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Physiological Cybernetics: Model of Osmolality and Volemia

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***Abstract*—The models of osmolarity and volemia are proposed in this paper. These two different models, characterized by a different time scale, represent a typical example of embedded physiological feedback control in medicine. Extensive simulation tests have been performed, showing that the models agree with the findings published in the literature of endocrine physiology and with medical practice. As a relevant example of application of the models, the diabetes insipidus pathology was considered. In the case of center insipidus diabetes, it is possible to predict effects of a therapy, giving out synthetic ADH for restoring homeostatic conditions. This model may be a helping tool in the study and development of micro-infusors with sensor and controllers embedded able to release a controlled drug quantity, accorded to the patient and optimized for avoiding hyper or ipo-concentrations of plasma ADH hormone.**

I. Introduction

WIENER in a seminal book [1] associated the ancient Greek word '$\kappa\breve{\upsilon}\beta\varepsilon\rho\nu\eta\tau\iota\kappa\circ\varsigma$' to the control of physiological systems. The biological control area gained an increasing attention in the 1960s, till early 1970s, with the development of several analytical models: the ambitious goal of researchers was to apply a mathematical framework for helping medical diagnostic techniques and new therapeutic protocols. Unfortunately physiological systems are intrinsically time variant and highly non linear. Moreover an effective balance of the model complexity is a difficult task to satisfy: low order models are usually too simple to be useful, on the other hand high order models are too complex for simulation purposes and have too many unknown parameters to be identified. Therefore, many clinical researchers do not consider a mathematical quantitative approach relevant for a practical progress in medicine. In more recent years the widespread use of friendly software packages for modelling, along with the development of powerful identification and control techniques have led to a renewed interest in control [2] and identification [3] of physiological systems. The term homeostasis [4] is a key word for describing equilibrium conditions of physiological models: this steady-state condition is usually due to the concurrent action of different physiological feedback mechanism with embedded controllers and sensors. A relevant consideration about homeostasis is that it may be representative both of normal conditions and of embedded compensatory changes after a pathology (e.g., the embedded regulation of cardiac output in normal conditions and after myocardial infarction).

The aim of this paper is the development of a model as simple as possible for describing osmolality control in the kidneys. The kidneys are responsible for regulating the volume and concentration of body fluids, by selectively filtering and reabsorbing materials from the blood [5]. This system is one of the most relevant example of embedded physiological feedback control in physiological homeostasis: it is a subject typical of humane endocrine system and like every model correlated with endocrinology it involves several effects acting concurrently on different organs. Therefore it constitutes a very complex model and requires a careful attention for achieving an effective simplification of the model itself. Furthermore maximum effort is due to linearize as much as possible the nonlinear functions involving different variable of interest. As many engineering models applied to complex systems, a major problem was due to the limited availability of experimental data collection useful for defining exact parameters, in terms of physiological-physics insights of the system: our efforts have been devoted to obtain modelling solutions similar to steady-state physiological data available in medical literature regarding hormonal concentrations, body fluid volume and osmolality, along with time constants matching with clinical observations. To authors' knowledge the subject at hand is rarely considered from control engineers: a unique interesting model of osmolality was dated at 1972 [6]. It was a complex and well-detailed model, based on the movements of body fluid between the intravascular, interstitial and intracellular compartments and to their reciprocal fluid interchanges.

The model proposed in this paper is simpler and considers a "whole-body" analysis, in order to select as output

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variables only the ones comparable with medical typical available data (e.g., acquired from a clinical dehydration test typical for checking diabetes insipidus). Furthermore dynamic nonlinearities are linearised, due to the consideration that only small variations with respect to homeostasis are allowed in practice, i.e., the model belongs to the class of small signal models, well-known, e.g., in the field of power electronics. Two different models have been considered: the first one is the embedded control of osmolality the second one is the volemia control, that includes both the effect of ADH (antidiuretic hormone) along with atrial natriuretic polypeptide (ANP) and aldosterone hormons. Simulation with two separate models, although strictly unnecessary, is a choice due to the goal to simplify simulation in terms of a simpler evaluation of the physiological phenomena. As a first task we decided to put into evidence osmolality, whose trend is much faster than the one related to modifications of the volume fluids. Osmotic regulation has time constants in a faster time scale, the volume regulation is characterized from a slower time scale. Furthermore model separation has the advantage to allow small signal models in a neighborhood of homeostatic conditions. In case of a large signal model strong nonlinearities due, for instance, to variations of concentrations should be considered.

