED-4004	
5.2	Develop an integrated Sigma 3 computer program system for retrieval and display of simulation data on the computer peripheral devices.		Completed-See TIR 741-MED-4019	
5.3	Plan, organize, perform, and report on simulation tests of physiological hypotheses utilizing systems developed under tasks 5.1 and 5.2 and mathematical model modifications formulated under task 4.2		Completed-See TIR 741-MED-4009	
6.0	DYNAMICALLY COMBINE SUBSYSTEM MODELS AND VERIFY RESPONSES			Completed - See TIR 741-MED-5008
	- Analyze and determine requirements necessary to integrate individual models into the whole-body algorithm.	Completed-See TIR 741-MED-3058		
	- Prepare a design specification (DM-109T) for the whole-body algorithm system. - Develop, checkout, and prepare a user's manual (DM-110T) for the whole-body algorithm.	Completed-See TIR 741-MED-4025		Completed - See TIR 741-MED-5009
7.0	DEVELOP AND IMPLEMENT A PLAN FOR COMBINING DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS WITH SUBSYSTEM AND WHOLE-BODY SIMULATIONS.			Completed - See TIR 741-MED-5006

tools in a way that would lead to their eventual compatibility as subsystem models for the whole-body algorithm. The primary effort under this task was to evaluate alternative candidate models for selection of a set of models representing the major body subsystems. The evaluation involved programming the models to operate on the available computer system and comparing the response with available experimental data. Several research studies were also required to investigate alternatives and develop approaches (such as identification analysis, stability and sensitivity analysis, boundary and initial value problem investigation, and improve physiological mechanisms and control functions). Some studies were also initiated under this task to investigate various approaches to interfacing these models and to develop compatibility between models with respect to their eventual use as subsystem models in the whole-body algorithm. Several models of these subsystems were also investigated and evaluated as possible alternatives such as the M. D. Anderson cardiovascular model and Milhorn's respiratory model. These studies resulted in recommendations which eventually altered the course of the contract work and the development of the whole-body algorithm. Among these were the decision to use Grodins' model for the respiratory subsystem model and the decision to develop a new model to simulate LBNP and tilt-table experiments based on the Croston cardiovascular model for exercise. This early task was very detailed with many subtasks identified and resulted in many TIR's in response to them as shown in Figure 1. This was true not only because of the better definition of the earlier tasks at the time the statement-of-work was written, but also because of the impact of this task on the course of the remaining tasks and ultimately the whole-body algorithm. The attention given to this task had an unquestionable contribution to the success of later major contract phases and the whole-body algorithm.

2.2 (TASK 2.0) CONTINUE AND COMPLETE DEVELOPMENT AND TESTING OF ALGORITHMS TO IDENTIFY AND CLASSIFY SELECTED PHYSIOLOGICAL CHANGES OCCURRING AS A RESULT OF SPACEFLIGHT

This task involves two major areas of investigation. The first area deals with applications for models and data systems in crew health status monitoring during spaceflight. Because of the impact of earlier contract studies and changing contract emphasis, this task was deferred to a later contract phase. The development of computerized data analysis systems, use of the simulation models for developing and testing zero-g hypotheses, and experience with Skylab physiological test and crew health status monitoring all had significant impact on the first part of this task. TIR 741-MED-5012 - "The Application of Computerized Data Systems and Simulation Models to Aid in Monitoring the Physiological and Health Status of Crewmen in Space" is a study report on this area of investigation.

The second part of this task involves the development of a Data Integration and Display System (DIDS) and a Statistical Evaluation System (SES) for the Sigma 3 computer. The development of these systems not only provided end-item programs for the Sigma 3, but also provided the basis for the eventual development of a data base and analysis system for the Univac 1108/1110 for Skylab data analysis.

2.3 (TASK 3.0) COMPLETE DESIGN AND IMPLEMENT A PLAN FOR COLLECTING, STORING, RETRIEVING AND COMPARING DATA COLLECTED WITHIN THE ENVIRONMENTAL PHYSIOLOGY BRANCH WITH GENERATED SUBSYSTEM ALGORITHM OUTPUT

This task resulted in the development of two major systems for the Univac 1108/1110 time-share system which complement the simulation models for analyzing spaceflight experimental data, developing and testing hypotheses, and researching the underlying physiological mechanisms. The first system is a data base and analysis system

which includes a data base for handling the Skylab major medical experiment data, a statistical and analysis package for analyzing and reducing the data, and a graphics display package for simultaneous display of data and model simulation results. The second system is an automated reference retrieval system. This library system acts as a repository for the Environmental Physiology Branch literature and has the capability to retrieve literature by subject, author, and key word.

2.4 (TASK 4.0) DEVELOP HYPOTHESES REGARDING PHYSIOLOGICAL SUBSYSTEM RESPONSES TO SKYLAB ENVIRONMENT AND STRESSES

This task and task 5.0 should be considered together because the process of developing and testing hypotheses is an iterative procedure. An initial hypothesis is postulated, formulated in the model, and tested by comparing the model response with experimental data. The hypothesis is then either revised or discarded and a new one is postulated and tested in the same manner. This procedure is continued until the iterative process converges toward the truth.

The systems analysis approach developed with the use of mathematical models in the earlier phases of this project was so encouraging as a potential method of formulating and testing hypotheses for physiological changes resulting from exposure to the spaceflight environment that the work under tasks 4.0 and 5.0 was expanded. This expanded work include a study to determine the feasibility and utility of using the simulation models and the systems analysis approach for analyzing actual Skylab inflight experiment data. This work was done under modification 4S to the basic contract and resulted in the successful demonstration of this approach using the cardiovascular models for exercise and LBNP simulation to formulate and test candidate hypotheses

related to these experiments by comparing preflight and inflight simulations with actual crew experiment data. The results of this study were reported in TIR 741-MED-4009 - "Skylab Medical Experiments Data Analysis - Phase I" which was a study report on the expanded work of tasks 4.0 and 5.0 under modification 4S.

2.5 (TASK 5.0) TEST PHYSIOLOGICAL SUBSYSTEM HYPOTHESES USING SKYLAB AND ENVIRONMENTAL PHYSIOLOGY BRANCH DATA

As mentioned above, task 5.0 should be considered with task 4.0 and the work under these two tasks was expanded to include a feasibility and utility study for the analysis of Skylab flight experiment data under modification 4S to the basic contract as reported in TIR 741-MED-4009. There was, however, a substantial amount of work done under these tasks under the basic contract which was preliminary to the expanded work under modification 4S which provided the basic capability to perform this work. This work was primarily centered upon converting the subsystem models to the Univac 1108/1110 time-share system and modifying them for interactive operation from remote terminals with graphic output capability. This work was necessary in order to provide the model capability necessary to perform the analysis under modification 4S. The interactive operation and graphic display capability on a much faster computer than the Sigma 3 was necessary to provide the operational capabilty to formulate and test hypotheses by direct comparison with Skylab experiment data.

