Title: Generalization of memories by spatial patterning of protein synthesis

Authors: Cian O'Donnell & Terrence J Sejnowski (Salk Institute for Biological Studies)

Summary

Despite the decades-old knowledge that the consolidation of both memories and synaptic plasticity requires the synthesis of new proteins, the computational benefit of this cellular process for learning remains unknown. Interestingly, protein expression during synaptic plasticity has been found to be spatially restricted to the activated neurons, and even to specific activated dendrites within those neurons. Using computational modeling we found that this spatial patterning of protein synthesis at both the single-cell and neural circuit levels can allow for selective memory consolidation. In this way the brain can simultaneously remember some items while forgetting others, based on each item's information content. We showed how the efficacy of this mechanism depends on the specificity of synaptic wiring on dendrites, and on the overlap of neural activity patterns at the circuit level. We used the framework to predict which specific brain circuits are the best places to look for this mechanism. Finally, we further used the framework to propose a novel model for memory generalization during slow-wave and REM sleep.

Further background

Behaviorally salient events that lead to strong memories are believed to cause a wave of protein synthesis at the time of memory encoding. These plasticity-related-proteins (PRPs) are synthesized rapidly (< 10 minutes) but degraded slowly (1-2 hours) (Kelleher et al., 2004). Although the molecular identities of the PRPs is unclear, their presence seems to be necessary for consolidating episodic memories - when PRP synthesis is blocked, the memories are rapidly forgotten. Interestingly, the PRPs that are synthesized in response to activation of one set of synapses can be shared within the activated neurons so that plastic changes at other synapses onto those same neurons can also be consolidated (reviewed by Redondo & Morris, 2012). The prevailing idea in the field (the 'synaptic tagging and capture' hypothesis) it that this temporally bounded PRP expression allows for the creation a ~2 hour time window within which other memory events are preferentially consolidated. However, this model ignores the fact that PRP expression is restricted not only in time, but also in space. Recent experiments have shown PRPs are localized to single dendrites (Govindarajan et al., 2011). Similarly at the neural circuit level, PRPs are presumably restricted to only the subset of activated neurons within the circuit. These two levels of spatial PRP restriction - the dendritic (Figure 1) and neuronal (Figure 2) - mean that only some synapses in a circuit will have access to the synthesized proteins, and hence have a chance to have their synaptic strength changes consolidated. We used a combination of mathematical modeling and computational simulations to quantify these additional benefits of this spatial patterning for selective memory consolidation, and to propose a novel model for a previously unexplained neural phenomenon: the generalization of memories during sleep.

