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# **Ion Diffusion and the Spatial Buffer Mechanism in the Brain-Cell Microenvironment**

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## Outline

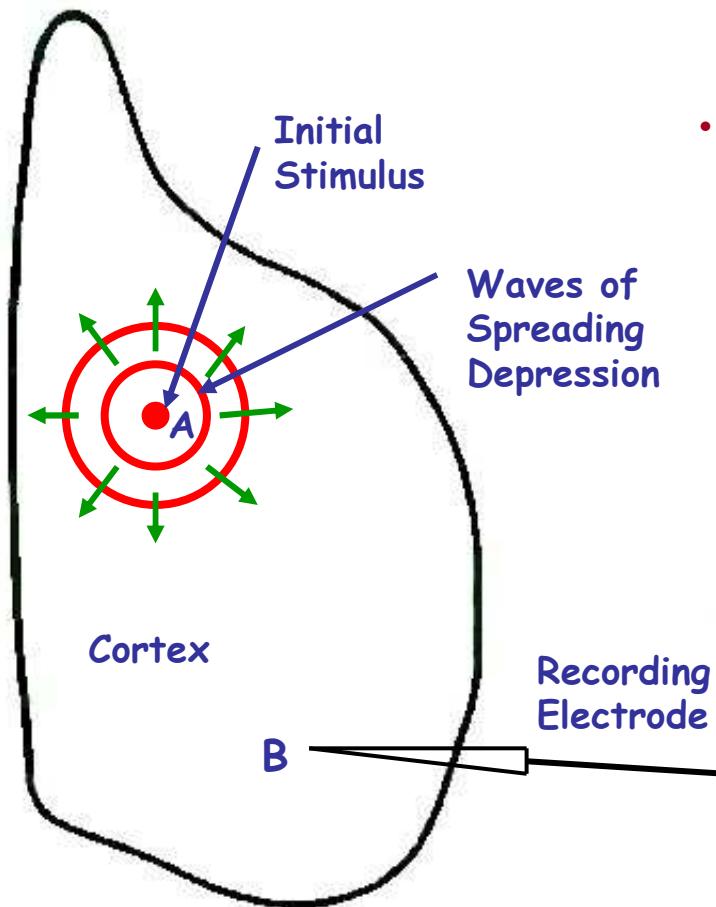
- Spreading Cortical Depression
- Brain-Cell Microenvironment
- Diffusion of Ions in the ECS and ICS
- Spatial Buffering

## Motivation

- Functional reasons
  - Spreading depression – connection with classic migraine
  - Seizures
- Structure of brain and diffusion paths of ions
  - Tortuosity
  - Volume fraction
  - Diffusion tensor imaging
- Ionic concentrations in the microenvironment of neurons
  - Maintain balance of ions during neural activity
  - Spatial buffering

## Spreading Cortical Depression (SD)

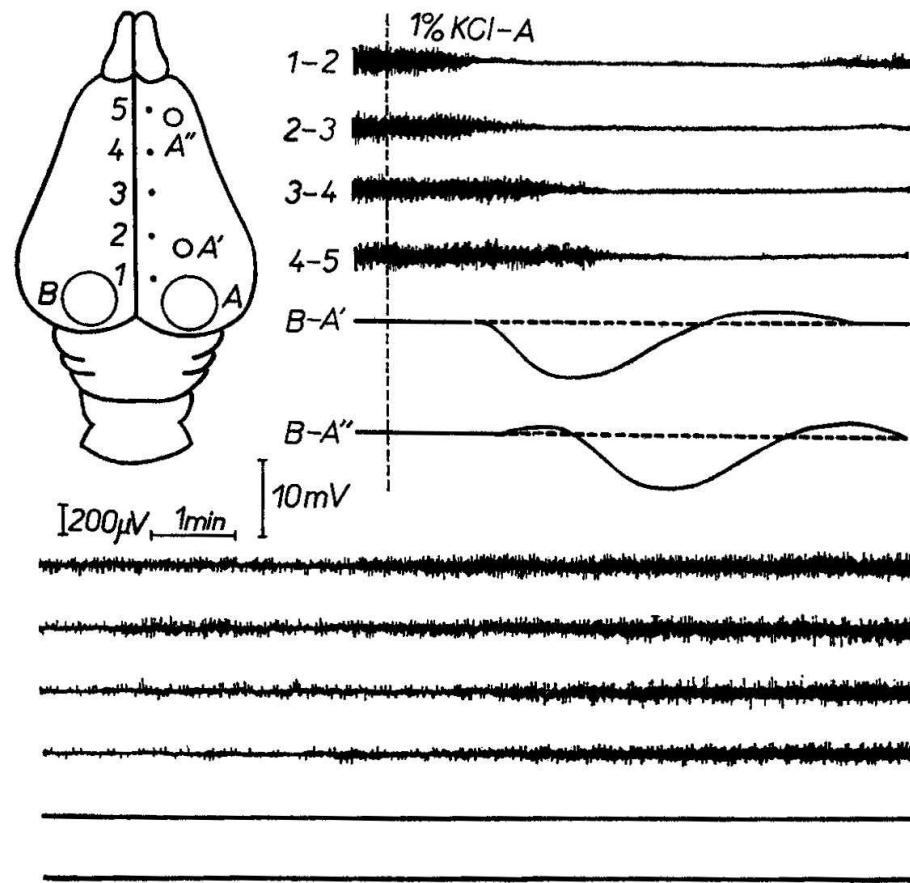
- Stimuli - chemical, electrical, mechanical, physiological
- Animals - rabbit, cat, rat, others (human?)
- Structures - cerebral cortex, retina, hippocampus, etc.



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

## Spreading Cortical Depression

- A.A. Leao - 1944 - Ph.D. Harvard, Epilepsy in rabbit
- Depression of the EEG - ~1-2 min



Bures, Buresova, and Krivanek (1974)

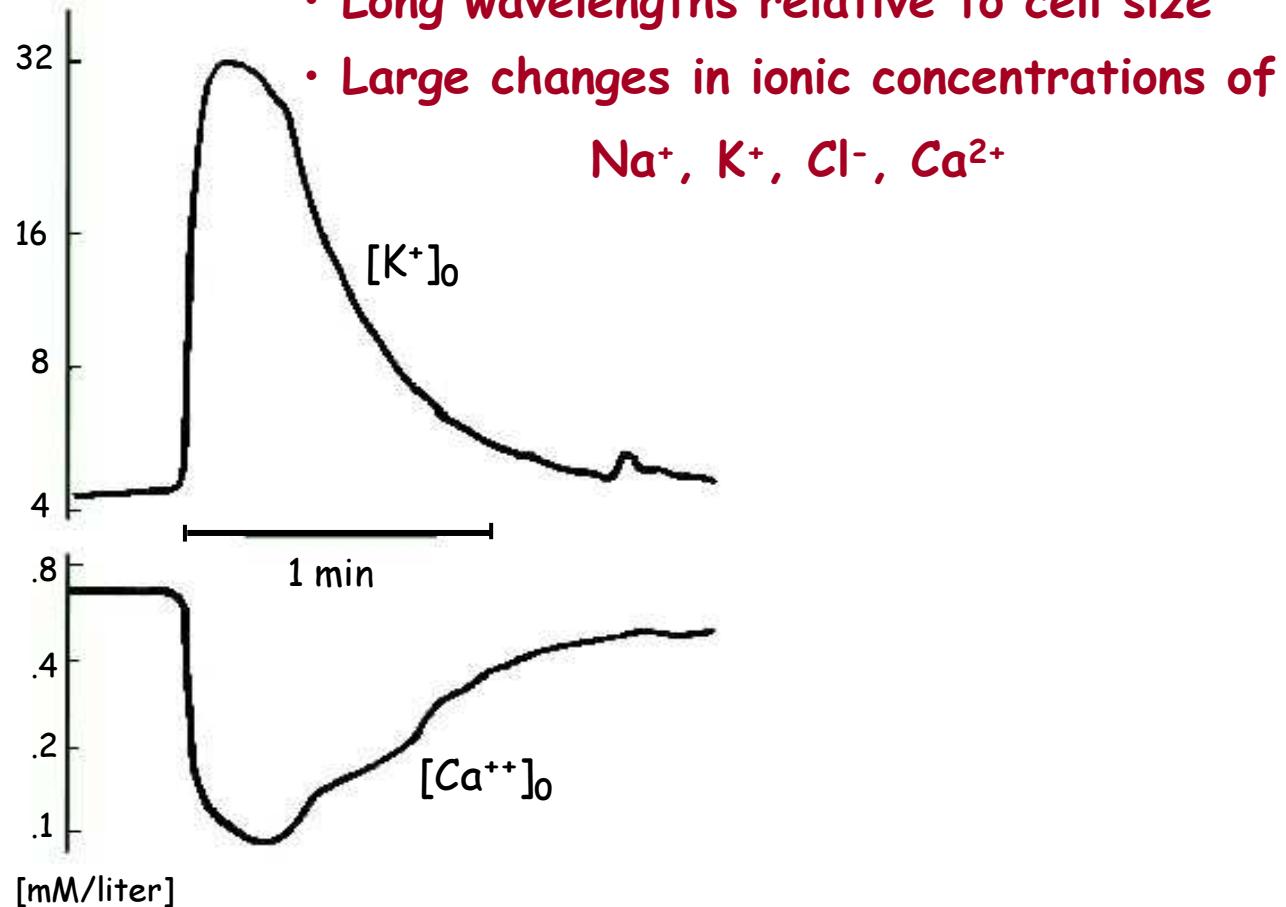
## Spreading Cortical Depression

- Instigation and propagation
- Properties similar to action potentials
  - solitary wave
  - all or none
  - refractoriness
  - multiple waves
  - annihilation upon collision

