CASE STUDY FROM
BIO-MATHEMATICAL MODELLING

A PHYSIOLOGICAL FLOW PROBLEM

(After Lin and Segel, Chapter 8)

How is water and salt expelled from the body, e.g. from the kidneys?

J. Diamond (1967): Salt is expelled from the body in a *non-direct way* by means of so-called *secondary channels,* which are consistently found in fluid secreting tissue.

- At the inner end of the secondary channels *chemical pumps* enter salt into the channel leading to a local high concentration of salt, and a salt concentration gradient towards the opening of the channels

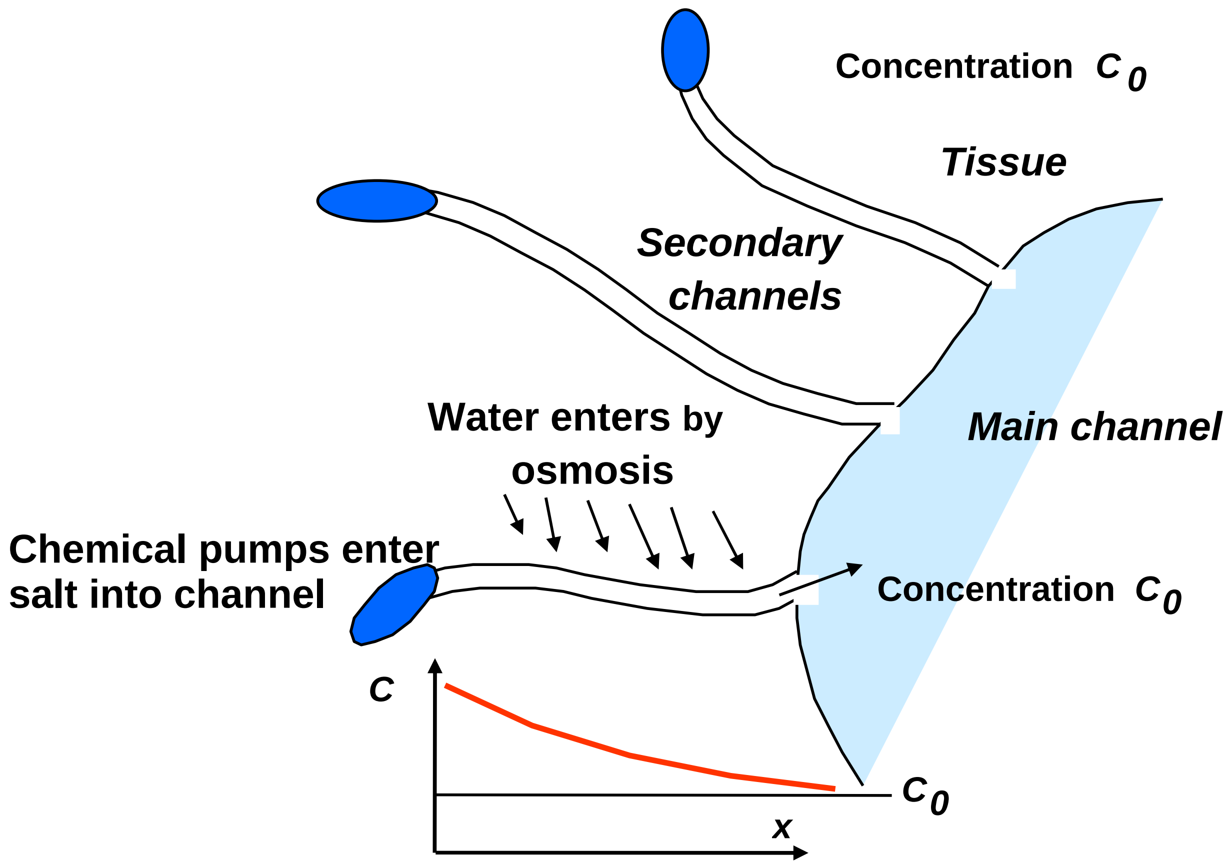
- ***Water*** enters the channel by *osmosis* through the walls

- ***Salt*** is moving in the channel by *diffusion* and *convection*

- At the outer end of the channel, the salt concentration is C_0 (body average)

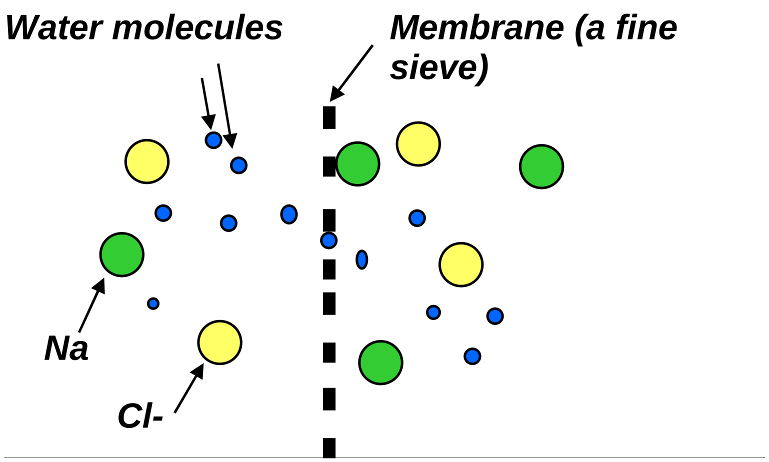
What determines the amount of salt coming out of the secondary channel under stationary (time independent) conditions?

