Mathematical modeling neuronal excitability

Georgi Medvedev

Department of Mathematics, Drexel University

December 12, 2008
Regular dynamics

- Steady state

\[ \dot{x} = x^2 - 1 \]

Fixed points: \( \bar{x} = \pm 1 \)

- Periodic motion

\[
\begin{align*}
\dot{x}_1 &= x_1 - x_2 - x_1 \left( x_1^2 + x_2^2 \right), \\
\dot{x}_2 &= x_1 + x_2 - x_2 \left( x_1^2 + x_2^2 \right)
\end{align*}
\]
Chaos

\[ \dot{x} = f(x), \quad x \in \mathbb{R}^3 \]

Sensitive dependence on initial data
Asymptotic states: maps

Quadratic family: \( x_{n+1} = f(x_n), \quad f(x) = \lambda x (1 - x) \)
Saddle-node bifurcation

\[
\begin{align*}
\dot{x} &= f(x, y, \alpha), \\
\dot{y} &= g(x, y, \alpha)
\end{align*}
\]

Frequency of the emerging limit cycle: \( \sim \sqrt{\alpha - \alpha_{SN}} \)
Andronov-Hopf Bifurcation

\[
\begin{align*}
\dot{x}_1 &= \alpha x_1 - \beta x_2 - x_1 \left( x_1^2 + x_2^2 \right), \\
\dot{x}_2 &= \beta x_1 + \alpha x_2 - x_2 \left( x_1^2 + x_2^2 \right)
\end{align*}
\]

\[\alpha < 0\]
\[\alpha = 0\]
\[\alpha > 0\]

Period: \( \frac{2\pi}{\beta} \)
Saddle-node bifurcation (maps)

\[ x_{n+1} = \alpha + (e^{-x_n} - 1) \]

\( \alpha < 0 \)

\( \alpha = 0 \)

\( \alpha > 0 \)

The passage time: \( \sim \sqrt{\alpha} \)
Period-doubling bifurcation (maps)

\[ x_{n+1} = -(1 + \alpha)x_n + x_n^3 \]

\[ \alpha < 0 \]

\[ \alpha > 0 \]
Quadratic family

\[ x_{n+1} = \lambda x_n (1 - x_n) \]

Sharkovski’s order: \[ 1 \rhd 2 \rhd 4 \rhd 8 \rhd \ldots \rhd 5 \cdot 2 \rhd 3 \cdot 2 \ldots \rhd 5 \rhd 3 \]
Feigenbaum universality:

\[
\lim_{n \to \infty} \frac{\lambda_n - \lambda_{n-1}}{\lambda_{n+1} - \lambda_n} = 4.669 \ldots, \quad \lambda_\infty \approx 3.57
\]

Schwarz derivative:

\[
Sf = \frac{f'''}{f'} - \frac{3}{2} \left( \frac{f'''}{f'} \right)^2
\]

Kneading theory, symbolic dynamics, \ldots
The Hodgkin-Huxley model

Current balance equation: \( I = I_{Na} + I_K + I_L + C \frac{dV}{dt} \)

Ionic currents:

\[
\begin{align*}
I_{Na} &= g_{Na} p (V - E_{Na}), \quad p = m^3 h, \\
I_K &= g_K n^4 (V - E_K), \\
I_L &= g_L (V - E_L)
\end{align*}
\]

- \( I_{Na} \): sodium current
- \( I_K \): potassium current
- \( I_L \): leak current
The Hodgkin-Huxley model

\[ C \dot{V} = -g_{Na}m^3h(V - E_{Na}) - g_Kn^4(V - E_k) - g_L(V - E_L) + I, \]

\[ \dot{m} = \frac{m_\infty(V) - m}{\tau_m(V)}, \]

\[ \dot{h} = \frac{h_\infty(V) - h}{\tau_h(V)}, \]

\[ \dot{n} = \frac{n_\infty(V) - n}{\tau_n(V)}. \]
Numerical integration of the HH model
The action potential

(a) V(t) and I(t)

(b) Upstroke and After-hyperpolarization

(c) Multiple action potentials
Classification of neural excitability

**TYPE I**

**TYPE II**
A 2D approximation of the Hodgkin-Huxley model (Krinsky and Kokoz, 1973)

\[
\begin{align*}
C \dot{V} &= -g_{Na} m^3 h (V - E_{Na}) - g_K n^4 (V - E_k) - g_L (V - E_L) + I, \\
\dot{m} &= \frac{m_\infty(V) - m}{\tau_m(V)}, \\
\dot{h} &= \frac{h_\infty(V) - h}{\tau_h(V)}, \\
\dot{n} &= \frac{n_\infty(V) - n}{\tau_n(V)}.
\end{align*}
\]
A 2D approximation of the Hodgkin-Huxley model (Krinsky and Kokoz, 1973)

Step 1.