## Spreading Cortical Depression

Time and space scales

- Slow wave phenomena - 1-15 mm/min
- Long wavelengths relative to cell size
- Large changes in ionic concentrations of  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ ,  $\text{Ca}^{2+}$



## Modeling 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)

## Model Equations

Consider only potassium and calcium:

$$K_t^o = D_K K_{xx}^o + \rho_1 g_{Ca}(V)(V - V_{Ca})(V - V_K) + P_K,$$

$$K_t^i = -\frac{\alpha}{1-\alpha} [\rho_1 g_{Ca}(V)(V - V_{Ca})(V - V_K) + P_K],$$

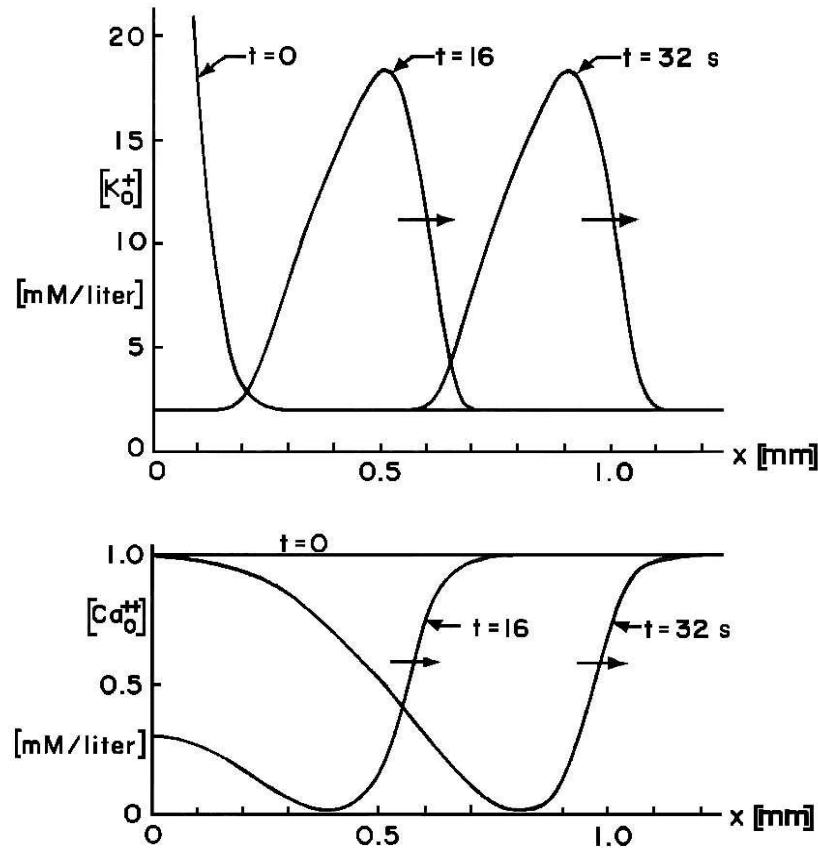
$$C_t^o = D_C C_{xx}^o + \rho_2 g_{Ca}(V)(V - V_{Ca}) + P_{Ca},$$

$$C_t^i = -\frac{\alpha}{1-\alpha} [\rho_2 g_{Ca}(V)(V - V_{Ca}) + P_{Ca}],$$

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

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 ( $K^+$ , $Ca^{2+}$ )



H. Ikeda and R.M. Miura, "Singular perturbation analysis of the solitary pulse solution for a model of spreading cortical depression".

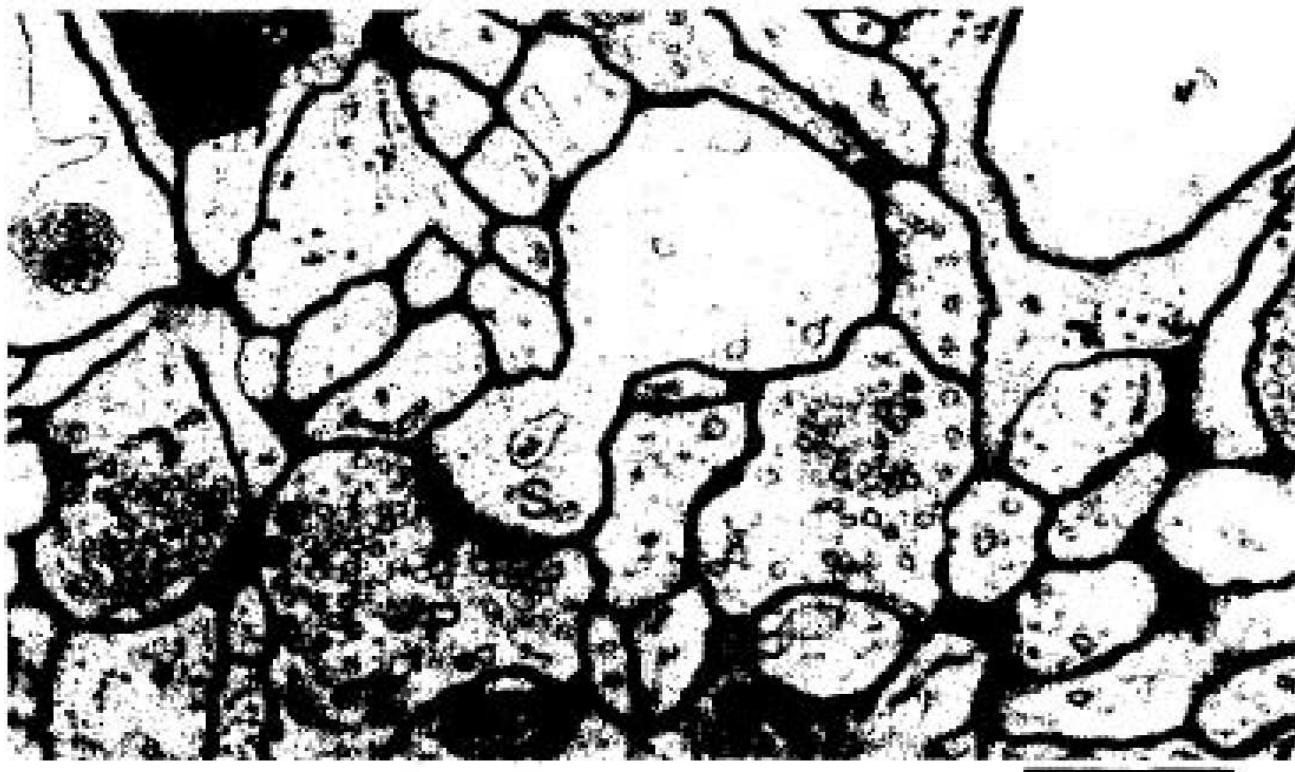
## Why Study SD Again?

- Lattice gas algorithm (brain as a porous medium, stable, computationally intensive)
- Brain structure effects
- Noncontinuum model in 2- and 3-dimensions
- Shapiro's computational model (J. Comp. Neurosci. 10 (2001), 99-120)
- Lack of correlation between SD and neurogenic inflammation in initiating classic migraine (Ann. Neurol., 49 (2001), 7-13)

# Dispersal of Ions in the Brain-Cell Microenvironment

- Influence of the geometric structure of the brain-cell microenvironment on the dispersal of ions
- No evoked spiking
- Ionic concentrations change very slowly so local equilibrium is achieved at each time step
- In the ECS and ICS, ions undergo pure diffusion
- Injection of potassium into the system

## Brain-Cell Microenvironment



Electron micrograph of a small region of the rat cortex (taken from C. Nicholson and E. Sykova, *Trends Neurosci.* **21** (1998), 207)

## Difficulties in Modeling 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) and between glial cells (gap junctions)
- Cell membranes with spatial distributions of ion channel densities

# Modeling Geometric Structure of the Brain-Cell Microenvironment

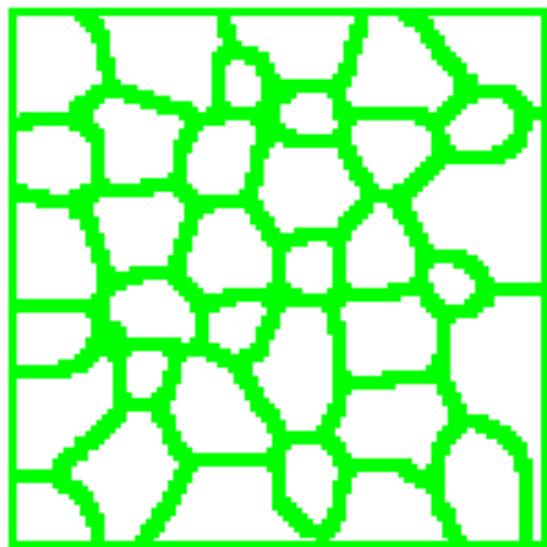
## I. Retrieving geometry from electron micrograph



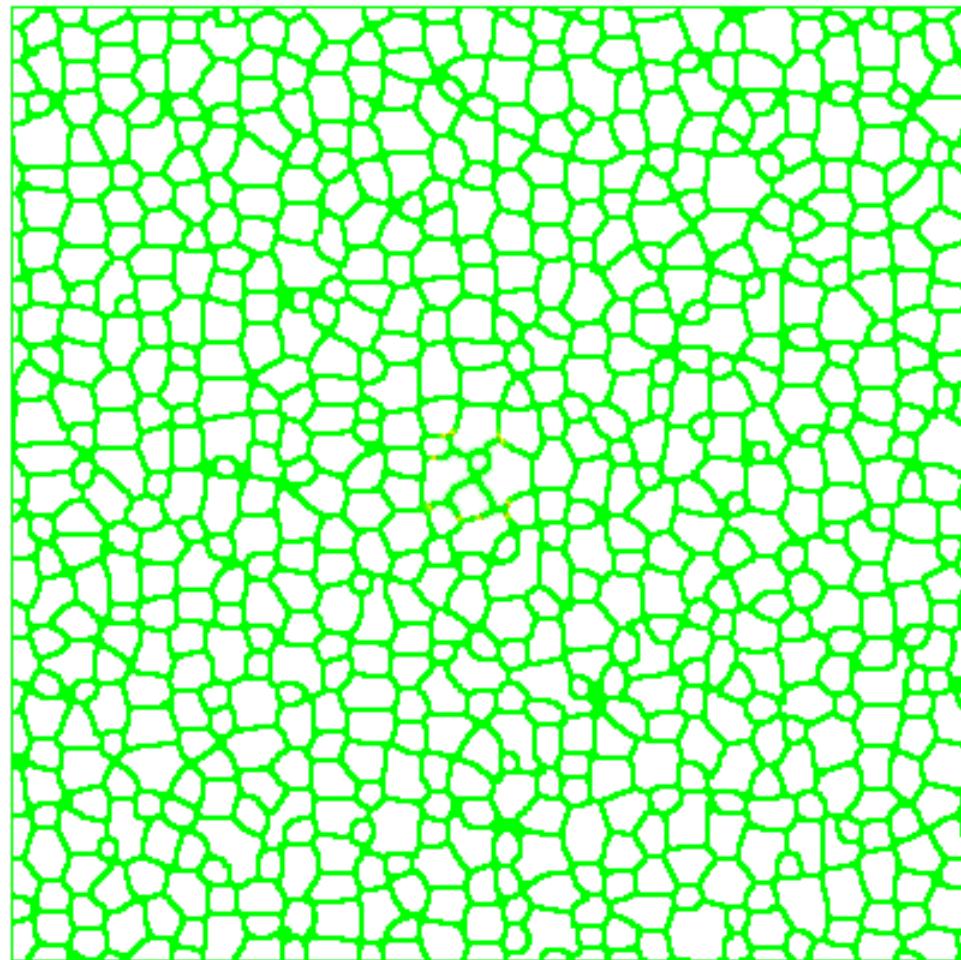
Retrieved components  
of the system:

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

## Generating Cellular Automata



Control parameters:  
Tortuosity: about 1.5  
Volume fraction: about 0.2



## Diffusion of Ions in the ECS and ICS

- Free diffusion of ions in the ICS and in the ECS , such as  $K^+$ ,  $Na^+$ ,  $Cl^-$ ,  $Ca^{++}$  are governed by

$$\frac{\partial C_{K,Na,Cl}^o}{\partial t} = D_{K,Na,Cl}^o \nabla^2 C_{K,Na,Cl}^o,$$

$$\frac{\partial C_{K,Na,Cl}^i}{\partial t} = D_{K,Na,Cl}^i \nabla^2 C_{K,Na,Cl}^i$$

- Solve using the lattice Boltzmann equation (LBE)

## Solving the Diffusion Processes using LBE

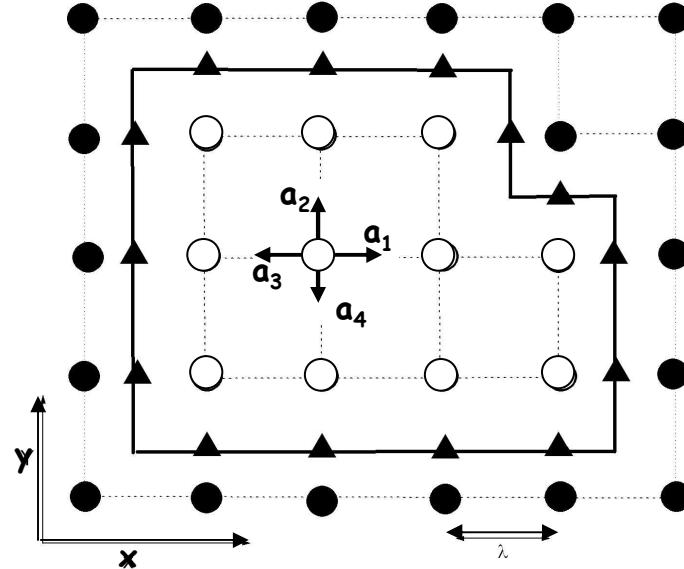
I. Ions move along the lattice nodes. The densities at each node, the LBE rule, and the corresponding diffusion coefficients are given by:

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

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

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

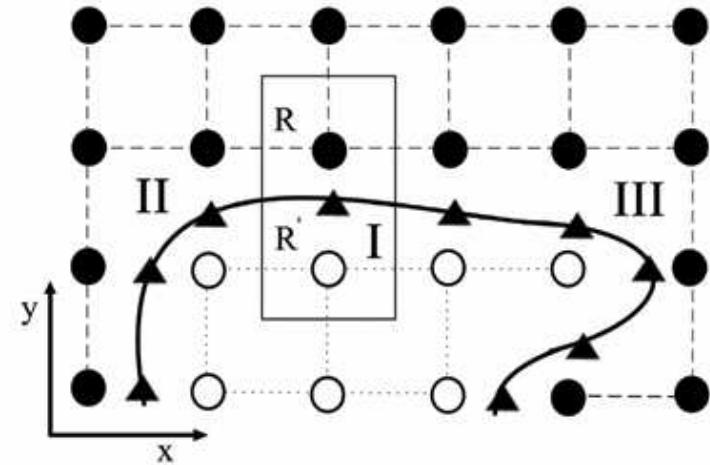
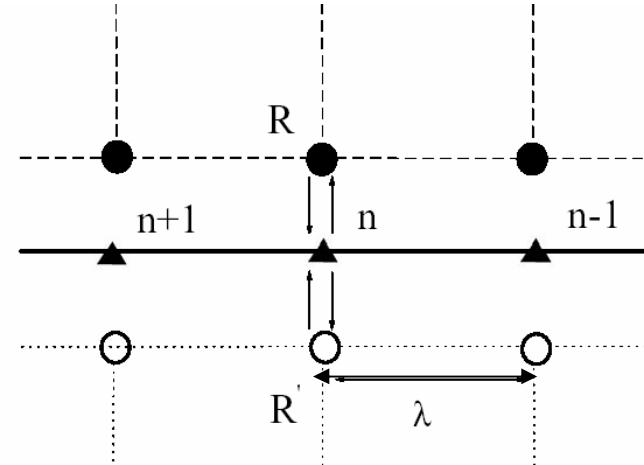
$$D_{K,Na,Cl} = \frac{\lambda^2}{4\tau} (1 - p_{0,K,Na,Cl}), \quad p_{j,l} = p_j = \frac{1 - p_{0,K,Na,Cl}}{4}$$



## II. Boundary condition between ICS and ECS

LBE rule for R and R' nodes

Geometric shape of the boundary between the ICS and ECS are classified into the three types: I, II, and III, and there are a total of 24 cases



## III. Boundary condition on the whole system: the concentration at the boundary nodes is always set to the value of the rest state

## Modeling Membrane Ionic Currents

Membrane potential is described by the Goldman-Hodgkin-Katz equation

$$V = \frac{RT}{F} \ln \left( \frac{P_1 [Na^+]^o + P_2 [K^+]^o + P_3 [Cl^-]^i}{P_1 [Na^+]^i + P_2 [K^+]^i + P_3 [Cl^-]^o} \right)$$

Membrane current has two parts: ionic channel current and active pumping current

$$I_{K,Na,Cl} = I_{K,Na,Cl}^c + I_{K,Na,Cl}^p$$

Ionic channel currents are

$$I_K^c = \bar{g}_K n_\infty^4 (V - V_K), \quad I_{Na}^c = \bar{g}_{Na} m_\infty^3 h_\infty (V - V_{Na}),$$

$$I_{Cl}^c = \bar{g}_{Cl} (V - V_{Cl}),$$

where  $m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}, \quad h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}, \quad n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}$

The pumping currents are modeled by:

$$I_{K,Na,Cl}^p = f_{K,Na,Cl} \{ 1 - \exp(-r_{K,Na,Cl} ([K, Na, Cl]_i^i - [K, Na, Cl]_R^i)) \} \\ - f_{K,Na,Cl}^*$$

