A Quick Look Into the Feedback System of a Simplified Kidney Model

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Abstract

The renal system plays various important roles in maintaining homeostasis, including waste elimination and nutrient reabsorption. In particular, the kidneys act as the body's primary filtration system, regulating electrolyte balance and removing unneeded waste and fluid products. In this paper, we explore the impact of electrolyte intake, namely sodium on tubular function. To focus on this specific aspect, the system of differential equations involved assumes constant values for the other physiological homeostatic mechanisms and a constant rate representing the interaction between both glomerular filtration and reabsorption. For instance, healthy values are used for the generalized filtration rate (encompassing glomerular filtration rate (GFR) and reabsorption rates) and blood flow. Using this simplified model, various test conditions (electrolyte sports drinks, seawater) were examined with a block diagram in Simulink. The results show only a minor difference between the control and experimental conditions, suggesting the fragility of homeostatic balance. With the human body being approximately 70% water, fluidic balance is of extreme importance. Current kidney research is limited, and this model seeks to offer further insights into the function and feedback system of the kidneys.

Key words: renal system, filtration, GFR, fluidic balance, waste management, nutrient reabsorption, homeostasis, kidneys, urination, electrolytes, sodium

I. Introduction

The kidneys are responsible for filtering nutrients to return to the body or to remove as waste (in the form of urea). This process is critical to regulating the body's balanced concentrations of minerals, nutrients, and water. When the body is dehydrated, especially for long periods of time, homeostatic imbalance ensues, causing the kidneys to alter filtration rates in an attempt to return the body to a balanced state. One key compound, sodium, is closely related to hydration levels and maintenance of homeostasis. Sodium is crucial for proper cell function and signaling, but overly high concentrations—especially over long periods of time—can increase blood pressure, leading to risk of serious injury of internal organs or stroke [1]-[2].

This project focuses on exploring the feedback system of sodium filtration, involving the fluid inputs, kidney response, and waste filtration rate. Many studies have attempted to represent the kidney, but due to its structural and physiological complexities, few all-encompassing models exist [3]-[7]. Nevertheless, the existing work is sufficiently complex to capture various important kidney components. Conversely, simplified models that focus on a sole region are less common; thus, there is a need for a simple kidney model that accurately represents the feedback system that controls electrolyte concentrations in order to meet the target levels for homeostasis and expel excess solutes via urine. The model described in this paper will study how varying electrolyte concentrations in drinks (ie. Gatorade, Powerade, and water) affect the reabsorption or excretion of salts (specifically, NaCl) in the kidney filtration feedback loop. It is anticipated that pure water will not have a significant effect on the control system while the electrolyte drinks will alter the output sodium concentration linearly (relative to their respective electrolyte concentrations).

The rest of the paper is organized as follows. Section 2 surveys the relevant physiological background and the basis of this model. Section 3 reviews the methodology, including mathematical premises, assumptions, parameters, and simulation cases. Section 4 outlines the results and possible sources of error. Lastly, Section 5 provides a discussion on future directions and implications. Note that the Appendix includes a list of figures, variables, and constants.

II. Physiological Premise

The renal system encompasses the kidneys, ureters, urinary bladder, and urethra, and has the primary function of eliminating nitrogenous waste from the body. In addition, the renal system uses the same mechanisms to filter waste products as it does to regulate water and concentration of essential minerals such as sodium, potassium, and chloride [8]. While the renal system as a whole is extremely complex, much of this complexity is contained within the many layers, compartments, and passages of the kidneys. Arguably, the kidneys, being majorly responsible for fluid filtration, are the principal

organ of the renal system. Within this, the kidneys are also responsible for retaining the appropriate balance of salt and water, which both play key roles in maintaining homeostasis and critical cell functioning.

