

Dynamic Model in the Proximal tubule of Rat Kidney

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Abstract

We developed a dynamic model of a male rat proximal tubule in order to investigate results brought by changes on different lumen boundary conditions. We examined how long it will take to reach a steady state again from a sudden change. We also investigated whether oscillation on a single parameter will result in similar oscillations on other parameters. We determined that these oscillations will not have a significant passive effect on proximal tubule's re-absorption. We also noticed several irregular phenomenon such as phase difference and amplitude difference on the oscillation pattern of concentrations in different part along the tubule. And we tried to explain these response by using physiological knowledge.

Keywords: Proximal tubule · Oscillations · Concentrations · Dynamic model

1 Model Formulation

In proximal tubule, cells and tight junctions between cells form a single-layer cell wall between lumen and bath. We build our model based on the steady state model that Anita Layton published. The model consider fifteen kinds of solutes, including Na^+ , K^+ , Cl^- , HCO_3^- , H_2CO_3 , CO_2 , HPO_4^{2-} , H_2PO_4^- , urea, NH_3 , NH_4^+ , H^+ , HCO_2^- , H_2CO_2 and glucose. Model contains four compartments (Lumen, cell, lateral space, bath). Solute are exchanged between different compartments through diffusion, transporters and coupled transporters. System equations are based on mass conservation and electronic neutrality.

1.1 Water Conservation

Water conservation in cell and lateral space (denoted by subscripts “C” and “P” respectively) is given by:

$$\frac{dV_C}{dt} = J_{v,LC} + J_{v,BC} + J_{v,PC} \quad (1)$$

$$\frac{dV_P}{dt} = J_{v,LP} + J_{v,BP} + J_{v,CP} \quad (2)$$

where the subscripts “L” and “B” denote lumen and bath respectively, and “v” denotes volume of water. Water conservation in lumen is given by:

$$0 = -\frac{\partial F_v}{\partial x} + 2\pi r(J_{v,CL} + J_{v,PL}) \quad (3)$$

where F_v means water flow in lumen, r means radius of lumen and partial derivative means along the lumen.

1.2 Solute Conservation

For non-reacting solute k , conservation equations are given by:

$$\frac{dV_C C_{k,C}}{dt} = J_{k,LC} + J_{k,BC} + J_{k,PC} \quad (4)$$

$$\frac{dV_P C_{k,P}}{dt} = J_{k,LP} + J_{k,BP} + J_{k,CP} \quad (5)$$

$$0 = -\frac{\partial (F_v C_{k,L})}{\partial x} + 2\pi r(J_{k,CL} + J_{k,PL}) \quad (6)$$

where $C_{k,i}$ denotes the concentration of solute k in compartment i and $J_{k,ij}$ denotes flux of solute k from compartment i to j .

For the reacting solutes, conservation is applied to the total buffers. Take the buffer HPO_4^{2-} and H_2PO_4^- for instance:

$$\frac{d}{dt} \left(V_i \left(C_{\text{HPO}_4^{2-},i} + C_{\text{H}_2\text{PO}_4^-,i} \right) \right) = \hat{J}_{\text{HPO}_4^{2-},i} + \hat{J}_{\text{H}_2\text{PO}_4^-,i} \quad (7)$$

where i corresponding to C or P. $\hat{J}_{k,i}$ denotes the net flux of solute k into the compartment i .

$$\frac{d}{dt} \left(F_v \left(C_{\text{HPO}_4^{2-},L} + C_{\text{H}_2\text{PO}_4^-,L} \right) \right) = \hat{J}_{\text{HPO}_4^{2-},L} + \hat{J}_{\text{H}_2\text{PO}_4^-,L} \quad (8)$$

The other buffer pairs $(\text{CO}_2, \text{HCO}_3^-, \text{H}_2\text{CO}_3)$, $(\text{HPO}_4^{2-}, \text{H}_2\text{PO}_4^-)$, $(\text{NH}_3, \text{NH}_4^+)$ all have above equations. The buffer pairs are in equilibrium:

$$\text{pH} = \text{pK}_A - \log \frac{C_{A,i}}{C_{B,i}} \quad (9)$$

where the buffer pairs (A,B) are $(\text{HCO}_3^-, \text{H}_2\text{CO}_3)$, $(\text{HPO}_4^{2-}, \text{H}_2\text{PO}_4^-)$, $(\text{NH}_3, \text{NH}_4^+)$, $(\text{HCO}_2^-, \text{H}_2\text{CO}_2)$. The conservation of hydrogen is given by:

$$\begin{aligned} & \frac{d}{dt} \left(V_i (C_{\text{H}^+} + C_{\text{NH}_4^+} - C_{\text{HCO}_3^-} - C_{\text{HPO}_4^{2-}} - C_{\text{HCO}_2^-}) \right) \\ &= \sum (\hat{J}_{\text{H}^+,i} + \hat{J}_{\text{NH}_4^+,i} - \hat{J}_{\text{HCO}_3^-,i} - \hat{J}_{\text{HPO}_4^{2-},i} - \hat{J}_{\text{HCO}_2^-,i}) \end{aligned} \quad (10)$$

1.3 Calculation

We discrete time-dependent term by Back-Euler Method. For the partial differential term, we simply regard F_v does not change too much along one cell's length along the tubule. For instance, solute conservation equation in lumen can be discrete as following: For non-reacting solute k , conservation equations are given by:

$$\frac{V_C^{n+1}C_{k,C}^{n+1} - V_C^n C_{k,C}^n}{\Delta t} = J_{k,LC}^{n+1} + J_{k,BC}^{n+1} + J_{k,PC}^{n+1} \quad (11)$$

where Δt means time step length, superscript n means the n -th time step.

