A Dynamic Simulator for the Management of Disorders of the Body Water Metabolism

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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 Antidiuretic Hormone Secretion; TBW, Total body water; U, Urine (or Urinary); UNa, Urinary sodium; UOsm, Urine osmolality; V, Volume; mEq, milliequivalents.

ABSTRACT

In this study, a simulation model is built to study the body water regulation and its disorders by focusing on the fundamental feedback mechanisms in the normal and disease physiology. This model is then extended to include related therapeutic interventions of the most common body fluid disorder, namely water intoxication/ hyponatremia, and a game version is produced to test the possible effects of a given set of treatment options on a simulated patient. The model is shown to adequately reproduce the changes in the body fluid balance in normal and diseased states. The interactive simulation game version of the model proves to be a useful experimental platform to describe changes that are known to occur after administration of various pharmacological means. Game results demonstrate that hypertonic saline should be given carefully concurrently with drugs that increase urine flow. The model and the game version constitute an experimental laboratory for a closed-loop therapy approach to hyponatremia.

1. INTRODUCTION

The homeostatic regulation of body fluids is important in almost every field of medicine and has been thoroughly investigated in this century. In health, total body water and its distribution throughout the body is maintained between narrow limits. This

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task is accomplished by two distinct but interactive systems that respectively regulate the extracellular sodium concentration/body water and the blood volume/sodium content.

The main feedback system for body water regulation is the Antidiuretic Hormone (ADH)-thirst system, and the main feedback mechanisms for sodium balance include the Aldosterone (ALD) and the Atrial Natriuretic Hormones (ANH), and the renal mechanisms. In ADH-induced hyponatremia, both the ADH and the thirst feedback loops are dysregulated, and the result is a lower sodium concentration and higher body water content, which may cause serious consequences.

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 EC sodium concentration, is the most important body fluid disorder with the potential for significant mortality. The treatment of hyponatremia constitutes a problem, partly because all available therapies have significant limitations. Furthermore, it is observed that a big 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 growing trend raised doubts related to 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 means, body water regulation and its disorders constitute a suitable area for system dynamics simulation modeling. However, no closed-loop therapy approach for disorders of dysnatremias has been yet attempted (Northrop, 2000). This study attempts to build a closed-loop system dynamics model for body water disorders, and particularly for ADH induced hyponatremia.

2. CLINICAL ABNORMALITIES OF BODY FLUID REGULATION

Any influence which alters the balance of the body water or sodium metabolism inevitably affects the balance of the other. Therefore, it is important to differentiate the clinical abnormalities of ECF volume/Na content from those of the TBW/osmolality regulation.

2.1 Disturbances of Body Sodium Content

As the major cation of the EC fluid, the sodium content determines the ECFV. Therefore disorders of sodium metabolism are always manifested as disorders of volume status. Moreover, due to the close interrelationship between ECFV and the mean arterial pressure (MAP), MAP is also dysregulated. 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), since 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 central nervous system.

In general, failure to maintain body water between narrow limits includes two components. The first one is associated with 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 component may still compensate this failure. (Jamison *et al*., 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. DYNAMIC MODELING OF PHYSIOLOGICAL SYSTEMS

3.1. Systems Theory in Physiological Models

Hippocrates held the idea that disease is cured by natural powers, but the corresponding 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 and suggested that physiological systems are dominated by negative feedback loops. The second pioneer of systems thinking in physiology, namely Arthur Guyton, was the first to introduce the concept of systems analysis to physicians, whose approach then led to the emergence of biomedical engineering.

3.2. Models for Fluid-Electrolyte Dynamics

The system for regulation of body fluid volume is important to understand diseases such as hypertension and dysnatremias. First models that represent certain aspects of renal control of body fluids belong to DeHaven and Shapiro (1967) and Reeve and Kulhanek (1967). Integrated models of body fluid regulation that also consider the circulatory system include those by Ikeda (1979) and Abbrecht (1980). However the most complex analysis of body fluid dynamics belongs to Guyton and co-workers, who constructed an overall circulatory model for examining the causes of hypertension. This model has inspired many other studies in this field, e.g. Cameron (1977), Badke (1972), and Uttamsingh (1981). Uttamsingh (1985) also extended his model for the clinical application of patients with renal failure. Recently, a long-term cardiovascular system model is developed by Karaaslan (2004) that integrates the previous models developed by Guyton, Uttamsingh and Coleman.

4. DESCRIPTION OF THE MODEL

The purpose of this modeling study is to develop a dynamic representation of our body fluid balance in normal and diseased states. For this purpose, this modeling study is divided into three parts. In the first part, the normal physiology of the body water balance and its stability will be clarified, and in the second part, the dynamics hyponatremia will be investigated. Lastly, the modified model of the second part will be used in an interactive simulation game for exploring the possible effects of therapeutic interventions, and finding a successful therapy.

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 all the regulated variables are taken as exogenous constants, e.g. the set point for ADH and the set point for blood volume. The effector organ of the body fluid system is the kidney.

The 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. In addition to these five sector groups, there are other structures in the model, which do not belong to any of these sectors but are used for the game, messages, extra measurements, time tracing converters, etc.

The initial states and parameters are standard values which are quoted frequently in the major medical textbooks and in earlier models. When available, published experimental data is also used. The model assumes a standard healthy human male of approximately 70 kg with 40 liters of body water.

4.1. Control of Total Body Water and Osmolality

The mechanism for the regulation of water balance is often referred to as the 'thirst-ADH mechanism'. The two most important factors that are monitored by this mechanism are EC osmolality and intravascular volume (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.

Under usual conditions, control of EC osmolality means almost the same thing as controlling the ECNa concentration, since ECNa is the substance that mostly contributes to the EC osmolality. Its importance in terms of water balance is that control of EC osmolality controls IC volume. Three facts about the body water and body sodium verify this argument: First, sodium is mostly restricted to the EC fluid; second, intracellular solute does not change easily, third, EC osmolality must equal IC osmolality. It should be noted that the mechanisms that control the ECNa "concentration" and the ECNa "amount" are different, albeit interacting. ECNa concentration has a normal value of 142 mEq/L, and is found by division of EC sodium content (ECNa) by ECFV.

Figure 4.1 provides a causal-loop diagram of the body water/osmolality control system. The 1st and the 2nd loops demonstrate the ADH-thirst feedback mechanism for EC osmolality and body water control. Increasing EC osmolality increases 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.

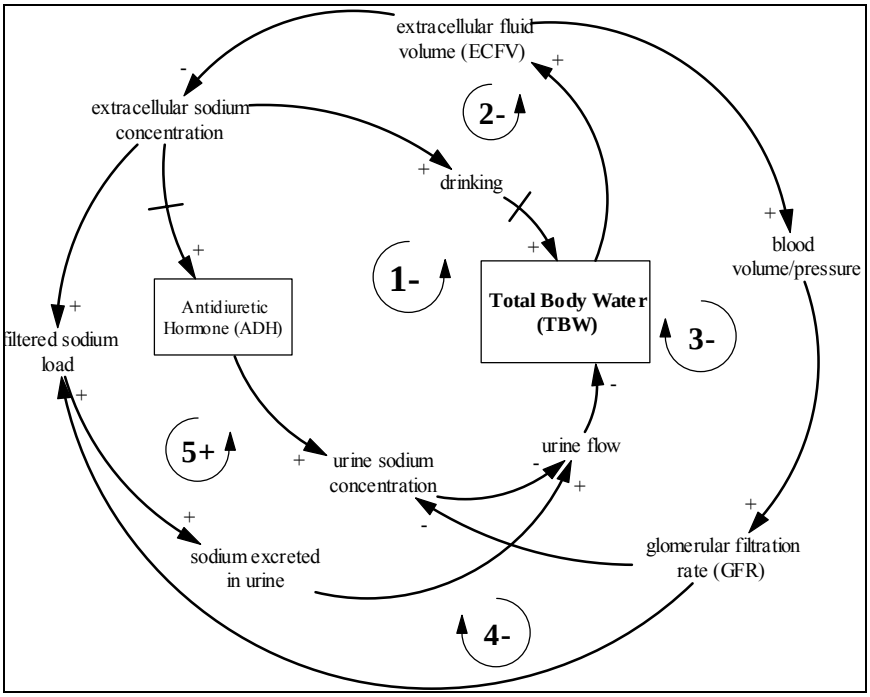

Figure 4.1. Causal-loop diagram for body water/osmolality control

Drinking is considered as the only source of fluid intake. Both continuous and discontinuous drinking options are modeled to simulate the drinking behavior. The model developed by Reeve and Kulhanek (1967) forms the basis regarding the drinking structure in this study. Accordingly, discontinous drinking is considered as a constant or variable rate mechanism governed by on-off switches and inhibitory feedback. For the continuous drinking structure, drinking rate is is defined as a function of EC osmolality (See Figure 4.2).