I. Models

Both models (osmolality and volemia) have been considered both with an analytical approach based on state space differential equations and with a compartmental approach typical of biomedical research [7] with similar results. Because of the easier implementation in case of static nonlinearities and time delays, in the following sections, the state-space analytical model will be presented.

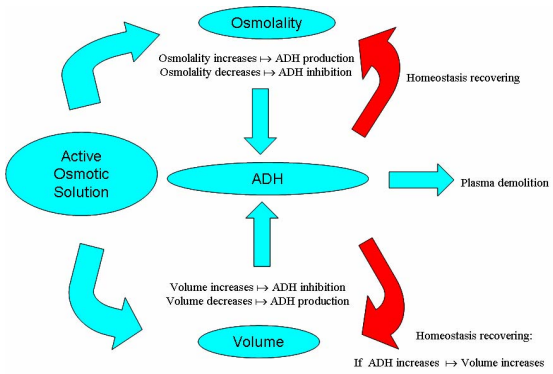

Fig. 1. ADH feedback action on osmolality and fluid volume

A. Osmolality

Consider now the state space model in a neighborhood of a homeostasis, corresponding to normal mean conditions of healthy and adult people: this starting hypothesis leads to linear models with thresholding nonlinearities. State variables for the osmolality model are the osmolality (x_1), ADH concentration (x_2) and the total body fluid volume (x_3). ADH release is a typical example of feedback control (Fig.1). As soon as the osmolality of the blood and body fluids is reduced, the receptors in the hypothalamus are no longer stimulated and the level of ADH stimulation is reduced, which signals to the kidneys to start excreting more water in the urine production, until the blood osmolality increases enough for the cycle to be started again [8].

Since body fluid osmolality is in equilibrium with plasma osmolality, consider two input signals in the model. The first one (u_1) is the quantity (in osmoles) of active solute of a salt solution injected via intravenous infusion, the second one (u_2) is the water volume injected via intravenous infusion. At the end of the infusion u_{1tot}/u_{2tot} is defined as the osmolality of the injected solution.

These considerations lead to the following mathematical model:

$$\dot{x}_1 = a_1 u_1 - a_2 u_2 - G_1(x_1) \tag{1}$$

$$\dot{x}_2 = G_2(x_1) + G_3(x_3) - a_7(x_2 - c_2) \tag{2}$$

$$\dot{x}_3 = a_8 u_2 - a_9(x_3 - c_3) + a_{10}(x_2 - c_2) \tag{3}$$

where:

$$G_1(x_1) = \begin{cases} -a_3(x_1(t-\tau) - c_1) & if \quad x_1 < c_1 \\ a_4(x_2(t-\tau) - c_2) & if \quad x_1 > c_1 \end{cases} \tag{4}$$

and $-a_3(x_1(t-\tau) - c_1)$ simplifies the nonlinear function $-(\frac{u_1 + x_1 x_3}{u_2 + x_3} - c_1)$ in the physiological hypothesis of $u_1 << (x_1 x_3)$ and $u_2 << x_3$.

$$G_2(x_1) = \begin{cases} a_5(x_1 - c_1) & if \quad x_1 > c_1 \\ 0 & if \quad x_1 < c_1 \end{cases} \tag{5}$$

$$G_3(x_3) = \begin{cases} a_6(c_3 - x_3) & if \quad x_3 < c_3 \\ 0 & if \quad x_3 > c_3 \end{cases} \tag{6}$$

In (1) is evidenced that an increase of osmolality is expected injecting osmoles of active solute u_1, while osmolality decreases injecting H_2O. Nonlinear function G_1 models the regulating action: if osmolality x_1 exceeds the threshold value c_1, the ADH hormone acts reducing x_1; on the contrary if x_1 decreases below its normal concentration c_1, ipoosmotic urine will increase, up to a new homeostatic condition. In (2) the ADH hormone dynamics is described if plasma osmolality exceeds the threshold value c_1, or if the total body fluid volume x_3 decreases below the threshold c_3. The last term models a fast reduction of ADH in case of overcoming its normal concentration c_2. In (3) is modelled the total body fluid volume x_3: it increases injecting H_2O and

in case of water retention due to ADH. The auxiliary term $a_9(x_3-c_3)$ was added for taking into account the total body fluid volume regulation: such term is a simplification due to the goal of a simple modelling of osmolality.

