Computational Neuroscience Summer School

Neural Spike Train Analysis

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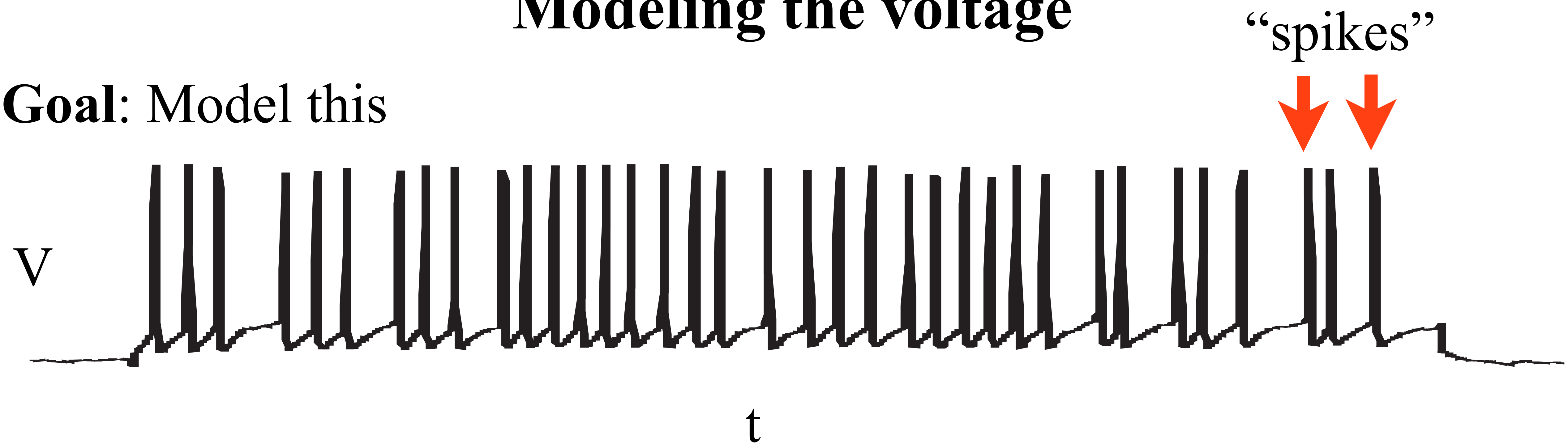
Boston University

An introduction to biophysical models (Part 3)

A dynamical model ... FitzHugh-Nagumo

Modeling the voltage

Goal: Model this



We proposed the Hodgkin-Huxely model:

$$
\begin{aligned}
C\,\frac{dV}{dt} &= I_{\text{input}}(t) - \bar{g}_{\text{K}} n^4 (V - V_{\text{K}}) - \bar{g}_{\text{Na}} m^3 h (V - V_{\text{Na}}) - \bar{g}_{\text{L}} (V - V_{\text{L}}) \\
\frac{dn}{dt} &= -\frac{n - n_\infty(V)}{\tau_n(V)} \\
\frac{dm}{dt} &= -\frac{m - m_\infty(V)}{\tau_m(V)} \\
\frac{dh}{dt} &= -\frac{h - h_\infty(V)}{\tau_h(V)}\,,
\end{aligned}
$$

4 coupled ODEs

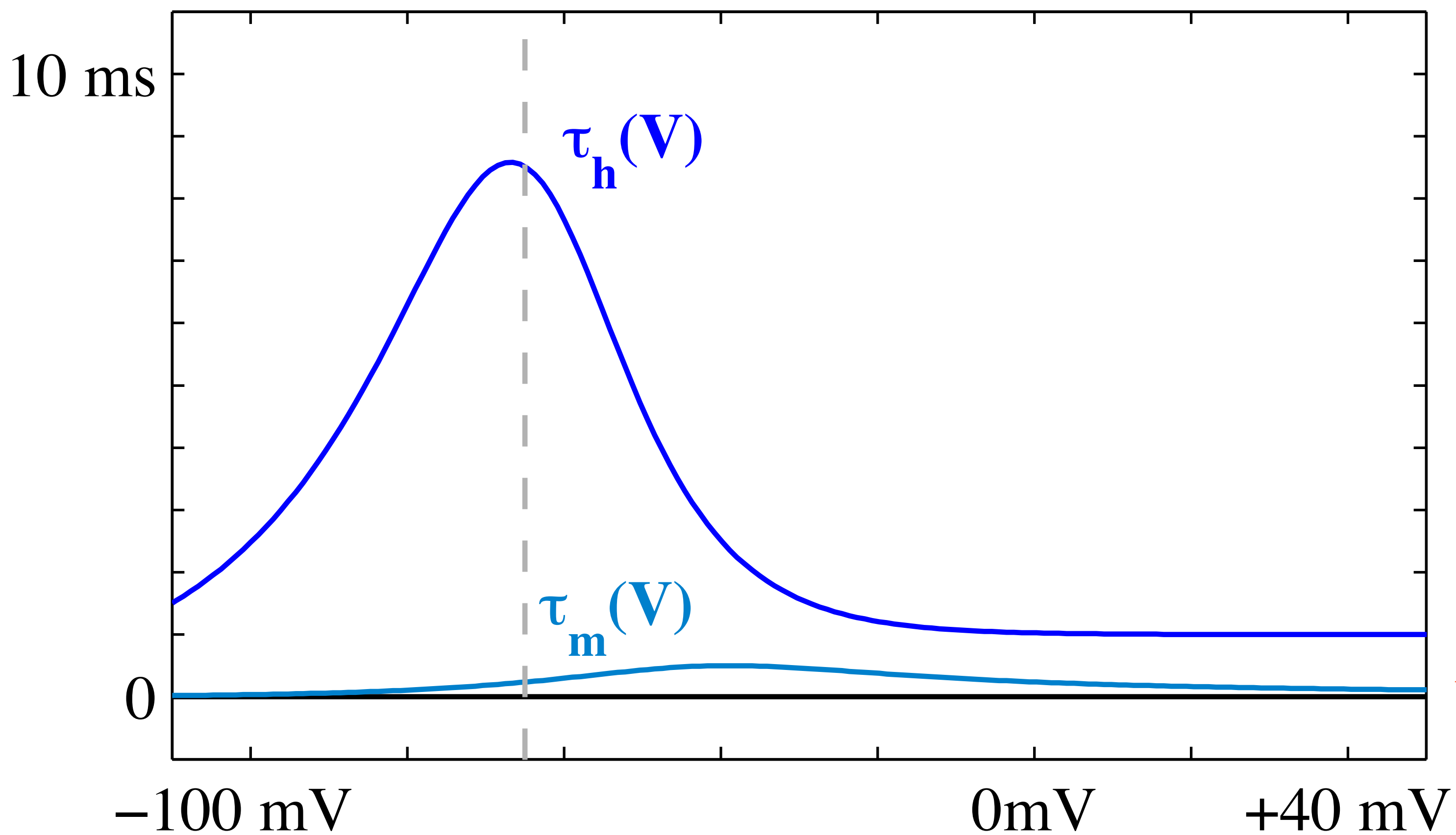
Let’s try to simplify ...

Simplify Hodgkin-Huxley

<u>Simplification 1</u>: Treat the variable m[t] as an instantaneous variable.

↑ (*sodium activation variable*)

time constants for Na.



Fast!

The m-gates swing open and closed ...

~~... quickly~~

... instantaneously.

$$\cancel{\frac{dm}{dt} = -\frac{m - m_\infty(V)}{\tau_m(V)}}$$

Replace m(t) with its steady state value.

$$m(t) \longrightarrow m_\infty(V)$$

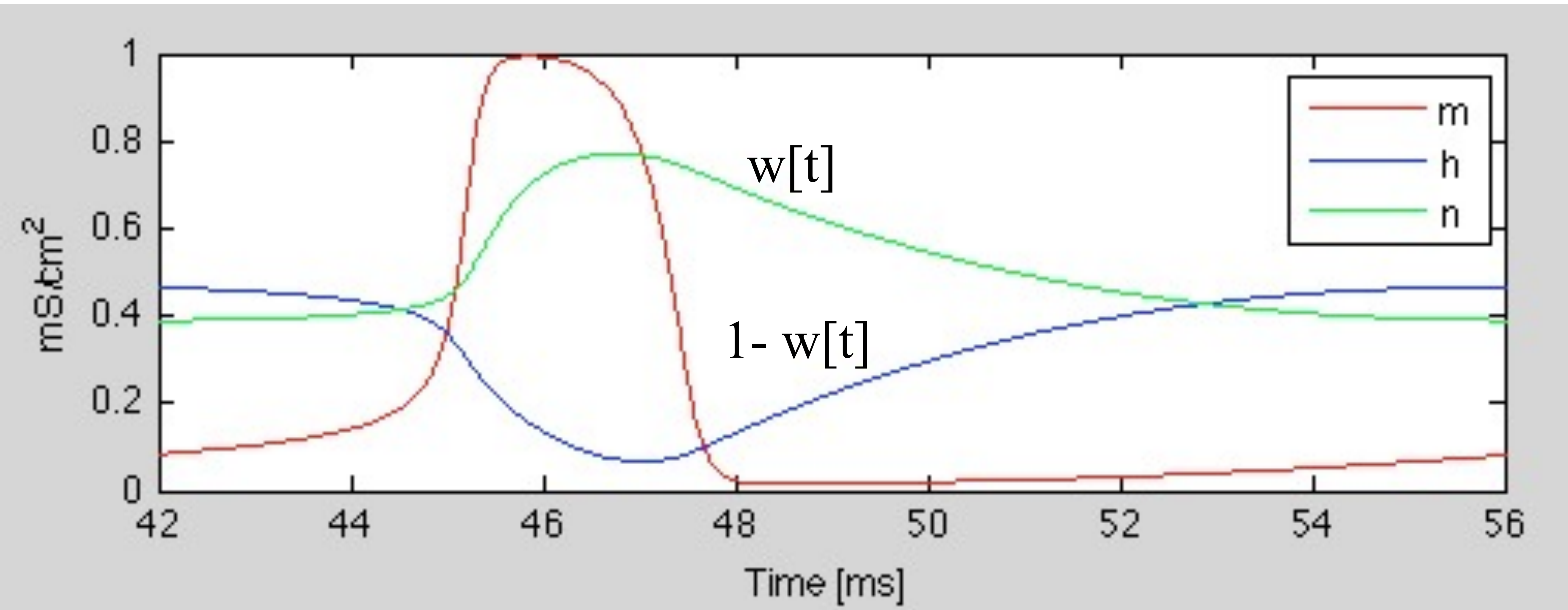
Simplify Hodgkin-Huxley

(*sodium inactivation variable*)

Simplification 2: Replace n[t] and h[t] with a single, new variable w[t].

(*potassium activation variable*)

Motivation: The n[t] and h[t] dynamics look related ... n[t] + h[t] ~ 1



Replace: n[t] with w[t]

h[t] with 1-w[t]

Simulate dw/dt using potassium gate dynamics (n).

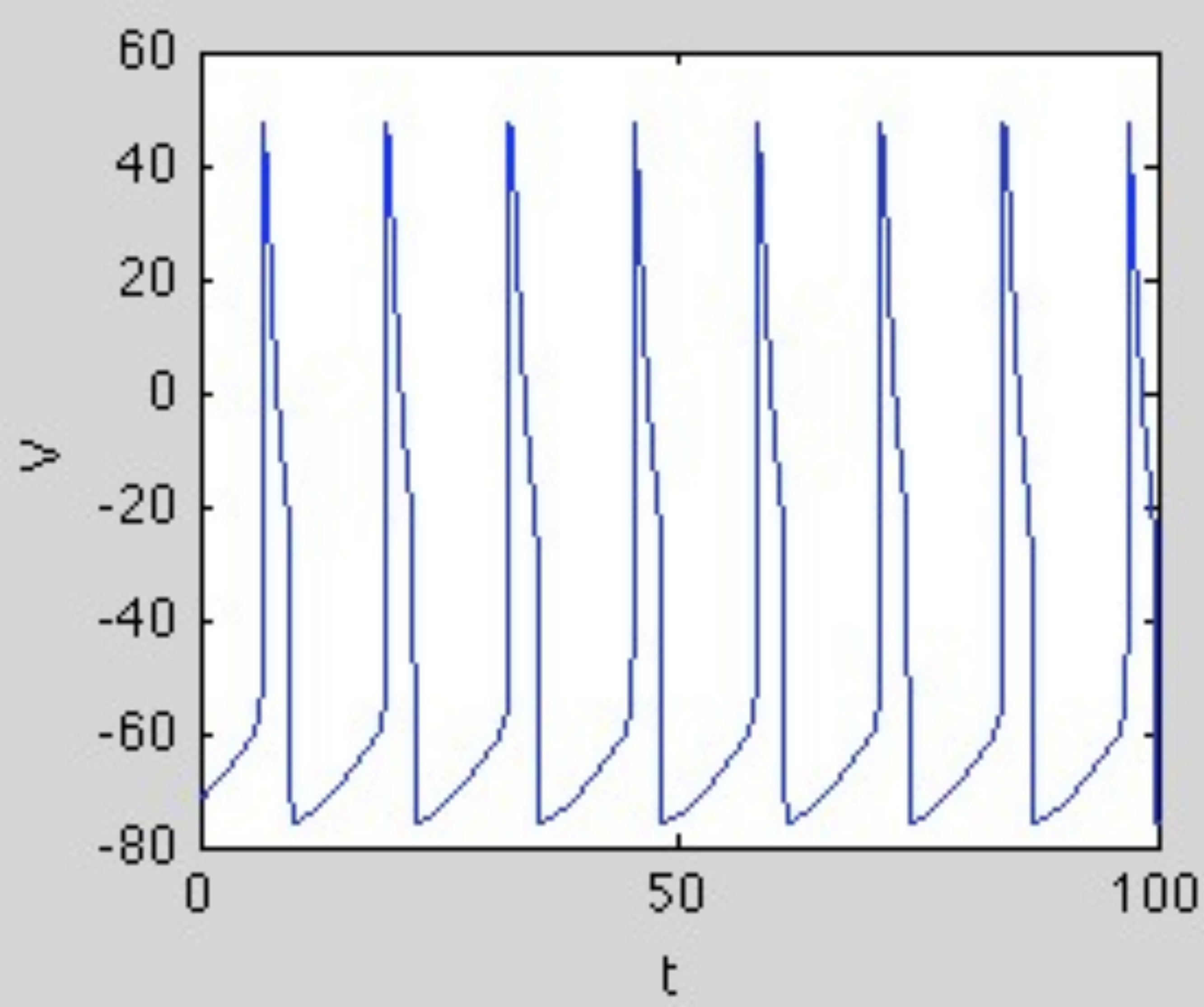
Simplify Hodgkin-Huxley

After these two simplifications:

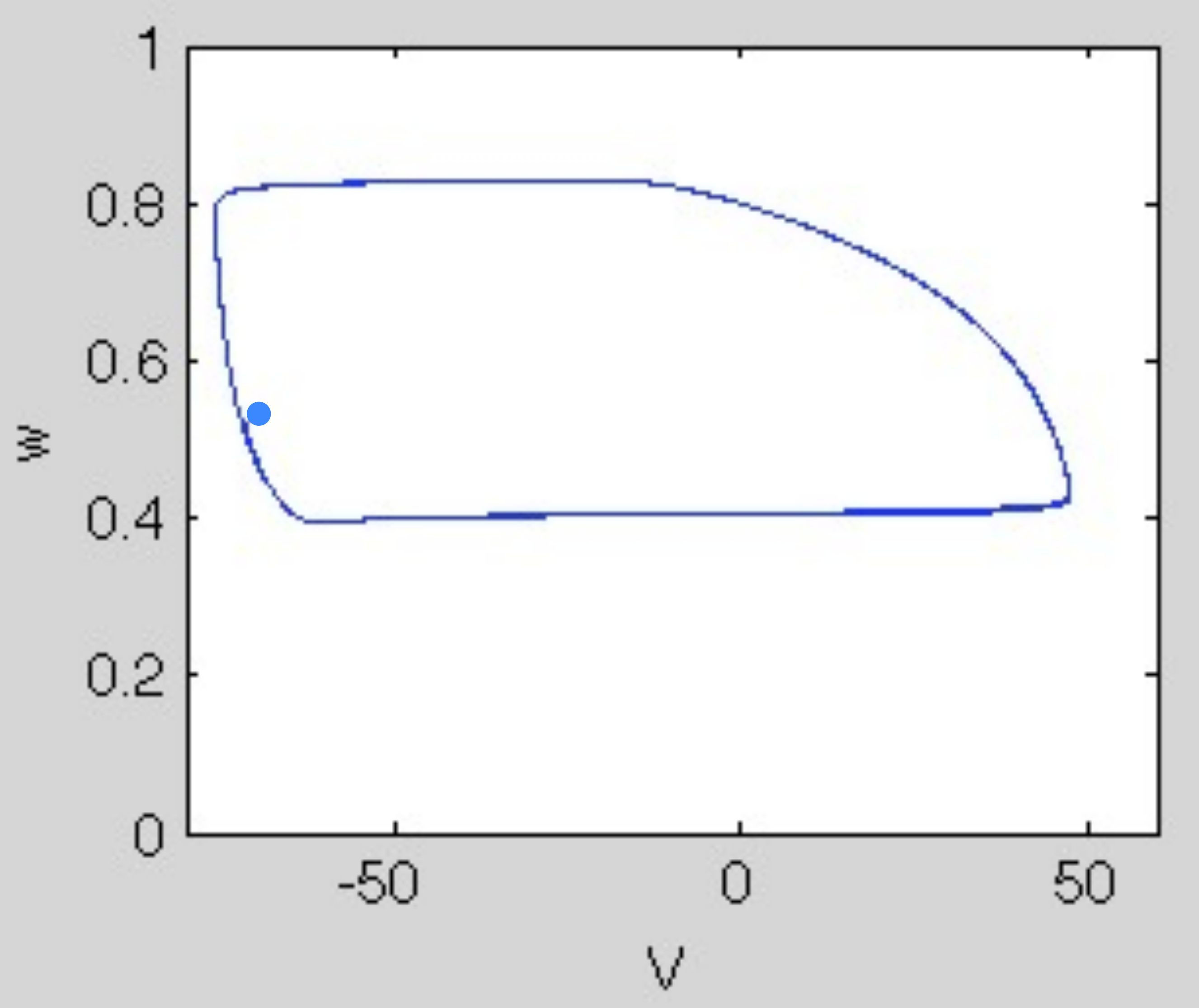
$(V, m, h, n) \longrightarrow (V, w)$ <u>Advantage</u>: 2-dim

Simulate reduced model (I big enough):

Plot phase space:



"spikes"



Q: What is this?

Simplify Hodgkin-Huxley

The simplified model is <u>not pretty</u> ...

The w dynamics depend on:

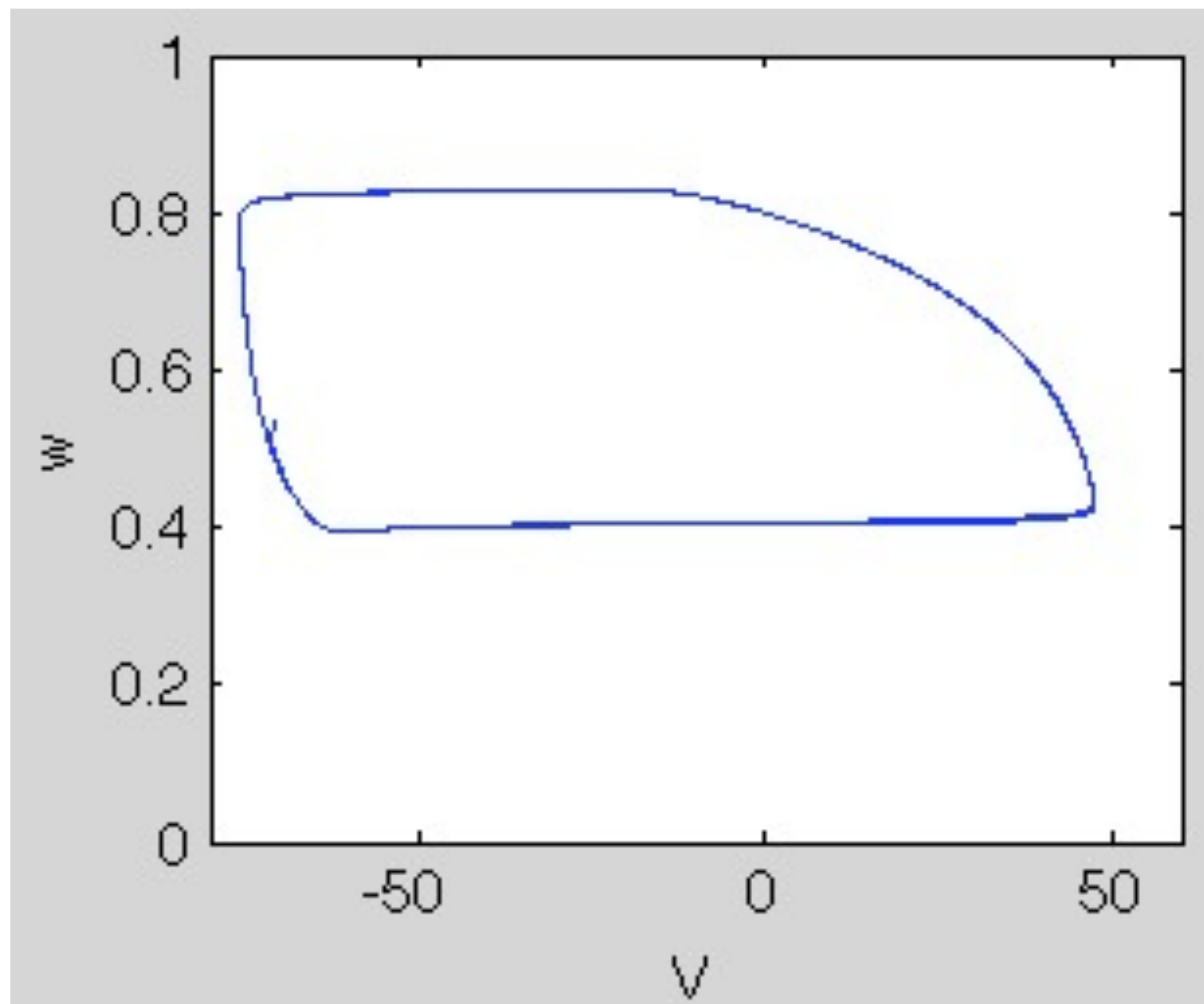
$$\alpha_n(V) = \frac{0.1 - 0.01(V+65)}{e^{1-0.1(V+65)} - 1}$$

$$\beta_n(V) = 0.125e^{(-V-65)/80}$$

Instead, consider an even simpler model ...

Goal:
mimic these spiking dynamics ...

allow notions of biology to become more abstract.



FitzHugh-Nagumo model

Consider instead the system:

$$\frac{dv}{dt} = v - \frac{1}{3}v^3 - w + I$$
$$\frac{dw}{dt} = \frac{v - a - bw}{\tau}$$

The FitzHugh-Nagumo model

Two variables: (v, w)

v = membrane potential

w = recovery variable (think: slow gating variable)

Parameters:

I = input current a, b, τ

Q: Does this model capture the spiking dynamics?

FitzHugh-Nagumo model

Let’s analyze this model.

– To do so, we’ll use XPPAUT.

http://www.math.pitt.edu/~bard/xpp/download.html

If you’d like, please download and install this software ...

and download the model:

http://math.bu.edu/people/mak/samsi/FHN.ode

FitzHugh-Nagumo model: *FHN.ode*

```
#The FitzHugh-Nagumo Model
```
comment

```
#Define the fixed parameters.
a=0.7
b=0.8
tau=12.5
```
Set model parameters

```
#Define the model equations.
dV/dt = V - V^3/3 - W + I
dW/dt = (V + a - b*W)/tau
```
Define model dynamics

```
#Define the initial conditions.
V(0)=0.1
W(0)=0.0
```
Set the initial conditions.

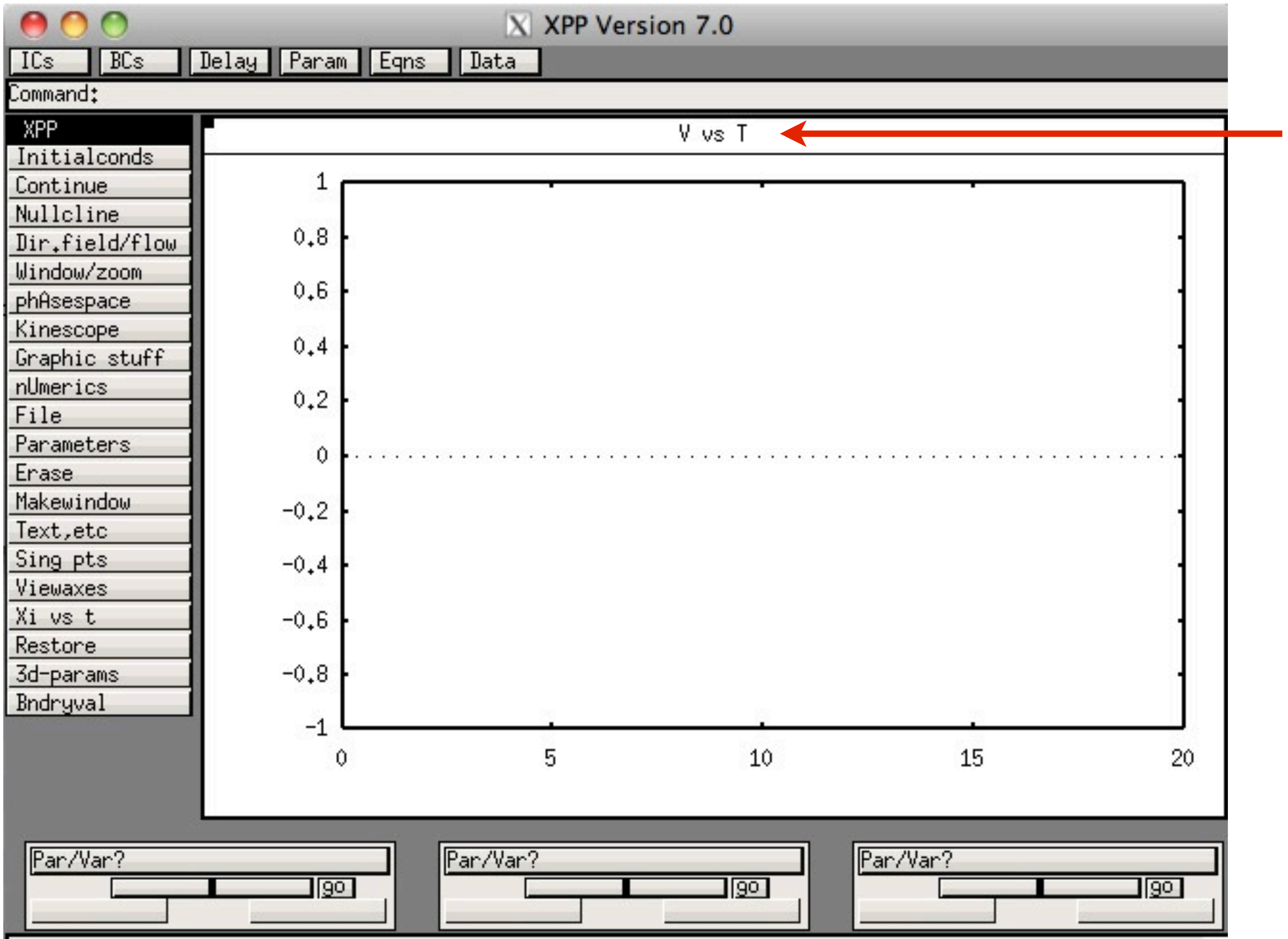
```
#Define the adjustable parameters.
param I=0
```
Specify one parameter to adjust

```
@ Total=500
@ dt=0.005
@ maxstor=500000
done
```
Set simulation features.