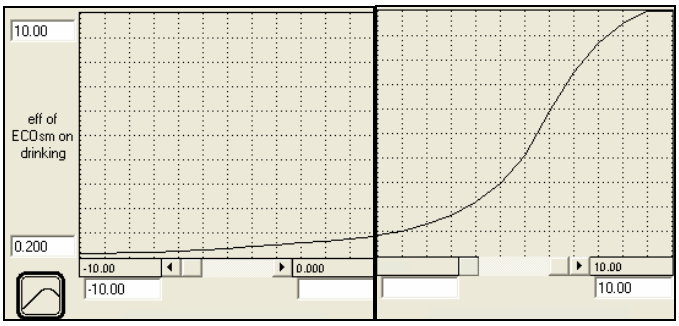

Figure 4.2. Effect of ECOsm on drinking

A constant water loss, which represents the continuous escape in the form of evaporation, and a varying urinary loss represent the two sources of loss of water from the body. The urine flow rate is determined by two variables, i.e. the urinary sodium concentration (UNa_conc), and the rate of sodium excretion (na_out_in_urine). The underlying assumptions are: 1-The rate of water transport is always proportional to the rate of solute transport, 2-The urine flow is inversely related to the urinary concentration assuming a given sodium outflow (Bray et al., 1989). Ordinarily the urine flow rate*urine osmolality (which equals to the amount of solute excreted) is relatively constant. The equation of the implied_UFlow is:

$$implied\_UFlow = \frac{na\_out\_in\_urine}{UNa\_conc \times 1000}$$

Under normal physiological conditions, the ADH level is the main determinant of urine osmolality. The upper limit to the maximal concentration of urine is about three-four times the osmolality of plasma (Janicic and Verbalis, 2003). Accordingly, the effect of ADH on UNa_conc is formulated with a graphical function (See Figure 4.3). The UNa concentration implied by ADH (implied_UNa_conc_by_ADH) is formulated by dividing the normal UNa concentration by the effect of ADH:

$$implied\_UNa\_conc\_by\_ADH = \frac{normal\_UNa\_conc}{eff\_of\_ADH}$$

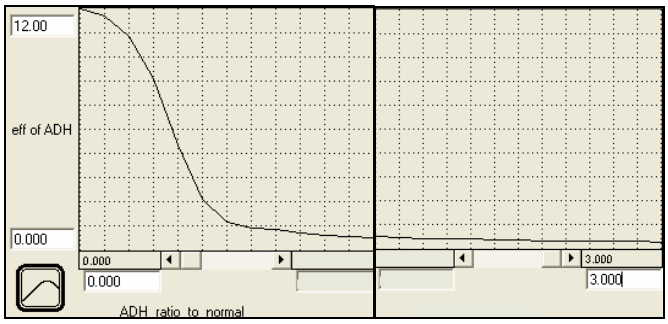

Figure 4.3.Effect of ADH on UNa concentration

However, there are other factors that can regulate urine osmolality and dilution in the absence or excess of ADH, i.e. the GFR. In addition to that, the effects of some drugs on urinary concentrating/diluting capacity of the kidney are also presented in the modified Game version of the model.

Other mechanisms that can influence the urine flow rate/urinary concentration are the Glomerular Filtration Rate (GFR) and the sodium excretion rate. GFR represents the amount of filtrate formed per minute and so it determines the amount filtered for any substance in the kidney. An increase in GFR increases urine flow via a decreased rinary concentration (3rd loop). As seen in the diagram, GFR and the EC sodium concentration influence the sodium excretion rate by changing the filtered sodium load (4th and 5th loops).

4.2. Control of Total Body Sodium and Extracellular Fluid Volume

Total body Na+ is restricted mostly to the ECF. Hence day to day variations in the amount of body Na+ represent variations in ECF volume (Bray et al., 1989). Since the EC and the IC osmolalities are always identical, and IC solute is assumed to be constant, the EC fluid volume (ECFV) is calculated as follows:

$$ECFV = TBW \times ECNa\_ratio\_to\_total / 1000$$

$$ECNa\_ratio\_to\_total = \frac{ECNa}{(ECNa + IK)}$$

In modern societies the sodium intake is always greater than necessary for homeostasis. Therefore, sodium intake rate is assumed to be constant in the model. According to the most recent knowledge, sodium excretion mainly involves three factors: the filtered load, ALD, and ANH.

Figure 4.4 provides a brief causal-loop diagram that demonstrates the causal mechanisms related to these three factors. The 1st and the 3rd loops are related to balancing 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 × plasma concentration of the substance (Guyton, 2000). Any change that causes an increase in the filtered load of sodium causes a rise in sodium excretion. On the other hand, the 2nd 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 remaining balancing loops relate to the effects of the ANH and ALD hormones. The response of ANH is assumed to take effect immediately, however ALD responds to the value of stimuli after a delay. Therefore, ALD is important for long-term adjustments of sodium excretion (Bray et al., 1989), whereas ANH (together with changes in filtered load) is responsible for short term adjustments.

The sodium excretion rate (na_out_in_urine) is formulated as as a multiplicative effect formulation:

$$na\_out\_in\_urine = Filtered\_Na \times normal\_fract \times eff\_of\_ANH\_on\_na\_excr \times eff\_of\_ALD\_on\_na\_excr$$

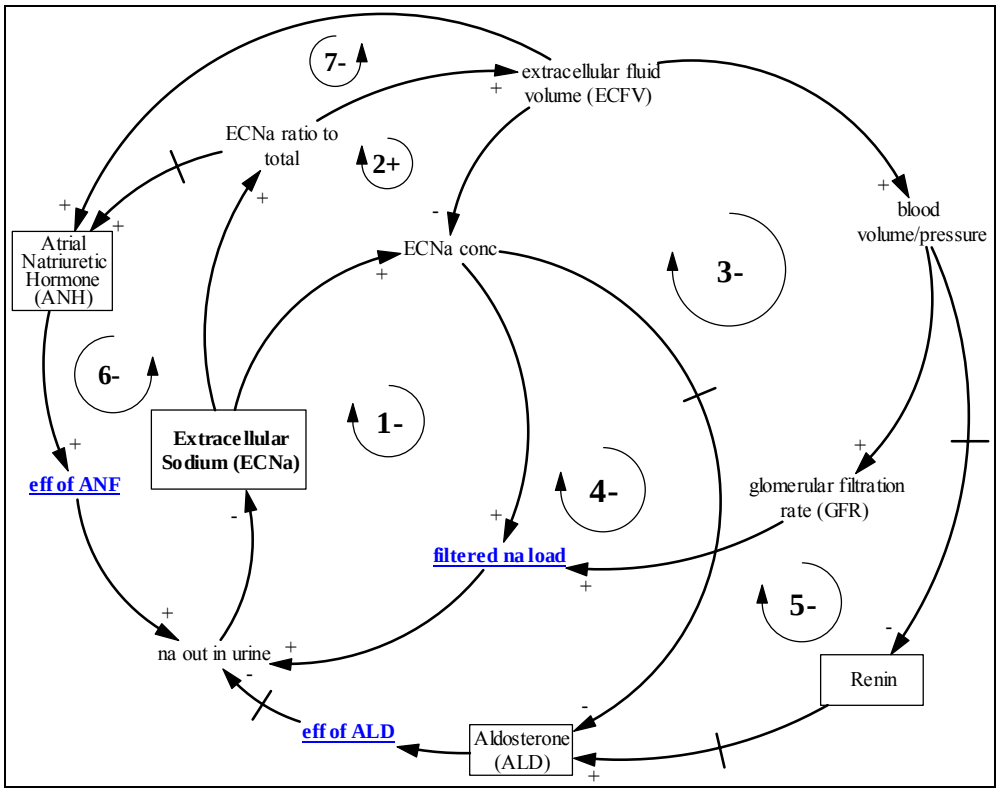

Figure 4.4. Simplified causal-loop diagram for sodium and ECFV regulation

4.3. Integrated Body Water and Sodium Regulation

Figure 4.5 gives an overall appreciation 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/Na content regulation from abnormalities of body water/osmolality.

In SIADH, the degree of water retention is limited due to the adaptive mechanisms of the body, i.e. the kidney adapts via a transient natriuresis and a persistent diuresis. In fact, the pathophysiology of this disease can be better understood when the causal-loop diagram presented below is examined carefully.

Main features of the SIADH are drastically decreased EC sodium concentration, a clinically normal ECFV, normal/mildly elevated blood pressure and an increased GFR. It is seen that the EC/blood volume regulation is appropriate; however the osmolality/TBW regulation is deranged. As the TBW increases due to increased ADH levels, both EC and the IC volumes increase. However a transient natriuresis induced by the ANH and ALD hormones acts to defend the EC volume and protects the body from a hypertensive state. Therefore, most of the excess fluid is accumulated in the IC fluid. However, to achieve a steady-state condition, fluid intake and output must be precisely balanced. Thus, a mild elevation in GFR can be considered as an adaptive response of the body to compensate the high urinary concentration induced by ADH.

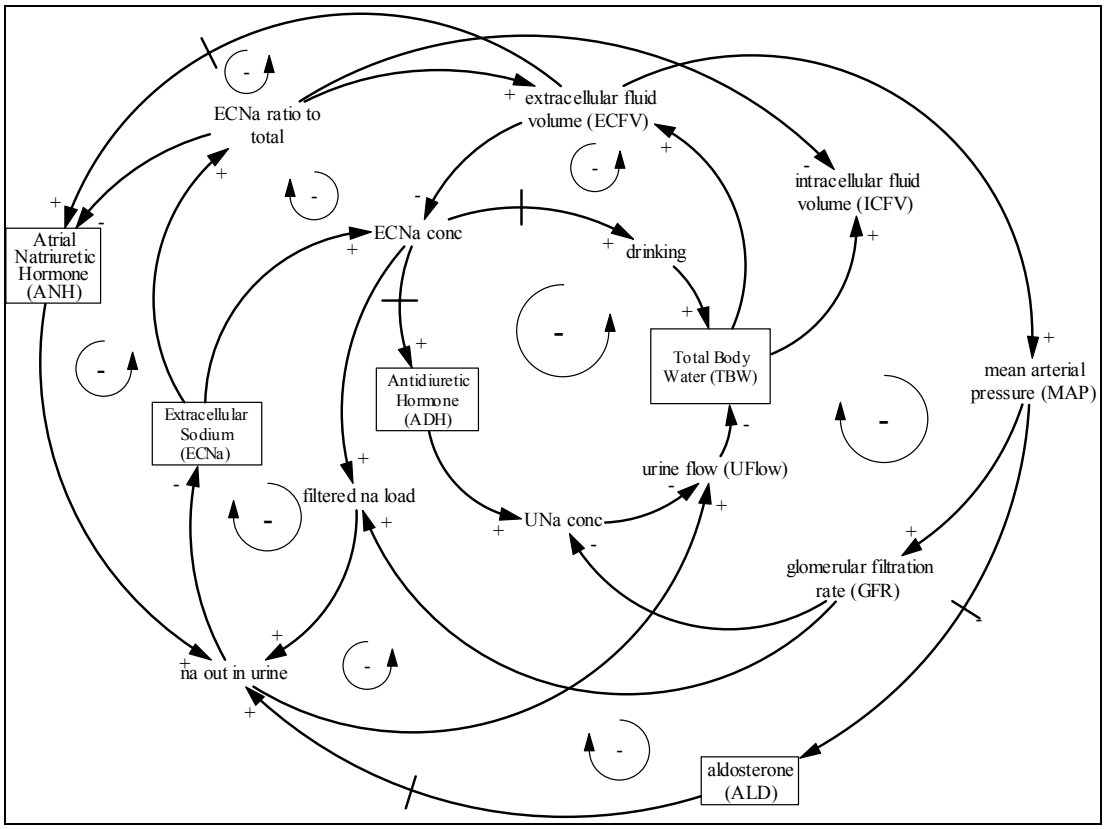

Figure 4.5. Overall regulation of body fluids by integrated control of body water and body sodium regulators

5. VALIDATION AND ANALYSIS OF THE MODEL

A formal validation process is followed in order to detect structural flaws of the model (Barlas, 1996) which is integrated to the model building process. Many direct structure tests are performed during the model building, which are not presented here. The validation of the model is basically demonstrated by performing "structure-oriented behavior tests" proposed in literature, such as extreme condition and behavior sensitivity tests, and a selected sample is presented. The model behavior is also compared with the real data, where data are available.