A list of variables and symbols used in simulation is reported in Appendix. Note that in case of unknown parameters, they are determined in order to obtain modelling solutions similar to steady-state physiological data available in medical literature regarding hormonal concentrations, body fluid volume and osmolality, along with time constants matching with clinical observations. A time delay (τ=30 min) is included in the model, that is representing the global control lag action of the organism with respect to the input.

B. Volemia

As in the previous model, consider the state space model in a neighbourhood of a homeostasis, corresponding to normal mean conditions of healthy and adult people. State variables for the volemia model are the plasma volume (x_1) and the aldosterone (x_2), ANP (x_3) and ADH (x_4) hormonal concentrations.

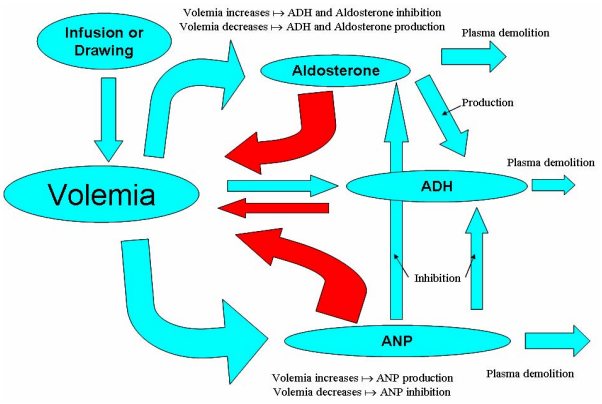

Fig. 2. ADH, Aldosterone and ANP feedback action on fluid volume. Black arrows indicate the homeostasis recovering feedback due to the hormones.

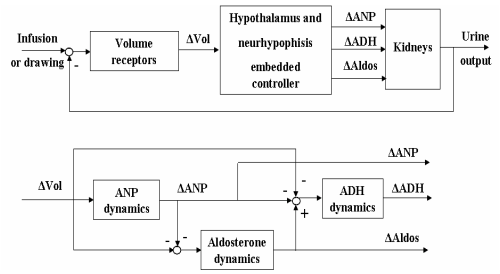

Fig. 3. Volemia feedback action in terms of a standard block diagram.

ADH is not the only hormone involved in the regulation of kidney function. Aldosterone hormone (from the adrenal cortex) affects the equilibrium condition and regulation of electrolyte content of the blood and body fluids. When aldosterone is present in the blood, the distal renal tubules increase their reabsorption of sodium and the secretion of potassium. With this action, more water is retained in the body and a person with high aldosterone content increases its water volume.

Aldosterone and ADH act with a stabilizing effect in case of hypovolemia: the aldosterone feedback loop increases volemia both directly at a renal level and indirectly, raising ADH production.

Atrial natriuretic polypeptide (ANP) is another hormone involved in natriuresis and the regulation of renal and cardiovascular homeostasis. It causes natriuresis, diuresis, and renal vasodilation; reduces circulating concentrations of renin, aldosterone, and ADH hormone; and therefore normalizes circulating blood pressure and volume. In plain words it is produced and released in case of hypervolemia and it determines high excretion rate both directly and indirectly, due to its inhibitory influence on the production of aldosterone and ADH.

Two time delays are included in the model: the first one ($\tau_1 = 45$ min) is representing the global control lag action of the organism with respect to the input, the second one ($\tau_2 = 15$ min) is typical of the hormonal cascade renin-angiotensin system and aldosterone.

