

OSMOTIC FORCES, GAP JUNCTIONS, AND SPREADING DEPRESSION: A COMPUTATIONAL MODEL.

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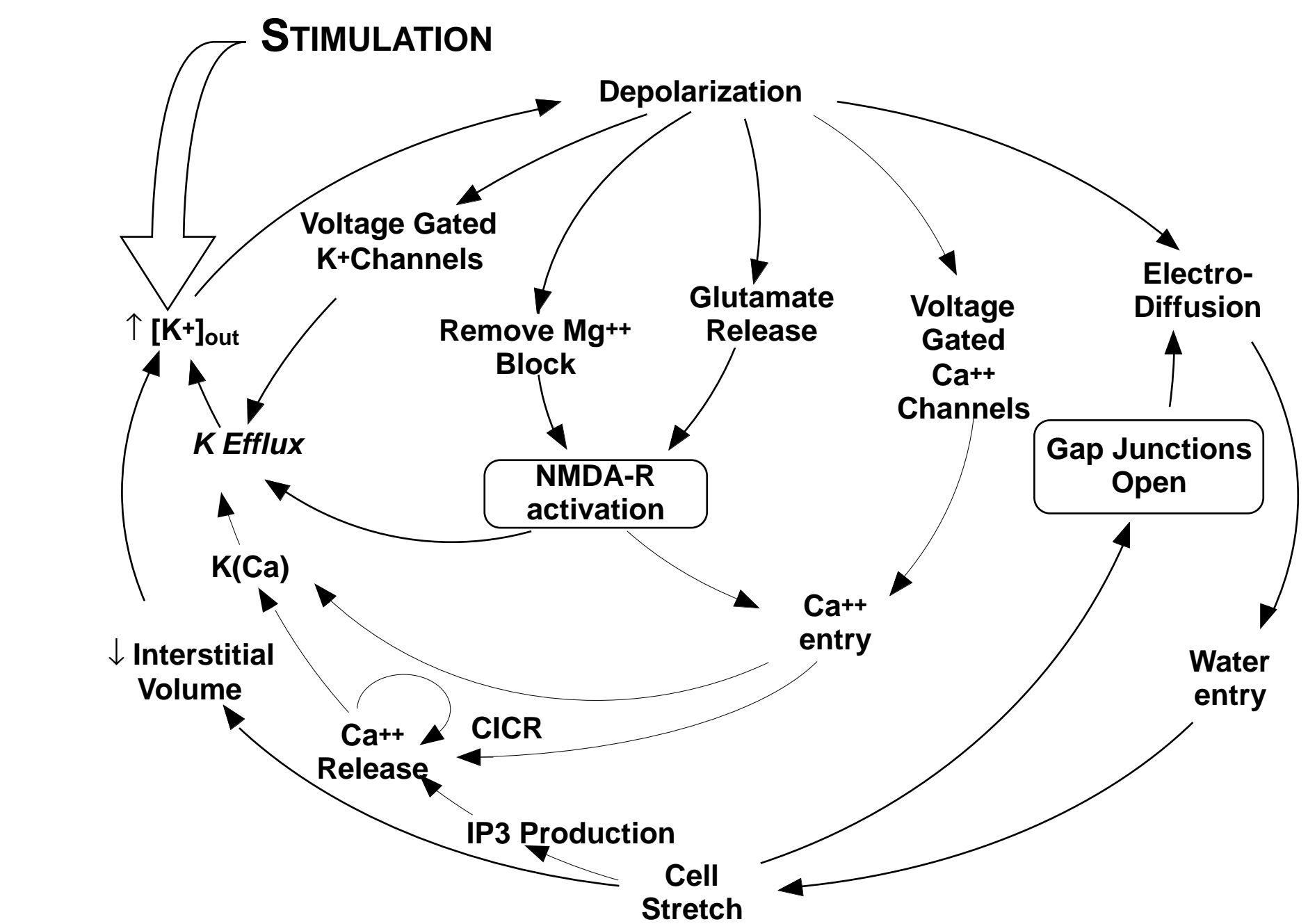
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INTRODUCTION

Spreading Depression (SD) consists of a slowly moving wave of membrane depolarization and a prolonged depression of EEG activity. It is accompanied by ionic concentration changes lasting for up to two minutes, and typically travels at 3 to 12 mm/min. Wave passage may be accompanied by increased blood flow and is followed by a prolonged vasodilation. SD is widely believed to cause migraine-with-aura, has been observed during cerebral ischemia, hypoxia, and concussion, and may even induce subsequent ischemic tolerance. There is no generally accepted theory of SD. Previous mathematical models are based on interstitial K⁺ diffusion, and have treated cytosolic concentrations as purely local. As such, they do not explain why gap junction poisons prevent SD. It seems unlikely that these gap junctions are glial since glial poisons do not prevent SD. The nearly 50% reduction in interstitial volume that occurs during SD has also not been previously modeled.

