Migraine With Aura: Treat It With Math

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Migraine and Aura

Migraine:

- a very painful type of headache that is very common
- pain can be excruciating and may incapacitate people for hours or even days
- symptoms are so severe that all you can think about is finding a dark, quiet place to lie down
- very sensitive to light and sound and may become nauseated and vomit
- three times more common in women than in men
- still no cure, although medications can help reduce the frequency of migraine and reduce the pain once it has started

Aura:

- in about 20% of people who have migraine, their headache is preceded by a sensory warning sign
- visual hallucination or illusion called an aura
- various forms, e.g., flashes of light, scintillating zigzag lines, blind spots, or temporarily vision loss

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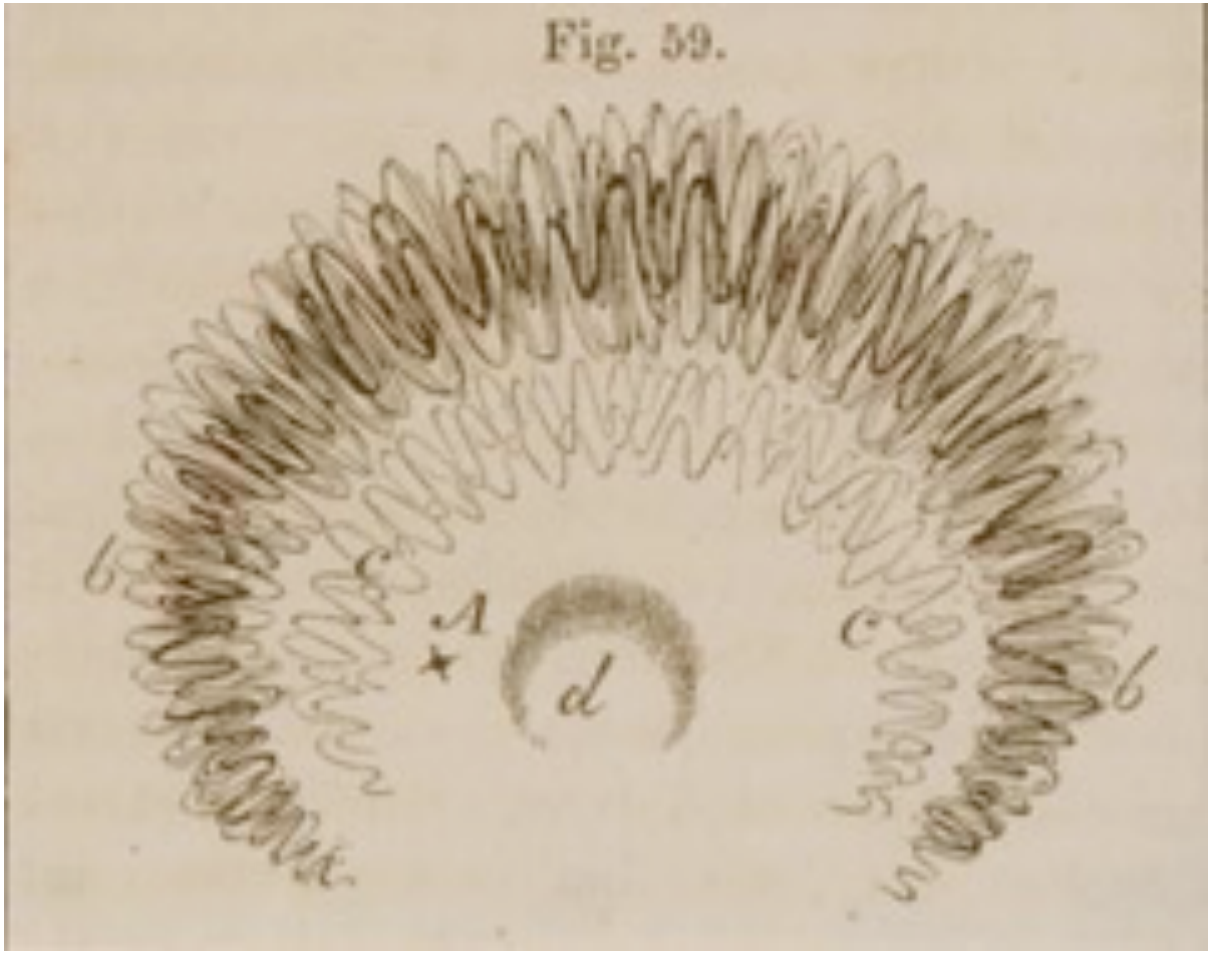
Aura



Christian Georg Theodor Ruete, Illustration of scintillating scotoma from "Textbook of Ophthalmology", 1845

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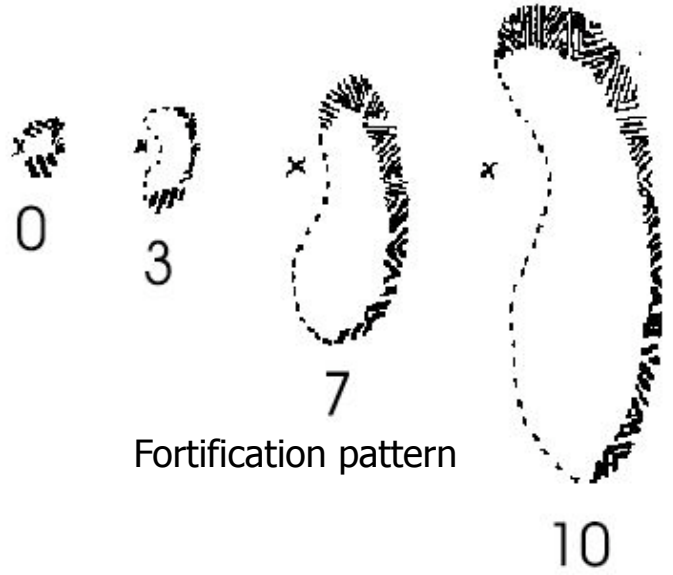
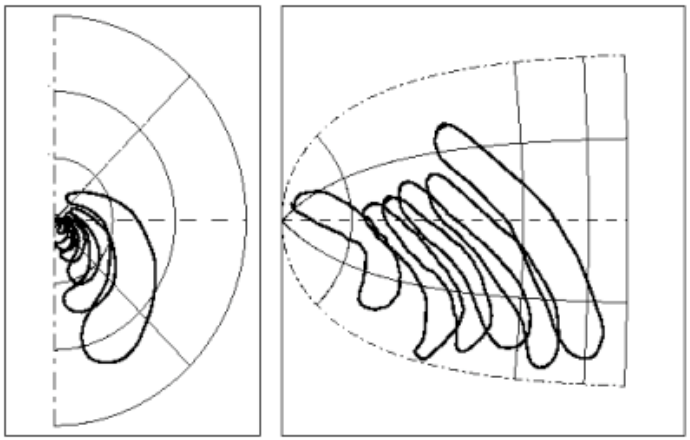
Migraine with Aura

Lashley (1941) for the first time made suggestions about connecting a propagating cerebral phenomenon to characteristic visual aura symptoms. The visual aura provides the only functional evidence so far of orientation tuning cells in human cortex.



