Analysis of a lumped model of neocortex to study epileptiform activity

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What is epilepsy?

Pathology

- Neurological disorder, affecting 1% of world population
- Characterized by increased probability of recurring seizures

Seizures

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EEG during a seizure

Goal of this research

Goals

- Study several models of neural activity in neocortex
- Identify correspondences between these models
- Extrapolate results from simpler models to more complex models

Results so far

- A large, detailed model describing activity of individual neurons in both normal and epileptiform states
- A simple, lumped model that has shown to have some similarity [Visser et al., 2010]

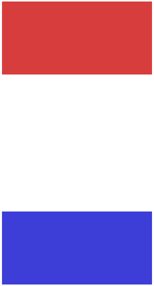
Motivation of model

Simulation on Youtube

Model

Two excitatory populations:

$$\dot{x}_1(t) = -\mu_1 x_1(t) - \mathcal{F}_1(x_1(t-\tau_i)) + \mathcal{G}_1(x_2(t-\tau_e))$$
$$\dot{x}_2(t) = -\mu_2 x_2(t) - \mathcal{F}_2(x_2(t-\tau_i)) + \mathcal{G}_2(x_1(t-\tau_e))$$



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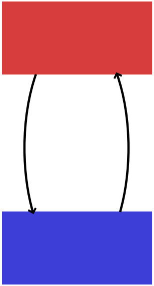

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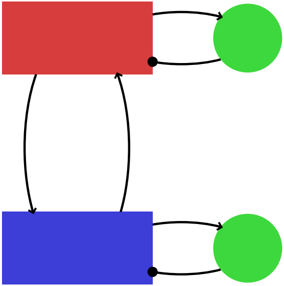

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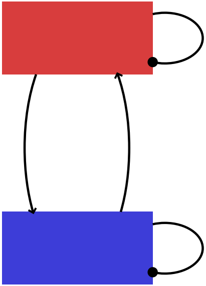


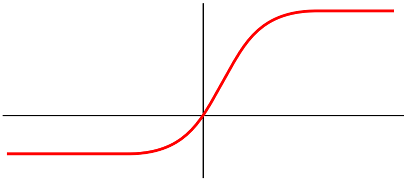
Simplifications

- Make system symmetric:

$$\mu_1 = \mu_2 := \mu \qquad \mathcal{F}_1 = \mathcal{F}_2 := \mathcal{F} \qquad \mathcal{G}_1 = \mathcal{G}_2 := \mathcal{G}$$

- Choose $\mathcal{F}(x)$ and $\mathcal{G}(x)$ as rescalings of:

$$S = (\tanh(x-a) - \tanh(-a)) \cosh^2(-a)$$



Time rescaling

Time is rescaled to non-dimensionalize system:

$$\dot{x}_1(t) = -x_1(t) - \alpha_1 S(\beta_1 x_1(t-\tau_1)) + \alpha_2 S(\beta_2 x_2(t-\tau_2))$$
$$\dot{x}_2(t) = -x_2(t) - \alpha_1 S(\beta_1 x_2(t-\tau_1)) + \alpha_2 S(\beta_2 x_1(t-\tau_2))$$

Introduce vector notation:

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}_t), \text{ with } \mathbf{x}_t \in C([-h,0],\mathbb{R}^2) \text{ and } h = \max(\tau_1,\tau_2).$$

Main parameters of interest: representing connection strengths between populations.

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Fixed points

Corollary

The origin is always a fixed point of the DDE.

Theorem

The DDE only has only symmetric fixed points, i.e.
$\mathbf{f}(\mathbf{x}) = 0 \implies \mathbf{x} = (x^*, x^*)$.

Linearization

The DDE is linearized about an equilibrium:

$$\dot{u}_1(t) = -u_1(t) - k_1 u_1(t-\tau_1) + k_2 u_2(t-\tau_2),$$
$$\dot{u}_2(t) = -u_2(t) - k_1 u_2(t-\tau_1) + k_2 u_1(t-\tau_2),$$

in which

$$k_1 := \alpha_1\beta_1 S'(\beta_1 x^*) \qquad k_2 := \alpha_2\beta_2 S'(\beta_2 x^*).$$

Note that k_1 and k_2 depend on the equilibrium at which we linearize.

