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A continuum approach to neuron modelling

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Overview

- Challenges with using the MEA
- Possible solutions (network- and microfluidic-based methods)
- A better solution (continuum)
- Literature precedent

Main challenge with the MEA

- Loss of spatial resolution, since we can no longer measure and perturb individual cells
- Emergent behaviours mean we can't study dynamics of individual neurons; would have to study network dynamics instead
- Too many unknowns to build a realistic network model. . .

Issues with the network model

- No geometric information
  - We can make a model of neuron networks, but there's no easy way to relate an agent in the network to the position of a living cell
  - This matters, as we can't predict the spatial dynamics, and therefore the effects of stimulating each electrode, without this information
- No topological information
  - We don't know who connects to who, in our neuron network
  - This means we can't produce an accurate network model
- Too many equations for simulations
  - 200,000 neurons is too many to simulate!
- Too many parameters to accurately determine
  - Even just coupling strength adds between 200,000 and 40,000,000,000 ($200{,}000^2$) extra parameters to the model

Some possible solutions

- Constrain the network geometry using on-chip microchannels
  - This has been done in the literature
  - Doesn't tell us much about connection strengths
  - Would be a very hard device to make
  - Requires making another new device
- Use synchronisation-based network models
  - Changing one of 200,000 network connection strengths probably won't change much in the dynamics
  - Can use this lack of sensitivity to make simpler models of neuron synchronisation
  - But, this synchronisation models won't work for any case other than synchronisation (limits the dynamics with specific assumptions)

A proposed alternative

- Assume we have an arbitrarily large number of neurons
- Every neuron connects to every other neuron within its local neighbourhood
- Treat it as a continuum (neural field, rather than point neurons)
- Build a PDE model

Benefits of a continuum model (1)

- No need to know the network geometry; any given ‘neuron’ is identified by its point in the domain
- No need to define a network topology; every ‘neuron’ interacts locally with those in its neighbourhood
- Far fewer parameters are required to characterise the system
  - Don’t need to specify a set of parameters for each agent in a network system
- Becomes tractable to study much more sophisticated dynamics than with the network model (beyond simple synchronisation!)
- We no longer care about what individual cells are doing, and can therefore get away with the lower spatial resolution of the electrodes
  - Instead, we’re measuring the average continuum value across some small region, which is a sufficient measurement; don’t need to know the state of every neuron in the network

Benefits of a continuum model (2)

- No need to individually perturb single neurons - it suffices to model a current input across some subdomain of the PDE's space
- Microfluidic electrodes have a very natural mathematical interpretation
  - For an accurate model, neurons can be thought of as 'solving' the continuum PDE across their network
  - Numerical methods for solving the model would typically use orthogonal collocation
  - A set of meshpoints are defined, and orthogonal basis functions are chosen such that they solve the PDE at those mesh points
  - The electrodes are therefore a physical analog of these collocation mesh points!
  - Very natural transition between numerical methods, and physical experiments

Literature precedent

- There's models for neural fields
  - Bressloff, Paul C. "Spatiotemporal dynamics of continuum neural fields." Journal of Physics A: Mathematical and Theoretical 45.3 (2011): 033001.
  - Seems to be based on some rather dubious assumptions (rate-based networks, assume SNIC neurons)
- There's also cable models for spatially extended neurons
  - Designed to model signal propagation down an axon
  - Could possibly produce a 2d spatially extended system as a continuum model?
  - I don't yet know how important the synaptic dynamics are on continuum dynamics

The Belousov-Zhabotinksy reaction

Chemical reaction, displaying complex dynamics away from equilibrium. I claim it behaves in the same way as neurons:

- Consider reactants as ‘ions inside a neuron’
- Consider products as ‘ions outside a neuron’
- Consider catalyst concentration as membrane potential
  - Stimulates the transition of reactants into products (and reverse)
  - Equivalently, stimulates the movement of ions into a cell (and out of it)

Dynamics of the BZ reaction are therefore analogous to neural dynamics

- Stirred system is like an ODE model
  - Can show mixed-mode bursting-like oscillations, and relaxation oscillations
- Unstirred system is like a spatially extended continuum neuron

The Belousov-Zhanosinsky reaction

- This is analogy interesting, as there's lots of research on the various behaviours of the BZ reaction that could be reapplied to predict dynamics of a large neural population.
- BZ reaction is a reaction-diffusion system, which Alan does lots of research on
- There's a literature precedent for bifurcation analysis of it

Controlling the BZ reaction

- The BZ reaction is a continuum system.
- Methods have been demonstrated for tracking its dynamics, suggesting that similar approaches may work for neural continuums
- These follow an OGY/ ETDF style approach.