In order to understand the intricacies involved in fluid filtration within the kidney, it is important to focus on the most basic functional unit: the nephron. The general pathway that fluid follows as it is being filtered throughout the nephron involves multiple steps. First, fluid goes through the glomerulus, a bundle of capillaries that connects the blood vessels to the proximal end of the nephron [9]. Next, excessive filtration occurs between the glomerular capillaries and the Bowman's capsule, where the tubular fluid is defined as ultrafiltrate— which is more concentrated than the fluid that is excreted [9]. Throughout the proximal section of the nephron, a process known as reabsorption will occur. Here, the ultrafiltrate solutes will be transported from the tubule back into the blood vessels in order to maintain proper solute concentration in the body [9]. As the tubular fluid travels along the nephron, reabsorption will occur, were some of the solute present in the ultrafiltrate will return to the blood vessels; however, this exchange will happen between the tubules and the peritubular capillaries, as the fluid flows throughout the nephron [9]. As it enters the distal section of the nephron, the tubular fluid will enter the collecting ducts, which will eventually lead to the bladder and be excreted during urination [9]. Because one's daily dietary intake of sodium often exceeds the body's cellular requirements, the amount of sodium excreted is often similar to the amount of sodium intake [9]. Due to intake being highly variable between people and throughout time, the kidneys need to constantly change their reabsorption rate in order to maintain homeostasis [9].

Due to the need to have variable reabsorption rates throughout the kidney, certain sections within the nephron are more involved in reabsorption than others (Figure 1). Approximately 60-70% of sodium in the ultrafiltrate is reabsorbed in the proximal nephron, composed of the proximal convoluted tubule and the proximal straight tubule, and 25-30% of sodium is reabsorbed in the thick ascending loop. Thus, at the distal section of the nephron, less than 10% of solute from the ultrafiltrate is expected to be present, having reabsorbed most of the extra solute filtered at the Bowman's capsule. However, in order to maintain the balance between the filtration of sodium at the Bowman's capsule (described by the glomerular filtration rate) and the reabsorption rates throughout the kidney, there is an additional negative feedback between the thick ascending loop and the glomerulus, which allows for balance between both rates in order to avoid both excessive and lacking absorption of sodium [9].

This process is very energy demanding, as approximately two thirds or more of renal oxygen uptake is used for active sodium reabsorption. However, the function of the glomerular filtration as well as reabsorption throughout the nephron allows the kidney to have variable concentrations in the urine output. This is necessary for homeostasis, as a variable amount of solute is ingested through one's diet.

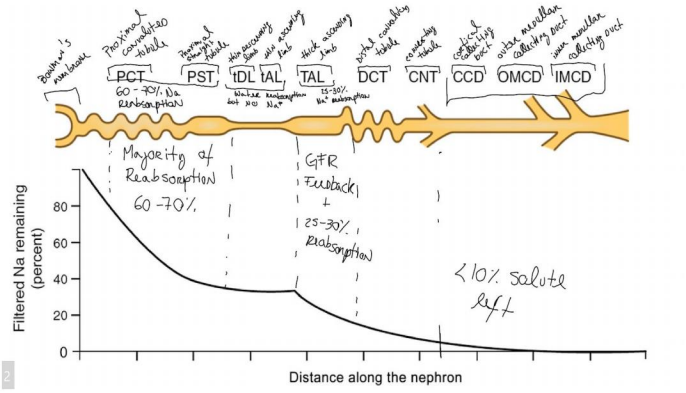

Figure 1: Annotated diagram demonstrating sodium reabsorption as it moves through a nephron [9].

Due to varying rates of reabsorption within the proximal section of the nephron as well as the thick ascending loop, a model deriving such interactions would be complex in nature. Thus, in order to investigate the generalized filtration response, a simplified model was developed, where all proximal nephron processes, including glomerular filtration and sodium reabsorption, are concatenated into a single rate. Thus, when varying glomerular filtration in conjunction with reabsorption, a single filtration rate was modified instead of separating these processes individually.

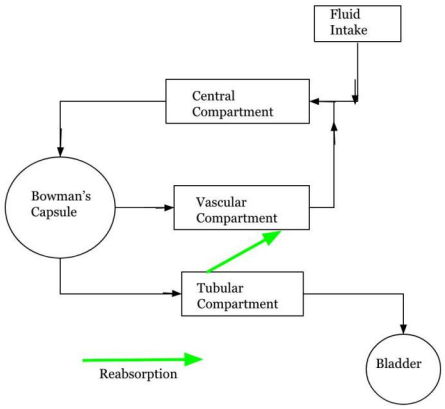

Figure 2: Modified biological block diagram, depicting the simplified kidney system described in this paper.

Considering the biological basis outlined in this section, the complex filtration system within the kidney can be simplified into a block diagram (Figure 2). This diagram maps the movement of fluid and solutes from the time of intake, proceeding through filtration, and ending in the bladder as waste.