Characteristic equation and eigenvalues

Consider solutions of the form $\mathbf{u}(t) = e^{\lambda t}\mathbf{c}, \mathbf{c} \in \mathbb{R}^2$. Non-trivial solutions of the system correspond with $\Delta(\lambda)\mathbf{c} = 0$, for:

$$\Delta(\lambda) = \begin{bmatrix} \lambda + 1 + k_1 e^{-\lambda\tau_1} & -k_2 e^{-\lambda\tau_2} \\ -k_2 e^{-\lambda\tau_2} & \lambda + 1 + k_1 e^{-\lambda\tau_1} \end{bmatrix}$$

Non-trivial solutions exist when $\det \Delta(\lambda) = 0$, or:

$$\underbrace{\left(\lambda + 1 + k_1 e^{-\lambda\tau_1} + k_2 e^{-\lambda\tau_2}\right)}_{:=\Delta_+(\lambda)} \underbrace{\left(\lambda + 1 + k_1 e^{-\lambda\tau_1} - k_2 e^{-\lambda\tau_2}\right)}_{:=\Delta_-(\lambda)} = 0.$$

This characteristic function has an infinite (but countable) number of roots.

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Symmetries of solutions

Theorem

Roots of Δ_- correspond to symmetric solutions, whereas roots of Δ_+ relate to asymetric solutions.

Proof.

Let $\mathbb{Z}_2$ act on $\mathbb{C}^2$ so that $-1 \in \mathbb{Z}_2$ acts as $\xi(x,y) : (x,y) \mapsto (y,x)$, then:

$$\Delta_-(\lambda) = 0 \Leftrightarrow \begin{cases} \Delta(\lambda)v = 0 \\ \xi v = v \end{cases}$$

$$\Delta_+(\lambda) = 0 \Leftrightarrow \begin{cases} \Delta(\lambda)v = 0 \\ \xi v = -v \end{cases}$$

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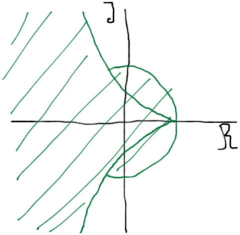
□

Roots of $|\Delta(\lambda)|$

Theorem

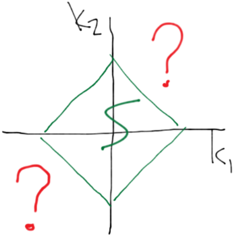
For $|\lambda| \geq C_0|e^{-\lambda h}|$ and $|\lambda| > C$, with $C \geq C_0$, $|\Delta(\lambda)| > 0$. Hence, $\Delta(\lambda)$ has a zero free right half-plane [Bellman and Cooke, 1963].



Minimal Stability Region

Theorem

For $|k_1| + |k_2| < 1$ *the system has no eigenvalues with positive real part.*

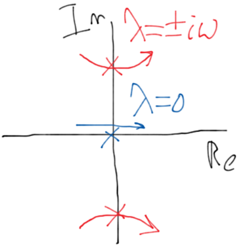


Bifurcations

Note:

As in ODEs, an equilibrium of a DDE loses its stablity when either

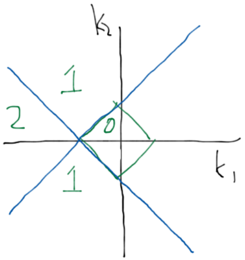
- a single real eigenvalue passes through zero (fold/transcritical), or
- a pair of complex eigenvalues passes through the imaginary axis (Hopf).



Fold/transcritical bifurcation

Theorem

Equilibria undergo a fold or transcritical bifurcation on the lines $1 + k_1 \pm k_2 = 0$ in (k_1, k_2)-space.



Hopf bifurcations

Theorem

Two curves, $\mathbf{h}_+(\omega)$ and $\mathbf{h}_-(\omega)$, exist along which the linearized system has a pair of complex eigenvalues $\lambda = \pm i\omega$.

