http://www.utdallas.edu/~kilgard/brain.jpg

Modeling Cortical Spreading Depression

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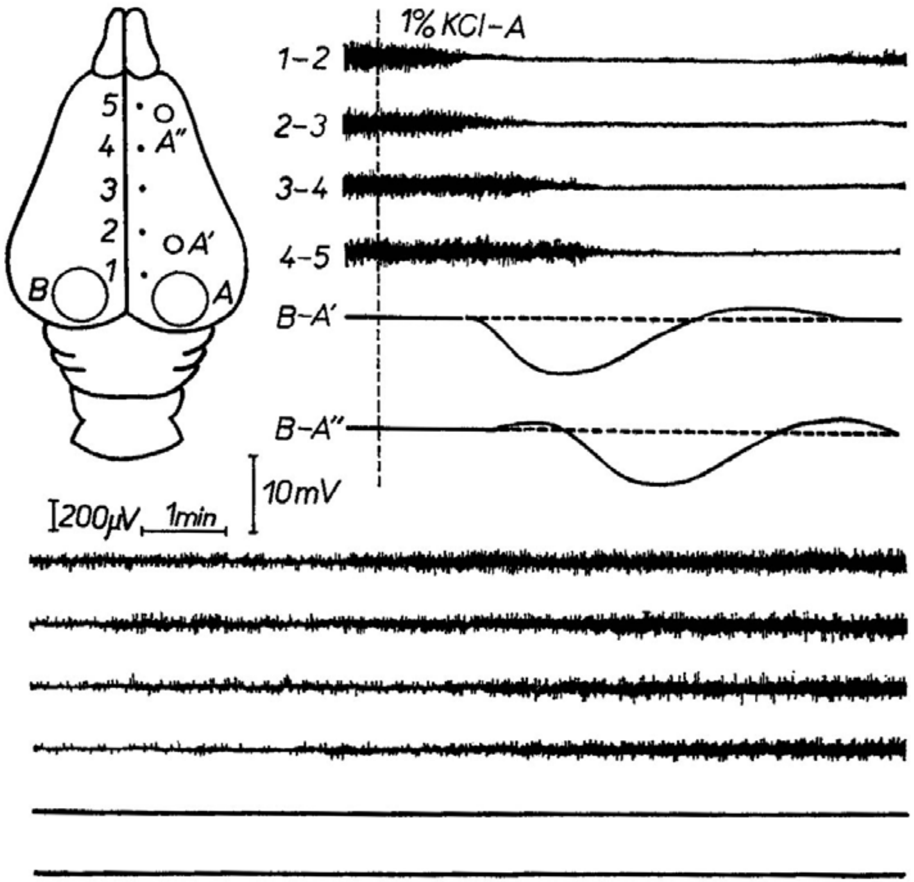
Outline

- Cortical Spreading Depression
- Ion Movements in the ECS and ICS
- Spatial Buffering and Cell Swelling
- Applications

Cortical Spreading Depression

- A.A. Leao - 1944 - Ph.D. Harvard, Epilepsy in rabbit
- Depression of the EEG - ~1-3 min



