Most currently available neuronal network models define learning as changes in the strength of synaptic connectivity (i.e., weight plasticity), with synaptic weights assumed to remain constant in the absence of such learning. However, our recent study on excitatory neuronal networks in the cerebral cortex has revealed that, in addition to activity-dependent plasticity, these networks exhibit intrinsic fluctuations in synaptic weight and widespread spontaneous synapse formation and pruning, with a time-course on the order of days. Our results indicate a coupling between weight plasticity and spine generation/elimination, and suggest that these mechanisms have complimentary but distinct functions in memory formation and maintenance.

Three principles of plasticity in spine synapses are presented here to facilitate construction of a new network model for the cerebral cortex.

One common assumption about synaptic connections is that they remain constant, in both real and artificial neuronal networks, in the absence of activity-dependent plasticity. In this line of thinking, the decay of memory, or forgetting, has been ascribed either to the failure of recollection processes or to activity-dependent overwriting of preexisting mnemonic traces.

Our recent study addressed this issue using two-photon, time-lapse imaging of dendritic spines in cultured CA1 pyramidal neurons from rat hippocampal slices. In this study, we precisely measured spine volumes over the course of days. We chose this metric because the volumes of spines have been shown to reflect the strength of synaptic connections, and thus, these volumes change with activity-dependent synaptic plasticity. During our experiments, we discovered daily random and spontaneous fluctuations in spine volume, even when activity-dependent plasticity was blocked by TTX and inhibitors of NMDA receptors. Such “intrinsic fluctuations” explain, for the first time, the commonly observed statistical distribution of spine volumes, and provide new explanations for the observed structural diversity of dendritic spines.

One important feature of the observed intrinsic fluctuations is the absence of “drift,” meaning if the volume of a spine on day $t$ is $V(t)$, the expected volume of the spine $V(t + 1)$ on day $t + 1$ is also approximately $V(t)$. This observation of zero drift is consistent with the idea that intrinsic fluctuations represent biologically inevitable instabilities.

Because of their zero drift nature, intrinsic fluctuations are consistent with most existing data and theories regarding synaptic structure and plasticity. For example, the presence of zero drift fluctuations is consistent with observations that long-term potentiation (LTP) involving many synapses can last a month or longer because, despite the fluctuations, the only change to the average volume of spines is a slow decay due to spine elimination.

The discovery of these fluctuations does, however, necessitate the reexamination of a few critical issues surrounding the physiological operation of cortical neuronal networks.
over the course of a single day (14 days in the case of the neocortex).\textsuperscript{5} The same equation also predicts the life expectancy of spines to be 30–50 days (1.5–2 years in the neocortex)\textsuperscript{5} if elimination is defined as the shrinkage of spines below the minimal volume recognized for spines (0.02 μm\textsuperscript{3}). Thus, our model provides a unifying explanation of weight fluctuations and synapse elimination, and suggests differences of one to two orders of magnitude between the timescale of changes in synaptic weight and the synaptic lifetime, presumably reflecting the different functions of these processes in distinct phases of memory. For example, there is little possibility that synaptic weight can be preserved for weeks or months, though synaptic weight can modulate the persistence of synapses as well as the accessibility of information stored therein.

### Spontaneous Generation of Spines

Intrinsic fluctuations also have another role in neuronal networks. Our observations and calculations, both in vitro\textsuperscript{5} and in vivo,\textsuperscript{18} have quantitatively demonstrated that spines, especially small ones, are frequently eliminated (Fig. 1B–D), and that there is abundant generation of new spines to balance these eliminations (Fig. 1A). Notably, spine elimination and generation occur continually, even in the absence of activity-dependent plasticity. Such spontaneous generation and elimination explain the observation that spines become stable only after the repeated formation and elimination of potential synapses.\textsuperscript{19,20} Synapse generation must be coupled with synapse elimination because space and resources are finite, so synapse elimination liberates the molecular resources and space needed for the generation of new synapses.