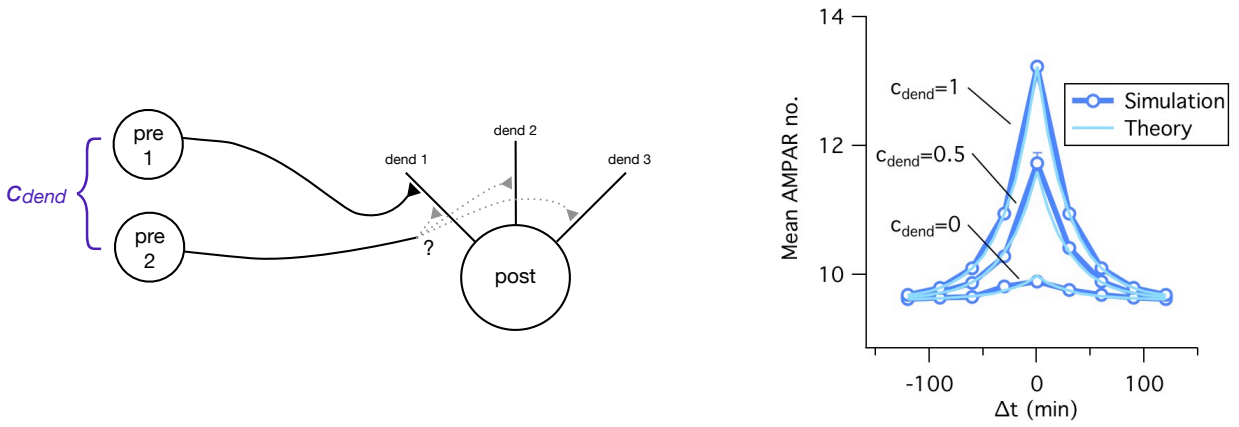

Figure 1. Consolidation as a function of the probability that synapses target the same dendrite. Left: two presynaptic neurons have a parameter (c_{dend}) that quantifies their bias to synapse onto the same postsynaptic dendrite. Right: Varying the bias parameter increases or decreases the mean consolidated synaptic strength change, as seen in the varying amplitude of the temporal consolidation window.

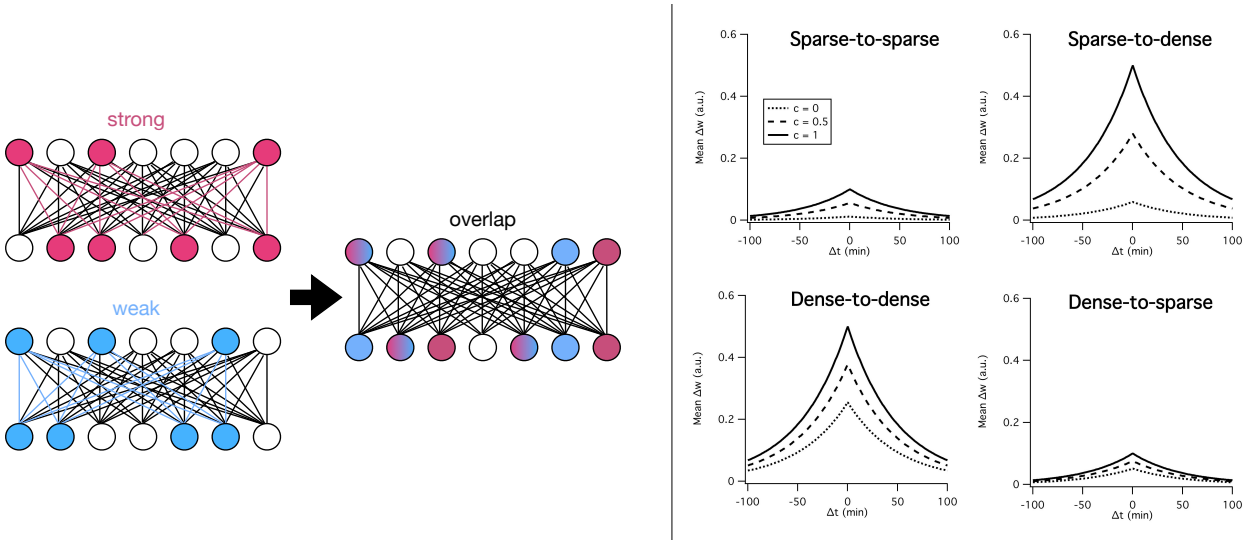

Figure 2. Consolidation of synaptic plasticity from a weak neural network activity pattern as a function of its overlap with a strong pattern. Left: Schematic of a 2-layer feedforward neural network with 'strong' and 'weak' activity patterns (left column) and their overlap (right column). Right: Calculated expected consolidated synaptic strength vs temporal interval for various levels of sparsity in the pre and postsynaptic layers of a 2-layer network. Different c parameter values represent different degrees of dendritic overlap (as in Figure 1).

References

- Govindarajan A, Israely I, Huang S-Y, Tonegawa S (2011) The dendritic branch is the preferred integrative unit for protein synthesis-dependent LTP. Neuron 69:132–146.
- Kelleher RJ, Govindarajan A, Tonegawa S (2004) Translational regulatory mechanisms in persistent forms of synaptic plasticity. Neuron 44:59–73.
- Redondo RL, Morris RGM (2011) Making memories last: the synaptic tagging and capture hypothesis. Nat Rev Neurosci 12:17–30.