Oxygen and seizure dynamics: II. Computational modeling

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Oxygen and seizure dynamics: II. Computational modeling. J Neurophysiol 112: 213–223, 2014. First published March 26, 2014; doi:10.1152/jn.00541.2013.—Electrophysiological recordings show intense neuronal firing during epileptic seizures leading to enhanced energy consumption. However, the relationship between oxygen metabolism and seizure patterns has not been well studied. Recent studies have developed fast and quantitative techniques to measure oxygen microdomain concentration during seizure events. In this article, we develop a biophysical model that accounts for these experimental observations. The model is an extension of the Hodgkin-Huxley formalism and includes the neuronal microenvironment dynamics of sodium, potassium, and oxygen concentrations. Our model accounts for metabolic energy consumption during and following seizure events. We can further account for the experimental observation that hypoxia can induce seizures, with seizures occurring only within a narrow range of tissue oxygen pressure. We also reproduce the interplay between excitatory and inhibitory neurons seen in experiments, accounting for the different oxygen levels observed during seizures in excitatory vs. inhibitory cell layers. Our findings offer a more comprehensive understanding of the complex interrelationship among seizures, ion dynamics, and energy metabolism.

hippocampus; hypoxia; bifurcation; epilepsy; potassium

The brain consumes 20% of the body’s metabolic energy with muscles and digestive system at rest, despite being only 2% of the human body mass (Attwell and Laughlin 2001). The majority of the brain’s metabolic energy is dedicated to supporting neural spiking activity, most of which is used by Na⁺-K⁺-ATP pumps that transport 3Na⁺ outwards with 2K⁺ inwards against their concentration gradients (Érecińska and Dagani 1990; Attwell and Laughlin 2001; Lennie 2003). Oxygen is an essential element for brain activity due to its central role in producing adenosine triphosphate (ATP). A complete lack of oxygen will result in the death of brain cells within tens of minutes (Hochachka and Guppy 1987).

The delicate balance between energy supply and expenditure becomes critically strained in pathological brain activity such as seizures and spreading depression, during which excessive O₂ demands transiently exceeded O₂ supply (Bahar et al. 2006; Galeffi et al. 2011). Although such oxygen changes with high levels of neural activity are well known, and patterns of damage to selectively vulnerable areas of the brain well characterized (such as Sommer’s sector in the hippocampus, see Aitken and Schiff 1986), the methodology to examine rapid oxygen changes at small spatiotemporal scales has only become recently available (Koo et al. 2004; Bahar et al. 2006). To improve the spatiotemporal limitations of O₂ sensing, we designed a ratiometric nano quantum dot (NQD) fluorescence resonance energy transfer (FRET) excited optical sensor to rapidly measure interstitial oxygen quantitatively from single cell microdomains to an entire hippocampal slice with high spatiotemporal resolution (Ingram et al. 2013). In a companion article (Ingram et al. 2014), we used this and related technologies to perform experiments relating seizure activity at the cellular level with simultaneous real-time oxygen microdomain measurements.

To better understand the relationship between seizures and oxygen dynamics, we here construct a biophysical model to account for experimental observations. We extend the Hodgkin-Huxley formalism by including the dynamics of Na⁺ and K⁺ ion concentrations as well as oxygen homeostasis. These ion concentrations are coupled to Na⁺-K⁺-ATP pump activity, a simplified glia-endothelium system, and diffusive transport from either the bath solution in a slice preparation, or the vasculature in the intact brain (Cressman et al. 2009; Ullah et al. 2009; Ullah and Schiff 2009 2010). We focus on oxygen consumption by Na⁺-K⁺-ATP pump activity, because most of the energy expenditure in active neurons is due to restoring ion gradients (Lennie 2003). We here demonstrate that a computational model incorporating basic features of oxygen metabolism can account for the broader spectrum of experimental observations including differential oxygen consumption between layers in the hippocampus, the delays to restore the O₂ deficit after intense activity, the mechanisms contributing to excitatory-inhibitory cell interplay, and how seizures can be supported only within a narrow range of tissue oxygen concentration (companion article, Ingram et al. 2014). Our work suggests the critical importance of modeling extracellular ion concentration and oxygen dynamics to properly understand the underlying mechanisms behind seizures and related phenomena.

MATERIALS AND METHODS

Our mathematical model builds on previous work (for review, see Schiff 2012). Instead of using constant ion concentrations, we modified the Hodgkin-Huxley formalism incorporating dynamics of sodium and potassium ion concentrations to account for the spontaneous periodic seizure events (Cressman et al. 2009; Ullah et al. 2009) observed in vitro following exposure to high extracellular [K⁺] (Traynelis and Dingledine 1988) or partial K⁺ channel blockade through 4-aminopyridine (4-AP) (Žiburkus et al. 2006, 2013). To investigate the relationship between seizures and available oxygen, we here add oxygen dynamics to the model.
Membrane potential dynamics. We used a single compartment model to represent neurons in this study to focus on the fundamentals of how oxygen and energy availability alters the fundamental dynamics of the neuronal membrane. Nevertheless, we find that such simplistic modeling accounts for several of the important features of our experiments. Our model contains transient sodium currents, delayed rectifier potassium currents, and specific leak currents for sodium, potassium, and chloride ions. The dynamics of the membrane potential, \( V \), are described with Hodgkin-Huxley equations:

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

\[
\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m
\]

\[
\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h
\]

\[
\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n
\]

where \( I_{\text{ext}} \) is the external applied current or synaptic current from other neurons and \( I_{Na} \) and \( I_K \) are the sodium and potassium currents passing through the voltage-gated ion channels including the sodium and potassium leak current, respectively. \( I_{Cl} \) is the chloride leak current. These currents can be expressed as:

\[
I_{Na} = G_{Na}m^2h(V - E_{Na}) + G_{NaL}(V - E_{Na})
\]

\[
I_K = G_Kn^4(V - E_{K}) + G_{Kl}(V - E_{K})
\]

