Spatiotemporal patterns in the wake of traveling wave solutions to the Morris-Lecar neuron model

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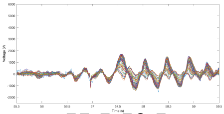
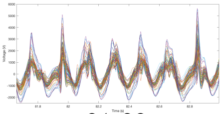
Seizure waves in the human brain

- A local field potential (LFP) recording was made from an 4mm x 4mm micro-electrode array of 96 electrodes implanted into the neocortex of an epilepsy patient.
- Series of traveling pulses are observed, often followed by interesting spatiotemporal behavior, such as secondary waves (sometimes traveling in a different direction), spots, or spirals.
- No current consensus on how seizures occur and what causes spatiotemporal patterns.

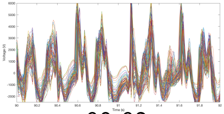
Seizure waves in the human brain



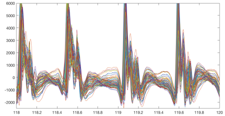
: 55.5-59.5s



: 81-83s



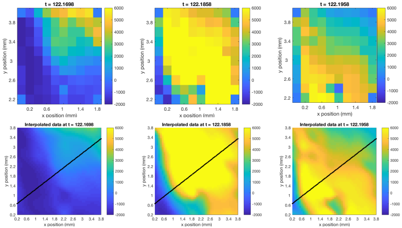
: 90-92s



: 118-120s

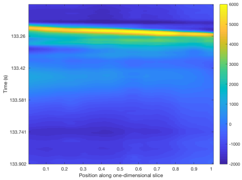
- The seizure lasts for roughly 140s.
- First 57 seconds: low electrical activity
- 57-83 seconds: oscillations that grow in amplitude over time
- 83-106 seconds: High amplitude pulses followed by complex spatiotemporal patterns
- 106-137 seconds: regularly-spaced planar pulses followed by secondary waves, before termination of seizure.

One-dimensional behavior

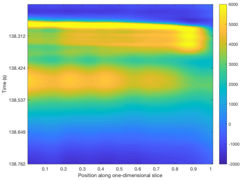


- First, we try to examine the one-dimensional behavior of the data. In the last third of the seizure, the primary events are planar waves.
- For these waves, estimate the direction of travel, and take one-dimensional slices after fitting a surface to the two-dimensional domain.

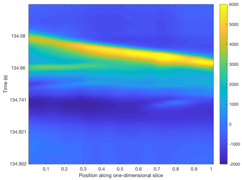
One-dimensional behavior



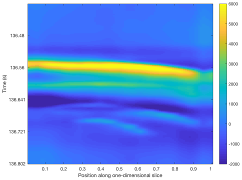
: Pulse with no patterns



: Long period of heightened activity



: Secondary waves in different direction



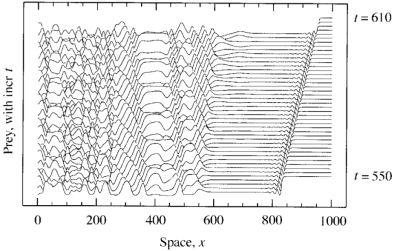
: Pulse followed by localized patterns

Goals

- We want to find a mathematical model of neural tissue that exhibits patterns in the wake of traveling pulses that match the behavior in our empirical data.
- Try to find a model that is as simple as possible while still generating the following patterns: secondary waves in different directions, spots, and localized oscillations. We will therefore focus on reaction-diffusion models with as few system variables as possible.
- Neuroscience motivation: understanding the mathematical properties of these patterns may give possible biological explanations for the mechanisms behind these patterns in seizures.
- Mathematical motivation: relatively few examples of patterns *in the wake of traveling waves*, and the phenomenon is not well-understood mathematically.

Spatiotemporal patterns in predator-prey models

- Invasion fronts in predator-prey models: introduction of predators to a prey-only domain induces an invasion front. Behind the invasion front are irregular oscillations.[1]
- The reaction terms typically have three fixed points: trivial, prey-only, and co-existence. In many cases, the coexistence state undergoes a supercritical Hopf bifurcation (fixed point loses stability and a stable limit cycle emerges).

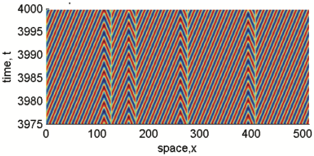


: From Kay and Sherrat, 1999.

