Numerical Solution to the Concentration Profile of a Given Nephron Density

Eleven (Shiyi) Chen sc7825@nyu.edu

May 14, 2022

Contents

1 Introduction

The nephron is a basic functional unit of the kidney. The blood goes through the Nephron before the urine is generated from the blood. Nephron plays a crucial role in the control of the volume and the Na^+ concentration in the extracellular fluid. In this project, we will first describe a single Nephron Model. This model has the limitation that the concentration of the urine cannot be bigger than e times the concentration of the blood plasma. However, there is no such limit in the nephron observed. To address this problem, a more complete multi-nephron model considering the length distribution of the Nephron is presented. To calculate the concentration in the urine, an integral equation is needed to be solved. In this project, a numerical scheme was used to solve the resulting integral equation of the model with any Nephron length distribution. The final result shows that given some distributions, the concentration in the urine can be arbitrary high without considering the water flux from the collecting duct. With the flux from the collecting duct being considered, however, the concentration in the urine is significantly decreased but still larger than e times the concentration in the plasma.

2 Math Model of the Nephron

In the nephron, the blood first enters the glomerulus. After filtration of the glomerulus, almost all the protein and blood cells in the blood are filtered out and go back into the blood, the leftover is called tubular fluid. The tubular fluid then enters the loop of Henle. Since the glomerulus is permeable to small molecules - like the water, and ions - the concentration of sodium in the initial tubular fluid is equal to that in the blood plasma. After entering the loop of Henle, the tubular fluid first goes through the descending loop of Henle(DLH), ascending loop of Henle(ALH), and finally through the distal convoluted tubule(DCT) and collecting duct(CT). Between ALH and DT, there is juxtaglomerular apparatus(JGA), which senses the sodium concentration of the tubular fluid and controls the rate of flow into the nephron thus controls the concentration in the urine. Here, we don't model the details about the mechanism and simply assume that

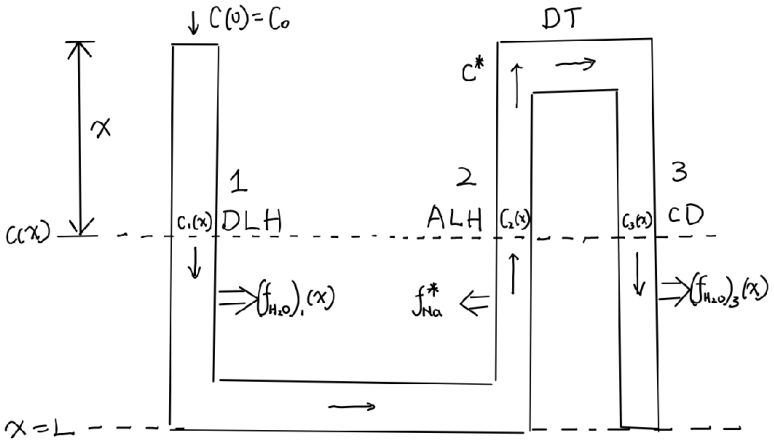

Figure 1: The model of one single nephron

Notation	Meaning
c_0	Sodium concentration in the blood plasma
$c(x)$	Sodium concentration in the interstatium at depth x.
$c_1(x)$	Sodium concentratonin the DLH at depth x.
$c_2(x)$	Sodium concentraton in the ALH at depth x.
$c_3(x)$	Sodium concentraton in the CD at depth x.
$(f_{H2O})_1(x)$	Flux of water at depth x of DLH.
$(f_{H2O})_3(x)$	Flux of water at depth x of CD.
f^*_{Na}	Flux of sodium at ALH.
c^*	Concentration of sodium in the tubule before entering DT.

this control mechanism is working and the concentration between the DT and ALH is equal to c^*. The graphic illustration is shown in Figure 1.

