The spatio-temporal dynamics of spontaneous activity in the developing retina

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Introduction

Retinal waves an are example of spontaneous correlated activity in the developing central nervous system which drive activity-dependent developmental programs prior to visual stimulus. [1] In order to understand their role in development, it is important to know: how do spatiotemporal wave properties depend on underlying physiology?

Generation of stage II waves [2]

- Spontaneous activity in Starburst Amacrine Cells (SACs) initates waves
- Dense, recurrent cholinergic connections between SACs propagates activity laterally
- Slow after-hyperpolarization of SACs creates shifting wave boundaries

Aims

- Develop simple, biophysical model capable of recapitulating dynamics of retinal waves
- Determine parameter regimes in which retinal waves exist
- Characterize spatiotemporal patterns of retinal waves

Model of stage II retinal waves

SACs obey Morris-Lecar dynamics [3] with an additional ACh conductance:

$$C_m V_t = -g_{Ca}(V - V_{Ca}) - g_K(V - V_K) - g_L^M(V - V_L) - g_{ACh}(V - V_{syn})$$

where

$$g_{ACh}(A) = g^M_{ACh}\frac{\delta A^2}{1+\delta A^2},$$
$$A_t = D\nabla^2 A + \beta(1+e^{-\kappa(V-V_0)})^{-1} - \frac{A}{\tau_{ACh}},$$
$$\tau_R R_t = \Lambda(V)(R_\infty - R) + \alpha S(1-R),$$
$$S_t = \gamma(1+e^{-\kappa(V-V_0)})^{-1} - \frac{S}{\tau_S}.$$

- Synaptic conductance g_{ACh} depends on local, extra-cellular concentration of acetylcholine A.
- Dense, lateral connectivity of SACs (not having axonal processes) modelled by the extra-synaptic diffusion of ACh. [2]
- Slow after-hyperpolarization variable S activated by depolarization and evolves on timescale τ_S, slower than timescale of R, τ_R.

Simulations

The model reproduces the spatiotemporal patterns of physiological waves.

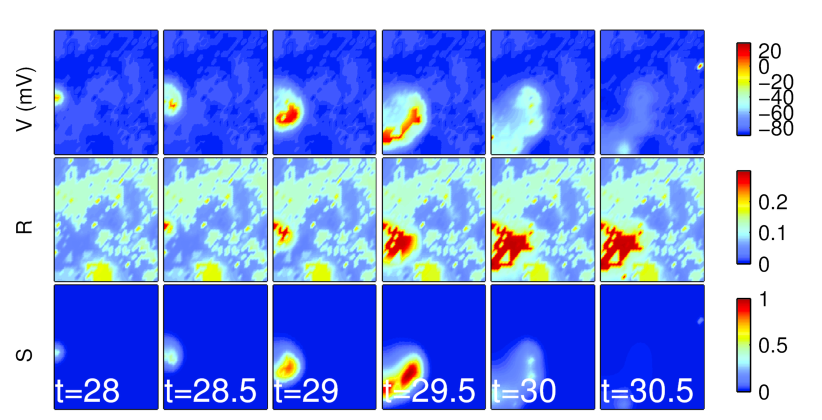

Figure 1: *Simulated stage II retinal waves. A 64x64 grid simulates 4mm² area of retina, such that each grid point corresponds approximately to one SAC. Each SAC depolarizes spontaneously at an average rate of once every 15 minutes.*

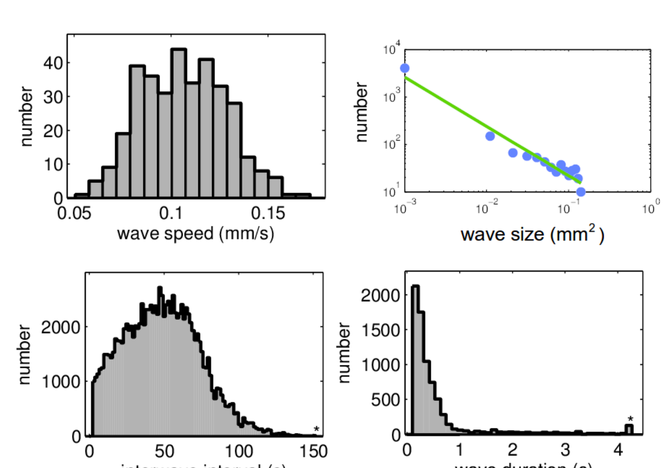

Figure 2: *Wave statistics following 5000s of simulated retinal wave activity.*

The developing retina as an excitable medium

For what parameters can physiological waves exist?

- Wave boundaries determined by refractory state of network – in a sufficiently non-refractory medium waves propagate large distances without decay
- Amacrine cell network modelled as a *reaction-diffusion* system

Singular perturbation analysis

$$V_t = f(V,R,S,A),$$
$$A_t = k(V,R,S,A) + \nabla^2 A,$$
$$R_t = \varepsilon g(V,R,S,A),$$
$$S_t = \varepsilon^2 h(V,R,S,A).$$

- Separate *fast* (voltage, V, and ACh concentration, A) and *slow* systems (refractory variables, R and S)
- As $\varepsilon \to 0$, both $R_t \to 0$ and $S_t \to 0$, only V and A are dynamic
- Stationary solutions in travelling frame, $\xi = x - c(R)t, t = t'$, are travelling fronts of speed c.
- *Heteroclinic* orbits connect rest and excited fixed points, computing using `HomCont` in AUTO.

