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Lens as an Osmotic Pump, a Bidomain Model

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Thanks to Weishi and Weizhang for inviting me
and Gloria for seeing that it all works

Mathematics Department

Kansas University

Lawrence KS USA

ABSTRACT

The lens of the eye has no blood vessels to interfere with vision. The lens is far too large for diffusion to provide food and clear wastes.

Experimental, theoretical and computational work has shown that the lens supports its own microcirculation. It is an osmotic pump that implements what physiologists have long believed "Convection provides what diffusion cannot."

We introduce a general (non-electro-neutral) model that describes the steady-state relationships among ion fluxes, water flow and electric field inside cells, and in the narrow extracellular spaces within the lens.

Using asymptotic analysis, we derive a simplified model exploiting the numerical values of physiological parameters. The model reduces to first generation 'circuit' models and shows the basis of computer simulations too large to easily understand. The full model helps resolve paradoxes that have perplexed molecular biologists: crucial physiological properties do not depend as expected on the permeability of the lens interior (to water flow).

Theme for Recent Lectures at Kansas U

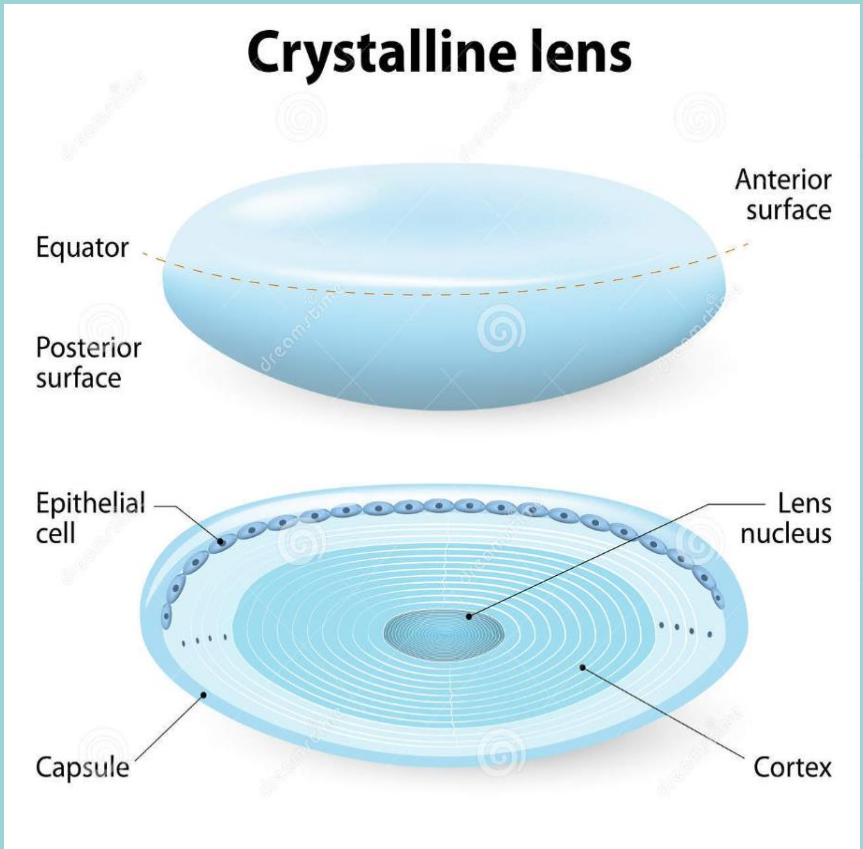
Bob Eisenberg

Examples of Precise Biophysics
at different scales, that yield
Physical Understanding of Biological Systems
and How They Work

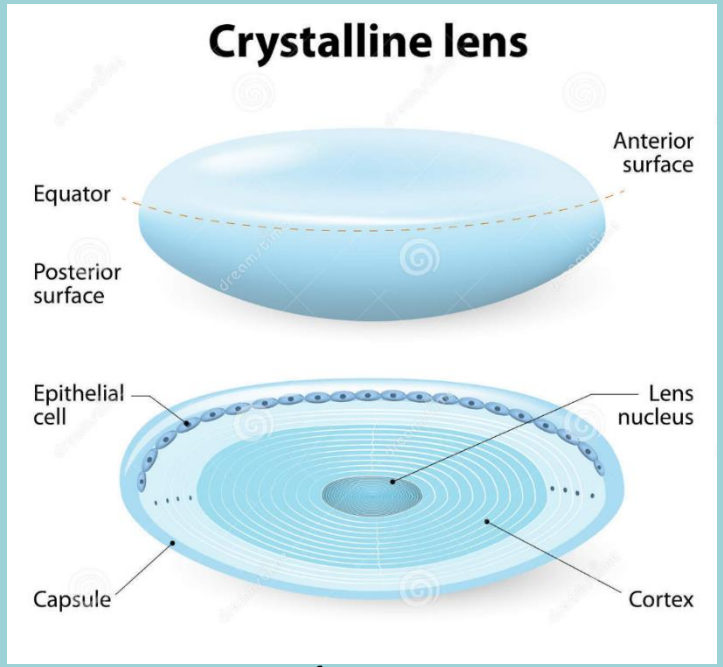
Checked by extensive experimentation

The Lens of the Eye:

Bidomain Model of an Osmotic Pump



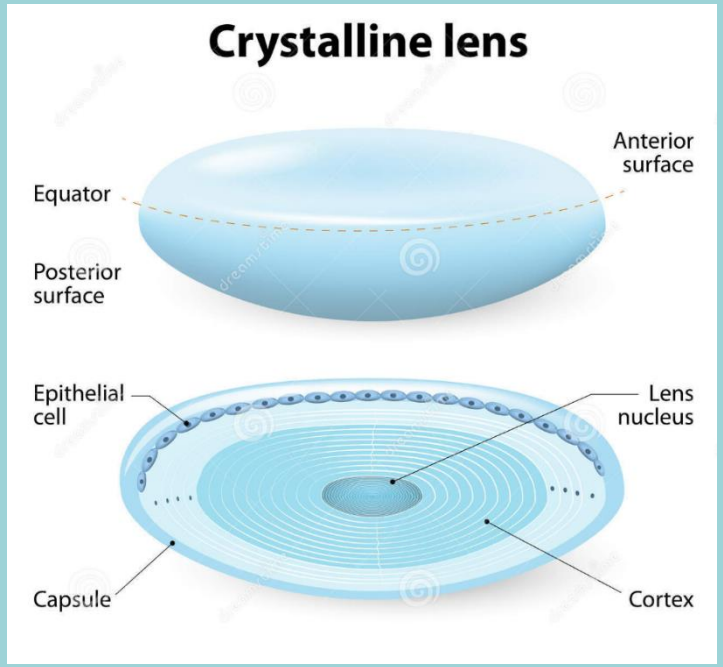
1 cm



The Lens is a Device to gather and focus light.

It is designed by evolution for a purpose:

To gather and refract light



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The Lens gathers and refracts light.

No blood vessels!!!

The Lens is a

Preparation

Chosen to Study

Convection and Circulation

By an Osmotic Pump

Without blood vessels!

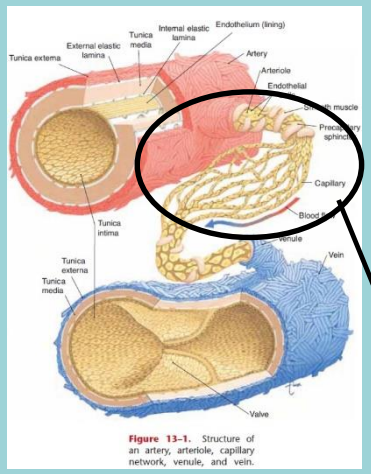
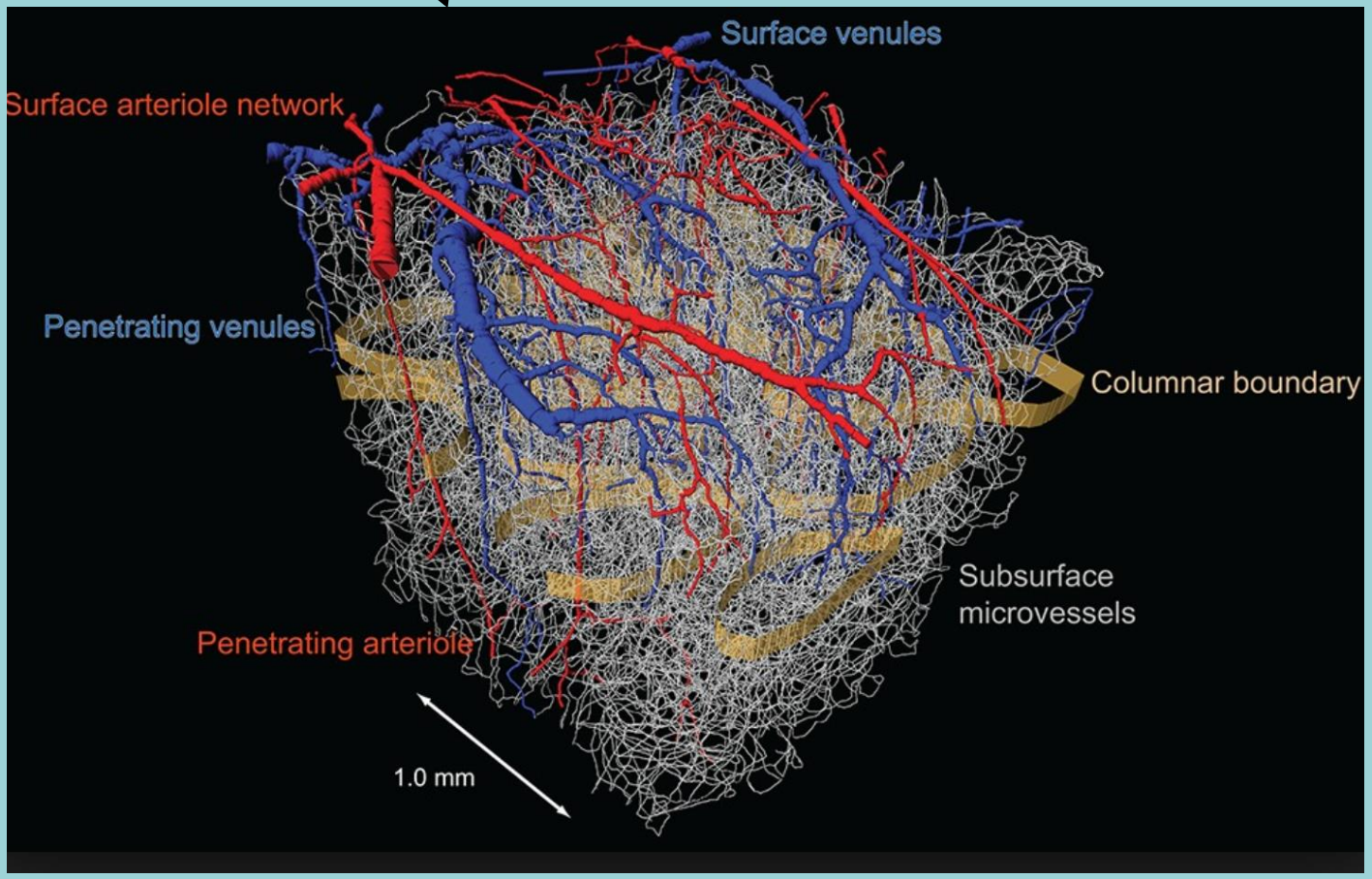


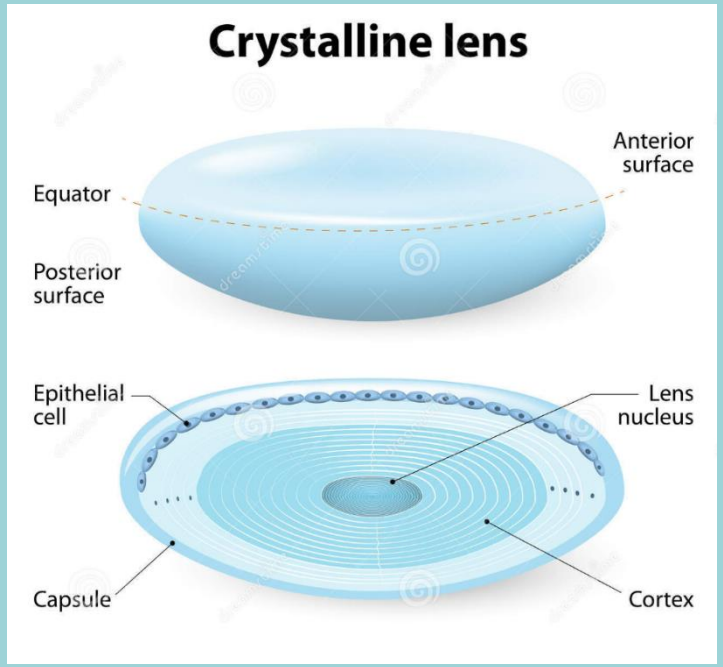
Figure 13–1. Structure of an artery, arteriole, capillary network, venule, and vein.

Circulatory System is Incredibly Dense.
Convection is needed.

Convection delivers what Diffusion cannot!

Diffusion is too slow to support life!!!





1 cm

Central Question:

How does the lens support circulation without blood vessels?

Central Idea of Biological Experiments

Preparation

We imagine that other biological systems use the same mechanism as the lens, most importantly the tiny extracellular spaces in the brain

Central Question:

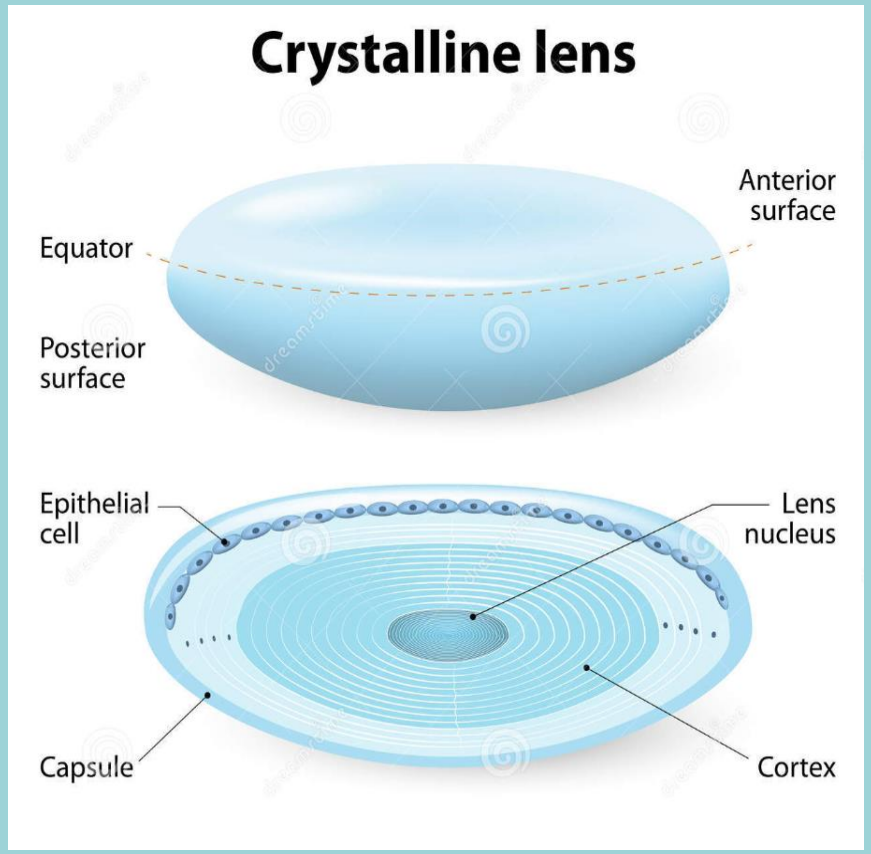
How does the lens support circulation

without blood vessels?

Central Question:

How does the lens support circulation without blood vessels?

ANSWER:
The Lens is an
Osmotic Pump



1 cm

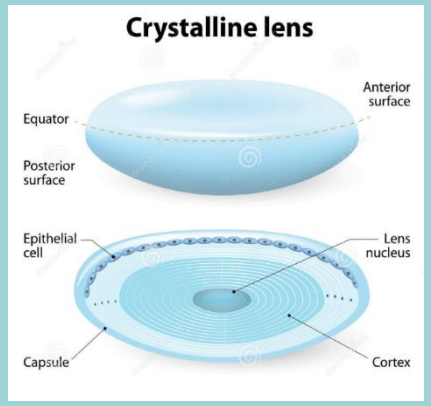
The Lens

An Osmotic Pump

Can we <u>prove</u> that the lens is an Osmotic Pump?

Are Osmotic Pumps a GENERAL BIOLOGICAL MECHANISM?

This is a seminar on Quantitative Biology as well as math



1 cm

Start with the Electrical Structure
because
Electrical Methods are Most Precise

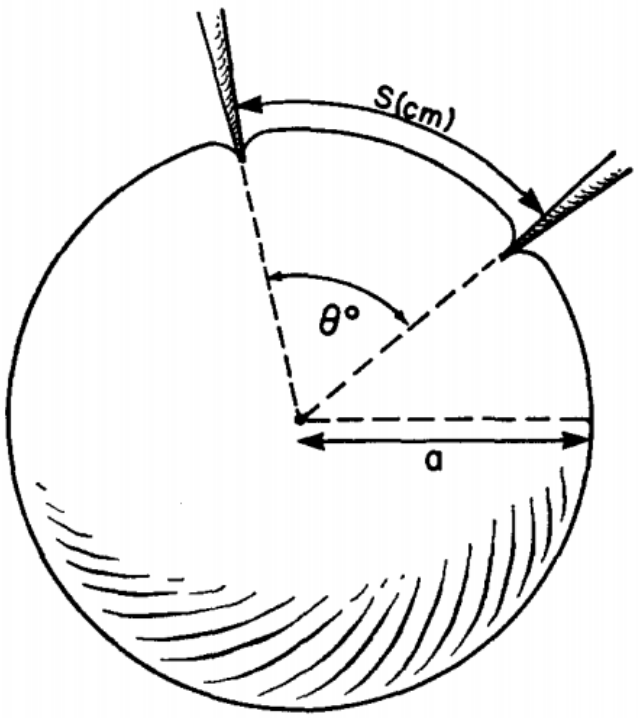
Structural Analysis of Electrical Properties

1. Qualitative Structure = Anatomy
2. Quantitative Structure Stereology
3. Electrical Model (from Poisson)
4. Impedance Measurements (DC to 10^4 Hz)
5. Parameter Estimation
6. Checking Parameter Invariance
7. Prediction of Biological Function

Structural Analysis of Electrical Properties uses **MATHEMATICS**

1.	Qualitative Structure = Anatomy	
2.	**Quantitative Structure Stereology**	**INVERSE PROBABILITY**
3.	**Electrical Model (from Poisson)**	**FIELD THEORY**
4.	**Impedance Measurements**	**CIRCUIT THEORY**
5.	**Parameter Estimation**	**INVERSE PROBLEM**
6.	**Checking Parameter Invariance**	**INVERSE PROBLEM**
7.	**Prediction of Biological Function**	**FIELD THEORY**

Electrical Methods are Most Precise
Spherical Cell



The steady-state solution can be written as

$$V_m = \frac{i_o R_m}{4\pi a^2}[\{1 - 2a/\Lambda\}\{1 + (a/\Lambda)D - (a/\Lambda)^2 E_o\} + (a/\Lambda)\csc\theta/2] \quad (1)$$

where

$$D = \ln\frac{\csc^2\theta/2}{1+\csc\theta/2}$$

$$E_o = \sum_{n=1}^{\infty}\frac{P_n(\cos\theta)}{n^2} \qquad n = 1, 2, 3, \cdots \quad (2)$$

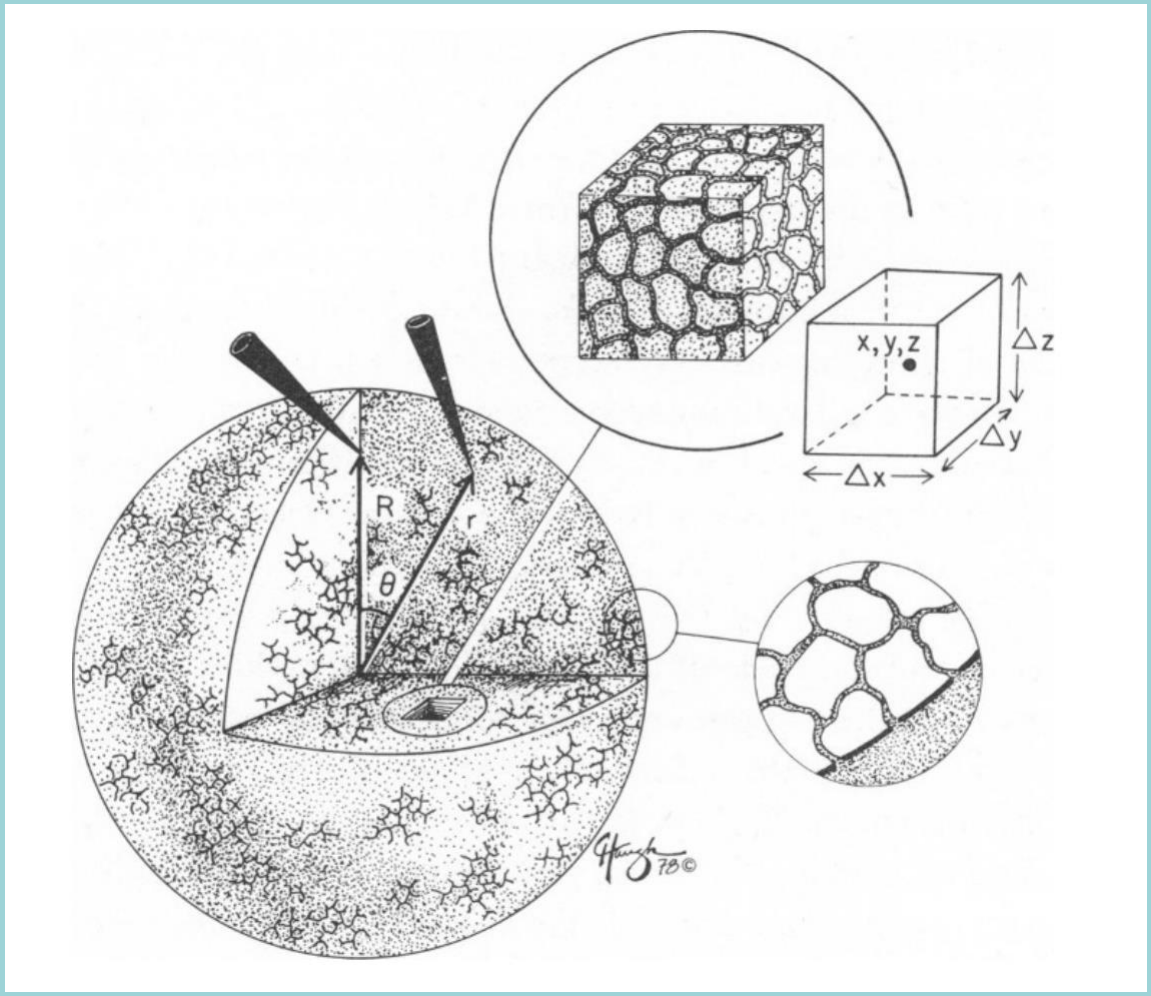
$$\frac{V_m}{i_o} \approx \frac{R_m}{4\pi a^2}\{1 + (a/\Lambda)\csc\theta/2\} = \frac{R_m}{4\pi a^2} + \frac{R_i}{4\pi a}\csc\theta/2 \quad (3)$$

Electrical Models often using Singular Perturbation Theory

exploiting membrane boundary condition

1. *J Gen Physiol, 1970.* ***55(6): p. 736-57.***
2. *Prog. Biophys. Mol. Biol. , 1970.* ***20: p. 1-65***
3. *SIAM J. Appl. Math., 1971.* ***21(2): p. 339-354.***
4. *Biophys J, 1972.* ***12(4): p. 384-403.***
5. *Annu Rev Biophys Bioeng, 1973.* ***2: p. 65-79.***
6. *J. Mathematical Biology, 1975.* ***2: p. 277-300.***
7. *J. Mathematical Biology, 1975.* ***2(4): p. 301-316.***
8. *SIAM J. Appl. Math., 1976.* ***30(2): p. 222-239.***
9. *Ann N Y Acad Sci, 1977.* ***303: p. 342-54.***
10. *Biophys J, 1977.* ***17(1): p. 57-93.***
11. *Biophys J, 1978.* ***23(2): p. 277-84.***
12. *CRC Crit Rev Bioeng, 1980.* ***4(3): p. 203-32.***
13. *Biophys J, 1983.* ***44(2): p. 225-48.***
14. *Biophys J, 1983.* ***42(1): p. 55-9.***
15. "*Membranes, Channels, and Noise 1984", p. 49-116.*
16. *Biophys J, 1985.* ***48(2): p. 253-67.***
17. **Kevorkian, J. and J.D. Cole,** ***1996***
    Multiple Scale & Singular Perturbation Methods.

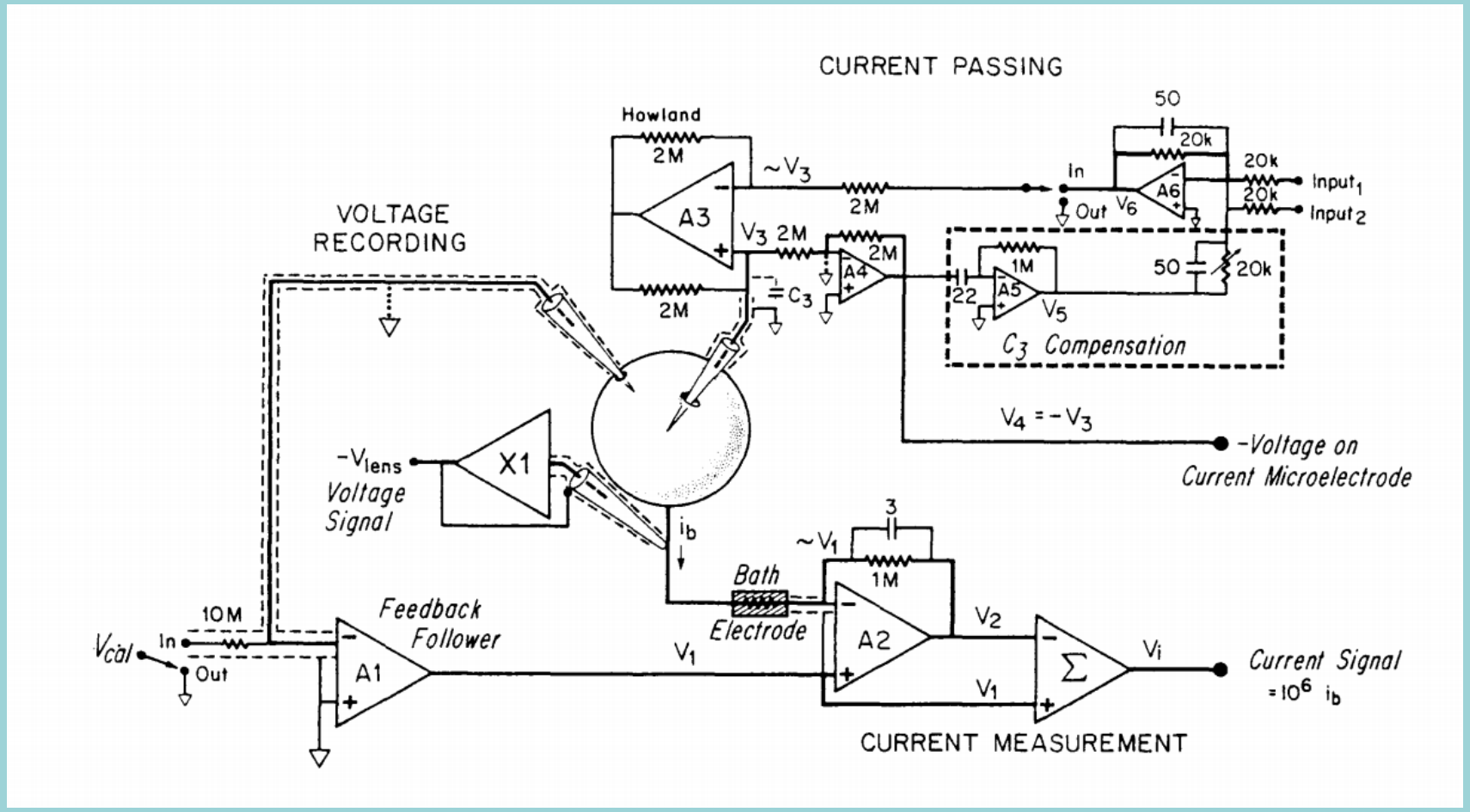
Electrical Models of Syncytia Can Be Derived Using Definitions of Vector Operators, Div and Grad



Eisenberg, Barcilon, and Mathias. Biophys. J. 25: 151-180 (1979).

The Lens: **An Osmotic Pump**

Electrical Methods are Most Precise
Impedance Measurements of Spherical Syncytia



Mathias, Rae, and Eisenberg. Biophys. J. 34: 61-85 (1981).

Electrical Measurements are Precise
Spherical Syncytia
TYPICAL DATA not selected for fit

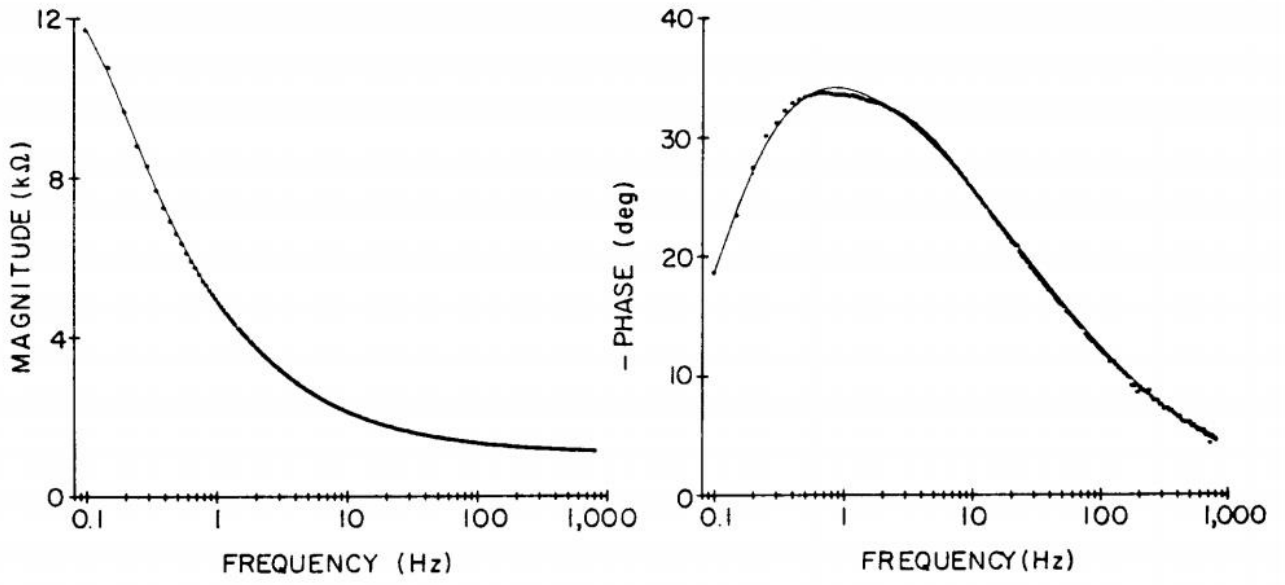


FIGURE 9 The magnitude, phase angle, and theoretical fit to impedance data of lens 2–8 taken from one electrode location. The electrode was at r_1 = 0.93 mm in a lens of radius a = 1.33 mm. The circuit parameters determined from the outermost location of the electrode are quite close to the average parameters determined from many locations (Table IV).

Rae, Mathias, and Eisenberg. Exp. Eye Res. 35: 471-490 (1982).

How is this precision possible?
Biology has Invariants!

Cell Interior is a (nearly) pure resistor
Membrane is a (nearly) a pure capacitor

Biology has Invariants!

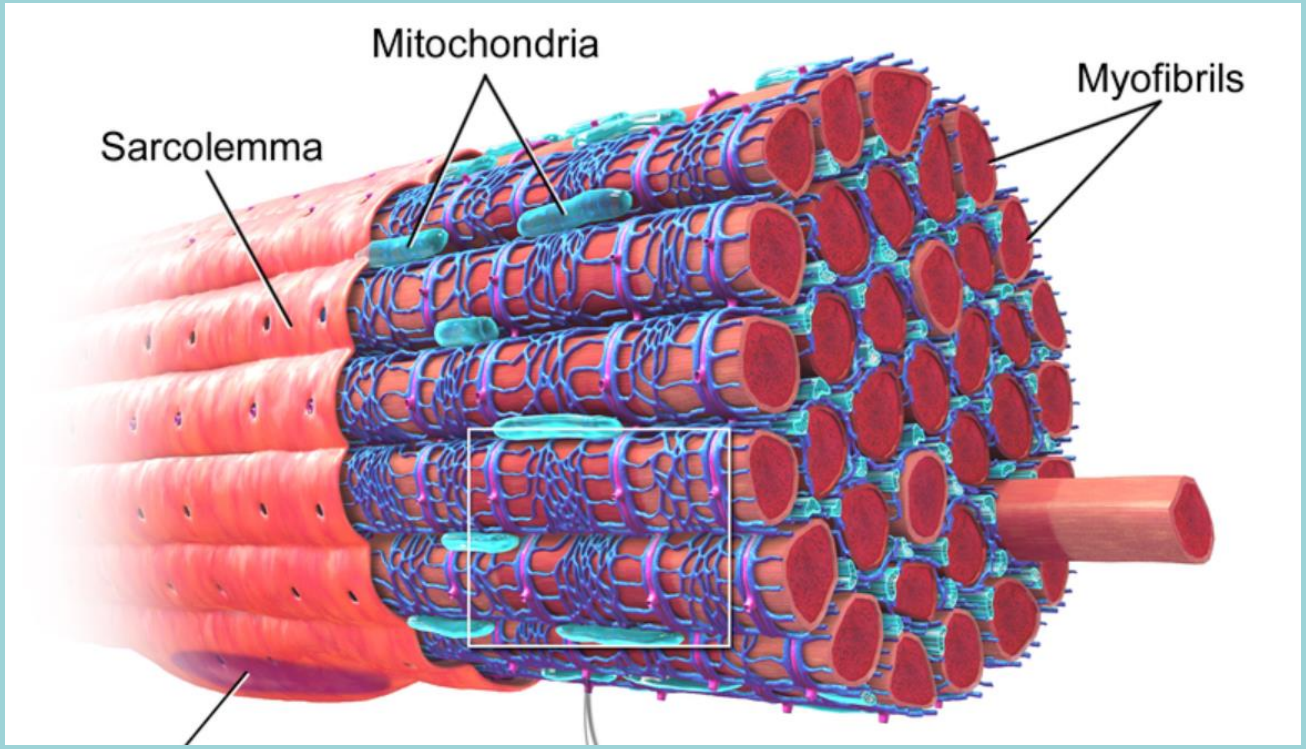
Cell Interior
is a (nearly) pure resistor

$$i = \frac{V}{R}$$

How is this precision possible?
Biology has Invariants!

Interior of Cells is (nearly) a pure resistor

even a muscle fiber

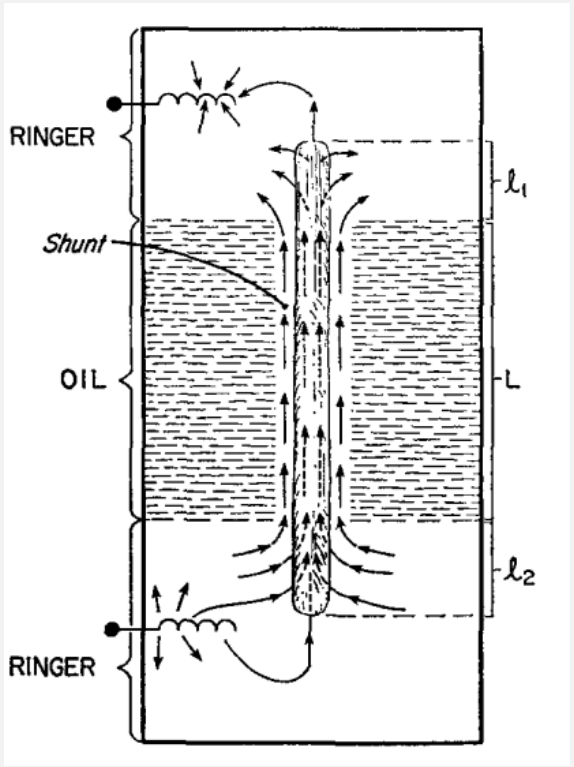


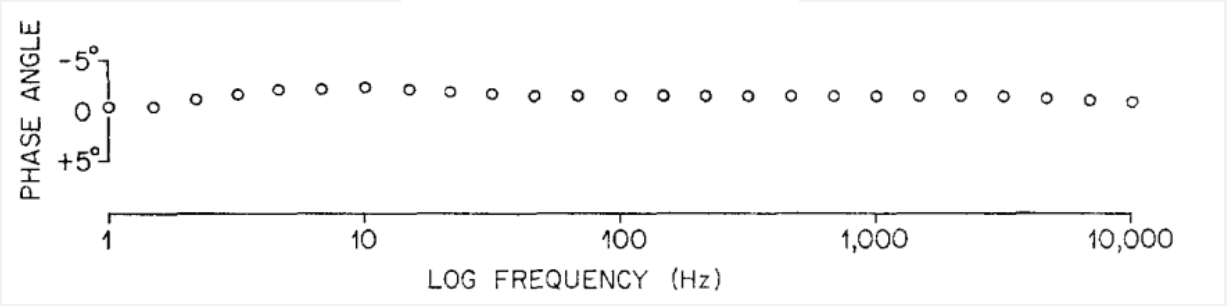
Muscle Interior is a Pure Resistor

Biology has Invariants

TABLE I
RESULTS FROM 14 MUSCLE FIBERS

	ϕmax
	degrees
	−1.48
	1.33
	0.74
	−2.45
	−2.42
	−2.22
	−1.58
	−1.60
	0.59
	0.68
	−1.79
	−0.62
	−1.86
	−2.25
Mean	−1.07
SD	1.34





Mobley, Leung, and Eisenberg, *J Gen Physiol, 1975. 65: p. 97-113.*

Interior of Cells is (nearly) a pure resistor
even a muscle fiber

How is this possible?

Electric Current Flows AROUND Obstacles

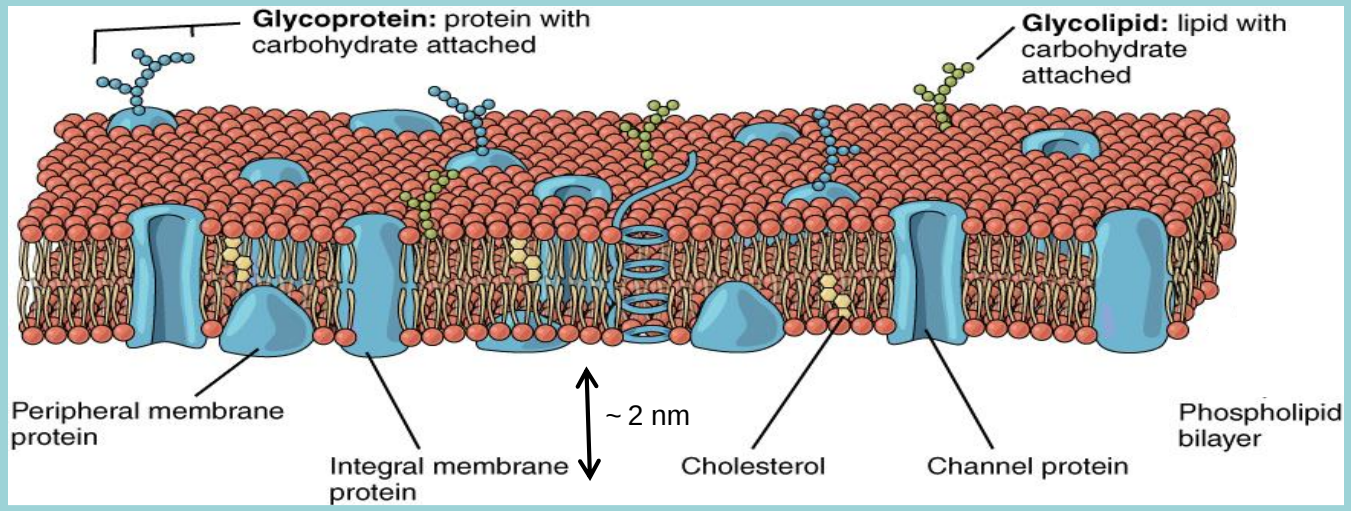
Electric Current Flows through Low Resistance Path

Property of PARALLEL RESISTORS

Biology has Invariants!

Cell Membrane
is a (nearly) pure capacitor

$$i = C\frac{\partial V}{\partial t}$$



Denis Haydon Life Work

Membrane is a (nearly) a pure capacitor

1. *J Theor Biol, 1965. 9(3): p. 433-43.*
2. *J Theor Biol, 1965. 9(3): p. 422-32.*
3. *J Theor Biol, 1965. 9(2): p. 278-96.*
4. *J Gen Physiol, 1965. 48: p. SUPPL:59-63.*
5. *J Mol Biol, 1968. 32(1): p. 149-50.*
6. *Br Med Bull, 1968. 24(2): p. 124-6.*
7. *J Theor Biol, 1968. 18(3): p. 371-9.*
8. *J Am Oil Chem Soc, 1968. 45(4): p. 230-40.*
9. *J Membr Biol, 1971. 5(3): p. 277-96.*
10. *Biochim Biophys Acta, 1979. 557(1): p. 259-63.*
11. *J Physiol, 1979. 287: p. 38P-39P.*
12. *J Physiol, 1979. 287: p. 2P.*
13. *Biophys J, 1980. 30(1): p. 129-36.*
14. *J Physiol, 1980. 309: p. 229-45.*

Estimated* Membrane Capacitance of Lens does NOT vary with ion concentrations

Expanded Scale

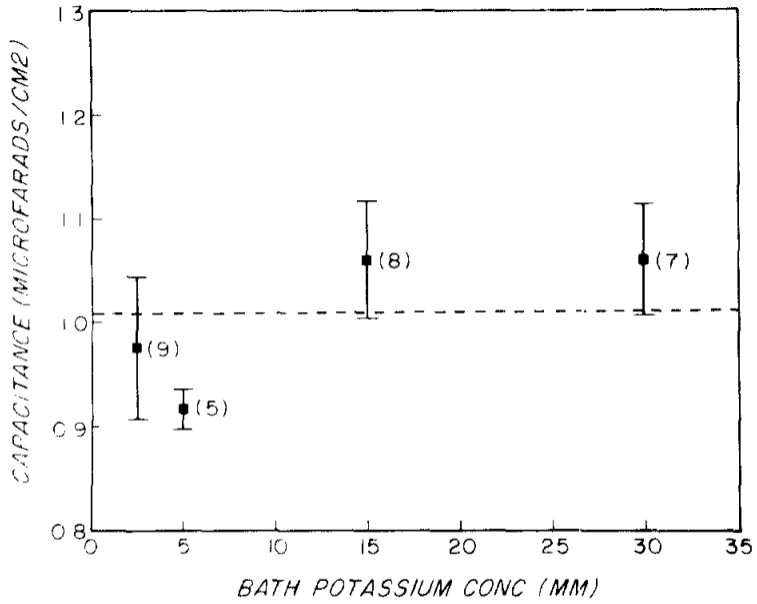


FIG. 3. Plot of the capacitance C_m of the inner membranes vs. the potassium concentration in the bath. The capacitance was determined by fitting the syncytial theory of Eisenberg et al. (1979), to the lens impedance data. Values are the mean ± S.D. with the number of lenses measured at each concentration given in parentheses. The mean capacitance determined from all measurements is shown (----).

*Note: this estimation involves structure, qualitative and quantitative, impedance measurement, field theory, and solving inverse problem. Errors in any of these will produce estimates that vary with concentration.

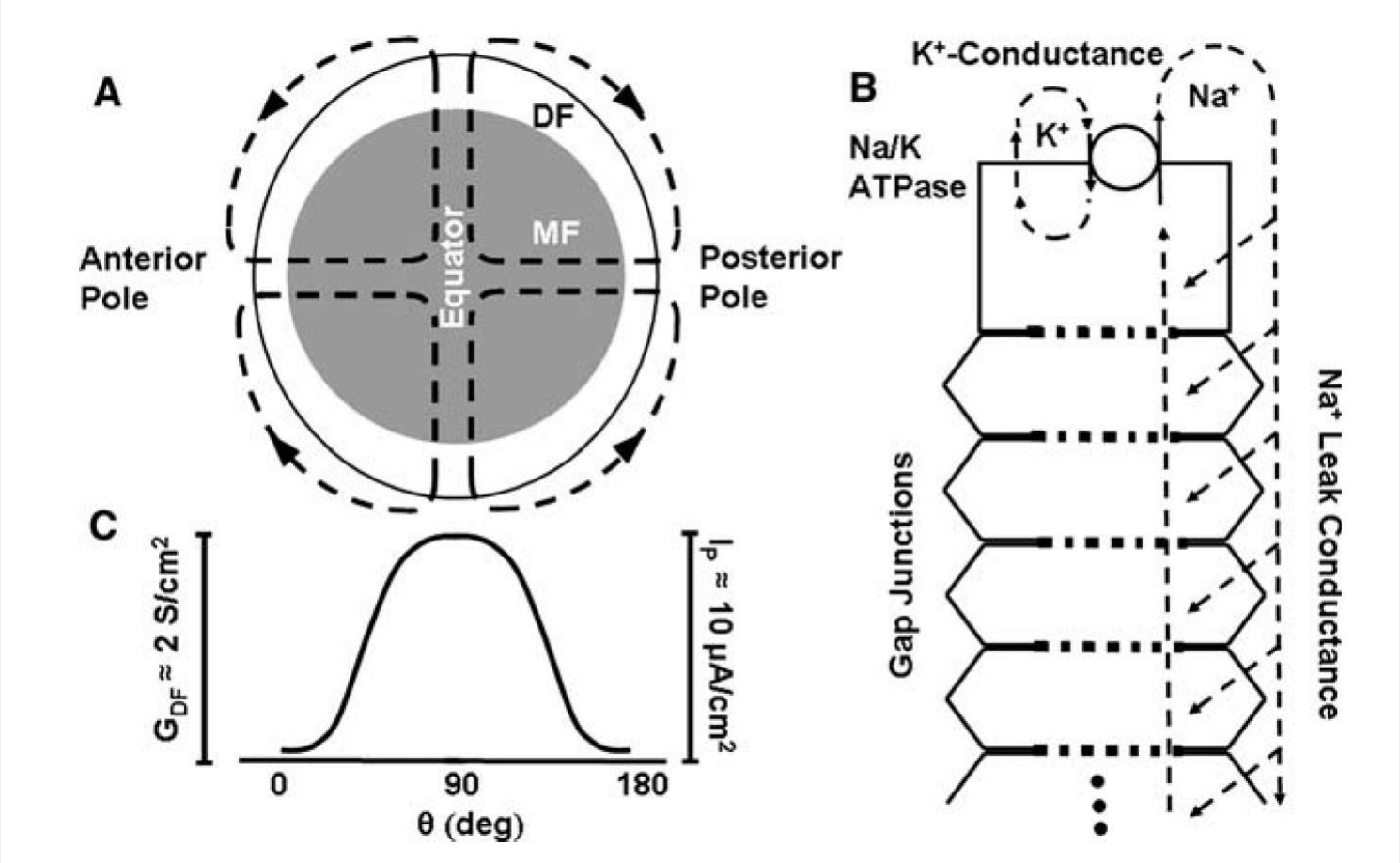
An Osmotic Pump

Can we <u>prove</u> that the lens is an Osmotic Pump?

Life work of Richard (Rick) Mathias

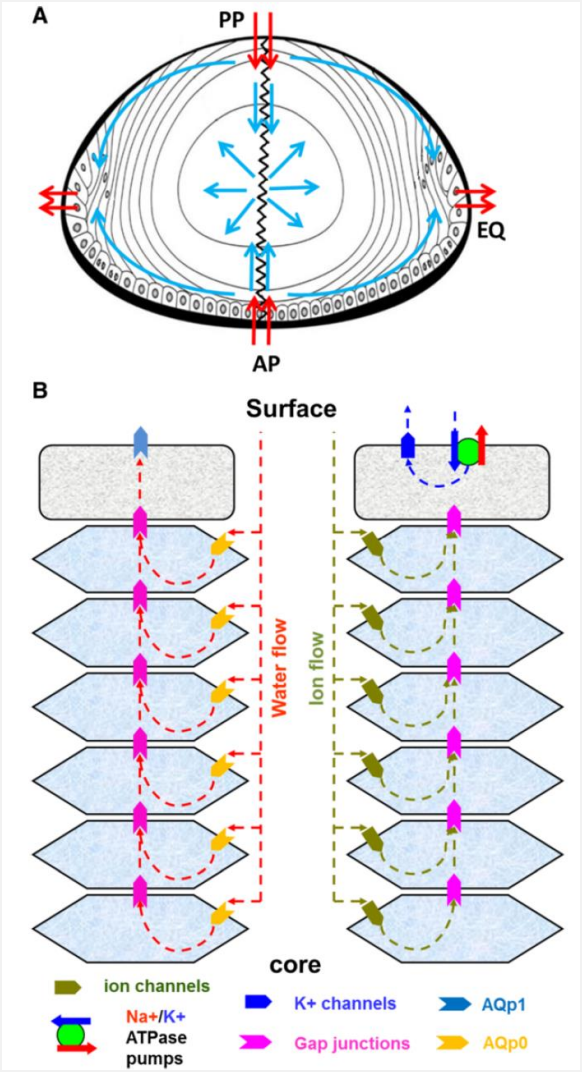
State University of New York SUNY Stony Brook

Too many papers to list! Do Google Search



Mathias, Kistler, and Donaldson,
J Membr Biol, 2007. 216(1): p. 1-16.

