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SUBJECT

Fluid and Electrolyte Control Systems in the Human Body - A Study Report

In this study report, research in the area of
modeling of the fluid and electrolyte system is
briefly reviewed and a model of this system which
is adequate for a basic description of the requisite
physiological processes is presented. The use of
this model as an individual subsystem model and as a
component of a more complete human model is discussed.

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Fluid and Electrolyte

Control Systems in the Human

Body - A Study Report

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Introduction

The recent advent and subsequent availability of sophisticated computing systems have stimulated a concurrent growth in mathematical modeling of physical systems of many types. Such modeling has played a necessary and even vital role in the development of present-day technology, particularly in relation to space exploration. One of the most interesting areas in which modeling is presently being utilized is related to physiological systems. Modeling of human body functions is a relatively new area of scientific endeavor that is interdisciplinary by its very nature, requiring expertise in physiology, physical chemistry, system control and numerical analysis. The human system consists of an aggregate of subsystems, each one of which is itself complicated, integrated so that the system as a whole maintains homeostasis. Each subsystem may be viewed as a type of feedback control system operating normally with negative feedback to restore stress conditions to normal conditions.

There is no unambiguous division of body functions into subsystems. In fact, any such division requires that the subsystems so defined have large overlapping areas and thus tend to be somewhat duplicative. In spite of this, it is convenient to regard the automatic control systems of the body as consisting of the cardiovascular system, the respiratory system, the thermal regulatory system, and the fluid and electrolyte system. Such a division has been utilized by

numerous researchers who have subjected these subsystems to close scrutiny. The ultimate 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 simulating the entire dynamic system.

In this study report research in the area of modeling of the fluid and electrolyte system will be briefly reviewed and a model of this system which is adequate for a basic description of the requisite physiological processes will be presented. The use of this model as an individual subsystem model and as a component of a more complete human model will be discussed.

Models of the Fluid and Electrolyte System

Fluid and electrolyte balance in the human system are controlled chiefly by the kidney acting in conjunction with the endocrine and circulatory systems. The complete specification of even an elementary model of this system requires that several compartments be included. These compartments will vary slightly from model to model depending on the approach and objective of the researcher, but usually will include interstitial, cellular, plasma, lymph, and kidney compartments. The present state of physiological knowledge of the fluid and electrolyte system is well summarized in several places (1), (2), (3), (4), (5) and will not be reviewed here.

The most detailed model of the kidney itself that has been constructed is that of Abbrecht (6). This model incorporates the most significant features of the architecture of the kidney and mathematically describes the functioning of the basic units in order to see to what extent such a model can explain the concentrative function of the kidney. The glomerular filtration rate is treated as an input parameter and the differential equations for transfer of water and solutes are developed under the assumption that the primary driving forces are the osmotic effect of the plasma proteins and the active transport of one solute across the walls of the nephric tubules. The resulting system of 20 to 30 ordinary differential equations are of the form of a multiple point boundary value problem of some complexity. Consequently the equations were not solved numerically and the main use of this model is conceptual in nature. Although interesting in itself because of its complexity, the model developed has little applicability in the area of overall fluid and electrolyte regulation. Other models developed by Abbrecht in areas somewhat related to renal dynamics include a mathematical model for the control system for erythropoiesis (7), and a model of the patient-artificial kidney system (8).

An extensive model of the nonequilibrium kinetics of water and major electrolytes in the human body has been prepared by Alvi and Lyman (9). This model, like the model of Abbrecht, is conceptual in nature since the relevent system of differential

equations is not solved numerically. The model considers water and four major electrolytes, Na^+, K^+, Ca^{++}, and Cl^-. The body is divided into the following compartments: plasma, red blood cells, interstitial fluid, intracellular fluid, connective tissue fluid, transcellular fluid, and exchangeable bone. The input comes from the gastrointestinal tract and the output is regulated by the nephrons of the kidney. Active and passive flux of each ion is considered across the various types of membranes that separate all the body compartments. Much of the known physiology and physical chemistry of the body is summarized by this model, but since a large number of the relevant parameters are unknown and difficult to determine the solution of the model equations would not be an easy task. Some of the equations given seem to be used out of context and there may be some question about the validity of these equations. In spite of this, the model does summarize a large number of facts about the fluid and electrolyte system in the body and thus represents a useful contribution to the literature.

Thomas G. Cleaver has developed a basic model of fluid flow and electrolyte balance in the body (10) that is amenable to numerical treatment. A modification of this model has been prepared by White and Neal for use by GE and NASA-MSC and a report is available (11) which details the physiology

and numerical analysis used by the model. Basically, the model is a three compartment model (plasma, interstitial fluid and cellular fluid) considering the dynamic changes in the levels of sodium, potassium, chloride and urea accompanying various oral input water loads. This model is an excellent one on which to learn how models work and what to expect from them. It is not large enough to be suitable for a model of long-term regulation of fluids and electrolytes since autonomic control is completely neglected and the circulatory subsystem model is quite crude.

