University of BRISTOL

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Experimental Bifurcation Analysis in Neurons Using Control-based Continuation

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My project

- Neurons are interesting
- We have lots of models of them
- These can explain most results from classical neuroscience using these models

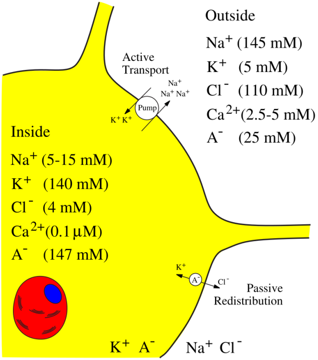
> "All models are wrong, but some are useful"
>
> — George Box

- Is there a better way?

Presentation plan

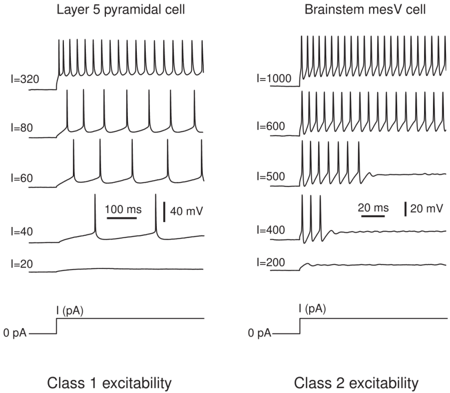
- A brief introduction to neurons
- Bifurcations as neural encodings
- Methods for bifurcation analysis
- Future work

But what is a neuron?



- Cell membrane, with salt inside and salt outside
- Different ion concentrations produce a voltage over the membrane
- Ion channels and pumps move the ions to change membrane potential

Neurons spike!

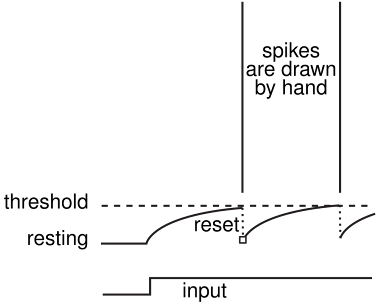


How do we model them?

- Membrane acts as a capacitor
- External currents charge it
- Ionic currents charge or discharge it

Neuron models seek to explain how currents charge and discharge the neuron

The integrate-and-fire neuron



$$\frac{\mathrm{d}V}{\mathrm{d}t} = \frac{1}{C} I(t) \tag{1}$$

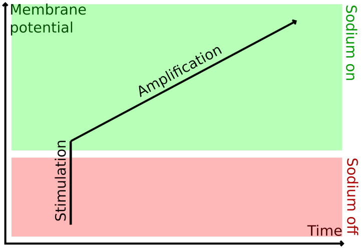
- If voltage $\geq$ threshold:
  - Say a spike was fired
  - Reset voltage
- Input current charges membrane, causing spiking
- Biophysical models just add more currents

Ionic currents

- The membrane contains ‘holes’ through which specific types of ions can pass
- These ion channels can open and close, so their resistance changes
- Changes in their conductance allow a neuron to spike

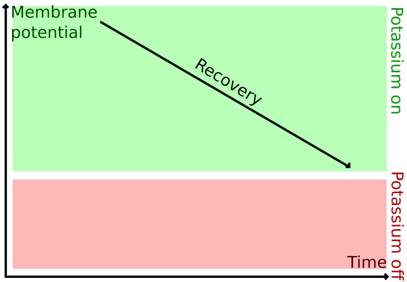
But how?

