Biophysical modelling of the intrinsic mechanisms of the autonomous starbust cells during stage II retinal waves

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Abstract

Retinal waves are spontaneous bursting activity propagating in the developing retina until vision is functional. In this work we propose a biophysical modelling of the mechanism that generates the spontaneous intrinsic cell-autonomous rhythmic bursting in Starbust Amacrine Cells (SACs), observed experimentally in [1] which is directly linked with the emergence of stage II retinal waves. We analyze this system from the dynamical system and bifurcation theory perspective.

Context & Motivation
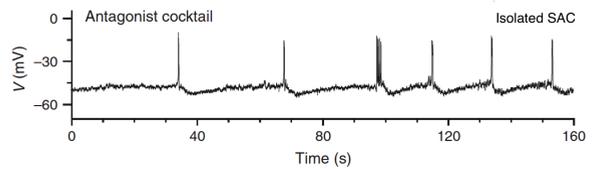
Cell-autonomous rhythmic bursts in SACs [1]

Experimental study of the mechanism underlying retinal waves

- In [1] it is shown that stage II retinal waves originate from cell-autonomous rhythmic bursts of SACs; the refractory process is dictated by a slow After HyperPolarisation (sAHP) current.
- Rhythmic bursts are shown experimentally in [1] to be consisted of fast oscillations, mediated by voltage-gated calcium channels.
- The refractory process inbetween the consecutive bursts is found in [1] to be modulated by calcium-dependent potassium channels inducing a sAHP current similar to I_{sAHP} reported in [2] for pyramidal neurons.
- Network interactions among SACs through cholinergic synapses ensure the necessary level of synchrony of activity which is the key to the wave generation, along with the existence of the aforementioned intrinsic periodic bursts [1].
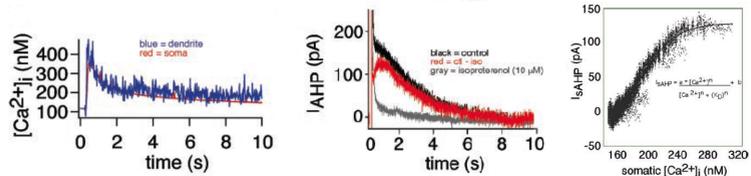
Calcium concentration (t)[2] $I_{sAHP}(t)$ [2] $I_{sAHP}(C)$ [2]

Experimental study on the mechanism of the $sAHP$

- The evolution of the intracellular calcium concentration C and the I_{sAHP} with time under voltage clamp is studied in [2]. Also, an experimentally fitted relationship between I_{sAHP} and C is deducted in the same work.

Motivation & Goals

- Finding a biophysical modelling reproducing these experiments and generating waves by taking into account the ionic mechanisms and tuning all parameters from the biophysical literature.
- Revisiting [3],[4] which do not correctly reproduce these fundamental effects in order to find a generic mechanism for stage II retinal waves.

Acknowledgements

Modelling Cell-Autonomous Bursts

Model   Experiment, Zheng et al.,2006 [1]
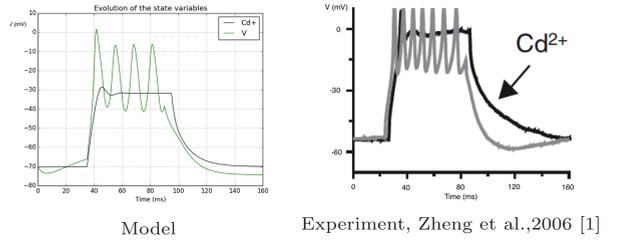
- Modelling the ionic mechanism of intrinsic bursts according to the experimental work of [1] based on extended Morris-Lecar equations.
- Fast oscillations of the voltage while applying an external current pulse of 150 pA followed by a subsequent AHP. Blocking all calcium related currents leads to the vanishing of both fast oscillations and AHP.

Slow After Hyperpolarization current

Ca^{+2} Concentration(t) $I_{sAHP}(t)$ $I_{sAHP}(C)$
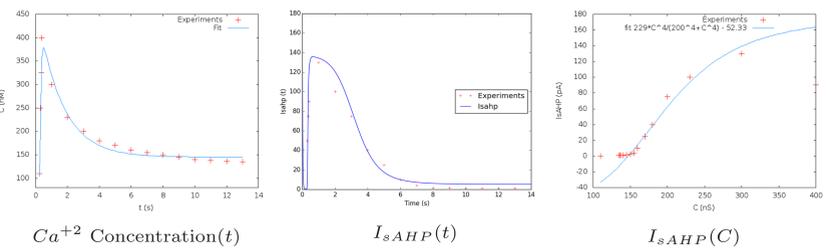
- Biophysical modelling of the mechanism of the slow AHP observed in [1] taking into account the ionic mechanism of Ca^{+2} gated K^+ currents. We extract the corresponding parameters using the experimental curves in [2] for the evolution of intracellular calcium concentration C, I_{sAHP} under voltage clamp and I_{sAHP} with respect to C.
- By fitting the experimental findings in [2], we model more realistically the sAHP current than [3],[4] which is crucial for the refractory process of the waves.