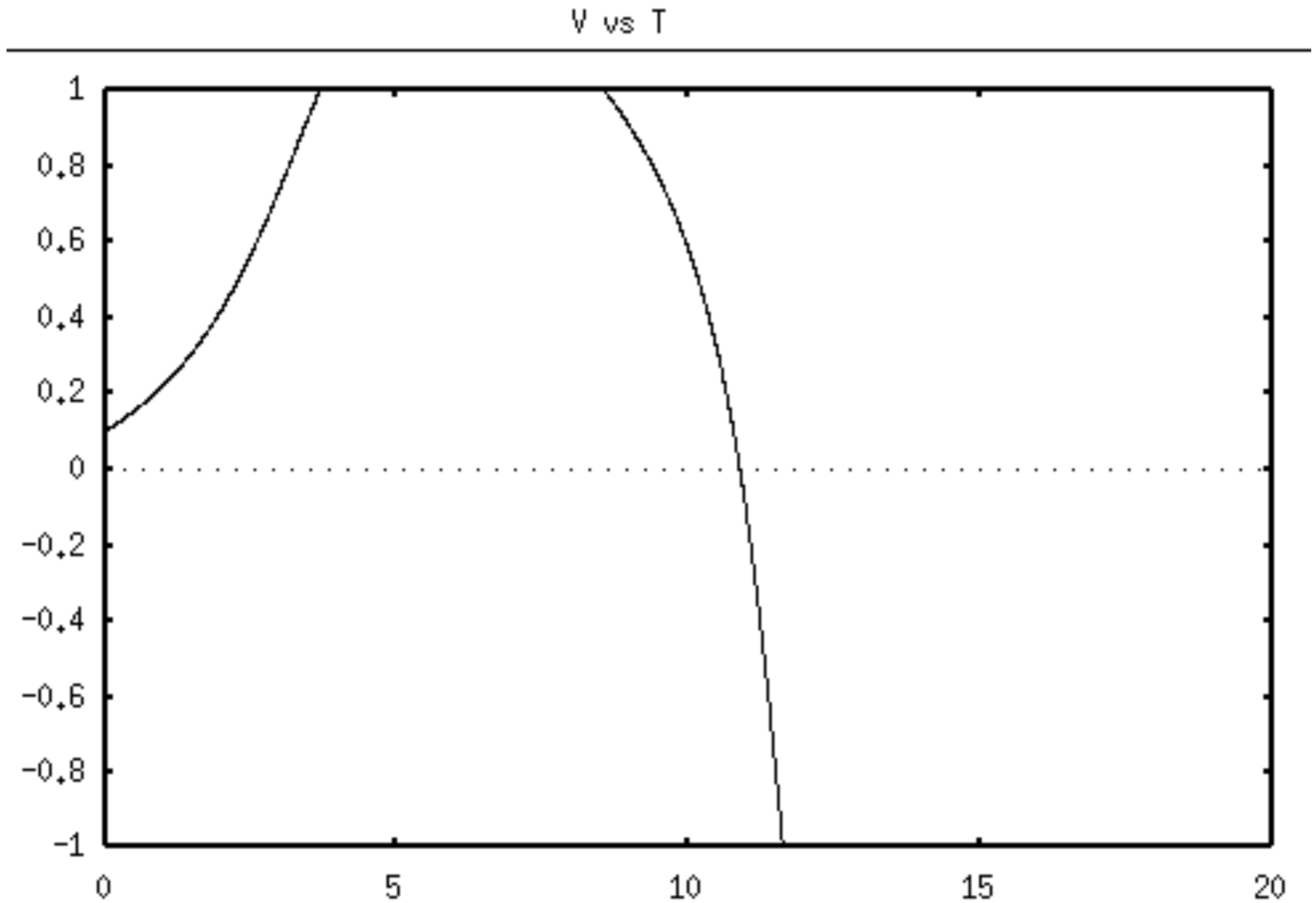
FitzHugh-Nagumo model

Let's run it in XPPAUT ...

- Locate and open the file *FHN.ode*



FitzHugh-Nagumo model: V vs t



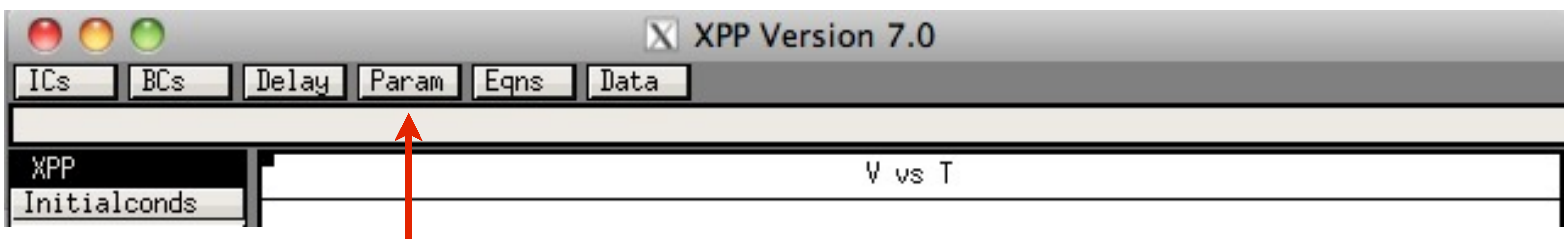
Keystrokes:

– *Initialconds - Go*

Improve visualization:

Xi vs t

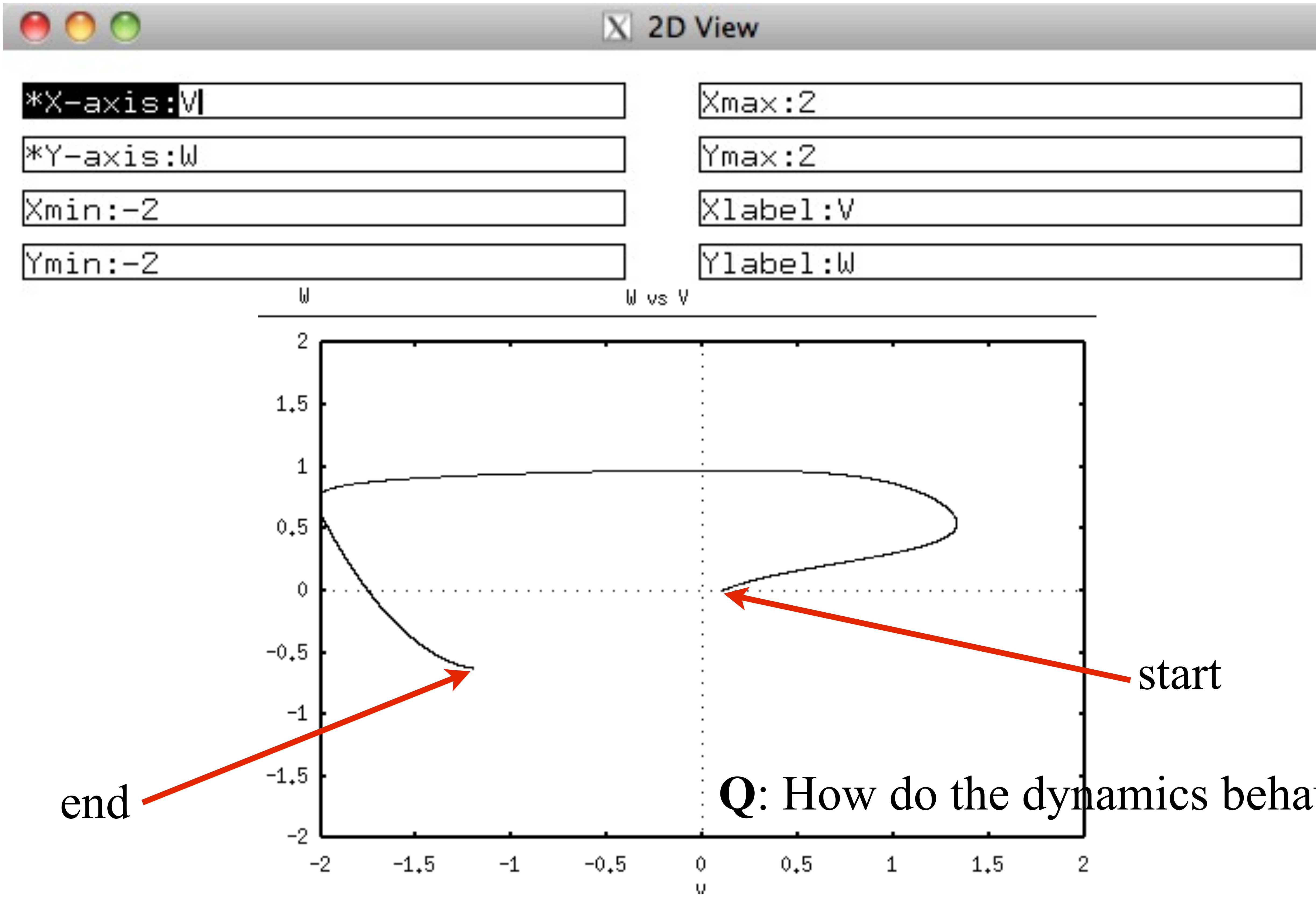
Q: What is the parameter I ? Param [box at top]



Q: How do the dynamics behave?

FitzHugh-Nagumo model: V vs w

Let's plot the phase space. *Viewaxes - 2D*



Q: How do the dynamics behave?

FitzHugh-Nagumo model: nullclines

Let's plot the <u>nullclines</u>.

<u>Keystrokes</u>:

– *Nullclines - New*

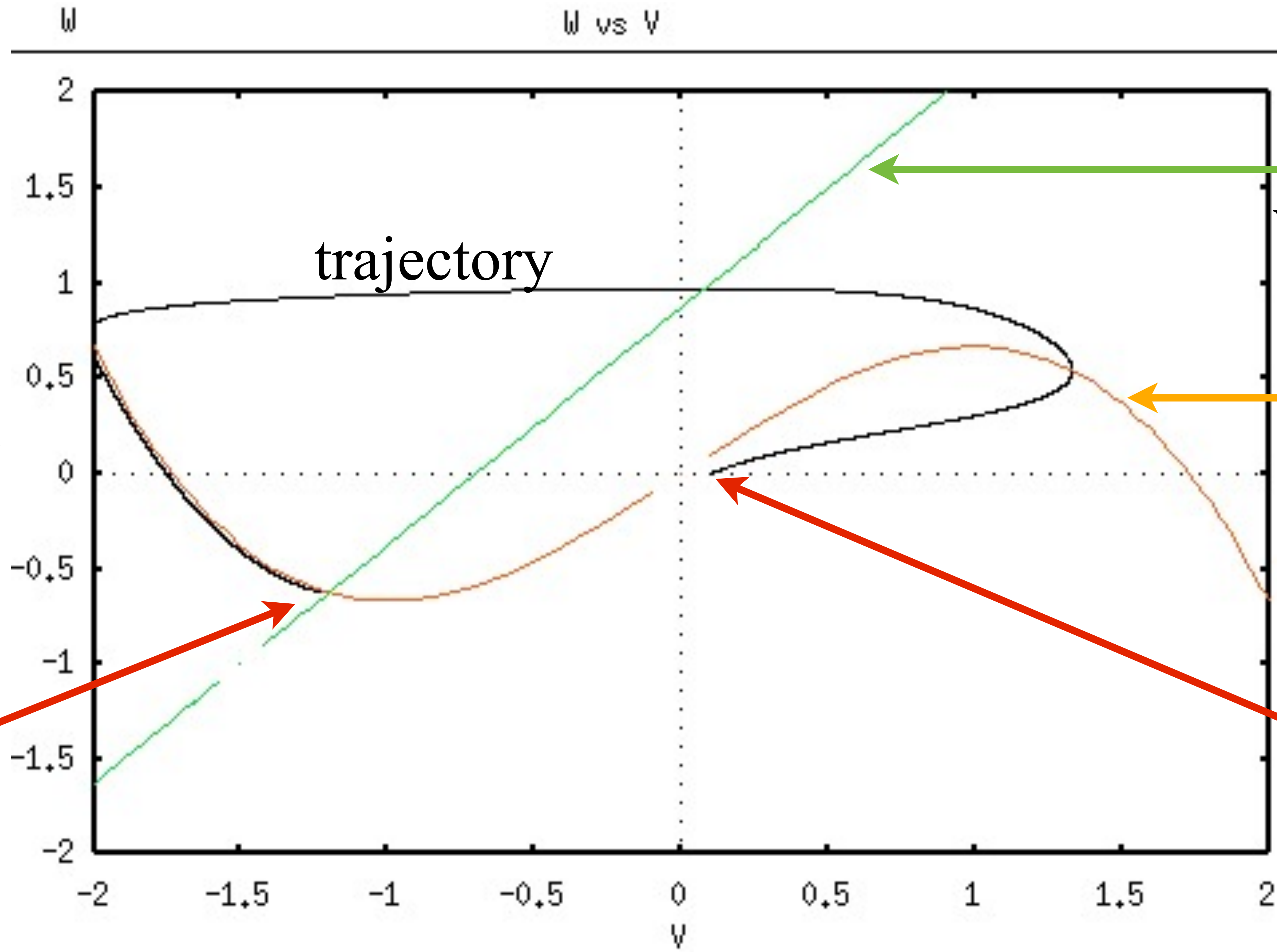
$$0 = \cancel{\frac{dv}{dt}} = v - \frac{1}{3}v^3 - w + I \quad \text{: v-nullcline}$$

$$0 = \cancel{\frac{dw}{dt}} = \frac{v - a - bw}{\tau} \quad \text{: w-nullcline}$$

