Ion Concentration Dynamics as a Mechanism for Neuronal Bursting

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We describe a simple conductance-based model neuron that includes intra- and extra-cellular ion concentration dynamics and show that this model exhibits periodic bursting. The bursting arises as the fast spiking behavior of the neuron is modulated by the slow oscillatory behavior in the ion concentration variables, and vice versa. By separating these time scales and studying the bifurcation structure of the neuron, we catalog several qualitatively different bursting profiles that are strikingly similar to those seen in experimental preparations. Our work suggests that ion concentration dynamics may play an important role in modulating neuronal excitability in real biological systems.

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I. INTRODUCTION

The Hodgkin-Huxley equations [1] are of fundamental importance in theoretical neuroscience. These equations assume that the intra- and extra-cellular ion concentrations of sodium and potassium are constant. While this may be a reasonable assumption for the squid giant axon preparation (for which the equations were originally developed), its validity in other cases is not clear. In the mammalian brain, for example, the neurons are much smaller and are more tightly packed, resulting in significantly smaller intra- and extra-cellular volumes. Thus, typical ionic currents can have a much larger effect on the ion concentrations in this case.

The effects of extracellular potassium ([K]o) accumulation on neuronal excitability have long been recognized [2,3], and deficiencies in [K]o regulation have been implicated in various types of epilepsy (for a review, see [6]) and spreading depression [7,8]. More recently, computational studies have begun to clarify the role of impaired [K]o regulation [9-12] as well as other varying ion concentrations [13,14].

In this work, we consider from a dynamical systems perspective the role of ion concentration dynamics in the generation of periodic bursting behavior. To emphasize the generality of our approach, we base our model on the standard Hodgkin-Huxley equations. We augment these with additional equations that describe the dynamics of both intra- and extra-cellular sodium and potassium. The inclusion of sodium is relatively novel and plays a crucial role in the dynamics described here. We also include terms describing pumps, extracellular diffusion, and a simple glial buffering system. A different analysis of this system was presented in [15].

II. MODEL

We begin by explicitly adopting the standard convention that an outward membrane current is defined as being positive [16]. Thus, the membrane potential V is given by

$$\frac{dV}{dt} = -I_{\text{membrane}}$$  (1)

where $I_{\text{membrane}}$ represents the sum of the various membrane currents. We aim in this work to consider a very simple and general model neuron. Hence we include only the standard Hodgkin-Huxley sodium current (with instantaneous activation), the delayed-rectifier potassium current, and leak current. We write the latter in terms of separate sodium, potassium, and chloride contributions [10]. Thus,

$$I_{\text{membrane}} = I_Na + I_K + I_{Cl}$$

$$I_{Na} = g_{Na}(m_{\infty}(V - E_{Na}) + g_{Na}L(V - E_{Na}))$$

$$I_{K} = g_{K}n^4(V - E_{K}) + g_{KL}(V - E_{K})$$

$$I_{Cl} = g_{Cl}(V - E_{Cl})$$

where the $g_i$ (i = Na, K, Cl) are maximum conductances. Time is measured in milliseconds, voltage in millivolts, and $C, I, I$ and $g$ are measured in units per unit of membrane area, i.e., $\mu F/cm^2$, $\mu A/cm^2$, and $mS/cm^2$, respectively. The reversal potentials $E_i$ are given in terms of the instantaneous intra- and extracellular ion concentrations by Nernst equations:

$$E_{Na} = 26.64 \ln \left(\frac{[Na]^i}{[Na]^o}\right)$$

$$E_{K} = 26.64 \ln \left(\frac{[K]^i}{[K]^o}\right)$$

We fix $E_{Cl} = -81.9386$ mV.

