# An ion-based model for swelling of neurons and astrocytes

Shujie Zhang 2024/5/7

# Contents

- **Biology Background**
- **Conclusions**
- **Model Details**
- **Brief comparison: Other Models**

# Biology Background

- Cell volume changes are ubiquitous in normal and pathological activity of the brain.
- Little known about the dynamics of swelling and the differential changes in pathological states

  - **Spreading depolarizations (SD)** under ischemic and non–ischemic conditions, and epileptic seizures.
  - **Anoxic depolarization (AD)**

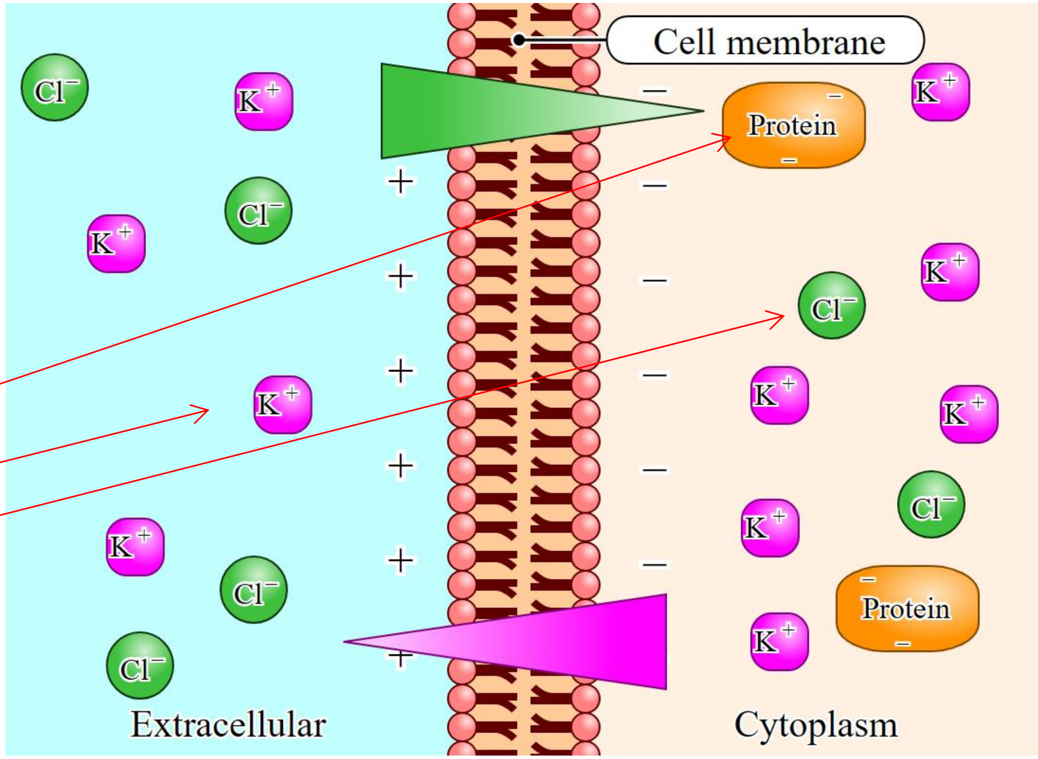
# Biology Background: What to model?

- Donnan equilibrium & Neutrality

> Charged particles near a semi-permeable membrane fails to distribute evenly across the two sides of the membrane.

- Negatively charged macromolecules (e.g., proteins)
- cations (e.g., sodium and potassium) to move to
- anions (e.g., chloride) tend to move away
- maintain overall electrical neutrality

& ion concentrations no longer the same




https://en.wikipedia.org/wiki/Gibbs%E2%80%93Donnan_effect

# Biology Background: What to model?

- **Donnan equilibrium & Neutrality**

$$\Pi_{i/e} = Na_{i/e} + K_{i/e} + Cl_{i/e} + \boxed{X_{i/e}} .$$

Impermeant particles to make sure of initial osmotic equilibrium and neutrality

$$\Pi_i = \Pi_e \ .$$

**AD & SD: Swelling Compensate**

$$\Pi_i > \Pi_e$$

$$\omega_{tot} = \omega_i + \omega_e \ .$$

# Biology Background: What to model?

- Free Energy–Starvation (FES)

In SD, ion gradients disrupted and requires a large amount of **ATP** to restore in an abrupt repolarization. Namely, energy is still extremely scarce.

