An Intracellular Ca^{2+} Subsystem as a Biologically Plausible Source of Intrinsic Bistability in a Network Model of Working Memory.

Christopher P. Fall and John Rinzel
New York University
Center for Neural Science

Abstract:
We explore a network model of working memory in an integrodifferential form similar to those proposed by Amari. The model incorporates an intracellular Ca^{2+} subsystem whose dynamics depend upon the level of the second messenger [IP3]. This Ca^{2+} subsystem endows individual units with intrinsic bistability for a range of [IP3]. This full network sustains [IP3]-dependent persistent ("bump") activity in response to a brief transient stimulus. The dynamics of network activation suggest that the time scales of second messenger activity relative to initiation of persistent firing deserves further exploration.

Summary of poster:

There is great interest in how the brain can maintain the persistent neural activity encoding recent stimuli that is thought to be the basis of working memory [1]. At least three theoretical mechanisms for the maintenance of persistent activity have been described [2], including local recurrent feedback, intrinsic persistent activity on a single-cell basis, and the "synfire chain" construct of Abeles [3]. Of these, recurrent excitation at the local circuit level has received the most attention, from Hopfield models through elaborated conductance unit networks [2, 4].

Wilson and Cowan suggested that meaningful insight into the behavior of neural ensembles might be gained by a mean field approach describing the average rate of firing over some coherent population [5]. Averaging on a local scale in combination with lateral connectivity described by a spatial kernel with wider support lead to a continuum, integrodifferential description of spatiotemporal neural activity [6]. At the same time, there is now renewed interest in the concept that individual neurons might have some inherent ability to sustain persistent activity without recurrence. The remarkable finding that individual cortical neurons can sustain graded persistent activity [7] is the perhaps most striking example to date, and a theoretical analysis suggests that regenerative intracellular Ca^{2+} release might play a role in intrinsic bistability [8]. At the intersection of these ideas is a model by Camperi and Wang which explores the idea of bistability in individual neurons within an Amari-type integrodifferential network model [9]. Camperi and Wang simulated a ring of individual cells, each with intrinsically bistable dynamics, connected by a lateral inhibition weight kernel that spanned the spatial domain.

Here we explore a Camperi-Wang-like model of working memory which incorporates an intracellular Ca^{2+} subsystem for generating slow timescale dynamics [10-12]. We treat the level of the second messenger IP3 as a proxy for the signaling cascade initiated by neuromodulators like dopamine. The Ca^{2+} subsystem is tunable for bistable, excitable and oscillatory dynamics with behavior that is dependent upon the level of [IP3]. The model

is able to sustain persistent ("bump") activity in response to a stimulus, and details of the dynamics of network activation suggest that the time scales of second messenger activity relative to initiation of persistent firing deserves further exploration.

The integrodifferential and kernel structure of the model, and "ring" geometry, is the same as the Camperi-Wang model [9], however the ad-hoc intrinsic bistability in the Camperi-Wang model is replaced by the Ca^{2+} subsystem. In our formulation, intracellular Ca^{2+} can be thought to facilitate postsynaptic neuronal input, which in turn contributes to intracellular [Ca^{2+}] via a plasma membrane Ca^{2+} flux through synaptic channels.

The equation describing the firing activity of each neuron is given by

$$\tau_0 \frac{dr}{dt} = -f(r) + g(I)(1 + \alpha[Ca^{2+}]_C).$$

The excitability of the Ca2+ subsystem shown in Fig. 1 is generated by IP3 modulated Ca^{2+} induced Ca^{2+} release (CICR) from the internal endoplasmic reticulum store with concentration $[Ca^{2+}]_E$. In this first pass model, we specify $[Ca^{2+}]_E$ as constant. The key property is positive feedback of cytosolic Ca^{2+} on to the IP3 sensitive Ca^{2+} channel (known as the IP3 receptor) interacting with SERCA calcium pumps having a nonlinear dependence on intracellular Ca^{2+}. The interplay of Ca^{2+} dependent rates of release and reuptake by these players results in a rich repertoire of dynamical behavior [10].