Trajectory ends ...

at nullcline intersection

fixed point



w-nullcline

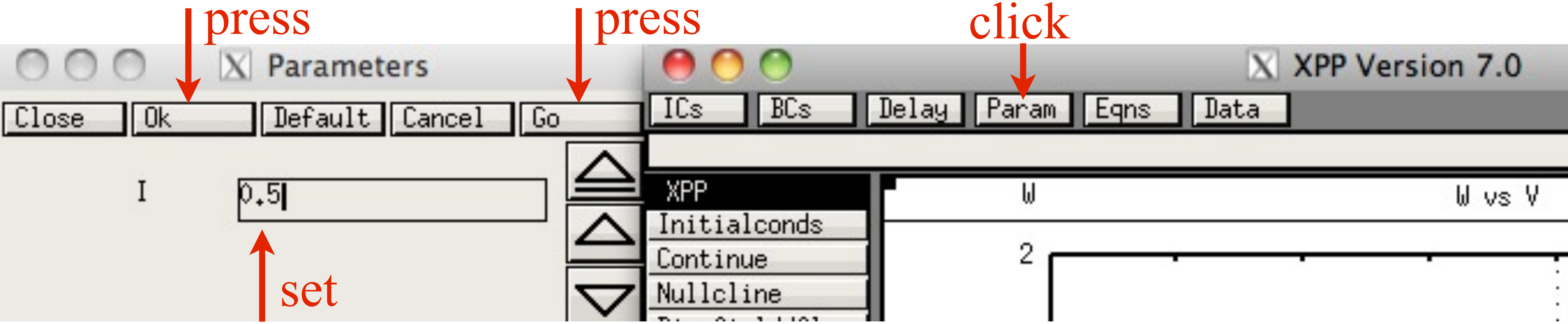
v-nullcline

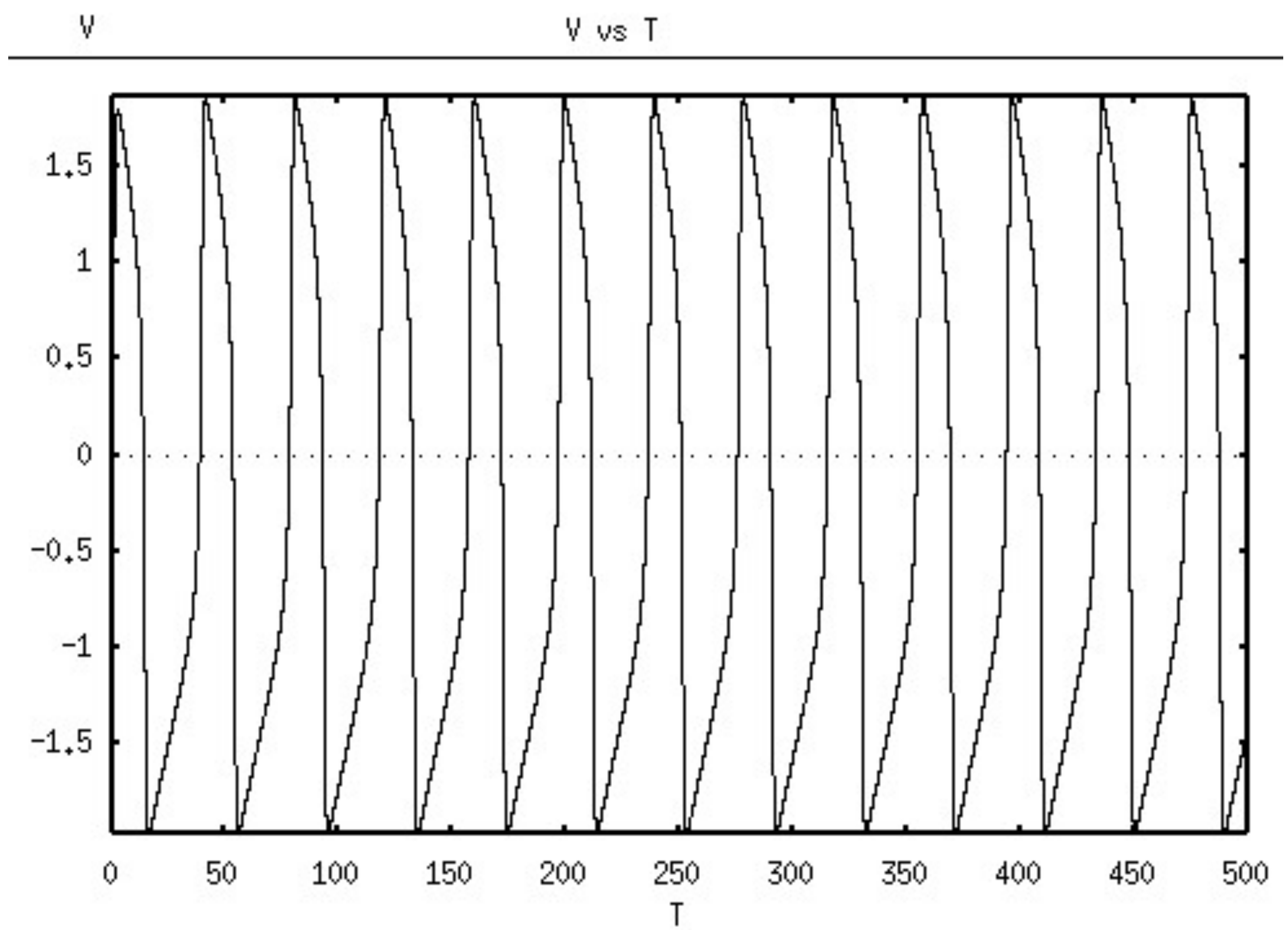
start

end

FitzHugh-Nagumo model: increase I

Let's increase the parameter I (i.e., deliver more "drive").





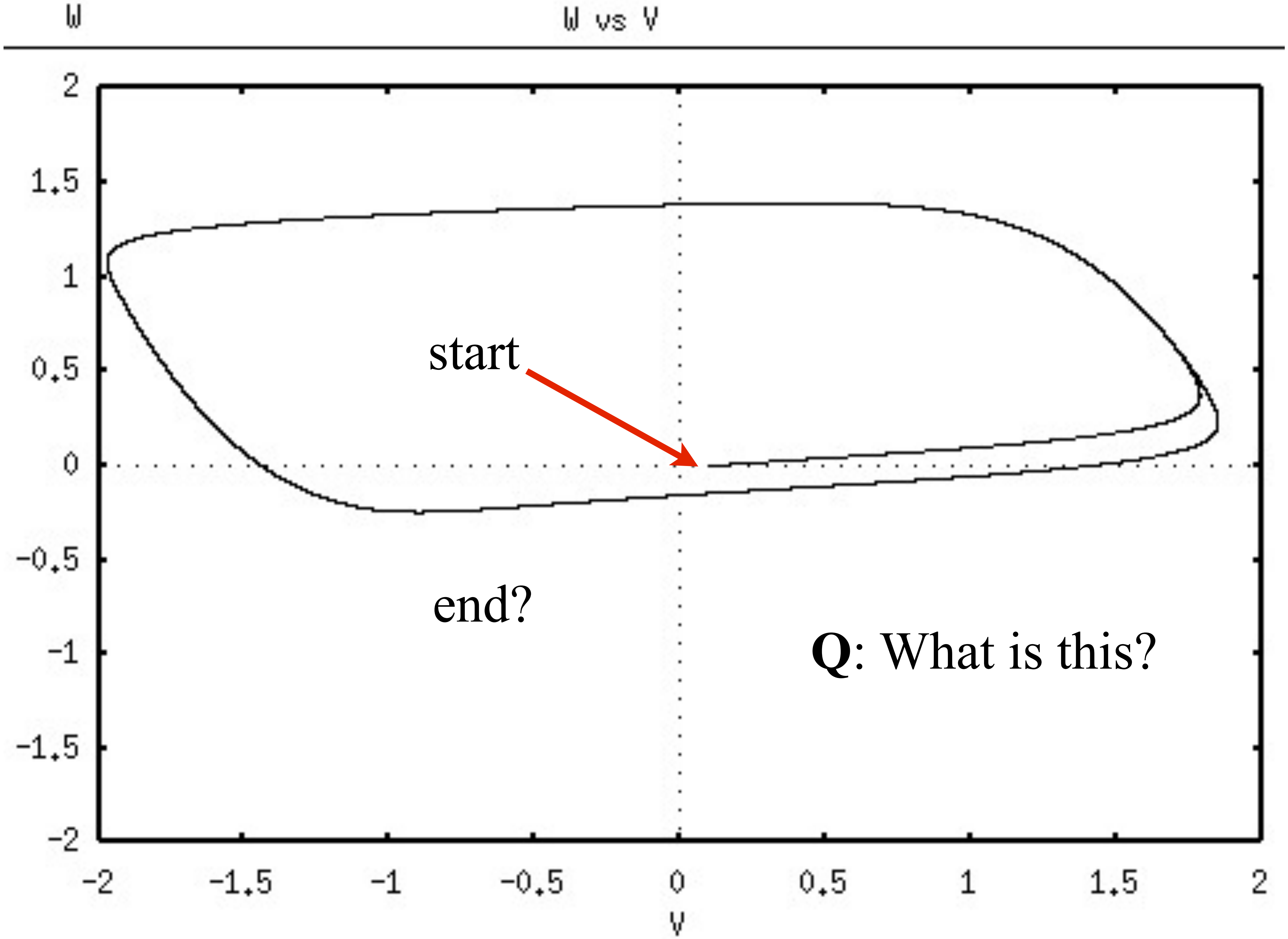
Plot: *Xi vs t*

Adjust axes: *Viewaxes - 2D*

Q: How do the dynamics behave?