In combined neuron–glia models, FES is metastable and appear after a strong enough stimulation, lasting about 80 sec.

# Biology Background: What to model?

- Electroneutral buffering and swelling of astrocytes

In FES, astroglial buffering becomes effective and help to recover the neuron by $K^+$ current rectifying.
Without the astrocytes, FES would be permanent.

$$\lambda^{upt.} = \lambda_1 \left(1.0 + \exp\left(\frac{5.5 - K_e}{2.5}\right)\right)^{-1}$$

$$J_{glia} = \lambda^{upt.} - \lambda^{rel.} \ .$$

$$N_e^K = N_e^{K,0} + N_i^{K,0} - N_i^K - \Delta N^K \ ,$$

$$\frac{\mathrm{d}\Delta N^K}{\mathrm{d}t} = J_{glia} \ .$$

$$N_e^{Na} = N_e^{Na,0} + N_i^{Na,0} - N_i^{Na} - \Delta N^{Na} \ ,$$

$$N_e^{Cl} = N_e^{Cl,0} + N_i^{Cl,0} - N_i^{Cl} - \Delta N^{Cl} \ ,$$

Electroneutrality

$$\Delta N^{Na} = (\chi - 1)\Delta N^K \ ,$$

$$\Delta N^{Cl} = \chi \Delta N^K \ .$$

# Method

- Hodgkin–Huxley type spiking dynamics + dynamic ion concentrations + simultaneous neuronal all in one
- .ode file run with XPPAUT

# Conclusion

- Elucidate :

1. Why glial cells swell more than neurons in SD and the special case of anoxic depolarization (AD)

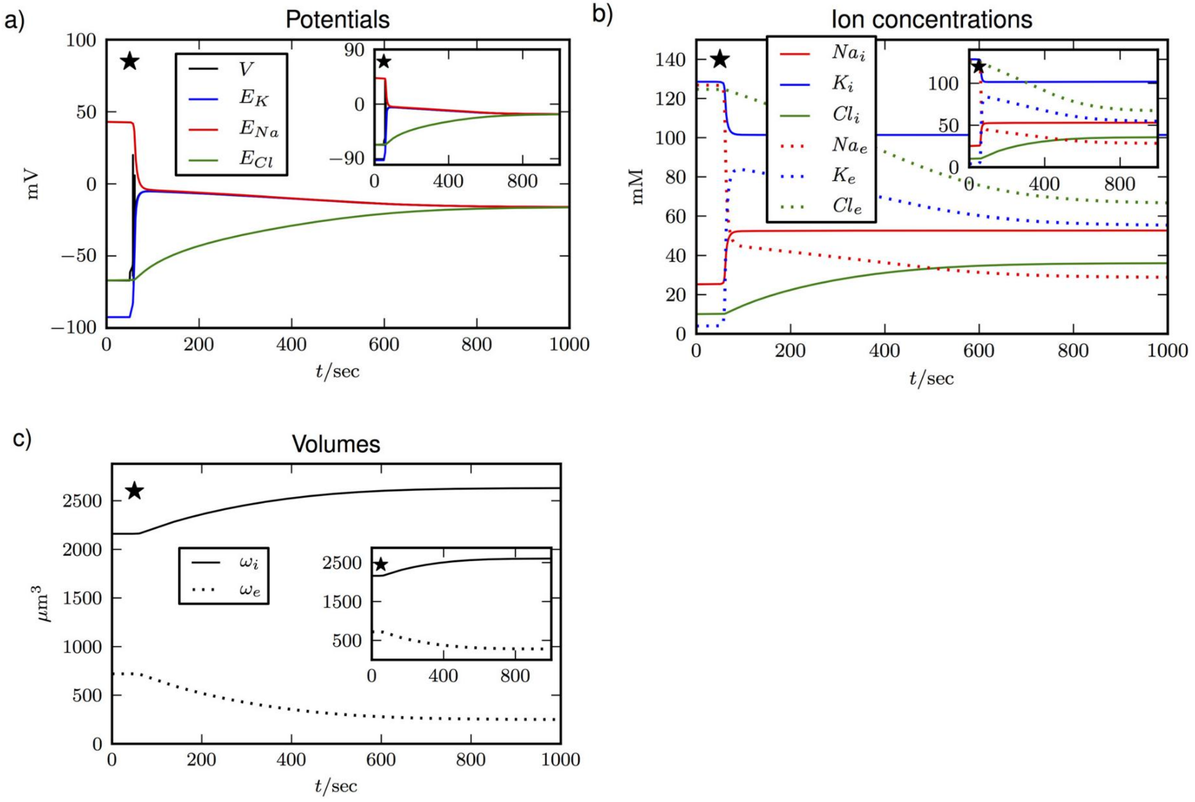
2. The relative contributions of the two cell types to tissue swelling.

