# A Biophysical Model of Metaplasticity Can Account for Homeostatic Synaptic-Scaling

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**Abstract**

Synaptic scaling has been described as a non-Hebbian, activity-dependent plasticity mechanism that globally adjusts the synaptic gain of a given neuron in response to changes in its firing activity (Turrigiano et al. 1998, Desai et al. 1998). It has been proposed that synaptic scaling is reminiscent of the sliding-threshold hypothesis of the BCM theory (Bienenstock et al. 1982, Frégnac 1998) and could act to maintain cortical stability and homeostasis *in vivo*; however, its mechanistic basis remains unexplained. We show that a biophysical model of BCM-type metaplasticity can account for the experimentally observed synaptic scaling, suggesting that these two phenomena – scaling and metaplasticity – could share a common underlying physiological mechanism.

*Keywords:* synaptic scaling, metaplasticity, homeostasis, calcium, NMDA.

The intrinsic instability of associative Hebbian plasticity (Hebb 1949) has long been addressed in theoretical studies. Stabilization mechanisms, such as fixed average weight (von der Malsburg 1973), synaptic decay (Oja 1982), hard boundaries (Miller et al. 1989) and sliding threshold (Bienenstock et al. 1982) have been proposed and implemented in a variety of artificial learning systems (for a recent review, see Gerstner and Kistler 2002). One early biological correlate of these stabilization theories is the observation that properties of synaptic plasticity self-adjust over time, according to the history of cortical or synaptic activity (Clothiaux and Bear 1991). This phenomenon is termed "metaplasticity" (Abraham and Bear 1996). Recently, much experimental effort has been devoted to the characterization of "synaptic scaling" (Turrigiano et al. 1998), which has also been suggested to play important role in homeostatic synaptic-gain regulation. The resemblance between scaling and metaplasticity is appealing, though systematic study relating these observations has not been performed. This work aims to link synaptic scaling with prior formulations of stabilization methods, as well as with metaplasticity, providing them with a possible common molecular basis.

In synaptic scaling experiments, miniature excitatory postsynaptic currents (mEPSC) are measured following chronic alteration of network activity in cultures of visual cortical cells (Turrigiano et al. 1998). Reduction of activity by bathing the cultures in tetrodoxin (TTX, a blocker of sodium action potentials) for 48 hours results in an increase of the mEPSC amplitudes. Conversely, increase of activity by bathing the cultures in bicuculline (an antagonist of the inhibitory neurotransmitter $GABA_A$) results in a reduction of these amplitudes. Analogous results are observed in experiments in rat visual cortex *in vivo* (Desai et al. 1998). There, developmental periods corresponding to increased frequency of quantal events (due to synaptogenesis) display smaller mEPSC amplitudes, while periods of decreased input activity (due, for example, to visual deprivation) lead to greater amplitudes relative to control.

To simulate these results, we use a recently proposed calcium-dependent biophysical plasticity model (CaDP) (Shouval et al. 2002), which provides a means for a mechanistic description of experiments in plasticity. The CaDP model is based on three central assumptions. First, the level of intracellular calcium concentration determines the sign and magnitude of synaptic plasticity, with increasing levels of calcium inducing, successively, no-plasticity, long-term depression (LTD) and long-term potentiation (LTP). Second, this calcium is accounted for by its influx through N-metyl-D-aspartate receptors (NMDAR). Finally, back-propagating action potentials (BPAP) have a long afterdepolarizing component, and contribute to plasticity through the voltage-dependence of the NMDAR. We simulate a point neuron with 100 synapses receiving homogeneous Poisson spike-trains with the same average rate across synapses. The CaDP alone, as typical of many Hebbian-associative models, is unstable.

We first examine whether traditional stabilizing methods, such as setting saturation limits to weight growth or adding a decay term to the learning equation, suffice to explain the results of synaptic scaling. The results are shown in Figure 1. In the presence of hard boundaries, the final synaptic weights saturate at the lower or the upper limits for low and high input rates, respectively (Fig. 1a). With a decay term, the weights converge asymptotically to a fixed point given by the learning curve (Fig. 1b). In either case, the synaptic weights grow with increasing activity level, contrary to the synaptic scaling observations. It is also clear, by definition, that synaptic scaling could not arise from a mechanism that normalizes synaptic weights.

Alternative approaches to homeostatic control of synaptic growth have previously been presented, notably, the metaplasticity as embodied by the sliding modification threshold of the BCM theory (Bienenstock et al. 1982). This theory proposes that, in order to stabilize plasticity, the threshold between LTD and LTP changes as a function of the cellular firing history. Postulates and predictions of the BCM theory are consistent with experimental observations (Kirkwood et al. 1996, Wang and Wagner 1999); however, its formulation has been so far phenomenological. Biological evidence suggests that a possible mechanism for metaplasticity depends on NMDAR dynamics. It has been shown that NMDAR conductance changes as a function of activity; and this can be produced either by altering the number of these receptors in the postsynaptic membrane (Watt et al. 2000) or by changing the ratios of the surface expression of different NMDAR subunits (Rao and Craig, 1997, Quinlan et al. 1999, Philpot et al, 2001). The biophysical CaDP formulation is particularly suitable for a mechanistic interpretation of metaplasticity. We incorporate a kinetic model of metaplasticity based on insertion and removal of NMDAR into and from the synaptic membrane. Let $g_i$ be the fraction of internal NMDAR and $g_m$ be the fraction of NMDAR inserted in the membrane. The transition rates between $g_i$ and $g_m$ depend on the time-averaged depolarization of the cell. Thus, at low levels of activity, the equilibrium shifts towards increased $g_m$, so more calcium flows into the cell, promoting potentiation; while at high levels, it shifts towards increased $g_i$, promoting depression (see Appendix). Similarities between this molecular correlate of metaplasticity and the phenomenological formulation of the sliding-threshold mechanism are evident.

Simulations of the combined plasticity-metaplasticity model produce the basic property of synaptic scaling: increasing levels of cellular activity lead to an overall down-regulation of the synaptic weights (Fig. 2a). It should be noted that no additional constraints for synaptic stabilization are needed with metaplasticity. Direct quantitative data comparison is difficult, because, in experiments, the activity of all excitatory or all inhibitory inputs are completely shut down, while here we investigate the response to graded modification of the stimuli. In addition, different setups induce different amounts of mEPSC amplitude change. In culture, treatment with TTX yielded an increase in mEPSC amplitudes to $192 \pm 16\%$, while treatment with bicuculline decreased the quantal amplitudes to $70 \pm 4\%$ of the control value (Turrigiano et al. 1998). Under monocular deprivation, the upscaling was to 123%; and during development, the downscaling was to 61% of control (Desai et al. 2002). In our simulations, the final synaptic weight corresponding to the lowest frequency (5 Hz) was 250% of its initial value and the weights corresponding to the highest frequency (40 Hz) was 59% of its initial value. These values depend

on the precise parameters of the metaplasticity learning, but the qualitative agreement with experimental results is apparent.

Downscaling of the weights does not reverse the increasing input-output relation; this indicates that the information contained in changes of the stimulating rate can still be propagated, but the increase is much more moderate than in the absence of metaplasticity (Fig. 2b). In addition, the final distribution of synaptic weights is unimodal (Fig. 3a), in agreement with theoretical predictions that follow from scaling experiments (van Rossum et al. 2001). Similar results can be obtained using a model involving differential regulation of the surface expression of the NMDAR subunits.

The existence of a long-term homeostatic regulation of synaptic weights raises two potential problems. First, there is evidence that AMPAR and NMDAR scale in the same direction (Watt et al. 2000); this opposes the idea that NMDAR dynamics counteracts excessive AMPAR growth. Second, these results are in apparent disagreement with the well-established rate-based LTD and LTP-inducing protocols, in which low-frequency stimulation elicits depression and high-frequency stimulation elicits potentiation of synaptic weights. Intuitively, it is difficult to predict what the fixed point of the synaptic evolution is if all of a cell's synapses undergo, for example, high-frequency stimulation. Both issues are elucidated when the time-scale of the NMDAR dynamics is taken into account.

Typically, experiments in which metaplasticity or scaling are carried out over hours or days, while the LTP and LTD experiments are performed in seconds or minutes. Therefore, the results of these experiments are compatible if the time constant for the changes in the AMPAR conductance is significantly shorter than that of NMDAR conductance. In this case, the evolution of these two conductances follows a push-pull behavior, as depicted in Fig. 3b. An abrupt change from a high input rate (40 Hz) to a low input rate (10 Hz) will initially elicit depression of the AMPAR. Because the cellular activity is low, NMDAR conductance slowly increases, followed by a subsequent potentiation of the synaptic weights. If the input rate switches from a low to a high rate, the weights are first potentiated, and then depressed. This implies that, under the conditions inducing synaptic scaling, the short-run modifications of the mEPSC amplitudes should have opposite directions relative to the long-run modifications. Thus far, the full temporal evolution of the mEPSC amplitudes, in these conditions, has not been observed; further experiments are needed to test this prediction.

NMDAR varies in response to the neuronal firing activity, not in response to the AMPAR conductance levels *per se*. However, a change in NMDAR conductance will inevitably lead to an AMPAR follow-up, in agreement with the observation that these two conductances are co-regulated by activity, as can also be seen in Fig. 3b. According to our model, blockage of NMDAR during scaling-inducing experiments should not lead to change in mEPSC amplitudes. To date, experimental data still do not agree as to whether activation of NMDAR plays a central role in the synaptic scaling (Lissin et al, 1998; Leslie et al, 2001).

Metaplasticity, and more recently, synaptic scaling, have been observed in a wide range of neuronal systems and across species (Abraham and Bear, 1996, Bear 1996, Turrigiano 1999). Theoretical and experimental studies have shown that both are homeostatic in nature, and each promotes stability and competition in the learning system. In particular, the BCM theory has been able to account for input selectivity and receptive field formation in complex input environments, under both phenomenological (Law and Cooper 1994) and biophysical (Yeung et al. 2002) formalisms. We have shown here that metaplasticity and scaling could be related processes, sharing a common underlying mechanism. We propose that this mechanism relies on the balance between a fast and a slow activity-dependent regulation of, respectively, AMPAR and NMDAR.

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**Figures and legends**

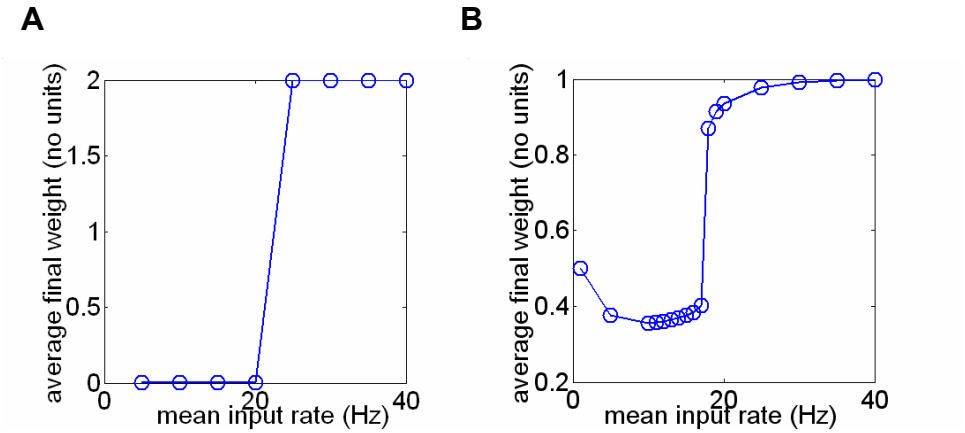


**FIG. 1.** Average of the 100 synaptic weights after stimulation at various frequencies. *A*: In the presence of hard boundary conditions, the weights saturate at the upper and lower limits. *B*: When the decaying term of the learning equation is different from zero, the fixed points of the weights is given by the U-shaped learning function. The results are independent of initial conditions. These different synaptic stabilization methods are not consistent with synaptic scaling observations.

