Yu Jiang, Srinivasa Chemudupati, Jan Morup Jorgensen, Zhong-Ping Jiang, and Charles S. Peskin, in Proceedings of the Joint IEEE Conference on Decision and Control and European Control Conference, Orlando, FL, USA, pp. 3688-3693, 2011.

Optimal Control Mechanism Involving The Human Kidney

Yu Jiang, Srinivasa Chemudupati, Jan Morup Jorgensen, Zhong-Ping Jiang, and Charles S. Peskin

***Abstract*— In this paper we study the control mechanism that regulates water and the concentration of sodium in human body. For this reverse engineering problem, a control system model is developed using a modification of the standard LQR theory. The control law derived in this paper reflects the realistic situation in which the body is in a supine position or a standing position, and also takes into account feedback time lag. The theoretical model is validated by experimental data fitting. Both computer simulations and experimental data fitting show that the proposed model can capture the main trends of water and salt outputs, and achieve tight control of the plasma concentration of salt as recorded in the experiment[7].**

I. Introduction

Feedback is an essential characteristic of all physiological systems [2]. All organisms, at many levels, rely on not only sensory but also feedback inputs in order to sustain life and procreate. The processes by which the body regulates its internal environment are collectively referred to as *homeostasis*, which in a general sense refers to regulation of an operating point or, stability of an equilibrium. Maintaining a stable internal environment requires constant monitoring and adjustments as conditions change. This adjusting of physiological systems within the body is called homeostatic regulation.

One major example of such a regulation mechanism is the tight control of the concentrations of various constituents of the extracellular fluid in the human body. Extensive research has been done in modeling various components in renal physiology in order to better understand the functioning of the kidney in mammals and the transport of ionic solutes in it (see, for example, [2], [6], [10], [11]).

The purpose of this paper is to study an optimal control mechanism involving the human kidney, and to validate the proposed control system model via experimental data. Having said that, the goal of our research is not to develop the most advanced feedback control laws, but to identify the best possible model that leads to good matching with physiological data. Based on the open-loop model developed in [3] and [8], we model regulation of the sodium ion using a state-space model for the human body wherein the states of extracellular volume (ECV) and sodium concentration are used to determine the control inputs that correspond to the actions of antidiuretic hormone (ADH) and aldosterone that control the water and salt permeability of the distal nephron. As a result of evolution after millions of years, it is reasonable to believe the control mechanism has achieved optimality properties with respect to some cost function. To address this reverse engineering problem, we attempt to adopt linear control models with a linear quadratic regulator which optimizes both an integral quadratic function and a badness function. This is done by a two-loop optimization. For given weight matrices, a feedback control law which minimizes the performance index is calculated in the inner loop, while in the outer loop, the weight matrices are optimized so as to reduce the data fitting error.

During the formulation of the control law, two special considerations have been made concerning the human body. The first consideration is to use a low-pass filter to model the delay-like dynamics of the process by which the human body senses the ECV and the sodium concentration, then secretes hormones. Another consideration is that of *autoinfusion*, which is defined as the gravity-governed phenomenon of sensing the extracellular fluid when a human subject lies down. Simulation results show that our model, to some extent, can capture the main trends of the outputs of urine and Na^+ during the experiment, as well as predict the sodium concentration in the ECV.

In Section 2, we review the mathematical model proposed in [3]. In Section 3, the LQR controller for the kidney flow regulation is developed which minimizes a cost function. Simulation results and experimental data fitting are given in Section 4. Finally, conclusions and discussions are provided in Section 5.

II. The Model

In this section, we review the mathematical model introduced in [3] and [8]. We will show the formulation of the single nephron model, solve the model under boundary conditions and a few assumptions. Then, we relate the nephron model to the water and sodium concentration in the whole organism.

A. The nephron model

As the basic structural and functional unit of the kidney, a nephron's main function is to regulate water and soluble substances by filtering the blood, reabsorbing what is needed and excreting the rest as urine. Fig. 1 shows the schematic of a nephron, which is composed of four parts: the descending limb, the ascending limb, the distal tubule, and the collecting duct. The loop composed of the descending limb and the

This work has been supported in part by the Poly and NYU Seed Grant and in part by NSF grant DMS-0906659.

Y. Jiang, S. Chemudupati and Z. P. Jiang are with the Department of Electrical and Computer Engineering, Polytechnic Institute of New York University, Brooklyn, NY 11201, USA.