FitzHugh-Nagumo model: increase I

Plot the phase space. *Viewaxes - 2D*



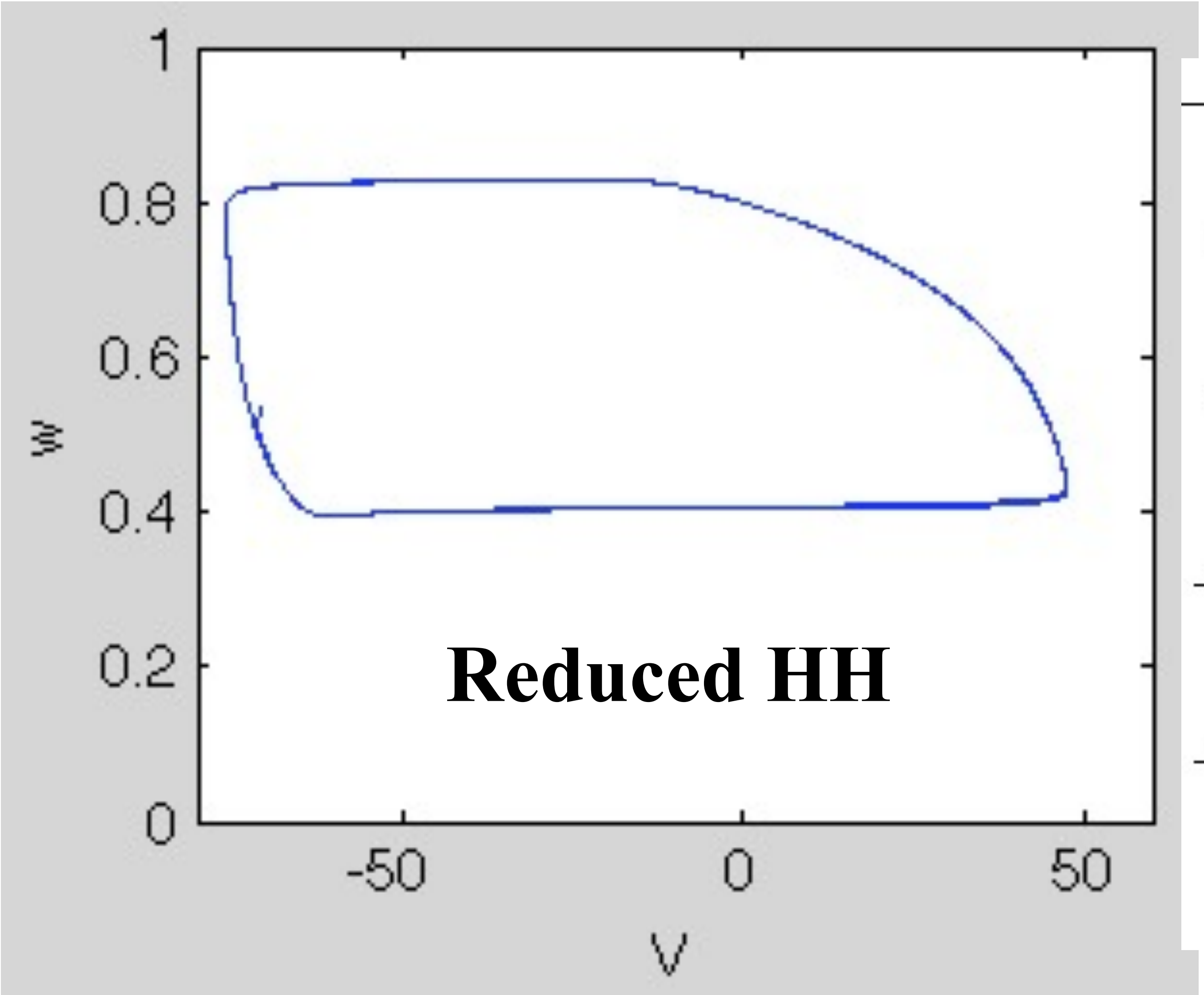
then

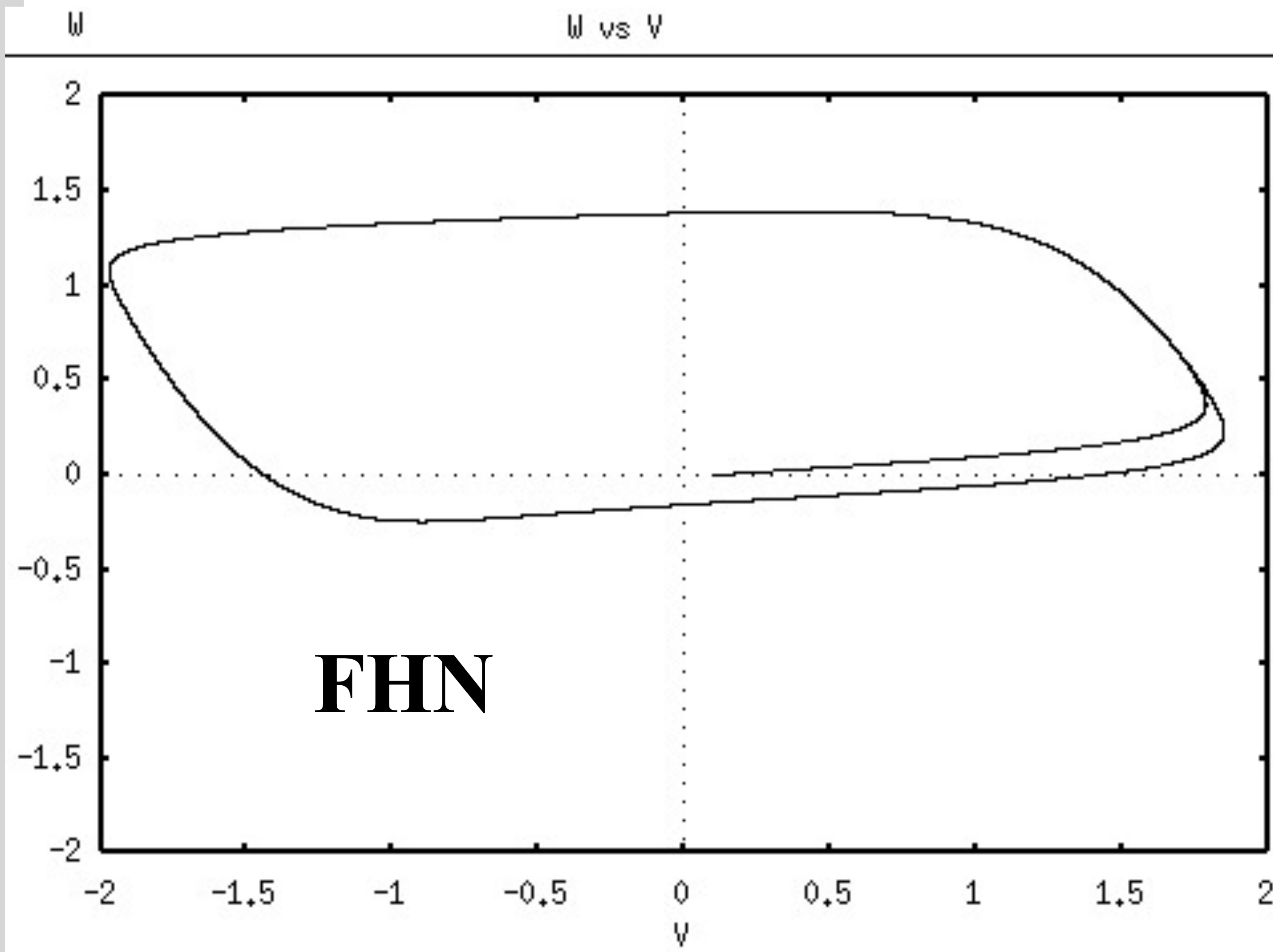
<u>NOTE</u>: If you see nullclines for I=0 case, *Nullcline - Manual*

FitzHugh-Nagumo model

Remember our reduced Hodgkin-Huxley model dynamics:

Goal: mimic these dynamics ....

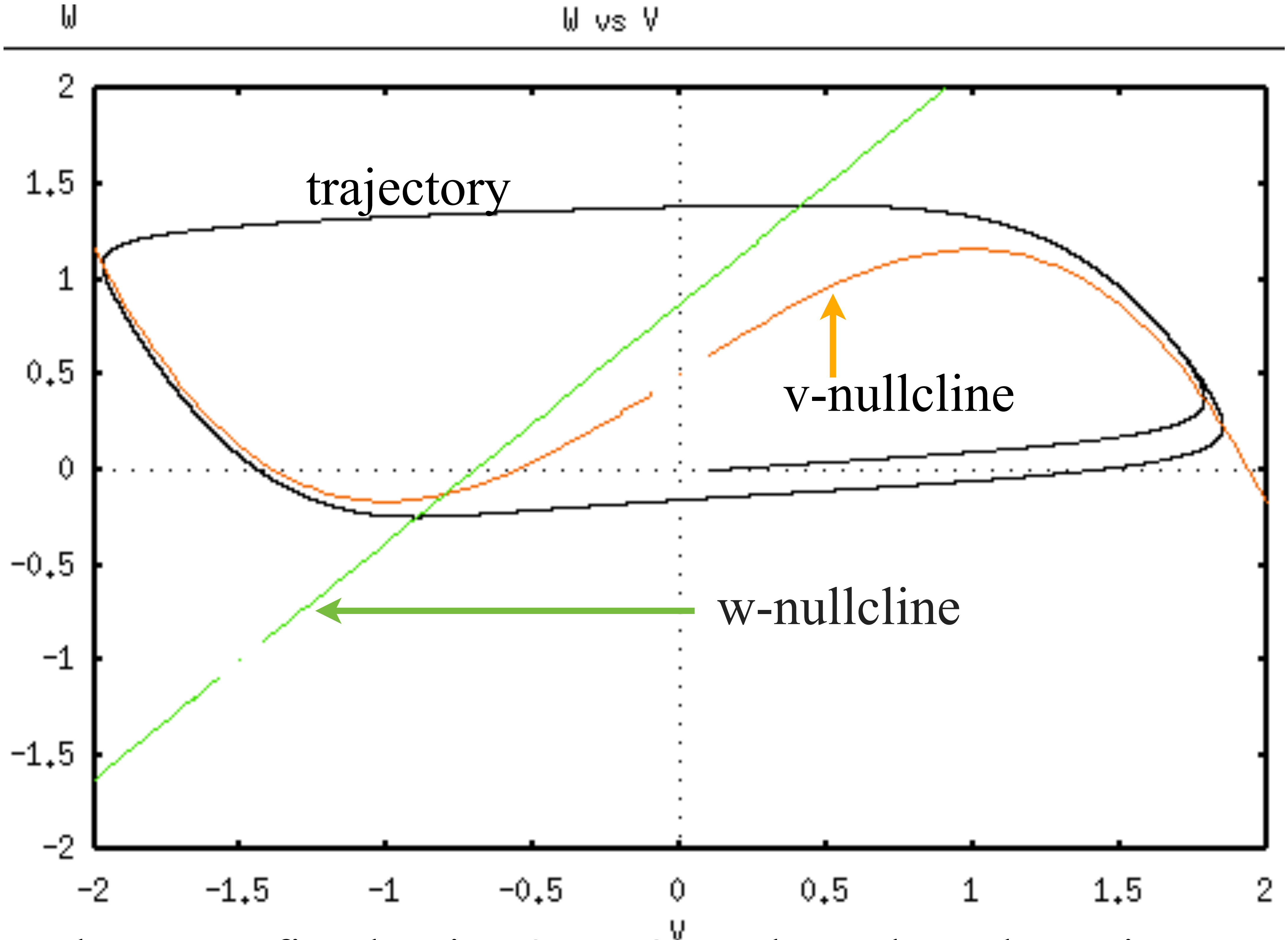




The FHN model qualitatively captures the reduced HH dynamics ...

FitzHugh-Nagumo model: nullclines

Let's plot the nullclines for I=0.5 *– Nullclines - New*



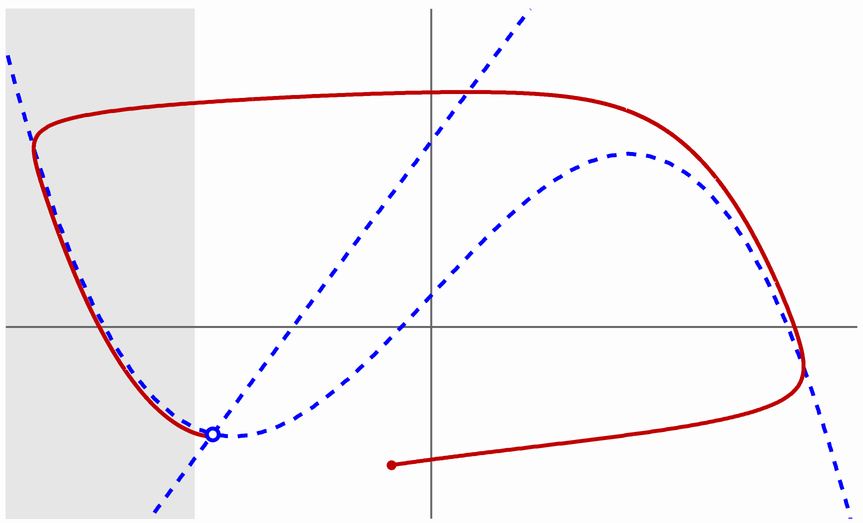
Q: Are there any fixed points? **Q**: Where does the trajectory go?

FitzHugh-Nagumo model: two values of I

We've considered FHN dynamics at two values of I:

I = 0

Dynamics approach ...



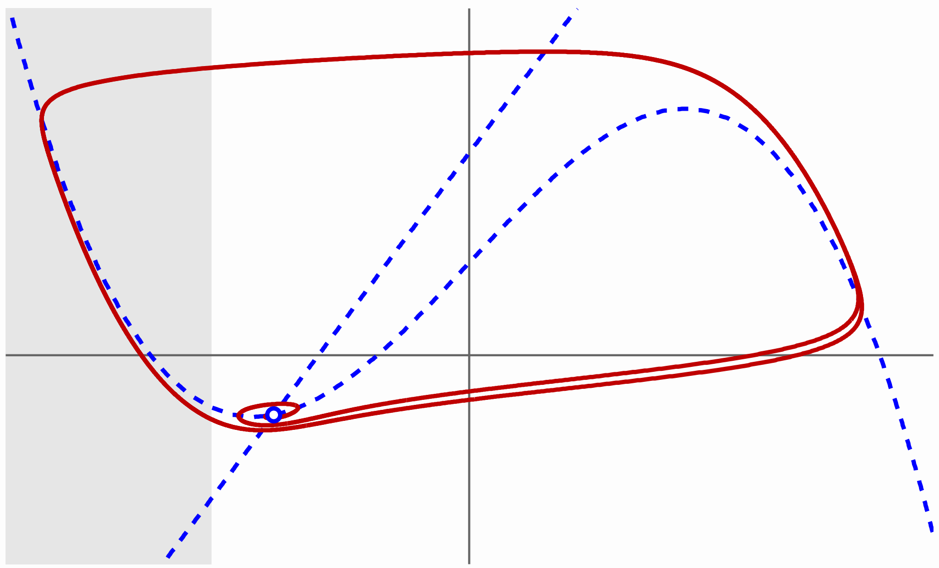
... a fixed point.

subthreshold "rest" state

Q: What happens in between?

I = 0.5

Dynamics approach ...



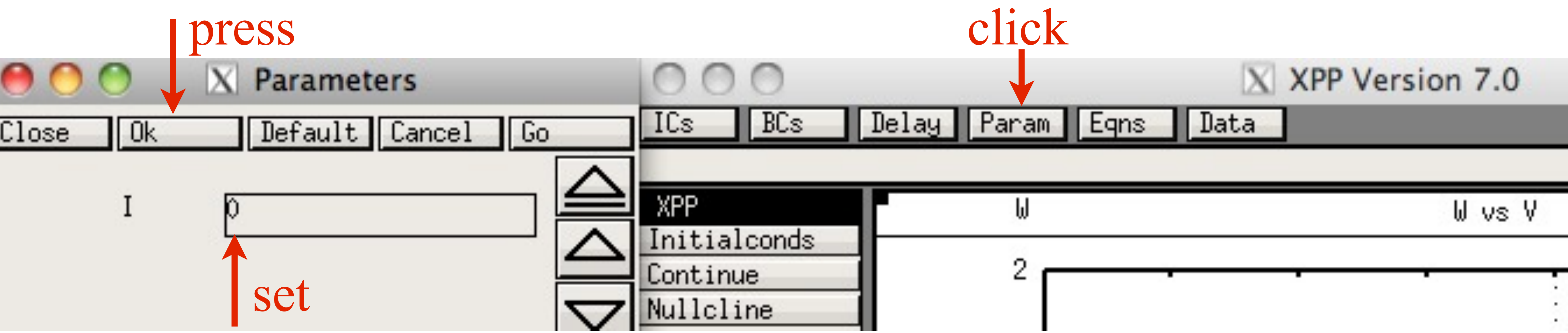
... a limit cycle.

"spikes"

Bifurcation diagram

We can compute a bifurcation diagram in XPPAUT
– a multi-step process.

1. Set I = 0.



2. Run the dynamics many times to approach the fixed point.

– *Initialconds* - *Go*

Then: – *Initialconds* - *Last*
Repeat!