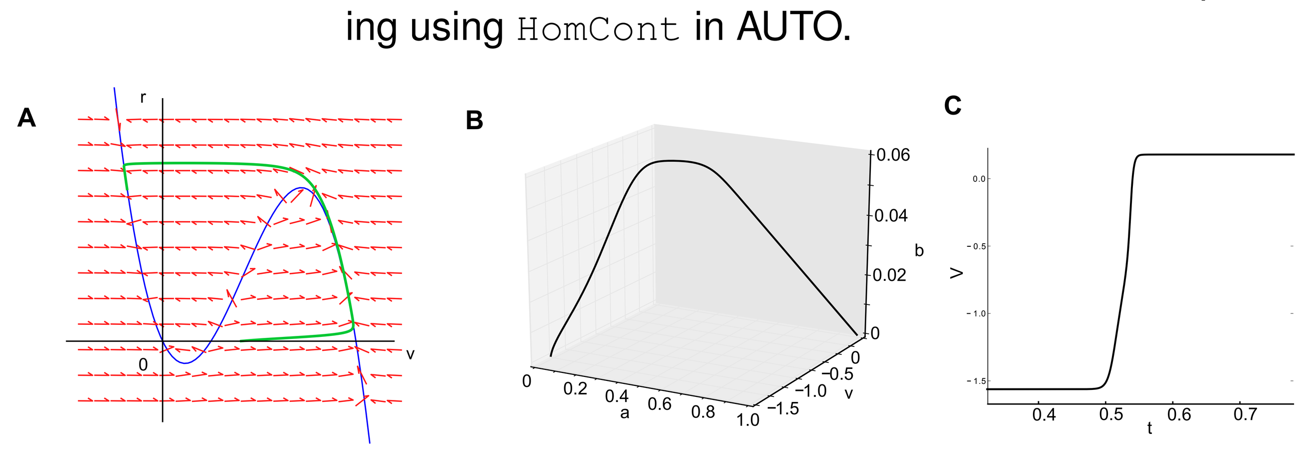

Figure 3: *Wave front dynamics. a) Fast-slow dynamics in Fitzhugh-Nagumo example b) trajectory of wave-front dynamics c) wave-front*

Excitability thresholds

Parameters where traveling fronts have a positive velocity are those where medium is excitable – supports waves able to travel across retina without decay.

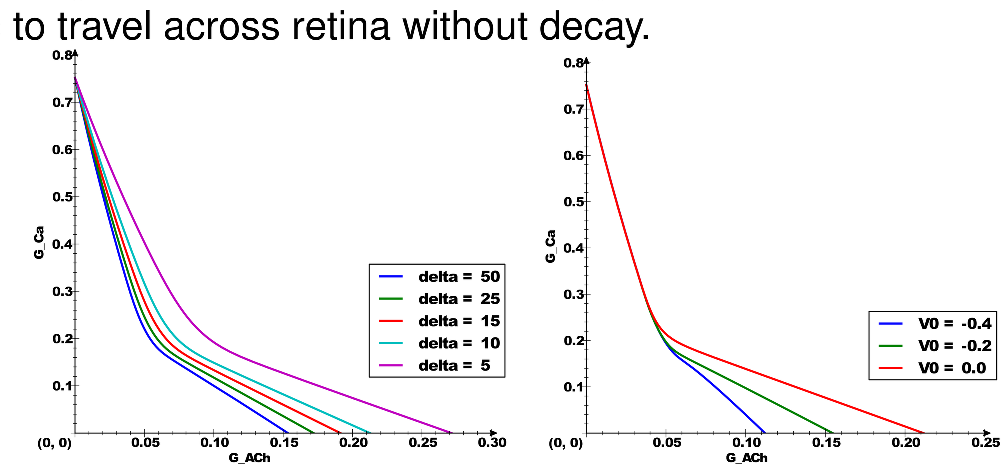

Figure 4: *Thresholds at which medium is 'excitable' – points to the right of each curve support forward travelling waves*

Critically configured spontaneous activity

What determines their spatiotemporal properties?

