Control of Clustered Action Potential Firing in a Mathematical Model of Entorhinal Cortex Stellate Cells

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Introduction

- The entorhinal cortex (EC) is a crucial component in spatial navigation systems and is one of the first areas to be affected in dementias featuring a tau pathology such as Alzheimer's Disease.
- Electrophysiological recordings from principal cells of the EC (layer II stellate cells, SCs) demonstrate subthreshold oscillations in the theta (4-12 Hz) range and clustered action potential firing, in which two or more action potentials are fired in quick succession followed by a quiescent period.
- Experimental models of tau-mediated dementias have revealed changes in clustered action potential firing in the dorsal EC (1).
- Here, we present a model of EC SCs. A numerical bifurcation analysis is performed on the model to understand the dynamic mechanisms underlying clustering in the model and explore causes of changes in dynamics in dementia.

Methods

We present a conductance based model with additive white noise on membrane potential, based on model of (2), given by $C\dot{V} = I_{\text{app}} - \Sigma g_X \psi_X (V - E_X) + \sigma\eta(t)$. Quantification of clustering is shown in Fig 1.

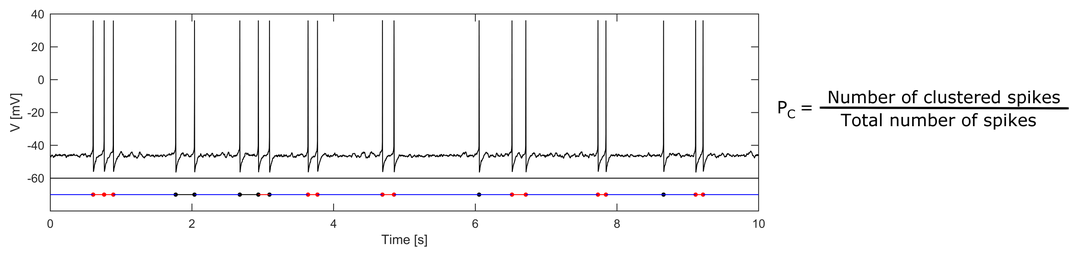

Fig. 1: Calculation of P_C. A cluster of spikes is defined as 2 or more spikes separated by an interspike interval (ISI) < 250 ms and preceeded and followed by an ISI > 300ms. Red dots are clustered, black dots are not. P_C is the fraction of clustered spikes. Here, $P_C = 13/20 = 0.65$.

Regimes of Clustering

The AHP and h currents are believed to be important in clustering, so P_C was calculated over a range of g_{AHP} and g_h. Regimes of realistic SC like clustering exist in the model (e.g. diamond in Fig 2).

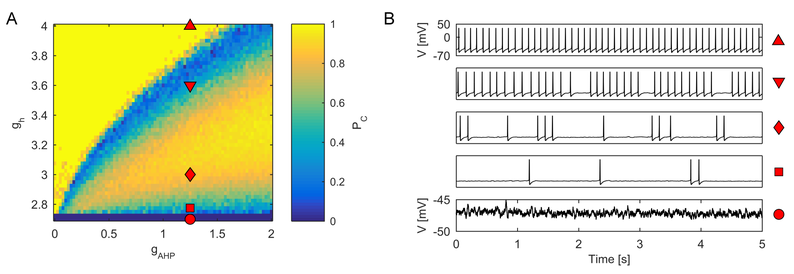

Fig. 2: (A) The value of P_C for different (g_{AHP}, g_h) regimes. (B) Example membrane potential traces at the parameter values indicated by the markers.

Potential Mechanisms in Dementia

Fig 3 demonstrates example paths through parameter space from P_C of the wild type (WT) animals to P_C of the transgenic (TG) animals (1). Experimental data suggests there is no change in g_h and an increase in g_{AHP} in the TG animals (1). Therefore paths e and f are most likely. However, path e exhibits unrealistic SC dynamics. Path f is therefore a potential mechanism by which the changes in clustering seen in dementia may arise.

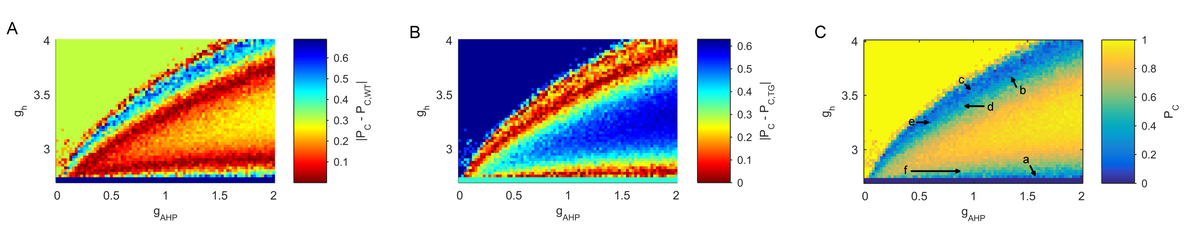

Fig. 3: (A) Magnitude of difference between P_C in model and P_C of WT data. Red means parameter regime is similar to that of WT data. (B) Similar to A, but for TG data. (C) Example paths from WT-like clustering to TG-like clustering.

Clustering arises due to flip bifurcations

Removing the noise term ($\sigma = 0$) from the model results in a system of ODEs on which a bifurcation analysis was performed. Deterministic clustering (periodic bursting) arises from tonic firing via a flip cascade through chaos. Flip bifurcations also take the system between regimes with different numbers of spikes per cluster.

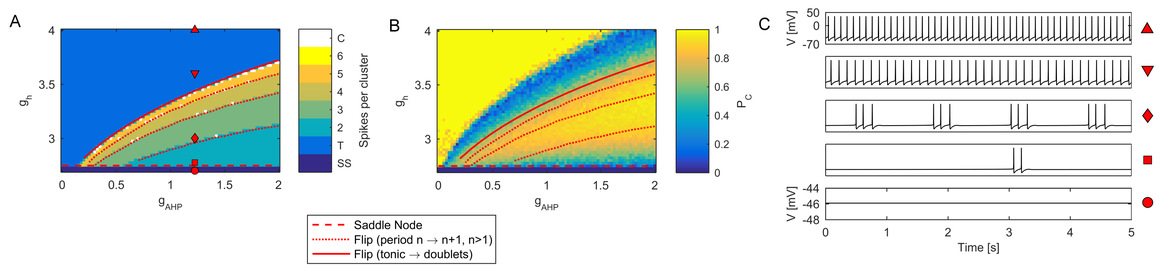

Fig. 4: (A) Heatmap showing different dynamic regimes in the deterministic system. Red lines show bifurcations. (B) Bifurcations in the deterministic system overlaid on the P_C heatmap for the stochastic system. (C) Example determinstic membrane potential traces at the parameter values indicated by the markers.

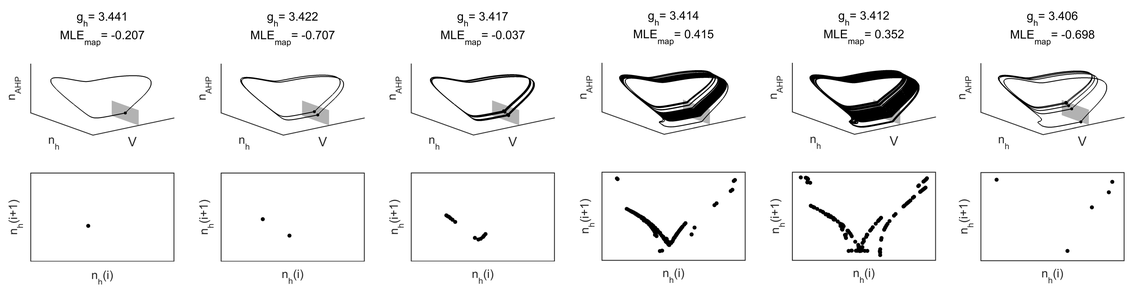

Fig. 5: Transition from tonic firing through chaos into period 5 clustered firing as g_h is decreased. Top row shows flows in the (V, n_h, n_{AHP}) subspace about the Poincaré section $V = 0$. Bottom row shows the Poincaré return map for n_h. Values at the top show g_h and the maximum Lyapunov exponent on the map, MLE$_{\text{map}}$. If MLE$_{\text{map}} > 0$, the system is chaotic.