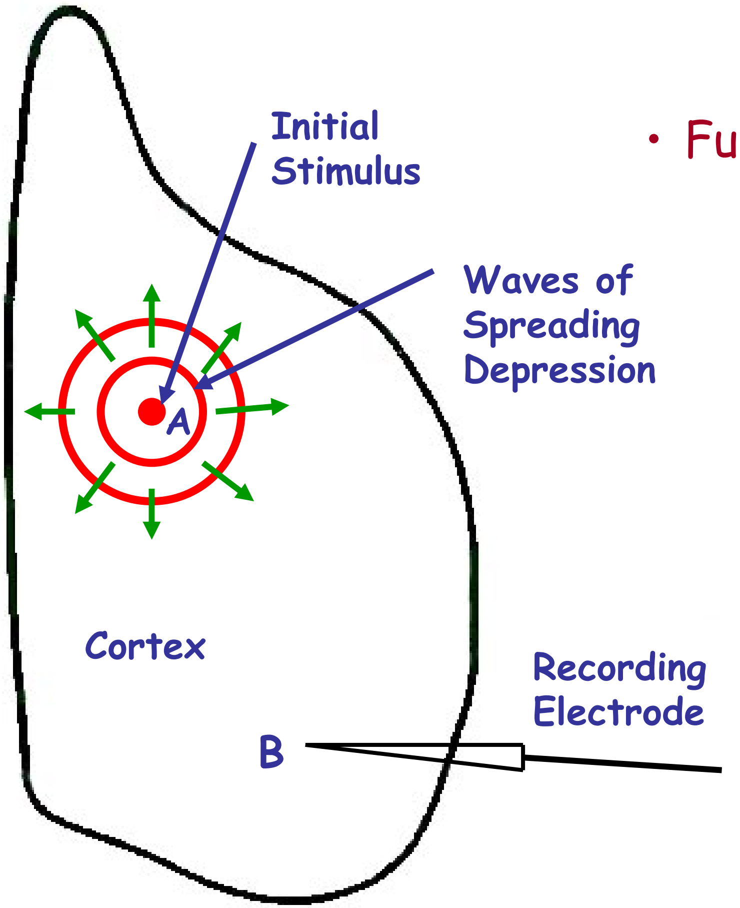
Bures, Buresova, and Krivanek (1974)

Why Study Cortical Spreading Depression?

- Discovered in 1944, but still do not understand SD
- Functional reasons
  - Seizures
  - Connection with (classic) migraine with aura
- Structure of the brain and diffusion paths of ions
  - Volume fraction
  - Tortuosity
- Ionic concentrations in the microenvironment of neurons
  - Large ion concentration changes in the ECS
  - Maintain balance of ions during neural activity

Cortical Spreading Depression (SD)

- Stimuli - chemical, electrical, mechanical
- Animals - rabbit, cat, rat, human, others
- Structures - cerebral cortex, retina, hippocampus, etc.



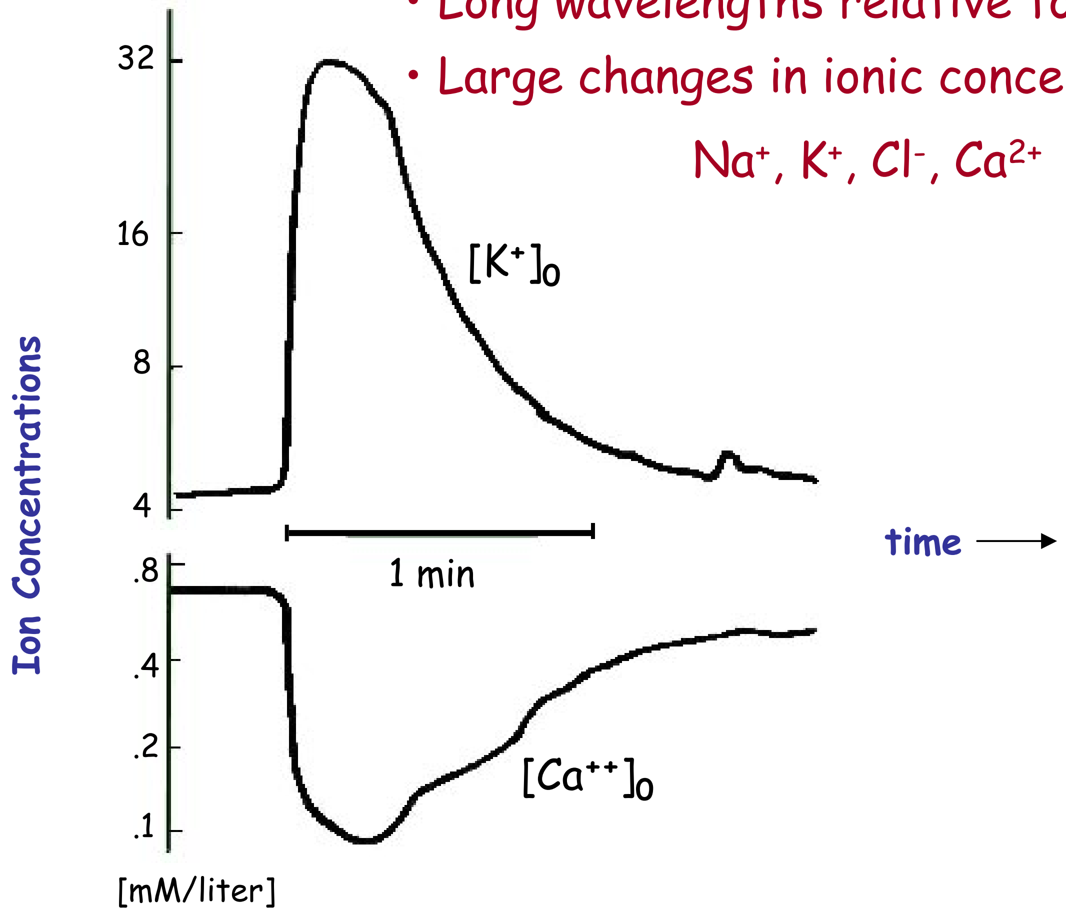
- Functional significance:
  - Physiologists - nuisance
  - Psychologists - learning and behavior
  - Physicians - migraine with aura