J. M. Jorgensen and C. S. Peskin are with the Department of Mathematics, Courant Institute of Mathematical Sciences, New York University, New York, NY 10012 USA. J. M. Jorgensen is also with the University of Copenhagen, Denmark.

Corresponding author, Z. P. Jiang, zjiang@poly.edu

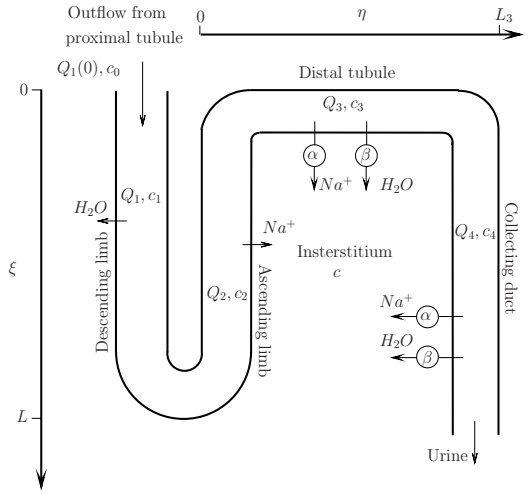

Fig. 1. The nephron model

ascending limb is called the *loop of Henle*. The proximal tubule, which precedes the loop of Henle, is not shown because the concentration of Na^+ does not change there.

Here each part is modeled separately, and all the parameters used in the nephron model are given in Table I.

1) The descending limb: Free permeability of water between the tubular fluid of the descending limb and the surrounding interstitium is assumed. This osmotically causes the concentrations of solutes in the two compartments to be equal at each level ξ. Impermeability to Na^+ is also assumed, thus

$$c(\xi) = c_1(\xi), \quad (1)$$

$$\frac{dQ_1(\xi)}{d\xi} = -f_1^{H_2O}(\xi), \quad (2)$$

$$\frac{dQ_1(\xi)c_1(\xi)}{d\xi} = 0. \quad (3)$$

2) The ascending limb: The ascending limb is impermeable to water, and we assume that the solute in the ascending limb is pumped out at a constant rate $f_2^{\mathrm{Na}^+}$, therefore

$$\frac{dQ_2(\xi)}{d\xi} = 0, \quad (4)$$

$$\frac{dQ_2(\xi)c_2(\xi)}{d\xi} = -f_2^{\mathrm{Na}^+}. \quad (5)$$

3) The distal tubule: For the distal nephron, both water and solute can leave and enter the tubule. We assume that the transmural flow rate per unit length is proportional to the osmotic pressure difference between the interstitial fluid and the tubular fluid. It is also assumed that the rate of reabsorption of sodium is proportional to the flux of sodium ions through the tubule, thus

$$\frac{dQ_3(\eta)}{d\eta} = \beta RT(c(0) - c_3(\eta)), \quad (6)$$

$$\frac{dQ_3(\eta)c_3(\eta)}{d\eta} = -\alpha c_3(\eta)Q_3(\eta). \quad (7)$$

4) The collecting duct: In the collecting duct, the same equations as in the distal convoluted tubule apply, but the relevant concentration difference is between the concentration in the collecting duct and in the interstitium.