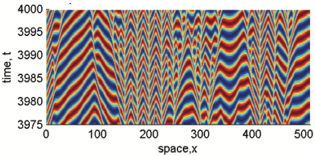
[1] Kay, A. L. and Sherratt, J. A. (1999). On the persistence of spatiotemporal oscillations generated by invasion. IMA journal of applied mathematics, 63(2):199–216.

Spatiotemporal patterns in $\lambda - \omega$ models

- Near a Hopf bifurcation, we can approximate the dynamics behind the front with a $\lambda - \omega$ system.
- Smith et al[2] studied a $\lambda - \omega$ system by generating initial conditions at periodic points on a domain.
- Convectively unstable wave trains result in periodic waves traveling in opposite directions, separated by slowly moving defects. On the other hand, absolutely unstable wavetrains devolve into chaotic patterns that persist.



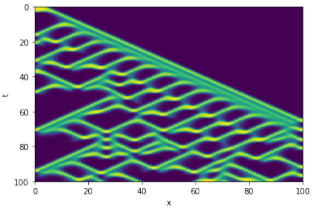
: Convectively unstable



: Absolutely unstable

[2] Smith, M. J., Rademacher, J. D., and Sherratt, J. A. (2009). Absolute stability of wavetrains can explain spatiotemporal dynamics in reaction-diffusion systems of lambda-omega type. SIAM Journal on Applied Dynamical Systems, 8(3):1136–1159.

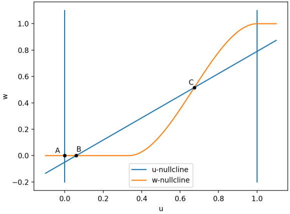
Backfiring in a model of excitable medium



- Model of carbon monoxide oxidation on a platinum surface (CO-Pt model) with two components: excitatory and inhibitory variables.
- "Backfiring" phenomenon: a traveling pulse emits secondary pulses in the opposite direction. Secondary pulses collide into one another and create chaotic patterns.[3]

[3] Or-Guil, M., Krishnan, J., Kevrekidis, I., and Bär, M. (2001). Pulse bifurcations and instabilities in an excitable medium: Computations in finite ring domains. Physical Review E, 64(4):046212.

Backfiring in a model of excitable medium



- Model has three rest states: A, B, and C. The bifurcation parameter controls the ratio of the time scales between the excitatory and inhibitory variables.
- Backfiring emerges along a curve of solutions containing a T-point, where a heteroclinic loop exists between A and B. Close to the T-point, solutions are pulses asymptotic to A with a "plateau" state near B.

Coupled network of Morris-Lecar neurons

$$\frac{dV^i}{dt} = D\frac{V^{i-1} - 2V^i + V^{i+1}}{(\Delta x)^2} + f(V^i, N^i; I)$$
$$\frac{dN^i}{dt} = g(V^i, N^i; I)$$

- Ring network of diffusively coupled neurons. V^i is the voltage and N^i is the inhibitory variable of the ith neuron.
- Behavior on the network depends on I, initial conditions, and the size of the network.
- Bifurcation parameter: I (external current).

Coupled network of Morris-Lecar neurons

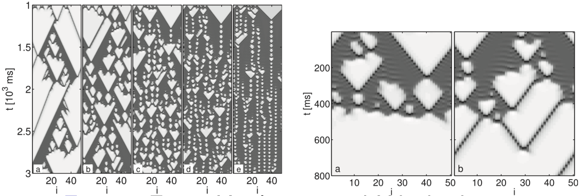


Figure: From Keplinger and Wackerbauer

- Chaotic patterns can appear when randomly selected neurons in the networked are perturbed from the rest state.[4]
- Patterns include spatially-localized oscillatory events at an excited state, with patches close to the rest state.
- Patterns are transient and collapse to either a rest state or a traveling pulse state.

[4] Keplinger, K. and Wackerbauer, R. (2014). Transient spatiotemporal chaos in the morris-lecar neuronal ring network. Chaos: An Interdisciplinary Journal of Non-linear Science, 24(1):013126.

Morris-Lecar model with diffusion

- Biological background: electrical activity in neurons propagated by ionic currents passing through channels in cell membrane.
- Flow of ions depends on the concentration and electric potential gradients. These forces balance each other out at the Nernst equilibria.
- Model neural tissue as a long cable: electric currents will propagate according to the diffusion equation.
- Some ionic channels have gates that activate based on electric potential: this allows sustained signals to propagate through a narrow axon.