Fortification pattern



Karl Spencer Lashley (1890-1958)

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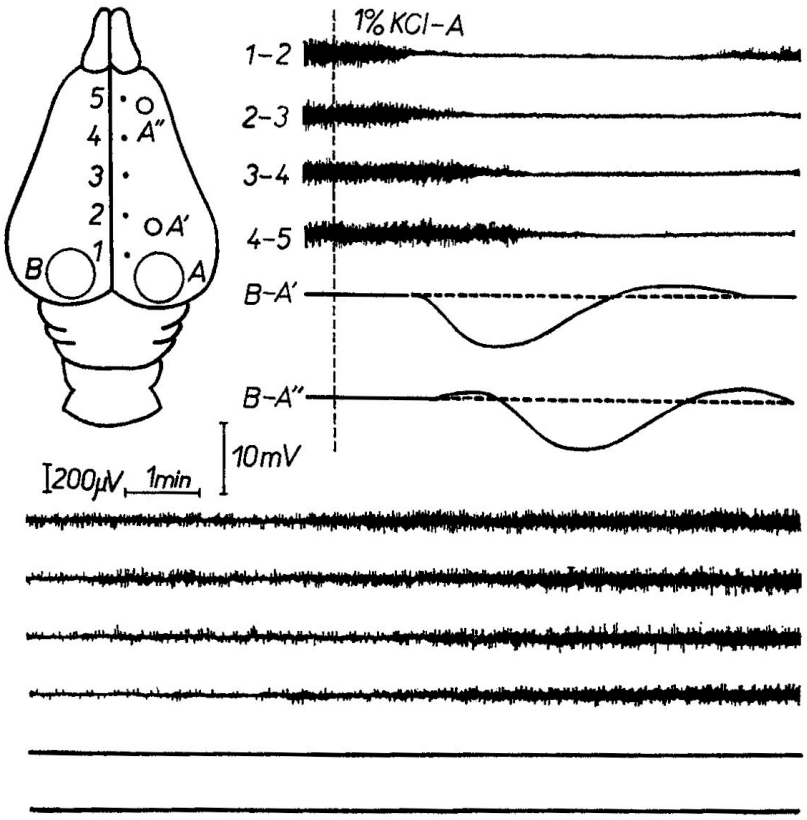
Cortical Spreading Depression (CSD)

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

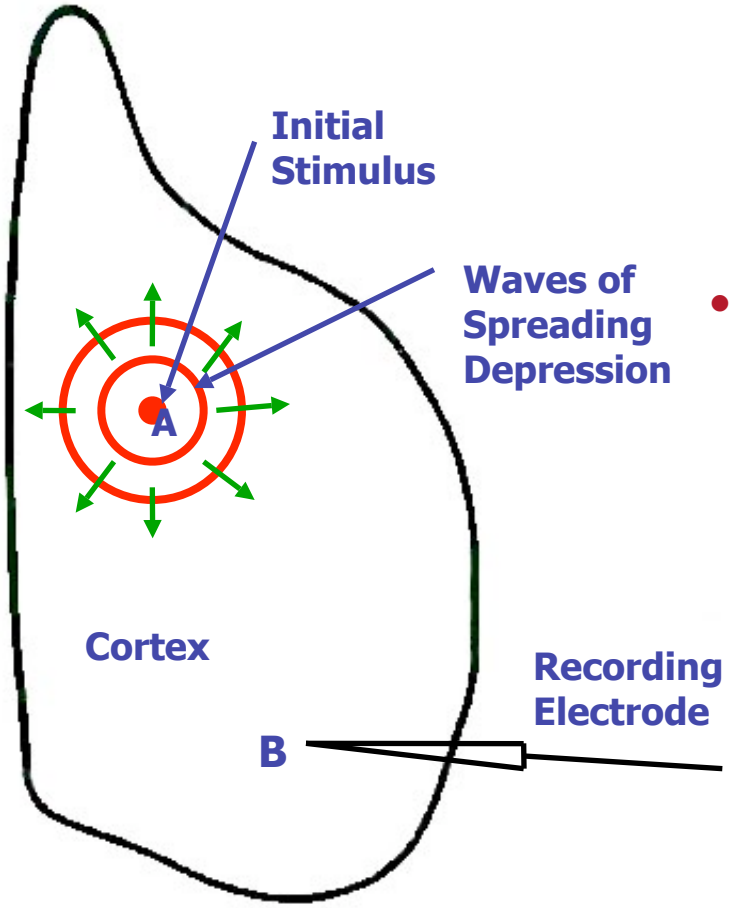


Bures, Buresova, and Krivanek (1974)

Aristides A.P. Leao (1914-1993)

Cortical Spreading Depression (CSD)

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



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

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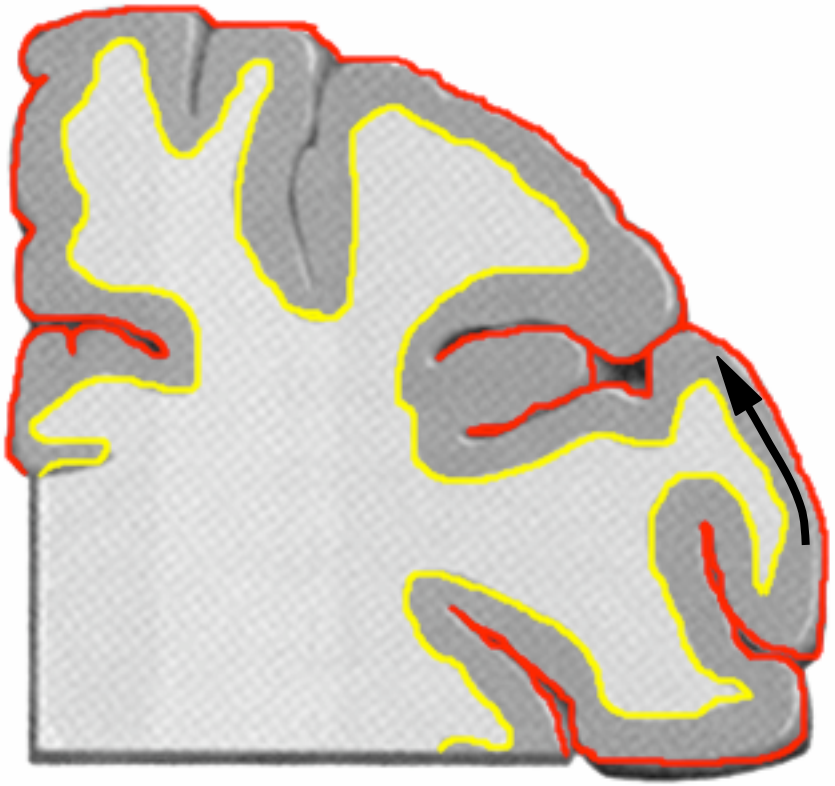
Cortical Spreading Depression (CSD)