Note that $\tau_m$ is small and use a steady state approximation: $m \approx m_\infty(V)$

\[
\begin{align*}
\dot{V} &= -g_{Na}m_\infty^3(V)h(V - E_{Na}) - g_Kn_\infty^4(V - E_K) - g_L(V - E_L) + I, \\
\dot{n} &= \frac{n_\infty(V) - n}{\tau_n(V)}, \\
\dot{h} &= \frac{h_\infty(V) - h}{\tau_h(V)}.
\end{align*}
\]
Step 2.
Approximate $h \approx 0.89 - 1.1n$

\[
\dot{V} = -g_{Na}m_{\infty}^3(V)(0.89 - 1.1n)(V - E_{Na}) - g_Kn^4(V - E_K) - g_L(V - E_L) + I,
\]
\[
\dot{n} = \frac{n_{\infty}(V) - n}{\tau_n(V)}.
\]
The rescaled 2D model

Rescale: \( V = k_V v \), \( t = k_i \tilde{t} \)

The slow-fast system:

\[
\begin{align*}
v' &= F(v, n) \\
\dot{n} &= G(v, n)
\end{align*}
\]

Small parameter: \( 0 < \epsilon \ll 1 \)

\[
\begin{align*}
F(v, n) &= -\tilde{g}_{Na} m_\infty^3(v) (1 - n) (v - \tilde{E}_{Na}) - \tilde{g}_K n^4(v - \tilde{E}_K) - \tilde{g}_L (v - \tilde{E}_L) + \tilde{I} \\
G(v, n) &= \frac{\tilde{n}_\infty(v) - n}{\tilde{\tau}_n(v)}
\end{align*}
\]
The slow-fast system

\[ \epsilon \dot{v} = F(v, n), \quad (\dot{v} = O(\frac{1}{\epsilon})) \]

\[ \dot{n} = G(v, n), \quad (\dot{n} = O(1)) \]

The slow subsystem (\( \epsilon = 0 \)):

\[ 0 = F(v, n), \quad \text{Slow manifold } S = \{(v, n) : F(v, n) = 0\} \]

\[ \dot{n} = G(v, n), \quad (v, n) \in S \]

The fast subsystem:  
Rescale time: \( \tau = \epsilon^{-1}t \), set \( \epsilon = 0 \)

\[ v' = F(v, n), \quad n' = 0 \]
Type I vs Type II models

Type I (Saddle-node bifurcation)

Type II (Andronov-Hopf bifurcation)
Saddle-node bifurcation: type I models
Andronov-Hopf bifurcation: type II models
Type I vs Type II models

**Type I**

Type I:  Frequency $\sim \sqrt{I - I_{SN}}$

**Type II**

Type II:  Frequency is bounded away from zero

Bursting Patterns: Example I

$I_{NaP} + I_K + I_{KM}$ (E. Izhikevich, Dynamical Systems in Neuroscience, Springer, 2007)
A three-variable model of pancreatic $\beta$–cell (Chay, Physica D, 1985)

Periodic spiking $\rightarrow$ doublets $\rightarrow$ ... $\rightarrow$ bursting (reverse period-adding separated by windows of chaotic dynamics)
The Chay Model (Chay, Physica D, 1985)

\[
\begin{align*}
\dot{v} &= g_I m_\infty^3(v) h_\infty(v) (E_I - v) + g_K n^4(E_K - v) + \frac{g_K C a u}{1 + u} (E_K - v) + l (E_l - v) \\
\dot{n} &= \frac{n_\infty(v) - n}{\tau(v)} \\
\dot{u} &= \rho \left( m_\infty^3(v) h_\infty(v) (E_{Ca} - v) - \gamma u \right),
\end{align*}
\]

Small parameter: \(0 < \rho \ll 1\)
Control parameter: \(g_K C\)

(Chay, 1985)
A one-dimensional map for the slow variable

\[ v_{\text{KC}} = 13 \]

\[ u \sim \text{[Ca}^{2+}] \]

Medvedev, 2005
A fixed point of $P$:  \[ P(\bar{u}) = \bar{u} \]

