Synaptic plasticity – the directed modulation of synaptic connections by specific activity histories or physiological signals – is believed to be a major mechanism for the modification of neuronal network function. This belief, however, has a ‘flip side’: the supposition that synapses do not change spontaneously in manners unrelated to such signals. Contrary to this supposition, recent studies reveal that synapses do change spontaneously, and to a fairly large extent. Here we review experimental results on spontaneous synaptic remodeling, its relative contributions to total synaptic remodeling, its statistical characteristics, and its physiological importance. We also address challenges it poses and avenues it opens for future experimental and theoretical research.

Synaptic Plasticity and Synaptic Tenacity
At a conceptual level, the central nervous system (CNS) comprises a vast network of excitable cells connected by specialized junctions known as synapses. Long before excitability and synaptic transmission were fully understood, scholars such as William James [1] suggested that changes to connections (‘tracts of conduction’), driven by sequential or concomitant activation of ‘elementary brain-processes’, might explain the formation of new associations and the learning of new tasks. In fact, James credits this idea to yet earlier scholars (e.g., Descartes, Locke) and notes that they ‘hit upon this explanation, which modern science has not yet succeeded in improving’ [1]. Years later, Donald Hebb rephrased this idea, using it as a cornerstone for constructs such as cell assemblies, thereafter used to explain network function and ultimately behavior in physiological terms [2]. Inspired by these theories, and armed with increasingly powerful methodologies, numerous investigators have convincingly demonstrated that activity histories (see Glossary) can influence and change such tracts of conduction, now largely identified as chemical synapses. The resulting changes, generally referred to as synaptic plasticity, are thus commonly viewed as evidence for this venerable theory.

The long-held framework described above has an implicit yet often ignored corollary, which is the supposition that synapses, when not driven to change by particular activity patterns or histories, retain their properties indefinitely. This supposition would seem to be essential because without it, spontaneously occurring changes might drive spurious modifications in network function or undo physiologically relevant ones. Thus, to fully appreciate the importance and limitations of synaptic plasticity, it is essential to measure and understand the capacity of synapses to maintain their particular properties (e.g., probability of release, total receptor conductance, size, morphology, ultrastructure, composition) over behaviorally relevant timescales. We refer to this capacity as synaptic tenacity [3–6].

The aim of this Opinion is to discuss challenges to the notion of synaptic tenacity that come from general biological considerations and experimental findings. Such findings collectively suggest that synaptic tenacity is inherently limited, since synapses do change spontaneously...
and to a fairly large extent. We survey these findings and discuss their implications in light of the supposition mentioned above. We then present principles emerging from recent literature on the manners by which spontaneous processes might govern dynamic and statistical properties of synaptic populations. We end by formulating several key questions concerning relationships between spontaneous remodeling, underlying biological processes, neuronal activity, and network function.

**Synaptic Tenacity: Inherent Challenges**

CNS synapses are micrometer-size, intricate assemblies of diverse molecules (e.g., receptors, ion channels, synaptic vesicle, scaffolding, cytoskeletal, adhesion, and signaling molecules). Typical lifetimes of synaptic molecules (i.e., days; see [7]) are orders of magnitude shorter than the lifetimes of many, if not most CNS synapses (weeks and months, and in some species probably years [8–10]; see [11] for a recent review). Consequently, the maintenance of synaptic connections involves continuous removal and degradation of molecules and their substitution with freshly synthesized copies. Given that CNS synapses are often remote from the neuron’s somatic biosynthetic machinery (residing at distances of many centimeters or even meters, in some organisms), long-term synaptic maintenance is a remarkable biological feat [12,13]. Importantly, however, given these logistic challenges and the low copy numbers of many molecules at individual synapses, it is probably unrealistic to expect that synapses maintain their particular contents and, by extension, their functional properties with pinpoint precision (see [14]). This expectation is further challenged by the fact that synapses are not rigid structures but rather are dynamic assemblies of molecules (and organelles) that continuously migrate into, out of, and between neighboring assemblies through lateral diffusion, active trafficking, endocytosis, and exocytosis [15,16]. These molecular dynamics are often further accelerated by cellular processes associated with synaptic transmission, such as membrane recycling and cytoskeletal dynamics.

Conceivably, challenges to synaptic tenacity posed by continuous molecular turnover and the myriad molecular dynamics might be met somehow, resulting in roughly stable synaptic properties. More likely, however, molecular dynamics coupled with imprecise proteostasis will drive spontaneous changes in synaptic properties that have little to do with specific activity histories [17]. As we show next, experimental evidence seems to favor the latter possibility.