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

where \( G \) represents conductance and the subscript \( L \) indicates the nonvoltage-sensitive leak. The activation and inactivation variables \( m, h, \) and \( n \) vary between 0 and 1 and represent the fraction of channels in the closed and open states. The parameters \( \alpha_m, \beta_m, \alpha_h, \beta_h, \alpha_n, \) and \( \beta_n \) are opening and closing rate constants of the ion channel state transitions that are dependent on \( V \). The equations of these rate constants are from a pyramidal cell model (Gloveli et al. 2005), originally derived from a model of hippocampal neurons (Traub et al. 1991), shown as follows:

\[
\alpha_m = 0.32(54 + V) / \{1 - \exp[-(V + 54)/4]\}
\]

\[
\beta_m = 0.28(V + 27) / \{\exp[(V + 27)/5] - 1\}
\]

\[
\alpha_h = 0.128\exp[-(50 + V)/18]
\]

\[
\beta_h = 4 / \{1 + \exp[-(V + 27)/5]\}
\]

\[
\alpha_n = 0.032(V + 52) / \{1 - \exp[-(V + 52)/5]\}
\]

\[
\beta_n = 0.5\exp[-(57 + V)/40].
\]

The reversal potentials of \( Na^+ \) (\( E_{Na} \)), \( K^+ \) (\( E_K \)), and \( Cl^- \) (\( E_{Cl} \)) are given by Nernst equations

\[
E_{Na} = 26.64\ln\left(\frac{[Na^+]_o}{[Na^+]_i}\right)
\]

\[
E_K = 26.64\ln\left(\frac{[K^+]_o}{[K^+]_i}\right)
\]

\[
E_{Cl} = 26.64\ln\left(\frac{[Cl^-]_o}{[Cl^-]_i}\right)
\]

where \([ \cdot ]_o\) and \([ \cdot ]_i\) represent concentrations inside and outside the cell, respectively. Unlike the Hodgkin-Huxley equations where various ion concentrations are fixed, our model adds potassium and sodium ion concentration dynamics. We do, however, assume that the chloride ion concentration is constant, with \([Cl^-]_o = 130.0 \text{ mM} \) and \([Cl^-]_i = 6.0 \text{ mM} \) (Cressman et al. 2009; Ullah et al. 2009). The units and description of all parameters used in this article are summarized in Table 1.

### Ion concentration dynamics

Each specific ion concentration is continuously updated by integrating the relevant ion currents. The extracellular potassium ion concentration, \([K^+]_o\), is a function of membrane potassium current (\(I_K\)), the neuronal \(Na^+-K^+\) pump current (\(I_{\text{pump}}\)), lateral diffusion of potassium (\(I_{\text{glu}}\)) from bath solution in vitro or blood vessel in vivo, glial uptake surrounding the neurons (\(I_{\text{gila}}\)) (Cressman et al. 2009), and glial \(Na^+-K^+\) pump current (\(I_{\text{glia}}\)) (Grisar 1984; Øyehaug et al. 2011)

\[
\frac{d[K^+]_o}{dt} = \gamma I_K - 2.0I_{\text{pump}} - I_{\text{diff}} - I_{\text{gila}} - 2.0I_{\text{glia}}
\]

where the dimensionless factor \( \gamma \) accounts for the ratio of the intracellular volume to the extracellular volume and \( \gamma = A/(F \times \text{Vol}) \) is a unit conversion factor that converts current from \( \mu \text{A/cm}^2 \) into \( \text{mM/s} \) (Cressman et al. 2009). \( A \) and \( \text{Vol} \) are the surface area and the volume of the cell with a radius of 7 \( \mu \text{m} \). \( F \) is the Faraday constant.

The intracellular sodium ion concentration, \([Na^+]_i\), is modeled based on the membrane sodium current (\(I_{Na}\)) and the \(Na^+-K^+\) pump current (\(I_{pump}\))

\[
\frac{d[Na^+]_i}{dt} = -\gamma I_{Na} - 3.0I_{\text{pump}}.
\]

We suppose that the flow of \(Na^+\) into the cell is compensated by the flow of \(K^+\) out of the cell and the total amount of sodium is conserved (Cressman et al. 2009). Thus the intracellular potassium, \([K^+]_i\), and extracellular sodium, \([Na^+]_o\), concentration dynamics are

