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# 1 A stochastic model of hippocampal 2 synaptic plasticity with geometrical 3 readout of enzyme dynamics

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14 **Abstract** Discovering the rules of synaptic plasticity is an important step for understanding  
15 brain learning. Existing plasticity models are either 1) top-down and interpretable, but not flexible  
16 enough to account for experimental data, or 2) bottom-up and biologically realistic, but too  
17 intricate to interpret and hard to fit to data. To avoid the shortcomings of these approaches, we  
18 present a new plasticity rule based on a geometrical readout mechanism that flexibly maps  
19 synaptic enzyme dynamics to predict plasticity outcomes. We apply this readout to a  
20 multi-timescale model of hippocampal synaptic plasticity induction that includes electrical  
21 dynamics, calcium, CaMKII and calcineurin, and accurate representation of intrinsic noise sources.  
22 Using a single set of model parameters, we demonstrate the robustness of this plasticity rule by  
23 reproducing nine published *ex vivo* experiments covering various spike-timing and  
24 frequency-dependent plasticity induction protocols, animal ages, and experimental conditions.  
25 Our model also predicts that *in vivo*-like spike timing irregularity strongly shapes plasticity  
26 outcome. This geometrical readout modelling approach can be readily applied to other excitatory  
27 or inhibitory synapses to discover their synaptic plasticity rules.

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## 29 Introduction

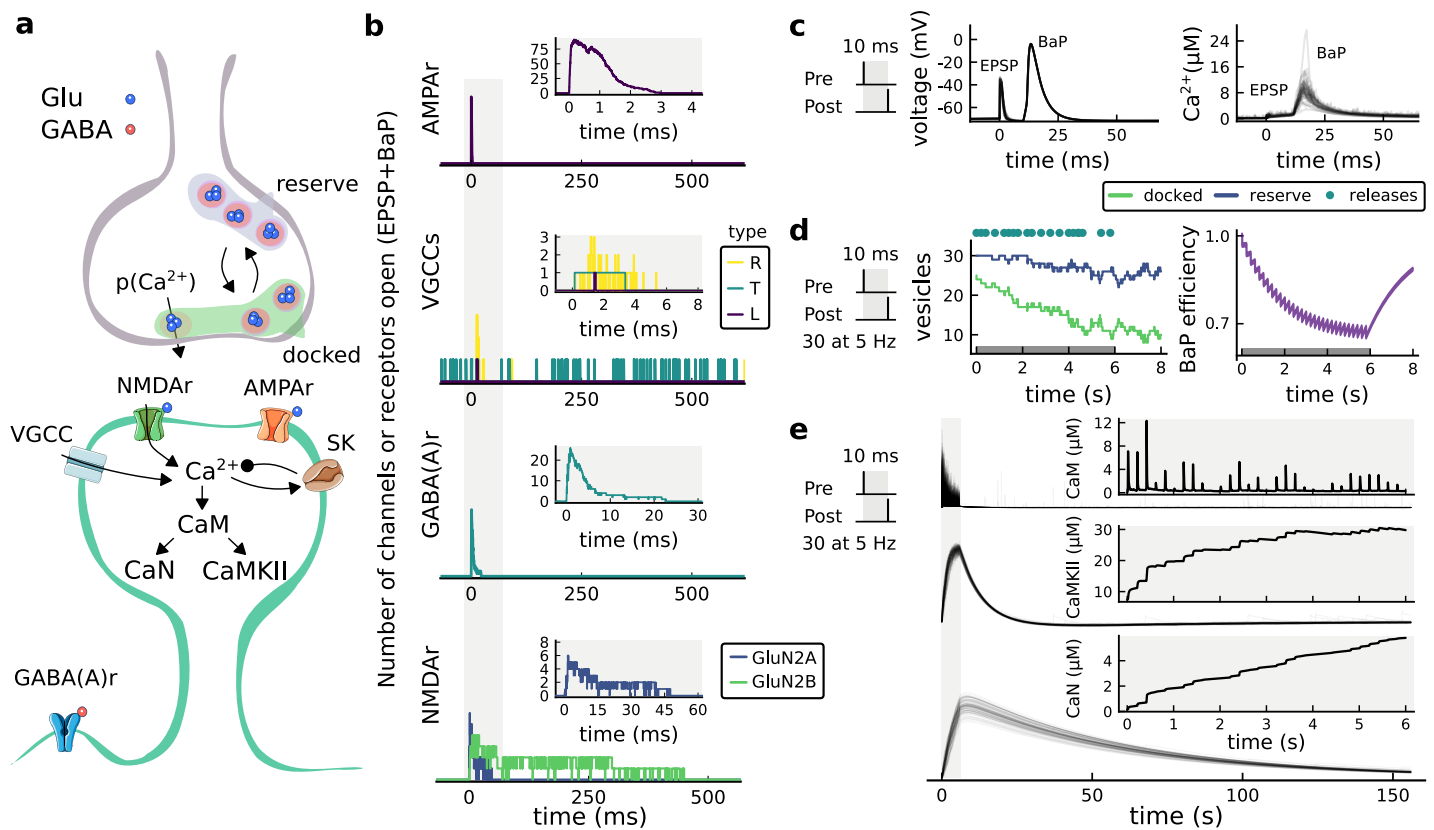
30 To understand how brains learn, we need to identify the rules governing how synapses change their  
31 strength in neural circuits. What determines whether each synapse strengthens, weakens, or stays  
32 the same? The dominant principle at the basis of current models of synaptic plasticity is the Hebb  
33 postulate (*Hebb, 1949*) which states that neurons with correlated electrical activity strengthen their  
34 synaptic connections, while neurons active at different times weaken their connections. In particu-  
35 lar, spike-timing-dependent plasticity (STDP) models (*Blum and Abbott, 1996; Gerstner et al., 1996;*  
36 *Eurich et al., 1999*) were formulated based on experimental observations that precise timing of  
37 pre- and post-synaptic spiking determines whether synapses are strengthened or weakened (*De-*  
38 *bienne et al., 1996; Tsodyks and Markram, 1997; Bi and Poo, 1998; Markram et al., 2011*). However,  
39 experiments also found that plasticity induction depends on the rate and number of stimuli de-  
40 livered to the synapse (*Dudek and Bear, 1992; Sjöström et al., 2001*), and the level of dendritic

41 spine depolarisation (*Artola et al., 1990; Magee and Johnston, 1997; Sjöström and Häusser, 2006;*  
42 *Golding et al., 2002; Hardie and Spruston, 2009*). The lack of satisfactory plasticity models based  
43 solely on neural spiking prompted researchers to consider simple models based on synapse bio-  
44 chemistry (*Castellani et al., 2001, 2005*). Following a proposed role for postsynaptic calcium ( $\text{Ca}^{2+}$ )  
45 signalling in synaptic plasticity (*Lisman, 1989*), previous models assumed that the amplitude of  
46 postsynaptic calcium controls long-term alterations in synaptic strength, with moderate levels of  
47 calcium causing long-term depression (LTD) and high calcium causing long-term potentiation (LTP)  
48 (*Shouval et al., 2002; Karmarkar and Buonomano, 2002*). However experimental data suggests  
49 that calcium dynamics are also important (*Yang et al., 1999; Mizuno et al., 2001; Wang et al., 2005;*  
50 *Nevean and Sakmann, 2006; Tigaret et al., 2016*). As a result, subsequent phenomenological mod-  
51 els of plasticity incorporated slow variables that integrate the fast synaptic input signals, loosely  
52 modelling calcium and its downstream effectors (*Abarbanel et al., 2003; Rubin et al., 2005; Rack-*  
53 *ham et al., 2010; Clopath and Gerstner, 2010; Kumar and Mehta, 2011; Graupner and Brunel, 2012;*  
54 *Honda et al., 2013; Standage et al., 2014; De Pittà and Brunel, 2016*). Concurrently, more detailed  
55 models tried to explicitly describe the molecular pathways integrating the calcium dynamics and  
56 its stochastic nature (*Cai et al., 2007; Shouval and Kalantzis, 2005; Miller et al., 2005; Zeng and*  
57 *Holmes, 2010; Yeung et al., 2004*). However, even these models do not account for data showing  
58 that plasticity is highly sensitive to physiological conditions such as the developmental age of the  
59 animal (*Dudek and Bear, 1993; Meredith et al., 2003; Cao and Harris, 2012; Cizeron et al., 2020*),  
60 extracellular calcium and magnesium concentrations (*Mulkey and Malenka, 1992; Inglebert et al.,*  
61 *2020*) and tissue temperature (*Volgushev et al., 2004; Wittenberg and Wang, 2006; Klyachko and*  
62 *Stevens, 2006*). The fundamental issue is that the components of these phenomenological models  
63 do not directly map to biological components of synapses, so they cannot automatically model  
64 alterations due to physiological and experimental conditions. This absence limits the predictive  
65 power of this class of plasticity models.

66 An alternative approach taken by several groups (*Bhalla and Iyengar, 1999; Jędrzejewska-Szmek*  
67 *et al., 2017; Blackwell et al., 2019; Chindemi et al., 2020; Zhang et al., 2021*) was to model the com-  
68 plex molecular cascade leading to synaptic weight changes. The main benefit of this approach  
69 is the direct correspondence between the model's components and biological elements, but this  
70 comes at the price of a large number of poorly constrained parameters. Additionally, the increased  
71 number of nonlinear equations and stochasticity makes fitting to plasticity experiment data diffi-  
72 cult (*Mäki-Marttunen et al., 2020*). Subtle differences between experimental STDP protocols can  
73 produce completely different synaptic plasticity outcomes, indicative of finely tuned synaptic be-  
74 haviour. This raises major challenges for both simple and complex models.

75 To tackle this problem, we devised a new plasticity rule based on a bottom-up, data-driven ap-  
76 proach by building a biologically-grounded model of plasticity induction at a single rat hippocampal  
77 CA3-CA1 synapse. We focused on this synapse type because of the abundant published exper-  
78 imental data that can be used to quantitatively constrain the model parameters. Compared to  
79 previous models in the literature, we aimed for an intermediate level of detail: enough biophysical  
80 components to capture the key dynamical processes underlying plasticity induction, but not the  
81 detailed molecular cascade underlying plasticity expression; much of which is poorly quantified for  
82 the various experimental conditions we cover in this study.

83 Our model is centred on dendritic spine electrical dynamics, calcium signalling and immediate  
84 downstream molecules, which we then map to synaptic strength change via a conceptually new  
85 dynamical, geometric readout mechanism. Crucially, the model also captured intrinsic noise based  
86 on the stochastic switching of synaptic receptors and ion channels (*Yuste et al., 1999; Ribault et al.,*  
87 *2011*). We found that, with a single set of parameters, the model can account for published data  
88 from spike-timing and frequency-dependent plasticity experiments, and variations in physiological  
89 parameters influencing plasticity outcomes. We also tested how the model responded to *in vivo*-  
90 like spike timing jitter and spike failures, and found that the plasticity rules were highly sensitive  
91 to these subtle input alterations.



**Figure 1. | The synapse model, its timescales and mechanisms.** **a**, Model diagram with the synaptic components including pre and postsynaptic compartments and inhibitory transmission (bottom left). **b**, Stochastic dynamics of the different ligand-gated and voltage-gated ion channels in the model. Plots show the total number of open channels as a function of time. AMPAr, NMDAr: AMPA- and NMDA-type glutamate receptors respectively; GABA(A)r: Type A GABA receptors; VGCC: R-, T- and L-type voltage-gated Ca<sup>2+</sup> channels; SK: SK potassium channels. The insets show a zoomed time axis highlighting the difference in timescale of the activity among the channels. **c**, Dendritic spine membrane potential (left) and calcium concentration (right) as function of time for a single causal (1Pre1Post10) stimulus (EPSP: single excitatory postsynaptic potential, "1Pre"; BaP: single back-propagated action potential, "1Post"). **d**, Left: depletion of vesicle pools (reserve and docked) induced by 30 pairing repetitions delivered at 5 Hz (Sterratt et al., 2011), see *Methods and Materials*. The same depletion rule is applied to both glutamate- and GABA-containing vesicles. Right: BaP efficiency as function of time. BaP efficiency phenomenologically captures the distance-dependent attenuation of BaP (Buchanan and Mellor, 2007; Golding et al., 2001), see *Methods and Materials*. **e**, Concentration of active enzyme for CaM, CaN and CaMKII, as function of time triggered by 30 repetitions of 1Pre1Post10 pairing stimulations delivered at 5 Hz. The vertical grey bar is the duration of the stimuli, 6 s. The multiple traces in the graphs in panels **c** (right) and **e** reflect the run-to-run variability due to the inherent stochasticity in the model.

## 92 Results

### 93 A multi-timescale model of synaptic plasticity induction.

94 We built a computational model of plasticity induction at a single CA3-CA1 rat glutamatergic synapse  
 95 (Figure 1). Our goal was to reproduce results on synaptic plasticity that explored the effects of  
 96 several experimental parameters: fine timing differences between pre and postsynaptic spiking  
 97 (Figure 2 and Figure 3); stimulation frequency (Figure 4); animal age (Figure 5); external calcium  
 98 and magnesium (Figure 6); stochasticity in the firing structure (Figure 7), temperature and exper-  
 99 imental conditions variations (Supplemental files). Where possible, we set parameters to values  
 100 previously estimated from synaptic physiology and biochemistry experiments, and tuned the re-  
 101 mainder within physiologically plausible ranges to reproduce our target plasticity experiments (see  
 102 *Methods and Materials*).

103 The model components are schematized in Figure 1a (full details in *Methods and Materials*).  
 104 For glutamate release, we used a two-pool vesicle depletion and recycling system, which accounts  
 105 for short-term presynaptic depression and facilitation. When glutamate is released from vesicles, it

106 can bind to the postsynaptic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-  
107 D-aspartate receptors (AMPArs and NMDAr, respectively), depolarizing the spine head by  $\sim 30$  mV  
108 (Kwon *et al.*, 2017; Jayant *et al.*, 2017; Beaulieu-Laroche and Harnett, 2018). The dendritic spine  
109 membrane depolarization causes the activation of voltage-gated calcium channels (VGCCs) and  
110 removes magnesium ( $[Mg^{2+}]_o$ ) block from NMDAr. Backpropagating action potentials (BaP) can  
111 also depolarize the spine membrane by up to  $\sim 60$  mV (Kwon *et al.*, 2017; Jayant *et al.*, 2017). As an  
112 inhibitory component, we modelled a gamma-aminobutyric acid receptor (GABA<sub>r</sub>) synapse on the  
113 dendrite shaft (Destexhe *et al.*, 1998). Calcium ions influx through VGCCs and NMDAr can activate  
114 SK potassium channels (Adelman *et al.*, 2012; Griffith *et al.*, 2016), which provide a tightly-coupled  
115 local negative feedback limiting spine depolarisation. Upon entering the spine, calcium ions also  
116 bind to calmodulin (CaM). Calcium-bound CaM in turn activates two major signalling molecules (Fu-  
117 jii *et al.*, 2013):  $Ca^{2+}$ /calmodulin-dependent protein kinase II (CaMKII) and calcineurin (CaN) phos-  
118 phatase, also known as PP2B (Saraf *et al.*, 2018). We included these two enzymes because of  
119 the overwhelming evidence that CaMKII activation is necessary for Schaffer-collateral LTP (Giese  
120 *et al.*, 1998; Chang *et al.*, 2017), while CaN activation is necessary for LTD (O'Connor *et al.*, 2005;  
121 Otmakhov *et al.*, 2015). Later, we show how we map the joint activity of CaMKII and CaN to LTP  
122 and LTD. Ligand-gated ion channels (ionotropic receptors) and voltage-gated ion channels have  
123 an inherent random behavior, stochastically switching between open and closed states (Ribault  
124 *et al.*, 2011). If the number of ion channels is large, then the variability of the total population  
125 activity becomes negligible relative to the mean (O'Donnell and Van Rossum, 2014). However in-  
126 dividual hippocampal synapses contain only small numbers of receptors and ion channels, for  
127 example they contain  $\sim 10$  NMDAr and  $< 15$  VGCCs (Takumi *et al.*, 1999; Sabatini and Svoboda,  
128 2000; Nimchinsky *et al.*, 2004), making their total activation highly stochastic. Therefore, we mod-  
129 elled AMPAr, NMDAr, VGCCs and GABA<sub>r</sub> as stochastic processes. Presynaptic vesicle release events  
130 were also stochastic: glutamate release was an all-or-none event, and the amplitude of each glu-  
131 tamate pulse was drawn randomly, modelling heterogeneity in vesicle size (Liu *et al.*, 1999). The  
132 inclusion of stochastic processes to account for an intrinsic noise in synaptic activation (Deperrois  
133 and Graupner, 2020) contrasts with most previous models in the literature, which either represent  
134 all variables as continuous and deterministic or add an external generic noise source (Bhalla, 2004;  
135 Antunes and De Schutter, 2012; Bartol *et al.*, 2015).

136 The synapse model showed nonlinear dynamics across multiple timescales. For illustration,  
137 we stimulated the synapse with single simultaneous glutamate and GABA vesicle releases (Figure  
138 1b). AMPAr and VGCCs open rapidly but close again within a few milliseconds. The dendritic  
139 GABA<sub>r</sub> closes more slowly, on a timescale of  $\sim 10$  ms. NMDAr, the major calcium source, closes  
140 on timescales of  $\sim 50$  ms and  $\sim 250$  ms for the GluN2A and GluN2B subtypes, respectively.

141 To show the typical responses of the spine head voltage and  $Ca^{2+}$ , we stimulated the synapse  
142 with a single presynaptic pulse (EPSP) paired 10 ms later with a single BaP (1Pre1Post10) (Figure  
143 1c left). For this pairing, the arrival of a BaP at the spine immediately after an EPSP, leads to a  
144 large  $Ca^{2+}$  transient aligned with the BaP due to the NMDAr first being bound by glutamate then  
145 unblocked by the BaP depolarisation (Figure 1c right).

146 Single pre or postsynaptic stimulation pulses did not cause depletion of vesicle reserves or sub-  
147 stantial activation of the enzymes. To illustrate these slower-timescale processes, we stimulated  
148 the synapse with a prolonged protocol: one presynaptic pulse followed by one postsynaptic pulse  
149 10 ms later, repeated 30 times at 5 Hz (Figure 1d-e). The number of vesicles in both the docked and  
150 reserve pools decreased substantially over the course of the stimulation train (Figure 1d left), which  
151 in turn causes decreased vesicle release probability. Similarly, by the 30th pulse, the dendritic BaP  
152 amplitude had attenuated to  $\sim 85\%$  ( $\sim 70\%$  BaP efficiency; Figure 1d right) of its initial amplitude,  
153 modelling the effects of slow dendritic sodium channel inactivation (Colbert *et al.*, 1997; Golding  
154 *et al.*, 2001). Free CaM concentration rose rapidly in response to calcium transients but also de-  
155 cayed back to baseline on a timescale of  $\sim 500$  ms (Figure 1e top). In contrast, the concentration of  
156 active CaMKII and CaN accumulated over a timescale of seconds, reaching a sustained peak during

157 the stimulation train, then decayed back to baseline on a timescale of  $\sim 10$  and  $\sim 120$  s respectively,  
158 in line with experimental data (*Quintana et al., 2005; Fujii et al., 2013; Chang et al., 2017*) (*Figure*  
159 *1e*).

160 The effects of the stochastic variables can be seen in *Figure 1b-d*. The synaptic receptors and  
161 ion channels open and close randomly (*Figure 1b*). Even though spine voltage, calcium, and down-  
162 stream molecules were modelled as continuous and deterministic, they inherited some random-  
163 ness from the upstream stochastic variables. As a result, there was substantial trial-to-trial variabil-  
164 ity in the voltage and calcium responses to identical pre and postsynaptic spike trains (grey traces  
165 in *Figure 1c*). This variability was also passed on to the downstream enzymes CaM, CaMKII and CaN,  
166 but was filtered and therefore attenuated by the slow dynamics of CaMKII and CaN. In summary,  
167 the model contained stochastic nonlinear variables acting over five different orders of magnitude  
168 of timescale, from  $\sim 1$  ms to  $\sim 1$  min, making it sensitive to both fast and slow components of input  
169 signals.

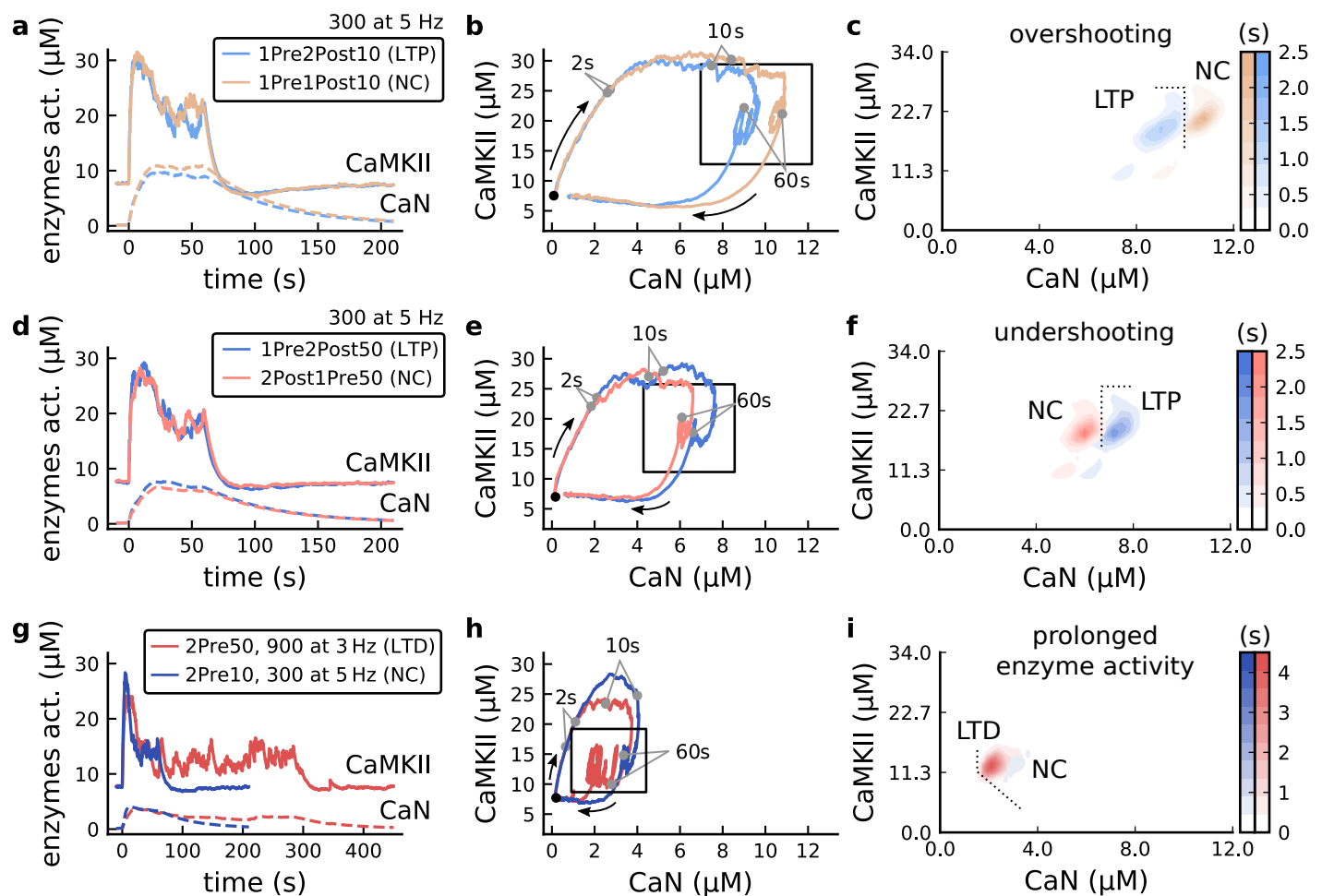
### 170 **Distinguishing between stimulation protocols using the CaMKII and CaN joint re-** 171 **sponse.**

172 It has proven difficult for simple models of synaptic plasticity to capture the underlying rules and ex-  
173 plain why some stimulation protocols induce plasticity while others do not. We tested the model's  
174 sensitivity by simulating its response to a set of protocols used by *Tigaret et al. (2016)* in a recent  
175 *ex vivo* experimental study on adult (P50-55) rat hippocampus with blocked GABA<sub>A</sub>r. We focused  
176 on three pairs of protocols (three rows in *Figure 2*). For each of these pairs, one of the protocols  
177 experimentally induced LTP or LTD, while the other subtly different protocol caused no change (NC)  
178 in synapse strength. Notably, three leading spike-timing and calcium-dependent plasticity models  
179 (*Song et al., 2000; Pfister and Gerstner, 2006; Graupner and Brunel, 2012*) could not fit these data  
180 (*Figure 3-Figure Supplement 1 a,b and c*). We thus asked if, by contrast, our new model could  
181 distinguish between each pair of protocols by assigning the correct plasticity outcome.