A Controversial Hypothesis

ing to this shrinkage is a matter of debate. Some studies support the hypothesis that during these pathologies astrocytes swell more than neurons [24, 25, 29, 33, 35], while others claim the opposite [34]. We will comment on some of these studies in the discussion of our results.

# Model Details(Figure 3, Donnan equilibrium)

**$c_{Cl^-}$ seems to have strong corelation with the volume**




$$\frac{N_i}{\omega_i^{eq}} = \frac{N_e}{\omega_e^{eq}} \quad \Rightarrow \quad \frac{N_{tot}}{\omega_{tot}} = \frac{N_i + N_e}{\omega_i^{eq} + \omega_e^{eq}} = \frac{N_i + N_i \frac{\omega_e^{eq}}{\omega_i^{eq}}}{\omega_i^{eq} + \omega_i^{eq} \frac{\omega_e^{eq}}{\omega_i^{eq}}} = \frac{N_i}{\omega_i^{eq}} \quad \Rightarrow \quad \omega_i^{eq} = \omega_{tot} \frac{N_i}{N_{tot}}\,, \qquad (28)$$

$$\omega_i^{eq} = \omega_i^0 \left(1.35 - 0.35 \exp\left(\frac{\Pi_e - \Pi_i}{20}\right)\right)\,. \qquad (25)$$

