Bifurcation, Bursting, and Spike Frequency Adaptation

Guckenheimer J, Harris-Warrick R, Peck J, Willms A.
Journal of Computational Neuroscience
Volume 4, 257-277, 1997

Mathematical Neuroscience
6.7.2007
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Outline

I. Introduction/Background
II. Bifurcations and transitions
    I. The properties of interspike intervals during transitions (spiking/quiescence)
    II. Test of theory on ML model
III. LP cell model
IV. Our results
V. Conclusions

Spike frequency adaptation

- Reduction in a neuron's firing rate
  - Opening channels hyperpolarizes neurons
  - Can lead to quiescence
- Observed in many neural systems and modulated by many neurotransmitters
  - Norepinephrine and other monoamines reduce activity of certain Ca^{2+} modulated K^{+} channels

Singularly perturbed dynamical systems

- Slowly varying, i.e. fast-slow timescales
- Fast time scale – dynamics involved with periodic firing
- General form:

$$x' = \varepsilon f(x,y)$$

$$y' = g(x,y)$$

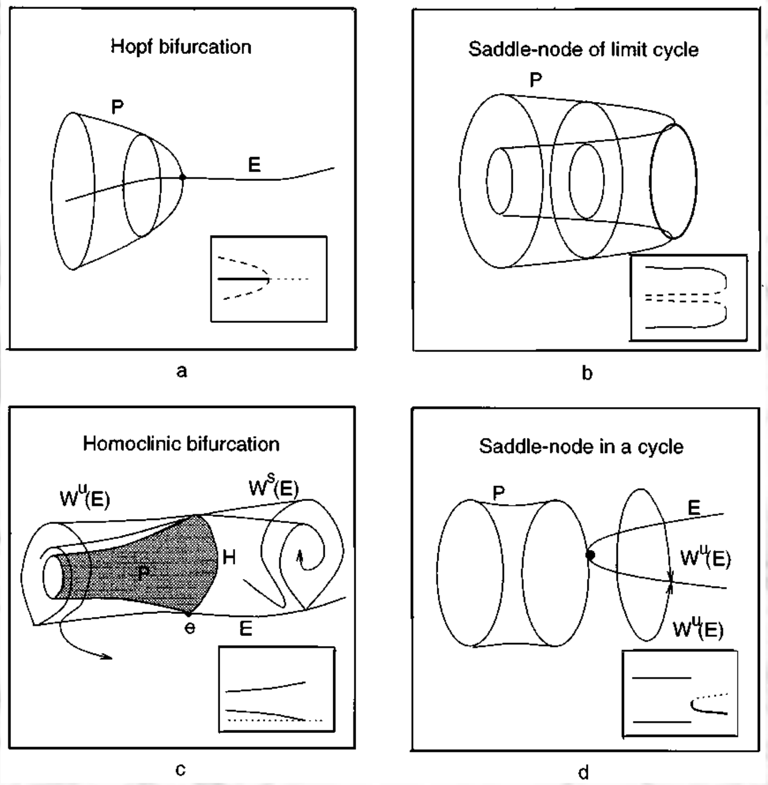
Thesis of paper

"Qualitative analysis of sequences of interspike intervals provides additional information that can be used to constrain the mechanisms underlying the termination of spiking."

Behavior at transitions

Bifurcation Types and Transitions

- Hopf Bifurcation - supercritical
  - Family of equilibrium points meets a family of periodic orbits
  - Oscillations decrease as HB point is approached
- Saddle-node limit cycle
  - Periodic orbits of differing stability but both with finite amplitude and period approach each other
  - Period of oscillations bounded with non-decaying amplitude
- Homoclinic Bifurcation
  - Periodic orbits terminate as the period grows without bound
  - Approach the same equilibrium from both forward and backward in time.
  - Lie in both stable and unstable manifolds
- SN of equilibria interrupting limit cycles
  - Stable periodic orbit approaches SN of equilibrium
  - Open region of trajectories at the EP of the bifurcation
  - Two equilibria following bifurcation: sink and saddle
  - Results in an excitable system



Guckenheimer et al., 1997

Properties of ISIs During HC Bifurcation

- Evolution near HC bifurcation based on x'= ε, with the distance from its critical value for bifurcation to quiescence $\varepsilon(t_h - t)$
- If $s = t_h - t$, instantaneous periods behaves like:

$$T_{\text{hom}(s)} = c_1 \ln(s^{-1}) + c_2 \ln(\ln(s^{-1})) + c_3$$

- Tested theory with simplified Morris-Lecar model

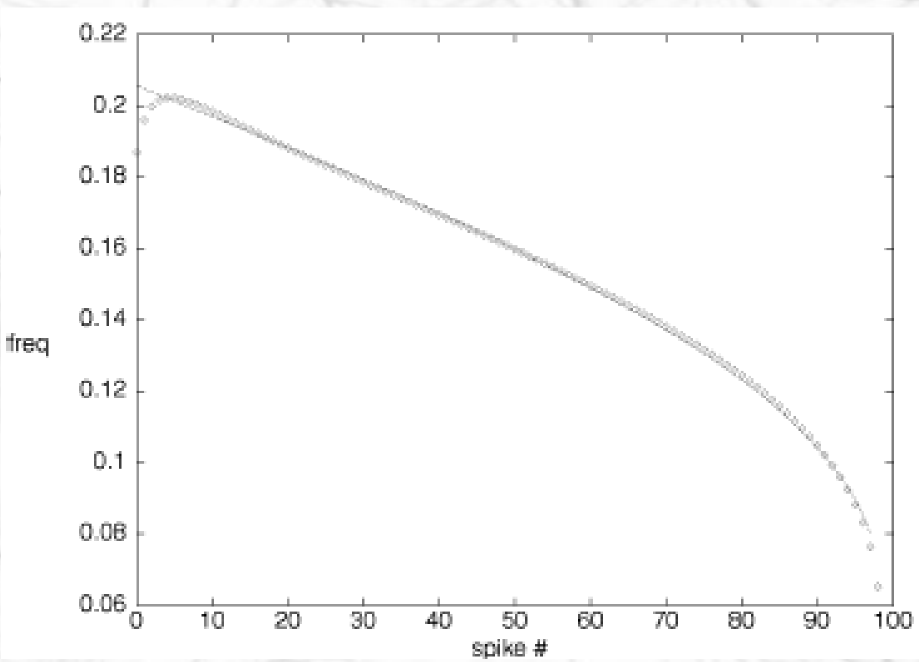


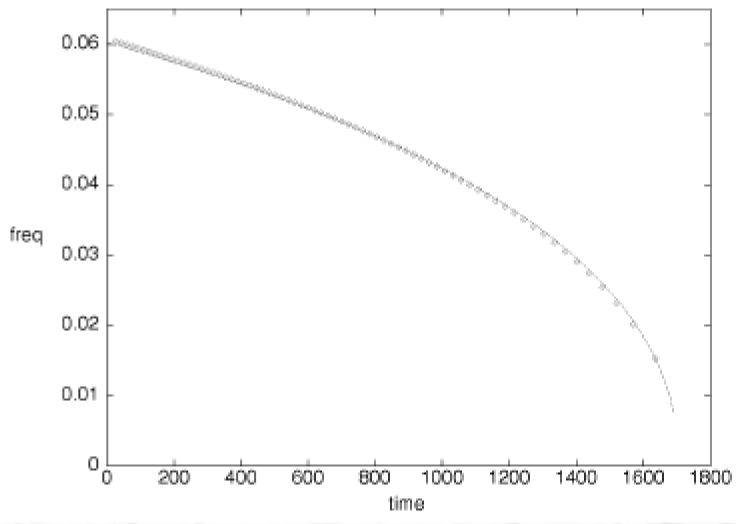
Table 4. Functional forms for instantaneous frequency.

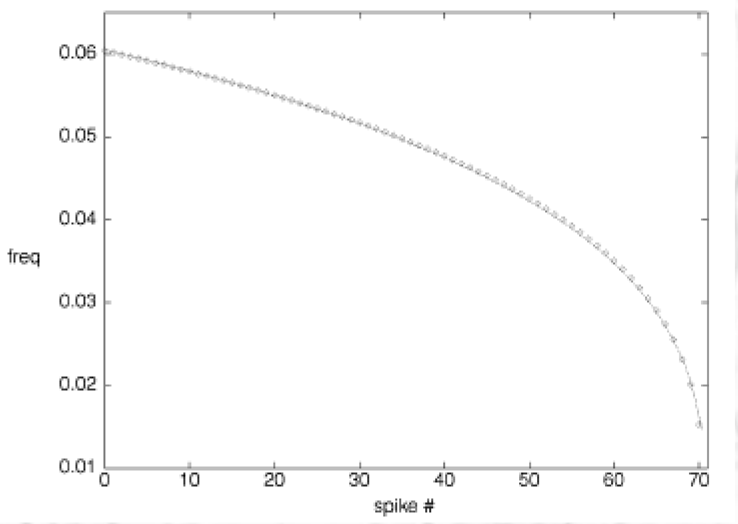
Type	Bifurcation	Frequency
Square root	Saddle-node	$\frac{1}{a+\frac{1}{\sqrt{b-ct}}}$
Logarithmic	Homoclinic	$\frac{1}{-a\log(b-ct)}$
Fractional linear	Hopf-Homoclinic	$\frac{1}{a+\frac{1}{b-ct}}$

Guckenheimer et al., 1997

Properties of ISIs During SN Bifurcation

- Theory predicts that evolution of vector field near SN bifurcation is approximated by solutions to $y' = y + x^2$
- Solution is of the form $I_{sn} = c_1 + c_2\ (-x)^{-1/2}$





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LP Neuron

$$C_m \dot{v} = -(\underbrace{\bar{g}_{\mathrm{Na}}\, m_\infty^3 h\, (v - E_{\mathrm{Na}})}_{I_{\mathrm{Na}}} + \underbrace{(\bar{g}_{\mathrm{Ca1}}\, a_{\mathrm{Ca1}}\, b_{\mathrm{Ca1}} + \bar{g}_{\mathrm{Ca2}}\, a_{\mathrm{Ca2}})\, (v - E_{\mathrm{Ca}})}_{I_{\mathrm{Ca}}} + \underbrace{\bar{g}_{\mathrm{K}}\, n^4 (v - E_{\mathrm{K}})}_{i_{\mathrm{K(V)}}}$$
$$+ \underbrace{\bar{g}_{\mathrm{K(Ca)}}\, a_{\mathrm{K(Ca)}}\, b_{\mathrm{K(Ca)}}\, (v - E_{\mathrm{K}})}_{I_{\mathrm{K(Ca)}}} + \underbrace{(\bar{g}_{\mathrm{Af}}\, b_{\mathrm{Af}} + \bar{g}_{\mathrm{As}}\, b_{\mathrm{As}}) a_A^3 (v - E_{\mathrm{K}})}_{I_A}$$
$$+ \underbrace{\bar{g}_h\, a_h\, (v - E_h)}_{I_h} + \underbrace{\bar{g}_s\, a_s\, (v - E_k)}_{I_s} + \underbrace{\bar{g}_l\, (v - E_l)}_{I_l}) + I_{\mathrm{ext}}$$

$$I_{\mathrm{Na}} : \begin{cases} m_\infty = (1 + 15\, e^{-(v+34)/13}\, \frac{(1-e^{-(v+6)/20})}{0.11(v+6)})^{-1} \\ \dot{h} = 500(0.08(1-h)e^{-(v+39)/8} - \frac{h}{1+e^{-(v+40)/5}}) \end{cases}$$

$$I_{\mathrm{Ca}} : \begin{cases} \dot{\mathrm{Ca}} = -300\, (\bar{g}_{\mathrm{Ca1}}\, a_{\mathrm{Ca1}}\, b_{\mathrm{Ca1}} + \bar{g}_{\mathrm{Ca2}}\, a_{\mathrm{Ca2}})\, (v - E_{\mathrm{Ca}}) + 360\, (0.05 - \mathrm{Ca}) \\ \dot{a}_{\mathrm{Ca1}} = 50((1 + e^{-(v+11)/7})^{-1} - a_{\mathrm{Ca1}}) \\ \dot{a}_{\mathrm{Ca2}} = 10((1 + e^{-(v-22)/7})^{-1} - a_{\mathrm{Ca2}}) \\ \dot{b}_{\mathrm{Ca1}} = 16((1 + e^{(v+50)/8})^{-1} - b_{\mathrm{Ca1}}) \end{cases}$$

$$i_{\mathrm{K(V)}} : \{ \dot{n} = 282(1 + e^{-(v-10)/22})^{-1}((1 + e^{-(v+25)/17})^{-1} - n)$$

$$I_{\mathrm{K(Ca)}} : \begin{cases} \dot{a}_{\mathrm{K(Ca)}} = 45(\frac{\mathrm{Ca}}{(1+e^{-(v+20+0.6\mathrm{Ca})/23})(1+e^{-(v+23+0.6\mathrm{Ca})/6})(2.5+\mathrm{Ca})} - a_{\mathrm{K(Ca)}}) \\ \dot{b}_{\mathrm{K(Ca)}} = 35(\frac{0.6}{0.6+\mathrm{Ca}} - b_{\mathrm{K(Ca)}}) \end{cases}$$