This expanded operational capability and rapid computational speed also proved necessary for implementing these subsystem models in the whole-body algorithm. The whole-body algorithm could never have been developed within contract limitations without the speed and rapid turnaround capability of the Univac 1108/1110 interactive

time-shared system operation. The basic effort under tasks 4.0 and 5.0, therefore, provided double payoff by providing the basic capability necessary for hypothesis testing and the development of the whole-body algorithm. Additionally, the work done under modification 4S which demonstrated the usefulness of the systems analysis approach and mathematical models for formulating and testing zero-g hypotheses through the analysis of Skylab medical experiment data was so promising that a new contract, which is currently in progress, was initiated to perform this analysis on all Skylab experiment data. This contract, NAS9-14532, will result in the formulation and testing of the individual subsystem hypotheses using the subsystem models and, ultimately, in the formulation of an integrated total body hypothesis for the physiological changes due to extended zero gravity exposure.

2.6 (TASK 6.0) DYNAMICALLY COMBINE SUBSYSTEM MODELS AND VERIFY RESPONSES

The successful completion of this task represents the accomplishment of the primary objective of this contract - to develop a whole-body algorithm. A great deal of study and research was required to develop a general approach to the design and implementation of the whole-body algorithm. Several consultants under subcontract were used to examine the model interface requirements for accurate physiological representation and to develop the approach. Much of this work is summarized in TIR 741-MED-3058 and the design specification (TIR 741-MED-4025). The results of this significant research effort is reported in TIR 741-MED-5008 and represents a major accomplishment of this contract work. This report also presents the validation of the whole-body algorithm by comparison of the simulation of the experiments of interest with experimental data from many different sources. A user's guide for the whole-body algorithm is given in TIR 741-MED-5009.

2.7 (TASK 7.0) DEVELOP AND IMPLEMENT A PLAN FOR COMBINING DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS WITH SUBSYSTEM AND WHOLE-BODY SIMULATIONS

Relatively little work has been done in the area of clinical applications of simulation models on the subsystem level. This area of investigation has a great deal of potential, but because of the relatively meager amount of information in the literature, the work under this task has been primarily concerned with investigating the need for such research and its applicability to the space program medical support requirements and research objects. A considerable amount of work and a major research program would be required to develop and implement the potential uses of simulation models in clinical diagnosis and therapy because such a project has not been attempted to date. However, the work of several Russian investigators, where this area of investigation has received a good deal of attention in connection with the Russian space program, has suggested the importance of examining this area of research much more carefully. The preliminary study under this task is reported in TIR 741-MED-5006.

2.8 SUMMARY

The systems analysis approach has been utilized primarily in the investigative areas of cardiovascular (LBNP, tilt) metabolic (exercise), endocrinology, fluid balance, and hematology. Five mathematical models have been developed under this program which include: a pulsatile model of the cardiovascular system (Croston), a model of the long term fluid and electrolyte balance (Guyton), a model of the thermoregulatory system (Stolwijk), a model of respiratory system (Grodins), and a model of erythropoiesis (GE). A more detailed correlation between NASA investigative areas and math models is shown in Figure 2.

