Calcium regulation of HCN supports persistent activity associated with working memory: a multiscale model of prefrontal cortex

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Introduction

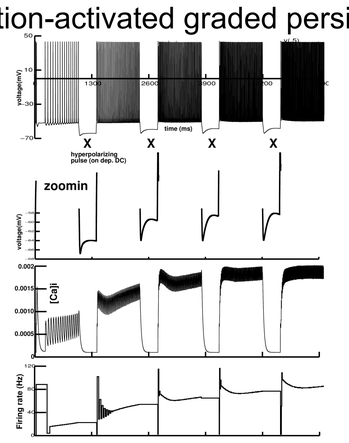
"Bump attractors" are hypothesized to enable short-term memory via persistent activation in prefrontal cortex (PFC). They have been primarily assessed in terms of electrical mechanisms, without attention to molecular events [1]. To assess this contribution, we developed a multiscale model going from molecular to network levels, assessing contribution of calcium (Ca) release from endoplasmic reticulum (ER) to Ca regulation of hyperpolarization-activated cyclic-nucleotide gated channels (HCN) thought to provide continued activity via rebound.

Methods

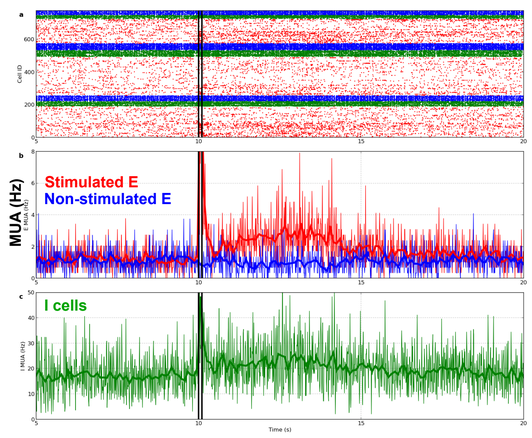
The network had 776 neurons arranged in 6 cortical layers. Layers consisted of populations of 5-compartment pyramidal neurons (E2: layer 2/3 pyramidals) and two populations of interneurons (basket: I2 and low-threshold spiking: IL2). Neurons contained Na, K, Ca, and HCN channels. Cells connected with AMPA/NMDA/GABAA synapses using data from primary motor cortex (M1). Metabotropic glutamate receptors (mGLUR) produced inositol triphosphate (IP_3). Intracellular components included: Ca, Ca buffers, ER Ca stores, IP_3, ER IP_3 receptors (IP_3Rs; release ER Ca), sarco/ER Ca-ATP-ase pumps (SERCA; pump Ca into ER), Ca extrusion pumps, and E cell HCN regulated by Ca-bound protein kinase [2].

Results

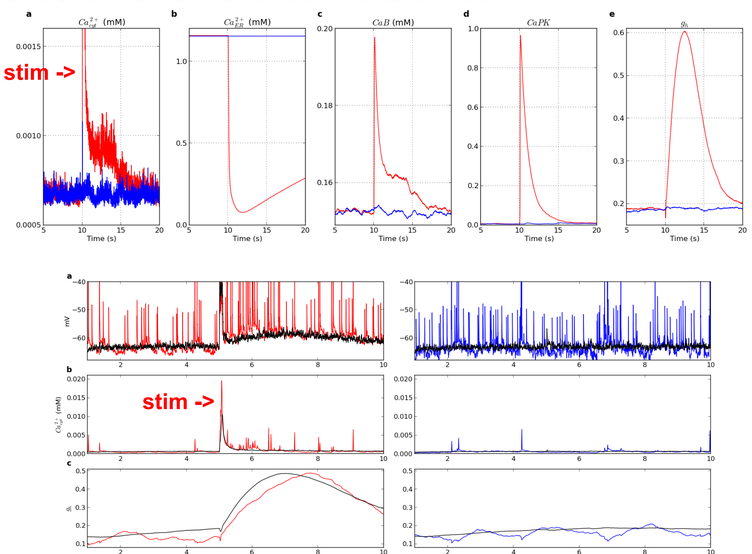
PFC pyramidal cells with calcium-regulated HCN display hyperpolarization-activated graded persistent activity [2,3].