$$I_A : \begin{cases} \dot{a}_A = 140((1 + e^{-(v+32)/16})^{-1} - a_A) \\ \dot{b}_{\mathrm{Af}} = 30((1 + e^{(v+75)/12})^{-1} - b_{\mathrm{Af}}) \\ \dot{b}_{\mathrm{As}} = 10((1 + e^{(v+75)/12})^{-1} - b_{\mathrm{As}}) \end{cases}$$

$$I_h : \{ \dot{a}_h = 0.1(1 + e^{-(v+100)/13})((1 + e^{(v+110)/12})^{-1} - a_h)$$

$$I_s : \{ \dot{a}_s = 0.0985((1 + e^{-(v-v_s)/4})^{-1} - a_s)$$

Parameter	Value	Meaning	Units
$\bar{g}_{\mathrm{Af}}$	1.5	Fast A current conductance	μS
$\bar{g}_{\mathrm{As}}$	1.3	Slow A current conductance	μS
$\bar{g}_{\mathrm{K(Ca)}}$	5	K(Ca) current conductance	μS
$\bar{g}_l$	0.05	Leak current conductance	μS
$\bar{g}_h$	0.1	Sag current conductance	μS
E_{K}	−86	Potassium reversal potential	mV
E_l	−52	Leak reversal potential	mV
E_h	−10	Sag reversal potential	mV
E_{Ca}	140	Ca reversal potential	mV
E_{Na}	50	Sodium reversal potential	mV
C_m	0.002	Membrane capacitance	nF

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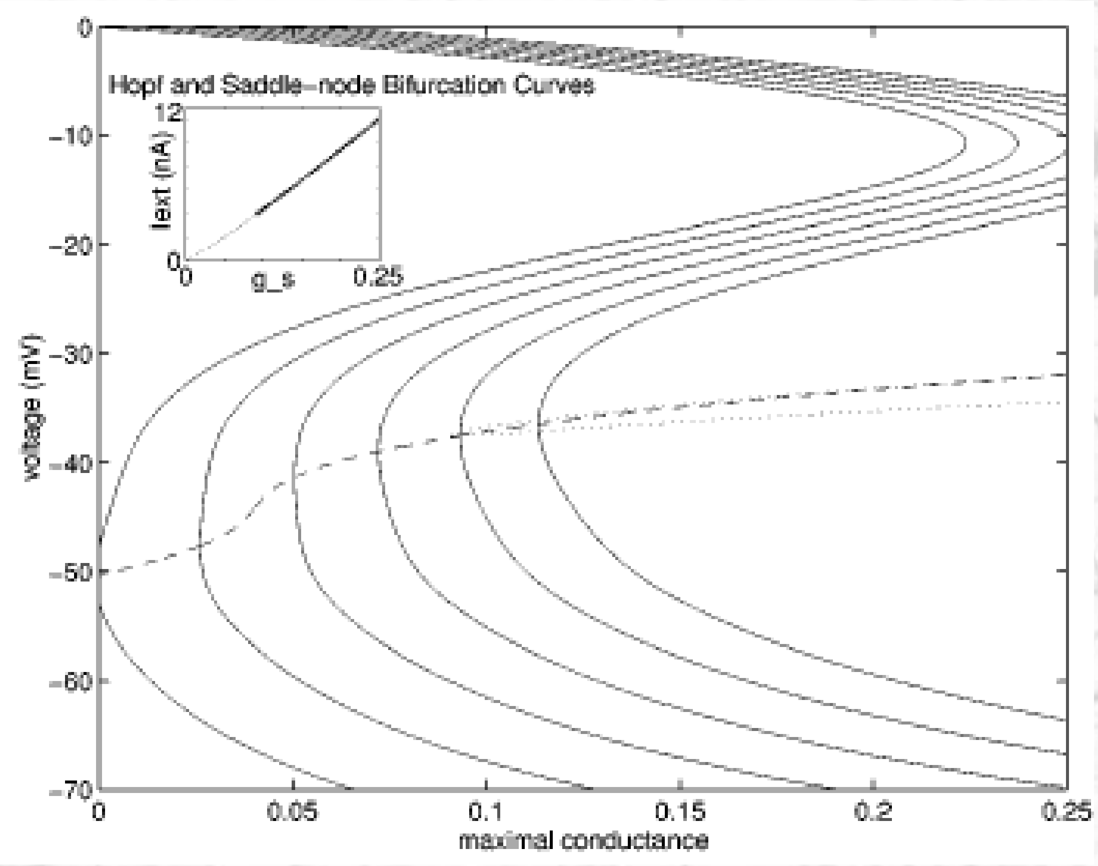
Properties of the Model

- LP neuron of somatogastric ganglion of *Panulirus interruptus*
- Single Compartment
- Multiple time scales
- Can be “frozen” by setting activation of slow current to 1 and varying maximal conductance
- Singularly perturbed system exhibits:
  - Saddle-node bifurcation
  - Homoclinic bifurcation
  - Subcritical Hopf bifurcation

P. Interruptus (California spiny lobster)

Bifurcation Plot

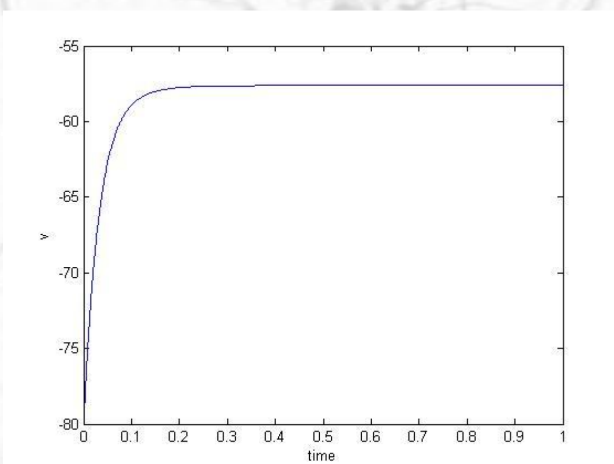


- Plots of equilibrium points while varying maximal conductance, for different values of applied current, I_{ext}
- Above dashed line: system unstable.
- Below dashed line: system stable
  - Global attracting equilibria