Computer Model
of Lens



Vaghefi, E., N. Liu, and P.J. Donaldson, *Biomed Eng Online, 2013.* ***12: p.85***

Direct Measurement of Pressure in the Lens

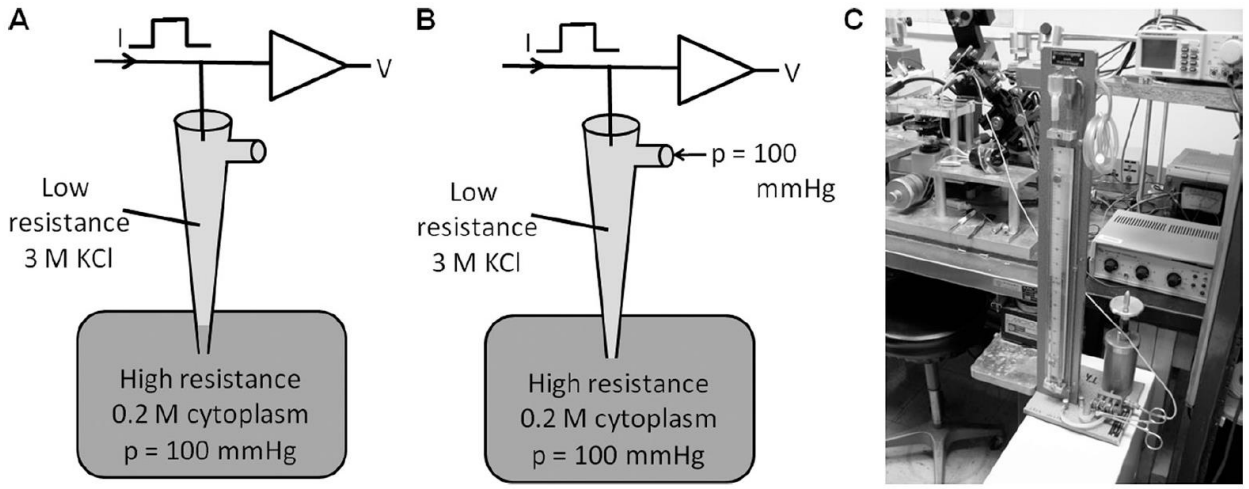
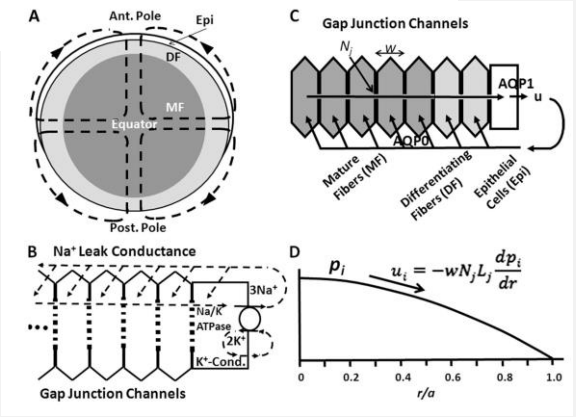


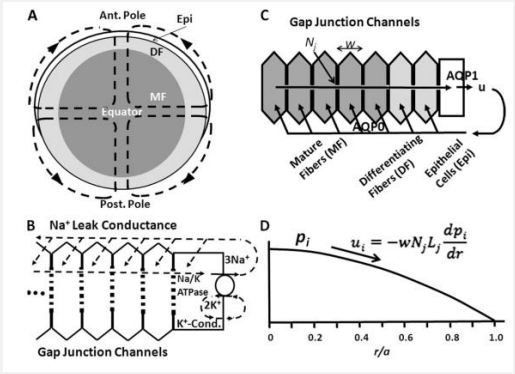
Figure 2. The intracellular pressure measuring system. (A) A sketch of the effect of intracellular pressure on the electrode–intracellular solution interface. An elevated intracellular pressure (e.g., 100 mmHg) over that in the bathing solution causes the interface to move up the shank of the electrode, thus filling the narrow tip with relatively high resistance cytoplasm. (B) When the same 100-mmHg pressure is applied to the port of the microelectrode, the interface moves back to the tip as shown, and the electrode resistance is restored to its relatively lower value recorded in the bathing solution. (C) The manometer used to adjust the hydrostatic pressure at the electrode port. The crank drives a piston to create the pressure, which is connected to the electrode port through the plastic tubing. When the electrode resistance is restored to its value in the bathing solution, such that an increase in applied pressure has no effect on resistance, whereas a small reduction in pressure causes a small increase in resistance, we assume the applied pressure equals the intracellular pressure. The value of applied pressure is then read from the column of mercury.



Gao, Sun, Moore, White, Brink, and Mathias,
J Gen Physiol, 2011. 137: 507-20.

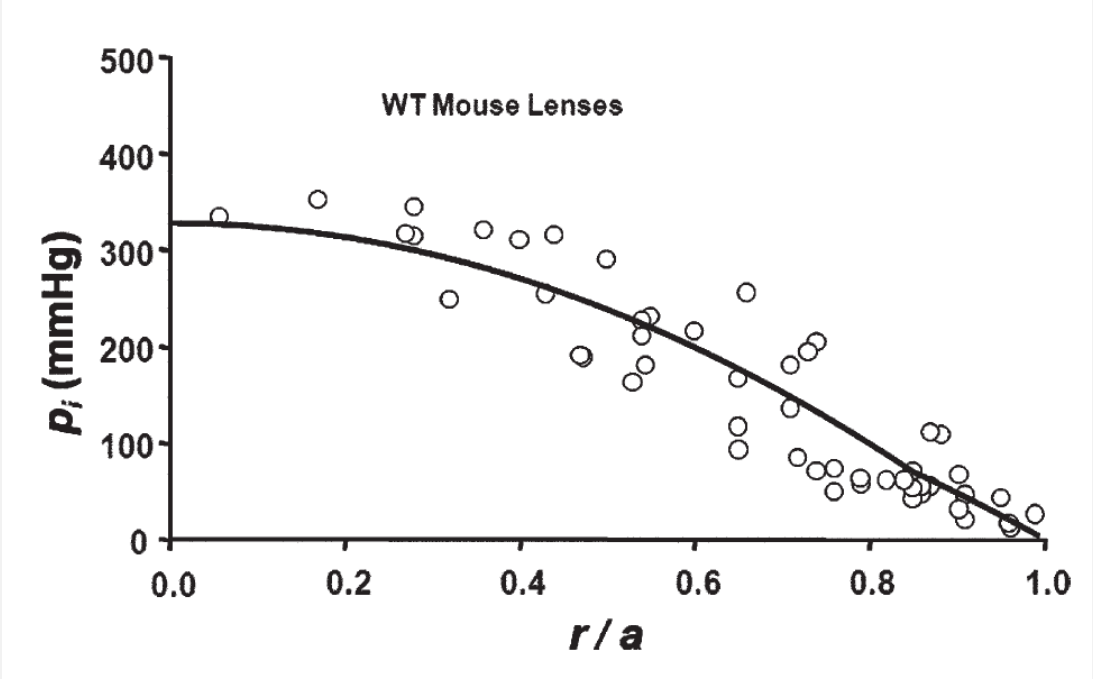
Direct Measurement of Pressure in the Lens

Theory

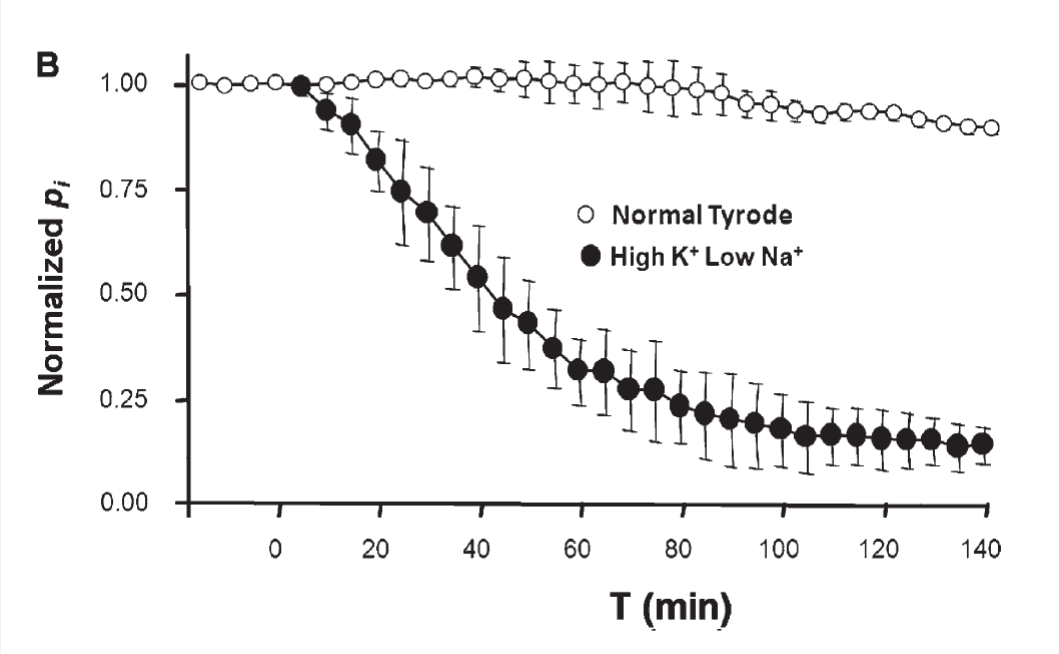


Gao, Sun, Moore, White, Brink, Mathias
J Gen Physiol, 2011
137: 507-20.

Experiment



Pressure with Reduced Transport in the Lens

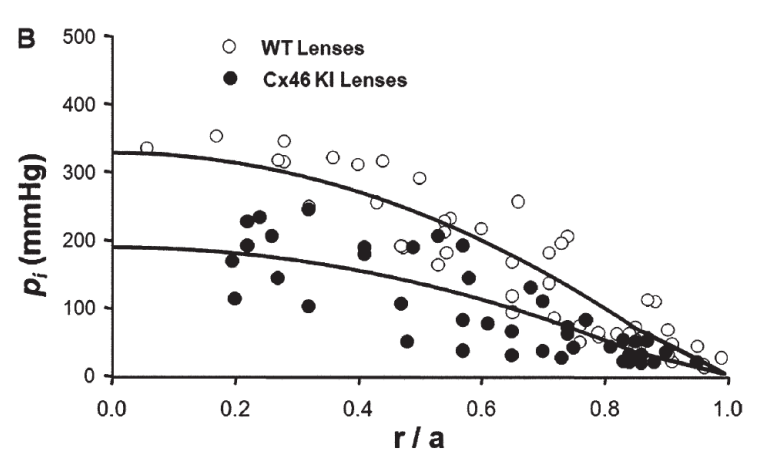


Normal Transport

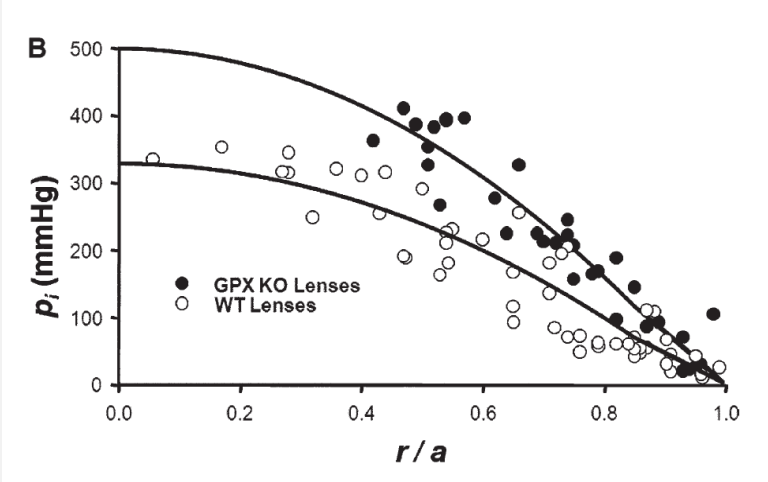
Reduced Transport

Gao, Sun, Moore, White, Brink, Mathias
J Gen Physiol, 2011
137: 507-20.