Proof.

For now, we consider only $\Delta_+(i\omega) = 0$; $\Delta_-(i\omega)$ is similar.

$$i\omega + 1 + k_1 e^{-i\omega\tau_1} + k_2 e^{-i\omega\tau_2} = 0$$

$$\begin{bmatrix} \cos(\omega\tau_1) & \cos(\omega\tau_2) \\ \sin(\omega\tau_1) & \sin(\omega\tau_2) \end{bmatrix} \begin{bmatrix} k_1 \\ k_2 \end{bmatrix} = \begin{bmatrix} -1 \\ \omega \end{bmatrix}$$

Hopf bifurcations

Proof cntd.

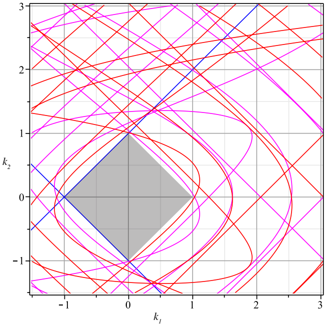
The matrix is invertible if $\det = \sin(\omega(\tau_2 - \tau_1)) \neq 0$, yielding:

$$\begin{bmatrix} k_1 \\ k_2 \end{bmatrix} = \mathbf{h}_+(\omega) := \frac{-1}{\sin(\omega(\tau_2 - \tau_1))} \begin{bmatrix} \sin(\omega\tau_2) & \cos(\omega\tau_2) \\ -\sin(\omega\tau_1) & -\cos(\omega\tau_1) \end{bmatrix} \begin{bmatrix} 1 \\ \omega \end{bmatrix}.$$

□

Bifurcations in (k_1, k_2)-space

- Very sensitive, complex branch structure
- Intersections correspond with codim-2 bifurcations.



$(\tau_1 = 11.6, \tau_2 = 20.3)$

Returning branches

Theorem

For a given $\omega_0 > 0$, $\Delta(\lambda)$ has no roots $\lambda = \pm i\omega, \omega > \omega_0$ inside the square $|k_1| + |k_2| < \sqrt{1+\omega_0^2}$.

Proof.

First, assume $i\omega$ is a root of Δ_+ (a similar argument holds for Δ_-):

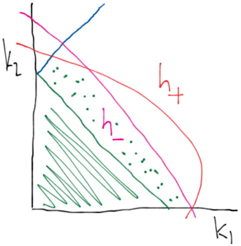
$$\begin{aligned} 0 &= |1 + i\omega + k_1 e^{-i\omega\tau_1} + k_2 e^{-i\omega\tau_2}|, \\ &\geq |1 + i\omega| - |k_1| - |k_2|. \end{aligned}$$

Then, this root lies outside the designated square for $\omega > \omega_0$. □

Revised stability region

Conjecture

For the considered parameters τ_1 and τ_2 the full stability region is bounded, connected and contains the origin.



The first Lyapunov coefficient

- Stability region partly bounded by curve of Hopfs
- The first Lyapunov coefficient is determined along the boundary
- Normal given by [Diekmann et al, 1995]:

$$
\begin{aligned}
c_1 = & \frac{1}{2} q^T D^3 \mathbf{f}(0)(\phi, \phi, \bar{\phi}) \\
& + q^T D^2 \mathbf{f}(0)(e^{0\cdot} \Delta(0)^{-1} D^2 \mathbf{f}(0)(\phi, \bar{\phi}), \phi) \\
& + \frac{1}{2} q^T D^2 \mathbf{f}(0)(e^{2i\omega\cdot} \Delta(2i\omega)^{-1} D^2 \mathbf{f}(0)(\phi, \phi), \bar{\phi}).
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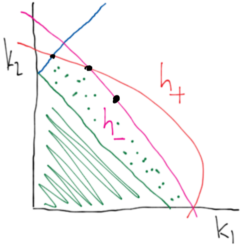
Codim 2 bifurcations

Generalized Hopf

- Lypunov coefficient passes through zero,
- Generalized Hopf bifurcation at boundary



Summary

Equilibria

- Only symmetric equilibria
- Stability region identified

Bifurcations of stability region

- Fold and transcritical bifurcations
- Hopf-bifurcations, both sub- and supercritical
- Zero-Hopf and Hopf-Hopf

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Numerical bifurcation analysis

One parameter

Identify stable and unstable manifolds of non-trivial equilibrium and periodic solutions for varying α_2.