5.1. Basis Dynamics of the Model

5.1.1. Base Behavior of the Model

The continuous version of the model shows a steady state behavior when all its levels are initialized at their equilibrium values, and the discontinuous drinking version of the model demonstrates the normal daily variations in the key variables (See Figures 5.1 and 5.2). It can be seen that the ECNa and the MAP show almost no change during the day. The main change can be seen in the dynamics of the urine flow, drinking, and the UNa concentration, since water is continuously lost and then replenished by drinking. As a result, the TBW is maintained within the normal limits.

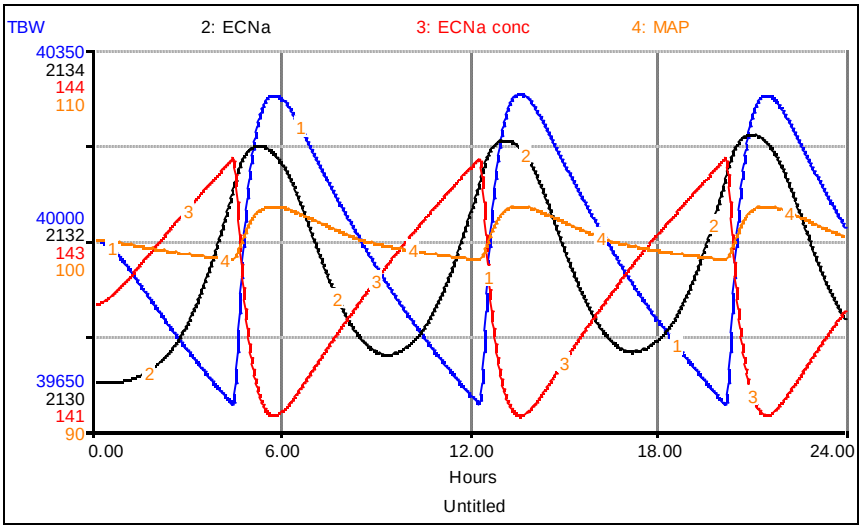

Figure 5.1 . Equilibria of the key variables with discontinuous drinking

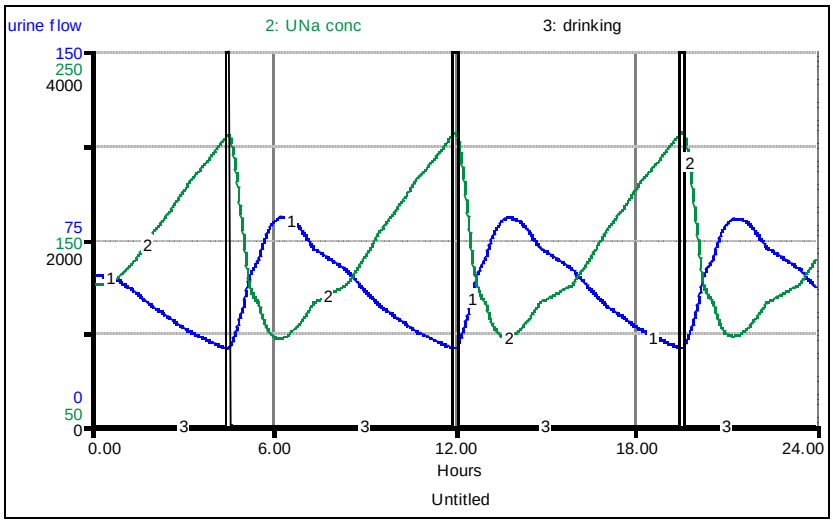

Figure 5.2. Equilibria of the key variables with discontinuous drinking-2

5.1.2. Water Loading

The dynamics of body fluids after water loading constitutes one of the fundamental tests of the interaction between body fluids and the kidney. For this simulation, the normal_drinking variable is set to 0, and a pulse of water input of 1000 ml is given at time 0. The urine flow rate increases about 11 fold in one hour, and after 3 hours it returns to its normal value (See Figure 5.3 and 5.4).

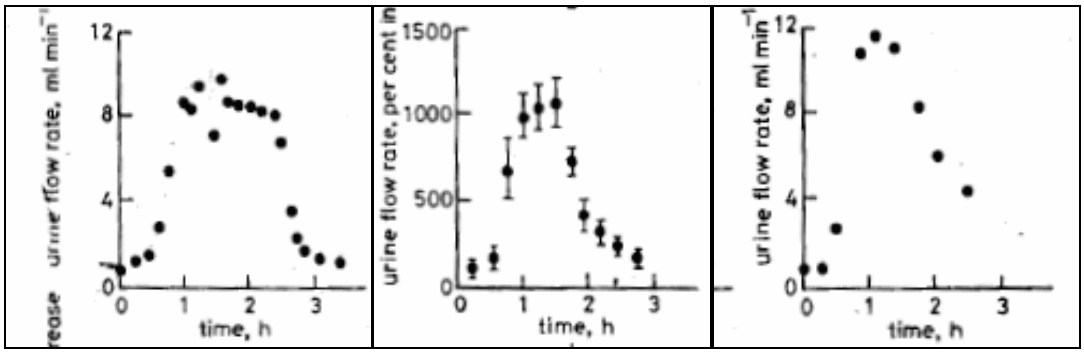

Figure 5.3. Urine flow following ingestion of 1 L of water;(a) data from Baldes and Smirk, 1934, (b) data for eight subjects, (c) data for one subject - (Uttamsingh, 1985)

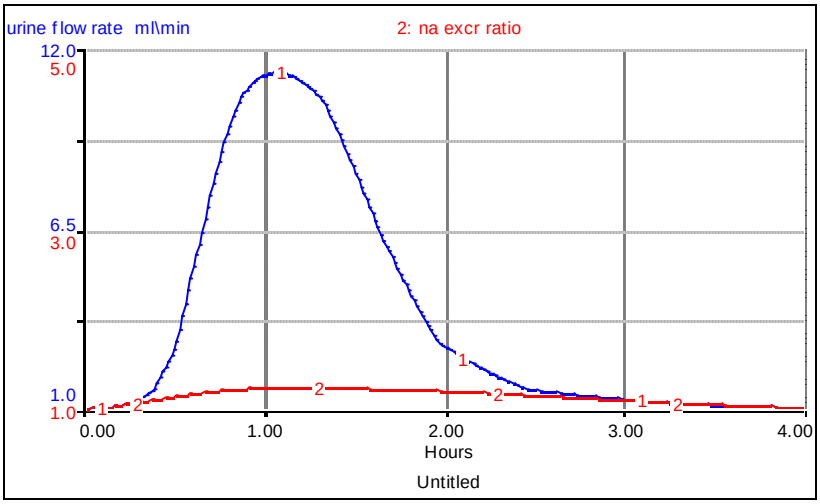

Figure 5.4. Base dynamics of urinary excretion following ingestion of 1 L of water

Figure 5.5 gives a schematic representation of the normal physiologic relationships among ECOsm, ADH concentrations, UOsm, and urine volume. Accordingly, urine osmolality is proportional to plasma ADH levels, but urine volume is inversely related to urine osmolality.

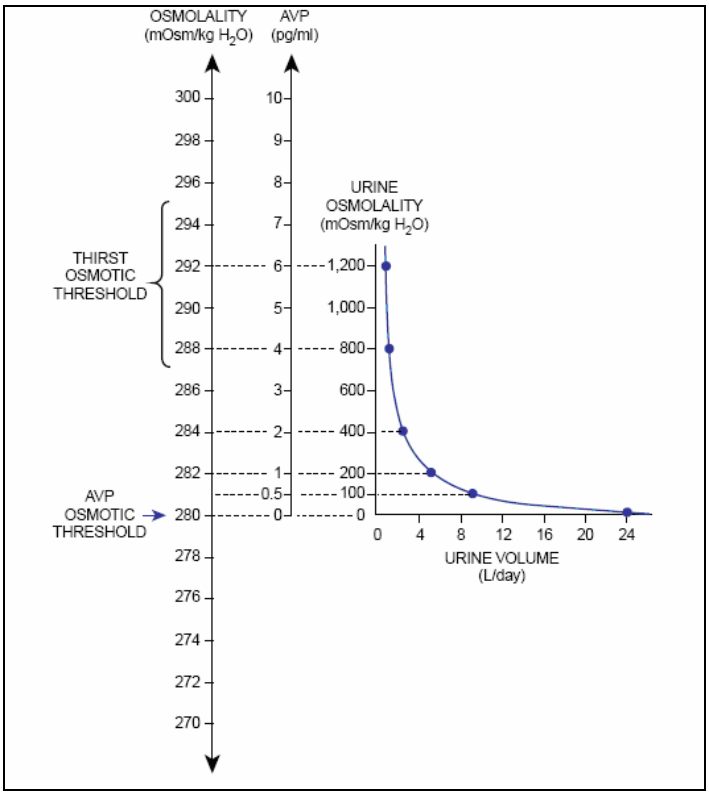

Figure 5.5 Normal physiologic relationships among EC osmolality, ADH concentration, urine osmolality, and urine volume in man (from Verbalis, 2003)

The model simulated results for the relationship between the urine flow and the UNa concentration in the base run and the water loading tests are given in Figure 5.6.