Besides facts about the nephron discussed above, the further assumptions are made to construct the model:

1. Nephron in the concentrating mode(ADH present). Moreover, we assume the permeability of DLH, DCT and CT are so huge that the concentration in the DT = concentration in the blood plasma, the concentration in the DT = ambient concentration in the interstitim. And the concentration in the CD also equal to ambient concentration in the interstitim. Thus, we have following relationships:

$$c_1(x) = c_3(x) = c(x)$$

Especially, we have:

$$c_1(0) = c(0) = c_0$$
$$c_3(L) = c(L) = \text{sodium concentration in the urine}$$

By the conversation of the tubular fluid, we have:

$$\frac{\partial Q_1}{\partial x}(x) + (f_{H_2\mathrm{O}})_1(x) = 0$$

2. We assume Juxaglomerulus Apparatus is working but we don't model the details of the mechanism, the simplified model satisfies that:

$$c_2(0) = c(0) = c^*$$

3. Sodium re-absorbance only happens at ALH, where the sodium is pumped out and the water remains the same(not the case for real nephron). This can be described as the total sodium at the bottom of DLH equal to the sodium pumped by ALH and sodium leaving at ALH.

$$c_1(L)Q_1(L) = f^*_{\mathrm{Na}}L + Q_1(L)c^*$$
$$\frac{\partial}{\partial x}\left(c_1(x)Q_1(x)\right) = \frac{\partial}{\partial x}\left(c(x)Q_1(x)\right) = 0$$

4. Local pick up of the sodium and the water: the concentration of the sodium in the interstitium at depth x consists of the water flux and the sodium flux at depth of x. Thus, for the single nephron model, we have:

$$f^*_{\mathrm{Na}} = c(x)(f_{H2O})_1(x)$$

The above shows the equations for the single nephron model. For the nephron model with a density distribution, those equations are similar. Except we need to express the flux of water and sodium with the distribution function. Now we define the density function of the nephron population to be:

$$\text{number of loops with L in the interval } (L_1, L_2) = \int_{L_1}^{L_2} \rho(L)dL$$

Next, we give two different models for the nephron distribution. When calculating the concentration in the interstitium, the first model only considers the flux from the DLH while the second model also considers the water flux from the collecting conduct. Thus, we would expect the first model gives a bigger $c(x)$ because there is less water in the interstitium. In the result section, we will show a more detailed numerical solution.
Case 1: Ignoring $\left(f_{\mathrm{H_2O}}\right)_3(x)$ into the contribution of $c(x)$:

$$c(0) = c_0$$
$$\frac{\partial Q_1}{\partial x}(x, L) + \left(f_{H_2\mathrm{O}}\right)_1(x, L) = 0$$
$$\frac{\partial}{\partial x}\left(c_1(x)Q_1(x, L)\right) = \frac{\partial}{\partial x}\left(c(x)Q_1(x, L)\right) = 0$$
$$c(L)Q_1(L, L) = f^*_{\mathrm{Na}}L + Q_1(L, L)c^*$$
$$c(x)\int_x^{L_{\max}} \left(\left(f_{H_2\mathrm{O}}\right)_1(x)\right)(x, L)\rho(L)\mathrm{dL} = f^*_{\mathrm{Na}}\int_x^{L_{\max}} \rho(L)\mathrm{dL}$$

Case 2: Considering $\left(f_{\mathrm{H_2O}}\right)_3(x)$ into the contribution of $c(x)$:

$$c(0) = c_0$$
$$\frac{\partial Q_1}{\partial x}(x, L) + \left(f_{H_2\mathrm{O}}\right)_1(x, L) = 0$$
$$\frac{\partial}{\partial x}\left(c(x)Q_1(x, L)\right) = 0$$
$$c(L)Q_1(L, L) = f^*_{\mathrm{Na}}L + Q_1(L, L)c^*$$
$$c(x)\int_x^{L_{\max}} \left(\left(f_{H_2\mathrm{O}}\right)_1(x)\right)(x, L)\rho(L)\mathrm{dL} + c(x)\left(f_{H_2\mathrm{O}}\right)_3(x) = f^*_{\mathrm{Na}}\int_x^{L_{\max}} \rho(L)\mathrm{dL}$$
$$\frac{\partial}{\partial x}\left(c(x)Q_3(x, L)\right) = 0$$
$$c^*\int_0^{L_{\max}} Q_1(L, L)\rho(L)\mathrm{dL} = c_0Q_3(0)$$

