Mathematical Foundations of Neuroscience - Lecture 9. Simple Models of Neurons and Synapses.

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Introduction

- Hodgkin-Huxley model is fairly biologically accurate, but is very slow - gating variables take most of the computing time
- Persistent instantaneous sodium + potassium ($I_{Na,p}$ - I_K) is more efficient (there is only one gating variable), but still it requires two computations of exponential functions per step. This model is still far too slow for large simulations.
- Exponential function requires a lot of computing since:

$$e^x = 1 + x + \frac{x^2}{2!} + \frac{x^3}{3!} + \frac{x^4}{4!} + ... + \frac{x^i}{i!} + ...$$

up to required accuracy

Actually direct summation of the series

$$e^x = 1 + x + \frac{x^2}{2!} + \frac{x^3}{3!} + \frac{x^4}{4!} + ... + \frac{x^i}{i!} + ...$$

would be numerically unstable, since both the numerator and denominator get very big. Instead it is better to express the i-th term with the previous one:

$$\text{term}_i = \frac{x^i}{i!} = \frac{x}{i}\frac{x^{i-1}}{(i-1)!} = \frac{x}{i}\text{term}_{i-1}$$

The algorithm is then

```
t=1;  s=1;
for(i=1;i<n;i++) {t=t*x/i; s=s+t;}
```

which in any case requires a lot of processing.

Simplified $I_{Na,p}$ - I_K

- Recall the $I_{Na,p}$ - I_K model:

$$C_m \frac{dV}{dt} = I - g_L(V - E_L) - g_{Na} m_\infty(V)(V - E_{Na}) - g_K n(V - E_K)$$
$$\frac{dn}{dt} = (n_\infty(V) - n)/\tau_n(V)$$

with $C_m = 1$, $E_L = -80$, $g_L = 8$, $E_{Na} = 60$, $g_{Na} = 20$, $E_K = -90$, $g_K = 10$, $m_\infty(V) = \frac{1}{1+\exp\left(\frac{-20-V}{15}\right)}$, $n_\infty(V) = \frac{1}{1+\exp\left(\frac{-25-V}{5}\right)}$, $\tau_n(V) = 1$, $I = 0$.

- Most of the computations performed each step are due to computation of the exponential functions.

Simplified $I_{Na,p}$ - I_K

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- Most of the computations performed each step are due to computation of the exponential functions.

Simplified $I_{Na,p}$ - I_K

- But we can try to approximate the sigmoid $\frac{1}{1+\exp(x)}$ with some simpler smooth function with similar properties.
- For example function:

$$f(x) = \begin{cases} \frac{1}{2(0.175 \cdot x - 1)^5} + 1; & x < 0 \\ \frac{1}{2(0.175 \cdot x + 1)^5}; & x \geqslant 0 \end{cases}$$

does a pretty good job and requires one branching instruction, 5 multiplications (why?), one division and one or two additions/subtractions.

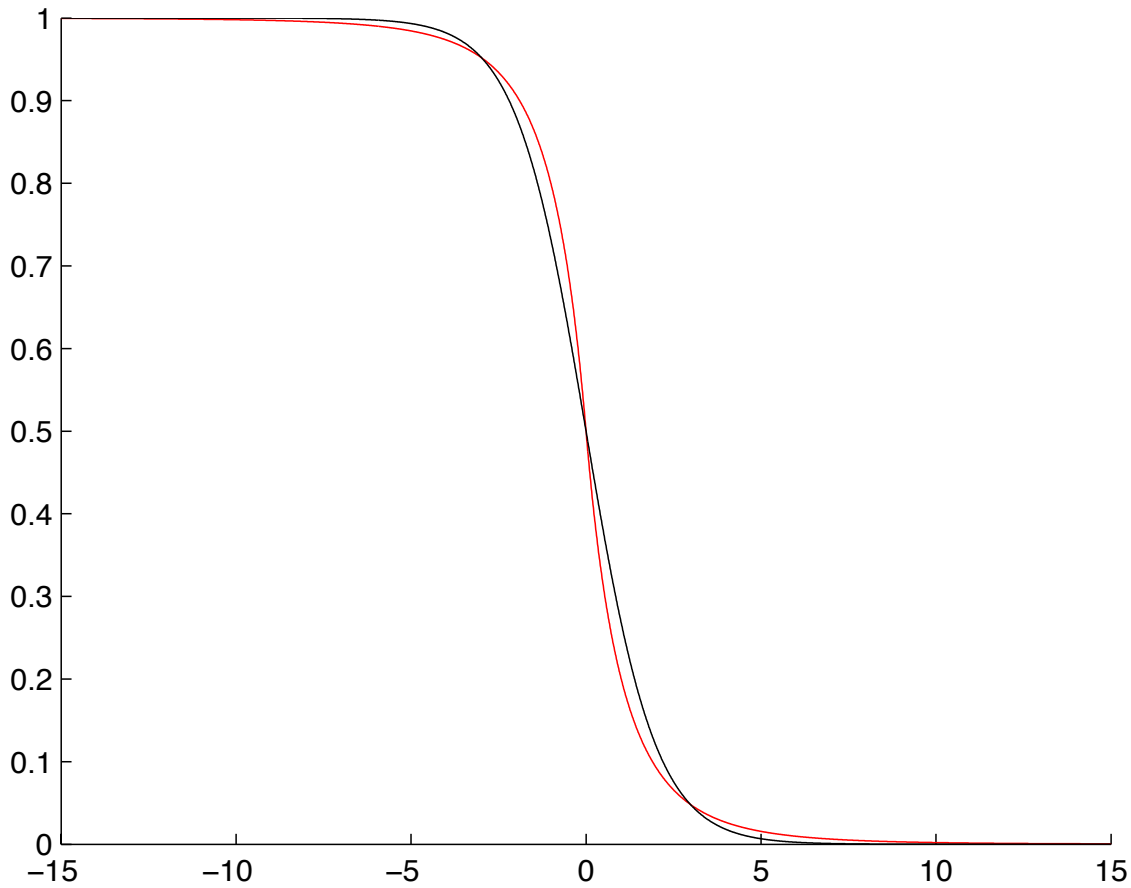


Figure: Two plots, function f from previous slide (red) and $\frac{1}{1+\exp(x)}$ sigmoid (black). The approximation is crude, but the function is far easier to compute, is smooth and differentiable.

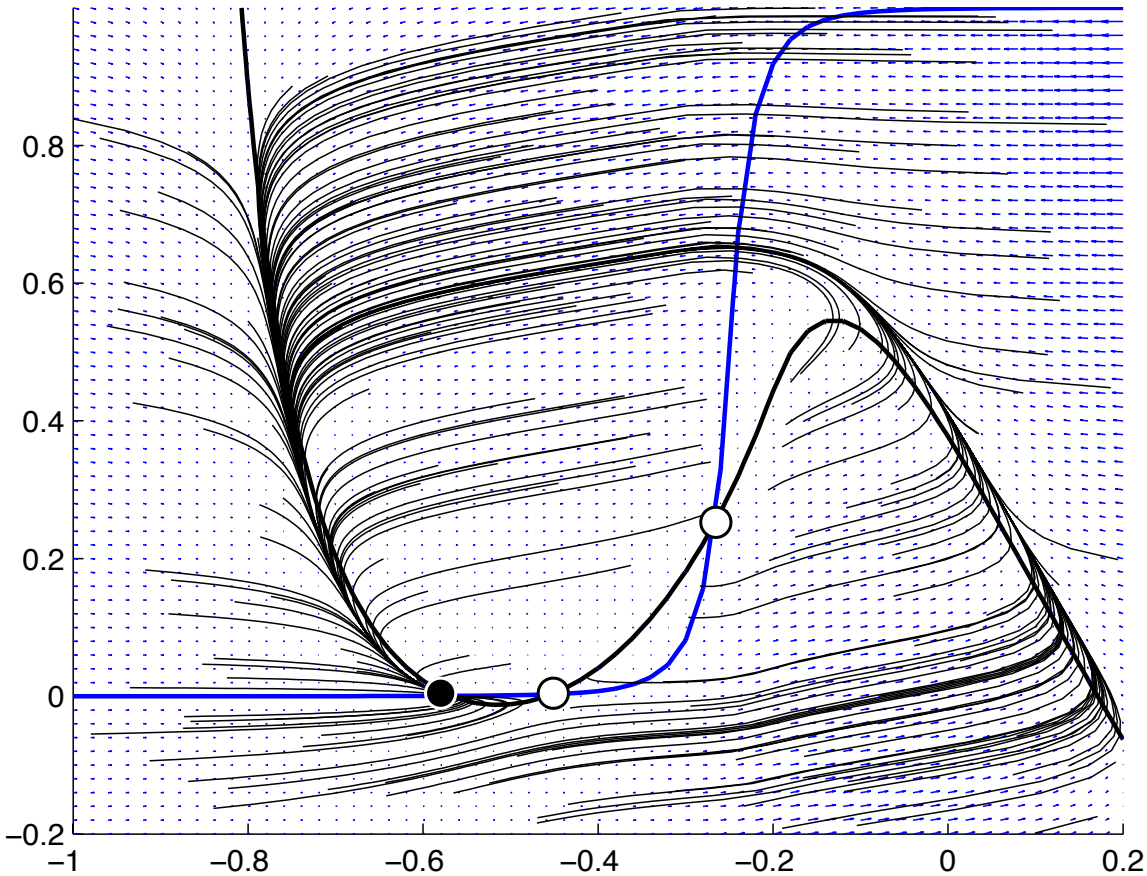
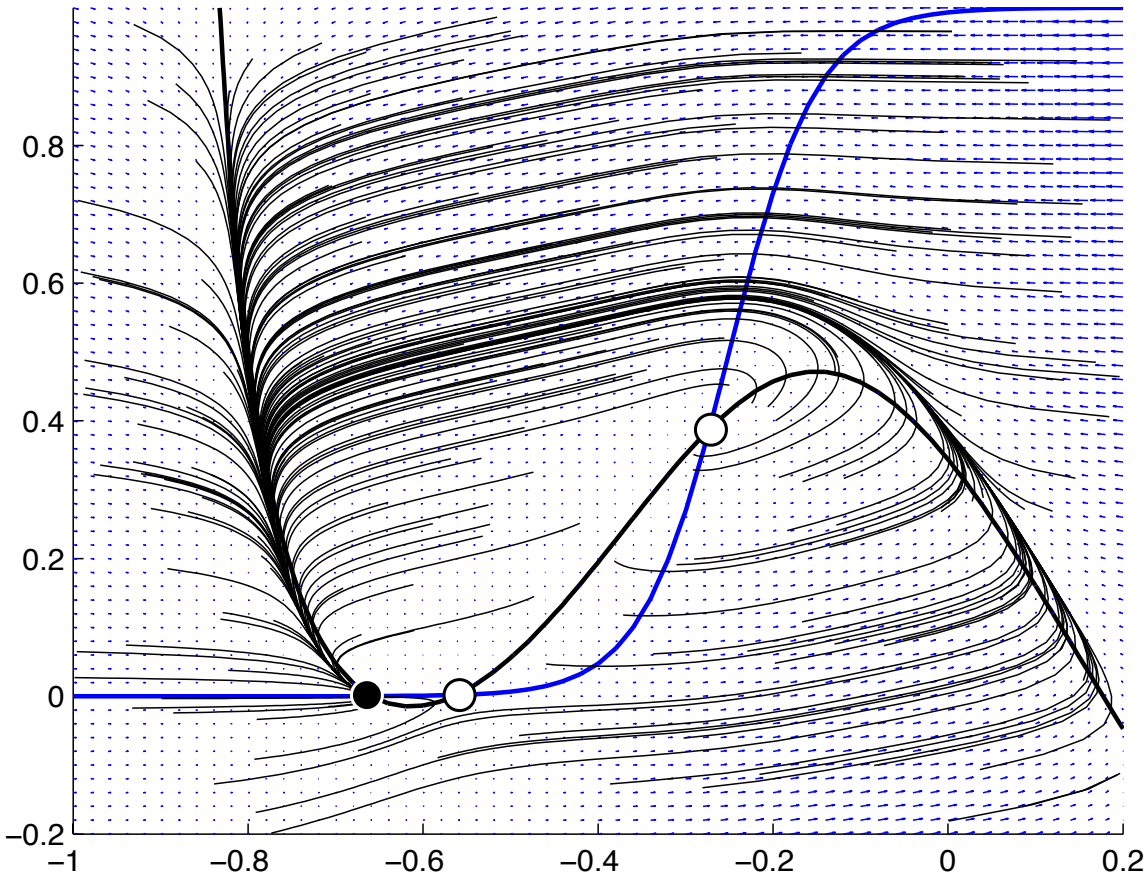


Figure: Phase portrait of the simplified $I_{Na,p}$ - I_K model with $m_\infty(V) = f((-20 - V)/15)$ and $n_\infty(V) = f((-25 - V)/2)$ and additional term $= -9$ added to the first equation. Compared with the original model.



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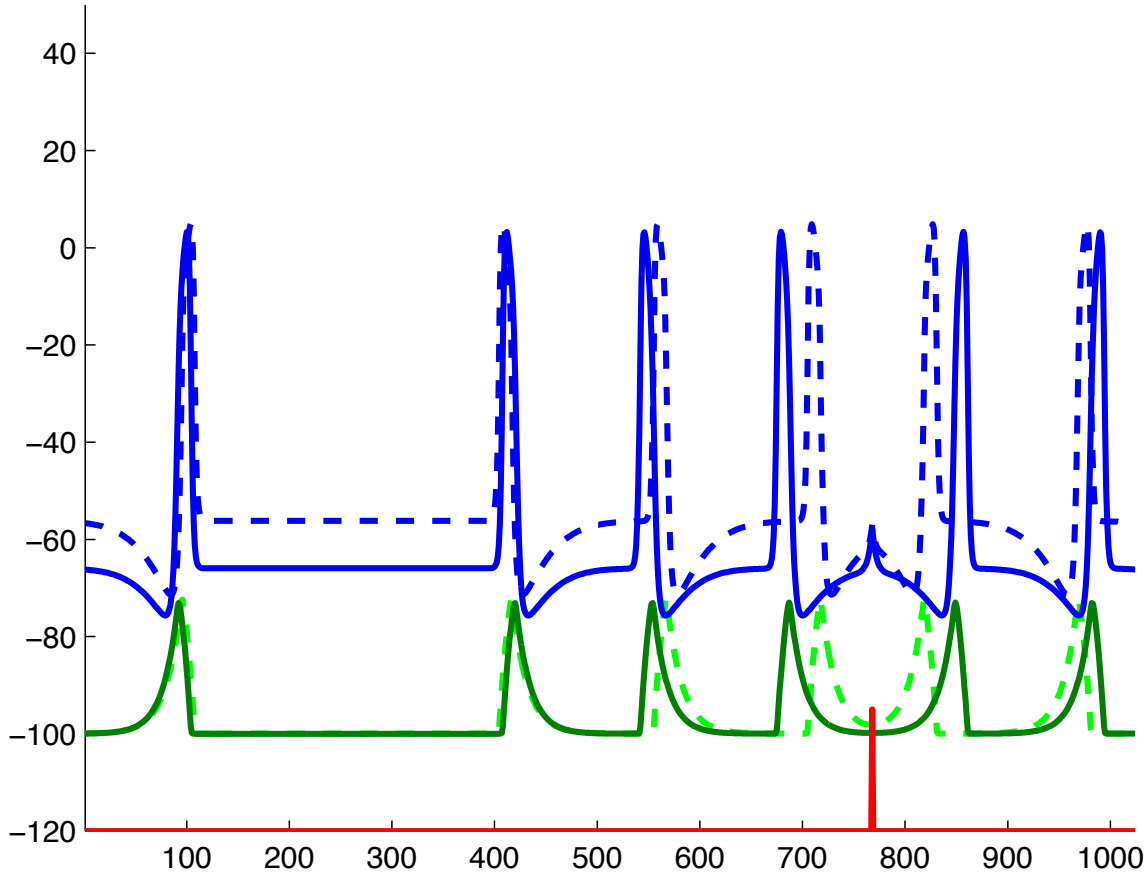


Figure: Comparison of the simplified (dashed line) and the original $I_{Na,p}$ - I_K model in a cable equation simulation. The spike propagation velocity and their shape are only slightly different.

- The rule is therefore to avoid any exp, sin, log, tan etc. functions, since their evaluation requires costly series expansion
- Even though we are still left with lots of possibilities, which are not as limited as one might expect
- We will begin with the simplest possible models, gradually increasing their complexity
- By the end of the section we will study a model that is quite efficient, though very accurately reproduces known spiking regimes

Integrate and fire

- The basic idea underlying integrators is that they store incoming current, and spike whenever the accumulated membrane potential exceeds some threshold
- This idea can be implemented with the so called integrate and fire neuron:

$$\frac{dV}{dt} = I - g_{\text{leak}}(V - E_{\text{leak}})$$

- Whenever V reaches certain value V_{th} an artificial spike is being generated (it is up to the programmer on how fancy the spike will be). After the spike V is set to V_{K} (a reset value) and the simulation continues.
- Even though the model is very simple, it can mimic the more complex integrators (like the $I_{\text{Na,p}}$ - I_{K}) quite well.

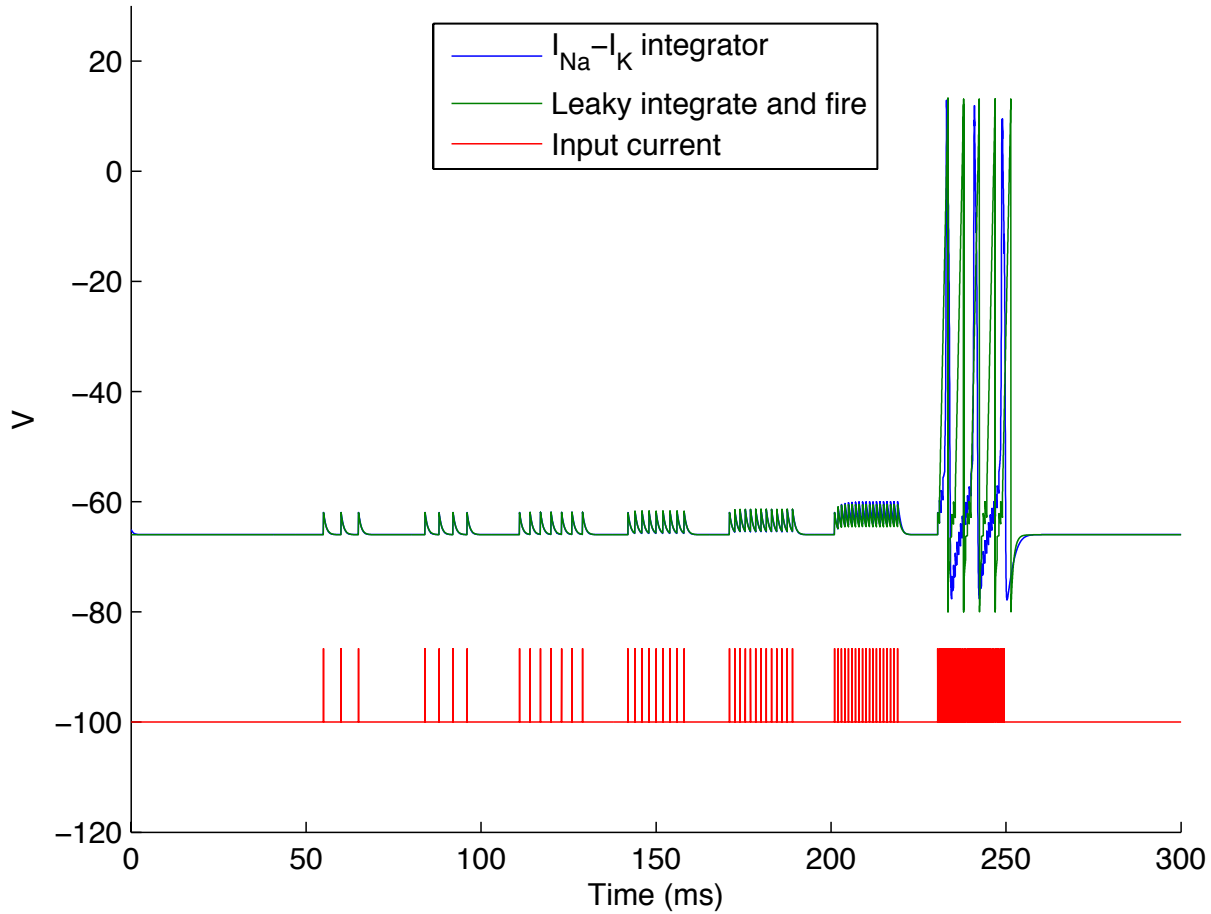
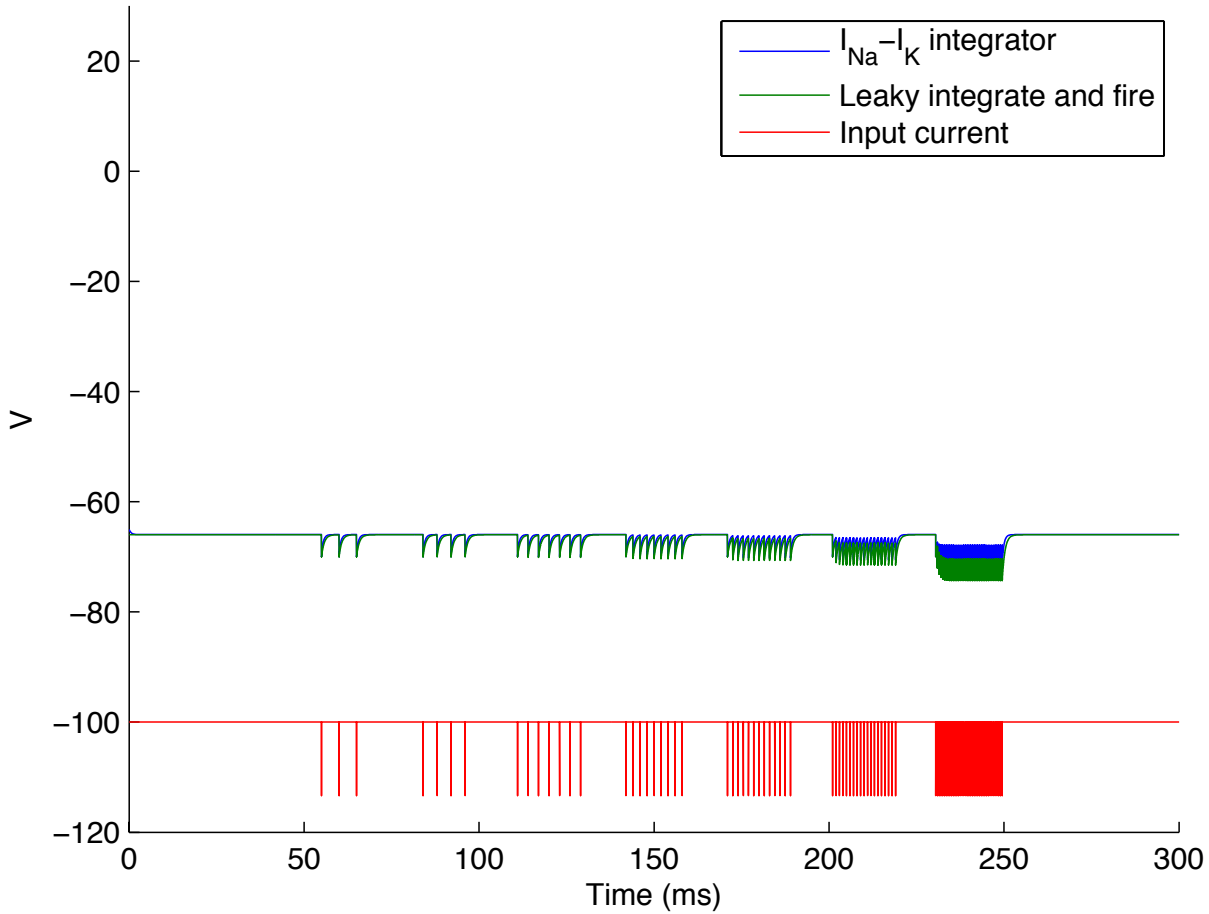


Figure: Comparison of the monostable $I_{Na,p}$ - I_K integrator with appropriately tuned leaky integrate and fire neuron in response to excitatory and inhibitory input.



