On Duration and Dopamine Modulation of Sustained Activity in Prefrontal Cortex Using Large, Conductance-Based Networks Models.

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Memory processes have wildly varying time scales, ranging from a few seconds to a lifetime. Thus, different memory mechanisms must exist. For example, long-term memory requires no willful participation and is normally associated with the modification of certain relevant physiological parameters, such as synaptic connections. Memories stored in this fashion can last for years.

On the other hand, working memory (a crucial cognitive function involved in organizing behavior, language, and thinking) is maintained by enhanced neuronal activity throughout its time span, typically of a few seconds. This enhanced activity is often known as "delay-period activity", and there is ample evidence that animals display memory-guided behavioral responses following it [1-8]. Sustained, memory-related activity is observed in many brain areas, such as parietal cortex, hippocampus, inferotemporal cortex and motor areas [3,9]. However, there is overwhelming evidence locating it predominantly in the dorsolateral prefrontal cortex (PFC), where it has been shown to be more robust and to persists even in the presence of interfering stimuli [3]. Moreover, some PFC neurons have been shown to fire maximally in tune with, for example, particular spatial memory cue locations ("memory fields" [4-7]).

It is also known that working memory processes are sensitive to dopaminergic neuromodulation [6-10]. Moreover, dopamine (DA) may also stabilize neural functions in PFC, increasing the robustness of sustained delay activity with respect to distracting input and noise [9].

In this work, we present a conductance-based network model exhibiting delayed-period sustained activity in the form of network bistability brought forth by graded recurrent excitation and inhibition. The conductances used are representative of those found in the relevant areas in the PFC. We focus on the relative importance of AMPA- and NMDA-like synapses in maintaining sustained activity (far from settled experimentally) and on possible mechanisms that may naturally limit the duration of such persistent activity. Moreover, we study dopaminergic neuromodulation by simulating natural and forced changes in local DA levels via the introductio of static and dynamically modulated changes in maximal conductances, thresholds, and synaptic strengths.

Recent theoretical works investigate network persistent activity [9-13]. The present work differs in various ways. For example, our model incorporates all relevant PFC conductances, and it addresses the effects of DA in originating, maintaining, modulating, and terminating delayed-period activity. Another important difference is that our simulations are carried on very large networks, using the parallel package NEUROSYS [14].

We consider a two-population, all-to-all network with AMPA-, NMDA-, and GABA-like synapses. Excitatory-excitatory synapses are recurrent and graded according to memory-field relative distances, while all others are uniform. Simulations range from N=100 to N=25,000, and we study the possible existence of a preferential excitatory-inhibitory cell ratio (which we find not to be the case provided that both are of the same order of magnitude).

As in other models, spatially localized transient inputs bring the network to an excited state, whereby synaptic recurrent excitation sustains the network activity after the input has been turned off. Moreover, due to the structured character of the recurrent excitation and to global inhibition, only a restricted number of cells with memory fields in the neighborhood of the input cue location remain active, thus providing a dynamical mechanism for memory keeping.

We address the issue of AMPA/NMDA relative dominance in maintaining sustained activity. We find that both are necessary, but the model produces more stable results when NMDA is highly dominant, although AMPA still needs to be present, albeit in small amounts.

Local or global abrupt parameter changes simulate direct changes in DA levels and iontophoresis of DA receptor [6-8]. The model exhibits selective potentiation or depression of memory fields [6]. We also demonstrate the existence of an optimal dopamine level for working memory processes -- levels above or below an optimal range impair performance [7].

A cascade effect, involving different inhibition and excitation mechanisms, is believed to be responsible for the timing of working-memory delay-period activity, which typically lasts a few seconds. However, it is not clear what the mechanisms could be or what the relative importance of the different inhibitory and excitatory components is. To study this, we consider a dynamical equation for DA concentration that depends on external sources and on internal afferent factors, as well as on local cortical activity. Maximal conductances, synaptic strengths, and thresholds are then modulated dynamically by this varying DA level, thus creating a dynamical loop which we use to study duration and stability of sustained activity. This is of course supplemented with a reasonable dose of white noise and external poisson processes. We find that this dynamical interplay of biophysical and random factors provides a convincing mechanism with realistic outcomes in terms of effect robustness and duration. Indeed, accepted experimental ranges for delay-period effects [4,5] enables us to gain insight on the inhibition-to-excitation "responsibility" ratio in the cascade process.

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