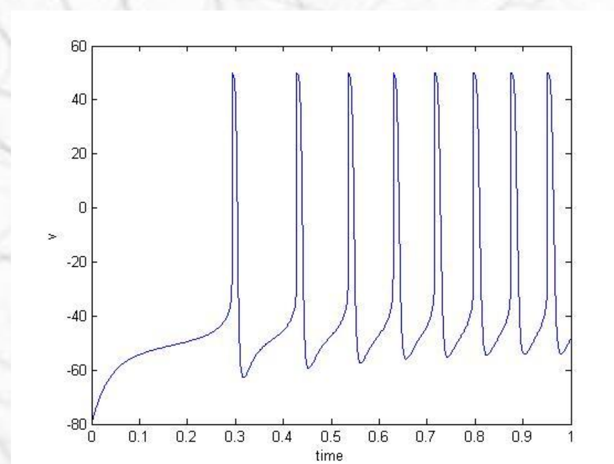
Guckenheimer et al., 1997

Equilibrium at SN Bifurcation

- For $I_{ext} < I_c$, a SN bifurcation occurs- depending on g_{max}: if right, stable fixed point, if left, stable limit cycle.
  - I_c is the current at which codimension two bifurcations begin (~ 4 nA with standard parameters)
- Approaching the bifurcation period increases (frequency decreases)



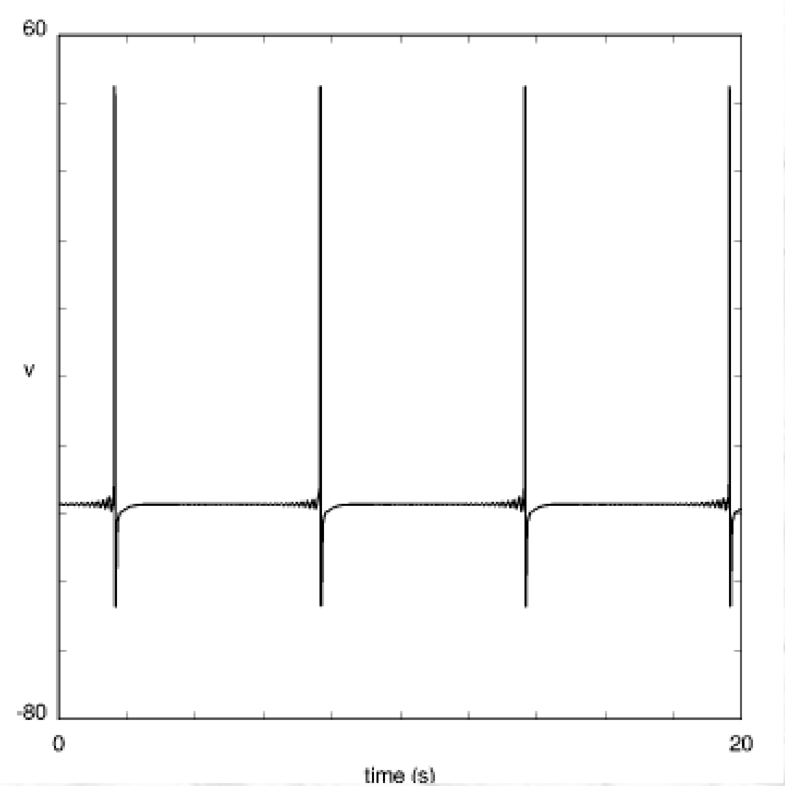
Quiescence



Tonic Firing

Equilibrium at Hopf Bifurcation

- When $I_{ext} > I_c$:
- Codimension two bifurcation
  - As g_s increases: start tonic firing
  - g_s passes SN bifurcation, no change in limit cycle
  - As g_s approaches HB, fast, low-amplitude, growing oscillations become evident during the rebound phase
  - Simultaneously, spiking frequency decreases



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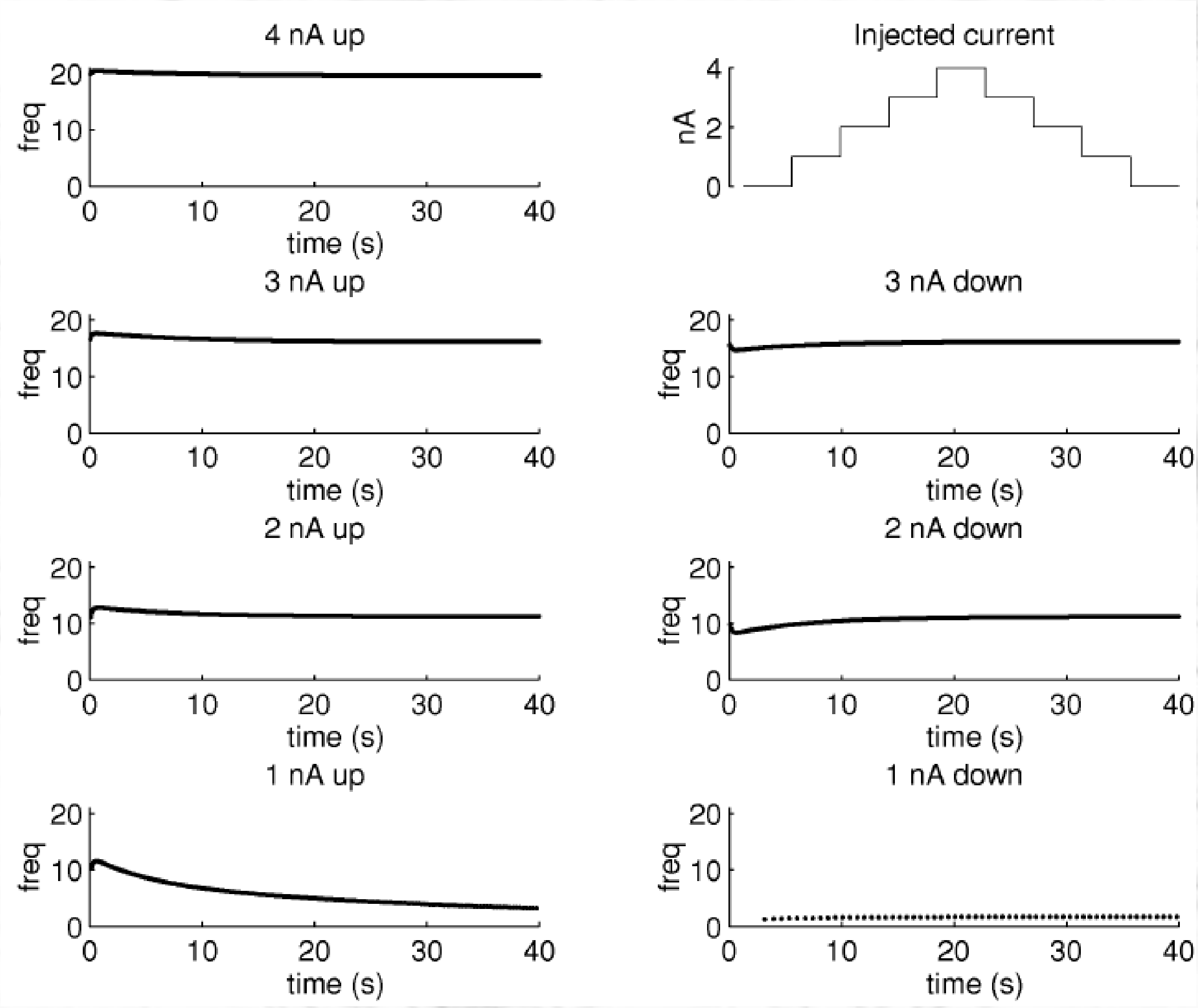
Spike Frequency Adaptation