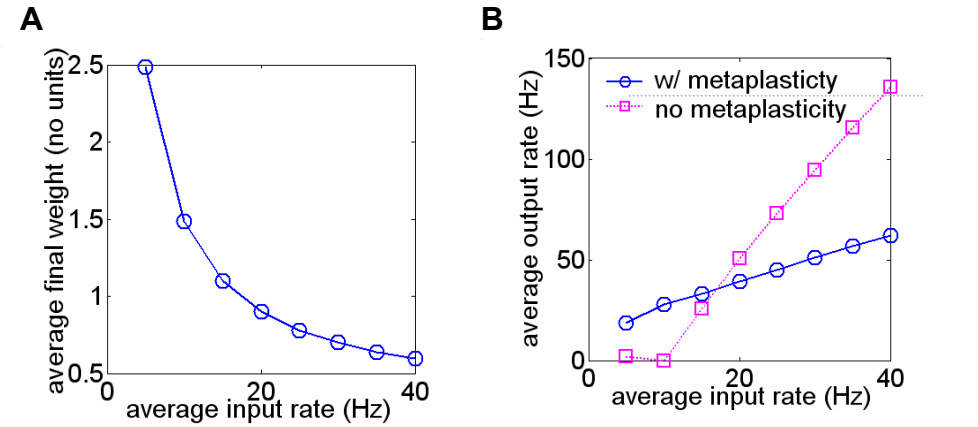


**FIG. 2.** Implementation of the CaDP and metaplasticity yields results comparable to those of synaptic scaling. *A*: Average final weight decays with increasing synaptic activity. *B*: The output rate still scales with the input rate. The input-output relation in the absence of metaplasticity (square) is shown, for comparison.

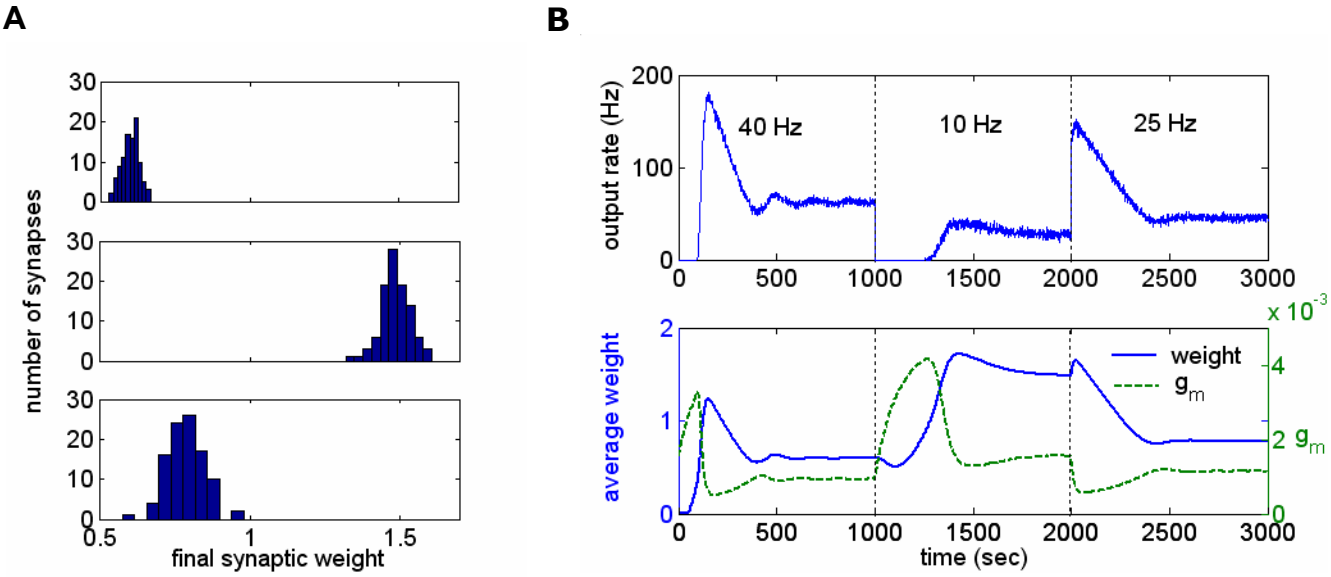


**FIG. 3.** *A*: The final distribution of the synaptic weights is a unimodal one, in agreement with the predictions of synaptic scaling. *B*: Time evolution of the output rates (top panel), the average synaptic weights (bottom panel, solid line) and the NMDAR conductance (bottom panel, dashed line) when the stimulating frequency switches from 40 Hz to 10 Hz at 1000 sec of simulated time, and from 10 Hz to 25 Hz at 2000 seconds of simulated time. The weights evolve first in one direction, then change direction as the effects of metaplasticity come to play.