QUALITATIVE MODEL



PHYSICAL MECHANISMS

OSMOSIS:



Salt ions are too large to pass through the membrane!

If the ion concentrations on each side of the membrane are C_1 and C_2, then the amount of water passing through the membrane per area and time units is

$$J = P(C_2 - C_1)$$

The constant *P* is called the ***permeability*****.**

$$J = P(C_2 - C_1)$$

Units:

$$[J] = \frac{Volume}{Area \times Time} = \frac{m^3}{m^2 s} = \frac{m}{s} \quad \text{(Same unit as velocity!)}$$

$$[C] = \frac{\text{\#ions}}{\text{Volume}} = \frac{osmol}{m^3}, \; (osmol = \text{Avogadro's number})$$

$$[P] = \frac{m/s}{osmol/m^3} = \frac{m^4}{osmol \cdot s}$$

(Note since the concentration of ions is about twice the concentration of salt, we may just as well think of *C* as the salt concentration)

DIFFUSION

Motion of salt in an otherwise stationary solution is due to concentration differences:

$$F = -D\frac{\partial C}{\partial x}$$

F is called the ***flux*** of salt *(*in the *x*-direction).

$\partial C / \partial x$ is the ***concentration gradient***.

D is called the ***diffusion coefficient****.*

Flux (in general a vector quantity!) is *amount passing through an imaginary surface in the fluid per time and area unit.* Units:

$$[F] = \frac{amount}{area \times time} = \frac{\mathrm{osmol}}{\mathrm{m^2 s}}$$

$$[C] = \frac{amount}{volume} = \frac{\mathrm{osmol}}{\mathrm{m^3}}$$

$$[D] = \frac{\mathrm{m^2}}{\mathrm{s}}$$

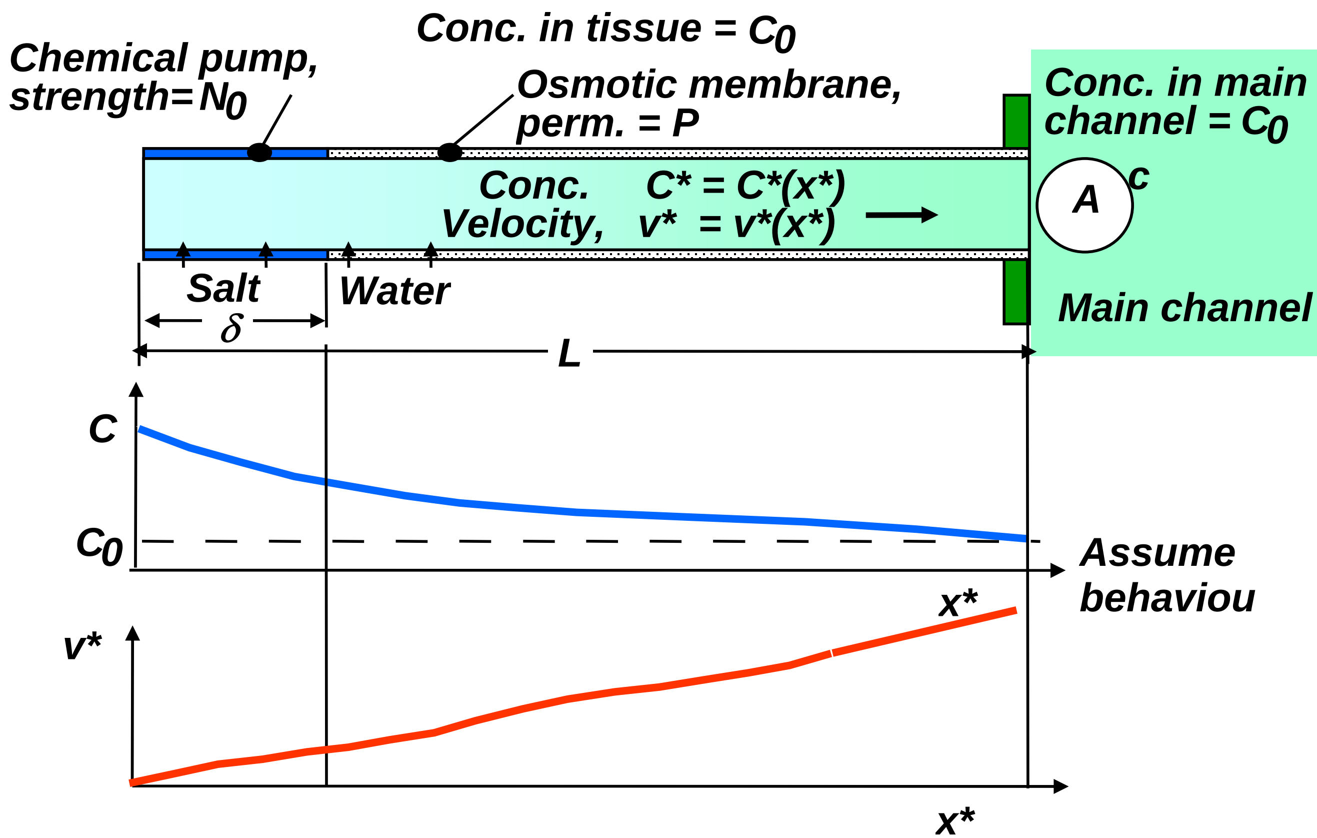
CHEMICAL PUMPS

Enter salt into the solution from the tissue by means of certain chemical mechanisms using energy (details not known!)

$$[N_0] = \frac{Amount}{Unit\ area\ wall \times time} = \frac{\text{osmol}}{\text{m}^2\text{s}}$$

THE NEXT STEP IS DEFINING THE GEOMETRY:

- The channels are *long and narrow*. Thus, we consider a 1d model.
- The inner end of the channel is closed.



Length: L

Cross sectional area: A

Circumference: c

Active zone for chemical pumps: δ

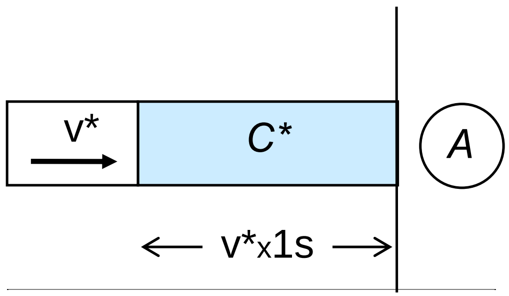
Water entering the channel through osmosis (per area unit):

$$J = P\left[C^*(x^*) - C_0\right]$$

Transport of salt in the channel:

A. Diffusion: $$F_D = -D dC^* / dx^*$$

B. Convection: *Passive transport due to the motion of the fluid*



$$F_c = \frac{v^* \cdot 1s \cdot A \cdot C^*}{A \cdot 1s} = v^* C^*$$

Total flux:

$$F^* = F_D + F_c = v^* C^* - D\frac{dC^*}{dx^*}$$

Chemical pumps (we do not include the end): $N_0(\delta c)$

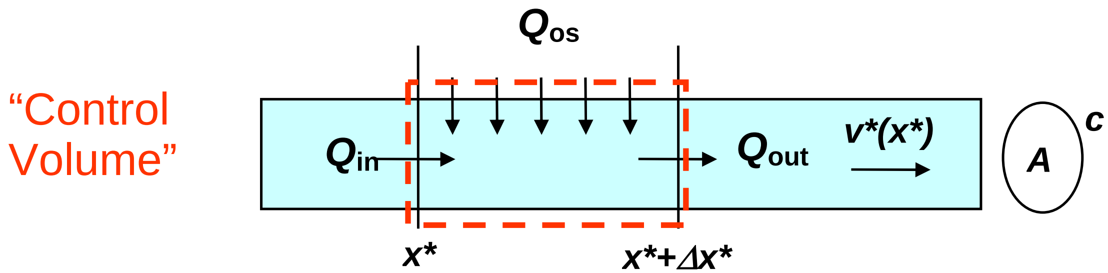
The problem presented to us is to determine the *emergent osmolarity* defined by $F^*(L) = v^*(L)Os^*$:

$$Os^* = \frac{F^*(L)}{v^*(L)} = \frac{v^*(L)C^*(L) - D\dfrac{dC^*}{dx^*}(L)}{v^*(L)}$$

Emergent osmolarity = the *apparent* concentration needed in order to have the same amount of output with the given fluid velocity and *no contribution from diffusion* (fictitious channel with constant concentration)

THE EQUATIONS: CONSERVATION OF WATER AND SALT!

WATER (Since the salt concentration is small, the density of water is assumed to be constant)



$$Q_{in} = Av^*(x^*)$$

$$Q_{out} = Av^*(x^*+\Delta x^*)$$

$$Q_{os} = P\left(C^*(x^*+\delta x^*) - C_0\right)\cdot\underbrace{\left(\Delta x^*\cdot c\right)}_{\text{wall area}}$$

$$Q_{out} - Q_{in} = Q_{os}$$

$$Av^*(x^*+\Delta x^*) - Av^*(x^*) = P\left(C^*(x^*+\delta x^*) - C_0\right)$$

$$(\Delta x^* \to 0) \Rightarrow \quad \frac{dv^*}{dx^*} = \frac{Pc}{A}\left(C^*(x^*) - C_0\right)$$

SALT

We use a conservation argument similar to for water:

$$Q_{out}^{salt} = AF^*(x^* + \Delta x^*)$$

$$Q_{in}^{salt} = AF^*(x^*)$$

$$Q_{ch.p.}^{salt} = N^*(x^*) \cdot \left(c\Delta x^*\right)$$

By letting Δx^* tend to 0:

$$A\frac{dF^*}{dx^*} = \begin{cases} N_0 c, & x^* \le \delta \\ 0, & x^* > \delta \end{cases}$$

The previous simple equation (for the salt) may be solved immediately:

$x^* \le \delta$:

$$A\frac{dF^*}{dx^*} = N_0 c \quad \Rightarrow \; F^* = \frac{N_0 c}{A} x^* \quad \text{(Since } F^*(0) = 0\text{)}$$

$x^* > \delta$:

$$A\frac{dF^*}{dx^*} = 0 \quad \Rightarrow \; F^* = \frac{N_0 c}{A} \delta \quad \text{(Since } F^* \text{ is continuous)}$$

Together, with the expression for the salt flux, this gives the following differential equation for *C**:

$$\boxed{C^* v^* - D\frac{dC^*}{dx^*} = \begin{cases} \dfrac{cN_0}{A} x^*, & 0 \le x^* \le \delta \\ \dfrac{cN_0}{A} \delta, & \delta \le x^* \le L \end{cases}}$$

BOUNDARY CONDITIONS AND MATCHING

CONDITIONS AT *x*=δ:

Closed end channel:

$$v^*(0) = 0,$$
$$F^*(0) = 0.$$

In fact,

$$\frac{dC^*}{dx^*}(0) = 0 \quad \left(\text{Since } F^*(0) = C^*(0)v^*(0) - D\frac{dC^*}{dx^*}(0)\right)$$

At the right end we assume that $C^*(L) = C_0$.

Finally, *matching* conditions at $x^*=\delta$:

$$F^*(\delta+) = F^*(\delta-)$$

$$v^*(\delta+) = v^*(\delta-)$$

$$C^*(\delta+) = C^*(\delta-)$$

$$\frac{dC^*}{dx^*}(\delta+) = \frac{dC^*}{dx^*}(\delta-) \quad \left(\text{Since } F^* = C^* v^* - D\frac{dC^*}{dx^*}\right)$$

(Not all conditions are needed in the final formulation)

FINAL FORMULATION

Differential equations (non-linear and coupled!):

$$\frac{dv^*}{dx^*} = \frac{Pc}{A}\left(C^*(x^*) - C_0\right), \quad 0 \le x^* \le \delta$$

$$C^* v^* - D\frac{dC^*}{dx^*} = \begin{cases} \frac{cN_0}{A} x^*, & 0 \le x^* \le \delta \\ \frac{cN_0}{A} \delta, & \delta \le x^* \le L \end{cases}$$

Boundary conditions:

$$v^*(0) = 0, \quad C^*(L) = C_0$$

$$v^*, C^* \text{ continuous for } x^* = \delta$$

Determine:

$$Os^* = \frac{F^*(L)}{v^*(L)} = \frac{cN_0\delta}{Av^*(L)}$$

SCALING

Parameter	Unit	Min. value	Typical value	Max. value
r	cm	10^{-6}	5×10^{-6}	10^{-4}
L	cm	4×10^{-4}	10^{-2}	2×10^{-2}
δ	cm	4×10^{-5}	10^{-3}	2×10^{-3}
D	cm^2/s	10^{-6}	10^{-5}	5×10^{-5}
N_0	$mOsm/cm^2s$	10^{-10}	10^{-7}	10^{-5}
P	cm^4/s mOsm	10^{-6}	2×10^{-5}	2×10^{-4}
C_0	$mOsm/cm^3$	-	3×10^{-1}	

(Table from Lin & Segel, p. 264)

Length scale: δ

Concentration scale: C_0

Velocity scale: $U = \dfrac{cN_0\delta}{C_0 A}$

Derivation of the velocity scale:

$$\underbrace{\frac{cN_0\delta}{A}A}_{\text{Salt out per time unit}} = C_0AU \Rightarrow U = \frac{cN_0\delta}{AC_0}$$

Scaled variables:

$$\boxed{\begin{aligned} x^* &= \delta x \\ C^* &= C_0 C \\ v^* &= Uv = \frac{cN_0\delta}{AC_0}v \end{aligned}}$$

THE SCALED EQUATIONS

$$\varepsilon \frac{dv}{dx} = C - 1, \ \ 0 \le x \le \lambda$$

$$Cv - \eta \frac{dC}{dx} = \begin{cases} x & 0 \le x \le 1 \\ 1 & 1 \le x \le \lambda \end{cases}$$

$$v(0) = 0, \ \ C(\lambda) = 1$$

$v, C, dC/dx$ continuous at $x = 1$.

$$\varepsilon = \frac{N_0}{PC_0^2}, \quad \eta = \frac{AC_0 D}{N_0 \delta^2 c}, \quad \lambda = \frac{L}{\delta}$$

$$\text{Determine } \ Os = \frac{1}{v(\lambda)}$$

Impossible to solve analytically!

Typical values of the non-dimensional parameters:

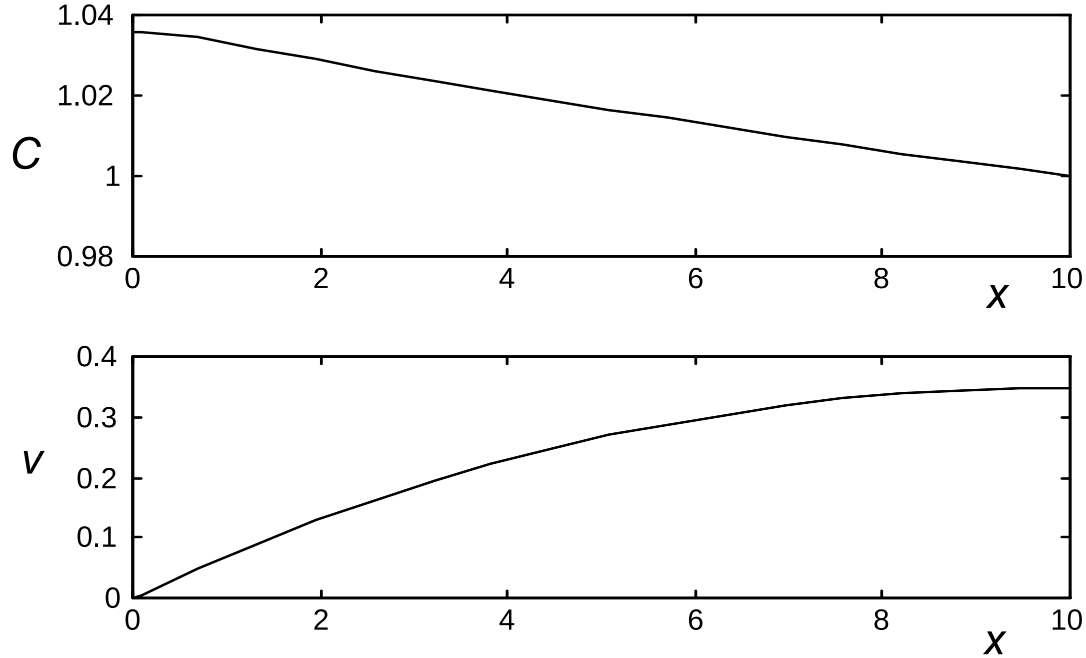
Parameter	Minimum	Typical	Maximum
ε	10^{-5}	$2{\cdot}10^{-2}$	10^{2}
η	$4{\cdot}10^{-3}$	75	10^{10}
λ	10(?)	10	500

SOME NUMERICAL SOLUTIONS

- obtained by means of a simple shooting method for

$$\lambda = 10, \quad \kappa = 1, \quad \varepsilon = .5$$

(The parameter κ will be defined below)



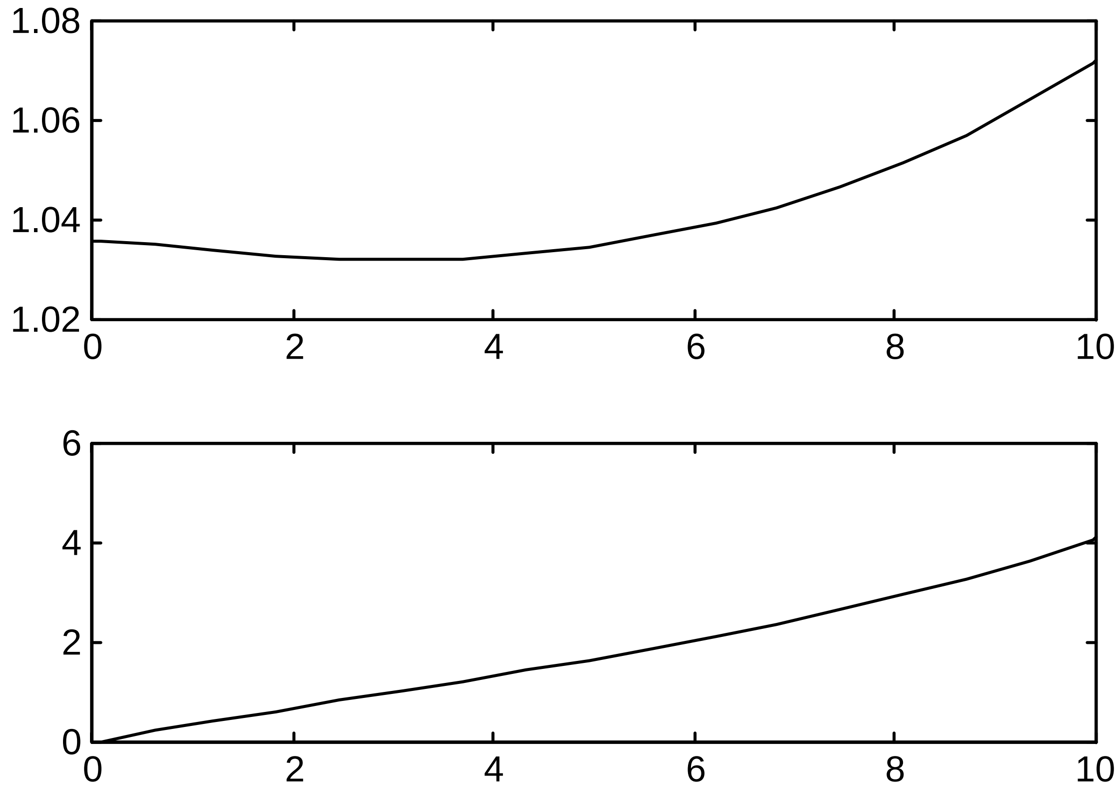
(Note: $C(0)$ = 1.0375)

MATLAB CODE:

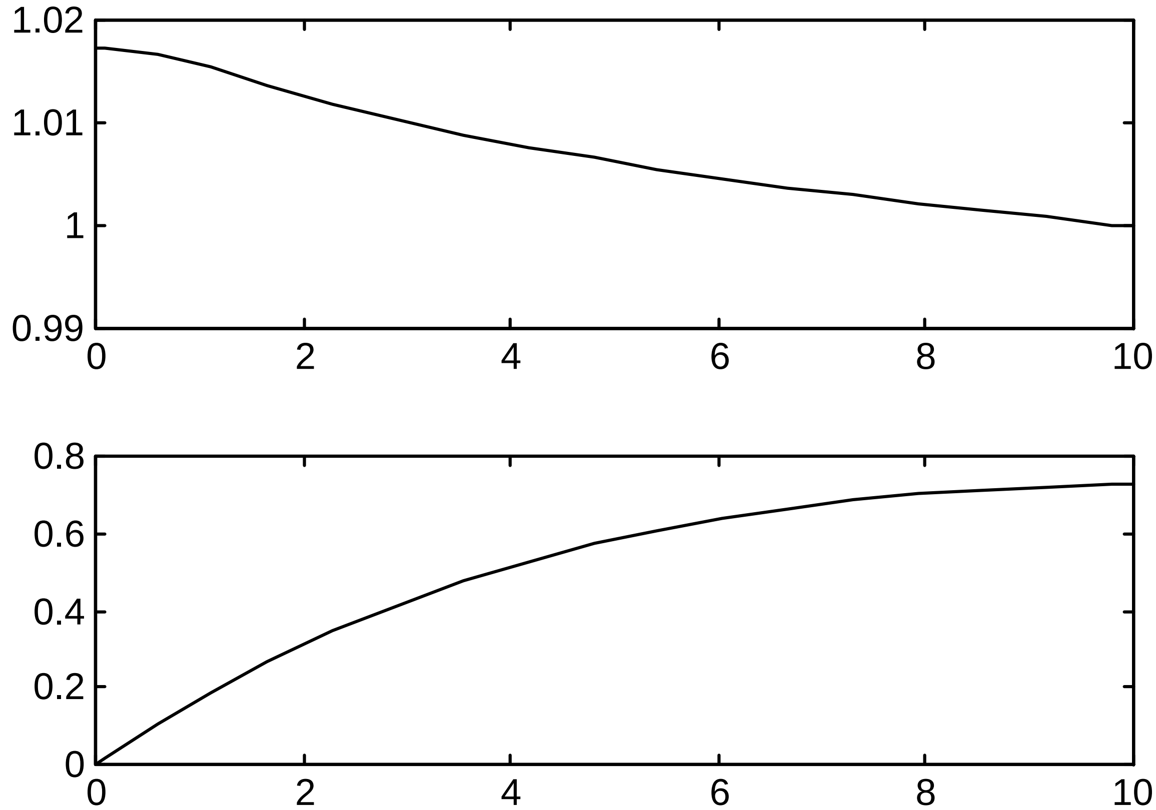
```
x0 =[0, 1.0355];
xspan = [0,10];
[t,x]=ode23('kidney',xspan,x0);
subplot(2,1,1); plot(t,x(:,2));
subplot(2,1,2); plot(t,x(:,1));


%L&S Eqn. 16a,b, Section 8.3: v=x(1), C = x(2):
function xdot = kidney(t,x)
lambda = 10.;
kappa = 1;
eps = .5;
f = (eps*kappa^2/lambda^2);
xdot(1)=( x(2)-1 )/eps;
xdot(2)=f*x(1)*x(2)-f*min(t,1);
```

$$\lambda = 10, \quad \kappa = 1, \quad \varepsilon = 0.1:$$

$C(0) = 1.0375$ (*Misses the target* $C(1) = 1!$):



$C(0)$=1.0173 (*Hits the target* $C(1) = 1!$):