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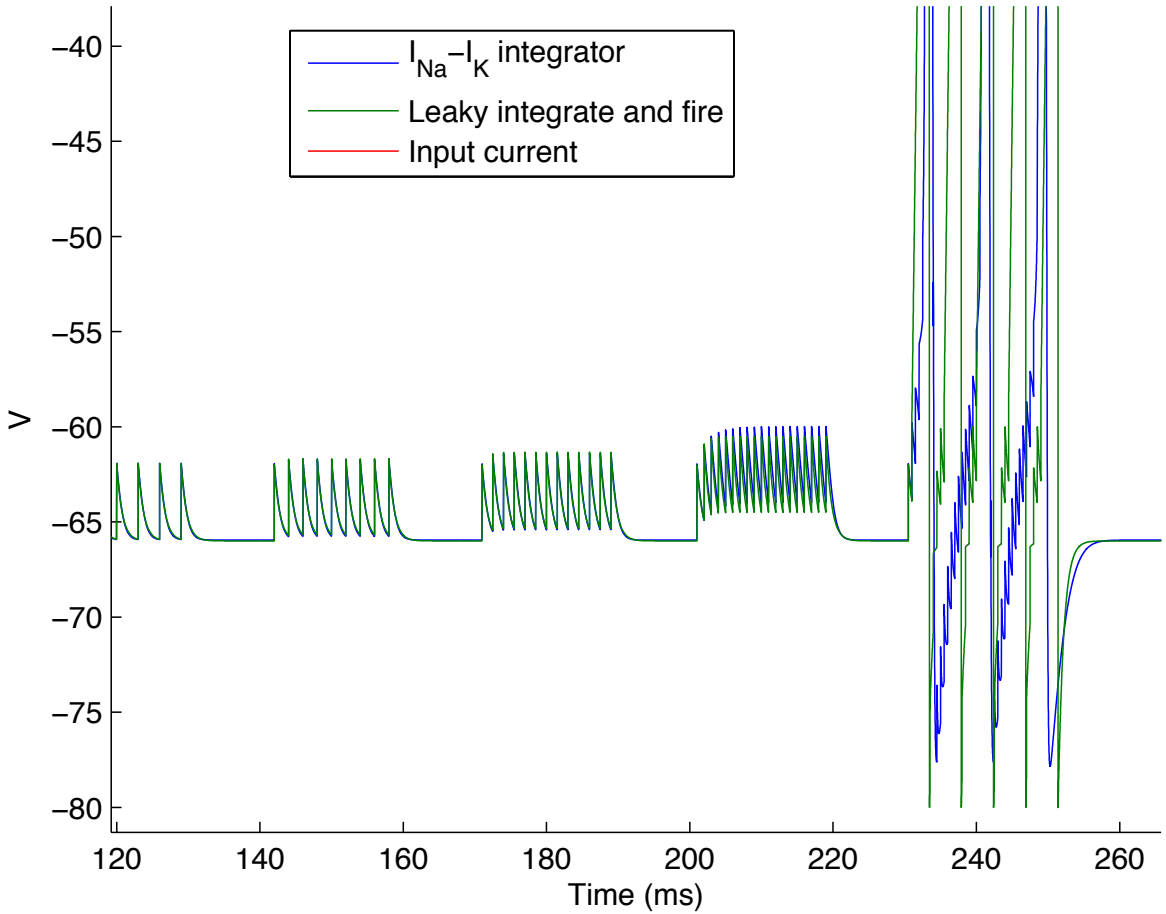


Figure: Comparison of the monostable $I_{Na,p}$ - I_K integrator with appropriately tuned leaky integrate and fire neuron in response to excitatory input (closeup).

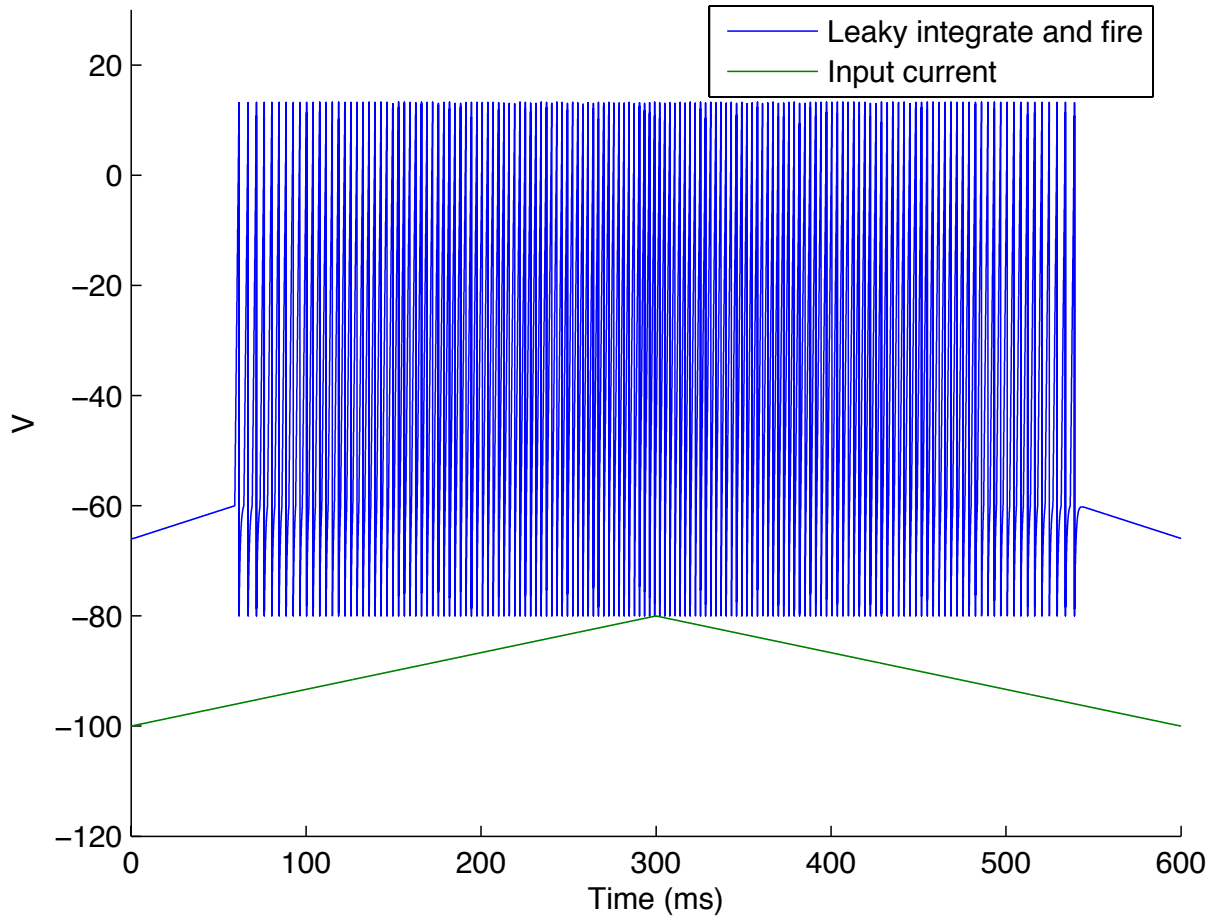


Figure: The leaky integrate and fire neuron in response to excitatory ramp current. The spiking frequency may get arbitrarily high.

Neuromime

- The spiking frequency of the leaky integrate and fire neuron can get arbitrarily high, which is not accurate from biological point of view.
- This weakness was addressed by French & Stein in 1970, by introducing the neuromime
- In this case the firing threshold is variable and depends on previous activity (which is far more plausible from the biological point of view).
- An input for neuromime is supplied to the first leaky integrator. Its output is then compared with the dynamical threshold Θ. If it exceeds Θ a spike is generated.
- The output spike is supplied back to another leaky integrator which is responsible for providing Θ. Therefore Θ gets increased, which causes further spikes less probable.

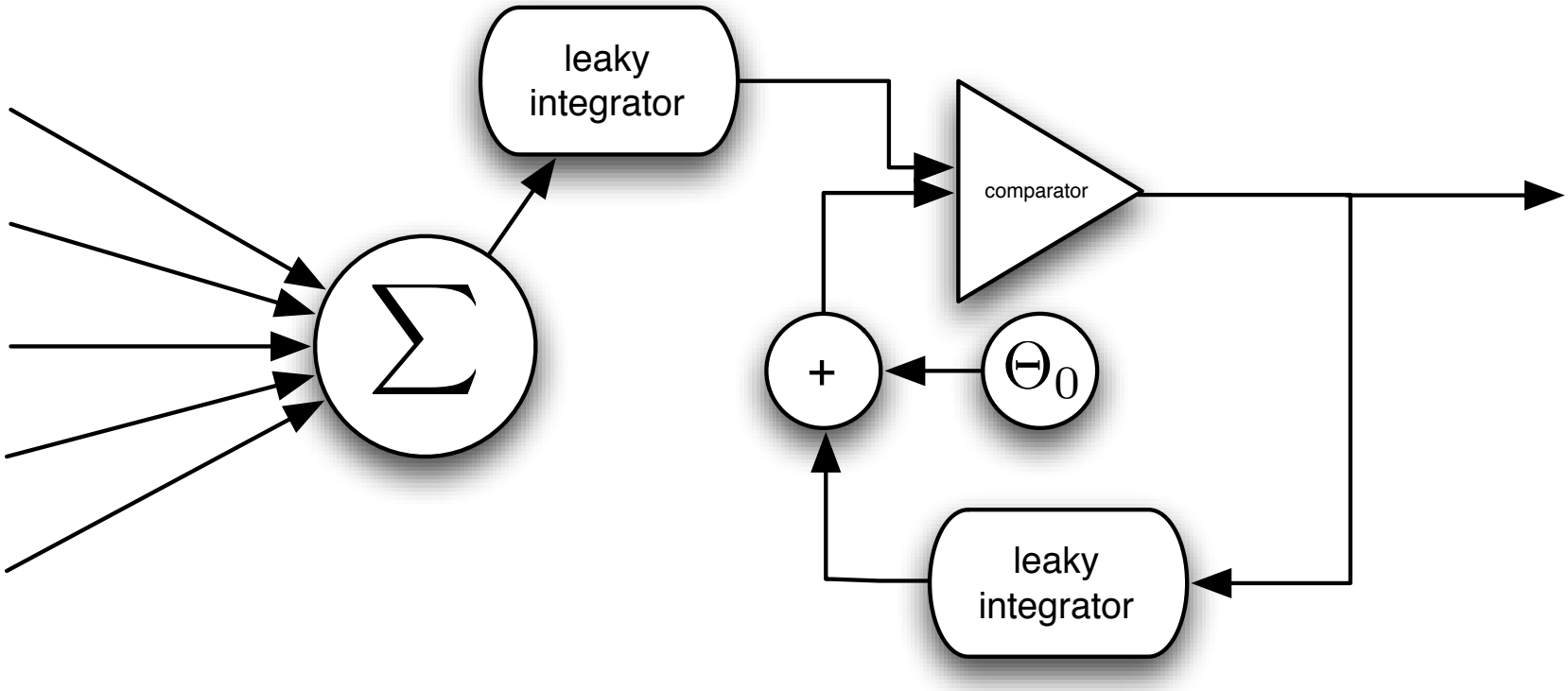


Figure: A sketch scheme of the neuromime model

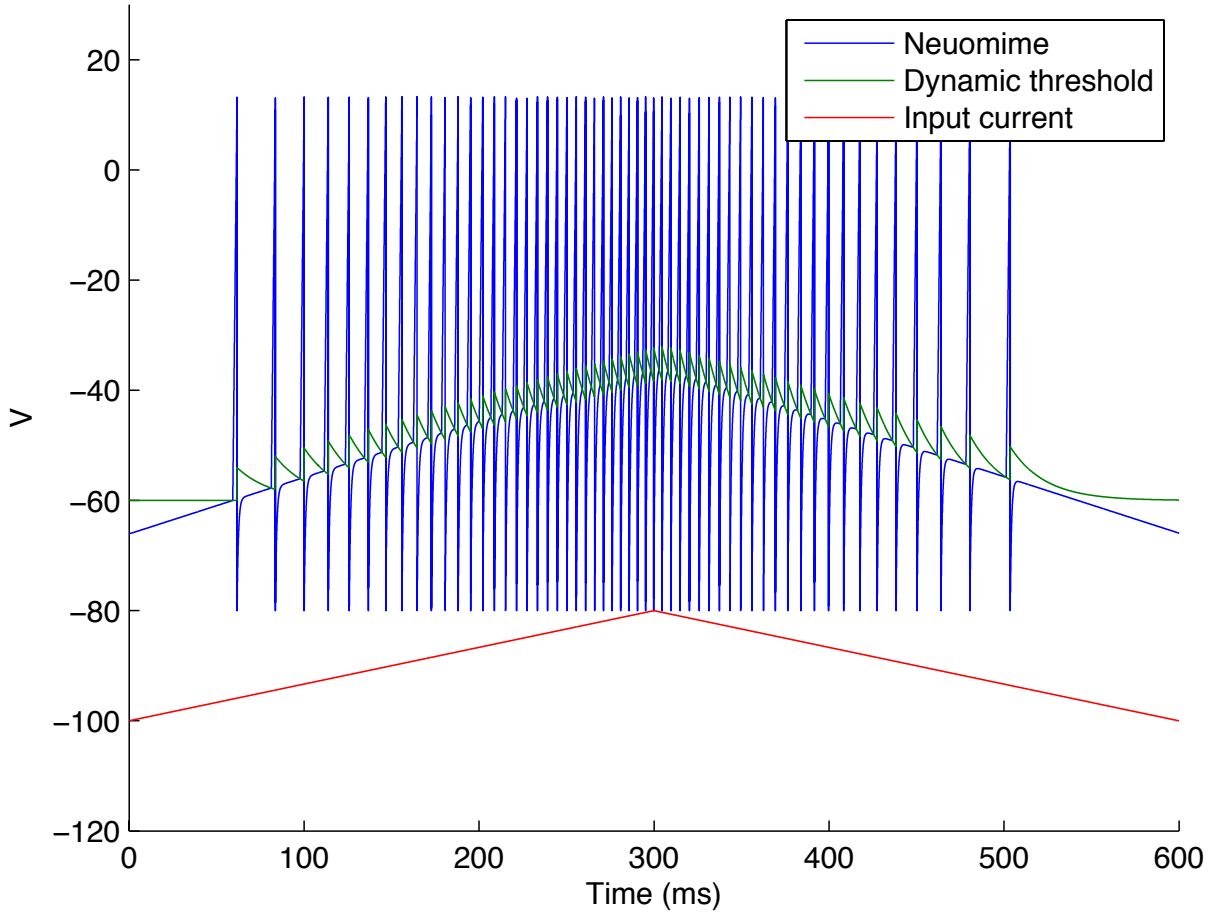


Figure: A response of neuromime to the ramp current.

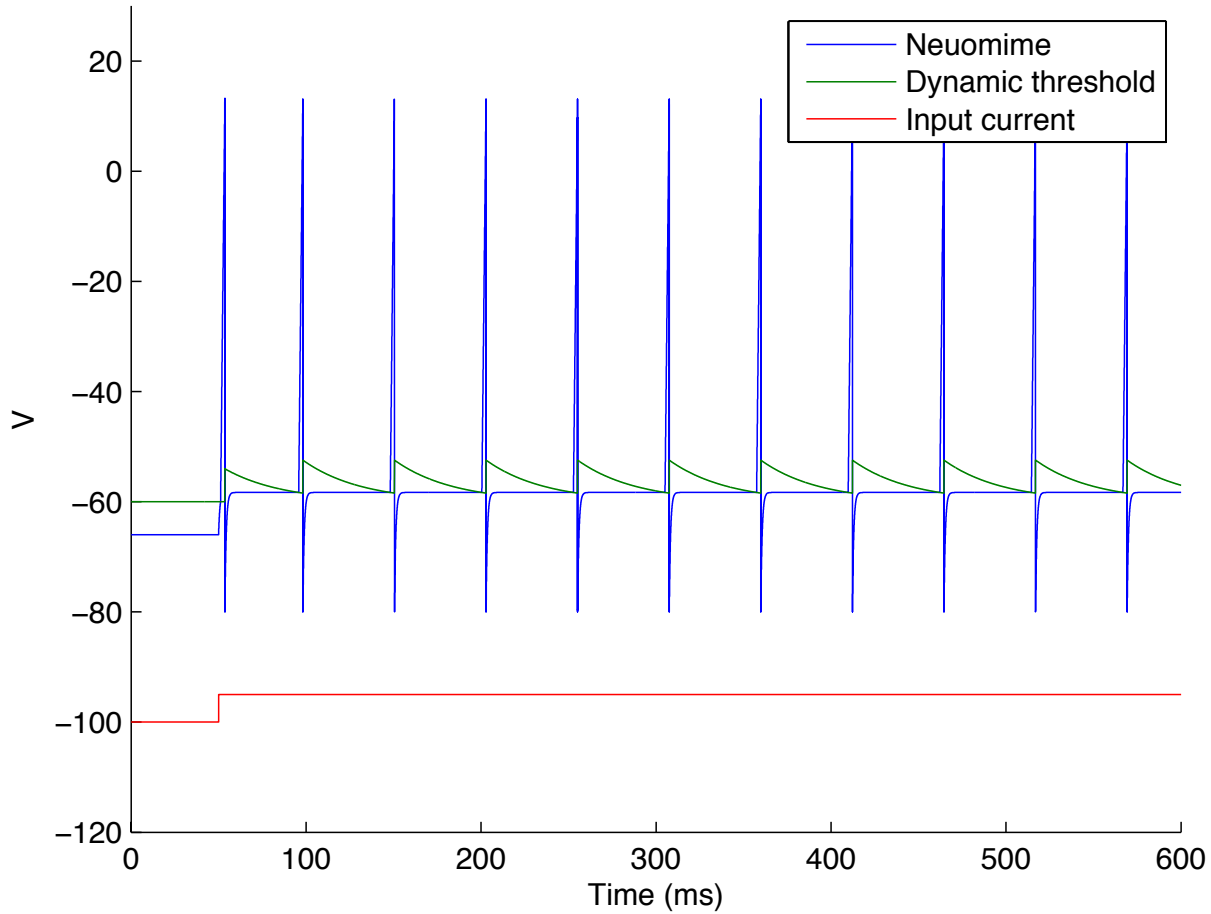
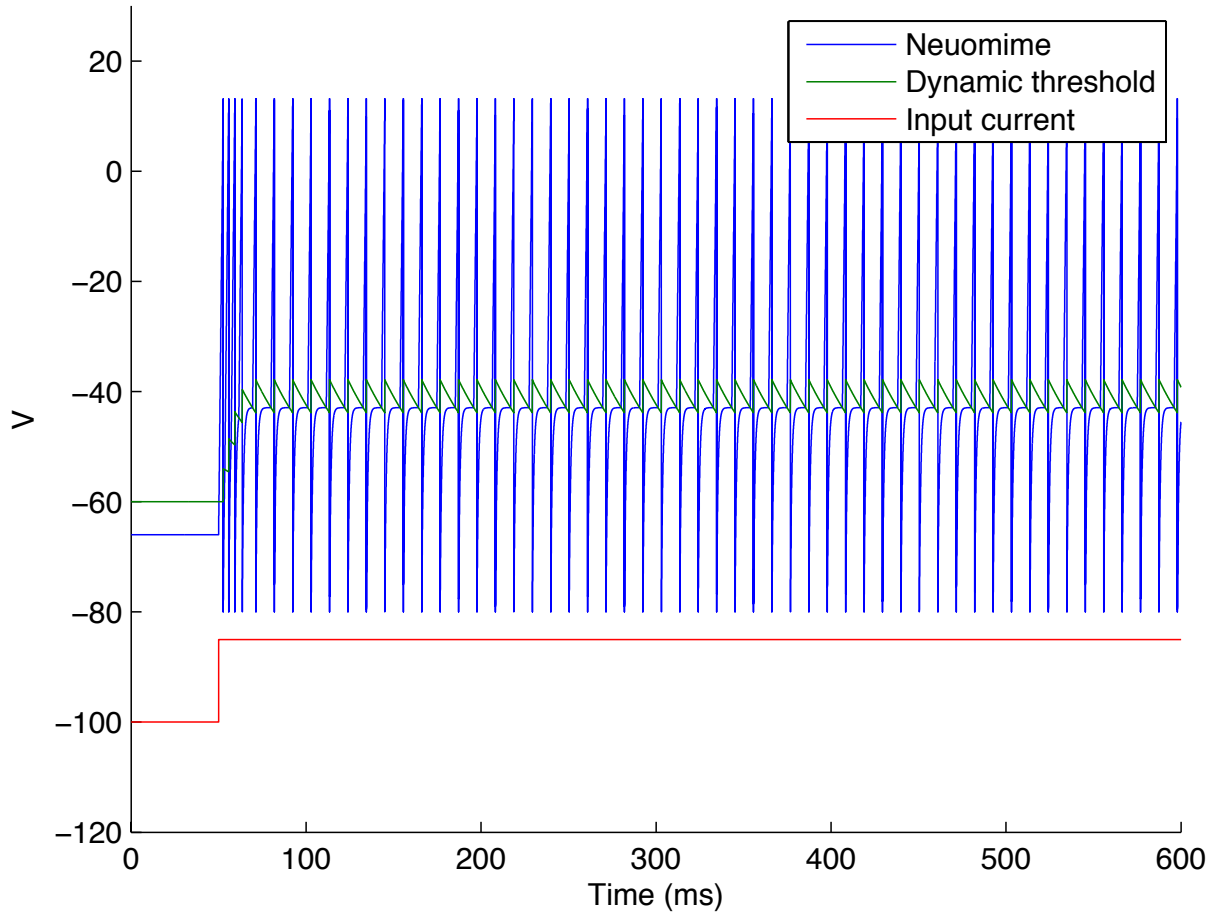


Figure: A response of neuromime to increasing step currents. Note the spike frequency accommodation.