- Hennig *et al* 2009 [3] observe power-law distributed wave size events from *in vitro* recordings, similar to avalanches of spontaneous activity observed in cortex [4]
- When does our model exhibit power-law distributed wave sizes?
- Drossel-Schwabl forest fire model (DS-FFM), a canonical model of *self-organized criticality* (SOC): [5] on a square lattice, at each time step
  1. Each excitable cell spontaneously fires with some probability f
  2. Each firing cell 'ignites' its excitable nearest neighbours
  3. Each firing cell becomes refractory (on next time step)
  4. Each refractory cell becomes excitable with some probability p

On 2D lattice, SOC observed when: [5]

$$(f/p)^{-1/2} \ll p^{-1} \ll f^{-1}. \qquad (1)$$

In our model, on a simulated lattice of n^2 cells, representing L^2 mm² of retina:

$$f = \frac{\pi n^2 c^2 \tau^2 \hat{f}}{L^2}, \quad p = \frac{\tau}{\rho},$$

for wave speed at rest refractory state c, per cell spontaneous firing rate $\hat{f}$, spike duration τ, and effective refractory period ρ.
From (1), observe SOC when:

$$\left[\frac{\pi n^2 c^2 \tau \hat{f} \rho}{L^2}\right]^{-1/2} \ll \frac{\rho}{\tau} \ll \frac{L^2}{\pi n^2 c^2 \tau^2 \hat{f}},$$

where c, τ and ρ are all relateable to parameters of underlying model through either simulation or numerical continuation.
In DS-FFM expect power-law distributed wave sizes with scaling exponent $\alpha = -1.15$, as $\theta = p/f \to \infty$.

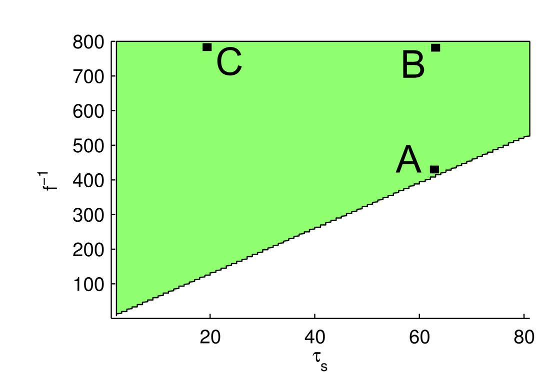

Figure 5: *Shaded region indicates where (1) is satisfied.* ***A*** $\theta = 1.5$*, log-linear least squares fit estimates* $\alpha = -1.45$ $(R^2 = 0.95)$*;* ***B*** $\theta = 3$*, log-linear least squares fit estimates scaling exponent* $\alpha = -1.10$ $(R^2 = 0.95)$*;* ***C*** $\theta = 10$*, log-linear least squares fit estimates* $\alpha = -1.14$ $(R^2 = 0.96)$.

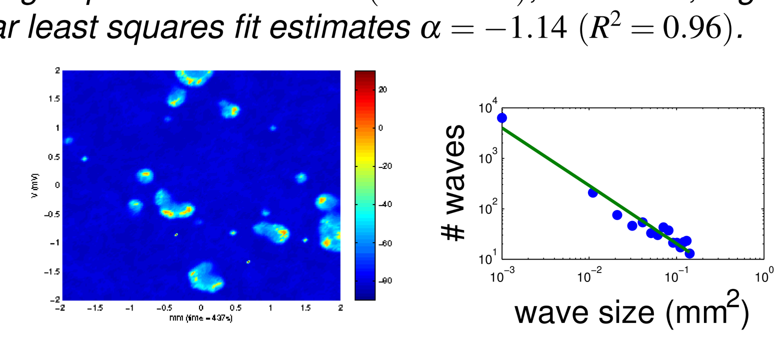

Figure 6: ***B*** *For* $\theta \to \infty$*, network approaches critical state characterized by power-law distributed events.*

Summary

- A combination of singular perturbation analysis, simulation and numerical continuation can be used to understand complex spatiotemporal patterns of stage II retinal waves
- Spontaneous activity in developing retina can be interpretted in terms of a classical self-organized critical forest fire model
- Future work: further statistical tests of power-law size distributions, criteria for other behaviour regimes (spiral waves, bimodal wave-size distributions)

The authors would like to thank Kevin Ford for discussions and feedback on this work.

References

[1] A. G. Blankenship and M. B. Feller, "Mechanisms underlying spontaneous patterned activity in developing neural circuits.," *Nature reviews. Neuroscience*, vol. 11, pp. 18–29, Jan. 2010.

[2] K. J. Ford, A. L. Félix, and M. B. Feller, "Cellular mechanisms underlying spatiotemporal features of cholinergic retinal waves.," *The Journal of neuroscience : the official journal of the Society for Neuroscience*, vol. 32, pp. 850–63, Jan. 2012.

[3] M. H. Hennig, C. Adams, D. Willshaw, and E. Sernagor, "Early-stage waves in the retinal network emerge close to a critical state transition between local and global functional connectivity.," *The Journal of neuroscience : the official journal of the Society for Neuroscience*, vol. 29, pp. 1077–86, Jan. 2009.

[4] J. M. Beggs and D. Plenz, "Neuronal avalanches in neocortical circuits.," *The Journal of neuroscience : the official journal of the Society for Neuroscience*, vol. 23, pp. 11167–11177, Dec. 2003.

[5] B. Drossel and F. Schwabl, "Self-organized critical forest fire model," *Physical review letters*, vol. 69, no. 11, pp. 1629–1632, 1992.