III. Methodology

As previously stated, many existing models attempt to capture the full complexity of the renal system and/or kidney function. In order to highlight the specific tubular process, initial attempts began with literature review for a more simplified system. Building off the assumptions in [10]-[11], a new mathematical model was derived and reproduced in Simulink. Section 3A reviews the relevant assumption and mathematical derivation, Section 3B reviews the basis for parameter constants, and Section 3C reviews the block diagram simulation.

A. Mathematical Modeling

Rather than simplifying from a full system model, the initial model is inspired from the mechanical kidney representation in Figure 3 [10]. As depicted, the authors effectively employ a two-compartment model. In pharmacokinetics, the central compartment represents the organs and tissues where drug distribution is instantaneous or near-instantaneous; the peripheral compartment (i.e. everything outside the central compartment) represents tissues where drug distribution occurs more slowly [12]-[13]. Though more commonly used in pharmacokinetics, this idea can be extended to regular physiological processes and thereby, the renal system. In the case of [10], the central compartment is essentially a single kinetically homogeneous block to describe highly-perfused organs external of the mechanical kidney system. The other blocks (e.g. Bowman's capsule, segments) represent more slowly-perfused tissues.

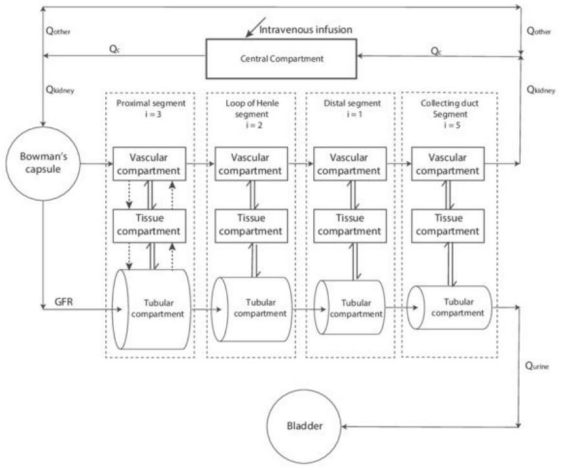

Figure 3: Schematic diagram of the mechanistic kidney model [10]

This two-compartment model was then further simplified to focus on a specific segment— in this case, the distal nephron. To achieve this, some modifications and assumptions were borrowed from [11]. Depicted in Figure 4, this model collapses the vascular compartment into a single vessel structure and the tubular compartments into a single tubule structure to create a more general system for measuring single-kidney function.

Combining Figures 3 and 4 to create the system modeled in this paper, Figure 3 enabled initial conceptualization of the biological block diagram (Figure 2). The model in Figure 4 proved to be a useful starting point to represent Figure 2, particularly given the differential solute concentration Equations (1) and (2).

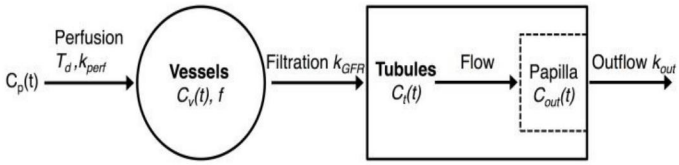

Figure 4: Modified two-compartment model, in which the kidney is reduced to a combination of the blood vessels structure and renal tubules structure [11].

Equations (1) and (2) were given in [11], along with the assumption prescribed by Equation (3).

Change in concentration of solute in the vascular compartment is described by:

$$\frac{dC_v(t)}{dt} = k_{perfusion}(C_p(t - T_d) - C_v(t)), \qquad (1)$$

where $k_{perfusion}$ is the perfusion rate constant, $C_v(t)$ is the concentration of solute in the vascular compartment, and $C_p(t - T_d)$ is the arterial input function.

Change in concentration of solute in the tubular compartment is described by:

$$\frac{dC_t(t)}{dt} = k_{GFR} \cdot C_v(t) - k_{out} C''_{out}(t), \qquad (2)$$

where $C_t(t)$ is the concentration of solute in the tubular compartment, k_{GFR} is a combined filtration rate constant (see Appendix B), k_{out} is the efflux rate constant, and $C''_{out}(t)$ is the concentration of solute in tubular transport.

