Mathematical Modelling of Renal Functions within a Simulated Clinical Environment

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Abstract

A mathematical model of the human renal system is presented within the context of a simulated clinical environment. The overall model contains a number of interrelated physiological subsystem models to represent hormonal and cardiovascular control and regulation of renal action for both water and electrolyte distribution. Control equations for each subsystem are solved numerically using VisSim, a powerful and easy to use Windows-based block-diagram language for system simulation. This simulation tool allows parameters to be varied as the simulation progresses which enables hypotheses to be investigated dynamically. The computer-based renal model is incorporated into a simulated clinical environment using the add-on utility VisSim-RT which provides an interface to custom built hardware located within a manikin. An overview of existing renal models is also given.

1 Introduction

A project has been initiated to develop computer simulations for a range of human physiological functions within the context of a clinical care environment. Initial work has centred on the mathematical modelling of renal functions using the software simulation package VisSim which allows dynamic systems to be represented in block diagram form. An additional programming tool, VisSim RT, has been used to couple the computer-based models to external hardware via embedded interfacing blocks.

The project consists of three phases:

1. an investigation of a range of existing renal models.
2. formulation and validation of a new model.
3. realisation of a simulated clinical environment.

The purpose of this paper is to provide a brief overview of existing renal models (phase one) and to report on progress to date with the implementation of phases two and three of the project.

2 Recent renal models

Existing mathematical models of the renal function may be broadly grouped into three main categories:

1. representations of specific aspects of renal functionality, in particular representation of the nephron and the dynamics of the medulla.
2. artificial kidney models which predict the changes in body fluid compositions due to patient-dialyzer interactions.
3. system models which account for the interrelationships between the kidney and other physiological systems.

The remainder of this section presents an overview of a selection of existing models in each of the above categories.

2.1 Nephron models

Chandhoke and Saidel [1] provide a detailed overview of many early models and their differing representations of medullary function. It is their belief that a realistic simulation model should include representations of both cortical and medullary vasculature and nephron heterogeneity. The key structural features of their own model were based upon anatomical studies of the rat kidney and incorporated representations of nephron structure, along with detailed subsystem models for both cortex and medulla.

Marsh [2] developed a range of simulations to investigate the concentrating mechanism of the medulla by dividing his models into numerous substructural representations of renal anatomical features.

A summary given by Stephenson and Berliner [3] of a number of differing hypotheses to explain the renal concentrating mechanism also references various simulation models developed during the 1970s and early 1980s. They concluded that whilst the workings of the inner medulla, when generating its concentration gradient, have been successfully represented in model form, results do not fully match experimental data.

The dynamic simulation models described by Barrett and Packer [4] utilised basic equations from earlier models but attempted to provide a more accurate representation of the functionality and anatomical aspects of the medulla, based on data from rodent studies. Whilst their results show good qualitative agreement to changes in antidiuretic hormone (ADH) level and offer a firm basis for investigating aspects of renal physiology, they concluded that a more detailed representation of medullary geometry would improve model equilibrium conditions.

Easton [5] contrasts a number of recent models, particularly the central core model of Stephenson [6] with the additional features of Leyton's model [7] which concerned the relationship between metabolic pump and water transfer coefficients. He also undertook a rigorous analysis of these models to produce solutions for a non-linear metabolic pump term and the resulting changes in solute concentration.

The recent work by Holstein-Rathlou and Marsh [8] reported a detailed investigation of renal blood flow autoregulation and the possible intrarenal control systems that govern it. Their simulation model includes 125 parallel representations of a single nephron with key parameters of specific nephrons set randomly across the normal physiological range. Their results indicate a good match with experimental data.

2.2 Artificial kidney models

The use of compartmental models to describe pharmacokinetic and metabolic processes in mathematical form has been widely applied to represent the exchange processes occurring during hemodialysis.

The clearly illustrated descriptions given by Sargent and Gotch [9] for formulating dialysis process models include mass balance equations for five dialysis processes, those of; urea and protein catabolism, heparin infusion, acetate metabolism, carbon dioxide balance and a generalised body base model.