Fig 3 the ion pumps are switched off after 50 sec

# Model Details(Figure 4)

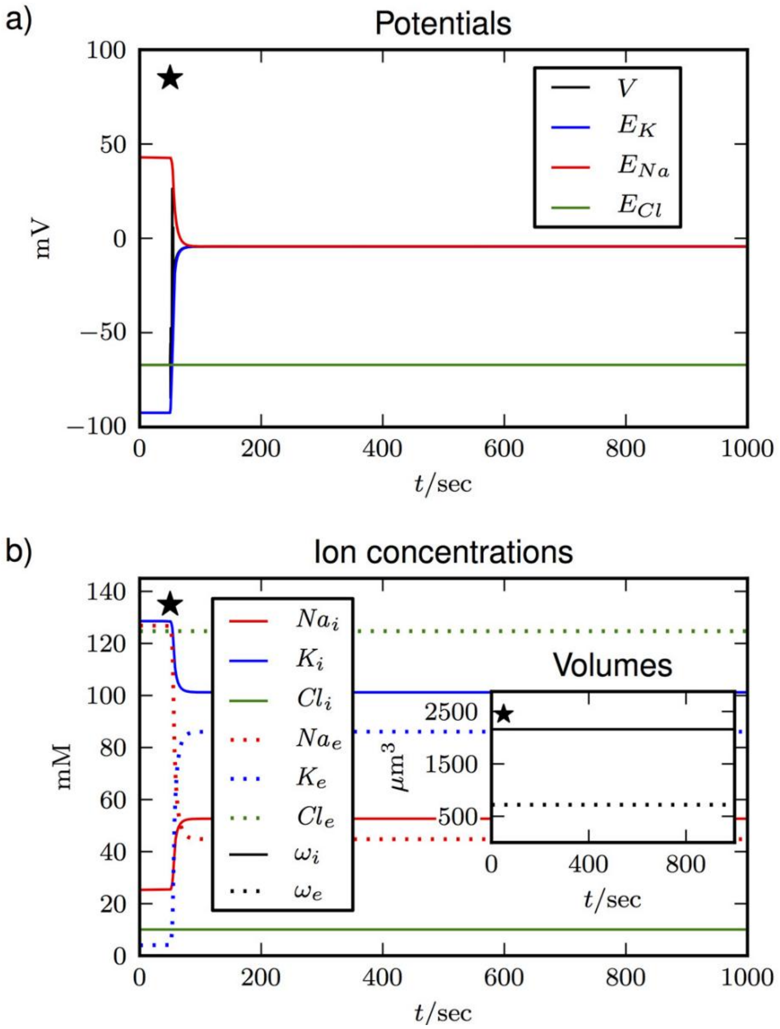



Fig 4  No $Cl^-$, no volumn change at all

This effect is gradual and swelling get slower the closer we get to $g_{Cl}$ = 0 $mS/cm^2$.