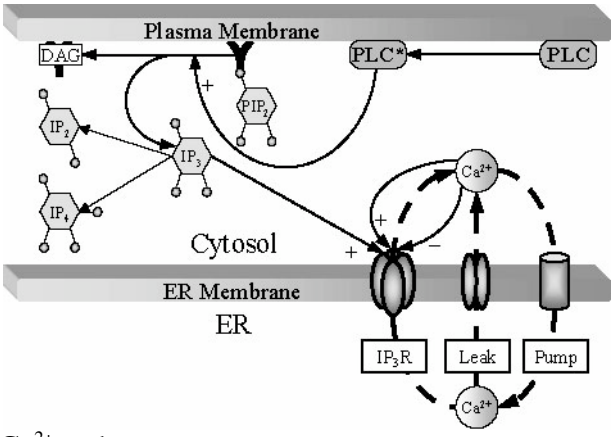


Fig1. Cartoon of the Ca^{2+} subsystem.

The equation describing the evolution of the cytosolic free Ca^{2+} concentration, $[Ca^{2+}]_C$, is

$$\frac{d[Ca^{2+}]_C}{dt} = f_C \cdot (J_{IP3R} - J_{SERCA} + J_{Leak} + \beta \cdot g(I)),$$

where, using the rapid buffer approximation [10], f_C is the fraction of free to total Ca^{2+} in the cytosol and β is a small parameter for the plasma membrane influx of Ca^{2+} from synaptic activity.

The time scale of the Ca^{2+} subsystem is controlled by the slow gating variable *h* that represents inactivation of the IP3-receptor channel by Ca^{2+}:

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau}, \text{ where } h_\infty = \frac{k_{inh}}{k_{inh} + [Ca^{2+}]_C}.$$

Several auxiliary expressions describe the fluxes outlined above as well as a leak term:

$$J_{IP3R} = v_{IP3R} m_\infty^3 h^3 ([Ca^{2+}]_E - [Ca^{2+}]_C)$$

$$m_\infty = \frac{[IP3]}{[IP3] + k_{IP3}} \frac{[Ca^{2+}]_C}{[Ca^{2+}]_C + k_{act}}$$

$$J_{Leak} = v_{Leak} ([Ca^{2+}]_E - [Ca^{2+}]_C)$$

$$J_{SERCA} = v_{SERCA} \frac{[Ca^{2+}]_C^2}{k_{SERCA}^2 + [Ca^{2+}]_C^2}.$$

The key expression in the Camperi-Wang model is the nonlinear function of the firing rate, $f(r) = c + r - ar^2 + br^3$, which in their model is tuned to be cubic in shape and results in intrinsic bistability. In our case the firing function is tuned to be monotonic and *not* intrinsically bistable.

The synaptic input to a neuron consists of recurrent input (given by the convolution over the weights and firing rates of other neuron) plus synaptic input from extrinsic neuronal sources:

$$I(\theta,t) = I^{ext}(\theta,t) + \int_{-\pi}^{\pi} \frac{1}{2\pi} W(\theta - \theta') r(\theta',t) d\theta'.$$

The total synaptic input, I, is thresholded

$$g(I) = I : I > 0$$
$$g(I) = 0 : I \le 0.$$

The weight kernel is given by

$$W(\theta) = -W_I + W_E \left(\frac{1 + Cos(m\theta)}{2} \right)^q.$$

The external input with constant (I_O) and transient (I_{cue}) components, is given by the very similar expression

$$I_{ext}(\theta,t) = I_O + H(t_{off} - t) \cdot I_{cue} \left(\frac{1 + Cos(n\theta)}{2} \right)^p,$$

where H is the Heaviside function and the stimulus is usually presented for 0.5 s. θ is the phase difference between neurons in the weight kernel and in the stimulus shape calculations. The shapes of these curves can be seen in Fig. 3B for standard parameters.

