Flushing Waste in the Central Nervous System in Sleep

A Glymphatic Hypothesis

K^+ in Optic Neve of Necturus

Bob Eisenberg
October 21, 2021

University of Illinois Chicago
Biomedical Engineering Seminar
October 22, 2021

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Thanks to James Patton, Jie Liang, and Tom Royston
for the kind invitation

Thanks to Tina Moore for all the support

and

Thanks to Rich Magin
for many fine interactions through the years

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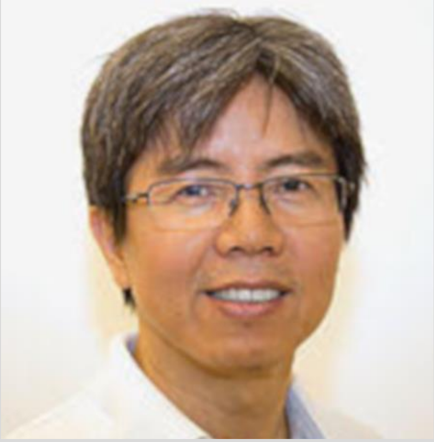
The central nervous system has a tiny extracellular space that can be filled with flows from nerve and glia. Potassium ions in that space can easily block signaling in nerve fibers and thus become a toxic waste. Sleep is said to flush toxic wastes from the brain, in the **glymphatic hypothesis,** proposed by others**.** Qualitative hypotheses like this are difficult to test and can lead to more discussion than knowledge. Numbers are needed because flows in complex structures are complex. We show how to construct models that are field theories built on conservation laws written as partial differential equations in three dimensions and time. These differential equations of nerve, glia and extracellular space fit experimental data in some detail, as do equations of the lens of the eye. Computation shows that extracellular potassium in optic nerve is maintained by bulk flow, mostly in the glia. The glia acts as a pipe that moves potassium by convection away from the nerve membrane, presumably into blood vessels, as proposed by the glymphatic hypothesis.

Collaborators

Project Leader



Yi Zhu
毅 朱

Huaxiong Huang
华雄 黄

Shixin Xu
士鑫 徐

1) arXiv:2105.14411. (2021) Derivation: Membranes in Optic Nerve Models
2) Biophysical Journal (2019) 116: p. 1171-1184 Lens of the Eye
3) Physics of Fluids (2021) 33(4): 041906. Physics of Model
4) Biophysical journal 120(15): 3008-3027. Biological Implications

Details are in Publications

Zhu, Y., S. Xu, R. S. Eisenberg and H. Huang (2021).
Optic nerve microcirculation: Fluid flow and electrodiffusion.
Physics of Fluids 33(4): 041906.

Zhu, Y., S. Xu, R. S. Eisenberg and H. Huang (2021).
A tridomain model for potassium clearance in optic nerve of Necturus.
Biophysical journal 120(15): 3008-3027.

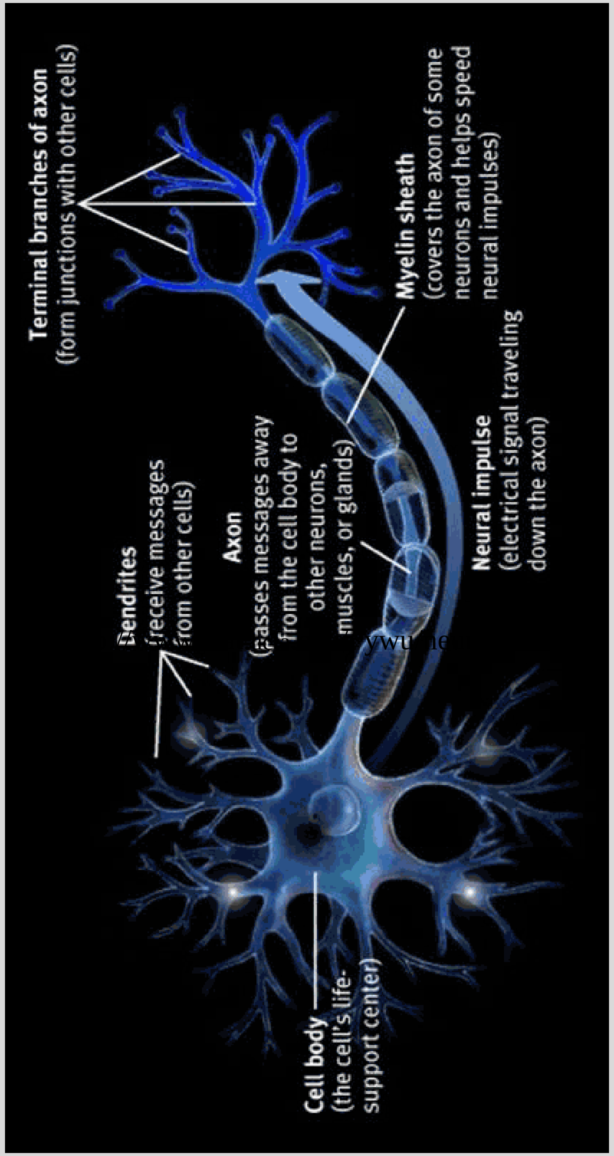
Supporting Publications

Xu, S., B. Eisenberg, Z. Song and H. Huang (2018).
Osmosis through a Semi-permeable Membrane: a Consistent Approach to Interactions.
arXiv preprint arXiv:1806.00646.

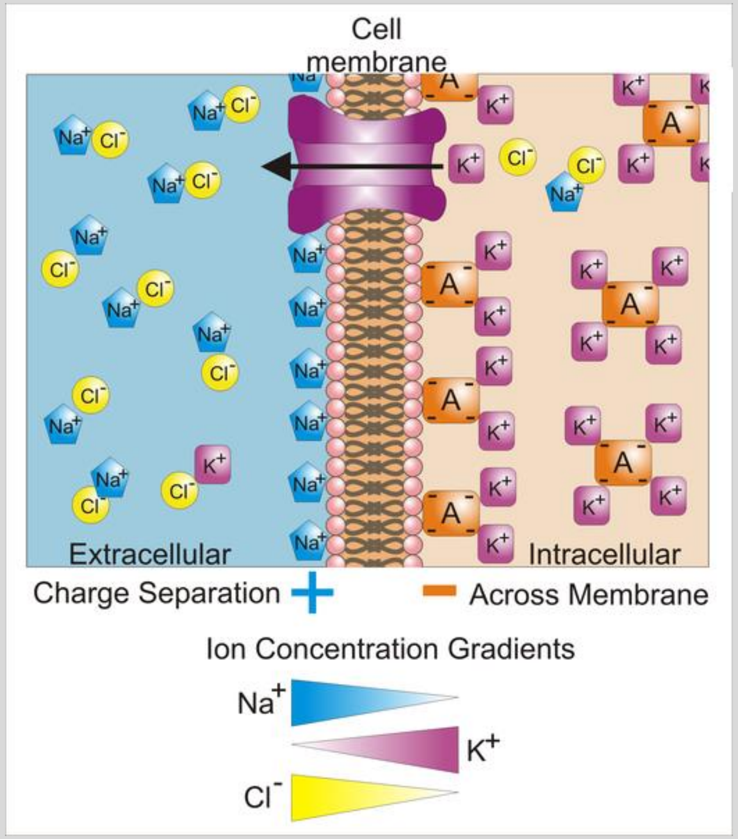
Zhu, Y., S. Xu, R. S. Eisenberg and H. Huang (2019).
A Bidomain Model for Lens Microcirculation
Biophysical Journal 116(6): 1171-1184
Preprint available on arXiv:1810.04162

Zhu, Y., S. Xu, R. S. Eisenberg and H. Huang (2021).
Membranes in Optic Nerve Models. arXiv preprint arXiv:2105.14411.

Nerve Signals



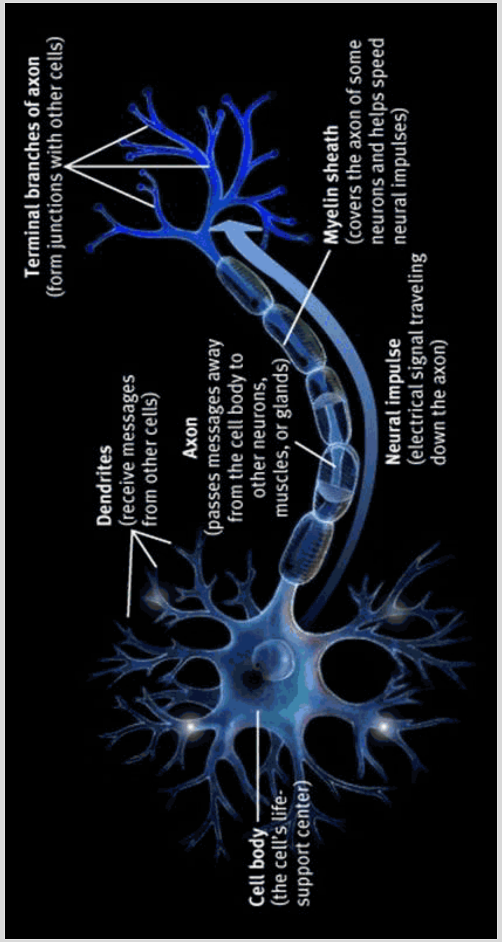
Move Potassium K^+ Out of Nerve Cells

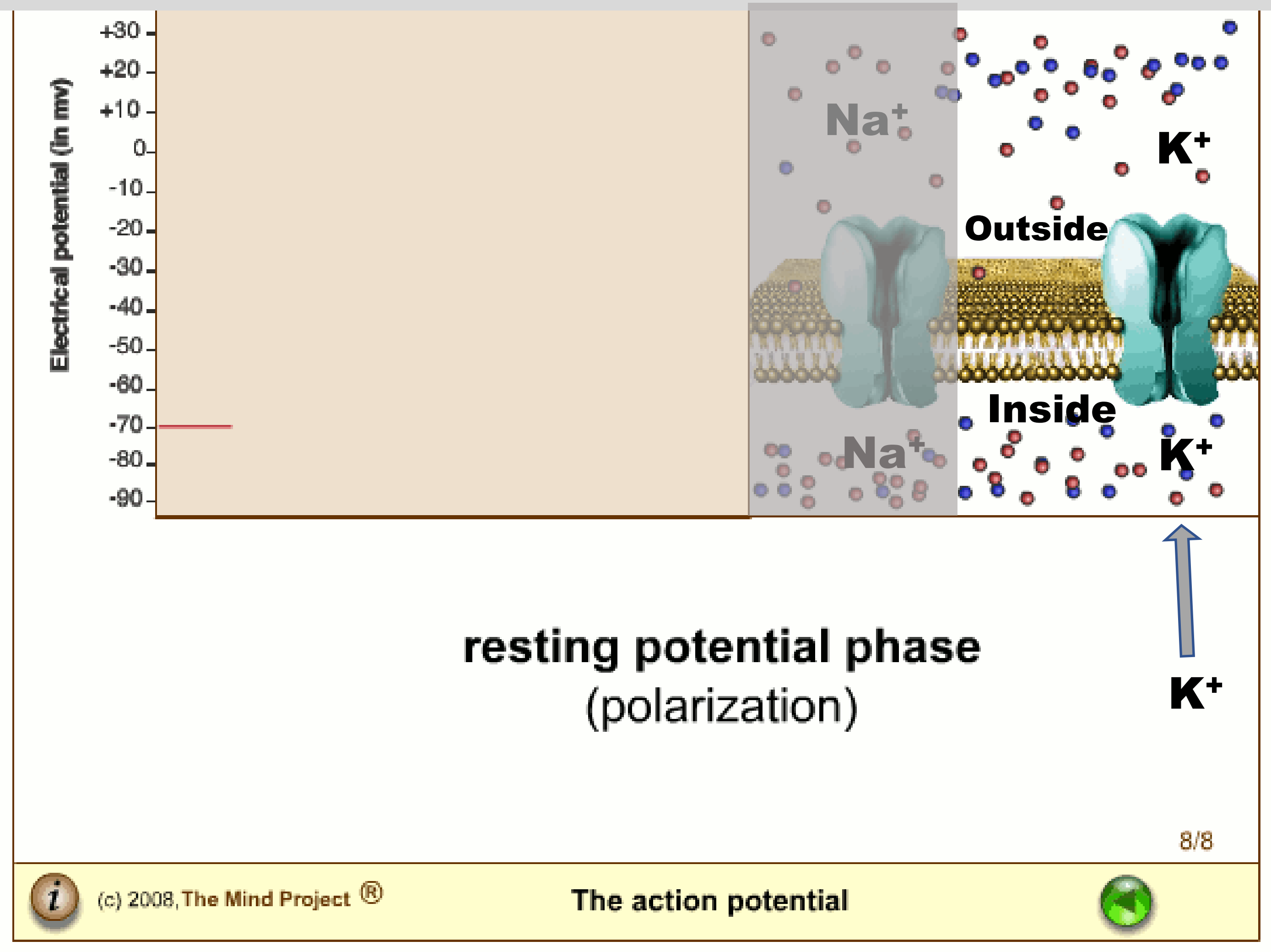


https://teachmephysiology.com/nervous-system/synapses/action-potential/

Nerve Signals ↔ **Action Potentials**

Move Potassium K^+ out of Nerve Cells

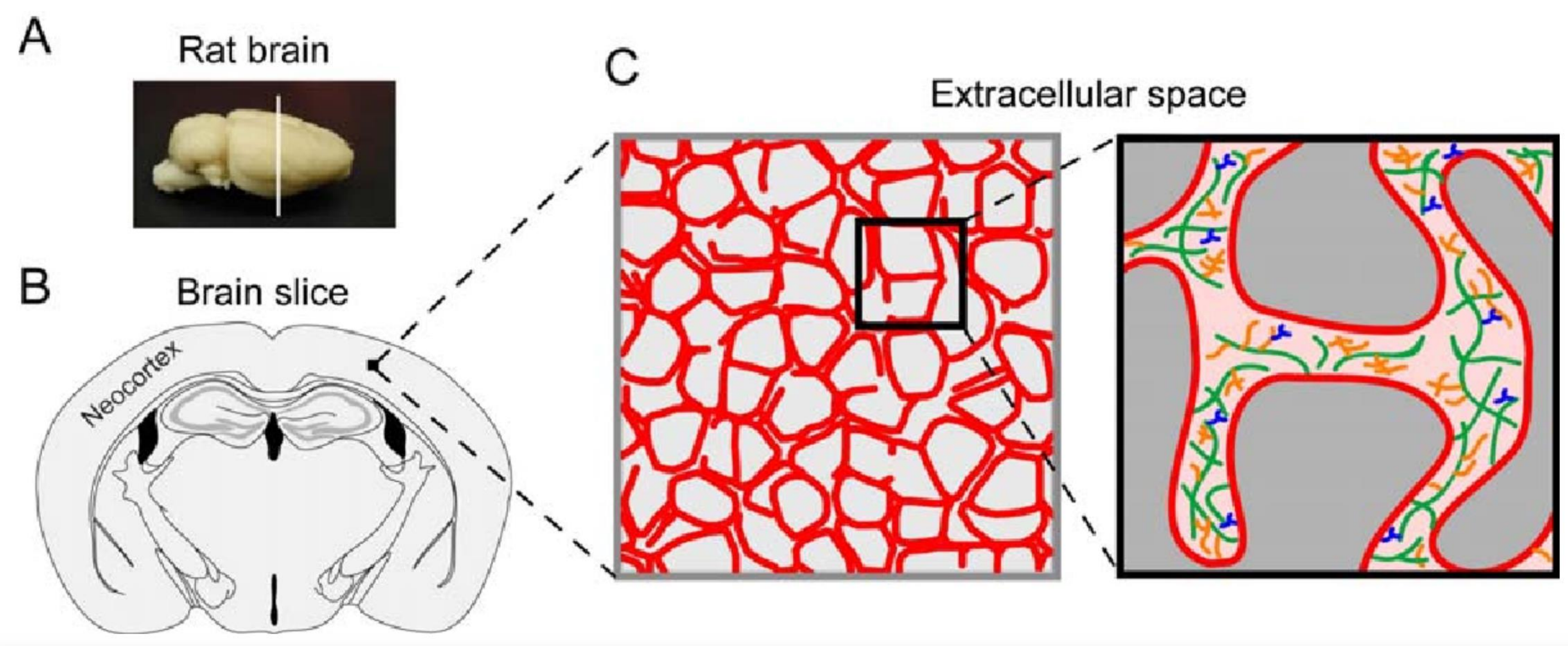




https://teachmephysiology.com/nervous-system/synapses/action-potential/

http://www.stat.ucla.edu/~ywu/neuron.html

Potassium Moves Out of Nerve Cells Into Extracellular Space

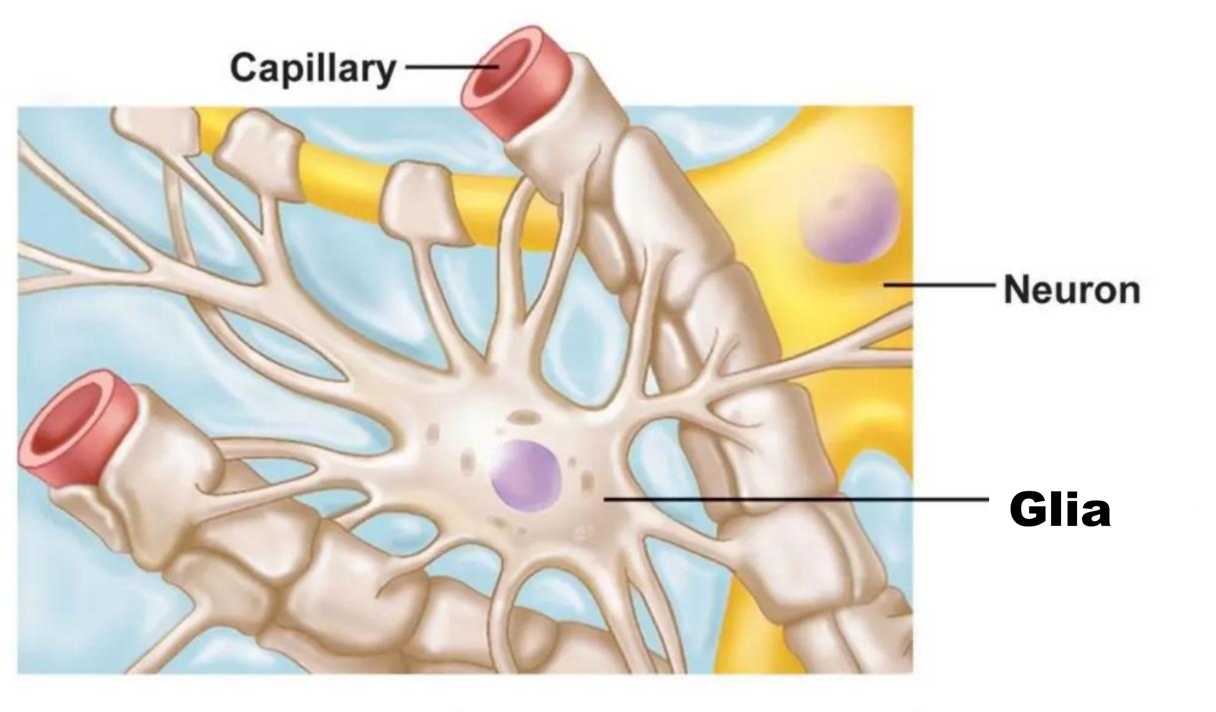


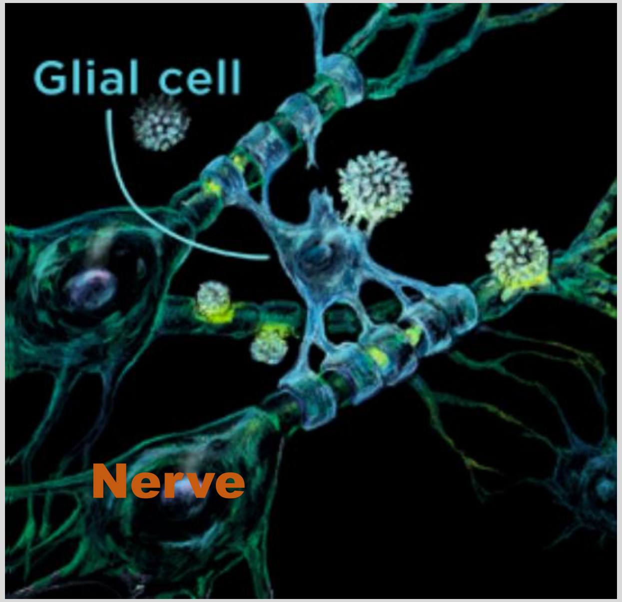
Sherpa, A. D. and S. Hrabetova (2016). "Astrocytes and diffusive spread of substances in brain extracellular space."
Diffusion fundamentals 25 4, S. 1-17

Nerve Fiber:
GLIA, Extracellular Space and Nerve Axons

Kuffler, Nicholls and Orkand (1966). J Neurophysiol 29: 768

= Necturus, mud puppy, salamander, amphibian





Glia is a Syncytium

Kuffler, Nicholls and Orkand (1966)
J Neurophysiol 29: 768-787

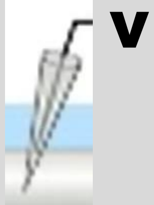
Microelectrodes Close Together

Microelectrodes Far Apart

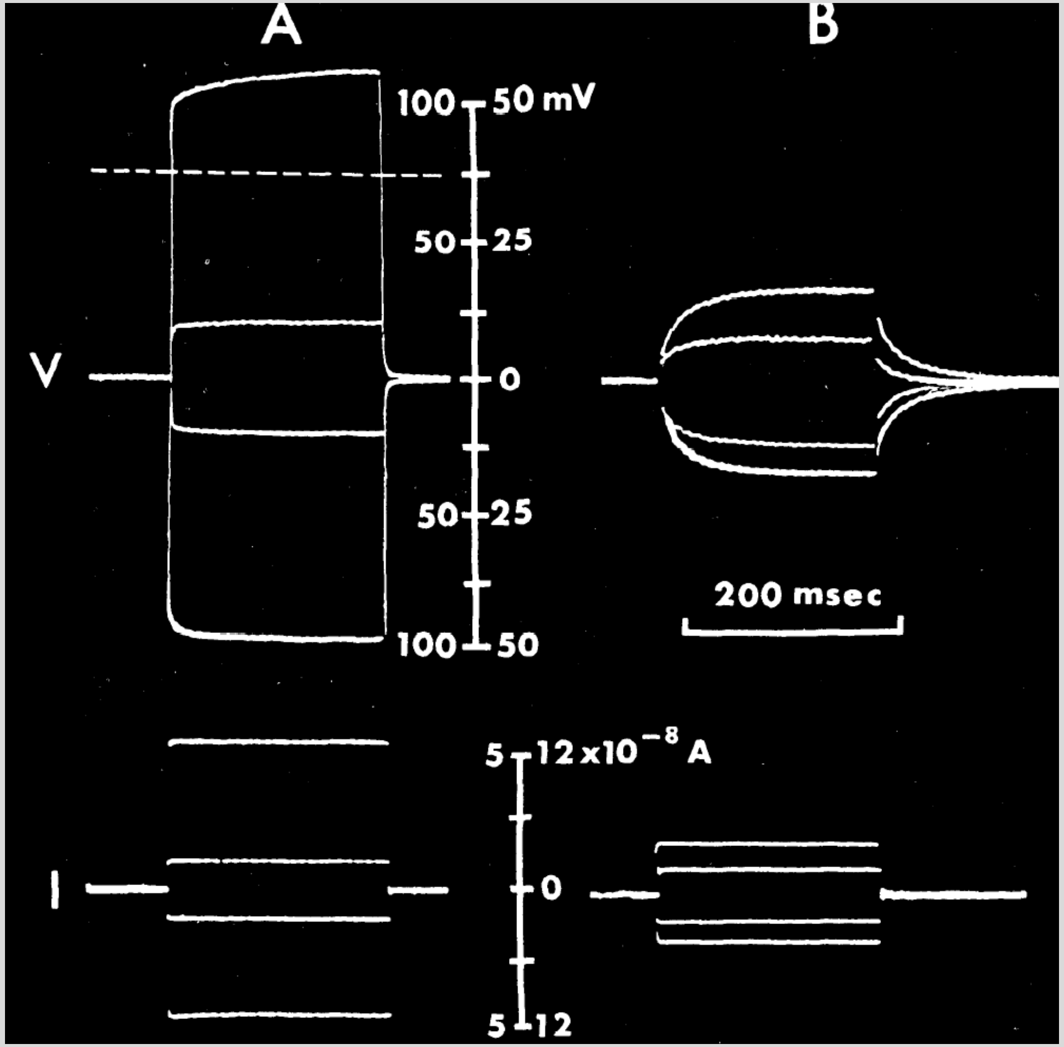
'Jump' in potential when microelectrodes are close together is effect of three dimensional spread of current

1} Eisenberg & Engel (1970)
J Gen Physiol 55: 736
2) Barcilon, Cole, Eisenberg (1971)
SIAM J. Appl. Math. 21: 339
3) Eisenberg & Rae (1976)
J Physiol 262(2): 285

Volage V Recording Microelectrode

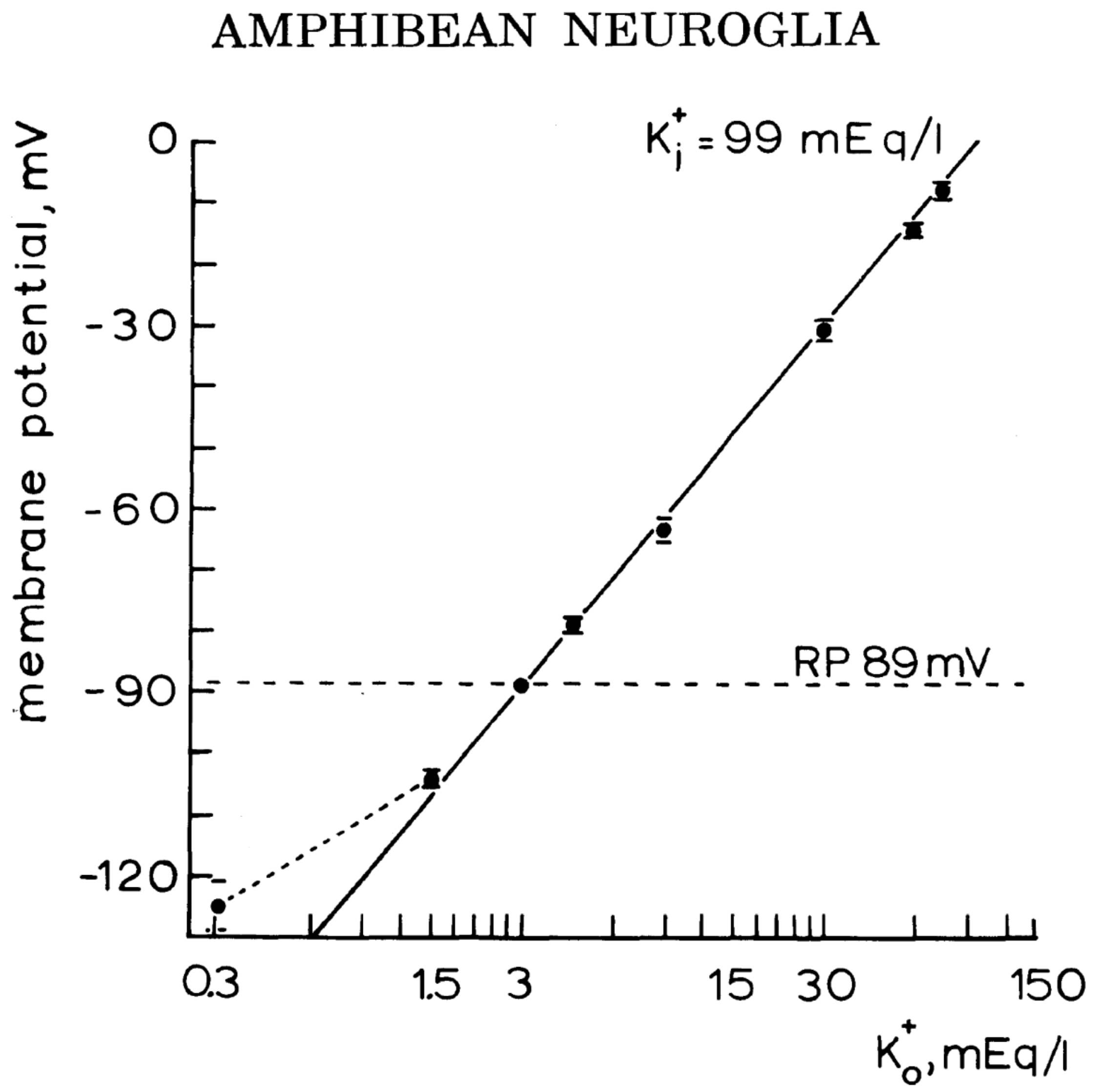


Current I Passing Microelectrode



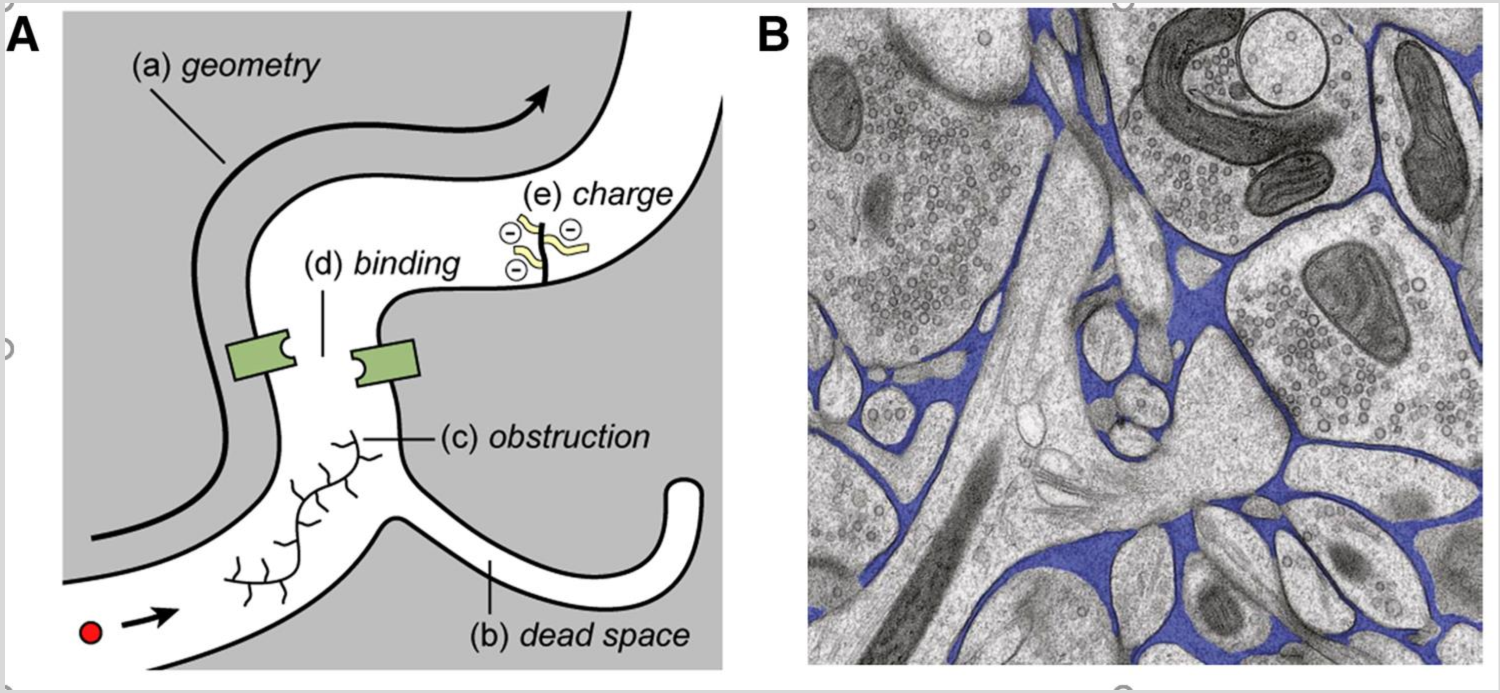
Glia Membrane Potential Measures Extracellular Potassium

Kuffler, Nicholls Orkand (1966)
J Neurophysiol 29(4): 768-787



"Brain Extracellular Space: The Final Frontier"

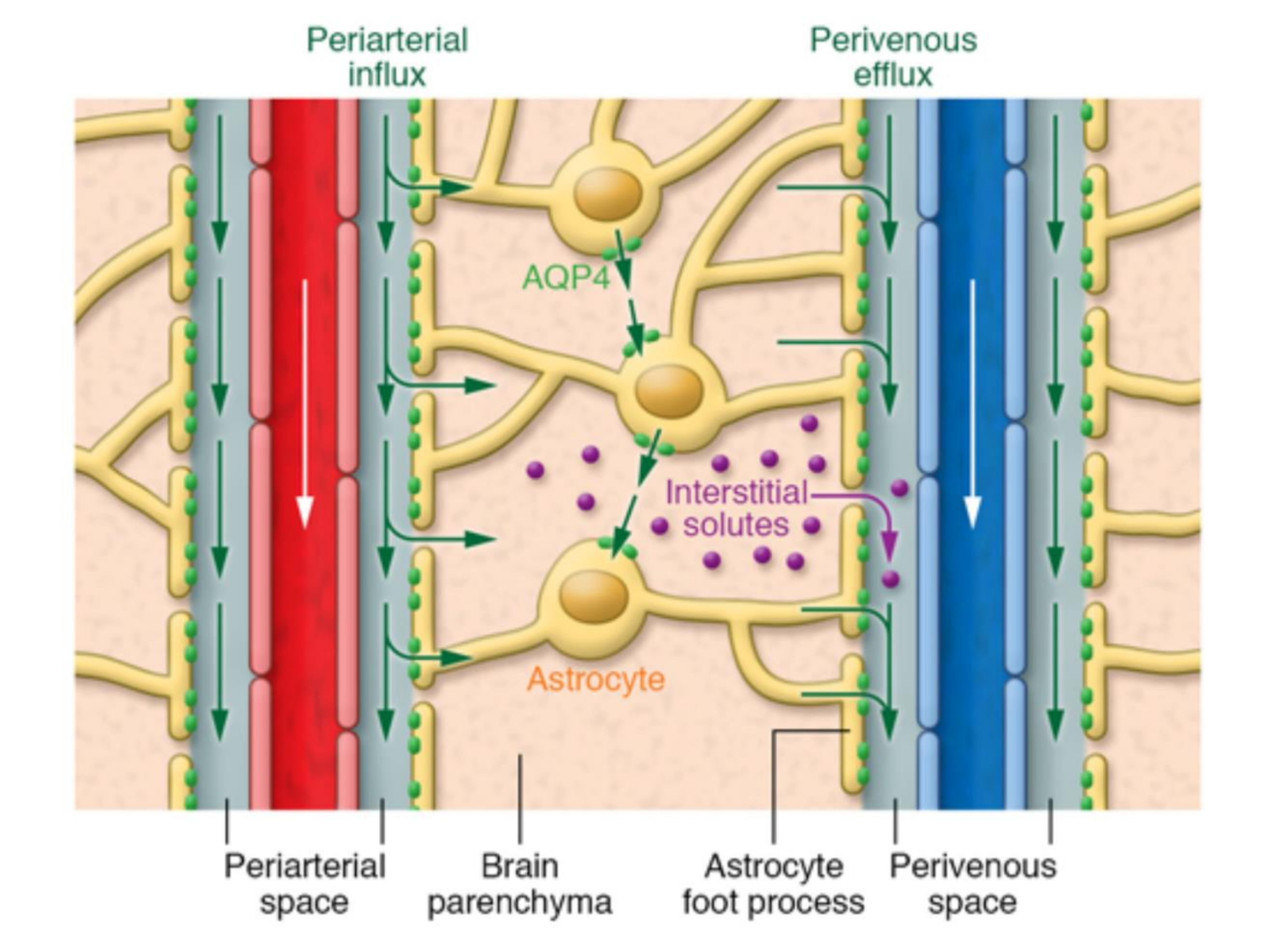
Nicholson and Hrabětová,
Biophysical Journal, 2017. 113: p. 2133-2142.

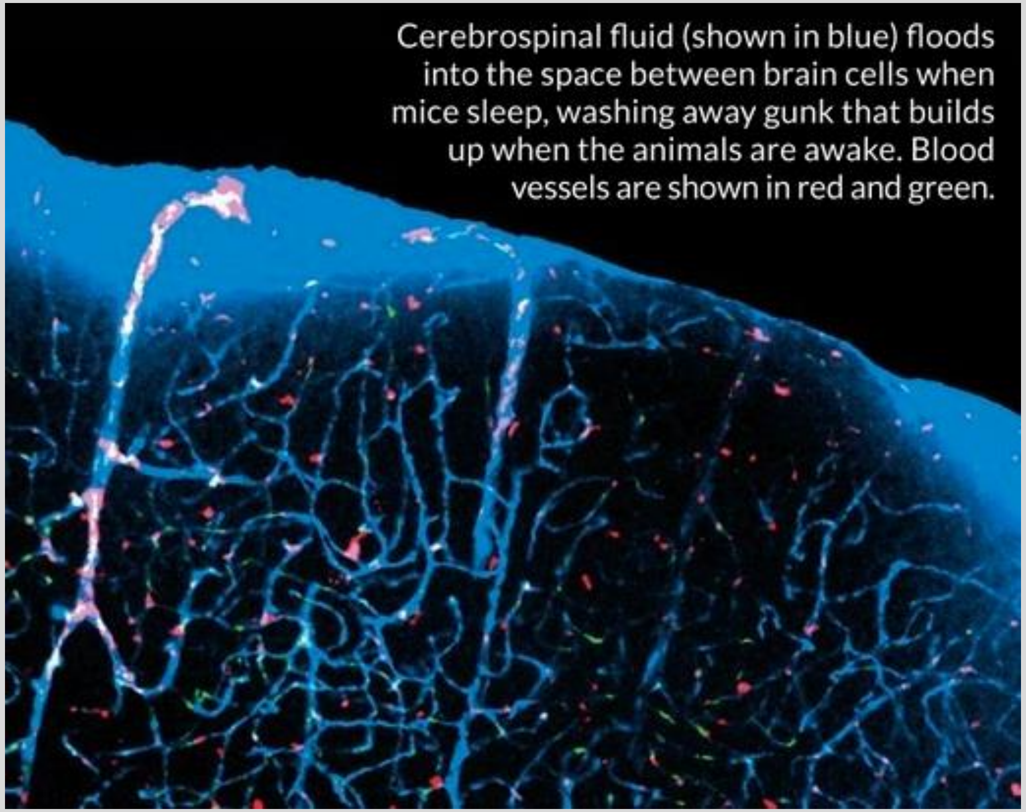


Stirred by Convection at work and in sleep
Driven by Electrochemical Potential for Water,
i.e., an **Osmotic Pump**

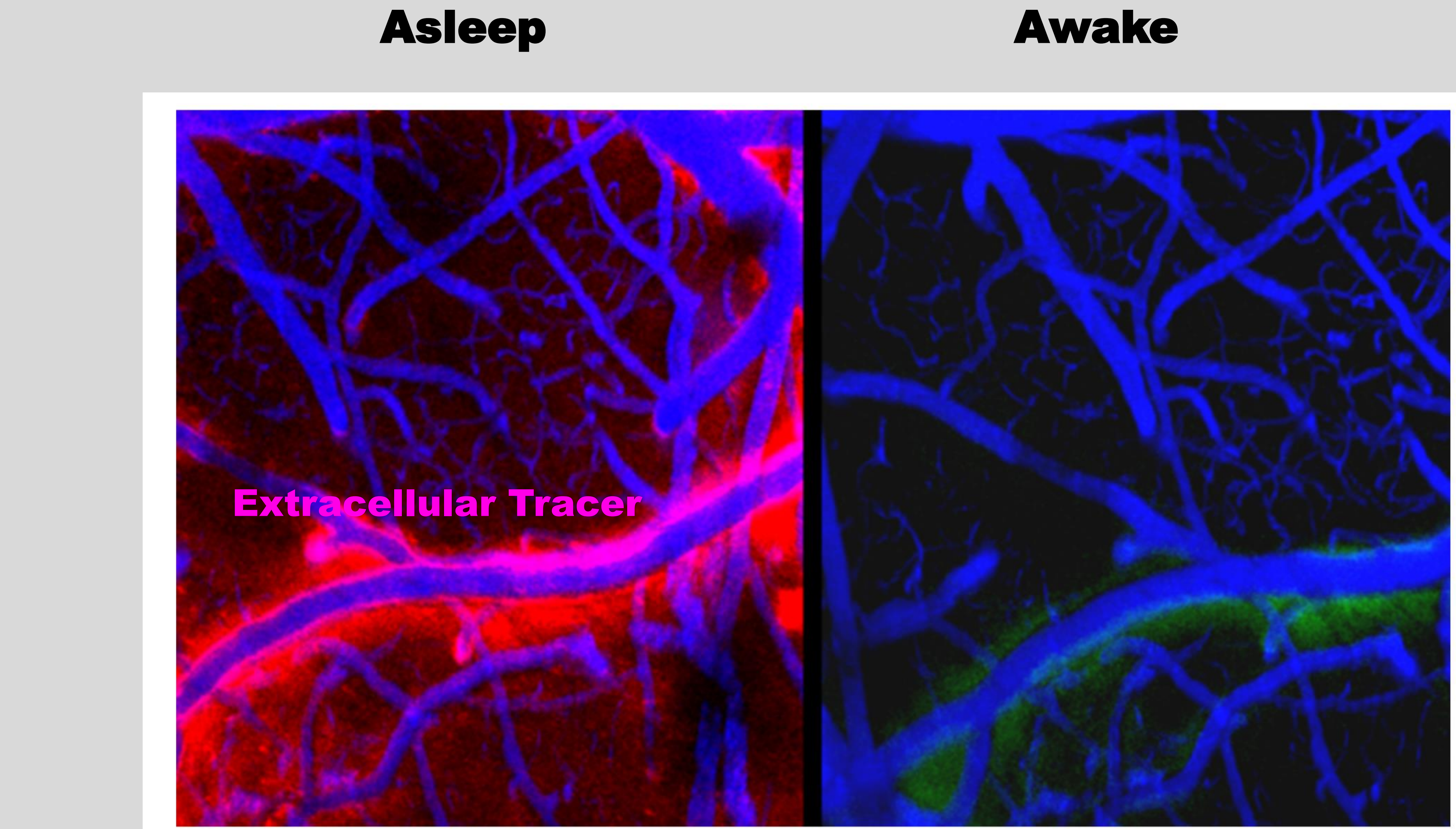
Glymphatic Hypothesis

Kaur, Davoodi-Bojd, Fahmy, Zhang, Ding, Hu, Zhang, Chopp and Jiang (2020).
"Magnetic Resonance Imaging and Modeling of the Glymphatic System." Diagnostics 10(6): 344.





Tina Saey **Science news,** November 16 2013



WIDE ASLEEP Colored tracers penetrate more deeply into a mouse's brain when it's asleep (left, red tracer) than awake (right, green tracer). The finding indicates that channels between brain cells open up during sleep and allow cerebrospinal fluid to wash debris out of the brain. Blood vessels are shown in blue.

L. XIE, H. KANG AND M. NEDERGAARD

(part of)

Glymphatic Hypothesis

Sleep Cleanses Waste from the Brain

Leading worker

"We need sleep. It cleans up the brain."

Dr. Maiken ***Nedergaard*** (Univ of Rochester)

https://www.upi.com/Health_News/2013/10/17/Brain-may-flush-toxins-out-during-sleep/20861382065779/

Mestre, H., Y. Mori and M. **Nedergaard** The Brain's Glymphatic System: Current Controversies. Trends in Neurosciences.
Nedergaard, M. (2013). **Garbage Truck of the Brain**. Science 340(6140): 1529-1530.
Xie, Kang, Xu, Chen, Liao, Thiyagarajan, O'Donnell, Christensen, Nicholson, Iliff, Takano, Deane and **Nedergaard** (2013). **Sleep Drives Metabolite Clearance from the Adult Brain**. Science 342(6156): 373-377.

Sleep Cleanses Waste from the Brain

“Sleep knits up the raveled sleeve of care”

William Shakespeare: Macbeth Act 2, Scene 2

Translation into modern American

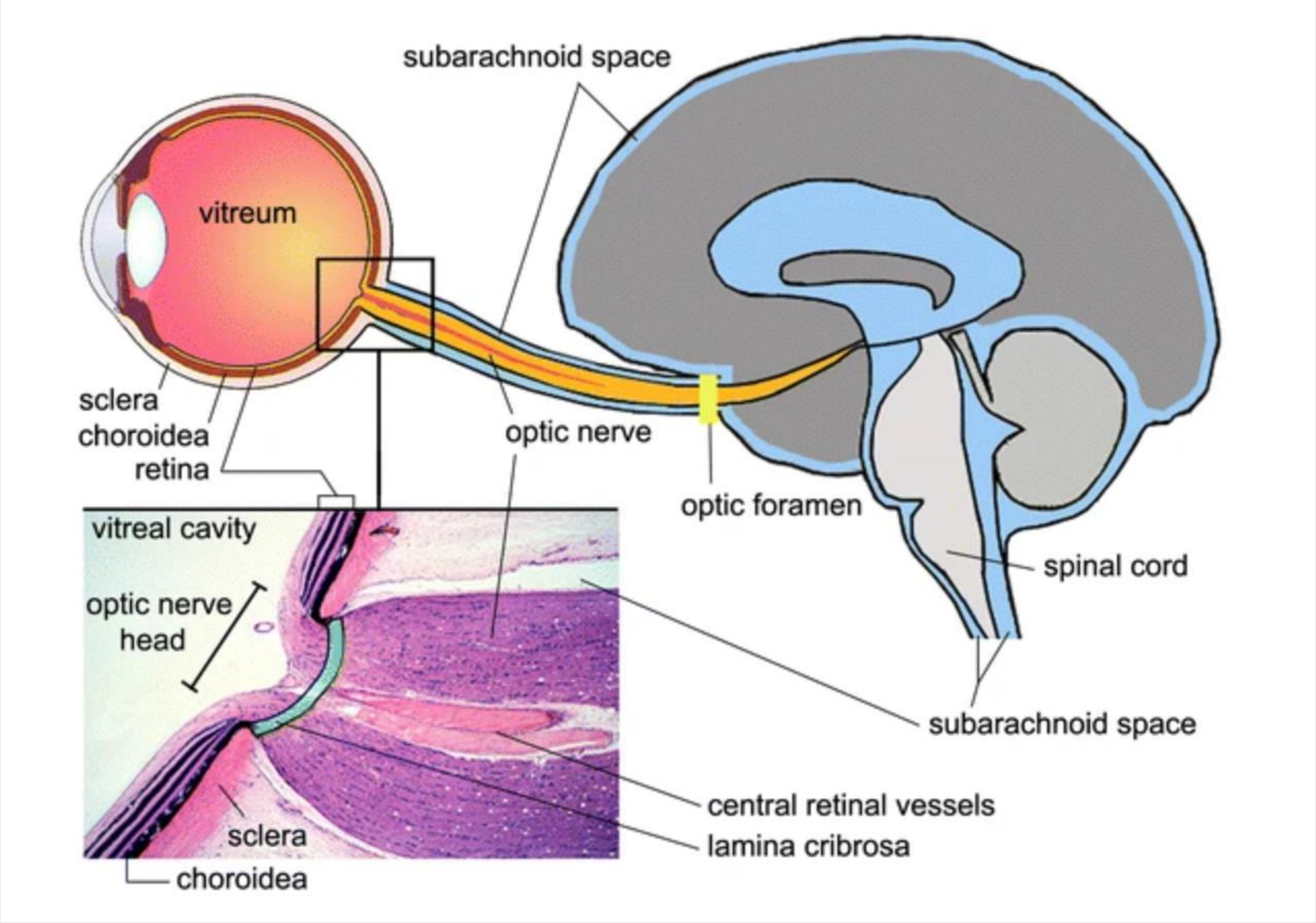
Sleep soothes away all our worries.

Sleep re-knits and repairs the sweater damaged by life’s worries

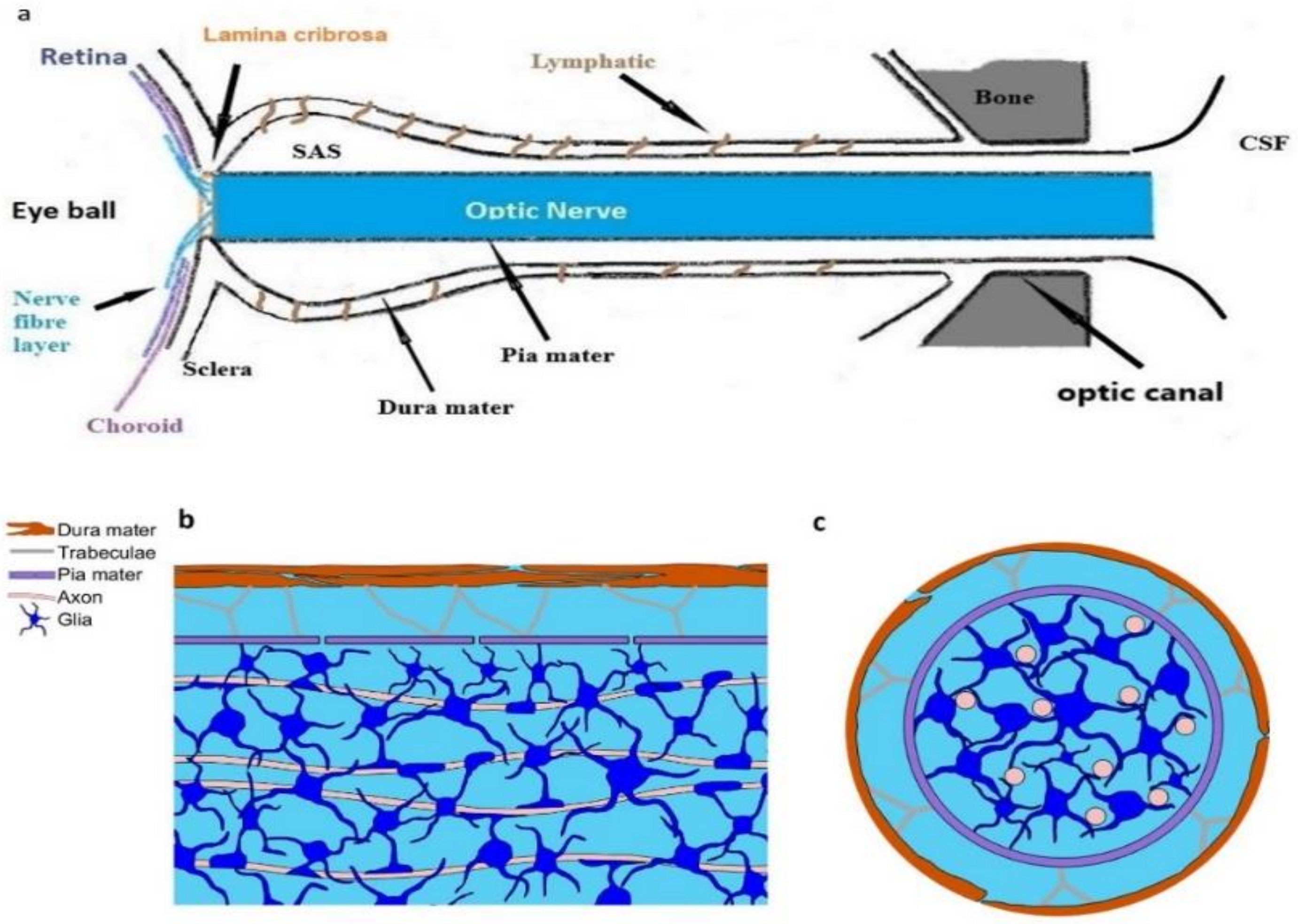
Wostyn, Van Dam, Audenaert, Killer, Paul and Groot (2015)

A new **glaucoma hypothesis**: A role of **glymphatic system dysfunction**

Fluids and barriers of the CNS 12: 16



Optic Nerve of Necturus



Plan of Action

Field Equations are Needed
of the Whole Optic Nerve

EVERYTHING INTERACTS WITH EVERYTHING ELSE

Partial differential equations are needed,
in time and space,
in neuron, glia, and extracellular space and across membranes
involving diffusion, migration, and convection of ions and water

In our work,

Compartment Models are derived from Field Equations
by mathematics: perturbation theory

Compartments are NOT assumed.

Plan of Action

Field Equations are Needed

even though they involve
Coupled Partial Differential Equations

Systems that use Complex Structures
must have theories that involve structure

Structure is in Three Dimensions
So Partial Differential Equations Appear Naturally

Plan of Action

Field Equations are Needed
of the **Whole Optic Nerve**
EVERYTHING INTERACTS WITH EVERYTHING ELSE

Compartment Models can be derived from Field Equations

by mathematics: perturbation theory

compared to numerical solution

**Combining perturbation theory and numerical analysis
Is very powerful**

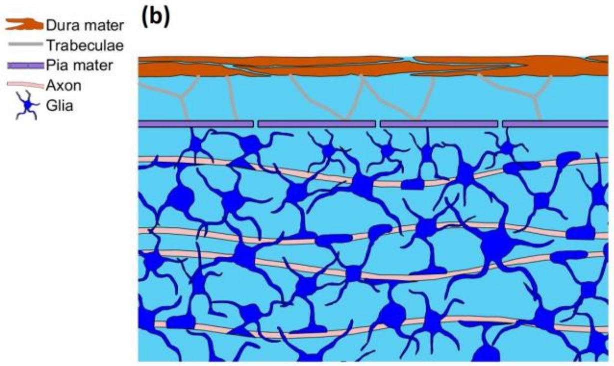
**Retains General Insight of Leading Simple Terms of Perturbation
Accuracy determined by numerics in a range of conditions
Without a difficult error analysis.**

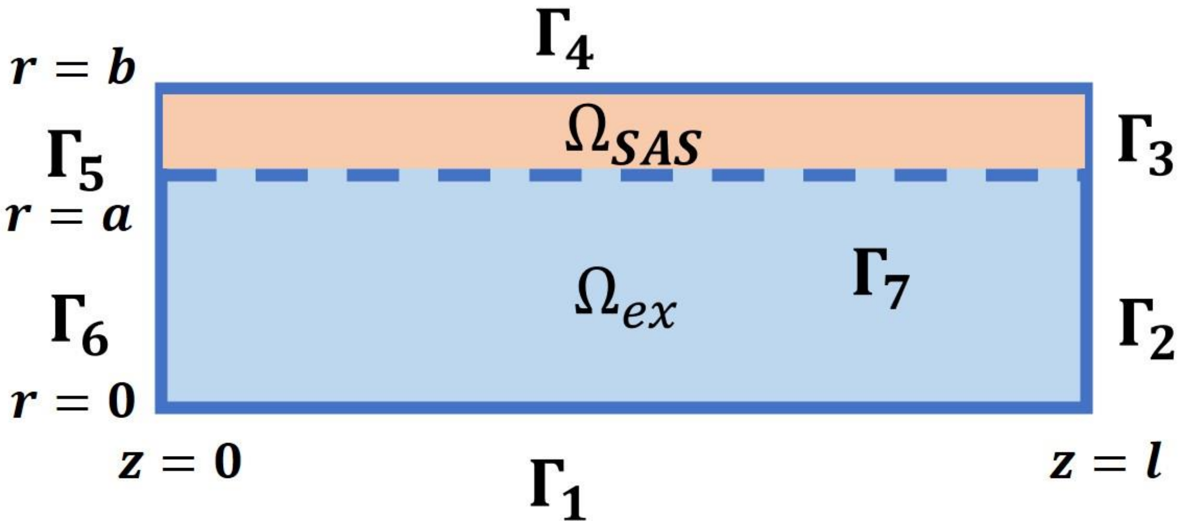
Mathematical Model

Necturus, mud puppy, salamander, amphibian

- Tridomain Model:
  - Each point is a mixture of optic nerve axons, glial cells and extracellular space with fraction $\eta_{ax}, \eta_{gl}, \eta_{ex}$.
  - Pumps and passive channels in cell membranes serve as source or sink for changing of concentrations and fluid.

$$\frac{\partial(\eta_l f_l)}{\partial t} + \nabla \cdot (\eta_l J_l) + \mathcal{M}_l(a_l + b_l) = 0$$





Mathematical Model is Needed

to deal with

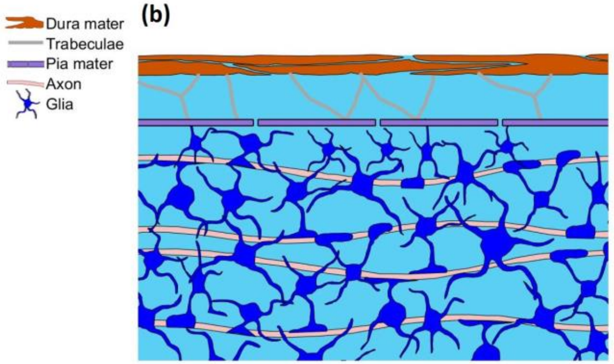
1) Structural Complexity that is ESSENTIAL in biology, as it is in engineering.
   Structural Complexity is in Boundary Conditions and parameters
2) Nerve, Glia, Extracellular Space
3) Flows of Ions and Water driven by
4) Diffusion Gradients, Osmotic Gradients, Migration of Charges

We use

Coupled Partial Differential Equations
with structural boundary conditions

Mathematical Model: Assumptions

- **Structure:**
  - We mainly focus on the intraorbital region, which is formed by axons, glial cells and extracellular space. Model will need to be extended to deal with glaucoma
  - Glial compartment and extracellular space are isotropic
  - **Axon compartment is anisotropic**
  - Subarachnoid space (SAS) is modeled as porous media
- **Ions**:
  - Only the Na^+, K^+, Cl^- and negative proteins are considered
  - Local ‘electroneutrality’ is used to couple PNP and cable models



- **Water**:
  - The loss of water in axons and glial cells is only through membranes flowing into or out of the extracellular space.
  - The trans-membrane water flux is proportional to the intra/extra-cellular hydrostatic pressure and osmotic pressure differences.
  - The glial cell and axons swell and shrink due to the water inflows and outflows. Axon is stiffer than glia compartment, so the volume change is smaller.

Mathematical Model: Water Flow

- **Darcy's law:** fluid is mainly driven by hydrostatic pressure and osmotic pressure
- **Mass conservation:** deformation of each compartment is induced by the water flow

$$\frac{\partial \eta_{gl}}{\partial t} + \mathcal{M}_{gl} L_{gl}^{m} \left(P_{gl} - P_{ex} - \gamma_{gl} k_B T \left(O_{gl} - O_{ex} \right) \right) + \nabla \cdot \left(\eta_{gl} \vec{\mathbf{u}}_{gl} \right) = 0$$

$$\frac{\partial \eta_{ax}}{\partial t} + \mathcal{M}_{ax} L_{ax}^{m} \left(P_{ax} - P_{ex} - \gamma_{ax} k_B T (O_{ax} - O_{ex}) \right) + \frac{\partial}{\partial z} (\eta_{ax} u_{ax}^{z}) = 0$$

$$\eta_{ex} + \eta_{gl} + \eta_{ax} = 1$$

$$\nabla \cdot \left(\eta_{gl} \mathbf{u}_{gl} \right) + \nabla \cdot \left(\eta_{ex} \mathbf{u}_{ex} \right) + \nabla \cdot \left(\eta_{ax} \mathbf{u}_{ax} \right) = 0$$

$$K_{gl} \left(\eta_{gl} - \eta_{gl}^{re} \right) = P_{gl} - P_{ex} - (P_{gl}^{re} - P_{ex}^{re})$$

$$K_{ax} \left(\eta_{ax} - \eta_{ax}^{re} \right) = P_{ax} - P_{ex} - (P_{ax}^{re} - P_{ex}^{re})$$

Fundamental Flow Equation was Derived

Generalization of Starlings Capillary Law

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

arXiv:1806.00646

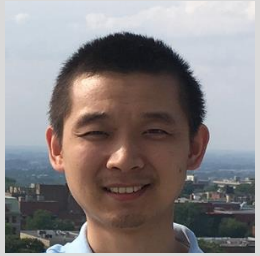
Project Leader

Shixin Xu

士鑫 徐

Huaxiong Huang

华雄 黄



Zilong Song

宋子龙

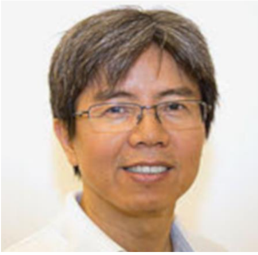
Excess potentials that characterize real, nonideal solutions have not yet been dealt with here, or elsewhere, as far as I know

Eisenberg (2013) "Interacting ions in Biophysics: Real is not ideal" Biophysical Journal 104: 1849-1866.

Shixin Xu
士鑫 徐

Numerical Method

Challenges Overcome



Huaxiong Huang
华雄 黄

- The whole model consist of 21 PDEs and 3 ODEs
- Model evolves different time scales from 1 ms to 10 s
- Domain decomposition: optical nerve region and outer region
- Domain decomposition: stimulated and unstimulated ergions
- Finite Volume Method is used to solve the whole system in order to ensure the conservation of mass and the continuity of flux across the all boundaries
- **MATLAB** is an enormous help, supplemented of course by custom code.

Validation

Model and Equations Validated by Analysis
and fitting of DETAILED experimental data
from the LENS of the EYE

and

Optic Nerve of Necturus (mud puppy, salamander an amphibian)

“Osmotic Pump” is fancy language

Osmosis is Diffusion of Water driven by the Chemical Potential of Water,

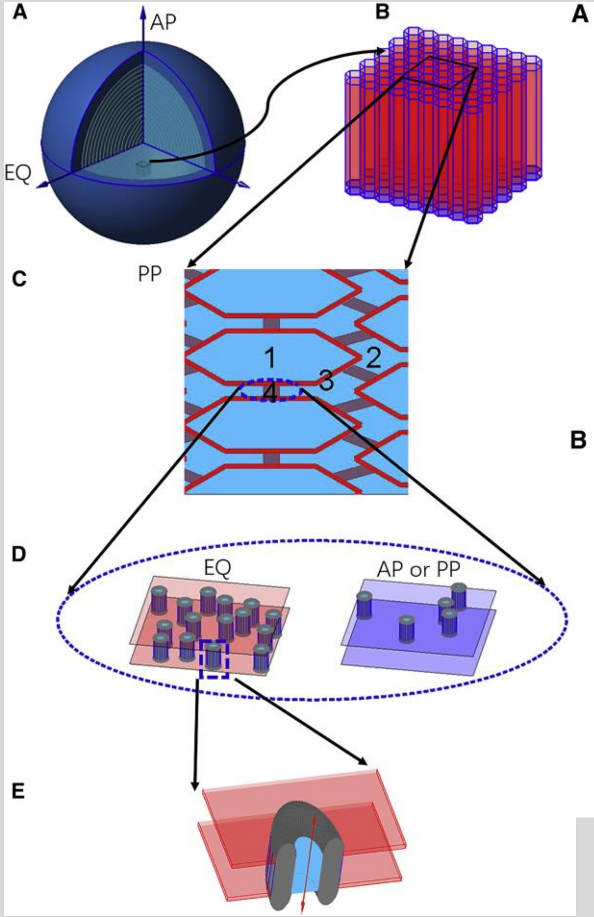
Precisely:

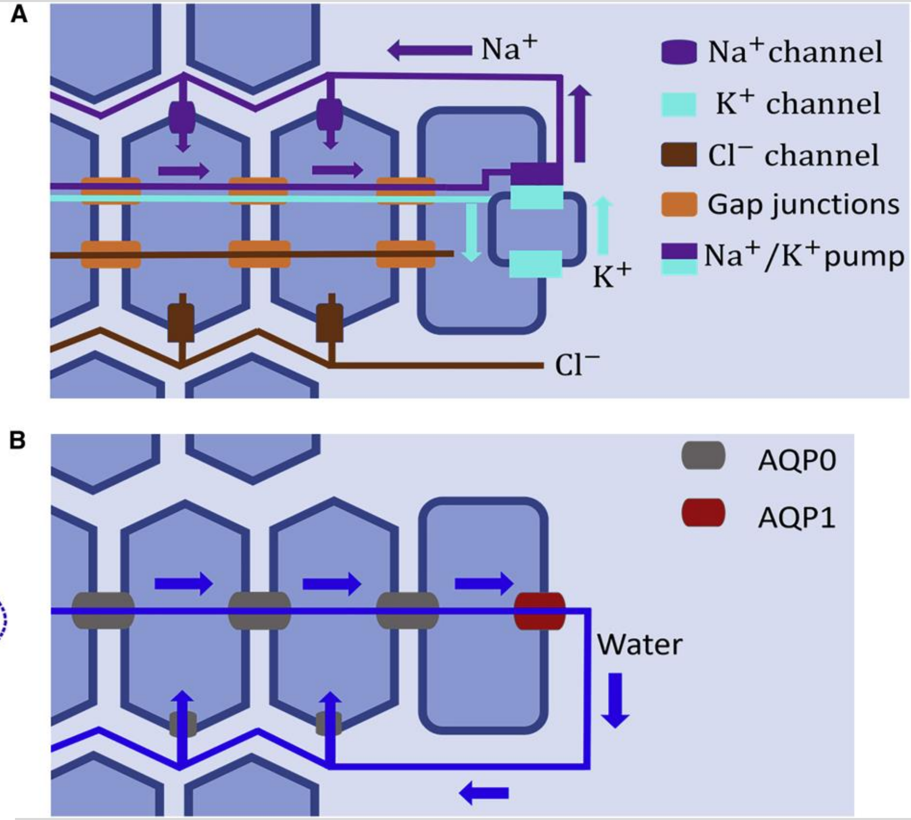
Osmotic flow

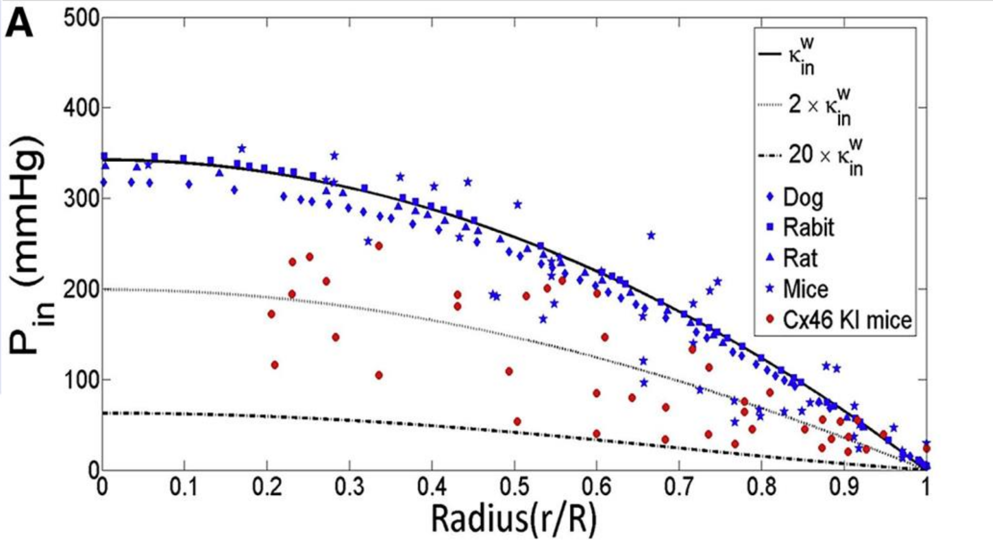
is driven by gradient of

Chemical Potential of water

Microcirculation in Lens



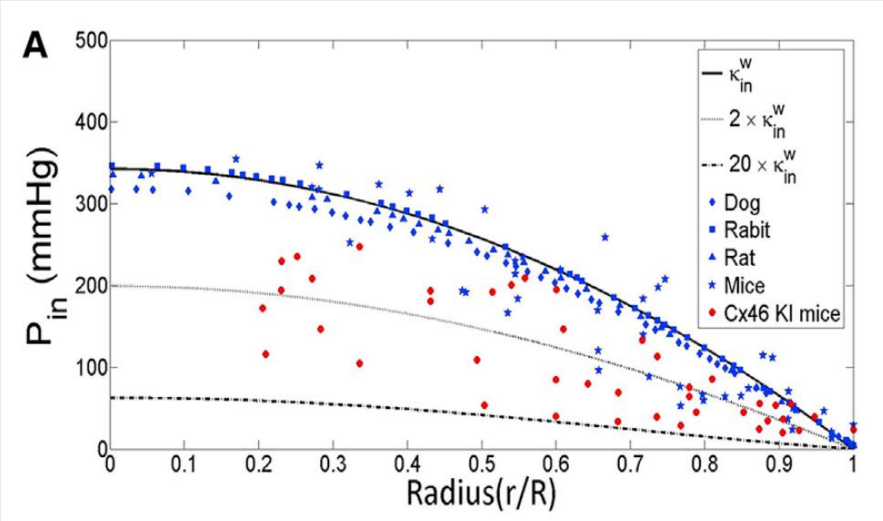




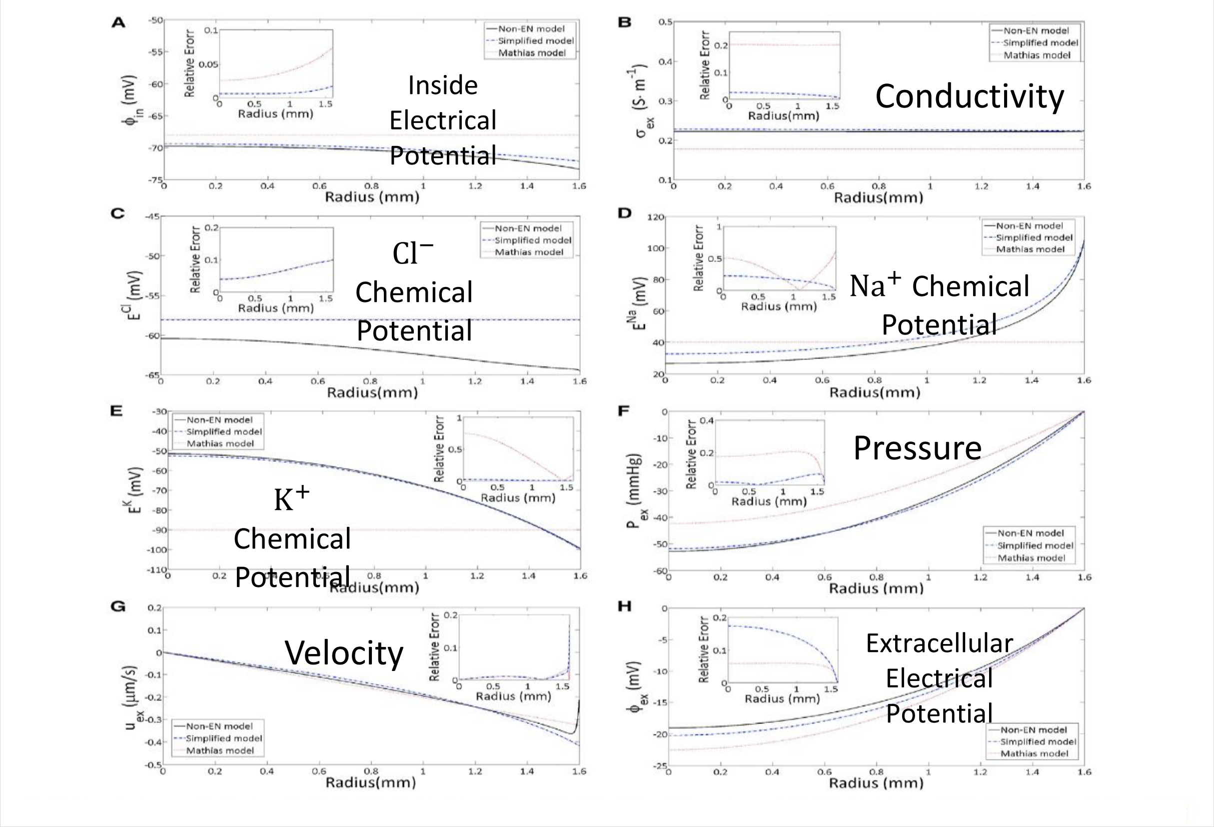
Zhu, Xu, Eisenberg & Huang, H. (2019). A bidomain model for lens microcirculation.
Biophysical journal, *116*, 1171-1184.

Comparison with Experimental Results
Lens of the Eye is an Osmotic Pump

Life work:
Richard (Rick) Mathias
CREATED and VALIDATED an Engineering Model of the Lens: an Osmotic Pump



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



We think we have proven that the lens is an Osmotic Pump

Zhu, Xu, Eisenberg and Huang (2019). "A Bidomain Model for Lens Microcirculation
Biophysical Journal 116(6): 1171-1184 and arXiv 1810.04162.

Field Theories
form a
FRAMEWORK

that can easily accommodate
Specialized Structure
Specialized Channels
Specialized Transporters
Structural Parameters determined by Structural Measurements

From which Engineering Models can be Derived

What experiments do we fit for nerve fibers?

