

# Corrections and Retraction

## CORRECTIONS

### NEUROSCIENCE

Correction for “Calcium-based plasticity model explains sensitivity of synaptic changes to spike pattern, rate, and dendritic location,” by Michael Graupner and Nicolas Brunel, which appeared in issue 10, March 6, 2012, of *Proc Natl Acad Sci USA* (109:3991–3996; first published February 22, 2012; 10.1073/pnas.1109359109).

The authors note that they omitted a reference to an article by Kumar and Mehta [Kumar A, Mehta MR (2011) Frequency-dependent changes in NMDAR-dependent synaptic plasticity. *Front Comput Neurosci* 5:38, 10.3389/fncom.2011.00038]. This reference should be cited on page 3993, right column, third full paragraph, after lines 5–10, “In this preparation, pairs of single pre- and postsynaptic spikes repeated at  $\theta$ -frequency yield LTD only (similar to our D region), whereas pairing a single presynaptic spike with a burst of two postsynaptic spikes yields curves that are similar to our DPD or P region, depending on the duration of the protocol.”

Additionally, on page 3992, left column, first full paragraph, line 12, “ $Noise(t) = \sigma\sqrt{\tau}\Theta[c(t) - \min(\theta_d, \theta_p)]\eta(t)$ ” should instead appear as “ $Noise(t) = \sigma\sqrt{\tau}\sqrt{\Theta(c(t) - \theta_d) + \Theta(c(t) - \theta_p)}\eta(t)$ ”.

www.pnas.org/cgi/doi/10.1073/pnas.1220044110

### NEUROSCIENCE, CHEMISTRY

Correction for “Marked difference in saxitoxin and tetrodotoxin affinity for the human nociceptive voltage-gated sodium channel ( $Na_v1.7$ ),” by James R. Walker, Paul A. Novick, William H. Parsons, Malcolm McGregor, Jeff Zablocki, Vijay S. Pande, and J. Du Bois, which appeared in issue 44, October 30, 2012, of *Proc Natl Acad Sci USA* (109:18102–18107; first published October 17, 2012; 10.1073/pnas.1206952109).

The authors note that the title appeared incorrectly. The title should instead appear as “Marked difference in saxitoxin and tetrodotoxin affinity for the human nociceptive voltage-gated sodium channel ( $Na_v1.7$ ).” The online version has been corrected.

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### SOCIAL SCIENCES

Correction for “How social and genetic factors predict friendship networks,” by Jason D. Boardman, Benjamin W. Domingue, and Jason M. Fletcher, which appeared in issue 43, October 23, 2012, of *Proc Natl Acad Sci USA* (109:17377–17381; first published October 8, 2012; 10.1073/pnas.1208975109).

The authors note that within the Acknowledgments, the line “a program project designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris” should instead appear as “a program project directed by Kathleen Mullan Harris and designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris at the University of North Carolina at Chapel Hill.”

Also within the Acknowledgments, the line “Persons interested in obtaining data files from Add Health should contact Add Health, Carolina Population Center, 123 W. Franklin Street, Chapel Hill, NC 27516-2524 (addhealth@unc.edu)” should instead appear as “Information on how to obtain the Add Health data files is available on the Add Health Web site (<http://www.cpc.unc.edu/addhealth>). No direct support was received from Grant P01-HD31921 for this analysis.”

Also within the Acknowledgments, the line “The authors also acknowledge funding from the National Institute of Child Health and Human Development (1R21HD071884)” should instead appear as “The authors also acknowledge cofunding from the National Institute of Child Health and Human Development and the Office of Behavioral and Social Sciences Research (OBSSR) (1R21HD071884).”

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## RETRACTION

### MEDICAL SCIENCES

Retraction for “Glycogen synthase kinase 3 $\beta$  transfers cytoprotective signaling through connexin 43 onto mitochondrial ATP-sensitive K<sup>+</sup> channels,” by Dennis Rottlaender, Kerstin Boengler, Martin Wolny, Astrid Schwaiger, Lukas J. Motloch, Michel Ovize, Rainer Schulz, Gerd Heusch, and Uta C. Hoppe, which appeared in issue 5, January 31, 2012, of *Proc Natl Acad Sci USA* (109: E242–E251; first published January 11, 2012; 10.1073/pnas.1107479109).

The authors wish to note the following: “In the course of intense investigations, the first author (D.R.) has admitted that he has committed intentional, systematic manipulation of the electrophysiological data collected in Cologne. Of note, the manipulation of data does not affect Western blots and infarct size data collected in Essen, Giessen, and Cologne, cell volume data collected in Essen, cell viability data collected in Salzburg and Cologne, or transgenic mice contributed from Essen and Lyon. Accordingly, we wish to retract the paper.”

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# Calcium-based plasticity model explains sensitivity of synaptic changes to spike pattern, rate, and dendritic location

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Multiple stimulation protocols have been found to be effective in changing synaptic efficacy by inducing long-term potentiation or depression. In many of those protocols, increases in postsynaptic calcium concentration have been shown to play a crucial role. However, it is still unclear whether and how the dynamics of the postsynaptic calcium alone determine the outcome of synaptic plasticity. Here, we propose a calcium-based model of a synapse in which potentiation and depression are activated above calcium thresholds. We show that this model gives rise to a large diversity of spike timing-dependent plasticity curves, most of which have been observed experimentally in different systems. It accounts quantitatively for plasticity outcomes evoked by protocols involving patterns with variable spike timing and firing rate in hippocampus and neocortex. Furthermore, it allows us to predict that differences in plasticity outcomes in different studies are due to differences in parameters defining the calcium dynamics. The model provides a mechanistic understanding of how various stimulation protocols provoke specific synaptic changes through the dynamics of calcium concentration and thresholds implementing in simplified fashion protein signaling cascades, leading to long-term potentiation and long-term depression. The combination of biophysical realism and analytical tractability makes it the ideal candidate to study plasticity at the synapse, neuron, and network levels.

computational model | frequency-dependent plasticity | bistable synapse

Numerous experiments have shown how synaptic efficacy can be increased [long-term potentiation (LTP)] or decreased [long-term depression (LTD)] by the relative spike timing [spike timing dependent plasticity (STDP)] (1–4) and firing rate of pre- and postsynaptic neurons (5, 6). Studies in different brain regions and under varying experimental conditions have revealed a plethora of different types of STDP (7). Experimental protocols using a diversity of spike patterns have furthermore highlighted the complexity and nonlinearity of plasticity rules in different systems (6, 8–11). However, how the diversity and nonlinearity of plasticity results emerge from the interplay between the underlying biochemical synaptic machinery and activity patterns remains elusive.

Molecular studies have identified two key elements for the induction of synaptic plasticity in hippocampus and neocortex. First, postsynaptic calcium entry mediated by NMDA receptors (NMDARs) (12) and voltage-dependent  $\text{Ca}^{2+}$  channels (VDCCs) (13–15) has been shown in many cases to be a necessary (15–17) and sufficient (18–20) signal for the induction of synaptic plasticity. Second, calcium, in turn, triggers downstream signaling cascades involving protein kinases (mediating LTP) and phosphatases (mediating LTD) (10, 21–23). Another G protein-coupled LTD induction pathway involves retrograde signaling by endocannabinoids (15, 24), whose efficiency is greatly modulated by postsynaptic calcium (15, 25, 26). Depending on type of synapse, age, and induction protocol, different types and combinations of signaling cascades provide the link between the activity-dependent postsynaptic calcium signal and expression mechanisms of synaptic plasticity, such as number and/or phosphorylation level of

postsynaptic AMPA receptors or changes in presynaptic transmitter release probability (12).

Despite the large amount of modeling studies on abstract and detailed implementations of biochemical signaling cascades (review in ref. 27), a mechanistic understanding of whether and how the calcium signal, combined with the multitude of identified signaling cascades, can give rise to the observed phenomenology of synaptic plasticity is still lacking. To make progress on this issue, we followed the path pioneered by Shouval et al. (28) and devised a biologically plausible but simplified calcium-based model that provides a link between stimulation protocols, calcium transients, protein signaling cascades, and evoked synaptic changes. The model implements in a schematic fashion two opposing calcium-triggered pathways mediating increases of synaptic strength (LTP; i.e., protein kinase cascades) and decreases of synaptic strength (LTD; i.e., protein phosphatase cascades or G-protein cascades). The model is shown to be able to account for a wide range of experimental plasticity outcomes in hippocampal cultures and hippocampal as well as neocortical slices. Fitting this data quantitatively allows us to predict differences in the underlying calcium dynamics between these different studies.

## Results

**Synaptic Efficacy Changes Induced by Calcium.** We consider a model of a single synapse submitted to trains of pre- and postsynaptic action potentials (APs). The model represents the state of a synapse as a synaptic efficacy variable,  $\rho(t)$ , whose temporal evolution is described by a first-order differential equation (Eq. 1):

$$\tau \frac{d\rho}{dt} = -\rho(1-\rho)(\rho_{\star} - \rho) + \gamma_p(1-\rho)\Theta[c(t) - \theta_p] - \gamma_d\rho\Theta[c(t) - \theta_d] + \text{Noise}(t). \quad [1]$$

In Eq. 1,  $\tau$  is the time constant of synaptic efficacy changes happening on the order of seconds to minutes. The first term on the right-hand side describes the dynamics of the synaptic efficacy in the absence of pre- and postsynaptic activity. Here, we choose a cubic function of  $\rho$  that endows the synapse with two stable states at rest: one at  $\rho = 0$ , a DOWN state corresponding to low efficacy, and one at  $\rho = 1$ , an UP state corresponding to high efficacy.  $\rho_{\star} = 0.5$  is the boundary of the basins of attraction of the two stable states. This bistable behavior is consistent with some experiments (29–31) as well as some biochemically detailed models (32, 33). It could be easily modified to account for more stable states or even a continuum of states without qualitatively modifying most of the results reported below.

Author contributions: M.G. and N.B. designed research; M.G. performed research; M.G. analyzed data; and M.G. and N.B. wrote the paper.

The authors declare no conflict of interest.

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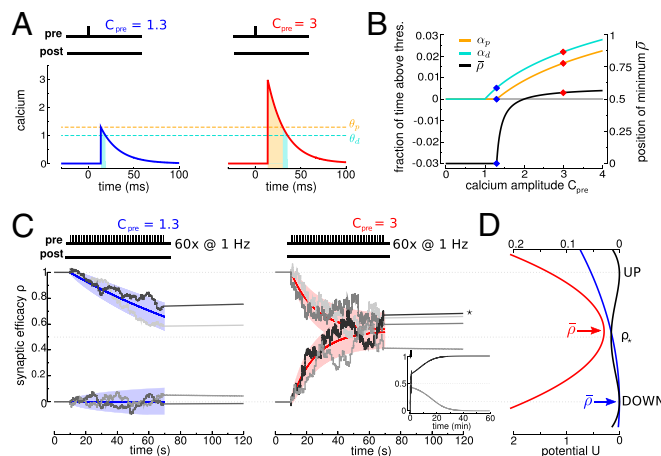
The next two terms in Eq. 1 describe (in a highly simplified fashion) calcium-dependent signaling cascades leading to synaptic potentiation (e.g., kinases) and depression (e.g., phosphatases or G protein-coupled pathways), respectively (similar to Wittenberg)\*. The synaptic efficacy variable tends to increase or decrease when the instantaneous calcium concentration,  $c(t)$ , is above the potentiation ( $\theta_p$ ) or depression threshold ( $\theta_d$ ), respectively ( $\Theta$  denotes the Heaviside function:  $\Theta[c - \theta] = 0$  for  $c < \theta$  and  $\Theta[c - \theta] = 1$  for  $c \geq \theta$ ).  $\gamma_p/\gamma_d$  measures the rates of synaptic increase/decrease when potentiation/depression thresholds are exceeded. The last term in Eq. 1 is an activity-dependent noise term,  $\text{Noise}(t) = \sigma\sqrt{\tau\Theta[c(t) - \min(\theta_d, \theta_p)]}\eta(t)$ , where  $\sigma$  measures the amplitude of the noise,  $\eta(t)$  is a Gaussian white noise process with unit variance density, and the  $\Theta$  function gives an activity dependence to noise (it is present whenever calcium is above the potentiation and/or depression thresholds). This term accounts for activity-dependent fluctuations stemming from stochastic neurotransmitter release, stochastic channel opening, and diffusion.

Changes in the synaptic efficacy are induced by the calcium concentration,  $c(t)$ , which is simply the linear sum of individual calcium transients elicited by pre- and postsynaptic APs. The calcium concentration makes a jump of size  $C_{\text{pre}}$  after each presynaptic spike (with a delay  $D$ ) and then decays exponentially with time constant  $\tau_{\text{Ca}}$ , which is on the order of milliseconds, modeling calcium influx induced by NMDAR activation (34) (Fig. 1A). Likewise, a calcium transient triggered by a postsynaptic spike mediated by VDCC activation is described by a jump of size  $C_{\text{post}}$  followed by an exponential decay with the same time constant as for the presynaptic spike,  $\tau_{\text{Ca}}$  (SI Appendix, Simplified Calcium Model). For simplicity, we neglect the NMDA nonlinearity, finite rise times, and different decay time constants for NMDA- and VDCC-mediated calcium transients here, and their impact on the model results is discussed in SI Appendix.

Importantly, the calcium-induced fast (approximately milliseconds) changes in the synaptic efficacy depend on the relative times spent by the calcium trace above the potentiation and depression thresholds. Increasing the evoked calcium amplitude increases the time spent above both thresholds (Fig. 1B). Repetitive presentations of the same calcium transients lead to the accumulation of changes in  $\rho$  caused by the slow time scale of  $\rho$  in the absence of activity (Fig. 1C, Inset). When calcium amplitudes and  $\gamma_p$  are sufficiently large, these accumulated changes provoke a transition from the DOWN to the UP state with high probability (that is, they induce LTP). Such a transition occurs stochastically because of the noise in the model (Fig. 1C). Also, the protocol has to be long enough for the variable  $\rho$  to have a chance to cross the unstable fixed point.

In the model, synaptic activity induces small but fast changes (within milliseconds) in the efficacy variable. In the absence of activity, the synaptic activity slowly decays to one of the stable steady states on a time scale of minutes (Fig. 1C, Inset). Slow dynamics after the induction protocol are seen in many experiments (3, 6, 10) but not experiments involving putative single synaptic connections (29, 31) that are consistent with abrupt changes between two discrete states. This discrepancy could be reconciled by a simple modification of the model, in which the synaptic efficacy would be determined by applying a threshold-nonlinear to the  $\rho$ -variable.

The model is simple enough, so that the probabilities to induce LTP and LTD can be calculated analytically. The analytical results reproduce the model behavior under two assumptions: (i) single calcium transients induce small changes in the synaptic efficacy (Fig. 1C), and (ii) the depression and potentiation rates ( $\gamma_d$  and  $\gamma_p$ ) are sufficiently large so that one can neglect the cubic term in Eq. 1 during synaptic stimulation (Fig. 1D, note the different scales for quadratic and double-well potentials). These assumptions reduce Eq. 1 to an Ornstein–Uhlenbeck process for which the potential of  $\rho$  during stimulation is quadratic with the minimum at  $\bar{\rho}$  (Fig. 1B and D and SI Appendix). The outcome of



**Fig. 1.** Repeated calcium transients induce transitions between the two stable states of synaptic efficacy. (A) A presynaptic spike at time  $t = 0$  ms induces a postsynaptic calcium transient of amplitude  $C_{\text{pre}}$  after a delay  $D = 13.7$  ms. *Left* and *Right* show transients with two different amplitudes that are indicated above the panels. The times spent above the depression (turquoise) and potentiation (orange) thresholds are indicated by shaded regions. (B) The higher the induced calcium transient,  $C_{\text{pre}}$ , the more time is spent above the depression (turquoise) and potentiation (orange) thresholds (left-hand y axis). Depression and potentiation together determine the average asymptotic value of synaptic efficacy  $\bar{\rho}$  (black; right-hand y axis) (SI Appendix). The two examples from A are indicated (◆). (C) Repeated calcium transients of high amplitude can lead to a transition from the DOWN to the UP state. The dynamics of  $\rho$  are shown in response to 60 presynaptic spikes at 1 Hz inducing calcium transients of low (*Left*) and high (*Right*) amplitude.  $\rho$  resides initially in the UP or DOWN state. Two instances of noise are shown for each initial condition (gray lines). ★, A DOWN to UP transition occurs for this case (*Right*). *Inset* shows the temporal evolution of  $\rho$  on a longer time scale for the two cases starting at the DOWN state in *Right*. The dynamics of the mean (colored line) and SD (shaded area) for the corresponding Ornstein–Uhlenbeck processes are depicted for each stimulation protocol and the two initial conditions. (D) During stimulation, the potential of the synaptic efficacy is approximately quadratic and has a single minimum at  $\bar{\rho}$  (indicated by a colored arrow and shown for the two cases of C; scale at the bottom). In the absence of activity, the potential has two minima (the black line corresponds to two stable states; scale at the top). Note the different scales of the potential during (scale at the bottom) and in the absence of (scale at the top) synaptic activity (because  $\gamma_p, \gamma_d \gg 1$ ; see text).

a particular plasticity protocol will be largely determined by whether  $\bar{\rho}$  is above or below the unstable fixed point  $\rho_* = 0.5$ . LTP tends to be induced if  $\bar{\rho} > \rho_*$  (Fig. 1C, *Right*), whereas LTD tends to be induced if  $\bar{\rho} < \rho_*$  (Fig. 1C, *Left*).