Neuronal activity can also potentiate the generation of spines.\textsuperscript{5,21,22} Such activity-dependent plasticity, however, cannot be synapse-specific (as there is no synapse before its generation), so initial generation must occur in a somewhat random fashion.

Our data have demonstrated that the volume, age, and life expectancy of spines are significantly correlated (Fig. 1B–E), with small spines likely to be newer and more frequently eliminated than large and stable spines such a long time due to spontaneous fluctuations (Fig. 1A) described by Langevin equation as $V' = (0.2V + 0.01)W'$. This equation indicates that since the coefficient of variation ($\sigma/V$) is approximately 0.2/day, the weight of a synapse can undergo changes of up to ~20% (1 SD)
spines. Thus, new spines are more transient, which is in accord with the generally accepted features of human memory. In fact, the logarithmic decay of new memory observed by Ebbinghaus can be well-predicted by the population behavior of small spines. These relationships suggest that intrinsic fluctuations facilitate the acquisition of new memory through the generation of new small spines.

The importance of spine generation in memory is also consistent with the fact that connections are rather sparse in the cerebral cortex, and there is thus ample opportunity for the formation of new circuits. It is also known that spontaneous generation of spines plays an essential role in early development, supporting the idea that continued spontaneous formation may play a role in learning throughout life.

**Key Principles for a Realistic Cortical Model**

 Newly generated spines can be tested and selectively strengthened via activity-dependent plasticity only after their generation—a process known as the generate-and-test operation. As we have found that a great number of small spines are randomly generated by intrinsic fluctuations, we posit that this random-generation-and-test mechanism may contribute to the adaptive and creative capacity of the brain in new, unpredictable environments.

Changes in spine volume likely depend upon the recent history of a spine. For example, synaptic plasticity may be modulated by recent spine enlargement events. On the scale of days, however, spine dynamics can be described as a Markov process, which facilitates the construction of a mathematical model.

We have also found that activity-dependent plasticity preferentially affects smaller spines (Fig. 1A). The preferential effects of activity-dependent plasticity on small spines can promote the persistence of large spines, meaning that large spines are thus somewhat protected from overwriting.

As such, we can summarize the rules of spine synapse plasticity with the following three principles.

1. Both generation and elimination of spine synapses occur at the minimum synaptic volume (0.02 μm³ in Fig. 1A).
2. Synaptic weights (V) show slow random fluctuations, V = (0.2V + 0.01)W.
3. Activity-dependent plasticity preferentially affects smaller synapses.

These rules do not provide specific details about individual incidences of spine generation, but are rather general principles followed in the generation of all spines. For example, we can assume that all spine generations are balanced by eliminations. A numerical illustration of our principles for synapses can be found at www.bm2.m.u-tokyo.ac.jp/spinedist/dl.html as a Mathematica notebook (SpineDynamics.nb) for versions 5 to 7.

Construction of network models that implement these realistic principles of synaptic plasticity is fundamental for the proper assessment of memory mechanisms in cortical neuronal networks. For example, we need to address how new memory is stored in a network, how it decays, and how it can be stabilized by repetitive learning. We further need to understand how old memory is embedded in the network, and what happens during memory reconsolidation. Once the basic foundation of the networks is elucidated, the function of temporary weight plasticity in the operation of these networks should be examined. Finally, it would be interesting to investigate how intrinsic fluctuations are optimized relative to activity-dependent plasticity to produce effective learning and ensure the persistence of memory, and how networks can resolve the plasticity-stability dilemma. From a clinical perspective, it would also be useful to examine what happens when intrinsic fluctuations or activity-dependent plasticity are impaired, as has been proposed in psychiatric disorders such as mental retardation, autism and schizophrenia. The realistic modeling of neuronal network can thus provide immediate, important contributions to the understanding of both normal and pathological cortical functions.

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