Concentration of solute in tubular transit is described by:

$$C''_{out}(t) = C'_{out}(t) - C_{out}(t), \qquad (3)$$

where $C'_{out}(t)$ is the concentration of solute from papillular perfusion, and $C_{out}(t)$ is the concentration of solute in the papilla that exits the body.

Using the aforementioned conceptualization, this system was extrapolated with two primary assumptions. First, Figure 4 organizes the papilla at the end of the tubules structure, and thus, it can be safely assumed that the papilla solute concentration is some fraction of the larger structure concentration.

Concentration of solute in the papilla is described by:

$$C_{out}(t) = d \cdot C_t(t), \qquad (4)$$

where d is the distal nephron component that describes the ratio of the papilla solute concentration.

Secondly, the vast majority of sodium reabsorption occurs at the proximal section of the nephron; thus, it can be assumed that the concentration of sodium left to reabsorb from the ultrafiltrate is negligible. Anatomically, the papilla is composed of the medullary collecting ducts of many nephrons merging into the papillary duct, which eventually leads to the bladder. At such a location in the kidney, there is a negligible concentration of sodium left to be reabsorbed. Less than 10% of solute remains from the ultrafiltrate at the collecting ducts; this percentage is expected to decrease as the tubular fluid leaves the collecting ducts and enters the papilla. Thus, the following assumption describing the ratio of solute concentration in the papilla to tubular transit can be made:

$$C''_{out}(t) = 0.1 \cdot C_{out}(t) \approx C_{out}(t) \quad , \qquad (5a)$$

$$C''_{out}(t) \approx C_{out}(t). \qquad (5b)$$

In the original equations, $C_t(t)$ is dependent on $C''_{out}(t)$, which in turn is dependent on $C'_{out}(t)$ and $C_{out}(t)$ — as seen in Equation (3). In this system, $C_{out}(t)$ is the desired measurable output and cannot physiologically be a system input, as it represents the concentration excreted. Conversely, Equation (5b) is a physiologically sensical representation.

These assumptions are critical for both mathematical and physiological simplification, as the tubular system is dependent on papilla output concentration. Thus, the final model to describe our system consists of Equations (1), (2), (4), and (5b).

B. Simulation Parameters

For simulation purposes, all parameters were defined considering average healthy adult conditions. Following Equations (1), (2), (4), and (5b), some components are assumed constant for ease of modeling.

The central compartment flow constant (*CC*) is a pre-system input gain of 20% (i.e. unitless gain of 0.2) to account for the fractional amount of renal blood flow (1 L/min) as compared to normal blood flow (5 L/min) [14]-[15]. T_d was assumed to be zero for ease of calculation and modeling. T_d represents the time delay between time of fluidic input (i.e. drinking a liquid) and time of arrival at the kidneys. By setting T_d to zero, the model essentially bypasses digestive processes to focus on kidney filtration. The distal nephron component (*d)* is set as 0.1 to represent the 10% ultrafiltrate reabsorption (refer to Section 2) occuring at this region.

For the rate constants, $k_{perfusion}$ is 1.3 mL/(min*mL), k_{GFR} is 100mL/(min*mL), and k_{out} is 0.5 mL/(min*mL) [16]-[18]. Note that $k_{perfusion}$ and k_{out} are directly taken from the literature, while k_{GFR} is based on the healthy adult GFR rate (90+).

For simulations, sodium is selected for analysis due to its abundance and importance in the human body. The baseline blood sodium concentration is set at 0.0547 mg/mL [19]-[20]. Sodium concentrations of all test conditions are calculated for 12 fluid ounces of each tested liquid. Water (control test case) has a concentration of 0.0507 mg/mL. Derived from nutritional values, Powerade has a concentration of 0.4225 mg/mL while Gatorade has 0.4507 mg/mL (realistic test cases). Seawater (extreme test case) has a sodium concentration of 3.5 mg/mL, derived from baseline salinity.

The initial conditions for integrator blocks are set to 3.22 mg/mL for the normal vascular sodium level and 2.3 mg/mL for the normal tubule sodium level [19]-[20].

C. Simulation Diagram

Using the final equations, (1), (2), (4), and (5b), to construct the Simulink block diagram in Figure 5, the filtration process within the kidneys with respect to sodium intake from a drink was tested with the four cases described above.