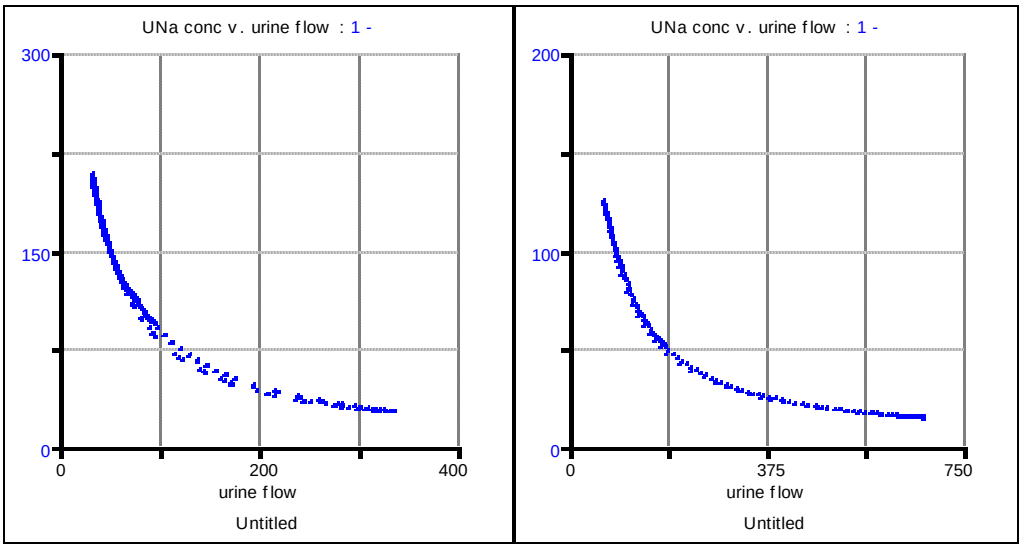

Figure 5.6. Simulated relationships among urine flow and UNa concentration (a) for the base run, (b) after ingestion of 1 L of water

5.2. Experiments with Changes in Daily Water Intake

This set of experiments is simulated by varying the daily water intake (normal_drinking) 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 elevated (decreased) water intake is a great fall (rise) in the UNa concentration and a consequent rise (fall) in the urine flow. There is almost no change in the TBW, MAP, and the ECNa, as long as the fluid intake and the fluid loss are precisely balanced. A representative dynamic of the key variables is given in Figure 5.7.

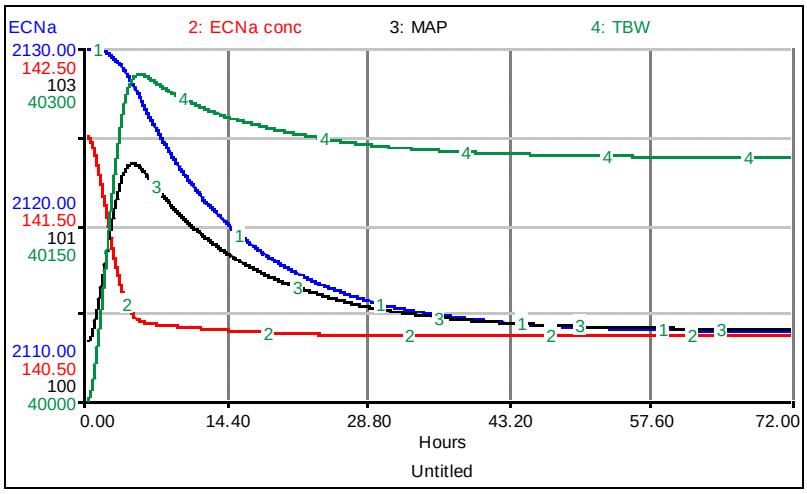

Figure 5.7. Dynamics of key variables in case of increased daily water intake

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, 2000). Figure 5.8 demonstrates the fact that the blood volume remains almost constant despite extreme changes in fluid intake. The simulated results are in accordance with the real case.

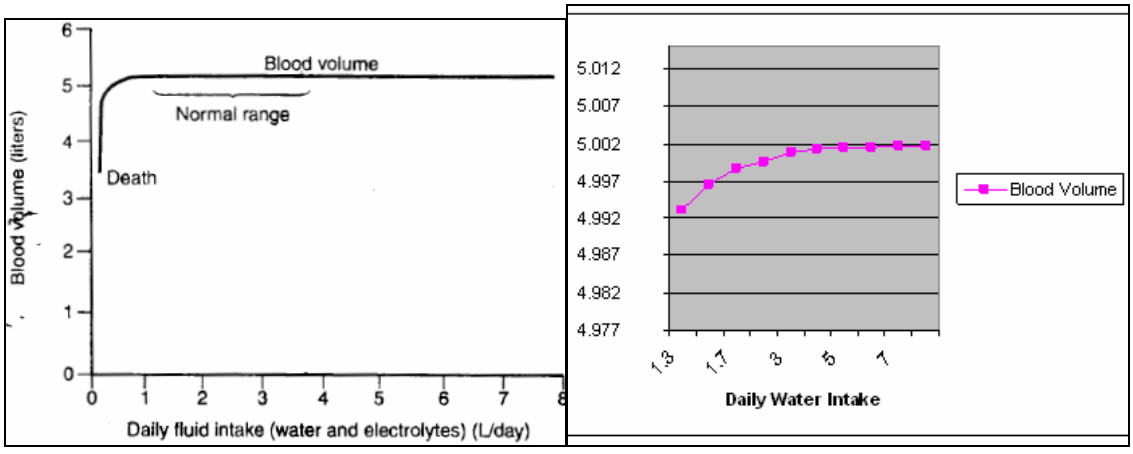

Figure 5.8 a) Approximate and b) simulated effect of changes in daily fluid intake on blood volume (b) from Guyton, 2000

5.3. Experiments with Changes in Daily Sodium Intake

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 little effect on the ECNa concentration and the TBW, but they have a great effect on the ECFV, BV, and MAP. A representative dynamics of the key variables is given in Figures 5.9 and 5.10.

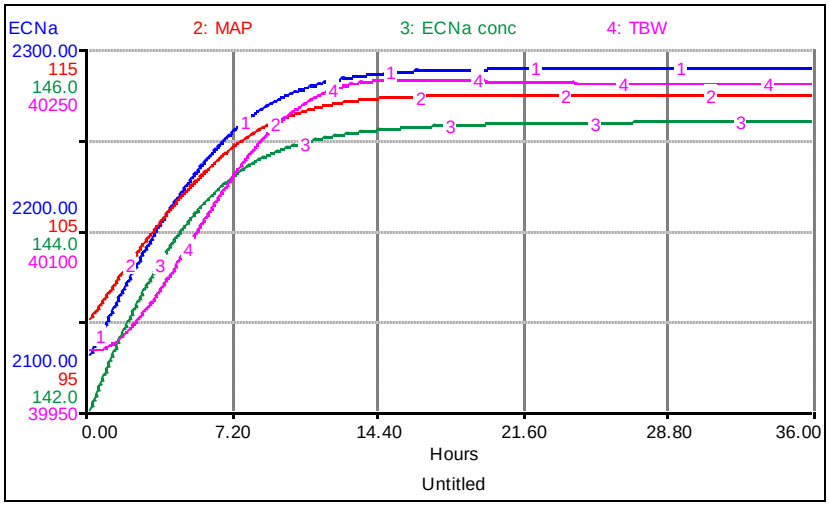

Figure 5.9. Dynamics of key variables in case of 4-fold increased sodium intake

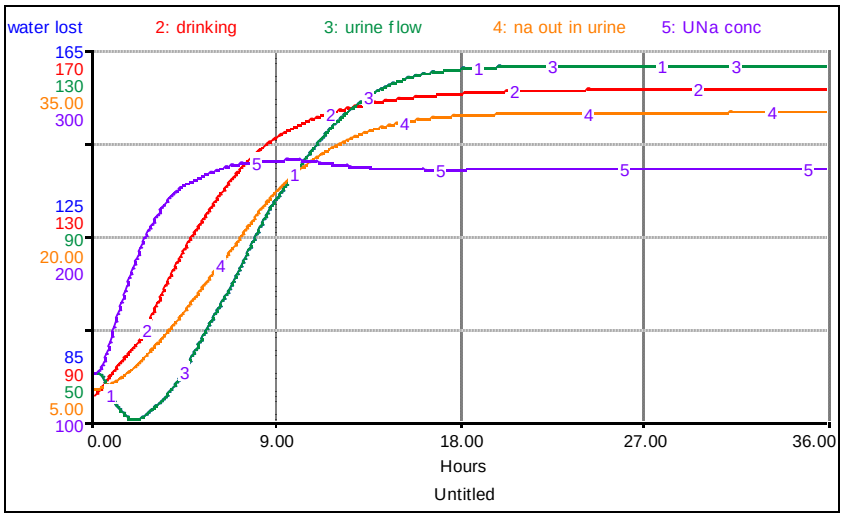

Figure 5.10. Dynamics of key variables in case of 4-fold increased sodium intake-2

Sensitivity of ECNa_concentration to Different Daily Sodium Intakes: In a normal person, ECNa concentration is controlled with reasonable effectiveness even with large changes in sodium intake, as long as water intake is enough to balance the losses (Guyton, 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 between 0.2 of normal salt intake and 5 times normal intake, a range of 25-fold. It is seen that ECNa

concentration is kept within 1% control limits when all feedback systems are intact (See Figure 5.11 and Table 5.1).