The solutions for each case are:
Case 1:

$$c(X) = c_0 \exp\left(\int_0^X \frac{\int_x^{L_{\max}} \rho(L)\mathrm{dL}}{\int_x^{L_{\max}} \frac{L\rho(L)}{1-\frac{c^*}{c(L)}}\mathrm{dL}}\mathrm{dx}\right) \tag{1}$$

In the limiting case when $c^* << c(L)$, we have:

$$c(X) = c_0 \exp\left(\int_0^X \frac{\int_x^{L_{\max}} \rho(L)\mathrm{dL}}{\int_x^{L_{\max}} \rho(L)L\mathrm{dL}}\mathrm{dx}\right) \tag{2}$$

Case 2:

$$c(X) = c_0 \exp\left(\int_0^X \frac{\int_x^{L_{\max}} \rho(L)\mathrm{dL}}{\int_x^{L_{\max}} \frac{L\rho(L)}{1-\frac{c^*}{c(L)}}\mathrm{dL} + \int_0^{L_{\max}} \frac{\left(\frac{c^*}{c(L)}\right)L\rho(L)}{1-\frac{c^*}{c(L)}}\mathrm{dL}}dx\right) \tag{3}$$

3 Numerical Methods

The quadrature rules are used to approximate the integration. Two quadrature rules are discussed blow: one is Trapezoidal rule and and another one is midpoint rule. Their formulas are listed below:

- Tropezoidal: $\int_a^b f(x)\mathrm{dx} \approx \Delta x \left(\frac{1}{2}f(a) + f(a+\Delta x) + \cdots + f(b-\Delta x) + \frac{1}{2}f(b)\right)$
- Midpoint Rule: $\int_a^b f(x)\mathrm{dx} \approx \Delta x(f(a+\Delta x/2) + f(a+3\Delta x/2) + \cdots + f(b-3\Delta x/2) + f(b-\Delta x/2))$

The midpoint rule was chosen in this project because one glitch when using the trapezoidal rule. This is when we consider evaluating $c(L_{max})$, the numerator and denominator are both 0. One can solve this problem by using L'Hôpital's rule. Since we are numerical dealing with any density function ρ, we choose to avoid this problem by choosing midpoint rule so we will never have this problem. All Equations, Equation 1, Equation 2, Equation 3 all have to evaluate the integral of the following form:

$$\int_0^X \frac{\int_x^{L_{\max}} f(L)\mathrm{dL}}{\int_x^{L_{\max}} g(L)\mathrm{dL}}\mathrm{dx}$$

By setting $A = \Delta x \begin{bmatrix} 1 & 1 & \cdots & 1 \\ & 1 & \ddots & 1 \\ & & \ddots & \vdots \\ & & & 1 \end{bmatrix}, F = \begin{bmatrix} f(\Delta x/2) \\ f(3\Delta x/2) \\ \vdots \\ f\left(L_{\max} - \Delta x/2\right) \end{bmatrix}, G = \begin{bmatrix} g(\Delta x/2) \\ g(3\Delta x/2) \\ \vdots \\ g\left(L_{\max} - \Delta x/2\right) \end{bmatrix}$ which A is a n by n matrix. F and G are all n by 1 column vector. Then the above double integral can be approximated as:

```
sum((A*F)./(A*G))*dx
```