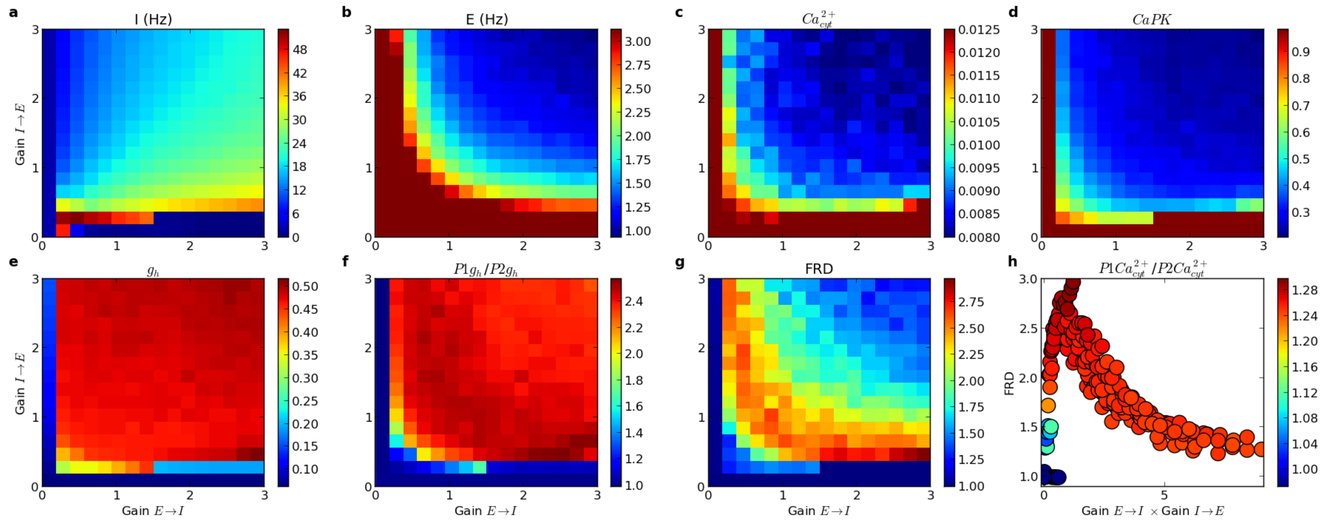
Network displays persistent activity after AMPA/NMDA/mGLUR stimulus



Intracellular calcium dynamics enable persistent activity. Stimulus-induced depolarization led to Ca influx via NMDA/L-type channels. After a delay, mGLUR activation led to ER Ca release via IP_3Rs. These factors increased HCN conductance and firing (0.5-3.5 Hz), lasting 5-10 s. Non-stimulated cells were suppressed from more inhibition via extra drive from activated E to I cells.

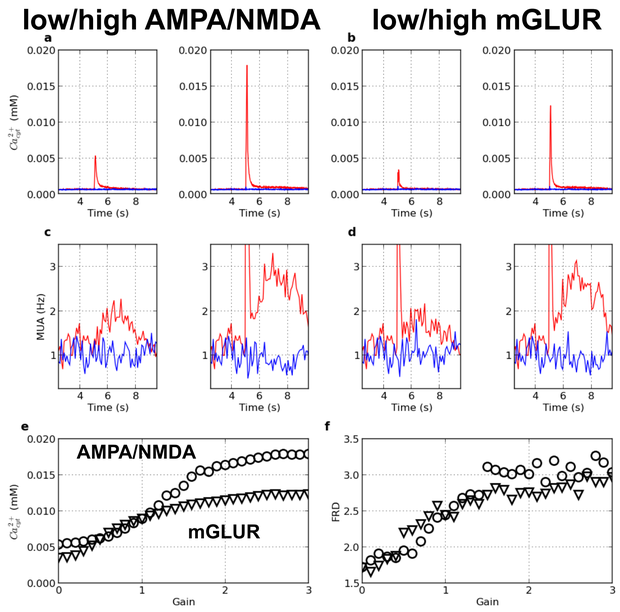


Excitation/inhibition balance regulates persistent activity & stimulus-representation (firing rate distinction; FRD). The model shows complex interplay among synaptic weights, excitation/inhibition network balance, altered firing rates and depolarization, changes in calcium levels, altered regulation of HCN, and FRD.