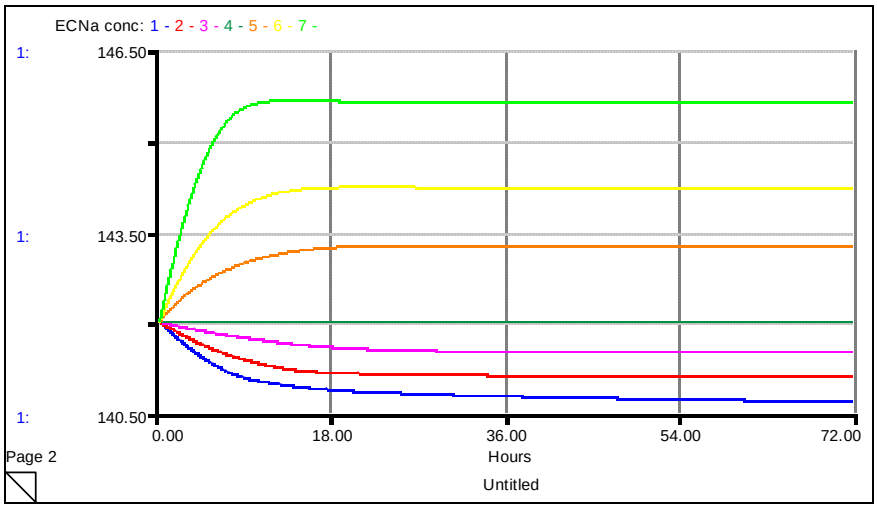

Figure 5.11. Sensitivity of ECNa concentration to different daily sodium intakes

Table 5.1: Simulated levels of ECNa concentration with different daily sodium intakes

Runs	Dietary Sodium (times normal)	ECNa concentration
1	0.2	140.63
2	0.50	141.11
3	0.8	141.5
4	1	142
5	2	143.27
6	3	144.23
7	5	145.66

In the second experiment, the effect of ADH-thirst feedback system on ECNa concentration is investigated. The experiment is repeated by blocking the ADH and then the thirst systems, and it is seen that each one of the ADH and the thirst systems can control the ECNa concentration on their own with reasonable effectiveness. On the other hand, if both of them are blocked simultaneously, ECNa concentration changes tremendously, as expected (See Figure 5.12 and 5.13).

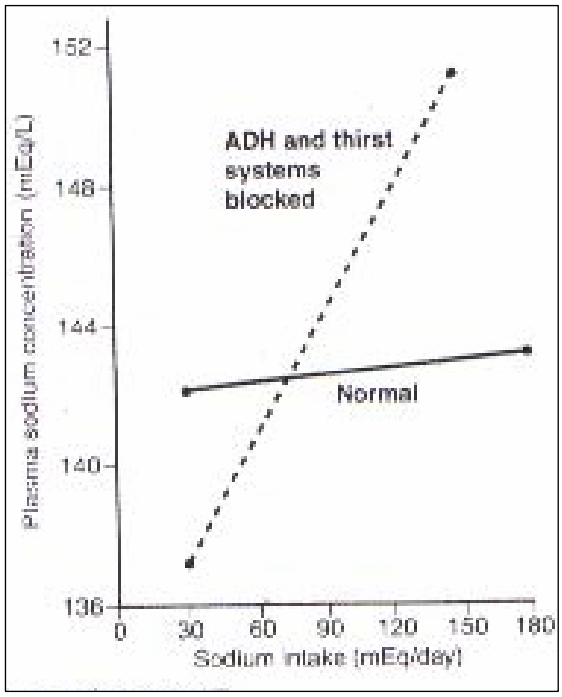

Figure 5.12. Effect of changes in sodium intake on ECNa concentration (1) under normal conditions (2) after the ADH-thirst feedback has been blocked -from Guyton (2000).

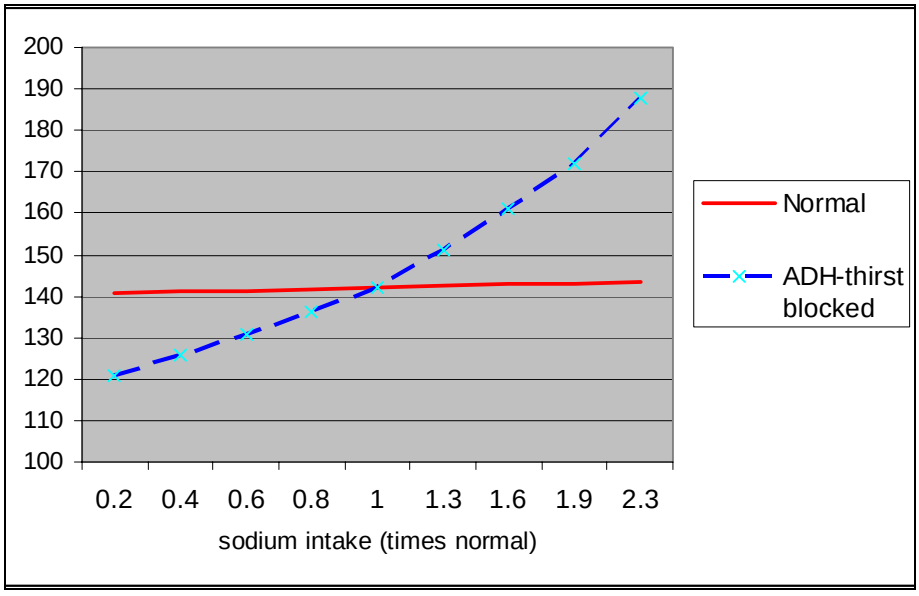

Figure 5.13. Simulated effect of changes in sodium intake on ECNa concentration (1) under normal conditions (2) after the ADH-thirst feedback has been blocked

In the third experiment, the effect of ALD feedback on ECNa concentration is sought, so the experiment is repeated by blocking the ALD feedback (See Figure 5.14 and 5.15). It is seen that ECNa concentration is almost equally well controlled with or without ALD feedback control, which demonstrates that the ECNa concentration is mainly controlled by the ADH-thirst system, and ALD has little effect on the ECNa concentration.

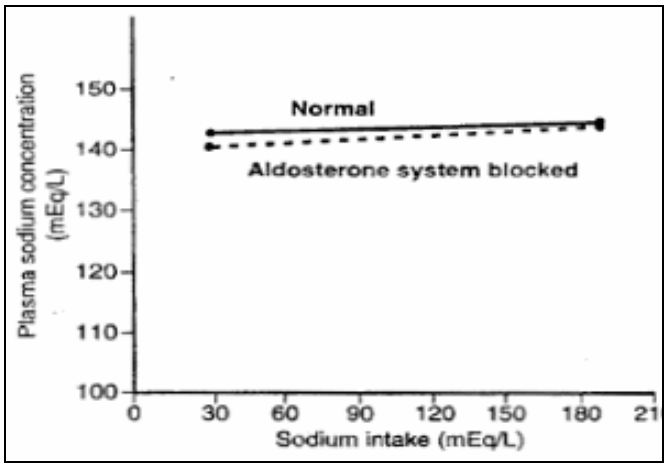

Figure 5.14. Effect of changes in sodium intake on ECNa concentration (1) under normal conditions (2) after the ALD feedback has been blocked-from Guyton (2000)

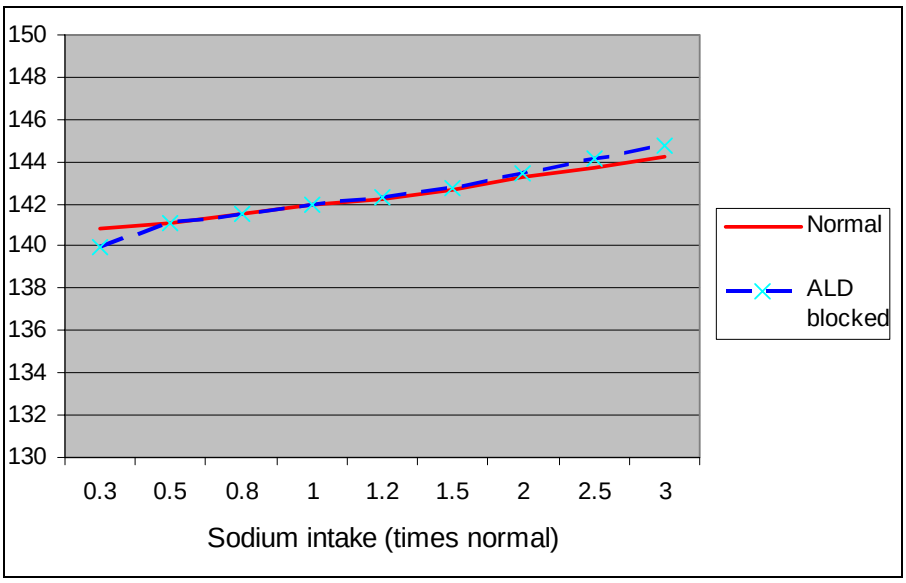

Figure 5.15. Simulated effect of changes in sodium intake on ECNa concentration (1) under normal conditions (2) after the ALD feedback has been blocked

6. THE INTERACTIVE DYNAMIC SIMULATOR (BWATERGAME)

6.1. Modification of the Model

First, some sectors or structures are added to the original model for representing the treatment options, and the variables for game related measurements. Second, some equations and graphical functions of the original model are modified to incorporate the effects of treatment options and of a disease process.

6.1.1. Structures Added to the Original Model

The treatment sector is composed of three sub-sectors, from which two of them are almost identical, i.e., Diuretic and Aquaretic (or ADH-Antagonist) sectors. These sectors represent the most commonly used drugs for treatment of hyponatremia. The drug metabolization structure used in *New Horizons in Virtual Medicine*- A Simple Model of Drug Metabolization of High Performance Systems, Inc. (1997) (See http://www.hps-inc.com/community/downloads/EducationDownloads.aspx) is evaluated to be appropriate for the scope of this study. The third subsector, i.e., intravenous fluid infusion constitutes another important part of the current standard therapy for treating severe hyponatremia. The three most commonly used categories are presented in the model, namely hypertonic, isotonic, and hypotonic fluids, which are classified according to their sodium content.

