MARK'S NOTES THAT MUSTN'T BE PRESENTED

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[2020-11-04 Wed]

1 Background

1.1 Today's agenda

Been writing my annual review recently. This presentation is aimed at giving an overview of that, as it nicely sums up what I've been up to so far, and what I want to get up to in the future. Wasn't quite sure how much depth to go into, so if you have any questions, stop me at any point and ask!

- **A brief summary of things**
- More CBC
- Results so far
- Current work

2 A brief summary of things

2.1 What am I doing?

- Neurons are interesting
  - Biological perspective: excitable cell; lots of reaction networks that produce surprisingly subtle functionalities within the cells
  - Philosophical perspective: individual cells are phenomenologically simple, yet collect them together into a brain and suddenly consiousness emerges. How? Why? Where from?

  - Mathematical perspective: neurons recieve their computational abilities from their intricate bifurcation structure, making them an excellent problem to study in nonlinear dynamics

- Nonlinear dynamics teaches us lots about neurons
  - We have lots of good neuron models
  - These models predict all sorts of different behaviours, and can, and do!, explain experimental observations
  - As mathematicians, we tend to focus entirely on the model; even if it's not a good electrophysiological representation of a neuron, it doesn't necessarily matter as long as it has some interesting dynamics

- Models are wrong
  - All models are wrong, but some are useful
  - The best models of the neurons are the cells themselves
  - What if we could perform our favourite analyses not on phenomenological models, but on the cells themselves?
  - Double win: we get interesting nonlinear dynamics to play with, *and* the results are biologically useful!

2.2 How am I doing it?

- Models are often analysed using numerical continuation
  - Nonlinear dynamics are usually hard to study
  - Instead of pen-and-papering everything, we can outsource the labour to a computer
  - Numerical continuation lets us take something we can easily find, eg. equilibria, and track them to spot things that are harder to find, eg. bifurcations
  - Very powerful tool; very widely used

- Numerical continuation needs a model
  - The model encodes our assumptions about how the cells work
  - If the assumptions are bad, the model will be unrepresentative, and the continuation results won't match reality

  - What if instead, we could run the same analysis without a model?

- Control-based continuation doesn't
  - CBC let's us perform continuation experiments without the need for a model
  - If a system is observable and controllable, it's CBCable
  - My overall goal is to study neurons using CBC

2.3 What needs to be done?

- Make it fast
  - Neurons have a finite lifespan
  - We could leave a mechanical system oscillating for days on end, but if we tried that with neurons, they would die
  - There's some very slow steps in CBC; new mathematical techniques might allow some big speed-ups here
- Make it noise-robust
  - CBC relies on experimental meausurements, which are often subject to lots of measurement noise
  - The CBC algo, solvers, etc. must therefore be robust in the face of noise
  - Furthermore, we could reasonably decide to model the neuron cells themselves as being a random dynamical system
  - Considerations of stochastic dynamics would be a whole new kettle of fish, and potentially a very interesting and useful one!
  - Stochastic continuation would be very useful eg. in aeroelastic flutter; perhaps treat turbulent fluid flow as a random influence, and see how the deterministic results change when randomness is considered
- Make it happen
  - Everything so far has been in silico
  - That means I've been simulating mathematical models, instead of using real cells
  - Of course, the end goal is to move beyond models, so I'll need to consider how these methods would need to change for an experiment