### Overview of the parameters in the model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C)</td>
<td>1 (\mu\text{F/cm}^2)</td>
<td>Membrane capacitance</td>
</tr>
<tr>
<td>(G_{Na})</td>
<td>30 (\text{mS/cm}^2)</td>
<td>Maximal conductance of sodium current</td>
</tr>
<tr>
<td>(G_K)</td>
<td>25 (\text{mS/cm}^2)</td>
<td>Maximal conductance of potassium current</td>
</tr>
<tr>
<td>(G_{NaL})</td>
<td>0.0175 (\text{mS/cm}^2)</td>
<td>Conductance of leak sodium current</td>
</tr>
<tr>
<td>(G_{Kl})</td>
<td>0.05 (\text{mS/cm}^2)</td>
<td>Conductance of leak potassium current</td>
</tr>
<tr>
<td>(G_{Cl})</td>
<td>0.05 (\text{mS/cm}^2)</td>
<td>Conductance of leak chloride current</td>
</tr>
<tr>
<td>([Cl^-]_i)</td>
<td>130 (\text{mM})</td>
<td>Intracellular chloride concentration</td>
</tr>
<tr>
<td>([Cl^-]_o)</td>
<td>6 (\text{mM})</td>
<td>Extracellular chloride concentration</td>
</tr>
<tr>
<td>(\gamma)</td>
<td>0.0445 ((\text{mM/s})/(\mu\text{A/cm}^2))</td>
<td>Conversion factor current to concentration</td>
</tr>
<tr>
<td>(\beta)</td>
<td>7</td>
<td>Ratio of intra-/extracellular volume</td>
</tr>
<tr>
<td>(\rho_{\text{max}})</td>
<td>1.25 (\text{mM/s})</td>
<td>Maximal Na-K pump rate</td>
</tr>
<tr>
<td>(G_{\text{glia}})</td>
<td>8 (\text{mM/s})</td>
<td>Glial uptake strength of potassium</td>
</tr>
<tr>
<td>(e_k)</td>
<td>0.33 (\text{s}^{-1})</td>
<td>Potassium diffusion rate</td>
</tr>
<tr>
<td>([K^+]_{\text{bath}})</td>
<td>4.0 (\text{mM})</td>
<td>Normal bath potassium concentration</td>
</tr>
<tr>
<td>(e_o)</td>
<td>0.17 (\text{s}^{-1})</td>
<td>Oxygen diffusion rate</td>
</tr>
<tr>
<td>(\alpha)</td>
<td>5.3 (\text{g/mol})</td>
<td>Conversion factor from pump current to oxygen concentration change</td>
</tr>
<tr>
<td>(\lambda)</td>
<td>1</td>
<td>Relative cell density</td>
</tr>
<tr>
<td>([O_2]_{\text{bath}})</td>
<td>32 (\text{mg/l})</td>
<td>Normal bath oxygen concentration</td>
</tr>
</tbody>
</table>
\[
\left[ K^+ \right]_o = 140 \text{ mM} + (18 \text{ mM} - \left[ Na^+ \right]_o) \\
\left[ Na^+ \right]_o = 144 \text{ mM} - \beta (\left[ Na^+ \right]_o - 18 \text{ mM})
\] (7)

The activity of \( Na^+\)-\( K^+\)-ATP pump, largely independent of membrane potential, is modulated by \( \left[ Na^+ \right]_o, \left[ K^+ \right]_o \), and ATP (Erecińska and Dagani 1990). The \( Na^+\)-\( K^+\)-ATP pump current can be expressed as (Cressman et al. 2009)

\[
I_{\text{pump}} = \frac{\rho}{1.0 + \exp[(25 - \left[ Na^+ \right]_o)/3]} \times \frac{1.0}{1.0 + \exp(5.5 - \left[ K^+ \right]_o)}
\] (8)

where \( \rho = \rho_{\text{max}} \) is a maximal \( Na^+\)-\( K^+\)-ATP pump rate for the fully oxygenated state. The extracellular potassium is not only actively regulated by neurons but also by glial cells. Several mechanisms in the glial membrane contribute to the regulation of \( \left[ K^+ \right]_o \), such as a glial \( Na^+\)-\( K^+\)-ATP pump (Grisar 1984; Øyehaug et al. 2011), the inward rectifying \( K^+ \) channels (Øyehaug et al. 2011), and the \( Na\)-\( K\)-\( Cl \) cotransporter (Øyehaug et al. 2011). The \( Na\)-\( K\) pump strength is modified by one-third for glia in our model because the relative resting energy consumption in neurons vs. glia is \( \sim 3:1 \) (Attwell and Laughlin 2001)

\[
I_{\text{gialpump}} = \frac{1}{3} \frac{\rho}{1.0 + \exp[(25 - \left[ Na^+ \right]_o)/3]} \times \frac{1.0}{1.0 + \exp(5.5 - \left[ K^+ \right]_o)}
\] (9)

Here, we assume a fixed intracellular sodium concentration \( \left[ Na^+ \right]_i = 18 \text{ mM} \) in the glial compartment. The inward rectified \( K^+ \) current and \( Na\)-\( K\)-\( Cl \) cotransporter are modeled as a simple glial buffer system for \( \left[ K^+ \right]_o \)

\[
I_{\text{gila}} = \frac{G_{\text{gila}}}{1.0 + \exp[(18 - \left[ K^+ \right]_o)/2.5]}
\] (10)

where \( G_{\text{gila}} \) is the maximal glial buffering rate of \( \left[ K^+ \right]_o \). The diffusion of potassium from the distant perfusion bath potassium concentration \( \left( K^+ \right)_{\text{bath}} \) to the extracellular space in a slice preparation is modeled by

\[
I_{\text{diff}} = \epsilon_i (\left[ K^+ \right]_o - \left[ K^+ \right]_{\text{bath}})
\] (11)

where \( \epsilon_i \) is the potassium diffusion constant (Cressman et al. 2009).

\textbf{Oxygen concentration dynamics.} Oxygen is in such high demand in the brain in large part to support neural spiking activity. Oxygen metabolism in the neuron is used for restoring and maintaining ionic balances in soma, axon, dendrite, and synaptic sites. In our single compartment model, the oxygen consumption can be estimated by the activity of \( Na^+\)-\( K^+\)-ATP pumps that transport \( 3Na^+ \) outward with \( 2K^+ \) inward against their concentration gradients for each ATP hydrolyzed (Attwell and Laughlin 2001; Erecińska and Dagani 1990; Lennie 2003). Typically, in the aftermath of a spike \( 2.4 \times 10^9 \) molecules of ATP may be consumed, 91% of which is consumed on \( Na^+\)-\( K^+\)-ATP pumps (Lennie 2003). As neural activity increases so does oxygen and ATP utilization.