# Model Details(Figure 5, FES)

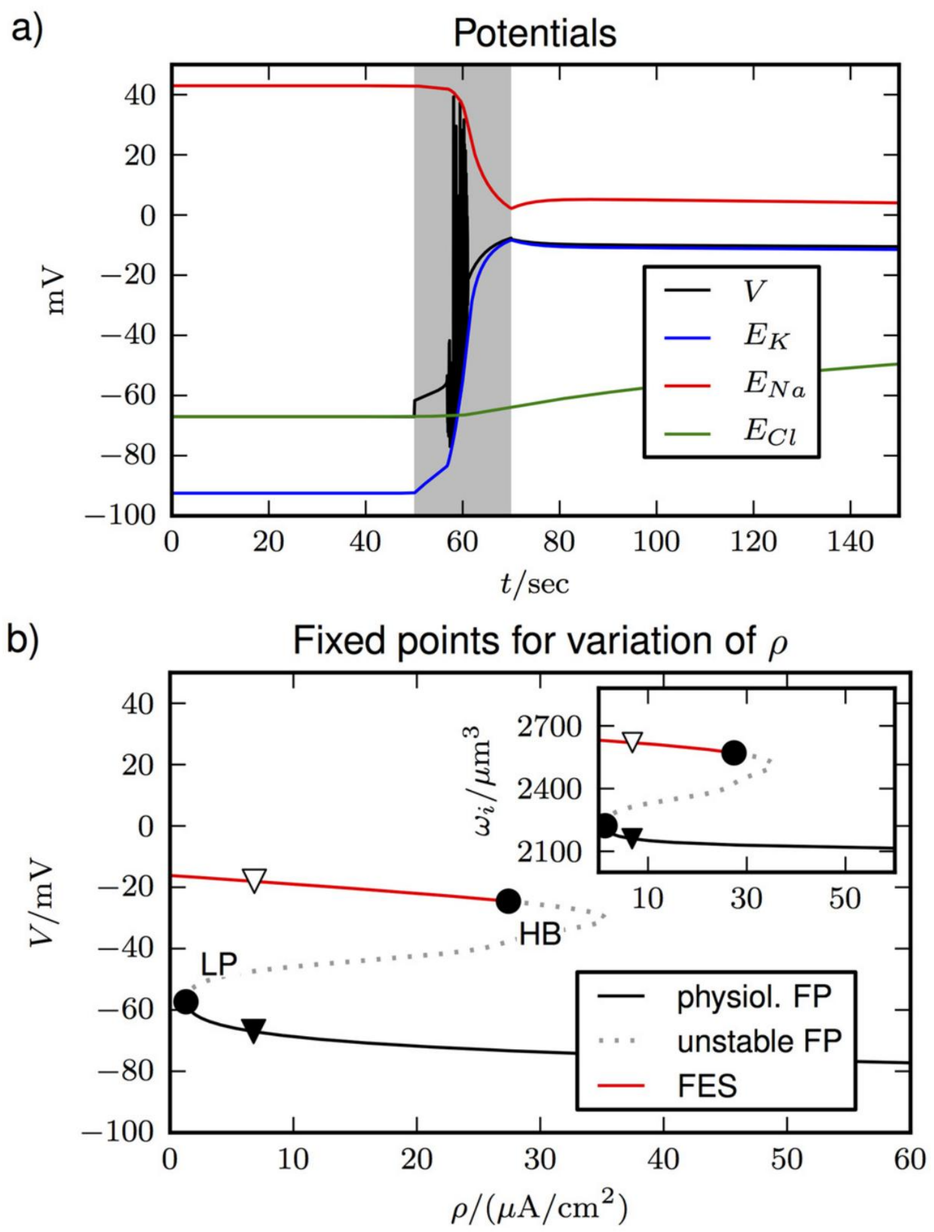



Fig 5 the pump activity is interrupted for 20 sec (shaded region) to show FES

# Model Details(Figure 3, 4 & 5)

```
############################################################
# choice between two volume models:                 #
# vli_inf0: equil. volume in derived model       #
# vli_inf1: equil. volume in exponential model   #
#############################################################
# n_i/e: total amount of particles in ICS/ECS        #
# p_i/e: total concentration of particles in ICS/ECS #
#############################################################
n_i      = n_nai + n_ki + n_cli + n_impi
n_e      = n_nae + n_ke + n_cle + n_impe
vli_inf0 = vl_tot * n_i / (n_i + n_e)
vli0     = 2160.
p_i      = n_i / vli * 1000.
p_e      = n_e / vle * 1000.
vli_inf1 = vli0 * (1.35 - 0.35*exp((p_e-p_i)/20.))
vli_inf  = (1-s) * vli_inf0 + s * vli_inf1
```