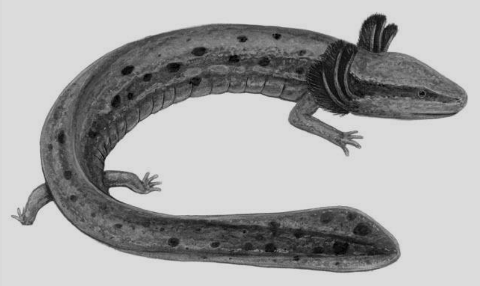
Harvard Group

at birth of Neurobiology

Studied Glia in Optic Nerve Preparation

of Necturus, mud puppy

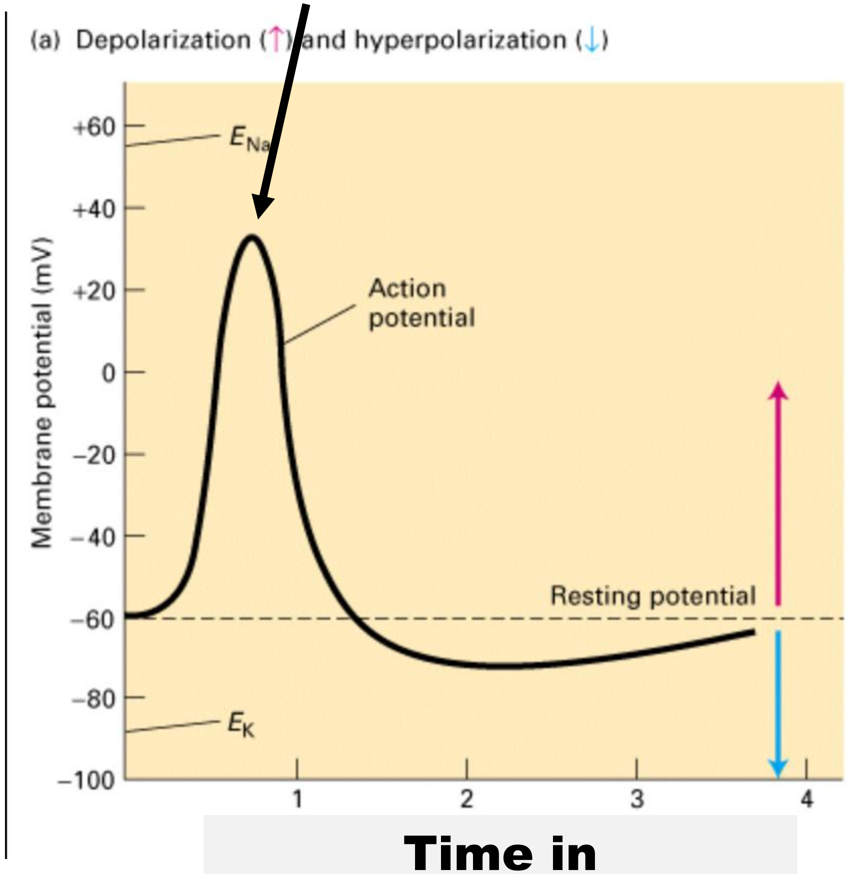
Importance of Choice of Preparation



Orkand, Nicholls, KUFFLER
J. Neurophysiology (1966) 29:788

Action Potential in Nerve and Glia

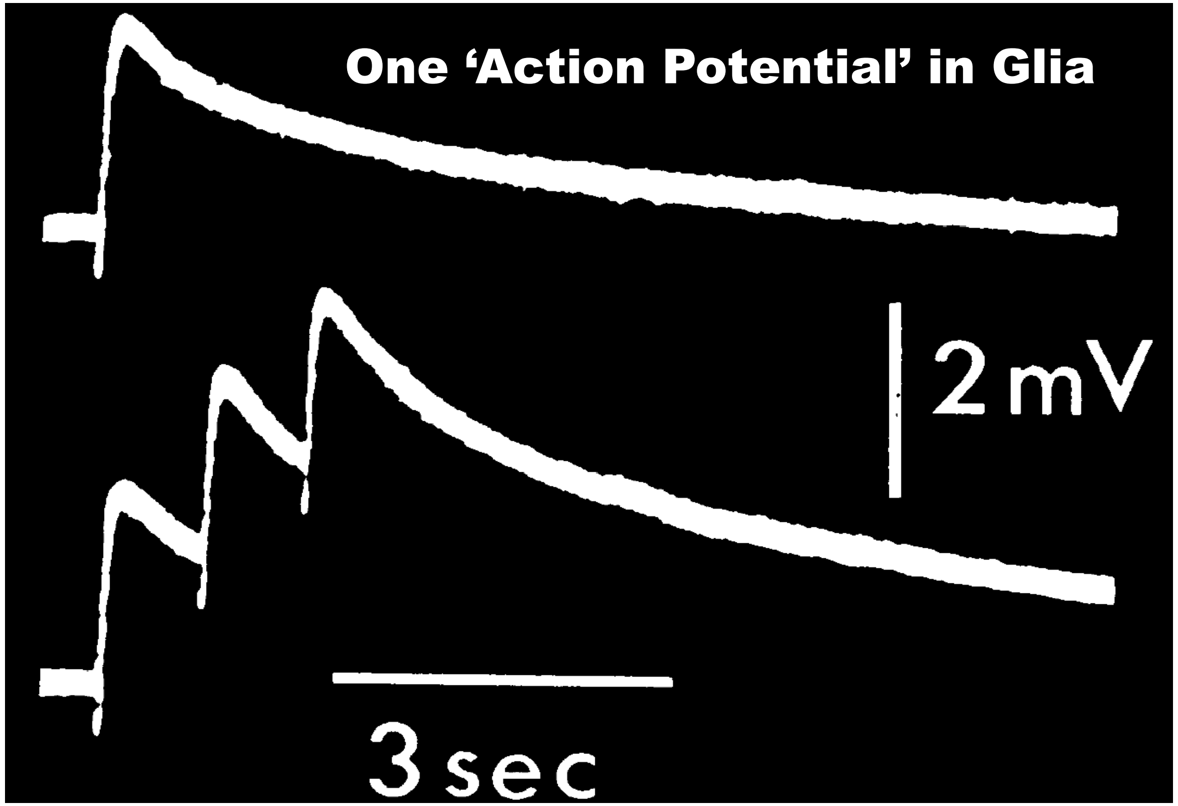
Nerve
50 mV



Time in MILLIseconds

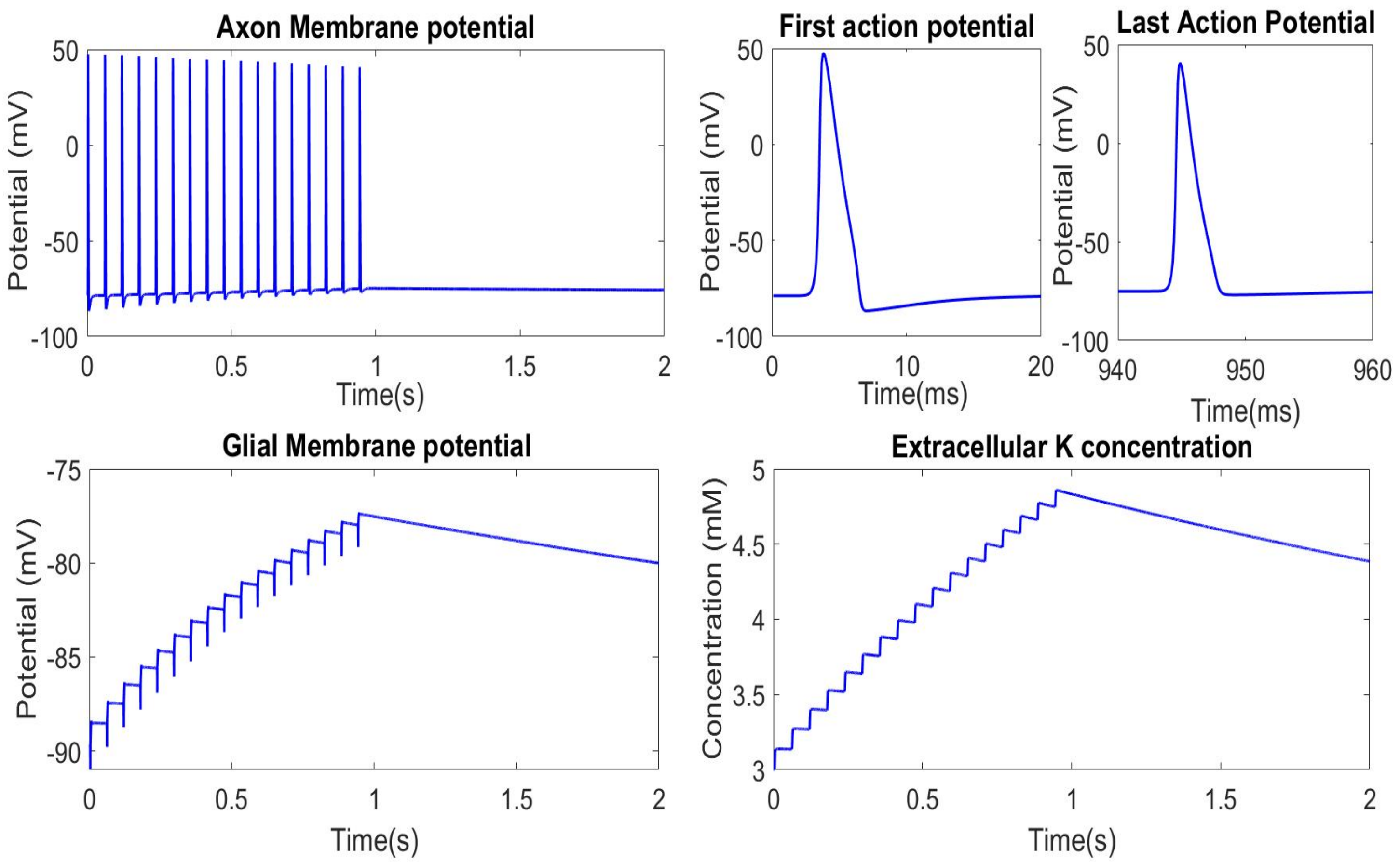
Glia
2 mV

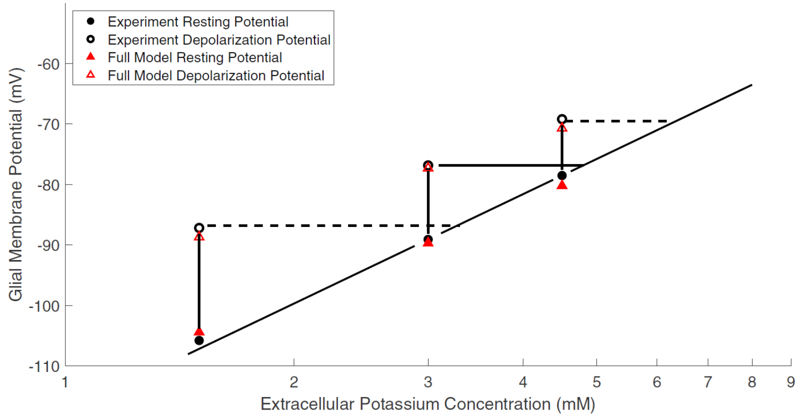
Orkand, Nicholls, Kuffler.
J. Neurophysiology (1966) 29:788



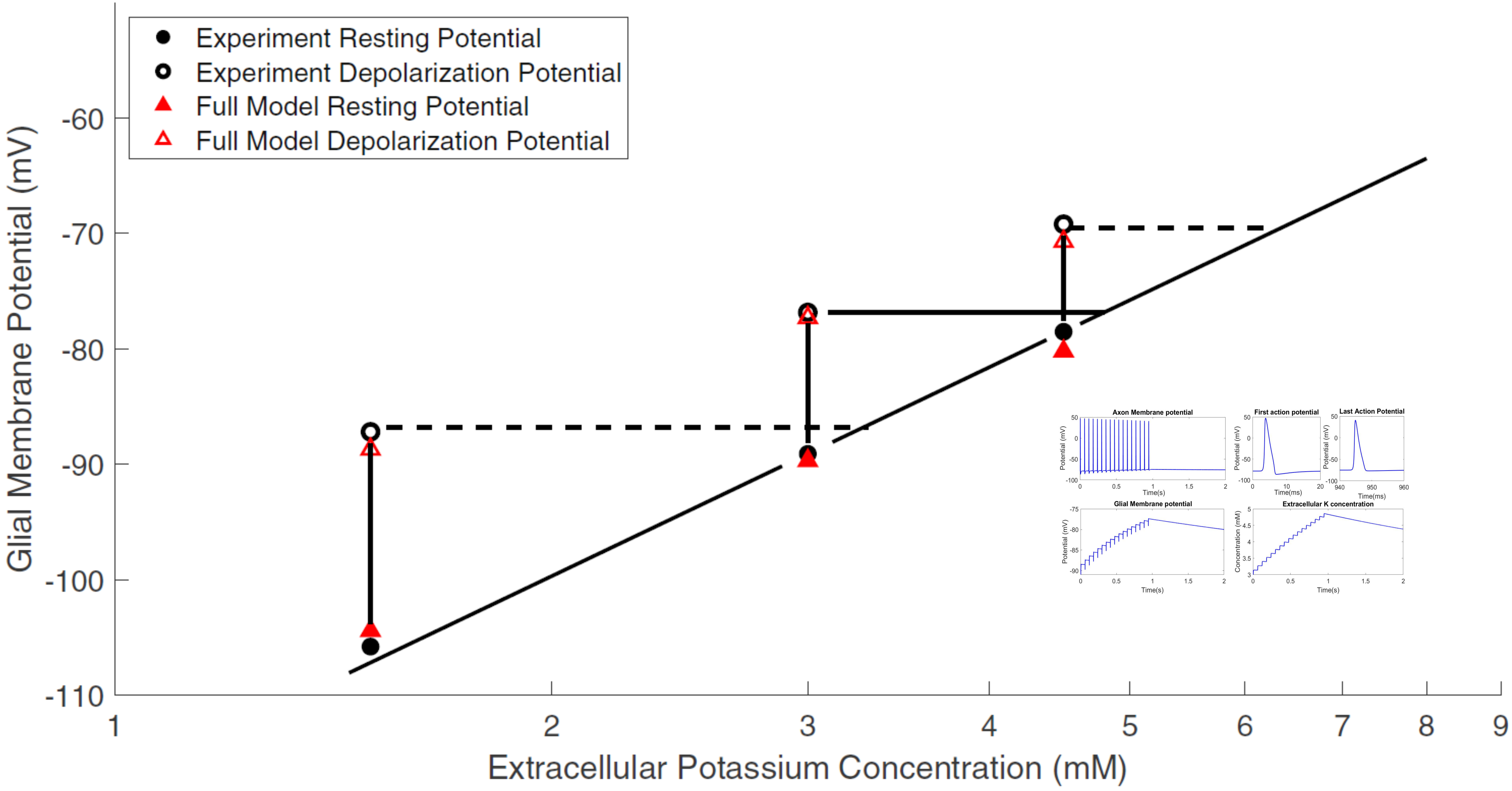
Time in SECONDS

Model Results: Calibration



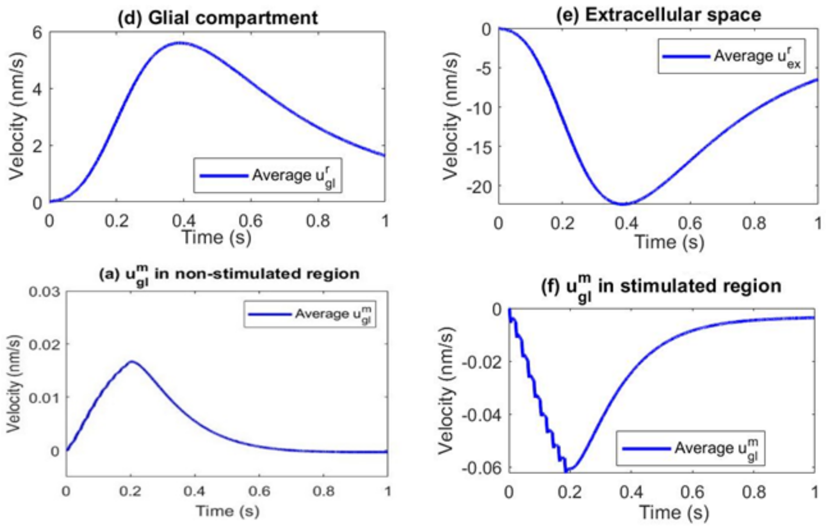


Model Results: Calibration

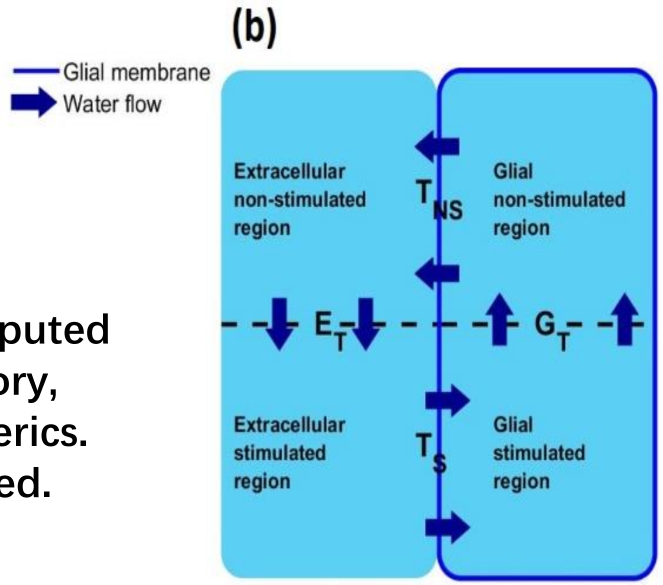


Microcirculation: Water Circulation

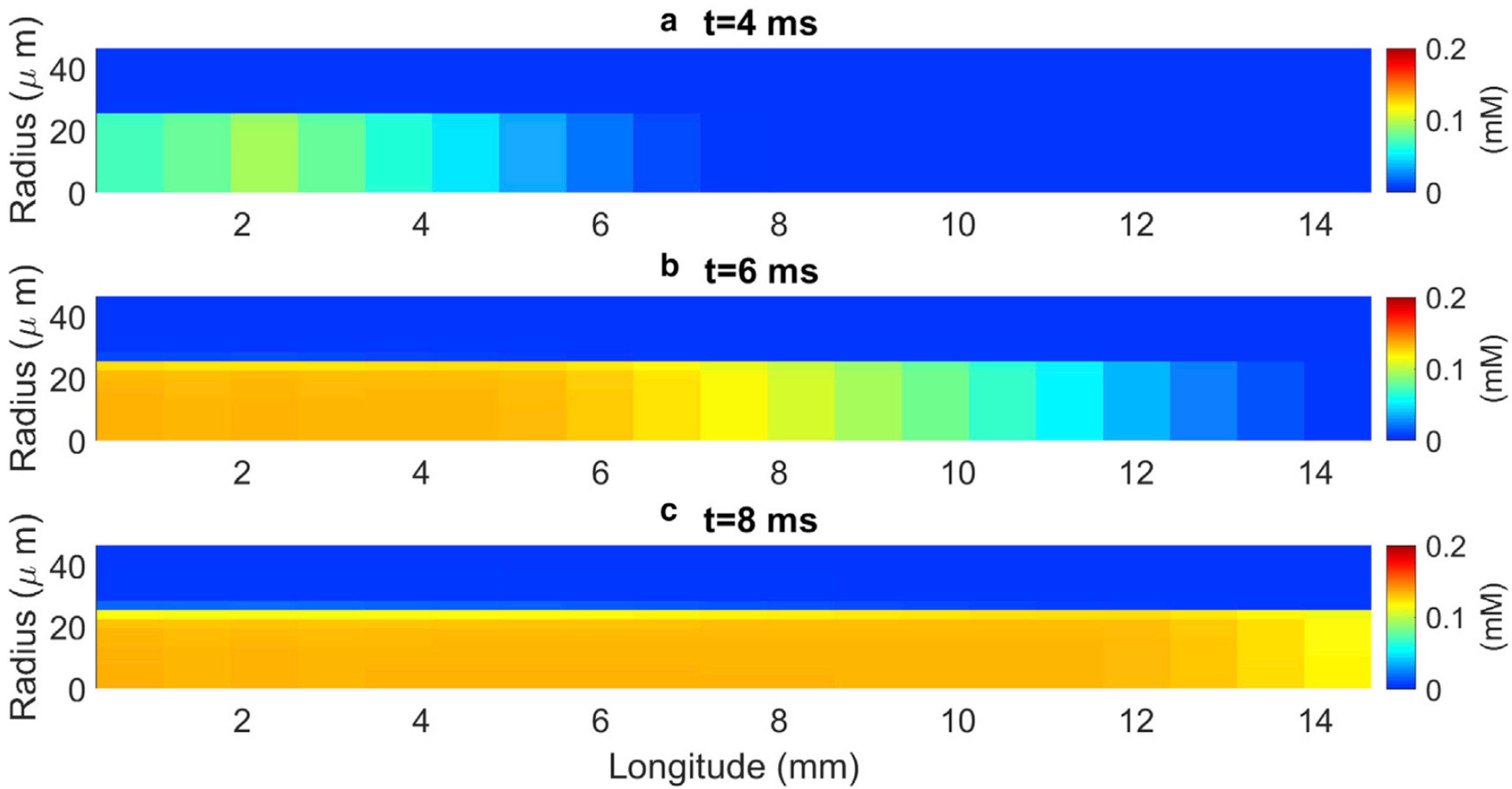
- Stimulus region: water flows into glial compartment from extracellular space due the decrease of osmotic pressure $\delta O_{ex} < 0$
- Inside the glial compartment, water flows from stimulus region to non-stimulus region due to the increase of hydrostatic pressure
- In the non-stimulus region, the water flows out of glial into the extracellular space
- In the extracellular space, water flows back to stimulus region due to the incompressibility of fluid.



Compartments are Computed by Perturbation Theory, and evaluated by numerics. They are NOT assumed.