182 The first pair of protocols differed in intensity. A protocol which caused no plasticity consisted  
183 of 1 presynaptic spike followed 10 ms later by one postsynaptic spike repeated at 5 Hz for one  
184 minute (1Pre1Post10, 300 at 5Hz). The other protocol induced LTP, but differed only in that it  
185 included a postsynaptic doublet instead of a single spike (1Pre2Post10, 300 at 5Hz), implying a  
186 slightly stronger initial BaP amplitude. We first attempted to achieve separability by plotting CaMKII  
187 or CaN activities independently. As observed in the plots in *Figure 2a*, it was not possible to set  
188 a single concentration threshold on either CaMKII or CaN that would discriminate between the  
189 protocols. This result was expected, at least for CaMKII, as recent experimental data demonstrates  
190 a fast saturation of CaMKII concentration in dendritic spines regardless of stimulation frequency  
191 (*Chang et al., 2017*).

192 To achieve better separability we set out to test a different approach, which was to combine the  
193 activity of the two enzymes, by plotting the joint CaMKII and CaN responses against each other on  
194 a 2D plane (*Figure 2b*). This innovative geometric plot is based on a mathematical concept of orbits  
195 from dynamical systems theory (*Meiss, 2007*). In this plot, the trajectories of two protocols can be  
196 seen to overlap for the initial part of the transient and then diverge. To quantify trial to trial vari-  
197 ability, we also calculated contour maps showing the mean fraction of time the trajectories spent  
198 in each part of the plane during the stimulation (*Figure 2c*). Importantly, both the trajectories and  
199 contour maps were substantially non-overlapping between the two protocols, implying that they  
200 can be separated based on the joint CaN-CaMKII activity. We found that the 1Pre2Post10 protocol  
201 leads to a weaker response in both CaMKII and CaN, corresponding to the lower blue traces in  
202 *Figure 2b*. The decreased response to the doublet protocol was due to the stronger attenuation of  
203 dendritic BaP amplitude over the course of the simulation (*Golding et al., 2001*), leading to reduced  
204 calcium influx through NMDARs and VGCCs (data not shown).

205 Using the second pair of protocols, we explored if this combined enzyme activity analysis could  
206 distinguish between subtle differences in protocol sequencing. We stimulated our model with



**Figure 2. | The duration and amplitude of the joint CaN-CaMKII activity differentiates plasticity protocols.** **a**, Time-course of active enzyme concentration for CaMKII (solid line) and CaN (dashed line) triggered by two protocols consisting of 300 repetitions at 5 Hz of 1Pre2Post10 or 1Pre1Post10 stimulus pairings. Protocols start at time 0 s. Experimental data indicates that 1Pre2Post10 and 1Pre1Post10 produce LTP and no change (NC), respectively. **b**, Trajectories of joint enzymatic activity (CaN-CaMKII) as function of time for the protocols in panel **a**, starting at the initial resting state (filled black circle). The arrows show the direction of the trajectory and filled grey circles indicate the time points at 2, 10 and 60 s after the beginning of the protocol represented as 2, 10 and 60 s. The region of the CaN-CaMKII plane enclosed in the black square is expanded in panel **c**. **c**, Mean-time (colorbar) spent by the orbits in the CaN-CaMKII plane region expanded from panel **b** for each protocol (average of 100 samples). For panels **c**, **f** and **i** the heat maps were based on enzyme activity throughout the protocol plus a further 10 s after the stimulation ended. **d-f**, CaN-CaMKII activities for the protocols 1Pre2Post50 (LTP-inducing) and 2Post1Pre50 (NC) depicted in the same manner as in panels **a-c**. **g-i**, CaN-CaMKII activities for the LTD-inducing protocol 2Pre50 (900 repetitions at 3 Hz) and the NC protocol 2Pre10 (300 repetitions at 5 Hz) depicted in the same manner as in panels **a-c**.

207 one causal pairing protocol (EPSP-BaP) involving a single presynaptic spike followed 50 ms stimu-  
 208 lated our model with one causal pairing protocol (EPSP-BaP) involving a single presynaptic spike  
 209 followed 50 ms later by a doublet of postsynaptic spikes (1Pre2Post50, 300 at 5Hz), repeated at  
 210 5 Hz for one minute, which caused LTP in *Tigaret et al. (2016)*. The other anticausal protocol invol-  
 211 ved the same total number of pre and postsynaptic spikes, but with the pre-post order reversed  
 212 (2Post1Pre50, 300 at 5Hz). Experimentally the anticausal (BaP-EPSP) protocol did not induce plas-  
 213 ticity (*Tigaret et al., 2016*). Notably, the only difference was the sequencing of whether the pre or  
 214 postsynaptic neuron fired first, over a short time gap of 50 ms. Despite the activations being ap-  
 215 parently difficult to distinguish (*Figure 2d*), we found that the LTP-inducing protocol caused greater  
 216 CaN activation than the protocol that did not trigger plasticity. Indeed, this translated to a horizon-  
 217 tal offset in both the trajectory and contour map (*Figure 2e-f*), demonstrating that another pair of  
 218 protocols can be separated in the joint CaN-CaMKII plane.

219 The third pair of protocols differed in both duration and intensity. We thus tested the com-  
220 bined enzyme activity analysis in this configuration. In line with a previous study (*Isaac et al.*,  
221 *2009*), *Tigaret et al. (2016)* found that a train of doublets of presynaptic spikes separated by 50  
222 ms repeated at a low frequency of 3 Hz for 5 minutes (2Pre50, 900 at 3Hz) induced LTD, while a  
223 slightly more intense but shorter duration protocol of presynaptic spike doublets separated by 10  
224 ms repeated at 5 Hz for one minute (2Pre10, 300 at 5Hz) did not cause plasticity. When we sim-  
225 ulated both protocols in the model (*Figure 2g-i*), both caused similar initial responses in CaMKII  
226 and CaN. In the shorter protocol, this activation decayed to baseline within 100 s of the end of the  
227 stimulation. However the slower and longer-duration 2Pre50 3Hz 900p protocol caused an addi-  
228 tional sustained, stochastically fluctuating, plateau of activation of both enzymes (*Figure 2g*). This  
229 resulted in the LTD-inducing protocol having a downward and leftward-shifted CaN-CaMKII trajec-  
230 tory and contour plot, relative to the other protocol (*Figure 2h-i*). These results again showed that  
231 the joint CaN-CaMKII activity can predict plasticity changes.

### 232 **A geometrical readout mapping joint enzymatic activity to plasticity outcomes.**

233 The three above examples demonstrated that plotting the combined CaN-CaMKII activities in a 2D  
234 plane allowed us to distinguish between subtly different protocols with correct assignment of plas-  
235 ticity outcome. We found that the simulated CaN-CaMKII trajectories from the two LTP-inducing  
236 protocols (*Figure 2a* and *Figure 2d*) spent a large fraction of time near  $\sim 20 \mu\text{M}$  CaMKII and  $7\text{--}10 \mu\text{M}$   
237 CaN. In contrast, protocols that failed to trigger LTP had either lower (*Figure 2d and g*), or higher  
238 CaMKII and CaN activation (1Pre1Post10, *Figure 2a*). The LTD-inducing protocol, by comparison,  
239 spent a longer period in a region of sustained but lower  $\sim 12 \mu\text{M}$  CaMKII and  $\sim 2 \mu\text{M}$  CaN and acti-  
240 vation. The plots in *Figure 2c, f and g*, show contour maps of histograms of the joint CaMKII-CaN  
241 activity, indicating where in the plane the trajectories spent most time. *Figure 2c and f* indicate that  
242 this measure can be used to predict plasticity, because the NC and LTP protocol histograms are  
243 largely non-overlapping. In *Figure 2c*, the NC protocol response "overshoots" the LTP protocol re-  
244 sponse, whereas in *Figure 2f* the NC protocol response "undershoots" the LTP protocol response.  
245 In contrast, when we compared the response histograms for the LTD and NC protocols, we found a  
246 greater overlap (*Figure 2i*). This suggested that, in this case, the histogram alone was not sufficient  
247 to separate the protocols, and that protocol duration is also important. LTD induction (2Pre50)  
248 required a more prolonged activation than NC (2Pre10). We thus took advantage of these joint  
249 CaMKII-CaN activity maps to design a minimal readout mechanism connecting combined enzyme  
250 activity to LTP, LTD or no change (NC). We reasoned that this readout would need three key prop-  
251 erties. First, since the CaMKII-CaN trajectories corresponding to LTP and LTD were not linearly sep-  
252 arable, the readout requires nonlinear boundaries to activate the plasticity inducing components.  
253 Second, since LTD requires more prolonged activity than LTP, the readout should be sensitive to  
254 the timescale of the input. Third, a mechanism is required to convert the 2D LTP-LTD inducing  
255 signals into a synaptic weight change. After iterating through several designs, we satisfied the first  
256 property by designing "plasticity regions": polygons in the CaN-CaMKII plane that would detect  
257 when trajectories pass through. We satisfied the second property by using two plasticity inducing  
258 components with different time constants which low-pass-filter the plasticity region signals. We sat-  
259 isfied the third property by feeding both the opposing LTP and LTD signals into a stochastic Markov  
260 chain which accumulated the total synaptic strength change. Overall this readout mechanism acts  
261 as a parsimonious model of the complex signalling cascade linking CaMKII and CaN activation to  
262 expression of synaptic plasticity (*He et al., 2015*). It can be considered as a two-dimensional exten-  
263 sion of previous computational studies that applied analogous 1D threshold functions to dendritic  
264 spine calcium concentration (*Shouval et al., 2002; Karmarkar and Buonomano, 2002; Graupner*  
265 *and Brunel, 2012; Standage et al., 2014*).

266 We now elaborate on the readout design process. We first drew non-overlapping polygons  
267 of LTP and LTD "plasticity regions" in the CaN-CaMKII plane (*Figure 3a*). We positioned these re-  
268 gions over the parts of the phase space where the enzyme activities corresponding to the LTP- and



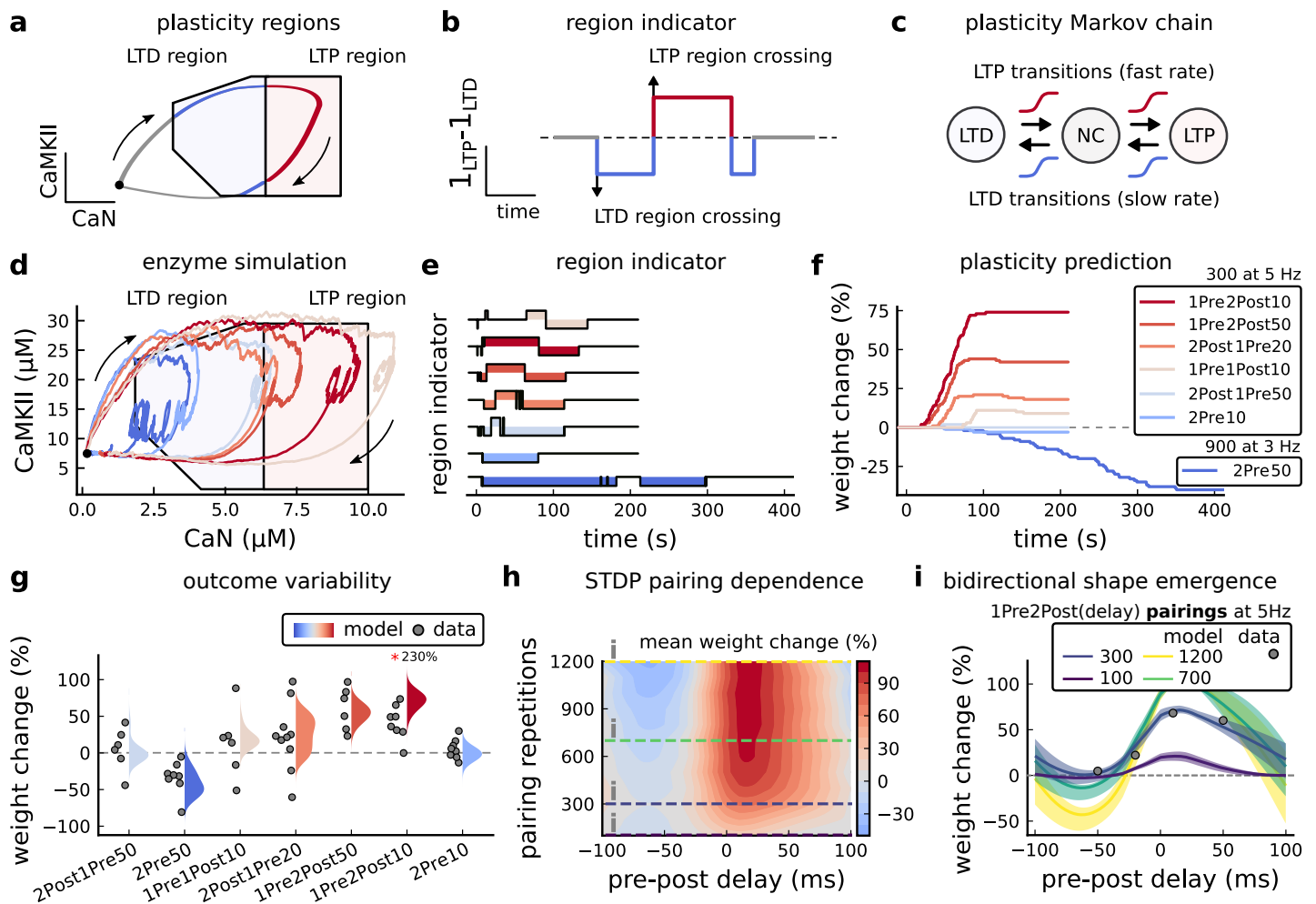
269 LTD-inducing protocols were most different (*Methods and Materials*), as shown by trajectories in  
270 *Figure 2*. When a trajectory enters in one of these plasticity regions, it activates LTD or LTP indica-  
271 tor variables (*Methods and Materials*) which encode the joint enzyme activities (trajectories in the  
272 phase plots) transitions across the LTP and LTD regions over time (*Figure 3b*). These indicator vari-  
273 ables drove transition rates of a plasticity Markov chain used to predict LTP or LTD (*Figure 3c*), see  
274 *Methods and Materials*. Intuitively, this plasticity Markov chain models the competing processes  
275 of insertion/deletion of AMPARs to the synapse, although this is not represented in the model. The  
276 LTD transition rates were slower than the LTP transition rates, to reflect studies showing that LTD  
277 requires sustained synaptic stimulation (*Yang et al., 1999; Mizuno et al., 2001; Wang et al., 2005*).  
278 The parameters for this plasticity Markov chain (*Methods and Materials*) were fit to the plastic-  
279 ity induction outcomes from different protocols (*Table 1*). At the beginning of the simulation, the  
280 plasticity Markov chain starts with 100 processes (*Destexhe et al., 1998*) in the state No Change  
281 (NC), with each variable representing 1% weight change, an abstract measure of synaptic strength  
282 that can be either EPSP, EPSC, or field EPSP slope depending on the experiment. Each process can  
283 transit stochastically between NC, LTP and LTD states. At the end of the protocol, the plasticity out-  
284 come is given by the difference between the number of processes in the LTP and the LTD states  
285 (*Methods and Materials*).

286 In *Figure 3d*, we plot the model's responses to seven different plasticity protocols used by  
287 *Tigaret et al. (2016)* by overlaying example CaMKII-CaN trajectories for each protocol with the LTP  
288 and LTD regions. The corresponding region indicators are plotted as function of time in *Figure*  
289 *3e*, and long-term alterations in the synaptic strength are plotted as function of time in *Figure 3f*.  
290 The three protocols that induced LTP in the *Tigaret et al. (2016)* experiments spent substantial  
291 time in the LTP region, and so triggered potentiation. In contrast, the 1Pre1Post10 overshoots  
292 both regions, crossing them only briefly on its return to baseline, and so resulted in little weight  
293 change. The protocol that induced LTD (2Pre50, purple trace) is five times longer than other pro-  
294 tocols, spending sufficient time inside the LTD region (*Figure 3f*). In contrast, two other protocols  
295 that spent time in the same LTD region of the CaN-CaMKII plane (2Post1Pre50 and 2Pre10) were  
296 too brief to induce LTD. These protocols were also not strong enough to reach the LTP region, so  
297 resulted in no net plasticity, again consistent with *Tigaret et al. (2016)* experiments.

298 We observed run-to-run variability in the amplitude of the predicted plasticity, due to the inher-  
299 ent stochasticity in the model. To ensure that stochastic components are necessary for adequate  
300 model behaviour, we compared stochastic and deterministic versions of the model with and with-  
301 out discrete presynaptic release and found that adding stochastic components indeed modified  
302 the model's behaviour (*Figure 3-Figure Supplement 2*). Also, we confirmed that VGCCs are neces-  
303 sary for accurate modelling of *Tigaret et al. (2016)* data as blocking these channels reproduced the  
304 data obtained in VGCC blockers by Tigaret i.e. no potentiation could be elicited (*Figure 3-Figure*  
305 *Supplement 3*). Finally, we stress in *Figure 3-Figure Supplement 4* that the horizontal boundaries  
306 (related to CaMKII activity) are indeed necessary.

307 In *Figure 3g*, we plot the distribution of the predicted plasticity from all the protocols (colours) of  
308 Tigaret alongside the experimental data (*Tigaret et al., 2016*). We find a very good correspondence  
309 between the model and experiments. Of note, data fitting of the experiments in *Tigaret et al. (2016)*  
310 (*Figure 3g*) was more accurate with our model than the fitting obtained with existing leading spike-  
311 or calcium-based STDP models (*Song et al., 2000; Pfister and Gerstner, 2006; Graupner and Brunel,*  
312 *2012*), see *Figure 3-Figure Supplement 1*.

313 Experimentally, LTP can be induced by few pulses while LTD usually requires stimulation proto-  
314 cols of longer duration (*Yang et al., 1999; Mizuno et al., 2001; Wang et al., 2005*). We incorporated  
315 this effect into the geometrical readout model by letting LTP have faster transition rates than LTD  
316 (*Figure 3c*). *Tigaret et al. (2016)* found that 300 repetitions of anticausal post-before-pre pairings  
317 did not cause LTD, in contrast to the canonical spike-timing-dependent plasticity curve (*Bi and Poo,*  
318 *1998*). We hypothesized that LTD might indeed appear with the anticausal protocol (*Table 1*) if  
319 stimulation duration was increased. To explore this possibility in our model, we systematically



**Figure 3. | Read-out strategy to accurately model Tigaret et al. (2016) experiment.** **a**, Illustration of the joint CaMKII and CaN activities crossing the plasticity regions. Arrows indicate the flow of time, starting at the filled black circle. Time is hidden so that changes in active enzyme concentrations are seen more clearly. **b**, Region indicator showing when the joint CaN and CaMKII activity crosses the LTD or LTP regions in panel **a**. For example, the LTP indicator is such that  $1_{LTP}(x) = 1$  if  $x \in LTP$  and 0 otherwise. Leaving the region activates a leaking mechanism that keeps track of the accumulated time inside the region. Such leaking mechanism drives the transition rates used to predict plasticity (*Methods and Materials*). **c**, Plasticity Markov chain with three states: LTD, LTP and NC. There are only two transition rates which are functions of the plasticity region indicator (*Methods and Materials*). The LTP transition is fast whereas the LTD transition is slow, meaning that LTD change requires longer time inside the LTD region (panel **a**). The NC state starts with 100 processes. **d**, Joint CaMKII and CaN activity for all protocols in Tigaret et al. (2016) (shown in panel **f**). The stimulus ends when the trajectory becomes smooth. Trajectories correspond to those in Figure 2b,e and h, at 60 s. **e**, Region indicator for the protocols in panel **f**. The upper square bumps are caused by the protocol crossing the LTP region, the lower square bumps when the protocol crosses the LTD region (as in panel **d**). **f**, Synaptic weight (%) as function of time for each protocol. The weight change is defined as the number (out of 100) of states in the LTP state minus the number of states in the LTD state (panel **c**). The trajectories correspond to the median of the simulations in panel **g**. **g**, Synaptic weight change (%) predicted by the model compared to data (EPSC amplitudes) from Tigaret et al. (2016) (100 samples for each protocol, also for panel **h** and **i**). The data (filled grey circles) was provided by Tigaret et al. (2016) (note an 230% outlier as the red asterisk). **h**, Predicted mean synaptic weight change (%) as a function of delay (ms) and number of pairing repetitions (pulses) for the protocol 1Pre2Post(delay), where delays are between -100 and 100 ms. LTD is induced by 2Post1Pre50 after at least 500 pulses. The mean weight change along each dashed line is reported in the STDP curves in panel **i**. **i**, Synaptic weight change (%) as a function of pre-post delay. Each plot corresponds to a different pairing repetition number (color legend). The solid line shows the mean, and the ribbons are the 2nd and 4th quantiles. The filled grey circles are the data means estimated in Tigaret et al. (2016), also shown in panel **g**.

**Figure 3-Figure supplement 1.** Standard models comparison for predicting plasticity fail to account for the data from Tigaret et al. (2016).

**Figure 3-Figure supplement 2.** Comparison showing different roles of stochasticity in the model.

**Figure 3-Figure supplement 3.** Effects of blocking VGCCs.

**Figure 3-Figure supplement 4.** Exclusively setting vertical boundaries (no CaMKII selectivity) fails to capture the correct outcome.