Cortex

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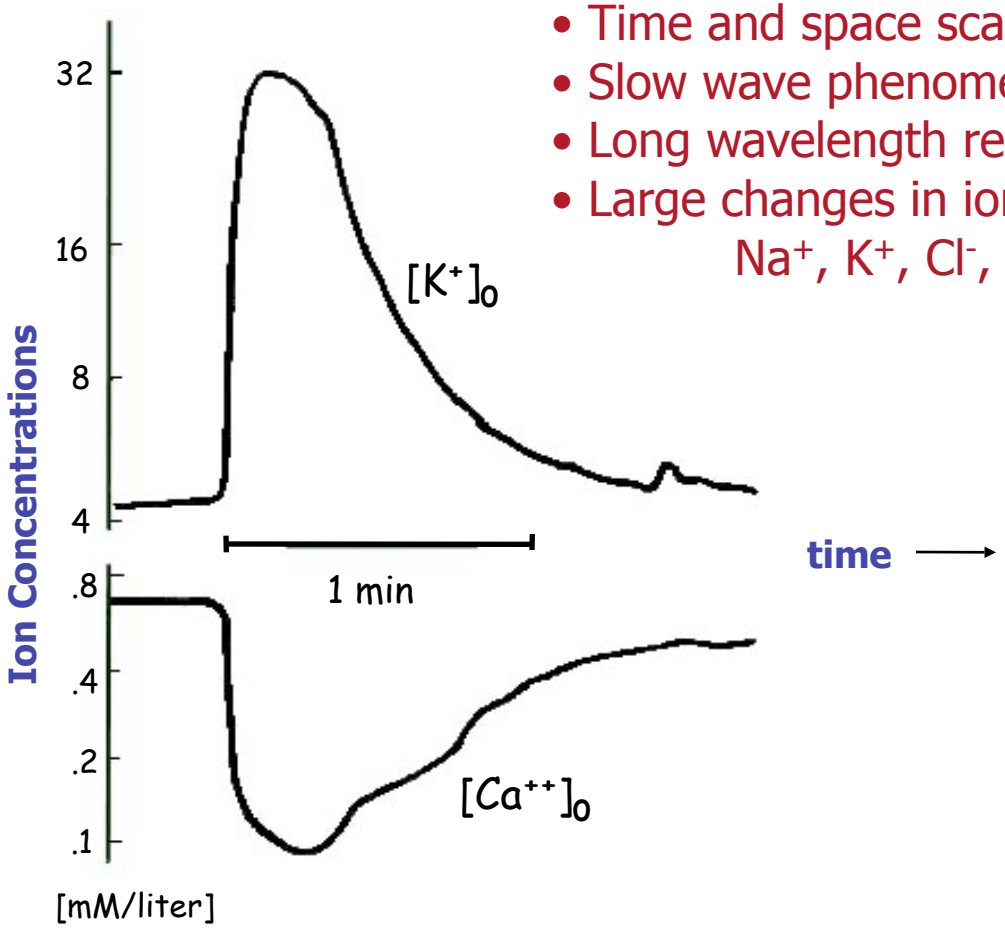
Cortical Spreading Depression (CSD)



- Instigation and propagation
- Properties similar to action potentials
- Time and space scales
- Slow wave phenomena - 1-15 mm/min
- Long wavelength relative to cell size
- Large changes in ionic concentrations of Na^+, K^+, Cl^-, Ca^{2+}

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Migraine with Aura and Cortical Spreading Depression

A connection between migraine with aura and cortical spreading depression had been conjectured for many years, but it wasn't until 2001 that Hadjikhani et al. in the Michael Moskowitz lab at Mass General, Harvard Medical School made a strong connection between the two phenomena. They used functional MRI with near-continuous recording to study three patients experiencing their visual auras.

They followed blood oxygenation level-dependent (BOLD) signal changes during the auras to show a number of characteristics of CSD.

1. Increase in BOLD signal (possible vasodilation).

2. BOLD change propagated over the occipital cortex, where the visual cortex is located, at a slow speed of approximately 3.5 mm/min, which is in the range of observed CSD speeds.

3. The BOLD signal was congruent with the movement of the retinotopy of the visual percept.

4. The BOLD signal then diminished (possible vasoconstriction).

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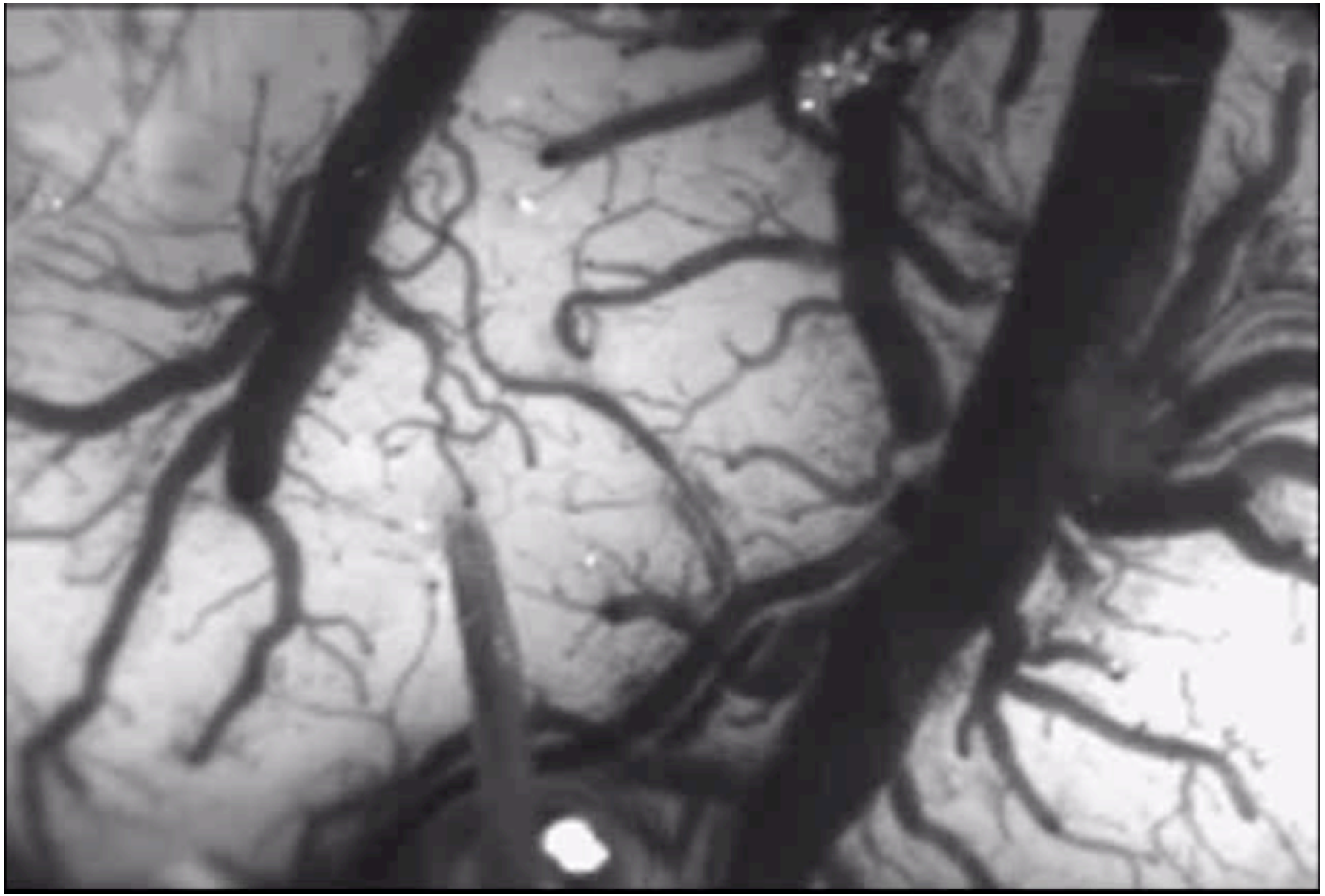