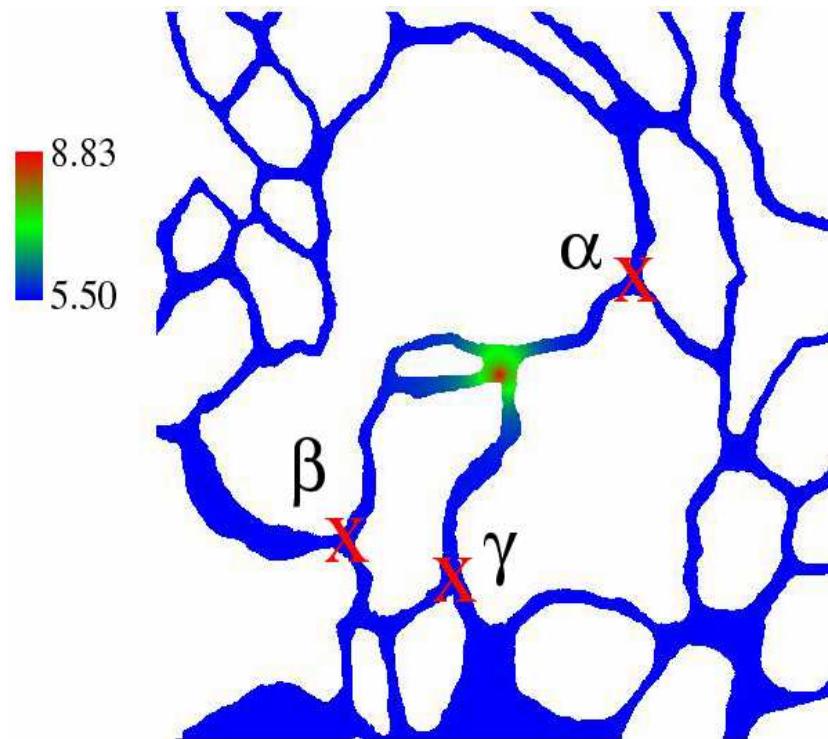
$$f_K^* = \bar{g}_K n_\infty^4 (V_r - V_K), \quad f_{Na}^* = \bar{g}_{Na} m_\infty^3 h_\infty (V_r - V_{Na}),$$

$$f_{Cl}^* = \bar{g}_{Cl} (V_r - V_{Cl})$$

The pumping current is determined to make the net current at rest crossing the membrane equal to zero.

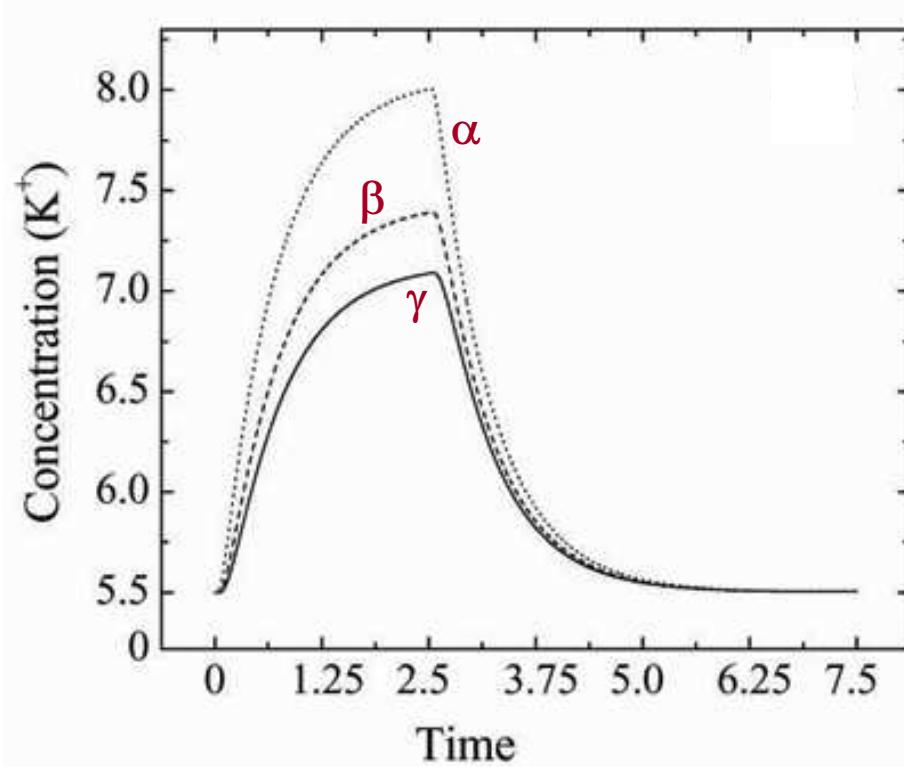
## Simulation of a Small System with Impermeable Membranes

- Potassium injection in the ECS



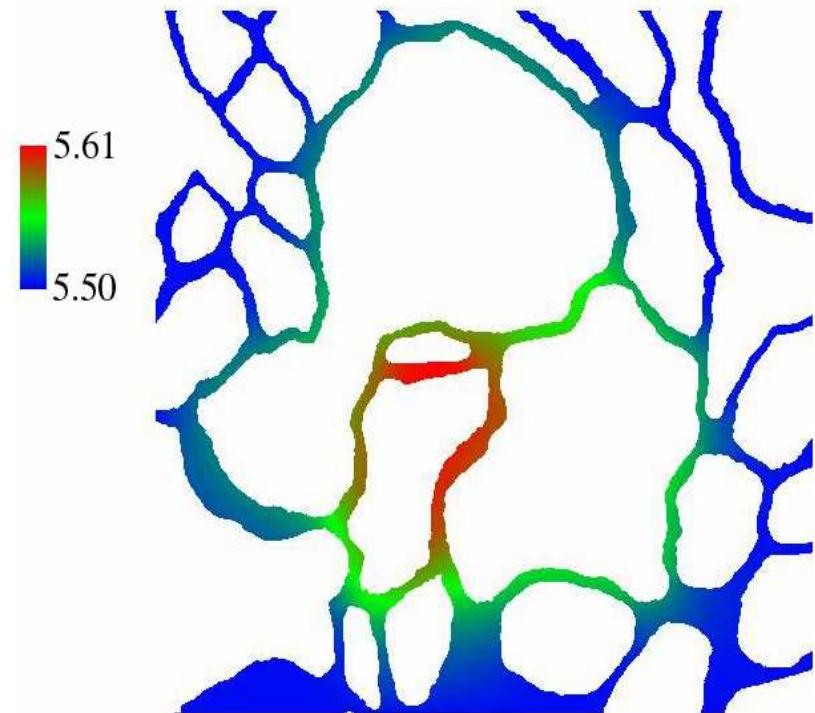
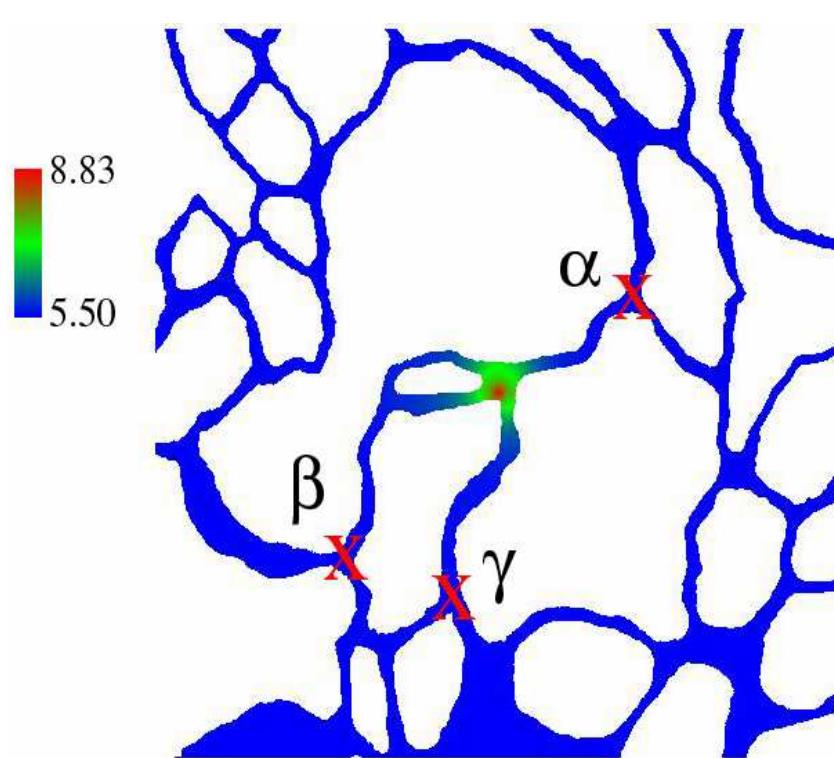
Potassium diffusion in the ECS at  $t=0.125$  ms. The injection stops at  $t=2.5$  ms.