A FIRST-TRY PERTURBATION EXPANSION

$$\varepsilon\frac{dv}{dx} = C - 1,\ \ 0 \le x \le \lambda$$

$$Cv - \eta\frac{dC}{dx} = \begin{cases} x & 0 \le x \le 1 \\ 1 & 1 \le x \le \lambda \end{cases}$$

$$C = C_0 + \varepsilon C_1 + \varepsilon^2 C_2 + \ldots$$

$$v = v_0 + \varepsilon v_1 + \varepsilon^2 v_2 + \ldots$$

To order ε^0**:**

$$C_0 - 1 = 0 \Rightarrow C_0 = 1,$$

$$1v_0 + \eta\frac{dC_0}{dx} = \begin{cases} x \\ 1 \end{cases} \Rightarrow v_0 = \begin{cases} x \\ 1 \end{cases},$$

To order ε^1:

$$C_1 = \frac{dv_0}{dx} = \begin{cases} 1 \\ 0 \end{cases} \Rightarrow C_1 \text{ is discontinuous!}$$

This is against our (physical) requirement that C should be continuous.

The problem is that η *tends to be large when* ε *is small!*

We introduce the modified parameter κ and eliminate η:

$$\eta = \frac{\left(\lambda^2 / \kappa^2\right)}{\varepsilon}$$

(The somewhat strange form is basically for making the expressions simpler!)

MODIFIED PERTURBATION EXPANSION

$$C - 1 = \varepsilon \frac{dv}{dx},\ \ 0 \le x \le \lambda$$

$$\varepsilon\kappa^2 C v - \lambda^2 \frac{dC}{dx} = \varepsilon\kappa^2 \begin{cases} x, & 0 \le x \le 1 \\ 1, & 1 \le x \le \lambda \end{cases}$$

$$\varepsilon << 1,\ \ \kappa, \lambda \sim O(1)$$

$$C = C_0 + \varepsilon C_1 + \varepsilon^2 C_2 + \dots$$

$$v = v_0 + \varepsilon v_1 + \varepsilon^2 v_2 + \dots$$

To order ε^0**:**

$$\left.\begin{array}{l} C_0 - 1 = 0 \\ \lambda^2 C_0' = 0 \end{array}\right\} \Rightarrow C_0 = 1,$$

To order ε^1:

$$\boxed{\left.\begin{array}{c} C_1 = v_0' \\ \kappa^2 v_0 C_0 - \lambda^2 C_1' = \kappa^2 \begin{pmatrix} x \\ 1 \end{pmatrix} \end{array}\right\} \Rightarrow \kappa^2 v_0 - \lambda^2 v_0'' = \kappa^2 \begin{pmatrix} x \\ 1 \end{pmatrix}}$$

Solution for $0 \le x \le 1$:

$$v_0 = x - K_1 \sinh\left(\frac{\kappa}{\lambda} x\right)$$

$$C_1 = v_0' = 1 - K_1 \frac{\kappa}{\lambda} \cosh\left(\frac{\kappa}{\lambda} x\right)$$

Solution for $1 \le x \le \lambda$:

$$v_0 = 1 - K_2 \cosh\left(\frac{\kappa}{\lambda} x + \Psi\right)$$

$$C_1 = v_0' = -K_2 \frac{\kappa}{\lambda} \sinh\left(\frac{\kappa}{\lambda} x + \Psi\right)$$

(since $C_1(\lambda) = 0$, $\Psi = -\kappa$)

The constants K_1 and K_2 are determined from the continuity requirements at $x = 1$:

$$K_1 = \frac{\lambda}{\kappa} \frac{\cosh(\kappa / \lambda - \kappa)}{\cosh(\kappa)}$$

$$K_2 = \frac{\lambda}{\kappa} \frac{\sinh(\kappa / \lambda)}{\cosh(\kappa)}$$

The *dimensionless osmolarity* at $x=\lambda$:

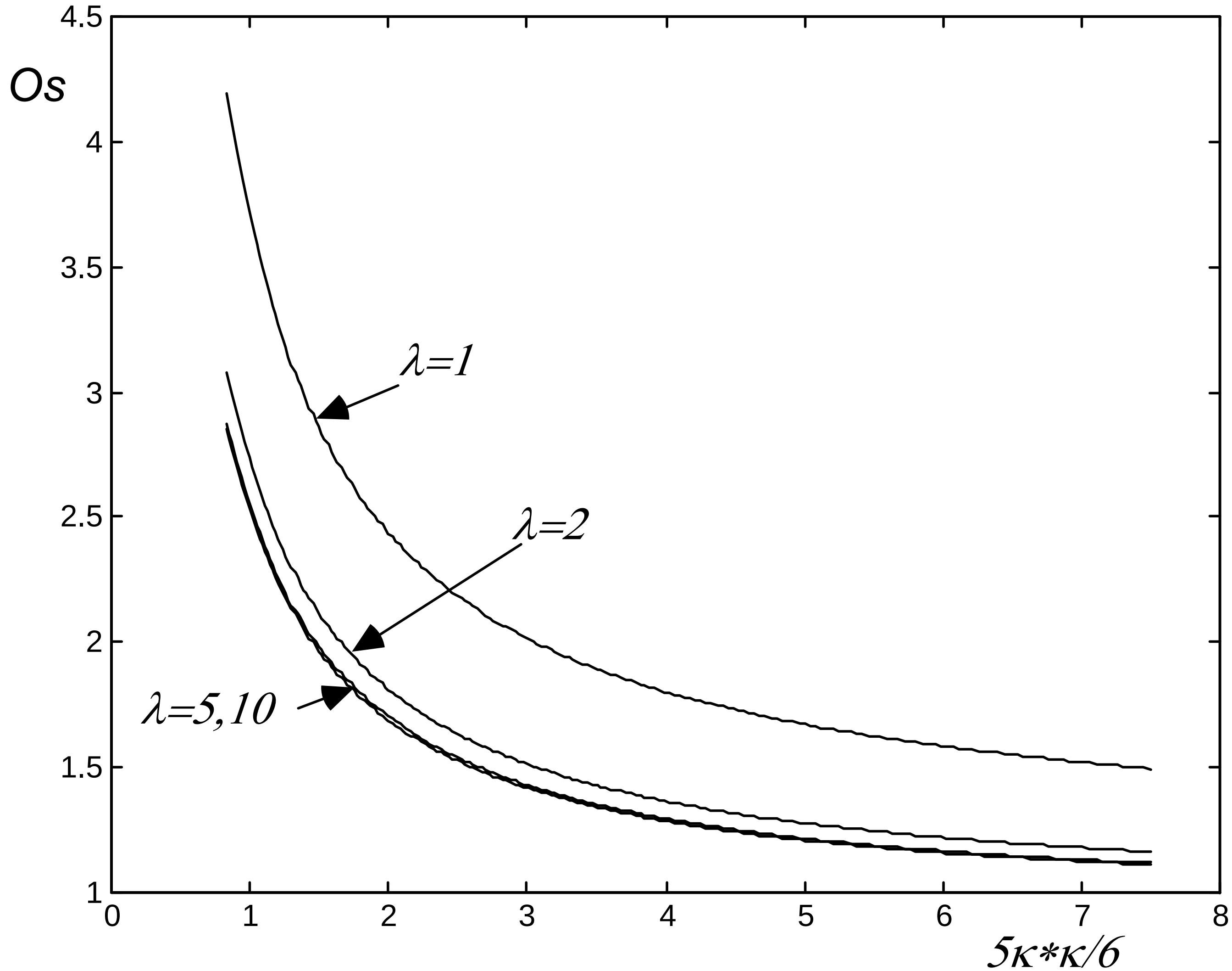
$$\boxed{Os = \frac{1}{v(\lambda)} \approx \frac{1}{v_0(\lambda)} = \frac{1}{1-K_2}}$$

Assume $\kappa/\lambda<1$:

$$Os \approx \frac{1}{1-K_2} \approx \frac{1}{1-\dfrac{1}{\cosh(\kappa)}} = \frac{\cosh(\kappa)}{\cosh(\kappa)-1}$$

When κ is small compared to 1, then

$$Os \approx \frac{\cosh(\kappa)}{\cosh(\kappa)-1} \approx \frac{1+\kappa^2/2+\ldots}{\kappa^2/2+\ldots} \approx \frac{2}{\kappa^2}$$



Os
4.5
4
3.5
3
2.5
2
1.5
1
0
1
2
3
4
5
6
7
8
λ=1
λ=2
λ=5,10
5κ*κ/6

ALL DIMENSIONLESS PARAMETERS MEAN SOMETHING IMPORTANT AND USEFUL!

$$\frac{\kappa^2}{2} = \frac{cPC_0 L^2}{AD2} \frac{\overline{C} - C_0}{\overline{C} - C_0} = \frac{\left(cLP(\overline{C} - C_0)\right)C_0 \frac{1}{A}}{D\left(\overline{C} - C_0\right)/(L/2)}$$

Now,

$$\underbrace{\left(cLP(\overline{C} - C_0)\right)C_0 \frac{1}{A}}_{\text{water in by osmosis}} \approx F_{conv.}$$

$$F_{diff} \approx -D \frac{dC^*}{dx^*}\bigg|_{ave} \approx D \frac{\overline{C} - C_0}{L/2}$$

That is,

$$\frac{\kappa^2}{2} \approx \frac{F_{conv.}}{F_{diff.}}$$

Thus,

$$Os = \frac{Os^*}{C_0} = \frac{F^*(L)}{v^*(L)C_0} = \frac{F_{conv.} + F_{diff}}{F_{conv.}} = 1 + \frac{F_{diff}}{F_{conv.}} \approx 1 + \frac{2}{\kappa^2}$$

THE STEPS OF THE ANALYSIS:

1. ***A qualitative idea of the model***
2. ***Identify physical mechanisms***
3. ***Sort out the geometry***
4. ***The modelling: Based on conservation principles!***
5. ***Scaling***
6. ***Perturbation analysis (not working!)***
7. ***Modified scaling***
8. ***Modified perturbation analysis (working!)***
9. ***Numerical experiments***
10. ***Final analysis***
11. ***Conclusions***