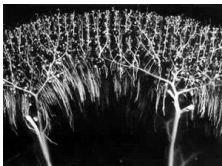


Well-posedness and qualitative properties of a kidney model

Magali Tournus, directed by Benoît Perthame, Aurelie Edwards, Nicolas Seguin

January 18, 2012



The kidney

Study of a simplified model

Well posedness and basic properties

The role of the pump

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- ▶ Blood composition has to stay constant in the body

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- ▶ Blood composition has to stay constant in the body
- ▶ The food intake vary (they depend on time, on each individual,..)

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- ▶ Blood composition has to stay constant in the body
- ▶ The food intake vary (they depend on time, on each individual,..)
- ▶ By filtering blood, kidney regulates homeostatsy

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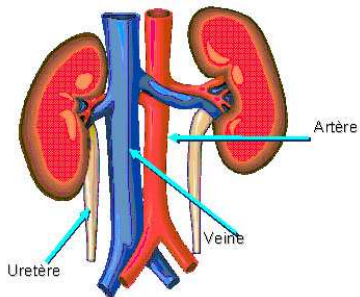


Figure:

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The concentrating mechanism

Exchanges of solutes between the tubes makes the solute concentration varying.

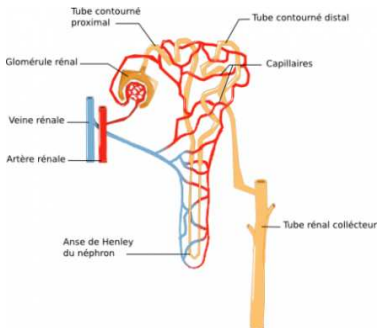


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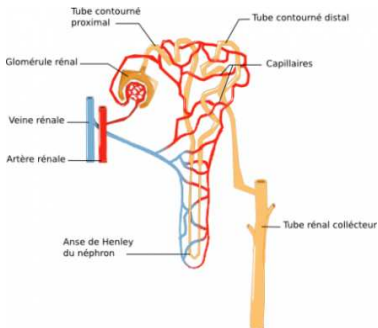


Figure:

Physiological attempts : At equilibrium, we expect a liquid with a high concentration “down below”.

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Study a simplified model to understand the mathematical problems underlying more realistic models

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- ▶ We suggest to consider a dynamic problem which would relax to the equilibrium

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- ▶ The biologists were interested in the equilibrium (lot of references in the domain)
- ▶ We suggest to consider a dynamic problem which would relax to the equilibrium
- ▶ They were Ok

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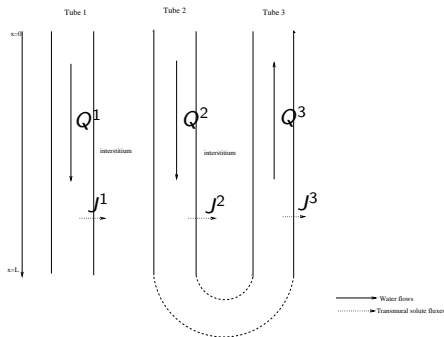


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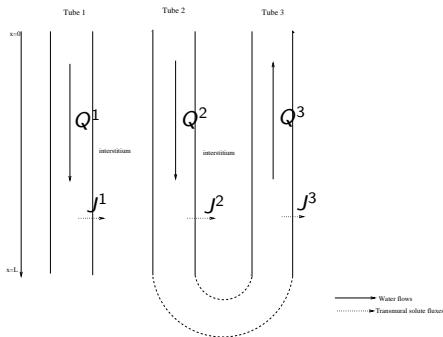


Figure:

- ▶ 3 tubes, with a specific architecture, are bathing in a common interstitium

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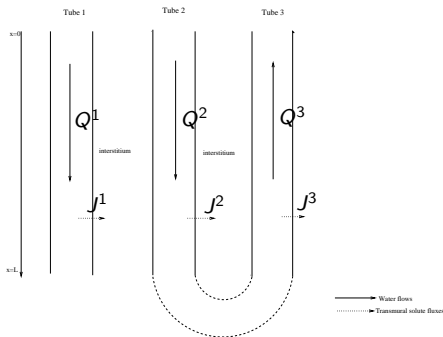