The following mathematical model holds:

$$\dot{x}_1 = b_1 u_1 + b_2 (x_4(t-\tau_1) - k_4) + \\ + b_3 (x_2(t-\tau_1-\tau_2) - k_2) - b_4 (x_3(t-\tau_1) - k_3) \tag{7}$$

$$\dot{x}_2 = -b_5 (x_2(t-\tau_2) - k_2) - F_1(x_3) + F_2(x_1) \tag{8}$$

$$\dot{x}_3 = -b_8 (x_3 - k_3) + b_9 (x_1 - k_1) \tag{9}$$

$$\dot{x}_4 = -b_{10} (x_4 - k_4) + F_3(x_1) + F_4(x_2) - F_5(x_3) \tag{10}$$

where:

$$F_1(x_3) = \begin{cases} b_6 (x_3 - k_3) & if \quad x_3 > k_3 \\ 0 & if \quad x_3 < k_3 \end{cases} \tag{11}$$

$$F_2(x_1) = \begin{cases} b_7 (k_1 - x_1) & if \quad x_1 < k_1 \\ 0 & if \quad x_1 > k_1 \end{cases} \tag{12}$$

$$F_3(x_1) = \begin{cases} b_{11} (k_1 - x_1) & if \quad x_1 < k_1 \\ 0 & if \quad x_1 > k_1 \end{cases} \tag{13}$$

$$F_4(x_2) = \begin{cases} b_{12} (x_2(t-\tau_2) - k_2) & if \quad x_2 > k_2 \\ 0 & if \quad x_2 < k_2 \end{cases} \tag{14}$$

$$F_5(x_3) = \begin{cases} b_{13} (x_3 - k_3) & if \quad x_3 > k_3 \\ 0 & if \quad x_3 < k_3 \end{cases} \tag{15}$$

As in the previous model, a list of variables and symbols used in simulation is reported in Appendix.

II. SIMULATION TESTS

The mathematical models have been implemented in a Matlab-Simulink environment for checking their effectiveness. In all following plots we considered tests with infusions or blood drawings at the maximum rate of 0.5l/30 min.

In Fig.3 osmolality and ADH hormone are plotted, in case of a hyperosmotic solution infused via intravenous infusion. Osmolality of the solution is four times greater than the physiological salt solution.

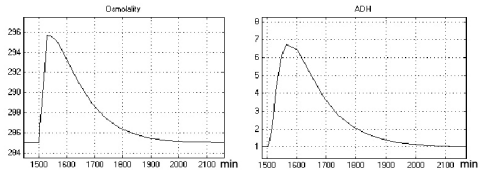

Fig. 4. Osmolality and ADH in case of injected hyperosmotic solution

Fig.4 shows that if a hyperosmotic solution is infused, the physiological control system reacts activating the ADH production. ADH acts increasing the volume of H_2O and osmolality reduces up to the homeostatic condition.

In Fig.5 an ipoosmotic solution is infused. ADH doesn't react and osmolality decreases for reaching again its homeostatic condition due to the body fluid volume control loop.

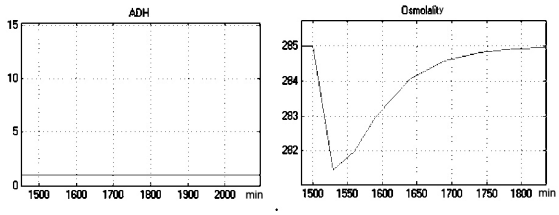

Fig. 5. ADH and osmolality in case of injected ipoosmotic solution

In Figg.6 and 7 the case of a blood drawing is shown. Plasma volume decreases, but recovers its homeostatic condition in a control mechanism involving the aldosterone, the increasing of ADH and the decreasing of ANP.

In Figg.8 and 9 the case of infusion of an isoosmotic solution is shown. Plasma volume decreases, but recovers its homeostatic condition in a control mechanism involving the aldosterone, the decreasing of ADH and the increasing of ANP.