# Model Details(Figure 7)

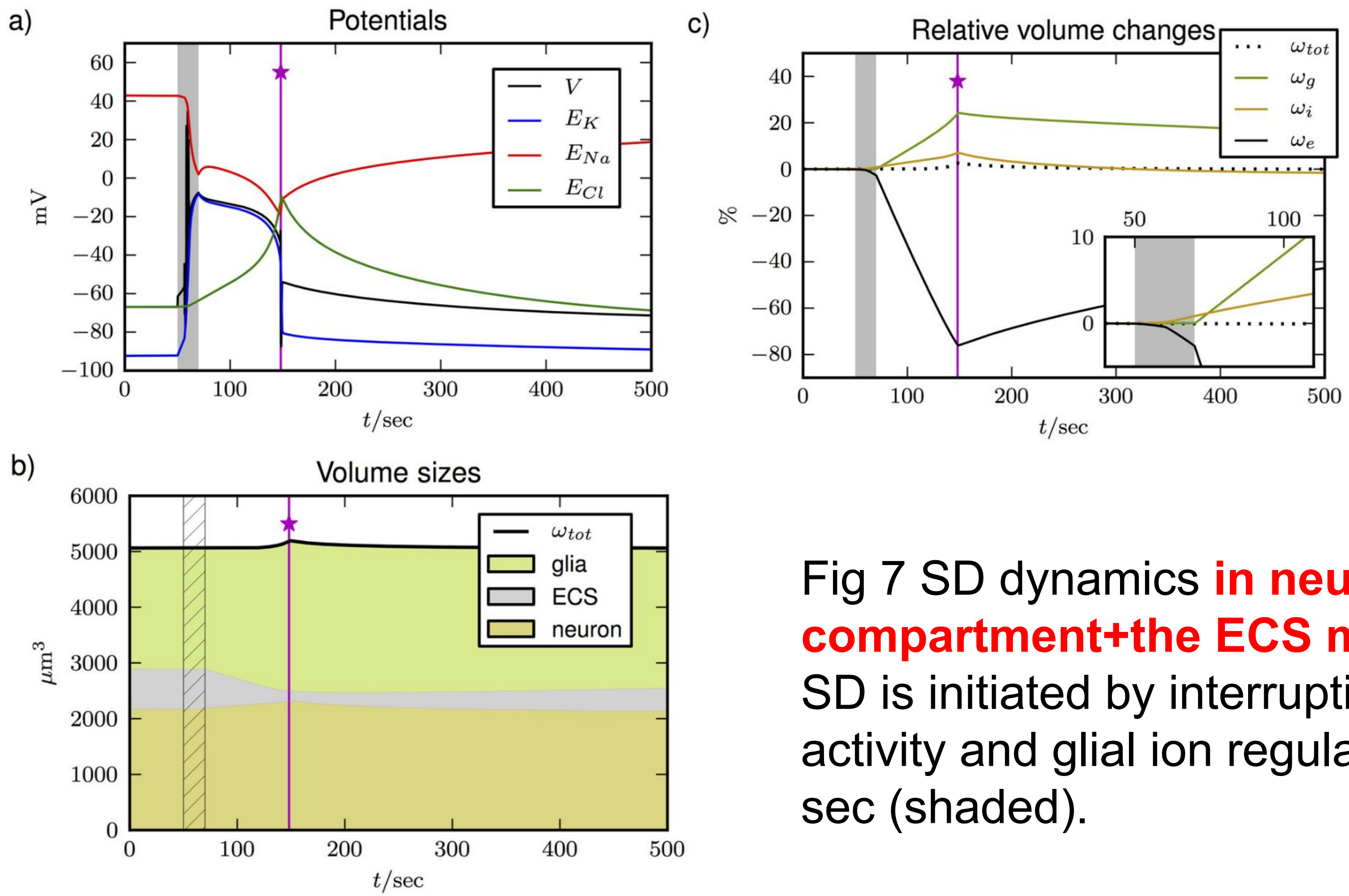



Fig 7 SD dynamics **in neuron+glial compartment+the ECS model.**
SD is initiated by interrupting pump activity and glial ion regulation for 20 sec (shaded).

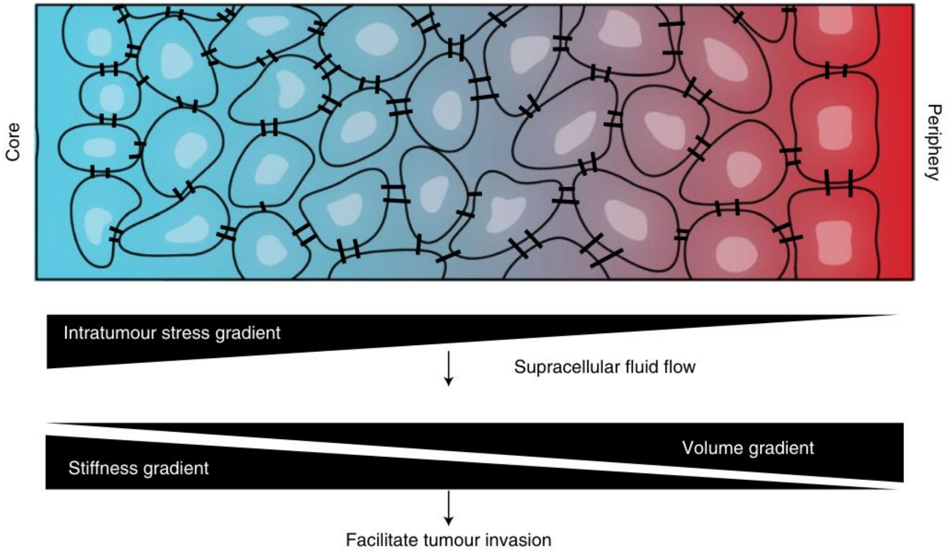
# Model Details(Figure 7 code)

```
################################################################################
################
# electroneutrality (first line) and mass conservation (second to fourth)  #
# conditions to compute ion amounts other than intracellular potassium and #
# chloride                                                                 #
################################################################################
################
n_nai = n_nai0 + n_ki0  - n_ki - n_cli0 + n_cli
dnna  =-dnk * (1-chi)
dncl  = dnk * chi
n_nae = n_nae0 + n_nai0 - n_nai + dnna
n_ke  = n_ke0  + n_ki0  - n_ki  + dnk
n_cle = n_cle0 + n_cli0 - n_cli + dncl

#####################
# glial buffering #
#####################
k1   = 1.75e-3
k2   = 6.2e-4
J_gl = (k2 - k1 / (1.0 + exp((5.5-ke)/2.5))) * f_gl
```