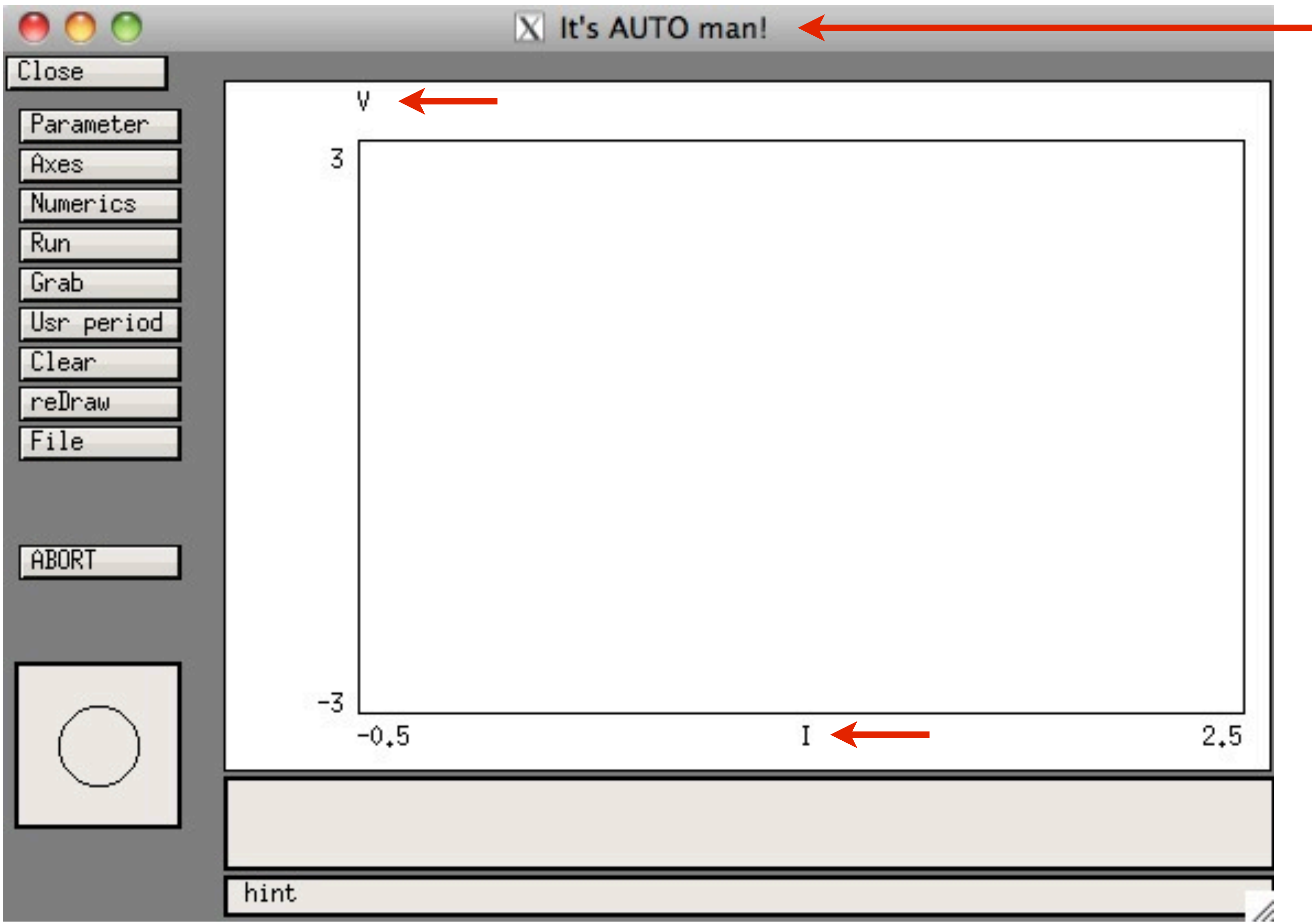
Use the last values of (v,w) and continue simulation.

Bifurcation diagram

3. Run AUTO

– *File - Auto*

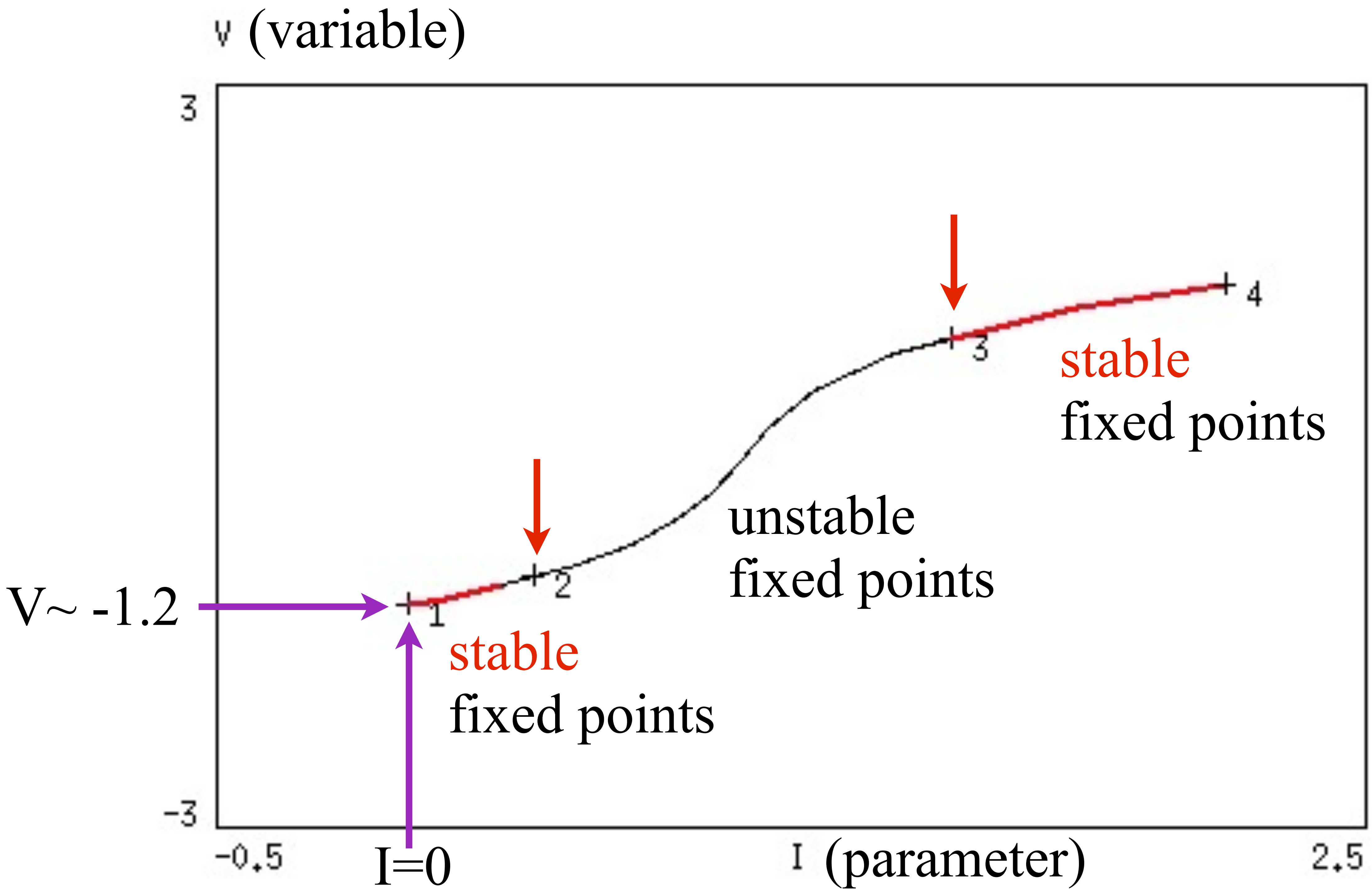
This screen should appear:



Bifurcation diagram

4. Follow the fixed points.

<u>IN AUTO</u>: *Run - Steady state*



Q: What happens at transitions?

Bifurcation diagram

Looks for terminal print out ...

```
Used 7 constants and 111 symbols
XPPAUT 7.0 Copyright (C) 2002-now  Bard Ermentrout
TrueColor visual:  no colormap needed

  BR    PT TY LAB     PAR(1)        L2-NORM         U(1)          U(2)
   1     1 EP   1  0.000000E+00  1.352139E+00 -1.199408E+00 -6.242600E-01
   1     7 HB   2  3.313016E-01  1.023602E+00 -9.674632E-01 -3.343290E-01
   1    16 HB   3  1.418717E+00  2.297925E+00  9.674697E-01  2.084337E+00
   1    18 EP   4  2.137627E+00  2.973547E+00  1.399077E+00  2.623846E+00
```

= I

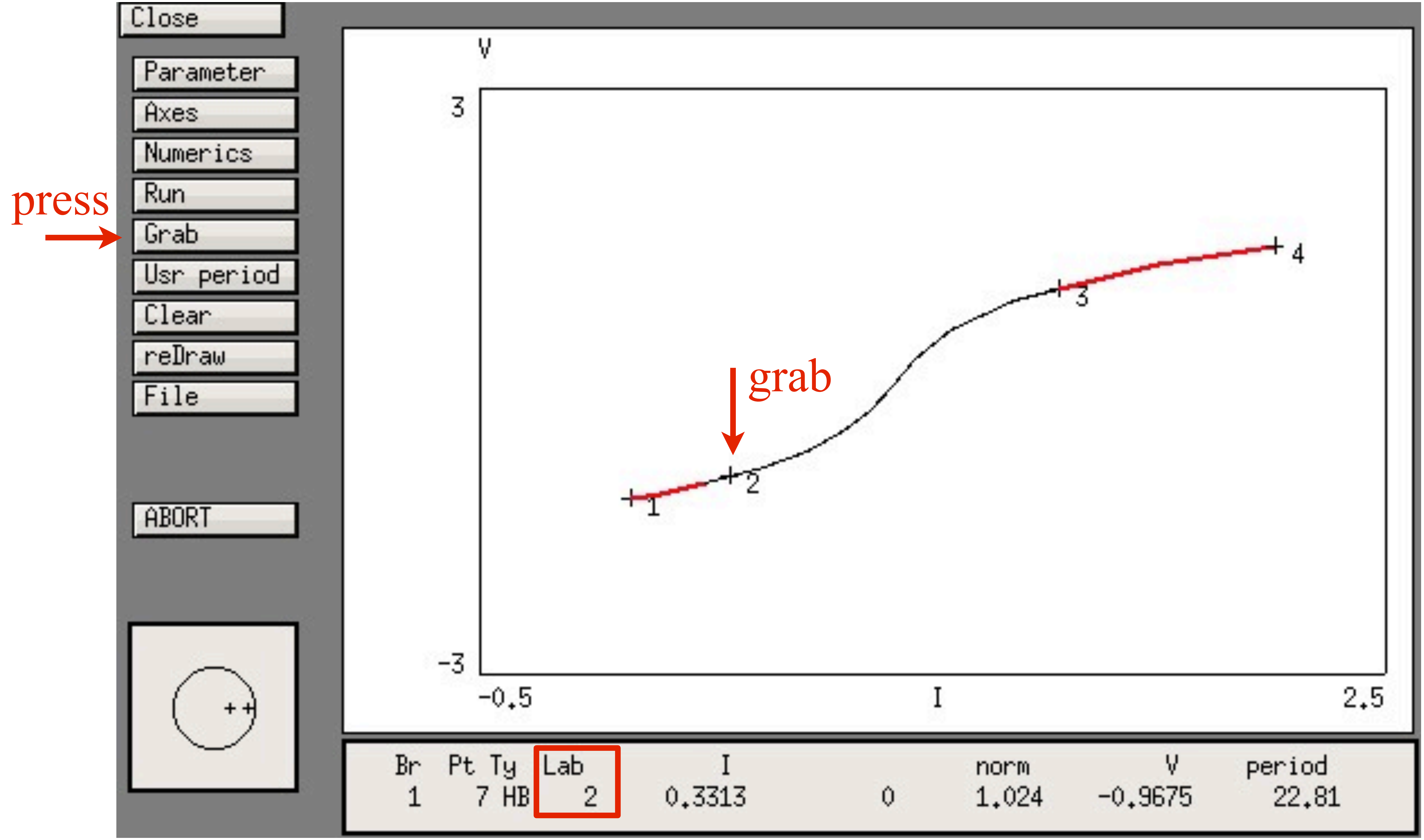
AUTO detects two “HB”   = Hopf bifurcations

At these HBs, a limit cycle appears / disappears ...

We can tract the limit cycles that emerge ...