2.4 How are those TODOs progressing?

- Efficiency
    - Current work; lots of problems, lots of progress
        - Currently studying how alternative discretisations could be employed to speed things up
        - Lots going wrong, but in research that seems to be a sign of good progress. . .
        - Very recently demonstrated it working for the first time; still lots of open questions, lots of issues about it not working how it should
- Noise-robustness
    - One paper under review
        - Has been discussed in my previous research update
        - Essential idea is to take time-series data, fit a nonparametric regression model to it, and use that model in place of the data
        - If we choose the models well, they'll accurately separate signal from noise
        - Acts like an adaptive filter, allowing us to keep all the signal information, and none of the random fluctuations
        - Downside is that I'd consider it to have a very limited set of usage cases; most of the time it wouldn't be a useful thing to do
    - Other ideas under consideration
        - Idea that's been mentioned a while ago but I'm yet to do anything with
        - Replace continuation equations with a different set of equations that encodes exactly the same thing
        - New equations should be noise-robust, and robust against discretisation approximation errors
        - Big bonus: new equations can be solved efficiently with gradient-free methods, which will improve point 1 of efficiency
        - Second big bonus: efficient solver methods are probabilistic, so will likely perform better in the face of noise

- Experiments
  - Minireview of literature
    - Had a look at microfluidic methods, electrode-based methods
    - Compared single-cell and multicell microfludidic approaches, in terms of captured nonlinear dynamics, and experimental viability
  - Some practical experience
    - Helped build some other microfluidics in the clean room, to get an understanding of how it's done and what they look like

3 More CBC

3.1 Today's agenda

- A brief summary of things
- **More CBC**
- Results so far
- Current work

3.2 Control-based continuation

This has been explained many times before, in the lab group meetings, so I'll keep things brief here and give only the very high-level overview.

- CBC works by tracking non-invasive control targets
  - This is a control target that corresponds to something the system was already doing
  - The controller therefore doesn't change how the system was behaving
  - The only difference between the controlled and uncontrolled system, in this case, is that unstable equilibria and periodic orbits are stabilised, so they become visible
  - Since they become visible, we can see how they move when we change a parameter

  - This 'seeing how they move' step is done with a continuation algo, in much the same way as with 'normal' continuation

- It has been tested on 'nice' systems, but biological systems aren't nice
  - By 'nice', I mean…
    - Deterministic: no randomness within the dynamics
    - Low noise in the observations
    - 'Simple' signals, with few high-frequency components; well-approximated by a shifted sine wave, as the dynamics are only weakly nonlinear
  - Biological systems, such as neurons, don't follow the niceness rules
    - Dynamics may be stochastic
    - There's often quite a lot of measurement noise
    - The signals are from a strongly nonlinear oscillator; have lots of high-frequency components; very very different to a sine wave

- Discretisation is a key part of this
  - Finding and tracking the noninvasive control targets requires us to solve for the fixed point of some map
  - This map maps from a function to a function
  - Instead of working with the continuous, infinite-dimensional map, we instead approximate it with a finite, lower-dimensional map, in a process called discretisation
  - We then attempt to solve the finite-dimensional equations using standard numerical methods, and hope that the results of the discretised case correspond to a solution of the original, continuous problem
  - I don't know if these hopes are actually valid, and nor would I know how to prove that

I'll get back to the topic of discretisation later, as that's a key part of my current research.

4 Results so far

4.1 Today's agenda

I have a couple of results so far. These are a tutorial paper, currently under review, and a conference paper, also currently under review. I'll talk briefly about these here.

- A brief summary of things
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4.2 Paper 1: 'Tutorial of . . . '

Tutorial of numerical continuation for systems and synthetic biology

- Already mentioned that numerical continuation is a very standard, widespread tool in nonlinear dynamics
- I spent a long time playing around with different continuation softwares while learning about neuronal dynamics
- This paper aims to bridge the gap between biologists and mathematicians
- Aims to expose numerical continuation, and some key ideas from nonlinear dynamics, to researchers without a nonlinear dynamics background
- Uses lots of examples to give a conceptual, high-level overview of the topic, so that readers can go on to understand work that builds on continuation, bifurcation theory, and so on

4.3 Paper 2: 'Bayesian local . . . '

Bayesian local surrogate models for the control-based continuation of multiple-timescale systems

- Noise-robustness is important in CBC
  - A point I touched on earlier

  - Lots of ways noise could enter the system
  - We can't treat noise as a negligable side-issue; we must pay active attention to dealing with it
  - This paper aims to do that, by using an adaptive filtering method