#### Spike Pair Stimulation Can Evoke a Plethora of Different STDP Curves.

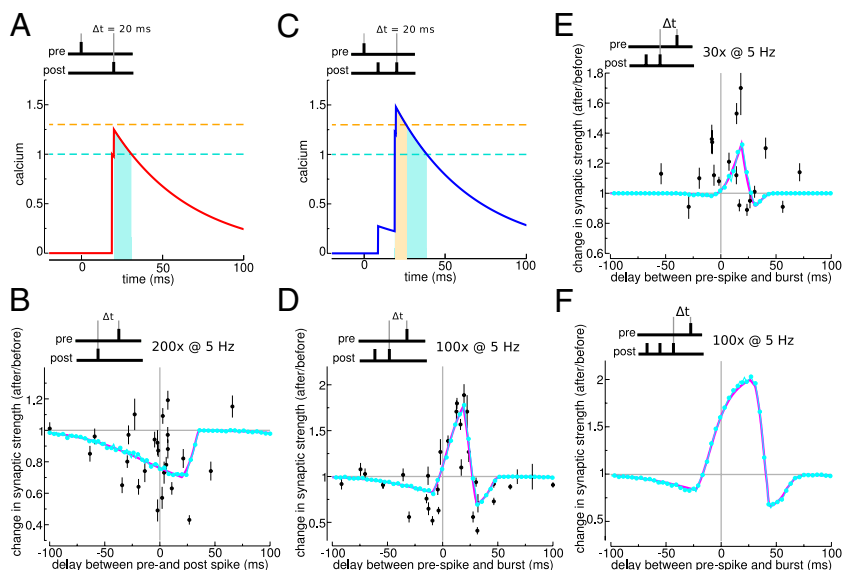
We start by explaining how the model reproduces the classical STDP curve (that is, depression for post-pre pairs and potentiation for pre-post pairs). Such a curve can be obtained when the potentiation threshold is larger than the depression threshold ( $\theta_p > \theta_d$ , consistent with ref. 22), the amplitude of the postsynaptic calcium transient is larger than the potentiation threshold ( $C_{\text{post}} > \theta_p$ ), and the amplitude of the presynaptic transient is smaller than the potentiation threshold ( $C_{\text{pre}} < \theta_p$ ). In addition, we impose that spike pairs with a large time difference should not evoke efficacy changes, which is the case if potentiation and depression rates balance on average during the protocol (i.e.,  $\bar{\rho} = 0.5$ ) (SI Appendix). These conditions yield the classical STDP curve (Fig. 2B).

For large  $\Delta t$ , pre- and postsynaptic calcium transients do not interact, and contributions from potentiation (because of the postsynaptic spike) and depression (because of the post- and presynaptic spikes if  $C_{\text{pre}} > \theta_d$ ) cancel each other, leading to no synaptic changes on average. For short negative  $\Delta t$ , the presynaptically evoked calcium transient rises above the depression threshold. Consequently, depression increases, whereas potentiation remains constant, which brings the potential minimum

\*Wittenberg G (2009) Synaptic decision making: flipping switch-like synapses with cubic autocatalysis. Front Syst Neurosci Conference Abstract, 10.3389/conf.neuro.06.2009.03.273.







**Fig. 3.** Numbers of postsynaptic spikes and repetitions of the stimulation motif qualitatively change the STDP curve. (A) Compound calcium trace evoked by a spike pair for  $C_{\text{pre}} = 1$ ,  $C_{\text{post}} = 0.276$ , and  $\Delta t = 20$  ms. For these parameter values, the calcium trace remains below the potentiation threshold ( $\theta_p = 1.3$ ,  $\theta_d = 1$ ). (B) For the parameters of A, spike pair simulation induces synaptic depression for small positive and negative values of  $\Delta t$ . (C) Adding a postsynaptic spike, resulting in a post-synaptic burst with an interburst interval of 11.5 ms, leads to crossing of the potentiation threshold. (D) Prespike and postburst stimulation results in a DPD curve. (E) Reducing the number of prespike and post-burst motif presentations from 100 to 30 turns the DPD curve into a PD curve exhibiting potentiation, with little depression at positive  $\Delta t$ . (F) Prespike and postburst stimulation with three postsynaptic spikes amplify potentiation at short positive  $\Delta t$  values. All data points are taken from plasticity experiments in hippocampal slices (mean  $\pm$  SEM) (11). Analytical results of changes in synaptic strength are shown in magenta, and simulation results are shown in cyan (see *SI Appendix, Table S2* for parameters).

tiation is seen when the duration of the protocol is reduced (Fig. 3E). The model parameters can be fitted quantitatively to the data of ref. 11 (*SI Appendix* and *Table S2*). The model can then be used to predict the plasticity outcomes for arbitrary protocols in the same experimental setting. For example, we predict that adding a third spike in the burst would yield broader and stronger LTP at positive  $\Delta t$  and short negative  $\Delta t$  (Fig. 3F).

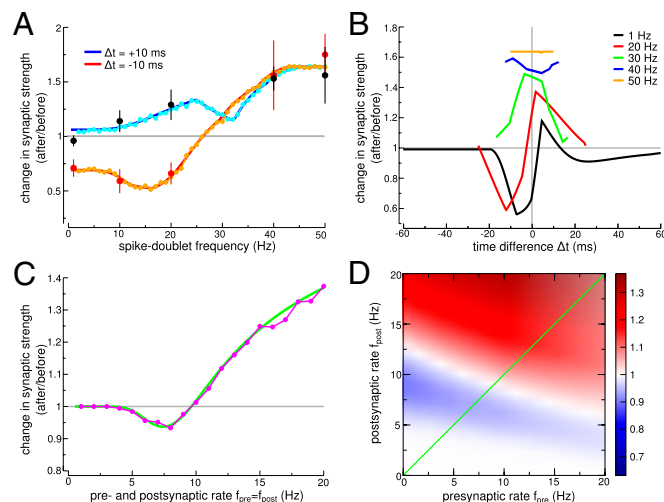
**Spike Triplets and Quadruplets.** We now show that our synapse model naturally reproduces nonlinearities of spike triplet and quadruplet experiments if calcium amplitudes of pre- and postsynaptically evoked transients have different amplitudes. In those experiments from hippocampal cultures, post-pre-post triplets and post-pre-pre-post quadruplets are shown to evoke LTP, whereas pre-post-pre triplets and pre-post-post-pre quadruplets induce no synaptic changes (or little potentiation) (10).