The extracellular potassium and intracellular sodium concentration dynamics are given by

$$\tau \frac{d[K]}{dt} = \gamma \beta I_K - 2\beta I_{\text{pump}} - \dot{I}_{\text{glia}} - \dot{I}_{\text{diffusion}}$$

$$\tau \frac{d[Na]}{dt} = -\gamma I_{Na} - 3I_{\text{pump}},$$

$$\tau = \tau$$

These equations describe the dynamics of the extracellular potassium and intracellular sodium concentrations, taking into account the effects of ion pumps, glial cells, and extracellular diffusion.

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where the concentrations are measured in millimolar (mM). \( \gamma = 4.45 \times 10^{-2} \) is a unit conversion factor that converts the membrane currents into mM/sec (see Appendix), and \( \beta = 7 \) is the ratio of the intracellular to extracellular volume [17]. The terms with tildes are the molar currents (mM/sec) given below, and \( \tau = 10^3 \) balances the time units.

The pump, glia, and diffusion molar currents are given by

\[
\begin{align*}
\tilde{I}_{\text{pump}} &= \rho \left( 1 + \exp \left( \frac{25-\left[Na_i\right]}{3} \right) \right)^{-1} \left( \frac{1}{1+\exp(5.5-\left[K_o\right])} \right), \\
\tilde{I}_{\text{glia}} &= G \left( 1 + \exp \left( \frac{18-\left[K_o\right]}{2.5} \right) \right)^{-1} \\
\tilde{I}_{\text{diffusion}} &= \varepsilon (\left[K\right]_o - k_{\text{bath}}).
\end{align*}
\]  

We set the default parameter values to \( \rho = 1.25 \text{ mM/sec} \), \( G = 66.666 \text{ mM/sec} \), and \( \varepsilon = 1.333 \text{ Hz} \). \( k_{\text{bath}} \) represents the potassium concentration in the reservoir, i.e., the bathing solution for a slice preparation, or the vasculature in vivo. We set \( k_{\text{bath}} = 4 \text{ mM} \) for normal physiological conditions.

The intracellular potassium and extracellular sodium concentrations are obtained from the following simplifying assumptions that allow us to reduce the dimensionality of the system [18]:

\[
\begin{align*}
\left[K\right]_i &= 140\text{mM} + (18\text{mM} - \left[Na_i\right]), \\
\left[Na\right]_o &= 144\text{mM} - \beta (\left[Na_i\right] - 18\text{mM}).
\end{align*}
\]  

The first assumption is that the sodium membrane current is the dominant means by which sodium is transported across the membrane, and that during the course of an action potential, the transport of sodium and potassium are simply related. The second assumption is that the total amount of sodium is conserved.

The remaining parameters and the equations for the gating variables are given in the Appendix.

III. RESULTS

A. Fixed ion concentrations

We begin with a discussion of the dynamical structure of our model subject to constant values of the ion concentrations. That is, we set \( \left[K\right]_o \) and \( \left[Na\right]_i \) to fixed predetermined values, and obtain the remaining concentrations using Equations (6). We then examine the behavior of the neuron as given by Equations (1) – (3).

Figure 4 shows bifurcation diagrams obtained under these conditions. The features in these diagrams clarify the neuron’s bursting behavior as the ion concentrations undergo slow oscillations, as explained below.

Figure 4A is constructed by holding \( \left[Na\right]_i \) fixed at 10mM and plotting the asymptotic values of the membrane potential \( V \) versus several fixed values of \( \left[K\right]_o \). Below approximately 5.7mM, the neuron is attracted to a stable equilibrium (shown as a solid line) that corresponds to the resting state. At approximately \( \left[K\right]_o = 5.7\text{mM} \), this equilibrium coalesces with a coexisting unstable equilibrium (dotted line) in a saddle-node bifurcation that occurs on an invariant closed curve (of infinite period) that appears simultaneously. This scenario is known as a SNIC bifurcation [4]. Beyond this, for values of \( \left[K\right]_o \) between 5.7mM and 35.2mM, a stable limit cycle appears, reflecting regular spiking in the neuron. This is depicted in the diagram by filled circles that mark the maximum and minimum values of the membrane voltage during a cycle. For increasing values of \( \left[K\right]_o \) approaching \( \left[K\right]_o = 35.2\text{mM} \) from below, the amplitude of this periodic orbit decreases and the orbit eventually merges...
with the coexisting unstable equilibrium in a supercritical Hopf bifurcation. For \([K]_0 > 35.2\text{mM}\), a stable equilibrium is found – this is the state of depolarization block \(22\).

