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Multi-timescale systems and slow-fast analysis

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Why multiple timescales?

Biological systems consist of interacting parts operating over many timescales

- Accurate models need a combination of slowly and rapidly changing variables
- Doing anything useful with these models requires ways of understanding timescale interactions

Simplest example

$$\dot{x} = f(x, y)$$

$$\dot{y} = \varepsilon g(x, y)$$

Subsystems and timescale separations

- Consider $\varepsilon \to 0$
- Let $\tau = \varepsilon t$

Fast subsystem:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x,y) \qquad (1)$$
$$\frac{\mathrm{d}y}{\mathrm{d}t} = 0$$

Slow subsystem:

$$f(x,y) = 0 \qquad (2)$$
$$\frac{\mathrm{d}y}{\mathrm{d}\tau} = g(x,y)$$

Example systems

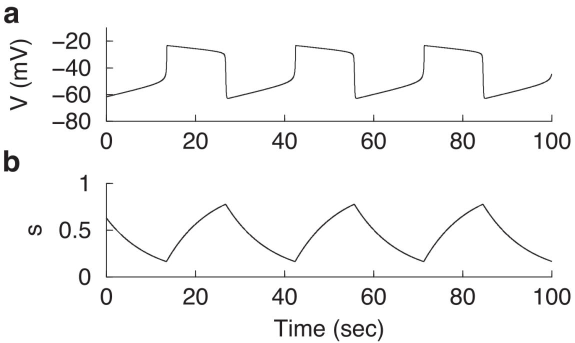
Mathematically interesting, and biologically useful: we can express lots of biology like this

- Pulsing behaviours
  - Heart beats, neuron spikes, hormone pulses
- Mixed-mode oscillations
  - Chemical systems, neuron voltage dynamics, pituitary cells
- Can classify neurons based on their fast subsystem topology

A test model

van-der-Pol oscillator is the classic planar slow-fast system; we consider a topologically equivalent bio model

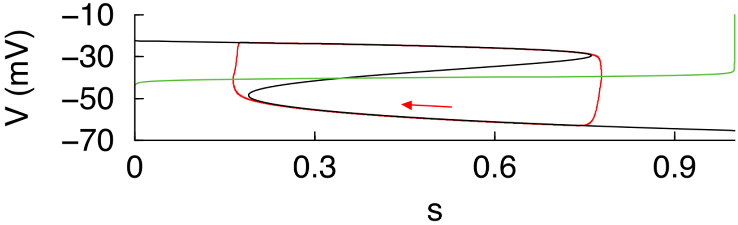
$$\frac{\mathrm{d}V}{\mathrm{d}t} = -(I_{Ca} + I_{Kdr} + I_{KATP} + I_{Ks} + I_l)$$
$$\frac{\mathrm{d}s}{\mathrm{d}t} = \frac{s_\infty(V) - s}{\tau_s} \tag{3}$$



Planar dynamics

Behaviours shown are typical of slow-fast systems

- States settle to equilibrium of fast subsystem
- Equilibrium evolves, disappears, reappears through changes in slow subsystem



Higher dimensions

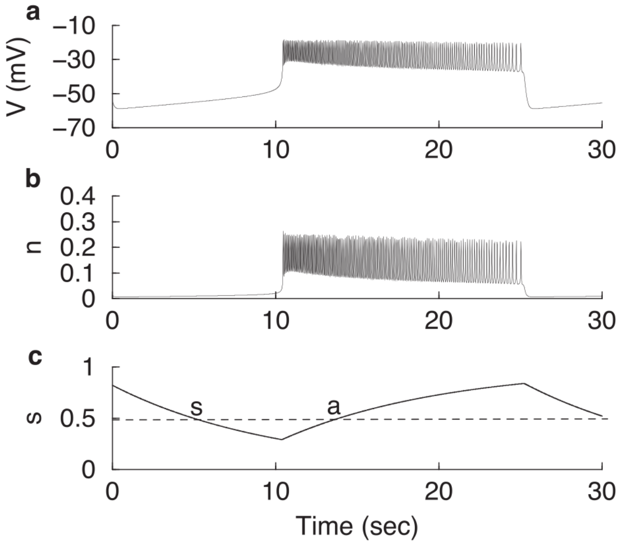
- Higher-dimensional models can also show relaxation oscillations, plus more
- Unlike the planar case, the fast subsystem attractor might no longer satisfy $f(x,y)=0$