The model demonstrates the ability to sustain bump-like working memory patterns that are dependent on the level of the second messenger IP3. As shown in Fig. 2(A-B), a low level of IP3 results in no sustained firing pattern. If IP3 is elevated Fig2(C-D), such as might be the case due to dopamine receptor activation, the model is able to sustain the bump pattern of activity.

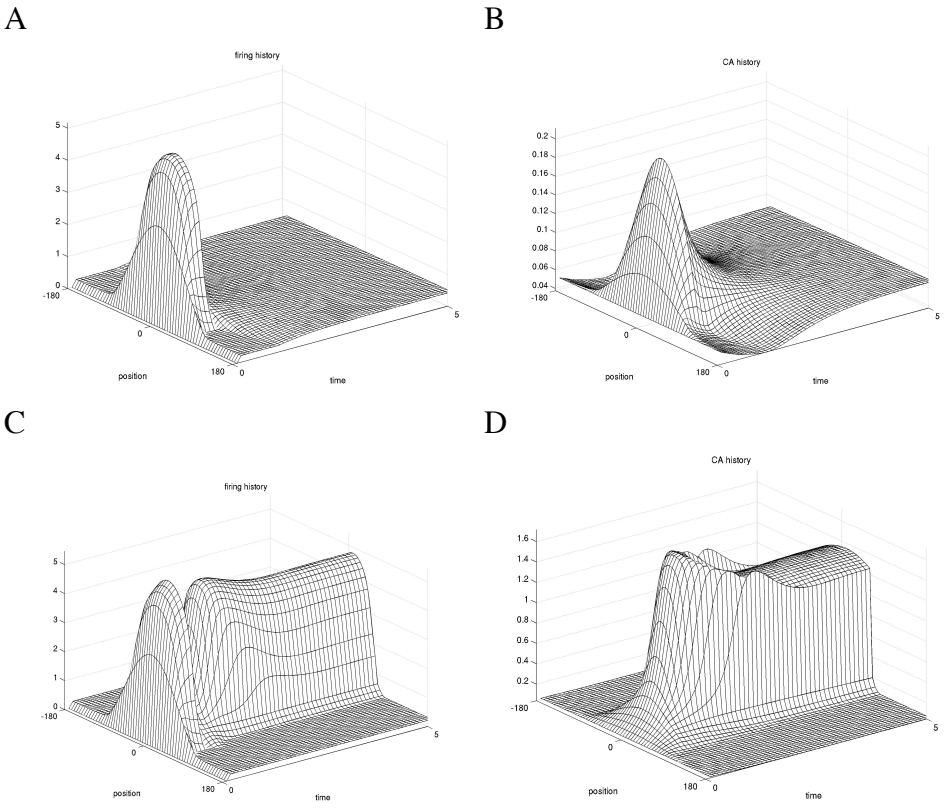
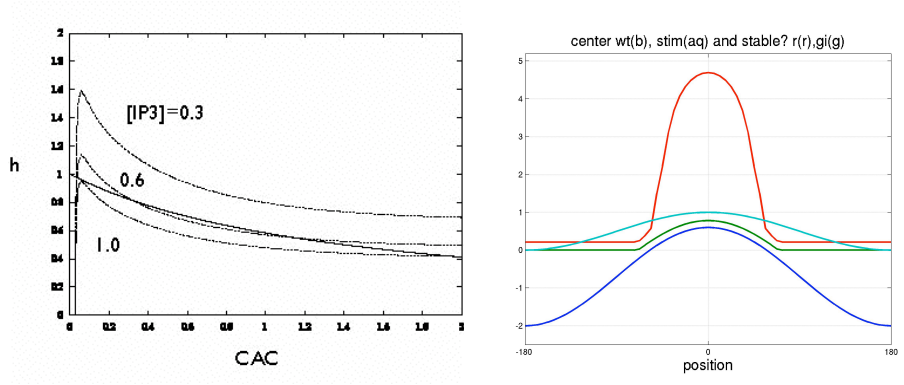


Fig. 2. Firing history and intracellular Ca^{2+} history for low and elevated [IP3]. (A) firing history for [IP3]=0.3uM (no persistent activity). (B) $[Ca^{2+}]_C$ for same condition as (A). (C) firing history for [IP3]=0.6, showing persistent activity. (D) $[Ca^{2+}]_C$ for same condition as (C).