Figure 1B is a two-dimensional bifurcation diagram which shows the location of the SNIC and Hopf bifurcations as the value of \([Na]_0\) is varied. These curves delineate the boundaries of different attracting behaviors of the neuron. To the left of the SNIC curve, the neuron is attracted to the resting equilibrium. Between the SNIC and the Hopf curves, the neuron exhibits regular spiking, and to the right of the Hopf curve, the neuron is attracted to the depolarization block equilibrium. (The detailed structure at the top of this diagram is discussed below.)

### B. Dynamic ion concentrations

We now describe the behavior of the full system, in which the ion concentrations are allowed to evolve dynamically. In Figure 2 we plot the asymptotic behavior of the ion concentrations for several values of \(k_{bath}\). Also included in the figure is a portion of the SNIC curve from Figure 1B.

At the default parameter values described above (with \(k_{bath} = 4.0\text{mM}\)), the entire system approaches a stable equilibrium resting state for which the membrane voltage and the ion concentrations assume fixed values. As \(k_{bath}\) is increased, these equilibrium values change and sweep out the solid curve shown on the left of Figure 2. At approximately \(k_{bath} = 7.615\text{mM}\), this curve collides with the SNIC boundary. Just beyond this value, the system jumps to a limit cycle. As \(k_{bath}\) continues to increase, the projection of this limit cycle onto the ion concentration variables drifts upward and to the right, as shown in the figure. Henceforth, for brevity, we refer to such limit cycle projections as “loops”.

Note that these large-amplitude loops straddle the SNIC curve. In addition, they have periods on the order of several tens of seconds. Consequently, as the system alternately transitions between the resting and the spiking regions, there is ample time to exhibit those asymptotic behaviors. That is, the neuron bursts. For example, for \(k_{bath} = 8.0\text{mM}\), the ion concentrations are attracted to the second (red) loop in Figure 2 and the corresponding behavior of the membrane voltage is shown below in Figure 4A.

At approximately \(k_{bath} = 9.0\text{mM}\), the large-amplitude loop disappears. For larger \(k_{bath}\), the ion concentrations exhibit very small-amplitude loops, as shown in the inset of Figure 2. Since this loop lies entirely within the spiking region, the neuron exhibits tonic spiking. Indeed, the loop itself represents the small changes in the ion concentrations due to individual action potentials.

We note in passing that we have observed multistability \(23, 25\). For values of \(k_{bath}\) approximately in the interval (8.8, 9.0) mM, a bursting solution coexists with a tonically-spiking state for the same parameter values. This is consistent with the analysis based on a reduced model in \(18\).

### C. Catalog of bursting types

The results presented above demonstrate that for parameter values in appropriately chosen ranges, the system evolves on a limit cycle whose projection onto the ion concentration variables forms a loop that straddles the SNIC curve, and the neuron bursts. Bursting behaviors of various qualitatively different kinds can be exhibited by the system if similar ion concentration loops straddle the bifurcation curves of Figure 1B in different ways. Accordingly, we can catalog all the possible arrangements, and examine the nature of the resulting bursting patterns.

Figure 3 shows four different ion concentration loops labeled A, B, C, and D. Loop A is the \(k_{bath} = 8.0\text{mM}\) loop discussed above, and the corresponding membrane voltage trace is shown in Figure 4A. Loop B (\(G = 20, \epsilon = 0.133\), and \(k_{bath} = 22\)) straddles both the SNIC and the Hopf bifurcation curves, and hence displays a qualitatively different bursting pattern. As the loop is traversed, the ion concentration trajectory moves from the rest-
continued to the upper right and forms a cusp with another
moclinic bifurcations (HC). The saddle-node branch con-
tinues up from the lower left corner, a codimension-
order. The loops are traversed in a counter-clockwise manner.
The dotted and solid lines are the SNIC and Hopf bifurcation
curves, respectively.