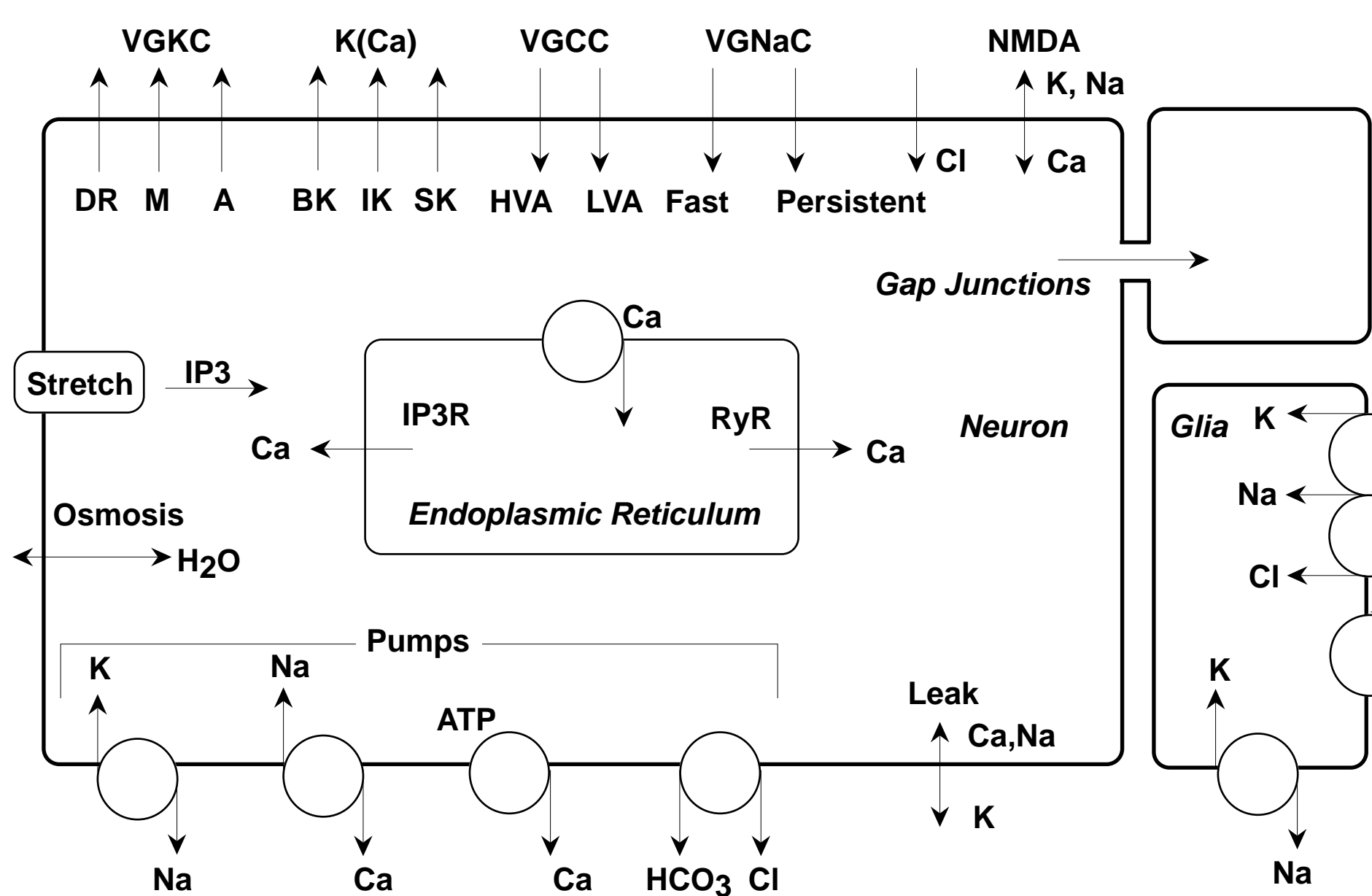
METHOD

A novel model of spreading depression has been developed that differs from previous ones in that it incorporates the effects of (a) gap junctions, (b) intracellular voltage gradients, and (c) osmotically induced volume changes. Ions are allowed to propagate in a neuronal syncytium of gap-junction connected cells. Because large ionic shifts and dendritic voltage gradients occur during SD, standard compartmental, cable-based, or reaction-diffusion models are inappropriate. Thus a full electrodiffusion model is used. Electrodiffusion pushes cytoplasmic K⁺ away from the stimulation. This movement, along with depolarization-induced Na⁺ and Cl⁻ fluxes, leads to an osmotic imbalance. This is countered by the flow of water into or out of cells, causing the cells to expand or contract. These cellular volume changes are spatially limited by the surrounding parenchyma (expansion) and intracellular organelles (contraction).



MEMBRANE CURRENTS

The neuronal membrane has three voltage gated K⁺ currents (VGKC), three Ca⁺⁺ dependent K⁺ currents (K(Ca)), two voltage gated Ca⁺⁺ currents (VGCC), two voltage gated Na⁺ currents (VGNaC), a passive Cl⁻ flux, three independent NMDA fluxes (K⁺, Ca⁺⁺, Na⁺), three leak currents and four ion pumps. The glial model has three ion pumps. The ER is treated as a large Ca⁺⁺ buffer with IP3-sensitive Ca⁺⁺ channels (IP3R), ryanodine-sensitive Ca⁺⁺ channels (RyR) and a Ca⁺⁺ pump. IP3 is produced from PIP2 by membrane stretch. Ion channels are described by Hodgkin-Huxley models.



MATHEMATICAL MODEL

ELECTRODIFFUSION EQUATION

$$\text{Continuity Equation: } \nabla \cdot \mathbf{J} + \frac{\partial c}{\partial t} = S \quad (S = \text{Source Terms})$$

$$\text{Nernst-Planck Equation: } \mathbf{J} = -D(\nabla c + \frac{zF}{RT}c\nabla E)$$

$$\text{Electrodiffusion Equation: } \frac{\partial c}{\partial t} = \nabla \cdot (D\nabla c) + \frac{zF}{RT}\nabla \cdot (Dc\nabla E) + S$$