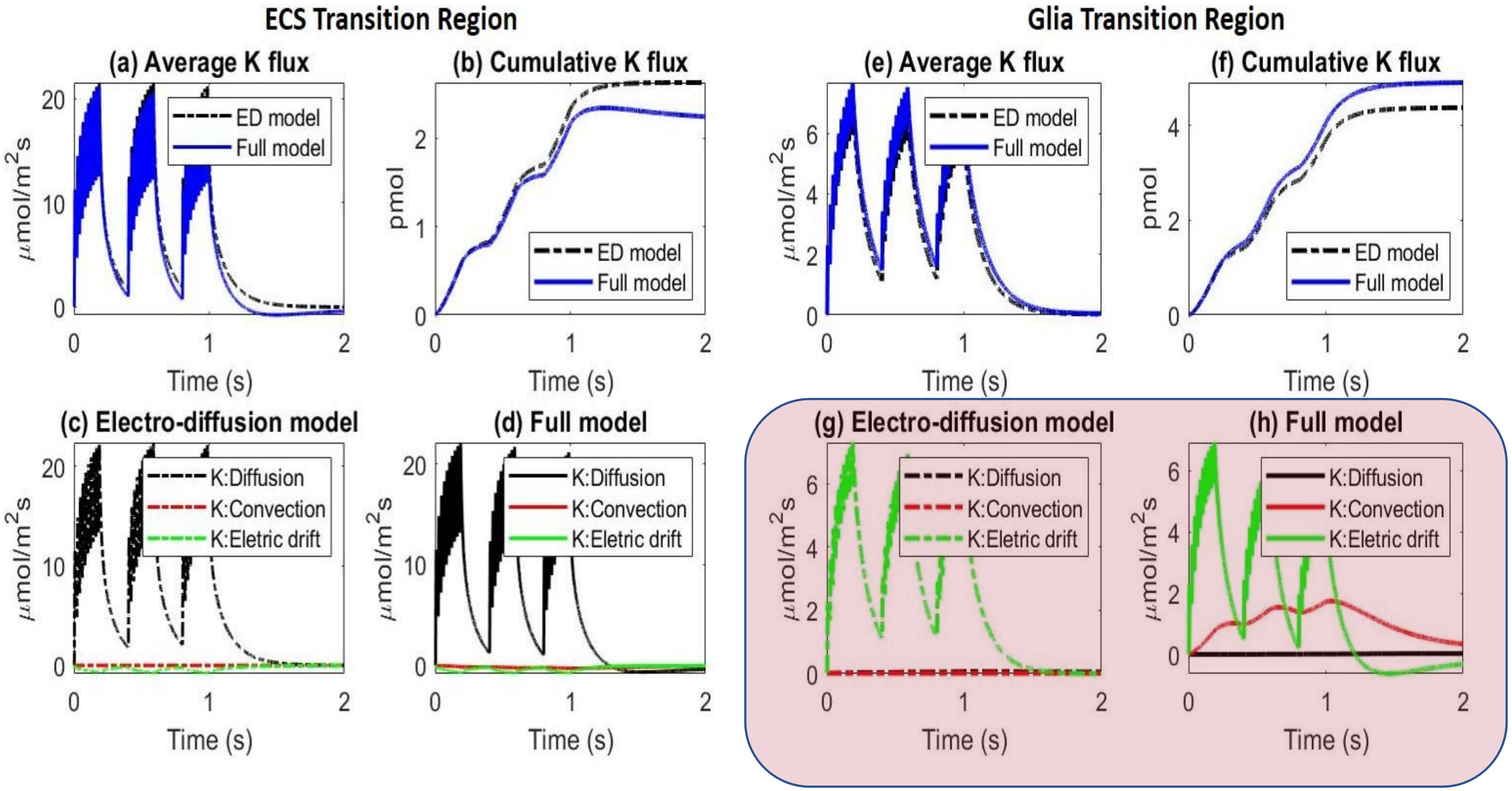
Clearance of Potassium



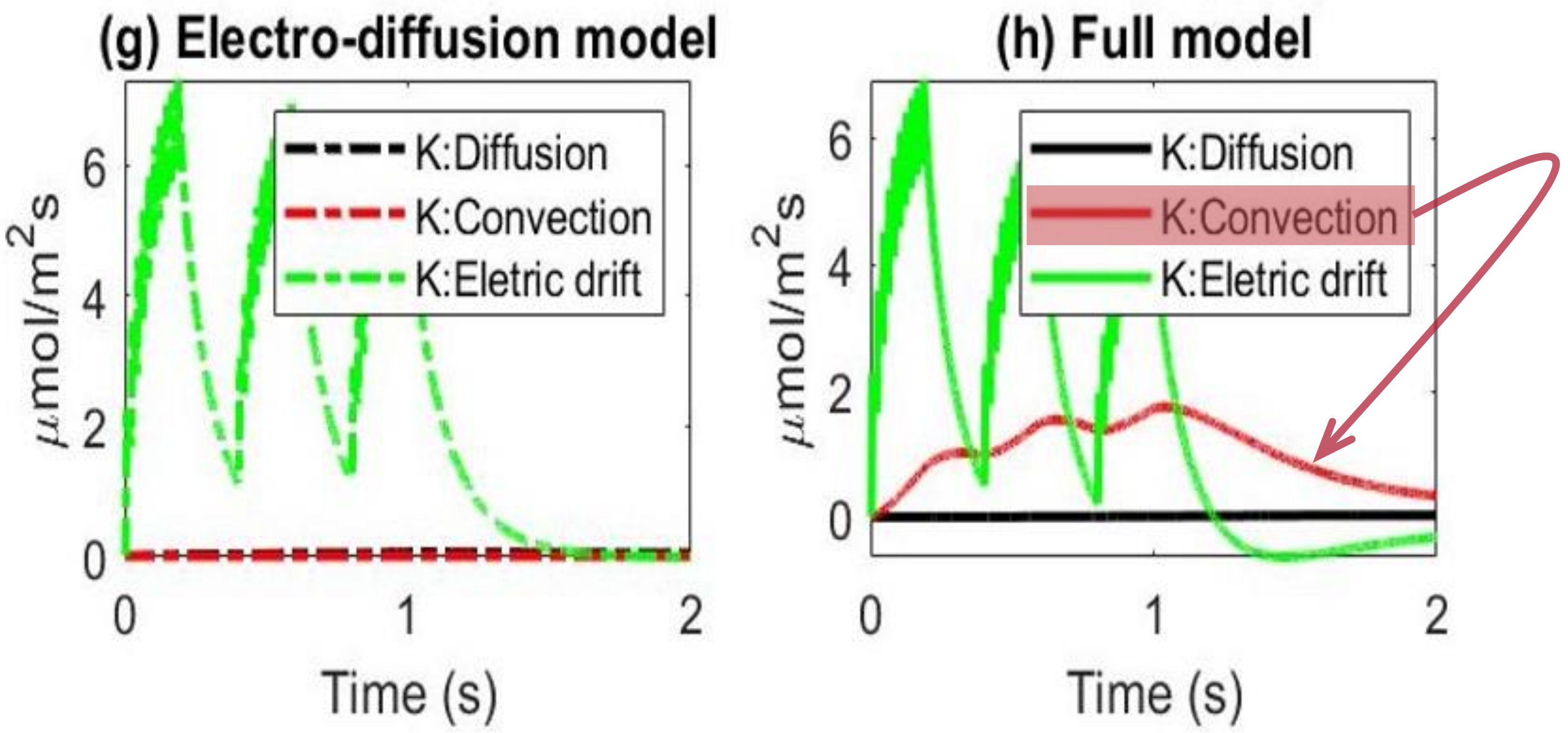
Spatial distribution of potassium changes from the resting state. To see this figure in color, go online.

Water Flow Enhances Glial Space Buffering

Field Theory gives so much detail, it is easy to overlook what is happening!!!



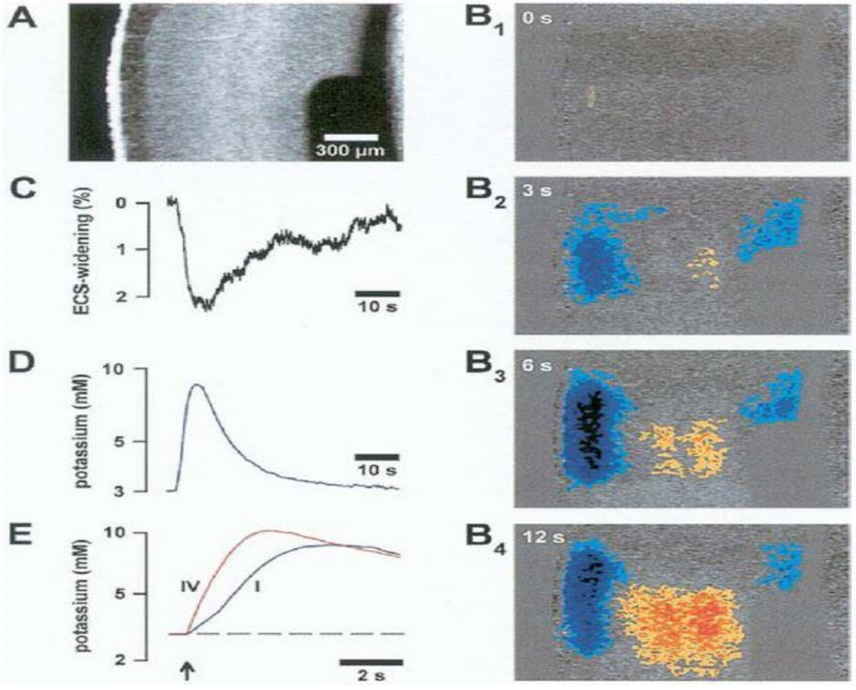
Water Flow Enhances Glial Space Buffering



Potassium Clearance

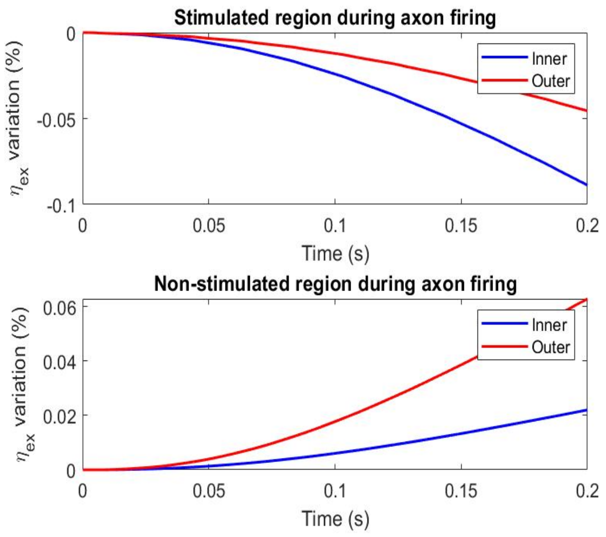
POTASSIUM BUFFERING
CENTRAL NERVOUS SYSTEM

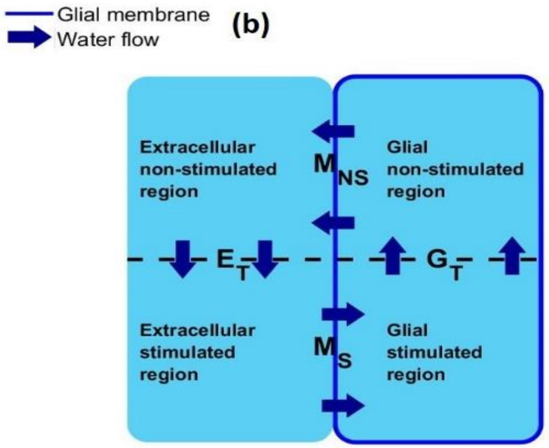
Holthoff &Witte. Glia 2000;29:288–292



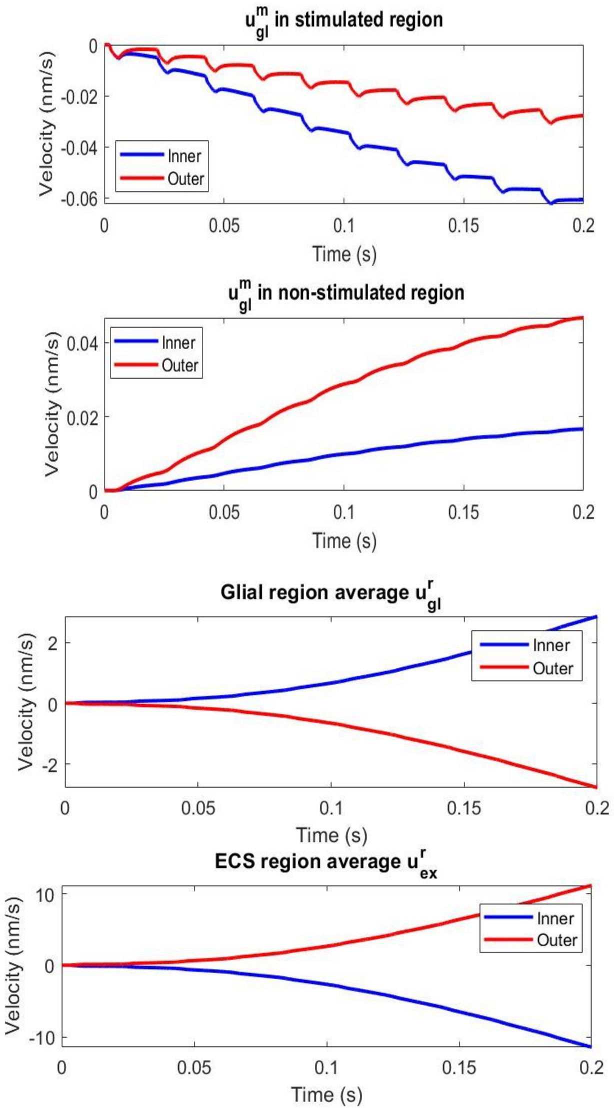
Brightening reports **Shrinkage** of the extracellular space

Darkening reports **Swelling** of the extracellular space (Fig. 1C)