- Approach HB by increasing injected current, frequency decreases
- Move away from it by decreasing injected current, frequency increases *slightly*



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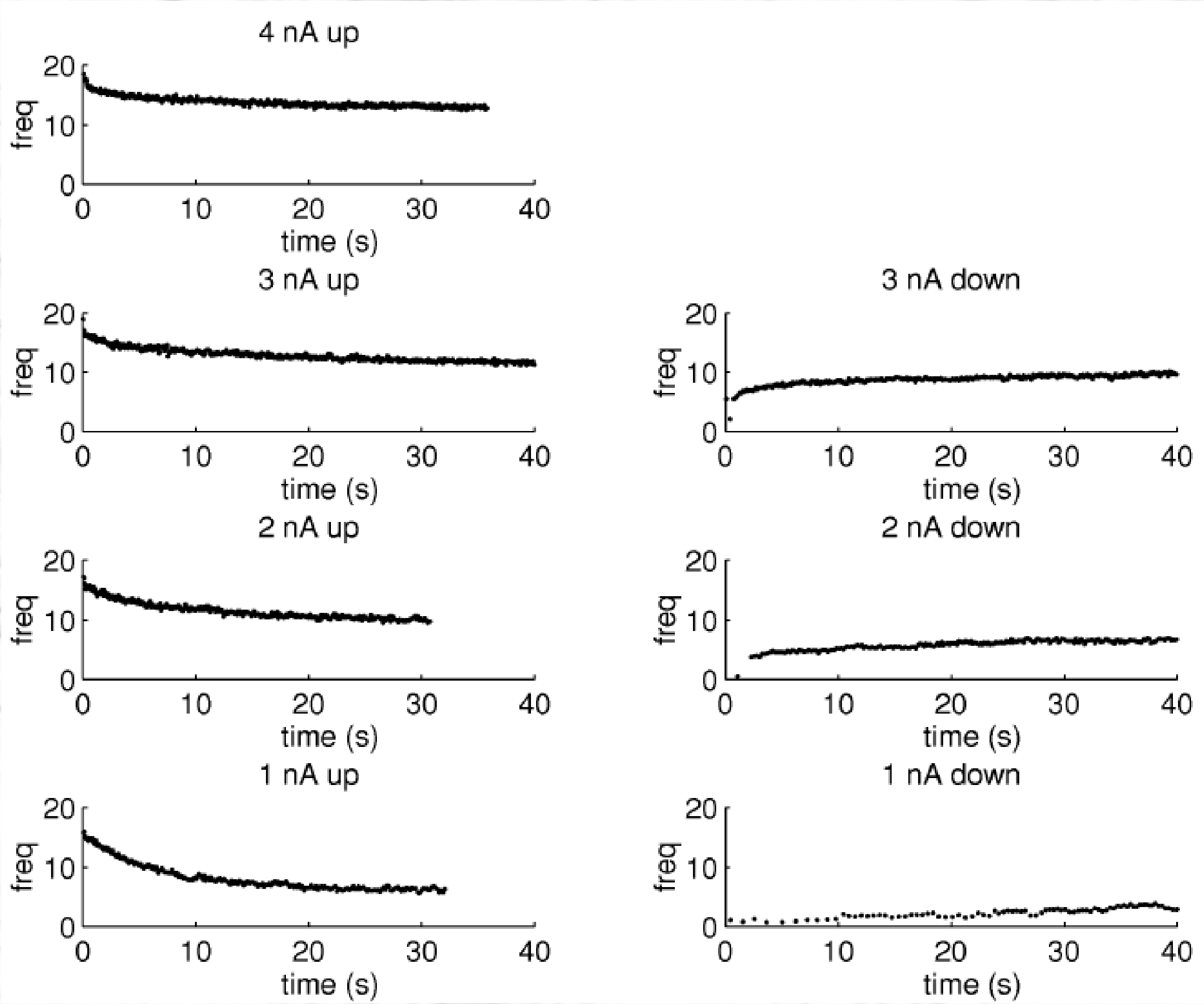
Compared to Experimental Data