$$\frac{dQ_4(\xi)}{d\xi} = \beta RT(c(\xi) - c_4(\xi)), \quad (8)$$

$$\frac{dQ_4(\xi)c_4(\xi)}{d\xi} = -\alpha c_4(\xi)Q_4(\xi). \quad (9)$$

TABLE I

PARAMETERS IN THE NEPHRON MODEL

Name	Description	Value	Dimension
c_0	Concentration of Na^+ in the extracellular fluid		mM
$c(\xi)$	Concentration of Na^+ in interstitium		mM
$Q_1(\xi)$	Flow in descending limb		L/s
$c_1(\xi)$	Concentration of Na^+ in descending limb		mM
$Q_2(\xi)$	Flow in ascending limb		L/s
$c_2(\xi)$	Concentration of Na^+ in ascending limb		mM
$Q_3(\eta)$	Flow in distal tubule		L/s
$c_3(\eta)$	Concentration of Na^+ in distal tubule		mM
$Q_4(\xi)$	Flow in collecting duct		L/s
$c_4(\xi)$	Concentration of Na^+ in collecting duct		mM
Q_{in}	Rate of water ingestion		L/s
Q_{in}^*	Standard value of Q_{in}	2.89×10^{-5}	L/s
Q_{out}	Rate of renal water excretion		L/s
α	Control function for regulating Na^+ excretion		$1/\mathrm{m}$
α^*	Standard value of α	82.6	$1/\mathrm{m}$
β	Control function for regulating water excretion		$\frac{10^3\mathrm{L}^2}{\mathrm{m\cdot s\cdot J\cdot mole}}$
β^*	Standard value of β	1.07×10^{-14}	$\frac{10^3\mathrm{L}^2}{\mathrm{m\cdot s\cdot J\cdot mole}}$
T	Body temperature	310	K
R	Ideal gas law constant	8.32	$\frac{\mathrm{J}}{\mathrm{mole\cdot K}}$
L	Length of Henle's loop	0.015	m
L_3	Length of distal tubule	0.01	$\frac{\mathrm{m\cdot mole}}{\mathrm{s\cdot m}}$
$f_2^{\mathrm{Na}^+}$	Pumping constant	2.5×10^{-6}	m
$f_1^{\mathrm{H_2O}}(\xi)$	Rate of water leaving the descending limb		$\frac{\mathrm{L}}{\mathrm{m\cdot s}}$
K_{T}	Tubuloglomerular feedback constant	7.35×10^7	$\frac{\mathrm{s}}{\mathrm{m\cdot mole}}$

B. Solving the equations

In order to study the influence of aldosterone and ADH on the ECV and sodium concentration, we need to solve the model (1)-(9), so that the flow and sodium concentration at the end of the nephron can be completely determined by α and β. This can be done by using the boundary conditions, assumptions for the interstitum[3], and by introducing a simple model of tubuloglomerular feedback (TGF).

1) The boundary conditions: By continuity, for flows and concentrations at each part of the nephron, we have the following boundary conditions

$$c(0) = c_1(0) = c_2(0), \quad c(L) = c_1(L) = c_2(L), \quad (10)$$

$$c_2(0) = c_3(0), \quad c_3(L_3) = c_4(0), \quad (11)$$

$$Q_1(L) = -Q_2(L), \; Q_2(0) = -Q_3(0), \; Q_3(L_3) = Q_4(0). \quad (12)$$

An equation for $Q_1(0)$ will be given below.

2) The interstitium: The concentration in the interstitium is the ratio of the active flux of sodium out of the ascending limb and the flux of water out of the descending limb, thus

$$c(\xi) = \frac{f_2^{\mathrm{Na}^+}}{f_1^{\mathrm{H_2O}}(\xi)}. \quad (13)$$

The above equation is derived based on three crucial assumptions. First, it is assumed that the peritubular capillaries pick up all the solute and solvent *locally*. Second, it is assumed that the local rate of Na^+ picked up by the peritubular capillaries is proportional to the local interstitial concentration of Na^+ , $c(\xi)$. Finally, steady-state is assumed, i.e., rate at which solute is pumped out of the ascending limb is equal to the rate at which solute is picked up by the peritubular capillaries.

3) The tubuloglomerular feedback: TGF is the mechanism whereby the individual nephron regulates the glomerular filtration rate, based on the sodium concentration at the beginning of the distal tubule, and our function for the tubuloglomerular feedback is

$$Q_1(0) = \frac{1}{K_{\mathrm{T}} c_2(0)}, \quad (14)$$

where K_{T} is a constant that determines the overall gain of this feedback law.

From (1)-(5), (10), (13), and (14), we can solve for $c_3(0)$ and $Q_3(0)$. The standard values are $c_3(0) = 44.7\mathrm{mM}$ and $Q_3(0) = 1.28 \times 10^{-10}\mathrm{L/s}$, and these values vary slightly depending on the current value of c_0. Therefore, given α and β, the flow $Q_4(L)$ and concentration $c_4(L)$ at the end of the nephron can be numerically solved, by approximating (6)-(9) using difference equations, where $c_4(L)$ is the Na^+ concentration of the tubular fluid as it exits the nephron, and $Q_4(L)$ is the rate of excretion of water by the nephron.

C. The whole-organism model

The rates of changes of V and c_0 with respect to time are given by the following differential equations

$$\frac{dV}{dt} = Q_{in} - Q_{out}, \quad (15)$$

$$\frac{dVc_0}{dt} = F_{in} - F_{out}, \quad (16)$$

where V and c_0 denote the ECV and plasma sodium concentration, whose standard values are $V^* = 15L$ and $c_0^* = 142mM$, respectively. F_{in} and F_{out} are the rates of ingestion and excretion of Na^+, and where Q_{in} and Q_{out} are the rates of ingestion and excretion of water. We regard F_{in} and Q_{in} as given functions of time, but F_{out} and Q_{out} are determined by the nephron model described above, in the following manner

$$F_{\mathrm{out}} = nc_4(L)Q_4(L), \quad (17)$$

$$Q_{\mathrm{out}} = nQ_4(L), \quad (18)$$

where n is the total number of nephrons (counting those in both kidneys), which we take to be $n = 2 \times 10^6$[2].