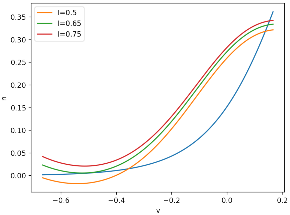
Morris-Lecar model with diffusion

$$\underbrace{\partial_t(v) = \partial_x^2(v)}_{\text{Diffusion}} + I - \underbrace{g_l \cdot (v - v_l)}_{\text{Leak}} - \underbrace{g_{Ca} \cdot m_{ss}(v) \cdot (v - v_{Ca})}_{Ca^+} - \underbrace{n \cdot (v - v_k)}_{K^+}$$

$$\partial_t(n) = \varepsilon \cdot \lambda_{ss}(v) \cdot [n_{ss}(v) - n]$$

- Non-dimensionalized model, where v is a measure of voltage and n is the fraction of open K^+ channels. Three types of channels in this model: leak (passive flow), Ca^+, and K^+.
- g_x and v_x are the respective conductances and Nernst equilibria for each channel. m_{ss}, n_{ss}, and λ_{ss} describe the activation curves of the ionic channels.
- Note: $\varepsilon \ll 1$ is a time constant that governs the lag of the channels. Thus, K^+ channels evolve on a longer time scale than the voltage. The Ca^+ channels respond instantaneously to voltage.

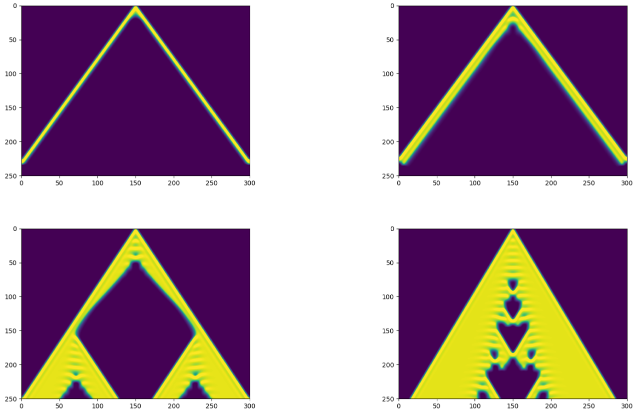
Morris-Lecar model



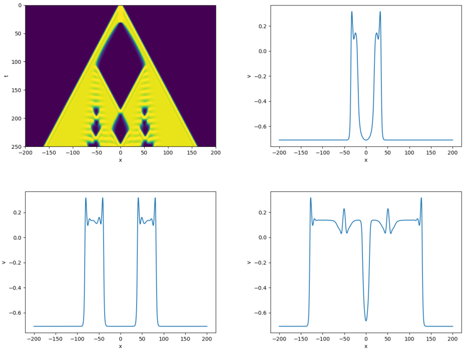
- Reaction terms have three fixed points: A, B, and C.
- A is a stable rest state, B is an unstable rest state, and C is an unstable excited state.
- The model undergoes a saddle-node bifurcation as I increases. During the bifurcation, A and B merge and disappear. Afterwards, a stable limit cycle emerges.

Direct simulations

- Fix large domain of length 400 under periodic boundary conditions. Initiate waves with a Gaussian function of v centered in middle of the domain with different values of I and ε. Different type of solutions: stable pulses, pulses with "backfiring", fronts with spatiotemporal patterns.

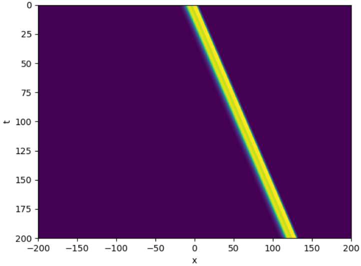


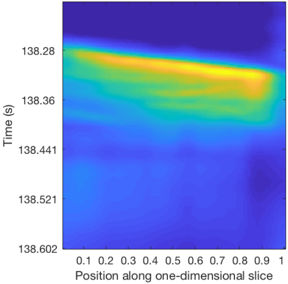
Direct simulations



- Changing the model parameters I and ε induce different types of waves. Recall: ε affects the time lag of the inhibitory gating variable.
- Different initial conditions also affect the resulting behavior. Parameters we tested: height, width, time duration of the initial perturbation. Thus, different waves appear to be selected depending on the initial conditions.

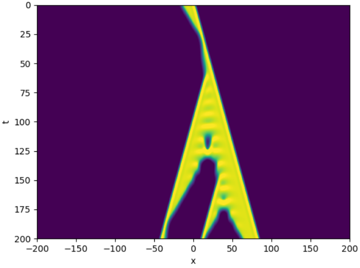
Direct simulations

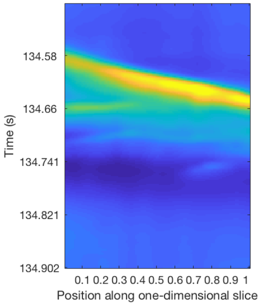




- Some of the qualitative one-dimensional behavior from the LFP data are reproduced in the simulations.
- Example: traveling pulses with a stable bump of activity following the initial increase.