Changing Cell to Cell Coupling by Molecular Genetics



Increasing the Number of Junction Proteins

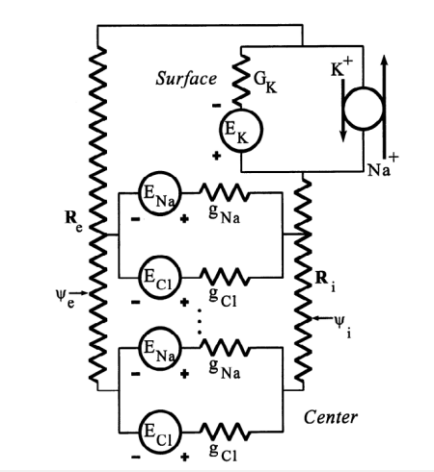


Reducing the Number of Junction Proteins

Gao, Sun, Moore, White, Brink, Mathias
J Gen Physiol, 2011
137: 507-20.

p. 509 of Gao, Sun, Moore, White, Brink, and Mathias,
J. General Physiology, 2011, 137: 507-520

“A comprehensive model of lens transport, including osmotic and hydrostatic pressure gradients in both the intracellular and extracellular compartments of the lens, is beyond the scope of this paper.”



Mathias, Rae, and Baldo (1997) Physiological Reviews 21-50.

Our Contributions

are to Derive Consistent Field Equations and Solve Them

Multiple Fields are Hard to Deal with Consistently without Variational Methods
(in engineering models or computations)

A great deal of confusion can result from nonmathematical reasoning Including paradoxes

Osmosis through a Semi-permeable Membrane
a Consistent Approach to Interactions
arXiv:1806.00646


Shixin Xu


Zilong Song


Huaxiong Huang

A Bidomain Model for Lens Microcirculation
Biophysical Journal (2019) 116: p. 1171-1184


Yi Zhu

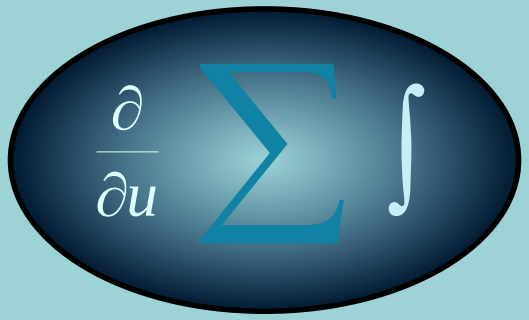

Shixin Xu


Huaxiong Huang

Inconsistent Models

produce confusion
even when correct

Mathematics



replaces
Inconsistent Models Models
with **Consistent**
Partial Differential Equations
and boundary conditions

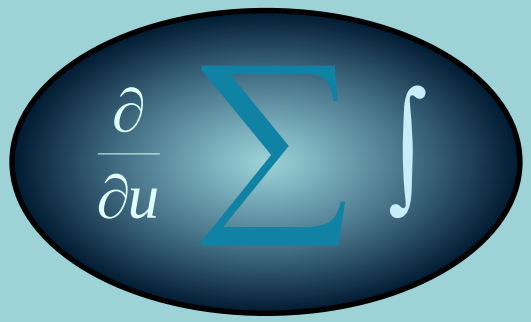
Scientists and Poets can Reach but

Engineers must Grasp

and not just reach
if
Devices are to Work
Uncalibrated Devices do not Work!

Poets
hope we will never learn the difference between dreams and realities

“Ah, … a man's reach should exceed his grasp,
Or what's a heaven for?”
Robert Browning
"Andrea del Sarto", line 98



Mathematics Creates our Standard of Living*

Partial Differential Equations
are needed to describe
Flow
driven by multiple fields

**e.g., Electricity, Computers, Fluid Dynamics, Optics, Structural Mechanics, …..*

We begin at the beginning:

Ionic Solutions are Complex Fluids

in which

‘everything interacts with everything else’

and

Flows are driven by convection, and diffusion.

Shixin Xu, Eisenberg, Song, and Huang
(2018)
arXiv:1806.00646, 35 pages.

Bulk Solutions and Membranes are described by Consistent Analysis of Coupled Water and Ionic Diffusion and Flow

The **Energy Variational Principle and Sharp Boundary Methods**
have been applied to a variety of membrane models,
allowing **density of solutions to be a function of concentrations**,
as is seen every day in chemistry laboratories
apparently for the first time

Unfortunately, so far, analysis has only been performed for **ideal solutions.**

Challenge

No one seems to know
how to formulate coupled water and ion **flow** and diffusion,
in the realistic nonideal case found in biology and electrochemistry
NOT equilibrium, not ideal,
must deal with saturation and finite size ions

Shixin Xu, Eisenberg, Song, and Huang (2018)
arXiv:1806.00646, 35 pages.

Challenge

No one seems to know
how to formulate coupled water and ion **flow** and diffusion,
in the realistic nonideal case found in biology and electrochemistry
NOT equilibrium, not ideal,
must deal with saturation and finite size ions.

Suggestion:
Combine EnVarA with Poisson Fermi approach of Jinn Liang Liu,
more than anyone else

Starling's Law has been derived: water flow is proportional to hydrostatic and osmotic difference from the Energy Variational Principle and a Sharp Boundary Methods

Total Energy Functional.

$$
\begin{aligned}
\mathrm{E}^{\mathrm{tot}} &= E_{kin} + E_{int} + E_{\Gamma} \\
&= E_{kin} + E_{es} + E_{ion} + E_{\Gamma} \\
&= \sum_{\pm} \int_{\Omega^{\pm}} (e_{kin}^{\pm} + e_{es}^{\pm} + e_{ion}^{\pm}) dx + \int_{\Gamma} (e_{\Gamma} + \gamma_0) dS \\
&= \sum_{\pm} \int_{\Omega^{\pm}} \left\{ \frac{1}{2} \rho^{\pm} |\mathbf{u}^{\pm}|^2 + \frac{1}{2} \mathbf{E}^{\pm} \cdot \mathbf{D}^{\pm} + k_B T \sum_i c_i^{\pm} \ln \left(\frac{c_i^{\pm}}{c_0} \right) \right\} \mathrm{dx} \\
&\quad + \int_{\Gamma} \left(\frac{C_m}{2} [\phi]^2 + \gamma_0 \right) dS
\end{aligned}
\tag{3}
$$

NOT unique
This is a PHYSICAL Model
e.g. it does not include Saturation produced by Finite size of ions

where c_0 is a characteristic ion density, C_m is membrane capacitance, γ_0 is the membrane surface tension. In the following, square brackets always denote the jumps across the interface.

$\sum_{\pm} \int_{\Omega^{\pm}} f^{\pm} dx = \int_{\Omega^{+}} f^{+} dx + \int_{\Omega^{-}} f^{-} dx$ is the sum of integration in left and right compartments weighted by the corresponding value of f.

The **dissipation functional** is defined as

$$
\begin{aligned}
\Delta = &\sum_{\pm} \int_{\Omega^{\pm}} 2\eta^{\pm} \left| \boldsymbol{D}_{\eta}^{\pm} \right|^2 dx + \sum_{\pm} \int_{\Omega^{\pm}} \lambda^{\pm} |\nabla \cdot \boldsymbol{u}^{\pm}|^2 dx + \frac{1}{k_B T} \sum_{\pm} \int_{\Omega^{\pm}} \sum_i D_i^{\pm} c_i^{\pm} |\nabla \tilde{\mu}_i^{\pm}|^2 dx \\
&+ \int_{\Gamma} G_1([\tilde{\mu}_i]) dS + \int_{\Gamma} G_2(Q_{\rho}) dS
\end{aligned}
\tag{4}
$$

Dissipation IS NOT unique
This is a PHYSICAL Model
e.g. it must it time and concentration dependence and much more
BUT
Mathematics must be consistent with the
TOTAL ENERGY FUNCTIONAL

Where $\boldsymbol{D}_{\eta} = (\nabla \boldsymbol{u} + (\nabla \boldsymbol{u})^T)/2$ is rate of strain, $\eta^{\pm}$ and $\lambda^{\pm}$ are the two Lame constants[109], $\tilde{\mu}_i^{\pm} = \tilde{\mu}_i^{\pm}(c_i^{\pm}, \phi^{\pm}, \rho^{\pm})$ and $D_i^{\pm}$ are the chemical potential and diffusion coefficient of i_{th} ion. The first three terms in dissipation functional are the dissipation induced by fluid friction, volume change and ion diffusion in the bulk region. The last two terms are the dissipation induced by irreversible osmosis .on the membrane. The forms of $G_1(x) \geq 0$ and $G_2(x) \geq 0$, for any x, will be discussed later.

Intracellular and Extracellular Velocities (1)

The intracellular velocity depends on the gradients of hydrostatic pressure and osmotic pressure (41,51,62), and the extracellular velocity is determined by the gradients of hydrostatic pressure and electric potential (41,67),

$$u_{ex} = -\frac{\kappa_{ex}}{\mu}\tau_c\frac{d}{dr}P_{ex} - k_e\tau_c\frac{d}{dr}\phi_{ex} \tag{2a}$$

and

$$u_{in} = -\frac{\kappa_{in}}{\mu}\left(\frac{d}{dr}P_{in} - \gamma_m k_B T\frac{d}{dr}O_{in}\right), \tag{2b}$$

where ϕ_l is the electric potential in the l space, τ_c is the tortuosity of extracellular region, μ is the viscosity of water, k_e is introduced to describe the effect of electro-osmotic flow, and κ_l is the permeability of the intracellular region ($l = in$) and the extracellular region ($l = ex$), respectively.

Flows and Coupling

Then, we obtain the following system for intra- and extracellular velocities in domain $\Omega = [0, R]$:

Coupling:

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2\mathcal{M}_{ex}u_{ex}\right) = -\mathcal{M}_v L_m\left(P_{ex} - P_{in} + \gamma_m k_B T\left(O_{in} - O_{ex}\right)\right) \tag{1a}$$

and

Conservation:

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2\left(\mathcal{M}_{ex}u_{ex} + \mathcal{M}_{in}u_{in}\right)\right) = 0, \tag{1b}$$

where u_l and P_l are the velocity and pressure in the intracellular and extracellular space, respectively, and O_l is the osmotic pressure with definition

Osmolarities:

$$O_{ex} = \sum_i C^i_{ex}, \quad O_{in} = \sum_i C^i_{in} + \frac{A_{in}}{V_{in}},$$

where C^i_l is the concentration of ith species ion in l space and A_{in}/V_{in} is the density of the permanent negatively charged protein. In this work, we assume the permanent negative charged protein is uniformly distributed within intracellular space with a valence of $\bar{z}$. Here, $\mathcal{M}_l$ is the ratio of intracellular area ($l = in$) and extracellular area ($l = ex$), $\mathcal{M}_v$ is the membrane area per volume unit, γ_m is the intracellular membrane reflectance, L_m is intracellular membrane hydraulic permeability, k_B is the Boltzmann constant, and T is temperature.

Ion Circulation

With similar assumptions, the conservation of ion concentration yields the following ion flux system:

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2\mathcal{M}_{ex}J^i_{ex}\right) = \mathcal{M}_v j^i_m \tag{4a}$$

and

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2\left(\mathcal{M}_{ex}J^i_{ex} + \mathcal{M}_{in}J^i_{in}\right)\right) = 0. \tag{4b}$$

The ion flux in the intracellular region J^i_{in} and ion flux in the extracellular region J^i_{ex} are defined as

$$J^i_{ex} = C^i_{ex}u_{ex} - D^i_{ex}\tau_c\frac{d}{dr}C^i_{ex} - D^i_{ex}\tau_c\frac{z^i e}{k_B T}C^i_{ex}\frac{d}{dr}\phi_{ex}, \tag{5a}$$

Membrane Flux of Ions

$$j^i_m = \frac{g^i}{ez^i}\left(\phi_{in} - \phi_{ex} - E^i\right), \tag{6a}$$

$$j^i_s = \frac{G^i}{ez^i}\left(\phi_{in} - \phi_{ex} - E^i\right), \tag{6b}$$

where $E^i = k_B T/ez^i \log(C^i_{ex}/C^i_{in})$ is the Nernst potential (an expression of the difference of chemical potential) of the ith species ion.