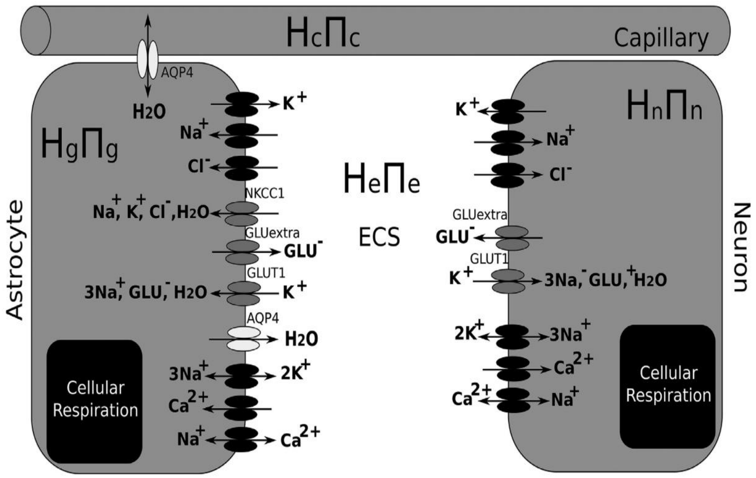
# Other Models About Cell Swelling

- Cell swelling, softening and invasion in a three-dimensional breast cancer model



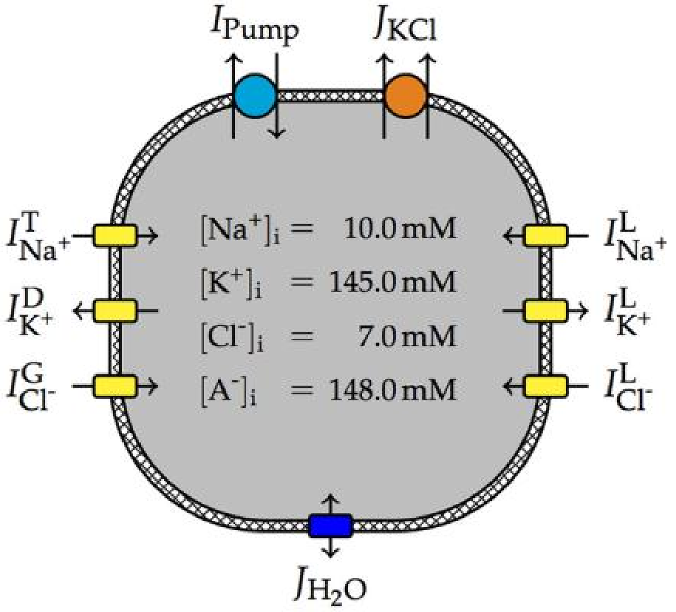

Attributed to macroscopic liquid flow

- A mathematical model of cellular swelling in Neuromyelitis optica




- Transport of water and ions through cell membranes
- disruption of cell membranes
- the metabolic state of the cell, specifically ATP

- A Biophysical Model for Cytotoxic Cell Swelling




- Ion Flow and Kinetics
- ATP-dependent pumps
- Chloride channels
- Donnan equilibrium

# Questions

Here fixed pattern are modeled on an unfamiliar platform.
How to integrate them in dynamic ECS modeling?

# Reference

[1] Hübel N, Ullah G (2016) Anions Govern Cell Volume: A Case Study of Relative Astrocytic and Neuronal Swelling in Spreading Depolarization. PLoS ONE 11(3): e0147060. doi:10.1371/journal.(ModelDB 187599)

[2] Han, Y.L., Pegoraro, A.F., Li, H. et al. Cell swelling, softening and invasion in a three-dimensional breast cancer model. Nat. Phys. 16, 101–108 (2020). https://doi.org/10.1038/s41567-019-0680-8

[3] Simão Laranjeira, Mkael Symmonds, Jacqueline Palace, Stephen J. Payne, Piotr Orlowski, A mathematical model of cellular swelling in Neuromyelitis optica, Journal of Theoretical Biology, Volume 433, 2017, Pages 39-48, ISSN 0022-5193, https://doi.org/10.1016/j.jtbi.2017.08.020.

[4] Dijkstra K, Hofmeijer J, van Gils SA, van Putten MJ. A Biophysical Model for Cytotoxic Cell Swelling. J Neurosci. 2016 Nov 23;36(47):11881-11890. doi: 10.1523/JNEUROSCI.1934-16.2016. PMID: 27881775; PMCID: PMC6604918.

# THANKS!