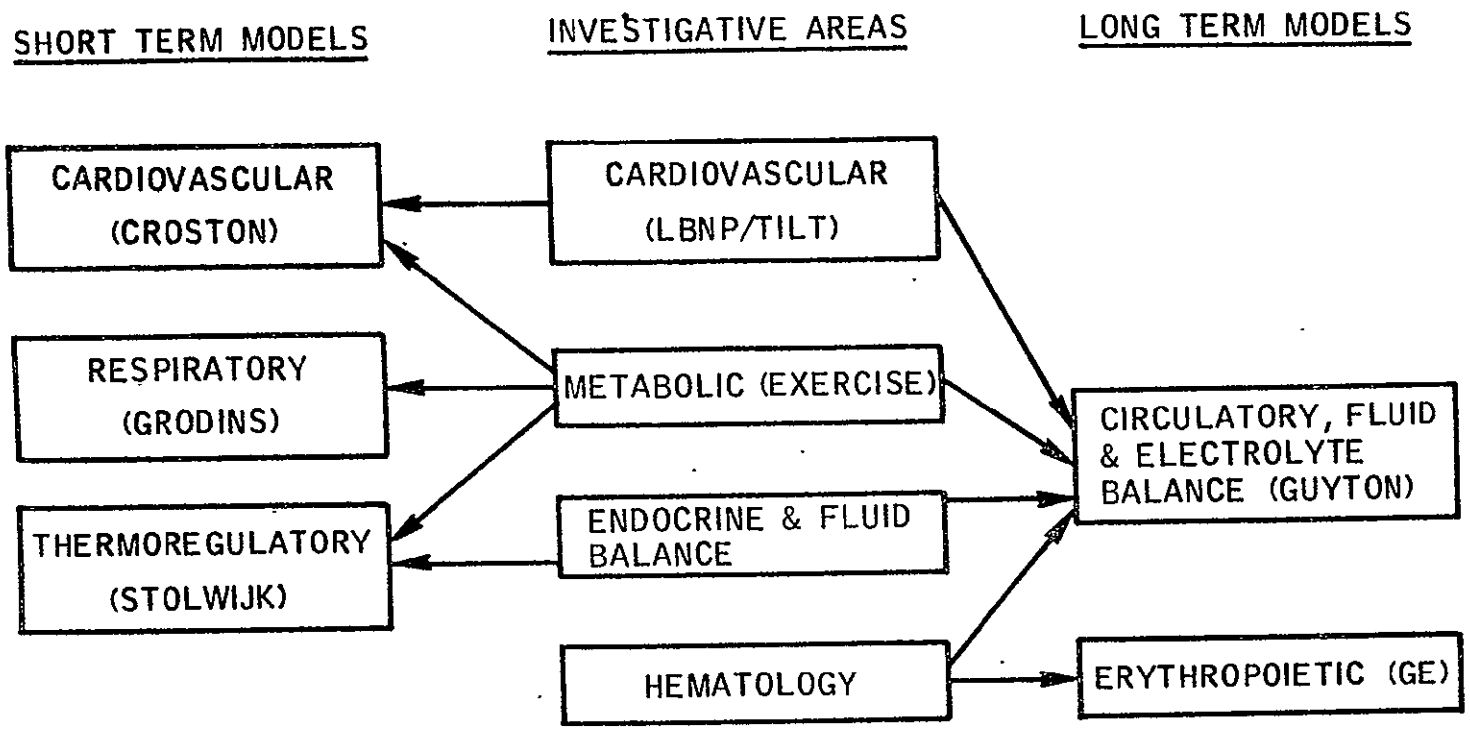

FIGURE 2 SIMULATION MODEL ASSOCIATION WITH INVESTIGATIVE AREAS

These physiological math models are the product of original research sponsored by NASA or have been selected from among existing models and modified to incorporate the specific functional relationships required to simulate experiments in the associated investigative areas. These physiological math models have been thoroughly documented in open scientific literature and in the Technical Information Releases (TIR's) submitted to NASA as out lined in section 5.0. The major subsystem models have further been integrated into a whole-body algorithm which will be capable of simulating dynamic subsystem interactions for long term adaptation and short term experimental stresses. These models are currently being used as an effective method for assembling knowledge about the physiological systems under investigation in a systematic way, and, therefore, to reveal the extent of existing knowledge and point out gaps in knowledge requiring further investigation.

In addition to the development of the whole-body algorithm, several supporting objectives of the data integration and display program have been completed. A data base structure has been completed for the storage, retrieval, and display of Skylab experimental data. Mathematical models and a supporting data handling system have been integrated on a time-sharing computer to produce direct graphical comparison of model output to experimental data. This system provides a convenient method for testing or validating existing concepts of new hypotheses by comparing the properties and behavior against reality. The validated models and supportive software are currently being used to formulate and integrate zero-g hypotheses. For this application, features of these models which provide good representation of the system function are used to predict system properties or behavior that were not measured in vivo.

3.0 CONCLUSIONS

The usefulness of systems analysis and simulation models is becoming well established in medicine and physiological research. The work done under this contract has been significant in advancing the knowledge in this area of research and has been successful in demonstrating its usefulness. The simulation model can provide insight into the system under study which is not obtainable by other means. Simulation techniques are particularly suitable for studying human physiological systems where it is not possible to make direct measurements or perform invasive experiments. Much of the work done under this contract has been concerned with developing these techniques and applying them to the study of the physiological responses of the human system in the spaceflight environment. Once a system model is developed and validated, it is possible to predict quantitative responses of the human system for many sets of conditions and constraints. A good example of this in the manned space flight program is the use of a human thermoregulatory model to predict thermal comfort conditions under a wide range of environmental conditions and metabolic demands which led to the successful designs of Apollo and Skylab life support control systems. In support of manned space flight, simulation can also provide predictive extrapolation for real-time supporting decisions by ground-based personnel.

In physiology research, the use of mathematical models and computer simulations has also proved to be of great value. The formulation of the model, based on a wide variety of observations on the real system, provides insight into the organization of the system elements, the processes within the elements, and the multiple pathways connecting these elements. During simulation the dynamic interactions between various subsystems of the model become more apparent.

Simulation enables an investigator to understand in greater detail how a biological system works through variation of the system's parameters. Mathematical models can indicate existing gaps in physiological data and suggest the type of experiment needed to obtain missing information. A model can be considered a framework on which all known observations of the system can be integrated and tested for consistency under a range of conditions. Thus, the model unifies the system so that an overall dynamic response can be considered. This use of mathematical models provides a new way to look at physiological systems and adds another dimension to experiment physiology.

The studies performed under this contract can be seen to follow a logical flow in a process that fully utilizes the systems analysis approach in studying physiological systems in both 1-g and weightlessness, for short term and long rerm experiments, for clinical as well as more basic physiological research. Important physiological subsystems are identified and simulation models are developed, modified, and validated. This is a continuous process because new physiological mechanisms are always being uncovered and new experiments are constantly being performed to challenge the model. The formulation of a whole-body system, by combining these subsystems, is a natural outgrowth of this process since it allows important inter-system pathways to be included and can permit a stress in one subsystem to reveal its influence on other subsystems. The inclusion of automatic data base systems and statistical analysis capabilities adds a new dimension to the systems analysis approach. With this tool the simulationist/experimenter can rapidly scan large amounts of data (such as Skylab medical data), graphically visualize correlations between variables and test hypotheses statistically. Acceptable candidate hypotheses can

be used to predict the effects of the hypotheses on other subsystems. These predictions may then become the basis for additional data analyses, the design of new experiments, or perhaps new model refinements.

Other uses of computer simulation in medicine and physiology can be realized when major subsystems/models are joined together to simulate the interaction between major body systems. For example, simulation could be used for real-time monitoring of patients, providing extrapolations of trends in important parameters, identifying the critical parameters in a system and the level of accuracy needed in their measurement, aiding in diagnosis, and indicating patient response to simulated therapy. Some of these applications will be discussed in more detail in section 4.0.

A common thread that runs through these interdisciplinary studies is a continuous emphasis on state-of-the-art surveys, identification of alternate models, software systems, technical approaches and trade studies for helping to evaluate the best candidates to meet each particular requirement. This approach is important because the entire effort represents a pioneering effort of applying automated systems analysis techniques to physiological/medical aerospace problems. Rapid advances are being made in physiological research, systems theory, and digital computer software which, while perhaps not originally intended for aerospace applications, can and should be identified, evaluated, and integrated into the total system design. The value of this systems analysis approach is demonstrated and confirmed by the successful accomplishment of the whole-body algorithm within the cost and schedule constraints of this contract.

A very important finding in this study is that the selected design approach, which is consistent with sound systems analysis procedures, has provided a whole-body algorithm simulation model that not only

meets the stated objectives and requirements of this contract but also:

1) provides a flexible structure for making changes in the model without total disruption of the entire system.

2) provides a central repository for collecting individual and total system hypotheses for physiological changes due to the space flight environment.

3) provides a simulation model which is capable of testing multiple system interaction and total system hypotheses related to any of the stresses for which it is designed to simulate.

4) provides the basic capability to simulate multiple and sequential stresses with little or no basic change to the model.

5) provides the basic structure for adding new subsystem models, improved sections in the subsystem models, and the mechanisms and/or interface changes necessary to simulate additional stresses including pathophysiological stresses.