Consider our neuron model again, without the steadystate assumption on I_{Kdr}

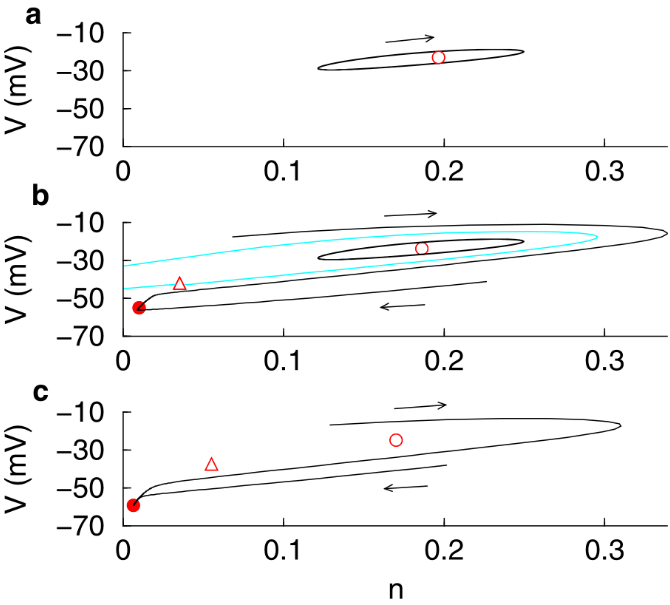
$$
\begin{aligned}
\frac{\mathrm{d}V}{\mathrm{d}t} &= -(I_{Ca} + I_{Kdr} + I_{KATP} + I_{Ks} + I_l) \\
\frac{\mathrm{d}s}{\mathrm{d}t} &= \frac{s_\infty(V) - s}{\tau_s} \\
\frac{\mathrm{d}n}{\mathrm{d}t} &= \frac{n_\infty(V) - n}{\tau_n}
\end{aligned} \tag{4}
$$

Bursting

Our new model produces bursting oscillations!



Busting phase plane



Higher dimensional models

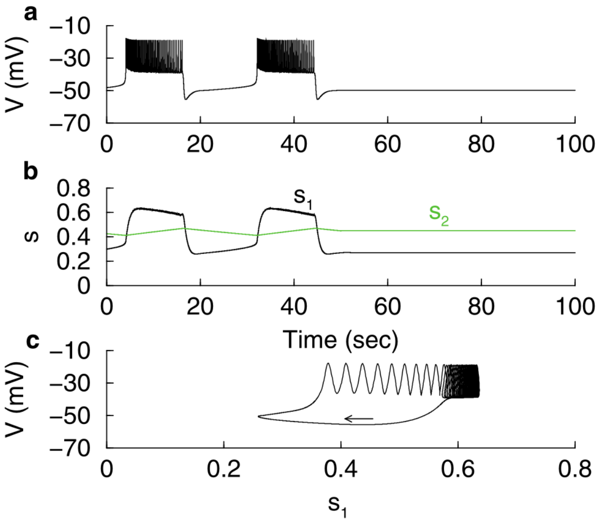
What happens if we have two slow variables?