**Figure 3-Figure supplement 5.** Varying Tigaret et al. (2016) experimental parameters.

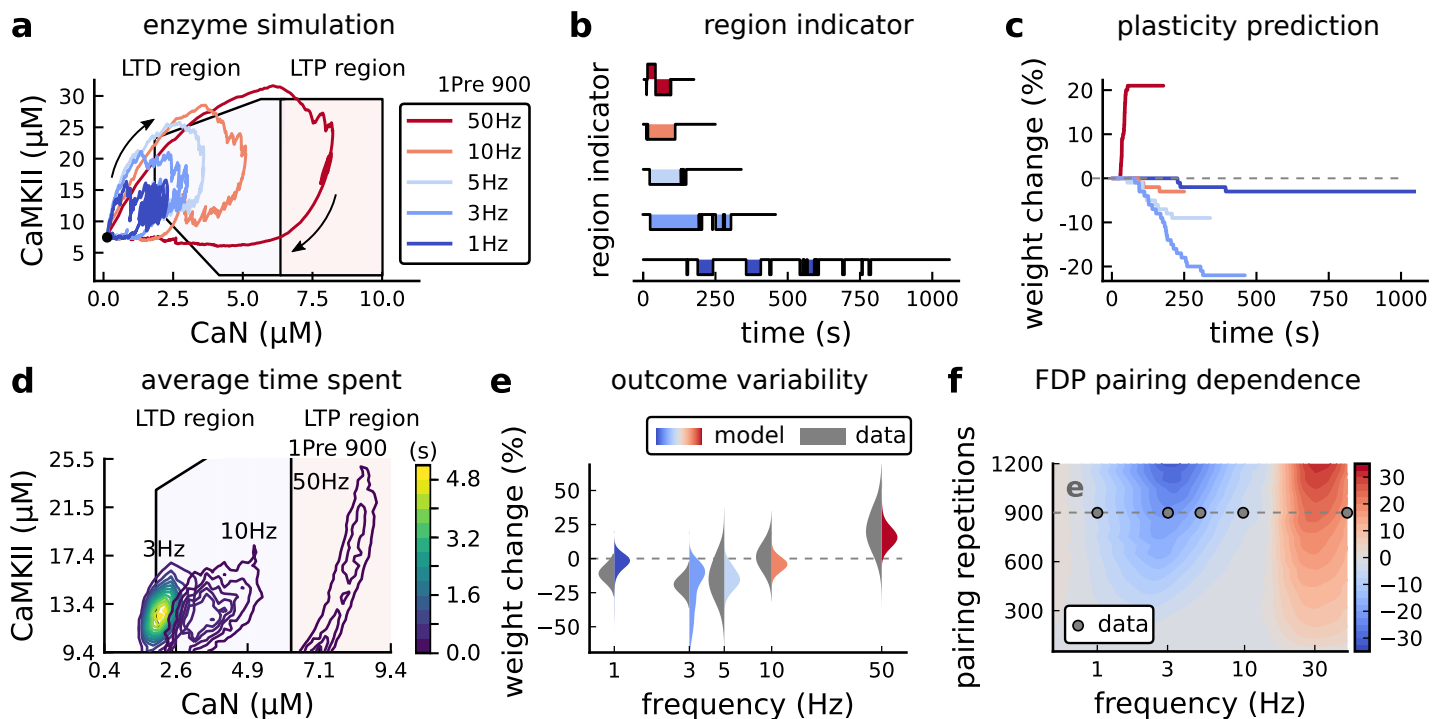
320 varied the number of paired repetitions from 100 to 1200, and also co-varied the pre-post delay  
321 from -100 to 100 ms. **Figure 3h** shows a contour plot of the predicted mean synaptic strength  
322 change across for the 1Pre2Post(delay) stimulation protocol for different numbers of pairing rep-  
323 etitions. In **Figure 3h**, a LTD window appears after ~500 pairing repetitions for some anticausal  
324 pairings, in line with our hypothesis. The magnitude of LTP also increases with pulse number, for  
325 causal positive pairings. For either 100 or 300 pairing repetitions, only LTP or NC is induced (**Figure**  
326 **3i**). The model also made other plasticity predictions by varying **Tigaret et al. (2016)** experimen-  
327 tal conditions (**Figure 3-Figure Supplement 5**). In summary, our geometrical readout reveals that  
328 the direction and magnitude of the change in synaptic strength can be predicted from the joint  
329 CaMKII-CaN activity in the LTP and LTD regions.

### 330 **Frequency-dependent plasticity**

331 The stimulation protocols used by **Tigaret et al. (2016)** explored how subtle variations in pre and  
332 postsynaptic spike timing influenced the direction and magnitude of plasticity (see **Table 1** for ex-  
333 perimental differences). In contrast, traditional synaptic plasticity protocols exploring the role of  
334 presynaptic stimulation frequency did not measure the timing of co-occurring postsynaptic spikes  
335 (**Dudek and Bear, 1992; Wang and Wagner, 1999; Kealy and Commins, 2010**). These studies found  
336 that long-duration low-frequency stimulation induces LTD, whereas short-duration high-frequency  
337 stimulation induces LTP, with a cross-over point of zero change at intermediate stimulation fre-  
338 quencies. In addition to allowing us to explore frequency-dependent plasticity (FDP), this stimu-  
339 lation paradigm also gave us further constraints to define the LTD polygon region in the model  
340 since in **Tigaret et al. (2016)**, only one LTD case was available. For FDP, we focused on modelling  
341 the experiments from **Dudek and Bear (1992)**, who stimulated Schaffer collateral projections to  
342 pyramidal CA1 neurons with 900 pulses in frequencies ranging from 1 Hz to 50 Hz. In addition to  
343 presynaptic stimulation patterns, the experimental conditions differed from **Tigaret et al. (2016)** in  
344 two other aspects: animal age and control of postsynaptic spiking activity (see **Table 1** legend). We  
345 incorporated both age-dependence and EPSP-evoked-BaPs in our model (**Methods and Materials**).  
346 Importantly, the geometrical readout mechanism mapping joint CaMKII-CaN activity to plasticity  
347 remained identical for all experiments in this work.

348 **Figure 4a** shows the joint CaMKII-CaN activity when we stimulated the model with 900 presy-  
349 naptic spikes at 1, 3, 5, 10 and 50 Hz (**Dudek and Bear, 1992**). Higher stimulation frequencies drove  
350 stronger responses in both CaN and CaMKII activities (**Figure 4a**). **Figure 4b,c** show the correspond-  
351 ing plasticity region indicator for the LTP/LTD region threshold crossings and the synaptic strength  
352 change. From this set of five protocols, only the 50 Hz stimulation drove a response strong enough  
353 to reach the LTP region of the plane (**Figure 4a and d**). Although the remaining four protocols drove  
354 responses primarily in the LTD region, only the 3 and 5 Hz stimulations resulted in substantial LTD.  
355 The 1 Hz and 10 Hz stimulations resulted in negligible LTD, but for two distinct reasons. Although  
356 the 10 Hz protocol's joint CaMKII-CaN activity passed through the LTD region of the plane (**Figure**  
357 **4a and d**), it was too brief to activate the slow LTD mechanism built into the readout (**Methods**  
358 **and Materials**). The 1 Hz stimulation, on the other hand, was prolonged, but its response was too  
359 weak to reach the LTD region, crossing the threshold only intermittently (**Figure 4b, bottom trace**).  
360 Overall the model matched well the mean plasticity response found by **Dudek and Bear (1992)**, see  
361 **Figure 4e**, following a classic BCM-like curve as function of stimulation frequency (**Abraham et al.,**  
362 **2001; Bienenstock et al., 1982**).

363 We then used the model to explore the stimulation space in more detail by varying the stim-  
364 ulation frequency from 0.5 Hz to 50 Hz, and varying the number of presynaptic pulses from 50  
365 to 1200. **Figure 4f** shows a contour map of the mean synaptic strength change (%) in this 2D  
366 frequency-pulse number space. Under **Dudek and Bear (1992)** experimental conditions, we found  
367 that LTD induction required at least ~300 pulses, at frequencies between 1Hz and 3Hz. In contrast,  
368 LTP could be induced using ~50 pulses at ~20Hz or greater. The contour map also showed that  
369 increasing the number of pulses (vertical axis in **Figure 4e**) increases the magnitude of both LTP



**Figure 4. | Frequency dependent plasticity, *Dudek and Bear (1992)* dataset.** **a**, Example traces of joint CaMKII-CaN activity for each of *Dudek and Bear (1992)* protocol. **b**, Region indicator showing when the joint CaMKII-CaN activity crosses the LTD or LTP regions for each protocol in panel **a**. **c**, Synaptic weight change (%) as a function of time for each protocol, analogous to *Figure 3c*. Trace colours correspond to panel **a**. The trajectories displayed were chosen to match the medians in panel **e**. **d**, Mean (100 samples) time spent (s) for protocols 1Pre for 900 pairing repetitions at 3, 10 and 50 Hz. **e**, Comparison between data from *Dudek and Bear (1992)* and our model (1Pre 900p, 300 samples per frequency, see *Table 1*). Data are represented as normal distributions with the mean and variance of the change in field EPSP slope taken from *Dudek and Bear (1992)*. **f**, Prediction for the mean weight change (%) when varying the stimulation frequency and pulse number (24x38x100 data points, respectively pulse x frequency x samples). The filled grey circles show the *Dudek and Bear (1992)* protocol parameters and the corresponding results are shown in panel **e**.

**Figure 4-Figure supplement 1.** Varying experimental parameters in *Dudek and Bear (1992)* and Poisson spike train during development.

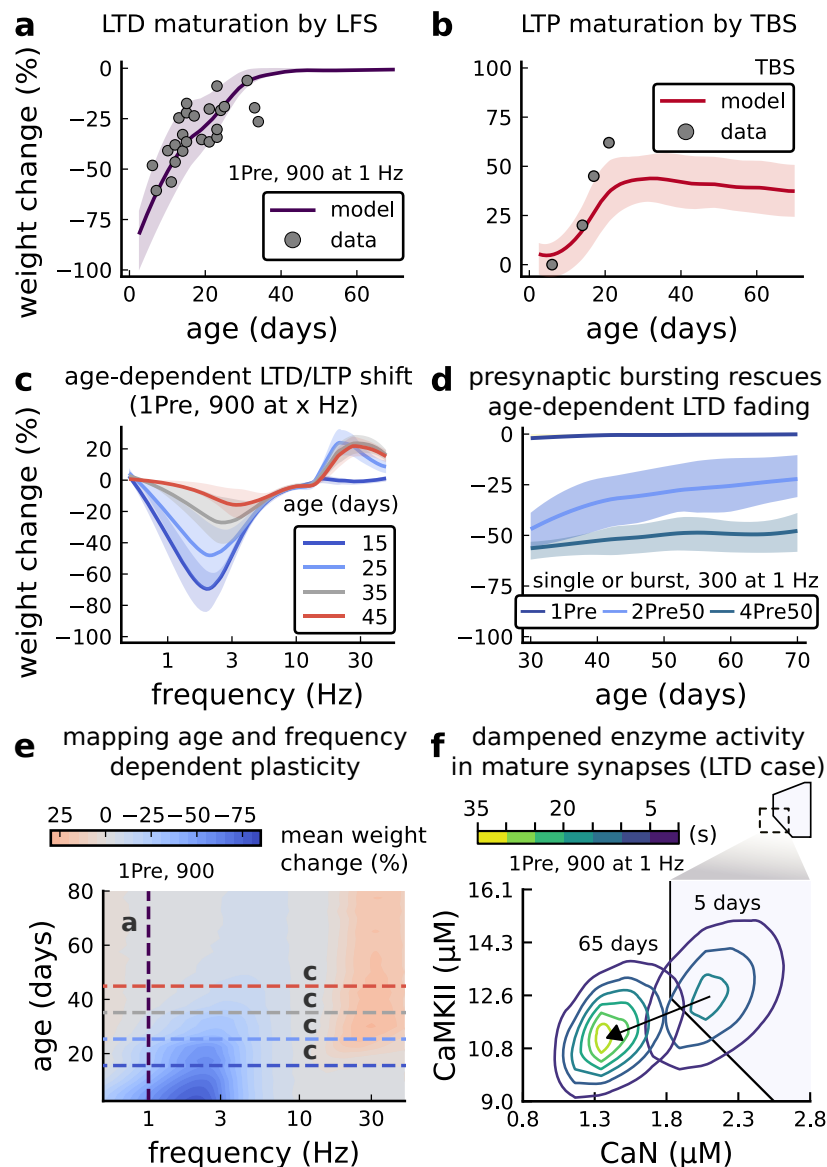
370 and LTD. This was paralleled by a widening of the LTD frequency range, whereas the LTP frequency  
371 threshold remained around ~20Hz, independent of pulse number.

372 The pulse-dependent amplification of synaptic weight predicted in *Figure 4* is also valid for  
373 *Tigaret et al. (2016)* experiment shown in *Figure 3h*.

374 *Ex vivo* experiments in *Dudek and Bear (1992)* were done at 35°C. However, lower tempera-  
375 tures are more widely used for *ex vivo* experiments because they extend brain slice viability. We  
376 performed further simulations testing temperature modifications for *Dudek and Bear (1992)* ex-  
377 periment, predicting a strong effect on plasticity outcomes (*Figure 4-Figure Supplement 1d-f*).

### 378 Variations in plasticity induction with developmental age

379 The rules for induction of LTP and LTD change during development (*Dudek and Bear, 1993; Cao*  
380 *and Harris, 2012*), so a given plasticity protocol can produce different outcomes when delivered to  
381 synapses from young animals versus mature animals. For example, when *Dudek and Bear (1993)*  
382 tested the effects of low-frequency stimulation (1 Hz) on CA3-CA1 synapses from rats of different  
383 ages, they found that the magnitude of LTD decreases steeply with age from P7 until becoming  
384 minimal in mature animals >P35 (*Figure 5a*, circles). Across the same age range, they found that a  
385 theta-burst stimulation protocol induced progressively greater LTP magnitude with developmental  
386 age (*Figure 5b*, circles). Paralleling this, multiple properties of neurons change during development:  
387 the NMDAR switches its dominant subunit expression from GluN2B to GluN2A (*Sheng et al., 1994;*  
388 *Popescu et al., 2004; Iacobucci and Popescu, 2017*), the reversal potential of the receptor (GABA<sub>R</sub>)



**Figure 5. | Age-dependent plasticity, Dudek and Bear (1993) dataset.** **a**, Synaptic weight change for 1Pre, 900 at 1 Hz as in *Dudek and Bear (1993)*. The solid line is the mean and the ribbons are the 2nd and 4th quantiles predicted by our model (same for panel **b**, **c** and **f**). **b**, Synaptic weight change for Theta Burst Stimulation (TBS - 4Pre at 100 Hz repeated 10 times at 5 Hz given in 6 epochs at 0.1 Hz, see *Table 1*). **c**, Synaptic weight change as a function of frequency for different ages. BCM-like curves showing that, during adulthood, the same LTD protocol becomes less efficient. It also shows that high-frequencies are inefficient at inducing LTP before P15. **d**, Synaptic weight change as a function of age. Proposed protocol using presynaptic bursts to recover LTD at  $\geq$  P35 with less pulses, 300 instead of the original 900 from *Dudek and Bear (1993)*. This effect is more pronounced for young rats. *Figure 5-Figure Supplement 1* shows a 900 pulses comparison. **e**, Mean synaptic strength change (%) as a function of frequency and age for 1Pre 900 pulses (32x38x100, respectively, for frequency, age and samples). The protocols in *Dudek and Bear (1993)* (panel **a**) are marked with the yellow vertical line. The horizontal lines represent the experimental conditions of panel **c**. Note the P35 was used for *Dudek and Bear (1992)* experiment in *Figure 4f*. **f**, Mean time spent for the 1Pre 1Hz 900 pulses protocol showing how the trajectories are left-shifted as rat age increases. **Figure 5-Figure supplement 1**. Duplets, triplets and quadruplets for FDP, perturbing developmental-mechanisms for LFS and HFS in *Dudek and Bear (1993)*, and age-related changes in STDP experiments (*Inglebert et al., 2020; Tigaret et al., 2016; Meredith et al., 2003*).

389 switches from depolarising to hyperpolarizing (*Rivera et al., 1999; Meredith et al., 2003; Rinetti-*  
 390 *Vargas et al., 2017*), and the action potential backpropagates more efficiently with age (*Buchanan*  
 391 *and Mellor, 2007*). These mechanisms have been proposed to underlie the developmental changes  
 392 in synaptic plasticity rules because they are key regulators of synaptic calcium signalling (*Meredith*  
 393 *et al., 2003; Buchanan and Mellor, 2007*). However, their sufficiency and individual contributions  
 394 to the age-related plasticity changes are unclear and this has not been taken into account in any  
 395 previous model. We incorporated these mechanisms in the model (*Methods and Materials*) by  
 396 parameterizing each of the three components to vary with the animal's postnatal age, to test if  
 397 they could account for the age-dependent plasticity data.

398 We found that elaborating the model with age-dependent changes in NMDAR composition,  
 399 GABA<sub>A</sub> reversal potential, and BaP efficiency, while keeping the same plasticity readout parame-  
 400 ters, was sufficient to account for the developmental changes in LTD and LTP observed by *Dudek*  
 401 *and Bear (1993)* (*Figure 5a,b*). We then explored the model's response to protocols of various stimu-  
 402 lation frequencies, from 0.5 to 50 Hz, across ages from P5 to P80 (*Figure 5c,e*). *Figure 5c* shows  
 403 the synaptic strength change as function of stimulation frequency for ages P15, P25, P35 and P45.  
 404 The magnitude of LTD decreases with age, while the magnitude of LTP increases with age. *Figure*

405 **5e** shows a contour plot of the same result, covering the age-frequency space.

406 The 1 Hz presynaptic stimulation protocol in *Dudek and Bear (1993)* did not induce LTD in adult  
407 animals (*Dudek and Bear, 1992*). We found that the joint CaN-CaMKII activity trajectories for this  
408 stimulation protocol underwent an age-dependent leftward shift beyond the LTD region (*Figure*  
409 *5f*). This implies that LTD is not induced in mature animals by this conventional LFS protocol due  
410 to insufficient activation of enzymes. In contrast, *Tigaret et al. (2016)* and *Isaac et al. (2009)* were  
411 able to induce LTD in adult rat tissue by combining LFS with presynaptic spike pairs repeated 900  
412 times at 3 Hz. Given these empirical findings and our modelling results, we hypothesized that LTD  
413 induction in adult animals requires that the stimulation protocol: 1) causes CaMKII and CaN activity  
414 to stay more in the LTD region than the LTP region, and 2) is sufficiently long to activate the LTD  
415 readout mechanism. With experimental parameters used by *Dudek and Bear (1993)*, this may be  
416 as short as 300 pulses when multi-spike presynaptic protocols are used since the joint CaMKII-CaN  
417 activity can reach the LTD region more quickly than for single spike protocols. We simulated two  
418 such potential protocols as predictions: doublet and quadruplet spike groups delivered 300 times  
419 at 1 Hz, with 50 ms between each pair of spikes in the group (*Figure 5d*). The model predicted that  
420 both these protocols induce LTD in adults, whereas as shown above, the single pulse protocol did  
421 not cause LTD. These findings suggest that the temporal requirements for inducing LTD may not  
422 be as prolonged as previously assumed, since they can be reduced by varying stimulation intensity.  
423 See *Figure 5-Figure Supplement 1* for frequency versus age maps for presynaptic bursts.

424 *Dudek and Bear (1993)* also performed theta-burst stimulation (TBS, *Table 1*) at different de-  
425 velopmental ages, and found that LTP is not easily induced in young rats (*Cao and Harris, 2012*),  
426 as depicted in *Figure 5b*. The model qualitatively matches this trend, and also predicts that TBS  
427 induces maximal LTP around P21, before declining further during development (*Figure 5b*, green  
428 curve). Similarly, we found that high-frequency stimulation induces LTP only for ages >P15, peaks  
429 at P35, then gradually declines at older ages (*Figure 5e*). Note that in *Figure 5b*, we used 6 epochs  
430 instead of 4 used by *Dudek and Bear (1993)* to increase LTP outcome which is known to washout  
431 after one hour for young rats (*Cao and Harris, 2012*).

432 In contrast to *Dudek and Bear (1993)* findings, other studies have found that LTP can be induced  
433 in hippocampus in young animals (<P15) with STDP. For example, *Meredith et al. (2003)* found that,  
434 at room temperature, 1Pre1Post10 induces LTP in young rats, whereas 1Pre2Post10 induces NC.  
435 This relationship was inverted for adults, with 1Pre1Post inducing no plasticity and 1Pre2Post10  
436 inducing LTP (*Figure 5-Figure Supplement 7*).

437 Together, these results suggest that not only do the requirements for LTP/LTD change with age,  
438 but also that these age-dependencies are different for different stimulation patterns. Finally, we  
439 explore which mechanisms are responsible for plasticity induction changes across development  
440 in the FDP protocol (*Figure 5-Figure Supplement 1*) by fixing each parameter to young or adult  
441 values for the FDP paradigm. Our model analysis suggests that the NMDAr switch (*Iacobucci and*  
442 *Popescu, 2017*) is a dominant factor affecting LTD induction, but the maturation of BaP (*Buchanan*  
443 *and Mellor, 2007*) is the dominant factor affecting LTP induction, with GABA<sub>r</sub> shift having only a  
444 weak influence on LTD induction for *Dudek and Bear (1993)* FDP.

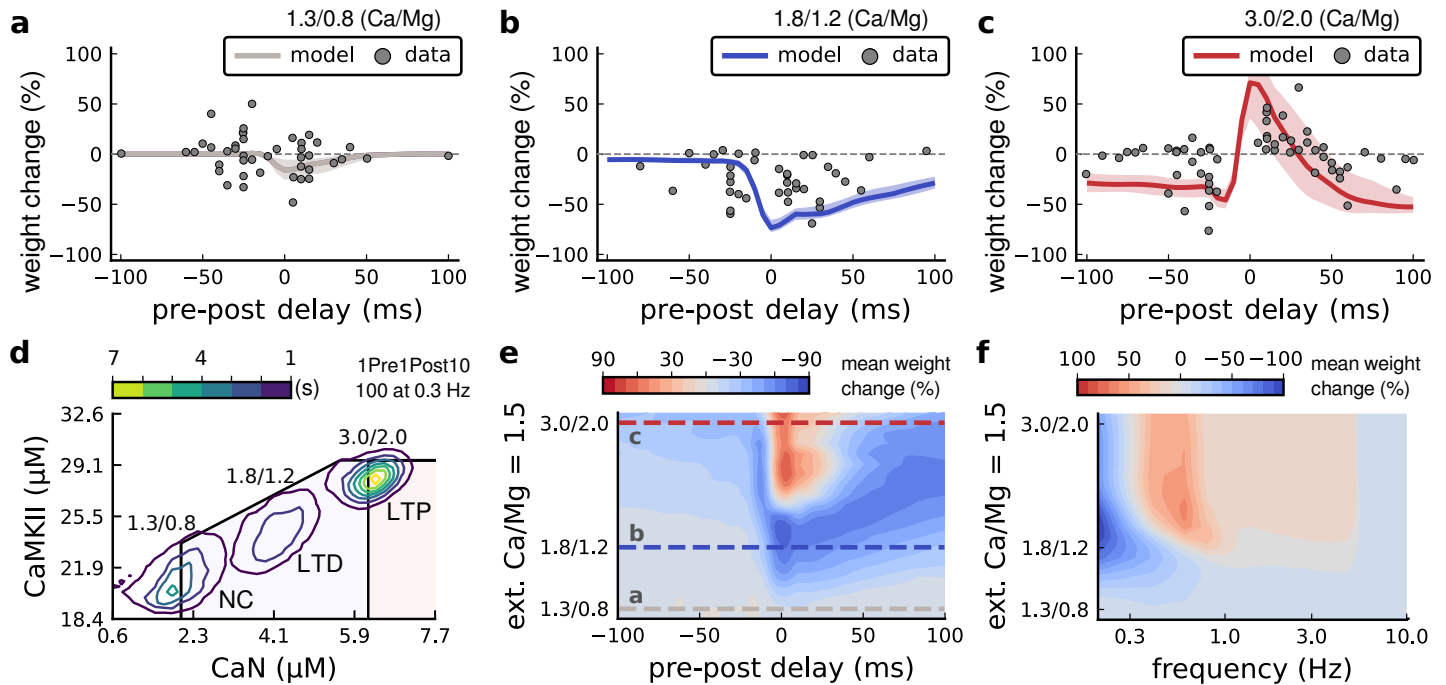
445 Plasticity requirements during development do not necessarily follow the profile in *Dudek and*  
446 *Bear (1993)* as shown by *Meredith et al. (2003)* STDP experiment. Our model shows that multiple  
447 developmental profiles are possible when experimental conditions vary within the same stimula-  
448 tion paradigm. This is illustrated in *Figure 6-Figure Supplement 2 a-c* by varying the age of STDP  
449 experiments done in different conditions. We fitted well the data from *Wittenberg and Wang (2006)*  
450 by adapting the model with appropriate age and temperature.

## 451 **Effects of extracellular calcium and magnesium concentrations on plasticity out-** 452 **come.**

453 The canonical STDP rule (*Bi and Poo, 1998*), measured in cultured neurons with high extracellular  
454 calcium ( $[Ca^{2+}]_o$ ) and at room temperature, was recently found not to be reproducible at physio-

455 logical  $[Ca^{2+}]_o$  in CA1 brain slices (*Inglebert et al., 2020*). Instead, by varying the  $[Ca^{2+}]_o$  and  $[Mg^{2+}]_o$ ,  
 456 *Inglebert et al. (2020)* found a spectrum of STDP rules with either no plasticity or full-LTD for phys-  
 457 iological  $[Ca^{2+}]_o$  conditions ( $[Ca^{2+}]_o < 1.8$  mM) and a bidirectional rule for high  $[Ca^{2+}]_o$  ( $[Ca^{2+}]_o > 2.5$   
 458 mM), shown in *Figure 6a-c*.