Sodium currents



- Sodium currents are positive charges flowing into the cell
- Sodium increases the membrane potential
- Higher membrane potential causes more sodium currents
- Positive feedback, causes upspike

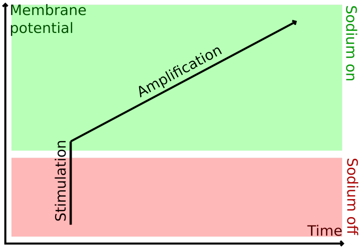
Ionic currents



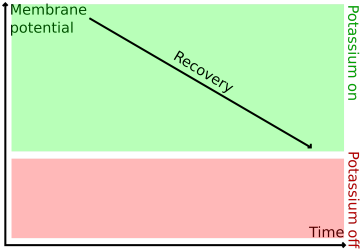
- Potassium currents are positive charges flowing out of the cell
- Potassium decreases membrane potential
- Higher membrane potential causes more potassium currents
- Negative feedback, causes downspike

Spiking mechanism

Disparate timescales cause spiking behaviour!



FAST



SLOW

What do ion models look like?

- Current = conductance × voltage
- Change in voltage = current ÷ capacitance

Hodgkin Huxley:

$$\begin{aligned}
C\dot{V} &= I - \overbrace{\bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}})}^{I_{\mathrm{K}}} - \overbrace{\bar{g}_{\mathrm{Na}} m^3 h (V - E_{\mathrm{Na}})}^{I_{\mathrm{Na}}} - \overbrace{g_{\mathrm{L}} (V - E_{\mathrm{L}})}^{I_{\mathrm{L}}} \\
\dot{n} &= \alpha_n(V)(1-n) - \beta_n(V)n \\
\dot{m} &= \alpha_m(V)(1-m) - \beta_m(V)m \\
\dot{h} &= \alpha_h(V)(1-h) - \beta_h(V)h \,,
\end{aligned}$$

Presentation plan

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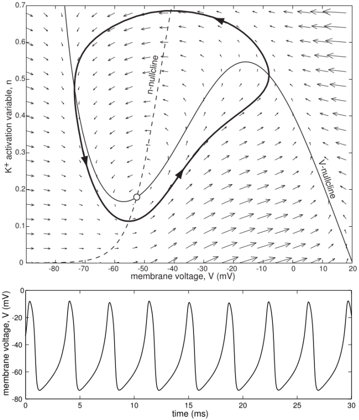
Hodgkin Huxley again

- We can replace really fast currents with their asymptotic values, to simplify things
- That input current I is really interesting!

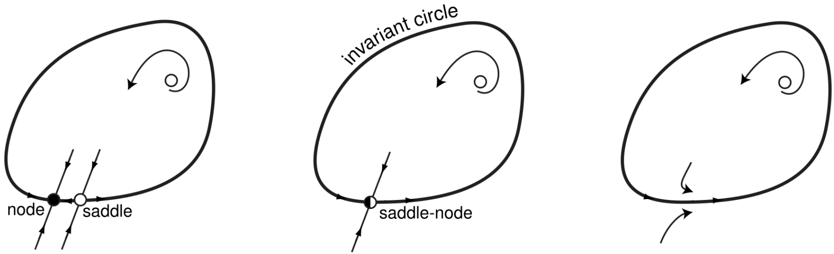
$$
\begin{aligned}
C\dot{V} &= I - \overbrace{\bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}})}^{I_{\mathrm{K}}} - \overbrace{\bar{g}_{\mathrm{Na}} m^3 h (V - E_{\mathrm{Na}})}^{I_{\mathrm{Na}}} - \overbrace{g_{\mathrm{L}} (V - E_{\mathrm{L}})}^{I_{\mathrm{L}}} \\
\dot{n} &= \alpha_n(V)(1-n) - \beta_n(V)n \\
\dot{m} &= \alpha_m(V)(1-m) - \beta_m(V)m \\
\dot{h} &= \alpha_h(V)(1-h) - \beta_h(V)h \ ,
\end{aligned}
$$

Spiking dynamics



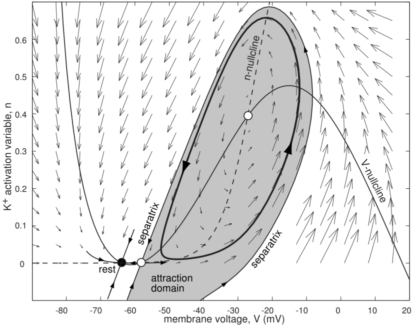
How can we turn these spikes on and off?