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- ▶ 3 tubes, with a specific architecture, are bathing in a common interstitium
- ▶ A fluid circulates in the tubes

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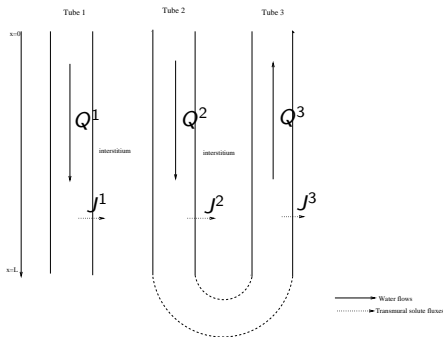


Figure:

- ▶ 3 tubes, with a specific architecture, are bathing in a common interstitium
- ▶ A fluid circulates in the tubes
- ▶ C is concentration of a solute dissolved in the fluid (it can be any intensive quantity)

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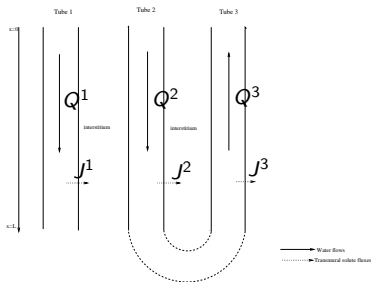


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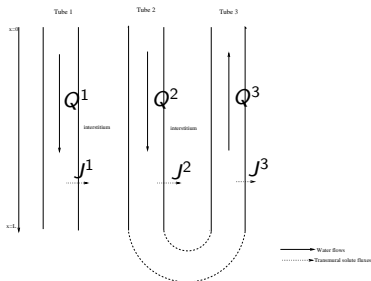


Figure:

Assumptions:

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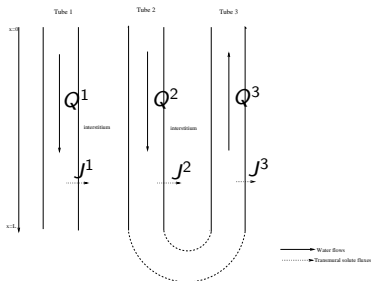


Figure:

Assumptions:

- ▶ Tubes are water impermeable
- ▶ Solute movements across the wall tubes is driven by

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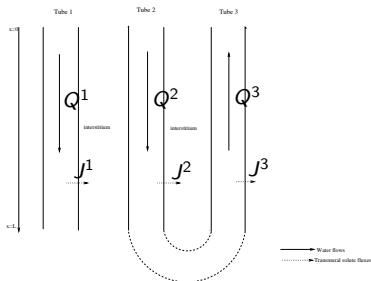


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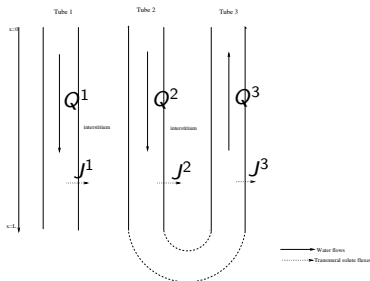


Figure:

Assumptions:

- ▶ Tubes are water impermeable
- ▶ Solute movements across the wall tubes is driven by
 1. solute diffusion
 2. solute active transport in tube 3 : a pump extracts solute from tube 3 to the intersitium

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The equations

$$\left\{ \begin{array}{l} Q^1 \frac{dC^1(x)}{dx} = J^1(x), \quad x \in [0, L], \\ Q^2 \frac{dC^2(x)}{dx} = J^2(x), \quad x \in [0, L], \\ Q^3 \frac{dC^3(x)}{dx} = J^3(x), \quad x \in [0, L], \\ C^1(0) = C_0^1, \quad C^2(0) = C_0^2, \quad C^3(L) = C^2(L), \end{array} \right.$$

C_0^1 et C_0^2 : Solute concentration at the inlet

Q^i : Water flow in tube i

J^i : Solute flux across wall tube i .

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Fluxes

$$J^1(x) = P^1(x)(C^{int}(x) - C^1(x)),$$

$$J^2(x) = P^2(x)(C^{int}(x) - C^2(x)),$$

$$J^3(x) = P^3(x)(C^{int}(x) - C^3(x)) - F(C^3(x), x),$$

P^i : Solute permeability of i

C^{int} : Interstitial concentration

$F(C^3, x) > 0$: Active transport
with the condition

$$J^1(x) + J^2(x) + J^3(x) = 0.$$

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with the condition

$$J^1(x) + J^2(x) + J^3(x) = 0.$$

- ▶ There is no solute accumulation in the interstitium
- ▶ This condition enables us to calculate C^{int} .