- When the membrane is impermeable, pure free diffusion in the ECS at three points



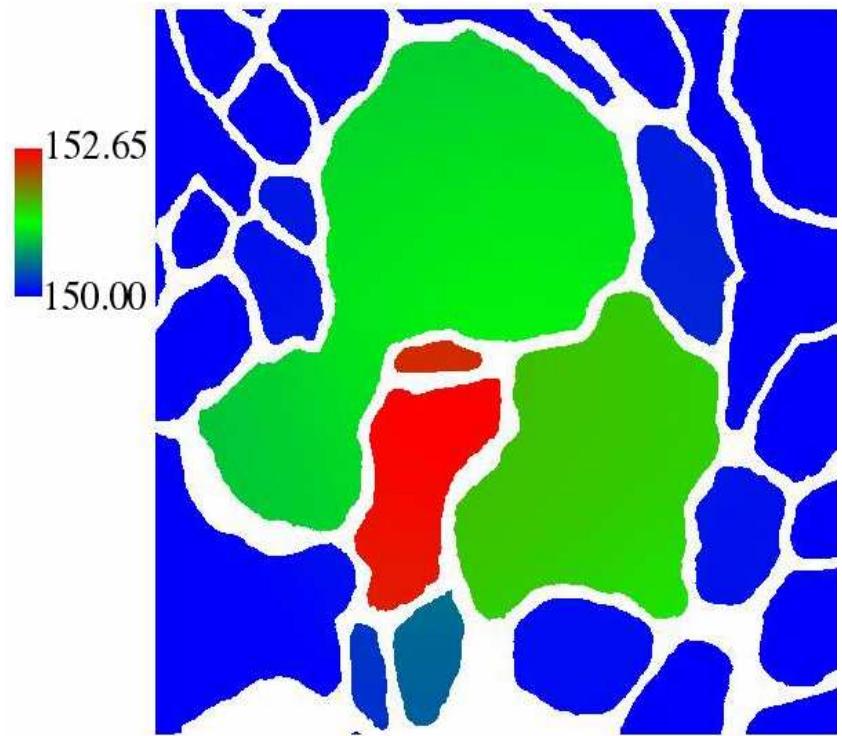
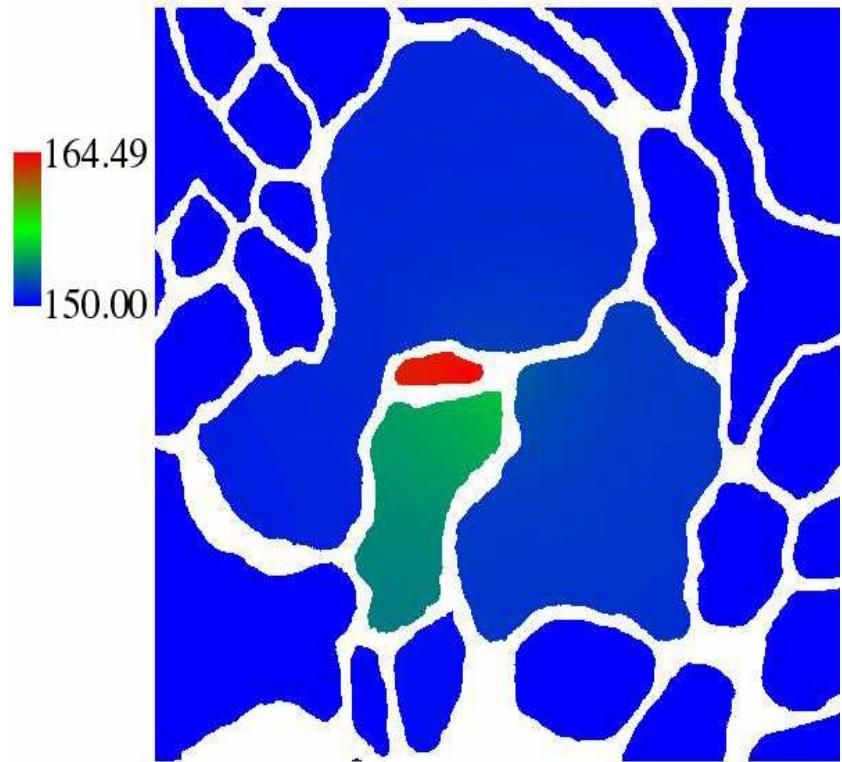
## Simulation of a Small System with Permeable Membranes

- Potassium injected in the ECS



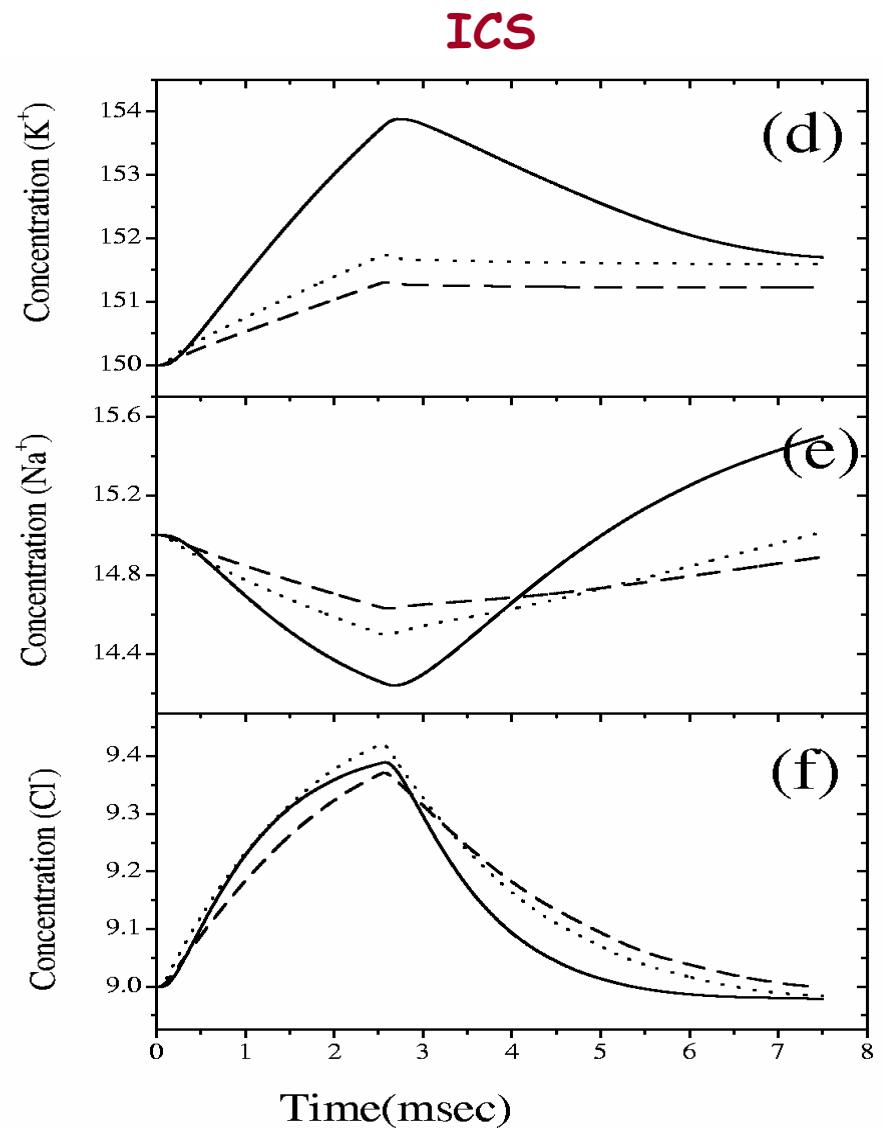
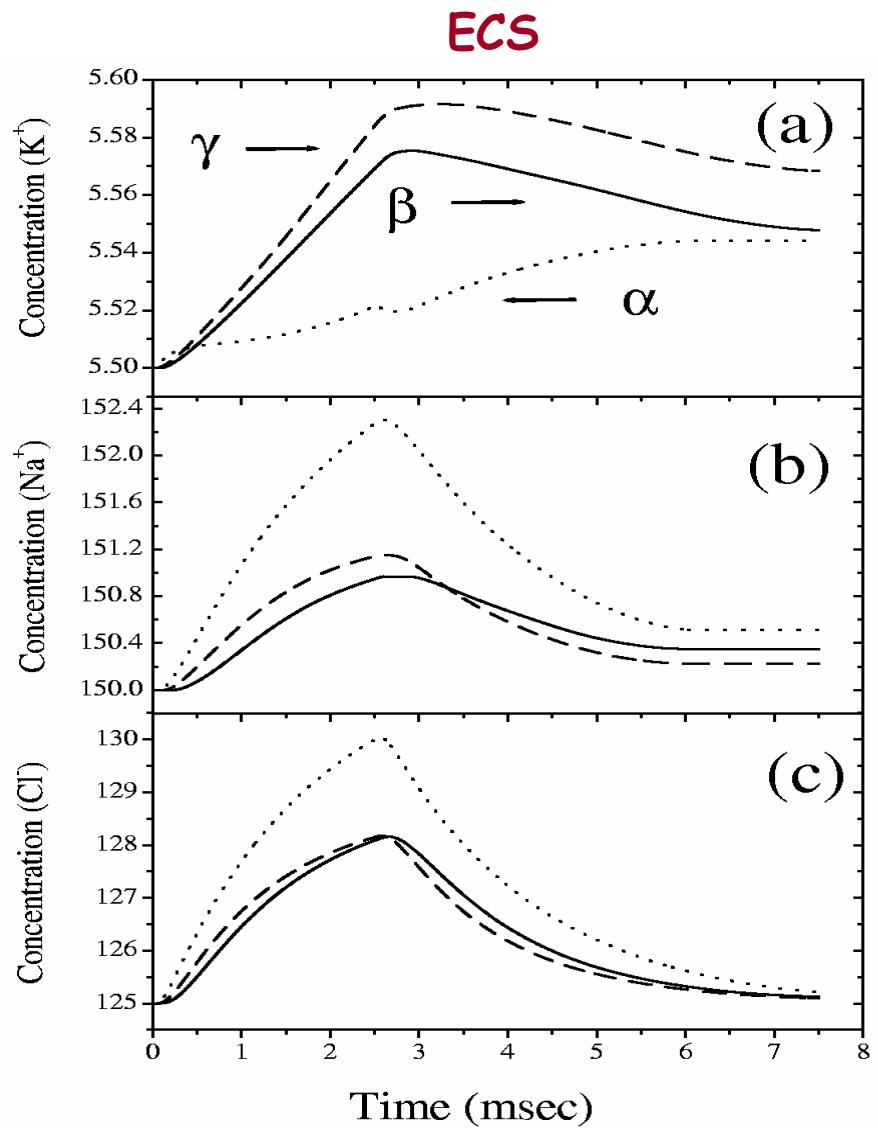
Potassium diffusion in the ECS at  $t=0.125\text{ms}$  and  $t=5\text{ms}$ . The injection stops at  $t=2.5\text{ ms}$ .