The SNIC bifurcation



- Like a regular saddle-node, but it occurs on a limit cycle
- Period of the cycle goes to infinity as it approaches the SNIC
- Causes spiking to stop / start

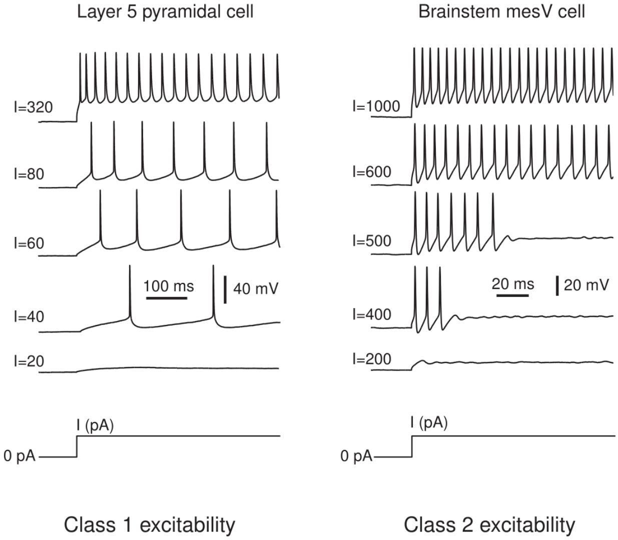
The SN bifurcation



Regular saddle-node bifurcations are interesting too

- Rest state disappears in saddle-node bifurcation
- Dynamics jump onto spiking limit cycle

Bifurcations encode information!



More bifurcations

- We can explain all neuron behaviours in terms of four bifurcations!
- (Usually) an input current drives the neuron dynamics across a bifurcation, causing spiking to start and stop
  - Ionic currents and can also cause bifurcations (see bursting neurons bonus section)
  - Pharmacological agents can make this happen, too
- The types of bifurcation a neuron undergoes can explain its behaviours and stimulus responses

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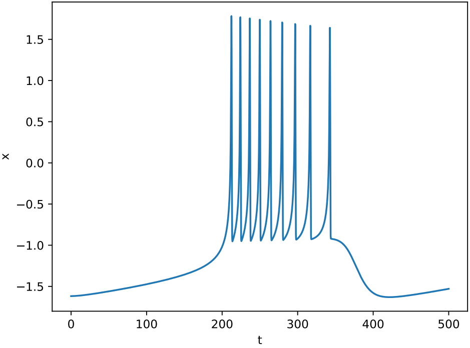
Bursting neurons



- Bursting is a type of mixed-mode oscillation
- Helps cells communicate through noisy channels, promotes calcium release
- Seems somewhat counter-intuitive
- Can we figure out how cells do this?

The Hindmarsh-Rose model

$$
\begin{aligned}
\frac{\mathrm{d}x}{\mathrm{d}t} &= y - ax^3 + bx^2 - z + I \,, \\
\frac{\mathrm{d}y}{\mathrm{d}t} &= c - dx^2 - y \,, \\
\frac{\mathrm{d}z}{\mathrm{d}t} &= \varepsilon \left[s(x - x_r) - z \right] \,,
\end{aligned}
$$

where $|\varepsilon| \ll 1$.

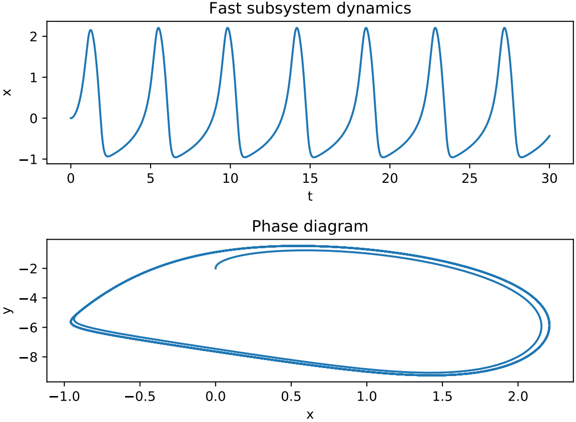
- x and y are the fast subsystem variables
- z is the slow subsystem variable
- As $\varepsilon \to 0$, z stops changing
- $\dot{z} = 0$ means z can be treated like a parameter
- Let's treat z as a parameter and do a bifurcation analysis on it!