459 We attempted to reproduce *Inglebert et al. (2020)* findings by varying  $[Ca^{2+}]_o$  and  $[Mg^{2+}]_o$  with  
 460 the following consequences for the model mechanisms (*Methods and Materials*). On the presyn-  
 461 aptic side,  $[Ca^{2+}]_o$  modulates vesicle release probability. On the postsynaptic side, high  $[Ca^{2+}]_o$   
 462 reduces NMDAR conductance (*Maki and Popescu, 2014*), whereas  $[Mg^{2+}]_o$  affects the NMDAR  $Mg^{2+}$   
 463 block (*Jahr and Stevens, 1990*). Furthermore, spine calcium influx activates SK channels, which hy-  
 464 perpolarize the membrane and indirectly modulate NMDAR activity (*Ngo-Anh et al., 2005; Griffith*  
 465 *et al., 2016*).



**Figure 6. Effects of extracellular calcium and magnesium concentrations on plasticity.** **a**, Synaptic weight (%) for a STDP rule with  $[Ca^{2+}]_o = 1.3$  mM (fixed ratio, Ca/Mg=1.5). According to the data extracted from *Inglebert et al. (2020)*, the number of pairing repetitions for causal/positive (anti-causal/negative) delays is 100 (150), both delivered at 0.3 Hz. The solid line is the mean, and the ribbons are the 2nd and 4th quantiles predicted by our model (all panels use 100 samples). **b**, Same as **a**, but for  $[Ca^{2+}]_o = 1.8$  mM (Ca/Mg ratio = 1.5). **c**, Same as **a**, but for  $[Ca^{2+}]_o = 3$  mM (Ca/Mg ratio = 1.5). **d**, Mean time spent for causal pairing, 1Pre1Post10, at different Ca/Mg concentration ratios. The contour plots are associated with the panels **a**, **b** and **c**. **e**, Predicted effects of extracellular Ca/Mg on STDP outcome. Synaptic weight change (%) for causal (1Pre1Post10, 100 at 0.3 Hz) and anticausal (1Post1Pre10, 150 at 0.3 Hz) pairings varying extracellular Ca from 1.0 to 3 mM (Ca/Mg ratio = 1.5). The dashed lines represent the experiments in the panel **a**, **b** and **c**. We used 21x22x100 data points, respectively calcium x delay x samples. **f**, Predicted effects of varying frequency and extracellular Ca/Mg for an STDP protocol. Contour plot showing the mean synaptic weight (%) for a single causal pairing protocol (1Pre1Post10, 100 samples) varying frequency from 0.1 to 10 Hz and  $[Ca^{2+}]_o$  from 1.0 to 3 mM (Ca/Mg ratio = 1.5). We used 21x18x100 data points, respectively calcium x frequency x samples.

**Figure 6-Figure supplement 1.** Effects of extracellular calcium and magnesium concentration on plasticity.

**Figure 6-Figure supplement 2.** Temperature and age effects.

466 *Figure 6a-c* compares our model to *Inglebert et al. (2020)* STDP data at different  $[Ca^{2+}]_o$  and  
 467  $[Mg^{2+}]_o$ . Note that *Inglebert et al. (2020)* used 150 pairing repetitions for the anti-causal stimuli and  
 468 100 pairing repetitions for the causal stimuli both delivered at 0.3 Hz. At  $[Ca^{2+}]_o = 1.3$  mM, *Figure*  
 469 *6a* shows that the STDP rule induced weak LTD for brief causal delays. At  $[Ca^{2+}]_o = 1.8$  mM, in  
 470 *Figure 6b*, the model predicted a full-LTD window. At  $[Ca^{2+}]_o = 3$  mM, in *Figure 6c*, it predicted a  
 471 bidirectional rule with a second LTD window for long causal pairings, previously theorized by *Rubin*  
 472 *et al. (2005)*.

473 **Figure 6d** illustrates the time spent by the joint CaN-CaMKII activity for 1Pre1Post10 using *In-*  
474 *glebert et al. (2020)* experimental conditions. Each density plot corresponds to a specific specific  
475 Ca/Mg ratio as in **Figure 6a-c**. The response under low  $[Ca^{2+}]_o$  spent most time inside the LTD  
476 region, but high  $[Ca^{2+}]_o$  shifts the trajectory to the LTP region. **Figure 6-Figure Supplement 1a**  
477 presents density plots for the anti-causal protocols.

478 *Inglebert et al. (2020)* fixed the Ca/Mg ratio at 1.5, although aCSF formulations in the literature  
479 differ (see **Table 1**). **Figure 6-Figure Supplement 1d** shows that varying the Ca/Mg ratio and  $[Ca^{2+}]_o$   
480 for *Inglebert et al. (2020)* experiments restrict LTP to  $Ca/Mg > 1.5$  and  $[Ca^{2+}]_o > 1.8$  mM.

481 Our model can also identify the transitions between LTD and LTP depending on Ca/Mg. **Fig-**  
482 **ure 6e** shows a map of plasticity as function of pre-post delay and Ca/Mg concentrations and the  
483 parameters where LTP is induced for the 1Pre1Post10 protocol. Since plasticity rises steeply at  
484 around  $[Ca^{2+}]_o = 2.2$  mM (see **Figure 6e**), small fluctuations in  $[Ca^{2+}]_o$  near this boundary could  
485 cause qualitative transitions in plasticity outcomes. For anti-causal pairings, increasing  $[Ca^{2+}]_o$  in-  
486 creases the magnitude of LTD (**Figure 6-Figure Supplement 1b** illustrates this with *Inglebert et al.*  
487 (2020) data).

488 *Inglebert et al. (2020)* also found that increasing the pairing frequency to 5 or 10 Hz results  
489 in a transition from LTD to LTP for 1Pre1Post10 at  $[Ca^{2+}]_o = 1.8$  mM (**Figure 6-Figure Supplement**  
490 **1c**), similar frequency-STDP behaviour has been reported in the cortex (*Sjöström et al., 2001*). In  
491 **Figure 6f**, we varied both the pairing frequencies and  $[Ca^{2+}]_o$  and we observe similar transitions to  
492 *Inglebert et al. (2020)*. However, the model's transition for  $[Ca^{2+}]_o = 1.8$  mM was centred around  
493 0.5 Hz, which was untested by *Inglebert et al. (2020)*. The model predicted no plasticity at higher  
494 frequencies, unlike the data, that shows scattered LTP and LTD (see **Figure 6-Figure Supplement**  
495 **1c**). Another frequency dependent comparison, **Figure 3-Figure Supplement 5c** and **Figure 6-Figure**  
496 **Supplement 1h**, show that *Tigaret et al. (2016)* burst-STDP and *Inglebert et al. (2020)* STDP share  
497 a similar transition structure, different from *Dudek and Bear (1992)* FDP.

498 In contrast to *Inglebert et al. (2020)* results, we found that setting low  $[Ca^{2+}]_o$  for *Tigaret et al.*  
499 (2016) burst-STDP abolishes LTP, and does not induce strong LTD (**Figure 3-Figure Supplement 5d**).  
500 For *Dudek and Bear (1992)* experiment, **Figure 4-Figure Supplement 1d**  $[Mg^{2+}]_o$  controls a sliding  
501 threshold between LTD and LTP but not  $[Ca^{2+}]_o$  (**Figure 4-Figure Supplement 1b**). For another direct  
502 stimulation experiment, **Figure 6-Figure Supplement 1c** shows that in an Mg-free medium, LTP  
503 expression requires fewer pulses (*Mizuno et al., 2001*).

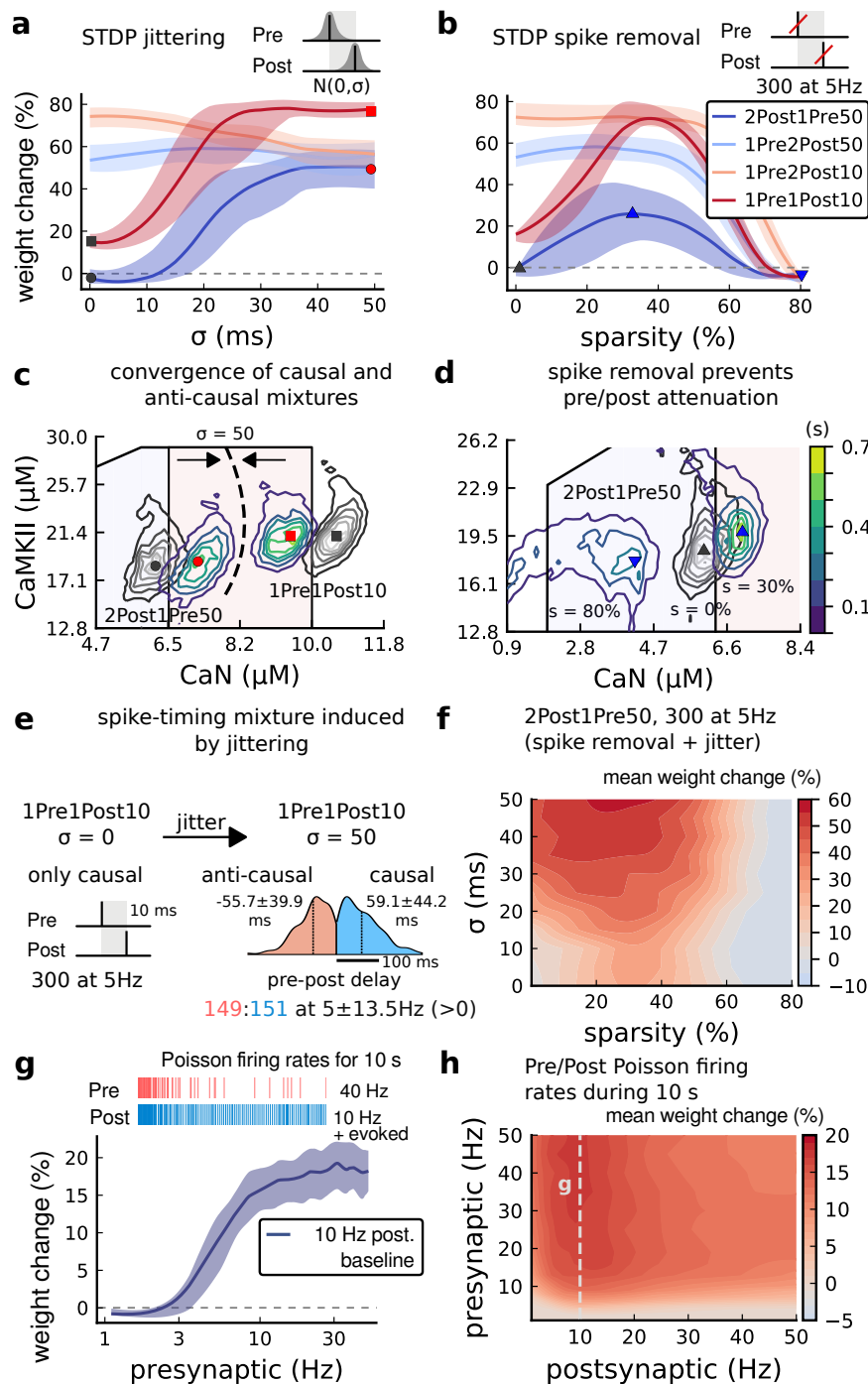
504 Despite exploring physiological  $[Ca^{2+}]_o$  and  $[Mg^{2+}]_o$  *Inglebert (Inglebert et al., 2020)* use a non-  
505 physiological temperature (30°C) which extends T-type VGCC closing times and modifies the CaN-  
506 CaMKII baseline (**Figure 6-Figure Supplement 2i**). **Figure 6-Figure Supplement 2g,h** show compara-  
507 ble simulations for physiological temperatures. In summary, our model predicts that temperature  
508 can change STDP rules in a similar fashion to  $[Ca^{2+}]_o$  (**Figure 6-Figure Supplement 1a,b**). Overall,  
509 we confirm that plasticity is highly sensitive to variations in extracellular calcium, magnesium, and  
510 temperature (**Figure 3-Figure Supplement 5a, Figure 6-Figure Supplement 2d-f**).

### 511 **In vivo-like spike variability affects plasticity**

512 In the above sections, we used highly regular and stereotypical stimulation protocols to replicate  
513 typical *ex vivo* plasticity experiments. In contrast, neural spiking in hippocampus *in vivo* is irregular  
514 and variable (*Fenton and Muller, 1998; Isaac et al., 2009*). Previous studies that asked how natural  
515 firing variability affects the rules of plasticity induction used simpler synapse models (*Rackham*  
516 *et al., 2010; Graupner et al., 2016; Cui et al., 2018*). We explored this question in our synapse model  
517 using simulations with three distinct types of additional variability: 1) spike time jitter, 2) failures  
518 induced by dropping spikes, 3) independent pre and postsynaptic Poisson spike trains (*Graupner*  
519 *et al., 2016*).

520 We introduced spike timing jitter by adding zero-mean Gaussian noise (s.d.  $\sigma$ ) to pre and postsy-  
521 naptic spikes, changing spike pairs inter-stimulus interval (ISI). In **Figure 7a**, we plot the LTP magni-  
522 tude as function of jitter magnitude (controlled by  $\sigma$ ) for protocols taken from *Tigaret et al. (2016)*.





**Figure 7. | Jitter and spike dropping effects on STDP and Poisson spike trains.** **a**, Mean weight (%) for the jittered STDP protocols (protocol color legend shown in **b**). The solid line is the mean, and the ribbons are the 2nd and 4th quantiles predicted by our model using 100 samples (same panels a, b and g). **b**, Mean weight (%) for the same (Tigaret et al., 2016) protocols used in panel a subjected to random spike removal (sparsity %). **c**, Mean time spent (s) varying jittering. Contour plot shows 2Post1Pre50 and 1Pre1Post10 (300 at 5 Hz) without (grey contour plot) and with jittering (coloured contour plot). The circles and squares correspond to the marks in panel a. **d**, Mean time spent (s) varying sparsity. Contour plot in grey showing 0% sparsity for 2Post1Pre50 300 at 5 Hz (see Figure 2f). The contour plots show the protocol with spike removal sparsities at 0% (NC), 30% (LTP), and 80% (NC). The triangles correspond to the same marks in panel a. **e**, Distribution of the 50 ms jittering applied to the causal protocol 1Pre1Post10, 300 at 5 Hz in which nearly half of the pairs turned into anticausal. The mean frequency is  $5 \pm 13.5$  Hz making it to have a similar firing structure and position in the LTP region. The similar occurs for 2Post1Pre50 (panel c). **f**, Mean weight change (%) combining both jittering (panel a) and sparsity (panel b) for 2Post1Pre50, 300 at 5 Hz. **g**, Mean weight change (%) of pre and postsynaptic Poisson spike train delivered simultaneously for 10 s. The plot shows the plasticity outcome for different presynaptic firing rate (1000/frequency) for a fixed postsynaptic baseline at 10 Hz. The upper raster plot depicts the released vesicles at 40 Hz and the postsynaptic baseline at 10 Hz (including the AP evoked by EPSP). **h**, Mean weight change (%) varying the rate of pre and postsynaptic Poisson spike train delivered simultaneously for 10 s. The heat map data along the vertical white dashed line is depicted in panel g.

523 With no jitter,  $\sigma = 0$ , these protocols have different LTP magnitudes (corresponding to Figure 3)  
 524 and become similar once  $\sigma$  increases. The three protocols with a postsynaptic spike doublet gave  
 525 identical plasticity for  $\sigma = 50$  ms.

526 To understand the effects of jittering, we plotted the trajectories of joint CaN-CaMKII activity  
 527 (Figure 7c). 2Post1Pre50 which "undershoots" the LTP region shifted into the LTP region for jitter  
 528  $\sigma = 50$  ms. In contrast, 1Pre1Post10 which "overshoots" the LTP region shifted to the opposite  
 529 direction towards the LTP region.

530 Why does jitter cause different spike timing protocols to yield similar plasticity magnitudes?  
 531 Increasing jitter causes a fraction of pairings to invert causality. Therefore, the jittered protocols  
 532 became a mixture of causal and anticausal pairings (Figure 7c). This situation occurs for all paired

533 protocols. So any protocol with the same number spikes will produce a similar outcome if the jitter  
534 is large enough. Note that despite noise the mean frequency was conserved at  $5 \pm 13.5$  Hz (see  
535 **Figure 7e**).

536 Next, we studied the effect of spike removal. In the previous sections, synaptic release prob-  
537 ability was  $\sim 60\%$  (for  $[Ca^{2+}]_o = 2.5$  mM) or lower, depending on the availability of docked vesicles  
538 (**Methods and Materials**). However, baseline presynaptic vesicle release probability is heteroge-  
539 neous across CA3-CA1 synapses, ranging from  $\sim 10 - 90\%$  (**Dobrunz et al., 1997; Enoki et al., 2009**)  
540 and likely lower on average *in vivo* (**Froemke and Dan, 2002; Borst, 2010**). BaPs are also heteroge-  
541 neous with random attenuation profiles (**Golding et al., 2001**) and spike failures (**Short et al., 2017**).  
542 To test the effects of pre and postsynaptic failures on plasticity induction, we performed simula-  
543 tions where we randomly removed spikes, altering the regular attenuation observed in **Tigaret**  
544 **et al. (2016)** protocols.

545 In **Figure 7b** we plot the plasticity magnitude as function of sparsity (percentage of removed  
546 spikes). The sparsity had different specific effects for each protocol. 1Pre2Post10 and 1Pre2Post50  
547 which originally produced substantial LTP were robust to spike removal until  $\sim 60\%$  sparsity. In con-  
548 trast, the plasticity magnitude from both 1Pre1Post10 and 2Post1Pre50 showed a non-monotonic  
549 dependence on sparsity, first increasing then decreasing, with maximal LTP at  $\sim 40\%$  sparsity.

550 To understand how sparsity causes this non-monotonic effect on plasticity magnitude, we plot-  
551 ted the histograms of time spent in the CaN-CaMKII plane for 2Post1Pre50 for three levels of spar-  
552 sity: 0%, 30% and 80% (**Figure 7d**). For 0% sparsity, the activation spent most time at the border  
553 between the LTP and LTD regions, resulting in no change. Increasing sparsity to 30% caused the  
554 activation to shift rightward into the LTP region because there was less attenuation of pre and  
555 postsynaptic resources. In contrast, at 80% sparsity, the activation moved into the LTD region be-  
556 cause there were not enough events to substantially activate CaMKII and CaN. Since LTD is a slow  
557 process and the protocol duration is short (60s), there was no net plasticity. Therefore for this pro-  
558 tocol, high and low sparsity caused no plasticity for distinct reasons, whereas intermediate sparsity  
559 enabled LTP by balancing resource depletion with enzyme activation.

560 Next we tested the interaction of jitter and spike removal. **Figure 7f** shows a contour map of  
561 weight change as a function of jitter and sparsity for the 2Post1Pre50 protocol, which originally  
562 induced no plasticity (**Figure 2**). Increasing spike jitter enlarged the range of sparsity inducing LTP.  
563 In summary, these simulations (**Figure 7a,b,f and h**) show that different STDP protocols have dif-  
564 ferent degrees of sensitivity to noise in the firing structure, suggesting that simple plasticity rules  
565 derived from regular *ex vivo* experiments may not predict plasticity *in vivo*.

566 How does random spike timing affect rate-dependent plasticity? We stimulated the model with  
567 pre and postsynaptic Poisson spike trains for 10s, under **Dudek and Bear (1992)** experimental condi-  
568 tions. We systematically varied both the pre and postsynaptic rates (**Figure 7h**). The 10s stimulation  
569 protocols induced only LTP, since LTD requires a prolonged stimulation (**Mizuno et al., 2001**). LTP  
570 magnitude monotonically increased with the presynaptic rate (**Figure 7g and h**). In contrast, LTP  
571 magnitude varied non-monotonically as a function of postsynaptic rate, initially increasing until a  
572 peak at 10 Hz, then decreasing with higher stimulation frequencies. This non-monotonic depen-  
573 dence on post-synaptic rate is inconsistent with classic rate-based models of Hebbian plasticity.  
574 We also investigated how this plasticity dependence on pre- and postsynaptic Poisson firing rates  
575 varies with developmental age (**Figure 4-Figure Supplement 1g-i**). We found that at P5 no plastic-  
576 ity is induced, at P15 a LTP region appears at around 1 Hz postsynaptic rate, and at P20 plasticity  
577 becomes similar to the mature age, with a peak in LTP magnitude at 10 Hz postsynaptic rate.

## 578 Discussion

579 We built a model of a rat CA3-CA1 hippocampal synapse, including key electrical and biochemical  
580 components underlying synaptic plasticity induction (**Figure 1**). We developed a novel geometric  
581 readout of combined CaN-CaMKII dynamics (**Figure 2-Figure 4**) to predict the outcomes from a

582 range plasticity experiments with heterogeneous conditions: animal developmental age (**Figure**  
583 **5**), aCSF composition (**Figure 6**), temperature (**Supplemental files**), and *in vivo*-like firing variability  
584 (**Figure 7**). This readout provides a simple and intuitive window into the dynamics of the synapse  
585 during plasticity. Our model is thus based on the joint activity of these two key postsynaptic en-  
586 zymes at both fast and slow time scales and considers the stochastic and adaptable dynamics of  
587 their activities dictated by the upstream calcium-dependent components at both the pre- and post-  
588 synapse. On this basis alone, our model is akin to biological processes where the outcome is jointly  
589 determined by several stochastic signaling components and a combination of multiple enzyme ac-  
590 tivities in time and space, i.e., are multi-dimensional. Our model is scalable, as it gives the pos-  
591 sibility for the readout to be extended to dynamics of  $n$  different molecules, using  $n$ -dimensional  
592 closed regions. It is abstract in the sense that we do not identify the readout components with  
593 specific synaptic molecules. Nevertheless, we anticipate that simple biochemical networks could  
594 implement the readout's functional mapping (**Alon, 2019**).

595 In addition to providing a new model of CA3-CA1 synapse biophysics, the main contribution  
596 of this work is the novel readout mechanism mapping synaptic enzymes to plasticity outcomes.  
597 This readout was built based on the concept that the full temporal activity of CaN-CaMKII over the  
598 minutes-timescale stimulus duration, and not their instantaneous levels, is responsible for changes  
599 in synaptic efficacy (**Fujii et al., 2013**). The readout follows the measurements of CaMKII and CaN  
600 molecular dynamics made using FRET imaging (**Fujii et al., 2013**). CaMKII and CaN were chosen be-  
601 cause they act upstream of several biochemical pathways implicated in the expression of plasticity  
602 and their inhibition blocks LTP and LTD, respectively (**O'Connor et al., 2005**). We expect that future  
603 studies using high temporal resolution measurements such as those provided by recent FRET tools  
604 available for CaMKII (**Chang et al., 2017, 2019**) will bring refinements to our model with the possi-  
605 bility to further test our readout predictions. In contrast, previous models assume that plasticity  
606 is explainable in terms of synaptic calcium or enzyme response to single BAP-EPSP pairings (**Shou-  
607 val et al., 2002; Karmarkar and Buonomano, 2002**). We instantiated this concept by analyzing the  
608 joint CaN-CaMKII activity in the two-dimensional plane and designing polygonal plasticity readout  
609 regions (**Figure 3a**). In doing so, we generalised previous work with plasticity induction based on  
610 single threshold and a slow variable (**Badoual et al., 2006; Rubin et al., 2005; Clopath and Gerstner,  
611 2010; Graupner and Brunel, 2012**) Given the high number of parameters in the model, we do not  
612 expect that the specific readout parameters we fit are unique. The addition of new datasets could  
613 better constrain the model fit. Here, we used only a two-dimensional readout, but anticipate a  
614 straightforward generalisation to higher-dimensions. The central discovery is that these trajec-  
615 tories, despite being stochastic, can be separated in the plane as a function of the stimulus (**Figure 3**).  
616 This is the basis of our new synaptic plasticity rule.

617 Let us describe the intuition behind our model more concisely. First, we abstracted away the  
618 sophisticated cascade of plasticity expression. Second, the plasticity regions, crossed by the trajec-  
619 tories, are described with a minimal set of parameters. Importantly, their tuning is quite straight-  
620 forward and done only once, even when the joint activity is stochastic. The tuning of the model is  
621 possible thanks to the decoupling of the plasticity process from the spine biophysics which acts as  
622 a feedforward input to the plasticity Markov chain and from the distributions of the different trajec-  
623 tories, which are well separated. It is expected that one could find other versions of this model  
624 (parameters or conceptual) instantiating our multidimensional readout concept that also match  
625 the data well. The separability afforded by the geometrical readout, along with the model flexibil-  
626 ity via fitting the plasticity regions, enabled us to reproduce data from nine different experiments  
627 using a single fixed set of model parameters. In contrast, we found that classic spike-timing (**Song  
628 et al., 2000; Pfister and Gerstner, 2006**) or calcium-threshold (**Graupner and Brunel, 2012**) models  
629 could not reproduce the range of protocols from **Tigaret et al. (2016)** (**Figure 3-Figure Supplement  
630 1**). More complicated molecular-cascade models have been shown to account for individual plas-  
631 ticity experiments (**Antunes et al., 2016; Jędrzejewska-Szmek et al., 2017; Mäki-Marttunen et al.,  
632 2020; Bhalla, 2017**), but have not been demonstrated to reproduce the wide range of protocols

633 presented here while considering experimental heterogeneity.

634 For some protocols, the CaMKII-CaN trajectories overshoot the plasticity regions (e.g. *Figure 3d*).  
635 Although abnormally high and prolonged calcium influx to cells can trigger cell death (*Zhivotovsky*  
636 *and Orrenius, 2011*), the effects of high calcium concentrations at single synapses are poorly under-  
637 stood. Notably, a few studies have reported evidence consistent with an overshoot, where strong  
638 synaptic calcium influx does not induce LTP (*Yang et al., 1999; Tigaret et al., 2016; Pousinha et al.,*  
639 *2017*).

640 Our model included critical components for plasticity induction at CA3-CA1 synapses: those af-  
641 fecting dendritic spine voltage, calcium signalling, and enzymatic activation. We were able to use  
642 our model to make quantitative predictions, because its variables and parameters corresponded  
643 to biological components. This property allowed us to incorporate the model components' depen-  
644 dence on developmental age, external Ca/Mg levels, and temperature to replicate datasets across a  
645 range of experimental conditions. The model is relatively fast to simulate, taking ~1 minute of CPU  
646 time to run 1 minute of biological time. These practical benefits should enable future studies to  
647 make experimental predictions on dendritic integration of multiple synaptic inputs (*Blackwell et al.,*  
648 *2019; Oliveira et al., 2012; Ebner et al., 2019*) and on the effects of synaptic molecular alterations  
649 in pathological conditions. In contrast, abstract models based on spike timing (*Song et al., 2000;*  
650 *Pfister and Gerstner, 2006; Clopath and Gerstner, 2010*) or simplified calcium dynamics (*Shouval*  
651 *et al., 2002; Graupner and Brunel, 2012*) must rely on ad hoc adjustment of parameters with less  
652 biological interpretability.

653 Intrinsic noise is an essential component of the model. How can the synapse reliably express  
654 plasticity but be noisy at the same time (*Yuste et al., 1999; Ribault et al., 2011*)? Noise can be re-  
655 duced either by redundancy or by averaging across time, also called ergodicity (*Sterling and Laugh-*  
656 *lin, 2015*). However redundancy requires manufacturing and maintaining more components, and  
657 therefore costs energy. We propose that, instead, plasticity induction is robust due to temporal  
658 averaging by slow-timescale signalling and adaptation processes. These slow variables display re-  
659 duced noise levels by averaging the faster timescale stochastic variables. This may be a reason  
660 why CaMKII uses auto-phosphorylation to sustain its activity and slow its decay time (*Chang et al.,*  
661 *2017, 2019*). In summary, this suggests that the temporal averaging by slow variables, combined  
662 with the separability afforded by the multidimensional readout, allows synapses to tolerate noise  
663 while remaining energy-efficient.

664 A uniqueness of our model is that it simultaneously incorporates biological variables such as  
665 electrical components at pre and postsynaptic sites some with adaptive functions such as attenua-  
666 tion, age and temperature, stochastic noise and fast and slow timescales. Some of these variables  
667 have been modelled by other groups, e.g. stochasticity, BaP attenuation or pre-synaptic plasticity  
668 (*Cai et al., 2007; Shouval and Kalantzis, 2005; Zeng and Holmes, 2010; Miller et al., 2005; Yeung*  
669 *et al., 2004; Shah et al., 2006; Deperrois and Graupner, 2020; Costa et al., 2015*), but generally in-  
670 dependently from each other. To position the uniqueness of our model in this broader context, we  
671 also provide a direct comparison of our model with some of the most recent leading models of ex-  
672 citatory synapse plasticity and the experimental work they reproduce (*Table 1-Table Supplement*  
673 *1 and Table 1-Table Supplement 2*).

674 We identified some limitations of the model. First, we modelled only a single postsynaptic spine  
675 attached to a two-compartment neuron (soma and dendrite), see Model Compartments in Online  
676 Methods. Second, the model abstracted the complicated process of synaptic plasticity expression.  
677 Indeed, even if this replicated the early phase of LTP/LTD expression in the first 30–60 minutes  
678 after induction, we did not take into account slower protein-synthesis-dependent processes, main-  
679 tenance processes, and synaptic pruning proceed at later timescales (*Bailey et al., 2015*). Third, like  
680 most biophysical models, ours contained many parameters (*Methods and Materials*). Although we  
681 set these to physiologically plausible values and then tuned to match the plasticity data, other com-  
682 binations of parameters may fit the data equally well (*Marder and Taylor, 2011; Mäki-Marttunen*  
683 *et al., 2020*) due to the ubiquitous phenomenon of redundancy in biochemical and neural systems

684 (*Gutenkunst et al., 2007; Marder, 2011*). Indeed synapses are quite heterogeneous in receptor  
685 and ion channel counts (*Takumi et al., 1999; Sabatini and Svoboda, 2000; Racca et al., 2000; Nim-*  
686 *chinsky et al., 2004*), protein abundances (*Shepherd and Harris, 1998; Sugiyama et al., 2005*), and  
687 spine morphologies (*Bartol et al., 2015; Harris and Stevens, 1989*), even within the subpopulation  
688 of CA1 pyramidal neuron synapses that we modelled here. It remains to be discovered how neu-  
689 rons tune their synaptic properties in this vast parameter space to achieve functional plasticity  
690 rules, or implement meta-plasticity (*Huang et al., 1992; Deisseroth et al., 1995; Abraham, 2008*).  
691 Fourth, the activation of clustered synapses could influence the plasticity outcome, and the num-  
692 ber of synapses activated during plasticity induction can be difficult to control experimentally. Our  
693 model concerns plasticity at a single synapse, which is also important during synaptic cluster acti-  
694 vation (*Ujfalussy and Makara, 2020*). We drew from data in *Tigaret et al. (2016)* where there is little  
695 indication of simultaneous clustered synaptic activation. Furthermore, our simulations are in good  
696 agreement with plasticity experiments using local field potential recordings (*Dudek and Bear, 1993*)  
697 where the number of activated synapses is uncertain. This indicates that the model proposed here  
698 can account for this aspect of synaptic plasticity heterogeneity. Finally, our readout model does  
699 not correspond to a specific molecular cascade beyond CaN and CaMKII activations. However, we  
700 anticipate that the same mapping could be implemented by simple biochemical reaction networks,  
701 with for example, transition rates based on Hill functions for the plasticity boundaries. Future work  
702 could try to match this readout to known synaptic molecules.

703 Several predictions follow from our results. Since the model respected the stochasticity of vesicle  
704 release (*Rizzoli and Betz, 2005; Alabi and Tsien, 2012*), NMDAr (*Nimchinsky et al., 2004; Popescu*  
705 *et al., 2004; Iacobucci and Popescu, 2017; Sinclair et al., 2016*), and VGCC opening (*Magee and John-*  
706 *ston, 1995; Sabatini and Svoboda, 2000; Iftinca et al., 2006*), the magnitude of plasticity varied from  
707 simulation trial to trial (*Methods and Materials, Figure 3g and Figure 4e*). This suggests that the  
708 rules of plasticity are inherently stochastic (*Bhalla, 2004; Antunes et al., 2016*) and that the vari-  
709 ability observed in these experiments (*Inglebert et al., 2020; Tigaret et al., 2016; Dudek and Bear,*  
710 *1992, 1993; Mizuno et al., 2001; Meredith et al., 2003; Wittenberg and Wang, 2006*) is partly due  
711 to stochastic signalling, in addition to the previously-documented heterogeneity in synapse prop-  
712 erties (*Nusser, 2018*) that we did not study here. By running extensive simulations over the space  
713 of protocols beyond those tested experimentally (*Figure 3h,i; Figure 4f; Figure 5c,e and f; Figure*  
714 *6e,f*), we made testable predictions for plasticity outcomes. For example, *Tigaret et al. (2016)* did  
715 not find LTD when using classic post-before-pre stimulation protocols, but the model predicted  
716 that LTD could be induced if the number of pairing repetitions was extended (*Figure 3h,i*). The  
717 model also predicts that the lack of LTD induced by FDP in adults can be recovered using doublets  
718 or quadruplet spike protocols (*Figure 5d*). We tested the model's sensitivity to spike time jitter and  
719 spike failure in the stimulation protocols (*Figure 7*). Our simulations predicted that this firing vari-  
720 ability can alter the rules of plasticity, in the sense that it is possible to add noise to cause LTP for  
721 protocols that did not otherwise induce plasticity.

722 What do these results imply about the rules of plasticity *in vivo*? First, we noticed that successful  
723 LTP or LTD induction required a balance between two types of slow variables: those that attenuate,  
724 such as presynaptic vesicle pools and dendritic BaP, versus those that accumulate, such as slow  
725 enzymatic integration (*Cai et al., 2007; Mizusaki et al., 2018; Deperrois and Graupner, 2020*). This  
726 balance is reflected in the inverted-U shaped magnitude of LTP seen as a function of post-synaptic  
727 firing rate (*Figure 7h*). Second, although spike timing on millisecond timescales can in certain cir-  
728 cumstances affect the direction and magnitude of plasticity (*Figure 3*), in order to drive sufficient  
729 activity of synaptic enzymes, these patterns would need to be repeated for several seconds. How-  
730 ever, if these repetitions are subject to jitter or failures, as observed in hippocampal spike trains *in*  
731 *vivo* (*Fenton and Muller, 1998; Wierzynski et al., 2009*), then the millisecond-timescale information  
732 will be destroyed as it gets averaged out across repetitions by the slow integration processes of  
733 CaMKII and CaN (*Figure 7a-d*). The net implication is that millisecond-timescale structure of individ-  
734 ual spike pairs is unlikely to play an important role in determining hippocampal synaptic plasticity

735 *in vivo* (Froemke and Dan, 2002; Sadowski et al., 2016; Graupner et al., 2016).

736 In summary, we presented a new type of biophysical model for plasticity induction at the rat  
737 CA3-CA1 glutamatergic synapse. Although the model itself is specific to this synapse type, the  
738 study's insights may generalise to other synapse types, enabling a deeper understanding of the  
739 rules of synaptic plasticity and brain learning.

## 740 Methods and Materials

### 741 Data and code availability

742 All simulations were performed in the Julia programming language (version 1.4.2). This choice  
743 was dictated by simplicity and speed (Parker, 2019). The code for the Markov chains is mostly  
744 automatically generated from reactions, and could be exported to an SBML representation for  
745 porting to other languages.

746 Simulating the synapse model is equivalent to sampling a piecewise deterministic Markov process,  
747 and this relies on the thoroughly tested Julia package [PiecewiseDeterministicMarkovProcesses.jl](#).  
748 These simulations are event-based, and no approximation is made beyond the ones required to  
749 integrate the ordinary differential equations by the LSODA method (Livermore Solver for Ordinary  
750 Differential Equations). We ran the parallel simulations in the Nef cluster operated by Inria.

**Table 1.** Table with the parameters extracted from the respective publications. To fit the data associated to publications displaying a parameter interval (e.g. 70 to 100) we used a value within the provided limits. Otherwise, we depict in parentheses the value used to fit to the data. For complete data structure on these publications and the ones used for method validation see github code. We allowed the AP to be evoked by EPSPs for these protocols: Mizuno et al. (2001), Dudek and Bear (1992) Dudek and Bear (1993). Note that Tigaret et al. (2016) used GABA(A)r blockers, which we modelled by setting the GABA<sub>A</sub> conductance to zero. Also, Mizuno et al. (2001) LTD protocol used partial NMDA blocker modelled by reducing NMDA conductance by 97 %.

**Table 1 - Table Supplement 1.** Comparison of recent computational models for plasticity.

**Table 2 - Table Supplement 2.** Comparison of the experimental conditions for the different reproduced datasets in recent computational models for plasticity.

Experiment	Paper	Repetitions	Freq (Hz)	Age (days)	Temp. (°C)	[Ca <sup>2+</sup> ] <sub>o</sub> (mM)	[Mg <sup>2+</sup> ] <sub>o</sub> (mM)
STDP	Tigaret et al. (2016)	300	5	56	35	2.5	1.3
STDP	Inglebert et al. (2020)	100, positive delays 150, negative delays	0.3	14–20 (21 for LTP)	30 (30.45 for LTP)	1.3–3	Ca/1.5
STDP	Meredith et al. (2003)	20	0.2	9–45	24–28	2	2
STDP	Wittenberg and Wang (2006)	70–100	5	14–21	24–30 (22.5–23)	2	1
pre-burst	Tigaret et al. (2016)	300 and 900	3 and 5	56	35	2.5	1.3
FDP	Dudek and Bear (1992)	900	1–50	35	35	2.5	1.5
FDP	Dudek and Bear (1993)	900	1	7–35	35	2.5	1.5
TBS	Dudek and Bear (1993)	3–4 (5) epochs	4Pre at 100 Hz (10x at 5Hz)	6, 14 and 17	35	2.5	1.5
LFS	Mizuno et al. (2001)	1–600	1	12–28	30 (26.5–31)	2.4	0

### 751 Notation

752 We write  $\mathbf{1}_A$  for the indicator of a set  $A$ , meaning that  $\mathbf{1}_A(x) = 1$  if  $x$  belongs to  $A$  and zero otherwise.

### 753 Vesicle release and recycling

754 Vesicle-filled neurotransmitters from the presynaptic terminals stimulate the postsynaptic side  
755 when successfully released. We derived a vesicle release Markov chain model based on a deter-  
756 ministic approach described in Sterratt et al. (2011). We denote by  $(t_1, \dots, t_n)$  the arrival times of  
757 the presynaptic spikes.

758 Vesicles can be in two states, either belonging to the docked pool (with cardinal  $D$ ) with fast  
759 emptying, or to the reserve pool (with cardinal  $R$ ) which replenishes  $D$  (Rizzoli and Betz, 2005).  
760 Initially the docked and reserve pools have  $D_0$  and  $R_0$  vesicles, respectively. The docked pool loses  
761 one vesicle each time a release occurs (Rudolph et al., 2015), with transition  $D \rightarrow D - 1$  (Figure

**Table 2.** Stochastic transitions used in the pool dynamics. Note that the rates depend on the pool's cardinal (*Pyle et al., 2000*).

Transition	Rate	Initial Condition
$(R, D) \rightarrow (R - 1, D + 1)$	$(D_0 - D) \cdot R / \tau_D$	$D(0) = D_0$
$(R, D) \rightarrow (R + 1, D - 1)$	$(R_0 - R) \cdot D / \tau_R$	$R(0) = R_0$
$(R, D) \rightarrow (R + 1, D)$	$(R_0 - R) / \tau_R^{ref}$	

762 **8).** The reserve pool replenishes the docked pool with transition  $(R, D) \rightarrow (R - 1, D + 1)$ . Finally, the  
 763 reserve pool is replenished with rate  $(R_0 - R) / \tau_D^{ref}$  with the transition  $(R, D) \rightarrow (R + 1, D)$ .

764 In addition to the stochastic dynamics in **Table 2**, each spike  $t_i$  triggers a vesicle release  $D \rightarrow$   
 765  $D - 1$  with probability  $p_{rel}$ :

$$p_{rel}(Ca_{pre}, [Ca^{2+}]_o, D) = \frac{(Ca_{pre})^s}{(Ca_{pre})^s + h([Ca^{2+}]_o)^s} \mathbf{1}_{D>0}, \quad h([Ca^{2+}]_o) = 0.654 + \frac{1.349}{1 + e^{4 \cdot ([Ca^{2+}]_o - 1.708 \text{ mM})}} \quad (1)$$

766 which is a function of presynaptic calcium  $Ca_{pre}$  and extracellular calcium concentration  $[Ca^{2+}]_o$   
 767 through the threshold  $h([Ca^{2+}]_o)$ . To decide whether a vesicle is released for a presynaptic spike  
 768  $t_i$ , we use a phenomenological model of  $Ca_{pre}$  (see **Figure 8a**) based on a resource-use function  
 769 (*Tsodyks and Markram, 1997*):

$$\begin{cases} \dot{Ca}_{pre} = -\frac{Ca_{pre}}{\tau_{pre}} & Ca_{pre}(0) = 0 \\ \dot{Ca}_{jump} = \frac{1 - Ca_{jump}}{\tau_{rec}} - \delta_{Ca} \cdot Ca_{jump} \cdot Ca_{pre} & Ca_{jump}(0) = 1. \end{cases} \quad (2)$$

770 Upon arrival of the presynaptic spikes,  $t \in (t_1, \dots, t_n)$ , we update  $Ca_{pre}$  according to the deterministic  
 771 jump:

$$Ca_{pre} \rightarrow Ca_{pre} + Ca_{jump}.$$

772 Finally, after  $Ca_{pre}$  has been updated, a vesicle is released with probability  $p_{rel}$  (**Figure 8b**).

773 Parameters for the vesicle release model are given in **Table 3**. The experimental constraints to  
 774 devise a release probability model are given by *Hardingham et al. (2006)* and *Tigaret et al. (2016)*.  
 775 Because  $[Ca^{2+}]_o$  modifies the release probability dynamics (*King et al., 2001*), we fixed an initial  
 776 release probability to 68 % for  $[Ca^{2+}]_o = 2.5 \text{ mM}$  as reported by *Tigaret et al. (2016)* (initial value in  
 777 **Figure 8b,d**). Additionally, *Hardingham et al. (2006)* reports a 38% reduction in the initial release  
 778 probability when changing  $[Ca^{2+}]_o$  from 2.5 mM to 1 mM. Taking these into account, the decreasing  
 779 sigmoid function in the **Figure 8e** depicts our  $[Ca^{2+}]_o$ -dependent release probability model ( $p_{rel}$ ).

780 **Figure 8e** shows that our  $p_{rel}$  function is in good agreement with a previous analytical model  
 781 suggesting that  $p_{rel}([Ca^{2+}]_o) \propto ([Ca^{2+}]_o)^2 \text{ mM}^{-2}$  (*King et al., 2001*). Our model also qualitatively  
 782 reproduces the vanishing of calcium dye fluorescence levels after 20 s of theta trains from *Tigaret*  
 783 *et al. (2016)* (in their Supplementary Materials). We interpret their fluorescence measurements as  
 784 an effect of short-term depression (see **Figure 8b**).

785 Despite our model agreeing with previous works, it is a simplified presynaptic model that does  
 786 not encompass the highly heterogeneous nature of vesicle release. Vesicle release dynamics are  
 787 known to be sensitivity to various experimental conditions such as temperature (*Fernández-Alfonso*  
 788 *and Ryan, 2004*), the age for some brain regions (*Rudolph et al., 2015*) or magnesium concentra-  
 789 tion (*Hardingham et al., 2006*). Furthermore, since our model of vesicle dynamics is simple,  $\tau_{rec}$   
 790 in **Equation 2** has two roles: to delay the  $p_{rel}$  recovery caused by  $Ca_{pre}$  inactivation (enforced by  
 791  $\delta_{Ca}$  in **Equation 2**) and to prevent vesicle release after HFS-induced depression (*King et al., 2001*;  
 792 *Rizzoli and Betz, 2005*). Later, we incorporate a higher number of experimental parameters (age,  
 793 temperature,  $[Ca^{2+}]_o$ ,  $[Mg^{2+}]_o$ ) with our NMDAr model, the main postsynaptic calcium source.

**Table 3. | Parameter values used in the presynaptic model.** Our model does not implement a larger pool called "resting pool" containing ~ 180 vesicles (CA3-CA1 hippocampus) (Alabi and Tsien, 2012). **Terminology note:** In other works, the larger pool with ~180 vesicles can be found with different nomenclatures such as "reserve pool" (Südhof, 2000) or "resting pool" (Alabi and Tsien, 2012). Furthermore, the nomenclature used in our model for the reserve pool is use in other studies as the "recycling pool", e.g. Rizzoli and Betz (2005) and Alabi and Tsien (2012).

Name	Value	Reference
<b>Vesicle release model (stochastic part)</b>		
initial number of vesicles at D	$D_0 = 25$	5 to 20 (Rizzoli and Betz, 2005; Alabi and Tsien, 2012)
initial number of vesicles at R	$R_0 = 30$	17 to 20 vesicles (Alabi and Tsien, 2012)
time constant R → D (D recycling)	$\tau_D = 5 \text{ s}$	1 s (Rizzoli and Betz, 2005)
time constant D → R (R mixing)	$\tau_R = 45 \text{ s}$	20 s (when depleted) to 5 min (hypertonic shock) (Rizzoli and Betz, 2005; Pyle et al., 2000)
time constant 1 → R (R recycling)	$\tau_R^{ref} = 40 \text{ s}$	20 to 30 s (Rizzoli and Betz, 2005)
release probability half-activation curve	$h$	see Equation 1
release probability sigmoid slope	$s = 2$	fixed for all $[Ca^{2+}]_o$
<b>Vesicle release model (deterministic part)</b>		
$C_{a_{pre}}$ attenuation recovery	$\tau_{pre} = 20 \text{ ms}$	50 - 500 ms with dye (Maravall et al., 2000) therefore < 50 to 500 ms without dye
deterministic jump attenuation recovery	$\tau_{rec} = 20 \text{ s}$	~ 20 s (Rizzoli and Betz, 2005)
deterministic jump attenuation fraction	$\delta_{ca} = 0.0004$	(Forsythe et al., 1998)

## 794 Model compartments

795 Our model is built over three compartments, a spherical dendritic spine linked by the neck to a cylin-  
 796 drical dendrite connected to a spherical soma. The membrane potential of these compartments  
 797 satisfy the equations below (parameters in Table 4). Since the dendrite is a single compartment,  
 798 the precise spine location is undefined. For more detailed morphological simulations to predict  
 799 plasticity see Ebner et al. (2019), Chindemi et al. (2020) and Jędrzejewska-Szmek et al. (2017). The  
 800 distance from the soma to the spine functionally mimics the BaP attenuation as shown in Golding  
 801 et al. (2001), and it is set to 200  $\mu\text{m}$  for all simulations, except in Figure 3-Figure Supplement 6c  
 802 and Figure 3-Figure Supplement 5e. In these panels, we modified this distance as described in the  
 803 graph y-axis to model Ebner et al. (2019) data. The different currents in the soma, dendrite and  
 804 spine are described as follows.

## 805 Membrane potential and currents

806 The membrane potential of these compartments satisfy the equations below (parameters in Table  
 807 4). The different currents are described in the following sections.

$$C_{sp} \cdot \dot{V}_{sp} = g_{neck} \cdot (V_{dend} - V_{sp}) + g_L^{sp} \cdot (E_{rev} - V_{sp}) + I_T + I_L + I_R + I_{NMDA} + I_{AMPA} + I_{SK} \quad (3)$$

$$C_{dend} \cdot \dot{V}_{dend} = g_{BaP}^{adapt} \cdot (V_{soma} - V_{dend}) + g_{neck} \cdot (V_{sp} - V_{dend}) + g_L^{dend} \cdot (E_{rev} - V_{dend}) + I_{GABA} \quad (4)$$

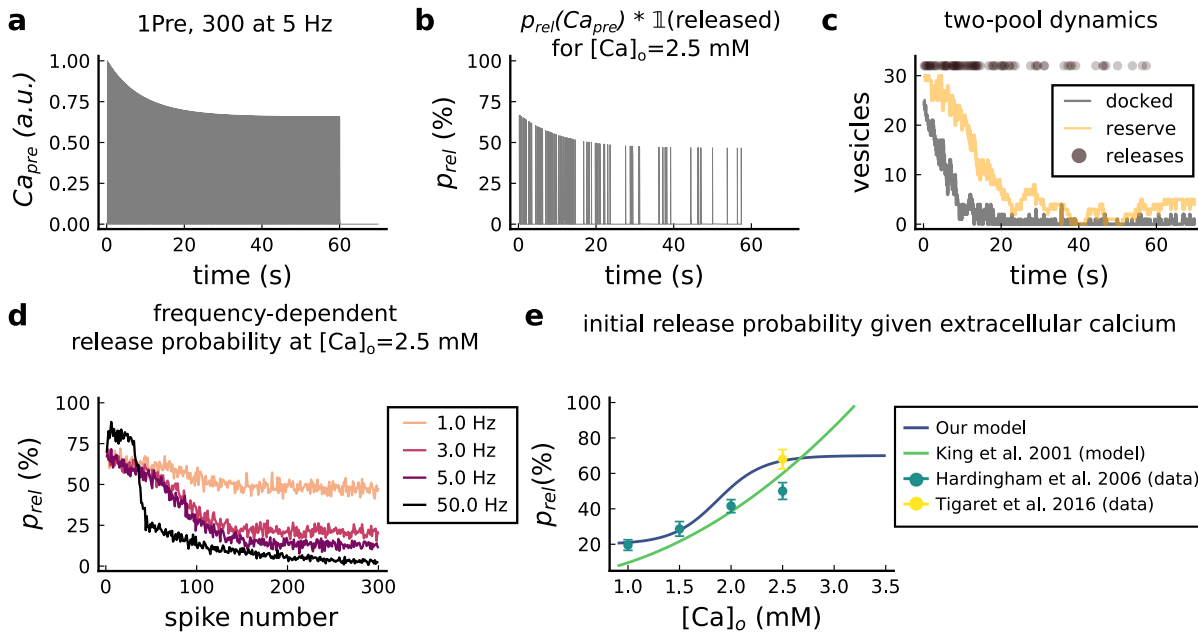
$$C_{soma} \cdot \dot{V}_{soma} = g_{BaP}^{adapt} \cdot (V_{dend} - V_{soma}) + g_L^{soma} \cdot (E_{rev} - V_{soma}) + \lambda_{age} \cdot (I_{BaP} + I_{Na}) + I_K \quad (5)$$

## 808 Action-potential backpropagation (BaP)

### 809 Postsynaptic currents

810 The postsynaptic currents are generated in the soma, backpropagated to the dendritic spine and  
 811 filtered by a passive dendrite. The soma generates BaPs using a version of the Na<sup>+</sup> and K<sup>+</sup> channel  
 812 models developed by Migliore et al. (1999). The related parameters are described in Table 5 (the  
 813 voltage unit is mV).





**Figure 8. | Presynaptic release.** **a**, Presynaptic calcium in response to the protocol 1Pre, 300 at 5 Hz displaying adaptation. **b**, Release probability for the same protocol as panel A but subjected to the docked vesicles availability. **c**, Number of vesicles in the docked and reserve pools under depletion caused by the stimulation from panel **a**. **d**, Plot of the mean (300 samples) release probability (%) for different frequencies for the protocol 1Pre 300 pulses at  $[Ca^{2+}]_o = 2.5$  mM. **e**, Release probability (%) for a single presynaptic spike as a function of  $[Ca^{2+}]_o$ . Note that *King et al. (2001)* model was multiplied by the experimentally measured release probability at  $[Ca^{2+}]_o = 2$  mM since their model has this calcium concentration as the baseline. Our model also does not cover the abolishing of release probability at  $[Ca^{2+}]_o = 0.5$  mM which can also be difficult to measure experimentally given the rarity of events (*Hardingham et al., 2006*).

#### Sodium channel

$$\begin{aligned}\alpha_m(V_{soma}) &= 0.4 \cdot \frac{V_{soma} + 30}{1 - e^{-\frac{V_{soma}+30}{7.2}}} \\ \beta_m(V_{soma}) &= 0.124 \cdot \frac{V_{soma} + 30}{e^{\frac{V_{soma}+30}{7.2}} - 1} \\ m_{inf}(V_{soma}) &= \frac{\alpha_m(V_{soma})}{\alpha_m(V_{soma}) + \beta_m(V_{soma})} \\ m_\tau(V_{soma}) &= \frac{1}{\alpha_m(V_{soma}) + \beta_m(V_{soma})} \\ \alpha_h(V_{soma}) &= 0.01 \cdot \frac{V_{soma} + 45}{e^{\frac{V_{soma}+45}{1.5}} - 1} \\ \beta_h(V_{soma}) &= 0.03 \cdot \frac{V_{soma} + 45}{1 - e^{-\frac{V_{soma}+45}{1.5}}} \\ \dot{h}(V_{soma}) &= \alpha_h(V_{soma}) \cdot (1 - h) - \beta_h(V_{soma}) \cdot h \\ \dot{m}(V_{soma}) &= \frac{m_{inf} - m}{m_\tau} \\ I_{Na} &= \gamma_{Na} \cdot m^3 \cdot h \cdot (Erev_{Na} - V_{soma}).\end{aligned}$$

#### Potassium channel

$$\begin{aligned}\alpha_n(V_{soma}) &= e^{-0.11 \cdot (V_{soma} - 13)} \\ \beta_n(V_{soma}) &= e^{-0.08 \cdot (V_{soma} - 13)} \\ n_{inf}(V_{soma}) &= \frac{1}{1 + \alpha_n(V_{soma})} \\ n_\tau(V_{soma}) &= \max\left(50 \cdot \frac{\beta_n(V_{soma})}{1 + \alpha_n(V_{soma})}; 2\right) \\ \dot{n}(V_{soma}) &= \frac{n_{inf} - n}{n_\tau} \\ I_K &= \gamma_K \cdot n \cdot (Erev_K - V_{soma})\end{aligned}$$

To trigger a BaP, an external current  $I_{BaP}$  is injected in the soma at times  $t \in \{t_1, \dots, t_n\}$  (postsynaptic input times) for a chosen duration  $\delta_{inj}$  with amplitude  $I_{amp}$  (nA), considering  $H$  as the Heaviside function this is expressed as:

$$I_{BaP} = \sum_{i=1}^n H(t_i) \cdot (1 - H(t_i + \delta_{inj})) \cdot I_{amp}.$$

**Table 4.** Parameters for the neuron electrical properties. \* The membrane leak conductance in the spine is small since the spine resistance is so high that is considered infinite ( $> 10^6 M\Omega$ ) (Koch and Zador, 1993). The current thus mostly leaks axially through the neck cytoplasm. The dendrite leak conductance is also small in order to control the distance-dependent attenuation by the axial resistance term  $g_{BaP}^{adapt}$  in Equation 4 and Equation 5.

Name	Value	Reference
<b>Passive cable</b>		
leak reversal potential	$E_{leak} = -70 mV$	69mV (Spigelman et al., 1996)
membrane leak conductance (for spine and passive dendrite)	$g_{leak} = 4 \cdot 10^{-6} nS/\mu m^2$	* see table legend (Koch and Zador, 1993)
membrane leak conductance (only soma)	$g_{soma} = 5.31 \cdot 10^{-3} nS/\mu m^2$	$3 \cdot 10^{-4}$ to $1.3 \cdot 10^{-3} nS/\mu m^2$ (Fernandez and White, 2010) 47 to $2.1 \cdot 10^3 nS$ (NeuroElectro:CA1)
membrane capacitance	$C_m = 6 \cdot 10^{-3} pF/\mu m^2$	$1 \cdot 10^{-2} pF/\mu m^2$ (Hines and Carnevale, 1997) 17 to 177 pF (NeuroElectro:CA1)
axial resistivity of cytoplasm	$R_a = 1 \cdot 10^{-2} G\Omega\mu m$	$2 \cdot 10^{-3} G\Omega\mu m$ (Golding et al., 2001)
<b>Dendrite</b>		
dendrite diameter	$D_{dend} = 2 \mu m$	same as Yi et al. (2017)
dendrite length	$L_{dend} = 1400 \mu m$	apical dendrites, 1200 to 1600 $\mu m$ (Mendoza et al., 2018)
dendrite surface area	$A_{dend} = 8.79 \cdot 10^3 \mu m^2$	$\pi \cdot D_{dend} \cdot L_{dend}$
dendrite volume	$Vol_{dend} = 4.4 \cdot 10^3 \mu m^3$	$\pi \cdot (D_{dend}/2)^2 \cdot L_{dend}$
dendritic membrane capacitance	$C_{dend} = 52.77 pF$	$C_m \cdot A_{dend}$
dendrite leak reversal potential	$g_{leakdend} = 3.51 \cdot 10^{-2} nS$	$g_{leak} \cdot A_{dend}$
dendrite axial conductance	$g_{diff} = 50 nS$	$R_a \cdot A_{dend}$
<b>Soma</b>		
soma diameter	$D_{soma} = 30 \mu m$	21 $\mu m$ (Stuart et al., 2016) page 3
soma area (sphere)	$A_{soma} = 2.82 \cdot 10^3 \mu m^2$	$(4\pi/3) \cdot (D_{soma}/2)^3$ ; $2.12 \cdot 10^3 \mu m^2$ (Zhuravleva et al., 1997)
soma membrane capacitance	$C_{soma} = 16.96 pF$	$C_m \cdot A_{soma}$
soma leaking conductance	$g_{leaksoma} = 15 nS$	$g_{soma} \cdot A_{soma}$ (Fernandez and White, 2010)
<b>Dendritic spine</b>		
spine head volume	$Vol_{sp} = 0.03 \mu m^3$	Bartol et al. (2015)
spine head surface	$A_{sp} = 4.66 \cdot 10^{-1} \mu m^2$	$4\pi \cdot (3Vol_{sp}/4\pi)^{2/3}$
spine membrane capacitance	$C_{sp} = 2.8 \cdot 10^{-3} pF$	$C_m \cdot A_{sp}$
spine head leak conductance	$g_{leaksp} = 1.86 \cdot 10^{-6} nS$	$g_{leak} \cdot A_{sp}$
<b>Dendritic spine neck</b>		
spine neck diameter	$D_{neck} = 0.1 \mu m$	0.05 to 0.6 $\mu m$ (Harris et al., 1992)
neck length	$L_{neck} = 0.2 \mu m$	$0.7 \pm 0.6 \mu m$ (Adrian et al., 2017)
neck cross sectional area	$CS_{neck} = 7.85 \cdot 10^{-3} \mu m^2$	$\pi \cdot (D_{neck}/2)^2$
neck resistance	$g_{neck} = 3.92 nS \approx 255.1 M\Omega$	$CS_{neck}/(L_{neck} \cdot R_a)$ 50 to 550 $M\Omega$ ( $275 \pm 27 M\Omega$ ) (Popovic et al., 2015)

814 The current injected in the soma is filtered in a distance-dependent manner by the dendrite be-  
 815 fore it reaches the dendritic spine. Biologically, BaP adaptation is caused by the inactivation of  
 816 sodium channels and the difference of sodium and potassium channel expression along the den-  
 817 drite (Jung et al., 1997; Golding et al., 2001). We used a phenomenological model, implementing  
 818 distant-dependent BaP amplitude attenuation by modifying the axial resistance  $g_{BaP}^{adapt}$  (see Equa-  
 819 tion 4 and Equation 5) between the dendrite and the soma as follows (Figure 9c top):

$$g_{BaP}^{adapt} = \lambda \cdot g_{diff} \cdot \phi_{dist}(d_{soma}), \quad \phi_{dist}(d_{soma}) = 0.1 + \frac{1.4}{1 + e^{0.02 \cdot (d_{soma} - 230.3\mu m)}} \quad (6)$$

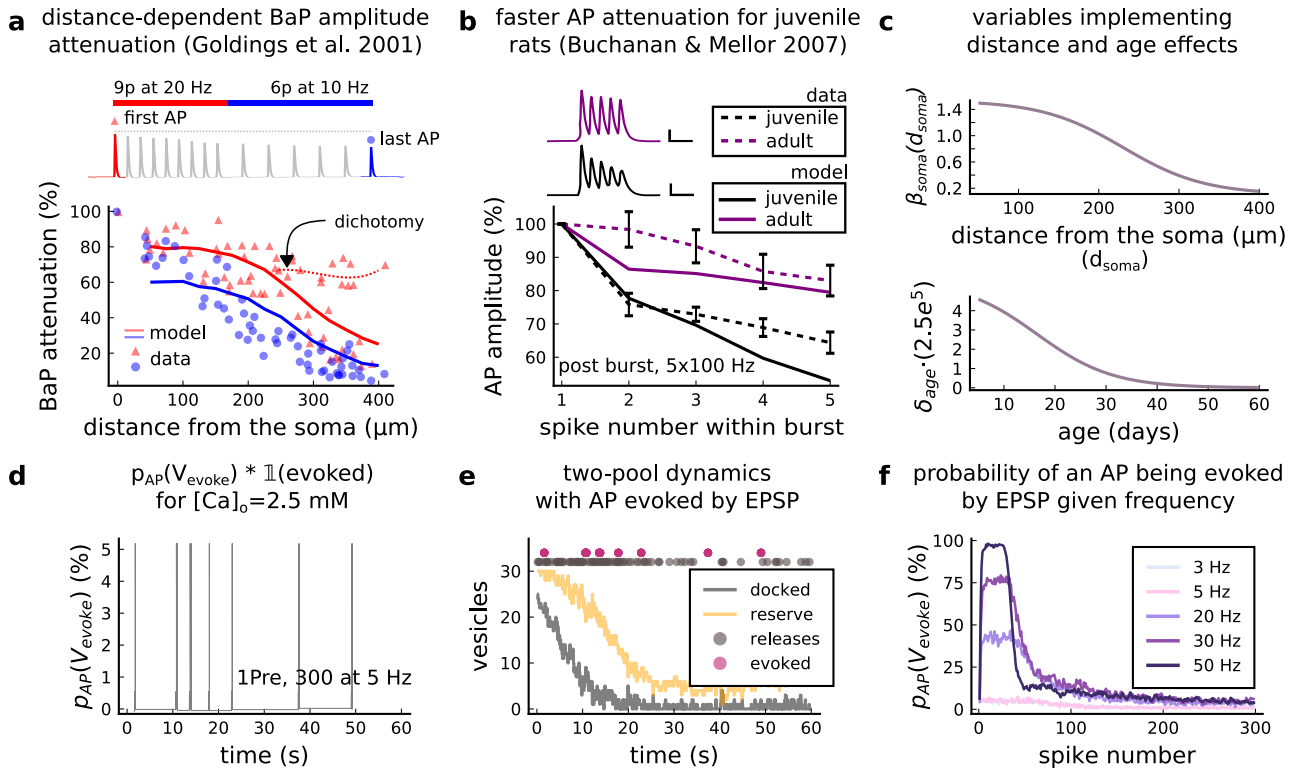
where  $d_{soma}$  is the distance of the spine to the soma and where the factor  $\lambda$  is dynamically regulated based on a resource-use equation from Tsodyks and Markram (1997) with a dampening factor  $\lambda_{aux}$  changing the size of the attenuation step  $\delta_{decay}$ :

$$\dot{\lambda} = \frac{1 - \lambda}{\tau_{rec}} - \delta_{decay} \cdot \lambda_{aux}^{-1} \cdot \lambda \cdot I_{BaP}(t)$$

$$\dot{\lambda}_{aux} = \frac{1 - \lambda_{aux}}{\tau_{rec}} - \delta_{aux} \cdot \lambda_{aux} \cdot I_{BaP}(t).$$

820 The BaP attenuation model is based on Golding et al. (2001) data for strongly attenuating neu-  
 821 rons. Therefore, the second type of attenuation (weakly attenuating) in neurons is not considered

822 (dichotomy in **Figure 9a**). **Figure 9a** compares Golding's data to our model and illustrates the effect  
 823 of BaP attenuation in the upper panels of **Figure 9a,b**.  
 824 **Table 5** shows the BaP attenuation parameters. The plasticity outcomes as function of the  
 825 dendritic spine distance from the soma are shown in **Figure 3-Figure Supplement 6c** and **Figure**  
 826 **3-Figure Supplement 5e**.



**Figure 9. | AP Evoked by EPSP.** **a**, Model and data comparison for the distance-dependent BaP amplitude attenuation measured in the dendrite and varying the distance from the soma. The stimulation in panel **a** is set to reproduce the same stimulation as *Golding et al. (2001)*. Golding described two classes of neurons: those that are strongly attenuated and those that are weakly attenuated (dichotomy mark represented by the dashed line). However, in this work we consider only strongly attenuated neurons. **b**, Attenuation of somatic action potential from *Buchanan and Mellor (2007)* and model in response to five postsynaptic spikes delivered at 100 Hz. The value showed for the model is the spine voltage with distance from the soma set to zero (scale 25 ms, 20 mV). **c**, Top panel shows the  $\lambda_{soma}$  used in *Equation 6* to modify the axial conductance between the soma and dendrite. Bottom panel shows the age-dependent changes in the step of the resource-use equation (*Equation 7*) that accelerates the BaP attenuation and decreases the sodium currents in *Equation 5*. **d**, Probability of evoking an AP multiplied by the successfully evoked AP ( $p_{AP}(V_{evoked}) \cdot \mathbb{1}(evoked)$ ) for the protocol 1Pre, 300 at 5 Hz (2.5 mM Ca). **e**, Two-pool dynamics with the same stimulation from panel D showing the vesicle release, the reserve and docked pools, and the evoked AP. **f**, Probability of evoking an AP for the protocol 1Pre 300 pulses at different frequencies (3 and 5 Hz have the same probability).

### 827 Age-dependent BaP adaptation

828 Age-dependent BaP attenuation modifies the neuronal bursting properties through the maturation  
 829 and expression of potassium and sodium channels (*Gymnopoulos et al., 2014*), therefore changing  
 830 the interaction of hyperpolarizing and depolarizing currents (see **Figure 9b**) (*Grewe et al., 2010*;  
 831 *Jung et al., 1997*). We reproduce *Buchanan and Mellor (2007)* somatic attenuation profiles (**Figure**  
 832 **9b**) with our model by including an age-dependent BaP amplitude attenuation factor. We define  
 833 the attenuation factor  $\lambda_{age}$  (**Figure 9c bottom**), as follows.

$$\lambda_{age} = \frac{1 - I_{age}}{\tau_{rec}^{age}} - \delta_{age} \cdot \lambda_{age} \cdot I_{BaP}(t), \quad \delta_{rec}^{age} = \frac{1.391 \cdot 10^{-4}}{1 + e^{0.135(age-16.482 \text{ days})}}. \quad (7)$$

834 In *Equation 5*, the age effects are introduced by multiplying the sodium  $I_{Na}$  and the ex-  
 835 ternal  $I_{BaP}$  currents by the attenuation factor  $\lambda_{age}$ .

### 836 AP evoked by EPSP

837 A presynaptic stimulation triggers a BaP if sufficient depolarization is caused by the EPSPs reach-  
 838 ing the soma (*Stuart et al., 2016*). We included an option to choose whether an EPSP can evoke  
 839 an AP using an event generator resembling the previous release probability model  $p_{rel}$  as in the  
 840 **Equation 1**. Like  $p_{rel}$ , the BaPs evoked by EPSPs are estimated before the postsynaptic simulation.  
 841 We use a variable  $V_{evoked}$  which is incremented by 1 at each presynaptic time  $t \in (t_1, \dots, t_n)$  and has  
 842 exponential decay:

$$\begin{cases} \dot{V}_{evoked} = -\frac{V_{evoked}}{\tau_v} & V_{evoked}(0) = 0 \\ V_{evoked} \longrightarrow V_{evoked} + 1. \end{cases} \quad (8)$$

843 Since the BaPs evoked by EPSPs are triggered by the afferent synapses and are limited by their  
 844 respective docked pools ( $D$ ), we use the previous  $p_{rel}$  to define the probability of an AP to occur.  
 845 We test the ratio of successful releases from 25 synapses to decide if a BaP is evoked by an EPSP,  
 846 setting a test threshold of 80%. Therefore, we express the probability of evoking an AP,  $p_{AP}(V_{evoked})$ ,  
 847 with the following test:

$$\frac{\sum^{25} \mathbf{1}(\text{rand} < p_{rel}(V_{evoked}, [Ca^{2+}]_o, D))}{25} > 80 \%$$

**Table 5.** The Na<sup>+</sup> and K<sup>+</sup> conductances intentionally do not match the reference because models with passive dendrite need higher current input to initiate action potentials (*Levine and Woody, 1978*). Therefore we set it to achieve the desired amplitude on the dendrite and the dendritic spine according to the predictions of *Golding et al. (2001)* and *Kwon et al. (2017)*.

Name	Value	Reference
<b>Soma parameters for Na<sup>+</sup> and K<sup>+</sup> channel</b>		
sodium conductance	$\gamma_{Na} = 8 \cdot 10^2 \text{ nS}$	0.32 nS/ $\mu\text{m}^2$ ( <i>Migliore et al., 1999</i> ) see legend commentary
potassium conductance	$\gamma_K = 40 \text{ nS}$	0.48 nS/ $\mu\text{m}^2$ ( <i>Migliore et al., 1999</i> ) see legend commentary
reversal potential sodium	$E_{rev_{Na}} = 50 \text{ mV}$	<i>Migliore et al. (1999)</i>
reversal potential potassium	$E_{rev_K} = -90 \text{ mV}$	<i>Migliore et al. (1999)</i>
<b>BaP attenuation parameters</b>		
attenuation step factor (age)	$\delta_{age}$	see <i>Equation 7</i> and <i>Figure 9b,c bottom</i> <i>Buchanan and Mellor (2007); Golding et al. (2001)</i>
attenuation step factor	$\delta_{decay} = 1.727 \cdot 10^{-5}$	adjusted to fit <i>Buchanan and Mellor (2007); Golding et al. (2001)</i>
auxiliary attenuation step factor	$\delta_{aux} = 2.304 \cdot 10^{-5}$	adjusted to fit <i>Buchanan and Mellor (2007); Golding et al. (2001)</i>
recovery time for the attenuation factor	$\tau_{rec} = 2 \text{ s}$	adjusted to fit <i>Buchanan and Mellor (2007); Golding et al. (2001)</i>
recovery time for the age attenuation factor	$\tau_{rec}^{age} = 0.5 \text{ s}$	adjusted to fit <i>Buchanan and Mellor (2007); Golding et al. (2001)</i>
<b>AP evoked by EPSP</b>		
decay time for $V_{evoked}$	$\tau_v = 40 \text{ ms}$	<i>Hines and Carnevale (1997)</i>
delay AP evoked by EPSP	$\delta_{delay-AP} = 15 \text{ ms}$	<i>Fricker and Miles (2000)</i>

848 The EPSP summation dynamics on the soma and dendrites depend on the complex neuron  
 849 morphology (*Etherington et al., 2010; Ebner et al., 2019*) which was not implemented by our model.  
 850 Therefore, our "AP evoked by EPSP test" intends to give a simplified way to produce BaPs similar  
 851 to an integrate-and-fire model (*Sterratt et al., 2011*).