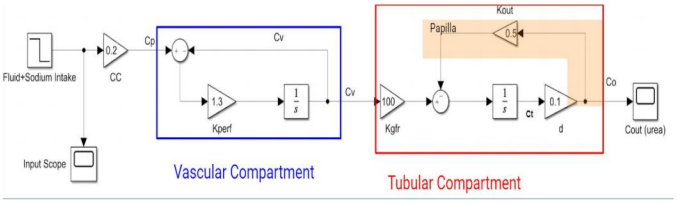

Figure 5: Simulink model of system. Vascular compartment representation is outlined in blue while tubular compartment representation is outlined in red.

The model uses a step function to represent the input or an initial impulse (i.e. the consumed liquid). The step value was set to the baseline sodium concentration found within a healthy adult, plus the sodium concentration of the liquid (i.e. described by each experimental case). The final value of the step function was also set at the baseline sodium concentration.

In order to maintain a similar structure as the system outlined in Figure 3, the *CC* gain of 0.2 was added to represent the central compartment. The input and *CC* gain feeds into a feedback loop representing the vascular compartment described by Equation (1). For this integrator block (Figure 5, blue), the initial condition is set to the normal vascular sodium level. The output of this loop (Cv) then feeds another loop representing the tubular compartment and papilla described by Equation (2). For this integrator block (Figure 5, red), the initial condition was set to the normal tubule sodium level. The output of this loop is then measured with a scope ($Cout$), representing the sodium concentration of urea within the bladder.

IV. Results

As stated in Section 3C, there are four test cases: the control test water, the realistic test cases of Powerade and Gatorade, and the extreme test case of seawater. Physiologically, even minor upsets to homeostatic balance can impede biological function; therefore, only marginal differences are expected between the control and realistic test cases.

A. Control Condition

Water was first tested to have a baseline for comparative analysis, as there is little sodium present in clean water. With the initial impulse, the output concentration jumped, but the system responded quickly and soon filtered the excess sodium out to reestablish the normal healthy baseline concentration (Figure 6).

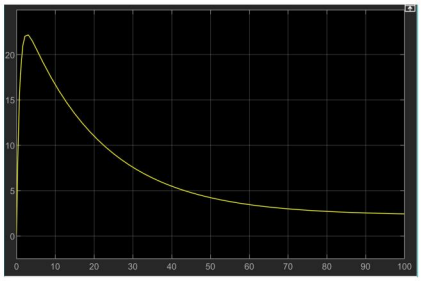

Figure 6: The control test case, water, is modeled showing a peak of 22.1 before returning to steady-state.

B. Test Conditions

Next, the two electrolyte drinks were tested. The output from both drinks followed the same pattern as that of water, peaking initially followed by a fairly quick return to baseline concentration (Figure 7). However, Powerade has a peak value 3.2% greater than the peak of water while Gatorade has a 3.4% greater peak. Although some may have brand loyalty or preference to one drink over the other, the physiological benefits are fairly similar, indicating no true physiological difference in choosing one over the other. The minimal difference between the two is attributed to their similar sodium concentrations.

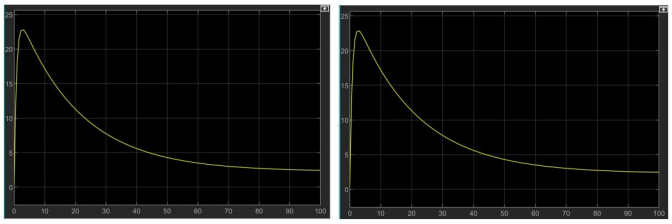

Figure 7: The realistic test cases, Powerade (left) and Gatorade (right), are modeled showing peaks of 22.8 and 22.86, respectively, before returning to steady-state.

Lastly, seawater was tested for an extreme comparison. Although it may appear that the change relative to water was also very minimal (Figure 8), further analysis reveals otherwise. The seawater peak is found to be 25% greater than that of water, which is substantially higher than the Powerade and Gatorade realistic test cases.

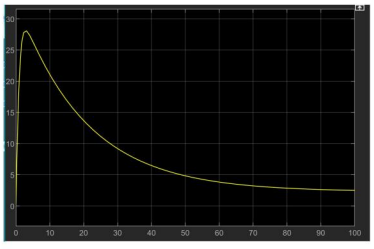

Figure 8: The extreme test case, seawater, is modeled showing a peak of 28.02 before returning to steady-state.

