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#### Research Focus Response

## Response to Melamed *et al.*: Coding and learning of behavioral sequences – open questions and potential solutions

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What are the neuronal mechanisms involved in learning behavioral sequences? This is a difficult and important question. Several recent studies have uncovered unforeseen problems involved in solving this question, and have offered novel solutions. In our recent work we focused on one of the problems involved – namely, the importance of replaying behavioral sequences at the relatively fast time scales of synaptic plasticity [1]. Neurons that encode events within a behavioral sequence, such as walking from place A to place B, are typically active over periods of a second or longer. However, to learn the behavioral sequence rapidly via NMDA-dependent synaptic plasticity these neurons should be activated in the same temporal order within ~10 ms. We presented a computational mechanism that could accomplish this task, made several predictions using this mechanism, and verified these predictions experimentally using data from hippocampal place cells [1]. In an accompanying article, Melamed *et al.* have raised several interesting open questions raised by our work [2]. Here, we point to potential solutions for three of these questions.

(i) ‘Combining a symmetrical receptive field with an oscillatory inhibition would lead to a phase precession and

then a recession, the result being that the spiking at a particular phase could not reliably represent the location’.

This would indeed be a problem if the position were encoded by the phase of a single symmetric place field. However, this is clearly not the case because a large number of hippocampal neurons are active at any given location. The position can be unambiguously encoded by the phases of symmetric receptive fields across a population of neurons with overlapping place fields. Indeed, several cortical receptive fields have a bell-shaped or symmetrical firing-rate profile as a function of certain physical variable. Whereas the firing rate of an individual cell provides ambiguous information about the physical variable, a population code consisting of firing rates of a large number of neurons with overlapping symmetric receptive fields is known to provide unambiguous information. Ditto for the temporal code. Of course, asymmetric firing rate and asymmetric temporal codes would remove the ambiguity in encoding a physical variable at a single-cell level using a rate or a temporal code, respectively.

(ii) ‘The problem is that, although Mehta and colleagues report a resetting of the symmetry, phase precession is always seen in previous reports’.

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Ours is the only study that has measured the correlation between phase and position as a function of experience in a behavioral sequence task such as running between two reward locations. In particular, the studies cited by Melamed *et al.* [3–5] have not made such measurements.

(ii) ‘...is the sequence learned before or after the asymmetry of the place field evolves?’

The two processes, asymmetric Hebbian synaptic plasticity and the hippocampal precise spike timing or temporal code, are mutually complementary. The receptive fields become asymmetric owing to Hebbian learning. When this asymmetry is coupled with a rhythmic input, it generates precise spike timing, which in turn produces more Hebbian learning and hence more asymmetric receptive fields. Thus, all that is required is an initial ‘small seed of asymmetry’ in the receptive field [6]. Such a seed of asymmetry could arise owing to a variety of mechanisms, including random fluctuations in the shape of the initial distribution of inputs, history-dependent processes such as recurrent inhibition, and short-term cellular or synaptic dynamics. Further, recent reports show that spike-timing-dependent plasticity (STDP) is history-dependent, too. In particular, if the presynaptic and postsynaptic neurons fire a burst of spikes, the amount of long-term potentiation and long-term depotentiation generated is governed largely by the relative timings of the first spike in the burst, and less by the relative timing of the subsequent spikes in the burst [7].

The initial seed of asymmetry could thus generate more precise spike timing, and hence rapid, flexible and more permanent learning of behavioral sequences [6,8]. Such a mechanism also makes behavioral sense: when an organism learns a new sequence, such as how to go from A to B, in the beginning there should be no preference for the sequence A to B over the sequence B to A. The neural circuits that by chance prefer A to B could be selectively strengthened by asymmetric experience, rhythmic inhibition and STDP to encode the behavioral sequence more permanently.

Consistent with our work, asymmetric and inseparable spatio-temporal receptive fields, similar to the hippocampal spatio-temporal receptive fields [1,6,8], have been found in direction-selective cells from various cortical regions such as

the cat striate cortex [9], *Xenopus* optic tectum [10] and mouse auditory cortex [11]. These asymmetric receptive fields probably developed with experience from primarily symmetric receptive fields, perhaps by similar mechanisms of asymmetric experience and Hebbian synaptic plasticity, because the removal of sequential experience abolishes the receptive field asymmetry as well as the direction selectivity of these neurons [12].

Future work in diverse areas of neuroscience, ranging from cellular to systems and computational neuroscience, would undoubtedly pose exciting new challenges that could bring us closer to understanding mechanisms governing the form and function of the neural code.

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## Letter

# Spines and dendrites cannot be assumed to distribute dye evenly

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In recent years, the increase in optical resolution offered by confocal and two-photon microscopy has allowed studies of the physiology of individual dendritic spines. To quantify or compare such variables as  $\text{Ca}^{2+}$  entry

into different spines, it is necessary to measure spine volume (e.g. see Refs [1,2]). Moreover, measurement of spine dimensions (e.g. see Refs [3,4]) and changes in such dimensions over time (e.g. see Ref. [5]) have also often depended on these light microscopy techniques. These are not trivial measurements, because the limit

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