Assumptions on the non-linearity

$$F(C^3, x) \geq 0, \quad F(0, x) = 0, \quad 0 \leq F_C(C^3, x) \leq \mu(x). \quad (1)$$

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- ▶ The pump can only transport the solute in one direction : from tube 3 to the intersitium

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- ▶ The pump can only transport the solute in one direction : from tube 3 to the intersitium
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- ▶ The pump can be saturated

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Example: A Michaelis-Menten type non-linearity

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Example: A Michaelis-Menten type non-linearity

$$F(C^3, x) = V(x) \frac{C^3}{1 + C^3}.$$

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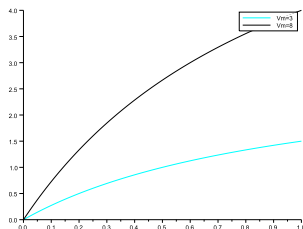


Figure:

The stationary and dynamic systems

The stationary system

$$\left\{ \begin{array}{l} \frac{dC^1(x)}{dx} = \frac{1}{3} [C^1(x) + C^2(x) + C^3(x) + F(C^3(x), x)] - C^1(x), \\ \frac{dC^2(x)}{dx} = \frac{1}{3} [C^1(x) + C^2(x) + C^3(x) + F(C^3(x), x)] - C^2(x), \\ -\frac{dC^3(x)}{dx} = \frac{1}{3} [C^1(x) + C^2(x) + C^3(x) + F(C^3(x), x)] - C^3(x) - F(C^3(x), x), \\ C^1(0) = C_0^1, \quad C^2(0) = C_0^2, \quad C^3(L) = C^2(L). \end{array} \right. \quad (2)$$

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The dynamic system $t \geq 0$ et $x \in [0, L]$,

$$\left\{ \begin{array}{l} \frac{\partial C^1}{\partial t} + \frac{\partial C^1}{\partial x} = \frac{1}{3} [C^1 + C^2 + C^3 + F(C^3, x)] - C^1, \\ \frac{\partial C^2}{\partial t} + \frac{\partial C^2}{\partial x} = \frac{1}{3} [C^1 + C^2 + C^3 + F(C^3, x)] - C^2, \\ \frac{\partial C^3}{\partial t} - \frac{\partial C^3}{\partial x} = \frac{1}{3} [C^1 + C^2 + C^3 + F(C^3, x)] - C^3 - F(C^3, x), \\ C^1(0, t) = C_0^1, \quad C^2(0, t) = C_0^2, \quad C^3(L, t) = C^2(L, t), \end{array} \right. \quad (3)$$

with initial conditions : $C^1(x, 0)$, $C^2(x, 0)$, $C^3(x, 0)$.

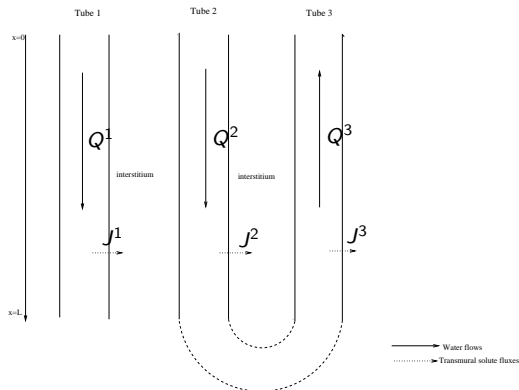
Main results

Theorem (Existence of a stationary solution)

Under assumptions (1), there is a weak solution to (5), and it is positive.

Theorem (Existence and uniqueness of the dynamic problem solution)

There is a unique weak solution to the initial value problem (3), which lies in $BV([0, L] \times [0, T])$.



