The Role of Oxygen on the Dynamics of Seizure and Spreading Depression

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Feb 14, 2018

Mathematical Modeling of Cortical Spreading Depression (SD) and Related Phenomena, University of Minnesota
Outline

• What is seizure?
• What is spreading depression?
• Commonality?
• What is missing in current model?
• Energy consumption in the brain
• Part I: oxygen and seizure dynamics
• Part II: oxygen and spreading depression
What is Seizure?

Epilepsy

• One of the most common brain disorders
• 1% world population, 3 million people in US
• characterized as the occurrence of repetitive Seizures

Seizure

• A sudden abnormal excessive neuronal activity
• Lasts from a few seconds to a few minutes

Cause

• Head trauma, stroke, brain infection etc.
What is Spreading Depression?

**Spreading Depression (SD)**
- a pathophysiologic phenomenon occurred during migraine, head trauma, and stroke.
- nearly complete depolarization
- propagates 2-5 mm/min

**SD can be induced by**

Hypoxia

![Hypoxia graph]

Czech et al., 1993 Brain Research

High potassium

![High potassium graph]

Brisson and Andrew, 2012, J Neurophysiol
The Commonalities

Seizures

Hypoxia Spreading Depression

Commonalities:
• Shifts of extracellular potential
• Redistribution of ions between intracellular and extracellular space
• Can be induced by low oxygen and high potassium, etc.


Czech et al., 1993 Brain Research
High $K^+$ Makes Seizures and SD

Timeline Spont. Seizures

8.5 mM

Traynelis & Dingledine 1988

26 mM

Anderson & Andrew, 2002 J Neurophys

40 mM

Zhou et al., 2010 Cereb Ctx

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Brains Hypoxic during Seizures and SD

*In Vitro Seizure*

[Bahar et al., 2006 NeuroReport](#)

[O_2] Determines Duration SD

[Takano et al. 2007](#)

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What is Missing in Current Models?

Hodgkin–Huxley Model: assumes ion concentrations are constant.

Seizures or SD: loss of ionic homeostasis.

Current Models: assumes energy (oxygen) is infinitely available.

Cressman et al., 2009, Ullah et al., 2009: Seizure model
Bazhenov et al., 2004, Krishnan et al., 2011: Seizure model
Energy consumption in brain

Distribution of Energy Used in Spikes:

1. **Restore Ion Gradient**
2. **Transmitters Release and Recycling**

\[ \text{Na/K pump} \]

\[ 3 \text{Na}^+ + \text{ATP} \rightarrow 2 \text{K}^+ \]

\[ \text{Out} \]

\[ \text{In} \]

\[ \text{Na}^+ \]

\[ \text{K}^+ \]

\[ \text{Cl}^- \]

\[ \text{Presynaptic Ca}^{2+} \]

\[ \text{Glutamate Cycling} \]

\[ \text{Axon} 33\% \]

\[ \text{EPSPs} 52\% \]

\[ \text{Soma} 6\% \]

\[ \text{Dendrites} \]

\[ \text{The Cost of Cortical Computation} \]

Lennie, 2003, Current Biology

\[ \text{C}_6\text{H}_{12}\text{O}_6 + 6 \text{O}_2 \rightarrow 6 \text{CO}_2 + 6 \text{H}_2\text{O} + 36 \text{ATP} \]
Part I: Oxygen and Seizure
Experimental $O_2$ Observations

1) Seizure
=> $O_2$ Deficit

2) Narrow Band $O_2$
=> Seizure

3) E & I Interplay
=> $O_2$ Interplay

Ingram et al., 2014 J Neurophys

Mathematical Model

Membrane Potential Dynamics: (Hodgkin Huxley Equations)

\[
\frac{dV}{dt} = \frac{1}{C}(-I_{Na} - I_{K} - I_{Cl})
\]

\[
I_{Na} = G_{Na} m^3 h (V - E_{Na}) + G_{NaL} (V - E_{Na})
\]

\[
I_{K} = G_{K} n^4 (V - E_{K}) + G_{KL} (V - E_{K})
\]

\[
I_{Cl} = G_{Cl} (V - E_{Cl})
\]

\[
E_x = 26.64 \ln\left(\frac{[x]_o}{[x]_i}\right), x = Na, K, Cl
\]

Ion Concentration Dynamics: Cressman et al. 2009

\[
\frac{d[K]_o}{dt} = \gamma \beta I_{K} - 2 \beta I_{pump} - I_{glia} - I_{diff}
\]

\[
[K]_i = 140 + (18 - [Na]_i)
\]

\[
\frac{d[Na]_i}{dt} = -\gamma I_{Na} - 3I_{pump}
\]

\[
[Na]_o = 144 - \beta([Na]_i - 18)
\]
Mathematical Model

Diffusion, Pump and Glial Uptake Currents:

\[ I_{\text{diff}} = \varepsilon_k ([K]_o - [K]_{\text{bath}}) \]

\[ I_{\text{pump}} = \frac{\rho}{1.0 + \exp((25 - [Na]_i) / 3)} \times \frac{1.0}{1.0 + \exp(5.5 - [K]_o)} \]

\[ I_{\text{gliapump}} = \frac{1}{3} \frac{\rho}{1 + \exp((25 - [Na]_{ig}) / 3)} \times \frac{1.0}{1.0 + \exp(5.5 - [K]_o)} \]

\[ I_{\text{glia}} = 2I_{\text{gliapump}} + \frac{\text{glia}}{1.0 + \exp((18 - [K]_o) / 2.5)} \]

Oxygen Dynamics:

\[ \frac{d[O_2]_o}{dt} = -\alpha \lambda (I_{\text{pump}} + I_{\text{gliapump}}) + \varepsilon_o ([O_2]_{\text{bath}} - [O_2]_o) \]
Mathematical Model

Diffusion, Pump and Glial Uptake Currents:

\[ I_{\text{diff}} = \varepsilon_k ([K]_o - [K]_{\text{bath}}) \]

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Oxygen Dynamics:

\[ \frac{d[O_2]_o}{dt} = -\alpha \lambda (I_{\text{pump}} + I_{\text{gliapump}}) + \varepsilon_o ([O_2]_{\text{bath}} - [O_2]_o) \]

\[ \rho = \frac{\rho_{\text{max}}}{1 + \exp((20 - [O_2]_o) / 3)} \]

the Na/K ATPase as a Function Of O2

Petrushanko et al. 2007
Potassium-induced Spontaneous Seizure

Experiment

Timeline Spont. Seizures

Model

Traynelis & Dingledine 1988

Experiment

Model
Oxygen Dynamics around Single Cell

Experiment

Ingram et al., 2014 J Neurophys
Oxygen Dynamics around Single Cell

Experiment

Model

Ingram et al., 2014 J Neurophys

Wei, Ingram, Ullah, Schiff, 2014 J Neurophys
Bifurcation Analysis with Fixed Ion Concentrations

Bazhenov et al 2004 J Neurphysiol ; Krishnan and Bazhenov, 2011 J Neurosci; Barreto et al 2011 J Biol Phys; Wei, Ingram, Ullah, Schiff, 2014 J Neurophys

**Hopf Bifurcation (HB):** a limit cycle decreases until it is reduced to a point and disappears.

**Saddle Node Bifurcation (SN):** two equilibrium points collide and disappear.
Bifurcation Analysis

\[
\frac{d[O_2]_o}{dt} = -\alpha \lambda (I_{pump} + I_{gliapump}) + \varepsilon_o ([O_2]_{bath} - [O_2]_o)
\]

![Graph showing bifurcation analysis with [O_2] values and corresponding V values and time].

K_o, Na_i, constrained K_i, Na_o

Wei, Ingram, Ullah, Schiff, 2014 J Neurophys
Bifurcation in Normal $[K^+]_{\text{bath}}$

Experiment

Model

Ingram et al., 2014 J Neurophys

Wei, Ingram, Ullah, Schiff, 2014 J Neurophys
[O₂]_{bath} Bifurcation in Normal [K^+]_{bath}

Wei, Ingram, Ullah, Schiff, 2014, J Neurophys
Excitatory and Inhibitory Interplay

Experiment


Ingram et al., 2014 J Neurophysiol.
Gradient, Not Spikes, Drives O2 Use

Model

![Graph of gradient, not spikes, drives O2 use](image)

Wei, Ingram, Ullah, Schiff, 2014 J Neurophysi
Short Summary

- **O₂ Deficit after Seizure**
- **Hypoxia Induces Seizures**
- **Neuron vs. Oxygen Interplay**

