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# A Dynamic Simulator for the Management of Disorders of the Body Water Homeostasis

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A dynamic model is built to study the water regulation of human body and related disorders, focusing on the fundamental feedback mechanisms involved in their normal and abnormal physiology. The simulation model is extended to include therapeutic interventions related to the most common body fluid disorder, namely, water intoxication/hyponatremia. The modeling approach is based on system dynamics methodology. Comparisons with experimental and field data show that the model adequately reproduces typical dynamics of the body fluid variables in their normal and diseased states. Finally, an interactive game version is developed to test the possible effects of alternative treatment options on a simulated patient. Simulation and game results reveal the subtleties involved during and after administration of various pharmacological interventions. For example, hypertonic saline should be administered concurrently and in delicate balance with drugs that increase urine flow. The simulator offers a virtual laboratory for experimental research and education on diagnosis and alternative therapies of body water disorders in general and hyponatremia in particular.

*Subject classifications:* simulation; system dynamics; health care: diagnosis/treatment; games.

*Area of review:* Special Issue on Operations Research in Health Care.

*History:* Received December 2006; revisions received November 2007, March 2008, May 2008; accepted June 2008.

What am I, Life?

A thing of watery salt

Held in cohesion by unresting cells,

Which work they know not why, which never halt

Myself unwitting where their master dwells,

I do not bid them, yet they toil, they spin . . .

John Masefield, "What Am I, Life?"

## 1. Introduction

Hippocrates held the idea that disease is cured by natural powers, but the term of "homeostasis" was first used far later by Walter Cannon, in his book *The Wisdom of the Body* (1932). Cannon made a qualitative use of the concepts of today's dynamic systems theory and suggested that physiological systems are dominated by negative (compensating) feedback loops. Another pioneer of systems approach to physiology, Arthur C. Guyton, was the first to introduce the concept of systems analysis to physicians (Guyton et al. 1972), whose approach then led to the emergence of biomedical engineering. Recently, there has been a growing interest in the modeling and OR community to provide model support in personalized diagnosis and treatment of some important diseases: Agur et al. (2006) develops a method for optimal patient-specific chemotherapy scheduling for cancer treatment. Similarly Romeijn et al. (2006) uses a new linear programming approach

to determine optimal radiation treatment plans for cancer patients. Ryu et al. (2004) utilizes a mathematical programming technique called isotonic prediction in disease prognosis and illustrates it on two medical applications. Craft et al. (2005) builds a comprehensive system of a differential equations model to understand how best to respond to a bioterror anthrax attack. Abdel-Hamid (2002) models the dynamics of human energy regulation using system dynamics simulation and studies the implications for alternative obesity treatments. Other recent applications of system dynamics and systems science to health care include Hirsch and Immediato (1999), Bar-Yam (2006), Sterman (2006), Jones et al. (2006), and Incioğlu (2007).

Our focus in this paper is the system of regulation of body fluids, which is critical to control diseases such as hypertension and dysnatremia (dehydration and water intoxication being two examples). Early models that represent certain aspects of renal control of body fluids belong to DeHaven and Shapiro (1967), Reeve and Kulhanek (1967), and Toates and Oatley (1970, 1977). Integrated models of body fluid regulation that also consider the circulatory system include those by Ikeda et al. (1979) and Abbrecht (1980). The drinking mechanism developed by Reeve and Kulhanek (1967) forms the basis of the main approach and assumption regarding the drinking structure in our study, as will be seen later in §3. Finally, the most complete analysis of body fluid dynamics belongs to Guyton and coworkers,

who constructed an overall circulatory model for examining the causes of hypertension (Guyton and Coleman 1967, Guyton et al. 1972). Uttamsingh et al. (1985) extended his model for the clinical application of patients with renal failure. Recently, a cardiovascular system model was developed by Karaaslan (2004), integrating the previous models developed by Guyton et al. (1972), Uttamsingh et al. (1985), and Coleman and Hall (1992). The fundamental water and sodium regulation mechanism described in this series of publications by Guyton and coworkers has been an important contributor to the foundations of our model. In §3, we shall more specifically refer to these publications in places where concrete results by prior modeling research have been used in our work. But as will be seen, our model is different enough from these prior models in purpose, time frame, and aggregation level, implying that we had to write our own original equations to a large extent. Perhaps the greatest utility of the prior modeling and physiology literature has been in their numeric and/or qualitative data that we used in estimating the parameters of our equations.

The homeostatic regulation of body fluids is important in almost every field of medicine. In health, total body water and its distribution in the body is maintained between narrow limits. This task is accomplished by two distinct but interactive feedback systems: The main feedback system for body water regulation is the thirst-Antidiuretic Hormone (ADH) system, and the main feedback mechanisms for sodium balance include the Aldosterone (ALD) and the Atrial Natriuretic Hormones (ANH), and the renal mechanisms (Guyton and Hall 2000).

Problems associated with body fluid disorders are very common in hospitalized patients. Among these, water intoxication (or hyponatremia) defined as an abnormally low level of extracellular sodium concentration, is the most important body fluid disorder with the potential for significant mortality. Extreme cases of low sodium concentration and high body water content may have serious consequences. The treatment of hyponatremia constitutes a problem, partly because all available therapies have significant limitations. Furthermore, it is observed that a large portion of hyponatremia incidences are in fact “hospital-acquired.” Most of these patients acquire hyponatremia as they receive intravenous fluids, which is a very common practice in hospitals. Today, more than 75% of currently recommended intravenous fluids are in the form of electrolyte-free water, which is known to aggravate hyponatremia (Halperin and Bohn 2002). This situation has raised concerns about hyponatremia, and inspired many studies on its diagnosis and optimum therapy (Shafiee et al. 2003).

Due to the feedback complexity of the underlying structure and its interactions with various pharmacological therapies, body water regulation and its disorders constitute a suitable area for system dynamics modeling. However, no closed-loop, systemic therapy approach for disorders of dysnatremias has yet been attempted (Northrop 2000). Our study builds a closed-loop system dynamics model of body

water regulation and its disorders, focusing particularly on hyponatremia.

## 2. Clinical Abnormalities of Body Fluid Regulation

Any influence that alters the balance of the body water or sodium metabolism inevitably affects the balance of the other. It is important to differentiate the dynamics and clinical abnormalities of extracellular (EC) fluid volume and/or sodium content from those of the total body water.

### 2.1. Disturbances of Body Sodium Content

As the main substance of the EC fluid, the sodium content determines the EC fluid volume. Therefore, disorders of sodium metabolism are always manifested as disorders of volume status. Moreover, mean arterial pressure (MAP) is also affected due to the close interrelationship between EC fluid volume and the MAP. Disorders of sodium metabolism commonly coexist with disorders of water and fluid-electrolyte balance.

### 2.2. Disturbances of Water Metabolism: Dysnatremias

Disorders of water metabolism are clinically manifested by disorders of EC sodium concentration (dysnatremias) because the regulatory systems controlling water metabolism do so by maintaining a constant EC sodium concentration. Loss of water leads to hypernatremia and widespread functional disturbances in the brain. On the other hand, accumulation of water leads to hyponatremia, cell swelling, and disturbances in the central nervous system.

In general, failure to maintain body water within narrow limits is associated with two functions. The first one involves the capability to dilute or concentrate urine appropriately, and the second one is associated with the thirst function. If one of these components fails to function properly, the other one may still compensate for this failure (Jamison and Oliver 1982).

Hyponatremia is the most common and potentially serious electrolyte abnormality in hospitalized patients (Shafiee et al. 2003). It is defined as an EC sodium concentration of less than 135 mEq/L. The most common causes of hyponatremia are the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) (38%), incorrect hydration (19%), and continuous diuretic treatment (30%) (Halperin and Bohn 2002).

## 3. Description of the Model

The purpose of this modeling study is to develop a dynamic representation of the body fluid balance in normal and pathological states so as to test alternative treatment strategies of dysnatremia. The study has three main parts, corresponding to three research goals: (1) to offer

a dynamic model that explains the main feedback mechanisms involved in the normal physiology/stability of body water balance and osmolality, (2) to extend the model to generate common medical disorders of body water regulation, namely, dysnatremias, and (3) to explore effective treatment strategies for a virtual patient with acute hyponatremia. For this last purpose, an interactive game version of the model is constructed whereby players can interactively test their own strategies by simulated experience. (Extensive gaming experiments by players with different backgrounds, carried out with suitable design of experiments and statistical analysis is our ongoing research.)

Two major systems that are involved in the homeostatic regulation of body fluids are the system that regulates the osmolality/body water and the system that regulates the blood volume/sodium content. In this study, the central controller is the hypothalamus, and thus the normal values of the main regulated variables are taken as exogenous constants, e.g., the set point for ADH (Antidiuretic Hormone) and the set point for blood volume.

The model is built using a system dynamics approach (Sterman 2000, Barlas 2002). According to this method, the dynamics of a system are represented by formulating the rates of *changes* (or *flows*) of a set of *stock* (or *state*) variables. Converters are intermediate variables linking a flow (or a converter) variable to other variables at some point in time. A system dynamics model thus consists of a set of coupled differential/difference equations. The general forms of equations are:

$$\frac{d}{dt} \text{Stock} = \text{inflows} - \text{outflows},$$

$$\text{Flows} = f(\text{stocks}, \text{converters}, \text{flows}),$$

$$\text{Converters} = f(\text{stocks}, \text{converters}, \text{flows}).$$

Simple examples of these three types of variables in our model (to be discussed later) are:

$$\frac{d}{dt} \text{ADH}_{\text{inPlasma}} = \text{Actual\_ADH\_Release} - \text{ADH\_Clear} \quad (\text{a stock equation}),$$

$$\text{Actual\_ADH\_Release} = \text{Desired\_ADH\_Release} \times \text{Eff\_of\_ADH\_Avail}$$

(a flow of the above stock),

$$\text{Eff\_of\_ADH\_Avail} = f(\text{ADH\_Pool}, \text{MaxPoolCapac})$$

(a converter equation),

where  $f(\cdot)$  will be specified in the complete model as a logistic function reaching a saturation level.

A typical model consists of many equations and functions  $f(\cdot)$  most of which may be nonlinear and/or time-delayed.

Such set of nonlinear, delayed differential/difference equations are almost always impossible to solve analytically. That is why simulation is an integral part of the methodology. Models are presented typically as stock-flow diagrams (in which stocks are represented by boxes and flows by valves). The polarity of causal relations and feedback loops between variables are presented in causal loop diagrams. (See Figures 3.1 and 3.4 for examples.)