We fitted the synapse model to experimental plasticity results from protocols with spike triplets and quadruplets (*SI Appendix, Fig. S3*) (10). The resulting parameter sets are located in the DP region, consistent with the experimental results on spike pairs in hippocampal cultures (3, 10). The fit consistently yields a large, postsynaptically evoked calcium amplitude  $C_{\text{post}} > C_{\text{pre}}$  (*Discussion* and *SI Appendix, Fig. S3A*). Consequently, post-pre-post triplets lead to stronger activation of potentiation compared with pre-post-pre triplets (*SI Appendix, Fig. S3B*). Together with a potentiation rate that is larger than the depression rate ( $\gamma_p > \gamma_d$ ), this model creates an imbalance in plasticity outcomes between pre-post-pre and post-pre-post triplets (*SI Appendix, Fig. S3C and D*). The model is also able to fit the quadruplet data (*SI Appendix, Fig. S3E*), again because of the pronounced difference between pre- and postsynaptically evoked calcium transients. Finally, parameters that best fit triplet and quadruplet data also reproduce the pair data (*SI Appendix, Fig. S3F*).

**Plasticity Vs. Firing Rate.** Here, we show that the firing rate dependence of plasticity results emerges naturally in the model because of interactions between successive calcium transients. In visual cortex slices, spike pairs at very low frequency induce no significant changes for short positive  $\Delta t$  ( $\Delta t = 10$  ms) (1, 6), whereas pronounced LTD is obtained for short negative  $\Delta t$  ( $\Delta t = -10$  ms). However, pairings at high frequency induce LTP only (6).

We successfully fitted the synapse model to data obtained with pre-post ( $\Delta t = 10$  ms) and post-pre spike pairs ( $\Delta t = -10$  ms) presented at frequencies ranging from 0.1 to 50 Hz (Fig. 4) (6). The fit results reside in the DPD and DPD' regions (*SI Appendix, Fig. S2*) and lead to STDP curves for low frequencies, which are biased to depression for the small  $|\Delta t|$  except for short positive  $\Delta t$

values at which no or little potentiation is evoked (Fig. 4B). Increasing the stimulation frequency naturally leads to an increase in time spent by the calcium trace above the potentiation threshold, because successive calcium transients start to interact with each other, which progressively leads to LTP at all time differences, consistent with the information in ref. 6 (Fig. 4A; compare Fig. 4B



**Fig. 4.** Plasticity vs. firing frequency. (A) Periodic pre-post pairs ( $\Delta t = 10$  ms) evoke no change at low-presentation frequencies and LTP at high frequencies, whereas post-pre pairs ( $\Delta t = -10$  ms) lead to depression at low frequencies and potentiation at high frequencies. Data points are taken from plasticity experiments in cortical slices (6) (mean  $\pm$  SEM). Analytical results of changes in synaptic strength are shown in blue and red, and simulation results are shown in cyan and orange. (B) Change in synaptic strength as a function of  $\Delta t$  for various frequencies  $f$  (as indicated). Low presentation frequencies (black line) of spike pairs lead to a DPD curve with a narrow LTP region. Potentiation is recruited when consecutive calcium transients start to interact at high frequencies, leading to potentiation only above 29 Hz for all  $\Delta t$ . (C) Pre- and postsynaptic Poisson firing at equal rates ( $f_{\text{pre}} = f_{\text{post}}$ ) evokes no synaptic changes at low rates, LTD at intermediate rates, and LTP at high rates. Analytical results of changes in synaptic strength are shown in green, and simulation results are shown in magenta. (D) The change in synaptic strength (analytical results) in response to Poisson stimulation is shown for all combinations of pre- and postsynaptic rates. The green diagonal illustrates the values depicted in C (see *SI Appendix, Table S2* for parameters).

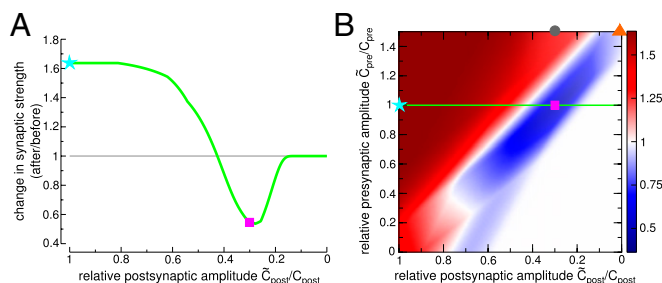
with figure 7 in ref. 6). Our model, furthermore, qualitatively reproduced experimental plasticity results in response to random firing in which spike times of both pre- and postsynaptic neurons are jittered and LTD is evoked at low frequencies, whereas high frequencies elicit LTP (*SI Appendix, Fig. S4*) (6).