A wide variety and large number of stresses as well as different stress levels have been simulated including environmental disturbances (ambient temperature changes, hypoxic and hypercapnic gas mixtures), metabolic changes (supine and sitting exercise), and special experimental situations (tilt-table studies, LBNP, and bed rest). Simulation of short term stresses resulted in simultaneous and integrated responses from the cardiovascular, respiratory, and thermoregulatory subsystems and the accuracy of a large number of responding variables was verified. The capability of simulating significantly longer responses was demonstrated by validating a four-week bed rest study. In this case, the long term subsystem model was found to reproduce many experimentally observed changes in circulatory dynamics, body fluid-electrolyte regulation and renal function.

Perhaps one of the most important conclusions which has been reached in this study is that the selected approach has yielded a whole-body algorithm simulation model which is extremely stable. This is true not only from the standpoint of response to stimuli or input conditions, but also from the operational viewpoint. The model seems to respond with reasonably good results even when gross inaccuracies or inadequacies were present during the development phase. Guyton has made similar observations concerning his model and attributes this phenomena to the extreme stability of the real system. Perhaps this observation confirms the idea that interacting subsystem models better represent the overall regulatory capability of the real system, and, therefore, inherit some of its innate stability and compensatory characteristics.

Even though this first version of the whole-body algorithm is an initial attempt to develop a total body system model, it provides a very powerful research tool and may be found to have many and varied practical applications as well. This program has been directed toward its development and verification for the specific purposes for which it was designed and, therefore, does not address the many possibilities for important applications. For that matter, applications of the model for which it was designed are not included in this program. Although a great deal was learned in the design and development of the whole-body algorithm, the next step is most certainly to put this powerful tool to use.

While the whole-body algorithm has reached the end of this first phase of development and already has very significant simulation capabilities, this is not to say that the work in this area is complete. Quite the contrary; the first version of the whole-body algorithm is only a start toward developing a total body simulation system. Many

subsystems have yet to be represented, particularly in the biochemical and neurological areas. Many improved mechanisms in the existing subsystems are being developed by other investigators and should be included. Many other experimental stresses and verified physiological hypotheses should be represented in the model.

4.0 RECOMMENDATIONS

This section presents some recommendations for future work based on the several studies and the results of work done under this contract. Some of these recommendations are already in the planning stages and Figure 3 presents a perspective of these recommended projects with respect to completed and on-going contract work.

4.1 IMPROVEMENTS IN THE FIRST VERSION OF THE WHOLE-BODY ALGORITHM

Many specific recommendations for improvements, additions, and more validation have been formed during the development of the first version of the whole-body algorithm. The more important ones are:

1) Add new compartmentization in the long term model to represent the legs since many of the important long term changes occurring in zero-g and bed rest involve the legs.

2) Add the capability to simulate postural changes in 1-g to the long term model for better simulation of the postflight readaptation to 1-g.

3) 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.

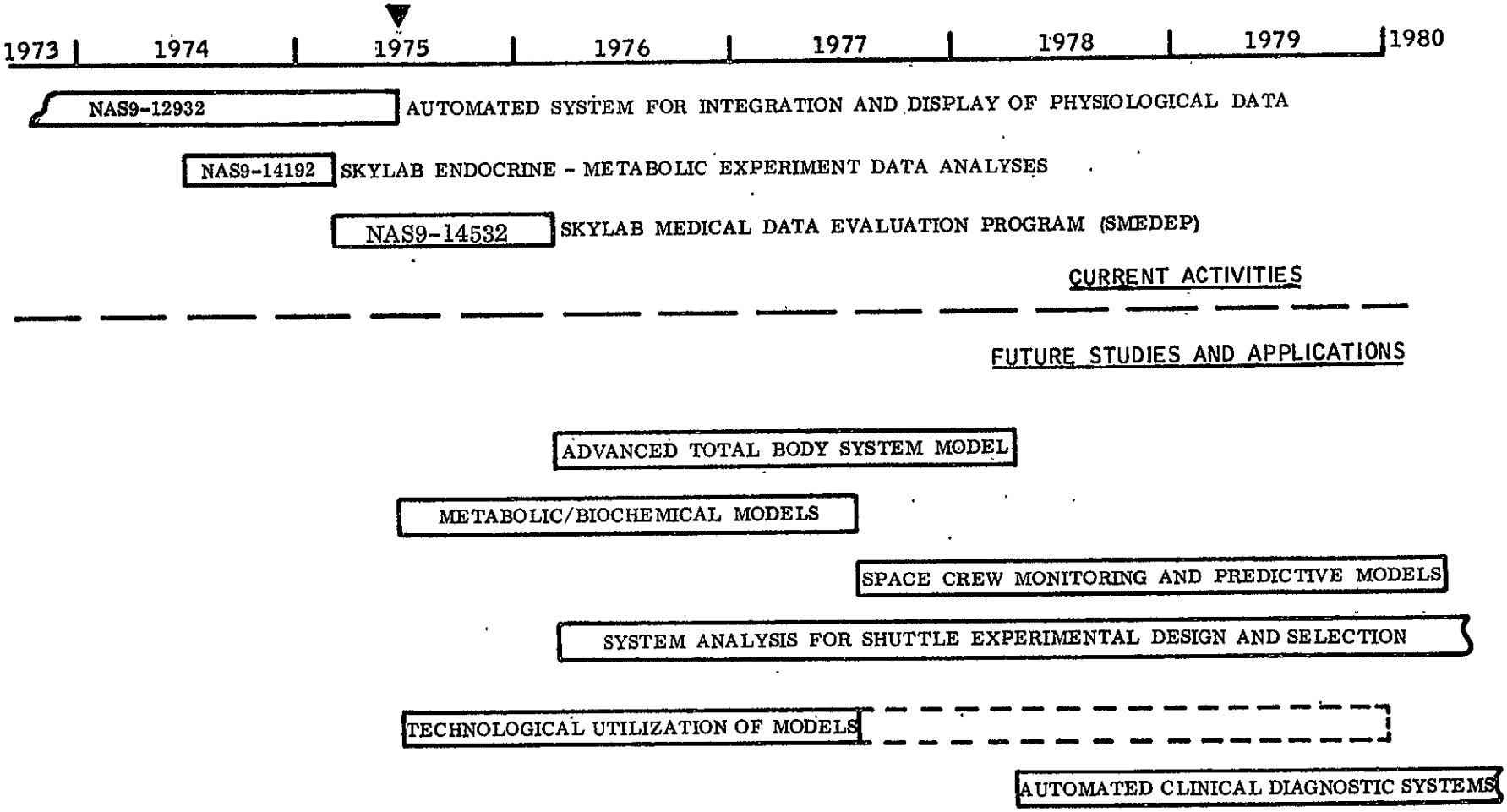

FIGURE 3 PHYSIOLOGICAL SYSTEMS ANALYSIS, MODELING, AND COMPUTER SIMULATION OF BIOMEDICAL EXPERIMENTS

4) 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) and are needed to produce the transient response in the system for the next hour or so.