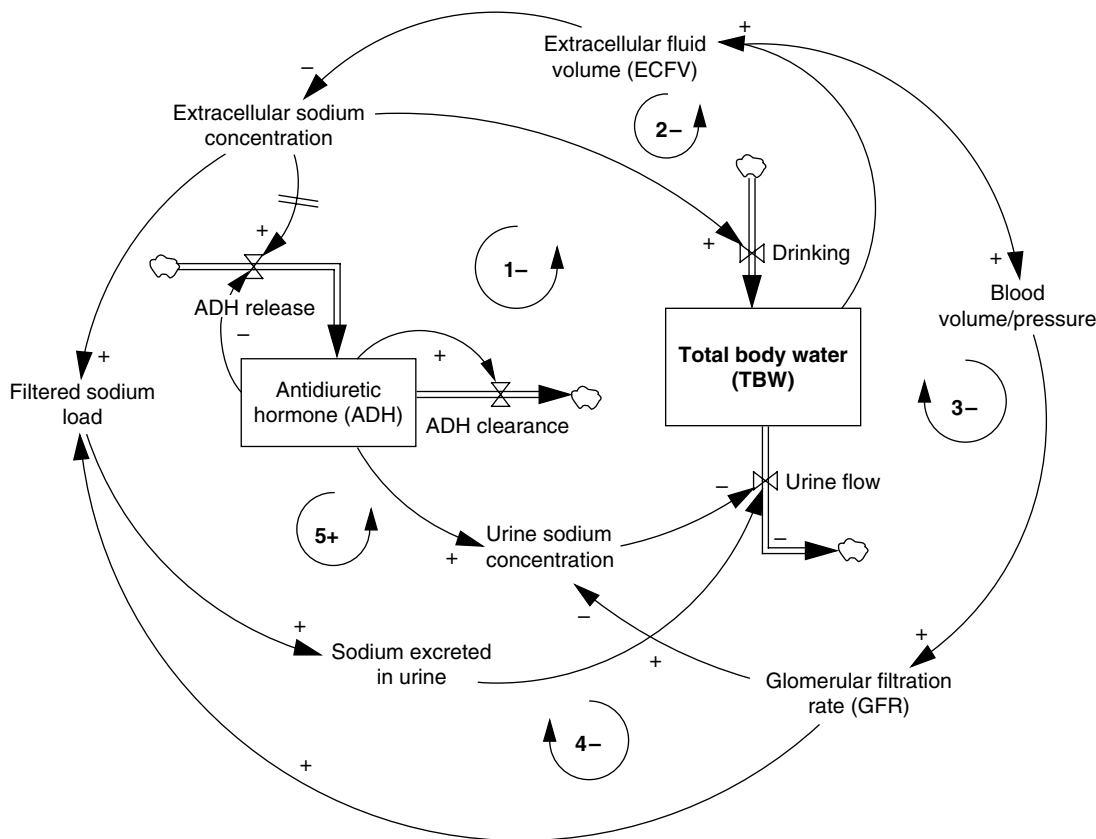
Our model is composed of nine sectors grouped under five sector groups. These sector groups correspond to *body water*, *sodium*, *hormonal system*, *urinary sodium concentration*, and *treatment*. The initial states and parameters (see the online supplement that can be found at <http://or.journal.informs.org/>) are standard values typically used in the major medical textbooks and in earlier models. When available, published experimental data are used. The model assumes a standard healthy human male of 70 kg with 40 liters of body water.

### 3.1. Regulation of Total Body Water and Osmolality

The mechanism for the regulation of water balance is often referred to as the “thirst-Antidiuretic Hormone (ADH) mechanism.” The two most important factors that are monitored by this mechanism are extracellular (EC) osmolality and blood volume. EC osmolality represents the number of particles in a given mass of water, usually expressed as millimoles (or milliequivalents) per kilogram of water. In usual conditions, control of EC osmolality is almost the same as controlling the EC sodium concentration because EC sodium is the substance that mostly contributes to the EC osmolality. Its importance in terms of water balance is that the control of EC osmolality indirectly controls intracellular (IC) volume. (Three facts about the body water/sodium are relevant: first, “mobile” sodium is mostly restricted to the EC fluid; second, intracellular solute does not change easily; and third, EC osmolality must equal IC osmolality except for very fast transients.) It should be noted that the mechanisms that control the EC sodium “concentration” and the EC sodium “amount” are different, albeit interacting (Bagby and Bennett 1998). EC sodium concentration has a normal value of 142 mEq/L, and is found by division of EC sodium content (ECNa) by EC fluid volume.

Figure 3.1 provides a simplified version of the stock-flow diagram of the body water/osmolality control sector of our model. The first and the second control (negative) loops demonstrate the ADH-thirst feedback mechanism for EC osmolality and body water control. An increase in EC osmolality raises the level of ADH, and as a consequence of increased urinary concentration, water excreted in urine decreases. At the same time, thirst perception is stimulated and water intake is increased. It is assumed that stimuli acting on ADH secretion do so as an additive sum, and the response of ADH takes effect immediately (Toates and Oatley 1977). GFR (Glomerular Filtration Rate) represents the amount of filtrate formed per minute, so it

Figure 3.1. Simplified stock-flow diagram for body water/osmolality control.



determines the amount filtered for any substance in the kidney. An increase in GFR increases urine flow via a decreased urinary concentration (third loop). As seen in the diagram, GFR and the EC sodium concentration influence the sodium excretion rate by influencing the filtered sodium load (fourth and fifth loops).

Drinking is considered as the only source of fluid intake. Both continuous and discontinuous-periodic drinking are modeled as options to simulate the drinking behavior. In either case, there is a 1/2 to 1 hour delay for all of the water drunk to become distributed in the body (Northrop 2000). The model developed by Reeve and Kulhanek (1967) forms the basis regarding the drinking structure. Accordingly, the discontinuous drinking version of the model represents a switch-on and switch-off structure, which only acts under some threshold body water level, and this level is maintained within  $\pm 0.5$  L of a mean (Reeve and Kulhanek 1967). For the continuous drinking structure, the drinking rate is approximated as a variable that may vary around its normal value, depending on varying levels of the EC osmolality (see Figure 3.2):

$$\text{UnrestrictDrinking} = \text{NormalDrinking} \times \text{Eff\_of\_ECOsm\_on\_Drinking}.$$

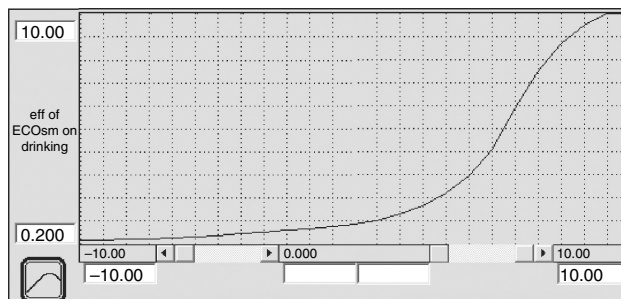
A constant insensible water loss, which represents the continuous escape in the form of evaporation (about 0.9 L/day), and a variable urination flow represent the

two sources of loss of water from the body. The urinary excretion can be divided into a constant component and a variable “free water excretion.” The constant rate or the *MinUrineFlow* is referred to as the obligatory urine loss, which is necessary to clear out the wastes of the body and it is imposed as a constraint. Consequently, the equation for the *UrineFlow* becomes

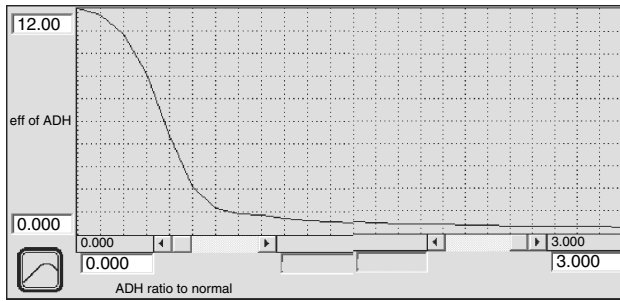
$$\text{UrineFlow} = \text{MAX}(\text{MinUrineFlow}, \text{ImpliedUFlow}).$$

The urine flow rate is in turn determined by two variables, i.e., the urinary sodium concentration (*UNaConc*) and the rate of sodium excretion (*NaOutUrine*). The implied urine flow rate is linearly related to sodium excretion because the rate of water transport is always proportional to the rate of

Figure 3.2. Effect of EC osmolality on drinking.



**Figure 3.3.** Effect of ADH on urine sodium concentration.



solute transport (Guyton and Hall 2000). The equation of the *ImpliedUFlow* is

$$ImpliedUFlow = \frac{NaOutUrine}{UNaConc \times 1,000}$$

The above equation depicts the inverse relationship between urine osmolality and urine flow rate (assuming a given sodium outflow). Ordinarily, the urine flow rate  $\times$  urine osmolality (equal to the amount of solute excreted) is relatively constant and independent of flow rate (Bray et al. 1989). Thus, the kidney adjusts the urine flow rate without markedly affecting its handling of sodium and other solutes.

The capability to dilute or concentrate urine appropriately depends on various factors; however, under normal physiological conditions, the ADH level is the main determinant of urine osmolality (Guyton and Hall 2000). ADH influences water excretion by promoting concentration of urine, but the  $Na^+$  excretion is unaffected by ADH. Accordingly, the effect of ADH on urine concentration is formulated with a decreasing sigmoidal graphical function (see Figure 3.3).

From the graph, it can be seen that the renal response to ADH saturates when ADH concentration reaches approximately three times its normal level, after which urinary osmolality is maximal and cannot increase further despite additional increases in ADH levels. With maximal concentrations of ADH (maximal antidiuresis), as little as 0, 4–0, 5 L of urine may be excreted per day with a urine osmolality of about 1,200 mEq/L (Bray et al. 1989, Janicic and Verbalis 2003.) It can also be seen that even when ADH is totally absent, the maximum amount of urine to be excreted cannot increase indefinitely.

On the other hand, there is a combination of factors other than ADH, i.e., the Glomerular Filtration Rate (GFR), that act in the absence or presence of ADH and change the urinary concentration, which is an indicator of the complexity and importance of the urinary concentration dynamics.

Accordingly, the UNa concentration implied by ADH and GFR (*ImpliedUNaConc*) is calculated by the following effect formulation:

$$ImpliedUNaConc = ImpliedUNaConcByADH \times Eff\_of\_GFR\_on\_UNa,$$

where

$$ImpliedUNaConcByADH = \frac{NormalUNaConc}{Eff\_of\_ADH}$$

### 3.2. Regulation of Total Body Sodium and Extracellular Fluid Volume

In the average adult human, about five-eighths of the body fluids constitute the intracellular (IC) fluid and three-eighths remain extracellular (EC), or 25 liters are IC fluid and 15 liters are EC. Sodium is the principal determinant of the total EC fluid volume (ECFV). Indeed, the human body regulates the ECFV by regulating its  $Na^+$  content (Bray et al. 1989). Because the EC and the IC osmolalities are always equal (except for very short transients) and the total “mobile”  $Na^+$  and  $K^+$  are mostly kept in their respective compartments, the ECFV is derived by the following equations:

$$\frac{ECNa}{ECFV} = \frac{ICK}{ICFV}, \text{ where}$$

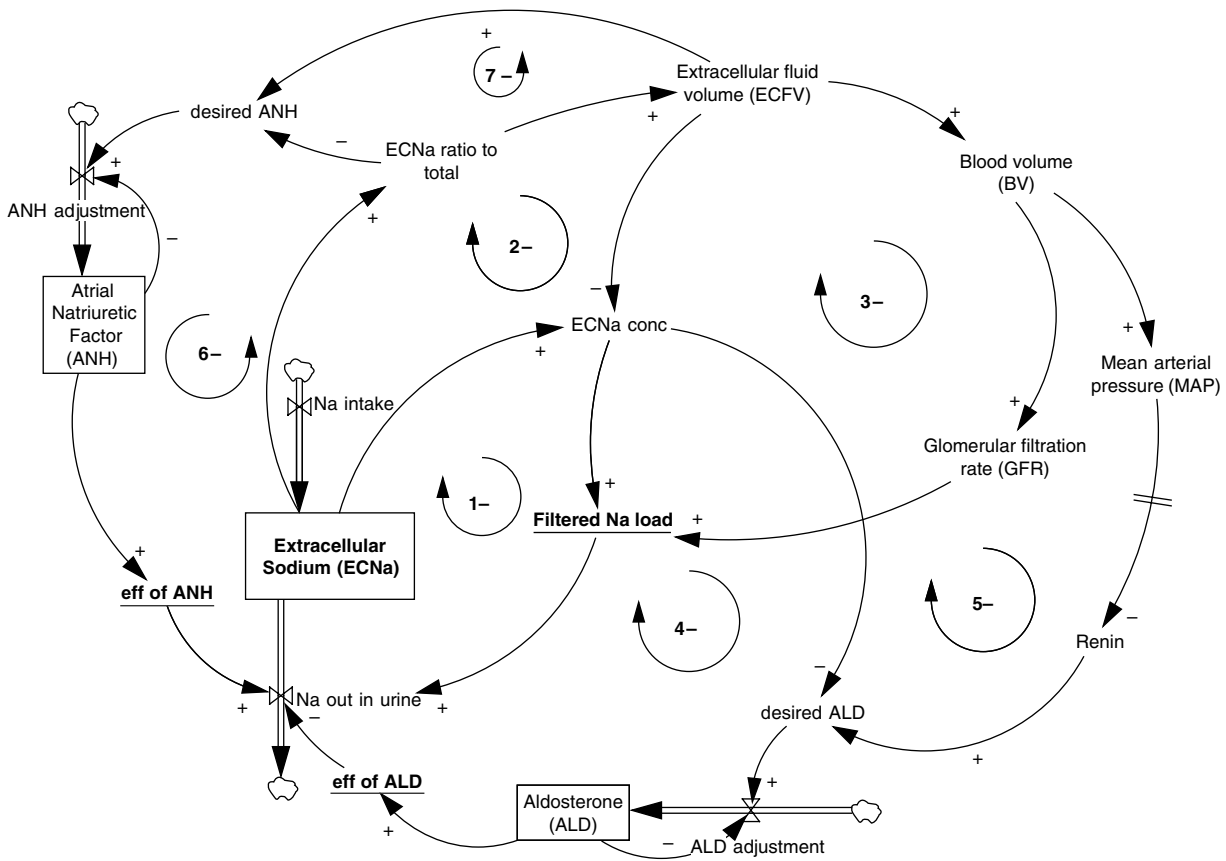
$$ECFV + ICFV = TBW, \text{ yielding}$$

$$ECFV = TBW \times \frac{ECNa}{(ECNa + ICK)} / 1,000.$$

Maintenance of normal ECNa and thereby a normal ECFV requires a refined intake and excretion for  $Na^+$  ions. However, related literature suggests that the regulated component has to be sodium excretion because regulation of intake, i.e., the sodium appetite regulation in modern societies, mostly depends on habits rather than the requirement and is almost always greater than necessary for homeostasis. Therefore, the sodium intake rate is assumed to be constant in the base model. Sodium excretion is affected by various factors; however, only the most important ones are explicitly represented in the model: the Glomerular Filtration Rate (which affects the filtered load of sodium in the kidney), the Renin-Angiotensin-Aldosterone hormone system, and the recently found Atrial Natriuretic Hormone.

Figure 3.4 shows our simplified stock-flow diagram depicting the causal mechanisms related to these three factors. The first and the third loops are related to balancing the effects of the filtered load. *Filtered load* refers to the rate at which substances are filtered in the kidney. It is found by the equation:  $GFR \times$  Plasma Concentration of the substance (Guyton and Hall 2000). For any substance, the amount excreted in the urine is the algebraic sum of the amounts filtered, reabsorbed, and secreted by the tubules. Any change that causes an increase in the filtered load of sodium causes a rise in sodium excretion. On the other hand, the second loop indicates that an increase in ECNa also has a decreasing effect on ECNa concentration due to the fluid shift between the IC and the EC compartments. The other balancing loops relate to the effects of the ANH and ALD hormones on reabsorption of Na from the kidneys. The response of ANH is assumed to take effect immediately; however, ALD is effective only in long-term adjustments of sodium excretion (Bray et al. 1989).

**Figure 3.4.** Simplified stock-flow diagram for sodium and EC fluid volume regulation.



Sodium excretion rate ( $NaOutUrine$ ) is formulated by a multiplicative effect formulation. The effects of ALD and ANH on sodium excretion are formulated with graphical functions with reference to their normal concentrations (see the online supplement for all functions):

$$NaOutUrine = FilteredNa \times NormalFraction \times Eff\_of\_ANH\_on\_NaExcret \times Eff\_of\_ALD\_on\_NaExcret,$$

where

$$FilteredNa = GFR \times ECNaConc / 1,000.$$

It is clear that changes in GFR or ECNa concentration will change the sodium load presented to the kidney. Under normal conditions, 99% of the filtered sodium is reabsorbed back to blood. Therefore, the filtered load is multiplied by a normal fraction to find the normal sodium excretion rate.

### 3.3. Integrated Regulation of Body Water and Sodium

Figure 3.5 gives an overall summary of how the two control systems of body water and body sodium integrate to produce a tight control system. This diagram may also help to differentiate the clinical abnormalities of EC fluid

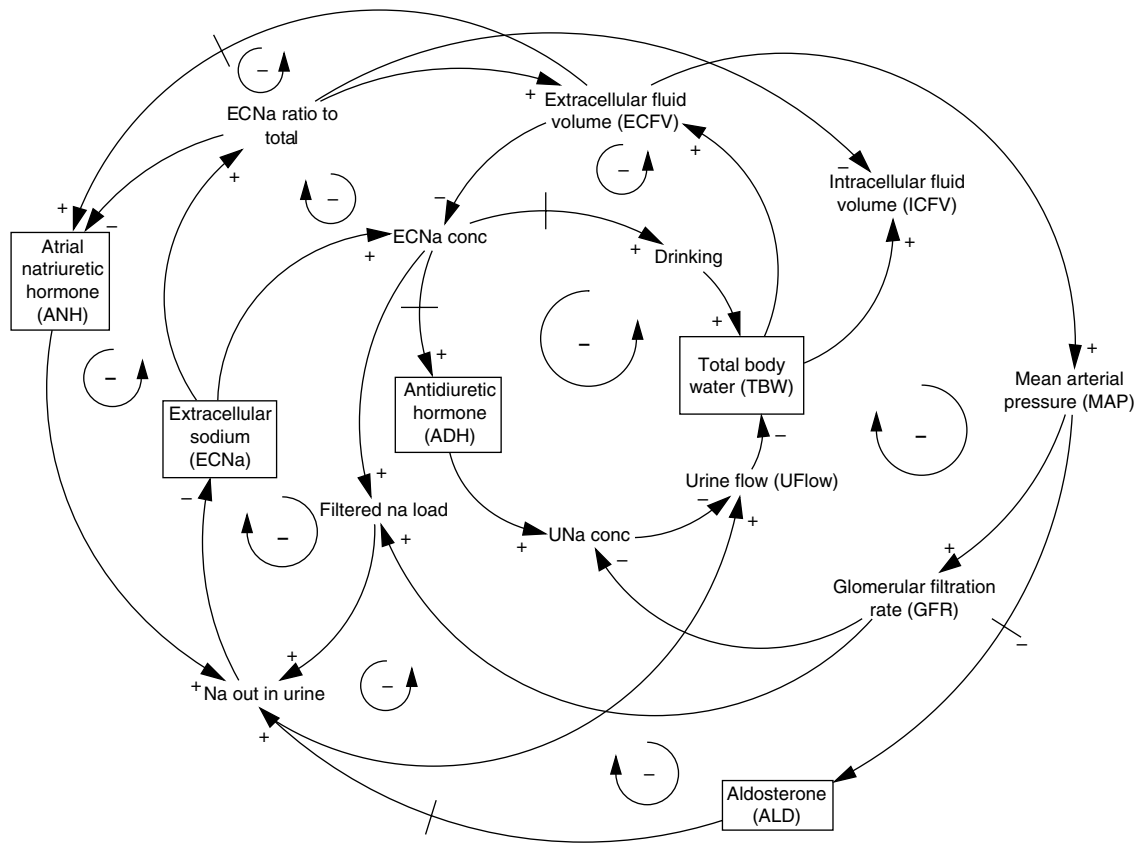
volume/sodium content regulation from abnormalities of body water/osmolality.

In SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion), the degree of water retention is limited due to the adaptive mechanisms of the body. The pathophysiology of this disease can be better understood when the causal-loop diagram presented in Figure 3.5 is examined. Main features of the SIADH are drastically decreased EC sodium concentration, a clinically normal EC fluid volume, normal/mildly elevated blood pressure, and an increased glomerular filtration rate (Schwartz et al. 2001). It is seen that the EC/blood volume regulation is appropriate; however the osmolality/TBW regulation is deranged. As the total body water increases due to increased ADH levels, both the EC and the IC volumes increase. However, a transient natriuresis induced by the ANH and ALD hormones acts to defend the EC volume. Therefore, most of the excess fluid is accumulated in the IC fluid. A mild elevation in glomerular filtration rate can be considered as an adaptive response of the body to compensate the high urinary concentration induced by ADH. (SIADH will be simulated and discussed again in §4.4.2.)

### 4. Validation and Analysis of the Model

The model is simulated in Stella software (isee Systems, Inc., <http://www.iseesystems.com>). The basic time unit is

**Figure 3.5.** Overall regulation of body fluids by integrated control of body water and body sodium.



hours and a sufficiently small time step (1/32 hr.) is used to assure numerical accuracy in simulation. Because some of the system behavior becomes evident only in the medium term, the simulation time horizon is set somewhere between 24 and 72 hours in most runs. (It is as high as 500 hours in some scenarios where long-term dynamics are of particular interest.) A formal validation process is followed to detect any structural flaws of the model (Barlas 1996). Numerous direct structure tests are performed during model building, which are not presented here due to space limitations (see Karanfil 2005). Validation of the model is next demonstrated by performing “structure-oriented behavior tests” (indirect structure tests), such as extreme condition and behavior sensitivity tests (Barlas 1989, 1996), and selected illustrations are presented below. Finally the model behavior is also compared with the real data, to the extent that experimental or field data are available, as will be seen below.