Models of Cortical Spreading Depression

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

Bernice Grafstein

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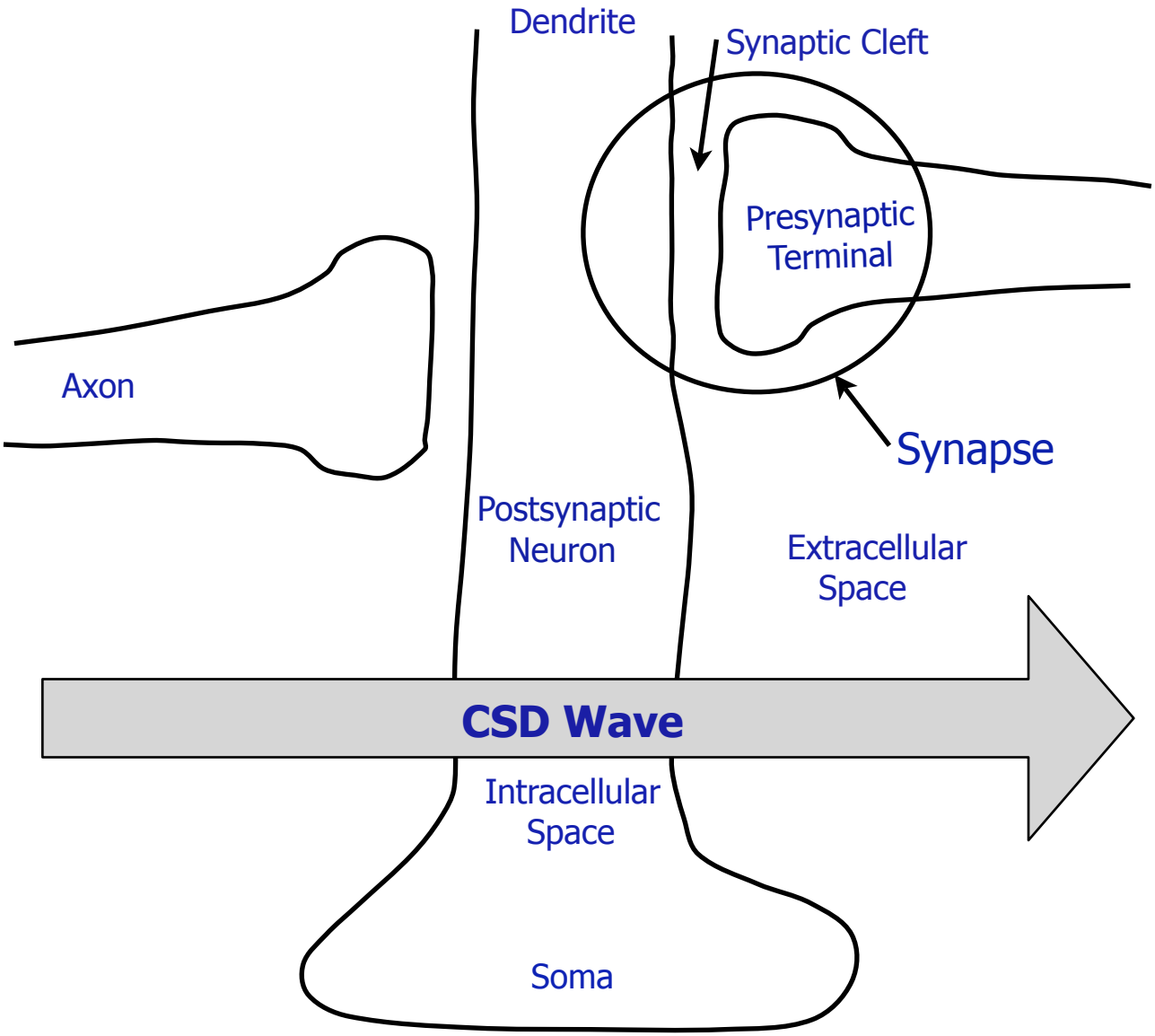
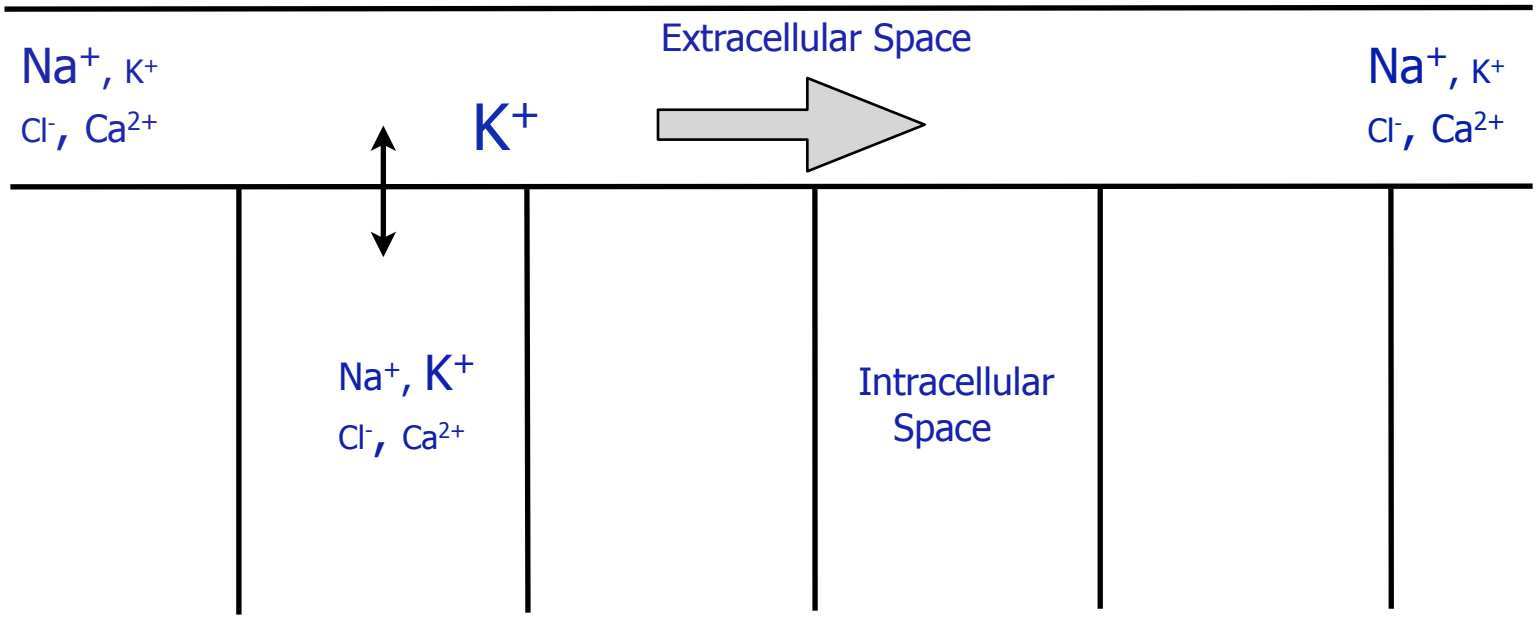
Simplified Continuum Model



Simplified Continuum Model Equations



Simplified Model Equations

- Neurotransmitter mechanism (Tuckwell and M.)
- Continuum model – only K^+ ($\mathbf{K}$) and Ca^{2+} ($\mathbf{C}$)

$$
\begin{aligned}
\mathbf{K_t^o} &= \mathbf{D_K K_{xx}^o} + \rho_1 \left(\mathbf{I_K} + \mathbf{P_K}\right), \\
\mathbf{K_t^i} &= -\frac{1}{1-\alpha}\rho_1 \left(\mathbf{I_K} + \mathbf{P_K}\right), \\
\mathbf{C_t^o} &= \mathbf{D_C C_{xx}^o} + \rho_2 \left(\mathbf{I_C} + \mathbf{P_C}\right), \\
\mathbf{C_t^i} &= -\frac{1}{1-\alpha}\rho_2 \left(\mathbf{I_C} + \mathbf{P_C}\right), \\
& \quad -\infty < \mathbf{x} < \infty, \quad \mathbf{t} > \mathbf{0}
\end{aligned}
$$

