What is the appropriate description level for synaptic plasticity?

Harel Z. Shouval[1]

Department of Neurobiology and Anatomy, University of Texas Medical School at Houston, Houston, TX 77030

The hypothesis that learning memory and some aspects of development are mechanistically implemented by synaptic plasticity has gained significant experimental support (1, 2). At the cellular and molecular level synaptic plasticity is a very complex phenomenon, involving hundreds of molecular species, depending on the structure of dendrites and on ion channel concentrations. If we are to understand how high-level processes arise from synaptic plasticity, and not simply that they arise from synaptic plasticity, we must know how to best characterize plasticity theoretically. Such a characterization should account for key experimental results, yet at the same time it should be as simple as possible so that we can use it to explain how plasticity can lead to learning and memory. The article by Gjorgjieva et al. (3) in PNAS argues that a sufficient model of synaptic plasticity can depend only on spike pairs and triplets and that more-complex biophysical and molecular processes might not be needed. It also shows a correspondence between this triplet-based rule and the well-known phenomenological Bienenstock Copper Munro (BCM) learning rule (4).

Many of the early theories of synaptic plasticity were not formulated on the basis of low-level experimental evidence. Instead, they were motivated by the consequences of plasticity observed at a higher level, for example receptive field plasticity in visual cortex. To account for such high-level plasticity, theorists postulated phenomenological low-level mechanisms that can account for such higher-level phenomena. In the mid-1970s von der Malsburg (5) proposed rate-based network models that included synaptic plasticity and competition between cells to account for the formation of orientation selectivity and ocular dominance maps in visual cortex. The plasticity model he used was very simple: synaptic potentiation that is proportional to the product of presynaptic and postsynaptic activity variables, coupled with a normalization of the total synaptic weight. Later work has shown the limitations of this plasticity model (6). The BCM model (4) was also formulated to explain receptive field plasticity in visual cortex, and like other rate-based phenomenological models, is formulated in terms of abstract pre- and postsynaptic activity variables. The BCM theory (Fig. 1*A*) is based on two principles, formulated by two equations. First, the plasticity equation:

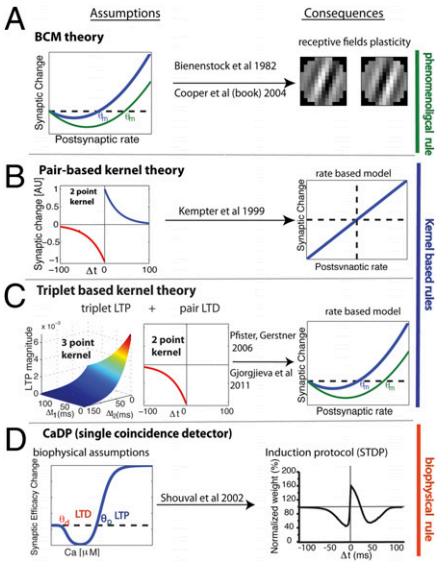

Fig. 1. Models of synaptic plasticity. (*A*) In BCM, a rate-based model of synaptic plasticity, the sign and magnitude of plasticity is determined by postsynaptic activity (*Left*). If activity is lower than θ_m, LTD is induced; otherwise, LTP is induced. The modification threshold changes as a function of the history of postsynaptic activity. BCM can account for receptive field plasticity in visual cortex (*Right*). (*B*) Pair-based kernel model of synaptic plasticity. LTD (red) is induced if the postsynaptic spike comes before the presynaptic spike; otherwise, LTP (blue) is induced. This rule is consistent with a rate-based rule that is linear in postsynaptic activity. (*C*) In a triplet-based theory, pair-based LTD plus triplet-based LTD can together account for various experimental results and for the rate-based BCM model. (*D*) CaDP, a biophysical model of synaptic plasticity, assumes that the level of postsynaptic calcium determines synaptic plasticity. Moderate calcium levels produce LTD, higher levels LTP. It can account for rate-based plasticity induction protocols and STDP; however, STDP has a second LTD region.

$$\frac{dw_i}{dt} = x_i \phi(y, \theta_m) \qquad [1]$$

states that the change of the synaptic efficacy (w_i) in synapse i is a product of the presynaptic activity (x_i) and a nonlinear function (ϕ) of the postsynaptic activity (y). The ϕ function is negative at low values of y and becomes positive when y exceeds the modification threshold (θ_m). The second principle, metaplasticity (7), which states the modification threshold (θ_m) is modifiable, serving as a negative feedback, is implemented in the equation:

$$\theta_m = \langle y^{1+\mu} \rangle_t, \qquad [2]$$

where the angled brackets denote a sliding temporal average, and $\mu > 0$ ensures stability (4). In Fig. 1*A* we show the form of the ϕ function for two different levels of the modification threshold.