**4.1. Validity of the Output Dynamics of the Model**

**4.1.1. Base Behavior of the Model.** Both continuous and discontinuous drinking options are modeled to simulate the drinking behavior of humans. When all its stocks are initialized ideally at their equilibrium values, the continuous version of the model correctly shows a constant equilibrium behavior, and the discontinuous drinking version

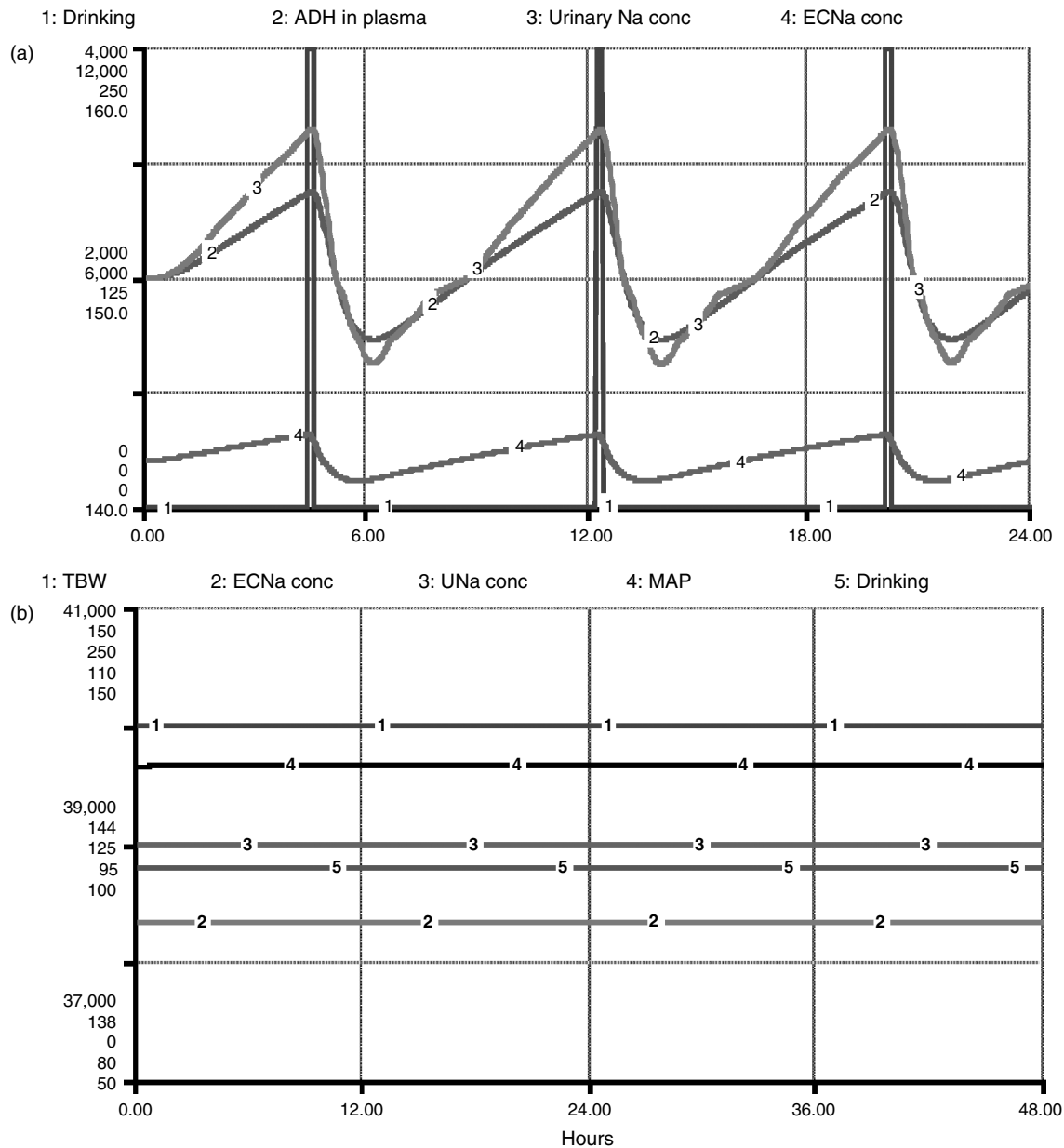
demonstrates the normal periodic variations in the key variables around the equilibrium points (see Figure 4.1). Discontinuous-periodic drinking represents a switch-on and switch-off structure that only acts under some threshold body water level, which is a more realistic representation of the drinking behavior. The EC sodium and the mean arterial pressure show almost no change during the day. The ECNa concentration varies between 141 mEq/L and 143 mEq/L, which is a small variation. The main change can be seen in the dynamics of the urine flow, drinking, the urine concentration, and ADH. Because water is continuously lost and then replenished by drinking, ADH adjusts the urine concentration to prevent higher fluctuations in the ECNa concentration in the case of highly varying fluid intake. ADH can thus be quite variable under normal conditions. As a result, the total body water (TBW) is maintained within the normal limits. The above equilibrium runs (both continuous and discontinuous-periodic) are obtained primarily as a demonstration of the structural validity of the model. Output behavior validity is discussed in the following sections.

**4.1.2. Water Loading.** Examining the dynamics of body fluids after water loading constitutes an extreme (“stress”) test (Barlas 1996) to assess the validity of interactions between body fluids and related hormones in the model. For this simulation, the *NormalDrinking* variable is

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**Figure 4.1.** Equilibria of the key variables with (a) discontinuous-periodic drinking, (b) continuous drinking.



set to zero, and a pulse of water input of 1,000 ml is given at time 0. The urine flow rate increases by about 11 fold in one hour, and after three hours it returns to its normal value. The validity of model behavior in this case is demonstrated by comparing its output behavior against real data (see Figures 4.2 and 4.3).

Figure 4.4 gives a schematic representation of the normal physiologic relationships among EC osmolality, ADH concentrations, urine osmolality, and urine volume, based on real data. Accordingly, urine osmolality is proportional to plasma ADH levels, but urine volume is inversely related to urine osmolality.

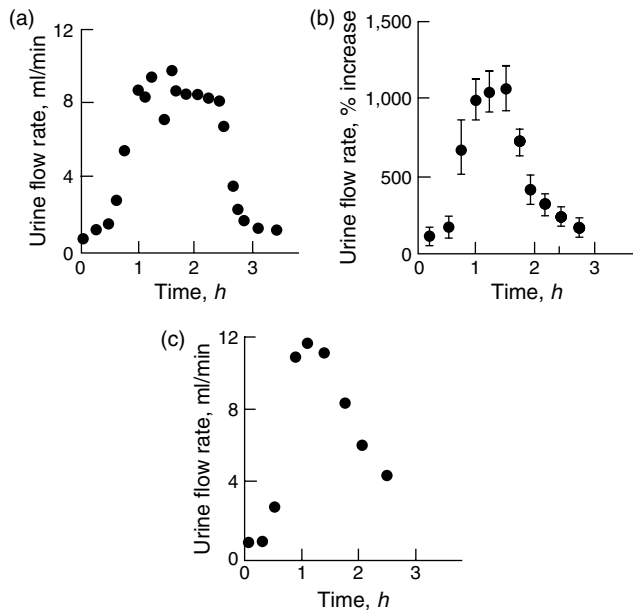
The model-simulated results on the relationship between the urine flow and the urine sodium concentration in the

base run and in the water-loading scenario are given in Figure 4.5, again agreeing with empirical evidence provided in Figure 4.4.

#### 4.2. Experiments with Changes in Daily Water Intake

Exploring the dynamics of body fluids after changing the water intake provides a tool to disturb the model from its equilibrium and test the validity of the resulting behavior. So, this set of experiments is simulated by varying the daily water intake (*NormalDrinking*) of the person from its normal value, which is about 2.2 liters, and resetting the thirst feedback on drinking. The main effect of an increased

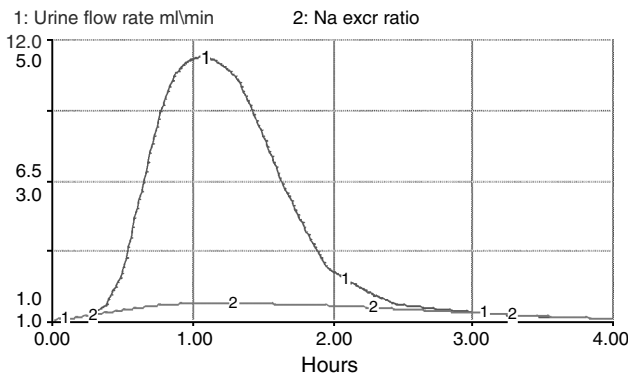
**Figure 4.2.** Urine flow rate following ingestion of 1 L of water; (a) data from Baldes and Smirk (1934), (b) data for eight subjects, (c) data for one subject (Uttamsingh et al. 1985).



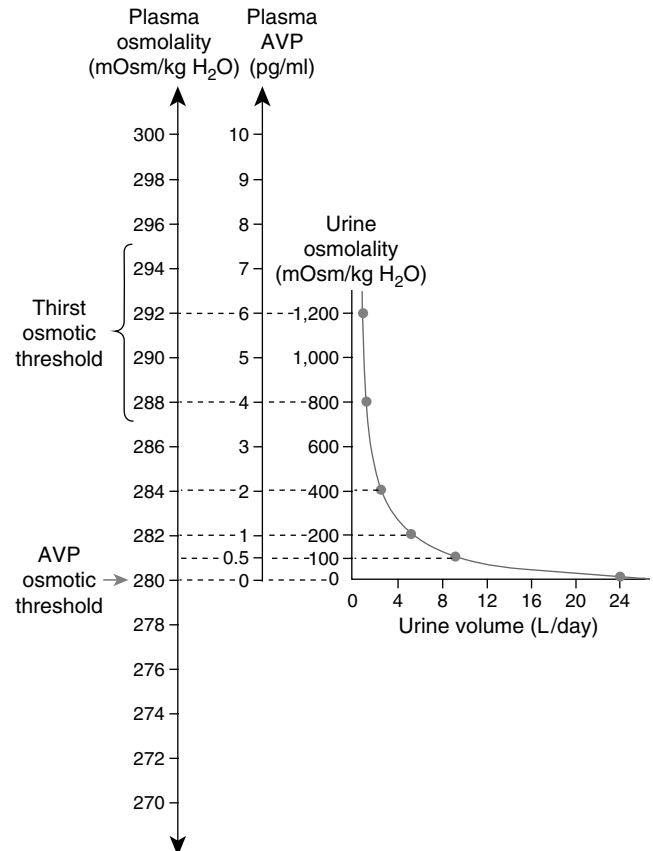
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(or decreased) water intake is a big fall (or rise) in the urine sodium concentration and a consequent rise (or fall) in the urine flow. There is almost no change in the total body water, mean arterial pressure, and the EC sodium, as long as the fluid intake and the fluid loss are precisely balanced. So, these critical indicators of the body are not sensitive to an increase or decrease in water intake, which is a demonstration of the resilience of the negative feedback structure. Representative dynamics of the key variables in response to doubling the normal drinking value to 4.4 liters/day are given in Figure 4.6.

**Figure 4.3.** Simulated urine flow following ingestion of 1 L of water for comparison against real data of Figure 4.2.



**Figure 4.4.** Normal physiologic relationships among EC osmolality, ADH (also termed Arginine Vasopressin or AVP) concentration, urine osmolality, and urine flow in man (from Verbalis 2003).



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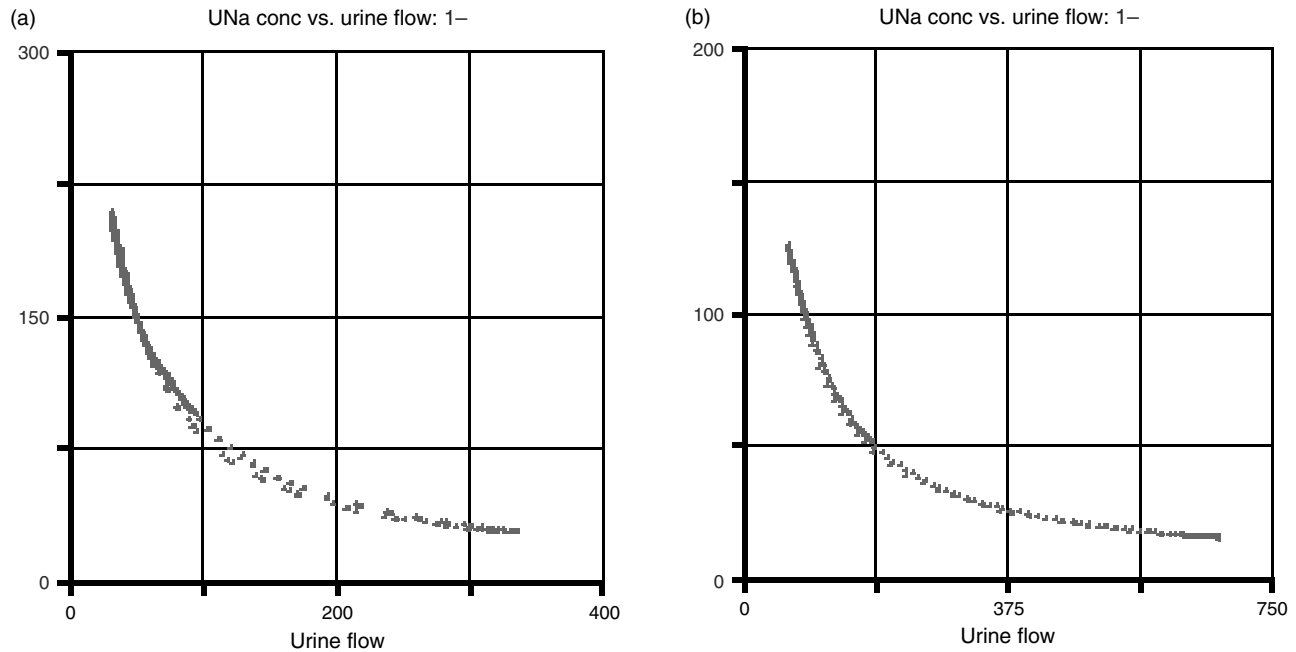
**4.2.1. Sensitivity of Blood Volume to Different Levels of Daily Water Intake.** Under normal conditions, blood volume is not affected by changes in fluid intake (Guyton and Hall 2000). Real-world data in Figure 4.7(a) demonstrate the fact that the blood volume remains almost constant despite extreme changes in water intake—the power of homeostasis. The simulated results of Figure 4.7(b) are again in accordance with this empirical evidence from Guyton and Hall (2000).

**4.3. Experiments with Changes in Daily Sodium Intake**

Similarly, changing the sodium intake presents another test to explore the validity and limits of the body water and sodium control feedback mechanisms of the model and to validate its behavior against empirical data. Thus, this set of experiments is simulated by varying the daily sodium intake of the person from its normal value. The results demonstrate that changes in sodium intake have very little effect on the ECNa concentration and the TBW, but they have a greater effect on the urine concentration, drinking, and

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**Figure 4.5.** Simulated relationships between urine osmolality and urine flow (a) for the base run, (b) after ingestion of 1 L of water, to be compared with real data in Figure 4.4.

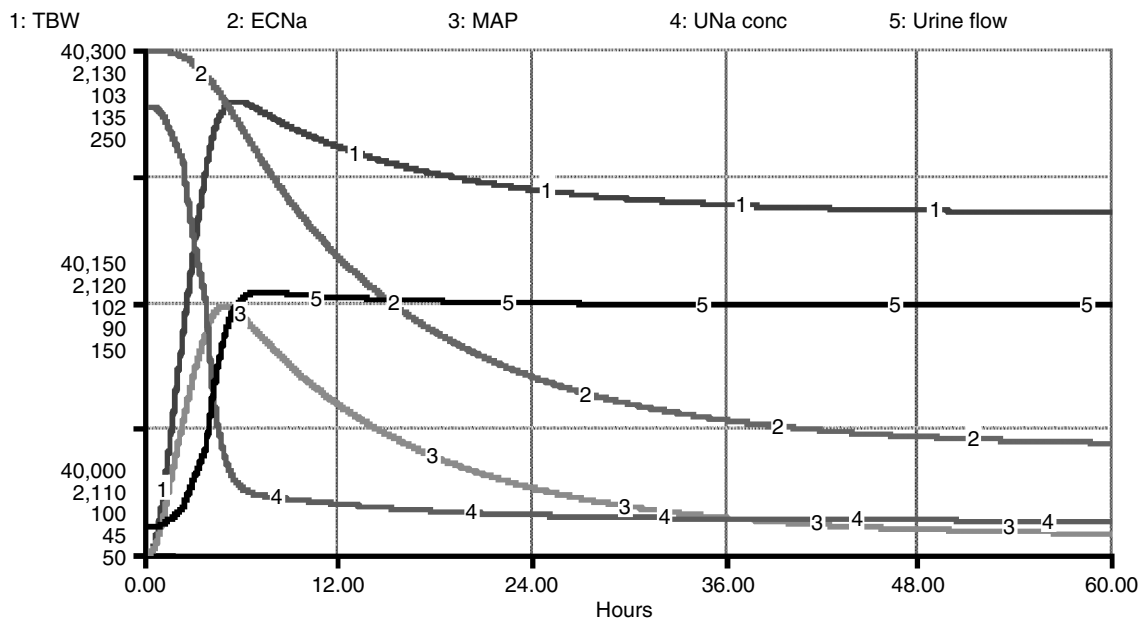


urine flow. A representative dynamics of the key variables after a four-fold increase in sodium intake are given in Figure 4.8. In this simulation, the EC fluid volume increases by 5%, whereas the change in the ECNa concentration, IC fluid, and the TBW remains between 1%–2% because water is shifted between the EC and the IC compartments. Increased salt intake causes an increase in the ECNa concentration, which stimulates thirst and increases drinking, and urine flow increases to match the elevated water intake. The resulting urine is much more concentrated than normal,

as expected; urine concentration and drinking increase by about 100%. These results corroborate the prevailing theory in the literature: “Consequently, NaCl ingestion only transiently increases ECF volume and Na content. Even a sustained increase in daily NaCl intake causes remarkably small increases in ECF volume/Na content (<5%)” (Bagby and Bennett 1998, p. 171).

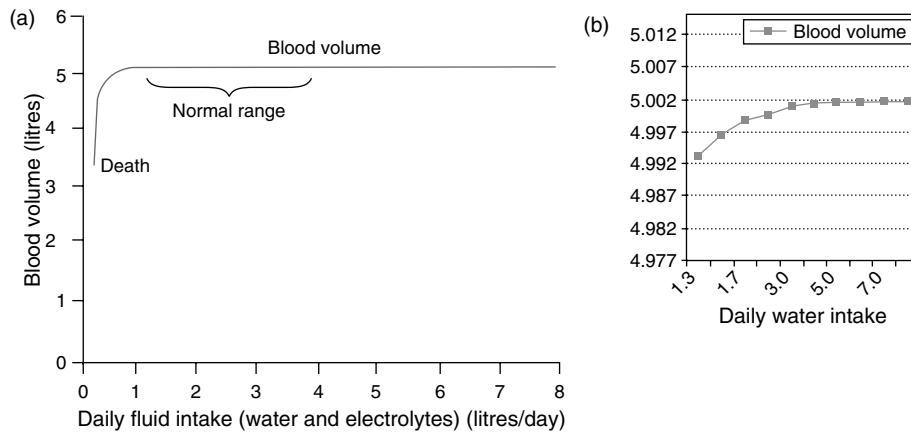
**4.3.1. Sensitivity of ECNa Concentration to Different Daily Sodium Intakes.** In a normal person, ECNa concentration is controlled quite effectively even with large

**Figure 4.6.** Dynamics of key model variables in case of increased daily water intake.



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**Figure 4.7.** (a) Approximate real (from Guyton and Hall 2000) and (b) simulated effects of changes in daily water intake on the blood volume level.



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changes in sodium intake, as long as water intake is enough to balance the losses (Guyton and Hall 2000). In this experiment, the effectiveness of body feedback mechanisms to control the ECNa concentration is investigated. The system is initialized with all variables being at their normal levels, and sodium intake is varied by a factor of 0.2 to 5 times normal salt intake, a range of 25-fold (the factors in between being 0.4, 0.6, 0.8, 1, 2, 3, and 4). It is seen that ECNa concentration remains remarkably within 1% control limits when all feedback systems are intact (see Figure 4.9).

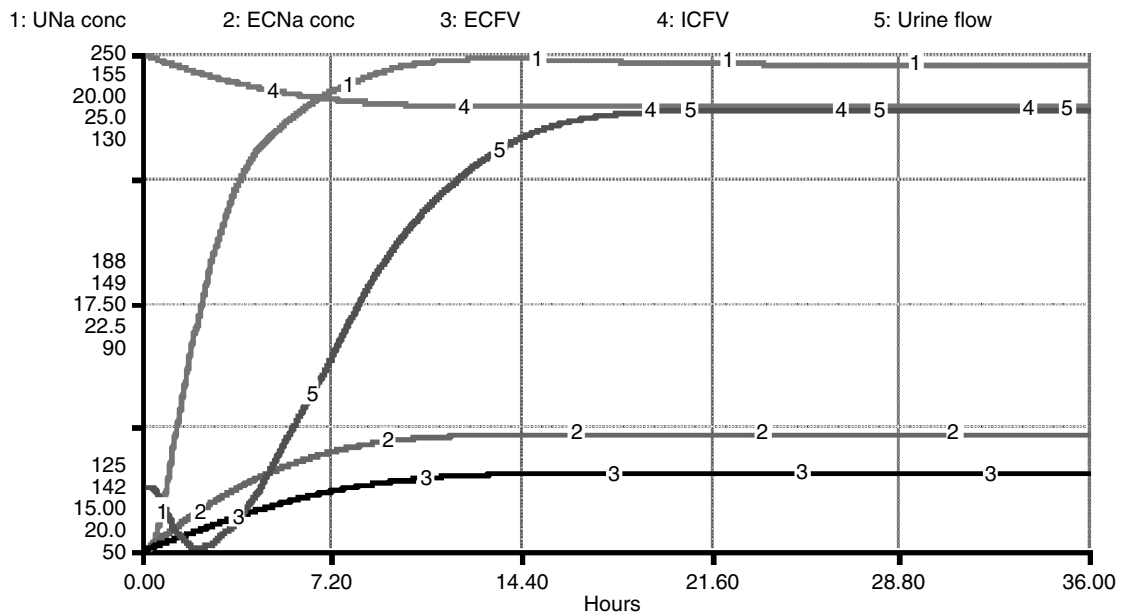
In the second experiment, the effect of the ADH-thirst feedback system on ECNa concentration is investigated. The above experiment is repeated by blocking the ADH and then the thirst control systems, and it is seen that each of the ADH and thirst control systems can regulate the

ECNa concentration on their own with reasonable effectiveness. On the other hand, if both systems are blocked simultaneously, the ECNa concentration changes tremendously, as expected by empirical evidence (see Figure 4.10).