From this expression, we can see the operation count actually is $O(n^2)$ because it involves the matrix vector product. We can reduce the operation count to $O(n)$ by the following way:

```
function S = midpoint(c0,fLL,gLL,h)
% swiping from the right to left
fLL = flip(fLL); gLL = flip(gLL);
uppint = cumsum(fLL)*h;
lowint = cumsum(gLL)*h;
Inner = uppint./(lowint);
Inner = flip(Inner);
S = c0*exp(cumsum(Inner)*h);
end
```

In this code, `fLL` represents the $f(LL)$ where LL are our mesh points. `gLL` represents $g(LL)$. And `h` is the mesh-width. From the above code, we can see that we reverse the order of summation in the inner integral. Thus, when we evaluate the next value in the outer integral, we can use the information we have already

calculated before instead of calculating them again.

To solve Equation 3, fix point iteration is been used to repeated approximate the solution. Given a initial guess $c(LL)$, we can calculate the right hand side using this guess. Then we plug in the new value to calculate it again. This process is repeated until the desired accuracy is achieved. The code for this process can be written as:

```
for i = 1:maxInter
thirdint = sum(((cstar./c).*LL.*rho(LL))./(1-cstar./c))*h;
c = midpoint(c0,f(LL),g(c,LL),thirdint,h);
end
```

Where the variable `thirdint` is the integral value $\int_x^{L_{\max}} \frac{L\rho(L)}{1-\frac{c^*}{c(L)}} \mathrm{dL}$.

4 Results

Uniform distribution case: $\rho(L) = \rho_0$ be constant. Considering c^* very small case(Equation 2), ρ is constant under this condition. From assumption 1, the concentration at X can be calculated as:

$$c(X) = c_0 \left(\frac{L_{\max} + X}{L_{\max}} \right)^2$$

At $L_{\max}$ we get the urine concentration.

$$c\left(L_{\max}\right) = 4c_0 > \mathrm{ec}_0$$

this tells us even the uniform distribution can be larger than the single nephron model.

Now we consider the density function $\rho(x)$ has the following form:

$$\rho(L) = \rho_0 \left(L_{\max} - L\right)^p$$

The initial value ρ_0 does not matter as it is canceled out in the numerator and denominator. Again, in the limiting when $c^* << c(L)$, we can calculate $c(x)$ by hand, the result is:

$$c(X) = c_0 \exp\left(\frac{(2+p)\left(-\log\left[L_{\max}\right] + \log\left[L_{\max} + X + pX\right]\right)}{1+p} \right)$$

In the case of $p = 0$, we recover the result from the uniform distribution as discussed before. In this case, we can calculate the exact solution and the numerical solutions as shown in Figure 2 with $p = 1$.

Especially, at $X = L_{\max}$:

$$c\left(L_{\max}\right) = (2+p)^{\frac{2+p}{1+p}} c_0$$

From this expression, we can see that we can make the $\left[\mathrm{Na}^+\right]$concentration in the urine arbitrary big with our choice of p. This is not the case, however, if we take into the geometric consideration. Consider the number of nephron presented within a radius r ball:

$$\text{number of nephron} = \int_{L_{\max}-r}^{L_{\max}} \rho_0 \left(L_{\max} - L\right)^p \mathrm{dL} \sim r^3$$

Thus, a reasonable choice would be $p = 2$ when the geometry is considered. In this case, the ratio is approximately 6.35 which is larger than when $p = 1$. Testing on this problem, we have the relationship between the error and the mesh width h is shown in Figure 3. The following is the fitting of errors and the mesh widths h, it shows that our implementation of integration is only first order accurate.

```
fit(hs', errors','power1')

ans =

General model Power1:
ans(x) = a*x^b
Coefficients (with 95% confidence bounds):
a =       7.717  (7.703, 7.731)
b =      0.9985  (0.9982, 0.9989)
xlabel('h'); ylabel('error');
```