Cortical Spreading Depression

Time and space scales

- Slow wave phenomena - 1-15 mm/min
- Long wavelengths relative to cell size
- Large changes in ionic concentrations of

Na^{+}, K^{+}, Cl^{-}, Ca^{2+}



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Models of Spreading Depression

- Analog to conduction of impulses in cardiac muscle (Wiener and Rosenblueth, Shibata and Bures)
- Computer simulation (Reshodko and Bures)
- Potassium, action potentials (Grafstein)
- Neurotransmitter mechanism (Tuckwell and M.)
- Osmosis and neuronal gap junctions (Shapiro, Kager et al.)

Simplified Model Equations

Continuum model, considering only potassium and calcium:

$$K_t^o = D_K K_{xx}^o + \rho_1 (I_K + P_K),$$

$$K_t^i = -\frac{\alpha}{1-\alpha} \rho_1 (I_K + P_K),$$

$$C_t^o = D_C C_{xx}^o + \rho_2 (I_{Ca} + P_{Ca}),$$

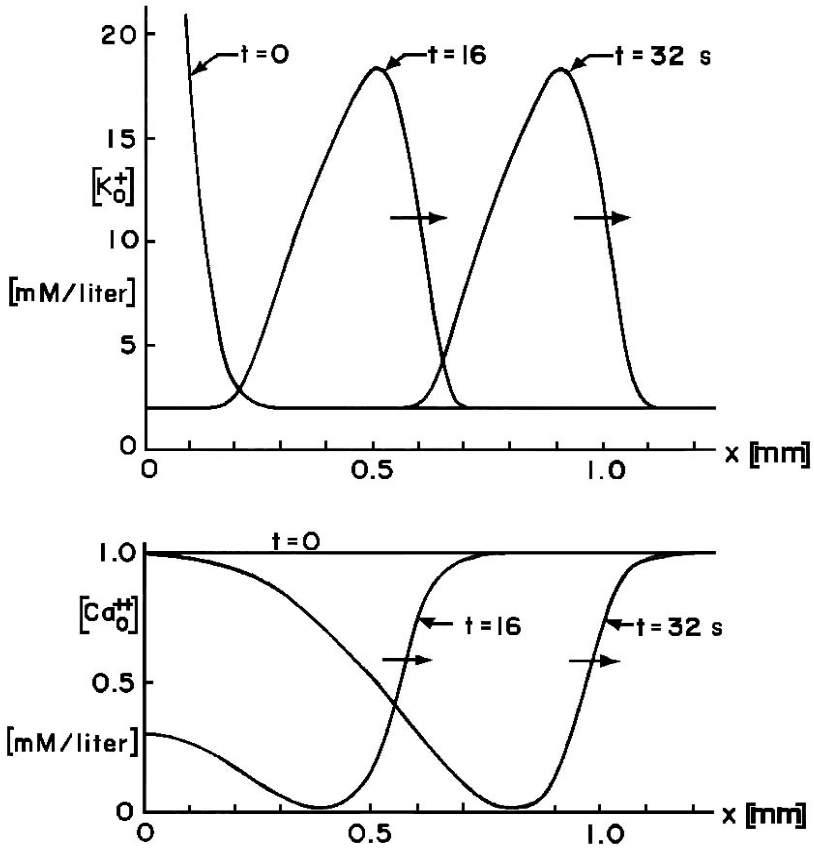
$$C_t^i = -\frac{\alpha}{1-\alpha} \rho_2 (I_{Ca} + P_{Ca}),$$