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Existence of a stationary solution

Sketch of the proof:

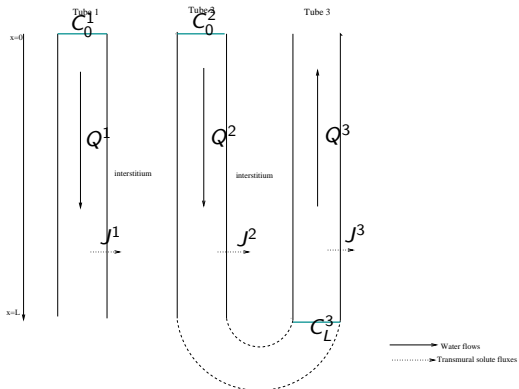


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Existence of a stationary solution

- For all $\alpha > 0$, there exists a solution in $(C[0, L])^3$ to the system

$$\left\{ \begin{array}{l} \frac{dC^1(x)}{dx} + \frac{2}{3}C^1(x) + \alpha C^1(x) = \frac{1}{3} [C^2(x) + C^3(x) + F(C^3(x), x)], \\ \frac{dC^2(x)}{dx} + \frac{2}{3}C^2(x) + \alpha C^2(x) = \frac{1}{3} [C^1(x) + C^3(x) + F(C^3(x), x)], \\ -\frac{dC^3(x)}{dx} + \frac{2}{3} [C^3(x) + F(C^3(x), x)] = \frac{1}{3} [C^1(x) + C^2(x)], \\ C^1(0) = C_0^1 > 0, \quad C^2(0) = C_0^2 > 0, \quad C^3(L) = C_L^3 \geq 0. \end{array} \right.$$

Tool : Banach Picard theorem

Existence of a stationary solution

Sketch of the proof:

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Tool : Banach Picard theorem

- ▶ Compactness of the family $(C_\alpha^1, C_\alpha^2, C_\alpha^3) \Rightarrow$ After extraction, the sequence converges toward a solution to

$$\left\{ \begin{array}{l} \frac{dC^1(x)}{dx} + \frac{2}{3}C^1(x) = \frac{1}{3} [C^2(x) + C^3(x) + F(C^3(x), x)], \\ \frac{dC^2(x)}{dx} + \frac{2}{3}C^2(x) = \frac{1}{3} [C^1(x) + C^3(x) + F(C^3(x), x)], \\ -\frac{dC^3(x)}{dx} + \frac{2}{3} [C^3(x) + F(C^3(x), x)] = \frac{1}{3} [C^1(x) + C^2(x)], \\ C^1(0) = C_0^1 > 0, \quad C^2(0) = C_0^2 > 0, \quad C^3(L) = C_L^3 \geq 0. \end{array} \right.$$

Existence of a stationary solution



$$\left\{ \begin{array}{l} \frac{dC^1(x)}{dx} + \frac{2}{3}C^1(x) = \frac{1}{3} [C^2(x) + C^3(x) + F(C^3(x), x)], \\ \frac{dC^2(x)}{dx} + \frac{2}{3}C^2(x) = \frac{1}{3} [C^1(x) + C^3(x) + F(C^3(x), x)], \\ -\frac{dC^3(x)}{dx} + \frac{2}{3} [C^3(x) + F(C^3(x), x)] = \frac{1}{3} [C^1(x) + C^2(x)], \\ C^1(0) = C_0^1 > 0, \quad C^2(0) = C_0^2 > 0, \quad C^3(L) = C_L^3 \geq 0. \end{array} \right.$$

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$$g : C_L^3 \mapsto C^2(L) - C^3(L)$$

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We have $\{g(0) > 0, \text{ and } C_L^3 \gg 1 \Rightarrow g(C_L^3) < 0\} \Rightarrow g \text{ cancels on } \mathbb{R}^+.$

□

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- ▶ Compact embedding $BV([0, T] \times [0, L]) \subset L^1((0, T) \times (0, L)) \Rightarrow$ Extraction of a subsequence which converges to C .

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- ▶ Compact embedding $BV([0, T] \times [0, L]) \subset L^1((0, T) \times (0, L)) \Rightarrow$ Extraction of a subsequence which converges to C .
- ▶ The limit function C is a weak solution (3).