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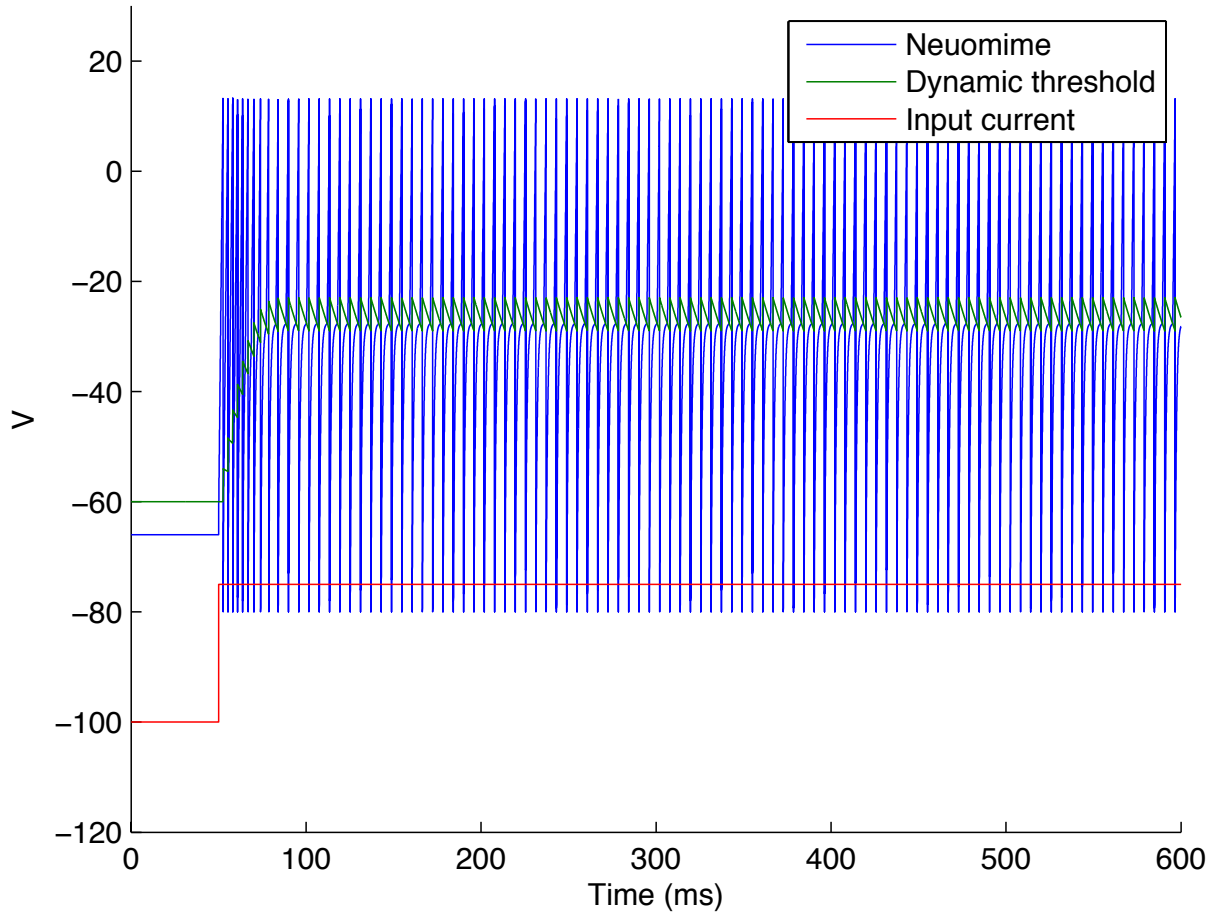

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Neuromime

- Neuromime is the basic unit for Pulse Coupled Neural Networks (PCNN), an approach to build neural like circuits for image segmentation and processing.
- Unlike integrate and fire neurons, neuromime accommodates its firing rate to the magnitude of input, but in contrast to biological neurons it lacks important dynamical features like subthreshold oscillations or excitation block.
- Lets now focus on a simple model that simulates a resonator.

Resonate and fire

- The resonate and fire neuron is given by a set of two equations:

$$C\frac{dV}{dt} = I - g_{\text{leak}}(V - E_{\text{leak}}) - W$$
$$\frac{dW}{dt} = (V - V_{1/2})/k - W$$

  where $V_{1/2}$ and k are parameters
- The model simulates the phase space near a focus node, but can also be equipped with artificial spike generation mechanism, whenever say V crosses certain V_{th}.

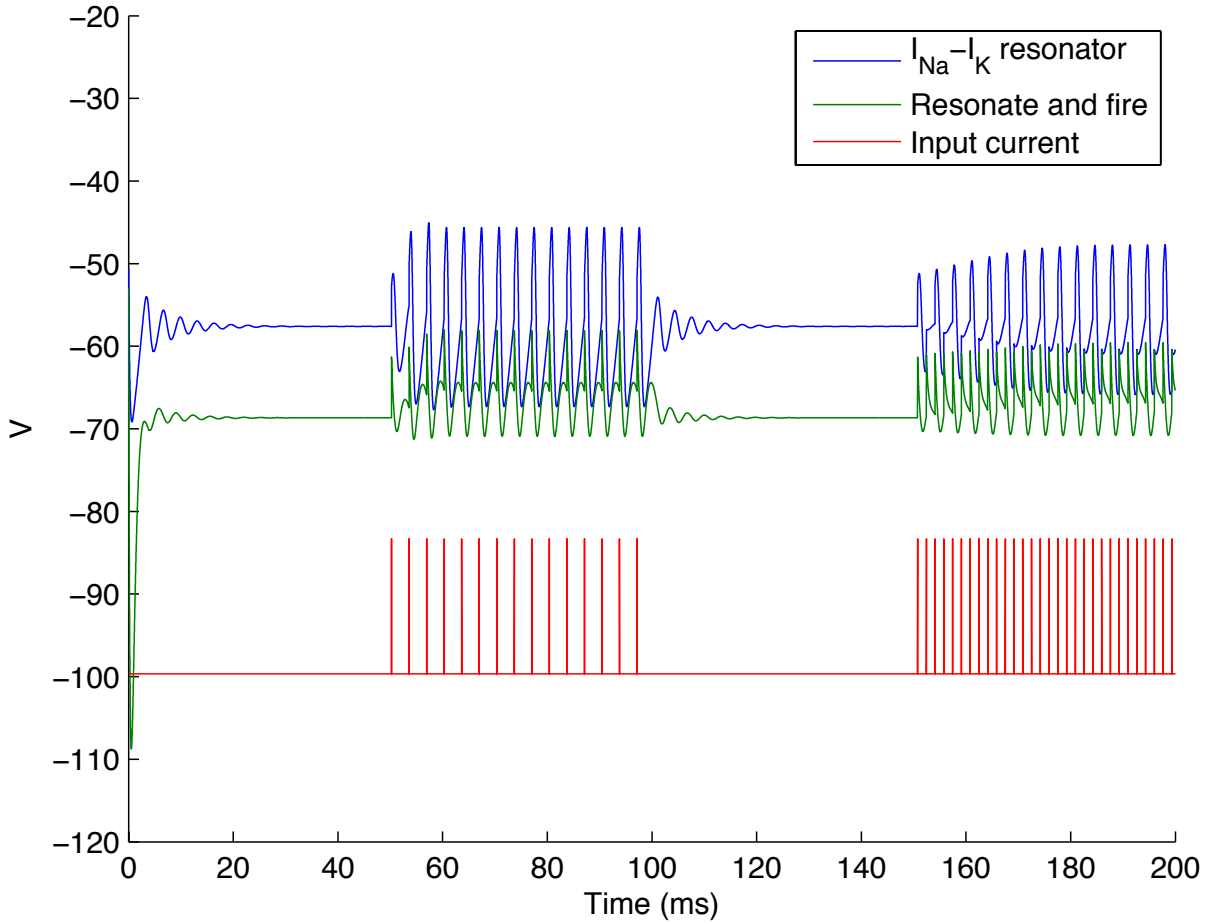
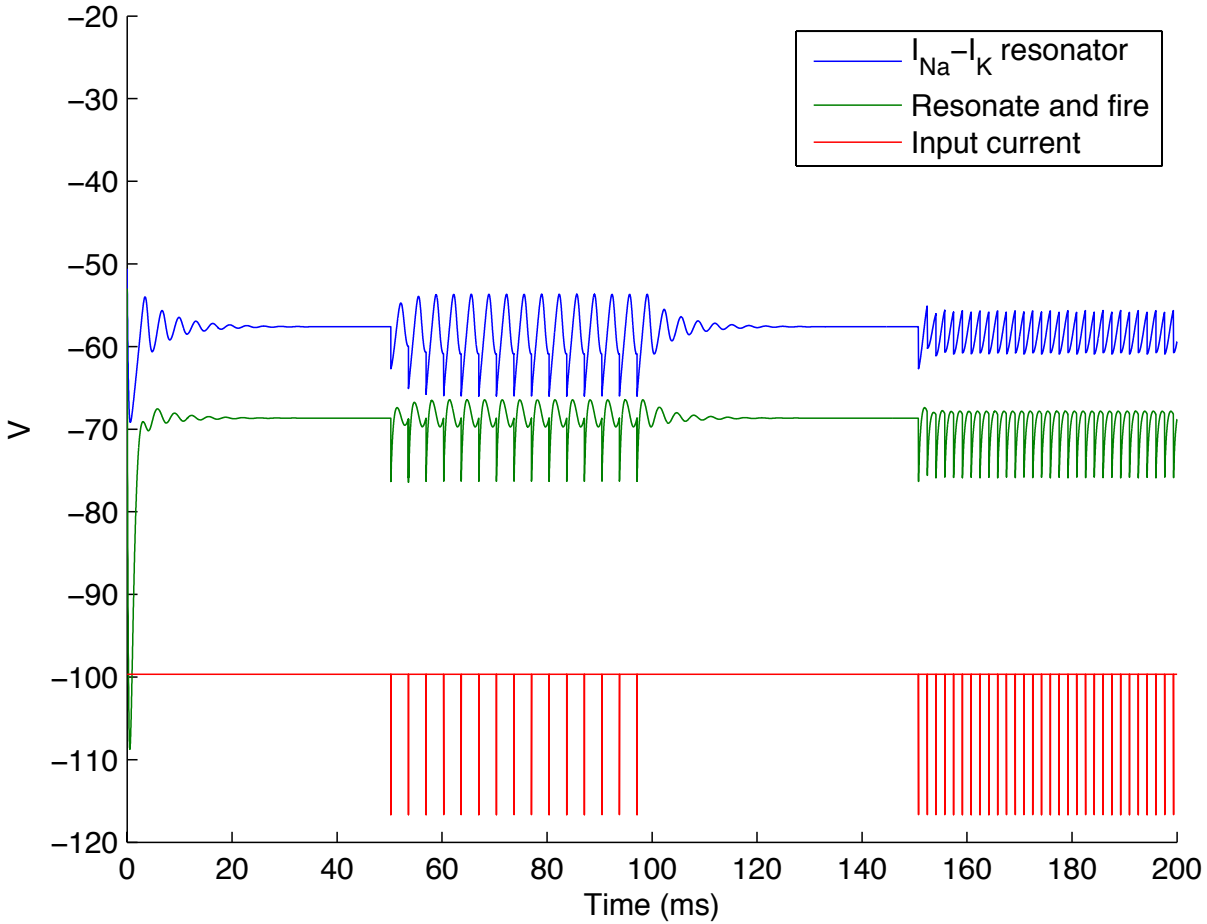


Figure: Comparison of the monostable $I_{Na,p}$ - I_K resonator with appropriately tuned leaky resonate and fire neuron in response to excitatory and inhibitory input.



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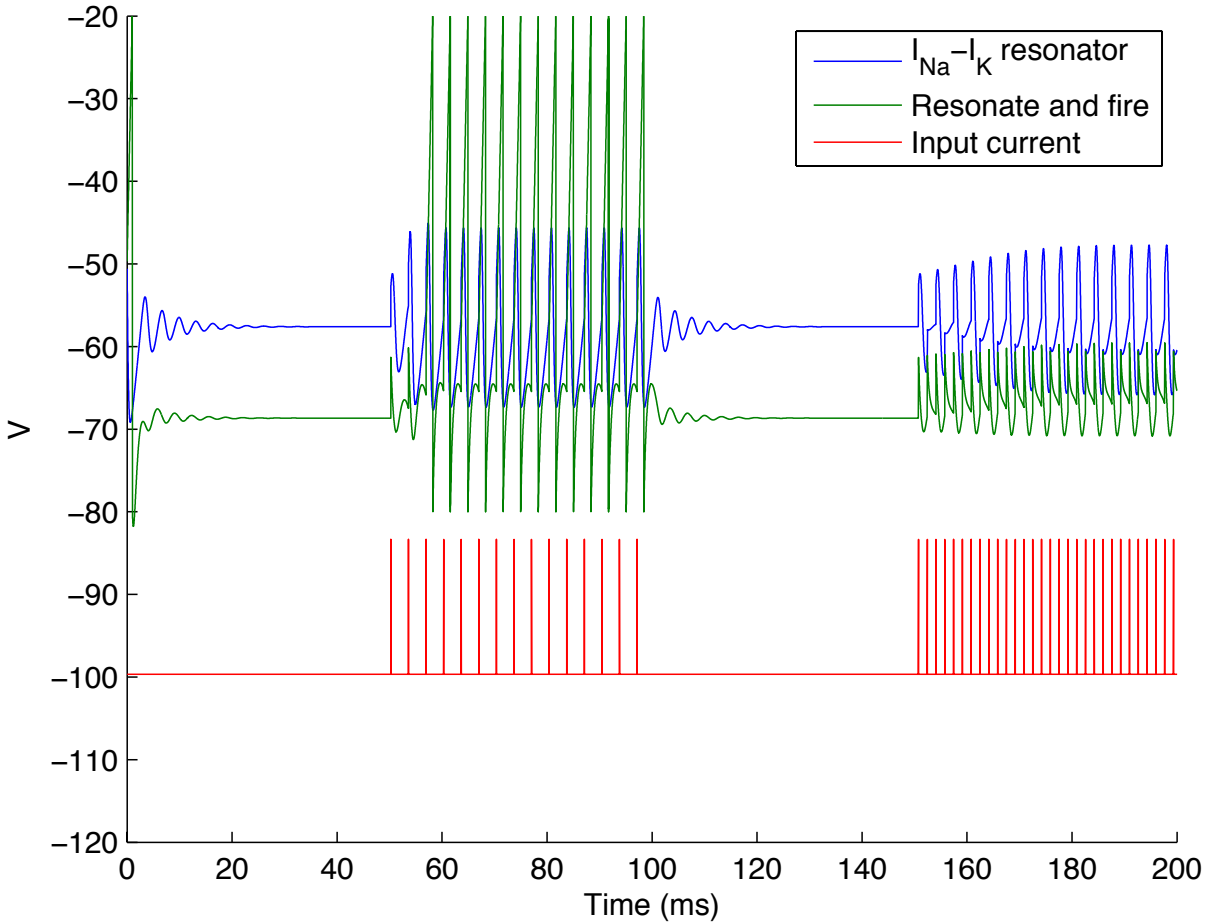


Figure: Comparison of the monostable $I_{Na,p}$ - I_K resonator with appropriately tuned leaky resonate and fire neuron. Good tuning of threshold allows to fire inhibitory induced (artificially generated) spikes.

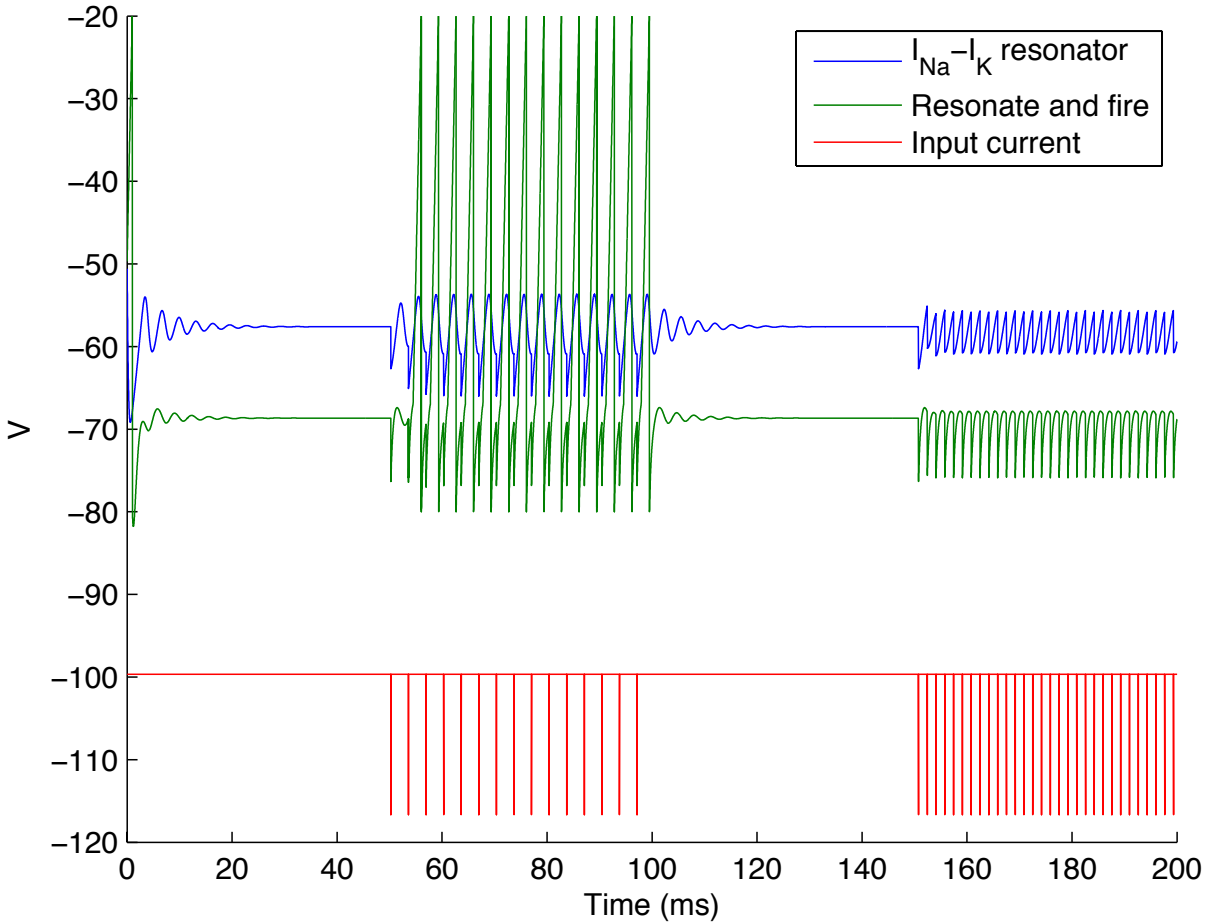


Figure: Comparison of the monostable $I_{Na,p}$ - I_K resonator with appropriately tuned leaky resonate and fire neuron. Good tuning of threshold allows to fire inhibitory induced (artificially generated) spikes.

- Leaky integrate and fire and resonate and fire models are not very useful for simulating real neurons. Neuromime can be good for engineering applications, but lacks many biological features.
- The approach taken by Richard FitzHugh in 1961 was to get rid of all the ionic conductances, and mimic the phase plane with simple polynomial and a linear function (Jin-Ichi Nagumo later created an electrtical device that implemented the model using tunnel diodes). The model is defined:

$$\frac{dV}{dt} = V - V^3 - W - I$$
$$\frac{dW}{dt} = 0.08(V + 0.7 + 0.8W)$$

(in general the V nullcline is a third degree polynomial, while W nullcline is linear).

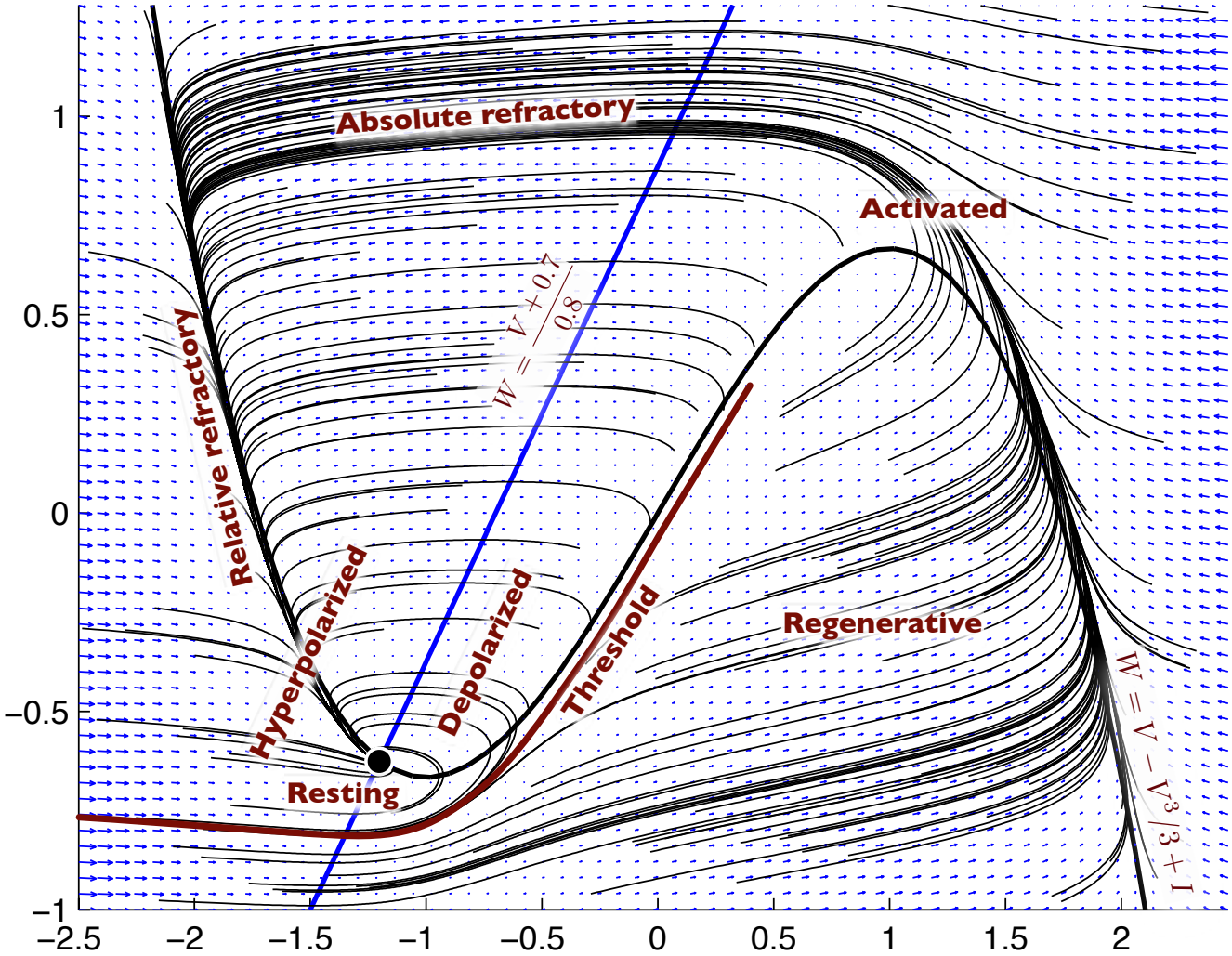


Figure: An annotated phase portrait of the FitzHugh-Nagumo model.