2 Numerical Experiment

After finishing the building of dynamic model, we can do various numerical experiments to observe changes along the time. In general, we did four kinds of experiments on boundary conditions separately :

- Increase a certain solute concentration level
- Add various frequency and amplitude oscillations on single nephron glomerular filtration rate (SNGFR)
- Add various frequency and amplitude oscillations a certain solute concentration
- Add oscillations on solute concentration and SNGFR simultaneously

And we found several interesting results and tried to explain them by physiological knowledge.

2.1 Recover Time

We increase glucose and urea concentration in lumen boundary condition separately. The proximal tubule plays an important role in re-absorption. Glucose are transported through transporter SGLT2 between lumen and cell, through transporter GLUT2 between cell and bath. Urea is a kind of inorganic chemicals with small molecule. It is transported by diffusion. Glucose and urea are both chemicals with no valence, meanwhile their concentrations are close in lumen. We calculate the convergence process to exam their difference in re-absorption. The transporter will accelerate the re-absorption process, thus we expect that the former experiment will reach the balance more quickly. Since we assume that lumen is incompressible, thus lumen concentrations will react to the sudden change almost simultaneously. Thus we observe cellular concentrations to judge the convergence. We find in both experiments the tubule will recover to steady state in 10-15 seconds. Moreover, if we increase other kind of solutes in similar scales, they can all reach the balance in 20 seconds. It

indicates that the proximal tubule have the ability of reacting to the changes in boundary conditions quickly and keeping the lumen environment in steady state.

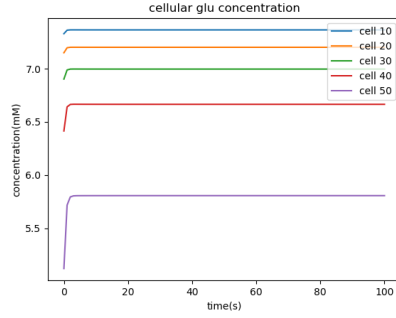


Figure 1: Glucose concentration

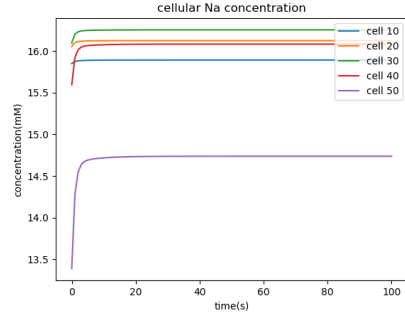


Figure 2: Sodium concentration

Figure 1 and Figure 2 is cellular glucose and sodium concentration trend after we increasing lumen boundary glucose concentration by 10 percents.

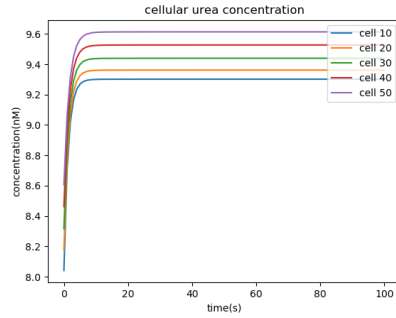


Figure 3: urea concentration

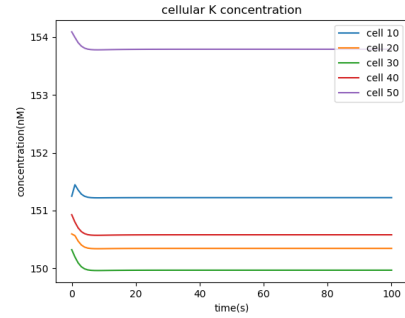


Figure 4: Potassium concentration

Figure 3 and Figure 4 is urea glucose and potassium concentration trend after we increasing lumen boundary urea concentration by 10 percents.

2.2 Oscillation on SNGFR

Experiments show that SNGFR has an oscillation of about 30 seconds time period. We include this oscillations in our numerical experiments to exam whether the oscillations will affect the tubule re-absorption function. We add oscillations as following form:

$$\text{SNGFR}(t) = \text{SNGFR}^0 * (1 + A \sin(\frac{2\pi t}{T})) \quad (12)$$

where $SNGFR^0$ means original SNGFR baseline, A and T denote amplitude and time period separately. We choose T as 15, 30 or 60, A as 0.1, 0.3 or 0.5 in the experiment.

3 Numerical Experiment

“I always thought something was fundamentally wrong with the universe” [1]

References

- [1] D. Adams. *The Hitchhiker’s Guide to the Galaxy*. San Val, 1995.