Phase Portrait and Bifurcations

Stable and Unstable Focus   Homoclinisation   After Saddle node bifurcation
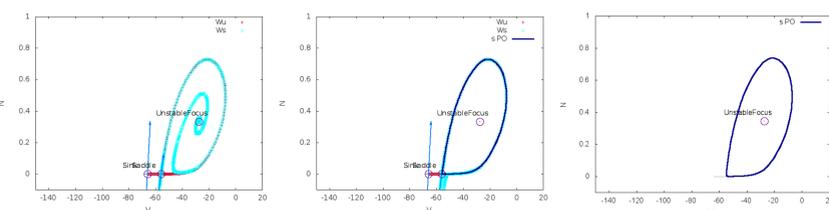
- Phase portrait of the Morris-Lecar system (two state variables: V,N). Illustrating the effect of sAHP on the dynamics by using it as a bifurcation parameter which varies from zero to negative values.
- There is a saddle node bifucation giving rise to an unstable focus which becomes a stable cycle by homoclinisation. As we increase more I_{sAHP}, there is another saddle node which destroys the low state stable fixed point.

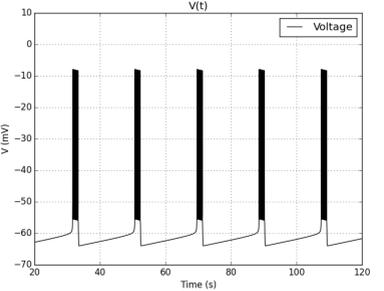## Simulating the intrinsic bursts and the sahp refractory mechanism

Figure A
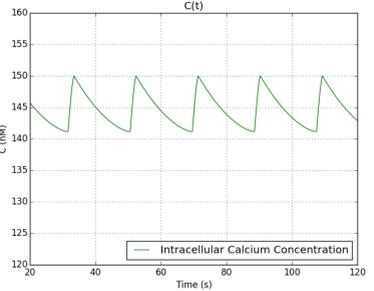Simulated Voltage Rhythmic bursts. Period 20s

Figure B
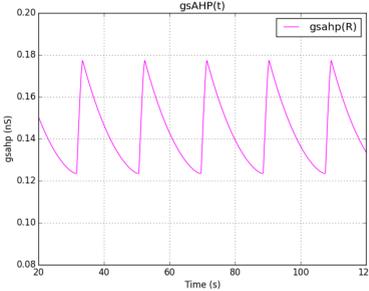Simulated Intracellular Calcium Loading/Offloading Mechanism
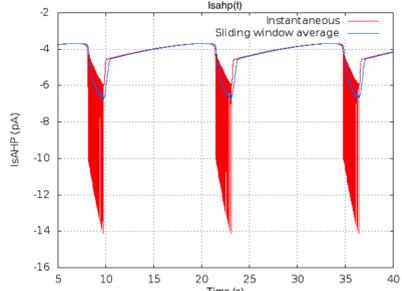
Figure C
Simulated $g_{sAHP}(t)$
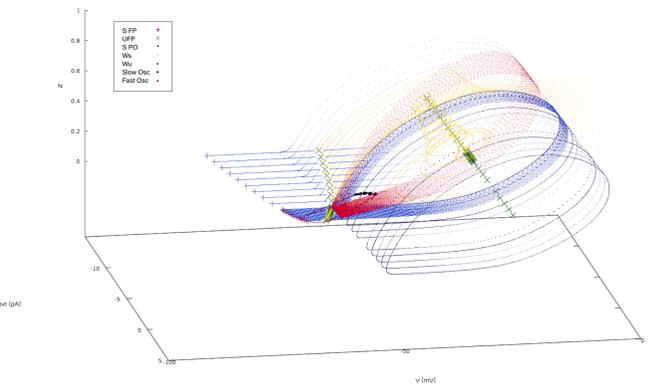
Figure D
Simulated $I_{sAHP}(t)$

Figure E
3D Bifurcation diagram of the mechanism generating rhythmic intrinsic bursts in SACs

Discussion

- We have exhibited a mechanism generating slow oscillations, based on the joint fast dynamics of Ca^{+2} and K^+ channels generating fast oscillations and a slow sAHP Ca^{+2} gated K^+ channels modulating slow oscillations.
- Slow oscillations are explained from the dynamical system aspect as switching constantly from a fixed point to a limit cycle, where I_{sAHP} acts as the bifurcation parameter.
- In figure E, we draw the 3D bifurcation diagram for V, N, I_{sAHP} showing the global view of the dynamical mechanism. When $I_{sAHP} = 0$, there exists a limit cycle during which we observe the fast oscillations during the bursts.

Proposed biophysical process:

SACs are in a regime where they can oscillate spontaneously. As they oscillate, the calcium load increases, so the effect of sAHP increases up to a point that oscillations stop, reaching a steady state where the level of the voltage is quite lower. As a consequence, intracellular calcium concentration unloads, I_{sAHP} decreases, until we reach a state where the effect of sAHP is small and oscillations start again.

Conclusions & Future perspectives

- We proposed a biophysical modelling of the spontaneous intrinsic cell-autonomous rhythmic bursting in Starbust Amacrine Cells during stage II retinal waves, directly extracted from experimental and biophysical data.
- Our model is able to generate spontaneously the observed rhythmic bursting, without the need of any external excitation to trigger the system, as opposed to [3] and [4].
- With our model we are able to explain biophysically and dynamically how the slow oscillations are generated and sustained in developing SACs.
- The next step would be to add the network effect to our modelling through cholinergic synapses, ensuring the necessary level of synchrony between neighbouring SACs to generate propagating waves.

References

1. Zheng J., Lee S., J.Zhou, A transient network of intrinsically bursting starbust cells underlies the generation of retinal waves, Nature Neuroscience, Volume 9, 2006
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3. M.Hennig, C. Adams, D. Willshaw, E.Sernagor, Early-Stage Waves in the Retinal Network Emerge Close to a Critical State Transition between Local and Global Functional Connectivity, JNeuroscience, 2009
4. Lansdell B., Ford K., Kutz N., A Reaction-Diffusion Model of Cholinergic Retinal Waves, PLOS Computational Biology, 2014