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

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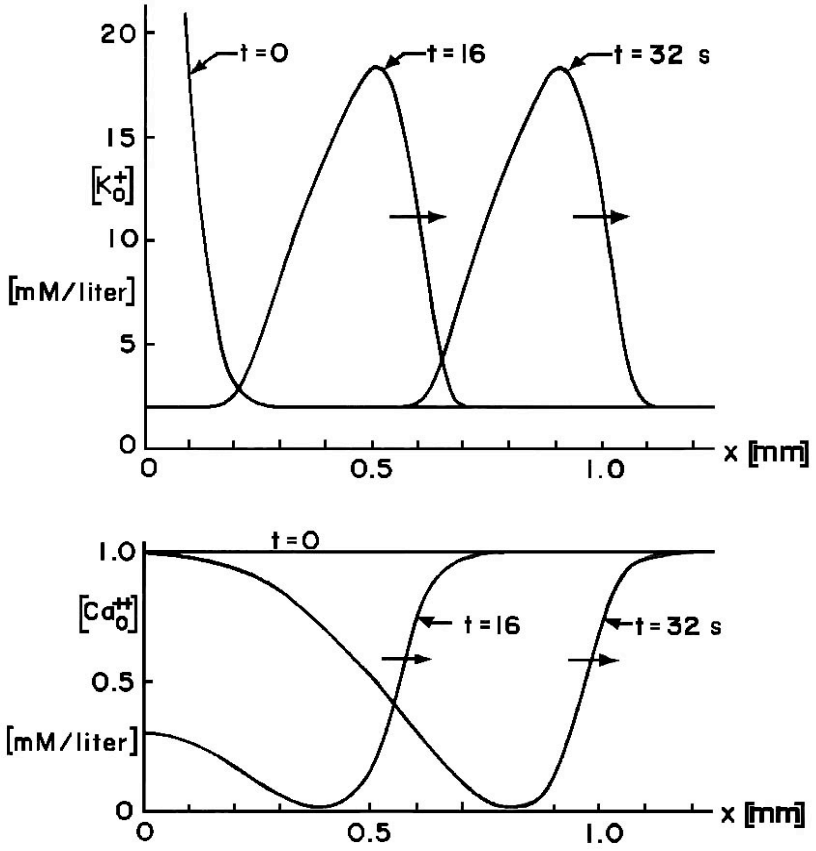
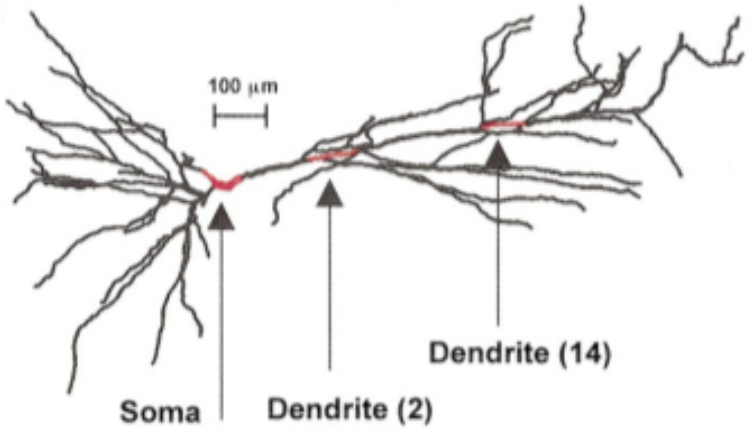
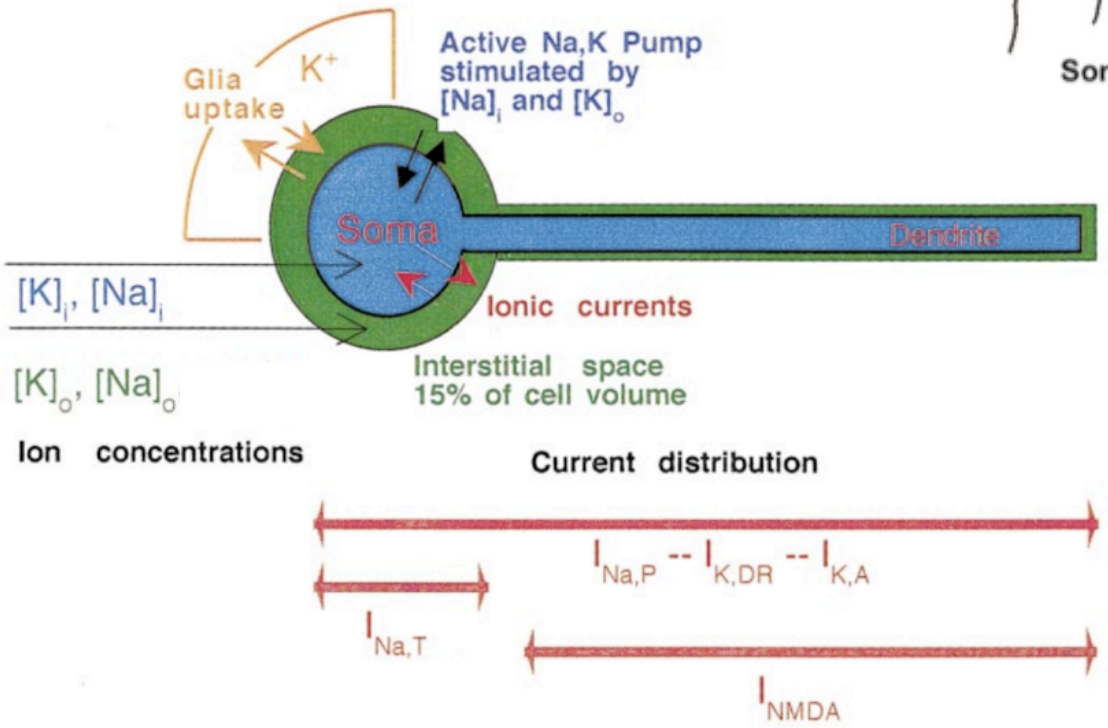
Solution of the Simplified SD Equations in One Space Dimension (K^+,Ca^{2+})



NOTE: Shape and speed approximately correct; however, ...

NEURON





Kager, Wadman, and Somjen, Simulated seizures and spreading depression in a neuron model incorporating interstitial space and ion concentrations, J. Neurophysiol. 84 (2000), 495-512.