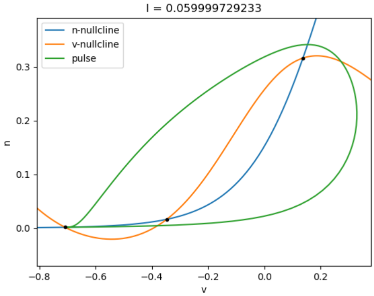
Direct simulations





- Example: pulses followed by secondary backfiring waves that get emitted from the primary pulse. Spatially-localized oscillations occur as secondary waves travel.

Traveling wave solutions



- Since we are interested in solutions traveling at constant speed, look for stationary solutions in the moving frame $\xi = x - ct$, where c is the wave speed. Apply change of variables to get ODE system:

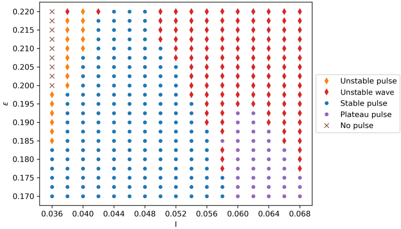
$$
\begin{aligned}
\dot{v} &= w \\
\dot{w} &= -cw - [I - g_l \cdot (v - v_l) - g_{Ca} \cdot m_{ss}(v) \cdot (v - v_{Ca}) - n \cdot (v - v_k)] \\
\dot{n} &= \varepsilon \cdot \lambda_{ss}(v) \cdot [n - n_{ss}(v)]/c.
\end{aligned}
$$

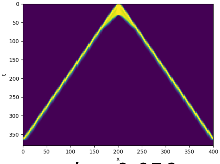
Computing branches of solutions using numerical continuation

- In the context of epilepsy, it is natural to see if changing the applied current I causes bifurcations in the system.
- Use numerical continuation in the traveling-wave ODE system with periodic boundary conditions to compute new solutions as I changes (keeping ε fixed).
- Result: curves of solution in the $I - c$ parameter plane, while all other parameters are fixed.
- Goal: study the solutions computed via numerical continuation to analyze their stability properties and locate their transition to backfiring.

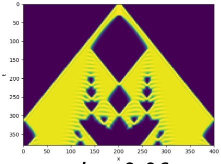
Computing branches of solutions using numerical continuation

- Focus on a curve of solutions starting with our solution at $(I, \varepsilon) = (0.06, 0.195)$.