Leaning and co-workers [10] proposed a dialysis system model which took account of the effects of dialysis therapy upon a number of interrelated physiological systems, including hormonal control, thermoregulation, the cardiovascular system, fluid-electrolyte balance and impaired renal function.

The extensive, multicompartment model formulated by Thews and Hutten [11] includes submodels for eleven specific processes. Variations between measured data and simulation results indicated mean differences of less than 0.5% of the measured value for pH, about 1% for electrolytes and about 5% for bicarbonate. The model may also be used to predict a patient's status during and after dialysis by estimating the onset of clinical complications such as hytotension and arrhythmias.

The approach made by Liberati and co-workers [12] provides a new bicompartmental model to allow urea concentration dynamics to be evaluated. Model verification is based upon extensive data tabulated for 14 dialysis patients. Whilst the model provides a close correlation to mean values, impedance measurement techniques to determine total body water show a much wider variation when contrasted with simulation predictions for individual patients. The use of the model to investigate post dialysis urea rebound is also reported.

A recent bicompartmental model formulated by Ursino and co-workers [13] for intradialytic sodium dynamics, may be used as an aid to defining patients'

ideal sodium dialystate concentrations relative to individual mass balance calculations.

2.3 Renal system models

The analysis and modelling of the kidney as a system whose functionality is governed by a range of control processes, including hormonal, blood volume, blood pressure and osmotic effects, is described in detail by Bigelow, DeHaven and Shapley [14]. The stress responses of their model to water loading, hypotonic saline infusion and urea ingestion compare well with experimental data and have helped in the understanding of renal control mechanisms, particularly the behaviour of ADH.

A general renal/body fluid system model developed by Uttamsingh and co-workers [15] draws together key features of many earlier models [10, 14] to provide a mathematical description which contains four sub-system blocks representing; the kidney, the cardiovascular system, hormonal control mechanisms plus fluid electrolyte and metabolite balance. It is this model that has been used as a basis for the implementation described in the next section of this paper.

3 Model formulation

The human renal system model presented in this paper is divided into the four physiological sub-systems illustrated in figure 1. The equations representing each of these four sub-systems were implemented using VisSim, version 2.0f, a dynamic system, block modelling language widely used for the simulation of engineering and control systems within a Microsoft or UNIX Windows environment [16]. The software also offers a powerful way of modelling physiological processes [17, 18].

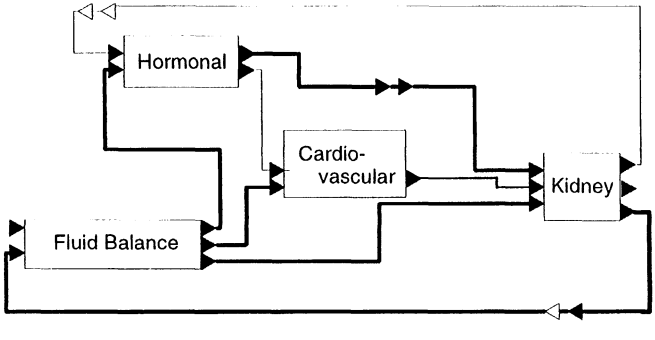


Figure 1: Top-level model representation.

Sub-system models were constructed as sequences of nested block diagrams, with each level in the overall block structure describing a specific mathematical function. Blocks are interconnected, or 'wired', using simple

point-and-click mouse operations. A modular approach was adopted which allowed sub-blocks to be tested and modified either independently of other function blocks, or as part of higher level blocks. This technique also permits differing versions of the same function to be evaluated concurrently.

The visual nature of the programming environment allows results to be presented graphically (using a range of display blocks) or exported to other applications, conversely data can also be imported from external spreadsheets or data-bases.

Two versions of the model have been developed. The first, KM1.VSM, utilises equations proposed by Uttamsingh et al [15] to describe sub-system blocks for renal function and hormonal control. The renal sub-system model contains linear piecewise approximation function blocks to represent four non-linear relationships; (i) glomerular filtration rate (GFR), (ii) fraction of water load reabsorbed in the distal tubule (EBDT), (iii) rate of reabsorbtion of sodium from the distal tubule (SDTR/SFDT), and (iv) rate of excretion of potassium due to aldosterone (UKAL). The swept output responses of each block are illustrated in figure 2. The main renal block equations are listed in table 1.