Electroneutral Expansion

from PNP = Poisson Nernst Planck,

named by Eisenberg & Chen, 1993, Biophysical Journal **64: A22.**

NOT electroneutral

Because of the capacitance of the cell membrane, assumptions of exact charge neutrality can easily lead to paradoxes because they oversimplify Maxwell's equations by leaving out altogether the essential role of charge. We use the analysis of (70) and thus introduce a linear correction term replacing the charge neutrality condition (41,51) without introducing significant error (see also (71)),

$$(1-\eta)\left(\sum_i ez^i C^i_{ex}\right) = -\mathcal{M}_v C_m(\phi_{in}-\phi_{ex}) \qquad (10a)$$

and

$$\eta\left(\sum_i ez^i C^i_{in} + \bar{z}e\frac{A_{in}}{V_{in}}\right) = \mathcal{M}_v C_m(\phi_{in}-\phi_{ex}), \qquad (10b)$$

where η is the porosity of intracellular region and C_m is capacitance per unit area.

Song, Cao, and Huang, *Physical Review E, 2018. 97(1): p. 012411*

Simplified Model

by well-defined
asymptotic expansion

With ordering

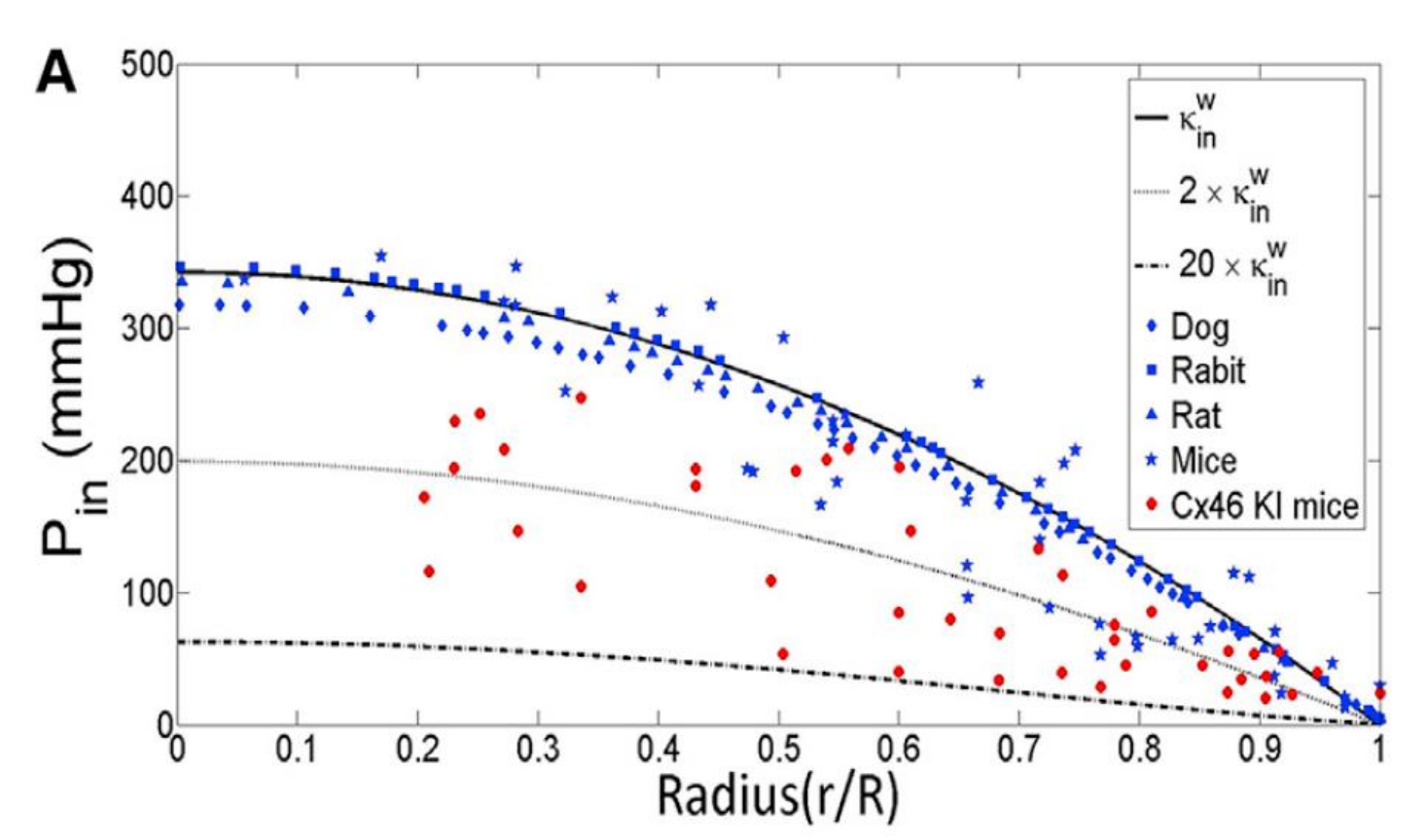
$$\{\delta_1, \delta_8\} \subset O(\varepsilon), \quad \{\delta_0, \delta_3\} \subset O(\varepsilon^2),$$
$$\{\delta_2, \delta_4, \delta_5, \delta_6, \delta_7\} \subset o(\varepsilon^2). \tag{16}$$

$\delta_9 = D_l^{Cl} - D_l^K$ and $\delta_{10} = D_l^{Cl} - D_l^{Na}$, $l = in, ex$, it yields

$$\delta_9 = O(\varepsilon^2), \quad \delta_{10} = O(\varepsilon). \tag{17}$$

$$\delta_0 = \frac{\mathcal{M}_{ex}}{\mathcal{M}_{in}},$$
$$\delta_1 = \frac{k_e \tau_c k_B T}{eRu_{ex}^*},$$
$$\delta_2 = \frac{\mu R u_{in}^*}{\kappa_{in} \gamma_m k_B T O^*},$$
$$\delta_3 = \frac{P^*}{\gamma_m k_B T O^*},$$
$$\delta_4 = \frac{\mathcal{M}_{in} u_{in}^*}{R \mathcal{M}_v L_m \gamma_m k_B T O^*},$$
$$\delta_5 = \frac{u_{in}^*}{L_s \gamma_s k_B T O^*},$$
$$\delta_6 = \frac{\mathcal{M}_v C_m k_B T}{e^2 C^* \eta},$$
$$\delta_7 = \frac{\mathcal{M}_v C_m k_B T}{e^2 C^* (1-\eta)}$$
$$\delta_8 = \frac{\mathcal{M}_{ex} D_{ex}^*}{\mathcal{M}_{in} D_{in}^*},$$
$$\delta_9 = \frac{D_l^{Cl} - D_l^K}{D_l^*}, \; l \in \{in, ex\}$$
$$\delta_{10} = \frac{D_l^{Cl} - D_l^{Na}}{D_l^*}, \; l \in \{in, ex\}$$
$$\delta_{11} = \frac{C_{in}^{Cl,0}}{C_{ex}^{Cl,0}},$$

Comparison with Experimental Results



Dependence on 'Connexin Permeability' κ_{in}

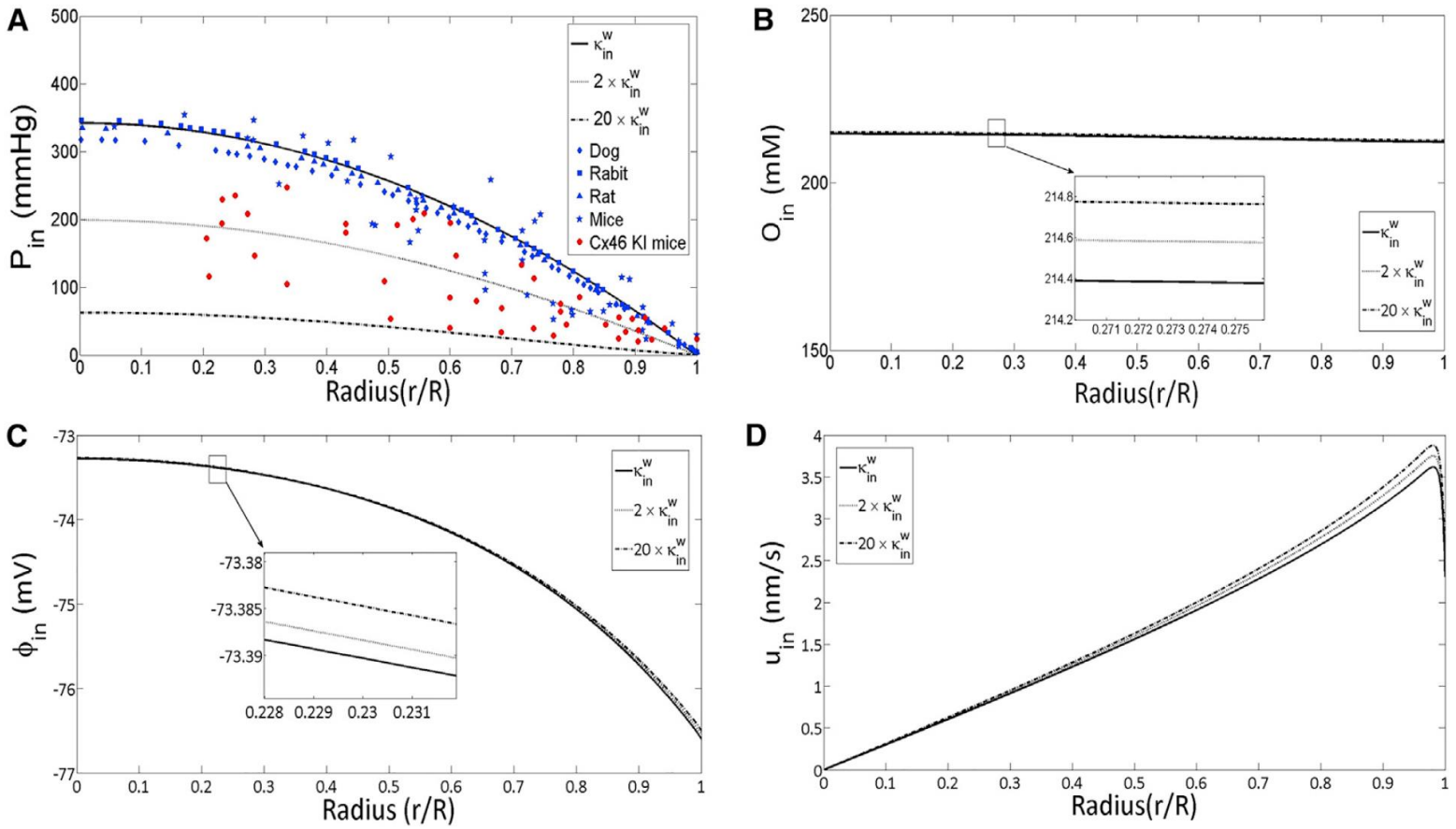
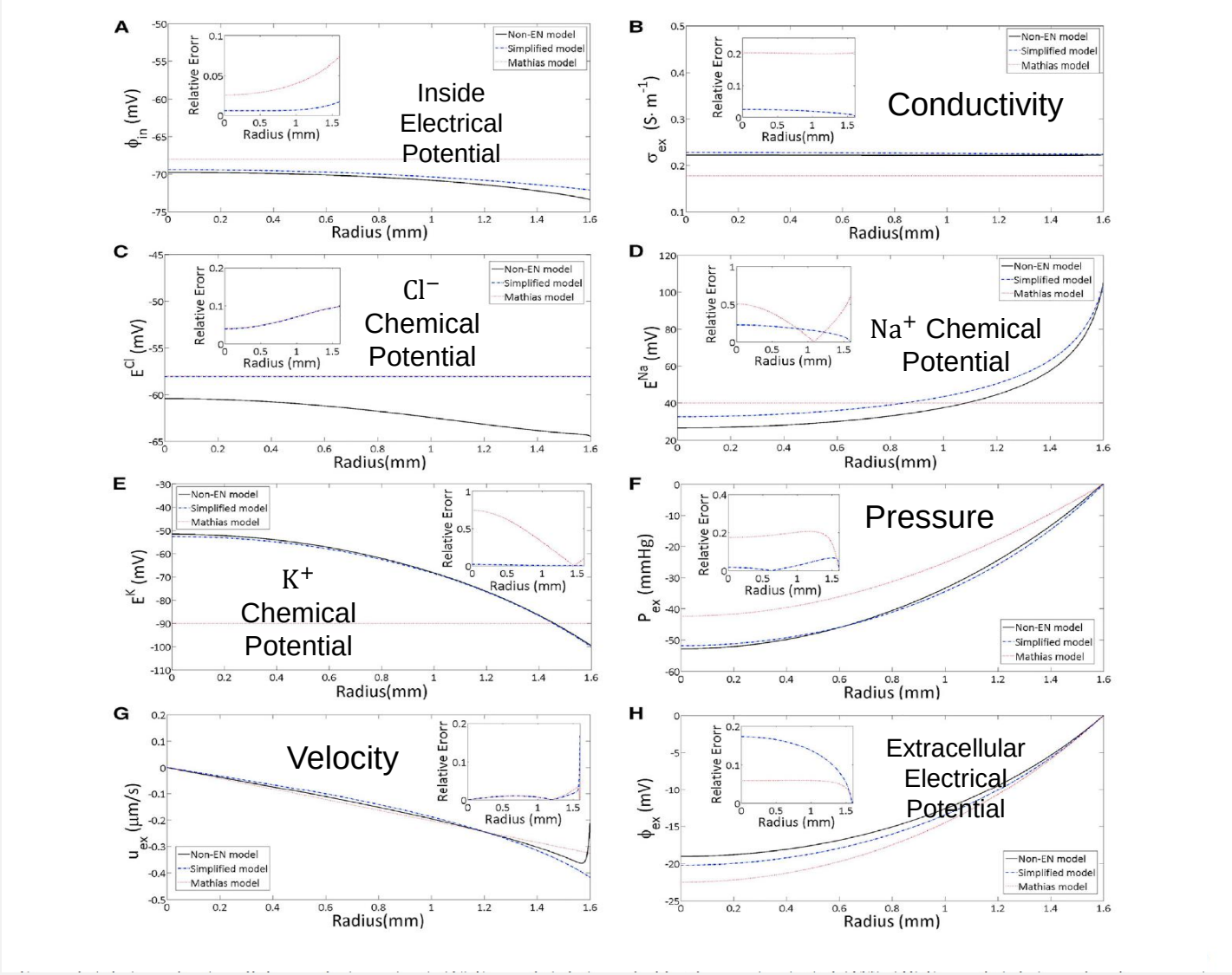