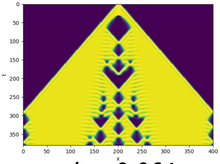




: $I = 0.056$

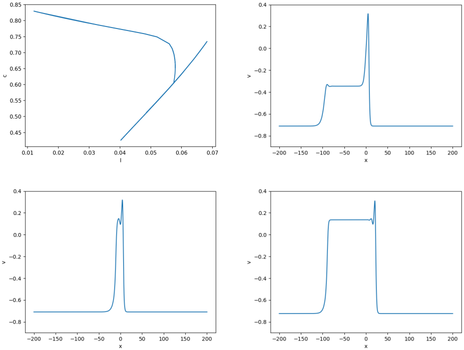


: $I = 0.06$



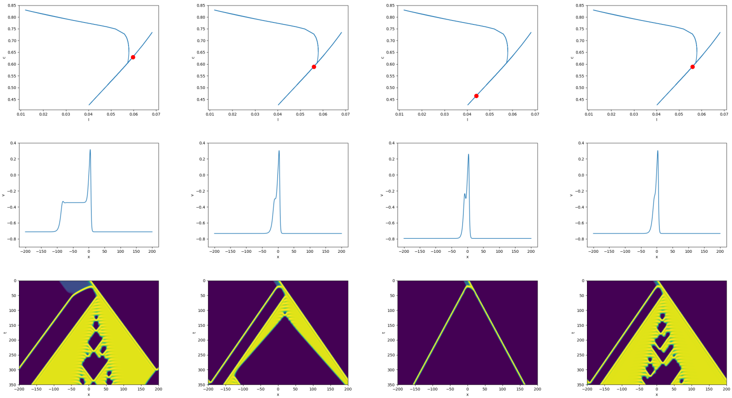
: $I = 0.064$

Computing branches of solutions using numerical continuation



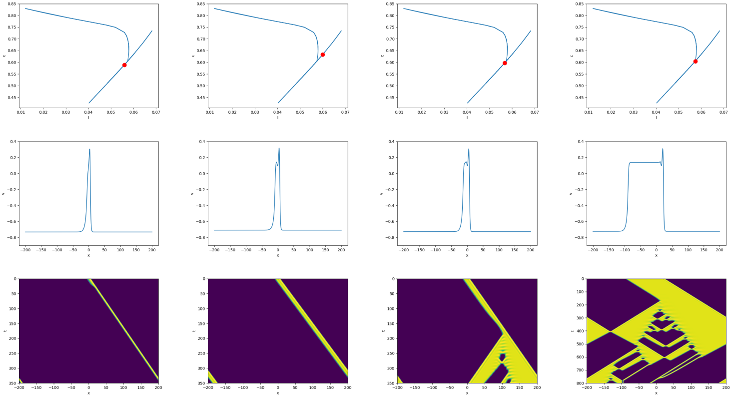
- Branch with two T-points computed for $\varepsilon = 0.195$. We vary I and compute new solutions using numerical continuation.
- First T-point: pulses with plateau at B. Second T-point: pulses with plateau at C.

Solutions near T-point



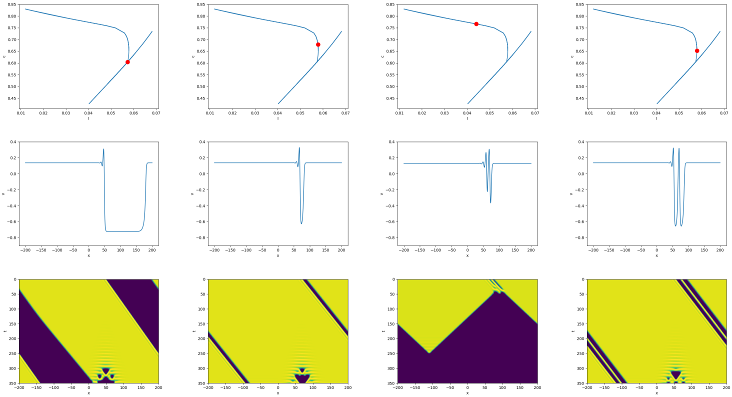
- The curve of solutions folds into the T-point in the $I - c$ parameter plane.
- For fixed I and ε, there may be more than one solution (with varying wave speeds and profile shape).

Solutions near T-point



- Pulses move between stable and unstable regimes along the branch of solutions.

Solutions near T-point

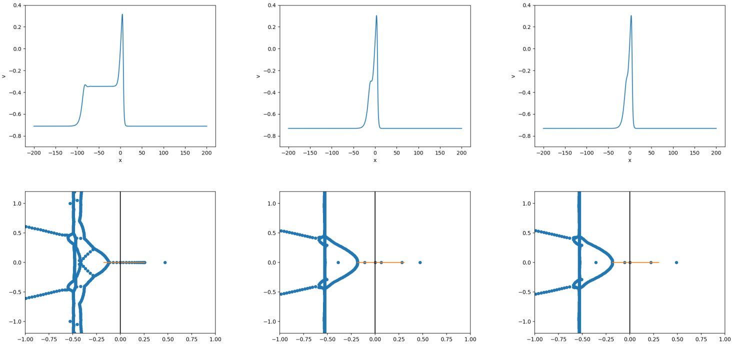


- The branch of solutions continues to another T-point.

Linear stability theory

- Linearize about a traveling pulse solution $(v_*(\xi), n_*(\xi))$. The spectrum of the resulting linear operator will consist of the essential spectrum (continuous) and the point spectrum (discrete) .
- The essential spectrum gives us information about the stability properties of the asymptotic states (stable in our case since the rest state A is stable).
- Unstable point spectrum corresponds to the pulse destabilizing in the middle.
- Absolute spectrum: not technically spectrum of an operator, but tells us if perturbations grow point-wise or get convected away.
- We computed spectra of the pulses from our branch of solutions, by discretizing the linearized operator about the pulse and solving for the eigenvalues of the resulting matrix.