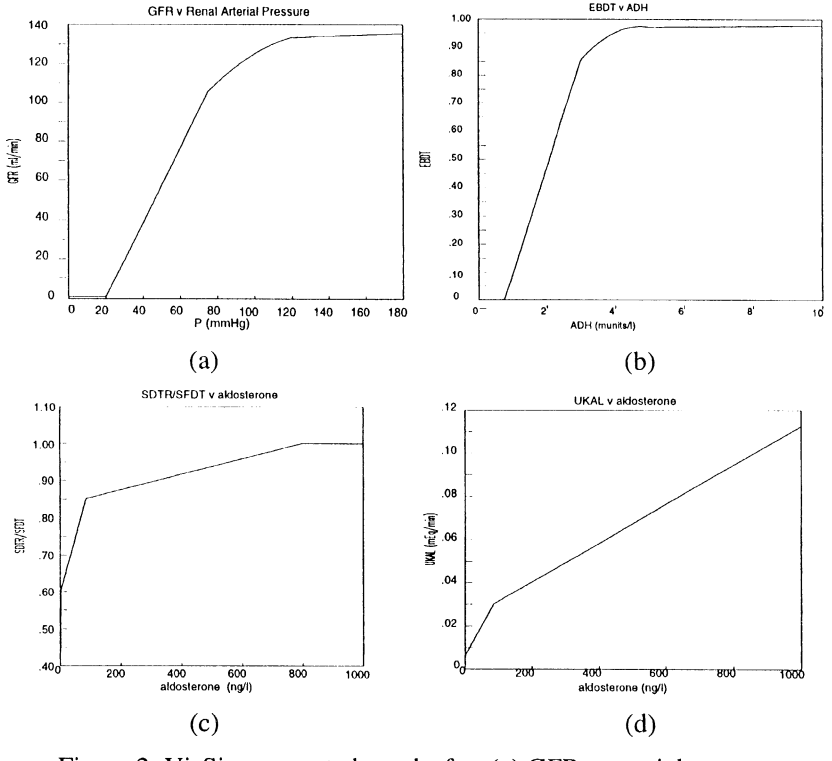


Figure 2: VisSim generated graphs for; (a) GFR *v* arterial pressure, (b) EBDT *v* ADH, (c) SDTR/SFDT *v* aldosterone, and (d) UKAL *v* aldosterone.

1.	FNA = GFR × PNA/1000	FNA PNA	Na filtration rate into proximal tubule extracellular conc of Na
2.	GTB = 5.815 - 0.0357 × PNA	GTB	glomerular-tubular balance
3.	SPTR = GTB × FNA	SPTR	Na reabsorption rate, proximal tubule
4.	SFLH = FNA - SPTR	SFLH	Na flow into loop of Henle
5.	EPTR = GTB × GFR	EPTR	Water reabsorption rate, prox tubule
6.	EFLH = GFR - EPTR	EFLH	Water flow into loop of Henle
7.	ELHR = 0.65 EFLH - 0.01 $EFLH^2$	ELHR	Water reabsorption rate, loop of Henle
8.	SLHR = 0.8 × SFLH	SLHR	Na reabsorption rate, loop of Henle
9.	EFDT = EFLH - ELHR	EFDT	Water flow into distal tubule
10.	SFDT = SFLH - SLHR	SFDT	Na flow into distal tubule
11.	EDTR = EBDT × EFDT	EDTR	Water reabsorption, distal nephron
12.	U_{flow} = EFDT - EDTR	U_{flow}	urine output
13.	Na_{EX} = SFDT - SDTR	Na_{EX}	sodium output
14.	UKH = 0.107 PK - 0.505	UKH PK	potassium excretion due to homeostasis extracellular concentration of potassium
15.	K_{EX} = UKH - UKAL	K_{EX}	potassium output

Table 1: Main equations for the kidney function block, adapted from Uttamsingh et al [15].