III. The modified LQR design

Based on the model developed in the previous section, we are ready to formulate the control mechanism for the problem of salt and water balance in the human body, using the LQR design technique. The LQR design comes from linear optimal control theory that aims to provide analytical designs of a special type: The closed-loop system resulting from the LQR design is not only stable, but also the best possible system of a particular type.

In this section, we will first give a state-space representation of the model, linearized at nominal values. Next we give two considerations concerning the human body, and then formulate the LQR control law.

A. State space model

The state-space model describing the water and salt balance in the human body can be written as

$$\dot{x} = f(x, u, d), \quad (19)$$

where

$$x = \begin{bmatrix} V \\ c_0 \end{bmatrix}, \quad u = \begin{bmatrix} \alpha/\alpha^* \\ \beta/\beta^* \end{bmatrix}, \quad d = \begin{bmatrix} Q_{in} \\ F_{in} \end{bmatrix},$$

x is the state vector describing the state of the extracellular fluid using extracellular volume V and plasma sodium concentration c_0. u is the control input in the form of variables actuating sodium and water reabsorption α and β in the distal tubule of the nephron. The starred values α^* and β^* are the corresponding normal values of α and β respectively for a healthy human. These values are those inputs that give rise to the nominal state of V^* and c_0^*. d is the vector of water intake Q_{in} and salt intake F_{in}. The disturbances proposed in the model are the disturbances in d, i.e., differences between actual values of intake and standard values Q_{in}^* and F_{in}^* of intake for humans. Finally f is a nonlinear function whose values can be numerically determined as outlined in the previous section.

The linearized version of the system around its nominal values takes the following form

$$\dot{\tilde{x}} = A\tilde{x} + B\tilde{u} + E\tilde{d}, \quad (20)$$

where

$$\tilde{x} = \begin{bmatrix} V - V^* \\ c_0 - c_0^* \end{bmatrix}, \ \tilde{u} = \begin{bmatrix} \alpha/\alpha^* - 1 \\ \beta/\beta^* - 1 \end{bmatrix}, \ \tilde{d} = \begin{bmatrix} Q_{\mathrm{in}} - Q_{\mathrm{in}}^* \\ F_{\mathrm{in}} - F_{\mathrm{in}}^* \end{bmatrix},$$

and by making small changes to ξ and η, matrices A and B are numerically obtained as follows

$$A = \begin{bmatrix} 0 & 0.0289 \\ 0 & -0.2737 \end{bmatrix} \times 10^{-4},$$

$$B = \begin{bmatrix} 0.3145 & 1.9083 \\ -0.9864 & -18.0743 \end{bmatrix} \times 10^{-4}.$$

B. The low-pass filter

The first consideration before formulating the control law is that of introducing "delay-like" dynamics transforming the system error state vector $\tilde{x}$ into error sensed output vector $\tilde{x}_{\rm s}$. This is done by passing the states through a first order low-pass filter and then using the outputs of the filters as the sensed signal for the control law formulation, thus

$$\dot{\tilde{x}}_{\rm s} = S(\tilde{x} - \tilde{x}_{\rm s}), \tag{21}$$

where $S = \begin{bmatrix} \frac{1}{\tau_V} & 0 \\ 0 & \frac{1}{\tau_{c_0}} \end{bmatrix}$, and τ_V, τ_{c_0} are two positive time constants of the filter, and also will be determined in the next section. The controller we consider takes the following form

$$\tilde{u} = g(\tilde{V}_{\rm s}, \tilde{c}_{0\rm s}), \tag{22}$$

where $\tilde{V}_{\rm s}$ and $\tilde{c}_{0\rm s}$ denote the sensed deviations of volume V and concentration c_0.