FIGURE 3 Comparison between different κ_{in}. (*A*) Comparison between simulation results and experimental results. The experimental data of dog, rabbit, and rat come from (47). Mice and Cx46 KI mice come from (28). According to (28), the Cx46 KI mice lens has twice the number density of lens gap-junction channels compared to mice. The parameter $\kappa_{in}^w = 4.6830 \times 10^{-20}/\mathrm{m}^2$, and radius is written in dimensionless units for different species. (*B*) Space distribution of intracellular osmotic pressure (O_{in}). (*C*) Space distribution of intracellular electric potential (ϕ_{in}). (*D*) Space distribution of intracellular water velocity (u_{in}). To see this figure in color, go online.

Non-Electroneutral Model *vs.* Simplified, *and* Mathias Models

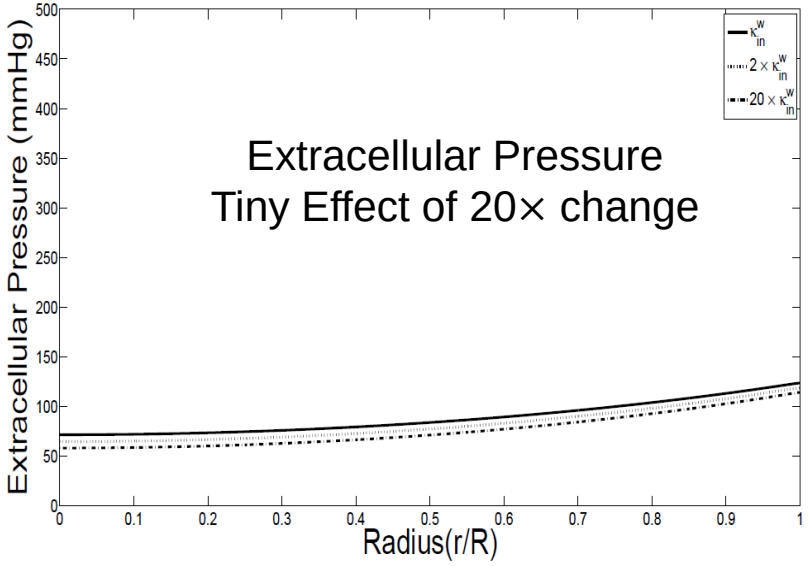


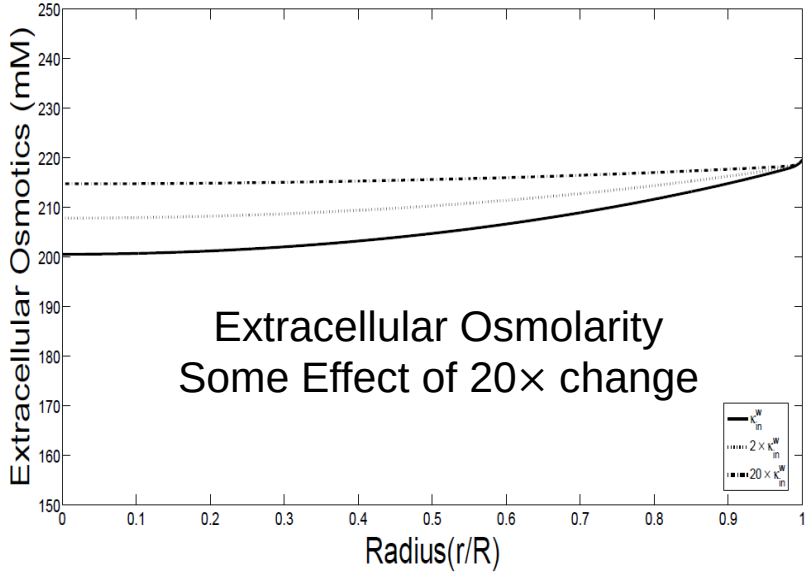
Resolution of Troubling Paradoxes in our Models

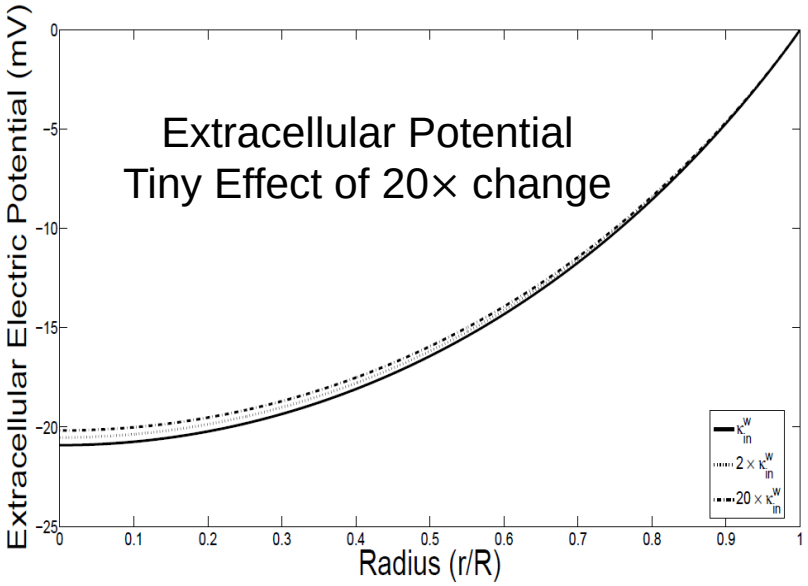
Perturbation Expansion shows that
Many intracellular and extracellular quantities are INSENSITIVE to increases in permeability EVEN BY A FACTOR of 20×

Because many quantities
depend only on the extracellular potential,
and the
Extracellular Potential is Insensitive
to
Permeability

Effect of Permeability κ_{in}







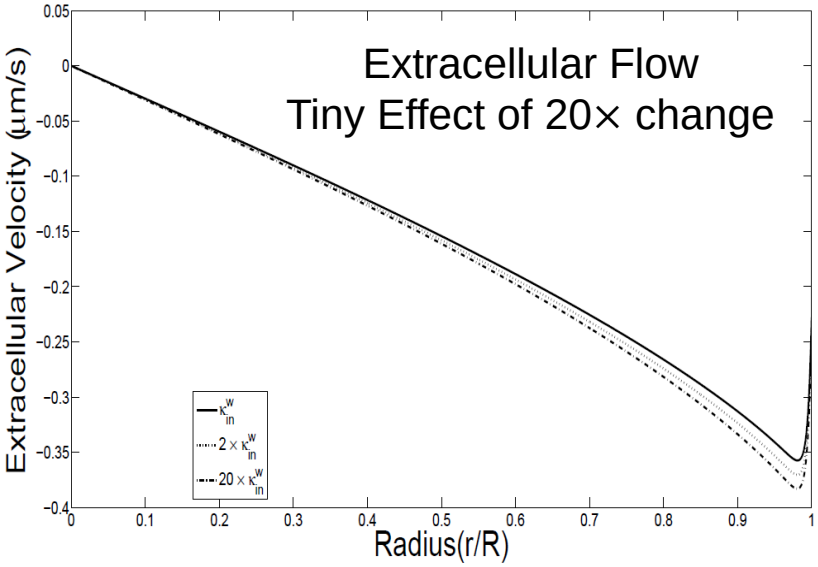
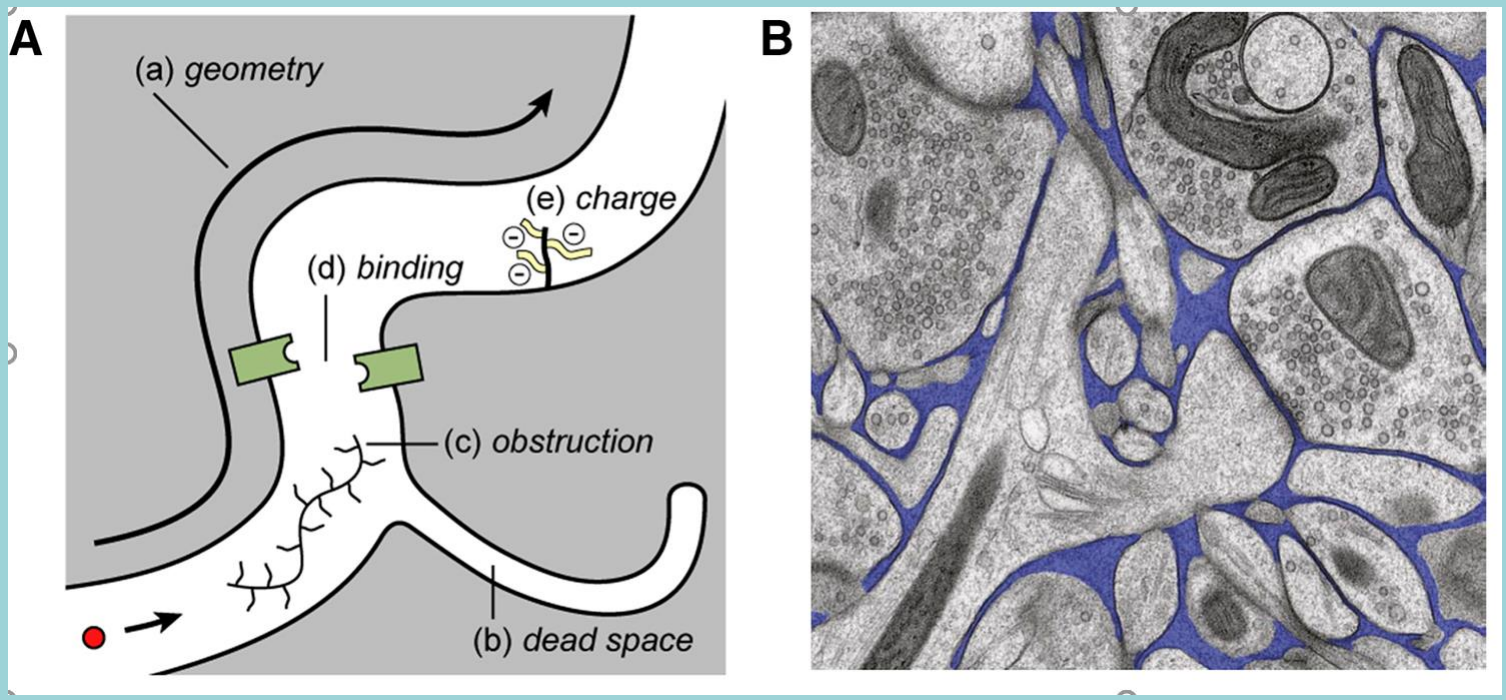


Figure D.5: Comparison between different κ_{in}.

“Brain Extracellular Space: The Final Frontier”

Nicholson and Hrabětová,
Biophysical Journal, 2017. 113: p. 2133-2142.



Stirred by an Osmotic Pump
like the lens,
at work and in sleep ??

Any Questions ?