- Potassium in the ICS



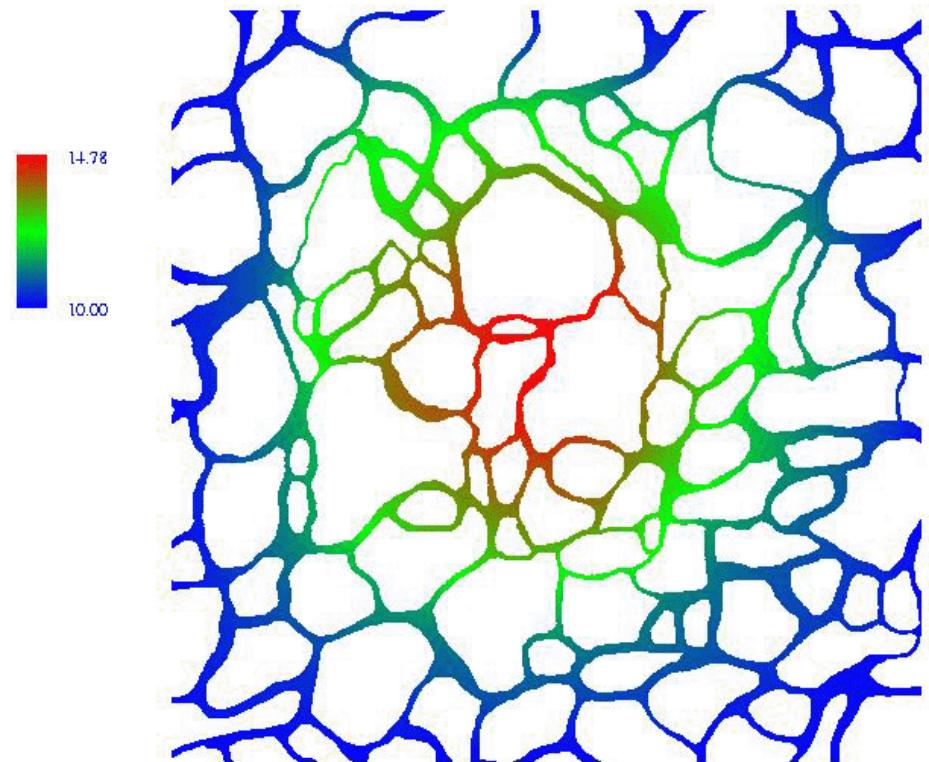
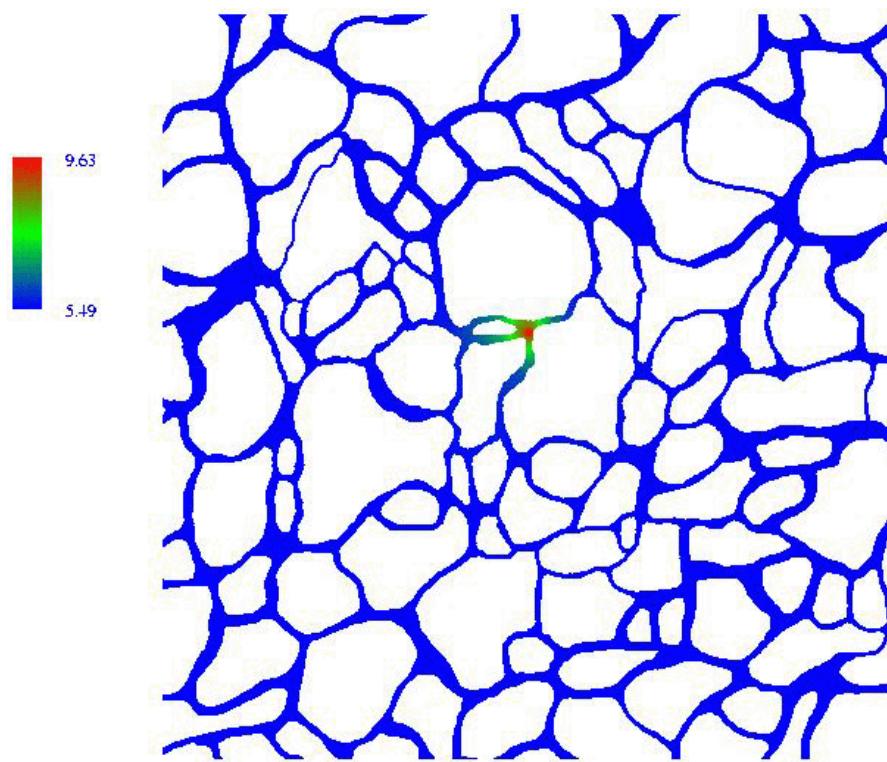
Potassium diffusion in the ICS at  $t=0.125\text{ms}$  and  $t=5\text{ms}$ .  
The injection stops at  $t=2.5\text{ ms}$ .

- Concentration changes with time at three points specified above



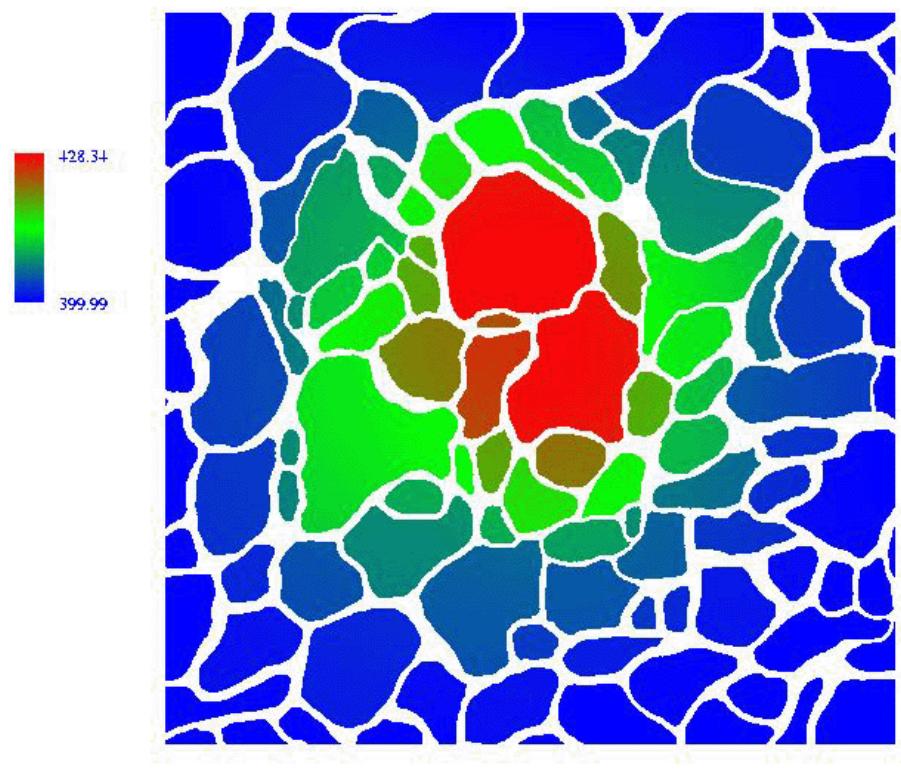
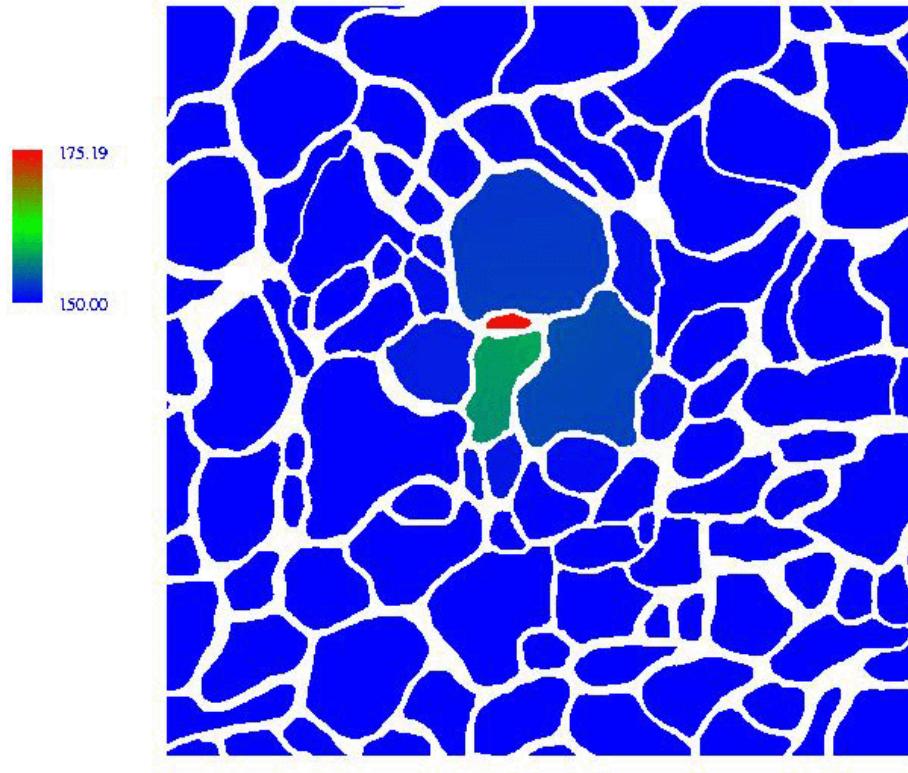
## Simulation of a Large System