C. Autoinfusion

Another consideration is that of *autoinfusion*, which is defined as the gravity-governed phenomenon of sensing an increased extracellular fluid volume (which can be viewed as the subject receiving a fictitious "infusion" to the "self" and hence the name) when a human subject lies down. This effect of autoinfusion is taken into account as a fixed step-like increase in the sensed extracellular volume for every subject. In this paper, this effect is assumed to be instantaneous for simplicity. Therefore, during the actuation, at the instant in which the subject lies down, an additional parameter $V_{\rm af}$ is introduced into the control law such that the apparent increase in V is accounted for, thus

$$\tilde{u} = \begin{cases} g(\tilde{V}_{\rm s} + V_{\rm af}, \tilde{c}_{0\rm s}), & \text{in supine position,} \\ g(\tilde{V}_{\rm s}, \tilde{c}_{0\rm s}), & \text{in standing position.} \end{cases} \tag{23}$$

where the constant parameter $V_{\rm af}$ will also be fit with the experimental data in the next section.

D. The LQR controller

In formulating the LQR controller, we assume there is no autoinfusion, and $\tilde{d} = 0$, i.e., water and salt are ingested at the standard rate. The overall system of (20) and (21) can be described as follows

$$\dot{X} = \begin{bmatrix} A & 0 \\ S & -S \end{bmatrix} X + \begin{bmatrix} B \\ 0 \end{bmatrix} \tilde{u}, \tag{24}$$

$$\tilde{x}_{\rm s} = HX, \tag{25}$$

where $H = [0 \;\; I]$ with I denoting the 2×2 identity matrix. $X = \left[\tilde{x}^T, \tilde{x}_{\rm s}^T\right]^T$ is the state, and $\tilde{x}_{\rm s}$ is the measurement output.

The objective of our problem is to find a static output feedback (SOF) controller in the form of

$$\tilde{u} = -K\tilde{x}_{\rm s}, \tag{26}$$

such that the following performance index

$$J = \frac{1}{2}\int_0^\infty \left[\tilde{x}^T \mathcal{Q} \tilde{x} + \tilde{u}^T \mathcal{R} \tilde{u}\right] dt, \tag{27}$$

where $\mathcal{Q} \geq 0$ and $\mathcal{R} > 0$ are two symmetric matrices, is minimized. The problem can be solved from the following algebraic equations, via iteration algorithms (see [9] for example)

$$0 = \begin{bmatrix} \mathcal{Q} & 0 \\ 0 & K^T \mathcal{R} K \end{bmatrix} + PA_c + A_c^T P, \tag{28}$$

$$0 = I + A_c M + M A_c^T, \tag{29}$$

$$K = \mathcal{R}^{-1} B^T P M H^T (HMH^T)^{-1}, \tag{30}$$

where $A_c = \begin{bmatrix} A & -BK \\ S & -S \end{bmatrix}$ is the closed-loop system matrix, P and M are symmetric positive definite solutions of (28) and (29), respectively. The choice of the matrices $\mathcal{Q}$ and $\mathcal{R}$ will be explained in the next section.

IV. Data fitting and numerical simulations

In this section we will validate the proposed LQR methodology and fit the parameters in our model, using experimental data from [7]. After briefly summarizing this experiment, we will define a "badness function", which is the scaled sum of squares of the differences between the experimental data and the corresponding theoretical prediction. The purpose of the data fitting is to minimize this badness function.

A. A brief summary of the experiment

An experiment was conducted [7], in which the hemodilution, central blood volume and renal responses in humans were measured after infusing isotonic saline in one group while using another group as controls (i.e. no infusion). The experiment specifies the intakes Q_{in} and F_{in} for the two groups, where the saline group underwent an infusion of 1500ml of isotonic saline over a period of 21 minutes starting from the 4-th hour of the experiment but the controls group did not undergo the infusion. However, subjects in *both* groups lay down when the infusion for the saline group started, and continued to lie down for the duration of the experiment.

TABLE II

Experimental urine outputs

Saline (infusion) group

Time(h)	1	2	3	4	5	6	7	8	9
$q_{\rm o}^{\rm i}$	2.9	3.5	4.1	6.0	5.5	6.0	5.0	5.2	5.4
$f_{\rm o}^{\rm i}$	85	95	120	205	280	380	360	350	365

Control group

Time(h)	1	2	3	4	5	6	7	8	9
$q_{\rm o}^{\rm c}$	2.5	3.1	5.6	4.8	4.5	4.0	3.6	4.7	3.2
$f_{\rm o}^{\rm c}$	70	80	180	190	200	205	200	220	190

TABLE III

Experimental $\rm Na^+$ concentration in the blood plasma

Saline (infusion) group

Time(h)	2	3	3.5	4	5	6	7	9
$c_0^{\rm i}$	140.0	140.6	140.4	140.6	140.8	140.8	141.1	140.7

