**A general theory of learning and memory with complex synapses**

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An incredible gulf separates theoretical models of synapses, often described solely by a single scalar value denoting the size of a postsynaptic potential, from the immense complexity of molecular signaling pathways underlying real synapses. To elucidate the functional contribution of such molecular complexity to learning and memory, it is essential to expand our theoretical conception of a synapse from a single scalar to an entire dynamical system with many internal molecular functional states. Moreover, theoretical considerations alone demand such an expansion; network models with scalar synapses assuming finite numbers of distinguishable synaptic strengths have strikingly limited memory capacity [Amit/Fusi92]. This raises the fundamental question, how does synaptic complexity give rise to memory?

To address this, we develop new mathematical theorems elucidating the relationship between the structural organization and memory properties of complex synapses that are themselves molecular networks. We consider an extremely general class of models where memories are stored in a population of N synapses each with M internal molecular functional states, where potentiation and depression each induce an arbitrary network transition between states, parameterized by a pair of MxM stochastic transition matrices. The cascade model of [Fusi…05] for example is one member of this model class. We find that no molecular network can achieve a memory capacity that exceeds N^(1/2) M, or have a memory curve that exceeds a power law envelope with exponent -1. Molecular networks achieving optimal capacity at any given time correspond to a simple linear chain of states, but have highly suboptimal memory at other times, and model independent tradeoffs between storing proximal and distal memories necessitate synaptic complexity.

Overall, we uncover general design principles governing the functional organization of complex molecular networks, and suggest new experimental observables in synaptic physiology, based on first passage time theory, that connect molecular complexity to memory.

**Additional Detail**

**Significance:** We are extremely excited about this work as we feel we have achieved several conceptual and mathematical breakthroughs in our ability to understand the space of all possible models of complex synapses. In contrast, the entire theoretical foundations underlying our current understanding of memory is based almost entirely on synaptic models that are far too simplistic (i.e. scalar synaptic strengths). As explained above, such scalar models are ruled out both experimentally as well as theoretically. Moreover, the very little work that has been done on more complex synaptic models has only focused on the behavior of very specific models (e.g. the cascade model [Fusi…05]). If we wish to understand essential biological structure-function relationships in molecular networks underlying synaptic plasticity, it is vital to theoretically explore the space of all possible molecular networks so that we can develop a correspondence between the topological features of these networks and desirable/undesirable memory properties of the synapse. This will help us impose some theoretical order on the bewildering complexity found in studies of synaptic plasticity at the molecular level. To our knowledge, we are the first to have done this; we have generated a rigorous analytical theory carving out the space of all possibilities in terms of synaptic memory and network topology that has actually lead to new mathematical theorems that have neurobiological relevance. Hence we have requested a talk.

**Methods:** We model synaptic plasticity with two Markov processes between the internal states, one for potentiation and one for depression (see fig.1). These are responsible for the initial creation of a memory and its subsequent forgetting due to ongoing plasticity. The performance of the synapse is quantified by a memory curve defined by the signal-to-noise ratio (SNR) quantifying the decaying fidelity with which the initial memory trace can be recalled as function of time. The formalism is entirely consistent with the work of [Fusi…05], but here we consider the performance of all possible models in this model class, rather than focus on a single one.

**Figure 1:** Models of complex synapses. (a) The complex synapse has a number of internal states, some of which correspond to a strong synaptic strength (red) and some to weak. (green) (b,c) Potentiation and depression induce different stochastic transitions between these states. This yields an entirely general family of complex plasticity models, where each choice of two stochastic transition matrices, and each assignment of strength to internal states, determines a choice of model in this family.

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By employing the theory of first passage times in stochastic processes, we prove that if we order the states from left to right according to the mean first passage time (in the stochastic process of forgetting) from each state to the set of potentiated states, then any memory model that optimizes the area under its memory curve must necessarily assume a linear chain topology in which potentiation moves states from left to right, while depression moves states from right to left, with no shortcuts along the chain allowed. By computing the area under the memory curve of the optimal chain we find the area cannot exceed N^(1/2) M where N is the number of synapses and M is the number of internal states. This automatically imposes the **same area limit on any model within this model family**. Thus synaptic complexity (quantified by M) can be a more powerful contributor to memory storage capabilities than the number of synapses N. This area bound also translates into a memory lifetime bound (the time at which the SNR is reduced to 1 is less than N^(1/2) M for any model).

We can also optimize the memory at any fixed time. We find that at times O(t), no memory model can achieve a memory capacity larger than O(N^(1/2) M t^-1). **This yields a power law memory envelope beyond which the memory curve of any model whatsoever can never cross**. The model that does achieve this limit is again a chain topology with transition rates tuned to match t. Such models have memory curves dominated by a single time scale matched to t. However, the chain topology with parameters optimized for t, while touching the envelope at time t, is far from the envelope at other times.

This leads to a model independent formulation of the tradeoff between storing proximal and distal memories that has been observed in any model that has been written down: if you optimize the memory at one point in time, you take a hit at other points. Thus if you want a memory model that is not too suboptimal at any given time (in terms of not being too far from the memory envelope) it cannot come very close to the memory envelope at any other time. Such models turn out not to be linear chains but more complex models with intricate topological transition networks and multiple timescales. Thus negotiating this tradeoff emerges as a fundamental driver of synaptic complexity.

**In summary**: By being able to, for the first time, analyze fundamental limits and tradeoffs in memory capacity for the space of all possible models of complex synapses within an extremely general model class, we feel we have taken an important step forward to understanding general principles governing the relationship between subsynaptic molecular network complexity and systems level measures of memory performance. These results should be of great interest to the Cosyne community.