DeHaven and Shapiro have presented large-scale "chemical" models of certain aspects of renal control of body fluids and electrolytes (12), (13). These models are of a considerably different nature from most of the other models presented in this report. The various body compartments (urine, plasma, red cells, interstitial fluid, intracellular fluid, and plasma gaseous phase) are considered to be homogeneous phases separated by membranes which maintain fixed concentration ratios of various chemical species in various phases. A total of 129 chemical species defined by 29 components plus antidiuretic hormone are utilized in the most recent of these models. The body is assumed to be in an idealized standard steady-state condition and the chemical composition problem is solved to obtain standard "equilibrium" constants or free-energy parameters. Stress is introduced into the system

by varying values of the composition of one or several species.
The chemical composition problem is then solved for the
"new" values of the concentration of the species using the
previously calculated standard free-energy parameters (by
minimizing the relevant functional numerically). Stress is
assumed to produce no change in the standard free-energy
parameters. Time is introduced by requiring that the input
to the plasma at time t_0 + h be exactly the output of the
urine at time t_0. This model considers no direct dynamic
simulation. This type of model is important because it demonstrates
clearly that very large chemical composition problems can be
handled effectively. The model may also be suitable for use
in certain types of experimental situations (which do not seem
to be clearly defined). Although chemical processes may be
dominant in these situations, there are many other situations
where the circulatory system, the neural system, and the
endocrine system act in concert with the intrinsic intraphase
and transmembrane chemical processes to regulate fluids and
electrolytes. It seems likely that a combination of a chemical
model like this one and a physical flow model like Cleaver's
(10), (11) would produce more useful results than either one
would by itself. This area merits serious study in the future.

A simulation of hemodynamics and fluid and electrolyte
balance in the body designed to give medical students an
interactive routine capable of reacting, in a gross sense,

like an average patient has been prepared by Dickinson (14).
This program produces data relevant to a patient's condition
including statements made directly by the patient. The model
is not truly dynamic, but utilizes a steady-state analysis at
the end of four-hour intervals. The model accomplishes its
desired objectives, but the amount of emiricism included
in certain segments (as in urine output calculations) tends
to go beyond accepted physiology.

Electronic analogues of the renal electrolyte system
have been prepared by several researchers (15), (16), (17).
Each of these models provides a number of important conceptual
ideas on regulation of water and electrolytes, but each has
certain deficiencies which cause the models themselves to have
only limited direct applicability. The model of Koshikawa
and Suzuki (15) omits many of the components of long term
regulation like the circulatory system. Levine's model (16)
leads to a set of simultaneous equations that was not solved
and so the model is mainly conceptual. Reeve and Kulhanek
(16) present a model which incorporates a thirst mechanism
but holds body solutes at fixed levels. The interaction between
the circulatory system and the fluid balance system is also
omitted. Thus the model does not tend to be of wide utility.

An Adequate Basic Model of Fluid and Electrolyte Control

The best, most comprehensive model of fluid and electrolyte control presently available has been constructed by Guyton and co-workers (18). The relevant systems analysis has been divided into 18 major systems that enter into circulatory, fluid, and electrolyte control. The subsystems involved include circulatory dynamics, capillary membrane dynamics, tissue fluids, electrolytes and cell water, pulmonary dynamics and fluids, angiotensin, aldosterone, and antidiuretic hormone control, thirst and drinking, kidney dynamics and excretion, muscle and non-muscle blood flow, autonomic control, heart rate and stroke volume, heart deterioration, red cell and blood viscosity, non-muscle oxygen delivery, and vascular stress relaxation. Most of the analysis was based on actual experimental data and has been tested extensively. The model illustrates quite clearly the importance of considering the interaction between various subsystems in predicting fluid volumes and electrolyte levels. The system modeled and the model itself are extremely stable, so much so that the function of any single control mechanism can be in error by as much as ±50% without significantly affecting the overall output of the system. One of the most important features of this model is that it is large enough to obtain this stability level. Because of this stability, the model is adequate for predicting the outcome of many experiments in spite of the fact that

each subsystem is modeled in a gross sense only with many minute details omitted.

Some of the experiments which have been performed with this model are simulation of the development of hypertension in a salt loaded, renal deficient patient, simulation of congestive heart failure, simulation of nephrosis, simulation of circulatory changes during severe muscle exercise, simulation of unilateral heart failure of the right or left side, simulation of the effects of the removal of the sympathetic nervous system on circulatory function, simulation of infusions of various types, simulation of the effects of extreme reduction of renal function on circulatory function and others. The model performed adequately in almost every case and represents an effective subsystem model.