Control group

Time(h)	2	3	3.5	4	5	6	7	9
$c_0^{\rm c}$	141.0	140.9	141.1	140.6	140.8	140.9	140.9	141.0

The experimental values are listed in Table II and III, in which $q_{\rm o}^{\rm i}$ and $f_{\rm o}^{\rm i}$ are the output water ($\rm mL/min$) and sodium ($\rm mmole/min$) for the saline group, respectively, recorded at hourly intervals for nine hours. $c_0^{\rm i}$ is the sodium concentration ($\rm mole/L$) for the saline group, recorded over the stretch of the experiment at eight unequally spaced but specified times. The quantities $q_{\rm o}^{\rm c}$, $f_{\rm o}^{\rm c}$, $c_0^{\rm c}$ are their counterparts in the control group, respectively. (Note that "o" for output should not be confused with "0" used previously.)

B. The badness function

For the purpose of data fitting, we define the badness function as the scaled mean square difference between experimental and predicted data of the renal outflows of sodium and water along with the measurements of the extracellular sodium concentration in the blood plasma at various instants in time. The badness function is defined as follows

$$\begin{aligned} B = \frac{1}{2}\sum_{j=1}^{9}\Bigg[&\frac{\left(q_{\rm o}^{\rm i}(j)-\hat{q}_{\rm o}^{\rm i}(j)\right)^2}{(\bar{q}_{\rm o}^{\rm i})^2}+\frac{(f_{\rm o}^{\rm i}(j)-\hat{f}_{\rm o}^{\rm i}(j))^2}{(\bar{f}_{\rm o}^{\rm i})^2}\\ &+\frac{\left(q_{\rm o}^{\rm c}(j)-\hat{q}_{\rm o}^{\rm c}(j)\right)^2}{(\bar{q}_{\rm o}^{\rm c})^2}+\frac{(f_{\rm o}^{\rm c}(j)-\hat{f}_{\rm o}^{\rm c}(j))^2}{(\bar{f}_{\rm o}^{\rm c})^2}\Bigg]\\ +\frac{1}{2}\sum_{k=1}^{8}&\left[\frac{(c_0^{\rm i}(k)-\hat{c}_0^{\rm i}(k))^2}{(\bar{c}_0^{\rm i})^2}+\frac{(c_0^{\rm c}(k)-\hat{c}_0^{\rm c}(k))^2}{(\bar{c}_0^{\rm c})^2}\right], \end{aligned} \tag{31}$$

where $q_{\rm o}^{\rm i}(j)$, $q_{\rm o}^{\rm c}(j)$, $f_{\rm o}^{\rm i}(j)$ and $f_{\rm o}^{\rm c}(j)$ are from the j-th column of Table II, $c_0^{\rm i}(k)$ and $c_0^{\rm c}(k)$ are from the k-th column of Table III. $\hat{q}_{\rm o}^{\rm i}(j)$ and $\hat{f}_{\rm o}^{\rm i}(j)$ are the average values of the computational results $Q_{\rm out}$ and $F_{\rm out}$ on the interval from the $(j-1)$-th hour to the j-th hour, and $\hat{c}_0^{\rm i}(k)$ is the predicted sodium concentration at the same time in the experiment when $c_{\rm o}^{\rm i}$ is recorded. $\hat{q}_{\rm o}^{\rm c}(j)$, $\hat{f}_{\rm o}^{\rm c}(j)$ and $\hat{c}_0^{\rm c}(k)$ are similarly defined for the control group. Finally, $\bar{q}_{\rm o}^{\rm i}$, $\bar{q}_{\rm o}^{\rm c}$, $\bar{f}_{\rm o}^{\rm i}$, $\bar{f}_{\rm o}^{\rm c}$, $\bar{c}_0^{\rm i}$, and $\bar{c}_0^{\rm c}$ are the average values of the last three numbers in the experimental data $q_{\rm o}^{\rm i}$, $q_{\rm o}^{\rm c}$, $f_{\rm o}^{\rm i}$, $f_{\rm o}^{\rm c}$, $c_0^{\rm i}$, and $c_0^{\rm c}$, respectively.