- Surrogate modelling is a possible route towards noise-robust experiments

  - Instead of running CBC using raw noise-corrupted experimental measurements, we could instead filter the data
  - Filtering needs to be done carefully!
    - If we whack the data through a simple low-pass filter, we'll cut off the all-important high-frequency information
  - Instead of using a simple low-pass filter, let's use a complicated one!
  - Take the time series data
  - Fit a nonparametric regression model to it
  - With a well-chosen model, we can filter out the noise
  - This works because a statistical model of the time series will describe the data as signal + noise; we fit a model to the signal part of it, and throw away the noise residuals
  - We can then use the surrogate in place of the original data, to perform whichever analyses we wanted to do
  - We can discretise the surrogate more accurately than we can the original data

5 Current work

5.1 Today's agenda

That's a very brief summary of what I'm trying to acheive and what I've finished working on so far. Now we're going to move on to what I'm currently working on, and what I want to achieve next.

- A brief summary of things
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5.2 Periodic splines discretisation

- Discretisation is important
  - The continuation equations are infinite-dimensional
  - We have a map that takes a function as its input, and gives a function as its output
  - We're searching for a function that remains unchanged when passed through this map
  - Such a function exists, but to find it we need to reduce the problem to something more tractable
  - This is where discretisation comes in
  - We approximate the infinite-dimensional problem with a finite-dimensional problem
  - The finite-dimensional problem is then tackled using standard numerical methods
- Efficiency is also important
  - Another point I touched on earlier
  - We want the experiments to run quickly, so that our cells survive
  - A big issue in making this happen is the gradient step
  - We're using numerical solvers on our continuation equatiosn
  - Virtually all numerical solvers require a gradient to work
  - Finding the gradient of an experimental system requires finite differences
  - This means perturbing the input vector slightly, and noting how the output vector changes
  - More elements in the input vector means more time spent perturbing, running to convergence, and measuring
  - This all takes time
  - Therefore, to speed things up, we want the fewest elements possible in our vector
  - IE. we need a low-dimensional discretisation
- Splines could be efficient discretisors
  - Neuronal signals have lots of high-frequency energy

  - This HF energy is what gives the signals their spiking shapes
  - The issue with this is that Fourier discretisation, as used so far in CBC, would require huge numbers of Fourier harmonics
  - This gives a big discretisation, which means slow finite differences, and inefficient experiments
  - Spline models are smooth piecewise-polynomial models
  - We can make them periodic, too
  - We can fit very complex curves by connecting the dots with pieces of polynomial
  - This makes them a good discretisor candidate!
  - Ideal: replace the Fourier basis functions with spline basis functions, for a novel discretisation
  - This is my current work
  - Bonus: spline discretisation might be more noise-robust, too
  - Or it might not be

5.3 Current issues

- Newton solvers don't converge on a solution
  - The discretised continuation equations are a set of nonlinear equations whereby we put in some vector, and get a vector as an output
  - If the vector represents a noninvasive control target, the continuation equations will give the zero-vector as their output
  - Therefore, the Newton iterations seek some input vector that solves these equations, and we know we've solved them when we plug the solution in and get zero out
  - Unfortunately, the Newton iterations converge on a vector that doesn't actually solve the system
  - The steps become negligable, but the resulting vectors don't solve the equations
  - This is a problem, as it means the accepted results are wrong
  - Nevertheless, a solution must exist, as it can be found using non-Newton solving methods
  - My current hunch is that the issues are arising as a result of difficulties in calculating the gradient accurately

- The solution curve becomes numerically unstable
    - As seen in the diagram, the solution jumps shortly after the second fold
    - The real (analytic) solution does not jump, so clearly this is the result of something going wrong with the numerics
    - My hope is that if I can find a solution to the gradient problem, it will fix this too
- Current work is therefore trying to fix this, so that I can test out the novel discretisation methods on neuronal data; all my discretisor experiments so far are on the weakly nonlinear Duffing oscillator