Other structures that are added to the game are related to the measurements of the game variables, finding the hourly and daily EC sodium concentration correction rates, time tracing converters, and initialization variables.

6.1.2. Modified Structures of the Original Model

Both thirst function and ADH have to be dysregulated to bring about hypoosmolality in the SIADH. Therefore, first the set-level of the ADH concentration is increased, and then the thirst function of the potential patient is modified. Accordingly, the patient has an elevated normal fluid intake and she cannot sufficiently suppress her water intake by hypoosmolality. The equations for the UNa 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 since a mild or severe water restriction can be imposed on the patient as a treatment option. The modified drinking equation is:

```
Drinking=unrestricted_intake*(unrestricted_drinking)+mild_water_restriction*(IF(mild/24)<(u
nrestricted_drinking)THEN(mild/24)ELSE(unrestricted_drinking))+severe_water_restriction*((
IF(severe/24)<(unrestricted_drinking)THEN(severe/24)ELSE(unrestricted_drinking)))
```

6.1.3. Validation and Analysis of the Modified Model

To verify the new drug sectors of the modified model, they are first simulated in isolation, and then a series of experiments are done to test the validity of the treatment options. Yamamura *et al*. (1993) investigated the responses to a series of intravenous doses of Aquaretics in a group of healthy, normally hydrated men. The real cumulative urine volume and the model behavior are presented in Figures 6.1 and 6.2.

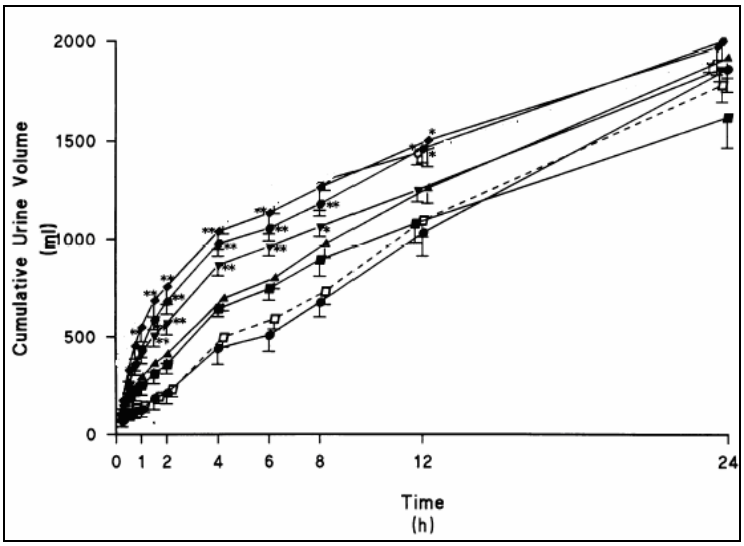

Figure 6.1. Cumulative volume-time relationship of a series of doses of Aquaretic in comparison to placebo (dotted lines) (Modified from Yamamura *et al.*, 1993)

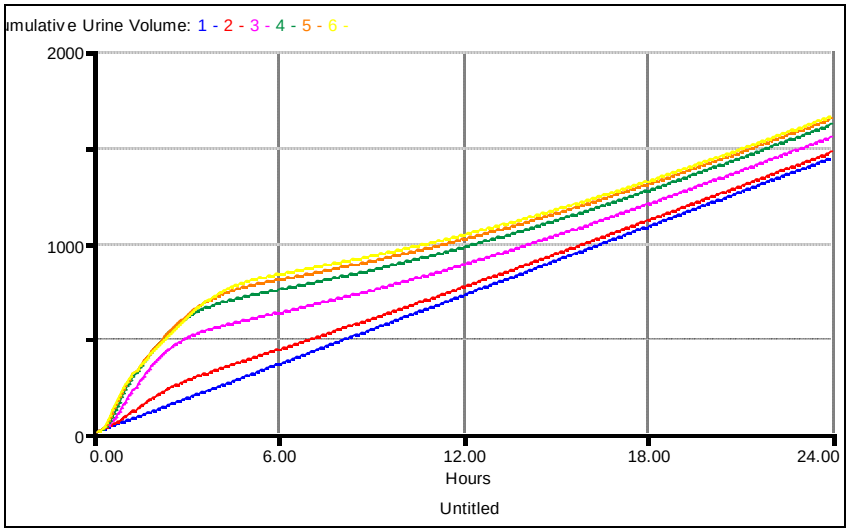

Figure 6.2. Model behavior

The modified model is then used to demonstrate the appearance of hyponatremia in the SIADH. To develop hyponatremia, both ADH and the thirst function have to be dysregulated. This fact is demonstrated by simulating the modified model 1st, by increasing the ADH level without changing the thirst function, and 2nd, by disturbing the thirst function without changing the ADH function. It is seen that the resulting decrease in *ECNa_conc* is very small.

However when both ADH and the thirst function are dysregulated, there is no mechanism that can preserve the level of the body water and the *ECNa_conc*. An example dynamic for the appearance of hyponatremia are given in Fig 6.3. In five days, the *ECNa_conc* of the patient falls to 120 mEq/L, and the *TBW* is increased by about 5 liters. The final values of this simulation are used for the initialization of the game.

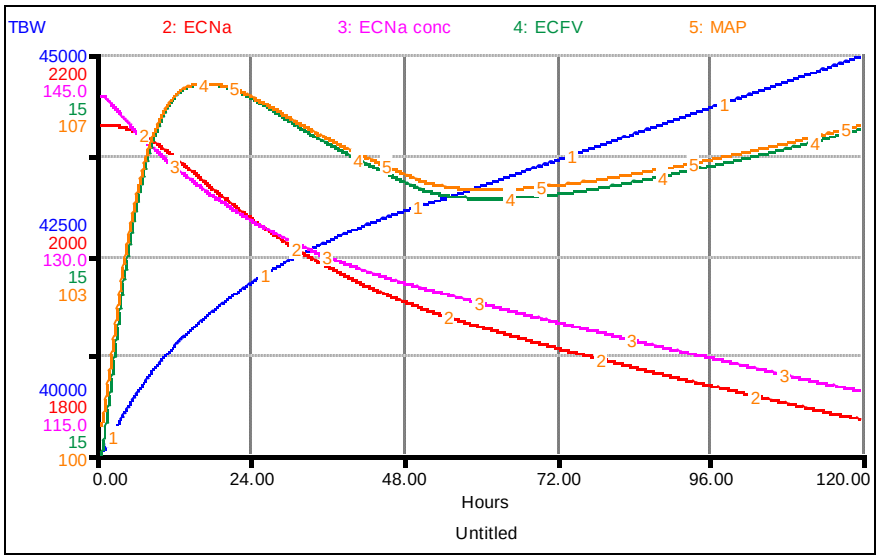

Figure 6.3. Appearance of hyponatremia when both ADH and the thirst functions are dysregulated

6.3. Game Description

The player plays the part of a physician, who is trying to treat a hyponatremic patient by seeking a delicate balance among weighing the risks of hyponatremia itself and those associated with rapid correction of hyponatremia. The patient has an ECNa conc. of 120 mEq/L and an excess body water of about 5 L.

The primary goal is to increase and sustain the EC Sodium Concentration (ECNa_conc.) to its normal levels, which is about 140 mEq/L. At the same time, the TBW should be decreased to its normal value of 40 liters as well as the EC & the IC water volumes. The challenge is to achieve these goals in balance, since rapid correction of severe hyponatremia can cause brain edema. The total duration will be 160 hours, or 20 decision rounds. The player should revise his decisions at each step, by making use of the provided analysis tools. The decisions made by the player are: Dose Diuretic, Dose Aquaretic (ADH-Antagonist), Isotonic Saline, Hypotonic Saline, and Hypertonic Saline. 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.