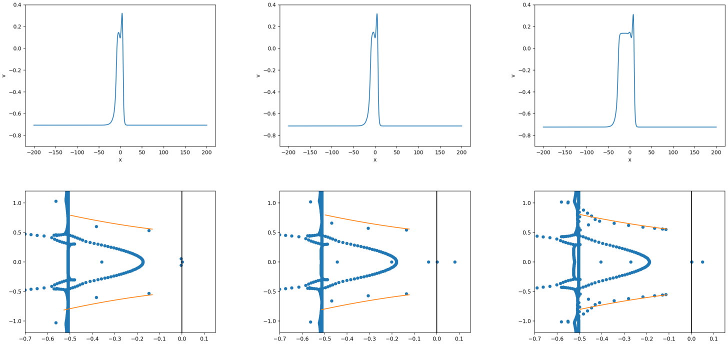
Spectrum of pulses along computed branch of solutions



- As domain length grows to infinity, the spectrum of a pulse to A with a plateau near B converges to a union of the essential spectrum of A, part of the absolute spectrum of B, and a finite number of discrete eigenvalues.[5]
- In this case: the point spectrum and absolute spectrum of B are both unstable.

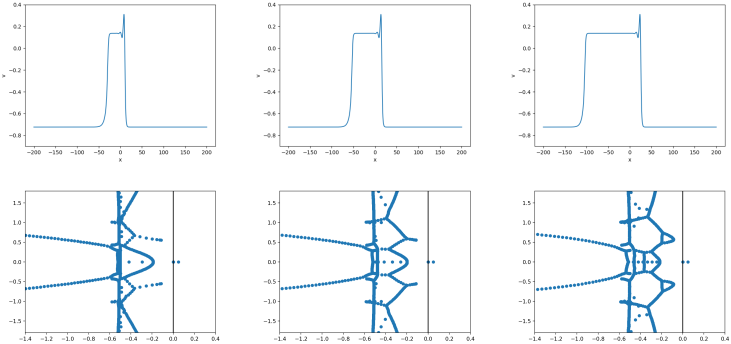
[5]Sandstede, B. and Scheel, A. (2000). Gluing unstable fronts and backs together can produce stable pulses. Nonlinearity, 13(5):1465.

Spectrum of pulses along computed branch of solutions



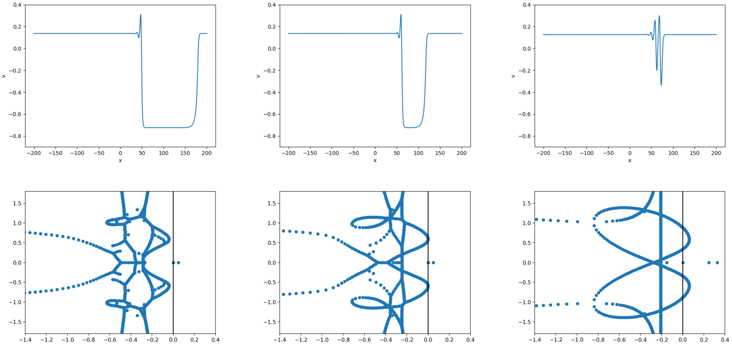
- The analogous result holds for pulses with a plateau near C. For our solutions, the absolute spectrum of C is *stable*.

Spectrum of pulses along computed branch of solutions



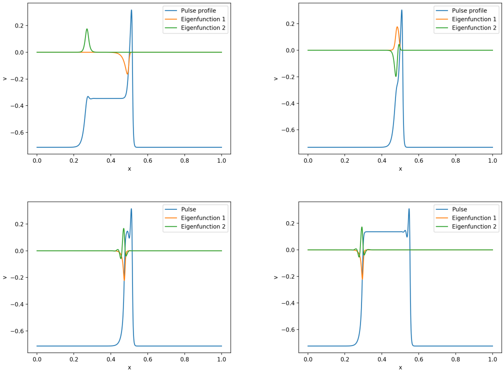
- However, the above result doesn't apply if the plateau length is too large relative to our domain length.

Spectrum of pulses along computed branch of solutions



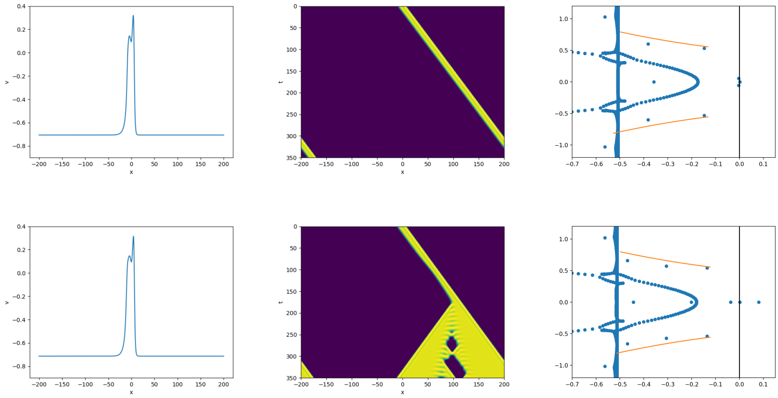
- When the plateau at C is large enough, the spectrum will start to resemble the *essential* spectrum of C. While the absolute spectrum of C is stable, the essential spectrum of C is unstable.