Fast-slow analysis of clustering

Two slow variables drive bursting - activation of persistent sodium (m_{NaP}) and inactivation of the slow A-type potassium current (h_{Kas}). A two parameter bifurcation analysis of the fast sub-system demonstrated a region of bistability between steady state and tonic firing. In the full system, the evolution of the slow variables moves through this parameter space, driving the fast subsystem through a hysteresis loop and periodically switching between firing and steady state, resulting in bursting.

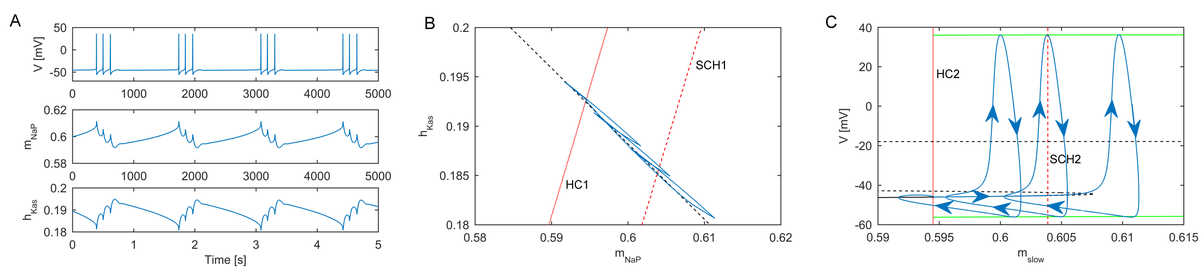

Fig. 6: (A) Deterministic dynamics of membrane potential and slow variables in a bursting regime. (B) Bifurcation analysis of the fast sub-system shows a homoclinic bifurcation (HC1) and a subcritical Hopf bifurcation (SCH1). The flow of the full system (blue) periodically moves across these bifurcations, resulting in periodic bursting. (C) Bifurcation analysis in which the slow subsystem is reduced to a single slow variable via a linear transformation.

Subthreshold Resonance

In a subthreshold regime, the deterministic system is in a focus steady state with theta band resonant frequency. Noisy perturbations to this steady state give rise to a power spectral peak in the theta band consistent with data.

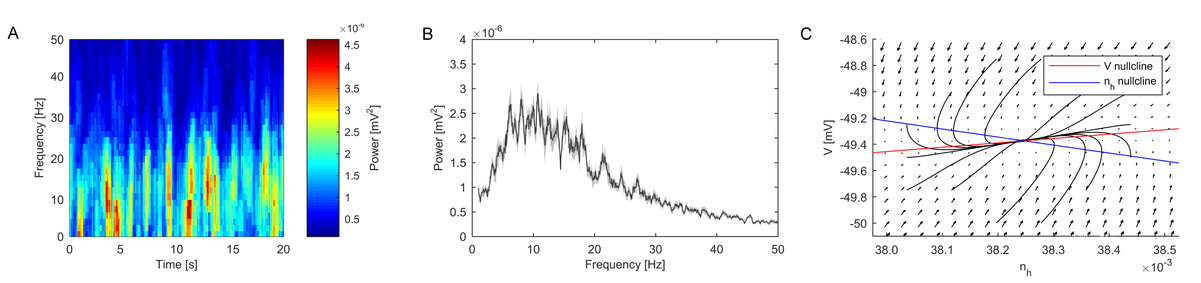

Fig. 7: (A) Spectrogram of example 20 second simulation in a subthreshold regime. (B) Average power spectrum of an ensemble of simulations. (C) The deterministic system is at a focus, meaning flows tend to 'spiral' into the steady state with resonant frequency in the theta band.

References & Acknowledgements

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2. J.T. Dudman and M.F. Nolan. *PLoS Comput Biol* 5(2):e1000290, 2009.

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