Mathematical Modeling in the Kidney: Characterizing a Long-Looped Nephron

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What is this "Kidney" you speak of?

- Production of urine
- Functional unit: Nephron
- Nephron $\rightarrow$ Kidney as the Neuron $\rightarrow$ Brain
Structure of the Long-Looped Nephron

\[ G : \text{Glomerulus, THAL : Thin Ascending Limb, TAL : Thick Ascending Limb, MD : Macula Densa} \]
Purpose
- Regulate chloride concentration

Key Features of Long-Looped Model
- Long-looped nephrons → slightly higher concentrated urine
- Thin ascending limb (THAL)
That’s riveting, but where’s the math?

**Mathematical Analysis**
- Partial Differential Model of Long-Looped Nephron
- Simplify PDE → ODE
- Bifurcation Analysis of the TGF System

**Key Parameters of Analysis**
- **Delay**: TGF time delay ($\tau$)
- **Gain**: TGF sensitivity to signal ($\gamma$)
Chloride and Flow Rate Model Equations

\[ C : \text{Chloride Concentration}, \quad F : \text{Fluid Flow Rate} \]
\[ R : \text{Tubular Radius}, \quad P : \text{Permiability} \]

\[
\pi R^2(x) \frac{\partial}{\partial t} C(x, t) = -F(t) \frac{\partial}{\partial x} C(x, t)
- \pi R(x) \left( \frac{V_{\text{max}}(x) C(x, t)}{K_M + C(x, t)} + P(x)(C(x, t) - C_e(x)) \right) \quad \text{(Conservation)}
\]

\[
F(t) = 1 + K_1 \tanh(K_2(C_{ss} - C(1, t - \tau))) \quad \text{(TGF Response)}
\]
Derivation of the Characteristic Equation

Model equations for $C(x, t)$ and $F(t)$

⇓

Nondimensionalization

⇓

Linearization; $C(x, t) = S(x) + \epsilon D(x, t)$

⇓

Separation of Variables; $D(x, t) = f(x)e^{\lambda t}$
Characteristic Equation

\( C \) : Chloride Concentration, \( R \) : Tubular Radius
\( S \) : Steady State Chloride Concentration, \( P \) : Permiability

\[
1 = \frac{-\gamma e^{-\lambda \tau}}{R(1)} \int_0^1 R(x) \cdot \exp \left( - \int_x^1 f(R, V_{\text{max}}, S, P, C_e) \, dy \right) \, dx.
\]

Key Parameters

- **Delay** : Time (\( \tau \))
- **Gain** : Sensitivity (\( \gamma \))
- **Solution Behavior** : \( \lambda = \rho + i\omega \) (\( \lambda \in \mathbb{C} \))
- **Real Part** : Growth/Decay (\( \rho \))
- **Imaginary Part** : Frequency (\( \omega \))
Bifurcation Diagram or Rorschach Test?

Bifurcation Diagram

$\rho_6 = 0$

$\rho_5 = 0$

$\rho_4 = 0$

$\rho_3 = 0$

$\rho_2 = 0$

$\rho_1 = 0$

$\rho_n < 0$
Long-Loop vs. Short-Loop Bifurcation
## Varying Lengths of Model THAL

<table>
<thead>
<tr>
<th>Case</th>
<th>THAL Length (cm)</th>
<th>TAL Length (cm)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Case</td>
<td>0.125</td>
<td>0.5</td>
<td>.25:1</td>
</tr>
<tr>
<td>Case 1</td>
<td>0.25</td>
<td>0.5</td>
<td>.5:1</td>
</tr>
<tr>
<td>Case 2</td>
<td>0.5</td>
<td>0.5</td>
<td>1:1</td>
</tr>
<tr>
<td>Case 3</td>
<td>1.0</td>
<td>0.5</td>
<td>2:1</td>
</tr>
</tbody>
</table>
Bifurcation Variance in Model Cases

Base Case (.25:1)

- $\rho_6 = 0$
- $\rho_5 = 0$
- $\rho_4 = 0$
- $\rho_3 = 0$
- $\rho_2 = 0$
- $\rho_1 = 0$
- $\rho_n < 0$

Case 3 (2:1)

- $\rho_6 = 0$
- $\rho_5 = 0$
- $\rho_4 = 0$
- $\rho_3 = 0$
- $\rho_2 = 0$
- $\rho_1 = 0$
- $\rho_n < 0$

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But what does it all mean?!

**Bifurcation Analysis**
- Higher tendency towards oscillatory solutions in Long Loop vs. Short Loop
- Within Long Loop, longer THAL $\Rightarrow$ more stable TGF system

**What’s Next?**
- Numerical analysis of full model equations
- Verify bifurcation analysis results
Thank you!
Any Questions?

Slides and references are available upon request: