A time-dependent central core model and a schematic model for passive mechanism

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Outline

Time-dependent model

Compartments

Multiphasic medulla on the domain $(0, L)$ (superficial $\rightarrow$ deep).

1. Central core ($k = 0$)
2. Descending tubule ($k = \mathrm{D}$)
3. Ascending tubule ($k = \mathrm{A}$)
4. Collecting tubule ($k = \mathrm{C}$)

Cross-sectional areas

Cross-sectional areas α_k (cm^2) satisfy

$$\sum_k \alpha_k = \alpha_* \tag{1.1}$$

where $\alpha_* : (0, L) \to \mathbb{R}_+$ is the fixed medullary cross-sectional area.

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$$\frac{\partial \alpha_k}{\partial t} + \frac{\partial}{\partial x}(\alpha_k u_k) = -\beta_k w_k, \quad k = \mathrm{D}, \mathrm{A}, \mathrm{C}, \tag{1.2}$$

$$\frac{\partial \alpha_0}{\partial t} + \frac{\partial}{\partial x}(\alpha_0 u_0) = \sum_{k=\mathrm{D},\mathrm{A},\mathrm{C}} \beta_k w_k. \tag{1.3}$$

u_k: axial flow *velocity* (cm/s); w_k: transmural flux (cm/s); β_k: total tubular circumferences (cm)

Water flow and transport

Poiseuille's equation:

$$\frac{8\pi\eta_k u_k}{\alpha_k} = -\frac{\partial p_k}{\partial x}, \quad k = 0, \mathrm{D}, \mathrm{A}, \mathrm{C}, \tag{1.4}$$

η_k: viscosity (mmHg·s), p_k: pressure (mmHg).

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Water transport:

$$w_k := \zeta_k \left(\psi_k - \psi_0\right), \quad k = \mathrm{D}, \mathrm{A}, \mathrm{C} \tag{1.5}$$

$$\left.\begin{aligned} \psi_k &:= p_k - \pi_k, \\ \pi_k &:= RT\left(2c_{\mathrm{s}}^k + c_{\mathrm{u}}^k\right), \end{aligned}\right\} \quad k = 0, \mathrm{D}, \mathrm{A}, \mathrm{C}. \tag{1.6}$$

ζ_k: water permeability (mmHg·s); c_i^k: concentration (mmol/cm^3)

Pressure-compliance relationship

Given tubular compliance ν_k (mmHg^{-1}), we assume

$$\nu_k(p_k - p_0) = \frac{\alpha_k}{\bar{\alpha}_k} - 1, \quad k = \mathrm{D}, \mathrm{A}, \mathrm{C}. \tag{1.7}$$

Note that p_0 is determined by the medullary volume conservation (1.1).

Solute dynamics

$$\frac{\partial}{\partial t}\left(\alpha_k c_i^k\right) = -\frac{\partial}{\partial x} f_i^k - \beta_k g_i^k, \quad k = \mathrm{D}, \mathrm{A}, \mathrm{C}, \tag{1.8}$$

$$\frac{\partial}{\partial t}\left(\alpha_0 c_i^0\right) = -\frac{\partial}{\partial x} f_i^0 + \sum_{k=\mathrm{D},\mathrm{A},\mathrm{C}} \beta_k g_i^k, \tag{1.9}$$

f_i^k: Axial solute flow (mmol/s):

$$f_i^k := \alpha_k \left(-D_i^k \frac{\partial c_i^k}{\partial x} + u_k c_i^k\right), \quad k = 0, \mathrm{D}, \mathrm{A}, \mathrm{C}. \tag{1.10}$$

D_i^k: diffusion coefficient (cm^2/s).

g_i^k: transmural solute flux ($\mathrm{mmol}/\mathrm{cm}^2 \cdot \mathrm{s}$),

solute transport

g_i^k: transmural solute flux (mmol/cm^2·s), (adapted from Stephenson et al. [1987, 1989]):

$$g_i^k := j_i^k + h_i^k, \quad k = \mathrm{D}, \mathrm{A}, \mathrm{C}, \tag{1.11}$$

$$j_i^k = \gamma_i^k \left(c_i^k - c_i^0 \right), \quad k = 0, \mathrm{D}, \mathrm{A}, \mathrm{C}. \tag{1.12}$$

γ_i^k: solute permeability (cm/s).

h_i^k: active transport:

$$h_{\mathrm{s}}^{\mathrm{A}} = \begin{cases} \frac{h_{\mathrm{s,max}}^{\mathrm{A}}}{1+M/c_{\mathrm{s}}^{\mathrm{A}}} & \text{in} \quad (0, \frac{L}{3}) \\ 0 & \text{in} \quad [\frac{L}{3}, L), \end{cases} \tag{1.13}$$

where M is the Michaelis-Menten constant.

Boundary condition: central core

No flux at the bottom:

$$u_0(t, L) = 0, \tag{1.14}$$

$$f_i^0(t, L) = 0, \quad i = \mathrm{s}, \mathrm{u}. \tag{1.15}$$

Dirichlet boundary at the cortico-medullary junction:

$$p_0(t, 0) = P_\mathrm{v}(t), \tag{1.16}$$

$$c_i^0(t, 0) = c_i^\mathrm{v}(t). \tag{1.17}$$

Boundary condition: descending tubule

Input from the PCT:

$$(\alpha_{\mathrm{D}}\, u_{\mathrm{D}})(t,0) = F_{\mathrm{PCT}}(t), \tag{1.18}$$

$$c_i^{\mathrm{D}}(t,0) = c_i^{\mathrm{PCT}}(t), \quad i = \mathrm{s}, \mathrm{u}, \tag{1.19}$$

Tip of the loop of Henle:

$$(\alpha_{\mathrm{D}}\, u_{\mathrm{D}} + \alpha_{\mathrm{A}}\, u_{\mathrm{A}})(t,L) = 0, \tag{1.20}$$

$$\left(f_i^{\mathrm{D}} + f_i^{\mathrm{A}}\right)(t,L) = 0, \tag{1.21}$$

$$p_{\mathrm{D}}(t,L) = p_{\mathrm{A}}(t,L), \tag{1.22}$$

$$c_i^{\mathrm{D}}(t,L) = c_i^{\mathrm{A}}(t,L) \tag{1.23}$$

Boundary condition: modification by distal tubules

Assumption: salt from the ascending tubule is further reabsorbed so that only a fraction of $q \in (0,1)$ are left at the collecting tubule; formally,

$$\left(f_{\mathrm{u}}^{\mathrm{A}} + f_{\mathrm{u}}^{\mathrm{C}}\right)(t,0) = 0, \tag{1.24}$$

$$\left(q f_{\mathrm{s}}^{\mathrm{A}} + f_{\mathrm{s}}^{\mathrm{C}}\right)(t,0) = 0. \tag{1.25}$$

Further, we assume that

$$p_{\mathrm{A}}(t,0) = p_{\mathrm{C}}(t,0), \tag{1.26}$$

$$f_i^{\mathrm{A}}(t,L) = (\alpha_{\mathrm{A}}\, u_{\mathrm{A}}\, c_i^{\mathrm{A}})(t,L), \quad i = \mathrm{s},\mathrm{u}, \tag{1.27}$$

$$(2c_{\mathrm{s}}^{\mathrm{C}} + c_{\mathrm{u}}^{\mathrm{C}})(t,0) = \mathrm{osm}_{\mathrm{cortex}}(t), \tag{1.28}$$

where the cortical osmolarity $\mathrm{osm}_{\mathrm{cortex}}$ is given.

Boundary condition: papillary outflow

$$p_{\mathrm{C}}(t, L) = P_{\mathrm{p}}(t), \tag{1.29}$$

$$f_i^{\mathrm{C}}(t, L) = (\alpha_{\mathrm{C}} u_{\mathrm{C}} c_i^{\mathrm{C}})(t, L), \quad i = \mathrm{s}, \mathrm{u}, \tag{1.30}$$

where P_{p} is the papillary pressure.

Rescaling

Introduce spatial rescaling and advective timescale:

$$x = L\hat{x}, \quad t = \tau\hat{t}, \quad \tau := \frac{L}{p_*/\rho_* L} = \frac{8\pi\eta_* L^2}{\bar{\alpha} c_* R T} \tag{1.31}$$

where the subscript $*$ denotes the typical magnitude of physical quantities; here $p_* = c_* R T$ and $\rho_* = 8\pi\eta_*/\bar{\alpha}$ are those of pressure and hydraulic resistivity with $\bar{\alpha} = \frac{1}{L}\int_0^L \alpha_*(x)\, dx$.

Unknowns:

$$\alpha_k = \bar{\alpha}\hat{\alpha}, \quad c_i^k = c_* \hat{c}_i^k, \quad p_k = p_* \hat{p}_k = c_* R T \hat{p}_k. \tag{1.32}$$

Dimensionless model

$$\frac{\partial \hat{\alpha}_k}{\partial \hat{t}} + \frac{\partial}{\partial \hat{x}} \left(\hat{\alpha}_k \hat{u}_k \right) = -\hat{w}_k, \tag{1.33}$$

$$\frac{\partial \hat{\alpha}_0}{\partial \hat{t}} + \frac{\partial}{\partial \hat{x}} \left(\hat{\alpha}_0 \hat{u}_0 \right) = \sum_k \hat{w}_k, \tag{1.34}$$

$$\hat{\nu}_k \left(\hat{p}_k - \hat{p}_0 \right) = \frac{\hat{\alpha}_k}{\hat{\bar{\alpha}}_k} - 1, \tag{1.35}$$

$$\hat{\alpha}_0 + \sum_k \hat{\alpha}_k = \hat{\alpha}_*, \tag{1.36}$$

$$\frac{\partial}{\partial \hat{t}} \left(\hat{\alpha}_k \hat{c}_i^k \right) = -\frac{\partial}{\partial \hat{x}} \hat{f}_i^k - \hat{g}_i^k, \tag{1.37}$$

$$\frac{\partial}{\partial \hat{t}} \left(\hat{\alpha}_0 \hat{c}_i^0 \right) = -\frac{\partial}{\partial \hat{x}} \hat{f}_i^0 + \sum_k \hat{g}_i^k, \tag{1.38}$$

Dimensionless flows and transports

$$\hat{u}_k := -\frac{\hat{\alpha}_k}{\hat{\rho}_k}\frac{\partial \hat{p}_k}{\partial \hat{x}}, \tag{1.39}$$

$$\hat{f}_i^k := \hat{\alpha}_k\left(-\hat{D}_i^k\frac{\partial \hat{c}_i^k}{\partial \hat{x}} + \hat{u}_k\hat{c}_i^k\right), \tag{1.40}$$

$$\hat{w}_k := \hat{\zeta}_k\left(\hat{\psi}_k - \hat{\psi}_0\right), \quad \hat{\psi}_k := \hat{p}_k - \left(2\hat{c}_{\mathrm{s}}^k + \hat{c}_{\mathrm{u}}^k\right), \tag{1.41}$$

$$\hat{g}_i^k := \hat{j}_i^k + \hat{h}_i^k, \quad \hat{j}_i^k = \hat{\gamma}_i^k(\hat{c}_i^k - \hat{c}_i^0). \tag{1.42}$$

$$\hat{h}_{\mathrm{s}}^{\mathrm{A}} = \begin{cases} \frac{\hat{h}_{\mathrm{s,max}}^{\mathrm{A}}}{1+\hat{M}/\hat{c}_{\mathrm{s}}^{\mathrm{A}}} & \text{in} \quad (0, \frac{1}{3}) \\ 0 & \text{in} \quad [\frac{1}{3}, 1) \end{cases} \tag{1.43}$$

Parameters and boundary conditions

Parameters (note that β_k is absorbed into $\hat{\zeta}_i^k, \hat{\zeta}_{\mathrm{w}}^k$):

$$\hat{\rho}_k = \frac{8\pi\eta_k}{\rho_*}, \quad \hat{\nu}_k = p_*\nu_k, \quad \hat{\bar{\alpha}}_k = \frac{\bar{\alpha}_k}{\bar{\alpha}}, \quad \hat{\alpha}_* = \frac{\alpha_*}{\bar{\alpha}}$$

$$\hat{D}_i^k = \frac{\tau}{L^2} D_i^k, \quad \hat{\zeta}_k = \frac{\beta_k p_* \tau}{\bar{\alpha}} \zeta_k, \quad \hat{\gamma}_i^k = \frac{\beta_k p_* \tau}{\bar{\alpha} c_*^2} \gamma_i^k,$$

$$\hat{h}_{\mathrm{s}}^{\mathrm{A}} = \frac{\beta_{\mathrm{A}} \tau}{\bar{\alpha} c_*} h_{\mathrm{s}}^{\mathrm{A}}, \quad \hat{M} = \frac{M}{c_*}.$$

Boundary conditions are the same but with $\hat{\cdot}$ notation where

$$F_{\mathrm{PCT}} = \frac{\bar{\alpha} L}{\tau} \hat{F}_{\mathrm{PCT}}, \quad P_{\mathrm{p}} = p_* \hat{P}_{\mathrm{p}}, \quad P_{\mathrm{v}} = p_* \hat{P}_{\mathrm{v}},$$

$$c_i^{\mathrm{v}} = c_* \hat{c}_i^{\mathrm{v}}, \quad \mathrm{osm}_{\mathrm{cortex}} = c_* \widehat{\mathrm{osm}}_{\mathrm{cortex}}.$$

Numerical simulation

- Approximation: backward difference for time derivatives and central difference for spatial derivatives. Then, use an iterative method.
- Most parameters except for D_i^k when $k \neq 0$, η_k, P_{v}, P_{p}, ν_k, q are available in Stephenson et al. [1987, 1989] which uses transfusion data in rabbit; these 6 will be chosen empirically.
- The simulated solution appears to converge to a steady state.

Parameters

Physical and geometric parameters (take $\bar{\alpha}_k = \pi r^2$, $\beta_k = 2\pi r_k$, $\alpha_* = \sum_k \bar{\alpha}_k$):

D_{s}^0	D_{u}^0	$D_i^k,\ k \neq 0$	η_k	ν_k	r_0	r_{D}	r_{A}	r_{C}
($\times 10^{-4}$ cm^2/s)			(cP $\approx 7.5 \times 10^{-6}$ mmHg·s)	(mmHg^{-1})	($\times 10^{-3}$ cm)			
2.5	2	0.15	0.6915	0.0517	2.5	0.8	1	1.2

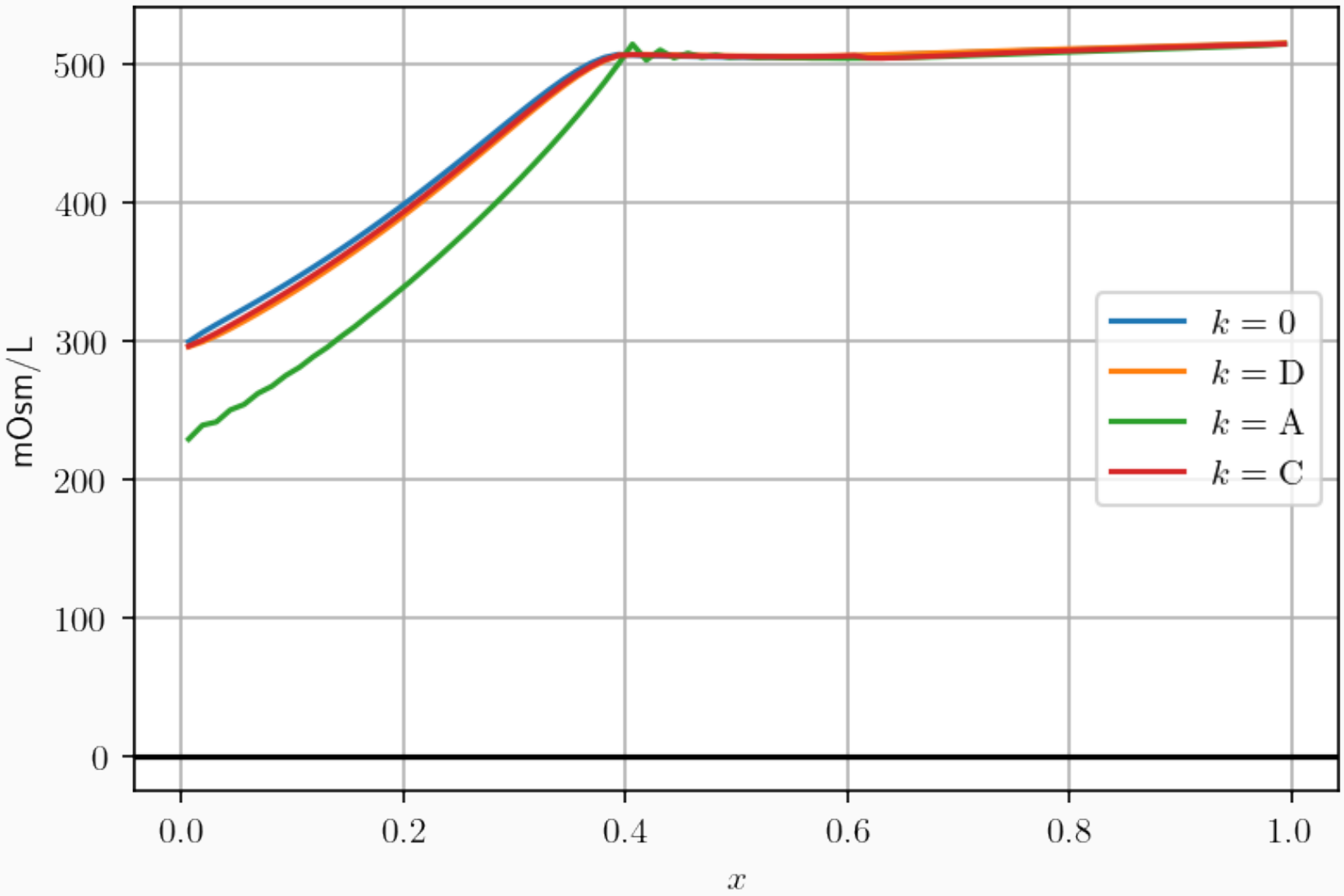
Transport parameters:

ζ_{D}	ζ_{A}	ζ_{C}	$\gamma_{\mathrm{s}}^{\mathrm{D}}$	$\gamma_{\mathrm{s}}^{\mathrm{A}}$	$\gamma_{\mathrm{s}}^{\mathrm{C}}$	$\gamma_{\mathrm{u}}^{\mathrm{D}}$	$\gamma_{\mathrm{u}}^{\mathrm{A}}$	$\gamma_{\mathrm{u}}^{\mathrm{C}}$	$h_{\mathrm{s,max}}^{\mathrm{A}}$	M
($\times 10^{-8}$ cm/mmHg·s)			($\times 10^{-5}$ cm/s)						($\frac{10^{-6}\text{mmol}}{\text{cm}^2\cdot\text{s}}$)	($\frac{\text{mmol}}{\text{cm}^3}$)
22.5	0	3.95	1.61	6.27	0.04	1.5	0.86	0	14.2	0.15
33.8	0	3.95	1.61	26.0	0.04	1.5	6.70	0	0	
26.4	0	3.95	1.61	26.0	0.04	1.5	6.70	1.5	0	

Boundary data

F_{PCT}	P_{p}	P_{v}	$c_{\mathrm{s}}^{\mathrm{v}}$	$c_{\mathrm{u}}^{\mathrm{v}}$	$\mathrm{osm}_{\mathrm{cortex}}$
($\times 10^{-7}\mathrm{cm}^3/\mathrm{s}$)	(mmHg)		(mmol/L)		
1.67	6.4	0	145	5	295

Result


500
400
300
200
100
0
mOsm/L
0.0
0.2
0.4
0.6
0.8
1.0
x
$k = 0$
$k = \mathrm{D}$
$k = \mathrm{A}$
$k = \mathrm{C}$

Schematic model for passive mechanism

Idea

- We want to have a clean picture of what makes passive mechanism working.
- Derive a schematic model of *inner medulla* based on the common explanation of passive mechanism:

Concept of passive mechanism

The net water and NaCl reabsorption preceding the inner medulla collecting tubules concentrate the urea enough that it diffuses out in the inner medulla. This in turn increases osmolality in the interstitium that drives the water reabsorption from the thin descending limbs, concentrating NaCl in the process. NaCl is then passively reabsorbed at the ascending tubule.

Model derivation

Consider a steady state of the previous dimensionless model but rescale $\hat{x} \in (0, 1)$ to be the *inner medulla* instead (from now on, we omit the $\hat{\cdot}$ notation). We further make simplifying assumptions that

- The descending and ascending tubule urea concentration and the collecting tubule salt concentration are negligible.
- Zero salt permeability in the descending tubule.

Rewriting $q_k = \alpha_k u_k$, $s_k = c_{\rm s}^k$, $u_k = c_{\rm u}^k$, $\gamma_s = \gamma_{\rm s}^{\rm A}$, $\gamma_u = \gamma_{\rm u}^{\rm C}$, and assuming that $1/\nu_k$ and D_i^k are small, we arrive at the leading order equations:

$$\frac{dq_{\rm D}}{dx} = -\zeta_{\rm D}\,(2s_0 + u_0 - 2s_{\rm D}) = -w_{\rm D}, \tag{2.1}$$

$$\frac{dq_{\rm A}}{dx} = 0, \tag{2.2}$$

$$\frac{dq_{\rm C}}{dx} = -\zeta_{\rm C}\,(2s_0 + u_0 - u_{\rm C}) = -w_{\rm C}, \tag{2.3}$$

$$\frac{dq_0}{dx} = w_{\rm D} + w_{\rm C}, \tag{2.4}$$

$$\frac{d}{dx}(s_{\rm D}\,q_{\rm D}) = 0, \tag{2.5}$$

$$\frac{d}{dx}(s_{\rm A}\,q_{\rm A}) = -\gamma_s(s_{\rm A} - s_0), \tag{2.6}$$

$$\frac{d}{dx}(s_0\,q_0) = \gamma_s(s_{\rm A} - s_0), \tag{2.7}$$

$$\frac{d}{dx}(u_{\rm C}\,q_{\rm C}) = -\gamma_u(u_{\rm C} - u_0), \tag{2.8}$$

$$\frac{d}{dx}(u_0\,q_0) = \gamma_u(u_{\rm C} - u_0). \tag{2.9}$$

9 unknowns: the water flow $q_{\mathrm{D}}, q_{\mathrm{A}}, q_{\mathrm{C}}, q_0$ and the solute concentrations $s_{\mathrm{D}}, s_{\mathrm{A}}, s_0, u_{\mathrm{C}}, u_0$. (Note that in the limit as $1/\nu_k \searrow 0$, p_k are identical.)

The ODEs are completed with 9 boundary conditions:

$$q_{\mathrm{D}}(0) = \frac{2S}{C}, \quad q_{\mathrm{A}}(1) = -q_{\mathrm{D}}(1), \quad q_{\mathrm{C}}(0) = \frac{U}{C}, \quad q(1) = 0. \tag{2.10}$$

$$2s_{\mathrm{D}}(0) = u_{\mathrm{C}}(0) = C, \tag{2.11}$$

$$\frac{2S}{C} + q_0(0) + q_{\mathrm{A}} + \frac{U}{C} = q_{\mathrm{C}}(1), \tag{2.12}$$

$$S + q_{\mathrm{A}}(0)s_{\mathrm{A}}(0) + s_0(0)q_0(0) = 0, \tag{2.13}$$

$$U + u_0(0)q_0(0) = u_{\mathrm{C}}(1)q_{\mathrm{C}}(1). \tag{2.14}$$

The problem can be reduced even further!

After some tedious calculation, we can explicitly solve for q_{A}, q_0, s_{D}, s_0, u_0 in terms of q_{D}, q_{C}, s_{A}, u_{C}. Hence, this problem is equivalent to

$$\frac{dq_{\mathrm{D}}}{dx} = -\zeta_{\mathrm{D}} \left(2s_0 + u_0 - \frac{2S}{q_{\mathrm{D}}} \right) \tag{2.15}$$

$$\frac{ds_{\mathrm{A}}}{dx} = -\frac{\gamma_s}{q_{\mathrm{A}}}(s_{\mathrm{A}} - s_0), \tag{2.16}$$

$$\frac{dq_{\mathrm{C}}}{dx} = -\zeta_{\mathrm{C}}(2s_0 + u_0 - u_{\mathrm{C}}), \tag{2.17}$$

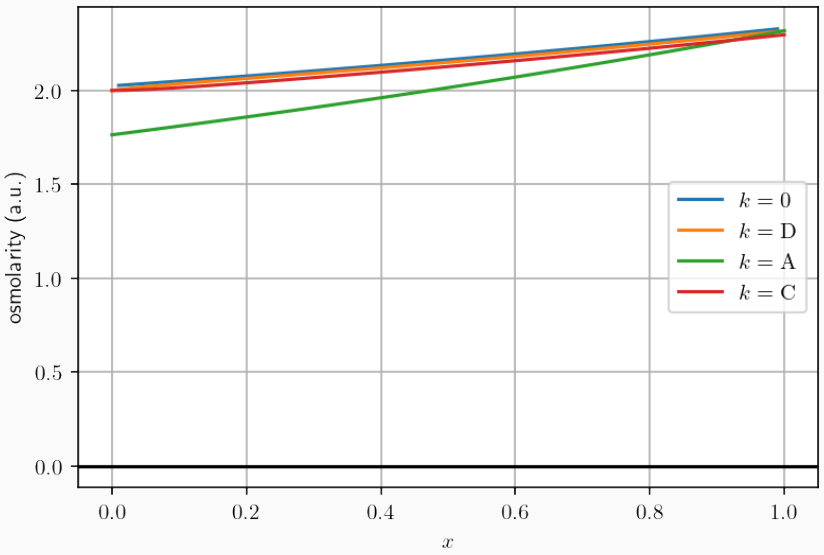
$$\frac{du_{\mathrm{C}}}{dx} = \frac{1}{q_{\mathrm{C}}} \left(\zeta_{\mathrm{C}} u_{\mathrm{C}}(2s_0 + u_0 - u_{\mathrm{C}}) - \gamma_u(u_{\mathrm{C}} - u_0) \right), \tag{2.18}$$

with boundary conditions

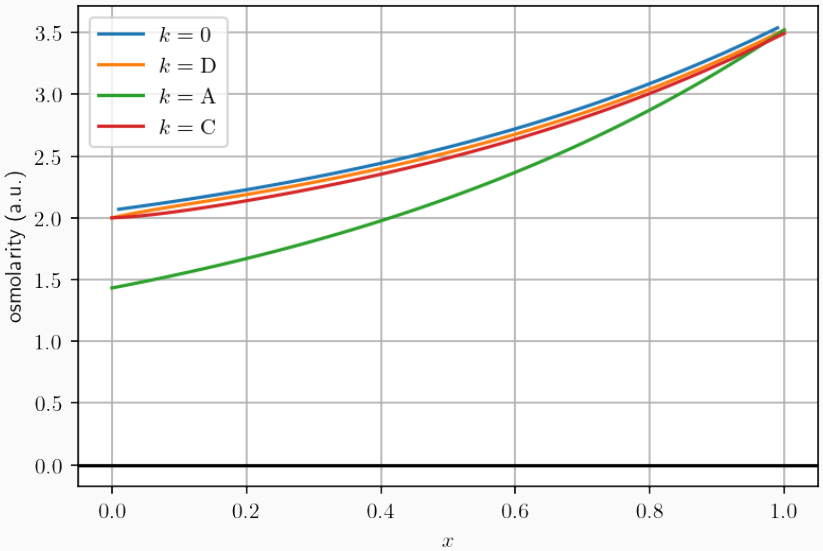
$$q_{\mathrm{D}}(0) = \frac{2S}{C}, \quad s_{\mathrm{A}}(1) = S/q_{\mathrm{D}}(1), \quad q_{\mathrm{C}}(0) = \frac{U}{C}, \quad u_{\mathrm{C}}(0) = C. \tag{2.19}$$

Exploring passive mechanism

The system of ODEs is approximated using central difference scheme, then solved using an iterative method.

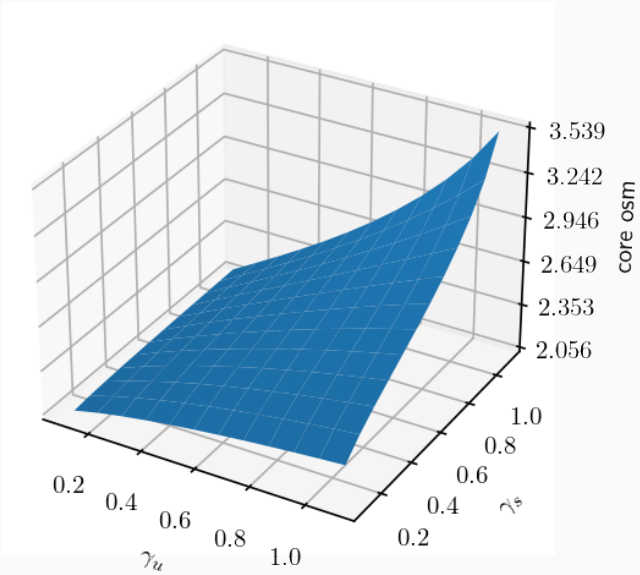


(a) $\gamma_u = \gamma_s = 0.1$

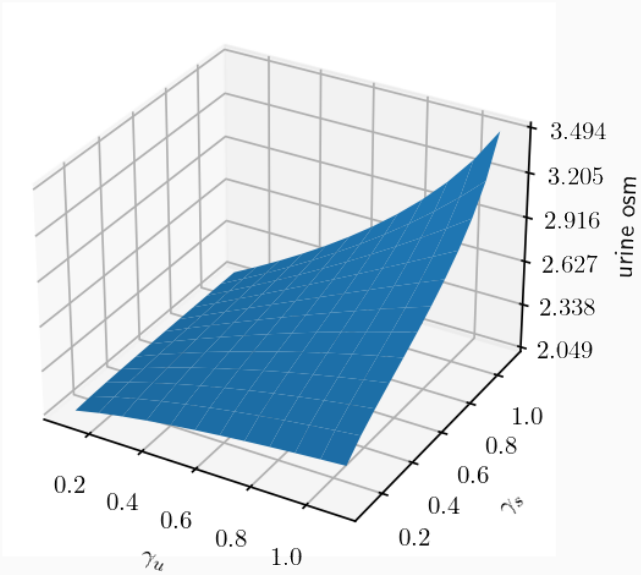


(b) $\gamma_u = \gamma_s = 1.2$

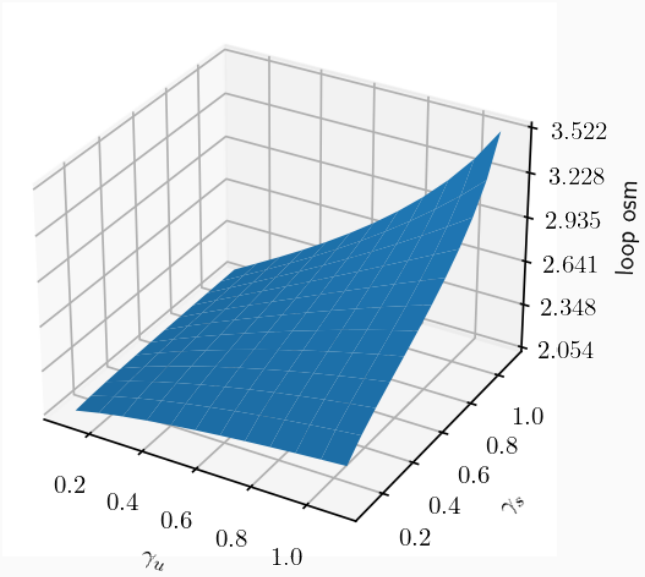
Figure 1: $\zeta_{\mathrm{D}} = \zeta_{\mathrm{C}} = 10,\ S = 1,\ U = 2,\ C = 2$



(a) papillary core osmolarity



(b) urine osmolarity



(c) osmolarity at the turning of Henle's loop

Conclusion #1: urea is an ‘enabler’ of salt reabsorption, while both salt and urea act as sources of osmotic drive.

Long-short loop proportion

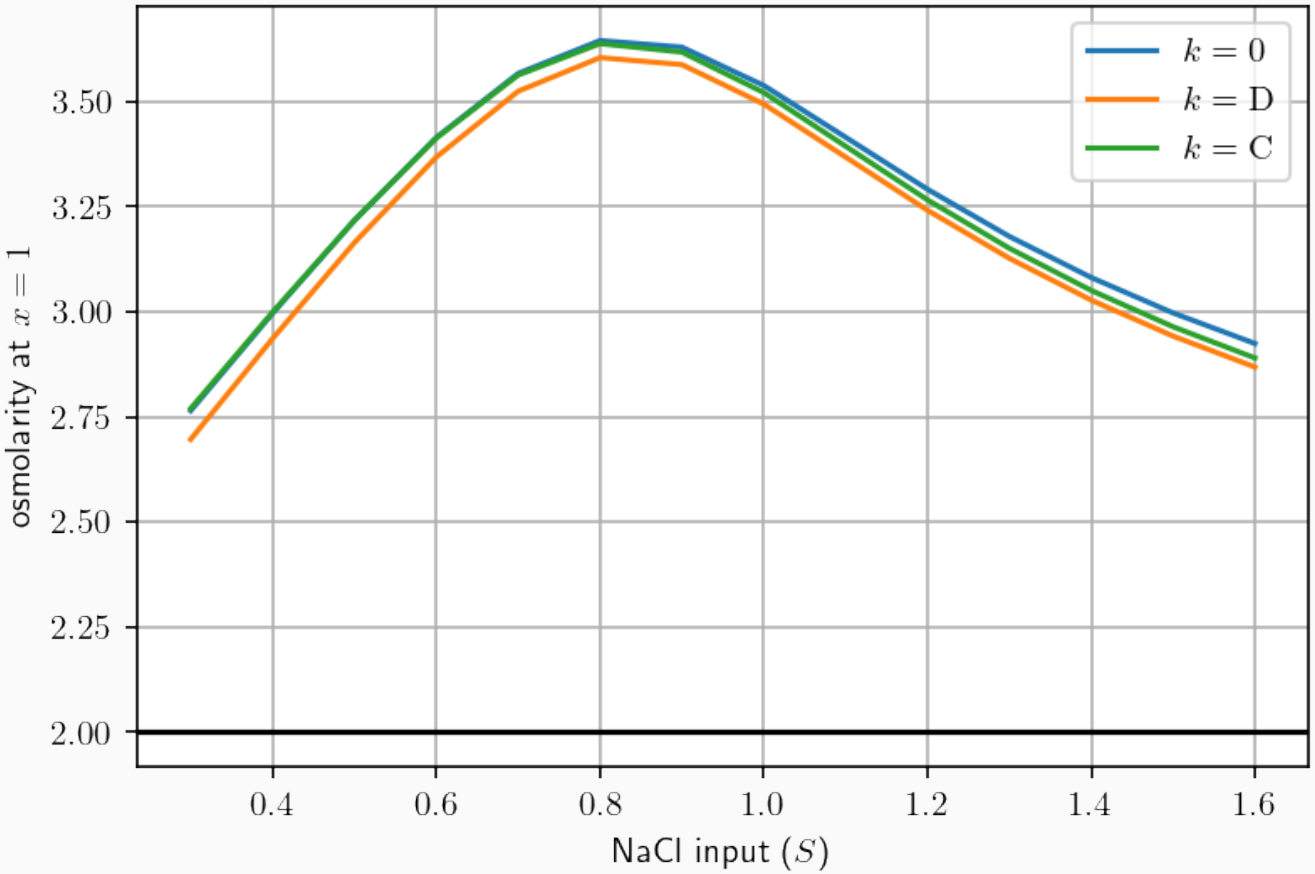


Figure 3: $\zeta_{\mathrm{D}} = \zeta_{\mathrm{C}} = 10,\ \gamma_u = \gamma_s = 1.2,\ U = 2,\ C = 2$

References

J. L. Stephenson, Y. Zhang, A. Eftekhari, and R. Tewarson. Electrolyte transport in a central core model of the renal medulla. *American Journal of Physiology-Renal Physiology*, 253(5):F982–F997, November 1987. doi: 10.1152/ajprenal.1987.253.5.f982. URL https://doi.org/10.1152/ajprenal.1987.253.5.f982.

J. L. Stephenson, Y. Zhang, and R. Tewarson. Electrolyte, urea, and water transport in a two-nephron central core model of the renal medulla. *American Journal of Physiology-Renal Physiology*, 257(3):F399–F413, September 1989. doi: 10.1152/ajprenal.1989.257.3.f399. URL https://doi.org/10.1152/ajprenal.1989.257.3.f399.