C. Experimental data fitting

For simplicity, assume both $\mathcal{Q}$ and $\mathcal{R}$ in (27) are diagonal matrices, hence

$$\mathcal{Q}=\begin{bmatrix} q_1 & 0\\ 0 & q_2\end{bmatrix},\quad \mathcal{R}=\begin{bmatrix} r_1 & 0\\ 0 & r_2\end{bmatrix},$$

where $q_1\geq 0$, $q_2\geq 0$, $r_1>0$, and $r_2>0$ are parameters to be fit. Besides, as mentioned in the previous section, we need to fit the autoinfusion constant $V_{\rm af}>0$, and two constants $\tau_V>0$ and $\tau_{c_0}>0$ for the low pass filters in (21). Also, we will fit the initial value of the ECV at the beginning of the experiment, denoted by $V_{\rm initial}$. However, since the sodium concentration is nearly constant, assume the initial value c_0 is its standard value.

This constrained nonlinear optimization problem is numerically solved using a MATLAB routine called *fminsearchbnd* which uses the Nelder-Mead algorithm to find a minimum without the need for numerical or analytic gradients while making sure that the parameters with respect to which we are optimizing are within a valid range. The optimized values are shown as follows:

$$\begin{aligned} &B=0.4088, \quad V_{\rm af}=0.4485L, \quad V_{\rm initial}=15.1452L,\\ &q_1=0.3501, \quad q_2=0.7132, \quad r_1=66.5249,\\ &r_2=13.7602, \quad \tau_V=1722s, \quad \tau_{c_0}=4213s. \end{aligned} \tag{32}$$

The optimal feedback gain matrix is

$$K = \begin{bmatrix} 0.2404 & -0.1457\\ -0.0104 & -0.0351\end{bmatrix}. \tag{33}$$

D. Numerical simulation

Based on the above controller, we simulate the experiment by plotting the predicted water and $\rm Na^+$ outputs, as well as the sodium concentration in continuous-time. The resulting curves are shown in Fig. 2-4. It can be observed that the renal responses of both groups were the same until the infusion happened. The jumps of $\rm Na^+$ output in both groups after $t=3h$ were caused by autoinfusion. Meanwhile, in both groups, sodium concentrations were tightly controlled.

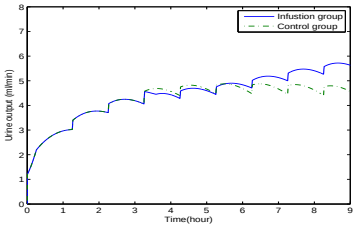

Fig. 2. Profile of urine output in both groups

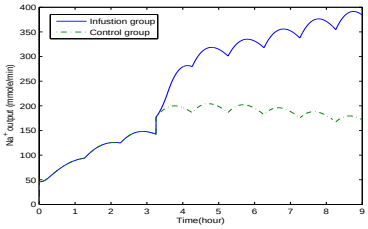

Fig. 3. Profile of $\rm Na^+$ output in both groups

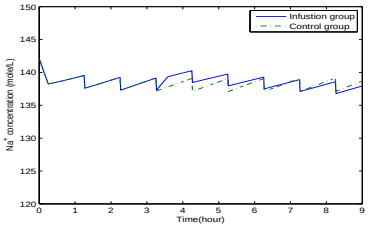

Fig. 4. Profile of $\rm Na^+$ concentration output in both groups

E. Comparison with experimental data

The data fitting results are shown in Figs. 5-10, in which the solid dots represent experimental data and the circles represent their corresponding theoretical predictions. We can clearly notice that our closed-loop model has successfully achieved tight regulation of plasma sodium concentration, and, to some extent, captures the main trends of the water and sodium outputs in both groups.