$$-\infty < x < \infty, \quad t > 0.$$

Tortuosity and volume fraction.

H.C. Tuckwell and R.M. Miura, "A mathematical model for spreading cortical depression," Biophysical J. 23 (1978), 257-276.

Solution of the SD Equations in One Space Dimension (K^+,Ca^{2+})



Difficulties in Modelling and Computations

- Complicated 3-D geometric structures of ICS and ECS
- Different kinds of cells and processes, such as neurons, glial cells, axons, synapses
- Many different kinds of ions with distinct diffusion coefficients and coupled dynamics
- Connections between neurons (synapses, gap junctions) and between glial cells (gap junctions)
- Cell membranes have spatial distributions of ion channel densities
- Cell swelling (moving cell membranes)

Modelling Geometric Structure of the Brain-Cell Microenvironment

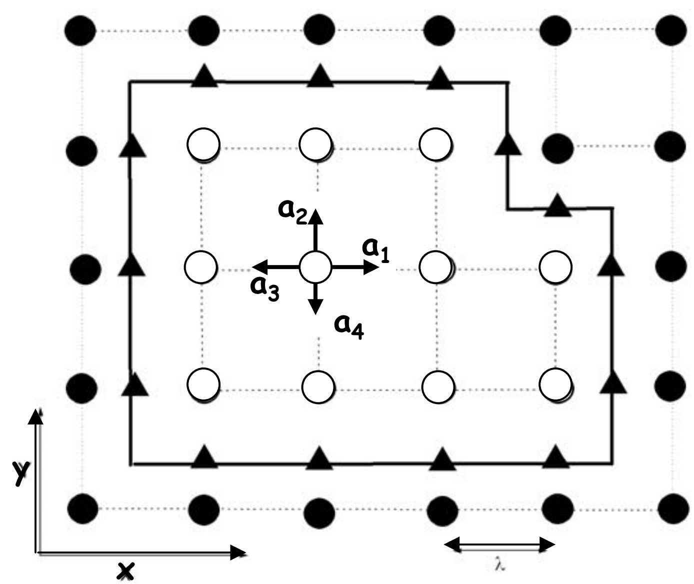
Retrieving geometry from electron micrograph

Retrieved components of the system:

1. ECS and ICS structure
2. Cell shape and membrane

Solving the Diffusion Processes using LBE

Ions move along the lattice nodes. The densities at each node, the LBE rule, and the corresponding diffusion coefficients are given by:



$$C^{i,o}(\vec{r},t) = \sum_{j=0}^{4} N_j^{i,o}(\vec{r},t),$$

$$N_j^{i,o}(\vec{r},t) \rightarrow N_j^{i,o}(\vec{r} + \vec{v}_j, t + \tau)$$

$$N_j^{i,o}(\vec{r},t) = \sum_{l=0}^{4} p_{j,l}(\vec{r},t) N_l^{i,o}(\vec{r} - \vec{v}_l, t),$$

$$D_{K,Na,Cl} = \frac{\lambda^2}{4\tau}(1 - p_{0,K,Na,Cl}), \quad p_{j,l} = p_j = \frac{1 - p_{0,K,Na,Cl}}{4}$$