5) Improve representation and/or validation of long term adaptation/acclimatization (particularly since this is an area of interest in space flight) to long term stress. Data from people living in hot and cold climates and at high altitudes may provide a starting place for such study.

6) Improve respiratory - thermoregulatory subsystem interface (other than through the cardiovascular subsystem) to improve simulation of respiratory heat losses and thermal influences on respiratory control.

7) Improve the flexibility for simulating different population responses to stress such as the effect of training/conditioning, age, etc.

8) Continue validation particularly in the areas of transient responses (both on and off) such as to exercise and thermal stress and multiple stresses for which data are available such as exercise and environmental stress, dehydration and exercise, tilt and environmental stress, and combined environmental stresses. More testing of bed rest hypotheses is also needed.

It is anticipated that, as the SMEDEP work (Contract NAS9-14532) develops a total system integrated hypothesis for the physiological

changes due to exposure to the space environment, there will be a requirement to modify the whole-body algorithm to include the formulation of these mechanisms. This would, in effect, make the whole-body algorithm capable of simulating the response to above stresses in the zero-g environment. The whole-body algorithm could then be used to examine the physiological interactions between the major subsystems for the zero-g hypothesis. In this way the whole-body algorithm could be used to test the integrated total body zero-g hypothesis whereas only the individual subsystem hypotheses can be tested separately on the individual subsystem models.

4.2 SMEDEP FOLLOW-ON ACTIVITIES

There are several outgrowths and applications that are expected to be based on the results of this program. Among these are the use of the models with the zero-g hypothesis mechanisms formulated in them for predicting responses of unmeasured variables, for assisting with experimental design for both ground-based and Shuttle flights to verify the hypothesis, and for real-time physiological monitoring of the crews for Shuttle flights. The individual subsystem models can produce very accurate responses to the major medical experiment stresses in a 1-g environment. It is easy to postulate many uses of these models if they could also be made capable of accurately duplicating the responses to these stresses for the space flight environment. They could be used as predictors of many important response variations for different conditions as well as indicate the values of those not measured, and as translators of events from the well-known 1-g response to the little-known zero-g response.

4.3 SYSTEMS ANALYSIS AS AN AID FOR DESIGNING MEDICAL EXPERIMENTS ON FUTURE SPACE MISSIONS

The great expense of space flights and the limitations on payloads and personnel make it incumbent for space mission planners to choose

carefully those experiments which offer the greatest return. This is often a value judgement based on immediate and long term scientific goals as well as political and economic realities. Scientists and planners should be provided with as much information as possible for this task as well as analysis techniques that will help assimilate and integrate this information. The broad area of systems analysis has proven to be a valuable approach for systematically organizing information and in deducing from this network the consequences of alternative plans.

An important use of simulation models has been to predict experimental results or stress responses which cannot be determined directly because of excessive risk, cost, or delay. The more highly developed the model the greater the predictive capabilities. However, a powerful use of simulation models is as a research tool to aid in designing and interpreting experiments rather than to take the place of experimentation. For these purposes, it is not always necessary that the model be an exact description of reality; a gross approximation will often be sufficient. Certain special techniques, such as sensitivity analysis, error analysis, and parameter estimation, have been developed that greatly enhance the use of simulation models in this regard. The following outline briefly discusses many of the uses that simulation models afford the scientist/planner in designing experiments (details have been omitted in the interest of brevity only; the techniques discussed have been developed sufficiently to begin applying them immediately to any physiological system which is not well understood and for which a gross descriptive model has been formulated):

(1) Models can be used to rapidly simulate long term experiments. An experiment that would take weeks to perform, but can be simulated in a relatively short period of time should be simulated first to establish the exact conditions that are desired.

(2) Models that predict unsteady state responses can be used to indicate the times when variables are changing more rapidly and thus suggest the time protocol for making data measurements.

(3) Traditional methods of stressing systems, such as inducing single step changes in a system parameter, often do not produce as much insight into a system as more unusual types of stresses such as multiple, sequential or time varying stresses. Models can usually predict, better than human intuition, the effects and advantages of using these types of experimental stresses.

(4) Sensitivity analysis is a systematic and quantitative method of identifying the most important parameters of a system; i.e., those that have the greatest influence on given response variables. This method would provide a rational basis for deciding priority of experimental measurements and cost allocations.

(5) Error analysis, when combined with sensitivity analysis, can lead to an even more powerful ordering of priorities. This technique provides an estimate of the relative contribution of errors of the major system parameters to the final system response. This information can be used to define the limits of allowable experimental error and hence suggest acceptable measurement techniques.

(6) Simulation may be used to design decisive experiments by determining those conditions under which competing theories or hypotheses predict the most divergent experimental results.

(7) Physiological function of a particular system (such as the circulatory or respiratory system) is often evaluated clinically by measuring only a few system variables (such as heart rate, tidal volume, etc.). As more knowledge is gained, these "performance criteria" are reevaluated and improved (e.g., the recent advent of

using exercise stress and non-invasive measurements to evaluate cardio-respiratory function). Simulation can be used to aid in this process of developing performance criteria which are sensitive to deteriorating physiological function. This can be done by testing complex combinations of parameters and correlating them with simulated stress and pathological states. This in turn would suggest experiments to test any favorable simulated results.

(8) The interpretation of experimental results can also be aided and extended by modeling. Parameter estimation procedures involve adjusting parameter values in a model until certain simulated responses compare favorably with experimental measurements. This results in estimating values for parameters and responses of the system that would otherwise be difficult or impossible to measure directly.

These examples show some of the ways in which models by themselves can benefit experimental design and interpretation. However, this is only part of the process. Full potential of the systems analysis method is realized when there exists an iterative cycle between model development and experimental observation. That is, the model, which represents the sum knowledge of a particular system, is used to suggest hypotheses and experiments, which in turn leads to refinements in the model and new model responses that must be tested experimentally... and so on. Thus, experimental design always follows directly from a highly organized search of the most critical elements in the system based on the most recent integrated system hypotheses.

4.4 ADVANCED TOTAL BODY SYSTEM MODELS

One of the important functions of the systems analysis approach and math modeling is to point out the area in which much more work is needed. It is already apparent that there are several voids in the

models currently available for studying the physiological processes of interest much less the pathological process and the complications of translating even the well understood process into the space environment. Much work is needed in the areas of modeling metabolic and biochemical processes, renal function, vestibular function, and a host of others. There has been little done in the area of modeling to understand disease processes on a subsystem or system level.