- Potassium injected in the ECS



Injection time= 200 msec. The snapshots are taken at  $t=0.125$  ms  
and  $t=2000$  ms

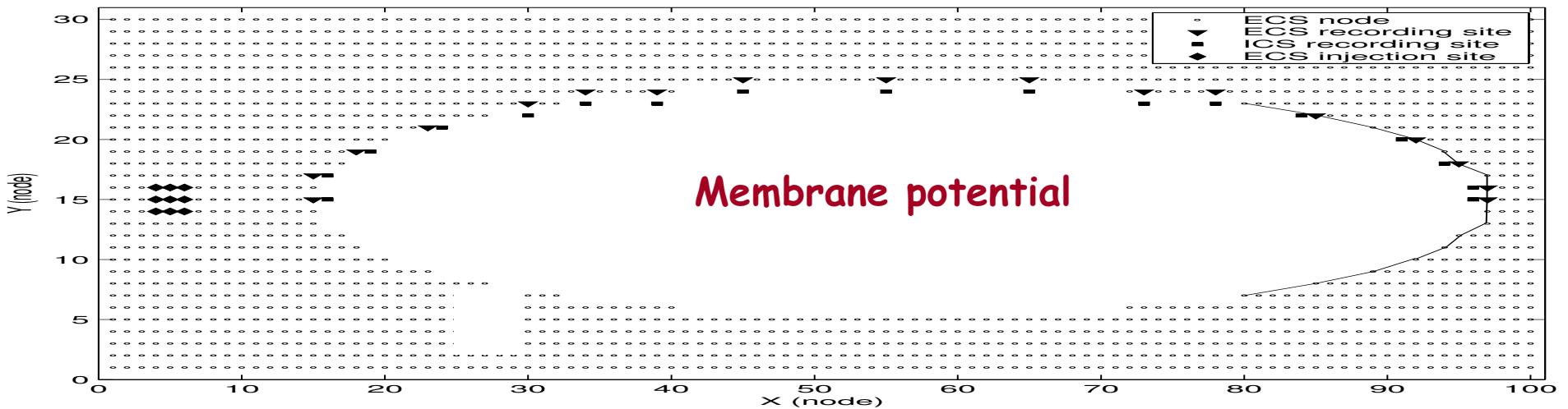
- Potassium in the ICS



Injection time = 200 msec. The snapshots are taken at  $t=0.125$  ms  
and  $t=2000$  ms

## Spatial Buffering

Single cell microenvironment with injection of potassium

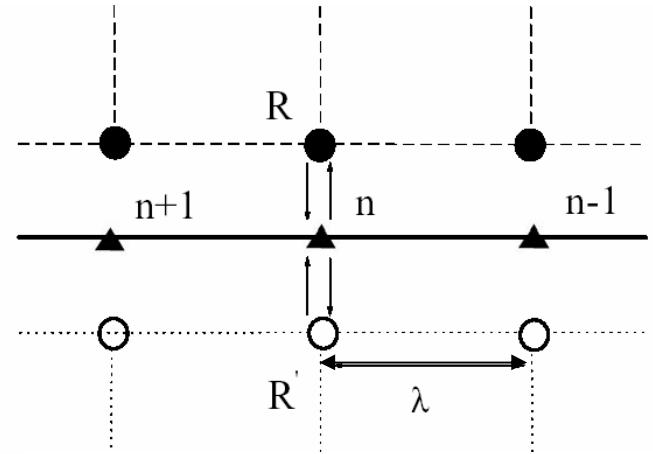


Chen and Nicholson, Biophys. J. 78 (2000), 2776-2797.

## Modeling Membrane Potential

The membrane potential is calculated by solving:

$$\frac{\partial V}{\partial t} = u \nabla^2 V - \sum I_j$$

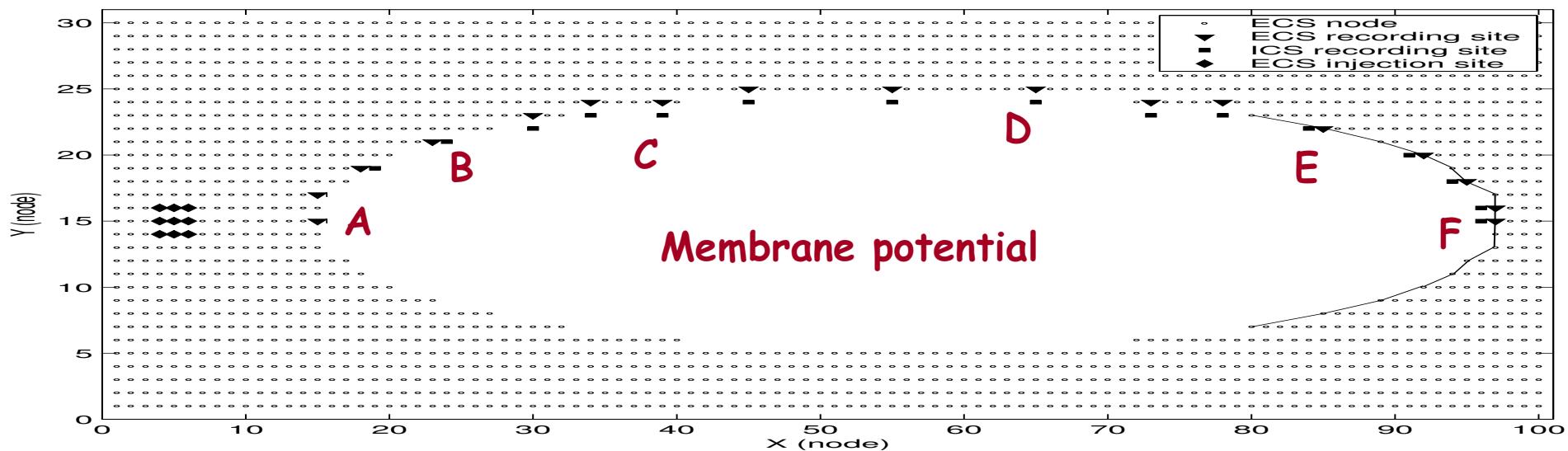


Employing finite differences:

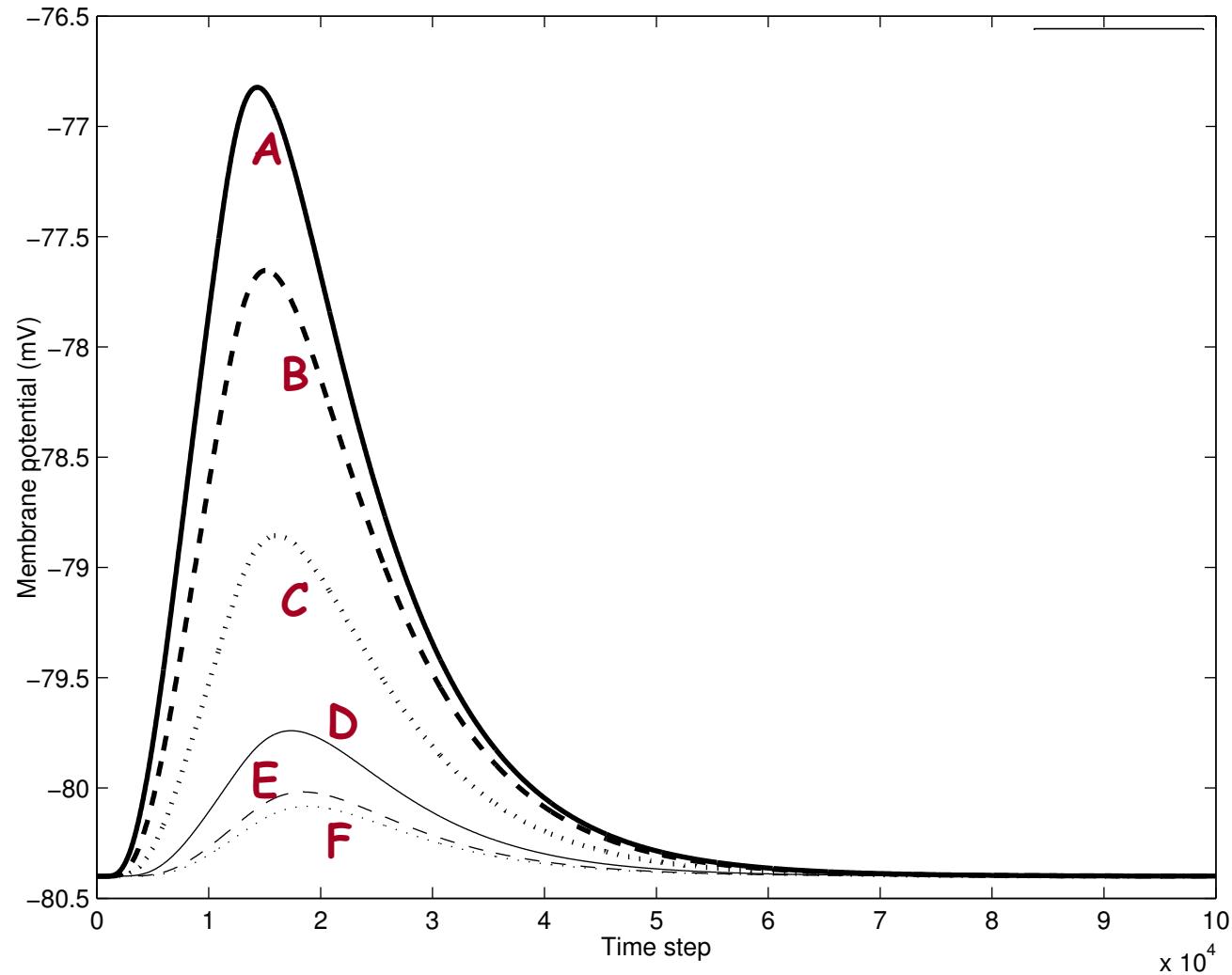
$$V(n, t + \tau) = V(n, t) + u\tau \frac{V(n+1, t) + V(n-1, t) - 2V(n, t)}{\lambda^2} - \tau \sum I_j$$