System analysis

- Initially, fix parameters at their Wikipedia recommended values
  - Let I = 2, to get some spikes going
  - Let z = 0, arbitrarily
  - $a = 1, b = 3, c = 1, d = 5, \varepsilon = 0.001, x_r = -1.6$
- Choose some arbitrary initial conditions

1. Simulate the system to get some idea of what happens

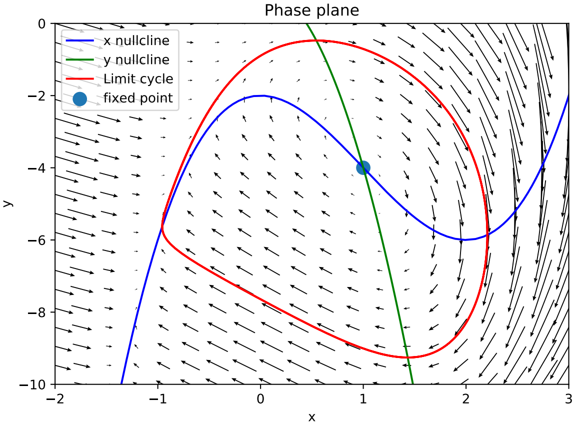
Sampling some trajectories



System analysis

1. Simulate the system to get some idea of what happens
2. There's a limit cycle, so do a phase plane analysis and search for an equilibrium inside it

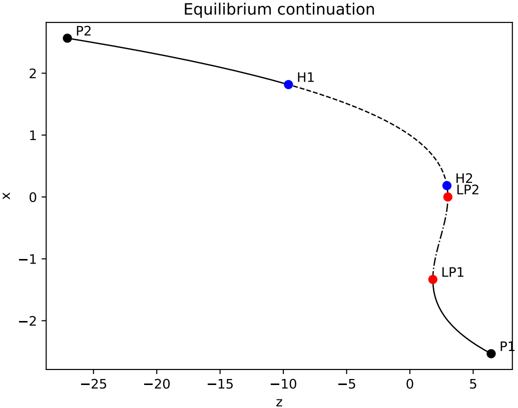
Phase plane analysis



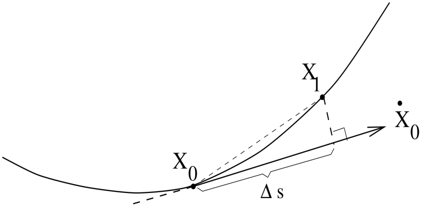
System analysis

1. Simulate the system to get some idea of what happens
2. There's a limit cycle, so do a phase plane analysis and search for an equilibrium inside it
3. Track how the equilibrium changes as the slow subsystem variable z changes

Equilibrium point curve



A first look at numerical continuation



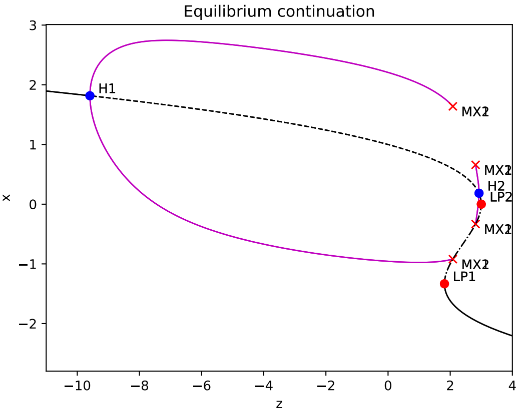
Predictor corrector scheme:

- Produce linear estimate of equilibrium point curve
- Use that to approximate the new equilibrium position
- Use a corrector to improve the estimate
- Prediction step $\perp$ correction step
- Extra variable and constraint regularises the problem