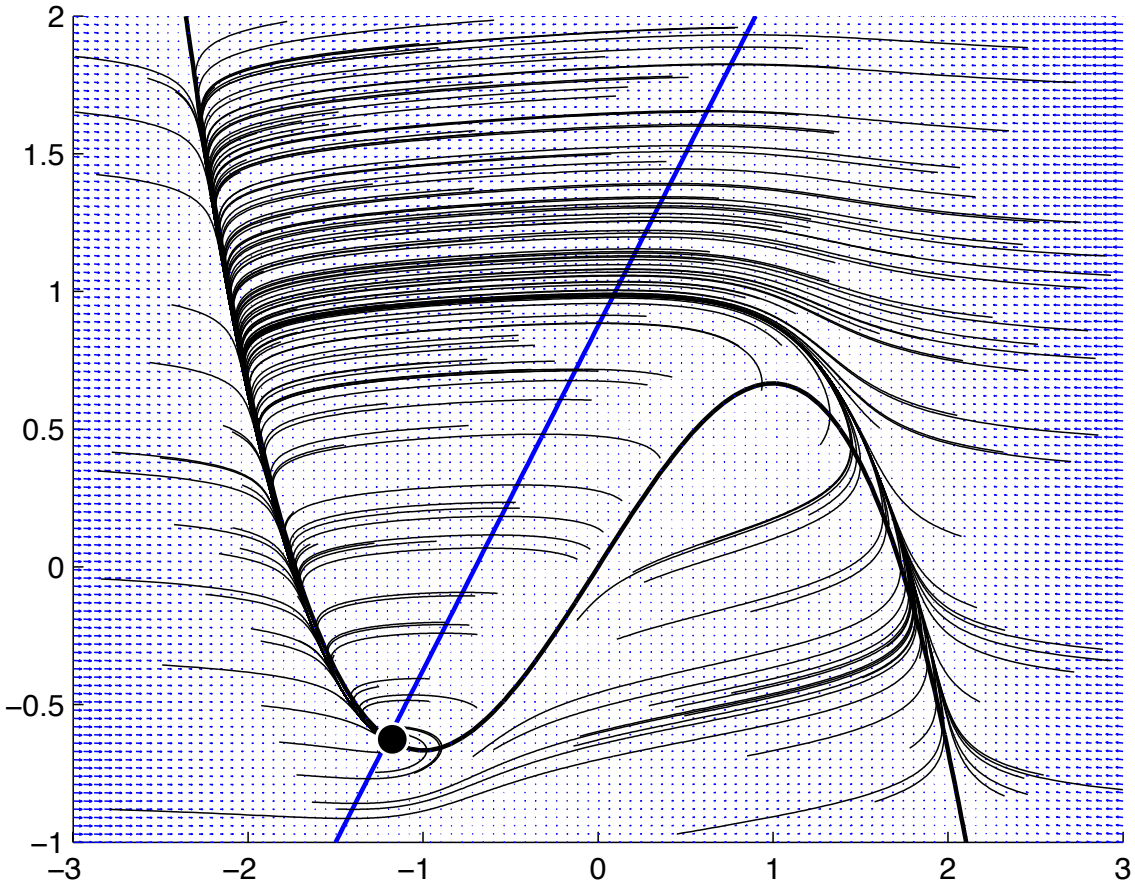
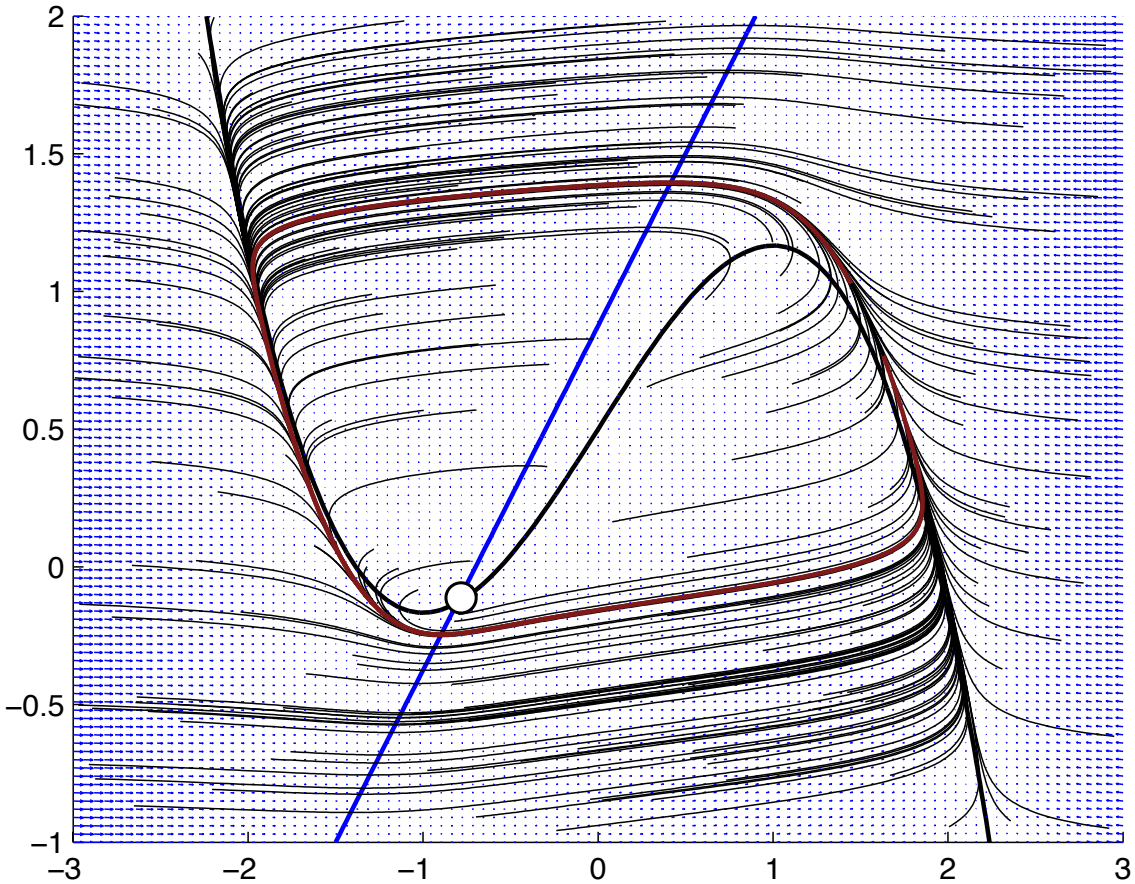


Figure: Phase portraits of the FitzHugh-Nagumo model (as given in previous slide) for $I = 0$ and $I = 0.5$ the stable focus looses stability at some point in between.



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FitzHugh-Nagumo model

- The more general form for the model is

$$\frac{dV}{dt} = V(a - V)(V - 1) - W - I$$
$$\frac{dW}{dt} = bV - cW$$

  by varying dimensionless parameters a, b and c one can obtain a system which has 1,2 or 3 intersections of nullclines exhibiting most of the known dynamical neuronal properties.
- The system much like the $I_{Na,p}$ - I_K model undergoes all of the bifurcations discussed on previous lectures, but evaluation of the right hand side function requires only at most three multiplications (one extra multiplication is required for the time step) .

FitzHugh-Nagumo model

- The model is also a good choice for cable equation and general reaction-diffusion systems

$$\frac{dV}{dt} = \alpha \frac{\partial^2 V}{\partial x^2} + V(a - V)(V - 1) - W - I$$
$$\frac{dW}{dt} = bV - cW$$

  The code implementing the FitzHugh-Nagumo cable equation model can fit on a single slide!

- Check out http://www.scholarpedia.org/wiki/images/ftp/FitzHugh_movie.mov

```
function cableFN()
ff=figure;
N=1024; % Number of spatial compartments (spatial resolution)
V=ones(1,N)*(-1);  W=ones(1,N)*(-0.5);  I=zeros(1,N); i=1;
tau = 0.1; tspan = 0:tau:1000;
% Second order derivative operator (sparse matrix)
S=sparse([1:N 1:N 2:N 1],[1:N 2:N 1 1:N ],[-2*ones(1,N) ones(1,2*N) ]);
for t=tspan
    if (t>0) I(1,N/4+N/2)=30; end; % to ignite any interesting action
    V = V + tau*((S*V')'-V.^3./3+V-W+I);
    W = W + tau*0.08*(V+0.7-0.8*W);
    if (mod(i,25)==0)
       cla; hold on;
       plot(1:N,V+1,1:N,W/3-2,1:N,I/40-2.5,'Linewidth',2);
       hold off;  axis([1 N -3 4]); legend('V','n','I');  drawnow;
    end;
    i=i+1;
end;
```

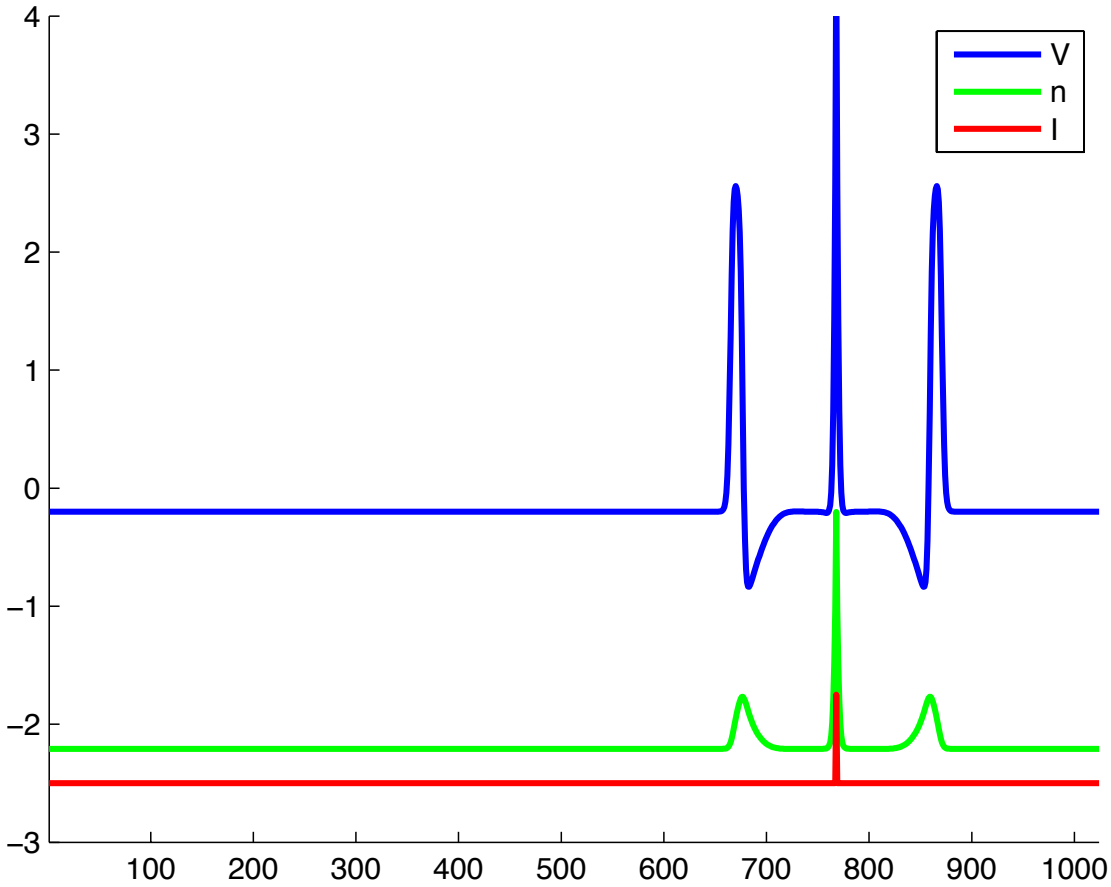


Figure: A screen of the cable equation simulation done by the code on previous slide.

Simple Model of Eugene M. Izhikevich

- Recall that the quadratic integrate and fire model with reset is a canonical model for the saddle-node homoclinic orbit bifurcation and depending on the reset value can exhibit various phenomena.
- E. Izhikevich noticed, that the important decision whether to spike or not is performed near the left knee of the "cubic" nullcline, whereas the exact shape of the action potential is not very important in large scale neural simulations
- As a result he combined a two parameter model of the left knee of "cubic" nullcline (approximated with the quadratic parabola) with the reset (which is performed on both variables).
- The resulting model, depending on parameters, can mimic dynamic behavior near many bifurcations.

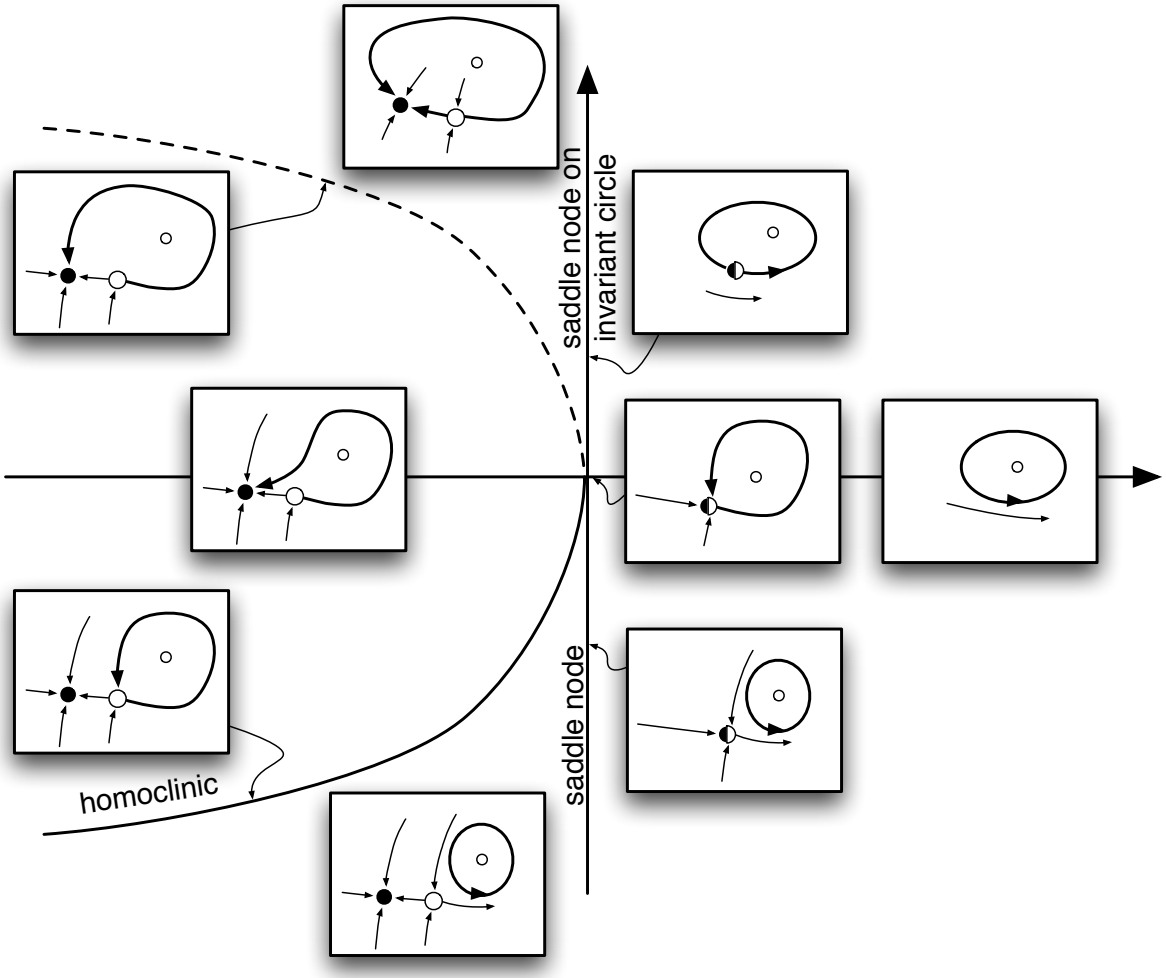


Figure: Saddle-node homoclinic orbit bifurcation diagram and corresponding canonical models with reset value.

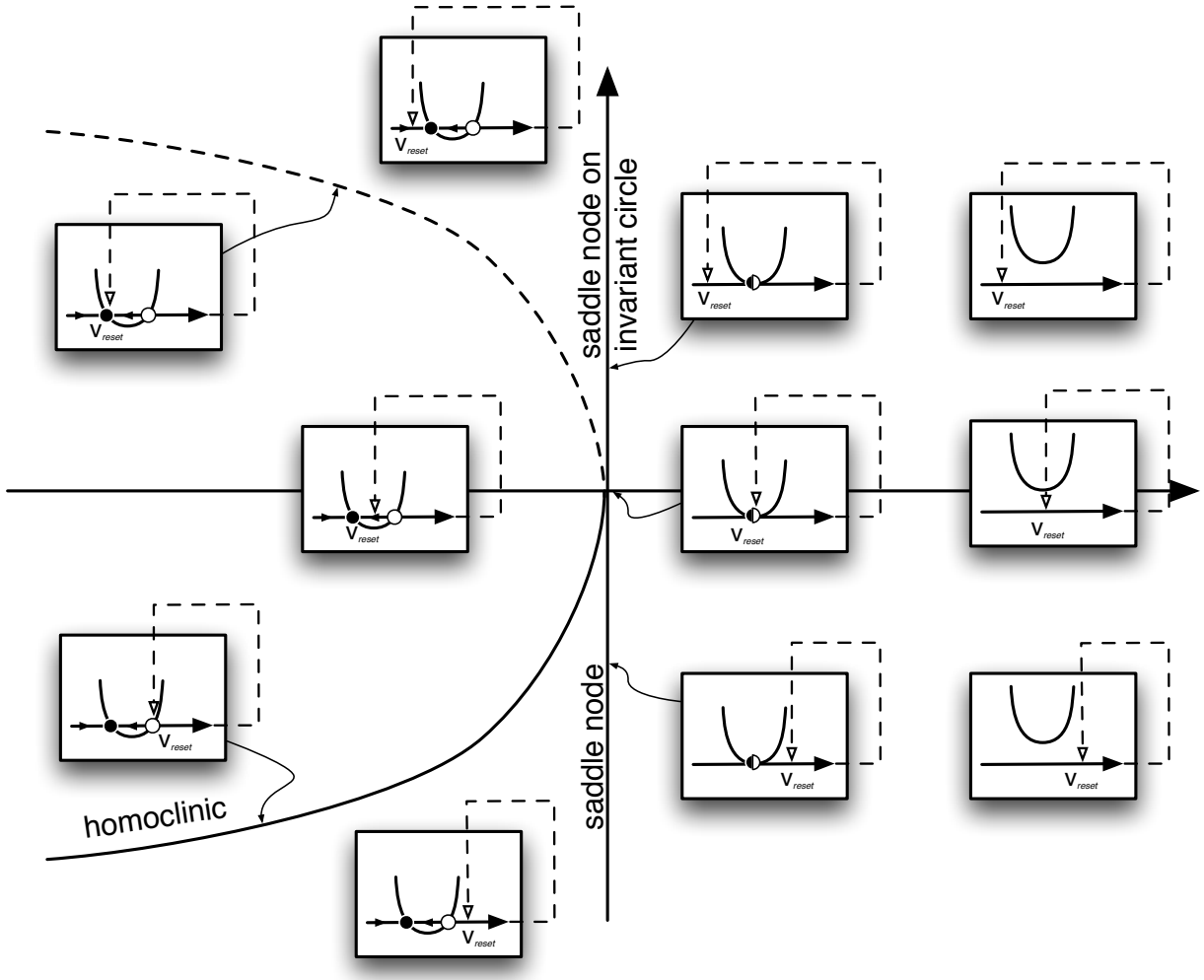


Figure: Saddle-node homoclinic orbit bifurcation diagram and corresponding canonical models with reset value.

Simple Model of Eugene M. Izhikevich

- The model defined as follows:

$$\begin{aligned} C\frac{dV}{dt} &= k(V - V_r)(V - V_t) - U + I \\ \frac{dU}{dt} &= a\,(b(V - V_r) - U) \end{aligned}$$

  moreover if $V > V_{peak}$ $V := c$ and $U := U + d$.
  $a, b, c, d, V_{peak}, k, C, V_r, V_t, I$ are parameters (there are ten parameters, but in fact there are only four independent parameters)
- Much like 1d quadratic integrate and fire with reset can mimic 2d system near saddle-node homoclinic orbit bifurcation, the 2d Simple Model with reset can mimic a 3d system near various bifurcations!

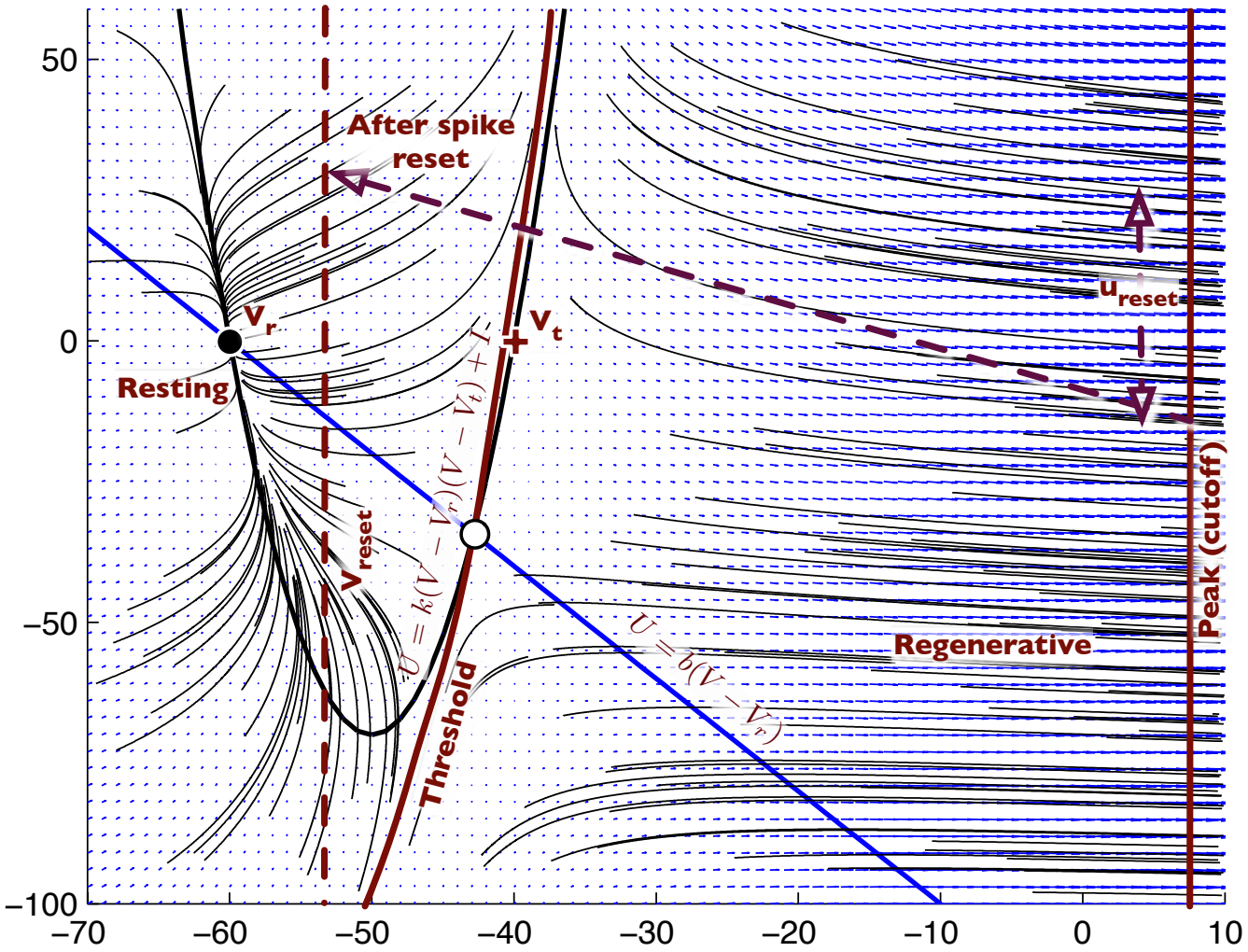


Figure: An annotated phase portrait of the Izhikevich Simple Model.