## Spatial Buffering

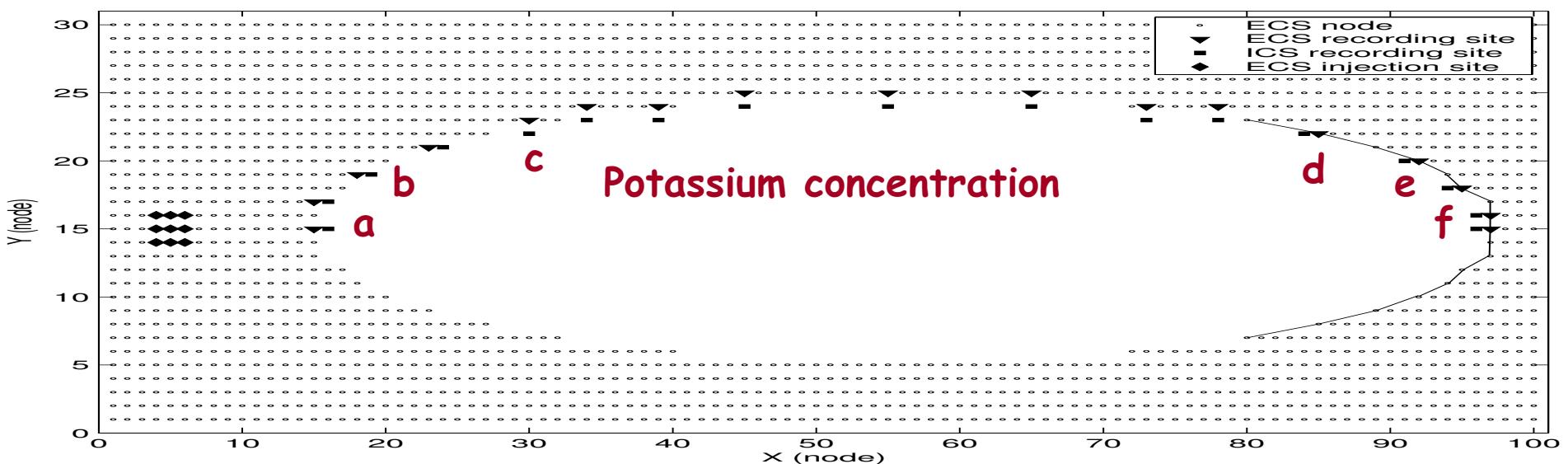
Single cell microenvironment with injection of potassium



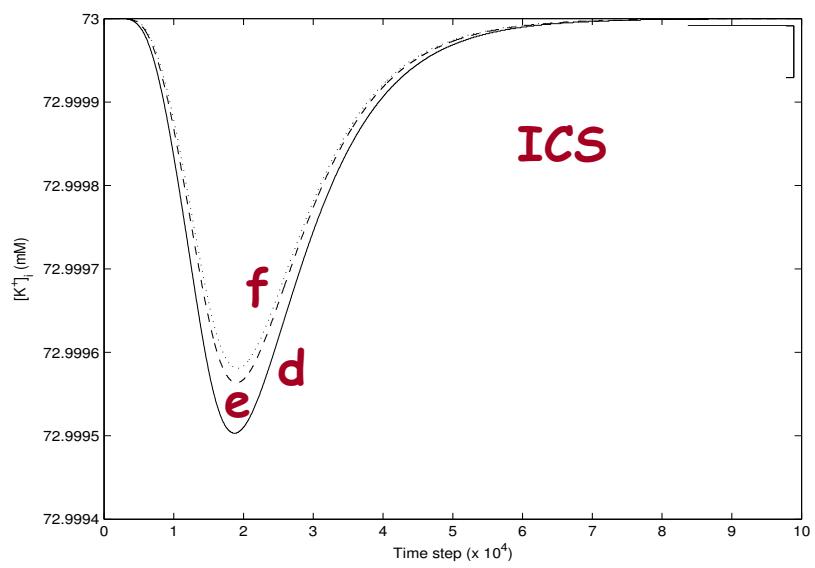
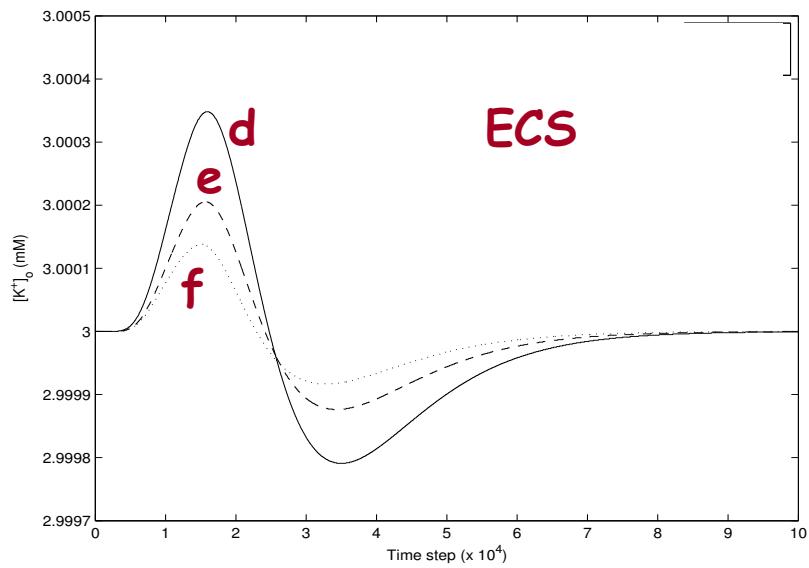
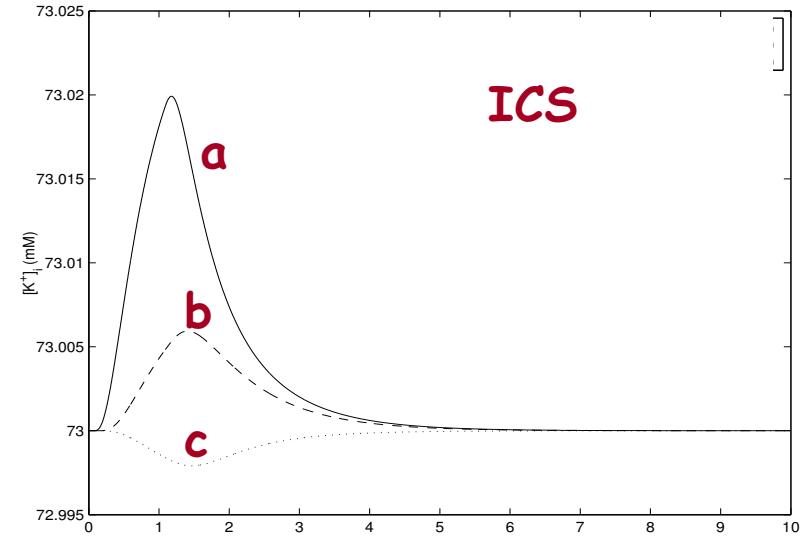
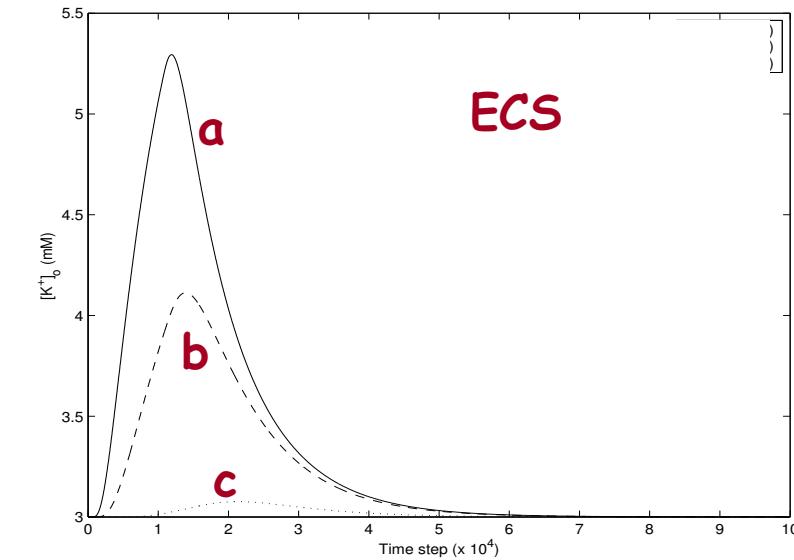
**Local depolarization due to potassium injection  
spreads electrotonically along the membrane surface**



## Single cell microenvironment with injection of potassium



## Time course of ECS and ICS Potassium



## Summary

- Spreading Cortical Depression
- Brain-Cell Microenvironment
- Diffusion of Ions in the ECS and ICS
- Spatial Buffering