**Spontaneous Synaptic Remodeling in Developing Networks**

During development the brain is strongly influenced by experience and activity, yet it seems that activity is largely dispensable for synapse formation per se. Although this conclusion is well established [18,19] (see [20] for a review of earlier work), recent studies have highlighted observations that are particularly pertinent to this Opinion.

Studies in primary culture have shown that general properties of excitatory and inhibitory synapses are largely preserved even when networks develop in the complete absence of activity. For example, chronic suppression of neurotransmitter release or network activity in primary cultures of hippocampal neurons does not appear to affect synaptic spatial densities, colocalization of pre- and postsynaptic molecules, or the synaptic contents of important postsynaptic density (PSD) proteins (e.g., PSD-95/Dlg4, CaMKIIα, SynGAP, Gephyrin) and neurotransmitter receptor subunits (Gria2/3, GABAAR2) [18,19]. Recently, these findings were confirmed and extended to additional preparations, including the intact brain. In one study [21] (see also [22]), spine types, spine spatial densities, and synaptic currents were examined in hippocampal organotypic cultures prepared from mice in which presynaptic release was
abolished (by eliminating the presynaptic proteins Munc13-1 and Munc13-2). These synaptic features were found to be similar to those observed in preparations from control animals, although postsynaptic currents were slightly reduced and less correlated with spine volume. In a second study [23], the near-complete suppression of presynaptic glutamate release in the mouse forebrain (by tetanus toxin expression) was found to have relatively modest effects on synapses and their properties, at least as judged by morphological measures. Although synapse numbers and spine densities were reduced in some brain regions (but not others), dendritic spines of all types formed at normal proportions.

These observations – that synapses of all sizes and types form at normal proportions – have profound implications: when synapses and dendritic spines are initially formed, they generally have small volumes and PSDs (e.g., [24–27]). Their subsequent conversion into large, mushroom-shaped spines is often thought to be driven by activity-dependent potentiation (reviewed in [28,29]; see also [30,31]). However, as mentioned above, large synapses, including mushroom-shaped spines, develop in normal proportions even when activity is essentially nonexistent [18,19,21,23]. It thus seems that activity-independent processes can generate the full repertoire of synaptic sizes [17], highlighting the potency of spontaneous synaptic remodeling.

Spontaneous Synaptic Remodeling in Established Networks
Longitudinal observations of individual CNS synapses over many days in mature networks, both in vitro and in vivo, indicate that most synapses are persistent over these timescales, (e.g., [10,32] but see [9]; reviewed in [8]), although significant synapse formation and elimination are also observed (reviewed in [33–35]). Closer examination reveals, however, that properties of individual synapses, such as spine volume (e.g., [17,24,36–38]), presynaptic bouton volume [39,40], synaptic vesicle number [4,5,41], active zone (AZ) molecule content (Bassoon, Munc13-1) [4,42,43], and PSD protein content (PSD-95, Gria2, Gephyrin, GKAP, Shank, Zip45/Homer1c) [3,5,6,27,43–49] fluctuate considerably over these timescales (as illustrated for PSD-95 in Figure 1). Given the strong correlations between these measures and functional synaptic features such as synaptic vesicle release [42] and synaptic current amplitudes (reviewed in [8,29,50]), these fluctuations are likely to have functional consequences. Indeed, comparable fluctuations in connection strengths are observed when measured directly [51–53]. Furthermore, fluctuations tend to occur simultaneously in pre- and postsynaptic scaffolds of the same synapses [43], further supporting their functional significance.

As synapses in the aforementioned studies were embedded in active networks, their fluctuations reflect both spontaneous and activity-history-driven processes. Yet even when spontaneous activity is suppressed or eliminated altogether, fluctuations persist [3,6,17,40,54], although their characteristics can change (see below). These results suggest that in mature networks, as in developing networks, spontaneous synaptic remodeling is significant.

Relative Contributions of Specific Activity Histories and Spontaneous Processes to Synaptic Remodeling
The presence of significant activity-independent synaptic remodeling raises an important question: what are the relative contributions of specific activity histories and spontaneous processes to synaptic remodeling? This question might be addressed by comparing the magnitudes of changes they induce. As a rough estimate, changes to PSD sizes following experimental paradigms that induce long-term potentiation (measured using fluorescently tagged variants of PSD-95 and Homer1b) (e.g., [30,31]) seem to be of magnitude similar to
that of baseline PSD size fluctuations observed in vivo using similar approaches [47,49]. However, these comparisons are made among different experimental systems and conditions (e.g., rat hippocampus CA1 pyramidal cells in cultured slices [30,31] and mouse layer 2/3 cortical pyramidal cells in vivo [47,49]).