The Simple Neuron model can be written in the form

$$\frac{dV}{dt} = \alpha V^2 + \beta V + \gamma - U$$
$$\frac{dU}{dt} = a(bV - U)$$

for some parameters. Recall the normal form of Bogdanov-Takens bifurcation:

$$\frac{dx}{dt} = y$$
$$\frac{dy}{dt} = c_1 + c_2 x + x^2 + \sigma xy$$

The simple model can exhibit Bogdanov-Takens bifurcation (integrator - resonator transition).

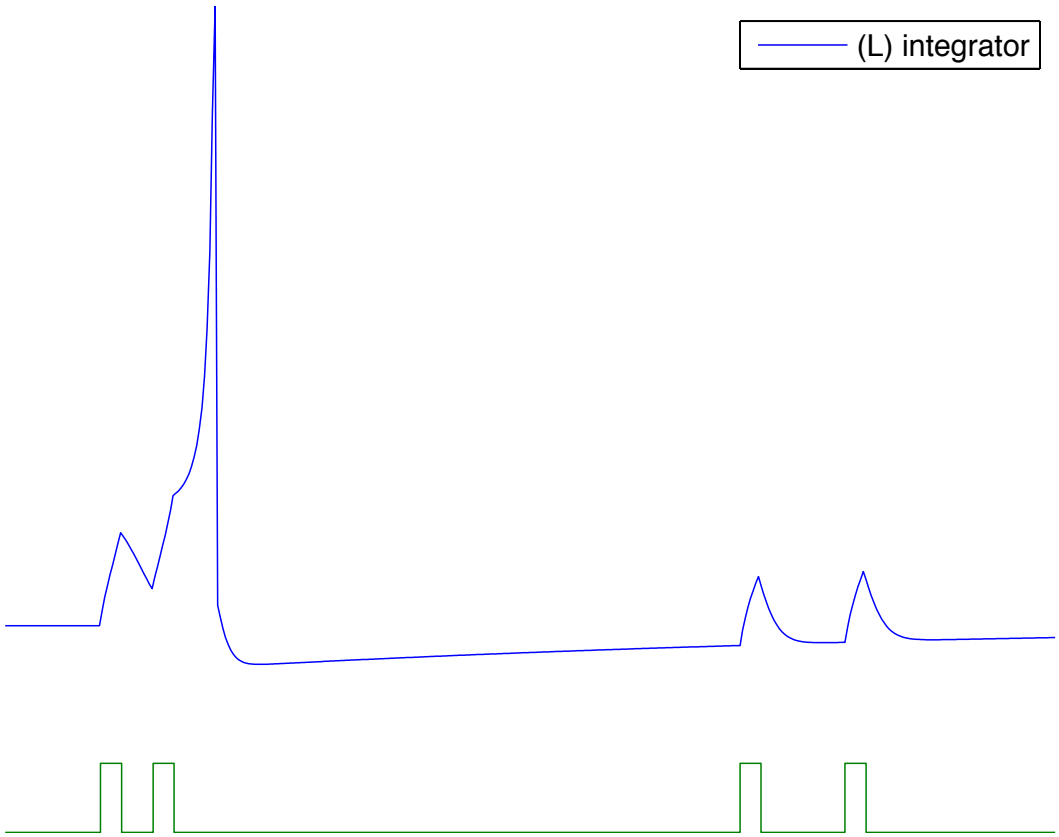
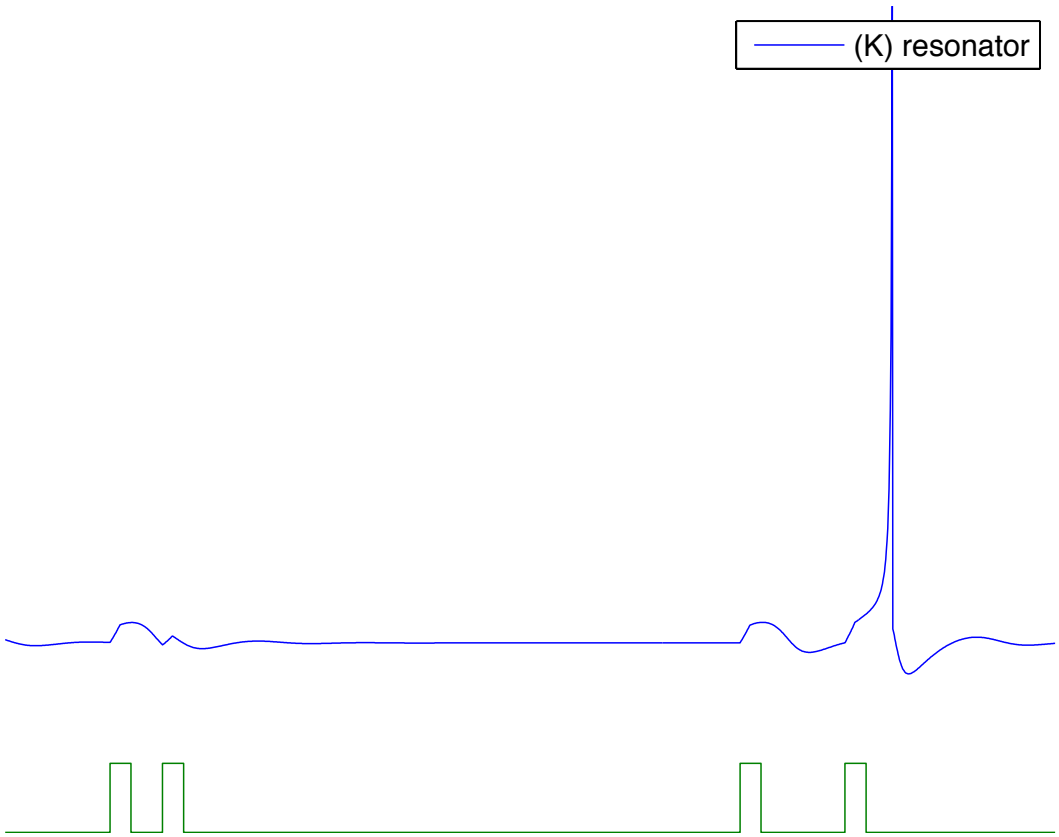


Figure: Dynamic regimes exhibited by the simple model by Eugene M. Izhikevich, see http://www.izhikevich.org/publications/whichmod.htm figure1.m for parameters.



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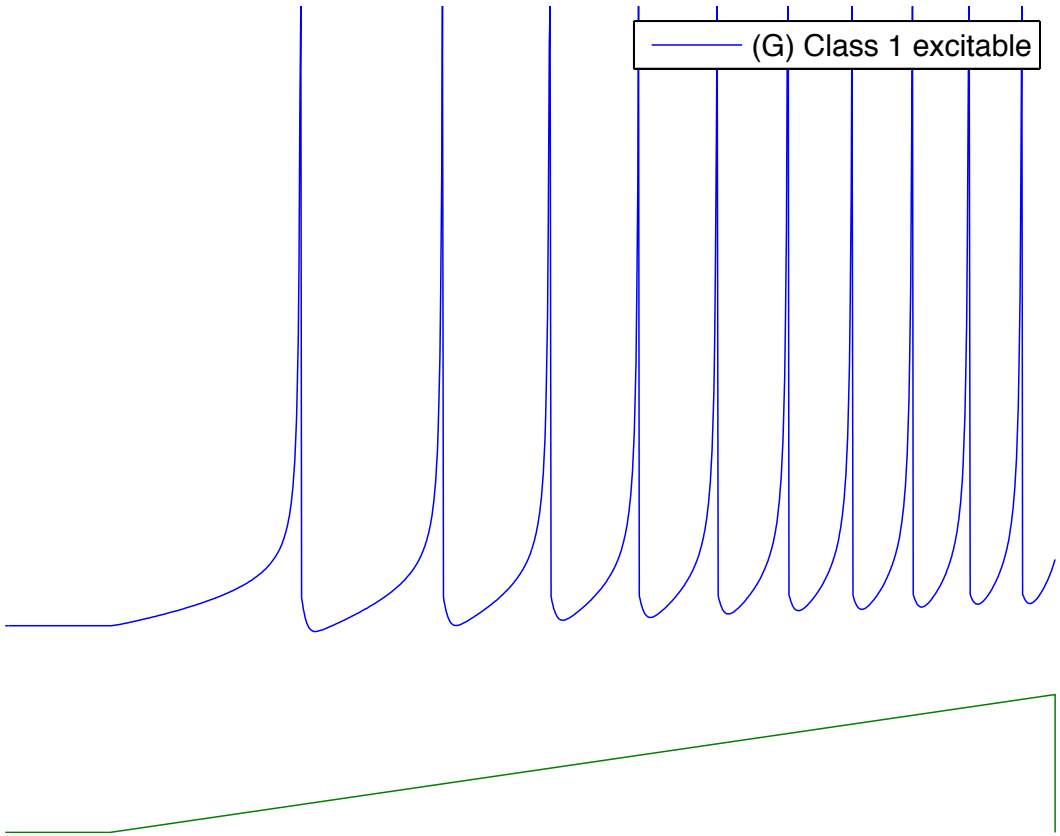

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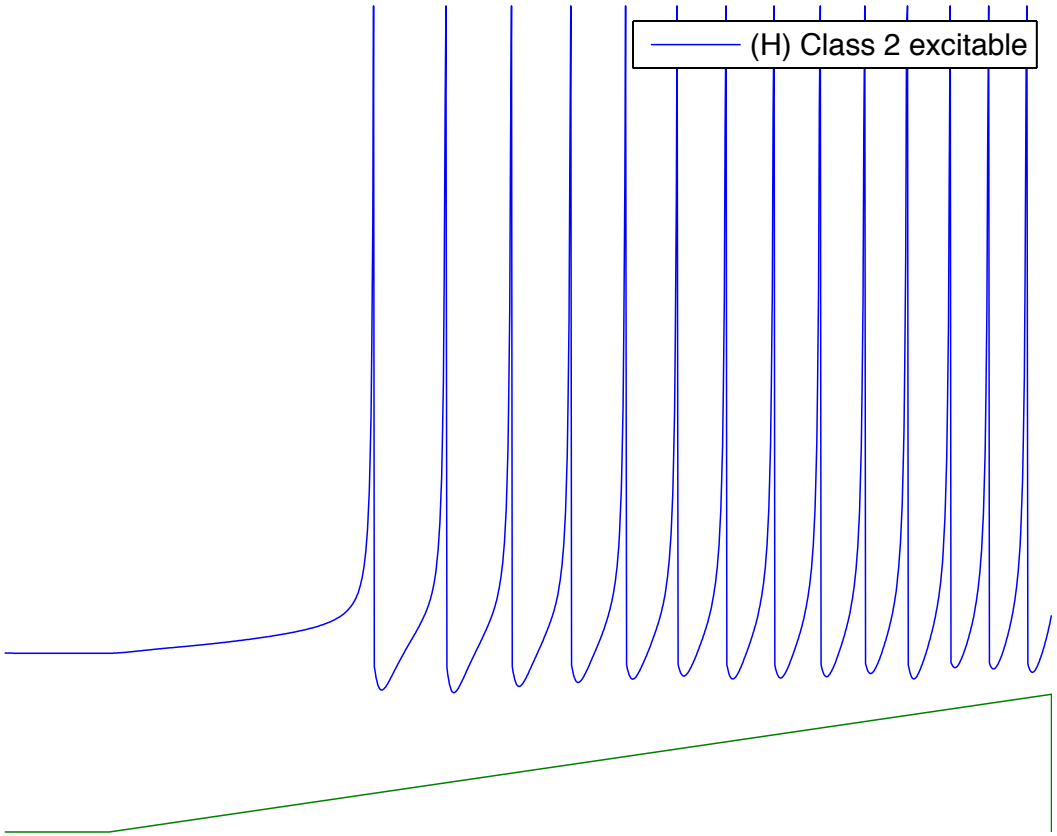

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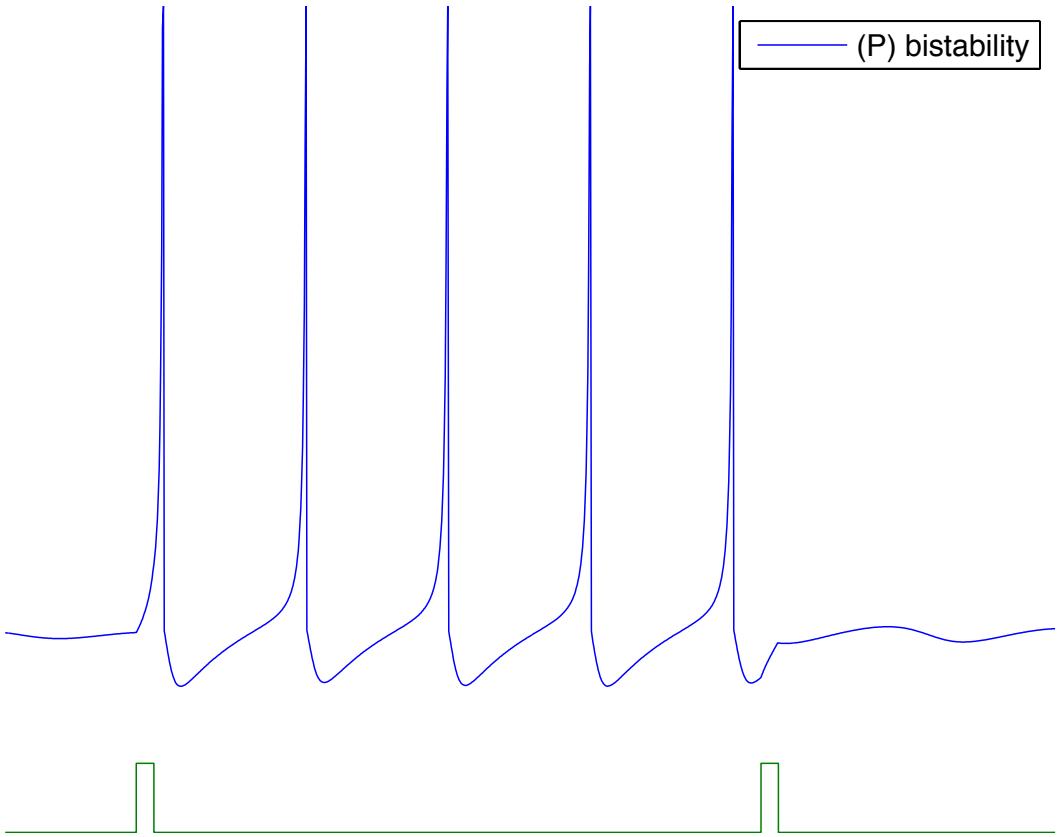

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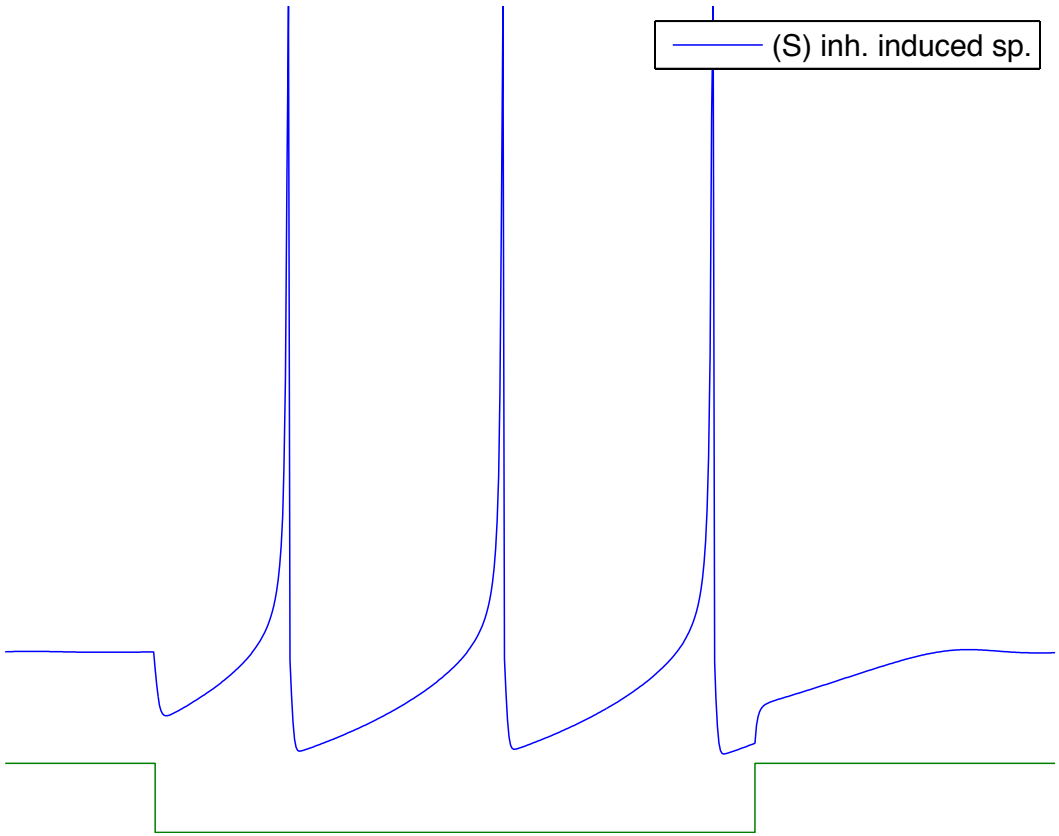

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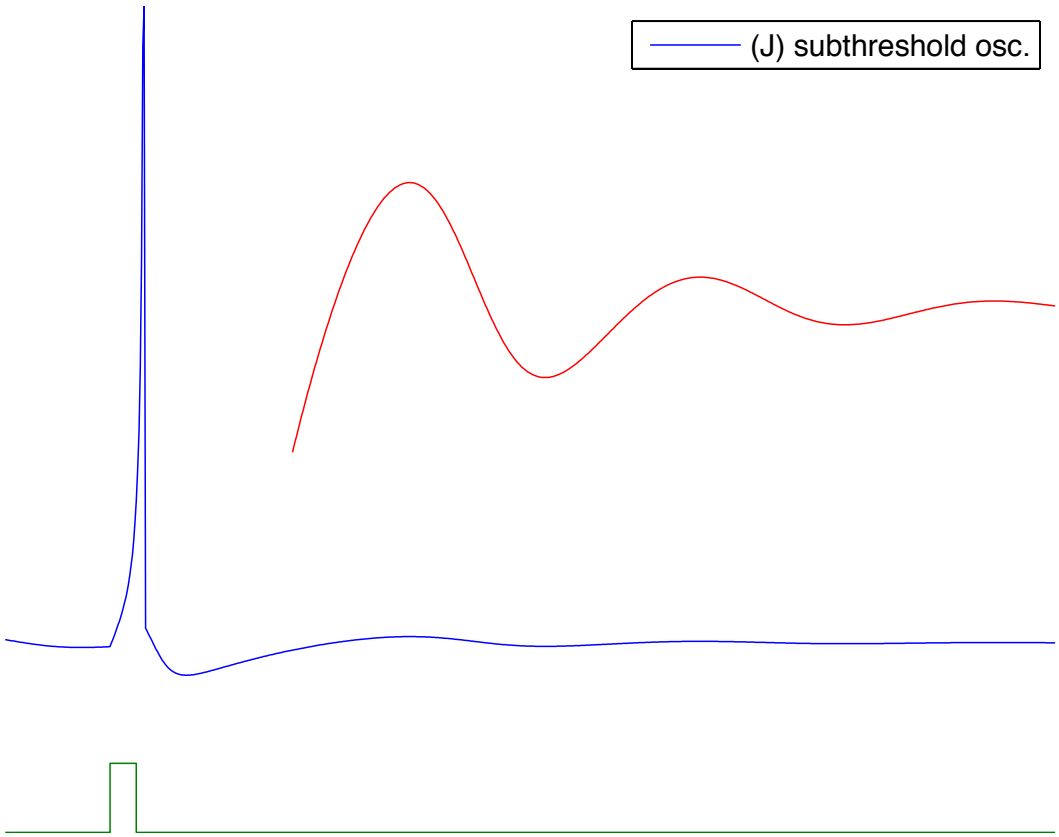

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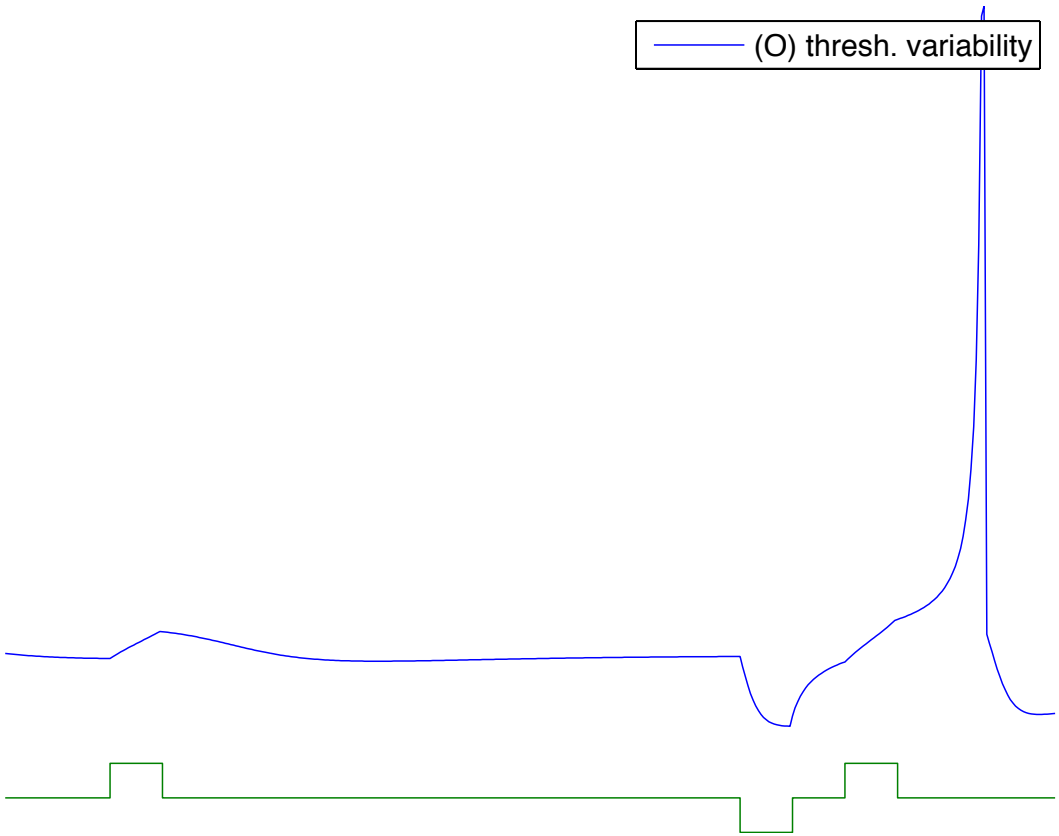