- We see that it is very similar



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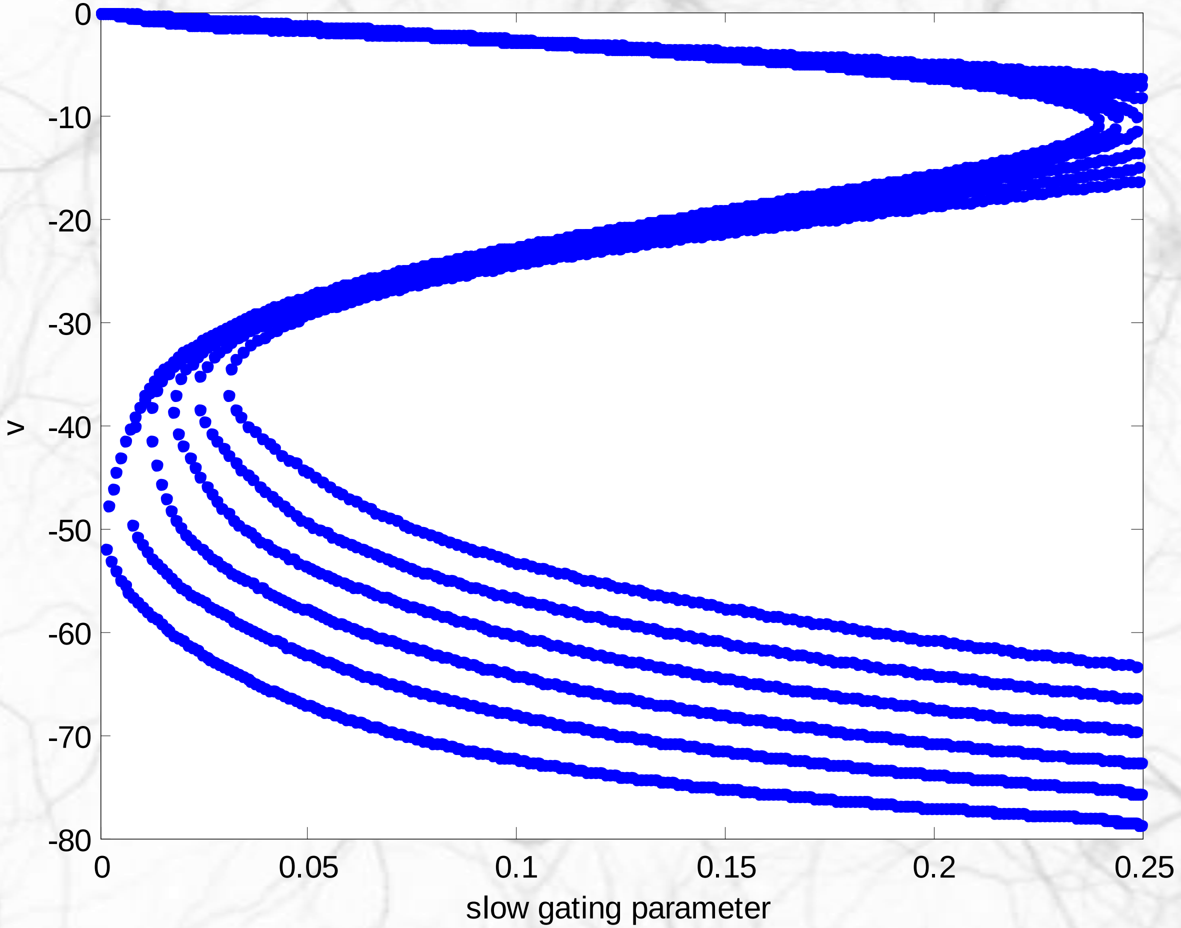
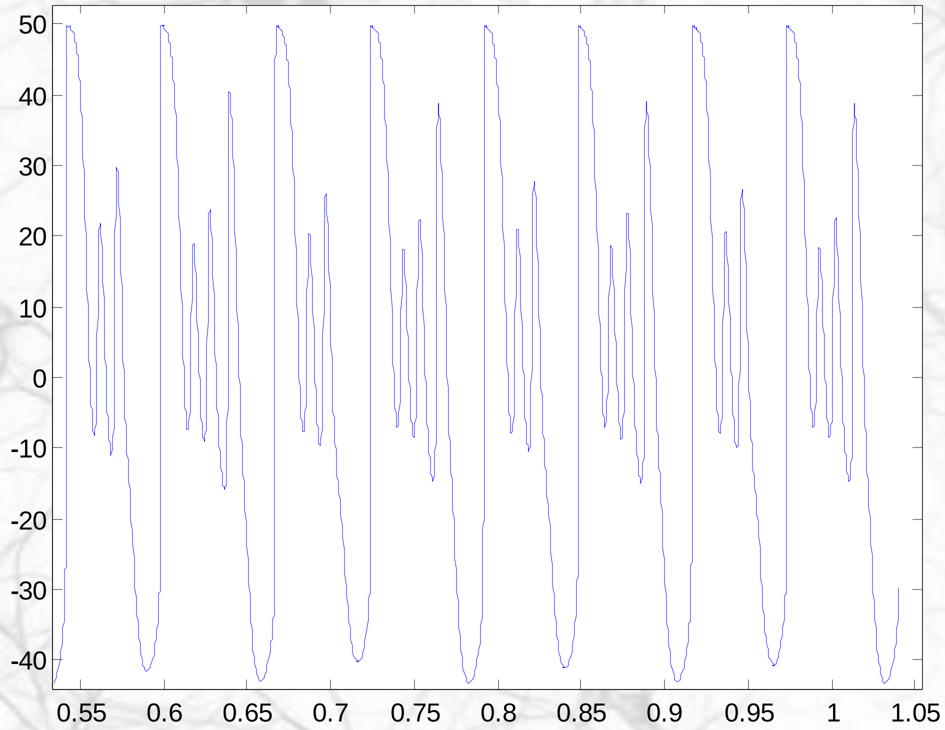
Our Results – Bifurcation Diagram

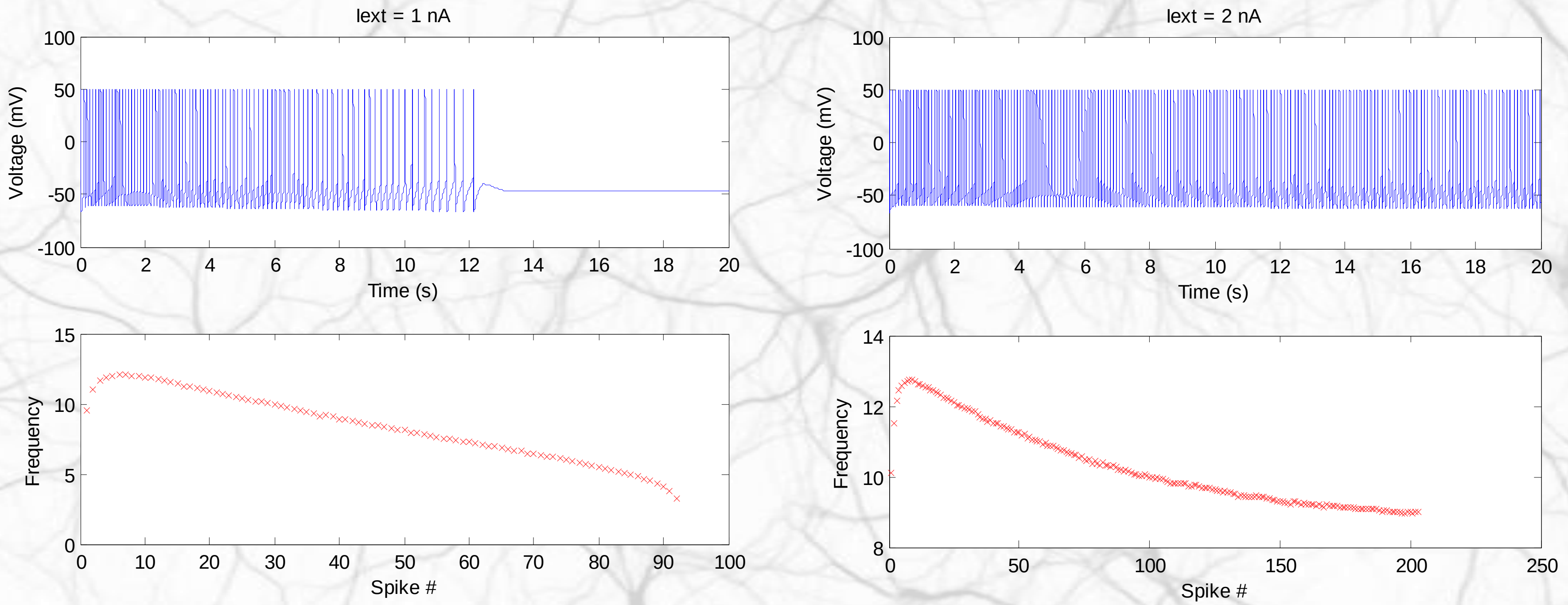


Near the Hopf Bifurcation



- Frozen LP model (x' = ε)
- I_{ext} = 8 nA
- Model in Matlab has trouble running for more that 10 seconds
  - Can't adjust to time scales
- See same