In the third experiment, the effect of ALD (Aldosterone) feedback on ECNa concentration is sought, so the experiment is repeated by blocking the ALD feedback (see Figure 4.11). It is seen that ECNa concentration is almost equally well controlled with or without the ALD feedback mechanism, which demonstrates that the ECNa concentration is mainly regulated by the ADH-thirst system, and the ALD system has little role in this regulation.

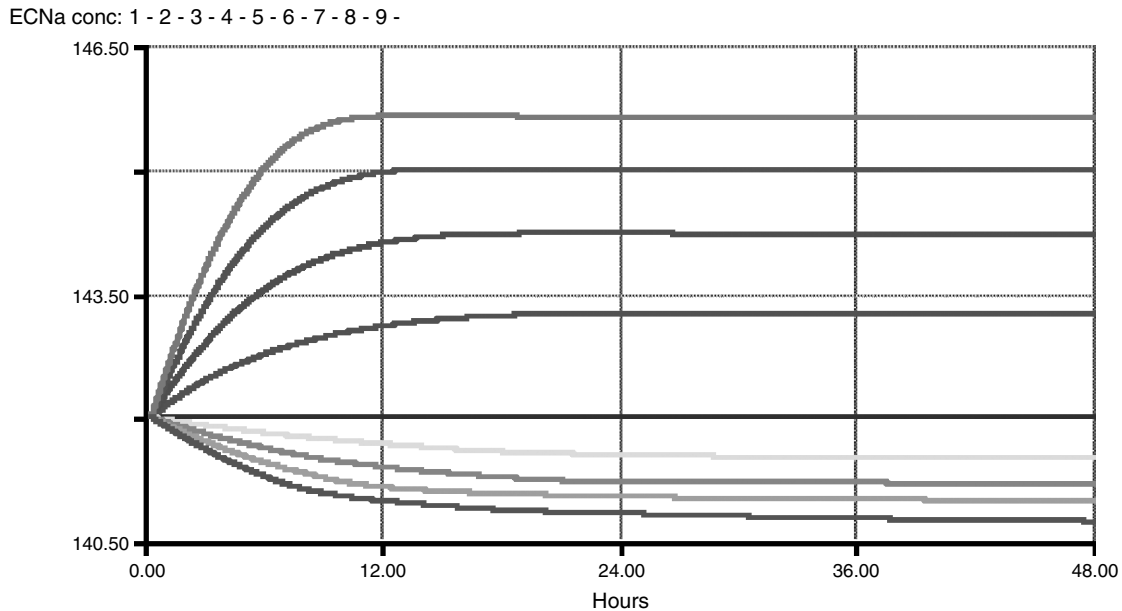
The general results above corroborate the prevailing theory for the Na homeostasis, stating that simultaneous changes in body sodium (and potassium) are accompanied

**Figure 4.8.** Dynamics of key variables in the case of four-fold increased sodium intake.



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**Figure 4.9.** Sensitivity of EC sodium concentration to different daily sodium intakes.



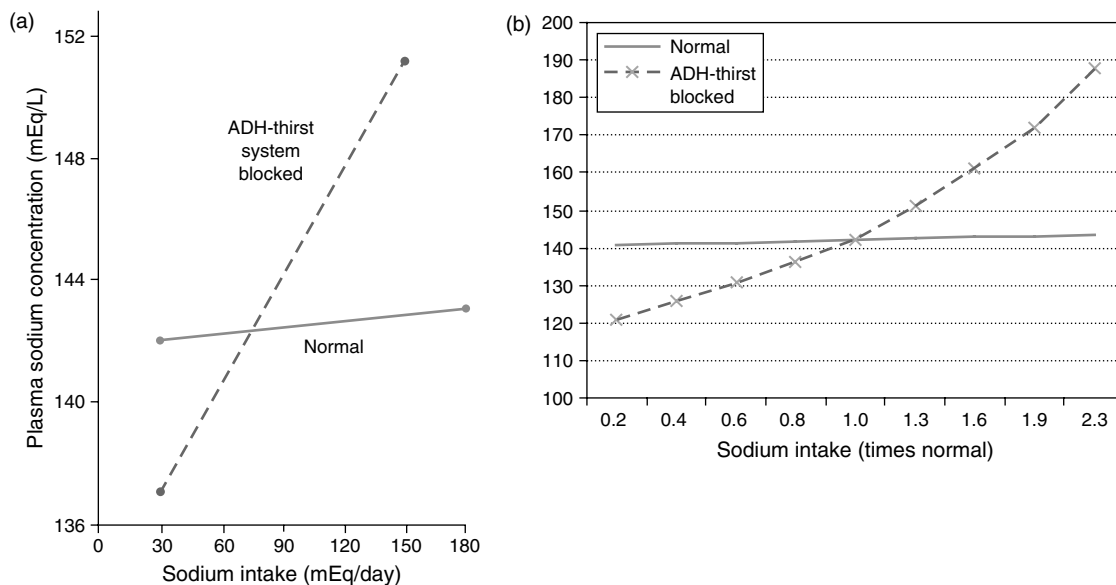
by osmotically adequate changes in TBW, and that osmo-control effectively adjusts TBW to its major substances Na (and K). Recently, a new concept of Na homeostasis was put forward by Titze et al. (2003), claiming that during Na retention, large portions of Na (up to 75%) are stored in an osmotically inactive form. In contrast, a recent study by Seeliger et al. (2005) does not support this notion, arguing that there is no positive proof for this Na storage because K balances were not assessed, and response to changes in Na

intake varies among species. Both our model and the recent study by Seeliger et al. (2005) reveal that further studies are needed to explore the subtleties of body sodium dynamics, especially by including the body potassium dynamics.

#### 4.4. Representing Diseases (Dysnatremia) and Treatment Options

The model discussed above represents the fundamental feedback structures of body water and osmolality regulation

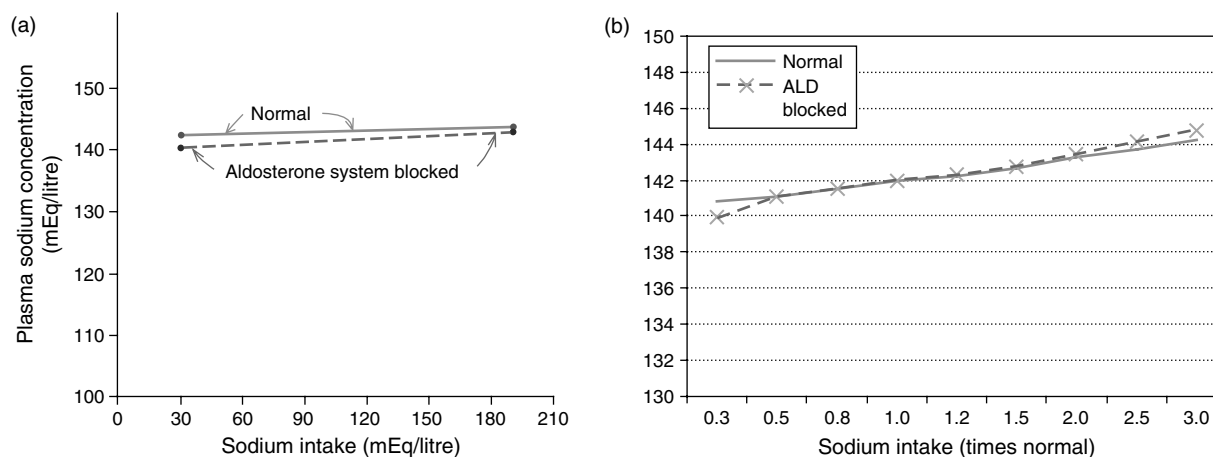
**Figure 4.10.** Effects of changes in sodium intake on EC sodium concentration (a) under normal conditions (solid line) and (b) after the ADH-thirst feedback has been blocked (dashed line). Empirical data (part a) from Guyton and Hall (2000) versus simulation results (part b).



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**Figure 4.11.** Effects of changes in sodium intake on EC sodium concentration (a) under normal conditions (solid line) and (b) after the ALD feedback has been blocked (dashed line). Empirical data (part a) from Guyton and Hall (2000) versus simulation results (part b).



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in a healthy person. Because the ultimate goal would be to provide assistance in the diagnosis and treatment of related diseases, the next step is to modify the model so as to replicate some common body water-sodium regulation disorders and to test alternative treatments. To this end, structures are modified or new structures are added to the original model to represent disease physiology and the treatment options, and some new variables are added for disease-related output measures.

**4.4.1. Representation of Hypernatremia (Diabetes Insipidus as a Common Type).** Increased levels of ECNa concentration or hypernatremia is typically seen when there is excess loss of water (Haslett et al. 2002). Diabetes Insipidus (DI) is the most common type of pathologic condition that is associated with hypernatremia. Insipidus means “tasteless,” therefore the term “Diabetes Insipidus” distinguishes excessive urine flow caused by inability to conserve water, from Diabetes Mellitus in which urine flow is enhanced due to excessive glucose excretion. In DI, deficiencies of ADH lead to the production of large amounts of dilute urine, which may reach up to 20–30 liters a day in severe cases. More commonly, however, urine volume is moderately increased (2.5 to 6 L/day). Consequently, the person becomes dehydrated.

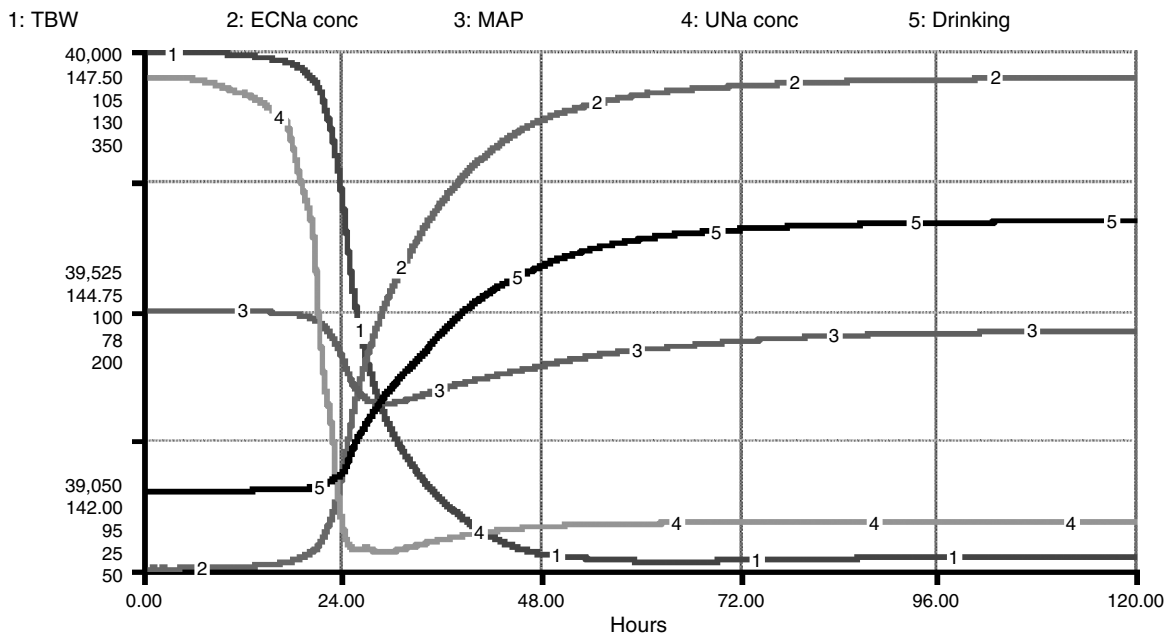
To simulate an extreme case of DI, the pool capacity of ADH is decreased by 90% (Figure 4.12). It is seen that the TBW can no longer be conserved, and the ECNa concentration can only be kept at an elevated level (Verbalis 2003). On the other hand, the blood pressure is kept constant at its normal level of 100 mmHg. The urine flow and hence drinking—to replace the loss—are highly elevated (drinking becomes extremely frequent in the discrete drinking version of the model). The urine concentration is very low, as expected. The daily water turnover of this patient is

about 11 liters, which is far greater than the normal value of 2–3 liters.