The above-studied deterministic spike patterns are at odds with experimentally recorded spike trains in vivo, which show a pronounced temporal variability similar to a Poisson process. We, therefore, turn to investigate the model in response to uncorrelated Poisson spike trains of pre- and postsynaptic neurons (*SI Appendix, Fig. S10*). The synapse model predicts that pre- and postsynaptic firings contribute in a similar way to synaptic efficacy changes in visual cortex: no change for low pre- and post rates, LTD for intermediate rates, and LTP for high rates (Fig. 4 C and D). The model also predicts that LTP occurs for purely post synaptic activity at high frequency. Such a behavior could, however, be prevented through a frequency-dependent attenuation of the postsynaptically induced calcium transients, modeling failure in backpropagating consecutive APs at high frequencies.

**Synaptic Plasticity and Dendritic Location.** While fitting our model to the plasticity results above, we have so far neglected any influence of dendritic filtering such as attenuation of the backpropagating AP. We show here that the model reproduces the switch from LTP, for proximal layer 5 to layer 5 synapses, to LTD for distal neocortical layer 2/3 to layer 5 synapses, since attenuation of AP backpropagation leads to reduced calcium influx (38).

Using the parameter set obtained from fitting our model to plasticity outcomes at proximal cortical synapses (Fig. 4) and varying only the evoked calcium amplitudes reproduces a bulk of experimental data on the location dependence of plasticity. (i) LTP turns into LTD at distal synapses when the postsynaptic calcium amplitude drops to 30%, which is in agreement with the experimentally observed magnitude of calcium influx reduction at distal dendrites (Fig. 5, magenta square). (ii) Large excitatory postsynaptic potentials (EPSPs) induced experimentally by extracellular stimulation or boosting of single synaptic inputs, leading to higher presynaptically evoked calcium influx ( $C_{\text{pre}}$ ) paired with APs, rescue LTP at distal dendrites (Fig. 5B, gray circle). (iii) Strong distal presynaptic input alone evokes LTD (Fig. 5B, orange triangle). All these results are naturally explained by the dependence of the amplitude of the calcium transient on dendritic location, and no parameter tuning is needed to reproduce them.

Another study on dendritic location dependence of plasticity in the somatosensory cortex showed that proximal LTP turns into LTD at distal synapses for pre-post pairing, whereas proximal LTD turns into distal LTP for post-pre pairings (39). These results can be explained in the framework of our model by a DPD plasticity window that shifts to negative  $\Delta t$  at distal synapses because of delayed NMDAR activation.



**Fig. 5.** LTP turns into LTD at distal synapses because of reduced calcium influx. (A) Reducing the postsynaptically evoked calcium amplitude because of the attenuation of the backpropagating AP turns LTP into LTD (magenta square, reduction to 30%). (B) Change in synaptic strength as a function of deviations of the pre- and postsynaptically evoked calcium amplitudes from the parameters used in Fig. 4 (*SI Appendix, Table S2*). The green line illustrates the dependence of plasticity on the postsynaptic amplitude as in A. LTP can be rescued by boosting presynaptic stimulation (gray circle), but strong presynaptic stimulation alone evokes LTD (orange triangle).

## Discussion

The model presented here posits that synaptic changes are driven by calcium transients evoked by pre- and postsynaptic spikes through potentiation and depression thresholds that represent (in a simplified fashion) protein signaling cascades leading to LTP and LTD. This model allows us to analytically compute plasticity outcomes as a function of model parameters for deterministic as well as stochastic protocols. This feature enabled us to fully characterize the behavior of the model in response to standard STDP protocols and show its ability to fit a large set of experimental data in different preparations. Because of the properties of calcium transients, our synaptic learning rule (as the experimental data) is naturally sensitive to both spike timing and firing rates of both pre- and postsynaptic neurons. The model illustrates that the calcium trace together with the nonlinear calcium-dependent activation of signaling cascades are potentially sufficient to explain the diversity and nonlinearity of plasticity outcomes.

Our model makes several predictions. We predict how Poisson stimulation shapes synaptic plasticity in cortical slices, hippocampal cultures, and hippocampal slices and predict that the plasticity results exhibit very different overall behaviors (Fig. 4D and *SI Appendix, Fig. S10 C and D*). For Poisson stimulation in cortical slices, we predict that decreasing calcium amplitudes (e.g., by partially blocking calcium intracellularly) shift the threshold for LTP induction to higher frequencies (*SI Appendix, Fig. S5B*). Conversely, boosting calcium amplitudes (e.g., by increasing extracellular calcium concentrations) should move the threshold to lower frequencies. We predict, furthermore, that reproducing the classical STDP curve (DP) requires single postsynaptic calcium transients to activate both potentiation and depression cascades. Contributions from both pathways cancel for single postsynaptic spikes, whereas blocking potentiating or depressing cascades should disrupt that balance and reveal LTD or LTP, respectively, for postsynaptic stimulation alone.