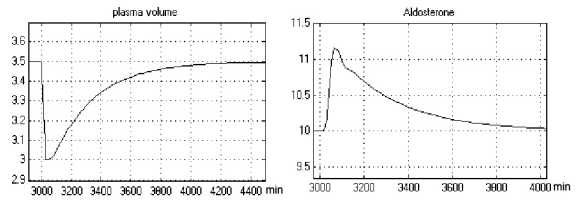

Fig. 6. Plasma volume and aldosterone in case of blood drawing

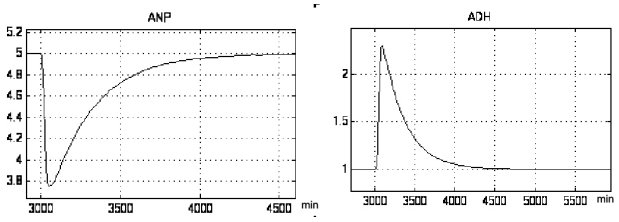

Fig. 7. ANP and ADH in case of blood drawing

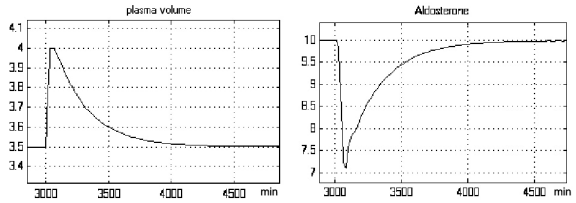

Fig. 8. Plasma volume and aldosterone in case of injected isoosmotic solution

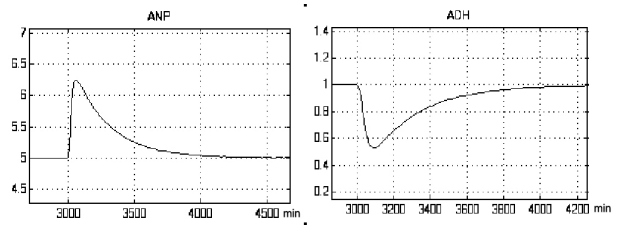

Fig. 9 ANP and ADH in case of injected isoosmotic solution

From these examples we can see that the plots generated by the proposed models are coherent with the medical practice of endocrinology.

III. APPLICATION: THE DIABETES INSIPIDUS CASE

The concentration of urine (also called the osmolality or specific gravity) may be important in diagnosing abnormal kidney function.

As a relevant example of application of the models proposed, consider the diabetes insipidus case. This pathology is strictly correlated with a failure in the embedded control loop of osmolality.

It can be classified into two main categories. The first category is the central diabetes insipidus case: it usually results from the decreased production of ADH, hormone regulating the amount of water in the body and causes

excessive production of very dilute urine (polydipsia) with a severe increasing of osmolality, unless the patient doesn't assume a great deal of water, to compensate for the fluid lost in urine.

The second one is the nephrogenic diabetes insipidus: it is a disorder characterized by the passage of large volumes of urine due to a defect of the kidney tubules. In this pathology ADH is normally produced, but the kidney defect usually produces a partial or complete failure of receptors located on or within the kidney tubules to respond to ADH. Also in this pathology patients are unable to control osmolality and the effects are similar to the ones previously described.

With the model for the osmolality we have simulated both pathologies; first consider the case of center insipidus diabetes, the most interesting for an application of the model proposed, since in this pathology it is possible a therapy giving out synthetic ADH for restoring homeostatic conditions.

The Simulink implementation of the model in case of pathologic conditions is simple: parameters involved in the ADH production are set to zero and an external input represents the synthetic ADH infusion, active if the osmolality exceeds the physiological value. The time delay characteristic of the ADH synthesis has been eliminated in the hypothesis of a direct infusion of ADH at a rate of 0,5 pmol/l per minute.

In Fig. 10 a hyperosmotic solution is infused, like in the experiment shown in Fig.3. In case of pathologic conditions the patient doesn't react activating the ADH production. In Fig. 11 the case of ADH infused is shown: this therapeutic control action reduces osmolality to steady-state conditions.

