Interval time representation through a self-organizing single cell neural integrator

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Behavioral and electrophysiological evidence indicates that animals actively anticipate forthcoming events following the observation of predictive cues (in contrast to the classical bottom-up S-R behavioristic view). In particular in prefrontal cortex, neural activity is often specifically correlated with an anticipated event rather than with preceding or current situational cues (Quintana & Fuster, 1999; Rainer et al., 1999). This anticipatory activity often takes a particular form: If a predictive cue and a subsequent choice situation are separated by a delay, as in a working memory task, anticipatory activity slowly climbs throughout the delay period (termed 'climbing activity') towards a maximum reached with target presentation.

In addition to being able to predict forthcoming events, animals can also predict quite accurately the time of occurrence of an anticipated events following a predictive stimulus, i.e. the temporal interval between a predictive stimulus and a predicted event. Climbing activity as recorded in various brain regions, besides being correlated with anticipated events, has a number of properties which make it a likely candidate for representing interval time: 1) Climbing activity might span widely different delay time intervals from hundreds of milliseconds to tens of seconds, 2) it is often surprisingly linear, and 3) its temporal slope adjusts within a few trials to the current temporal interval, as observed recently by Komura et al. (2001).

Here I suggest a computational model of how climbing, temporal integrator-like activity might be generated at the single neuron level, how it might adjust to different time intervals, and how single neurons might self-organize into a biophysical configuration that allows them to work as timers. Single cells were modeled as spiking leaky-integrate-&-fire (LIF) neurons equipped with additional (conductance-based) mechanisms for spiking-driven Ca^{2+} influx and Ca^{2+}-gated after-depolarizing (inward) currents (I_{ADP}). Ca^{2+}-gated inward currents can maintain spiking in isolated neocortical pyramidal cells in vitro for minutes (Haj-Dahmane & Andrade, 1998; Egorov et al. 2002). Although climbing activity is a single neuron property in the present model, a model cell also received both recurrent (phase-locked; e.g. Pesaran et al., 2002) and uncorrelated (Poisson-like) background synaptic input through AMPA-, NMDA-, and $GABA_A$-like channels to simulate the kind of input a climbing neuron might receive from the cortical network environment within which it is embedded.

It is shown that climbing activity with time courses much slower than the intrinsic time constants of the system (up to at least two orders of magnitude) can be generated through fine adjustment of a positive feedback loop between spiking-driven Ca^{2+} influx and the Ca^{2+} activated cation current I_{ADP}. In particular, climbing activity with arbitrary but constant slopes can be produced through a near-bifurcation dynamics, starting from a line attractor configuration where for a range of firing rates the amount of ADP conductance generated at each rate matches the amount required to maintain each of these rates. (Line attractor configurations were first found by optimization methods.) At the line attractor configuration, each firing rate is a stable fixed point of the single neuron dynamics. Recent experimental evidence in-vitro suggests that single pyramidal cells (isolated from network input) under cholinergic modulation in fact exhibit firing rate multistability as indicative of a line attractor configuration, based on the cellular mechanisms proposed here (Egorov et al. 2002). If the system is slightly dislocated from its line attractor configuration, a brief stimulus causes activity to slowly climb from ~30Hz to ~80Hz with a time course mainly determined by the distance (in parameter space) to the bifurcation point (or, more accurately, 'multifurcation line'), rather than by the intrinsic time constants of the system. The distance to the bifurcation point can be varied by adjusting the strength of recurrent or feedforward synaptic weights, a mechanism that retains the linearity of climbing activity. The weight adjustment that adapts the slope of climbing activity to the required temporal interval could be driven by a temporal-difference-error signal, based on the difference between the predicted time of occurrence (as signaled by the climbing neurons) and the actual time of occurrence.

It is furthermore shown that noise-induced variance in the firing rate output and in intracellular Ca^{2+} levels monotonically reaches a maximum as the cell's biophysical parameters approach a line attractor configuration. Intracellular Ca^{2+} fluctuations can therefore be exploited as an intracellularly accessible learning signal to guide the cell's ADP conductance parameters towards a regime where the cell can work as a temporal integrator. This is demonstrated by a simple gradient ascent (‘hill-climbing’) procedure.

Thus, the present study shows how arbitrarily slowly climbing activity, coding for different interval times, might be generated through a single cell feedback loop, and how single neurons might self-organize into a biophysical configuration required for temporal integration. The model makes specific predictions that could be tested in in-vitro and in-vivo experiments. For example, pharmacologically enhancing or diminishing I_{ADP} in vivo should lead animals to systematically under- or overestimate the time interval between a predictive stimulus and predicted event while disrupting the time course of climbing activity.

Note: Since a full length version of this work has already been submitted for journal publication, the 1000-word summary format was chosen although an oral presentation would be preferred.

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