Bifurcation diagram

5. Grab a HB.



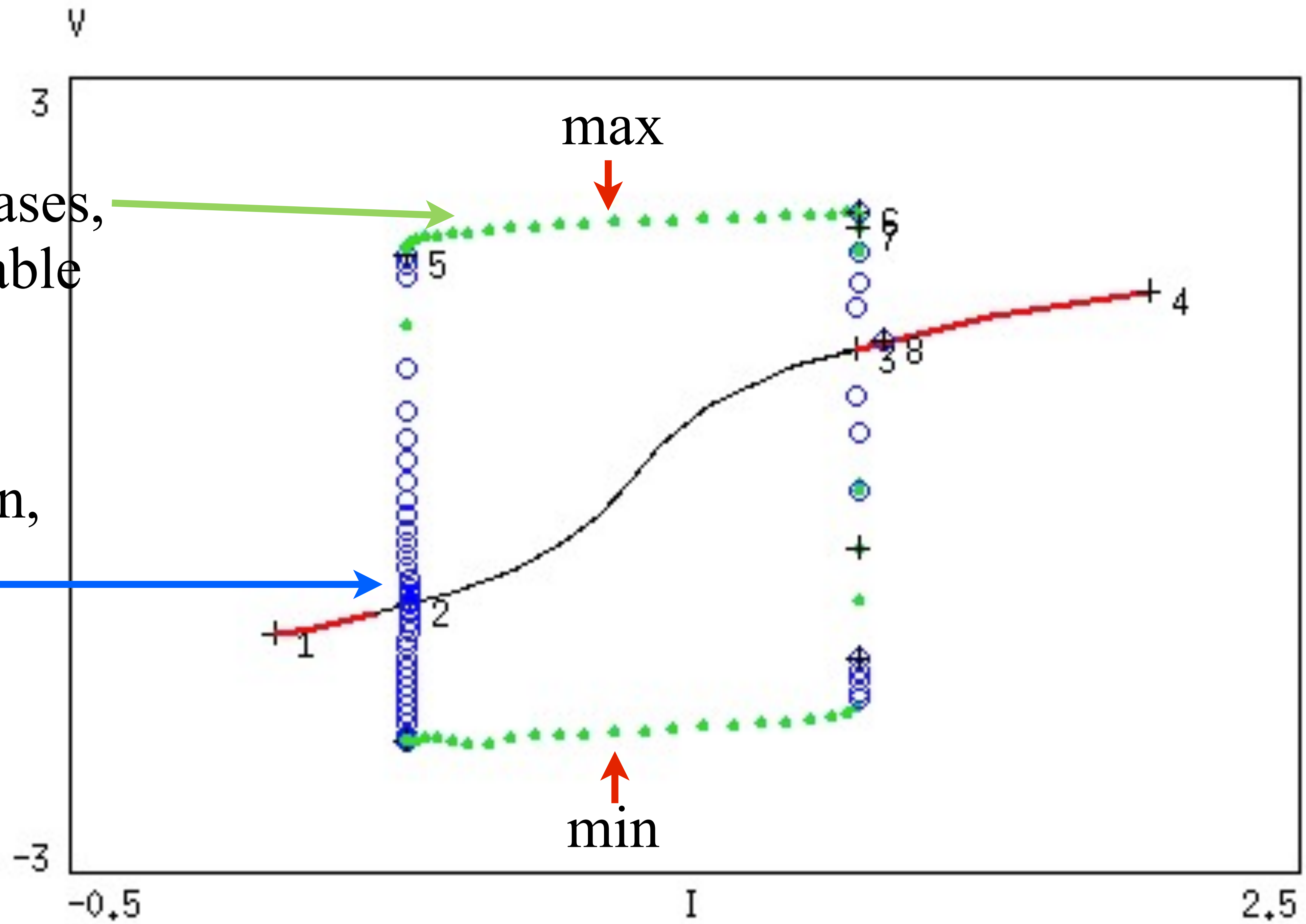
Bifurcation diagram

6. Follow the periodic orbit.

IN AUTO: *Run - Periodic orbit* <u>Note</u>: must grab HB first!

limit cycle amplitude increases, and becomes stable

limit cycle born, it's unstable

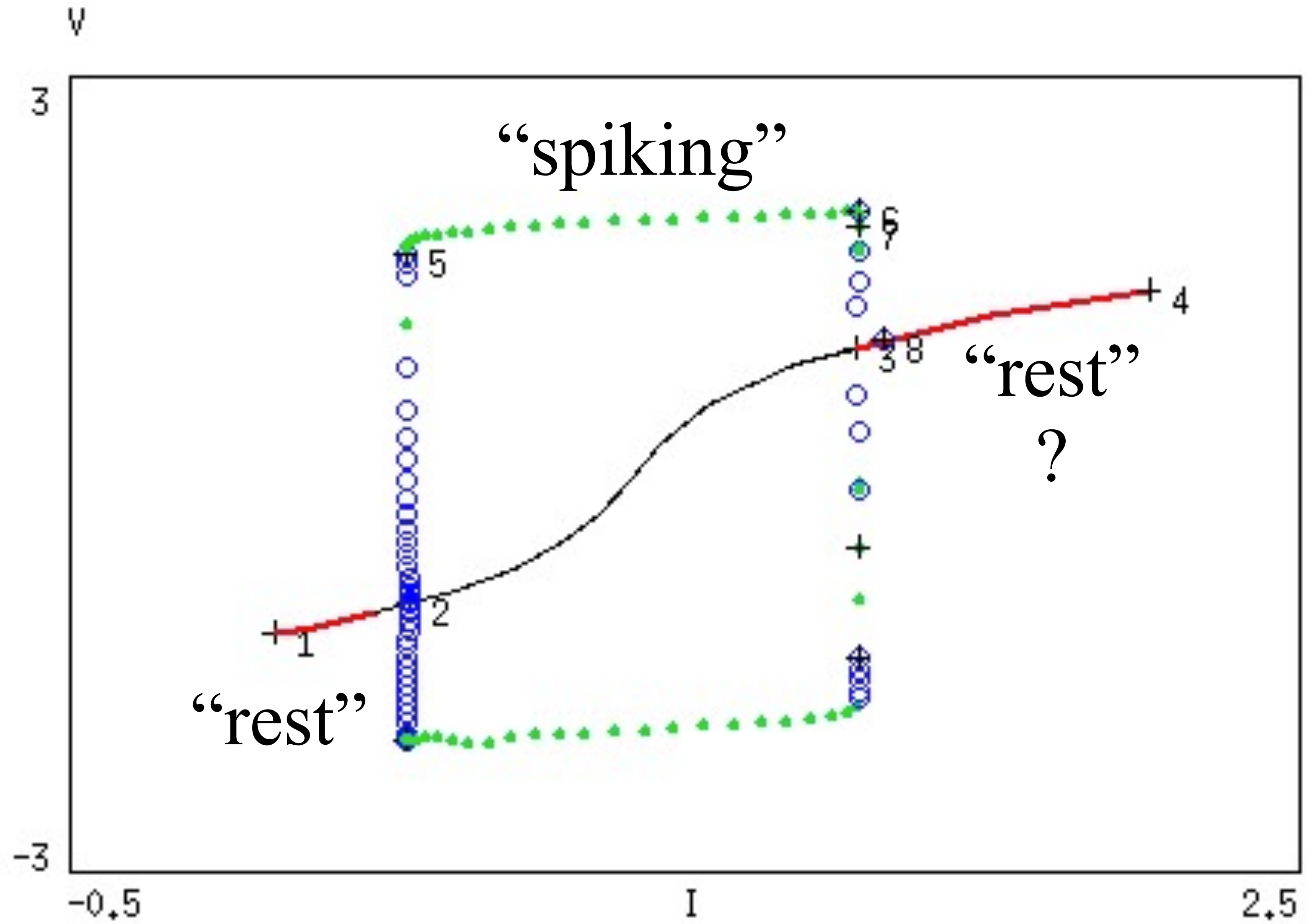


When fixed point is unstable, a stable limit cycle appears ...

FitzHugh-Nagumo model

In this way, we develop a deep understanding of FHN dynamics ...

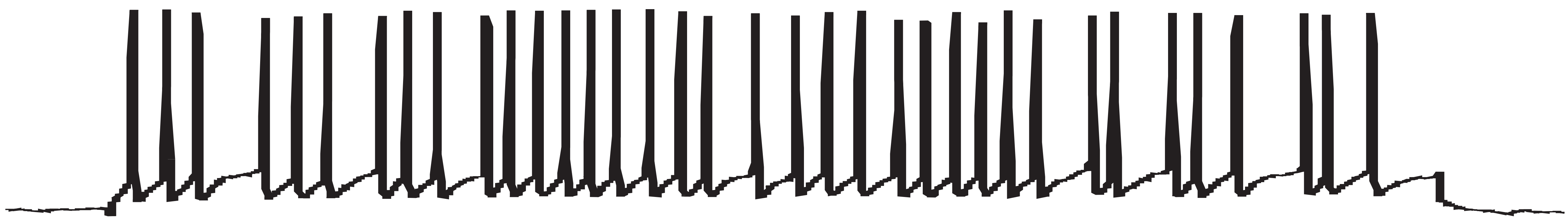
"As I increases, the transition from rest to spiking occurs at a (subcritical) Hopf bifurcation."



It's not "too difficult" to examine model dynamics in XPPAUT.

One last thing ...

In the past two days, we've considered two approaches to "understand" neuronal spiking data:



Statistical: firing rate, ISI, GLM, ...

Advantage: direct link to data.
Disadvantage: no biophysics.

Mathematical: I&F, Hodgkin-Huxley, FHN.

Advantage: incorporates biophysics / dynamics.
Disadvantage: indirect links to data.

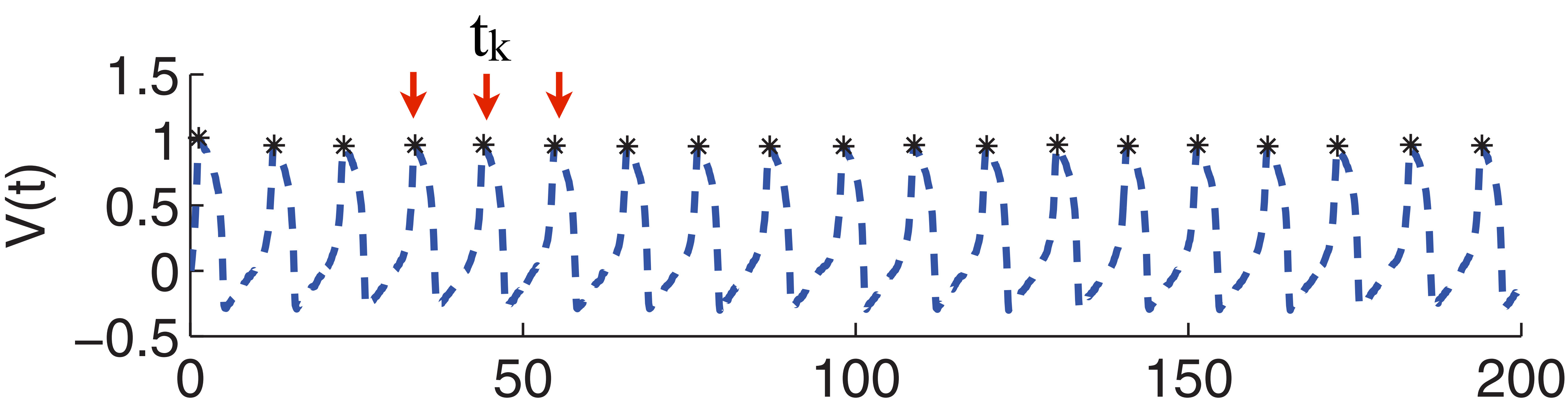
Q: Which approach is best?

Data assimilation

Q: Can we combine neuronal data and "expert knowledge" - as captured in a biophysical/dynamics model - to understand the brain?

A: Data assimilation. <u>Example</u> [Meng, Kramer, Eden, 2011]

Given data (spike times):



Data assimilation

And given a model: (Hodgkin-Huxley)

$$C\,\frac{dV}{dt} = I_{\text{input}}(t) - \boxed{\bar{g}_{\text{K}}}\,n^4(V - V_{\text{K}}) - \boxed{\bar{g}_{\text{Na}}}\,m^3h(V - V_{\text{Na}}) - \bar{g}_{\text{L}}(V - V_{\text{L}})$$

$$\frac{dn}{dt} = -\frac{n - n_\infty(V)}{\tau_n(V)}$$

$$\frac{dm}{dt} = -\frac{m - m_\infty(V)}{\tau_m(V)}$$

$$\frac{dh}{dt} = -\frac{h - h_\infty(V)}{\tau_h(V)}\,,$$

Q: Can we estimate the (hidden) model states (V,n,m,h) and parameters?

A: Maybe ... consider a particle filter.

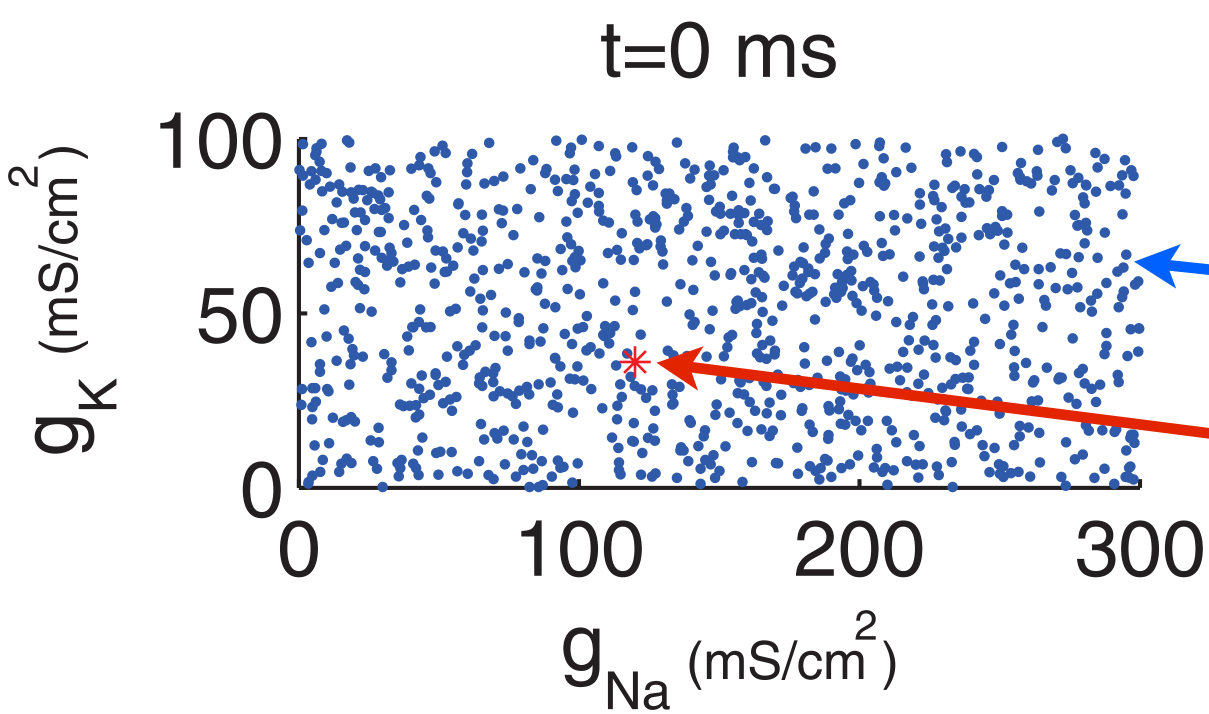
Each particle represents possible values for hidden quantities.