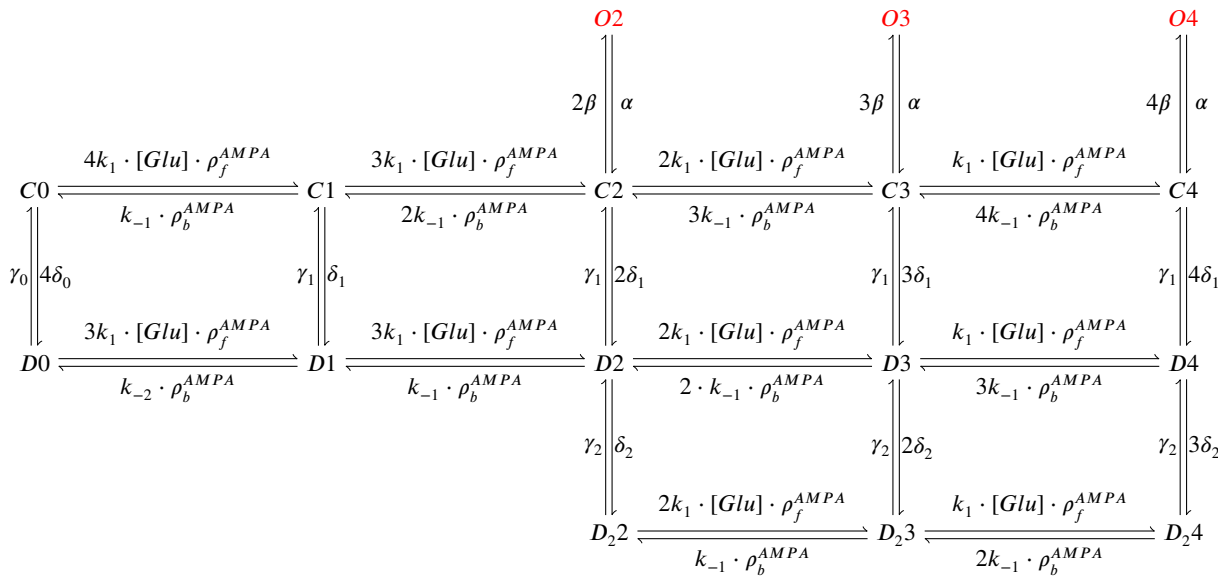
852 Previous work suggests that BaPs can be evoked with a ~5 % probability for low-frequencies in  
 853 the Dudek and Bear experiment ( $[Ca^{2+}]_o = 2.5 \text{ mM}$ ) (*Mayr and Partzsch, 2010*). Our model covers  
 854 this estimation, but the chance to elicit an AP increases with the frequency (*Etherington et al.,*  
 855 *2010*). This is captured by the  $V_{evoked}$  (in an integrate-and-fire fashion (*Stuart et al., 2016*)) as shown  
 856 in *Figure 9f*. The *Figure 9d,e* show how a 5 Hz stimulation evokes APs. The delay between the

857 EPSP and the evoked AP is set to  $\delta_{delay-AP} = 15ms$ , similar to the EPSP-spike latency reported for  
 858 CA1 pyramidal neurons (*Fricker and Miles, 2000*).

### 859 AMPAR

#### 860 Markov chain

861 The AMPAR is modeled with the Markov chain (**Figure 10**) described by *Robert and Howe (2003)* and  
 862 *Coombs et al. (2017)* and adapted to temperature changes according to *Postlethwaite et al. (2007)*.  
 863 Here, we introduce the additional parameters  $\rho_f^{AMPA}$ ,  $\rho_b^{AMPA}$  to cover AMPAR temperature-sensitive  
 864 kinetics (*Postlethwaite et al., 2007*). The corresponding parameters are given in **Table 6**.

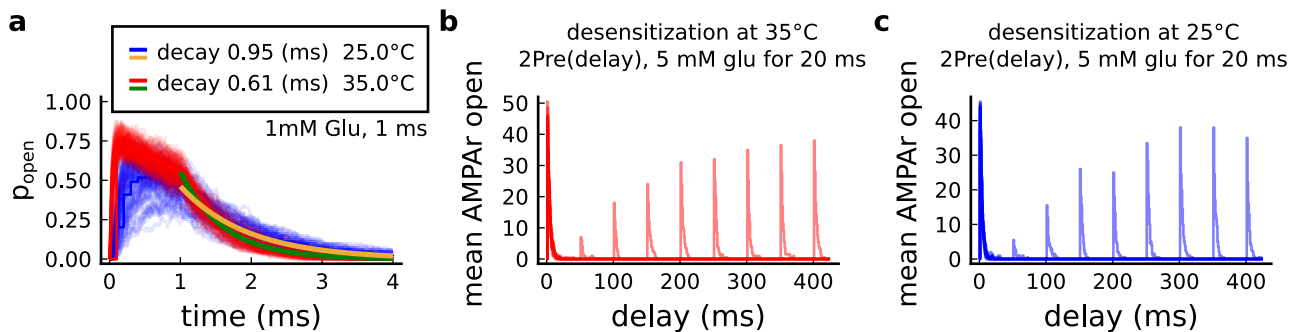


**Figure 10.** AMPAR Markov chain with three sub-conductance states and two desensitisation levels. It includes parameters  $\rho_f^{AMPA}$ ,  $\rho_b^{AMPA}$  (binding and unbinding of glutamate) which depend on temperature. Open states are O2, O3 and O4; closed states are C0, C1, C2, C3 and C4; desensitisation states are D0, D1, D2, D3 and D4; deep desensitisation states are D22, D23 and D24.

865 The AMPAR current is the sum of the subcurrents associated to the occupancy of the three  
 866 subconductance states O2, O3 and O4 of the Markov chain in **Figure 10** and described as follows:

$$I_{AMPA} = (E_{rev_{AMPA}} - V_{sp}) \cdot (\gamma_{A2} \cdot O2 + \gamma_{A3} \cdot O3 + \gamma_{A4} \cdot O4).$$

867



**Figure 11. | Effect of temperature in the AMPAR. a**, Probability of AMPAR opening ( $\frac{O2+O3+O4}{N_{AMPA}}$ ) and the decay time at different temperatures in response to 1 mM glutamate during 1 ms (standard pulse). *Postlethwaite et al. (2007)* data (our model) suggests that AMPAR decay time at 35°C is  $\sim 0.5 ms$  ( $\sim 0.6 ms$ ) and at 25°C is  $\sim 0.65 ms$  ( $\sim 0.95 ms$ ). This shows a closer match towards more physiological temperatures. **b**, Desensitization profile of AMPAR at 35°C showing how many AMPAR are open in response to a glutamate saturating pulse (5 mM Glu during 20 ms) separated by an interval (x-axis). **c**, Same as in panel **b** but for 25°C.

868 The adaptation of the Markov chain from *Robert and Howe (2003)* is made by changing the  
 869 forward  $\rho_f^{AMPA}$  and backward  $\rho_b^{AMPA}$  rates in a temperature-dependent manner matching the decay  
 870 time reported by *Postlethwaite et al. (2007)*:

$$\rho_f^{AMPA} = \frac{10.273}{1 + e^{-0.473 \cdot (T - 31.724^\circ C)}}, \quad \rho_b^{AMPA} = \frac{5.134}{1 + e^{-0.367 \cdot (T - 28.976^\circ C)}}.$$

871 The effects of temperature change on AMPAR dynamics are presented in *Figure 11*, which also  
 872 shows that the desensitisation is not altered by temperature changes (*Figure 11b,c*). The recovery  
 873 time from desensitisation is the same as at room temperature (*Robert and Howe, 2003*). Desensi-  
 874 tisation measurements are required to account for a temperature-dependent change in the rates  
 875 of the "vertical" transitions in *Figure 10*, see *Postlethwaite et al. (2007)*. This can be relevant for  
 876 presynaptic bursts.

**Table 6.** Parameter values for the AMPAR Markov chain and glutamate release affecting NMDAR, AMPAR. Properties of GABA release are the same as those for glutamate.

Name	Value	Reference
<b>Glutamate parameters</b>		
duration of glutamate in the cleft	$glu_{width} = 1 \text{ ms}$	<i>Spruston et al. (1995)</i>
concentration of glutamate in the cleft	$glu_{amp} = 1 \text{ mM}$	<i>Spruston et al. (1995)</i>
glutamate variability (gamma distribution $\Gamma$ )	$glu_{cv} = \Gamma(1/0.5^2, 0.5^2)$	<i>Liu et al. (1999)</i>
glutamate signal	$Glu$	$glu_{cv} \cdot glu_{amp}$ for AMPAR, NMDAR and copied to GABA neurotransmitter
<b>AMPA parameters</b>		
number of AMPARs	$N_{AMPA} = 120$	<i>Bartol et al. (2015)</i>
reversal potential	$E_{rev_{AMPA}} = 0 \text{ mV}$	<i>Bartol et al. (2015)</i>
subconductance O2	$\gamma_{A2} = 15.5 \text{ pS}$	16.3 pS ( <i>Coombs et al., 2017</i> )
subconductance O3	$\gamma_{A3} = 26 \text{ pS}$	28.7 pS ( <i>Coombs et al., 2017</i> )
subconductance O4	$\gamma_{A4} = 36.5 \text{ pS}$	37.8 pS ( <i>Coombs et al., 2017</i> )
glu binding	$k_1 = 1.6 \cdot 10^7 \text{ M}^{-1} \text{ s}^{-1}$	<i>Robert and Howe (2003)</i>
glu unbinding 1	$k_{-1} = 7400 \text{ s}^{-1}$	<i>Robert and Howe (2003)</i>
glu unbinding 2	$k_{-2} = 0.41 \text{ s}^{-1}$	<i>Robert and Howe (2003)</i>
closing	$\alpha = 2600 \text{ s}^{-1}$	<i>Robert and Howe (2003)</i>
opening	$\beta = 9600 \text{ s}^{-1}$	<i>Robert and Howe (2003)</i>
desensitisation 1	$\delta_1 = 1500 \text{ s}^{-1}$	<i>Robert and Howe (2003)</i>
desensitisation 2	$\delta_2 = 170 \text{ s}^{-1}$	<i>Robert and Howe (2003)</i>
desensitisation 3	$\delta_0 = 0.003 \text{ s}^{-1}$	<i>Robert and Howe (2003)</i>
re-desensitisation 1	$\gamma_1 = 9.1 \text{ s}^{-1}$	<i>Robert and Howe (2003)</i>
re-desensitisation 2	$\gamma_2 = 42 \text{ s}^{-1}$	<i>Robert and Howe (2003)</i>
re-desensitisation 3	$\gamma_0 = 0.83 \text{ s}^{-1}$	<i>Robert and Howe (2003)</i>

### 877 Postsynaptic $Ca^{2+}$ influx

878 The effects of experimental conditions on the calcium dynamics are due to receptors, ion channels  
 879 and enzymes. A leaky term models the calcium resting concentration in the *Equation 9*. The cal-  
 880 cium fluxes from NMDAR and VGCCs (T, R, L types) are given in *Equation 10*. The diffusion term  
 881 through the spine neck is expressed in *Equation 11*. Finally, the buffer, the optional dye and the  
 882 enzymatic reactions are given in *Equation 12* (parameter values given at the *Table 7*):

$$\dot{Ca} = \frac{Ca_\infty - Ca}{\tau_{Ca}} + \quad (9)$$

$$\frac{Ca_{NMDA} + I_T + I_R + I_L}{2 \cdot F \cdot A_{sp}} + \quad (10)$$

$$\frac{\max(Ca_\infty, Ca/3) - Ca}{\tau_{CaDiff}} - \quad (11)$$

$$Bu \dot{f}_{Ca} - Dye + enzymes. \quad (12)$$

883 Despite the driving force to the resting concentration,  $Ca_{\infty} = 50 \text{ nM}$ , the tonic opening of T-type  
 884 channels causes calcium to fluctuate making its mean value dependent on temperature, extracel-  
 885 lular calcium and voltage. The effects of this tonic opening in various experimental conditions are  
 886 shown in **Figure 6-Figure Supplement 2c**. To avoid modelling dendritic calcium sources, we use a  
 887 dampening term as one-third of the calcium level since calcium imaging comparing dendrite and  
 888 spine fluorescence have shown this trend (*Segal and Korkotian, 2014*). **Equation 11** implements  
 889 the diffusion of calcium from the spine to the dendrite through the neck. The time constant for the  
 890 diffusion coefficient  $\tau_{CaDiff}$ , is estimated as described in *Holcman et al. (2005)*. The calcium buffer  
 891 and the optional dye are described as a two-state reaction system (*Sabatini et al., 2002*):

$$\begin{aligned} \text{Buf} f_{Ca} &= k_{on}^{Buf} \cdot (\text{Buf} f_{con} - \text{Buf} f_{Ca}) \cdot Ca - k_{off}^{Buf} \cdot \text{Buf} f_{Ca} \\ \text{Dye} &= k_{on}^{Fluo5} \cdot (\text{Fluo5} f_{con} - \text{Dye}) \cdot Ca - k_{off}^{Fluo5} \cdot \text{Dye}. \end{aligned} \quad (13)$$

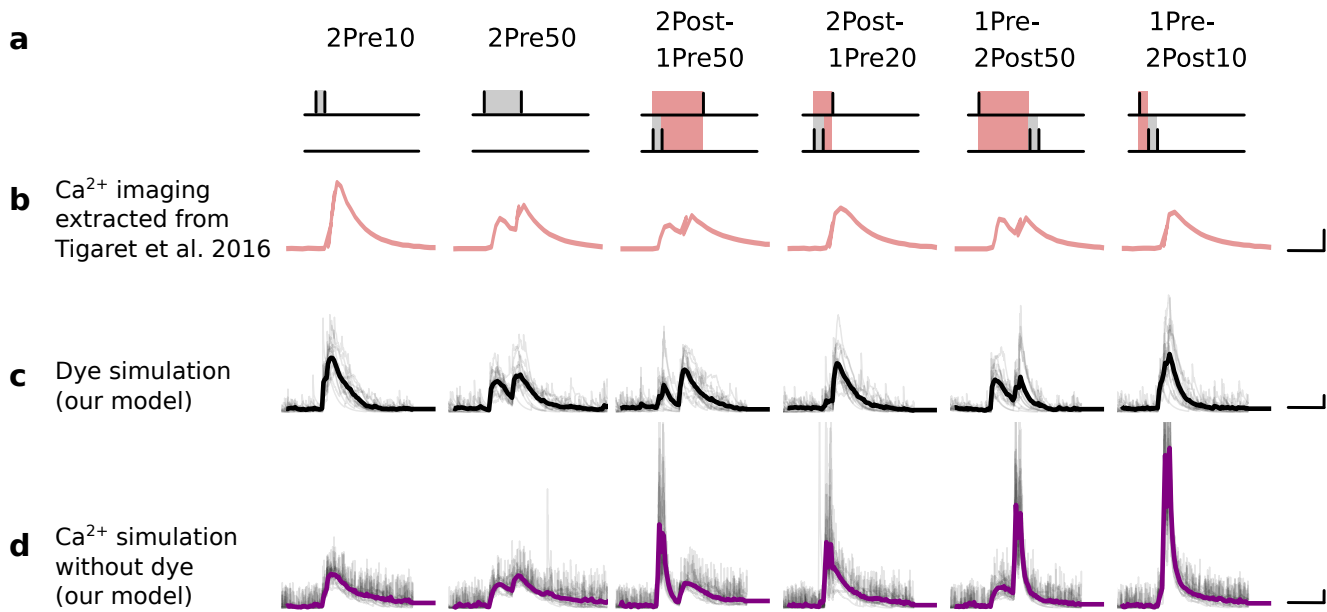
**Table 7.** Postsynaptic calcium dynamics parameters.

Name	Value	Reference
<b>Buffer and dye</b>		
association buffer constant	$k_{on}^{Buf} = 0.247 \mu\text{M}^{-1}\text{ms}^{-1}$	<i>Bartol et al. (2015)</i>
dissociation buffer constant	$k_{off}^{Buf} = 0.524 \text{ms}^{-1}$	<i>Bartol et al. (2015)</i>
buffer concentration	$\text{Buf} f_{con} = 62 \mu\text{M}$	$76.7 \mu\text{M}$ ( <i>Bartol et al., 2015</i> )
<b>Calcium dynamics</b>		
Calcium baseline concentration	$Ca_{\infty} = 50 \text{ nM}$	$37 \pm 5$ to $54 \pm 5 \text{ nM}$ ( <i>Maravall et al., 2000</i> )
Calcium decay time	$\tau_{Ca} = 10 \text{ ms}$	50 to 500 ms for with dye ( <i>Maravall et al., 2000</i> ) therefore < 50 to 500 ms undyed (unbuffered)
Calcium diffusion	$D_{Ca} = 0.3338 \mu\text{m}^2\text{ms}^{-1}$	0.22 to $0.4 \mu\text{m}^2\text{ms}^{-1}$ ( <i>Bartol et al., 2015; Holcman et al., 2005</i> )
Calcium diffusion time constant	$\tau_{CaDiff} = \frac{V_{ol_{sp}}}{2D_{Ca}^2 \cdot D_{neck}} + \frac{l_{neck}^2}{2D_{Ca}} = 0.5 \text{ ms}$	8 ms for a $V_{sp} = 0.7 \mu\text{m}^3$ ( <i>Holcman et al., 2005</i> )
<b>GHK equation</b>		
temperature	$T = 35^{\circ}\text{C}$	converted to Kelvin in the <b>Equation 14</b> given the protocol
faraday constant	$F = 96.485 \text{ C mol}^{-1}$	<i>Hille (1978)</i>
gas constant	$R = 8.314 \text{ J K}^{-1} \text{ mol}^{-1}$	<i>Hille (1978)</i>
Calcium permeability	$P_{Ca} = 0.045 \mu\text{m ms}^{-1}$	adjusted to produce $3 \mu\text{M}$ Calcium in response to a Glu release supplementary files from <i>Chang et al. (2017)</i>
Calcium ion valence	$z_{Ca} = 2$	<i>Hille (1978)</i>

892 Unlike other calcium-based plasticity models (*Graupner and Brunel, 2012*) using the dye fluo-  
 893 rescence decay as an approximation to calcium decay, our model is based on receptor and ion channel  
 894 kinetics. Additionally, our model can simulate the dye kinetics as a buffer using **Equation 13** when  
 895 appropriate. See **Figure 12** that highlights differences between calcium and dye dynamics which  
 896 is affected by the laser-induced temperature increase (*Wells et al., 2007; Deng et al., 2014*). We  
 897 estimated the calcium reversal potential for the calcium fluxes using the Goldman-Hodgkin-Katz  
 898 (GHK) flux equation described in *Hille (1978)*. The calcium ion permeability,  $P_{Ca}$ , was used as a free  
 899 parameter adjusting a single EPSP to produce a calcium amplitude of  $\sim 3 \mu\text{M}$  (*Chang et al., 2017*).

$$\begin{aligned} \phi(V_{sp}, T) &= z_{Ca} \cdot V_{sp} \cdot F / R \cdot (T + 273.15\text{K}) \\ \Phi_{Ca}(V_{sp}, [\text{Ca}^{2+}]_i) &= -P_{Ca} \cdot z_{Ca} \cdot F \cdot \phi(V_{sp}, T) \cdot \frac{[\text{Ca}^{2+}]_i - [\text{Ca}^{2+}]_o \cdot e^{-\phi}}{1 - e^{-\phi}} \end{aligned} \quad (14)$$

900  $\Phi_{Ca}(V_{sp}, [\text{Ca}^{2+}]_i)$  (**Equation 14**) is used to determine the calcium influx through NMDAr and VGCC  
 901 in the **Equation 15**, **Equation 16**, **Equation 17** and **Equation 18** using the spine membrane voltage  
 902 and calcium internal concentration ( $[\text{Ca}^{2+}]_i$ ). Note that for simplicity the calcium external concen-  
 903 tration ( $[\text{Ca}^{2+}]_o$ ) was kept fixed during the simulation and only altered by experimental conditions  
 904 given by the aCSF composition.

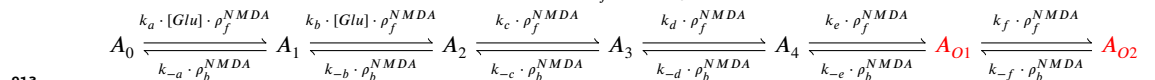


**Figure 12. Differences between dye measurements and simulated calcium.** **a**, Pre and postsynaptic stimuli as used in *Tigaret et al. (2016)*. **b**, Calcium imaging curves (fluorescence  $\Delta F/A$ ) elicited using the respective stimulation protocols above with Fluo5 200  $\mu M$  (extracted from *Tigaret et al. (2016)*). Scale 100 ms, 0.05  $\Delta F/A$ . **c**, Dye simulation using the model. The dye is implemented by increasing temperature to mimic laser effect on channel kinetics and decreases the interaction between NMDAR and voltage elicited by BaP. Temperature effects over NMDAR are shown in *Korinek et al. (2010)*. Also, the effects of temperature on calcium-sensitive probes shown in *Oliveira et al. (2012)* (baseline only, likely related to T-type channels). Other examples of laser heating of neuronal tissue are given in *Deng et al. (2014)*. Such a dye curve fitting was obtained by increasing temperature by  $10^\circ C$  to mimic laser-induced heating (*Wells et al., 2007; Deng et al., 2014*). We achieved a better fit by decreasing the amplitude of the BaP that reaches the dendrite. Additionally, for fitting purposes, we assumed that a temperature increase lead to a decrease in BaP amplitude. Scale 0.6  $\mu M$  dye, 100 ms. **d**, Calcium simulation without dye. Scale 0.85  $\mu M$   $Ca^{2+}$ , 100 ms.

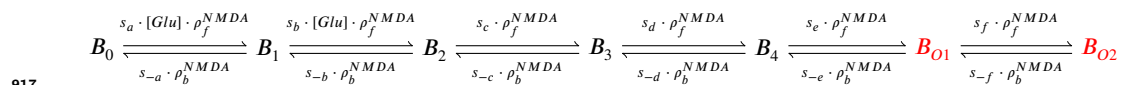
## 905 NMDAr - GluN2A and GluN2B

### 906 Markov chain

907 In hippocampus, NMDARs are principally heteromers composed of the obligatory subunit GluN1  
 908 and either the GluN2A or GluN2B subunits. These N2 subunits guide the activation kinetics of  
 909 these receptors with the GluN1/GluN2B heteromers displaying slow kinetics ( $\sim 250ms$ ) and the  
 910 GluN1/GluN2A heteromers displaying faster kinetics ( $\sim 50ms$ ). We modeled both NMDA subtypes.  
 911 The NMDAR containing GluN2A is modeled with the following Markov chain (*Popescu et al., 2004*)  
 912 where we introduce the additional parameters  $\rho_f^{NMDA}, \rho_b^{NMDA}$ :



914 The NMDAR containing GluN2B is modeled with a Markov chain based on the above GluN2A  
 915 scheme. We decreased the rates by  $\sim 75\%$  in order to match the GluN2B decay at  $25^\circ C$  as published  
 916 in *Iacobucci and Popescu (2018)*.



918 The different rates are given in *Table 8*.

### 919 NMDAr and age switch

The age-dependent expression ratio of the subtypes GluN2A and GluN2B ( $r_{age}$ ) was obtained from experimental data of mouse hippocampus (*Sinclair et al., 2016*). We added noise to this ratio



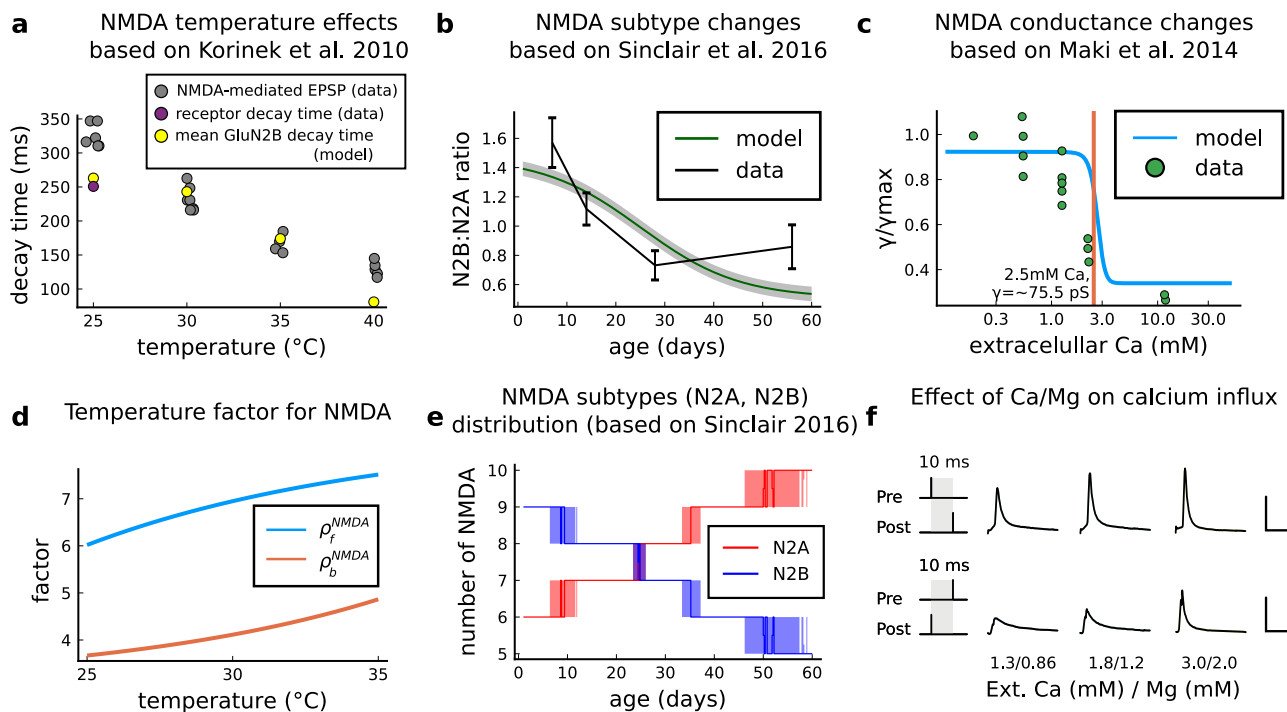
causing  $\sim 1$  NMDAr subunit to flip towards GluN2A or GluN2B (see **Figure 13e**). The population of 15 NMDAr is divided in the two subtypes according to the ratio plotted in **Figure 13b** as a function of age. The ratio to define the number NMDAr subtypes as function of age reads:

$$r_{age} = 0.507 + \frac{0.964}{1 + e^{0.099 \cdot (age - 25.102 \text{ days})}} + \mathcal{N}(0, 0.05)$$

$$N_{GluN2B} = \text{round} \left( \frac{N_{NMDA} \cdot r_{age}}{r_{age} + 1} \right)$$

$$N_{GluN2A} = \text{round} \left( \frac{N_{NMDA}}{r_{age} + 1} \right).$$

920 The round term in the two previous equations ensures that we have an integer value for the  
921 NMDAr subtypes, making the stair shaped curve seen in **Figure 13e**.