Eigenfunctions



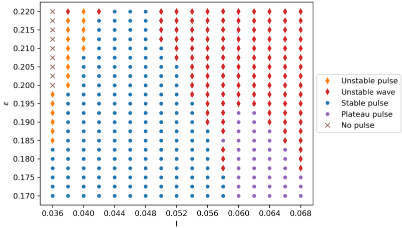
- Look at the corresponding eigenfunctions. Orange: eigenfunction for the most unstable point eigenvalue. Green: eigenfunction for the most unstable part of the absolute spectrum of the plateau state.
- Pulses with a plateau near B destabilize in the back and the front. Pulses with a plateau near C destabilize only in the back.

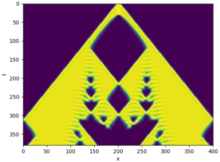
Onset of backfiring behavior

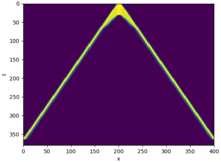


- Recall that we are interested in understanding how the backfiring behavior emerges.
- Point spectrum destabilizes via a Belyakov transition: stable conjugate eigenvalues collide and turn into stable and unstable real eigenvalues.

Computing branches of solutions using numerical continuation

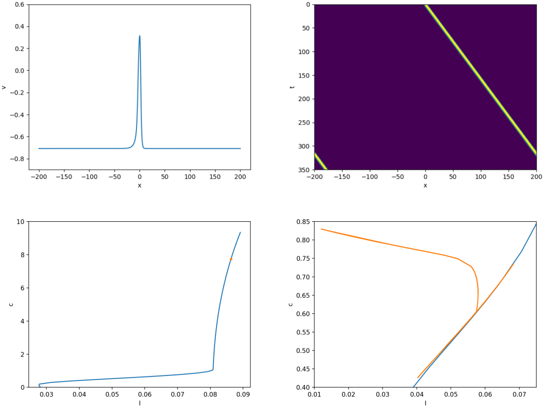






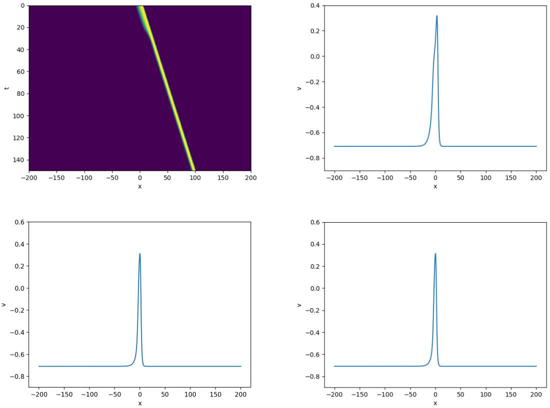
- Recall: the curve of solutions was found by taking a direct simulation from $(I, \varepsilon) = (0.06, 0.195)$. Our goal was to study how these solutions change when I is varied.
- Starting with a solution from $(I, \varepsilon) = (0.052, 0.195)$, we computed a second branch of pulse solutions.

Computing branches of solutions using numerical continuation



- The second curve of solutions contain stable pulses with no plateau. Past the saddle-node bifurcation, the solutions approximate periodic orbits.
- The two curves intersect with one another in the $I - c$ plane.

Computing branches of solutions using numerical continuation



- A solution from one curve can "jump" onto the second curve.

Two-dimensional behavior

- Our electrode array approximates a two-dimensional domain.
- A lot of information is not captured by a one-dimensional slice, e.g. absolute direction and speed of secondary waves.
- In the intermediate stage of the seizure, there are two-dimensional spatiotemporal patterns such as spots, spirals, and spatially-localized oscillations.

Simulations in two spatial dimensions

- The two-dimensional analogue of our previous numerical experiments is using a single Gaussian point source to initiate waves from the center of the domain.
- Single point source experiments: circular rings expand from the point source. Backfiring rings can move back towards the center of the domain, but the behavior is locally one-dimensional.