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Uniqueness of the dynamic problem solution

$$C^i(t=0) \geq 0, \quad C^i(t=0) \in L^1(0, L), \quad \frac{d}{dx} C^i(t=0) \in L^1(0, L). \quad (4)$$

Theorem (Contraction principle)

If $C(x, 0)$ et $\tilde{C}(x, 0)$ are two initial conditions, then the weak solutions satisfy

$$\int_0^L [|C^1 - \tilde{C}^1| + |C^2 - \tilde{C}^2| + |C^3 - \tilde{C}^3|](x, t) dx \leq \int_0^L [|C^1 - \tilde{C}^1| + |C^2 - \tilde{C}^2| + |C^3 - \tilde{C}^3|](x, 0) dx,$$

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Sketch of the proof:

- ▶ If C et \tilde{C} are two solutions to (3), we define

$$d^i(x, t) := |C^i(x, t) - \tilde{C}^i(x, t)|, \quad i = 1, 2, 3.$$

$$G(x, t) := |F(C^3(x, t), x) - F(\tilde{C}^3(x, t), x)| \leq \mu(x) d^3(x, t).$$

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- ▶ We subtract the equations on C and \tilde{C} .

We multiply each line by $\text{sign}(C^i(x, t) - \tilde{C}^i(x, t))$

- ▶ We obtain

$$\begin{cases} \frac{\partial d^1}{\partial t} + \frac{\partial d^1}{\partial x} \leq -\frac{2}{3}d^1 + \frac{1}{3}(d^2 + d^3 + G), \\ \frac{\partial d^2}{\partial t} + \frac{\partial d^2}{\partial x} \leq -\frac{2}{3}d^2 + \frac{1}{3}(d^1 + d^3 + G), \\ \frac{\partial d^3}{\partial t} - \frac{\partial d^3}{\partial x} \leq -\frac{2}{3}(d^3 + G) + \frac{1}{3}(d^2 + d^1). \end{cases}$$

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- ▶ Summing the line and integrating over $[0, L]$,

$$\frac{d}{dt} \int_0^L [d^1 + d^2 + d^3] dx \leq -d^1(L, t) - d^3(0, t) \leq 0,$$

□

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Convergence of the dynamical solution toward stationary state

Theorem (Long time behavior and uniqueness of the stationary problem solution)

The solution C to the dynamic system converges to the unique solution \bar{C} to the stationary system in L^1 ,

$$\|C(x, t) - \bar{C}(x)\|_{L^1} \underset{t \rightarrow \infty}{\searrow} 0.$$

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- ▶ We construct super solution to (5) as large as wanted

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- ▶ We prove that when the initial condition is a super/sub solution to the stationary state, the dynamic profile is monotonic in time for all x and converge to the steady state

Convergence of the dynamical solution toward stationary state

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- ▶ We prove that when the initial condition is a super/sub solution to the stationary state, the dynamic profile is monotonic in time for all x and converge to the steady state
- ▶ 0 is a subsolution
- ▶ We stuck every initial condition between 0 and a super solution.

Numerical method

These results give us that

- ▶ There is a unique solution to the stationary system
- ▶ We can efficiently approach this solution by solving the dynamic problem and let the time evolve

We use a finite-volume type scheme.

The CFL condition :

$$\Delta t \leq \frac{3\Delta x}{3 + 2\Delta x + 2\Delta x V}.$$

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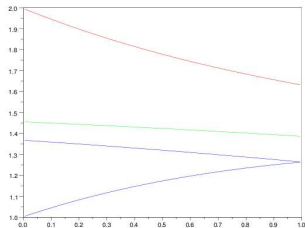
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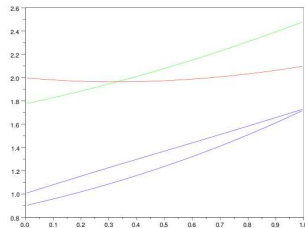
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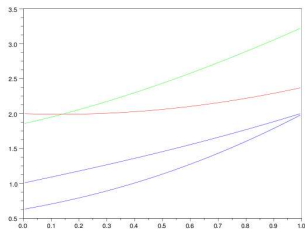
The role of the pump



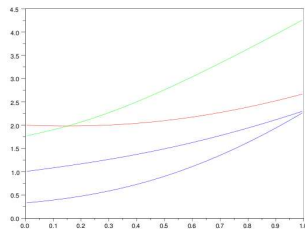
($V_m=0$)



($V_m=3$)



($V_m=5$)



($V_m=8$)