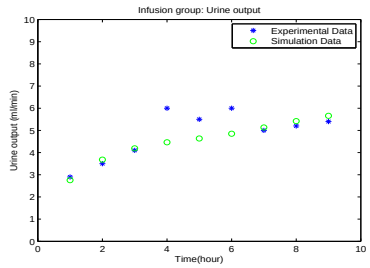

Fig. 5. Urine output of the infusion group

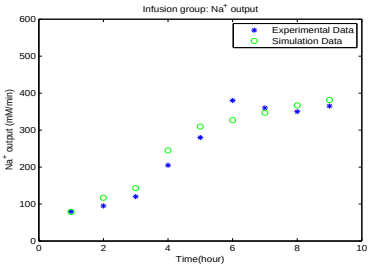

Fig. 6. Na^+ output of the infusion group

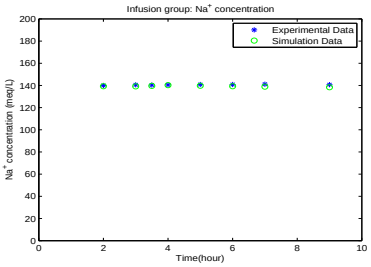

Fig. 7. Sodium concentration of the infusion group

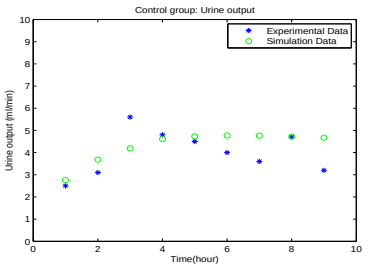

Fig. 8. Urine output of the control group

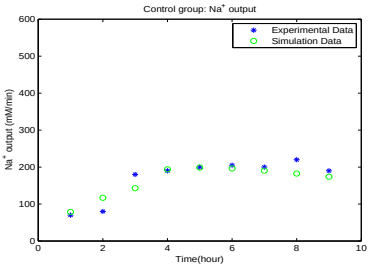

Fig. 9. Na^+ output of the control group

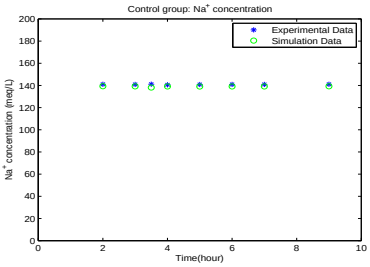

Fig. 10. Sodium concentration of the control group

V. Conclusions and Future Work

In this paper, linearized systems with LQR regulator are developed to model the mechanism that regulates water and sodium concentration in human body. Simulation results show that our model is able to capture the main trends of water and Na^+ outputs, while simultaneously achieve tight control of the sodium concentration.

Because of the complexity of physiological systems, the actual regulation mechanism in the human body may involve strong nonlinearities. Therefore, one way to improve the accuracy of our model is to consider nonlinear controllers. Unfortunately, we are unable to find a nonlinear control system model which yields better experimental results than the proposed linear LQR-based model. Also, the data that we fit are from a single experiment and the model should be tested on other experiments as well. One such experiment has been done by Heer *et al.* and is described in detail in [4]. Simulating this and other experiments may help us better understand the physiological meaning of optimality in control of sodium and water in the human body.

References

[1] S. Chemudupati, "Control techniques to model the salt water balance in the human body", M. S. thesis, Polytechnic Institute of NYU, Brooklyn, NY, Feb. 2010.

[2] A. Guyton and J. Hall, *Textbook of Medical Physiology*, Elsevier, Philadelphia, PA, 1981.

[3] F. C. Hoppensteadt and C. S. Peskin, *Modeling and Simulation in Medicine and the Life Sciences*, Springer, 2002.

[4] M. Heer, F. Baisch, J. Kropp, R. Gerzer, and C. Drummer, "High dietary sodium chloride consumption may not induce body fluid retention in humans", *American Journal of Physiology: Renal Physiology*, vol. 278(4), pp. 585-595, 2000.

[5] B. D. O. Anderson and J. B. Moore, *Optimal Control, Linear Qudratic Methods*, Prentice Hall, NJ, 1990.

[6] H. W. Smith, *The kidney – Structure and Function in Health and Disease*, Oxford Medical Publications, 1951.

[7] L. Johansen, P. Bie, J. Warberg, N. J. Christensen, M. Hammerum, R. Videbaek, and P. Norsk, "Hemodilution, central blood volume, and renal responses after an isotonic saline infusion in humans", *Integrative and Comparative Physiology*, vol. 272(2), pp. 549-556, 1997.

[8] J. M. Jorgensen and C. S. Peskin, "Mathematical model of human water and salt balance demonstrating loss of volume with Na^+ loading for constant water intake", Preprint, Feb. 2009.

[9] W. S. Levine and M. Athans, "On the determination of the optimal constant output feedback gains for linear multivariable systems", *IEEE Transactions on Automatic Control*, vol. 15(1), 1970, pp. 44-48.

[10] E. Kompanowska-Jezierska, C. Emmeluth, L. Grove, P. C. J. Sadowski, and P. Bie, "Mechanism of vasopressin natriuresis in the dog: role of vasopressin receptors and prostaglandins", *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*, vol. 274(6), pp. 1619-1625, 1998.

[11] A. M. Weinstein, "A mathematical model of rat cortical collecting duct: determinants of transtubular potassium gradient", *American Journal of Physiology: Renal Physiology*, vol. 280(6), pp. 1072-1092, 2001.