Addressing these voids must be among the objectives of an advanced total body system model. However, to go beyond interacting four major subsystem models into an algorithm for studying interactions between these subsystems, one must consider an even more basic problem than filling the voids of these models. It almost seems like a conflict in terms, but the model must be simplified before much can be done, which may require a totally different approach than building a total body model by connecting subsystem models together. The first version of the whole-body algorithm is already unwieldy and difficult to work with as well as being very time consuming and expensive to operate. Expanding to fill voids and simplifying, however, are not conflicting terms in systems analysis. In fact, at the very heart of the systems approach is an iterative process of improving and simplifying to preserve and enhance the essentials and discarding or reducing to essential the non-essential. It is, therefore, expected that by the time the first version of the whole-body algorithm is outdated, a second will begin to emerge and the best approach to the building of a total body system model, if it is different, will be clear.

4.5 BIOCHEMICAL/METABOLIC MODELS

Human biochemical and metabolic functions have received relatively little attention in the present systems analysis effort. Indeed there have only been a few outstanding attempts in general to

subject whole-body biochemical functions to the rigors of systems analysis, modeling, and simulation. This neglect can be related to the difficulty of studying these massively complex and interrelated systems on a whole-body basis. The enormous number of body chemical constituents, both organic and inorganic, enzymes and hormones, are believed to be regulated to a fine degree in the fluids that bathe and protect the tissues and organs. And yet there is also a high degree of interaction, either directly or indirectly, between most of these substances. This suggests a very complex network of multiple pathways and feedback loops. The difficulty of attempting to gain insight into even a portion of this sytem is compounded by experimental obstacles such as: inaccurate and cumbersome methods of assaying enzymes and hormones, the uncertainty of obtaining samples from the micro-compartments of interest, and the often times large number of chemical components that need to be assayed. The array of data collected during the metabolic and body fluid experiments aboard Skylab is indicative of the scope of the data analysis problems investigators are faced with in attempting to gain insight into the biochemical and metabolic changes associated with long duration space flight.

Recently, however, a clearer picture is emerging of the organization of the body's biochemistry and its relationship to the regulation of other physiological systems such as the circulatory, respiratory, and renal systems. Physiologists have successfully isolated certain organ systems and determined experimental transfer functions relating plasma concentrations of effector chemicals to enzyme or hormone response. In some cases models of certain biochemical and metabolic systems have been constructed and experiments have been designed specifically to provide parameter values, transfer functions, and validation data for these models. For example, models have been developed

that attempt to describe the thyroid-iodine regulating system, calcium metabolism, adrenocortical steroid regulation, and insulin-glucose regulation. Several renal models now exist that describe electrolyte-fluid regulation and include mechanisms for the action of antidiuretic hormone, aldosterone, and the angiotension-renin cycle. Modeling has also seen some exciting application in basic physiological studies of cells and tissues. A significant body of systems analysis literature exists on capillary exchange, transport across biological membranes, intra-tissue diffusivity, and mitochondrial energy production.

There is a need, however, to integrate much of this work and extend it to account for whole-body function. A more complete description of such important phenomena as acid-base balance, fluid-electrolyte balance, and hormonal response and effects will enhance a model's ability to more accurately simulate the major physiological functions that are of concern in the present research effort (i. e., respiratory, thermoregulatory, and circulatory function). The recent Skylab program has revealed that some lack of understanding still exists in many biochemically related areas such as calcium metabolism regulation of sodium and potassium, fluid distribution, and red blood cell production. An understanding of the production of metabolites during exercise seems to be important to an accurate description of cardio-respiratory regulation during this stress. An area which has recently demonstrated a certain degree of success is the whole-body modeling of pharmacokinetics. The application of these models for drug uptake studies and chemotherapy would be important both in the space and earth environment. Solutions to a small portion of these problems have already been addressed in the models currently in use, but they are incomplete and not fully validated.

A program for incorporating a more complete description of biochemical and metabolic systems into the existing framework of simulation models should have many benefits as suggested above. Such a program should initially concentrate on defining specific needs and applications, reviewing existing models and the current physiological literature and developing algorithms that would meet the identified requirements. A second phase would proceed along lines similar to that followed in developing current models: identifying mission information, collecting data for verification and validation, and incorporating these algorithms into the whole-body model.

4.6 AUTOMATED DIAGNOSTIC SYSTEM

Since the physiological math models provide an accurate simulation of the human system's response to stress, they can be used to understand the human physiological process and physiological changes so that both can be analyzed and predicted. The use of these models in a predictive mode assumes that the models have been verified for the response of interest in the environment of interest and "tuned" for the individual being observed. If this procedure has given the observer confidence that the model can accurately "predict" the "normal" response to a given stress, then the individual's response to this stress can be compared to the model response and a safety margin or "redline" boundary established for the safe operating range for that individual to determine when a given stress should be terminated. In the same sense, any pathological process due to disease which is understood can be modeled and the human system's response to the pathological stress can be simulated. And, again, the model would establish a "normal" response to candidate disease states under the environmental stress situation and the individual's response compared

to it to establish a candidate diagnosis. Various courses of treatment could also be evaluated on the model before administering to the individual.

The use of models in this way may become important in space because the "classic" symptoms from which diseases are normally diagnosed on earth may be significantly altered by the zero-g environment. A model which is capable of responding to a given disease state in a 1-g simulation with the "classic" response and which has been verified as an accurate simulator of the space flight environment may be a very powerful tool for translating these "classic" terrestrial responses into "classic" space flight environment responses. In the same way, earthbound treatment procedures may be inadequate or inaccurate when applied to the spacebound patient. Of course, the remoteness of the patient from the physician and diagnostic equipment (such as x-ray and laboratory equipment) make any other available methods more important.

The use of simulation models in this mode is certainly not new to the space program. Many problems encountered in spacecraft systems while in flight were isolated and resolved on the ground through the use of simulation. The system simulation was used as a surrogate to isolate the source of the problem in the real system by failing various parts to match the symptoms observed in the real system. Once the failure was "diagnosed", a workaround procedure (treatment) was tested on the surrogate before attempting the procedure on the real system.

The use of these deterministic types of models are a very important consideration for the development of an automated diagnostic system for the space environment applications because of lack of knowledge with respect to disease processes in the presence of these unusual stresses. However, to be complete, and to take full advantage

of the capability of modern computers, other types of models (such as stochastic models) and data analysis systems should be evaluated for use in conjunction with deterministic models. A total system approach for automated diagnosis would be designed as an adjunct to and in support of the needs of a flight surgeon or physician. Such a system would be needed whether the physician were onboard or on the ground whereby the physician would either be remote from this patient or from his laboratory and library. In any case, the space environment of his patient, as mentioned above, may require the use of special aids to address the diagnostic and treatment problem. The design of the system would certainly differ depending upon the circumstances. A block diagram of one concept is shown in Figure 4.