The extracellular oxygen concentration, \( \left[ O_2 \right]_o \), around a single neuron is supplied diffusively by the bath solution in in vitro experiments. Therefore, \( \left[ O_2 \right]_o \) can be modeled as:

\[
d\left[ O_2 \right]_o \over dt = -\alpha I (I_{\text{pump}} + I_{\text{gialpump}}) + \epsilon_o (\left[ O_2 \right]_{\text{bath}} - \left[ O_2 \right]_o)
\] (12)

where \( \left[ O_2 \right]_{\text{bath}} \) is the bath oxygen concentration in the perfusion solution, with a normal value at \( \sim 32 \text{ mg/l} \), when aerated with 95\% \( O_2\)-4\% \( CO_2 \) at 32–34°C. The diffusion rate \( \epsilon_o \) obtained from Fick’s law, is \( \epsilon_o = D/\Delta x^2 \). We used a diffusion coefficient \( D = 1.7 \times 10^{-5} \) \text{ cm/}^2/\text{s} for oxygen in brain tissue (Homer 1983) and \( \Delta x = 100 \mu\text{m} \) for the average distance from electrode tip to the surface of the slice. \( \lambda \) is a relative cell density, usually set to be 1. \( I \) is a conversion factor that converts charge carrier utilization (mM/s) to the rate of oxygen concentration change (mg\text{ l}^{-1}\text{ s}^{-1})

The detailed calculation of \( \alpha \) is shown as follows. When the \( Na^+\)-\( K^+\)-ATP pump current is 1 mM/s, it transports 3 mM/s \( Na^+ \) outward and 2 mM/s \( K^+ \) inward. The amount of ATP required to be hydrolyzed for this process is 1 mM/s. The pump is fueled primarily by oxidative phosphorylation, which yields up to 36 molecules of ATP from the complete oxidation of 1 glucose with 6 oxygen molecules:

\[
C_6H_{12}O_6 + 6 O_2 \rightarrow 6 CO_2 + 6 H_2O + 36 \text{ ATP}
\]

The amount of oxygen needed to generate 1 mM/s ATP is 1/6 mM/s. Since the molar mass of \( O_2 \) is 32 g/mol, the concentration of oxygen expended on 1 mM/s pump current is 5.3 mg\text{ l}^{-1}\text{ s}^{-1}. Therefore, the conversion factor \( \alpha \) between pump current (mM/s) and oxygen concentration change (mg\text{ l}^{-1}\text{ s}^{-1}) was set to 5.3 g/mol.

With oxygen dynamics in the model, we have modified the \( Na^+\)-\( K^+\)-ATP pump rate \( \rho \) in Eqs. 8 and 9 according to a sigmoid function of \( \left[ O_2 \right]_o \) (Petrusansko et al. 2007)

\[
\rho = \frac{\rho_{\text{max}}}{1 + \exp[(20 - \left[ O_2 \right]_o)/3]}
\] (13)

Both the neuronal and glial \( Na^+\)-\( K^+\)-ATP pump are modified so that they depend on the available oxygen concentration in the extracellular space. This dynamic microenvironment will be found essential to account for our experimental findings.

\textbf{Two-neuron model.} To account for the temporal interplay between excitatory pyramidal cells and inhibitory or OLM cells seen in experiments (Ziburkus et al. 2006, 2013), as well as metabolism dynamics observed in the their cell body layers stratum (sh) pyramidal and st. oriens (Ingram et al. 2014) in the hippocampus, we used the same neuron model for both cells and coupled them through synaptic interactions and potassium diffusion. Each cell has its own extracellular microenvironment, such as potassium diffusion from bath solution (\( e_k \)), glial uptake of extracellular potassium (\( G_{\text{gila}} \)), and relative cell densities (\( \lambda \)). The membrane potentials of pyramidal cell (\( V_c \)) and OLM interneuron (\( V_i \)) are modeled as

\[
\frac{dV_c}{dt} = \frac{1}{C} (I_{\text{ext},c} - I_{\text{Na},c} - I_{\text{K},c} - I_{\text{Cl},c} - I_{\text{syn},c})
\]

\[
\frac{dV_i}{dt} = \frac{1}{C} (I_{\text{ext},i} - I_{\text{Na},i} - I_{\text{K},i} - I_{\text{Cl},i} - I_{\text{syn},i})
\]

where the equations modeling inhibitory (\( I_{\text{syn},c} \)) and excitatory (\( I_{\text{syn},i} \)) synaptic inputs are adopted from Ullah and Schiff (2010) and are given as follows:

\[
I_{\text{syn},c} = G_{\text{ie}} \cdot S_{\text{ie}} \cdot \exp(-\chi_{\text{ie}}/5) \cdot (V_c - E_{\text{ie}})
\]

\[
I_{\text{syn},i} = G_{\text{ei}} \cdot S_{\text{ei}} \cdot \exp(-\chi_{\text{ei}}/5) \cdot (V_i - E_{\text{ei}})
\]

\[
\tau_{\text{ie}} = 20/(1 + \exp(-(V_i + 20)/3)) \cdot (1 - S_{\text{ie}}) - S_{\text{ie}}
\]

\[
\tau_{\text{ei}} = 20/(1 + \exp(-(V_c + 20)/3)) \cdot (1 - S_{\text{ei}}) - S_{\text{ei}}
\]

\[
\chi_{\text{ie}} = \eta_{\text{ie}} \cdot (V_i + 50) - 0.4 \cdot \chi_{\text{ie}}
\]

\[
\chi_{\text{ei}} = \eta_{\text{ei}} \cdot (V_c + 50) - 0.4 \cdot \chi_{\text{ei}}
\]