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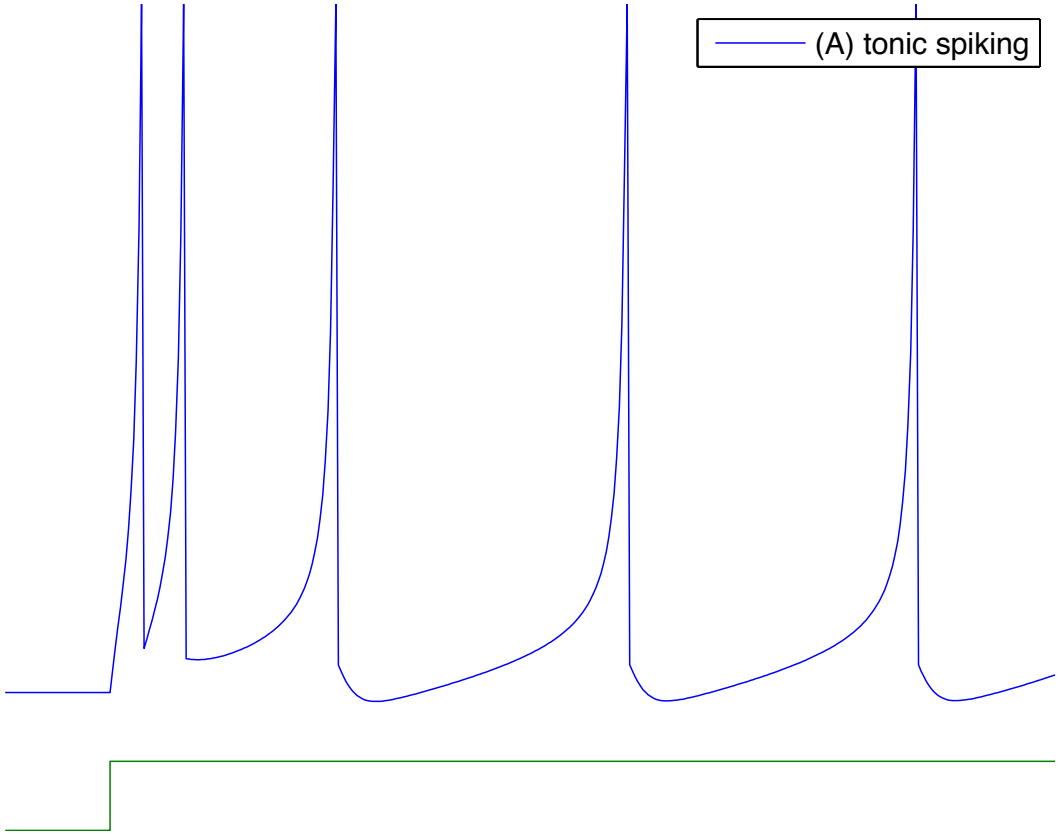

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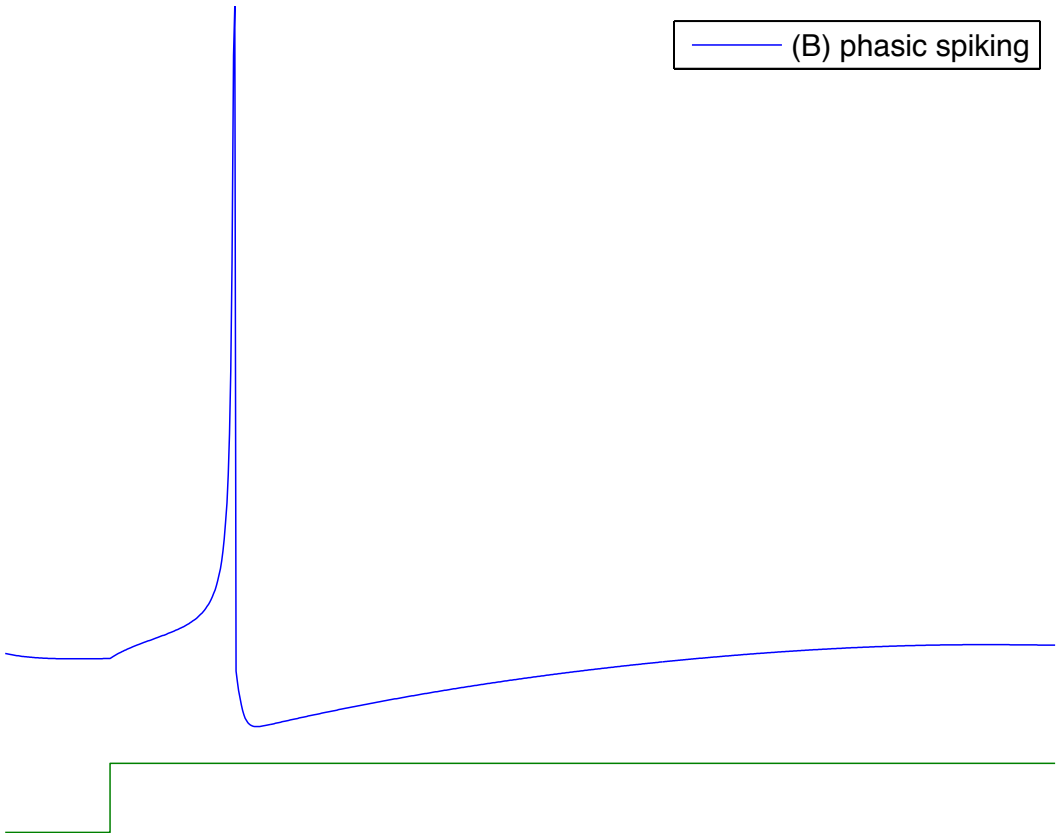

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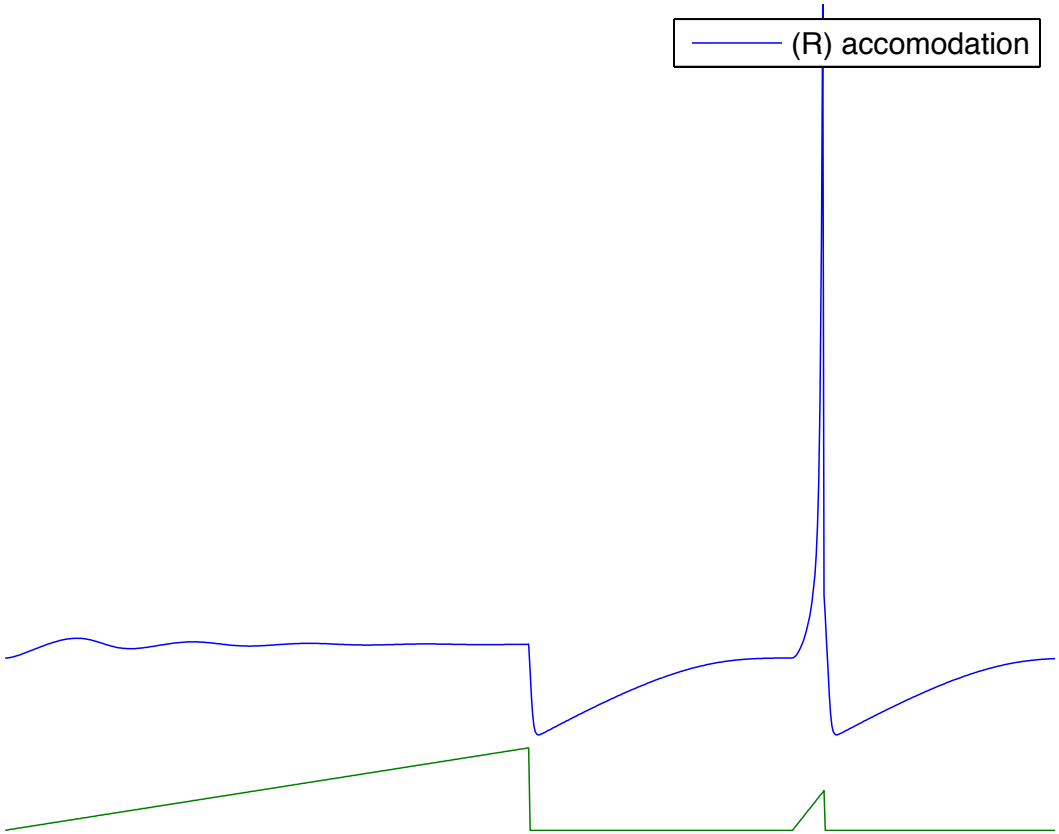

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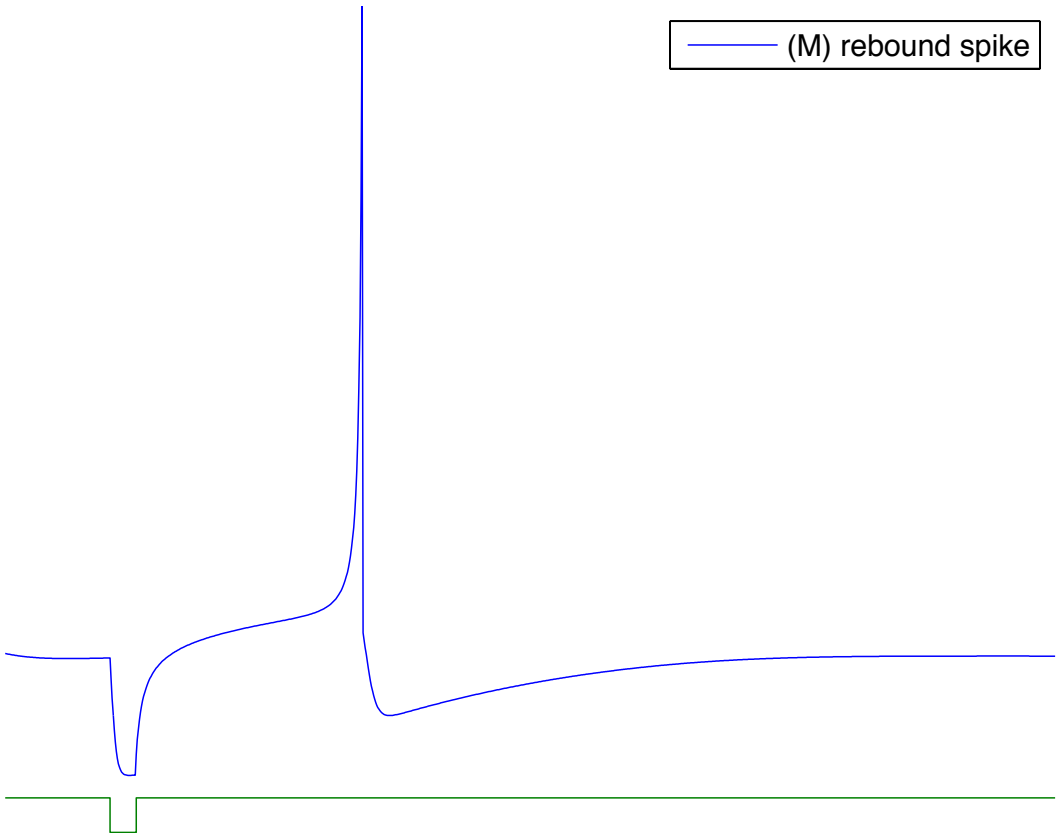

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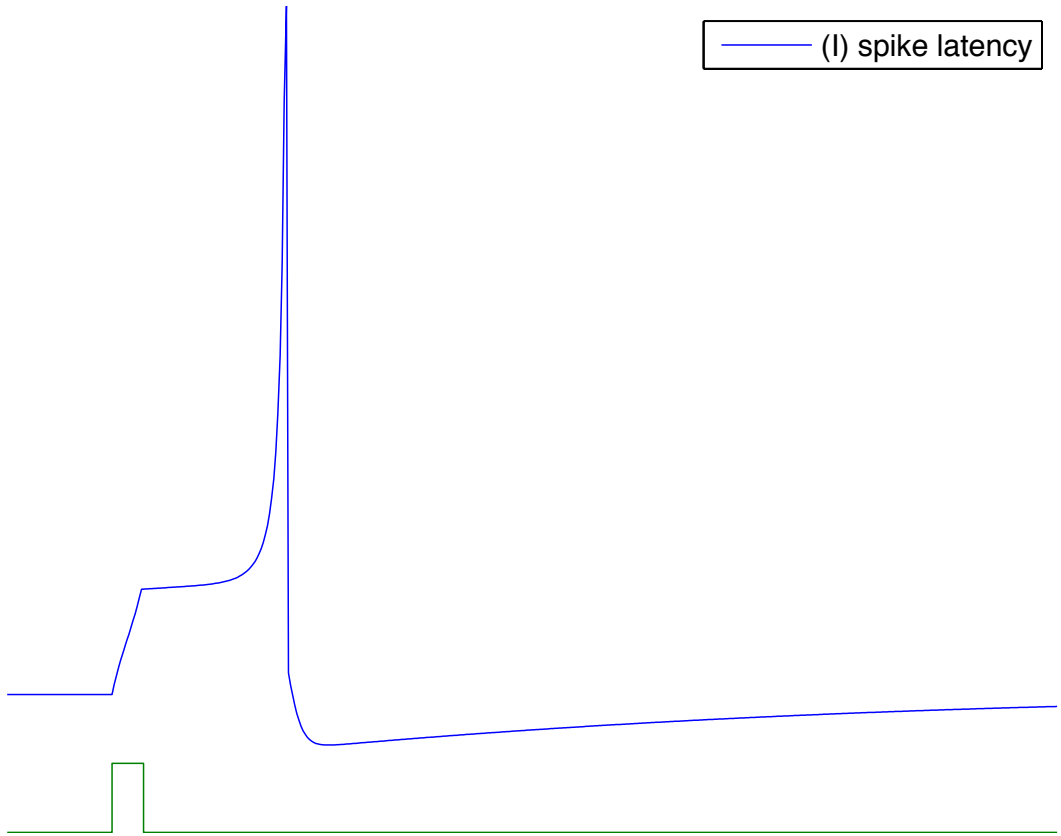

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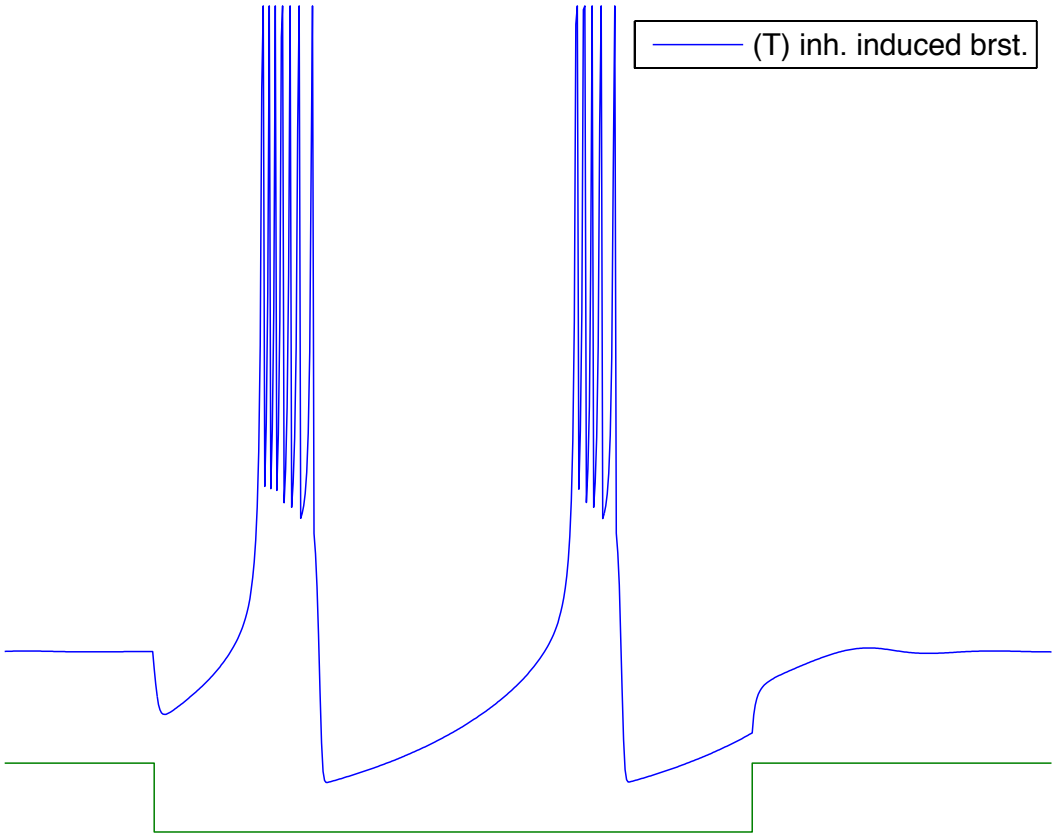

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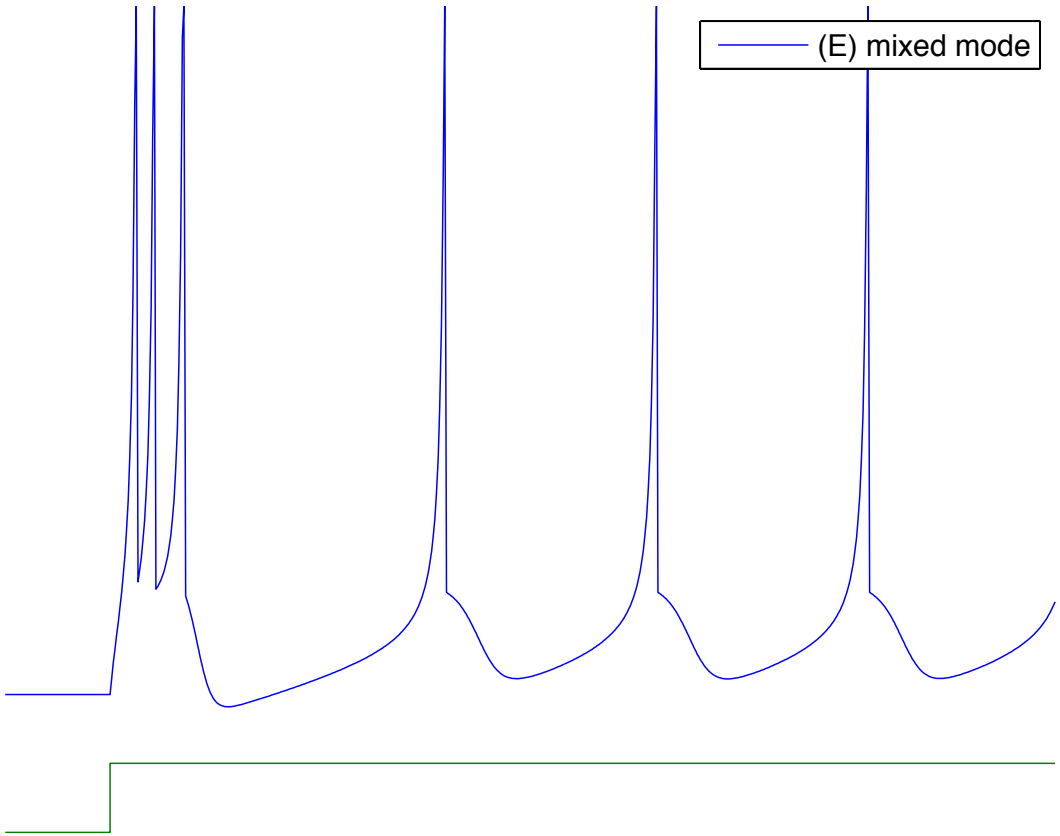

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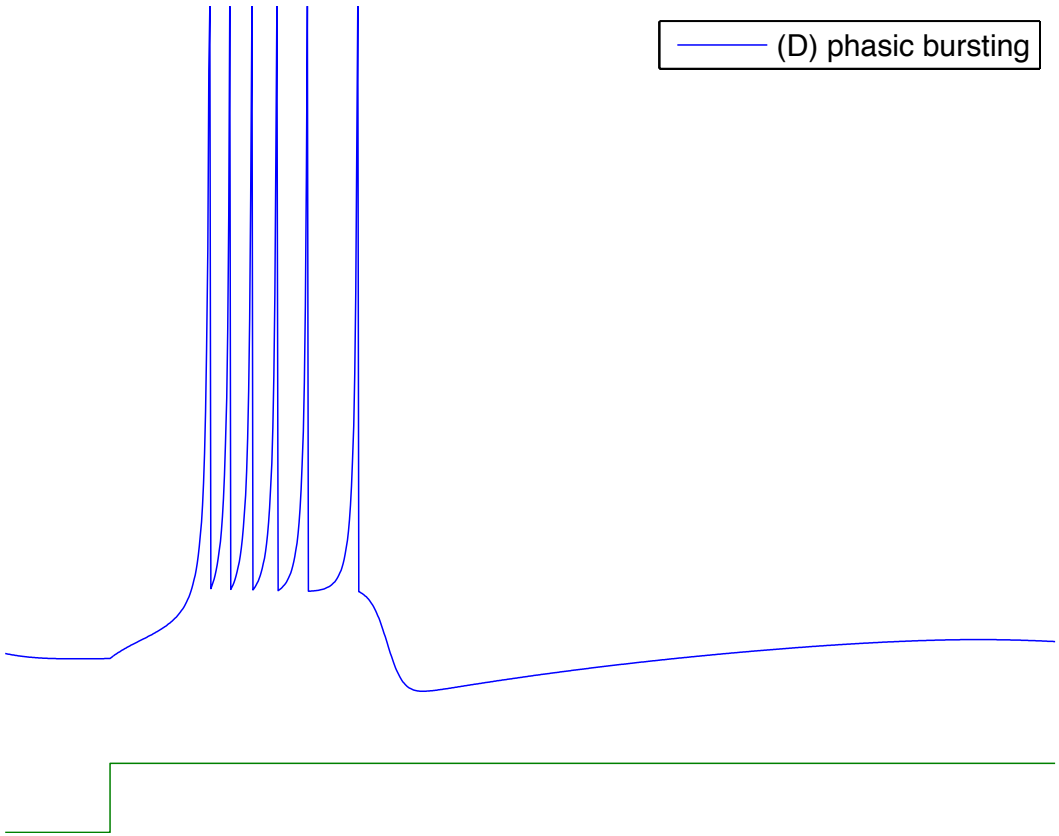