4.7 SPACE CREW MONITORING AND PREDICTIVE MODELS

There are many applications for physiological models which are capable of operating in a predictive mode. As has been mentioned above, the predictive mode of model operation is based upon the ability of the model to accurately simulate the response of the real system to a given stress or combination of stresses under controlled conditions. This capability is particularly important for combinations of stresses for which the response is not easily produced experimentally (such as those including zero gravity in combination with other stresses) and for observing individual responses which do not fit the normal pattern of expected response because they do not fit the class of subjects from which the data base was derived. The ability of a physiological model to "predict" a response of interest is based upon confidence that the model can faithfully reproduce a known response to usual stresses under controlled circumstances and its integrity is preserved after imposing additional stresses or after the addition of a change in the

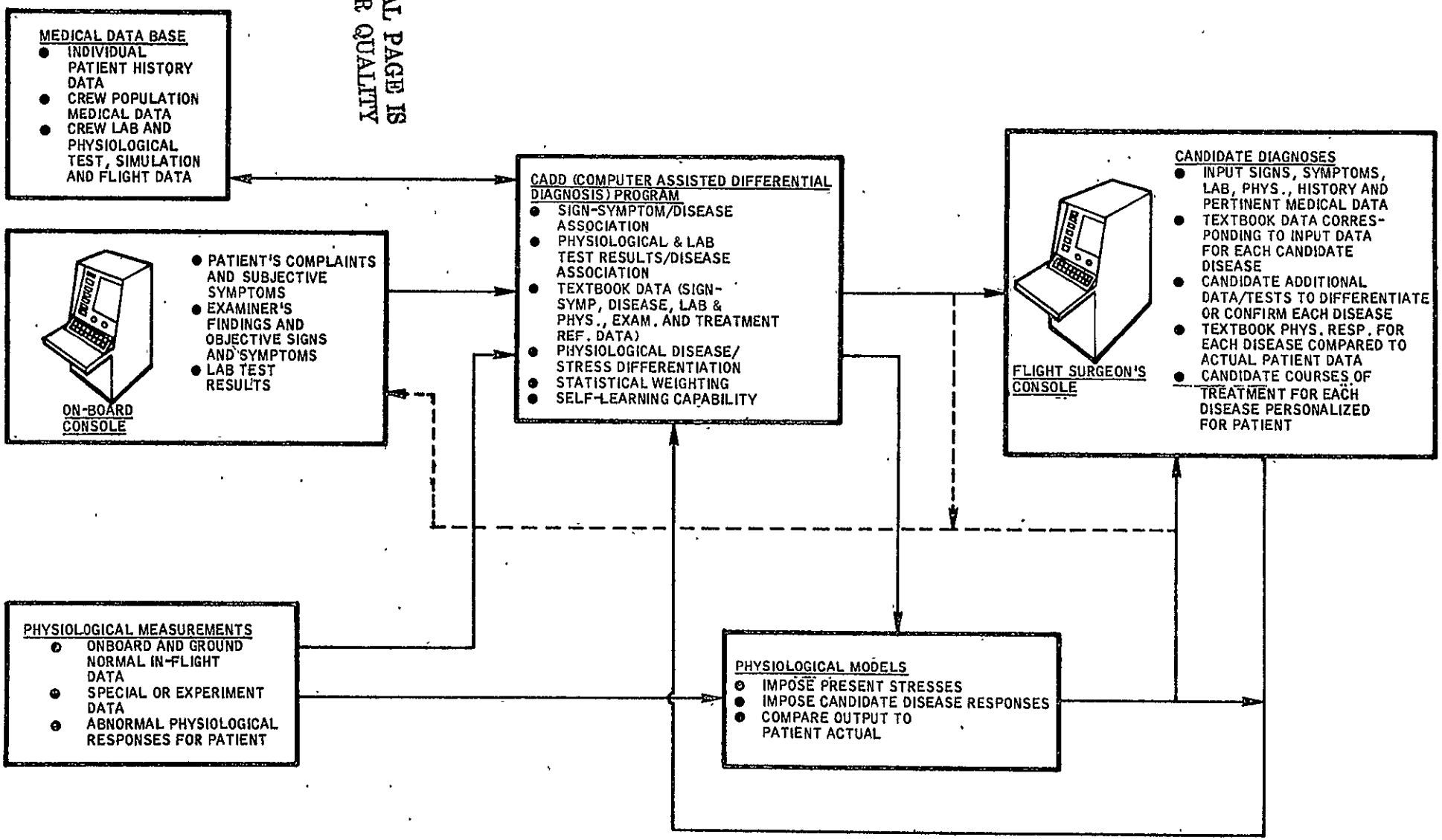

FIGURE 4 CONCEPT FOR AN AUTOMATED DIAGNOSTIC SPACE SYSTEM

model which represents mechanism of a physiological change in the real system for which the prediction is desired. This predictive mode is useful not only for pathological responses (to disease stresses), but is also useful for monitoring physiological responses to unusual stresses or combinations of stresses or unusual individuals both in space and during ground-based experiments.

The output of a predictive model system which represents the predicted "normal" or "safe" range of response for a given set of circumstances can be used as a basis of comparison for the response of an individual or a group undergoing the stress or stresses being simulated by the model. In this way the monitor can determine when a stress should be terminated based on a measurement or a unique combination of measurements which reached a "redline" condition as predicted by the model system. The model system can be made up of physiological models, or statistical (stochastic) models based on accumulated and analyzed biomedical data, or some combination of both. Such a system could be used as a real-time monitor of biological data during an experiment or a space flight, either as a separate system or in combination with an Automated Diagnostic System as discussed above. Figure 5 is a block diagram of one concept of a biomedical monitoring system.

4.8 SPECIAL PURPOSE SIMULATION MODELS

There are many potential special purpose applications of physiological math models which are just beginning to be developed by some investigators such as drug uptake analysis and chemotherapy studies. One of the most promising areas of investigation of this type is in determining the values of various measurements which require invasive techniques by using models to simulate the real system and calculate the values.