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Figure 3 shows a magnification of the upper part of
loop D from Figure 4 which represents the termination of
the burst event. With the increased magnification, it can be
seen that this portion of the ion concentration limit cycle
indeed does not cross the Hopf curve. Instead, it crosses
the two saddle-node curves. To clarify the nature of the
burst termination, we show in the left panel of Figure
(b) the one-dimensional bifurcation diagram analogous to Figure 4A for $[Na]_i = 37.2$ mM, along with the burst termination portion of the system’s trajectory. Also included is an inset showing the membrane voltage
versus time for one complete burst event. It can be seen
that the termination (arrows) occurs when the trajectory
tracking the upper stable equilibrium branch encounters
the second saddle-node bifurcation and drops to the lower
stable equilibrium branch.

The additional detail in Figure 5 permits the identi-
fication of a fifth type of bursting pattern exhibited by
our system (obtained with $\rho = 0.9$, $G = 10$, $\epsilon = 0.5$, $k_{bath} = 20$, and $\gamma = 0.25$). E labels the upper portion of
an ion concentration loop that is slightly lower than the D
loop. It can be seen that this portion of loop E crosses, in
order, the Hopf, saddle-node, and homoclinic bifurcation
curves. The remaining portion of loop E (not shown)
is similar to loop B, and indeed the membrane voltage
traces are similar, but the termination mechanisms are
different. Notably, this type of burst terminates after
a few small-amplitude spikes via homoclinic rather than
SNIC bifurcation; see Figure 6E.

Finally, we note that we have also identified parameter
sets that give rise to loops that encircle the BT point in
Figure 5 while lying entirely above the SL point, as well
as similar loops occurring upward and to the right of
this, including ones that straddle only the two SN curves.
However, the separation of time scales is less clear in
these cases. And although it might exist, we were not
able to find a loop that crosses the SNIC and Hopf curves
and then returns above the saddle-node cusp. Such a
loop would exhibit a burst termination that transitions
from depolarization block to the rest state smoothly and
without a sudden drop in membrane potential.

IV. DISCUSSION

In this paper, we have presented a simple model of
a single neuron with dynamic intra- and extra-cellular
sodium and potassium concentrations that exhibits pe-
riodic bursting behavior. Our goal has been to present
a catalog of the wide variety of qualitatively different
bursting patterns exhibited by this model based on an
understanding of the underlying bifurcation structure.

FIG. 3: (Color) Loops A-D represent the time evolution of the
ion concentrations as the system exhibits limit cycle behav-
ior. The loops are traversed in a counter-clockwise manner.
The dotted and solid lines are the SNIC and Hopf bifurcation
curves, respectively.
FIG. 4: Four qualitatively different bursting patterns corresponding to the four loops shown in Figure 3. In the lower panels, solid curves represent $[K_o]$ (left vertical axes), and dotted curves represent $[Na_i]$ (right vertical axes). The event in (D) recurs with a period of approximately 16.5 seconds, but for clarity, only a portion of one such event is shown.

To do this, we have taken advantage of the large separation of time scales inherent in the model: that of spikes, which occur on the order of milliseconds, and that of the bursting events, which occur on the order of tens of seconds. We have focused attention on the nature of the fast spiking dynamics by freezing the slow ion concentration variables and identifying the asymptotic behavior of the neuron under these conditions. This clarifies how oscillations in the slow variables modulate the neuron’s excitability and give rise to bursting.

A crucial aspect of our model that is typically not present in comparably simple models (to our knowledge) is the inclusion of sodium concentration dynamics. Thus, we have two slow variables ($[Na_i]$ and $[K_o]$) instead of one, and it is therefore possible for the slow system to undergo bifurcations to oscillatory states. Analysis complementary to the work presented here, in which bifurcations in the slow dynamics are analyzed by removing the fast dynamics via averaging, has been presented in [18].