Two parameters

Continue boundaries of stable solutions in α_1 and α_2.

Software

- DDE-BIFTOOL [Engelborghs et al., 2002]
- PDDE-CONT/Knut [Roose and Szalai, 2007]

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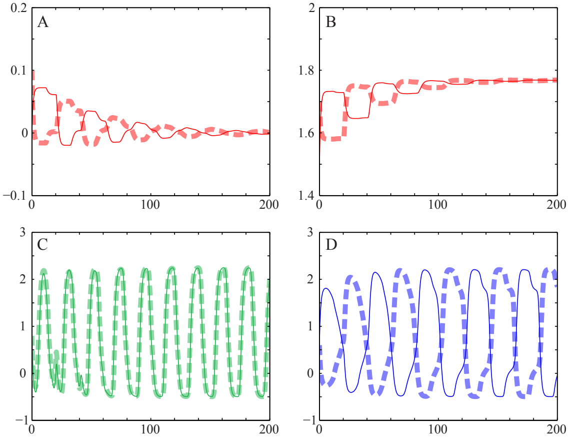

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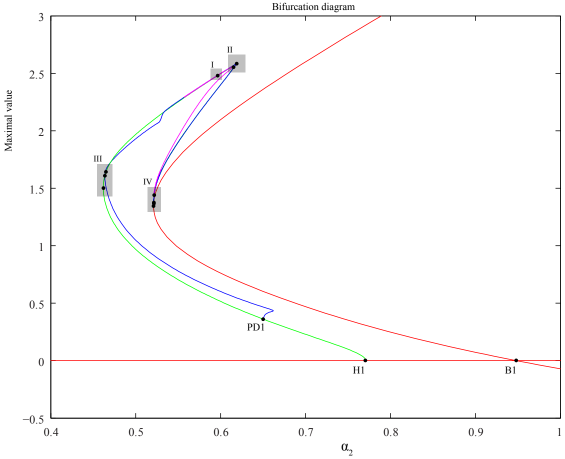

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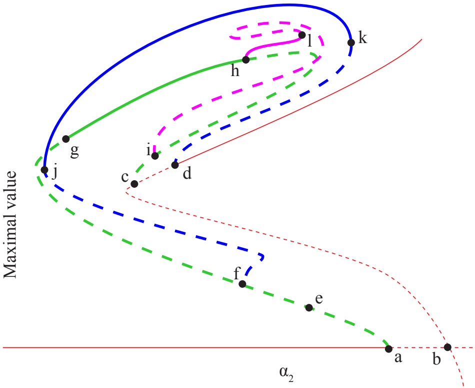
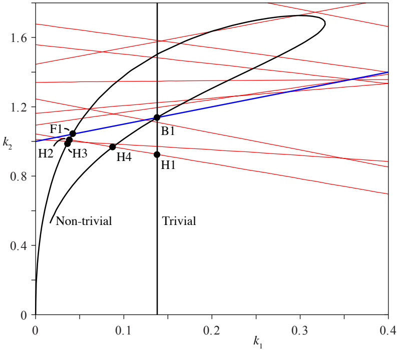
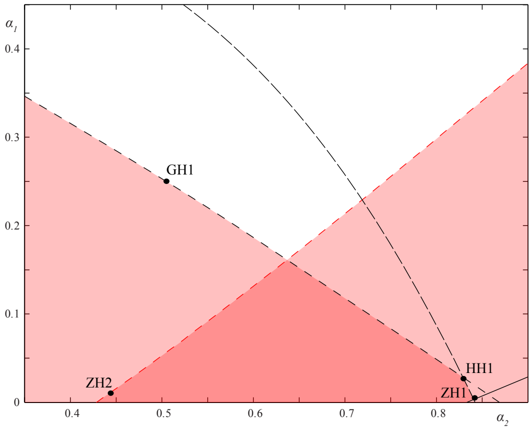