As time evolves, keep those particles most consistent with the data.

Data assimilation

Example particle evolution.

Distribution of two parameter values (g_K, g_{Na}) for each particle:



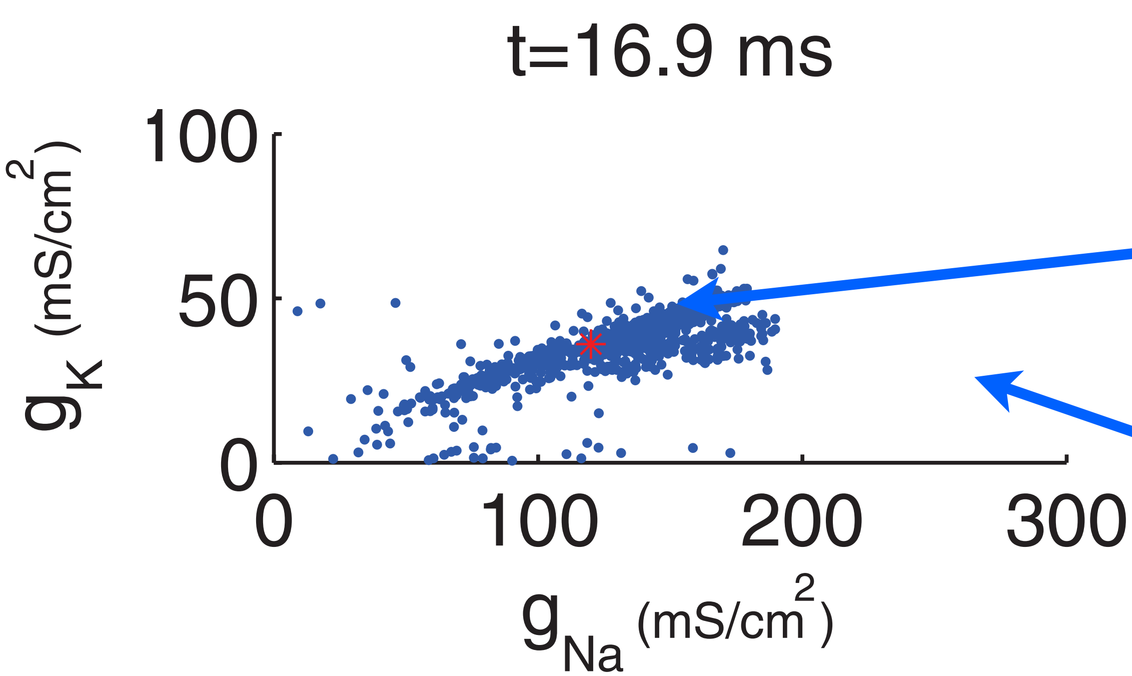
Before observing any data ...

... a non-informative prior

Particle: (g_K, g_{Na})

True value

Observe data ...



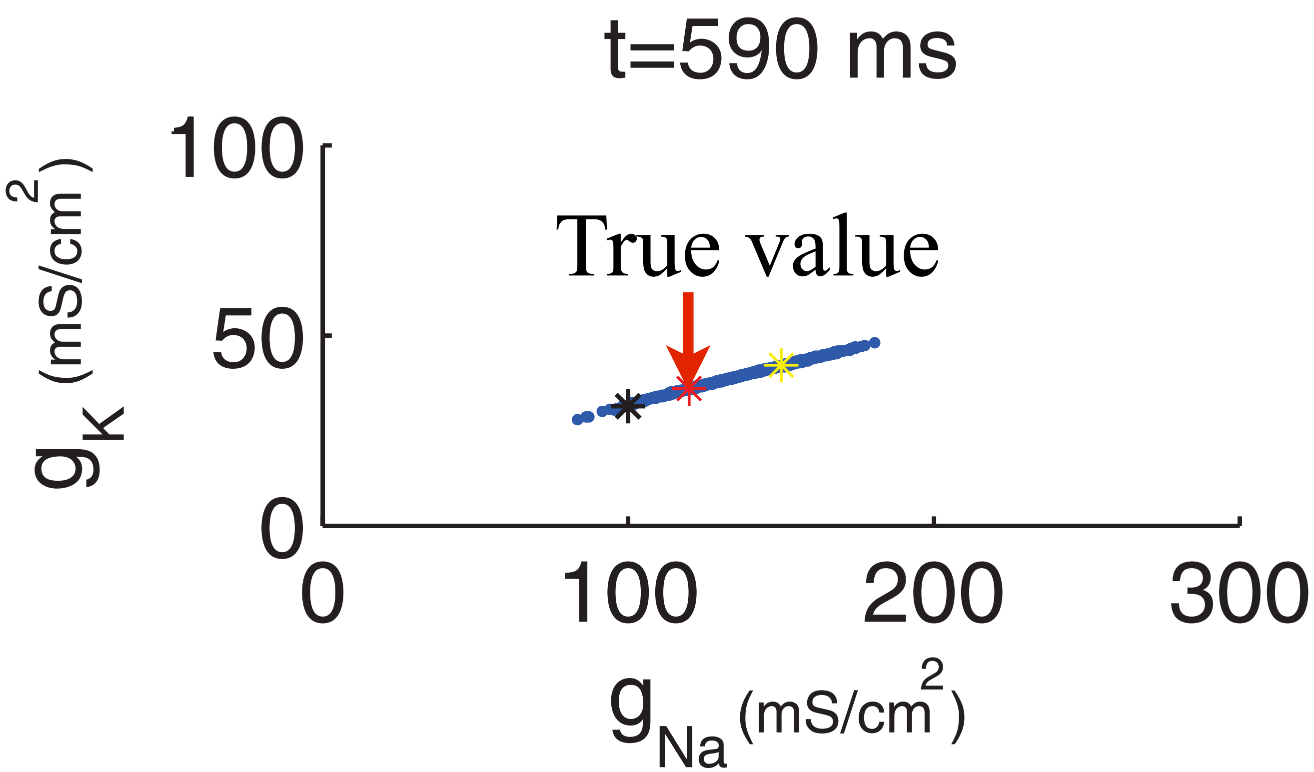
Only a subset of (g_K, g_{Na}) survive.

(g_K, g_{Na}) consistent with observed spike times

(g_K, g_{Na}) inconsistent with observed spike times

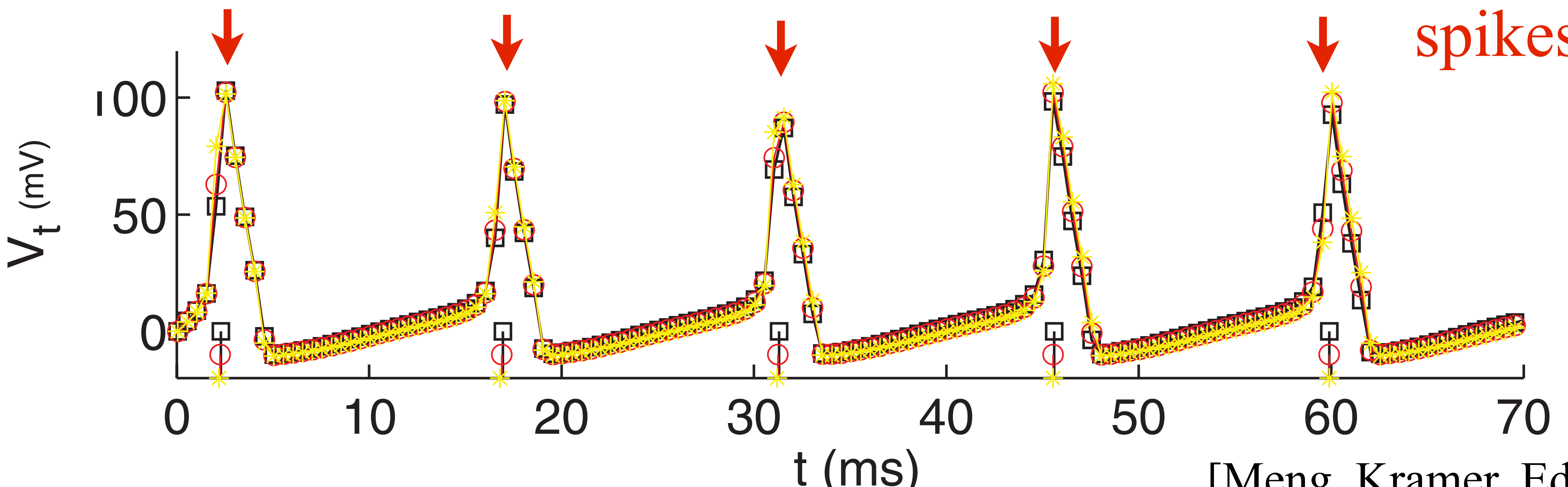
Data assimilation

Continue to observe data ...



A manifold of parameter pairs consistent with observed data ...

Many pairs of (g_K, g_{Na}) that produce spike times consistent with the observed data ...



[Meng, Kramer, Eden, 2011]

Data assimilation

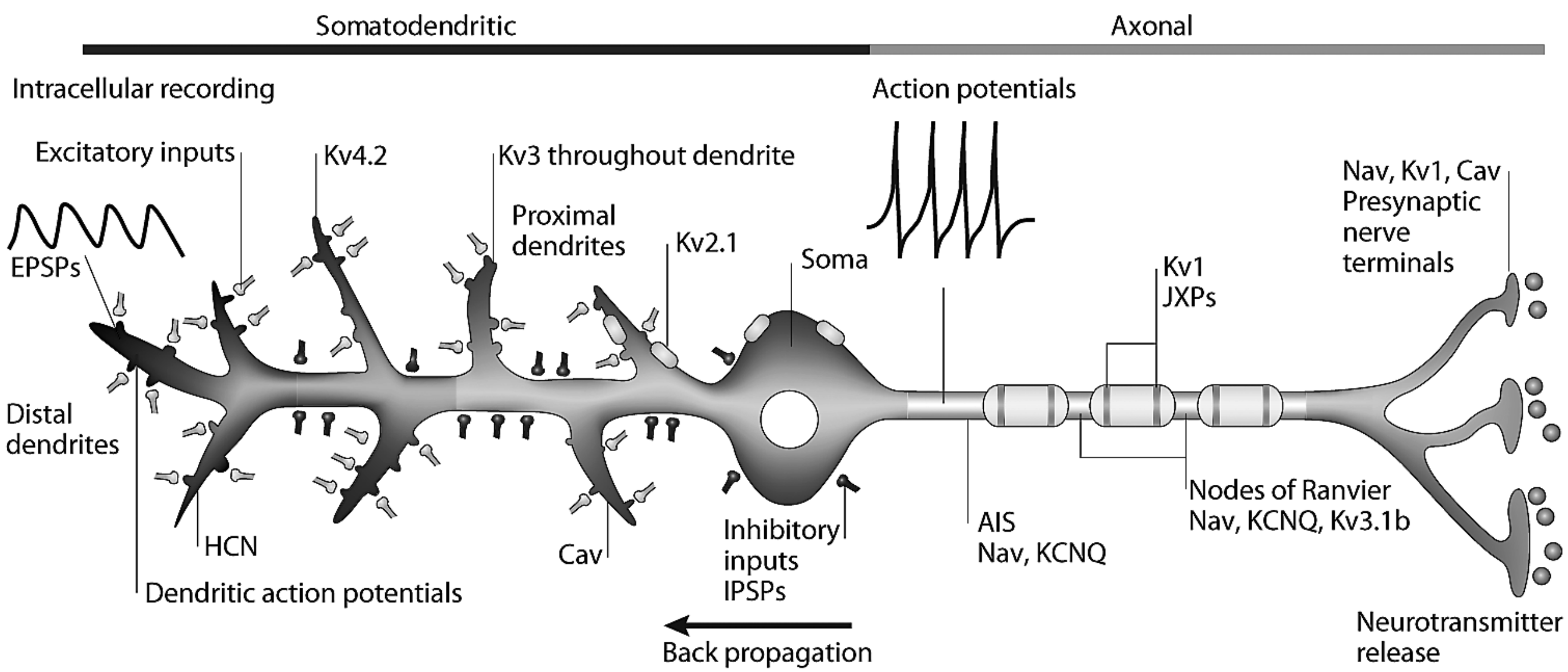
In simulation,

– often works well.

In practice,

– many challenges exist.

– A big one: models are inadequate ...



geometry,
currents,
synapses,
...

[Schiff 2012]

... we’re fitting the wrong model to the data.

Q: How do we address these and related challenges?

Summary

Many approaches to analyze spike train data ...

- Statistical
- Mathematical (biophysical / dynamical)

Today: an introduction to some mathematical modeling approaches,

- I&F, LIF
- Hodgkin-Huxley
- FitzHugh-Nagumo

References (a subset)

Koch, *Biophysics of Computation*

Izhikevich, *Dynamical Systems in Neuroscience*

Ermentrout and Terman, *Mathematical Foundations of Neuroscience*

Ermentrout, *Simulating, Analyzing, and Animating Dynamical Systems (XPPAUT)*

Thanks

Workshop Organizers:

Hongtu Zhu, Thomas Witelski

Organizing Committee:

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