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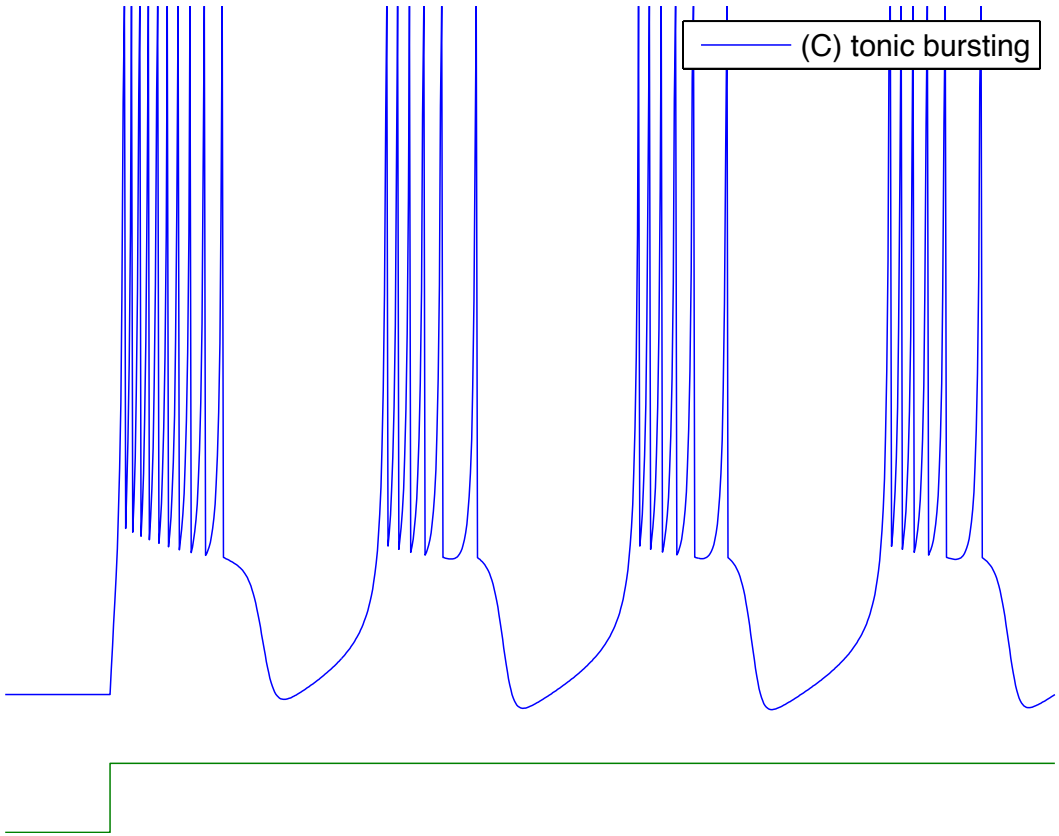

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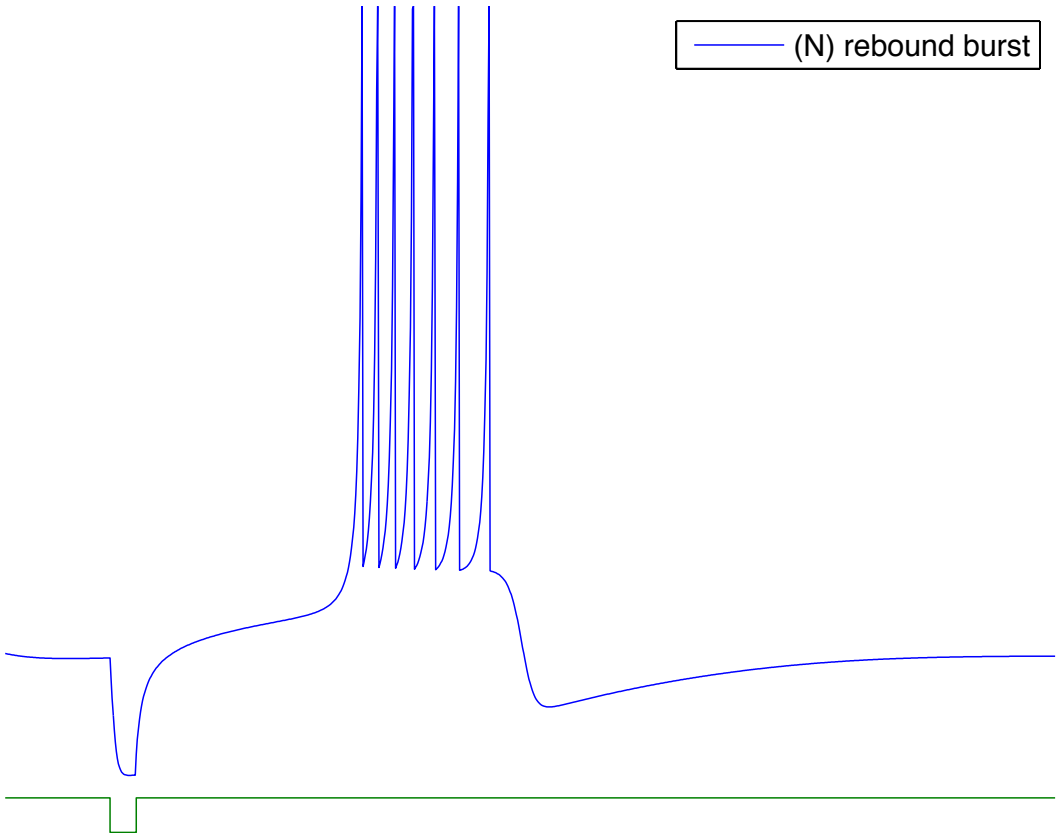

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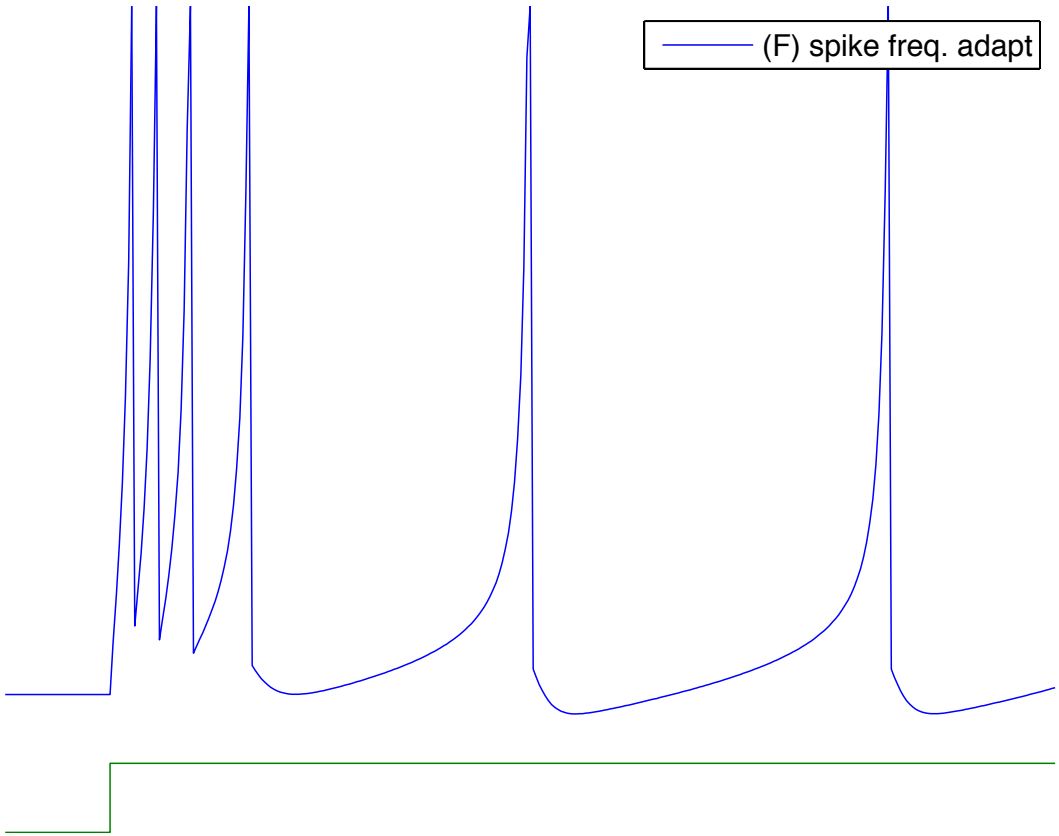

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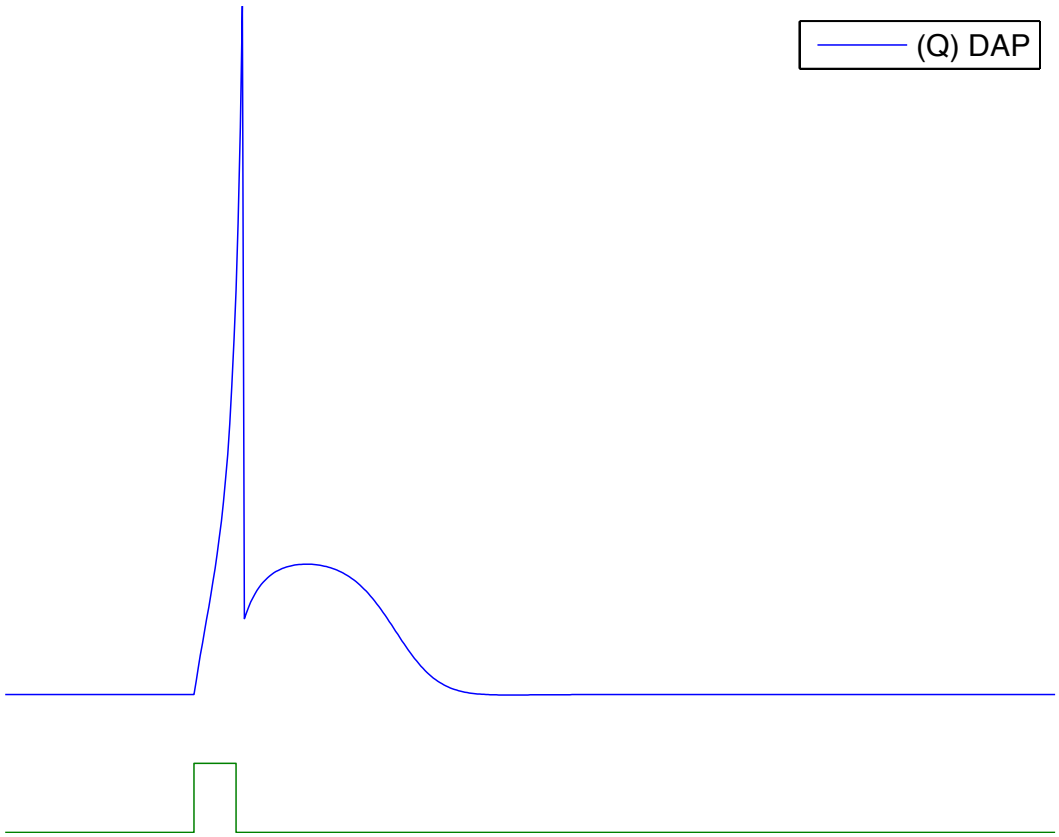

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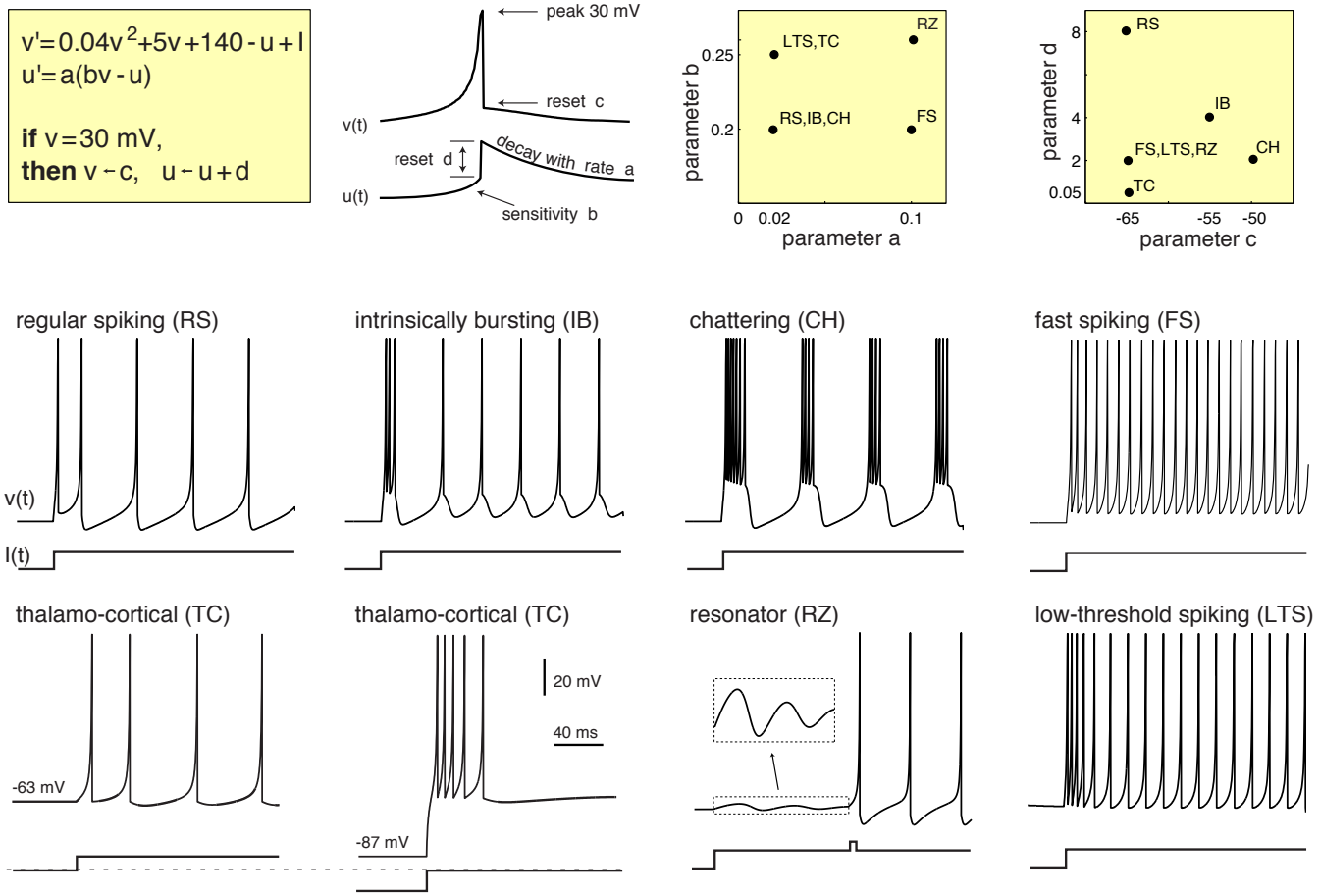

Figure: A summary of possible regimes in the Izhikevich Simple Model with respect to parameters. Reproduced from http://www.izhikevich.org/publications/spikes.htm with permissions.

```
% Created by Eugene M. Izhikevich, February 25, 2003
% Excitatory neurons    Inhibitory neurons
Ne=800;                 Ni=200;
re=rand(Ne,1);          ri=rand(Ni,1);
a=[0.02*ones(Ne,1);     0.02+0.08*ri];
b=[0.2*ones(Ne,1);      0.25-0.05*ri];
c=[-65+15*re.^2;        -65*ones(Ni,1)];
d=[8-6*re.^2;           2*ones(Ni,1)];
S=[0.5*rand(Ne+Ni,Ne),  -rand(Ne+Ni,Ni)];
v=-65*ones(Ne+Ni,1);    firings=[];   % Initial values of v and spike timings
u=b.*v;                 % Initial values of u
for t=1:1000            % simulation of 1000 ms
  I=[5*randn(Ne,1);2*randn(Ni,1)]; % thalamic input
  fired=find(v>=30);    % indices of spikes
  firings=[firings; t+0*fired,fired];
  v(fired)=c(fired);
  u(fired)=u(fired)+d(fired);
  I=I+sum(S(:,fired),2);
  v=v+0.5*(0.04*v.^2+5*v+140-u+I); % step 0.5 ms
  v=v+0.5*(0.04*v.^2+5*v+140-u+I); % for numerical
  u=u+a.*(b.*v-u);                 % stability
end;
plot(firings(:,1),firings(:,2),'.');
```

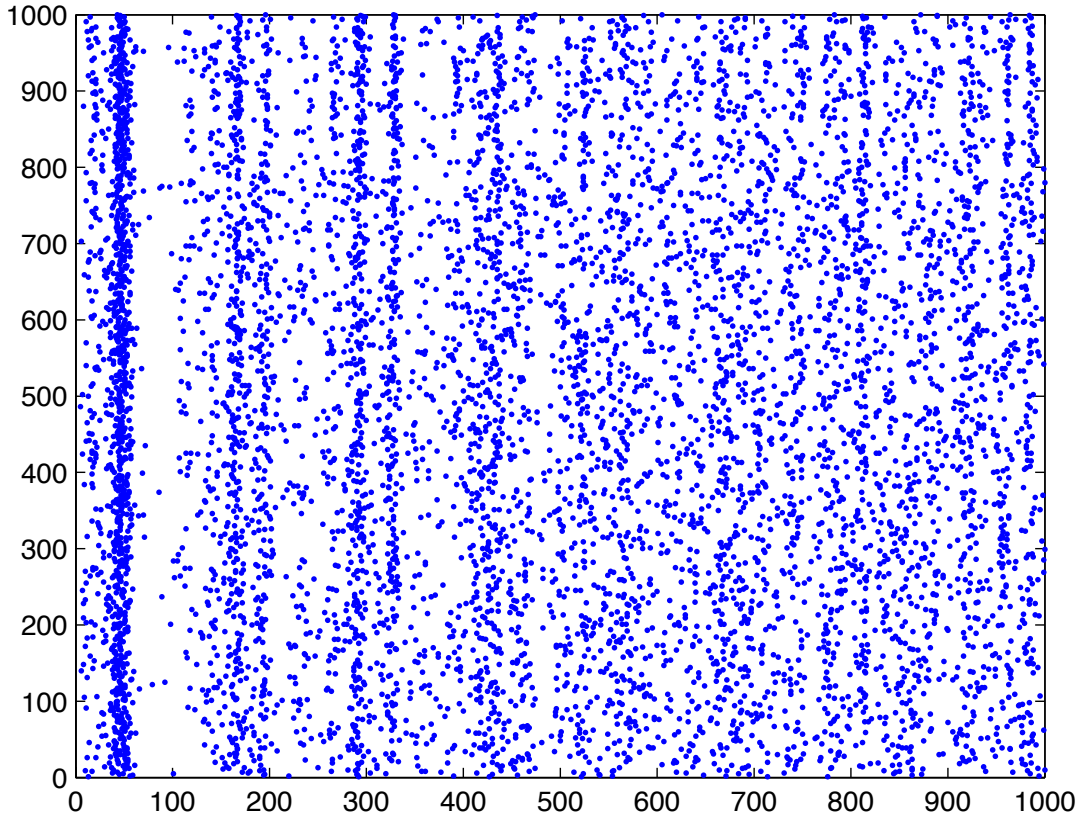

Figure: A spike train computed by the script from previous slide. See `http://www.izhikevich.org/publications/spikes.htm`

Synapses

- Every nerve impulse eventually reaches the axon, and has to be somehow transmitted to another neuron.
- This is accomplished by the synapses, small spaces where two neuronal membranes come close together.
- However small, synapses are far from being simple. There are two main types of synapses:**electrical** (sometimes called **gap junctions**) and **chemical**.
- Chemical synapses work by releasing a chemical messenger substance (neurotransmitter) which binds to the receptors at the postsynaptic neuron.
- Electrical synapses seem to exchange the membrane excitation directly, via sodium/potassium gradients.

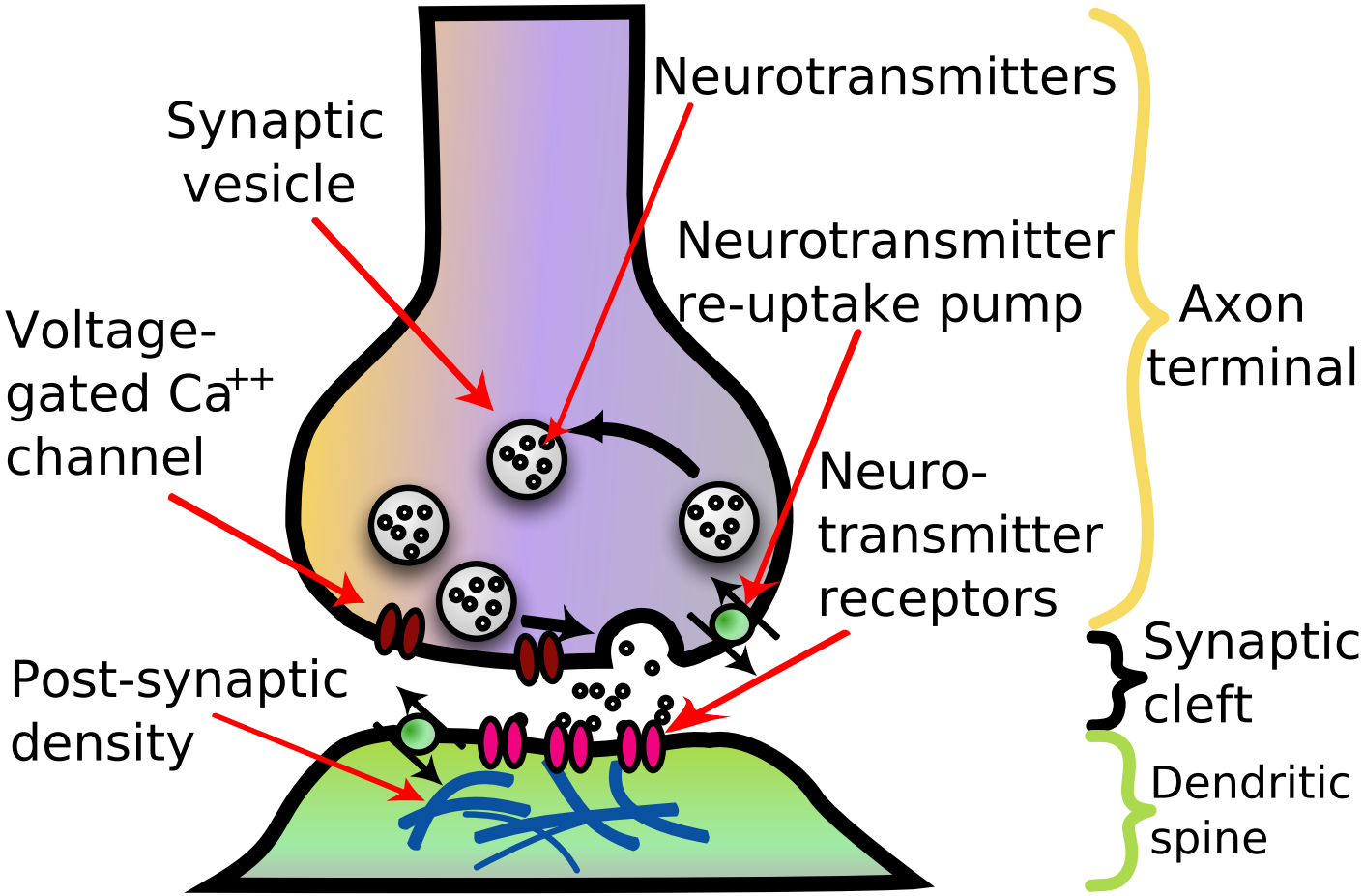

Figure: A chemical synapse. Modified from http://en.wikipedia.org/wiki/File:Synapse_Illustration2_tweaked.svg

Types of synapses

- Chemical synapses can be distinguished by the neurotransmitters and receptors they use for signaling. The most common neurotransmitters are:
  - Glutamate (salts of glutamic acid) - bind to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) and N-methyl-D-aspartic receptor (NMDA). Both excite the postsynaptic neuron.
  - γ-Aminobutyric acid (GABA) - binds to GABA receptors which can be divided into two main types $GABA_A$ and $GABA_B$. Both Inhibit the postsynaptic neuron.
- Each binding of neurotransmitter to a receptor opens an ionic channel increases membrane conductance.
- The postsynaptic excitation/inhibition depends on the synapse strength (size), available amount of neurotransmitter, and the postsynaptic membrane polarization.