The hormonal control sub-system also contains piecewise approximation function blocks for; (i) release rate of antidiuretic hormone (ADHS) as dependant upon changes in extracellular fluid volume, (ii) clearance rate of antidiuretic hormone (DADH), and (iii) release rate of aldosterone (ALSA) due to the concentration of angiotensin in plasma. The swept responses of these blocks are shown in figure 3, whilst the main equations are listed in table 2.

1.	concentration of ADH in plasma; ADH (dt) = ∫ [ADHS - (ADH × DADH)] / PV (dt) where plasma vol., PV = 0.6 blood volume
2.	concentration of renin in plasma; R (dt) = ∫ [RS - 0.135 R] / PV (dt) where renin release, RS = 0.0163 - 0.0093 SFDT
3.	concentration of angiotensin II in plasma; A (dt) = ∫ [AS - 4.04 A] / PV (dt) where angiotensin formation, AS = 583.3 R × PV
4.	concentration of aldosterone in plasma; ALD (dt) = ∫ [ALS - 0.62 ALD] / PV (dt) where net excretion of aldosterone, ALS = (3.0 ALSA + ALSK) / 4.0 aldosterone release rate due to plasma potassium conc., ALSK = 21.64 PK - 55.5

Table 2: Main equations for the hormonal control block, adapted from Uttamsingh et al [15].

For this first version, KM1.VSM, both the cardiovascular and fluid balance sub-systems were implemented as simplified models. The cardiovascular block contains equations for blood volume (V_{BL}) and mean arterial pressure (P_A) based, in part, upon the Guyton-Coleman model described by Rideout [19] where V_{BL} is related to extracellular fluid volume, V_{EX}, as,

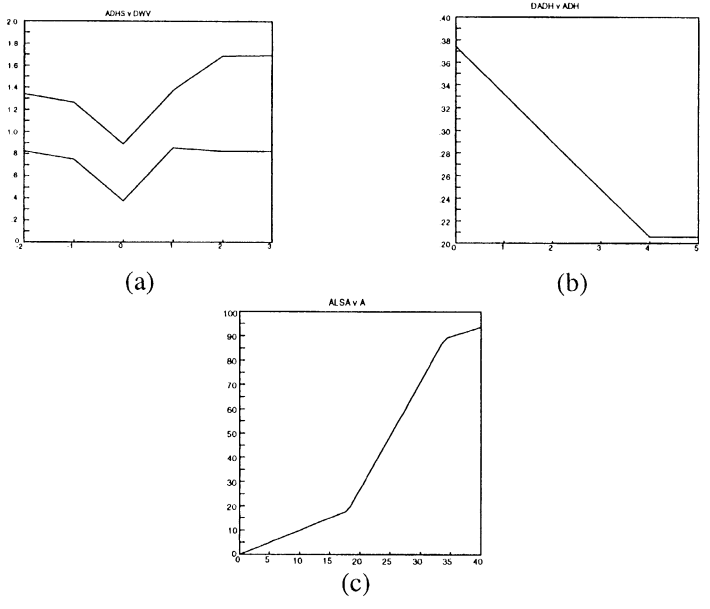
$$V_{BL} = 0.33(V_{EX}) \{\text{limit } V_{EX} \leq 6 \text{ litres}\}$$

and mean systemic pressure, P_{MS}, is,

$$P_{MS} = 3.5(V_{BL} - 3)$$

such that,

$$P_A = P_{MS} / 0.07$$



(a) (b) (c)

Figure 3: VisSim generated graphs for; (a) ADHS *v* changes in extracellular fluid volume, (b) DADH *v* ADH, (c) ALSA *v* angiotensin concentration.