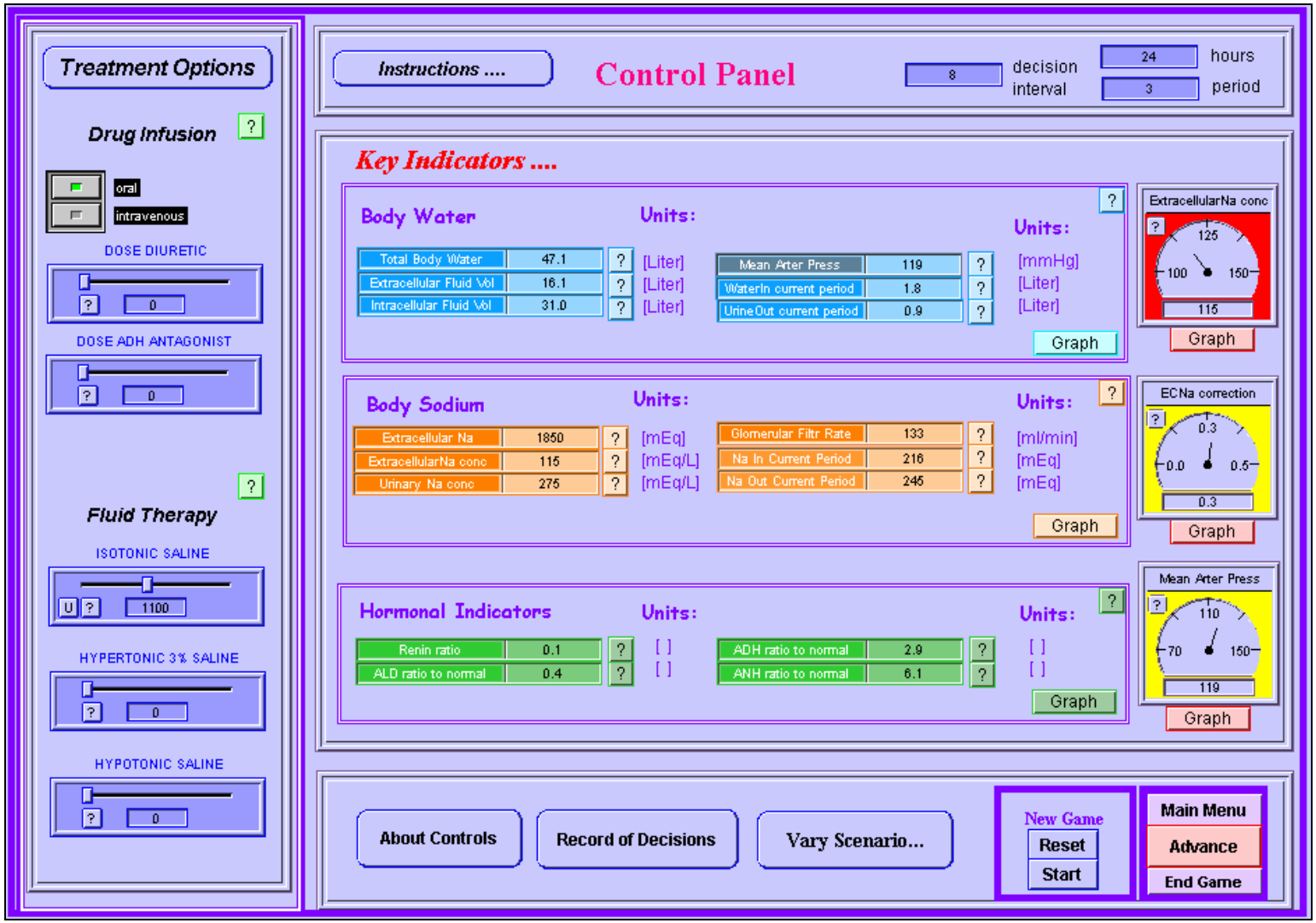

Figure 6.4. Game/Control Panel Screen

6.4. Results of the Game Tests by Players

The game was played by five graduate students of Industrial Engineering Department of Boğaziçi University. Each of these players played the game several times and applied different strategies in their trials.

The following figures represent the dynamics of the key measures obtained from a representative player. Figure 6.5, 6.6, and 6.7 display the dynamics of the player's saline infusion decisions, ECNa concentration, TBW, MAP, urine output, and hourly correction rate, respectively.

As can be seen from the figures below, the representative player initially was unable to prevent the decline of the ECNa concentration to levels below 115 mEq/L, but then he succeeded to increase it to mildly hyponatremic levels towards the end of the game. He used a combination of Aquaretics and Diuretics to increase urine flow via a decreased UNa concentration, and also applied a combination of hypertonic and isotonic saline during his trial. The TBW first increased by 1.5 L, and then it tended to decrease. At the end of the game, the simulated patient still has about 4 L of excess water. The correction rates were between their normal health limits during simulation. The player first wrongly chose to give hypertonic solution without drugs, but this only resulted in a fall in ECNa concentration and a rise in blood pressure. Hypertonic saline combined with urine flow increasing drugs later caused an elevated sodium balance and negative water balance.

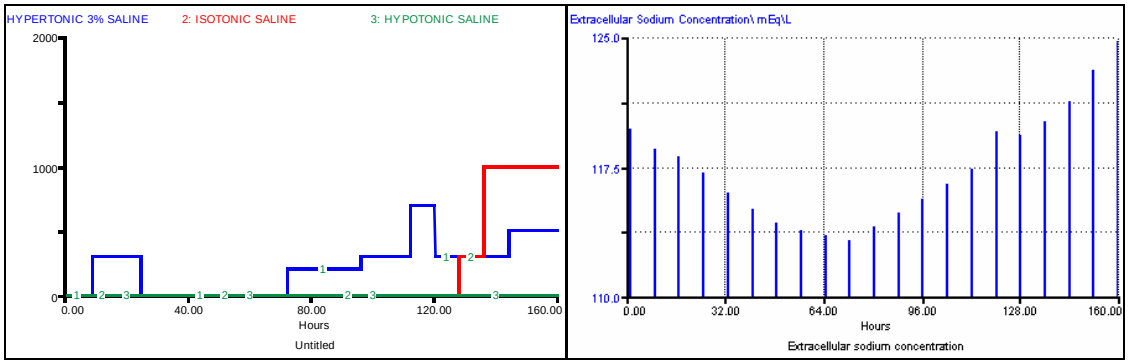

Figure 6.5. a) Saline infusion decisions and b) Dynamics of ECNa concentration for the representative player

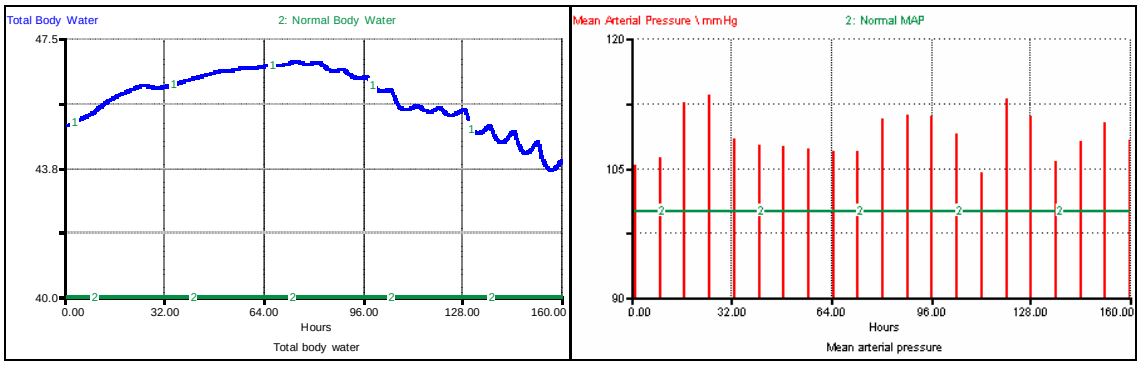

Figure 6.6. Dynamics of a) TBW and b) MAP

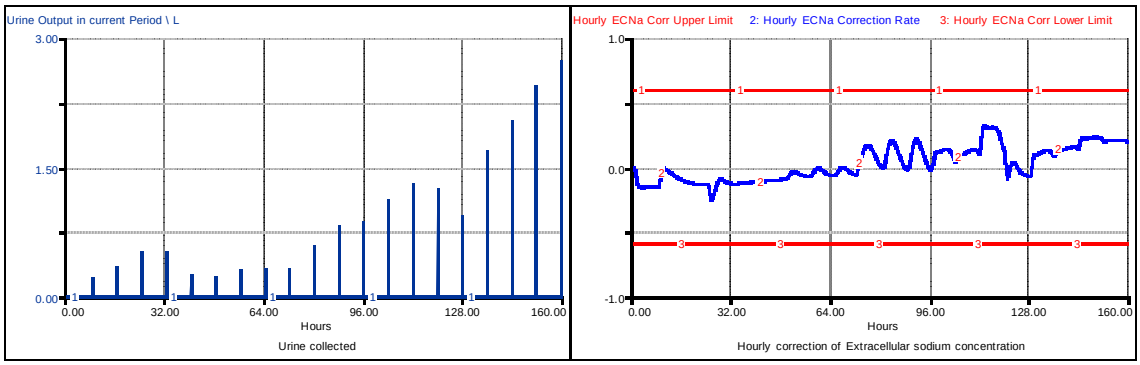

Figure 6.7. Dynamics of a) urine output and b) hourly ECNa correction rate

There is no single correct set of decision for players, but they should take into account certain critical measures during their trials. As mentioned before, the correction rate is a vital concern while correcting 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. Therefore the players that used Diuretics instead of Aquaretics had to administer high amounts of saline.

On the other hand, Aquaretics may decrease the UNa concentration to levels below its normal; however 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 thus Diuretics reduced the effects of Aquaretics in these 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. Since 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, both due to decreased sodium, and due to decreased urine flow. Normally, SIADH patients have a normal or slightly elevated MAP level, and this level should be closely monitored. Low MAP levels may inhibit the urine flow increasing strategies, and a very high level of MAP is also unwanted due to its negative consequences.

We now focus on a comparative evaluation of some key performance measures for the players. Figure 6.8 displays the ECNa concentration with respect to the corresponding trials of these five players. Player 1 first decreased and then slowly increased the ECNa concentration. Player 4 did not change the ECNa concentration noticeably, and player 3 decreased it. The trials of players 2 and 5 were the most successful ones; Player 5 continuously increased the ECNa concentration, however player 2 could not sustain the elevated level towards the end of the game.

In general, the TBW shows a variable decreasing trend for the 5 players as can be seen from the graph in Figure 6.9, except player 3. Figure 6.10 depicts that the MAP levels for the players stay close to normal levels, except players 1 and 3. Player 3 had

fluctuating high levels of MAP. On the other hand, player 1 had the highest levels of MAP during his trial, and also he ended with the second lowest level of ECNa concentration. Figure 6.11 displays the hourly correction rate of the ECNa concentration. As can be seen, all the players acted patiently throughout their simulation except player 3. Figure 6.12 displays the sodium intake decisions of the players. Among the two successful players, player 2 used a constant high amount of hypertonic saline, whereas player 5 used graded amounts of saline. However the amount of sodium lost is consistently high for the 2nd player. On the other hand it stays at low levels for player 5 and does not increase further with increasing sodium intake. Since player 3 administered a high amount of isotonic saline on the 76th hour, both the ECNa and the body water increased abruptly and simulation stopped due to coma resulting from exceeding of the hourly correction limits.