Simulations in two spatial dimensions

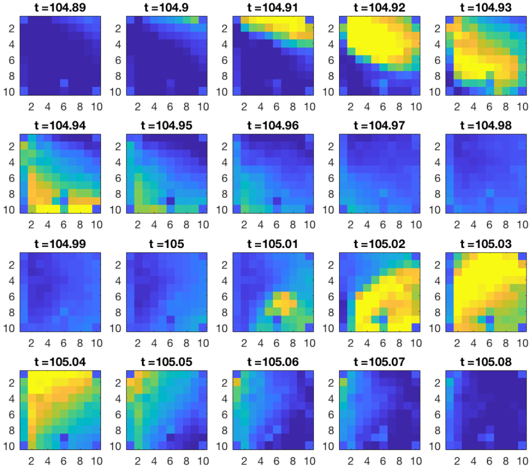
- Instead of a single point source, try initiating waves with two point sources. We fix the distance between the point sources and initial conditions, while varying the model parameters I and ε.
- When the waves from the two point sources collide, they emerge and produce two-dimensional spatiotemporal patterns.

Reproducing two-dimensional patterns

- The microelectrode array covers a small area of the brain. To make an apt comparison with our two-dimensional simulations, focus on small sections of the domain.
- When 10x10 patches in the large 400x400 domain are examined, the primary traveling pulse is approximately planar. Behind the primary pulse, localized secondary behavior is observed.
- Examples: spirals and spots in the simulations look similar to the secondary patterns found in the seizure. In some cases, secondary waves traveling in a different from the primary pulse is also found.

Reproducing two-dimensional patterns

- Traveling pulses followed by second pulse from a different direction.



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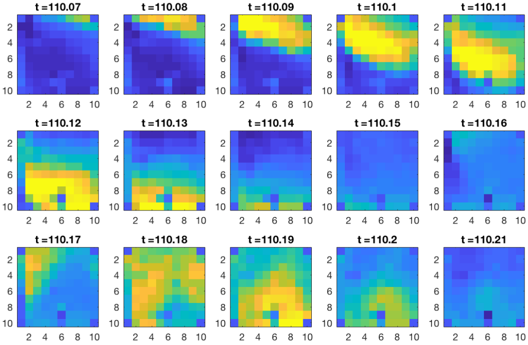
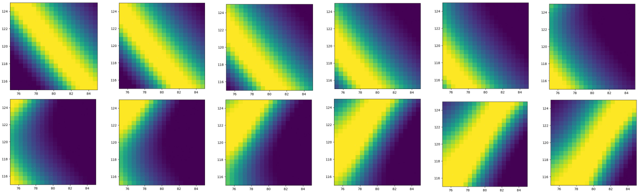
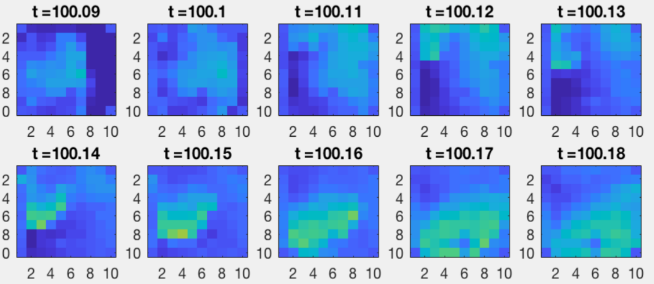
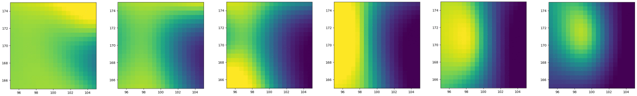




Reproducing two-dimensional patterns

- Spots following a traveling pulse





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Conclusions

- We found a reaction-diffusion model of neural tissue that exhibits behavior qualitatively similar to empirical data. We computed a branch of solutions that transitions from stable to unstable pulses. The destabilizing mechanism bears many similarities to that of the CO-Pt model.
- There are many branches of solutions in $I - \varepsilon - c$ space, and it is unclear how solutions are selected by the initial condition.
- In two spatial dimensions, single point source experiments display backfiring waves, but the behavior is locally one-dimensional.
- Two point sources are needed to produce two-dimensional spatiotemporal patterns. Our numerical experiments suggest that these patterns are caused by wave interactions between the backfiring waves.

Future work

- More quantitative characterization of the spatiotemporal patterns, such as frequency of local oscillations, length and time scales of spirals and spots, and of the rate of phase change of electrodes during spiral waves.
- Amplitude secondary patterns in LFP recordings are often of lower amplitude than the primary patterns. In our simulations, the amplitudes are roughly the same.
- Changing model parameters over time may help us find bifurcations between the different stages of a seizure.
- Alternative hypothesis of a seizure mechanism: moving the location of the stimulus source.