Model Simulation: voltage time course and instantaneous frequency plots



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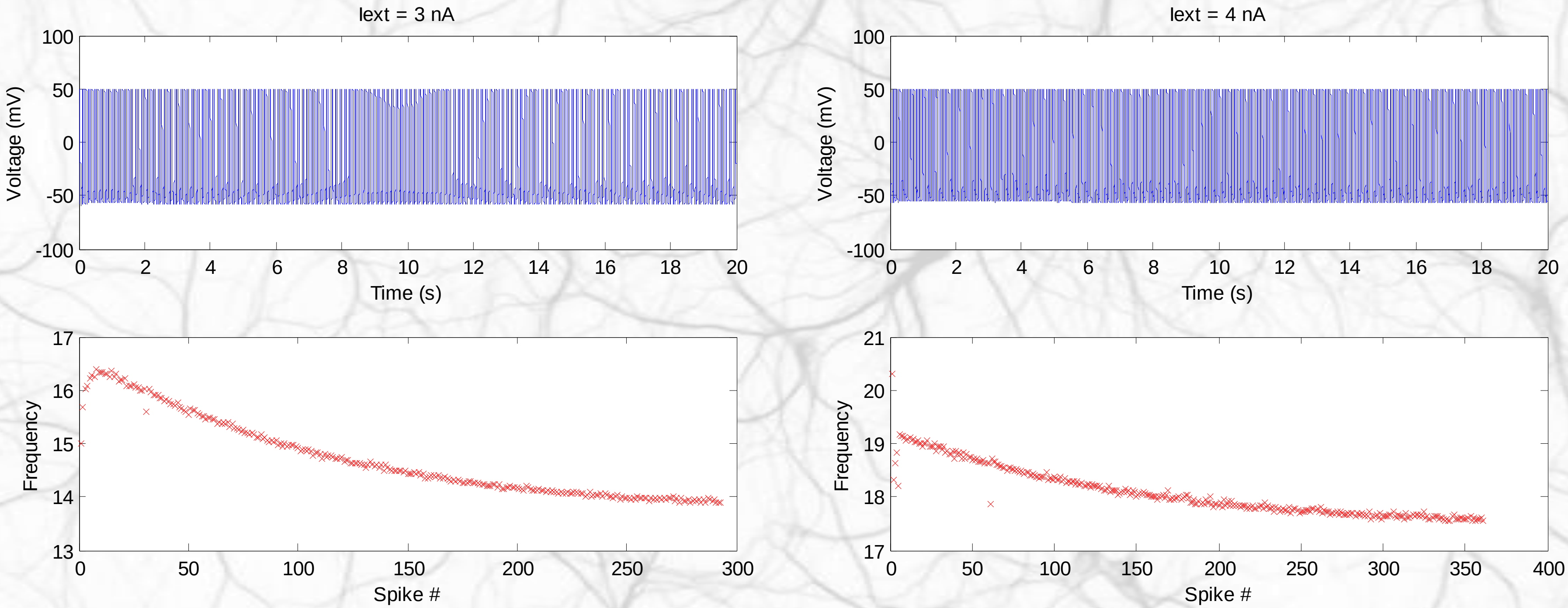
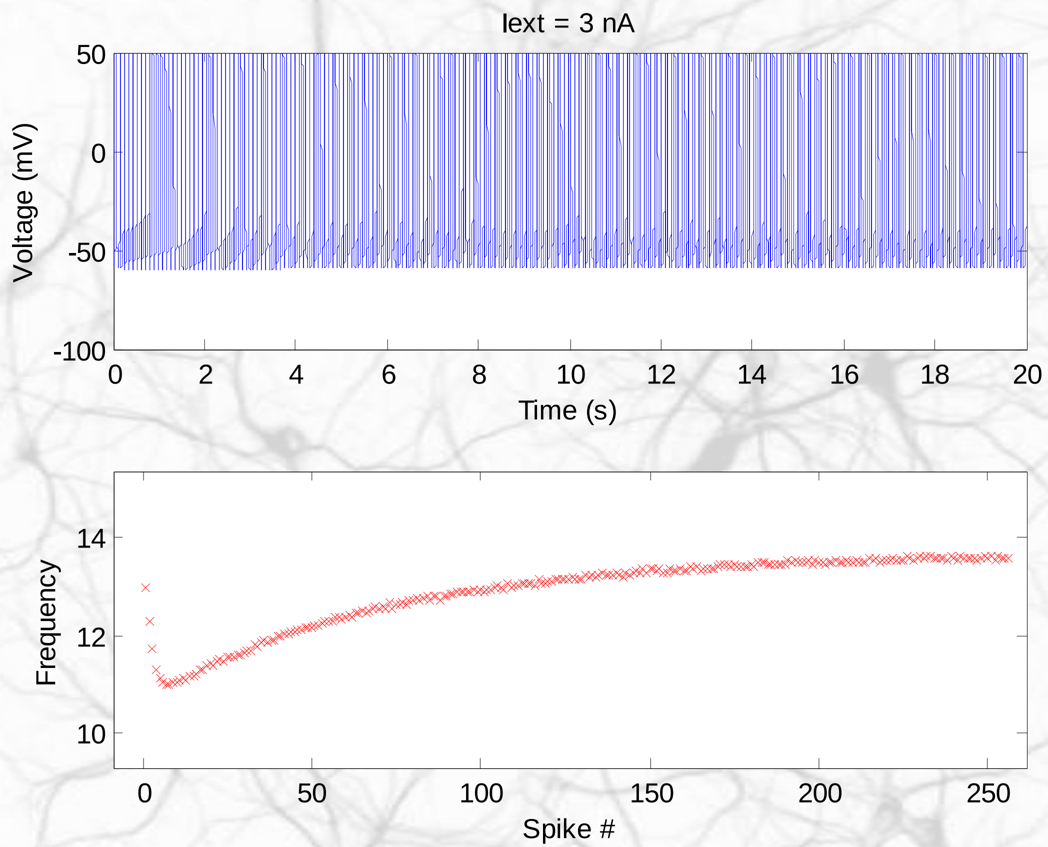
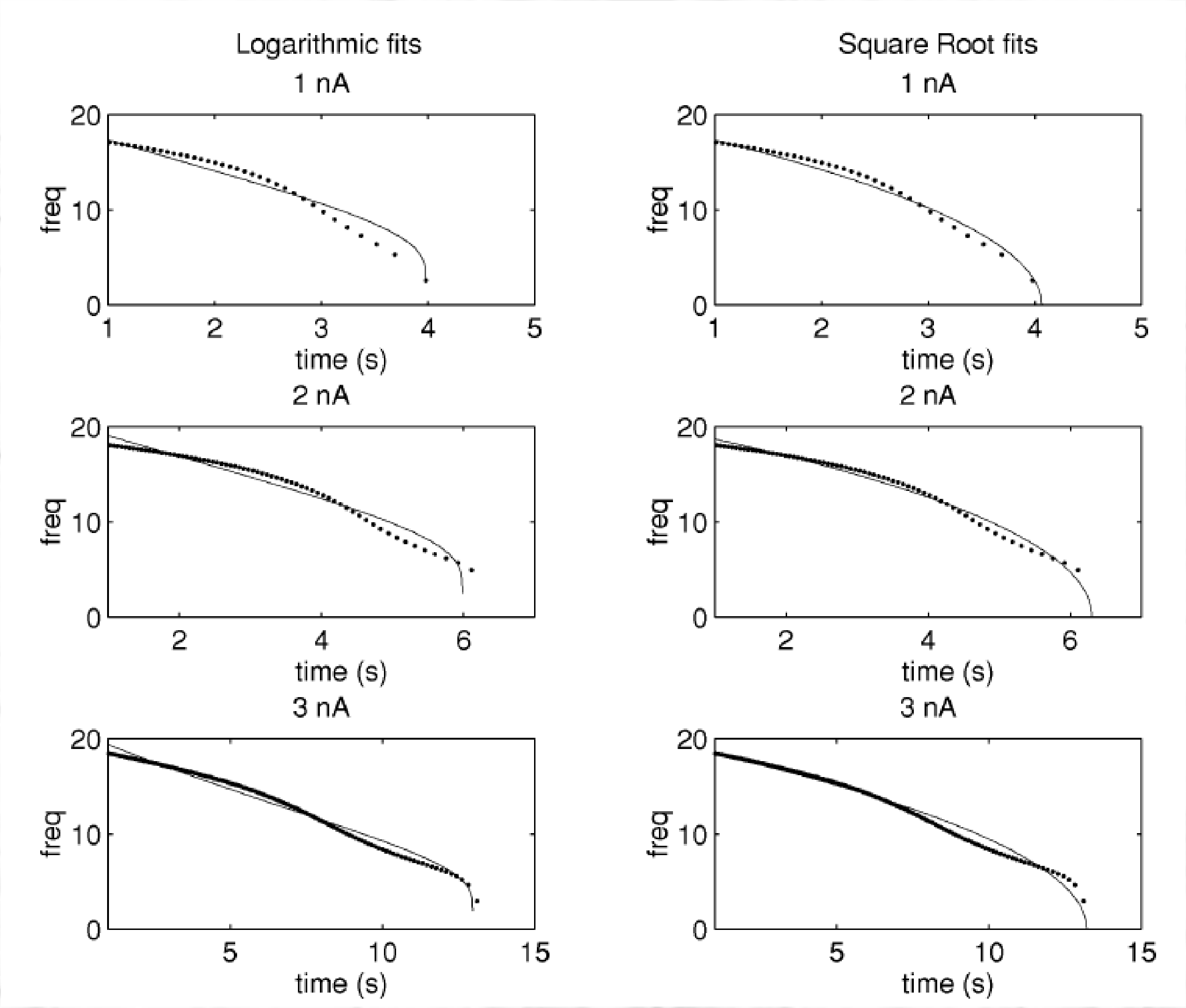