Probably the most serious weakness in the model is the lack of a description of hydrogen ion regulation. Hydrogen ion levels are controlled by the renal system, the buffering system of the body, and the respiratory system acting together and, in fact, are one controller of respiration (19). Thus, the hydrogen ion control system should be included in a model of circulatory and renal function if that model is to be used as a component of a whole body model including respiration since it is one of the main connecting links between the

circulatory and renal systems and the respiratory system. The
basic knowledge required to simulate hydrogen ion control is
available and is summarized in several places (2), (20), (21),
(22), (23).

Hydrogen ion control will be added to the presently
available Guyton model in order to produce a model which
could adequately serve not only as a valuable subsystem model
but also could function as a component of an overall body model.

References

(1) A. C. Guyton, Textbook of Medical Physiology, 4th ed.,
     W. B. Saunders Co., Philadelphia, 1971.

(2) R. F. Pitts, Physiology of the Kidney and Body Fluids,
     2nd ed., Yearbook Medical Publishers, Chicago, 1968.

(3) D. Black, Essentials of Fluid Balance, 4th ed., F. A. Davis
     Co., Philadelphia, 1968.

(4) W. T. W. Potts, "Osmotic and Ionic Regulation," Ann. Rev.
     Physiol. 30:73, 1968.

(5) C. T. Ray, "Water and Electrolyte Balance," in W. A.
     Sodeman, Jr. (eds.), Pathologic Physiology, 4th ed.,
     W. B. Saunders Co., Philadelphia, 1967.

(6) J. A. Jacquez, B. Carnahan, and P. Abbrecht, "A Model
     of the Renal Cortex and Medulla," Math. Biosci. 1:227,
     1967.

(7) K. C. Mylrea, and P. H. Abbrecht, "Mathematical Analysis
     and Digital Simulation of the Control of Erythropoiesis,"
     J. Theor. Biol. 33:279, 1971.

(8) P. H. Abbrecht, and N. W. Prodany, "A Model of the Patient-
     Artificial Kidney System," IEEE Trans. BME, 18:257,
     1971.

(9) Z. M. Alvi, and J. H. Lyman, "Development of a Mathematical
     Model for the Nonequilibrium Kinetics of Major
     Electrolytes in the Human Body," Biotechnology Laboratory
     Report No. 45, University of California at Los Angeles,
     1969.

(10) T. G. Cleaver, University of Louisville, private communication.

(11) R. J. White, and L. Neal, "A Simple Model of Fluid Flow
     and Electrolyte Balance in the Body," private report, 1972.

(12) J. C. DeHaven, and N. Z. Shapiro, "Intrinsic Control of
     Body Fluid and Electrolyte Distribution and Urine
     Formation," Supplementum ad Nephron 4:1, 1967.

(13) J. C. DeHaven, and N. Z. Shapiro, "Simulation of the Renal
     Effects of Antidiuretic Hormone (ADH) in Man"
     J. Theor. Biol. 28:261, 1970.

(14) C. J. Dickinson, "MacPee," University of London, unpublished.

(15) S. Koshikawa, and K. Suzuki, "Study of Osmo-Regulation
      as a Feedback System," Med. Biol. Engng. 6:149, 1968.

(16) S. N. Levine, "A Model for Renal-Electrolyte Regulation,"
      J. Theor. Biol. 11:242, 1966.

(17) E. B. Reeve, and L. Kulhanek, "Regulation of Body Water
      Content: A Preliminary Analysis," in Physical
      Bases of Circulatory Transport: Regulation and
      Exchange (E. B. Reeve, and A. C. Guyton, ed.),
      W. B. Saunders, Philadelphia, 1967.

(18) A. C. Guyton, T. G. Coleman, and H. J. Granger, "Circulation:
      Overall Regulation," Ann. Rev. Physiol. 34:13, 1972.

(19) F. S. Grodins, J. Buell, and A. J. Bart, "Mathematical
      Analysis and Digital Simulation of the Respiratory
      Control System," J. App. Physiol. 22:260, 1967.

(20) H. W. Davenport, The ABC of Acid-Base Chemistry, 4th ed.
      University of Chicago Press, Chicago, 1958.

(21) H. N. Christensen, Body Fluids and the Acid-Base Balance,
      2nd ed., W. B. Saunders Co., Philadelphia, 1964.

(22) J. R. Robinson, Fundamentals of Acid-Base Regulation,
      3rd ed., F. A. Davis Co., Philadelphia, 1967.

(23) W. J. Waddell, and R. G. Bates, "Intracellular pH,"
      Physiol. Rev. 49:285, 1969.