Under healthy conditions, the body is incredibly apt at maintaining homeostasis, and can return to homeostasis even under extreme conditions (as seen in the seawater

case). Since Gatorade and Powerade are developed for human intake at a portioned rate, the small changes in the system are logical. However, if one were to drink a much larger portion of seawater over a longer period of time, the body and kidney function would most likely begin to falter due to a cascade of homeostatic issues.

C. Errors and Observations

Due to the simplifications and assumptions made to create this system, there are a variety of possible errors. As mentioned in previous sections, the literature review revealed that some subsystems in the renal system played only minor roles in filtration, and were thus collapsed into the more relevant components. Although this approach was necessary to build the model, it is also the likely culprit for the majority of potential errors.

Physiologically, there exists an additional feedback component between the thick ascending loop and the glomerulus, which maintains the balance between the glomerular filtration rate (GFR) and the reabsorption rate [9]. Because of the simplification choice to concatenate GFR with the reabsorption rates, this feedback loop was lost.

In addition to baseline system simplification, the initial conditions may have caused errors related to the rate constants. Constant parameters derived from the average "healthy adult" baseline may also contribute to errors; finding these values proved challenging. A final source of error could stem from modeling the time delay at zero for instantaneous urination.

V. Discussion and Conclusions

This project adapted a two-compartment model in order to represent a simplified "black box" version of the kidney and observe the response specifically at the renal papilla, concatenating all other portions of the nephron. The model was outfitted with constant parameters describing healthy adult conditions as further simplification. This simplification is necessary due to computational limitations: (i) physiological complexities that cannot fully be defined by mathematical approximations and (ii) processing capacity of Simulink. Extending these limitations to clinical settings, such as dialysis machines, the simplified system described in this paper would be insufficient for practical applications. Moreover, mathematical models are most clinically beneficial for unhealthy systems, typically involving homeostatic imbalance. At this time, existing research of physiologically accurate constant parameters is also limited.

The filtration process was displayed using four test cases, revealing minimal differences between the control case and the realistic input cases. Using the extreme seawater case as a comparison, this is reasonable. A potential clinical application of this model is to attempt to capture urinary hesitancy, a condition in which one may have issues when starting to urinate or when maintaining urine flow. This condition could potentially be modeled using the simplified system but altering the time delay to represent the "hesitancy" aspect [21].

Through this project, it has become clear why the bulk of existing literature opts for more complex models. With the intricacies of the renal system, extracting one component (e.g. the kidneys) still results in quite a convoluted model. In this paper, the kidney filtration system was simplified to the very basic elements of filtration and feedback. Although this oversimplification does not fully preserve the integrity of the system, the sole fact that the model could output change in sodium concentration over time, with relative accuracy, is promising. The reasonable success of the simplified system implies that future iterations can utilize similar principles (i.e. reducing components to a compartmental level) to achieve greater accuracy. Through slightly more complex models, future research can still hone in on a specific element to further knowledge on how the kidney filtration system operates in tandem with the renal system. By advancing our understanding of the renal system, even at a simplified feedback system, advances towards understanding the full, more complex kidneys and renal system can one day be made. The simplified model created here shows promising results for kidney models in the future, and hopefully strides towards solving clinical mysteries as well.

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IX. Appendix

A. *List of Figures*

B. *List of Variables and Constants*

Variable	Definition
$C_v(t)$	Concentration of solute in the vascular compartment
$C_p(t)$	Arterial input function, concentration of solute from the abdominal aorta
$C_t(t)$	Concentration of solute in the tubular compartment
$C''_{out}(t)$	Concentration of solute in tubular transport
$C'_{out}(t)$	Concentration of solute from papillular perfusion
$C_{out}(t)$	Concentration of solute in the papilla, exiting the body

Constant Parameter	Definition	Value
CC	Central compartment flow constant	0.2
T_d	Time delay between input of substance (drink liquid) and when it actually reaches the kidneys	0
k_{out}	Efflux rate constant, represented by the average renal clearance rate [17]	$0.5 \frac{mL}{min*mL}$
$k_{perfusion}$	Perfusion rate constant [16]	$1.3 \frac{mL}{min*mL}$
k_{GFR}	Combined rate constant of multiple transport rates including the rate of production of ultrafiltrate in the glomerulus and reabsorption rate [18]	$100 \frac{mL}{min*mL}$
d	Distal nephron component	0.1