Short term plasticity

- The short term plasticity models the available amount of neurotransmitter at a time.
- Some synapses exhibit facilitation (the amount of neurotransmitter becomes larger as the presynaptic neuron spikes) while other exhibit depression (the amount of neurotransmitter decreases in response to spikes, making the synapse weaker)
- The simplest formulation is:

$$\frac{dS}{dt} = (1 - S)/\tau_s$$

and $S := pS$ whenever an action potential is transferred. The synapse gets depressed for $p < 0$ and facilitated for $p > 0$.

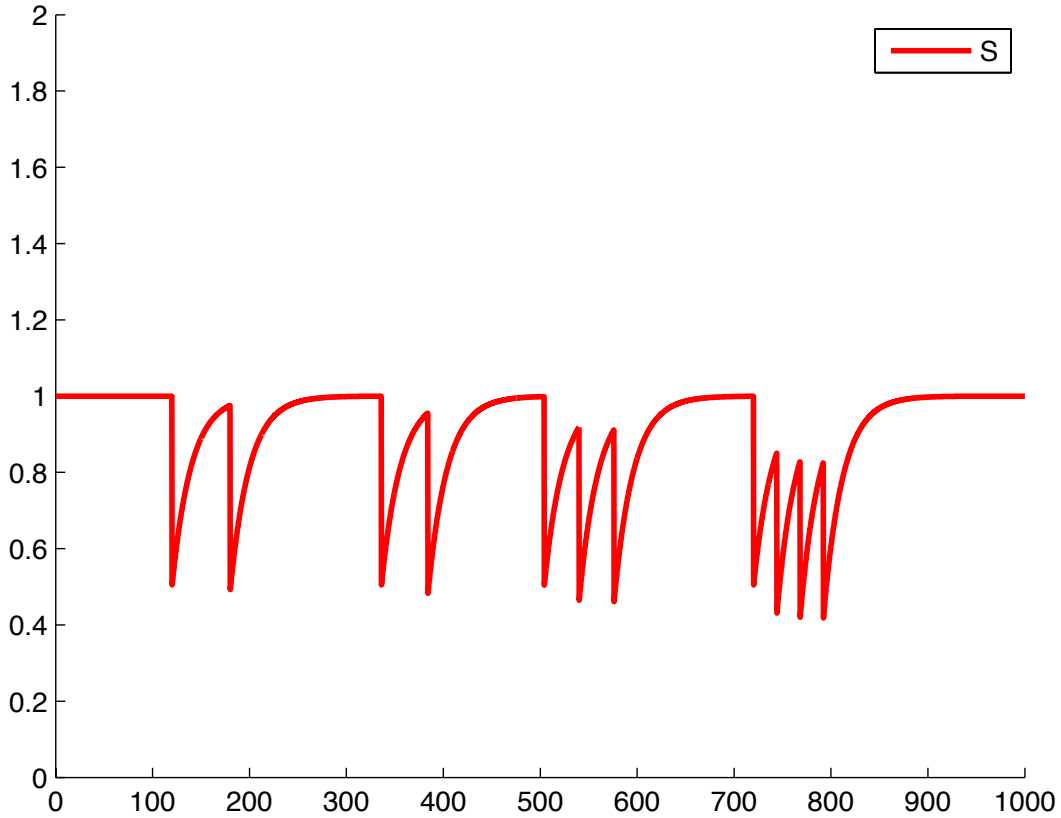

Figure: Simple synapse exhibiting depression (1) and facilitation (2).

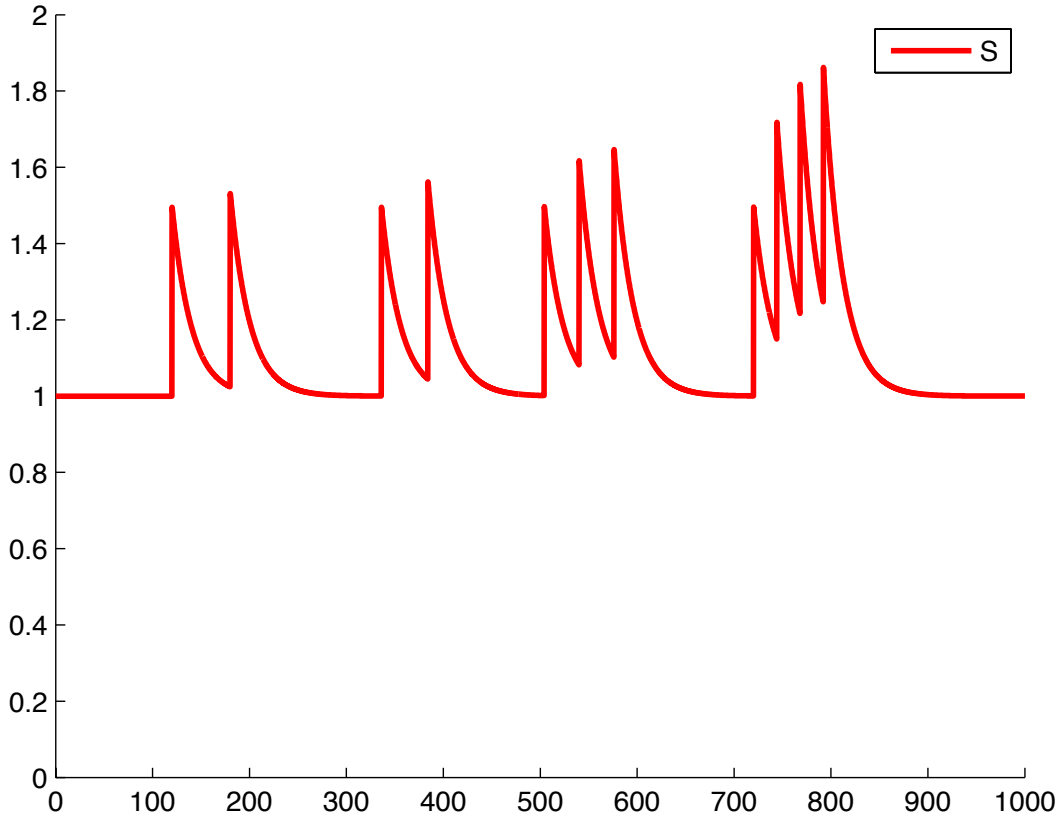

Figure: Simple synapse exhibiting depression (1) and facilitation (2).

Depression-Facilitation

- The recordings from real synapses look however rather different than those modeled by the simple synapse above (though the simple model is fairly accurate for very large simulations)
- Henry Markram and his collaborators introduced in 1998 a more accurate phenomenological model:

$$\frac{dR}{dt} = \frac{1-R}{D} \qquad \frac{dw}{dt} = \frac{U-w}{F}$$

where U, D, F are parameters. Whenever a spike is propagated through the synapse $R := R - Rw$ and $w := w + U(1-w)$. R is the depression variable and w is the facilitation variable. The total synaptic strength at time t is equal $S = Rw$

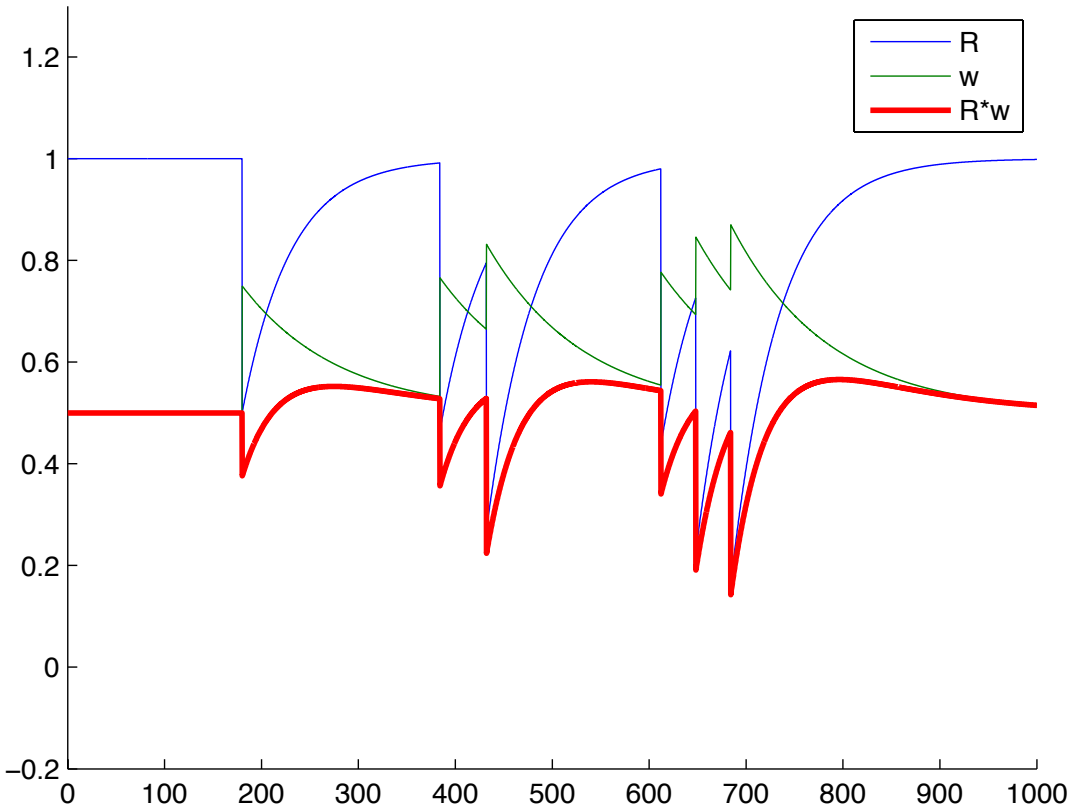

Figure: A synapse modeled by the phenomenological model of H. Markram exhibiting depression (1) $F = 50, D = 100, U = 0.5$ and facilitation (2) $D = 100, F = 50, U = 0.2$. By adjusting the parameters the model can reproduce conductances of various synapses.

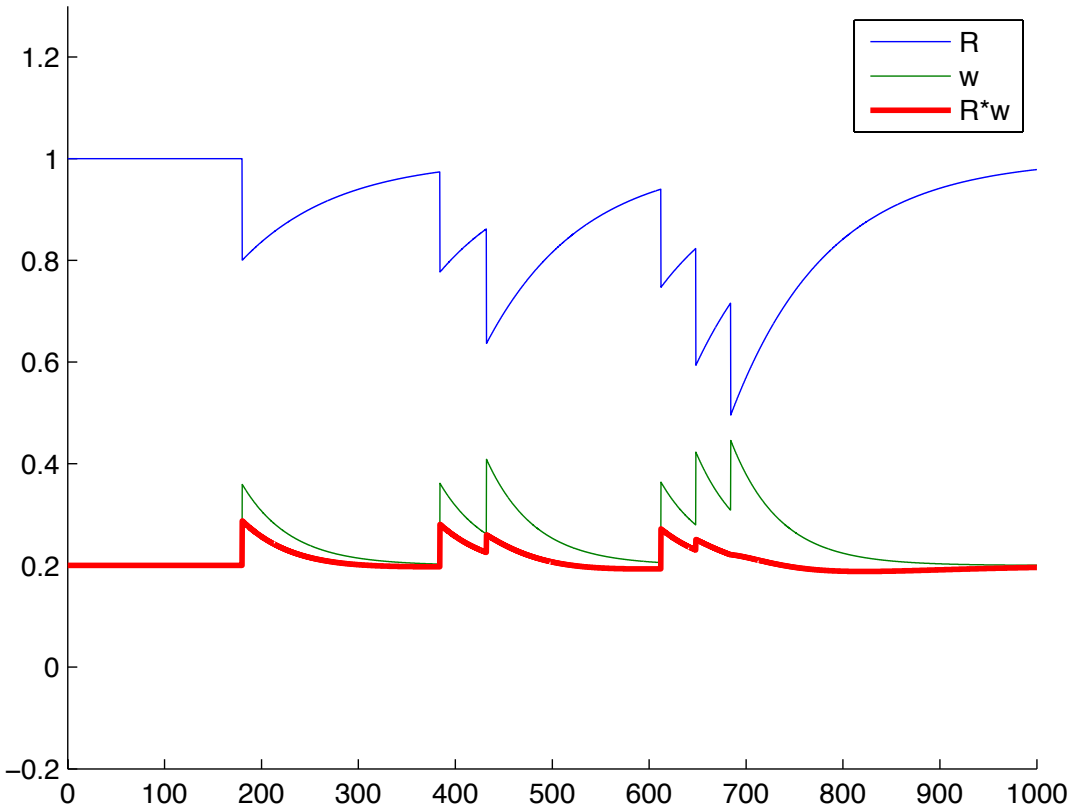

Figure: A synapse modeled by the phenomenological model of H. Markram exhibiting depression (1) $F = 50, D = 100, U = 0.5$ and facilitation (2) $D = 100, F = 50, U = 0.2$. By adjusting the parameters the model can reproduce conductances of various synapses.

- The value of the short term depression-facilitation influences the resulting receptor conductance. In the present scope we assume there are four conductances g_{AMPA}, g_{NMDA}, g_{GABA_A} and g_{GABA_B}. Each time a spike is propagated the appropriate conductances are increased by $c_{i\to j}S_i = c_{i\to j}R_i w_i$ (before depressing or facilitating) where $c_{i\to j}$ is the strength of the synapse from neuron i to neuron j.
- The conductances have their own kinetics, that is they diminish exponentially as

$$\frac{dg}{dt} = -g/\tau$$

where $\tau_{\text{AMPA}} = 5ms$, $\tau_{\text{NMDA}} = 150ms$, $\tau_{\text{GABA}_A} = 6ms$ and $\tau_{\text{GABA}_B} = 150ms$

- Once we have the synaptic conductances we have to look what currents they may cause through the membrane, depending on voltage V. We generally have that:

$$\begin{aligned} I_{\text{syn}} = {} & g_{\text{AMPA}}(E_{\text{AMPA}} - V) + \\ & + g_{\text{NMDA}} \frac{\left(\frac{V+80}{60}\right)^2}{1 + \left(\frac{V+80}{60}\right)^2}(E_{\text{NMDA}} - V) + \\ & + g_{\text{GABA}_A}(E_{\text{GABA}_A} - V) + \\ & + g_{\text{GABA}_B}(E_{\text{GABA}_B} - V) \end{aligned}$$

with $E_{\text{AMPA}} = 0$, $E_{\text{NMDA}} = 0$, $E_{\text{GABA}_A} = -70$, $E_{\text{GABA}_B} = -90$. NMDA current looks strange but the formula is a fit to empirical data.

Eventually, using say the Izhikevich Simple Neuron (with reset) we have (for single compartment model):

$$\begin{aligned}\frac{dV_i}{dt} =& 0.04V_i^2 + 5V_i + 140 - U_i + \sum_{j\to i} g_{\text{j,AMPA}}(0 - V_i) + \\ &+ \sum_{j\to i} g_{\text{j,NMDA}} \frac{\left(\frac{V_i+80}{60}\right)^2}{1+\left(\frac{V_i+80}{60}\right)^2}(0 - V_i) + \sum_{j\to i} g_{\text{j, GABA}_A}(-70 - V_i) + \\ &+ \sum_{j\to i} g_{\text{j,GABA}_B}(-90 - V_i) + \sum_{j\in \text{gap}(i)} g_{\text{gap}j\to i}(V_j - V_i)\end{aligned}$$

$$\frac{dU_i}{dt} = a(bV_i - U_i)$$

- Now, since we have the equation, the only thing left would be to discretize and solve it numerically.
- There is however one catch. Assume the neuron is at rest with $V = -65$, and g_{GABA_A} is large due to previous activity. Then $g_{\mathrm{GABA}_A}(-70 + 65) = -5g_{\mathrm{GABA}_A}$ is a strong inhibitory input. Assume that input manages to hyperpolarize the membrane so that at the next time step $V = -76$. Now $g_{\mathrm{GABA}_A}(-70 + 76) = 6g_{\mathrm{GABA}_A}$ is a strong excitatory input! The same applies to g_{GABA_A} which is even more vulnerable due to slower kinetics.
- In certain conditions that ping-pong can continue, and V will oscillate each time getting bigger in absolute value. This leads to numerical instability (V reaches spiking cutoff every time step causing indefinite increase of U and the whole simulation collapses).

- In order to avoid instability, one has to modify the numerical scheme (it is not sufficient to use smaller time step).
- Recall the Euler method is obtained as follows:

$$\frac{dx}{dt} = \lim_{\Delta t \to 0} \frac{x(t+\Delta t) - x(t)}{\Delta t} = F(x(t)) \;\Rightarrow\; x(t+1) \approx x(t) + \Delta t F(x(t))$$

- But on the other hand we have :

$$\frac{dx}{dt} = \lim_{\Delta t \to 0} \frac{x(t) - x(t-\Delta t)}{\Delta t} = F(x(t)) \;\Rightarrow\; x(t+1) \approx x(t) + \Delta t F(x(t+1))$$

we get the so called closed (or backward) scheme. The closed scheme is far more stable with respect to instabilities related to GABA conductances.

- The closed scheme is stable, but the solution is implicit, therefore it needs to be solved separately for every right hand side function F.
- Fortunately conductances depend linearly in V, so the implicit scheme is fairly easy to implement for that part of the equation. The rest (including neural dynamics) can be solved by the forward (explicit) scheme.

We have

$$V_i(t+1) = V_i(t) +$$

$$+\Delta t \left(0.04 V_i(t)^2 + 5 V_i(t) + 140 - U_i(t) + \sum_{j \to i} g_{\text{j,AMPA}} (0 - V_i(t+1)) + \right.$$

$$+ \sum_{j \to i} g_{\text{j,NMDA}} \frac{\left(\frac{V_i(t)+80}{60} \right)^2}{1 + \left(\frac{V_i(t)+80}{60} \right)^2} (0 - V_i(t+1)) + \sum_{j \to i} g_{\text{j, GABA}_A} (-70 - V_i(t+1)) +$$

$$\left. + \sum_{j \to i} g_{\text{j,GABA}_B} (-90 - V_i(t+1)) + \sum_{j \in \text{gap}(i)} g_{\text{gap}j \to i} (V_j - V_i(t)) \right)$$

$$U_i(t+1) = U_i(t) + \Delta t \left(a(bV_i(t) - U_i(t)) \right)$$

note that the coefficient of the NMDA conductance depends on $V(t)$ and is therefore computed explicitly.

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$$V_i(t+1) = V_i(t) +$$

$$+\Delta t \left(0.04 V_i(t)^2 + 5 V_i(t) + 140 - U_i(t) + \sum_{j \to i} g_{\text{j,AMPA}} (0 - V_i(t+1)) +\right.$$

$$+ \sum_{j \to i} g_{\text{j,NMDA}} \frac{\left(\frac{V_i(t)+80}{60} \right)^2}{1 + \left(\frac{V_i(t)+80}{60} \right)^2} (0 - V_i(t+1)) + \sum_{j \to i} g_{\text{j, GABA}_A} (-70 - V_i(t+1)) +$$

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$$+ \sum_{j \to i} g_{\text{j,NMDA}} \frac{\left(\frac{V_i(t)+80}{60} \right)^2}{1 + \left(\frac{V_i(t)+80}{60} \right)^2} (0 - V_i(t+1)) + \sum_{j \to i} g_{\text{j, GABA}_A} (-70 - V_i(t+1)) +$$

$$\left. + \sum_{j \to i} g_{\text{j,GABA}_B} (-90 - V_i(t+1)) + \sum_{j \in \text{gap}(i)} g_{\text{gap}j \to i} (V_j - V_i(t)) \right)$$

$$U_i(t+1) = U_i(t) + \Delta t \left(a(bV_i(t) - U_i(t)) \right)$$

note that the coefficient of the NMDA conductance depends on $V(t)$ and is therefore computed explicitly.

Consequently by solving with respect to $V_i(t+1)$

$$V_i(t+1) =$$

$$= \frac{V_i(t) + \Delta t \left(0.04 V_i(t)^2 + 5 V_i(t) + 140 - U_i(t) + \right.}{1 + \Delta t \left(\sum_{j \to i} g_{\text{j,AMPA}} + \sum_{j \to i} g_{\text{j,NMDA}} \frac{\left(\frac{V_i(t)+80}{60}\right)^2}{1+\left(\frac{V_i(t)+80}{60}\right)^2} + \right.}$$

$$\left. \frac{\left. -70 \sum_{j \to i} g_{\text{j, GABA}_A} - 90 \sum_{j \to i} g_{\text{j,GABA}_B} + \sum_{j \in \text{gap}(i)} g_{\text{gap}j \to i} (V_j - V_i(t)) \right)}{\left. \sum_{j \to i} g_{\text{j, GABA}_A} + \sum_{j \to i} g_{\text{j, GABA}_B} \right)}$$

$$U_i(t+1) = U_i(t) + \Delta t \left(a(bV_i(t) - U_i(t))\right)$$

The scheme is stable and ready to use for large scale simulations, see foe example:
http://www.izhikevich.org/publications/reentry.htm

- Computing exponential functions, sines etc. is very demanding!
- Integrate and fire and resonate and fire are simple models, useful for theoretical approach, but not good for simulations
- FitHugh-Nagumo model is simple (nullclines are polynomial), yet biologically plausible and particularly useful for reaction-diffusion systems
- Simple Model by E. Izhikevich is an efficient 2d model with a power of 3d model due to the reset
- Synapses can be electrical and chemical. Chemical synapses exhibit short term depression/facilitation
- Synaptic currents depend on neurotransmitter conductances and postsynaptic membrane voltage
- Explicit Euler scheme can be unstable for synaptic conductances(!)