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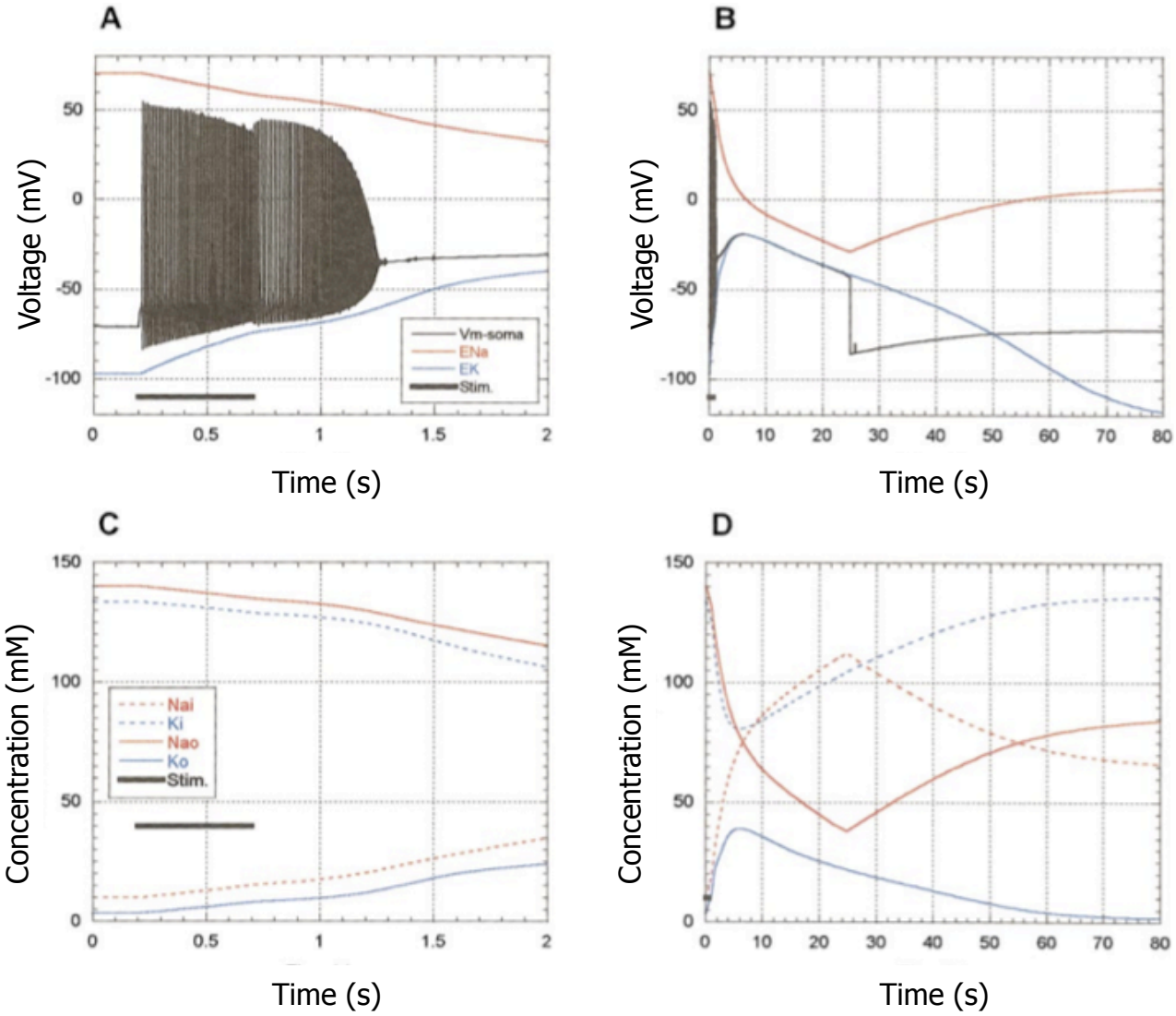
NEURON - Kager et al.



Simplified Continuum Model

Huaxiong Huang, Wei Yao, and M.

Consider only the soma and dendritic compartments with the following membrane currents:

$$
\begin{aligned}
C_m \frac{dE_m}{dt} &= -I = -I_{Na} - I_K - I_{Leak} - I_{Sti}, \\
I_{Na} &= I_{Na,T} + I_{Na,P} + I_{Na,NMDA} + I_{Na,Leak} + I_{Na,Pump}, \\
I_K &= I_{K,DR} + I_{K,A} + I_{K,NMDA} + I_{K,Leak} + I_{K,Pump}, \\
I_{Leak}, & \quad I_{Sti}, \\
I_{ion,GHK} &= m^p n^q \frac{P_{ion} g_{ion,GHK} E_m \left([ion]_i - \exp\left(-\frac{E_m}{\phi}\right) [ion]_e \right)}{\phi \left(1 - \exp\left(-\frac{E_m}{\phi}\right)\right)}, \\
I_{ion,HH} &= g_{ion,HH} \left(E_m - E_{ion}\right), \\
E_{ion} &= \phi \log \frac{[ion]_e}{[ion]_i}, \quad \phi \equiv \frac{RT}{zF}, \\
I_{Na,Pump} &= 3I_{Pump}, \quad I_{K,Pump} = -2I_{Pump}, \quad \text{where} \\
I_{Pump} &= \frac{I_{max}}{(1 + 3.5[K]_e^{-1})^2 (1 + 10[Na]_i^{-1})^3}.
\end{aligned}
$$

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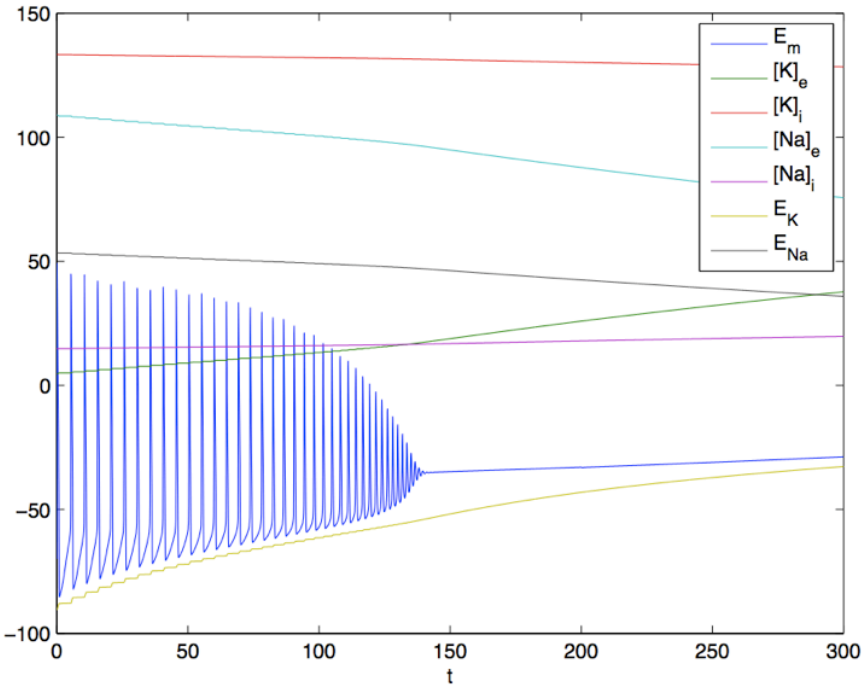
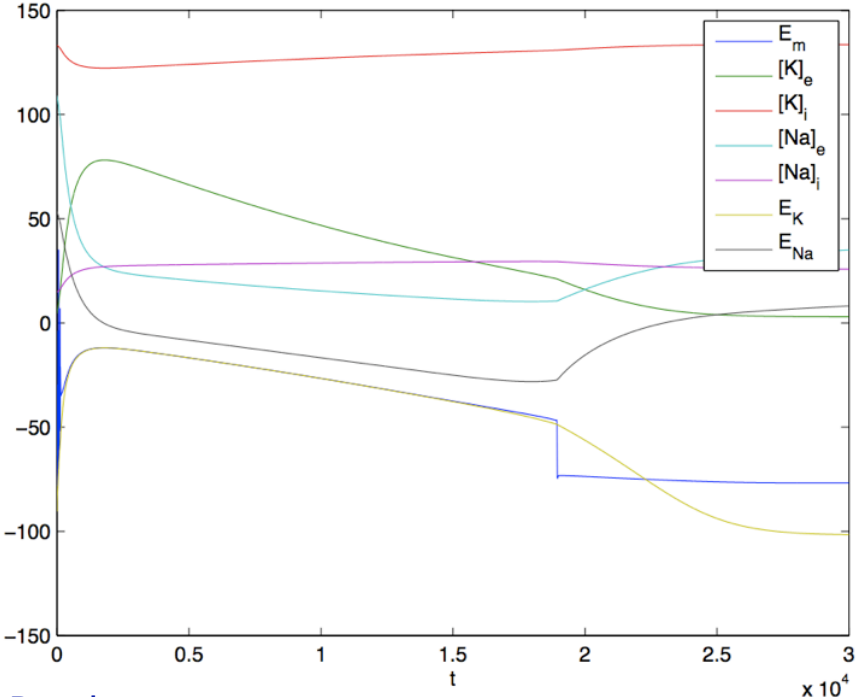
Simplified Continuum Model