Because we are interested in exploring biologically plausible intrinsic bistability, we have tuned the Ca^{2+} subsystem into a regime of bistability by using the intracellular second messenger IP3 as a control parameter (Fig 3). By increasing [IP3] from 0.3 μM through to 1.0 μM, the system passes from being monostable with a single stable steady state at a lower level of $[Ca^{2+}]$ through a region of bistability and then on to monostability with one stable elevated state.



A B

Fig 3. (A) $[Ca^{2+}]_C$ (dotted) and *h* (solid) nullclines for [IP3]=0.3 μM, 0.6 μM and 1.0 μM. (B) Overlaid plots showing connection weight value (blue) as a function of distance from any given neuron, cue stimulus (aqua) imposed for 0.5s at t=0.5s, the firing rate (red) as a function of space at t=5s, and the value of the thresholded input convolution gi (green), also at t=5s. Firing rate and convolution are shown for [IP3]=0.6, which sustains a bump pattern, however the stimulus shape and weight kernel are the same for both simulations.

The present work demonstrates that a biologically plausible source of intrinsic bistability can lead to persistent bump activity in a simple model of working memory. It is not clear yet how the initiation and maintenance of persistent activity in this paradigm might depend on the relative timescales of the Ca^{2+} subsystem and neuronal integration. Moreover, it will be interesting to see how the integrodifferential model responds to other dynamical regimes possible with this Ca^{2+} subsystem, such as excitability and oscillations. The biphasic bump initiation shown in Fig. 2 suggests that this topic deserves more exploration, and this is work in progress.

1. Fuster, J.M., *The prefrontal cortex*. 1988, New York: Raven Press.
2. Durstewitz, D., J.K. Seamans, and T.J. Sejnowski, *Neurocomputational models of working memory*. Nat Neurosci, 2000. **3 Suppl**: p. 1184-91.
3. Abeles, M., *Corticonics: neural circuits of the cerebral cortex*. 1991, New York: Cambridge University Press.
4. Wang, X.J., *Synaptic reverberation underlying mnemonic persistent activity*. Trends Neurosci, 2001. **24**(8): p. 455-63.
5. Wilson, H.R. and J.D. Cowan, *Excitatory and inhibitory interactions in localized populations of model neurons*. Biophys J, 1972. **12**(1): p. 1-24.
6. Wilson, H.R. and J.D. Cowan, *A mathematical theory of the functional dynamics of cortical and thalamic nervous tissue*. Kybernetik, 1973. **13**(2): p. 55-80.
7. Egorov, A.V., et al., *Graded persistent activity in entorhinal cortex neurons*. Nature, 2002. **420**(6912): p. 173-8.
8. Loewenstein, Y. and H. Sompolinsky, *Temporal integration by calcium dynamics in a model neuron*. Nat Neurosci, 2003. **6**(9): p. 961-7.

9. Camperi, M. and X.J. Wang, *A model of visuospatial working memory in prefrontal cortex: recurrent network and cellular bistability*. J Comput Neurosci, 1998. **5**(4): p. 383-405.
10. De Young, G.W. and J. Keizer, *A single-pool inositol 1,4,5-trisphosphate-receptor-based model for agonist-stimulated oscillations in Ca2+ concentration*. Proc Natl Acad Sci U S A, 1992. **89**(20): p. 9895-9.
11. Atri, A., et al., *A single-pool model for intracellular calcium oscillations and waves in the Xenopus laevis oocyte*. Biophysical Journal, 1993. **65**(4): p. 1727-39.
12. Li, Y.X. and J. Rinzel, *Equations for InsP3 receptor-mediated [Ca2+]i oscillations derived from a detailed kinetic model: a Hodgkin-Huxley like formalism*. Journal of Theoretical Biology, 1994. **166**(4): p. 461-73.