$$\text{One Dimensional Reduction: } \frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left(D \frac{\partial c}{\partial x} \right) + \frac{zF}{RT} \frac{\partial}{\partial x} \left(Dc \frac{\partial E}{\partial x} \right) - \frac{A}{V} J_m + S$$

CYTOSOLIC CONCENTRATIONS: ELECTRODIFFUSION EQUATION

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left(D \frac{\partial c}{\partial x} \right) + \frac{zF}{RT} \frac{\partial}{\partial x} \left(Dc \frac{\partial E}{\partial x} \right) - \frac{A}{V} J_m + f$$

$$\frac{\partial [K^+]_{in}}{\partial t} = \frac{\partial}{\partial x} \left(D_{K,in} \frac{\partial [K^+]_{in}}{\partial x} \right) + \frac{F}{RT} \frac{\partial}{\partial x} \left([K^+]_{in} D_{K,in} \frac{\partial E}{\partial x} \right) - \frac{A}{V} (j_A + j_M + j_{DR} + j_{BK} + j_{IK} + j_{SK} + j_{K,NMDA} + j_{K,leak} - j_{Na,K})$$

$$\frac{\partial [Ca^{++}]_{in}}{\partial t} = \frac{\partial}{\partial x} \left(D_{Ca,in} \frac{\partial [Ca^{++}]_{in}}{\partial x} \right) + \frac{2F}{RT} \frac{\partial}{\partial x} \left([Ca^{++}]_{in} D_{Ca,in} \frac{\partial E}{\partial x} \right) - \frac{A}{V} (j_{LVA} + j_{HVA} + j_{LVA} + j_{Ca,NMDA} + j_{Na,Ca} + j_{ATP}) + j_{IP3} + j_{Ryanodine} - j_{pump}$$

$$\frac{\partial [Na^+]_{in}}{\partial t} = \frac{\partial}{\partial x} \left(D_{Na,in} \frac{\partial [Na^+]_{in}}{\partial x} \right) + \frac{F}{RT} \frac{\partial}{\partial x} \left([Na^+]_{in} D_{Na,in} \frac{\partial E}{\partial x} \right) - \frac{A}{V} (j_F + j_P - \frac{3}{2} j_{Na,K} - j_{Na,Ca} + j_{Na,NMDA})$$

$$\frac{\partial [Cl^-]_{in}}{\partial t} = \frac{\partial}{\partial x} \left(D_{Cl,in} \frac{\partial [Cl^-]_{in}}{\partial x} \right) - \frac{F}{RT} \frac{\partial}{\partial x} \left([Cl^-]_{in} D_{Cl,in} \frac{\partial E}{\partial x} \right) - \frac{A}{V} (j_{Cl,bicarb} + j_{K,m} + j_{Na,m})$$