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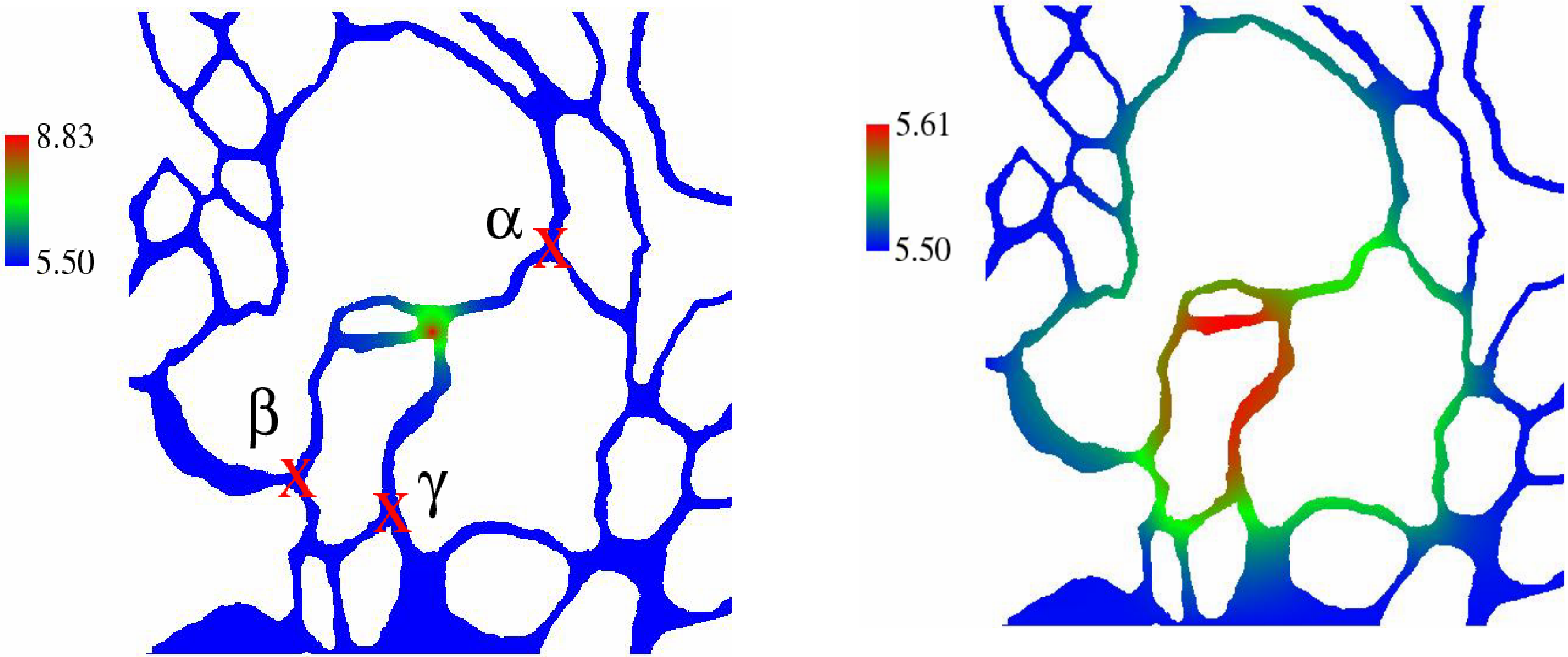