where \( \eta \) is 0.4 when \( V \) is in the range of \(-30 \text{ to } -10 \text{ mV} \). Otherwise, \( \eta = 0 \). The variable \( S_{\text{ie}} \) gives the temporal evolution of the synaptic input from the pyramidal cell to the interneuron, and \( S_{\text{ei}} \) is the synaptic
input from the interneuron to the pyramidal cell. The variables $\chi_a$ and $\chi_i$ take into account the firing interplay between pyramidal cells and interneurons (Ullah et al. 2009). The excitatory and inhibitory synaptic conductances are $G_e = 0.22 \, \text{mS/cm}^2$ and $G_i = 0.12 \, \text{mS/cm}^2$. The reversal potentials of inhibitory ($E_{i0}$) and excitatory ($E_{e0}$) synapses are $-80$ and $0 \, \text{mV}$, respectively. The time constants for the excitatory and inhibitory synapses are $\tau_e = 4$ and $\tau_i = 8$.

Pyramidal cell and OLM interneurons are also coupled with potassium diffusion. The potassium Eq. 5 for each neuron is updated by adding the following lateral diffusion terms ($I_{\text{lateral}}$):

$$I_{\text{lateral},e} = \frac{D_K}{\Delta x_{0}} ([K^{+}]_{0} - [K^{+}]_{e})$$

$$I_{\text{lateral},i} = \frac{D_K}{\Delta x_{0}} ([K^{+}]_{e} - [K^{+}]_{i})$$

where the subscript $o$ in $[K^{+}]_{o}$ and $[K^{+}]_{e}$ represents extracellular space, and the superscript $e$ and $i$ represent excitatory and inhibitory cells, respectively. The distance $\Delta x_{0}$ between two neurons is usually $30-200 \, \mu\text{m}$ (Žiburkus et al. 2006), and the potassium diffusion coefficient is $D_K = 2.5 \times 10^{-5} \, \text{cm}^2/\text{s}$ (Tuckwell and Miura 1978).

To mimic 4-AP and decreased magnesium in in vitro experimental seizures (Žiburkus et al. 2006) in the normal bath potassium solution, we reduced the voltage-gated potassium conductances $G_K$ of both cells to be $7.25 \, \text{mS/cm}^2$. We also increased the leak sodium conductance $G_N$ of pyramidal and OLM cells to be $0.0275 \, \text{mS/cm}^2$ to help represent the increased excitatory network activity under the influence of 4-AP. The different oxygen level in two layers is related to cell densities, since cells are more highly packed in the st. pyramidale layer than in the st. oriens layer, and we set the relative cell density $\lambda$ for pyramidal and OLM cells at 1 and 0.5, respectively.

**Bifurcations.** The bifurcation analysis of the neuronal model ordinary differential equations were performed using XPPAUT (Ermentrout 2002) and MATLAB (Mathworks, Natick, MA) software. We used the fourth-order Runge-Kutta method for integrating the differential equations.

**Code archive.** To facilitate dissemination of these results, the Matlab code required to reproduce the fundamental model, shown in Fig. 2 of this article, and the XPPAUT code required to reproduce the bifurcation diagram in Fig. 5 of this article are available in Supplemental Material archived with this article available online at the J Neurophysiol website.

**RESULTS**

**Oxygen dynamics during seizure-like events.** In slice preparations, network activity is typically quiescent in the absence of external input at normal $[K^{+}]_{\text{bath}} (\sim 4 \, \text{mM})$, while burst firing (Rutecki et al. 1985) and seizure-like events (Traynelis and Dingledine 1988) occur spontaneously and periodically at higher $[K^{+}]_{\text{bath}}$ concentrations (8.5 mM) in the CA1 region. In our model, we set $[K^{+}]_{\text{bath}}$ at 8.5 mM to generate periodic and spontaneous seizures (Fig. 1B) similar to experimental seizures in the slices (Traynelis and Dingledine 1988). Seizure events are accompanied by large amplitude oscillations of $[K^{+}]_o$ (Fig. 1B, bottom trace).

During seizures, a variety of voltage gated channels are activated resulting in substantial ion flux across the neuronal membrane. Energy (ATP) and $O_2$ are required to restore ionic gradients (as well as neurotransmitter release and recycling, not modeled here). We show experimental voltage and oxygen data from a seizure event of a typical single cell (Fig. 2, A and B, and data from Ingram et al. 2013) and the model (Fig. 2C) for comparison. The membrane potential and oxygen concen-

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**Fig. 1.** Periodic and spontaneous periodic seizures in the CA1 region at 8.5 mM potassium in the perfusate [reproduced with permission from Traynelis and Dingledine 1988]. B: in the model, membrane potential and local extracellular potassium concentration, $[K^{+}]_o$, shows periodic seizures occur with similarly elevated 8.5 mM bath potassium.
increases the extracellular $[K^{+}]_{o}$. At the beginning of a seizure, a sudden burst of neuronal firing decreases. All of these factors contribute to account for a substantial decrease in extracellular local $[O_2]_{o}$ during seizure events when the pumps work harder to replenish the oxygen deficit by diffusion from bath solution during and after a seizure event. The time course of $O_2$ deficit is similar to that observed experimentally.

Seizure-like events driven by hypoxia. With hypoxia occurring during seizure events, we investigated whether brief hypoxic periods can increase cell firing and push an excitable cell into a seizure state with a normal bath potassium concentration (see companion article, Ingram et al. 2014). In experiments, the slices are in a slightly hyperexcitable state by partially lowering Mg$^{2+}$ and Ca$^{2+}$ in the recording chamber perfused with normal oxygen ($\sim$32 mg/l). Lowering divalent cation concentrations tends to make neurons more excitable by changing intrinsic electrical properties through decreased charge screening (Frankenhaeuser and Hodgkin 1957) and decreasing the Mg$^{2+}$ blockade of NMDA channels (Dingledine et al. 1999). The chamber oxygen concentration was then decreased by switching from perfusate aerated with 95% $O_2$-5% $CO_2$ to one aerated with 95% $N_2$-5% $CO_2$ and then increased back to 95% $O_2$-5% $CO_2$. Seizure events were observed to occur experimentally only during a narrow range of bath oxygen pressure (Fig. 3A, gray region, and data from companion article, Ingram et al. 2014).

In our model, we injected a small amount of external positive current ($I_{ext} = 0.5 \mu A/cm^2$) into the neuron to mimic a slightly cellular excitable state with a normal bath potassium concentration (no divalent cation effects are in this model). The neuron was tonically firing but not in a seizure state with normal bath oxygen pressure (32 mg/l in experiments) as shown in Figs. 3B and Fig. 4B, which slightly elevated $[K^{+}]_{o}$ outside the seizure oscillation region. As we decreased $[O_2]_{bath}$, local available $[O_2]_{o}$ decreased, which decreased the maximal neuronal and glial Na$^{+}$-K$^{+}$-ATP pump strength, leading to
higher extracellular $[K^+]_o$ thus initiating seizures. In the model, we observed that hypoxia can induce large slow $[K^+]_o$ oscillations with a concentration range seen in periodic seizure-like events, which occurred within a narrow range of bath oxygen pressure as shown in Fig. 3B. The seizure-permissive $[O_2]_{bath}$ band was generally 24–29 mg/l in the model and slightly higher at 27–31 mg/l in experiments.

Under conditions of mild hypoxia, singlet spiking can become multistable, a dynamical bifurcation. Figure 4A shows the minimum and maximum of local potassium $[K^+]_o$ as a function of $[O_2]_{bath}$ in a hyperexcitable neuron ($I_{ext} = 0.5 \mu A/cm^2$) with $[K^+]_{bath} = 4.0 \text{ mM}$. Inset: small fast local $[K^+]_o$ oscillation during tonic firings. The calibration bars are 0.05 s (horizontal) and 0.05 mM (vertical). Membrane potential traces for the 3 regions of bifurcation diagram when $[O_2]_{bath}$ is reduced, oxidative metabolism becomes limited, resulting in a significant decline in ATP generation and a reduction of pump strength. When the pump cannot work fast enough to restore ion gradients, a region of large slow potassium $[K^+]_o$ oscillations appear forming a foundation for spontaneous seizures (Fig. 4C). When $[O_2]_{bath}$ decreases further, the neuron goes to a quiescent resting steady state as shown in Fig. 4D. In this hypoxic region, the pump is too weak to restore the sodium gradient, resulting in the inactivation of the neuron seen in anoxia. A further decrease in available $[O_2]_{bath}$ leads to a terminal “wave of death” (Zandt et al. 2011).

Bifurcation analysis. To further understand the relationship between oxygen and seizures, we performed a formal analysis of these dynamical bifurcations as a function of $[K^+]_o$ and $[Na^+]_i$. We set $[K^+]_o$ and $[Na^+]_i$ to fixed values for the following analysis. Figure 5A shows a bifurcation diagram of membrane potential $V$ by varying $[K^+]_o$ while holding $[Na^+]_i$ at 18 mM. We observed two of the common bifurcation mechanisms known to occur in such a neuronal model: the Hopf bifurcation (HB) and the saddle-node bifurcation (SN) (Barreto and Cress-...
seizures are related to mild hypoxia, while spreading depression is related to more severe hypoxia (Aitken et al. 1991; Bahar et al. 2000) and the mixture state of seizure and spreading depression seen in hypoxia (Czéh et al. 1993). The pattern from the red trace is also seen experimentally in OLM cells and occasionally pyramidal cells during seizures when they go into transient depolarization block (Žiburkus et al. 2006, 2013). Decreasing \([O_2]_{\text{bath}}\) further \((O_2)_{\text{bath}} = 10 \text{ mg/l},\) the blue dot in Fig. 6A is a quiescent steady-state point following a single spreading depression event. At a low oxygen concentration, the pump activity to restore ion gradients is limited, and the neuron remains inactivated.

We also studied the effect of oxygen diffusion constant \(e_x\) and relative cell density \(\lambda\) on neuron behavior, with normal oxygen bath concentration \((O_2)_{\text{bath}} = 32 \text{ mg/l}\). When the depth from the surface of the slice increases, the effective diffusion constant \(e_x\) decreases (see Oxygen concentration dynamics). We chose \(e_x = 0.68, 0.17, \) and \(0.0756 \text{ Hz, corresponding to the depth from the surface of the slice at } \Delta x = 50, 100, \) and \(150 \mu\text{m},\) respectively (Fig. 6B). As the depth from the surface increases, the interseizure intervals increase, because it takes more time to recover oxygen in deeper layer after seizures. Since the cell density is different in pyramidal cell body and oriens layers, we can change the value of relative cell density \(\lambda\) in the model. The highly packed pyramidal cell layer consumes more oxygen than the lower cell density in the oriens layer for comparable spiking rates and more easily induces seizure-like events (Fig. 6C). The interseizure interval gets longer as we lower \(e_x\) or increase \(\lambda\) because it takes more time to restore ion gradients with less available oxygen. Therefore, although neuron behavior (resting, spiking, bursting/seizure, spreading depression, or depolarization block) is mainly dependent on bath potassium concentration, oxygen, and tissue architecture substantially modify the resulting neuronal dynamics.