The fluctuations observed in the latter studies represent the sum of both activity-dependent and -independent processes. As a step toward separating their respective contributions, the effects of suppressing activity were examined. Such experiments (in culture) [17,54] have shown that suppressing all spontaneous activity reduces the magnitude of glutamatergic synapse size fluctuations, but only by a factor of about two. Interestingly, little to no change was observed for GABAergic synapses [6,40].

A more direct estimate of the relative contributions is obtained by comparing pairs of synapses formed between the same axons and dendrites (see Figure 2 for an illustration of this approach). Such pairs share common activation histories that should drive similar remodeling in the two synapses. Conversely, size or remodeling differences between synapses belonging to the same pair would reflect spontaneous, activity-history-independent processes occurring autonomously at each synapse. This rationale was applied in several recent studies using electron microscopy reconstructions of hippocampal tissue [55], a fully reconstructed volume of mouse neocortex [56], and long-term imaging of cortical neurons in culture [54]. In general, it was found that such synapse pairs tend to be more similar than randomly chosen pairs. However, remodeling covariance over 48-h periods, as well as correlation coefficients of instantaneous sizes (spine volumes and PSD areas) were relatively small (~0.25–0.35). This led to an estimate that at most 40% of synaptic remodeling could be attributed to specific activity histories [54].

Collectively these findings suggest that the contributions of spontaneous processes and specific activity histories to synaptic remodeling are of similar magnitudes.
Characteristics, Sources, and Implications of Spontaneous Remodeling Processes

It appears that spontaneous remodeling is a central, inherent feature of CNS synapses, which merits in-depth analyses of its characteristics, sources, implications, and physiological importance. We mention a few of these here.

In the framework of synaptic plasticity, significance is attached to the specific configuration of synaptic strengths (synaptic weights) in a network. Therefore, it is important to characterize the rates at which spontaneous remodeling might ‘erode’ configurations of synaptic input strengths (Figure 3). Imaging studies in primary culture indicate that synaptic configurations erode significantly over timescales of a few days [3–6,27,38]. This becomes evident when synaptic size is plotted against initial size at increasingly greater time intervals, as illustrated in Figure 3B [6,27]. Not only are correlations reduced, but linear regression fits gradually become shallower while their offset terms grow larger. Suppressing network activity slows this process, but only by a factor of about two [3]. Interestingly, erosion rates of GABAergic synapse configurations seem to be insensitive to activity levels and slower than those of glutamatergic synapses in the same neurons [6].

Given enough time, will synaptic configurations erode completely? In studies published to date, monotonic erosion of synaptic configurations was reported [3–6,27,38]; however, over the timescales of such experiments, configurations did not erode entirely. Perhaps, given sufficient time, they would (Figure 3D, red broken lines). Alternatively however, they might conserve a semblance of their original configuration even after long times (Figure 3D, green broken lines). This could reflect limited mixing due to sizes fluctuating around synapse-specific set points (Figure 3E) defined, for example, by relatively stable core scaffolds [4,16]. Another possibility is that synaptic tenacity varies in the population such that the sizes of some synapses fluctuate much more than others. At present the extent of mixing and the heterogeneity of synaptic.

Figure 2. Pairs of synapses formed between the same axons and dendrites. (A) An illustration of a pair of commonly innervated (Cl) synapses (red arrowheads); that is, synapses formed between the same axon (red) and the same dendrite (gray). Because of their shared axon and dendrite, such synapse pairs are assumed to have roughly similar activity histories. (B) Given their similar activity histories, the sizes of synapses belonging to the same Cl synapse pair (top) would be expected to be more similar than the sizes of synapses innervated by different axons (non-CI; bottom), exemplified by arrowheads with differing colors in A. (C) Similarly, a higher degree of remodeling covariance might be expected between Cl synapses (top) compared with a randomly chosen pair of synapses (bottom).
Figure 3. Erosion of Synaptic Configurations by Spontaneous Remodeling. (A) Illustration of a hypothetical dendritic segment at three consecutive time points. Sizes of individual spines are color coded according to the bar below. (B) Top: The size of each synapse at time \( t_2 \) is plotted against its size at an initial time \( t_1 \). Light-blue lines are the linear regression fits whereas broken gray lines indicate the identity relationship. Bottom: Linear regression fits at a later time \( t_3 \) typically exhibit a lower goodness of fit \( (R^2) \) value and a shallower slope. (C) Changes in synaptic size as a function of initial size. Linear regression fits are shown as purple unbroken lines. Such lines cross the abscissa at the mean synaptic size, showing that, for synapses smaller than this mean, changes tend to be positive, whereas for synapses greater than this mean changes tend to be negative. For longer time intervals, the linear regression slopes gradually increase. (D) \( R^2 \) values (top) and slopes (bottom) of linear regression fits as in B decrease with time, providing a time scale for the erosion of synaptic configurations. What happens after very long times? This depends on the degree of mixing (E). If sizes fluctuate around synapse-specific set points [i.e., exhibit limited mixing (illustrated for three synapses; top)], \( R^2 \) values and slopes will settle at intermediate values (green broken lines in (D)). If not (as illustrated for three synapses, bottom), they will diminish to zero (red broken lines in (D)); at that time, all relationships with original synaptic configurations will be lost (i.e., these will have eroded entirely).