Iext = 3 nA
Iext = 4 nA
Voltage (mV)
Time (s)
Frequency
Spike #
100
50
0
-50
-100
0
2
4
6
8
10
12
14
16
18
20
17
16
15
14
13
21
20
19
18
17
50
100
150
200
250
300
350
400



The differential equation solver in Matlab was not able to continue integration past a certain point without taking into account fast spiking (continuous integration)

Fit techniques → LP Neuron Model



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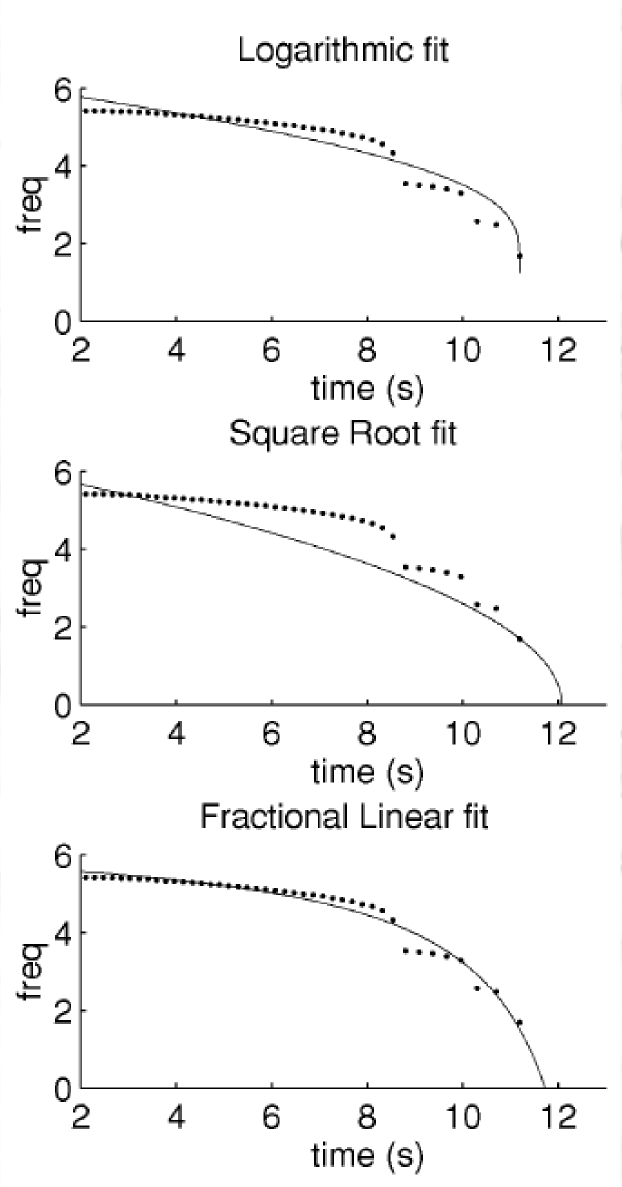

Conclusions

- By plotting the interspike interval data of a neuron and applying asymptotic analysis, one can determine the dynamical mechanism of spike termination
- It appears that because the LP neuron data is fit best by the fractional linear fit (see below), spike termination is the result of subcritical Hopf bifurcation
- A further prediction about the type of bifurcation is that the cell exhibits bistability
- Our reproduction of this model showed similar results

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