The BCM theory can indeed account for the formation of orientation selectivity and ocular dominance of cortical neurons in natural image environments and for various different deprivation experiments (6). Furthermore, the assumptions of BCM have influenced experimental studies of synaptic plasticity (8). However, it is difficult to tightly link BCM to physiological and biochemical experiments, owing to the abstract nature of the variables BCM uses.

In the late 1990s several experimental studies indicated that the precise timing of pre- and postsynaptic spikes have significant influence on the sign and magnitude of synaptic plasticity (9, 10) (Fig. 1*B*). According to this experimental observation, called spike timing-dependent plasticity (STDP), when a presynaptic spike comes before a postsynaptic spike [$\Delta t = (t_{post} - t_{pre}) > 0$], long-term potentiation (LTP) is induced, and if the order is reversed ($\Delta t = <0$), long-term depression (LTD) is induced. Such results cannot be accounted for by rate-based theories, which are designed to be independent of single spike times.

Because of the complexity of the mechanisms inducing synaptic plasticity, it was tempting to assume that all of synaptic plasticity can be captured by this simple curve and that plasticity that is induced by complex pre- and postsynaptic spike trains can be simply explained by the superposition of the plasticity induced by all spike pairs (11, 12). Such a theory does not provide a mechanistic description of synaptic plasticity; instead it postulates that the curve in Fig. 1*B* (*Left*) can be used to summarize all that needs to be known of plasticity. This curve is also called a two-point kernel. Kempter et al. (1999) (11) analyzed the correspondence between

Author contributions: H.Z.S. wrote the paper.

The author declares no conflict of interest.

See companion article on page 19383.

[1]E-mail: Harel.Shouval@uth.tmc.edu.

STDP and rate-based plasticity theories. By using a simple model neuron and assuming that presynatic spikes are generated by a Poisson process with a given rate, they were able to reduce a theory based on linear superposition of the STDP curves to a rate-based theory. Their analysis shows that the STDP rule corresponds to a rate-based rule that is linearly dependent on the postsynaptic firing rate (Fig. 1*B*, *Right*) and on the covariance between the different inputs. These results also show that pair-based STDP does not correspond to the BCM rule (13). Further inspection of pair-based STDP shows that it cannot account for many experimental observations (14). For example, experimentally (9) spike timing-dependent LTP was only induced if spike pairs were delivered at a frequency above 10 Hz, a result that cannot be explained by pair-based kernel theory (9, 14).

Motivated by the failure of the pair-based kernel model, Pfister and Gerstner (2006) (13) developed a kernel-based model that took into account both pairs and triplets. In other words, plasticity can be summarized by two- and three-point kernels. The triplet-based theory could account for more experimental results and in particular the frequency dependence of STDP (9, 15). Indeed, pair-based LTD and triplet-based LTP were sufficient to account for experimental observations in visual cortex (Fig. 1*C*).

The article by Gjorgjieva et al. (3) further analyzes the triplet-based model by adopting the techniques used previously for pair-based STDP (11). The article shows that triplet-based STDP reduces to a BCM-like rule and additional temporal correlation-dependent components. To obtain metaplasticity the authors postulated an additional mechanism whereby the magnitude of the pair-based STDP is an increasing function of the temporal average of postsynaptic activity. Consequently, the triplet-based rule has many of the same features as BCM, such as generating selective receptive fields when presented with linearly independent input vectors. The additional components to the learning rule mean that it can also accomplish tasks that BCM cannot; for example, it can separate between patterns that are separable only because of their correlational structure but would seem identical on the basis of firing rates alone. These results indicate that a triplet-based theory of synaptic plasticity may be sufficient, because it can account both for cell-based experimental protocols and for higher-level features.

However, various experimental results have not been accounted for by the triplet-based theory. For example, the rule designed to account for the frequency dependence of STDP (15, 16) cannot at the same time account for plasticity protocols induced directly by spike triplets and quadruplets in a different synapse within a similar neocortical preparation (16). Further, whereas low-frequency pairs do not cause LTP when the presynaptic stimulus is delivered by activating a single presynaptic cell, they might if delivered extracellularlly, thus activating multiple synapses (15) because in terms of single synapse kernel-based theories, these two conditions are identical.

An alternative to kernel-based theories are mechanistic theories in which plasticity induced by different induction protocols arises from a common mechanism. Mechanistic models fall into two categories: biophysical and phenomenological (17, 18). Phenomenological models assume an underlying mechanism that is not explicitly mapped onto biophysical processes, in contrast to biophysical models, which assume mechanisms based on realistic assumptions; often the boundary between these categories is not sharp.