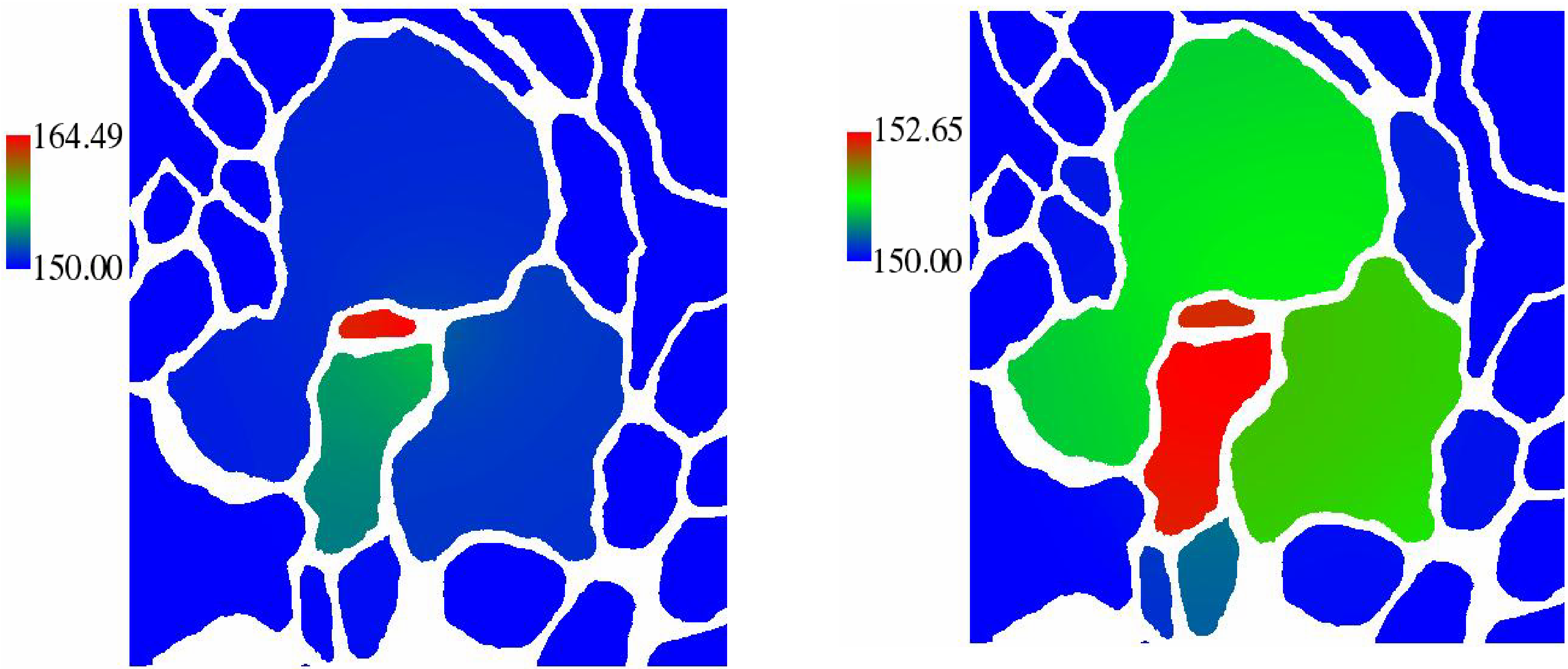
Simulation of a Small System with Permeable Membranes