The role of the pump

- ▶ The concentration increases in all tubes along the axis of x
- ▶ In kidney, the concentration at point $x = L$ is important : it is the point at which urine concentration is determined

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The role of the pump

- ▶ The concentration increases in all tubes along the axis of x
- ▶ In kidney, the concentration at point $x = L$ is important : it is the point at which urine concentration is determined

We want to identify the profile of C when $V \rightarrow \infty$.

$$\left\{ \begin{array}{l} \frac{dC^1(x)}{dx} = \frac{1}{3} \left[C^1(x) + C^2(x) + C^3(x) + V \frac{C^3(x)}{1 + C^3(x)} \right] - C^1(x), \\ \frac{dC^2(x)}{dx} = \frac{1}{3} \left[C^1(x) + C^2(x) + C^3(x) + V \frac{C^3(x)}{1 + C^3(x)} \right] - C^2(x), \\ -\frac{dC^3(x)}{dx} = \frac{1}{3} \left[C^1(x) + C^2(x) + C^3(x) + V \frac{C^3(x)}{1 + C^3(x)} \right] - C^3(x) - V \frac{C^3(x)}{1 + C^3(x)}, \\ C^1(0) = C_0^1, \quad C^2(0) = C_0^2, \quad C^3(L) = C^2(L). \end{array} \right. \quad (5)$$

Purpose: Explain the behavior of C_V when $V \rightarrow \infty$

Theorem (Asymptotics)

Solutions to (5) satisfy

$$(C_V^1, C_V^2, C_V^3) \xrightarrow{V \rightarrow +\infty} (C^1, C^2, C^3) \quad L^p(1 \leq p < \infty), \text{ a.e.},$$

$$\left(\frac{dC_V^1}{dx}, \frac{dC_V^2}{dx}, \frac{dC_V^3}{dx}\right) \xrightarrow{V \rightarrow +\infty} (\mu^1, \mu^2, \mu^3) \quad M^1[0, L].$$

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with

$$\begin{cases} C^1(x) = \frac{C_0^1 + C_0^2}{2} + \frac{C_0^1 - C_0^2}{2} e^{-x}, \\ C^2(x) = \frac{C_0^1 + C_0^2}{2} + \frac{C_0^2 - C_0^1}{2} e^{-x}, \\ C^3(x) = 0. \end{cases} \quad \begin{cases} \mu^1 = \frac{1}{2} [(C_0^2 - C_0^1) e^{-x} + B\delta_L], \\ \mu^2 = \frac{1}{2} [(C_0^1 - C_0^2) e^{-x} + B\delta_L], \\ \mu^3 = B\delta_L. \end{cases}$$

where

$$B = \lim_{V \rightarrow \infty} C_V^3(L).$$

A priori bounds and compact embeddings

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A priori bounds and compact embeddings

- ▶ The edges of the domain $C_V^1(L)$ and $C_V^3(0)$ are bounded in L^∞

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A priori bounds and compact embeddings

- ▶ The edges of the domain $C_V^1(L)$ and $C_V^3(0)$ are bounded in L^∞
- ▶ (C_V^i) is bounded in $BV[0, L] \cap L^\infty[0, L]$ and

$$V \|C_V^3\|_{L^1[0, L]} \leq K$$

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- ▶ $L^1[0, L] \subset\subset M^1[0, L] \Rightarrow$ existence of μ

Computation of the limit

From the estimation

$$V \|C_V^3\|_{L^1[0,L]} \leq K$$

we have

$$C^3 = 0.$$

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Computation of the limit

From the estimation

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- ▶ We choose test functions $\phi \in C^1[0, L]$ such that $\phi(0) = \phi(L) = 0$
 $\Rightarrow \mu^3 = 0$ on $]0, L[$.

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- ▶ We choose test functions $\phi \in C^1[0, L]$ such that $\phi(0) = \phi(L) = 0$
 $\Rightarrow \mu^3 = 0$ on $]0, L[$.
- ▶ We choose test functions $\phi \in C^1[0, L] \Rightarrow \mu^3 = B\delta_{x=L} - A\delta_{x=0}$.