For this study, we deliberately chose a single neuron with the classic Hodgkin-Huxley ionic currents in order to focus attention on the role of the ion concentration dynamics. Consequently, some quantitative aspects of the dynamics (e.g., the value of $[K_o]$ for the onset of depolarization block in Figure 4A) are not directly applicable to mammalian systems. More realistic models of mammalian systems would require additional currents and a network structure with significant synaptic activity. (For example, despite the intriguing similarity of Figure 4D to phenomena observed in spreading depression, it is known that spreading depression requires persistent sodium channels [17].) In addition, the absence of synaptic background activity means that our model neuron transitions abruptly from rest directly to bursting as
$[K]_o$ increases. In a more realistic setting, we would expect to see an intervening regime of tonic spiking due to network effects before the onset of bursting.

Although our approach has concentrated on identifying all possible bursting scenarios without regard to physiological relevance, we note that bursting morphologies similar to those that we catalog here have been observed in experimental models of epilepsy, including a high-potassium model [28], a high-potassium, low-calcium model [22], and a low-magnesium 4-aminopyridine model [29]. This suggests that despite the obvious limitations of our model, it is capturing aspects of the essential dynamics in these experiments. And, although there has been debate about whether a single neuron can undergo a “seizure” [12, 30], our single-neuron results suggest that ion concentration dynamics may well play an important role in epilepsy.

It is interesting to note that in order to obtain our type D burst, in which the burst termination transitions smoothly from depolarization block back to rest without exhibiting spikes (Figure 4D), we found it necessary to increase the parameter $\gamma$, which is inversely proportional to the volume of our assumed spherical cell (see the Appendix). With a smaller volume, the internal sodium concentration is more easily increased to sufficient levels to prevent spiking. Thus, our model predicts that this type of burst should be most easily observed in smaller neurons. Accordingly, this behavior has been seen in hippocampal interneurons (e.g., Figure 4a of [29]). Similar behavior in other cases, however, may well be due to different mechanisms (e.g., calcium [31] or chloride accumulation [32]), and future work will explore the consequences of including these and other ions [33], as well as a more realistic collection of channels.

**V. CONCLUSION**

We have found that a simple model of a single neuron, augmented by dynamic intra- and extra-cellular ion concentrations, can display various kinds of periodic bursting behavior. Our work emphasizes the importance of ion concentration homeostasis in the maintenance of the normal physiological state, and suggests that a breakdown in such homeostatic mechanisms may underlie pathological
conditions such as epilepsy.

VI. ACKNOWLEDGEMENTS

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Appendix A: Parameters and Equations for Gating Variables

Parameters not specified above were set as follows:

\[ C_m = 1 \mu F/cm^2 \]
\[ g_{Na} = 100 mS/cm^2 \]
\[ g_{NaL} = 0.0175 mS/cm^2 \]
\[ g_K = 40 mS/cm^2 \]
\[ g_{KL} = 0.05 mS/cm^2 \]
\[ g_{ClL} = 0.05 mS/cm^2 . \]

The sodium activation was instantaneous, with

\[ m_{\infty} (V) = \frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)} \]
\[ \alpha_m(V) = \frac{1}{\exp(-0.1(V+30))} \]
\[ \beta_m(V) = 4 \exp \left(-\frac{V+55}{18} \right) . \]

The remaining gating variables were governed by

\[ \frac{dq}{dt} = \phi [\alpha_q(V)(1-q) - \beta_q(V)q] , \quad q = h, n \]

with

\[ \phi = 3.0 \]
\[ \alpha_h(V) = 0.07 \exp \left(-\frac{V+44}{20} \right) \]
\[ \beta_h(V) = \frac{1}{\exp(-0.1(V+34))} \]
\[ \alpha_n(V) = \frac{1}{\exp(-0.1(V+34))} \]
\[ \beta_n(V) = 0.125 \exp \left(-\frac{V+44}{80} \right) . \]