INTERSTITIAL CONCENTRATIONS: REACTION/DIFFUSION EQUATION

$$\frac{\partial c_{out}}{\partial t} = D_{K,out} \frac{\partial^2 c_{out}}{\partial x^2} + \frac{(A/V)f}{1-f} j_{c,m} - j_{c,glia}$$

$$\frac{\partial [K^+]_{out}}{\partial t} = D_{K,out} \frac{\partial^2 [K^+]_{out}}{\partial x^2} + j_{K,glia} + \frac{(A/V)f}{1-f} (j_A + j_M + j_{DR} + j_{BK} + j_{IK} + j_{SK} + j_{K,NMDA} + j_{K,leak} - j_{Na,K})$$

$$\frac{\partial [Ca^{++}]_{out}}{\partial t} = D_{Ca,out} \frac{\partial^2 [Ca^{++}]_{out}}{\partial x^2} + \frac{(A/V)f}{1-f} (j_{LVA} + j_{HVA} + j_{LVA} + j_{Ca,NMDA} + j_{Na,Ca} + j_{ATP} + j_{Ca,NMDA})$$

$$\frac{\partial [Na^+]_{out}}{\partial t} = D_{Na,out} \frac{\partial^2 [Na^+]_{out}}{\partial x^2} + \frac{(A/V)f}{1-f} (j_F + j_P - \frac{3}{2} j_{Na,K} - j_{Na,Ca} + j_{Na,NMDA})$$

$$\frac{\partial [Cl^-]_{out}}{\partial t} = D_{Cl,out} \frac{\partial^2 [Cl^-]_{out}}{\partial x^2} + \frac{(A/V)f}{1-f} (j_{Cl,bicarb} + j_{K,m} + j_{Na,m})$$

OSMOTIC FORCES

By electroneutrality the number of impermeant cytosolic anions in dV is

$$N_A = V_{int} ([Na^+]_{int,rest} + [K^+]_{int,rest} - [Cl^-]_{int,rest})$$

By isotonicity the total external solute concentration [S]_{out} is

$$[S]_{out} = [Na^+]_{in} + [K^+]_{in} + [Cl^-]_{in} + \frac{N_A}{f dV_f}$$

Water flow across the membrane maintains isotonicity

$$\Delta dV / dV = \Delta N_S / N_S$$

where N_S is the total number of interstitial solute ions. Hence

$$\frac{dV}{dt} = \begin{cases} \left[\frac{1}{[S]_{out}} \sum \frac{d}{dt} ([c]_{in} V) \right] V \leq V_{max} \\ 0, & V > V_{max} \end{cases}$$

RESULTS

KEY PREDICTIONS

An increase in these parameters ↓	Causes a change in these →	Magnitude ↑ ↓	Speed ↑ ↓	Slope ↑ ↓	Duration ↑ ↓
Cytosolic diffusion constant		↑	↑	↑	↓
NMDA conductance		↑	↑	↑	↓
BK conductance		↑	↑	↑	↓
SK conductance		×	×	×	↓
IK conductance		×	×	×	↓
DR conductance		×	×	×	↑
A-channel conductance		×	×	×	↓
Na-channel conductance		↑	↑	↑	↓
HVA-channel conductance		↑	↑	↑	↓
LVA-channel conductance		×	×	×	↑
Interstitial Ca ⁺⁺ conc.		↑	↑	↑	↑
Diameter		↓	↓	↓	↓
Glial pumping rate		↓	↓	↓	×

PREDICTED DEPENDENCE ON VARIOUS BIOPHYSICAL PARAMETERS

The figures to the right show the dependence of predicted wave speed and magnitude (max [K⁺]_{out}) on various parameters. Each figure summarizes a large set of simulations in which only a single parameter was varied.