Interplay between pyramidal cell and inhibitory interneuron. Previous experiments reported a strongly interdependent pattern between excitatory pyramidal cells and OLM interneurons during spontaneously seizures in the hippocampus (Žiburkus et al. 2006, 2013). We probed oxygen dynamics around individual cell types in both st. pyramidale and st. oriens layers to see the metabolic energy demands during seizure events. Experimentally, we found that although OLM interneurons typically fire at higher rates than pyramidal cells, the maximal oxygen reduction was observed in the densely

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**Fig. 5.** Bifurcation analysis with fixed ion concentrations. A: bifurcation diagrams of membrane potential \(V\) with \([K^+]_o\) as a parameter for fixed intracellular \(Na^+\) concentration \([(Na^+]_i) = 18 \text{ mM}.\) Stable and unstable steady states are depicted as black and red lines, respectively. Stable limit cycles are depicted as green lines. Transition between stable and unstable attractors occurred at saddle-node bifurcation (SN) and Hopf bifurcation (HB) points. B: 2-parameter bifurcation diagram describes neuronal asymptotic behaviors to different fixed values of \([K^+]_o\) and \([Na^+]_i\). SN and HB lines indicate bifurcation curves corresponding to transitions between resting state and spiking state and between spiking state and depolarization block (DB) state, respectively.
packed cell body layer of CA1 st. pyramidale as shown in the companion article (Ingram et al. 2014).

In the model, pyramidal cells and OLM interneurons (Fig. 7A) share the same potassium bath concentration but have different local architecture and independent microenvironments, such as glial buffering of potassium and potassium diffusion rate. To study the parameter space of the ratio of $G_{\text{glia}}$ and $k_0$ (calculated as OLM/pyramidal) where the model exhibits firing interplay, we fixed the parameters of the pyramidal cell as in Table 1 and varied the parameters surrounding the OLM interneuron. The region between two lines shows that the region for alternating interplay within the parameter space is robust (Fig. 7B). Figure 7C shows a typical two neuron interplay example. OLM interneurons are more active at ictal onset, followed by a period of depolarization block when pyramidal cells exhibited runaway excitation as in Žiburkus et al. (2006, 2013). Our model also reproduces the different $[O_2]_o$ levels that we have observed in st. pyramidale and st. oriens layers during seizures (companion article, Ingram et al. 2014) by reflecting in the model that cells in the pyramidal layer, and therefore their Na-K-ATP pumps, are more densely packed than in oriens layer. This leads to more intense hypoxia in the pyramidal layer but preserves a higher level of $[O_2]_o$, and thus a higher energy charge (Atkinson 1968) in the oriens layer that is needed to recover inhibitory control (Fig. 7C). Although the interplay between pyramidal cell and inhibitory OLM interneuron shows they fire alternatively, local available oxygen increases and decreases simultaneously. This is a manifestation that oxygen consumption is not directly coupled to firing rates, which dissipate stored energy, but rather is directly related to restoring ion gradients. Because ion gradients reach their maximum collapse during depolarization block, energy requirements are highest at the peak of excitatory runaway excitation when inhibitory neurons may be in depolarization block. The model illustrates and offers an explanation for this
DISCUSSION

In this study, we constructed a computational model that incorporates sodium and potassium ion concentration dynamics as well as oxygen homeostasis to account for experimental observations. Our findings help elucidate the mechanisms of seizure development and termination as well as the interaction between seizure and energy metabolism. During neural activities, the greatest energy requirement is consumed in restoring ion gradients following action and synaptic potential activity, while neurotransmitter release and recycling are also demanding (Lennie 2003). Although we mainly consider the energy consumed by Na\textsuperscript{+}-K\textsuperscript{+}-ATP activity, the model reflects sufficient dynamics of oxygen metabolism to account for several experimental observations of the interrelationship between oxygen and seizures.

First, we observe prolonged oxygen depletion during and after high rates of neural activity such as seizure events. High levels of neural activity initiate extracellular K\textsuperscript{+} and intracellular Na\textsuperscript{+} accumulation, which increases the activation of the Na\textsuperscript{+}-K\textsuperscript{+}-ATP pump. The pump consumes ATP, leading to increased oxygen consumption, which decreases local tissue [O\textsubscript{2}] and impairs the ability of a cell to reestablish its ionic gradients in a positive feedback loop that leads cells first to increased excitability and then to reduced activity and potentially depolarization block. This basic finding is consistent with previous studies linking an increase in oxygen consumption with a concomitant rise in the extracellular potassium concentration (Erecińska and Dagani 1990). Our model further demonstrates the relatively long time scale of restoring cellular ionic gradients following intense seizure activity, which introduces an effective refractory period on such events seen in model, experiments, and clinical seizures.

Second, we have shown that hypoxia can drive a neuron into seizure states with a normal bath potassium concentration. This