Tenacity remain unknown. The rates at which synaptic configurations erode in vivo and how these might change with age [39] (see also [57]) or in association with various neurological disorders are not known either. These are crucial questions that call for very long measurements, particularly in vivo (see Outstanding Questions). Finally, the degree to which the observed erosion of synaptic configurations ultimately affects network function is unclear, but potential links between such erosion and memory decay [17] or declining mental abilities are plausible.

Although synaptic configurations deteriorate, the same analyses reveal other properties that emerge as stable invariants at the population level.

First, while single-synapse properties (e.g., spine volumes, PSD molecule contents) fluctuate, distributions of the same properties can be very stable [3,6,27,38]. Such distributions quantify the proportions of synapses of different sizes in the population; distribution stability implies that fluctuations in synaptic sizes are not merely diffusive (which would lead to the gradual broadening of size distributions) but reflect a dynamic equilibrium in which synaptic sizes are somehow constrained (Box 1). One way to appreciate the presence of such constraints is by plotting changes in synaptic sizes against their initial sizes at later times (Figure 3C). Such plots highlight the tendency of small synapses to grow larger and of large synapses to become smaller [3,6,27], with the magnitude such changes increasing with time.

Second, the shapes of distributions within synaptic populations (e.g., distributions of release probability, synaptic currents, spine volumes, PSD molecule and receptor contents) tend to be skewed; that is, to have a tail of particularly large or strong synapses (e.g., [6,18,19,27,58,59]; reviewed in [60]). It has been suggested that such distributions might be a consequence of
Box 1. Models of Synaptic Size Dynamics

How can stable, skewed size distributions arise in populations of synapses whose sizes fluctuate continually?

Suppose that all synapses start out having small sizes, and that their sizes change stochastically. At time \( t + 1 \) synaptic size is equal to its original size \( x_i \) plus some random value \( \eta_i \); that is, \( x_{i+1} = x_i + \eta_i \) or, in terms of change at time \( t \),

\[
\Delta x_t = \eta_t
\]

In such diffusive fluctuations (random walk), distributions expand indefinitely (Figure A). Consequently, no stable distribution is ever reached (even if the average of \( \eta \) is zero).

The divergence of these distributions can be curtailed by adding a restraining ‘force’ \( f(x) \) whose magnitude depends on \( x_i \) such that \( \Delta x_t = f(x_t) + \eta_t \). In this formulation of constrained fluctuations (Langevin dynamics), changes are still random but a deterministic restraining force acts, in analogy to a spring, to maintain sizes near some mean value. In the simplest case, where the force is linear \((-\gamma x_t)\) and fluctuations are Gaussian, the process becomes

\[
\Delta x_t = \gamma x_t + \eta_t
\]

Such dynamics give rise to stable distributions (Figure B) but these are Gaussian, not skewed, implying that additional assumptions are necessary to recapitulate the skewed distributions observed physiologically.

Skewed distributions are often associated with multiplicative noise, meaning that fluctuation magnitudes depend on the variable’s state (e.g., synaptic size). Multiplicative noise can be introduced through more complex formulations of \( x_{i+1} \) [17,38]; still, restraining forces are required to maintain stable distributions. In one study [17] good fits to experimental data were obtained by introducing restraining forces that differed for different synapse-size categories (as did state-dependent fluctuations). It is not obvious, however, how synapses would ‘know’ to which category they belong and when to switch the rules that govern their remodeling.