Appendix B: Derivation of Conversion Factors

To derive the conversion factor \( \gamma \), we consider a membrane current density \( I \), measured in \( \mu A/cm^2 \), and ask: how many ions exit a cell through a patch of membrane of area \( A \) (cm\(^2\)) in time \( \Delta t \) (sec) due to this current? Recalling the convention that membrane currents are positive-outward, the amount of charge that leaves is

\[ \Delta Q = (IA) \Delta t . \]

Assuming monovalent ions, the number of ions is

\[ \Delta N = \left( \frac{IA}{q} \right) \Delta t , \]

where \( q = 1.60 \times 10^{-19} \) Coulombs. Hence, the rate at which ions pass through the area \( A \) is

\[ \frac{dN}{dt} = \left( \frac{IA}{q} \right) . \]

Now assume a spherical cell of volume \( V_{in} \) (measured in cm\(^3\)) with an intracellular concentration \( c_{in} \) of positive ions measured in ions/cm\(^3\). We have

\[ c_{in} = \frac{N}{V_{in}} , \]

where \( N \) is the number of ions within the volume. Hence,

\[ \frac{dc_{in}}{dt} = \left( \frac{1}{V_{in}} \right) \frac{dN}{dt} = \frac{1}{V_{in}} \left( \frac{IA}{q} \right) . \]

The minus sign has been introduced because a positive (outward) current corresponds to a decrease in the number of (positive) ions within the cell.

We wish to express this rate-of-change of concentration in mM/msec. The expression on the right-hand side has units

\[ \frac{1}{cm^2} \cdot \frac{\mu A}{cm^2} \rightarrow \frac{10^{-6}}{cm^3} \cdot \frac{ions}{cm^3 \cdot sec} \rightarrow \frac{1}{10^3 N_A} \cdot \frac{msec}{mL} . \]

where \( N_A = 6.02 \times 10^{23} \) is Avogadro’s number. Since 1 millimole/L = 1 mM, we have

\[ \frac{dc_{in}}{dt} = - \left( \frac{1}{10^3} \right) \frac{IA}{N_A q V_{in}} . \]

We write

\[ \frac{dc_{in}}{dt} = - \left( \frac{1}{10^3} \right) \gamma I \]

(B1)

with

\[ \gamma = \frac{A}{N_A q V_{in}} = \frac{A}{F V_{in}} , \]

where \( F = N_A q \) is the Faraday constant. Equation (B1) is used for the intracellular sodium in Equation (4).

Now assume that the sphere has radius \( r \), and let \( A \) be its total surface area. (More correct would be to let \( A \) be just the area of the channel pores.) Then,

\[ \gamma = 3 \frac{A}{Fr} . \]

Using \( r = 7 \mu m \), we obtain \( \gamma = 4.45 \times 10^{-2} \). Conversely, for \( \gamma = 0.25 \) and 1.0, we obtain \( r = 1.24 \) and 0.31 \( \mu m \), respectively.

Consider now the concentration of positive ions in the extracellular space. The volume in the expression for \( \gamma \) must be replaced with the extracellular volume, and the negative sign in Equation (B1) must be removed. Let \( \beta = V_{in}/V_{out} \). Then \( \gamma \rightarrow \gamma \beta \), and we have

\[ \frac{dc_{out}}{dt} = \left( \frac{1}{10^3} \right) \gamma \beta I . \]

(B2)

Equation (B2) is used for the extracellular potassium in Equation (4).
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[34] SNIC stands for Saddle-Node on Invariant Circle (see, e.g., [20]). This codimension-one bifurcation has also been called a SNIPER bifurcation, for Saddle-Node Infinite-PERiod [21].
[35] This bifurcation [20, 21] has also been called a saddle-node homoclinic orbit bifurcation; see [20].