- By pump
- + from bath

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Part II: Oxygen and Spreading Depression
SD Model
-Adding Chloride and Volume

Osmotic Pressure:

\[ P_i = [\text{Na}^+]_i + [\text{K}^+]_i + [\text{Cl}^-]_i + A_i \]
\[ P_o = [\text{Na}^+]_o + [\text{K}^+]_o + [\text{Cl}^-]_o + A_o \]

Volume Regulation:

\[ \frac{d\text{Vol}}{dt} \sim (P_i - P_o) \]

Dreier, 2011
Nature Medicine
Dynamics for All Ions – Keep track of N

\[
\begin{align*}
\frac{dN K^+}{dt} &= \frac{1}{\tau} \left( \gamma_3 (I_K - 2 I_{pump}) - I_{diff} - I_{glia} - 2 \gamma I_{gliapump} + \beta I_{kcc2} + \beta I_{nkcc1} \right) \times Vol_o \\
\frac{dN K^+_i}{dt} &= \frac{1}{\tau} \left( -\gamma (I_K - 2 I_{pump}) - I_{kcc2} - I_{nkcc1} \right) \times Vol_i \\
\frac{dN Na^+}{dt} &= \frac{1}{\tau} \left( \gamma_3 (I_{Na} + 3 I_{pump}) + \beta I_{nkcc1} \right) \times Vol_o \\
\frac{dN Na^+_i}{dt} &= \frac{1}{\tau} \left( -\gamma (I_{Na} + 3 I_{pump}) - I_{nkcc1} \right) \times Vol_i \\
\frac{dN Cl^-}{dt} &= \frac{1}{\tau} \left( -\gamma_3 I_{Cll} + \beta I_{kcc2} + 2 \beta I_{nkcc1} \right) \times Vol_o \\
\frac{dN Cl^-_i}{dt} &= \frac{1}{\tau} \left( \gamma I_{Cll} - I_{kcc2} - 2 I_{nkcc1} \right) \times Vol_i \\
\end{align*}
\]

\[E_{Na} = 26.64 \ln \left( \frac{[Na^+]_o}{[Na^+]_i} \right)\]
\[E_{K} = 26.64 \ln \left( \frac{[K^+]_o}{[K^+]_i} \right)\]
\[E_{Cl} = 26.64 \ln \left( \frac{[Cl^-]_i}{[Cl^-]_o} \right)\]
Seizure and Spreading Depression

Wei, Ullah, Schiff, 2014 J Neuroscience
Model Variables during SD

Wei, Ullah, Schiff, 2014 J Neuroscience
Hypoxic SD

Wei, Ullah, Schiff, 2014 J Neuroscience

Czeh et al., 1993 Brain Research
Wave of Death (Zandt et al, 2011 PLOS ONE)
Increased O$_2$ Availability

$[O_2]$ Determines Duration SD

Takano et al 2007 Nat Neurosci

Wei, Ullah, Schiff, 2014 J Neuroscience
The Unification of Seizures and SD

Local potassium changes as a function of bath potassium and bath oxygen

\[
\begin{align*}
\text{Local potassium changes as a function of bath potassium and bath oxygen} \\
\text{[K^+]}_{\text{bath}} \text{ around 8 - 12 mM: bursting (Rutecki1985) and seizures (Traynelis1988)} \\
\text{[K^+]}_{\text{bath}} \text{ around 26 mM: spreading depression (Anderson 2002)}
\end{align*}
\]
Double Bifurcation Preserved with Goldman-Hodgkin-Katz current equation

\[ I_{HH} = G \times (V - E) = G \times (V - \frac{RT}{zF} \ln\left(\frac{C_o}{C_i}\right)) \]

\[ I_{GHK} = P \times \frac{z^2 F^2 V}{RT} \frac{C_i - C_o \exp\left(-\frac{zFV}{RT}\right)}{1 - \exp\left(-\frac{zFV}{RT}\right)} \]

Wei, Ullah, Schiff, 2014 J Neuroscience
Acknowledgements

Steven J. Schiff  Ghanim Ullah  Justin M. Ingram

US-German Collaborative Research in Computational Neuroscience (CRCNS)

Code Archive: https://scholarsphere.psu.edu/
Thanks for Your Attention and Any Questions?