One particularly simple formulation, which bypasses the need for arbitrary categories, is the Kesten process. Here, multiplicative noise is built into the restraining force by supplementing it with a random component \( \xi \):

\[
\Delta x_t = (-\gamma + \xi) x_t + \eta_t
\]

This process entails two types of changes to synaptic size: continuous downsampling (on average), which includes state-dependent fluctuations, and an additive term that contains state-independent fluctuations (Figure C). The Kesten process was shown to describe faithfully many experimental observations [3,6,27,46], including: size fluctuations; stable, skewed distributions; growth of new synapses; and synaptic scaling (Box 2).

Figure I. Shape and Stationarity of Synaptic Size Distributions Governed by Different Stochastic Processes. (A) Diffusion (random walk). (B) Langevin dynamics. (C) Kesten process. The top panels show the additive component (size independent; orange) and the restraining one (size dependent; blue) for each case, as well as their average sum (green). Bottom panels show the resulting distributions at three consecutive time points.
synaptic plasticity in several forms [61]. **Skewed distributions** emerge, however, even when activity is suppressed throughout network development [18,19], highlighting once again the significant contributions of spontaneous remodeling and its ability to generate full repertoires of synapses at correct proportions.

The realization that size fluctuations play crucial roles in synaptic remodeling has motivated several groups to explore this topic through computational modeling [17,27,29,38]. These models faithfully capture many of the experimental results and provide some insights into their potential origin. For example, they offer an explanation of how synaptic size fluctuations can give rise to skewed, stable size distributions (Box 1). They also provide an explanation for experimental findings showing that scaling of synaptic size distributions can occur without overt, uniform multiplicative scaling of individual synapse sizes [3,27] (Box 2).

A more recent computational study [62] has gone one step further, showing that all of these properties – size fluctuations and stable and skewed size distributions, as well as their scaling – can emerge naturally from stochastic assimilation and removal of synaptic molecules at synaptic sites, provided the two processes exhibit cooperativity. This model also recapitulates the internal spatial organization of synapses in the form of dynamic nanodomains (e.g., [63,64]). A more detailed model, where removal and aggregation are implemented by lateral diffusion of receptors bound to scaffold proteins, also provides good fits to measured distributions [65]. Since distribution properties can be described equally well by alternative mesoscopic models, further experimental and theoretical work is required to identify the key biophysical processes involved.

**Concluding Remarks**

The findings summarized above indicate that synaptic tenacity is inherently limited [3,4,6,43,54] or, using the terminology of Rumpel, Loewenstein, and others [34,35], that synapses are intrinsically ‘volatile’. How can the notions of synaptic plasticity and synaptic volatility be

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**Box 2. Synaptic Scaling as a Population-Level Phenomenon**

Distributions of synaptic properties (e.g., synaptic current amplitude, glutamate receptor content, PSD size) are known to change following manipulations of spontaneous network activity levels, sensory input, and neuromodulatory tone. In particular, distributions were shown to scale (namely, retain their shape on a stretched/compressed x-axis) following such manipulations as illustrated in Figure 1. This scaling is often attributed to a global multiplicative change in the measured property such that all synapses formed on the same neuron change by some global scale factor [66]. This interpretation is particularly appealing as it suggests a mechanism for preserving the relative strengths of synaptic inputs, amounting to neuron-wide renormalization.

Most studies concerning this phenomenon were based on population-wide comparisons of synaptic properties before and after a manipulation. When individual synapses are tracked throughout the scaling process, however, additional information is revealed suggesting that **distribution scaling** can occur without overt, uniform multiplicative scaling of individual synapse sizes [3,27,46]. Indeed, these analyses directly show that the fold change differs markedly among synapses belonging to the same neuron. A mechanism for distribution scaling that is consistent with the individual-synapse dynamics entails changes in statistical parameters that govern spontaneous remodeling (Box 1). For example, such manipulations might change the slope of continuous downscaling (the average restraining force, −γ, in Box 1), the average magnitude of additive processes (the mean of parameter η in Box 1), or, possibly, the magnitude of multiplicative and additive fluctuations as illustrated in Figure IA,C [3,6,27,46]. Therefore, synaptic scaling can emerge as a population-level phenomenon that does not necessarily preserve the relative strengths of synaptic inputs.