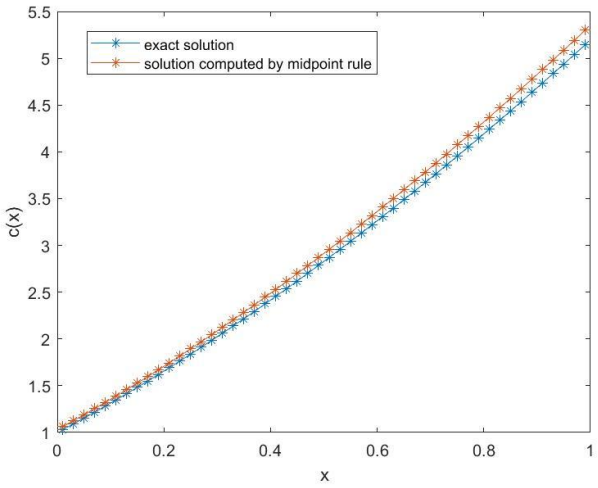

Figure 2: The exact solution and the approximated solution with 100 mesh points(Equation 2)

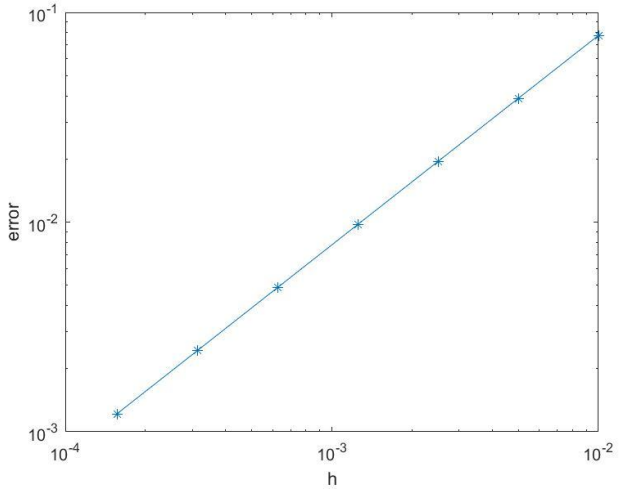

Figure 3: The relationship between the error and the meshwidth h

As for solving Equation 3 which corresponds to the case 2, choosing $p = 2$ with the initial guess being the approximating case $c^* << c(L)$, the $c(x)$ in each iteration is shown in Figure 4. Figure 5 shows the error to the exact solution with respect to each iteration. The exact result was chosen with respect to an iteration

number so large that the error is below the machine precision. From Figure 5, the linear convergence is observed for the fix point iteration.