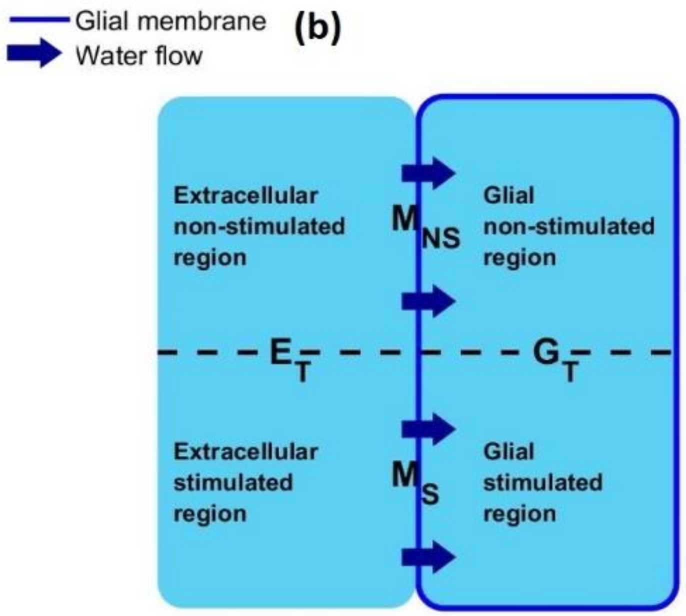


Compartments are Derived

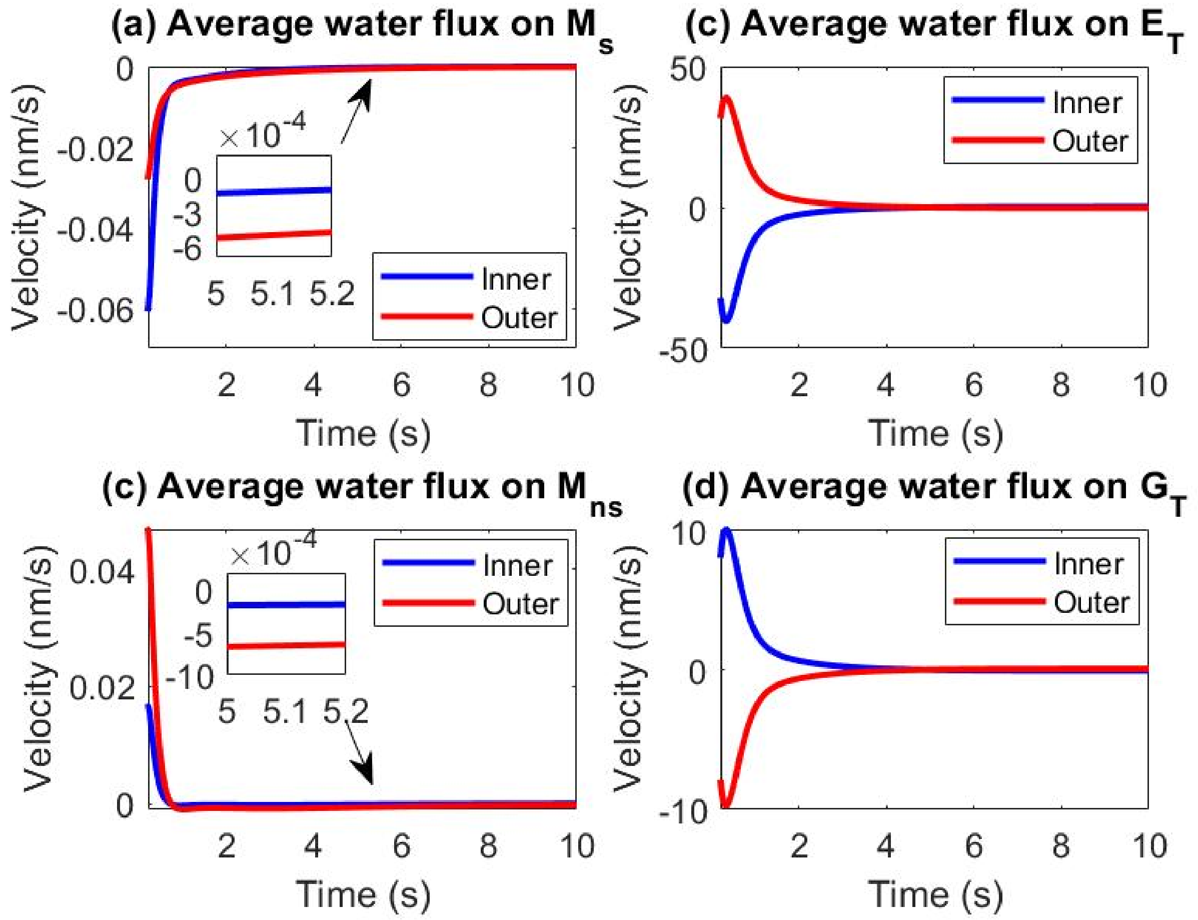


Potassium Clearance

Field Theory gives so much more detail,
than you want to understand

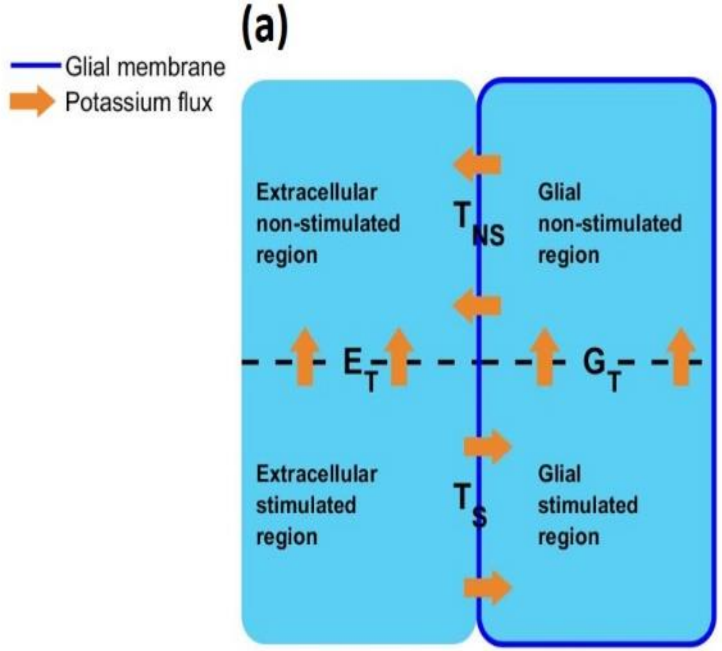


Compartments are Derived
By Singular Perturbation Analysis
They are NOT assumed



Microcirculation: Potassium

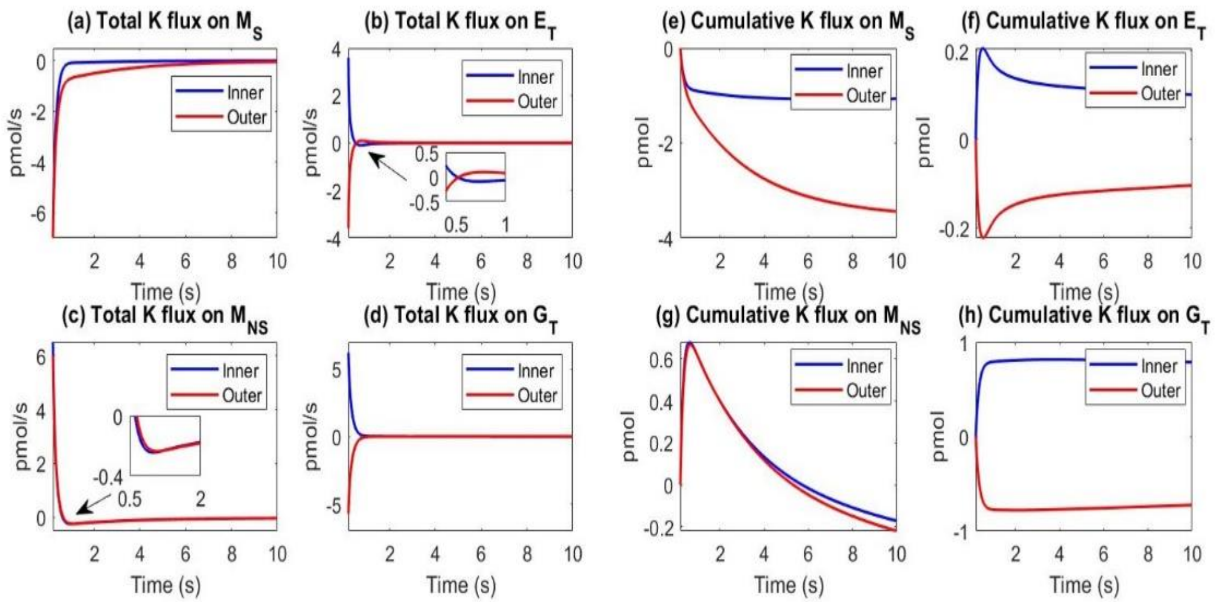
- Axon Stimulation moves extra potassium into the extracellular space
- Nernst potential of K^+ in the stimulus region increases ($E_k > [\phi]_{gl}$)
- K^+ flows into glial compartments from extracellular space
- Whole Glial compartment electric potential becomes more positive
- In the non-stimulus region, $E_k < [\phi]_{gl}$, K^+ flows out from glial compartment to extracellular space
- Also in the extracellular space, K^+ flows from stimulus region to the non-stimulus region due to the diffusion

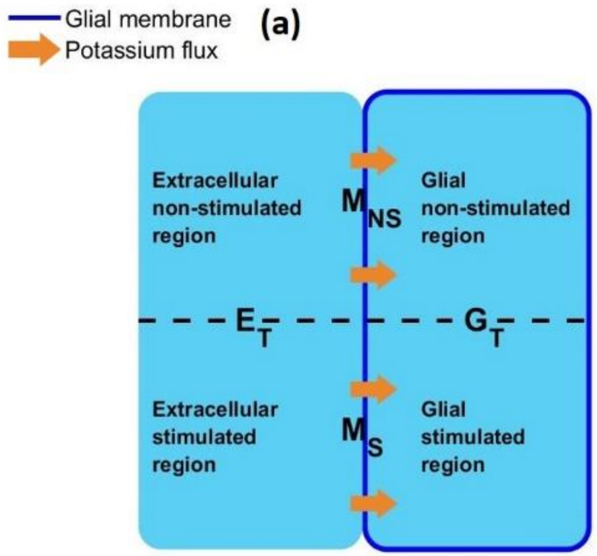


Compartments are Computed
by PerturbationTheory, NOT assumed

Potassium Clearance: Stimulus Region Effect

- After axon firing period $[T_{sti}, T_{all}]$





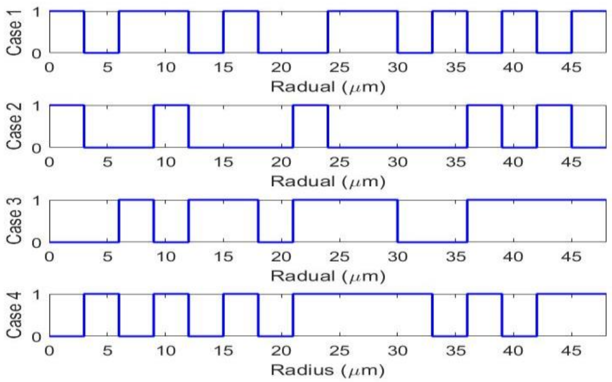
Compartments are Derived

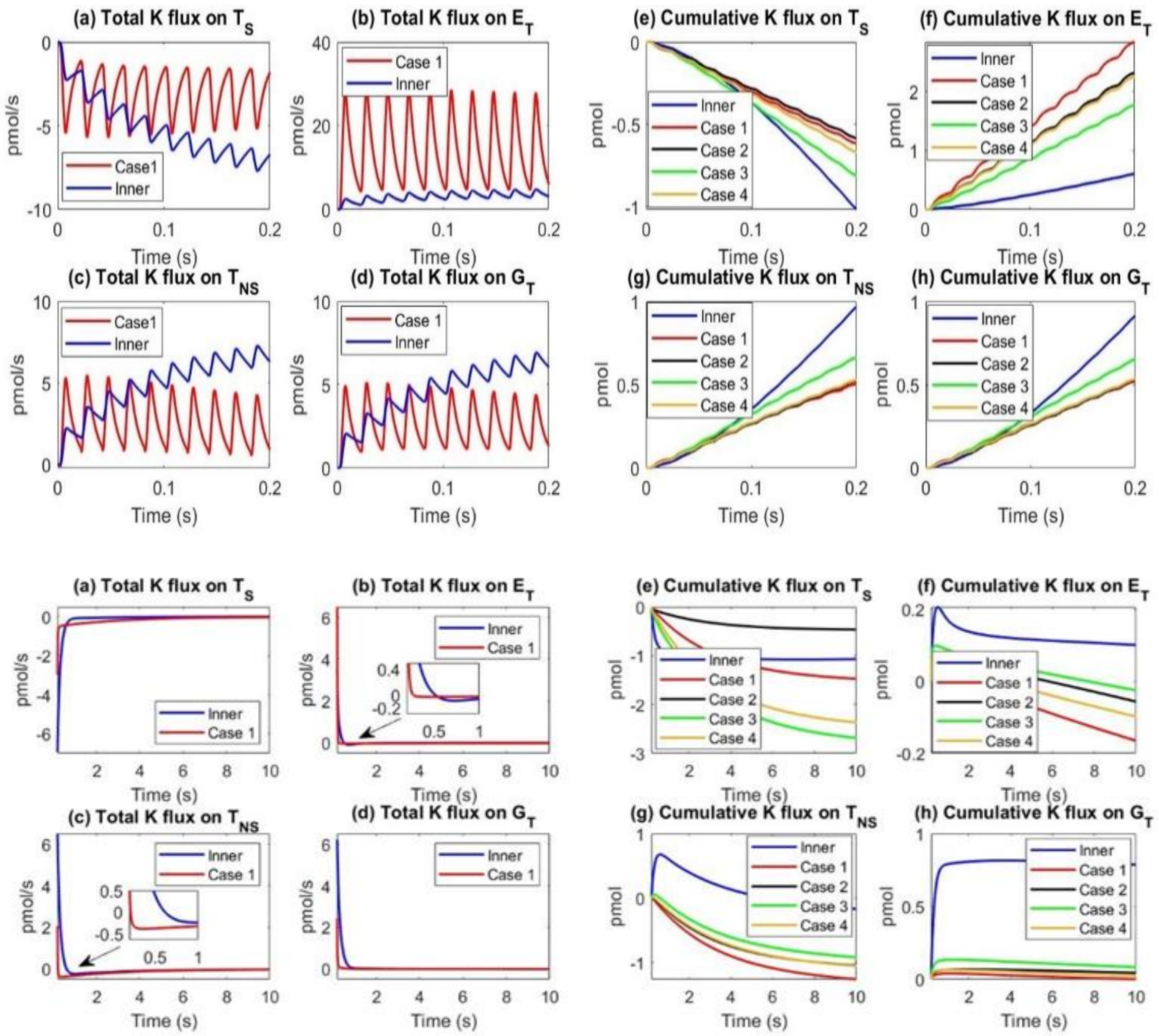
- The main potassium clearance mechanism is the **leakage from extracellular space to glial compartment through the glial membrane**;
- The potassium flux in extracellular region and glial compartment is negligible, i.e. both of them could be treated as a homogenous compartment;

Potassium Clearance: Random (in space)

Sensitivity to Spatial Distribution

Model is a Framework
that needs
More Experimental data





Sometimes Detail is Surprising
Must be actually computed
for that reason. This detail is hard
to capture robustly in compartment
and engineering models.

Results Depend on
Types and Locations of Channels and Transporters

Model can easily accommodate channel or transporters
in the detail established in future experiments

because

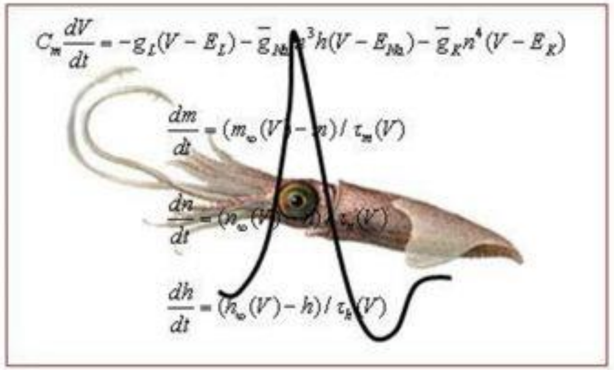
Model is a field theory with defined structure,
Allowing any property or location of channels or transporters

Model is a Framework

Model is a FRAMEWORK

that can easily accommodate
Specialized Structure
Specialized Channels
Specialized Transporters
Structural Parameters Determined by Sructural Measurements

Mathematical Model of Action Potential



- Ion concentration and electric potential
  - Mass conservation law
  - Local electroneutrality
  - Passive channel:
    - Potential dependent conductance on the axon membrane: Hodgkin-Huxley Model
    - Constant conductance on the glial cells' membrane: Ohm's Law $\frac{g_{gl}^i}{z^i e}\left(\phi_{gl}-\phi_{ex}-E_{gl}^i\right)$
    - Nernst Potential $E_{gl}^i = \ln\frac{C_{ex}^i}{C_{gl}^i}$

$$\frac{\partial(\eta_{gl}C_{gl}^i)}{\partial t}+\mathcal{M}_{gl}\left(a_{gl}^i+b_{gl}^i\right)+\nabla\cdot\left(\eta_{gl}\mathbf{J}_{gl}^i\right)=0$$

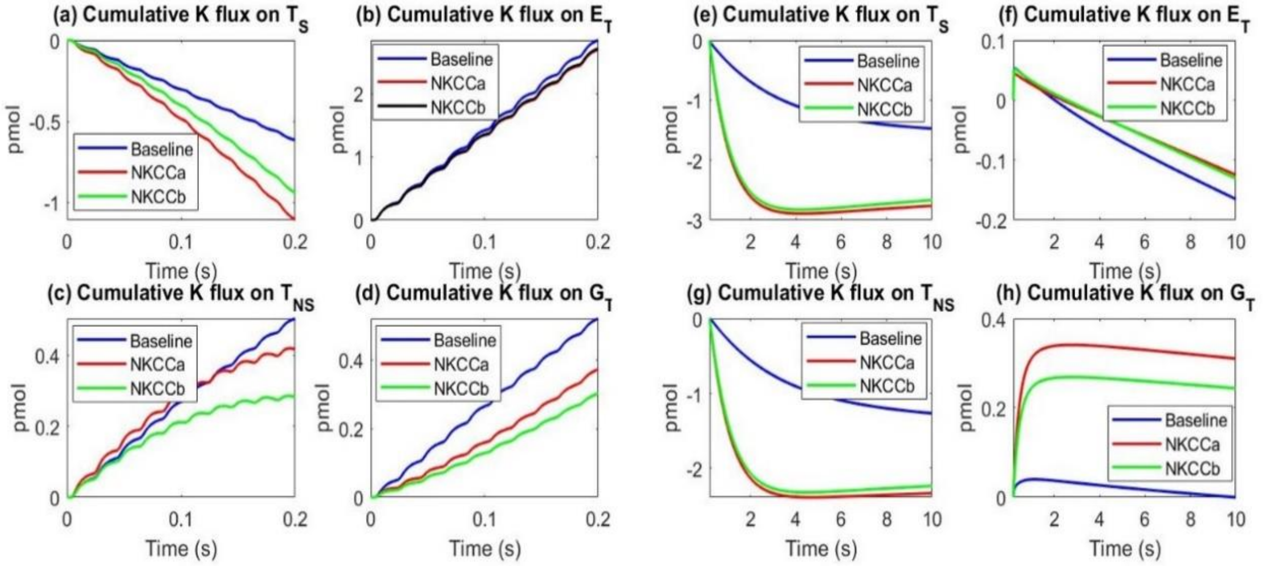
$$\frac{\partial(\eta_{ax}C_{ax}^i)}{\partial t}+\mathcal{M}_{ax}\left(a_{ax}^i+b_{ax}^i\right)+\frac{\partial}{\partial z}\left(\eta_{ax}J_{ax,z}^i\right)=0$$

$$\frac{\partial(\eta_{ex}C_{ex}^i)}{\partial t}-\mathcal{M}_{ax}\left(a_{ax}^i+b_{ax}^i\right)-\mathcal{M}_{gl}\left(a_{gl}^i+b_{gl}^i\right)+\nabla\cdot\left(\eta_{ex}\mathbf{J}_{ex}^i\right)=0$$

$$\eta_{gl}\sum_i z^i C_{gl}^i + z^{gl}A_{gl}\eta_{gl}^{re}=0,\qquad \eta_{ax}\sum_i z^i C_{ax}^i + z^{ax}A_{ax}\eta_{ax}^{re}=0,\quad \sum_i z^i C_{ex}^i=0,$$

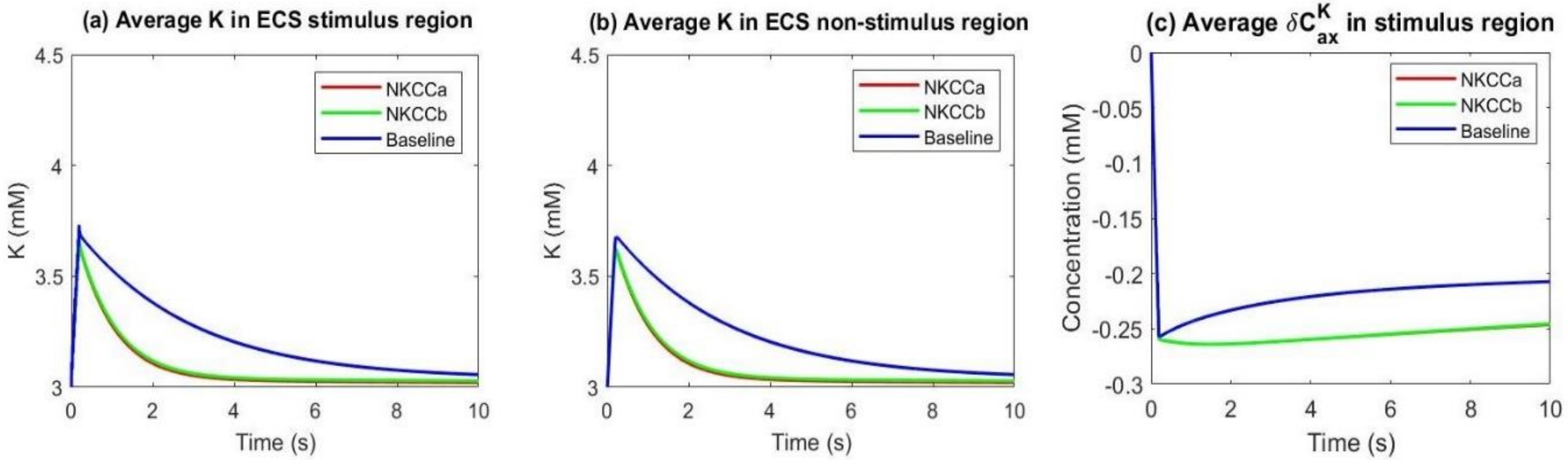
$Na^{+}/K^{+}/Cl^{-}$ NKCC transporter
Potassium Clearance

- $J_{NKCC}^{K} = -\frac{I_{max}^{NKCC}}{ez^{K}} log\left(\frac{C_{ex}^{K}}{C_{gl}^{K}}\frac{C_{ex}^{Na}}{C_{gl}^{Na}}\left(\frac{C_{ex}^{Cl}}{C_{gl}^{Cl}}\right)^{2}\right),$
- $J_{NKCC}^{Na} = -\frac{I_{max}^{NKCC}}{ez^{Na}} log\left(\frac{C_{ex}^{K}}{C_{gl}^{K}}\frac{C_{ex}^{Na}}{C_{gl}^{Na}}\left(\frac{C_{ex}^{Cl}}{C_{gl}^{Cl}}\right)^{2}\right),$
- $J_{NKCC}^{Cl} = 2\frac{I_{max}^{NKCC}}{ez^{Cl}} log\left(\frac{C_{ex}^{K}}{C_{gl}^{K}}\frac{C_{ex}^{Na}}{C_{gl}^{Na}}\left(\frac{C_{ex}^{Cl}}{C_{gl}^{Cl}}\right)^{2}\right).$
- With the help of $Na^{+}/K^{+}/Cl^{-}$ NKCC transporter, more potassium goes through the glial membrane in the simulated region during axon firing.



Potassium Clearance: NKCC transporter

- With the NKCC model, the potassium decays at a much faster rate than in the baseline model.
- However, the quicker potassium taken into glial compartment by the NKCC leads the slower stimulated axon compartment potassium concentration back to resting state.