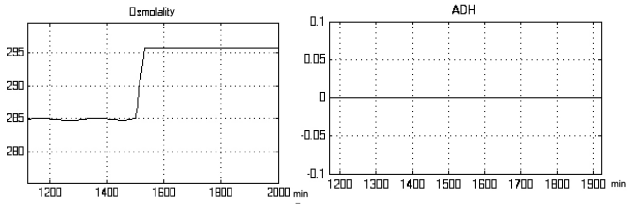

Fig. 10. Case of center insipidus diabetes and injected hyperosmotic solution: osmolality and ADH without ADH external infusion

Osmolality model and its effectiveness in case of center insipidus diabetes was checked with daily water deprivation clinical tests. In the example shown in Fig. 12 the patient had a water loss estimated in 2.5 l of water in 12 hours. Such loss was the input of the osmolality model.

Osmolality versus time in case of the clinical data and of the model prediction are compared: they are matching in a good agreement.

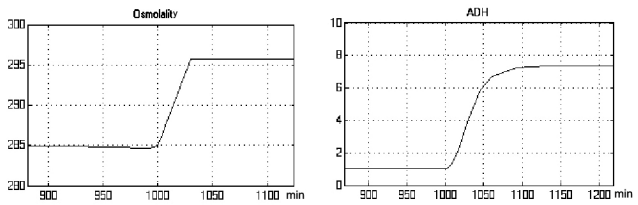

Fig. 11. Case of center insipidus diabetes and injected hyperosmotic solution: osmolality and ADH with ADH external infusion

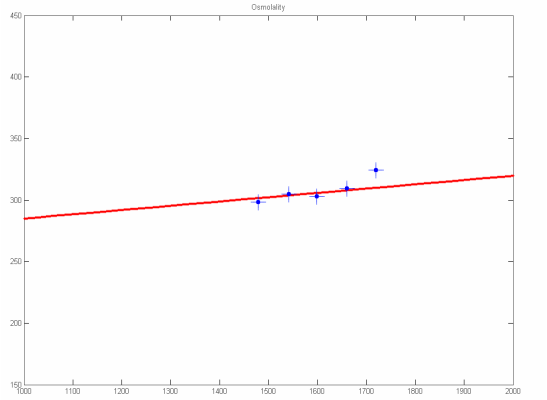

Fig. 12. Case of center insipidus diabetes and water deprivation test: experimental (dots) data and model output (continuous line) of osmolality vs. time

In Fig.13 the case of nephrogenic diabetes insipidus is considered in the presence of a infused hyperosmotic solution: the kidney tubules are unable to respond to ADH and the osmolality doesn't decrease.

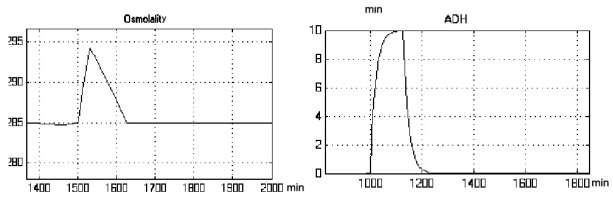

Fig. 13. Case of nephrogenic diabetes insipidus and injected hyperosmotic solution: osmolality and ADH

IV. Conclusion

The results obtained in simulation tests offer coherent values with the medical practice. Future goals of the research are devoted to a more strict validation of coefficients after an accurate analysis of clinical data

For improving the model accuracy, studies are in progress for adding different factors that interacts with the system, e.g., the rate of glomerulare filtration or the control of excretion of sodium and potassium.

The simplified simulation models may be a helping tool in the study and development of micro-infusors with sensor and controllers embedded able to release a controlled drug quantity [9], accorded to the patient and optimized for

avoiding hyper or ipo-concentrations of plasma ADH hormone. Work is in progress for joining a compartmental model with the analytical one: the compartmental approach [10] is under development for three main applications:

1. concurrent representation of the analytical models;
2. implementation of the model illustrated in [6]. It subdivides in a natural way the water compartments of the whole system;
3. in case of pathologies (e.g.: diabetes insipidus) a predictive analysis of drug release is studied to optimise therapies.

