

# Brain calculus: neural integration and persistent activity

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Tank and colleagues make *in vivo* intracellular recordings from neurons in a 'neural integrator' of the goldfish involved in maintaining eye position. In this circuit, 'working' memory may be the result of persistent changes in the state of the local network.

The brain must keep track of a large number of variables, both external and internal, in the normal, everyday guidance of behavior. Short-lived events, such as a traffic light turning green, may catch our attention and induce a memory of that occurrence and a change in our behavior. Likewise, each movement that we make, such as a change in the pressure applied to the gas pedal, changes our physical relationship to the world, and therefore must be registered (remembered) for the next movement to be accurately performed (if disaster is to be consistently avoided).

How does the brain perform this running tabulation, loosely referred to as 'working' memory? Numerous neurophysiological experiments, at levels of the nervous system from the brainstem to the neocortex, have demonstrated that persistent neuronal activity is correlated with, and presumably required for, maintaining such internal representations. The most widely accepted theory for the cellular mechanisms underlying this activity is that it results from sustained synaptic excitation generated by reverberatory interactions among an assembly of neurons. Although Rafael Lorente de Nó<sup>1</sup> and Donald Hebb<sup>2</sup> are often credited with this notion, the theory that memory occurs through persistent brain activity was proposed in the early 1700s by David Hartley (as vibrations), and later championed by Alexander Bain in the 1800s (who, incidentally, also stated the 'Hebb' hypothesis for synaptic plasticity decades before Hebb was born<sup>3</sup>). After such a long history of theory, the experimental test of this hypothesis has finally come of age in research<sup>4</sup> described on page 184.

As we visually examine an object, we

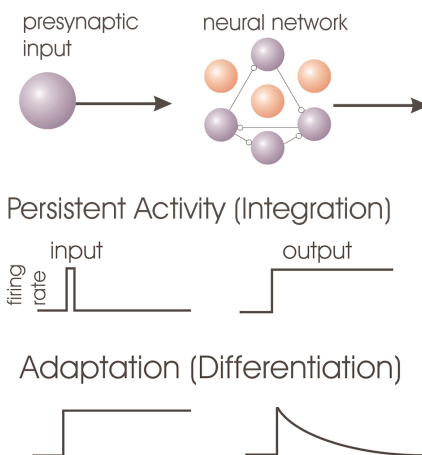
fixate on first one feature and then the next, with a rapid eye movement (a saccade) in between. Each fixation point requires continuous contraction of the eye muscles, without which the eyes would drift back to central gaze after each movement. This muscular exertion requires, in turn, persistent activity in some of the brainstem nuclei controlling eye movements—all in response to a very brief (tens of milliseconds) burst of action potentials generating the saccade to a new fixation point.

In a technical *tour de force*, Aksay and colleagues have examined the cellular mechanisms for the generation of this persistent activity in goldfish during periods of spontaneous visual fixation interleaved with horizontal saccades<sup>4</sup>. Goldfish continuously scan their visual world through a series of horizontal saccades, with each fixation point being maintained by the persistent activity of neurons in a brainstem region known as 'area I.' The inactivation of area I, for example, results in an inability to maintain a fixation point and, therefore, a slow slip back toward central gaze after each eye movement<sup>5</sup>. Neurons in area I, of which there are only approximately 30–50, are activated by a

brief burst of action potentials from premotor command neurons that generate the saccade. Through the mathematical equivalent of integration of this input (the integral of a brief input is a sustained output), area I neurons are able to respond with a persistent increase in activity that very slowly degrades, over tens of seconds, a time period that is insignificant in normal vision (Fig. 1).

How then do area I neurons generate a persistent change in activity in response to a brief input? Several possible mechanisms can be imagined for a persistent increase in activity, including the activation of prolonged depolarizing currents (or the turning off of hyperpolarizing currents) in single neurons, an increase in the rate of release of neurotransmitter at excitatory synapses (facilitation), the activation of re-entrant excitation among a network of neurons, or some combination of all three<sup>6,7</sup>.

By recording intracellularly from area I neurons in the awake, behaving goldfish during the generation of spontaneous eye movements, Aksay and colleagues obtained data that help to distinguish between these mechanisms. The maintenance of eye position was associated with step changes in membrane potential that were insensitive to move-



**Fig. 1.** Generation of persistent activity through neuronal integration and transient activity through adaptation. Through re-entrant excitation, a network of neurons may generate persistent activity in response to an input of short duration, in a manner similar to 'integration.' Alternatively, through adaptation, mediated by the activation of hyperpolarizing currents or synaptic depression, the network may respond only to changes in the input, similar to 'differentiation.'