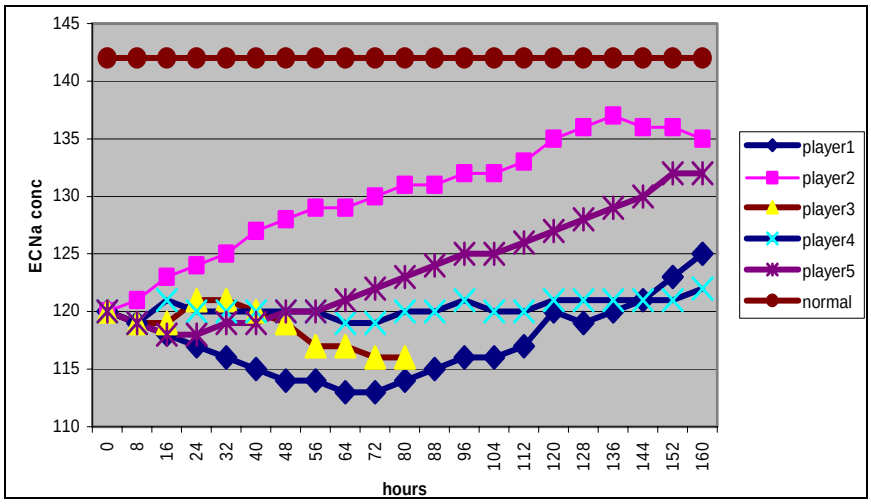

Figure 6.8. Dynamics of the ECNa concentration for five players

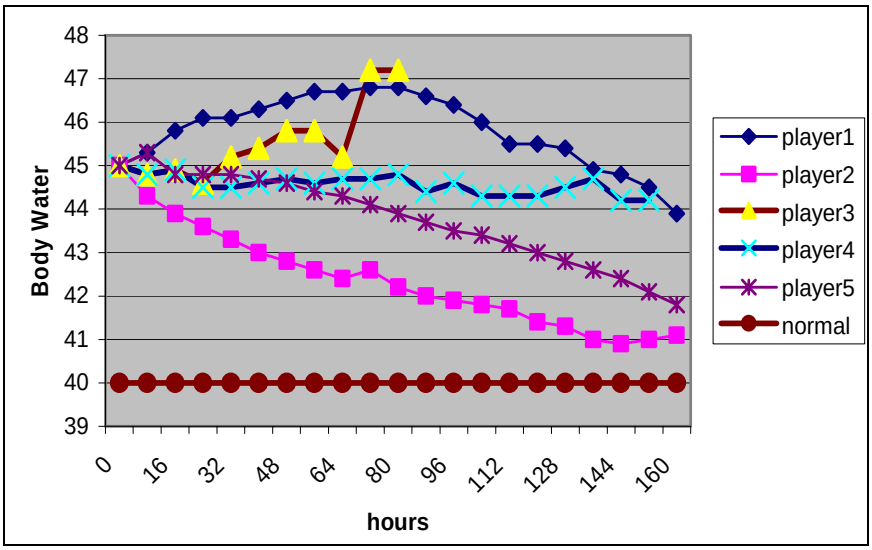

Figure 6.9. Dynamics of the TBW for five players

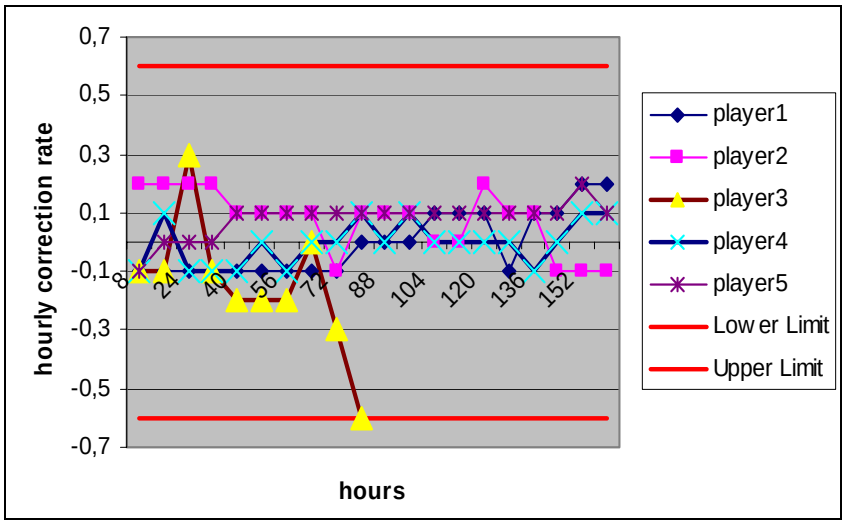

Figure 6.10. Dynamics of the hourly ECNa correction rate for five players

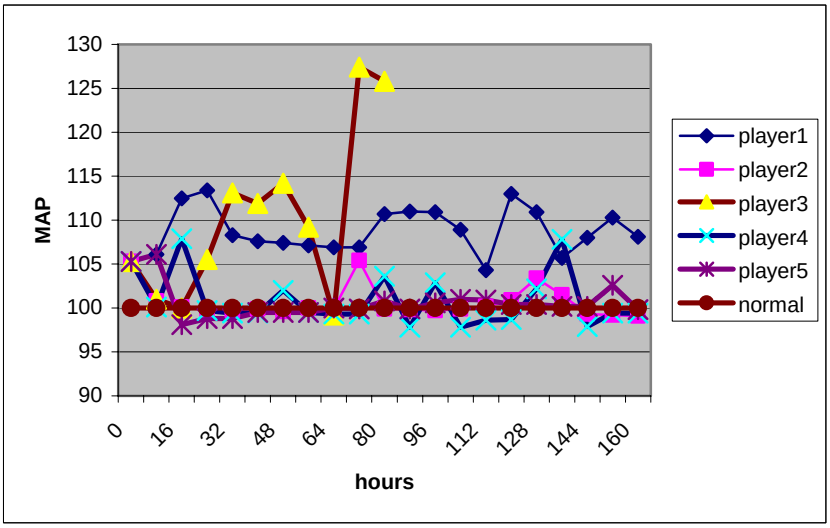

Figure 6.11. Dynamics of the MAP for five players

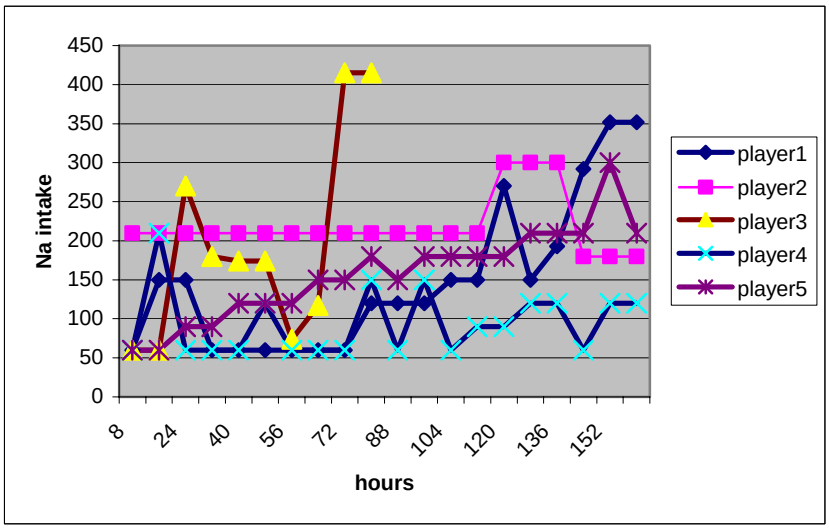

Figure 6.12. Sodium intakes resulting from decisions of five players

7. CONCLUSIONS AND FURTHER RESEARCH

The purpose of this research is to study the normal and disease physiology of the body water metabolism, and to develop an interactive simulation model for a particular body fluid disorder, namely water intoxication/hyponatremia. For this purpose, a system dynamics model is built representing the structure of the body water and sodium balance for a normal individual. Then, this model is modified to include the effects of disease processes, and example dynamics are reproduced for the development of ADH-induced hyponatremia. Finally, a game version of the modified model is constructed by including the most relevant treatment options, and necessary measurements for diagnosis. The game is then used as an experiment platform to test the possible effects of a given set of treatment options on a simulated patient. This interactive simulation game attempts to be a step towards a closed-loop therapy for the hyponatremia patients. It can also be used as a learning and teaching environment for the renal physiology, and especially for the differentiation between the concepts of "sodium content" and "sodium concentration", and related disorders.

As a result of extensive validity testing, the model is found to be a robust representation of the water-electrolyte balance in normal and various test conditions. 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. On the other hand, arterial pressure is mainly determined by "sodium intake", rather than water intake, which at first seems paradoxical, since arterial pressure is in fact determined by the "water volume" of the EC compartment.

The modified model for the development of hyponatremia reproduces all the cardinal features of the SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion). Dysregulated ADH-thirst system first causes an increase in the body fluids, but then transient sodium loss is promoted, and the extracellular fluid volume is only slightly elevated, despite the apparent expansion of the body water. Hence, it is the intracellular compartment which is mostly expanded in SIADH. As a result of dilution, extracellular sodium concentration falls drastically, but the arterial pressure is only slightly elevated. Moreover, urine is still highly concentrated due to the absent negative feedback between the extracellular sodium concentration and the ADH.

The interactive simulation game version yields meaningful results for various treatment options. Game results reveal that the effective correction of the SIADH can only be attained if a negative water balance can be maintained. Replacing the sodium deficits alone is worthless since blood pressure conserving mechanisms cause an increased sodium excretion rate following the intake. Moreover, it is demonstrated that graded doses of hypertonic saline infusion is the most useful solution for the treatment. However it should be administered carefully to prevent an overcorrection, and concurrently with drugs that increase the urine flow. In conclusion, the model and the game version constitute an experimental laboratory for a closed-loop therapy approach to hyponatremia.

There are several avenues in which this research can be expanded. One first step is converting 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. Moreover, more realistic initial conditions could be selected to represent a person who is inclined to become hyponatremic.

Since the focus of the modified model is the development and therapy of hyponatremia, other electrolytes have not been analyzed. However, hyponatremia occurs with many other electrolyte imbalances, and hypokalemia is the most common electrolyte disorder. An analysis of impacts of the treatment options of hyponatremia on potassium dynamics may reveal a broader range of possible physiological phenomena.

Another important electrolyte excluded from this study is the urea. We have assumed that urine osmolality is only determined by the sodium chloride; however in reality urea also contributes to 40 percent of the urine osmolality when the kidney is forming a maximally concentrated urine (Guyton, 2000).

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