Petrov, Valery, Michael J. Crowley, and Kenneth Showalter. "Tracking unstable periodic orbits in the Belousov-Zhabotinsky reaction." Physical review letters 72.18 (1994): 2955.
Petrov, Valery, Michael F. Crowley, and Kenneth Showalter. "An adaptive control algorithm for tracking unstable periodic orbits." International Journal of Bifurcation and Chaos 4.05 (1994): 1311-1317.

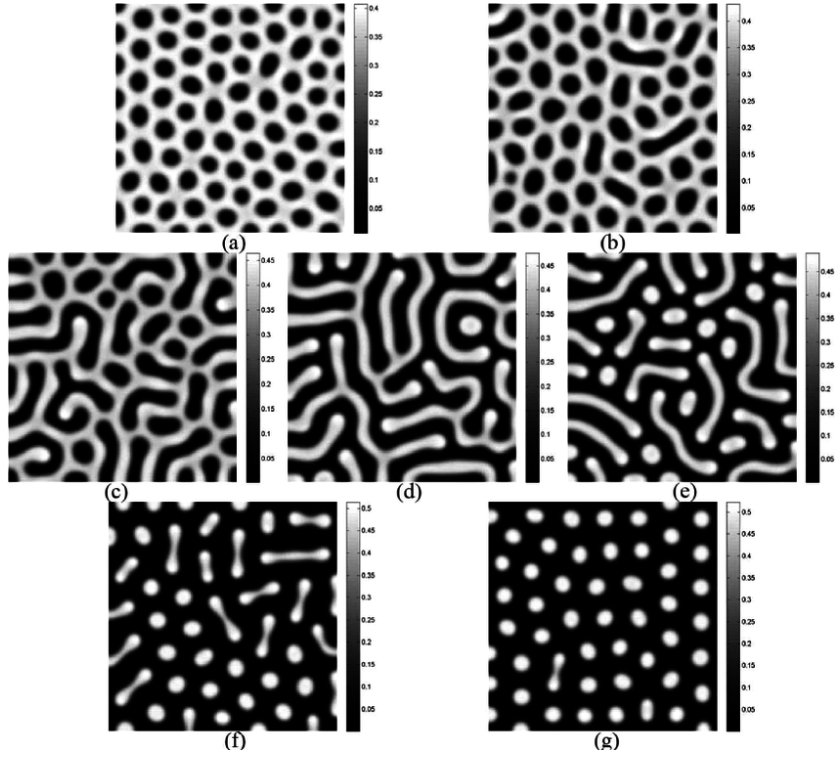
Epilepsy, coherent structures, and Turing instabilities

- Epilepsy is characterised by waves travelling across the surface of the brain [SOURCE?]
- Travelling waves are a type of ‘coherent structure’ (some structure that appears and persists in the dynamics)
- More generally, Turing patterns refer to the appearance of coherent structures in reaction-diffusion systems (like BZ reaction!)
- Since we’ve added a spatial domain, we now have new ways to bifurcate
  - Lose stability in temporal dimension - traditional bifurcation
  - Lose stability in spatial dimension - Turing instability
- Turing patterns and instabilities form new bifurcations we could control and test for
  - . . . possibly bifurcations that lead to epileptic dynamics?

Studying continuum models

- Turing patterns are a very well studied area - lots of literature to draw from
- There's also lots of literature on PDEs
- (I conjecture) it would be considerably easier to study bifurcations in the PDEs than in a massive network

Interlude for pretty pictures



Some issues

- The continuum model discussed in previous review is rate-based; doesn't generalise to arbitrary neurons, only good for cortical (SNIC) neurons
- A spatially extended cubic Lienard model would give the dynamics of arbitrary neuron populations, if and only if synaptic dynamics are non-critical

Possible project plan

- Produce a neuron normal form model
  - Krasi's cubic Lienard + a slow subsystem
- Generate a neural continuum model from a spatially extended normal form
- Analyse bifurcations etc. in the model, to get an idea of what the actual cells will do
- Develop a CBC approach to track those bifurcations

Note that a spatially extended neuron model might not be sufficient; the review cited earlier would be a good place to start on understanding good continuum models.

Possible project plan

Nice but not necessarily essential:

- Bigger MEA (more cells = more like a continuum)
- More electrodes (more collocation meshpoints = more accurate model)