- Potassium injected in the ECS



Potassium diffusion in the ECS at t=0.125ms and t=5ms. The injection stops at t=2.5 ms.

- Potassium in the ICS



Potassium diffusion in the ICS at t=0.125ms and t=5ms.
The injection stops at t=2.5 ms.

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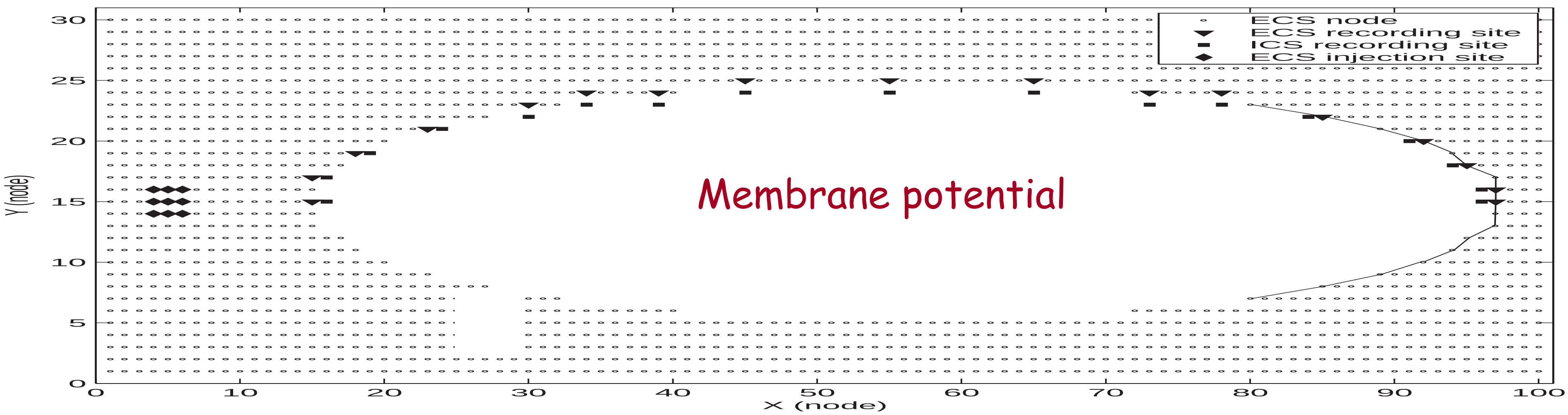
Spatial Buffering

Single cell microenvironment with injection of potassium

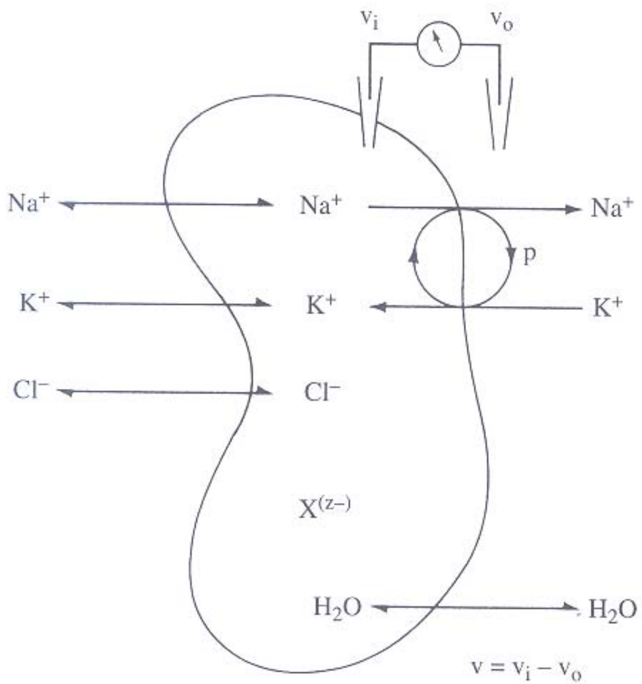


Chen and Nicholson, Biophys. J. 78 (2000), 2776-2797.

Steinberg, Wang, Huang, and Miura, Math. Biosci. Engin. 2 (2005), 675-702.

Osmosis & Cell Volume Change

- During SD, the extracellular space is compressed to about 25-50% of its original fraction of 20%.
- The swelling of cells caused by osmosis due to the movement of water molecules across a semi-permeable membrane.
- Na+, K+, Cl-, and water move through channels in the membrane.



- X molecules are trapped inside the cell.
- Isotonicity
- Electroneutrality

Applications

- SD is a cause of migraine with aura
- Diffusion tensor imaging
- Blood vessels (video)

Summary

- Spreading Cortical Depression
- Brain-Cell Microenvironment
- Ion Movements in the ECS and ICS
- Spatial Buffering
- Cell Swelling
- Applications to Migraine with Aura and Diffusion Tensor Imaging