$$\begin{aligned}
\frac{\mathrm{d}V}{\mathrm{d}t} &= -(I_{Ca} + I_{Kdr} + I_{Ks1} + I_{Ks2} + I_l) \\
\frac{\mathrm{d}n}{\mathrm{d}t} &= \frac{n_\infty(V) - n}{\tau_n} \\
\frac{\mathrm{d}s_1}{\mathrm{d}t} &= \frac{s_{1\infty}(V) - s_1}{\tau_{s1}} \\
\frac{\mathrm{d}s_2}{\mathrm{d}t} &= \frac{s_{2\infty}(V) - s_2}{\tau_{s2}}
\end{aligned} \tag{5}$$

Same model as earlier, only we now have two fast variables V and n, slow variable s_1, and super-slow variable s_2

Higher dimensional models

- Previously, the slow variable switched spiking on and off
- Now, the very-slow variable switches the system from bursting to either quiescence or tonic spiking
- The slow-variable oscillates, and changes direction during the active phase



More dimensions = more robustness

Planar bursting requires

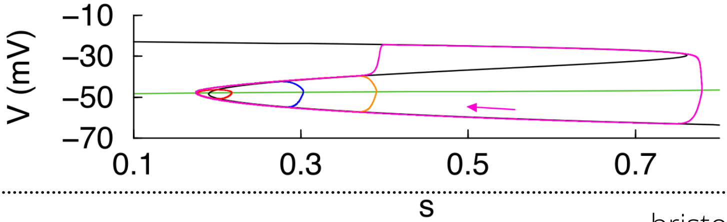
- Bistability in the fast subsystem
- The slow-subsystem nullcline to intersect in the right place

This limits the region of parameter space in which bursting can occur

- Not very good – biology is noisy and imprecise; if we need very specific values, things probably won't work
- Adding additional slow dynamics makes things more robuts
- Interpretation: instead of shifting the state around, the slow variables shift the entire bifurcation diagram back and forth

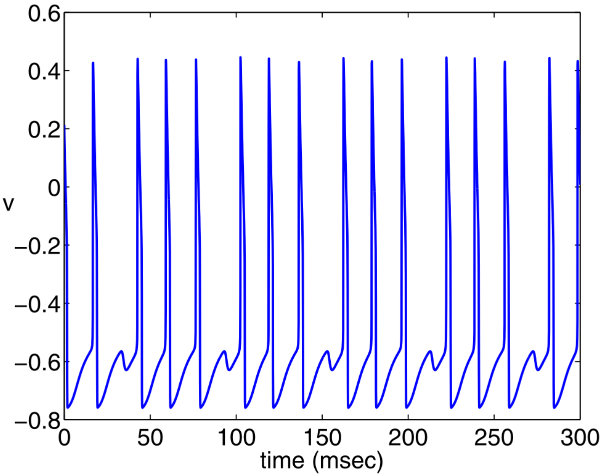
Canards

- Canards cause a rapid transition from quiescence to spiking
- Solution follows fast-subsystem unstable manifold
  - Torus canards follow branches of UPO
- Canards are non-robust in planar systems
  - Appear in exponentially small region of parameter space
- Complicated maths shows that these canards can appear robustly in non-planar systems



Mixed-mode oscillations

- Canards arise from the existence of a folded node singularity
- The same structure allows mixed-mode oscillations
    - System oscillates between bigger and smaller oscillations



Why are biologists interested?

An example: the spinal cord

- Synaptic coupling is all excitory
  - Expectation: active network, due to positive feedbacks
  - Reality: mostly silent, occasional activity; *why?*
- Proposed model: synaptic depression; cells that fire together unwire
  - Model shows relaxation oscillations
- Predictions from multiscale analysis:
  - Electrical perturbations will cause shift between activity and quiescence
  - Length of active, quiescent phase depends on perturbation timings
- Predictions confirmed experimentally, elucidating spinal cord neurology

Practical issues

- How do we identify how many timescales are present?
- How do we identify what those timescales are?
- How do we determine whether those timescales are distinct?
- How do we best partition multiple timescales, when it's not obvious what should be fast, medium, or slow?