APPENDIX

List of estimated parameters for osmolality

c_1: homeostatic concentration of osmolality (285mOsm/Kg of H_2O)

c_2: homeostatic concentration of ADH (1 pmol/l)

c_3: total volume of body fluids (40 l)

a_1: it indicates the effects on osmolality of a isoosmotic solution (Na^+) injected via intravenous infusion; a practical way for determining such value is the assumption: $x_1 = (c_1 c_3 + u_1)/c_3$ whose derivative w.r.t. u_1 is $1/c_3$. Therefore a_1=1/40.

a_2: it indicates the effects on osmolality of isoosmotic distilled water injection. It is considered the value that in case of a isoosmotic solution produces a null variation of osmolality. Therefore: $a_2=c_1/c_3$= 285/40.

a_3: it indicates the effects on osmolality of ADH (a_3=0,01).

a_4: it still indicates the effects on osmolality of ADH (a_4=0,01).

a_5: it indicates the effects on ADH of osmolality (a_5=0,03).

a_6: it indicates the effects on ADH of volume (a_6=0,3).

a_7: coefficient representing plasma degradation of ADH; such hormone has a half-life time of about 15 minutes. Therefore a_7=0,05.

a_8: the volume injected in plasma fluid adds to the total volume of body fluid (a_8 =1)

a_9: it represents a model approximation of the volemia regulation (a_9 =0.01)

a_{10}: it indicates the effects on volume of ADH (a_{10}=0,001).

List of estimated parameters for volemia

k_1: plasma volume (k_1 =3,51)

k_2: homeostatic mean concentration of aldosterone (k_2 =10 ng/dl)

k_3: homeostatic mean concentration of ANP (k_3 = 5 pmol/l)

k_4 homeostatic mean concentration of ADH (k_4 =1 pmol/l)

b_1: the volume injected in plasma fluid adds to the plasma volume (b_1 =1)

b_2: it indicates the effects on volume of ADH (b_2=0,001).

b_3: it indicates the effects on volume of aldosterone (b_3=0,0001).

b_4: it indicates the effects on volume of ANP (b_4=0,001).

b_5: coefficient representing plasma degradation of aldosterone; such hormone has a half-life time of about 15 minutes. Therefore b_5=0,05.

b_6: it indicates the effects on aldosterone of ANP (b_6=0,1).

b_7: it indicates the effects on aldosterone of volume (b_7=0,1).

b_8: coefficient representing plasma degradation of ANP; such hormone has a half-life time of about 3 minutes. Therefore b_8=0,2

b_9: it indicates the effects on ANP of volume (b_9=0,5).

b_{10}: coefficient representing plasma degradation of ADH; such hormone has a half-life time of about 15 minutes. Therefore b_{10}=0,05

b_{11}: it indicates the effects on ADH of volume (b_{11}=0,01).

b_{12}: it indicates the effects on ADH of aldosterone (b_{12}=0,06).

b_{13}: it indicates the effects on ADH of ANP (b_{13}=0,02).

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REFERENCES

[1] N. Wiener, *Cybernetics: Control and Communication in the Animal and the Machine,* John Wiley & Sons, 1961.

[2] D. T. Westwick and R.E. Kearney, *Identification of Nonlinear Physiological Systems*, John Wiley & Sons, 2003.

[3] M. C. Khoo, *Physiological Control Systems*, Prentice Hall, 2001.

[4] W. Cannon, *The Wisdom of the Body*, Norton, New York, 1939.

[5] P.C. Walsh et al., *Urologia di Campbell*; VII edizione, Verducci Editore, 1999.

[6] R. Merletti and H.R. Weed, "Nonlinear Model of body Fluid and Osmolality Control System," in *Proceedings of the 5th IFAC World Congress*, Paris, pp. 25.1-25.7, 1972.

[7] J.A. Jacquez, *Compartmental analysis in biology and medicine,* Biomedware, *1996*.

[8] A.C. Guyton, *Trattato di fisiologia medica*; IV edition, PICCIN, 1995.

[9] D. Maifeller et al., "*A high-performance silicon micropump for an implantable drug delivery system,*" Proc. of the 12th *IEEE MEMS 1999 Technical Digest*, Orlando, FL, USA, pp 541-546, 1999.

[10] G. Ciofani, A.Landi, D.Mazzei, and A. Mazzoldi, "*Osmolality control by inalation or microinfusion?,*" Proc. of the 6th Int. Conf. On Biomedicine 2005, Bologna, pp 559-571, 2005.