This result has important implications for relationships between activity and synaptic remodeling: it suggests that activity, in addition to driving remodeling through deterministic rules acting at the single-synapse level, can also modify steady-state properties of synaptic populations by parametrically affecting the features of stochastic processes that govern spontaneous remodeling.
reconciled? How can properties of individual neurons, such as sensory tuning and motor and place representation, as well as higher-level functions remain invariant if directed and spontaneous synaptic changes are, as suggested by various studies, of similar magnitude? Potential answers to these questions have been discussed in several recent reviews [33–35] and a subset of possible resolutions is summarized briefly in Box 3. Irrespective of interpretation, however, it is clear that the ideal notion of perfectly tenacious synapses is not supported by experimental findings (nor is it particularly plausible from a biological standpoint, given the

> **Box 3. Memory in the Presence of Limited Synaptic Tenacity**
>
> How can memory persist in the presence of significant spontaneous synaptic remodeling? This matter has been addressed in several recent reviews [33–35]. Some possible resolutions are listed briefly below.
>
> • Compound Connections: Connections between neurons are often based on multiple synapses resulting in compound connections (reviewed in [69]). Consequently, fluctuations at the single-synapse level might average out at the compound connection level, improving the signal-to-noise ratio (SNR) of connection strengths and their plasticity.
>
> • Strength in numbers: Persistent changes to network function might rely on the formation of new synapses and the elimination of others. The magnitude of spontaneous rewiring, however, seems to be comparable with directed rewiring [70], reviewed in [34, 35]. An elegant model [71] tied these findings to the idea of compound connections mentioned above, suggesting that learning involves transitions between two relatively persistent states; namely, connections with few (zero or one) synapses and compound connections (approximately four or five synapses).
>
> • Massive redundancy: Invariant function might involve vast numbers of neurons and synapses such that fluctuations at the single-synapse level become negligible. Indeed, the acquisition of a new motor skill in mice was estimated to involve ~4700 motor cortex neurons and ~410 000 synapses [72]. In this case, global properties other than specific patterns of synaptic weights might be the relevant system variables.
>
> • Diversity and selection: Spontaneous remodeling might be functionally important for the generation of diverse, partially random synaptic configurations from which ‘useful’ configurations are thereafter selected; for example, through interactions with the environment (reviewed in [35]).
>
> • Synaptic sampling: Spontaneous changes in synaptic properties might allow networks to explore and sample synaptic configurations for those most congruent with sensory input or desired functions and improve the ability of networks to generalize and compensate for unforeseen changes [73].
>
> • A paradigm shift? The possibility remains that none of the potential explanations listed above will prove to be sufficient and that a paradigm shift will be ultimately required to understand the physiological substrate of learning and memory [66, 67].
challenges to synaptic tenacity discussed above). Furthermore, spontaneous synaptic remodeling has important consequences that are not fully understood and are not always intuitive (see Outstanding Questions). When it comes to cognitive functions, long-term memory is one area where the notion of synaptic volatility raises perhaps some of the most challenging questions. In light of findings discussed in this Opinion article, and possibly others [34,66,67], age-old notions concerning relationships between histories of ‘elementary brain-processes’, connection strengths, and memory traces might need to be revisited; put differently (to paraphrase James [1]), modern science might need to improve on this explanation.

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Outstanding Questions

Mixing and timescales: Given sufficiently long times, will individual synapses ‘explore’ the full range of synaptic sizes? Stated differently, to what degree do synapse sizes mix? (Figure 3D,E)? If mixing of synaptic sizes is substantial, over what timescales does such mixing occur? How do such timescales compare with the lifespans of individual synapses? Imaging individual synapses at high temporal resolution for extended timescales might provide clues about this critically important question.

Internal set points: If mixing of synaptic sizes is limited, this would indicate that synaptic sizes fluctuate around synaptic-specific internal ‘set points’. What might define such set points? How might these be modified?

Relationships between activity and synaptic size fluctuations: Are size fluctuations manifestations of specific activity histories and deterministic ‘rules’ or does activity parametrically affect stochastic processes that govern spontaneous synaptic remodeling (in analogy to temperature in chemical reactions and diffusive processes)? Given the strong influence that activity has on the dynamics of many synaptic molecules, the latter possibility cannot be ignored.

Spontaneous remodeling and network function: How does spontaneous synaptic remodeling affect the input-output relationships of individual neurons? How does it affect the fidelity of signal propagation within neuronal networks?

Biological sources: What gives rise to spontaneous synaptic remodeling? How is it related to biophysical dynamic processes and to internal synaptic structure, such as nanodomain and specific molecular assemblies?

Spontaneous remodeling and aging: How does spontaneous synaptic remodeling change with development, during aging, or in relation to neurological disorders or neurodegenerative conditions?
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