Recall  \[ P(u) = e^{-\alpha T(u)} u + (1 - e^{-\alpha T(u)}) F(u) \]

Stability of $\bar{u}$:  \[ |P'(\bar{u})| < 1 \]
Superstable cycles of $P$: bursting

A cycle: $u_1 \rightarrow u_2 \rightarrow \ldots \rightarrow u_n \rightarrow u_1$
A piecewise linear approximation of $P$

Approximate $P$ with $P_l(u) = (1 - \alpha T_0)u + \alpha T_0 F_0$

The superstable stable cycles of $P$ undergo reverse period-adding bifurcations followed by small windows of complex (chaotic) bursting
Transition from tonic spiking to bursting: doublets and irregular spiking

Bifurcations: \( P(\bar{u}) = \pm 1 \) (saddle-node/period-doubling)

Attracting fixed point (spiking) \(\rightarrow\) PD cascade (doublets etc) \(\rightarrow\) bursting
Firing patterns generated by the Chay model

A three-variable model of pancreatic β−cell (Chay, Physica D, 1985)

Periodic spiking → doublets → ... → bursting (reverse period-adding separated by windows of chaotic dynamics)
Example I: $I_{NaP} + I_K + I_{KM}$ model

\[
\begin{aligned}
\dot{v} &= g_{NaP} m_\infty^3(v) h (E_{Na} - v) + (g_K n^4 + g_{KM} m_{KM}) (E_K - v) + g_L (E_L - v) \\
\dot{n} &= \frac{n_\infty(v) - n}{\tau_n} \\
\dot{m}_{KM} &= \alpha (\tilde{m}_\infty(v) - m_{KM}) ,
\end{aligned}
\]

Example II: $I_{NaP} + I_K$ model

\[
\begin{align*}
\dot{v} &= \left( g_{NaP}m_\infty^3(v)h + g_{Na}m_\infty^3(v)(1-n) \right) (E_{Na} - v) + g_Kn^4 (E_K - v) + g_L (E_L - v) \\
\dot{n} &= \frac{n_\infty(v) - n}{\tau_n} \\
\dot{h} &= \alpha (h_\infty(v) - h),
\end{align*}
\]

Butera, RJ, Jr., J. Rinzell, and JC Smith, J. Neurophys., 1999
Example III: $I_{Na} + I_K$ model

\[
\begin{align*}
\dot{v} &= g_K n^2 (E_K - v) + g_{Na} m^3 \infty (v) h (E_{Na} - v) + g_L (E_L - v) \\
\dot{n} &= \frac{n_\infty (v) - n}{\tau_n} \\
\dot{h} &= \alpha (h_\infty (v) - h),
\end{align*}
\]

A. Shilnikov and G. Cymbalyuk, PRL, 2005
Conclusions

The method of reduction of the differential equation models to 1D maps

– provide a compact description of the dynamical structure of the model
– retain the biophysical meaning of the parameters
– suggest two distinct scenarios for transition from spiking to bursting

References:

G.S. Medvedev, Reduction of a model of an excitable cell to a one-dimensional map, Physica D, 2005
G.S. Medvedev and J. Cisternas, Multimodal regimes in a compartmental model of the dopamine neuron, Physica D, 2004

Acknowledgments.

This work was partially supported by the National Science Foundation under Grant No. 0417624.
Multimodal Oscillations in a Model of the Dopamine Neuron

Interspike interval histograms (noise intensity: $\sigma = 0.01$)

Interspike interval distributions

Voltage time series

Hitczenko, Medvedev, in preparation
A family of multimodal periodic solutions

Firing number := \( \frac{N_l}{N_s + N_l} \), \( N_s(N_l) \) = number of small (large) oscillations

Medvedev and Cisternas, Physica D, 2004
Reduction to a 1D mapping

\[ P(\xi) = (1 - \alpha \Omega_1 T(\xi)) \xi + \alpha \Omega_2 T(\xi) \bar{f}(\xi), \quad \alpha = \frac{1}{\tau} \]
Multimodal Oscillations in a Model of the Dopamine Neuron

Medvedev, Cisternas, Physica D, 2004
Conclusions

The method of reduction of the differential equation models to 1D maps

– provide a compact description of the dynamical structure of the model
– may be used in simulations of large neuronal networks
– retain the biophysical meaning of the parameters
– suggest two distinct scenarios for transition from spiking to bursting

References:

G.S. Medvedev, Reduction of a model of an excitable cell to a one-dimensional map, Physica D, 2005
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