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ment of the membrane potential or changes in firing rate induced with the intracellular injection of current. This supports the network hypothesis, because if the step changes were generated through mechanisms intrinsic to the cell recorded, such as through the activation of a persistent depolarizing current, then hyperpolarization (or depolarization) of the cell with current injection should have affected these persistent changes. In addition, by determining (through the intracellular injection of current) how much the firing rate should change with a given change in membrane potential, the authors were able to demonstrate that the step changes in membrane potential during normal eye movements were of sufficient amplitude to explain the associated changes in firing rate. Although these findings do not rule out an important contribution of intrinsic membrane properties or synaptic plasticity, especially among neurons presynaptic to those recorded, they do support a role for recurrent excitation in generating persistent neuronal activity. Thus, the position of each eye fixation may be encoded as a specific pattern of activity in area I neurons, with each pattern being, at least in part, stably maintained through a balance of recurrent interactions. The arrival of a burst of action potentials corresponding to the command to generate a saccade to a new fixation point results in a persistent and stable shift in the pattern of activity in area I, and this, in turn, helps to maintain the new eye position.

The biophysical constraints placed on such a neural network have been explored in a computational model of persistent activity in the eye position neural integrator<sup>8</sup>. Creating a model network that could generate a continuum of stable discharge rates required the careful tuning of synaptic connections owing to the long time constant of the network (the eyes lose positional information only over tens of seconds in the dark) in comparison to the time constant of membrane properties of each of the constituent neurons (milliseconds). Prolonging the cellular time constant to approximately 100 ms by having the excitatory synapses be dominated by NMDA receptors increased the robustness of the network considerably, suggesting that this subtype of glutamate receptor may have a key role in the generation of persistent activity in neural assemblies. Similarly, a model of working memory-related activity in the prefrontal cortex also emphasized the importance of NMDA receptors for the

occurrence of persistent patterns of neuronal discharge<sup>9</sup>. The NMDA receptor has long been considered a key player in both short- and long-term memory, and these studies extend its possible role in these processes.

These results have broad implications for understanding the general operation of neural networks, because the activation of persistent neuronal discharge in response to brief stimuli is prevalent throughout the nervous system. Prominent examples are the generation of persistent activity in cells that signal the direction in which the head is pointing (head direction cells), as well as the generation of activity signaling the position of the animal in the environment (place cells), both of which occur in the rodent limbic system<sup>10</sup>. Perhaps the best-known example of persistent activity in the nervous system is the one that occurs in the prefrontal cortex during the performance of tasks that require information to be stored for brief periods (seconds). Extracellular recordings of a select subgroup of neurons in the prefrontal cortex reveal persistent increases in activity following the presentation of a stimulus to be remembered and before the performance of the appropriate motoric response<sup>11</sup>. Unlike area I neurons in the goldfish, the persistent activity in the primate prefrontal cortex can encode an upcoming movement long before it is performed. Again, the leading hypothesis for the cellular mechanisms of this activity is through re-entrant excitation within the cortical network<sup>9</sup>. Anatomically, cortical networks are replete with recurrent excitatory interconnections, and recent investigations have demonstrated the ability of local cortical cell assemblies to autonomously generate periods of sustained activity with relatively low rates of action potential discharge. Through a delicate balancing act with local inhibitory neurons and intrinsic membrane conductances, these local cortical networks are able to generate relatively stable patterns of activity for brief periods of time (seconds)<sup>12,13</sup>.

What about the opposite—generating a brief change in activity in response to a constant input, or neuronal ‘differentiation’? This is actually a common pattern of neuronal response in the nervous system and is represented by the process known as adaptation (Fig. 1). Adaptation allows for reduced responses to slowly changing or static stimuli and consequently emphasizes features or stimuli that are new or that change more rapidly.

Again, multiple cellular mechanisms are possible in this neuronal differentiation, including the activation of outward currents in response to neuronal activity, depression of excitatory synaptic transmission, and decreases in persistent network interactions. In contrast to integration, where the activation of persistent activity in neuronal networks seems to be the most common mechanism, neuronal adaptation typically results from either intrinsic membrane properties<sup>14</sup> or synaptic depression<sup>15</sup>.

Through the activation of persistent activity in both local and long-range neural networks, the brain is able to build a representation of the external environment, a ‘world view’ if you will, that is critical to the performance of goal-directed behaviors. Future challenges include detailing the mechanisms for robustness against distractors, membership of single neurons in multiple simultaneously active assemblies, the interaction of short- and long-term memory, and the reactivation of assemblies based on memory alone. Through an investigation of relatively simple networks, such as those generating sustained eye position in the brainstem, we are beginning to achieve a cellular understanding of these complex issues.

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