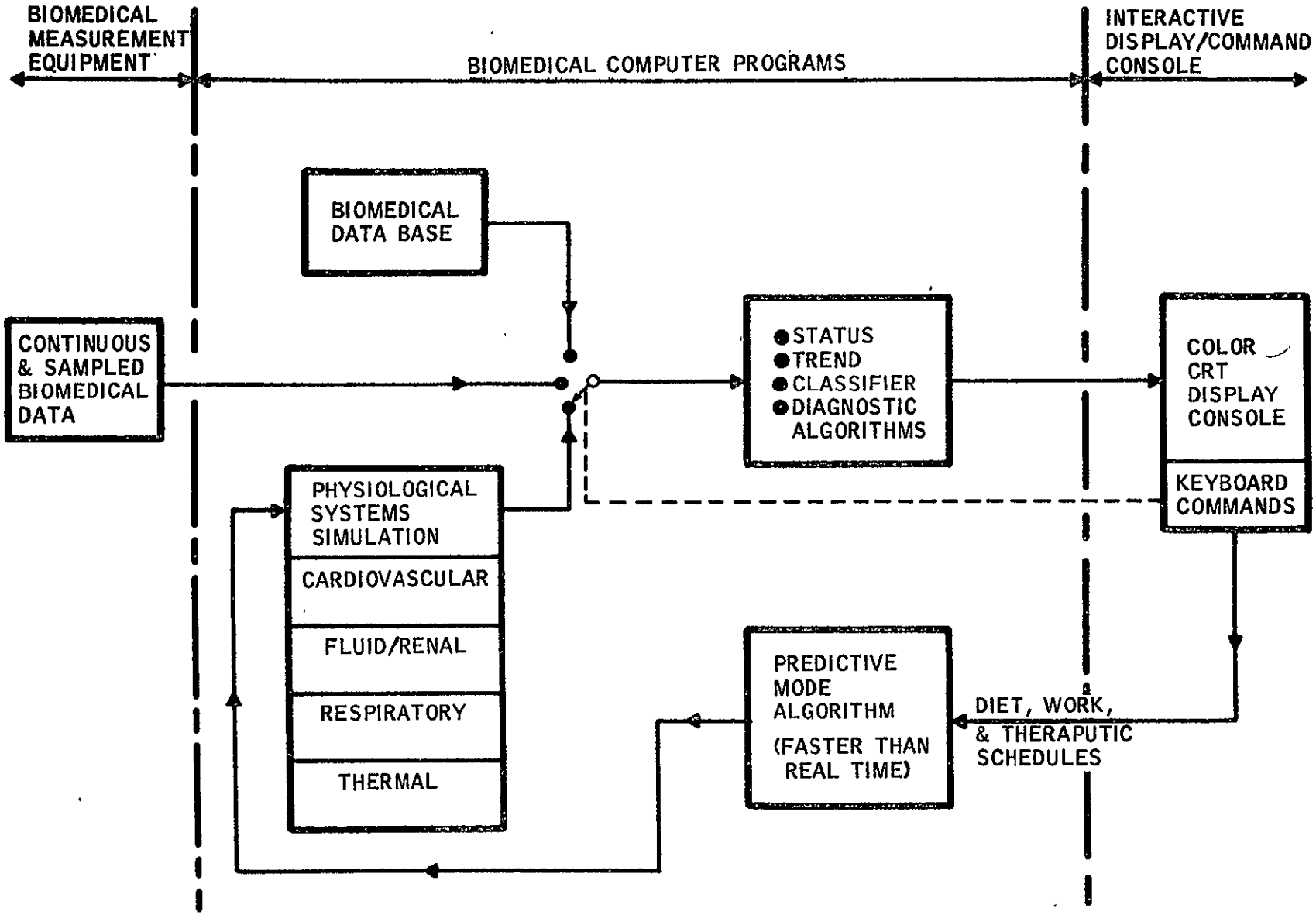

FIGURE 5 ADVANCED BIOMEDICAL COMPUTER SYSTEM CONCEPT

4.9 TECHNOLOGICAL UTILIZATION OF MODELS

Several investigators have suggested the need for a system which could make large complex computer simulation models available for general use. Most investigators are willing to make their models available, upon request, to other investigators, but the lack of commonality between computers and programming languages make the interchange of models between investigators difficult or costly. Also many investigators do not have the availability of a large computer which may be required for some of the models of interest. Educators and others have suggested a single repository concept whereby contributors could have access to each other's models. This concept is attractive for many reasons such as the idea of building upon the efforts of others which eliminates redundant effort for each category of problem. Also much of the work by these investigators has been done on government contract or grant and the results properly belong in the public domain. Any investigator embarking on a new problem area who wishes to make the maximum utilization of his resources will survey the state-of-the-art and capitalize on the works of others. A system is needed whereby this work can be made available to him and the system should maintain the state-of-the-art in modeling.

The best computer system currently available for this purpose would be a large nationwide time-share system. This type of system would allow contributors to put their models in place on the system which would satisfy the "central repository" concept. Each user would then access the system via a time-share terminal at his location and communicate by telephone line with the central computer. A regulatory body would be required to initiate and maintain the system. If a source of financing were made available, a panel of investigators from the major contributing research centers could be set up to

perform this function. This panel would first survey the state-of-the-art and select the best models of each type for inclusion in the system. The models would then be converted to the common computer and properly documented with user's instructions for all the models. As each user develops improvements to existing models or creates new ones, the panel would approve them for addition to the system and update the documentation periodically. A system of this type would provide an important additional capability to any research center, however, large and complete, but perhaps more importantly, it would make large complex models available to smaller facilities such as hospital and university laboratories. This system would also establish a very important system of communication between the research centers on a national level and provide a forum for new development. Such a communication system could provide an important national resource for all biomedical experiments and investigators.

This resource would also contribute to the future development and application of physiological modeling by making them available as a teaching tool as well as a research tool. Many larger universities and medical centers are currently using simple models as a teaching aid. These models are used in this way to demonstrate important physiological processes at all levels of detail. Larger more complex models could also be used in this way to demonstrate complex interactions between subsystems and to provide a much less costly source for student experiments than is currently available. Also many important human system experiments are either very difficult or impossible to duplicate in animals or in vivo human laboratory experiments. Harvard Medical School has developed an analog version of a circulatory model and made it available commercially as a teaching tool for medical students. It is manufactured in the form of an electronic device whereby switches and dials can be configured

to represent various circulatory system failures or pathological states and the output displays the proper response of the real system for this condition. Much more complex digital computer simulation programs of physiological systems could be used in the same way through a system like the one described above. The teaching institution would only be required to purchase or lease a time-share terminal and pay use time on the computer system and telephone lines for the availability of a large array of models capable of simulating the physiological and pathological processes for many body systems at several levels of detail.

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