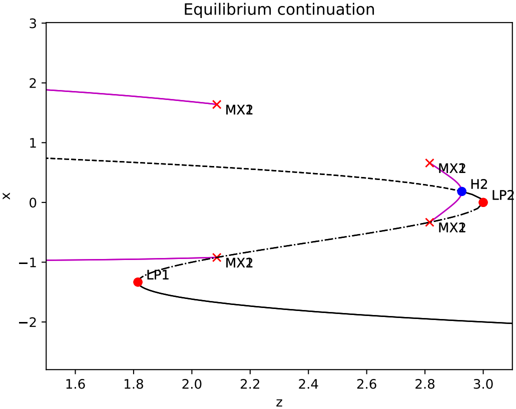
System analysis

1. Simulate the system to get some idea of what happens
2. There's a limit cycle, so do a phase plane analysis and search for an equilibrium inside it
3. Track how the equilibrium changes as the slow subsystem variable z changes
4. Track the limit cycles emanating from the Hopf

Periodic orbit continuation



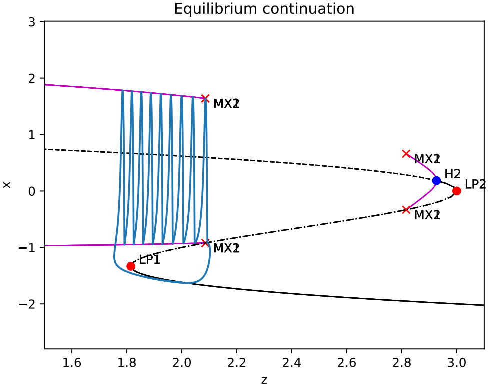
Periodic orbit continuation



System analysis

1. Simulate the system to get some idea of what happens
2. There's a limit cycle, so do a phase plane analysis and search for an equilibrium inside it
3. Track how the equilibrium changes as the slow subsystem variable z changes
4. Track the limit cycles emanating from the Hopf
5. Reintroduce the slow subsystem

Putting it all together



$$\dot{z}(t) = \varepsilon\left[s(x(t) - x_r) - z(t)\right]$$
$$\approx \varepsilon\left[s(\bar{x} - x_r) - z(t)\right]$$

Limitations of continuation

We now understand how a model bursts (hopefully!)
Caveat:

> “All models are wrong, but some are useful”
>
> — George Box

How much did we really learn about bursting cells, by looking at a phenomenological model with arbitrary parameters?

A novel alternative

- We can run continuation experiments on models, but those models aren't always meaningful
- Can we instead run a continuation procedure on a living cell?

Control-based continuation (CBC)

A model-free method for running bifurcation analysis experiments on black-box systems

Control-based continuation

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With CBC, we can...

- find stable and unstable equilibria

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With CBC, we can...

- find stable and unstable equilibria
- find stable and unstable periodic orbits

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With CBC, we can...

- find stable and unstable equilibria
- find stable and unstable periodic orbits
- track those under variations in parameters

Control-based continuation

Control-based continuation (CBC)

A model-free method for running bifurcation analysis experiments on black-box systems

With CBC, we can…

- find stable and unstable equilibria
- find stable and unstable periodic orbits
- track those under variations in parameters
- no need to use a model to do this!

Control-based continuation

Control-based continuation (CBC)

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- Can't use arbitrary simulations, so use a control system to make the system behave how we want it to

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- Can't use arbitrary simulations, so use a control system to make the system behave how we want it to
- No control action $\implies$ system acts under its natural dynamics

Control-based continuation

Control-based continuation (CBC)

A model-free method for running bifurcation analysis experiments on black-box systems

- Can't use arbitrary simulations, so use a control system to make the system behave how we want it to
- No control action $\implies$ system acts under its natural dynamics
- Goal: find a control target that can be stabilised with no control action

Control-based continuation

Goal

Find a control target $x_*(t)$ that can be stabilised with no control action

- Consider $\dot{x} = f(x, t)$
- A controller is a function $u(x, t)$, such that the controlled system

$$\dot{x}_c = f(x_c, t) + u(x_c, t) \tag{2}$$

satisfies $\lim_{t \to T} [x_c(t)] = x_*(t)$

Control-based continuation

Basically…

$u(x, t)$ pushes the system to make it do what we want!