$$\frac{d[Na]_i}{dt} = -\frac{S}{FV_i} I_{Na}, \quad \frac{d[Na]_e}{dt} = \frac{S}{FV_e} I_{Na},$$
$$\frac{d[K]_i}{dt} = -\frac{S}{FV_i} I_K, \quad \frac{d[K]_e}{dt} = \frac{S}{FV_e} I_K.$$





Preliminary Results

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Simplified Continuum Spatial Model

$$
\begin{aligned}
C_m \frac{\partial E_m}{\partial t} &= -I = -I_{Na} - I_K - I_{Leak} - I_{Sti}, \\
I_{Na} &= I_{Na,T} + I_{Na,P} + I_{Na,NMDA} + I_{Na,Leak} + I_{Na,Pump}, \\
I_K &= I_{K,DR} + I_{K,A} + I_{K,NMDA} + I_{K,Leak} + I_{K,Pump}, \\
I_{Leak}, & \quad I_{Sti}, \\
I_{ion,GHK} &= m^p n^q \frac{P_{ion} g_{ion,GHK} E_m \left([ion]_i - \exp\left(-\frac{E_m}{\phi}\right) [ion]_e \right)}{\phi \left(1 - \exp\left(-\frac{E_m}{\phi}\right)\right)}, \\
I_{ion,HH} &= g_{ion,HH} \left(E_m - E_{ion}\right), \\
E_{ion} &= \phi \log \frac{[ion]_e}{[ion]_i}, \quad \phi \equiv \frac{RT}{zF}, \\
I_{Na,Pump} &= 3I_{Pump}, \quad I_{K,Pump} = -2I_{Pump}, \quad \text{where} \\
I_{Pump} &= \frac{I_{max}}{(1 + 3.5[K]_e^{-1})^2 (1 + 10[Na]_i^{-1})^3}.
\end{aligned}
$$

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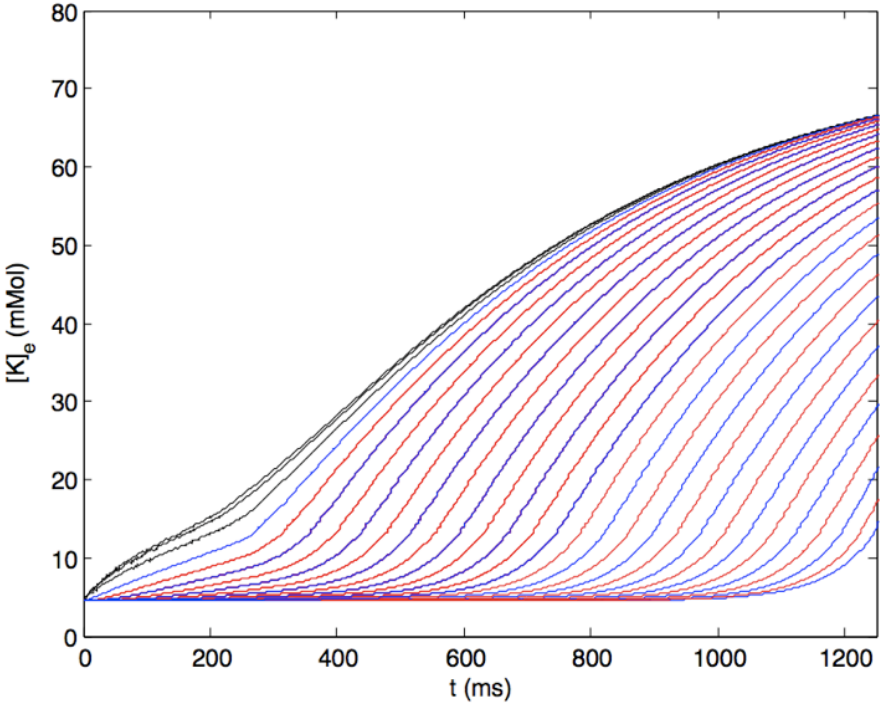
Simplified Continuum Spatial Model

$$
\begin{aligned}
\frac{\partial [Na]_i}{\partial t} &= -\frac{S}{FV_i} I_{Na}, \\
\frac{\partial [Na]_e}{\partial t} &= \frac{S}{FV_e} I_{Na} + D_{Na} \frac{\partial^2 [Na]_e}{\partial x^2}, \\
\frac{\partial [K]_i}{\partial t} &= -\frac{S}{FV_i} I_K, \\
\frac{\partial [K]_e}{\partial t} &= \frac{S}{FV_e} I_K + D_K \frac{\partial^2 [K]_e}{\partial x^2}.
\end{aligned}
$$