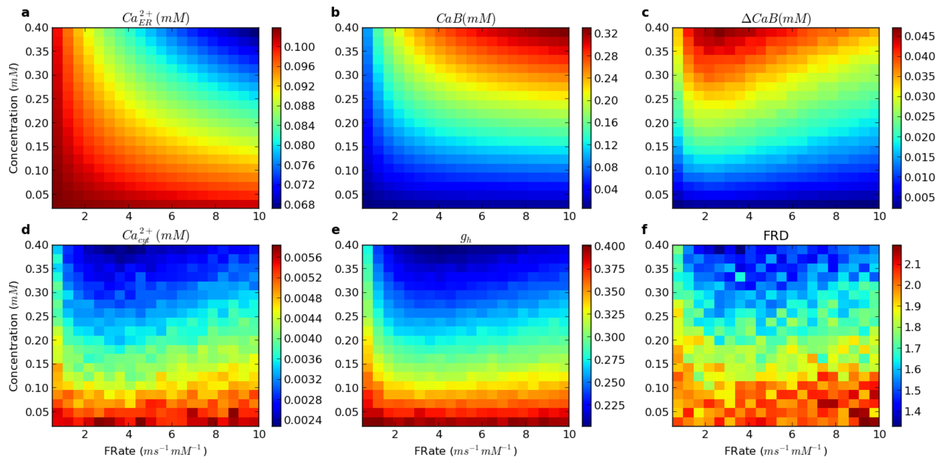


Multiple pathways to induction of persistent activity

low/high AMPA/NMDA low/high mGLUR

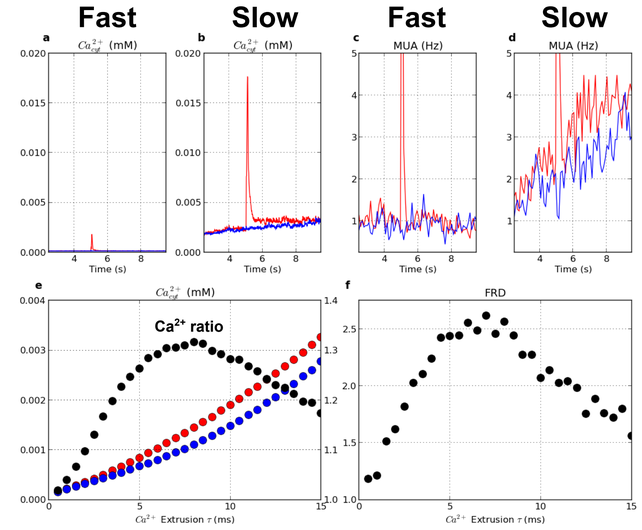


Calcium buffering efficacy regulates persistent activity. Increasing concentration or binding rate of Ca buffers reduces free Ca and its regulation of HCN, thereby reducing FRD.



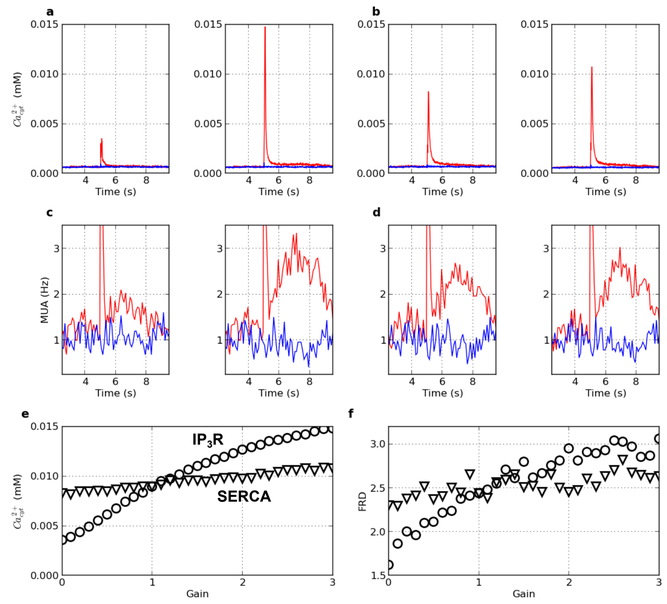
Calcium extrusion pump efficacy regulates FRD

Slow pump causes Ca to saturate all neurons; fast pump prevents Ca from having time to regulate neurons.



Factors regulating ER calcium liberation regulate persistent activity. Both IP_3R and SERCA density correlated positively with FRD, since both allow mGLUR stimulation to retrieve more ER Ca.

low/high IP_3R low/high SERCA



Conclusions:

1) We developed a multiscale model of PFC with scales ranging from the molecular to the neuronal network that exhibits persistent activity, which is hypothesized to enable working memory.

2) In contrast to prior models which depend on reverberant excitatory activity to trigger persistent activity, our model depends on a *preparatory* calcium signal, with inhibition *triggering* the induction of persistent activity.

3) The existence of multiple pathways for the induction of persistent activity (AMPA/NMDA and mGLUR) is a critical feature of biological systems, which are remarkably resistant to disruption. Several electrochemical interactions could lead to the persistent activity associated with working memory.

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References:

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[2] Hyperpolarization-activated graded persistent activity in the prefrontal cortex. Winograd et. al, PNAS 2008.

[3] Predictive Features of Persistent Activity Emergence in Regular Spiking and Intrinsic Bursting Model Neurons. Sidiropoulou & Poirazi, PLOS Computational Biology 2012.