Fixed points in (k_1, k_2)-space



Bifurcations of stable solutions in α_1 and α_2



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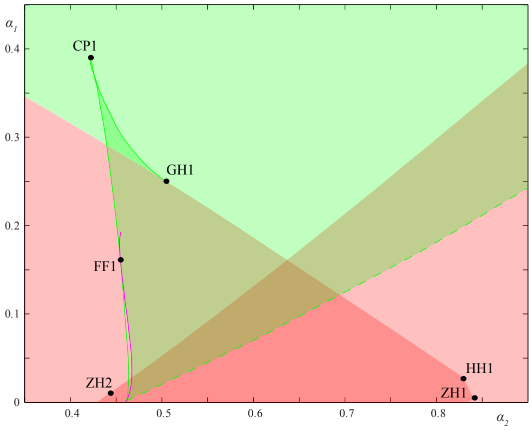

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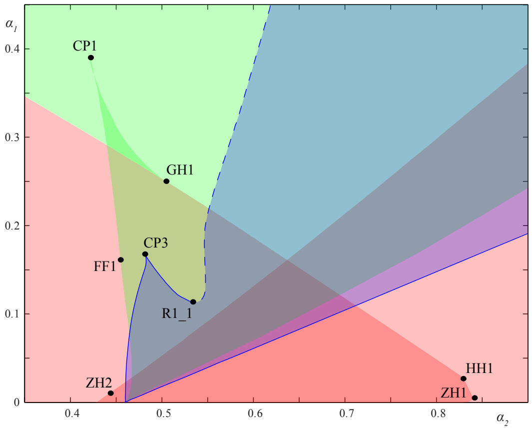
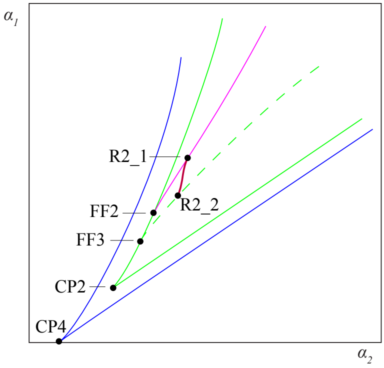
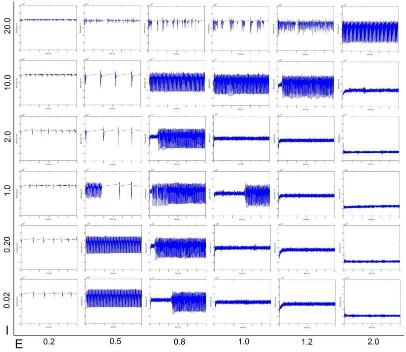


Complex bifurcation structure



Comparison

The bifurcation analysis is compared with a survey on the detailed model:



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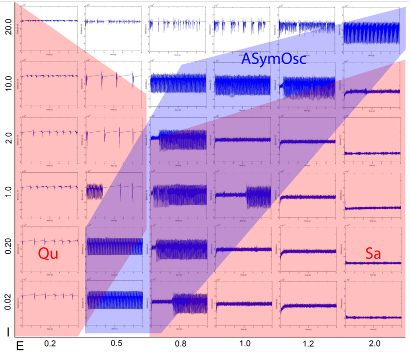

Summary and conclusions

Summary

- We studied a simple, lumped model for neural activity
- Parameter regions of steady states and periodic solutions are identified

Conclusions

- The behavior of both models varies similarly for changes of parameters
- Regions of multistability are of interest for studying epilepsy

Future work

Details

- Study the model's codim-2 bifurcations
- Proofs rather than conjectures

Next steps

- Expand model (e.g. break symmetry)
- Parameter estimation