Preliminary Result

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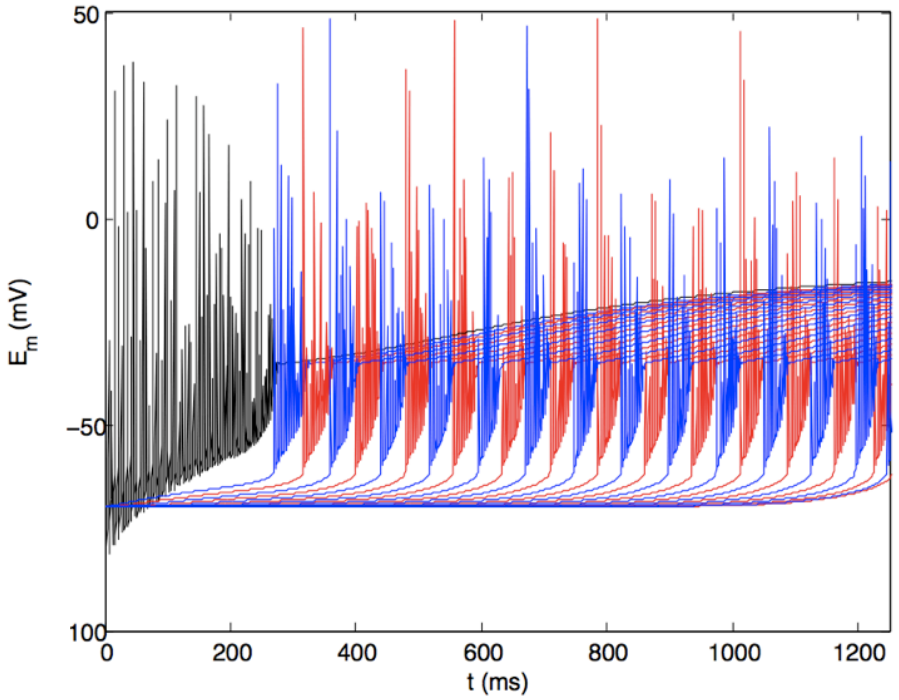
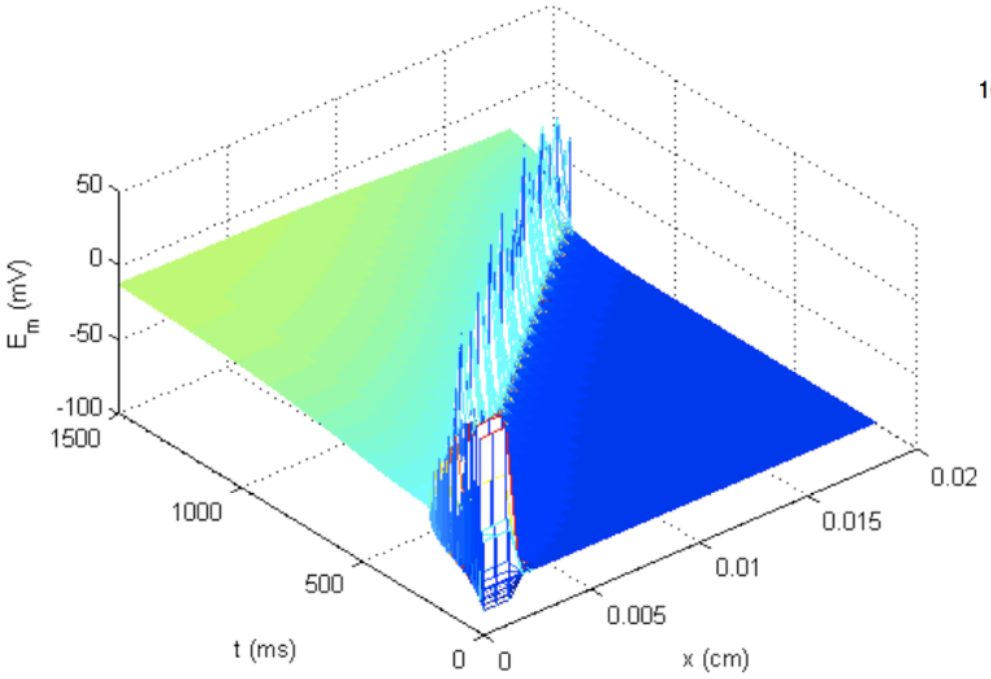
Simplified Continuum Spatial Model





Preliminary Results

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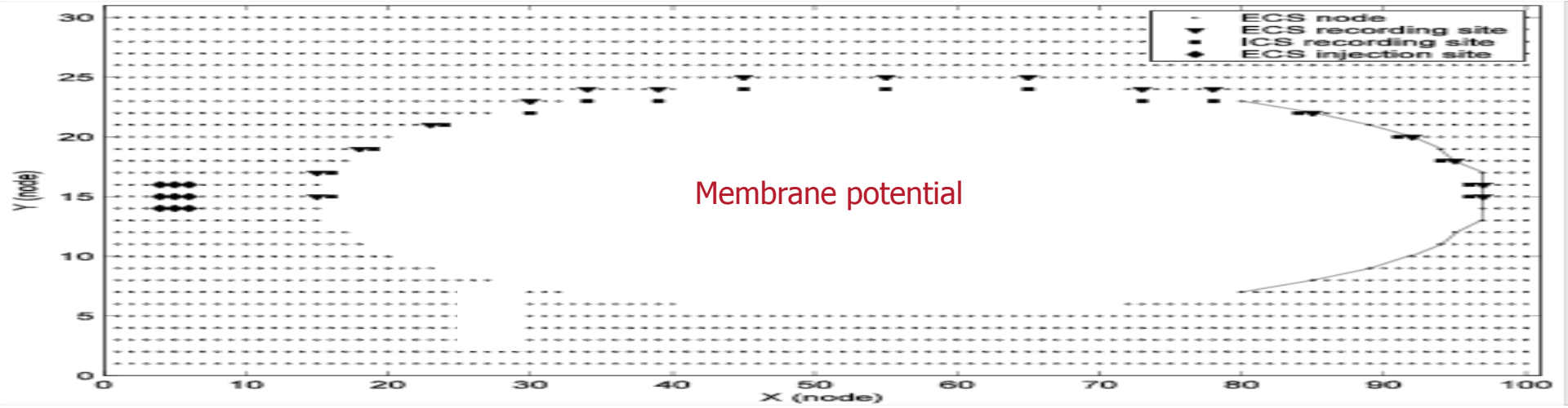
Other Mechanisms

Spatial Buffering

Single cell microenvironment with injection of potassium



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

Steinberg, Wang, Huang, and M., Math. Biosci. Engin. 2 (2005), 675-602.

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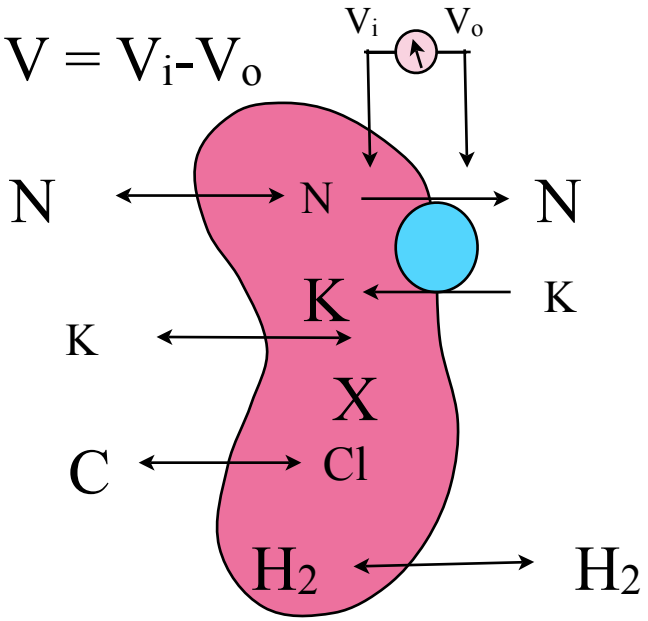
Other Mechanisms

Osmosis and Cell Volume Change

- During CSD, ECS compressed to about 25-50% of its original volume fraction
- Cell swelling due to osmotic movement of water across membrane
- Na+, K+, Cl-, and water move through channels in the membrane



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

Shapiro, Osmotic forces and gap junctions in spreading depression: A computational Model, J. Comp. Neurosci.10 (2001), 99-120.

Kager, Wadman, and Somjen, Conditions for the triggering of spreading depression studied with computer simulations, J. Neurophysiol. 88 (2002), 2700-2012.

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Other Problems

- Volume Fraction
- Tortuosity
- Discrete Model - Lattice Boltzmann
- Existence of Solitary Waves

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Summary

- Migraine with Aura
- Cortical Spreading Depression
- Models for SD
- Continuum Modeling
- Newer Models
- Spatial Buffering
- Cell Swelling
- Other Problems

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