Fig. 7. Interplay between pyramidal cell and inhibitory interneuron. A: structure of the hippocampal CA1 2-neuron model. The cell body of pyramidal cell (P, black) in stratum (st.) pyramidal layer and the cell body of oriens lacunosum moleculare (OLM; O, red) interneuron in the st. oriens layer. B: region for the alternating interplay in firing between 2-neuron model. When the ratio of G\textsubscript{glia} and OLM, calculated as OLM/pyramidal, are in the region bounded by the 2 lines, the 2 cells exhibit firing interplay. The ratios are calculated when the parameters of the pyramidal cell are fixed as in Table 1. An example of the interplay in the region of the square is shown in C. In C, the dual-layer model shows a nearly identical electrical and [O\textsubscript{2}] interplay as seen experimentally (Žiburkus et al. 2006, 2013, Ingram et al. 2014, companion article). When the OLM cell (Vo, red) goes into depolarization block the pyramidal cell (Ve, black) is released and exhibits runaway excitation behavior until the OLM cell resumes firing. Extracellular potassium concentrations of pyramidal cell (black) and OLM cell (red) are elevated during seizure events. Even though the OLM cell fires more than the pyramidal cell, local oxygen concentration around cell body in st. pyramidal (black) is lower than in st. oriens layer (red), which is due to the higher packing density of pyramidal cells. Note, importantly, that the maximal O\textsubscript{2} consumption occurs during depolarization block in the model, consistent with experimental observations, reflecting maximal stimulation of Na-K pump under conditions of maximal gradient collapse.
behavior occurs within a narrow range of oxygen concentration, which is consistent with experimental observations (companion article, Ingram et al. 2014). Our findings show that neurons are more likely to go into periodic seizures when the Na\(^{+}\)-K\(^{+}\) pump rate is reduced as overall oxygen availability to the neurons is reduced, consistent with the observations in Grisar (1984) that the activity of the Na\(^{+}\)-K\(^{+}\) pump may be reduced in human epilepsy patients. Our findings are also consistent with the early work of Foerster and Penfield (1930), who described how seizures could be reliably produced in scarred posttraumatic brain by gently pulling on the attached dura producing mild transient vascular compromise.

Third, we performed a detailed dynamical bifurcation analysis of the model. Since our model consists of a fast (neuron model) and a slow (ion concentration) subsystem, it is difficult to pinpoint the exact mechanism underlying the complex oscillatory behavior using the full model. Cressman et al. (2009) performed a bifurcation analysis with a simplified reduced model and showed that pump rate strength can be a bifurcation parameter that changes the model from steady state to oscillatory burst firing and seizures. Here we extended these results to oxygen driven bifurcations (Barreto and Cressman 2011; Krishnan and Bazhenov 2011; Øyehaug et al. 2011). By characterizing the trajectories of ion concentration from the full model in a phase plane where each point reflects dynamics solved from fixed ion concentrations, we can gain insight into the transition of rest, spiking and depolarization block state. We studied how oxygen parameters, such as bath oxygen concentration [O\(_2\)]\(_{\text{bath}}\), oxygen diffusion constant \(D_o\), and relative cell density \(\lambda\), change the seizure behavior of oscillatory ion concentrations. As [O\(_2\)]\(_{\text{bath}}\) decreases, the neuron can cycle from seizure to hypoxic spreading depression-like events and finally into quiescence. Less oxygen pressure in the tissue increases extracellular potassium concentration in vitro (Schiff and Somjen 1987). Although the local oxygen concentration is asymptotically dominated by oxygen bath concentration, the depth from the surface of slices in vitro or distance from the vasculature in vivo, and relative cell density, also change network behavior. When the distance from tissue surface is increased, or when cell density is higher, the cells have longer interseizure intervals because it takes longer to restore ion gradients with less oxygen available. Similarly, the cells would more readily transition into spreading depression in deeper layers since less oxygen is available. At the lowest levels of oxygen availability, cell ionic gradients will not be maintained and quiescence ensues.

Lastly, our model can accurately describe the cellular interplay as well as differential oxygen levels between pyramidal cells and OLM interneurons during seizure-like events in the same manner as seen in experiments (Žiburkus et al. 2006, 2013; companion article, Ingram et al. 2014). The most robust alternating firing interplay can be seen when \(\varepsilon_k\) surrounding OLM interneurons is lower than around pyramidal cells. This may be physically manifest by perineuronal nets of extracellular matrix ensheathing interneurons (Morris and Henderson 2000). Regarding differential oxygen levels, the simplest explanation is that the more densely packed CA1 pyramidal neurons contribute to the greatest change in ionic distribution and subsequently the greatest reduction in [O\(_2\)]\(_{\text{i}}\).

In this article, we demonstrated three biophysical routes to induce seizure-like events: high potassium, low oxygen, and 4-AP. By making the Na\(^{+}\)-K\(^{+}\)-ATP pump \(O_2\) dependent, our model accounts for several prominent features of experimental seizures. Oxygen concentration does not merely decrease as a result of intense neuronal activity during seizures, but differential [O\(_2\)]\(_{\text{i}}\) changes within layers and about specific neuronal types can help sculpt and orchestrate the neuronal spatiotemporal interplay seen in seizure patterns. Seizure foci in epileptic patients can be complex in structure, and oxygen availability is likely an important factor that can contribute to seizure initiation and dynamics. Our work also demonstrates that the complex relationship between seizure and spreading depression may be considerably simplified using a framework in which oxygen dynamics are taken into account.

In future work, it is important to include the cell volume in the model. Cell swelling during seizure or spreading depression would restrict the extracellular space and further restrict the diffusion of ions or oxygen. For simplicity, we did not model full dynamics of intracellular and extracellular Na\(^{+}\), K\(^{+}\), and Cl\(^{-}\), but more complete accounting for these analytes is required when volume is introduced. When modeling oxygen dynamics in vivo, we should take blood flow and pressure into consideration. We used deterministic models to seek an underlying bifurcation structure to account for experimental observations. Nevertheless, incorporating stochastic dynamics into such models to better reflect such effects in vivo will complicate this simple dynamical picture we have presented. To achieve simplicity, we also incorporated single compartment neuronal models. Although such simple models were successful in capturing some of the fundamental dynamics seen in a variety of experimental findings, a more accurate representation of the spatial structure of neurons with multicompartment models, and with larger ensembles of neurons embedded within more realistic tissue, will be important to better characterize the influence of oxygen on neuronal network dynamics. Such dynamics will, of course, be applicable to a broader range of phenomena than seizures.

Our findings confirm the critical need for including oxygen dynamics in our efforts to better understand the fundamental biophysical mechanisms that underlie patterns of normal or pathological neuronal activity.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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