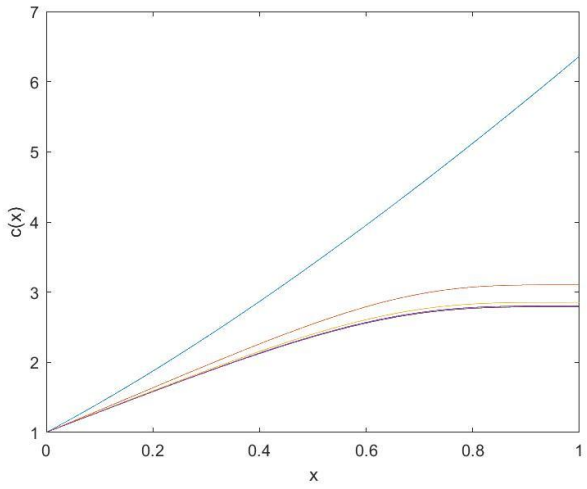

Figure 4: Solving Equation 3, $c(x)$ in each iterations

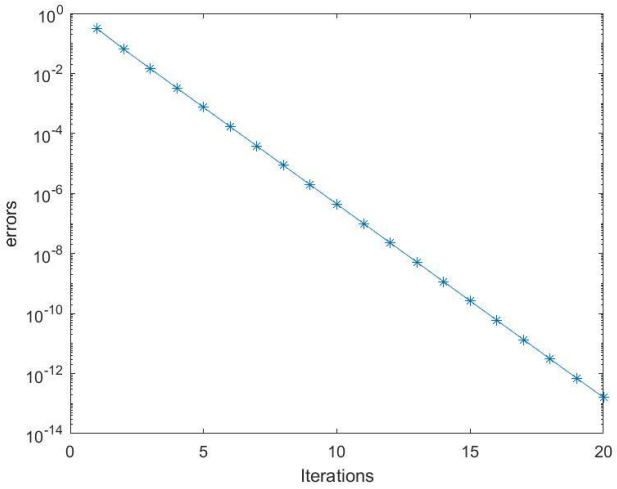

Figure 5: Error with respect to each iterations

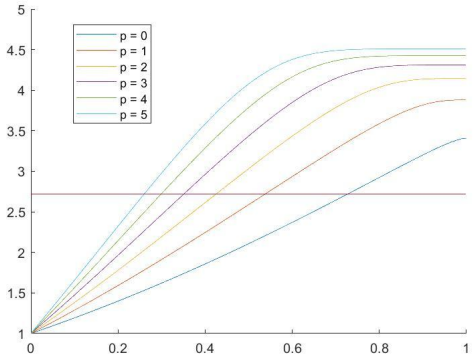

Figure 6: $c^* = 0.1c(0)$

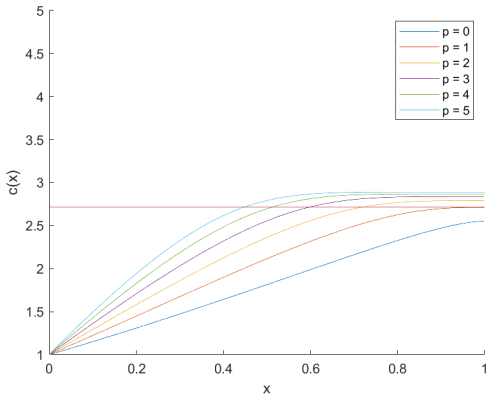

Figure 7: $c^* = 0.3c(0)$

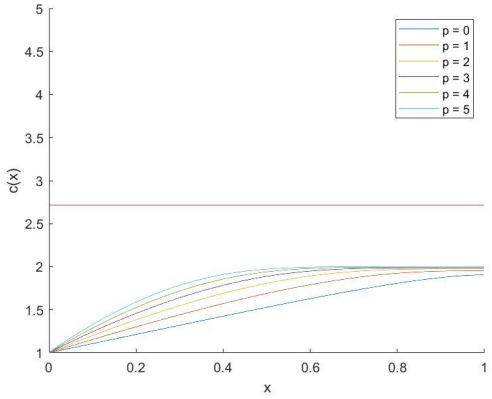

Figure 8: $c^* = 0.5c(0)$

Figure 6, Figure 7, Figure 8 show the profile $c(x)$ under different p values with Equation 3. The straight line shows the value of e. As we can see from the graph, when the target concentration value c^* is small, the nephron can create more concentrated urine.

5 Conclusion

In this project, three different models: single nephron model, nephron model with distribution profile with water flux(case 1) from CT considered and not considered are considered(case 2) are discussed. The urine concentration in the single nephron model cannot exceed the factor e while the other two models do not have this kind of limitation. However, for case 2 where the water flux from the CT is considered, the concentration in the urine is significantly smaller than case 1 when we do not consider the water flux from the CT. This can be explained as the water from the CT dilutes the urine and thus cannot produce concentrated urine. Moreover, we have also shown the numerical method to solve this problem with any given density distribution $\rho(x)$ by using the midpoint quadrature rule and the fix point iteration. The fix point iteration helps us to solve the equation even if $c(x)$ is involved in the integral.

6 Reference

The model is described in Chapter 4 of the book: Hoppensteadt, Frank C., and Charles S. Peskin. Modeling and simulation in medicine and the life sciences. Vol. 10. Springer Science & Business Media, 2012.