**4.4.2. Representation of Hyponatremia (SIADH as a Common Type).** SIADH is the most common cause of hyponatremia (38%). Both the thirst function and ADH action have to be deregulated to bring about hypoosmolality that occurs in SIADH. Therefore, first the set level of the ADH concentration is increased, and then the thirst function of the potential patient is modified in the model. Accordingly, the patient has an elevated normal fluid intake and she cannot suppress her water intake as a result of hypoosmolality. The equations for the urine sodium concentration are also modified to include the effects of a possible administration of the Aquaretic and the Diuretic drugs. The equation for drinking is modified so that a mild or severe water restriction can be imposed on the patient as a treatment option. (The terms “mild” and “severe” correspond to daily water intakes of 1,700 and 800 ml/day, respectively.)

The modified model is then used to demonstrate the appearance of hyponatremia in the SIADH. To develop hyponatremia, both ADH and the thirst functions have to be deregulated. This fact is demonstrated by simulating the modified model first by increasing the ADH level without changing the thirst function, and second, by disturbing the thirst function without changing the ADH function. It is seen that the resulting decrease in *ECNaConc* is very small. However, when both ADH and the thirst function are deregulated, there is no mechanism that can preserve the level of the body water and the *ECNaConc*. As an example, the dynamics of the emergence of hyponatremia is illustrated in Figure 4.13. In five days, the *ECNaConc* of the patient falls to 120 mEq/L, and the TBW is increased by about five liters. The final values of this simulation are used for the

**Figure 4.12.** Dynamics of the key variables in Diabetes Insipidus where ADH is incapacitated.

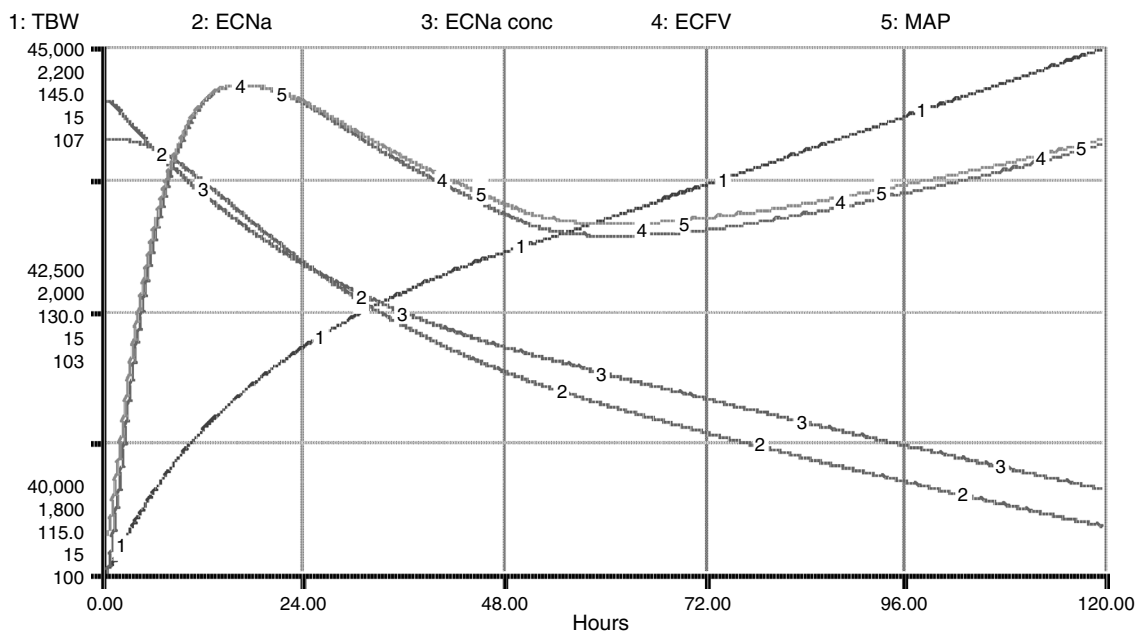


initialization of the interactive game, where a patient with acute hyponatremia is assumed to be admitted to a hospital.

**4.4.3. Treatment Sector for Hyponatremia.** An important intended application of the model and its game version is to test the effectiveness of different treatment options for specific diseases. In particular, we focus on the treatment of acute hyponatremia. The simulated patient is assumed to have an ECNa concentration of 120 mEq/L and an excess body water of about 5 L. The treatment goal

is to increase and sustain the ECNa concentration (*ECNa-Conc*) at its normal level, which is about 140 mEq/L. At the same time, the total body water should be decreased to its normal value (of 40 liters) and so should the EC and the IC water volumes. The new treatment sector is composed of three subsectors, two of which are almost identical, i.e., Diuretic and Aquaretic (or ADH-Antagonist) drug sectors. These two sectors represent the most commonly used drugs for treatment of hyponatremia (Yamamura et al. 1993, Saito et al. 1996, Shafiee et al. 2003). The drug metabolism

**Figure 4.13.** Appearance of hyponatremia when both ADH and the thirst functions are blocked.



structure used in Isee Systems (1997) is assumed to be appropriate for the scope of this research. The third subsector, i.e., intravenous fluid infusion, constitutes another standard therapy for treating severe hyponatremia. The three most commonly used types are represented in the model: hypertonic, isotonic, and hypotonic fluids, which are classified according to their sodium content. These treatment options are illustrated below in the interactive game section. (Also see the online supplement.)

## 5. The Interactive Dynamic Simulator (BWATERGAME)

### 5.1. Game Description

Finally, an interactive game version of the model is built, whereby players can diagnose hyponatremia and test various treatment strategies on a virtual patient. The player plays the part of a physician who is trying to treat an acute hyponatremic patient by weighing the risks of hyponatremia itself and those associated with rapid correction of the disease. The primary goal is to increase and sustain the ECNa concentration (*ECNaConc*) at its normal level, which is about 140 mEq/L. Simultaneously, the total body water volume, as well as the EC and the IC water volumes, should be decreased to their normal levels. The challenge is to achieve these goals in balance, keeping in mind that rapid correction of severe hyponatremia can cause brain edema. The total duration of the game is 160 hours, or 20 decision rounds. The player should revise her decisions at each step, by making use of the provided analysis tools. The treatment options available to the player are: Dose Diuretic, Dose Aquaretic (ADH-Antagonist), Isotonic Saline, Hypotonic Saline, and Hypertonic Saline (see the game control panel in the online supplement). Moreover, the player can change some of the game settings or impose water restriction to the patient by varying the scenario. A more detailed description of the game can be found in the user manual (see the online supplement and Karanfil 2005, 2006).

### 5.2. Results of BWATERGAME by Test Players

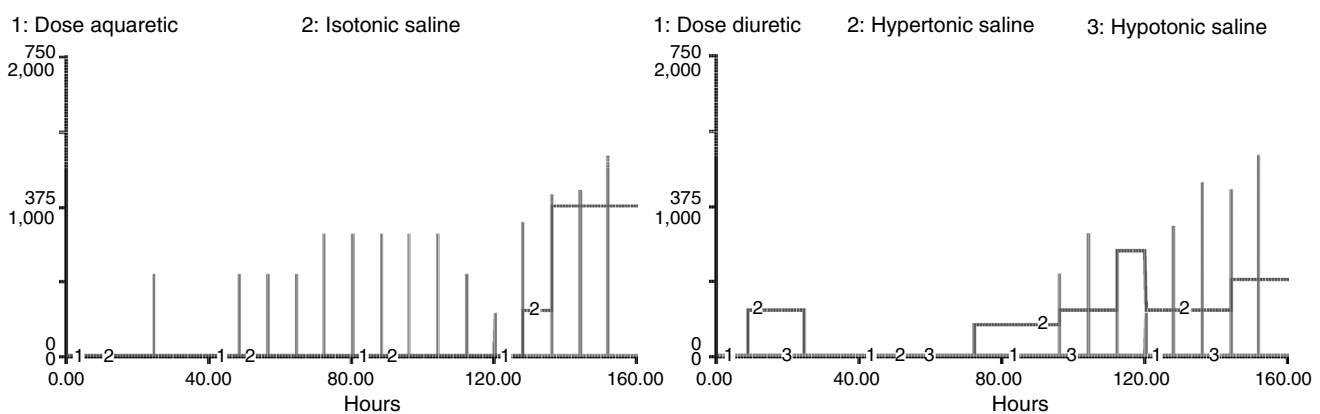
The game was tested by graduate students of the Industrial Engineering Department of Boğaziçi University, Istanbul. Each subject played the game several times and applied different strategies in their trials. The graphs in Figures 5.1–5.4 represent the dynamics of a few key measures obtained from a typical representative player. Figures 5.1 and 5.2 display the dynamics of the player's saline infusion and drug dose decisions, and Total body water, ECNa concentration, Urine Na concentration, and ECNa as outputs.

As can be seen in the figures, the representative player initially was unable to prevent the decline of the EC sodium concentration to levels below 115 mEq/L, but then he succeeded to increase it to mildly hyponatremic levels toward the end of the game. He used a combination of Aquaretics and Diuretics to increase urine flow via a decreased urine sodium concentration, and also applied a combination of hypertonic and isotonic saline during his trial. Total body water increased by 1.5 L in the initial phase, and then it decreased. At the end of the game, the simulated patient still has about 4 L of excess water. The player first wrongly chose to give hypertonic solution without drugs, but this only resulted in a fall in EC sodium concentration and a rise in blood pressure. Hypertonic saline combined with urine flow stimulating drugs later caused an elevated sodium balance and negative water balance.

Figures 5.3 and 5.4 on the other hand depict the game results of a player with a reasonably successful treatment strategy. The successful player used a combination of aquaretics and isotonic saline. In contrast to the representative player, he was able to reduce the urinary Na concentration to its normal levels by using the aquaretics alone, instead of a combination of diuretics and aquaretics that blunts the kidney's response. He was also able to replenish the sodium deficits. At the end of the game, he decreased the TBW to 42.2 liters, and the ECNa concentration rose to 133 mEq/L.