Control-based continuation

- Say $u(x,t) = 0$, when the control target is $x_*(t)$
- Controlled system is then given by

$$\begin{aligned}\dot{x} &= f(x,t) + u(x,t) \\ &= f(x,t) + 0 \\ &= f(x,t)\end{aligned}$$

- This is our original, open-loop system!

For control target $x_*(t)$, the control scheme is said to be noninvasive, and the system acts under its natural dynamics

Control-based continuation

Goal: find some $x_*(t)$ that doesn't reqire any pushing

Basic example

- Consider $\dot{x} = -x$
- We add a controller to stabilise an arbitrary point x_*
- We need to push the system to hold it at any $x \neq 0$
  - $x = 0$ is the only point requiring no pushing
  - $x = 0$ therefore drives $u(x, t)$ to zero, and is an equilibrium under open-loop dynamics

Typical CBC approach

- Let the system do its own thing; this gives us a start equilibrium

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- Find a controller that stabilises it with zero control action
- Change a parameter slightly
  - System state moves away from control target slightly
- Record what the system now does

Typical CBC approach

- Let the system do its own thing; this gives us a start equilibrium
- Find a controller that stabilises it with zero control action
- Change a parameter slightly
  - System state moves away from control target slightly
- Record what the system now does
- Update the control target to once again have a zero control action

Typical CBC approach

Updating the control target:

- Set control target to match what the system did

Typical CBC approach

Updating the control target:

- Set control target to match what the system did
- Run it under the new controller

Typical CBC approach

Updating the control target:

- Set control target to match what the system did
- Run it under the new controller
- Repeat until control target = system output

Typical CBC approach

Updating the control target:

- Set control target to match what the system did
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- Repeat until control target = system output
- This drives control force to zero

Typical CBC approach

Updating the control target:

- Set control target to match what the system did
- Run it under the new controller
- Repeat until control target = system output
- This drives control force to zero
- Under this method, we can track equilibria and limit cycles as a parameter changes!

Presentation plan

Hopefully you're not asleep yet!

- A brief introduction to neurons
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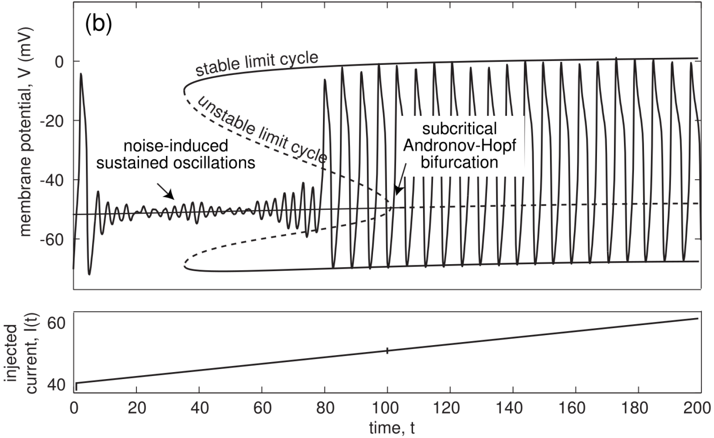
Questions to answer

- How do things change when we add noise?
- How do we control a stochastic system?
- How do we control a neuron when we can't observe its state variables?
- How do we control a neuron when we don't have any model of it?
- How can we study global bifurcations using CBC?

Global bifurcations

- Local bifurcations are those that can be understood entirely from changes in invariant set stability
  - Eg. Hopf, Saddle-Node
- Global bifurcations are those that can’t
  - Eg. homoclinic
- CBC allows us to track limit cycles and equilibria, but how can we change it to track global bifurcations?

Noisy bifurcations




That's all Folk