For g_{K,NMDA} (A) and g_{BK} (B) a parametric set of curves is shown. Each curve corresponds to a different g_{DR}. Wave speed and magnitude are both increasing functions of g_{DR} (C). Above a threshold value of g_{DR}, wave speed increases with g_{K,NMDA} and g_{BK}, wave magnitude increases with g_{BK}, but decreases with g_{K,NMDA}. The insets show the threshold values of g_{DR} for the parameters used in these simulations.

Predicted wave speed is an increasing function of g_{Na} (D) while wave magnitude decreases with g_{Na}. This suggests that Na⁺ currents facilitate SD at low levels and inhibit it at higher levels.

Both the predicted wave speed and wave magnitude decrease with average dendritic diameter (E). This suggests that waves may propagate more strongly in thinner processes.

CONCLUSIONS

GOALS

To model and predict the importance of:

- Volume changes
- Interneuron gap junctions
- in the propagation of spreading depression

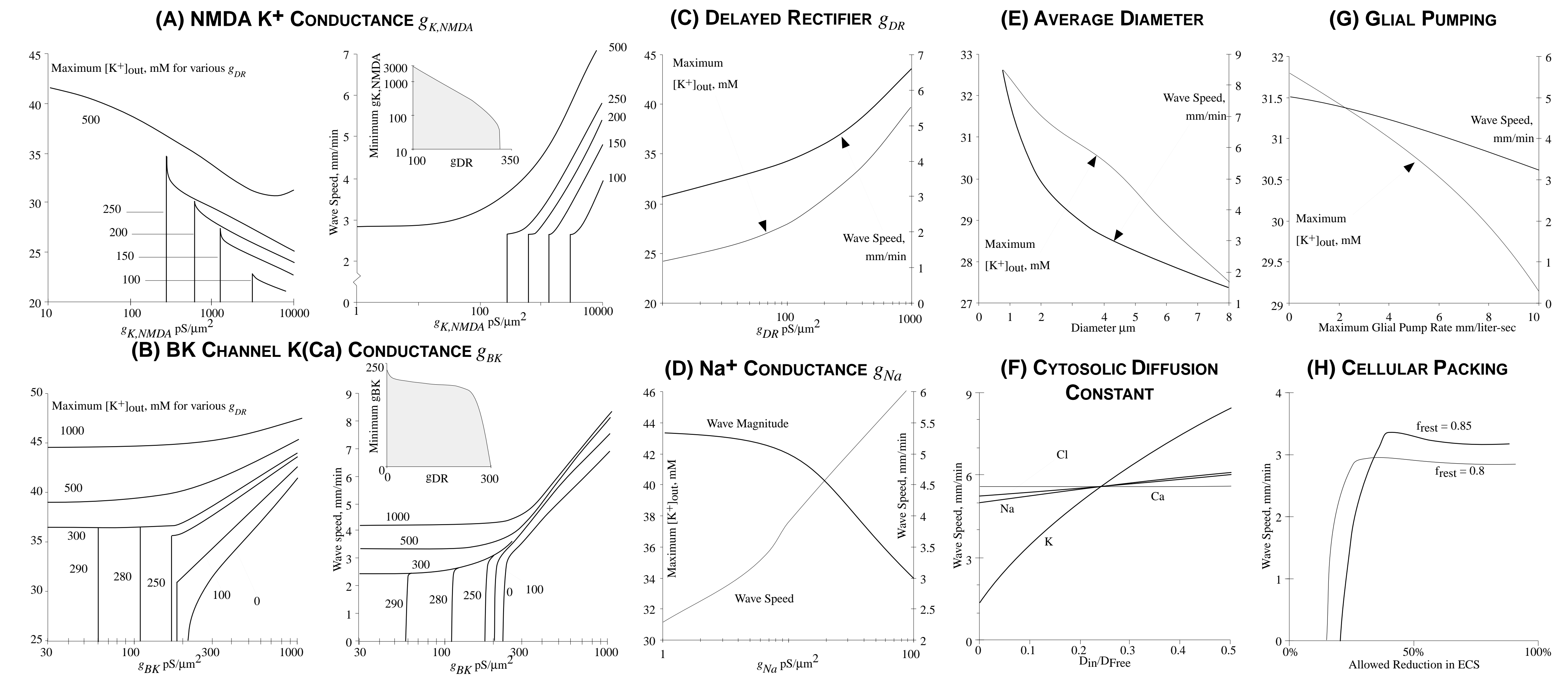
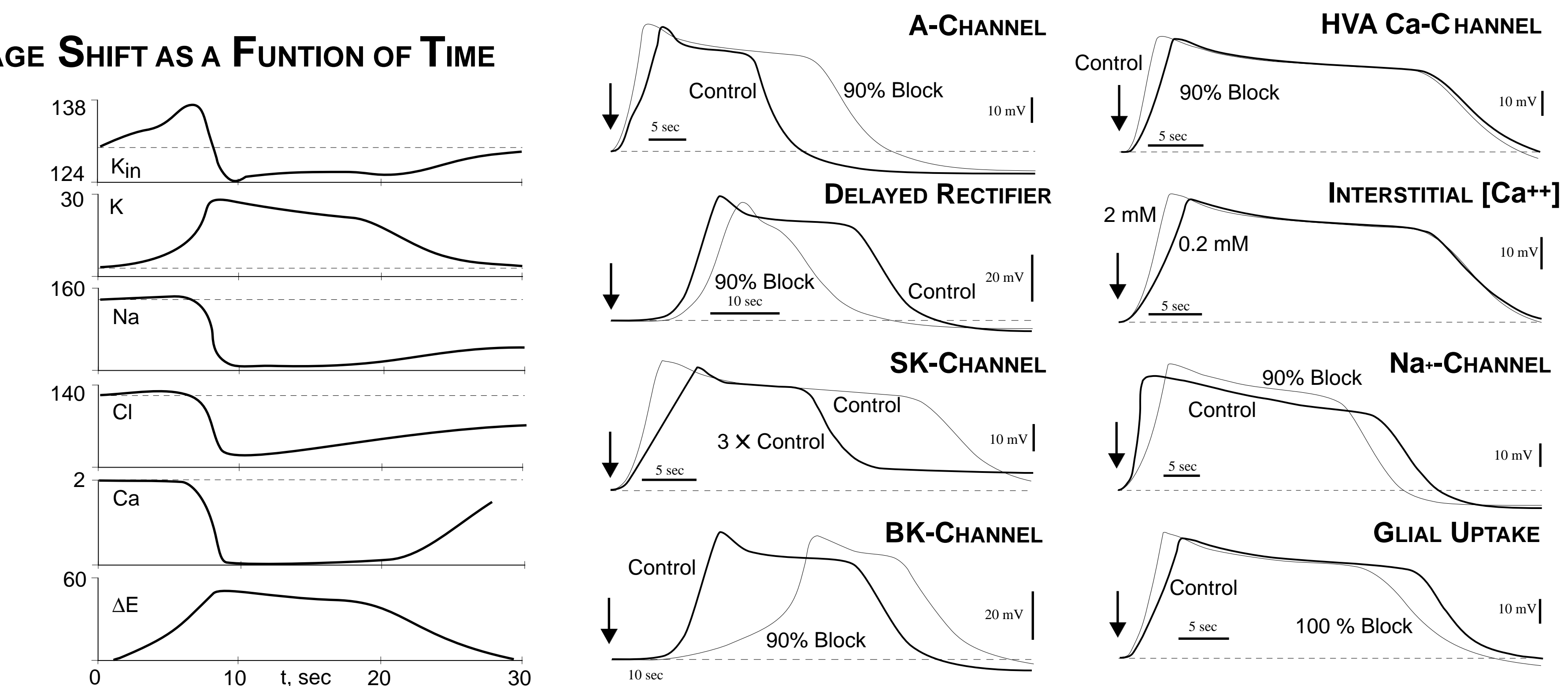
ASSUMPTIONS

- Osmotic forces cause water entry/efflux
- Cytoplasmic voltage gradients may be of significance
- Ions propagate through interneuron gap junctions

PREDICTED CONCENTRATION (mM) AND DC-VOLTAGE SHIFT AS A FUNCTION OF TIME

Spreading depression was induced by raising [K⁺]_{out} to 50 mM at the origin. The waveforms to the right are from a typical simulation with a predicted wave speed of 3.6 mm/min. The curves show the ionic concentrations (interstitial except [K⁺]_{in}) and DC-Voltage shift at a point 0.5 mm distant from the stimulation, as a function of time. Resting values are indicated by dashed lines.

The two columns on the far right show the effect of various parameters on the shape of the predicted waveform. Each figure corresponds to a different pair of simulations, in which only a single parameter value was varied. The predicted DC-Voltage shift, as observed at a fixed point (either 0.5 or 1.0 mm from the stimulation), is plotted as a function of time. Arrows give the time of stimulation and resting values are indicated by dashed lines. Other parameters vary from figure to figure. Note that the scales are different.



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