More Details: Microcirculation: Ion

- The **potassium** variation (δC_{ex}^{K}) in the extracellular

$$\frac{d(\eta_{ex}\delta C_{ex}^{K})}{dt} = -\left(\lambda_{gl}^{m,K} + \lambda_{ex}^{K}\right)\delta C_{ex}^{K}$$

$$\delta C_{ex}^{K}(iT) = \delta C_{ex}^{K}(iT) + \delta C_{sti}, \qquad i = 0,1\cdots$$

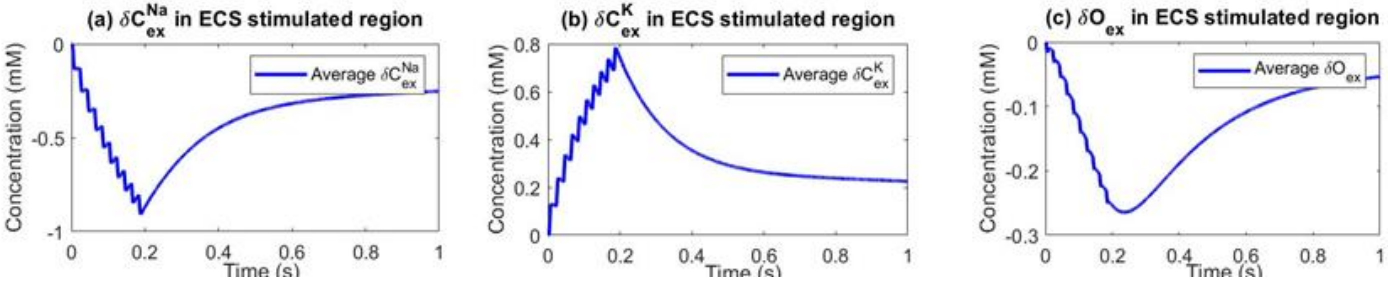
- The **sodium** variation (δC_{ex}^{Na}) in the extracellular region

$$\frac{d(\eta_{ex}\delta C_{ex}^{Na})}{dt} = -\lambda_{ex}^{Na,1}\delta C_{ex}^{Na} + \lambda_{ex}^{Na,2}\delta C_{ex}^{K},$$

$$\delta C_{ex}^{Na}(iT) = \delta C_{ex}^{Na}(iT) - \delta C_{sti}, \qquad i = 0,1\cdots$$

- The **Chemical Potential of Water (osmotic 'pressure')** variation (δO_{ex}) in the extracellular region

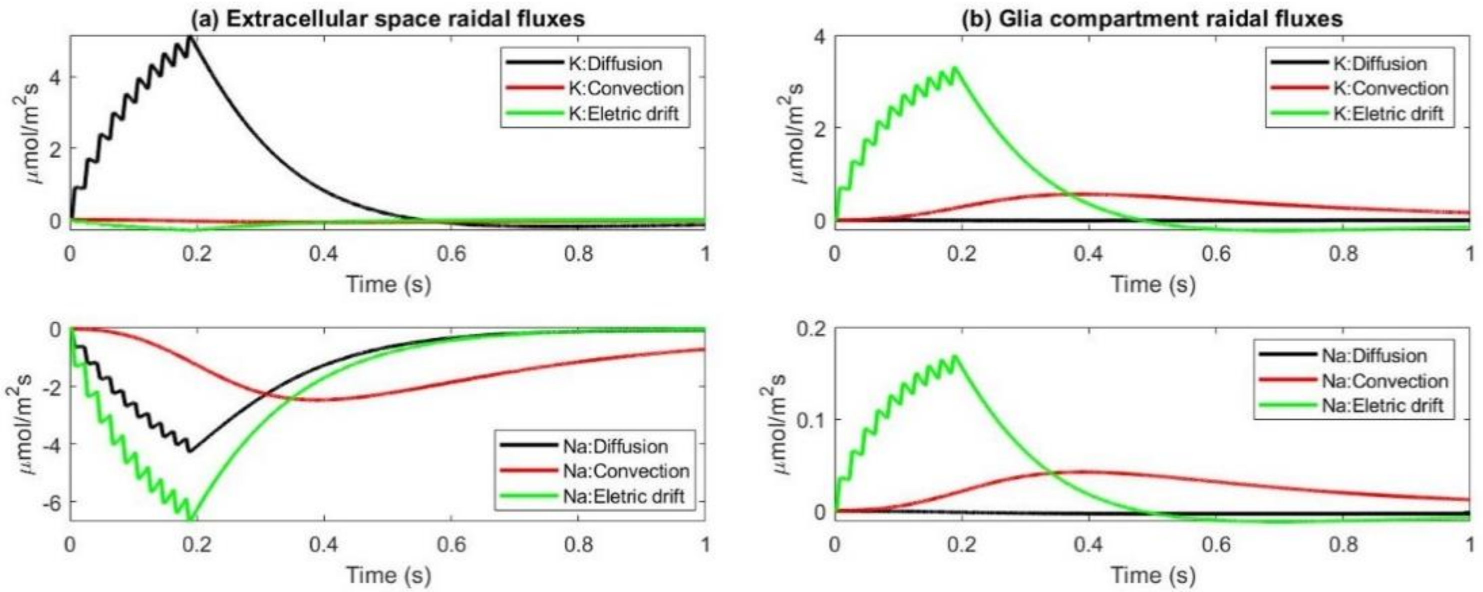
$$\delta O_{ex} = 2(\delta C_{ex}^{K} + \delta C_{ex}^{Na})$$



Where T is firing period, λ_{ex}^{K} describes the spatial effect of the extracellular communication between stimulated region and non-stimulated region, $\lambda_{gl}^{m,K}$ describes the effect of glial transmembrane flux, $\lambda_{ex}^{Na,1}$ describes the spatial effect of the extracellular communication between stimulated region and non-stimulated region, and $\lambda_{ex}^{Na,2}$ describes the effect of electric drift in the extracellular space

Microcirculation: Convection

- Extracellular space:
  - K^+: **diffusion flux** dominates
  - Na^+: same order



Qualitative Conclusions are from MATHEMATICAL Perturbation Analysis. They are NOT verbal vagueries.

Conclusions

Field Theory of Glymphatic Flow

- A tridomain model is developed to understand the microcirculation in the optic nerve and the potassium clearance mechanism.
- **Main pathway is Convection Through Glia**
  driven by electrochemical diffusion and migration of ions and water in axon and extracellular space

  This is a RESUT derived from a field theory of glymphatic flow
  without arbitrary compartments or simplifications. It is derived NOT assumed.
- The electrical syncytium property of the glial cells is critical for clearing potassium during nerve activity.
- Spatial distribution of pumps and channels can be included as they are discovered. Likely to have large effects. **New Experiments Needed**

Speculations and Future Work

- Do Localized Pumps Produce Increased Clearance ?
- Can Blood Vessels be included making a Four Domain Model?
- Can model account for Sleep Cleansing by up-regulation of localized pumps?
- Is the Glymphatic Hypothesis of Sleep Cleansing correct?

Questions ?

Scientists and Poets can Reach

for something

but

<u>Engineers must Grasp</u>

and not just reach for it

if

Devices are to Work

Uncalibrated Devices do not Work!

Poets

create beauty by mixing 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

Extra Slides

Inconsistent Models

produce confusion
even when correct

Mathematics

$$\frac{\partial}{\partial u} \sum \int$$

replaces
<u>In</u>consistent Models Models
with **Consistent**
Partial Differential Equations
and boundary conditions

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.

Our Contributions

are to Derive <u>Consistent</u> 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

$$\frac{\partial}{\partial u} \sum \int$$

Mathematics Creates our Standard of Living*

<u>Partial Differential Equations</u>
are needed to describe
<u>Flow</u>
driven by multiple fields

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

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,
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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

Field Equations are Needed
of the **Whole Optic Nerve**
EVERYTHING INTERACTS WITH EVERYTHING ELSE

Models of just one part of the system
Ignore membrane flows and interactions
that can dominate properties
Every scientist is sure their 'one part' is the right one.

Models with ARBITRARY compartments, that are not derived,
lead to more discussion than insight:
Every scientist is sure their compartments are right,
but none of their compartments are robust.

Potassium Clearance

in outermost Shell, Pia Mater

- Assume the water fluid goes through the non-selective pathway only depends on the hydro pressure difference

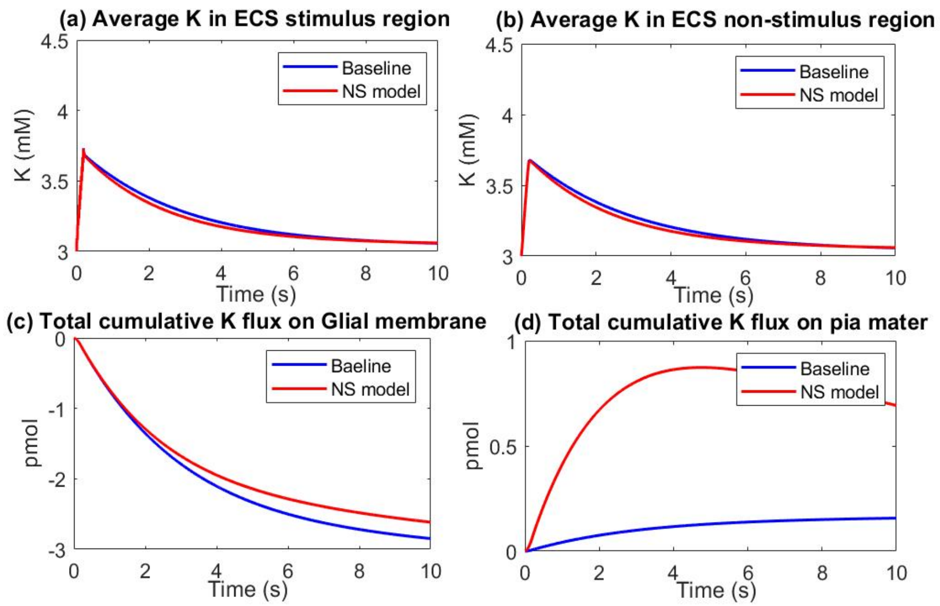
$$u_{pia}^{m} = L_{pia}^{m}\left(P_{ex}^{OP} - P_{ex}^{sas} - \gamma_{pia}k_B T\left(O_{ex}^{OP} - O_{ex}^{sas}\right)\right),$$

$$\boldsymbol{u_{pia}^{ns} = L_{pia}^{ns}(P_{ex}^{OP} - P_{ex}^{sas}).}$$

- The non-selective pathway between the cell clefts provides the additional pathway for diffusion, electric drift as well as convection for ions

$$\mathbf{J}_{ex}^{i,OP} \cdot \hat{r} = \mathbf{J}_{ex}^{i,SAS} \cdot \hat{r} = \frac{G_{pia}^{i} + G^{ns}}{z^{i} e}\left(\phi_{ex}^{OP} - \phi_{ex}^{SAS} - E_{pia}^{i}\right) + \boldsymbol{C_{ex}^{i} u_{pia}^{ns}},$$

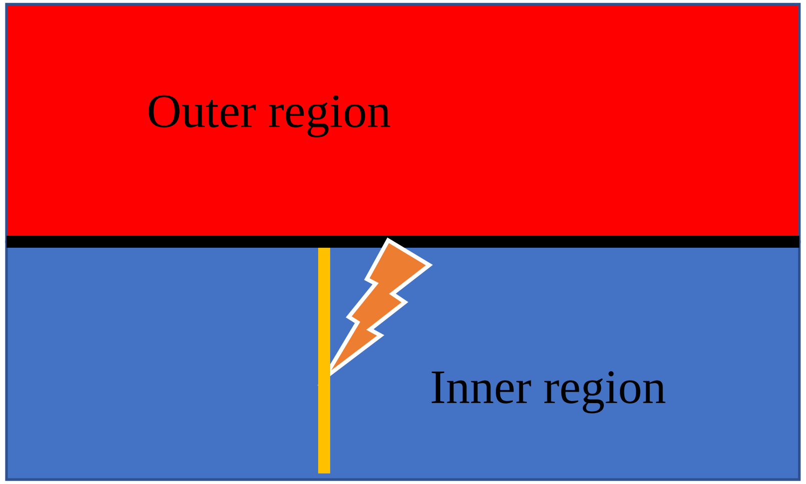
$i = \mathrm{Na}^{+}, \mathrm{K}^{+}$

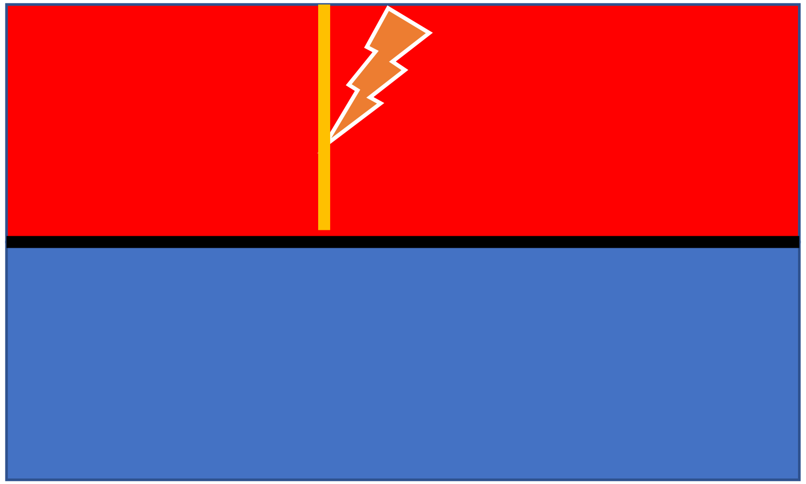


The amount of potassium leak out of the optic nerve through the pia boundary has dramatically increased in comparison with the baseline model. However, the dominate pathway of potassium clearance is still through the glial membrane part due to the contact area.

Potassium Clearance: Stimulus Region Effect

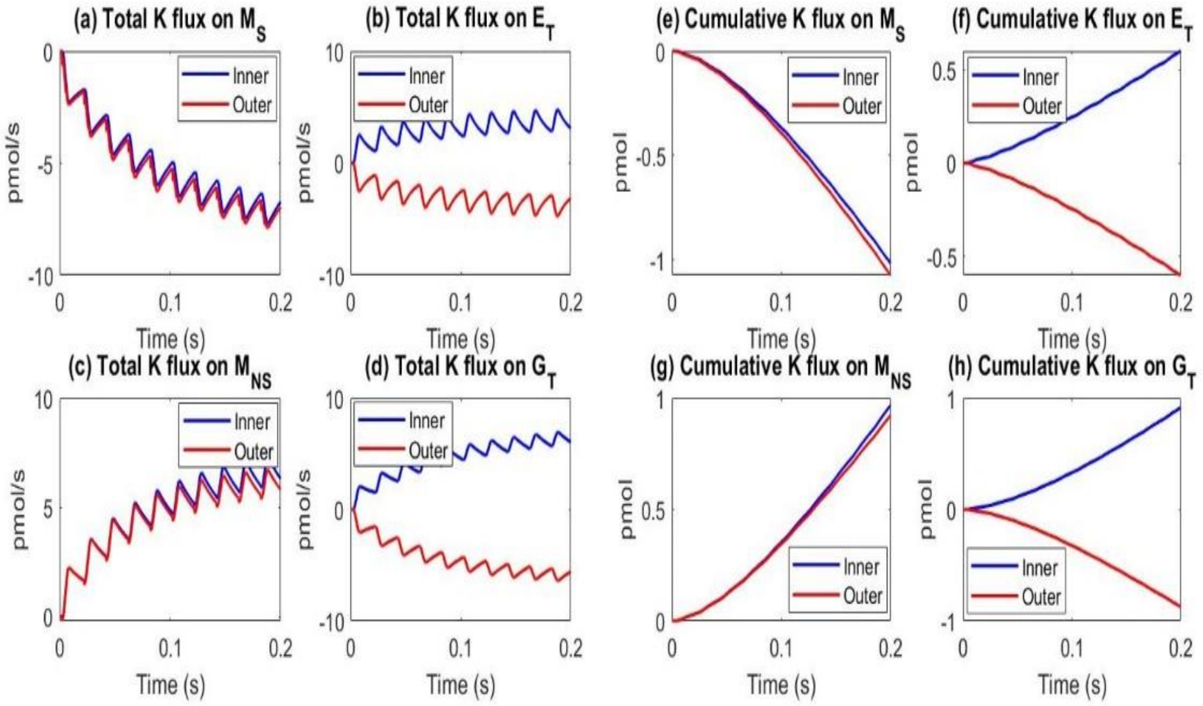
- Stimulus region
  - Inner region $\left[0, \frac{r^*}{2}\right] \times [0, L]$
  - Outer region $\left[\frac{r^*}{2}, r^*\right] \times [0, L]$
  - Transition region $r = \frac{r^*}{2}$
- Time period
  - Axon firing period $[0, T_{sti}]$
  - After firing period $[T_{sti}, T_{all}]$
  - $T_{sti} = 0.2s$ and $T_{all} = 10s$

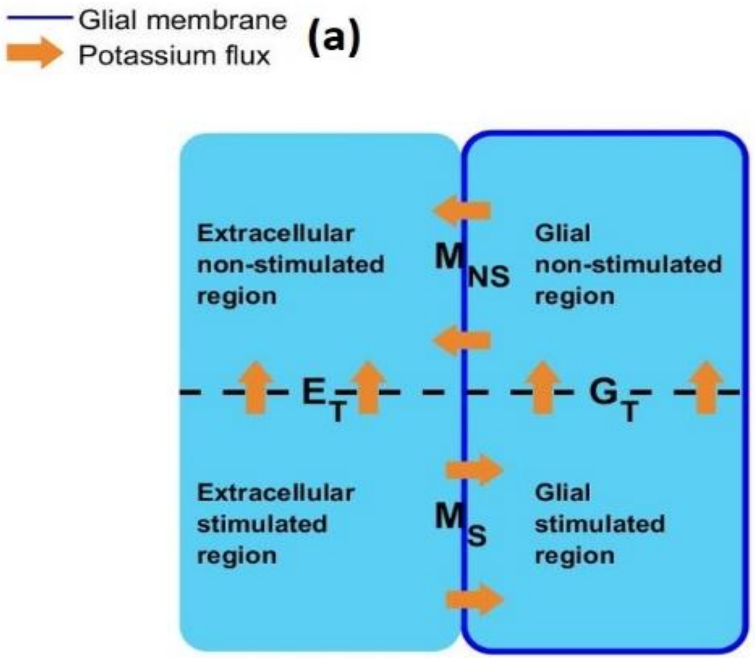




Potassium Clearance: Stimulus Region Effect

- During axon firing $[0, T_{sti}]$



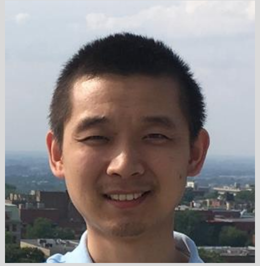


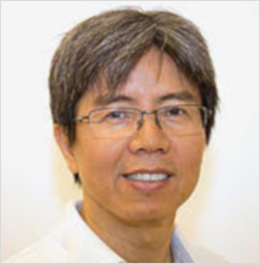
Both Glial compartment and ECS help potassium clearance. Glial compartment is more important.

Osmosis through a Semi-permeable Membrane

a Consistent Approach to Interactions

arXiv:1806.00646





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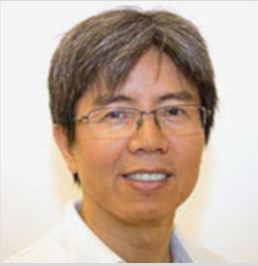
A Bidomain Model for Lens Microcirculation

Biophysical Journal (2019) 116: p. 1171-1184



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