The model also allows us to infer information about the calcium transients using the stimulation protocol and the observed plasticity outcomes. For example, AP backpropagation seems to be more efficient (e.g., through less attenuation or broader APs in hippocampal cultures, because only a single postsynaptic spike is required to elicit LTP as opposed to the requirement for postsynaptic bursts in hippocampal and cortical slices (11, 15). In line with that observation, fitting our model to hippocampal culture data yields a larger, postsynaptically evoked calcium amplitude for single APs (*SI Appendix, Fig. S2*). Furthermore, cortical slice parameters show that the maximal calcium amplitude does not predict the direction of synaptic changes, which was seen in cortical slice experiments (compare *SI Appendix, Fig. S1* with ref. 15). We predict that synaptic changes should be much more correlated with the times spent above specific calcium thresholds than with the amplitudes of the calcium transients. Conversely, the model provides a tool to predict changes in synaptic strength when the calcium dynamics or stimulation protocols are varied. In particular, we have shown that it naturally reproduces the dependence of synaptic plasticity on dendritic location (Fig. 5).

The model bears similarities with a number of previous synaptic plasticity models (28, 40–42). Shouval et al. pioneered the study of calcium-based models and showed how such models can reproduce a variety of experimental protocols (28). Our model can be seen as an additional simplification of this model, which allows us to (i) analytically compute plasticity outcomes and (ii) find that the standard STDP curve (DP in our terminology) can naturally be reproduced without any need for additional detectors of synaptic activity other than calcium. Brader et al. introduced bistability in a calcium-based model but did not attempt to fit experimental data with such a model (41). Additionally, the works of Pfister et al. (40) and Clopath et al. (42) use a similar approach as our approach of fitting a variety of experimental protocols to a simplified model. However, in contrast to our model, the works in refs. 40 and 42 use a purely phenomenological model (based on adding triplet terms and a voltage dependence to a simple STDP rule) that cannot be easily related to the biophysical properties



of the synapse. Furthermore, such models fail to produce the plethora of STDP curves (Fig. 2) and the nonlinear summation of synaptic changes seen when changing the number of motif presentations (Fig. 3). The strength of the calcium-based approach used here is the fact that we can investigate how synaptic plasticity is affected when biophysical parameters, such as the calcium amplitudes, are varied (Fig. 5).

Finally, we emphasize that our model could easily be generalized in various directions. One of such directions is the implementation of a Bienenstock-Cooper-Munro (BCM)-like sliding threshold as shown in *SI Appendix, Fig. S5*. A second generalization would be to include the effects of various neuromodulators that are known to affect synaptic plasticity (43). One simple way of implementing neuromodulation would be to add neuromodulatory dependence to specific model parameters as the thresholds or rates. Such an implementation could potentially lead to a more biophysical ground of reinforcement learning theories.

To conclude, our synaptic learning rule provides a bridge between activity patterns, the calcium signal, biochemical signaling cascades, and plasticity results. Its simplicity and analytical tractability make it an ideal candidate for investigating the effects of learning at the network level.

## Materials and Methods

**Analytical solution for transition probabilities.** The behavior of the model is governed by  $\alpha_D$  and  $\alpha_U$ , the fraction of time the calcium concentration spends above the potentiation and depression thresholds, respectively.  $\alpha_D$  and

$\alpha_U$  can be computed analytically for all the stimulation protocols considered here. The probability for a DOWN-to-UP transition,  $U$ , and for the reverse transition,  $D$ , can then be computed analytically using the Fokker-Planck formalism (*SI Appendix, Eqs. S13 and S15*).

**Synaptic strength, change in synaptic strength and simulations.** We take the synaptic strength linearly related to  $\rho$  as  $w = w_0 + \rho(w_1 - w_0)$ , where  $w_0/w_1$  is the synaptic strength of the DOWN/UP state. We assume that, before a stimulation protocol, a fraction  $\beta$  of the synapses are in the DOWN state. We consider the change in synaptic strength as the ratio between the average synaptic strengths after and before the stimulation, i.e.  $((1 - U)\beta + D(1 - \beta)) + b[U\beta + (1 - D)(1 - \beta)]/(\beta + [1 - \beta]b)$ , where  $b = w_1/w_0$ .

**Fitting the synapse model to experimental data.** Fitting procedures are described in *SI Appendix* and parameters are summarized in *SI Appendix, Table S2*.

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