Biophysical models of synaptic plasticity make specific testable assumptions about the biophysical mechanisms resulting in changes to synaptic efficacies. For example, it is well known that calcium ions flowing into the postsynaptic spine through NMDA receptors play a major role in synaptic plasticity in many systems. Additionally, experimental observations and theoretical ideas have led to the notion that low levels of calcium elevation lead to LTD, whereas higher levels lead to LTP. Hence, such assumptions have gone into several calcium-dependent plasticity (CaDP) models of synaptic plasticity (Fig. 1*D*) (14, 19). These assumptions can account for various induction protocols, including STDP, but surprisingly STDP in such models has a second LTD region at $\Delta t > 0$. A second LTD region exists in hippocampal slices (14) but probably not in neocortical slices. The failure of CaDP to account for neocortical plasticity might be traced back to its assumptions, because in neocortex spike timing-dependent LTD does not depend on postsynaptic NMDA receptors. Alternative theories with two coincidence detectors might fit the data better (20).

The appropriate description level for synaptic plasticity is still not known and might depend on what exactly we are trying to understand. More research is required to test whether kernel based models are sufficient for explaining higher-order phenomena, and how they arise from the cellular biophysics, or whether biophysical models must be used instead.

1. Martin SJ, Grimwood PD, Morris RG (2000) Synaptic plasticity and memory: An evaluation of the hypothesis. *Annu Rev Neurosci* 23:649–711.
2. Whitlock JR, Heynen AJ, Shuler MG, Bear MF (2006) Learning induces long-term potentiation in the hippocampus. *Science* 313:1093–1097.
3. Gjorgjieva J, Clopath C, Audet J, Pfister JP (2011) A triplet spike-timing–dependent plasticity model generalizes the Bienenstock–Cooper–Munro rule to higher-order spatiotemporal correlations. *Proc Natl Acad Sci* 108:19383–19388.
4. Bienenstock EL, Cooper LN, Munro PW (1982) Theory for the development of neuron selectivity: Orientation specificity and binocular interaction in visual cortex. *J Neurosci* 2:32–48.
5. von der Malsburg C (1973) Self-organization of orientation sensitive cells in the striate cortex. *Kybernetik* 14:85–100.
6. Cooper L, Intrator N, Blais BS, Shouval HZ (2004) *Theory of Cortical Plasticity* (World Scientific, Hackensack, NJ).
7. Abraham WC, Bear MF (1996) Metaplasticity: The plasticity of synaptic plasticity. *Trends Neurosci* 19:126–130.
8. Bear MF (2003) Bidirectional synaptic plasticity: From theory to reality. *Philos Trans R Soc Lond B Biol Sci* 358: 649–655.
9. Markram H, Lübke J, Frotscher M, Sakmann B (1997) Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 275:213–215.
10. Bi GQ, Poo MM (1998) Synaptic modifications in cultured hippocampal neurons: Dependence on spike timing, synaptic strength, and postsynaptic cell type. *J Neurosci* 18:10464–10472.
11. Kempter R, Gerstner W, van Hemmen L (1999) Hebbian learning and spiking neurons. *Phys Rev E* 59: 4498–4514.
12. Song S, Miller KD, Abbott LF (2000) Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. *Nat Neurosci* 3:919–926.
13. Pfister JP, Gerstner W (2006) Triplets of spikes in a model of spike timing-dependent plasticity. *J Neurosci* 26:9673–9682.
14. Shouval HZ, Wang SS, Wittenberg GM (2010) Spike timing dependent plasticity: A consequence of more fundamental learning rules. *Front Comput Neurosci* 4:19.
15. Sjöström PJ, Turrigiano GG, Nelson SB (2001) Rate, timing, and cooperativity jointly determine cortical synaptic plasticity. *Neuron* 32:1149–1164.
16. Froemke RC, Dan Y (2002) Spike-timing-dependent synaptic modification induced by natural spike trains. *Nature* 416:433–438.
17. Senn W, Markram H, Tsodyks M (2001) An algorithm for modifying neurotransmitter release probability based on pre- and postsynaptic spike timing. *Neural Comput* 13:35–67.
18. Clopath C, Büsing L, Vasilaki E, Gerstner W (2010) Connectivity reflects coding: A model of voltage-based STDP with homeostasis. *Nat Neurosci* 13: 344–352.
19. Shouval HZ, Bear MF, Cooper LN (2002) A unified model of NMDA receptor-dependent bidirectional synaptic plasticity. *Proc Natl Acad Sci USA* 99: 10831–10836.
20. Karmarkar UR, Najarian MT, Buonomano DV (2002) Mechanisms and significance of spike-timing dependent plasticity. *Biol Cybern* 87:373–382.