Computation of the limit

From the estimation

$$V \|C_V^3\|_{L^1[0,L]} \leq K$$

we have

$$C^3 = 0.$$

- ▶ We choose test functions $\phi \in C^1[0, L]$ such that $\phi(0) = \phi(L) = 0 \Rightarrow \mu^3 = 0$ on $]0, L[$.
- ▶ We choose test functions $\phi \in C^1[0, L] \Rightarrow \mu^3 = B\delta_{x=L} - A\delta_{x=0}$.

with

$$\lim_{V \rightarrow \infty} C_V^3(L) = B \geq 0, \quad \lim_{V \rightarrow \infty} C_V^3(0) = A \geq 0. \quad (6)$$

Then, we prove $A = 0$, report in the system and do “analytical computations”

The boundary layer

To perform numerical simulations, we have to precise the shape of the boundary layer.

Well-posedness and qualitative properties of a kidney model

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The kidney

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The boundary layer

To perform numerical simulations, we have to precise the shape of the boundary layer.

Theorem (The boundary layer)

The limits of the boundary values are

$$C_V^1(L) \xrightarrow{V \rightarrow +\infty} C_0^1 + C_0^2$$
$$C_V^2(L) = C_V^3(L) \xrightarrow{V \rightarrow +\infty} C_0^1 + C_0^2 + (C_0^2 - C_0^1)e^{-L}$$

The behavior of C_V^3 for $x \simeq L$ is given by the inequalities

$$C_V^3(x) \leq C_V^3(L) \exp\left(-\frac{2}{3}VM(L-x)\right) + \frac{K}{V} \left[1 - \exp\left(-\frac{2}{3}VM(L-x)\right)\right]$$

$$C_V^3(x) \geq C_V^3(L) \exp\left(-\frac{2}{3}V(L-x)\right) + \frac{\bar{K}}{V} \left[1 - \exp\left(-\frac{2}{3}V(L-x)\right)\right]$$

Numerical illustrations

The difficulties are : When V grows,

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- ▶ The CFL becomes tougher

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The difficulties are : When V grows,

- ▶ The CFL becomes tougher
- ▶ The number of mesh necessary to see the phenomenon becomes high next to L

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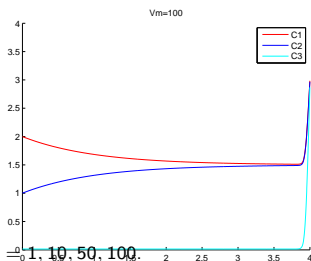
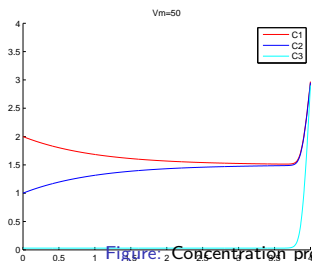
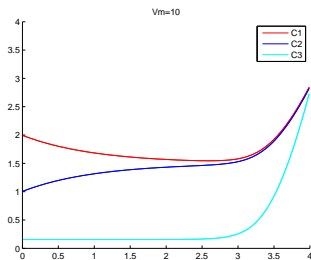
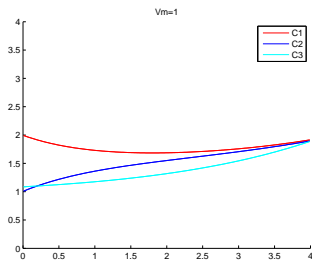


Figure: Concentration profiles for $V = 1, 10, 50, 100$.

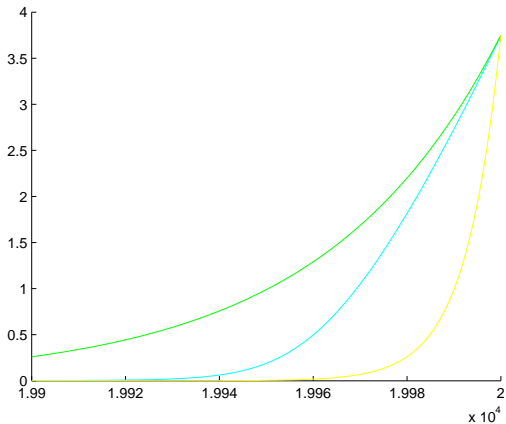
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Perspectives and ongoing projects

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- ▶ We also work on realistic models

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- ▶ We want to study the limit of the system for large L

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