The fluid balance block contains three basic relationships describing the rates of change of extracellular fluid volume (V_{EX}), extracellular sodium (Na_{EX}) and extracellular potassium (K_{EX}) in terms of their respective rates of ingested and excreted quantities where,

$d(V_{EX}) / dt$ = fluid ingested - urine flow (ml/min)

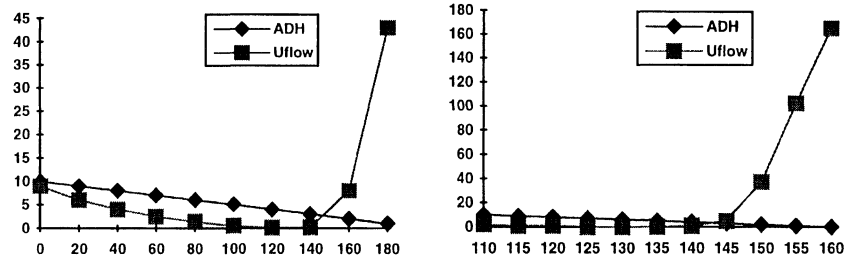
$d(Na_{EX}) / dt$ = Na ingested - Na excreted (mEq/min)

$d(K_{EX}) / dt$ = K ingested - K excreted (mEq/min)

The second version of the model, KM2.VSM, uses similar mathematical relationships for the kidney and hormonal blocks but contains more detailed descriptions for cardiovascular and fluid control blocks. Therefore the model may be validated over a wider range of physiological conditions. Further details of this model will be reported on at a later date.

4 Validation

Initial simulations of model KM1.VSM produced results for sodium, potassium and water excretion rates which appear to compare well with those reported by others [15, 20]. Preliminary testing of the kidney function block also confirmed earlier observations that clinically infeasible scenarios could result, e.g. negative urine output and negative urinary extraction of electrolytes [20]. Additional terms were then introduced to limit these occurrences and flag out of range physiological conditions.



(a) (b)

Figure 4: (a) Urine flow rate v changes in ADH levels and arterial pressure, (b) Urine flow v changes in ADH and extracellular sodium concentrations.

Tests were also performed to validate the model's ability to predict urine output and excretion rates for both sodium and potassium. Figure 4(a) illustrates urine output as both ADH concentration and arterial pressure are varied, whilst figure 4(b) shows the response as both ADH and extracellular sodium concentrations are swept. In both examples, all other inputs are held constant at their steady-state values.

Tests performed on the complete model, with all sub-systems connected as per figure 1, indicate that reliable steady-state conditions are reached for all variables within two minutes of simulation time. The optimisation of simulation step-time was achieved on a trial and error basis such that minimum initial instability was observed, whilst maintaining an acceptable run-time for a total model simulation time of four hours. A Runge-Kutta 4th order integration algorithm was used with a simulation step time of 1 second. The model contains approximately 850 active function blocks and provides acceptable levels of accuracy, with all key results confirming published steady-state values.

5 Simulated Clinical Environment

The third phase of this project will be the incorporation of the full model into a manikin and the provision of appropriate bedside monitoring and diagnostic

equipment to create a realistic, interactive teaching aid for renal and dialysis studies.

A Laerdal ALS training manikin [21], currently fitted with a Heartsim 2000 ECG interface, will be modified to include a target microcontroller system and hardware interfaces to the VisSim computer-based simulation model. Eventually the modelling software itself will be loaded into the target microcontroller using the C-code generator option provided with VisSim. Prototype circuitry has already been constructed to allow real-time control and monitoring of fluid flow rates and marker concentration levels, see figure 5.

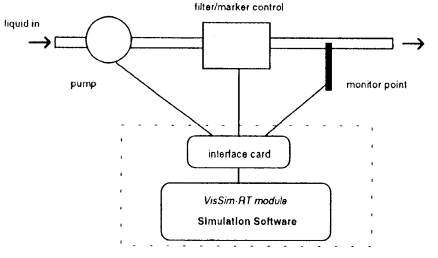


Figure 5: Simulation interface and control circuitry

The add-on facility, VisSim-RT, provides a direct link between the hardware interface and the simulation model. Additional software has been incorporated into the model KM2.VSM to scale simulation responses to the sampling rates of the hardware interface.

6 Conclusions

This paper has presented a short review of recent renal and dialysis models. Key features from several earlier renal models have been incorporated into a new model which has been implemented using the dynamic system, block-diagram software VisSim. The model provides realistic simulations over a range of physiological conditions. The model will eventually be used as part of a simulated clinical environment for both teaching and research purposes. It is anticipated that, following on from this initial phase of work, a number of associated physiological simulations will be integrated within a manikin to provide a sophisticated vehicle for the instruction and training of clinicians.

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