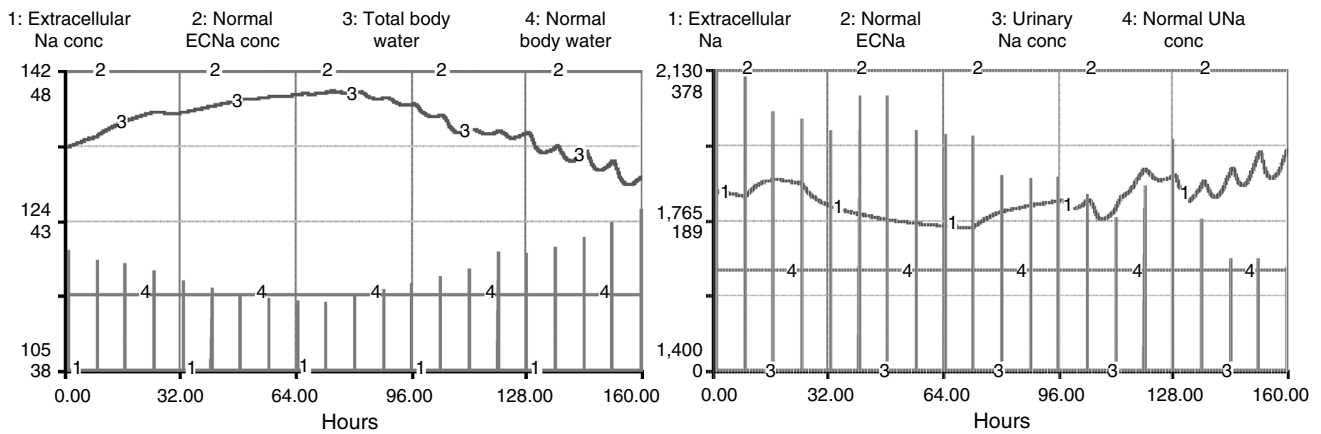
There is no single correct set of treatment decisions, as long as certain critical balances are simultaneously taken into account. (As mentioned before, the correction rate is

**Figure 5.1.** Saline infusion (seen as step functions) and drug dose decisions (seen in spikes) for a representative player.

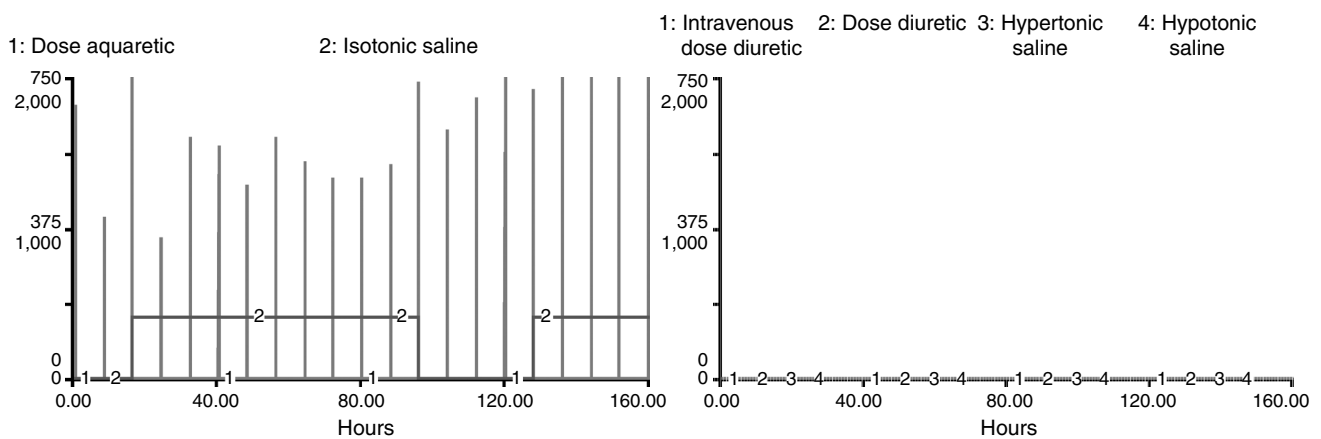




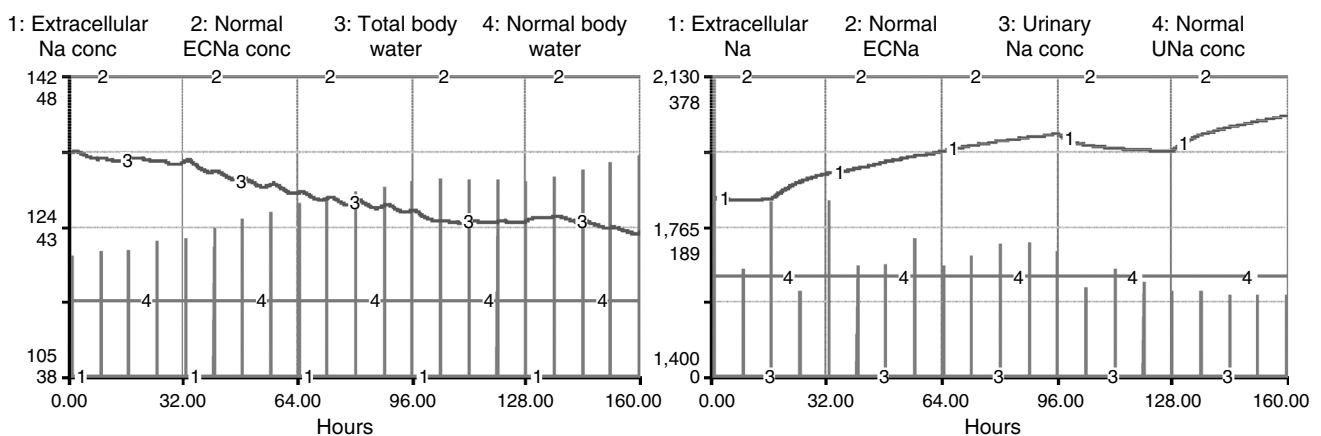
**Figure 5.2.** Dynamics of total body water, ECNa concentration (seen in spikes), UNa concentration (seen in spikes), and ECNa for a representative player.



**Figure 5.3.** Saline infusion (seen as step functions) and drug dose decisions (seen in spikes) for a player with a successful strategy.



**Figure 5.4.** Dynamics of total body water, ECNa concentration (seen in spikes), UNa concentration (seen in spikes), and ECNa for a player with a successful strategy.



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also a vital concern while managing the hyponatremia of the patient.) The two goals of the treatment should be considered concurrently: attaining a negative water balance and replenishment of the sodium deficits. Diuretics may be useful in correcting the excess body water, but should be supported by high amounts of sodium. So, the players that used Diuretics instead of Aquaretics had to administer high amounts of saline. While Aquaretics may decrease the urine sodium concentration to levels below its normal, Diuretics can only blunt the urinary concentration process, so they can decrease the UNa concentration at most to its normal level. Generally, players administered Diuretics and Aquaretics together, and Diuretics reduced the effectiveness of Aquaretics in those trials. This demonstrates that Diuretics should not be administered in severe cases of hyponatremia.

Another important point to note is the EC sodium level of the patient. Because the sodium-preserving systems are intact in an SIADH patient, the ECNa content is preserved at a lower steady-state value. However, sodium depletion may worsen the condition of the patient due to decreased sodium and decreased urine flow. SIADH patients typically have a normal or slightly elevated mean arterial pressure level, and this level should be closely monitored. Low arterial pressure levels may inhibit the urine flow increasing strategies, and a high level of arterial pressure is undesirable for obvious reasons.

The game results so far demonstrate that the interactive simulator (BWATERGAME) can be a useful experimental platform to study the subtleties involved in the administration of different pharmacological interventions (also see Karanfil 2005, 2006). Our current research involves more extensive testing of the simulator and statistical analysis of the experimental results.

## 6. Conclusions and Further Research

The goal of this research is to model the normal and abnormal physiology of the body water and sodium regulation in humans and to test treatment strategies for a particular body fluid disorder, namely, water intoxication/hyponatremia. For this purpose, first a system dynamics model is built representing the dynamics of the body water and sodium balance for a normal individual. Then, this model is extended to generate common disorders of body water regulation (both hypernatremia and hyponatremia) and to explore effective treatment strategies. Comparisons with experimental and field data show that the model adequately reproduces typical dynamics of the body fluid variables in normal and pathological states. Sensitivity results also agree with high resilience known to exist in the human body as a feedback control system. Based on the extended model, a game version is finally constructed whereby players can interactively treat a virtual patient with acute hyponatremia. The game is used as an experimental platform to test the effects of a typical set of treatment options on a simulated patient.

The model demonstrates that ADH (Antidiuretic Hormone) is extremely important for the control of sodium concentration, yet it has a relatively mild effect on the control of blood volume/pressure. The modified model for the development of hyponatremia reproduces all the cardinal features of the SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion). Blocking of the ADH-thirst system first causes an increase in the body fluids, but then transient sodium loss is promoted. As a result of dilution, ECNa concentration falls drastically, but the arterial pressure is only slightly elevated. Moreover, urine is still highly concentrated due to the absence of compensating feedback between the ECNa concentration and the ADH.

The interactive simulation game (BWATERGAME) yields meaningful results for various treatment options. Game results reveal that an effective correction of the SIADH can only be attained if a negative water balance can be maintained. Replacing the sodium deficits alone is worthless because, following a sodium intake, blood pressure conserving mechanisms cause an increased sodium excretion rate. It is demonstrated that Aquaretics (that increase the urine flow) are the most effective treatment, together with slow replenishment of body sodium stocks by graded doses of saline infusion. However, they should be administered carefully to prevent an overcorrection.

In conclusion, the model and the interactive game version constitute an experimental laboratory for systemic therapy of hyponatremia. They can be used as a research and teaching tool on renal physiology, on the important differentiation between the concepts of “sodium content” and “sodium concentration,” between their equilibrium and dynamics, and related disorders.

There are several avenues in which this research can be expanded. We are already working on more extensive gaming experiments by players with different backgrounds, carried out with a suitable design of experiments and subsequent statistical analysis of results. Another research step is modifying the current game model for the treatment of severe hyponatremia in an intensive care unit setting, by changing the initial conditions of the modified model and the treatment options.

Hyponatremia can occur with many electrolyte imbalances (other than sodium), hypokalemia (potassium deficit) being the most common electrolyte disorder. Another substance ignored in our model is the urea. We have represented the urine osmolality by its sodium chloride concentration only; however, in reality urea also contributes significantly to the urine osmolality when the kidney forms a maximally concentrated urine (Guyton and Hall 2000). Modeling of the interactions of the treatment options of hyponatremia with potassium and urea dynamics may reveal a broader range of possible physiological phenomena.

## 7. Electronic Companion

An electronic companion to this paper is available as part of the online version that can be found at <http://or.journal.informs.org/>.

## Appendix. Abbreviations

ADH	Antidiuretic Hormone
ALD	Aldosterone
ANG	Angiotensin
ANH	Atrial Natriuretic Hormone
BV	Blood volume
DI	Diabetes Insipidus
EC	Extracellular
ECFV	Extracellular fluid volume
ECNa	Extracellular sodium
ECOSm	Extracellular osmolality
GFR	Glomerular Filtration Rate
IC	Intracellular
ICFV	Intracellular fluid volume
ICOsm	Intracellular osmolality
K	Potassium
L	Liter
MAP	Mean Arterial Pressure
Na	Sodium
PV	Plasma volume
RAAS	Renin-Angiotensin-Aldosterone System
SIADH	Syndrome of Inappropriate ADH Secretion
TBW	Total body water
U	Urine (or Urinary)
UNa	Urinary sodium
UOsm	Urine osmolality
conc	concentration
eff	effect
mEq	milliequivalents

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