**Figure 13. | NMDAr changes caused by age, temperature and extracellular and magnesium concentrations in the aCSF. a** Decay time of the NMDAr-mediated EPSP recorded from neocortical layer II/III pyramidal neurons (grey) (*Korinek et al., 2010*) compared to the decay time from the GluN2B channel estimated by our model (yellow) and data from Iacobucci's single receptor recording (purple) (*Iacobucci and Popescu, 2018*). **b**, Comparison of our implementation of GluN2B:GluN2A ratio and the GluN2B:GluN2A ratio from the mouse CA1 excitatory neurons. **c**, Comparison of our implementation of NMDAr conductance change in response to the extracellular against data (*Maki and Popescu, 2014*). **d**, Forward and backwards temperature factors implemented to approximate NMDAr subtypes decay times at room temperature (*Iacobucci and Popescu, 2018*) and temperature changes observed in *Korinek et al. (2010)*. **e**, NMDAr subtype fluctuations in our model with age. We added noise to have a smoother transition between different ages. **f**, Calcium concentration changes for causal and anticausal protocols in response to different aCSF calcium and magnesium compositions with fixed Ca/Mg ratio (1.5). Scale 50 ms and 5  $\mu M$ .

## 922 NMDAr and temperature

923 We adjusted the GluN2A and GluN2B forward and backward rates to follow the temperature effects  
924 on NMDAr-mediated EPSP (*Korinek et al., 2010*), see **Figure 13a,d**. Because GluN2B dominates the  
925 NMDAr-mediated EPSP, we fit its decay time of the NMDAr-mediated EPSP as function of temper-  
926 ature as reported by *Korinek et al. (2010)* using logistic functions  $\rho_f^{NMDA}$  and  $\rho_b^{NMDA}$ . The decay  
927 time comparison is shown in **Figure 13a**. Then, we applied the same temperature factor  $\rho_f^{NMDA}$   
928 and  $\rho_b^{NMDA}$  for GluN2A. The decay times of GluN2A and GluN2B are similar to those reported by  
929 *Iacobucci and Popescu (2018)*. The forward and backward factors are described as follows:

$$\rho_f^{NMDA} = -1230.680 + \frac{1239.067}{1 + e^{-0.099 \cdot (T+37.631^\circ C)}}, \quad \rho_b^{NMDA} = 3.036 + \frac{1621.616}{1 + e^{-0.106 \cdot (T-98.999^\circ C)}}.$$

### 930 NMDAr current and Ca<sup>2+</sup>-dependent conductance

NMDAr conductance is modulated by external calcium and is modelled according to the next equations using NMDAr subconductances  $A_{O1}$  and  $A_{O2}$  (GluN2A), and  $B_{O1}$  and  $B_{O2}$  (GluN2B).

$$\gamma_{NMDA} = 33.949 + \frac{58.388}{1 + e^{4 \cdot ([Ca^{2+}]_o - 2.701 \text{ mM})}} pS$$

$$B(V_{sp}, [Mg]_o) = \frac{1}{1 + \frac{[Mg]_o}{3.57} \cdot e^{-0.062 \cdot V_{sp}}}$$

$$NMDA = (B_{O1} + B_{O2} + A_{O1} + A_{O2}) \cdot B(V_{sp}, [Mg]_o) \cdot \gamma_{NMDA}$$

$$I_{NMDA} = (Erev_{NMDA} - V_{sp}) \cdot NMDA$$

**Table 8.** NMDAr parameters.

Name	Value	Reference
<b>NMDAr (GluN2A)</b>		
glutamate binding	$k_a = 34 \mu M^{-1} s^{-1}$	Popescu et al. (2004)
glutamate binding	$k_b = 17 \mu M^{-1} s^{-1}$	Popescu et al. (2004)
forward rate	$k_c = 127 s^{-1}$	Popescu et al. (2004)
forward rate	$k_f = 580 s^{-1}$	Popescu et al. (2004)
opening rate	$k_e = 2508 s^{-1}$	Popescu et al. (2004)
opening rate	$k_j = 3449 s^{-1}$	Popescu et al. (2004)
closing rate	$k_{-f} = 662 s^{-1}$	Popescu et al. (2004)
closing rate	$k_{-e} = 2167 s^{-1}$	Popescu et al. (2004)
backward rate	$k_{-d} = 2610 s^{-1}$	Popescu et al. (2004)
backward rate	$k_{-c} = 161 s^{-1}$	Popescu et al. (2004)
glutamate unbinding	$k_{-b} = 120 s^{-1}$	Popescu et al. (2004)
glutamate unbinding	$k_{-a} = 60 s^{-1}$	Popescu et al. (2004)
<b>NMDAr (GluN2B)</b>		
glutamate binding	$s_b = 0.25k_b$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
glutamate binding	$s_c = 0.25k_c$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
forward rate	$s_e = 0.25k_e$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
forward rate	$s_d = 0.25k_d$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
opening rate	$s_e = 0.25k_e$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
opening rate	$s_f = 0.25k_f$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
closing rate	$s_{-f} = 0.23k_{-f}$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
closing rate	$s_{-e} = 0.23k_{-e}$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
backward rate	$s_{-d} = 0.23k_{-d}$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
backward rate	$s_{-c} = 0.23k_{-c}$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
glutamate unbinding	$s_{-b} = 0.23k_{-b}$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
glutamate unbinding	$s_{-a} = 0.23k_{-a}$	adapted from GluN2A (Popescu et al., 2004; Iacobucci and Popescu, 2018)
<b>other parameters</b>		
total number of NMDAr	$N_{NMDA} = 15$	5-30 (Spruston et al., 1995; Bartol et al., 2015; Nimchinsky et al., 2004)
distribution of GluN2A and GluN2B	defined by $r_{age}$	Sinclair et al. (2016)
NMDAr conductance depending on calcium	$\gamma_{NMDA}$	Maki and Popescu (2014)
NMDAr reversal potential	$Erev_{NMDA} = 0 \text{ mV}$	Destexhe et al. (1994)
fraction of calcium carried by NMDAr	$f_{Ca} = 0.1$	Griffith et al. (2016)

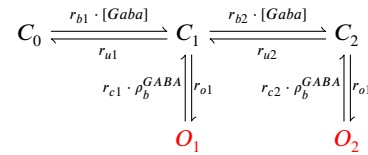
931 We modified the conductance  $\gamma_{NMDA}$  as a function of extracellular calcium from that reported  
 932 by **Maki and Popescu (2014)**. The reported NMDAr conductance at  $[Ca^{2+}]_o = 1.8 \text{ mM}$  is  $53 \pm 5 pS$ .  
 933 Here, we used the higher conductance  $91.3 pS$  for NMDAr (for both subtypes) at  $[Ca^{2+}]_o = 1.8 \text{ mM}$   
 934 to compensate for the small number of NMDAr reported by **Nimchinsky et al. (2004)**. Hence, we  
 935 adjusted **Maki and Popescu (2014)** data to take into account this constraint: this caused a right-shift  
 936 in the NMDA-conductance curve (**Figure 13c**). The calcium influx  $Ca_{NMDA}$  is modulated by the GHK  
 937 factor, **Equation 14**, as a function of the internal and external calcium concentrations and the spine  
 938 voltage:

$$Ca_{NMDA} = f_{Ca} \cdot \Phi_{Ca} \cdot NMDA. \quad (15)$$

939 The combined effect of extracellular Magnesium (**Jahr and Stevens, 1990**) and Calcium concen-  
 940 tration are displayed in **Figure 13f**.

### 941 GABA(A) receptor

942 Since the precise delay of GABA release relative to glutamate is not known, we assumed GABA  
943 and glutamate release are synchronized for simplicity (see **Table 6**). We used the GABA(A) receptor  
944 Markov chain (**Figure 14**) presented in **Busch and Sakmann (1990)**; **Destexhe et al. (1998)** and we es-  
945 timated temperature adaptations using the measurements reported by **Otis and Mody (1992)**.

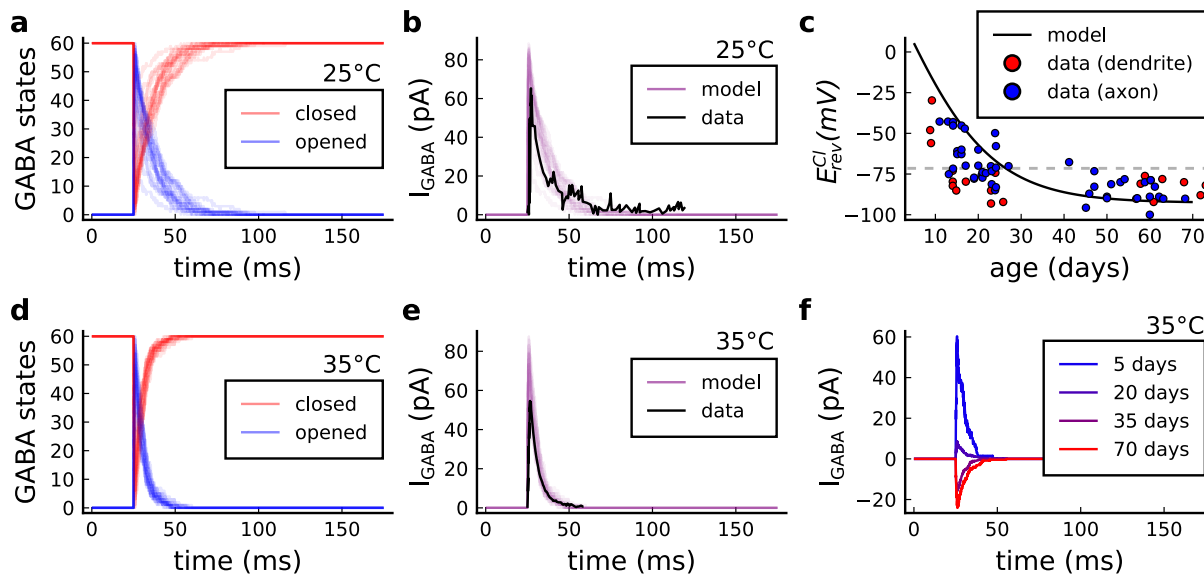


**Figure 14. | GABA<sub>A</sub> Markov chain model.** Closed states ( $C_0$ ,  $C_1$  and  $C_2$ ) open in response to GABA<sub>A</sub> and can go either close again or open ( $O_1$  and  $O_2$ )

### 946 GABA(A)r and temperature

947 Because the amplitude of GABA(A) current is altered by the GABA<sub>A</sub>r shift during development (**Rinetti-**  
948 **Vargas et al., 2017**), we applied temperature changes only to the closing rates using a logistic func-  
949 tion for  $\rho_b^{GABA}$ , estimated by fitting to the measurements from **Otis and Mody (1992)** (data compar-  
950 ison in the **Figure 15b,e**).

$$\rho_b^{GABA} = 1.470 - \frac{-1.279}{1 + e^{0.191 \cdot (T - 32.167)}}$$



**Figure 15. | GABA(A)<sub>r</sub> current, kinetics and chloride reversal potential.** **a**, States of GABA(A)<sub>r</sub> Markov chain at 25°C in response to a presynaptic stimulation. Opened =  $O_1 + O_2$ , closed =  $C_0 + C_1 + C_2$ . **b**, Model and data comparison (**Otis and Mody, 1992**) for GABA(A)<sub>r</sub> current at 25°C. Even though data were recorded from P70 at 25°C and P15 at 35°C, we normalize the amplitude to invert the polarity and compare the decay time. This is done since the noise around P15 can either make GABA<sub>A</sub>r excitatory or inhibitory as shown by  $E_{Cl}$  data in panel **c**. **c**, Chloride reversal potential ( $E_{rev}^{Cl}$ ) fitted to **Rinetti-Vargas et al. (2017)** data. Note that we used both profiles from axon and dendrite age-dependent  $E_{rev}^{Cl}$  changes since exclusive dendrite data is scarce. **d**, States of simulated GABA(A)<sub>r</sub> Markov chain at 35°C in response to a presynaptic stimulation. **e**, Model and data comparison (**Otis and Mody, 1992**) for GABA(A)<sub>r</sub> current at 25°C (same normalization as in panel **b**). **f**, Change in the polarization of GABA(A)<sub>r</sub> currents given the age driven by the  $E_{rev}^{Cl}$ .

### 951 GABA(A)r current and age switch

952 The GABA(A)<sub>r</sub>-driven current changes during development (**Meredith et al., 2003**) passing from de-  
953 polarizing (excitatory) to hyperpolarizing (inhibitory) (**Chamma et al., 2012**). The reversal potential  
954 of chloride ions permeating GABA(A)<sub>r</sub> shifts from above the membrane resting potential (inward

955 driving force - excitatory) to below the membrane resting potential (outward driving force - in-  
 956 hibitory) (*Rinetti-Vargas et al., 2017*). Such effect mediated by chloride ions is associated with the  
 957 KCC2 pump (K Cl co-transporter) which becomes efficient in extruding chloride ions during matu-  
 958 ration (*Rinetti-Vargas et al., 2017*). To cover the GABA(A)r age-dependent shift, we fit the chloride  
 959 reversal potential ( $E_{rev}^{Cl}$ ) using the data published by *Rinetti-Vargas et al. (2017)* (*Figure 15c*):

$$E_{rev}^{Cl} = -92.649 + \frac{243.515}{1 + e^{0.091 \cdot (\text{age} - 0.691 \text{ days})}}$$

$$I_{GABA} = (O_1 + O_2) \cdot (E_{rev}^{Cl} - V_{dend}) \cdot \gamma_{GABA}$$

960 **Table 9** presents the parameters to model the GABA<sub>A</sub> receptor.

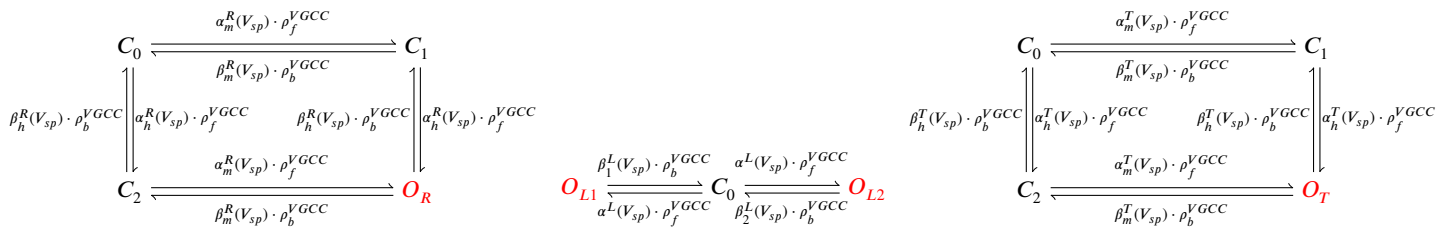
**Table 9.** GABA<sub>A</sub> receptor parameters.

Name	Value	Reference
<b>GABA(A) receptor</b>		
number of GABA	$N_{GABA} = 34$	30 ( <i>Edwards et al., 1990</i> )
chloride reversal potential	see age-dependent equation	<i>Rinetti-Vargas et al. (2017)</i>
GABA <sub>A</sub> receptor conductance	$\gamma_{GABA} = 36 \text{ pS}$	27 pS ( <i>Macdonald et al., 1989</i> )
binding	$r_{b1} = 20 \cdot 10^6 \text{ M}^{-1} \text{ s}^{-1}$	<i>Busch and Sakmann (1990)</i>
unbinding	$r_{u1} = 4.6 \cdot 10^3 \text{ s}^{-1}$	<i>Busch and Sakmann (1990)</i>
binding	$r_{b2} = 10 \cdot 10^6 \text{ M}^{-1} \text{ s}^{-1}$	<i>Busch and Sakmann (1990)</i>
unbinding	$r_{u2} = 9.2 \cdot 10^3 \text{ s}^{-1}$	<i>Busch and Sakmann (1990)</i>
opening rate	$r_{ro1} = 3.3 \cdot 10^3 \text{ s}^{-1}$	<i>Busch and Sakmann (1990)</i>
opening rate	$r_{ro2} = 10.6 \cdot 10^3 \text{ s}^{-1}$	<i>Busch and Sakmann (1990)</i>
closing rate	$r_{c2} = 400 \text{ s}^{-1}$	based on ( <i>Busch and Sakmann, 1990; Otis and Mody, 1992</i> )
closing rate	$r_{c2} = 9.8 \cdot 10^3 \text{ s}^{-1}$	based on ( <i>Busch and Sakmann, 1990; Otis and Mody, 1992</i> )

## 961 VGCC - T, R and L type

### 962 Markov chain

963 A stochastic VGCC model was devised using the channel gating measurements from rat CA1 (2-  
 964 8 weeks) pyramidal neurons by *Magee and Johnston (1995)* at room temperature. Our model  
 965 has three different VGCC subtypes described by the Markov chains in *Figure 16*: the T-type (low-  
 966 voltage), the R-type (medium-to-high-voltage) and the L-type (high-voltage).



**Figure 16.** From left to right, R-, L-, and T-type VGCCs Markov chain adapted from Magee and Johnston (*Magee and Johnston, 1995*). The R- (left scheme) and T- type (right scheme) have a single open state (red colour), respectively,  $O_R$  and  $O_T$ . The L-type VGCC (middle) has two open states,  $O_{L1}$  and  $O_{L2}$ .

967 The VGCC Markov chain derived from Magee and Johnston 1995 (*Magee and Johnston, 1995*) is  
 968 composed of two gates (h,m) for T- (*Figure 17a,d*) and R-types (*Figure 17b,e*) and a single gate for  
 969 L-type (*Figure 17c*), as described in the equations below.

### R-type h-gate rates

$$\begin{aligned}\tau_h^{R*} &= 100 \\ h_{inf}^{R*}(V_{sp}) &= \frac{1}{1 + e^{\frac{V_{sp}+39}{9.2}}} \\ \alpha_h^R(V_{sp}) &= \frac{h_{inf}^R}{\tau_h^R} \\ \beta_h^R(V_{sp}) &= \frac{1 - h_{inf}^R}{\tau_h^R}\end{aligned}$$

### L-type rates

$$\begin{aligned}\alpha^L(V_{sp}) &= \frac{0.83}{1 + e^{\frac{13.7-V_{sp}}{6.1}}} \\ \beta_1^L(V_{sp}) &= \frac{0.53}{1 + e^{\frac{V_{sp}-11.5}{6.4}}} \\ \beta_2^L(V_{sp}) &= \frac{1.86}{1 + e^{\frac{V_{sp}-18.8}{6.17}}}\end{aligned}$$

### T-type h-gate rates

$$\begin{aligned}\tau_h^{T*} &= 50 \\ h_{inf}^{T*}(V_{sp}) &= \frac{1}{1 + e^{\frac{V_{sp}+70}{6.5}}} \\ \alpha_h^T(V_{sp}) &= \frac{h_{inf}^T}{\tau_h^T} \\ \beta_h^T(V_{sp}) &= \frac{1 - h_{inf}^T}{\tau_h^T}\end{aligned}$$

### R-type m-gate rates

$$\begin{aligned}\beta_m^{R*} &= 40 \\ m_{inf}^{R*} &= \frac{1}{1 + e^{\frac{3-10}{8}}} \\ \alpha_m^{R*} r &= \beta_m^{R*} \cdot \frac{m_{inf}^{R*}}{1 - m_{inf}^{R*}} \\ \tau_m^R &= \frac{1}{\alpha_m^{R*} + \beta_m^{R*}} \\ m_{inf}^R &= \frac{1}{1 + e^{\frac{3-V_{sp}}{8}}} \\ \alpha_m^R(V_{sp}) &= \frac{m_{inf}^R}{\tau_m^R} \\ \beta_m^R(V_{sp}) &= \frac{1 - m_{inf}^R}{\tau_m^R}\end{aligned}$$

### T-type m-gate rates

$$\begin{aligned}\beta_m^{T*} &= 1 \\ m_{inf}^{T*} &= \frac{1}{1 + e^{\frac{-32+20}{7}}} \\ \alpha_m^{T*} r &= \beta_m^{T*} \cdot \frac{m_{inf}^{T*}}{1 - m_{inf}^{T*}} \\ \tau_m^T &= \frac{1}{\alpha_m^{T*} + \beta_m^{T*}} \\ m_{inf}^T &= \frac{1}{1 + e^{\frac{-32-V_{sp}}{7}}} \\ \alpha_m^T(V_{sp}) &= \frac{m_{inf}^T}{\tau_m^T} \\ \beta_m^T(V_{sp}) &= \frac{1 - m_{inf}^T}{\tau_m^T}\end{aligned}$$

## 970 VGCC and temperature

971 We used the same temperature factor for every VGCC subtype, respectively  $\rho_f^{VGCC}$  and  $\rho_b^{VGCC}$  (see  
972 **Figure 17f**), as follows:

$$\rho_f^{VGCC} = 2.503 - \frac{0.304}{1 + e^{1.048 \cdot (T-30.668)}}, \quad \rho_b^{VGCC} = 0.729 + \frac{3.225}{1 + e^{-0.330 \cdot (T-36.279)}}.$$

**Table 10.** VGCC parameters

Name	Value	Reference
<b>VGCC</b>		
VGCC T-type conductance	$\gamma_{CaT} = 12 \text{ pS}$	same as ( <i>Magee and Johnston, 1995</i> )
VGCC R-type conductance	$\gamma_{CaR} = 17 \text{ pS}$	same as ( <i>Magee and Johnston, 1995</i> )
VGCC L-type conductance	$\gamma_{CaL} = 27 \text{ pS}$	same as ( <i>Magee and Johnston, 1995</i> )
number of VGCCs	3 for each subtype	1 to 20 ( <i>Higley and Sabatini, 2012</i> )

973 The VGCC subtypes are differently sensitive to temperature, with temperature factors for decay  
974 times ranging from 2 (*Iftinca et al., 2006*) to 50-fold (*Peloquin et al., 2008*). It further complicates

975 if T-type isoforms are considered. Indeed, they can have temperature factors that accelerate or  
 976 slow down the kinetics. For instance, when passing from room to physiological temperatures, the  
 977 isoform  $Ca_v3.3$  has a closing time  $\sim 50\%$  faster (*Iftinca et al., 2006*) and the isoform  $Ca_v3.1$  becomes  
 978  $\sim 15\%$  slower. To simplify, the same temperature factor was adopted to all VGCC subtypes.

### 979 VGCC currents

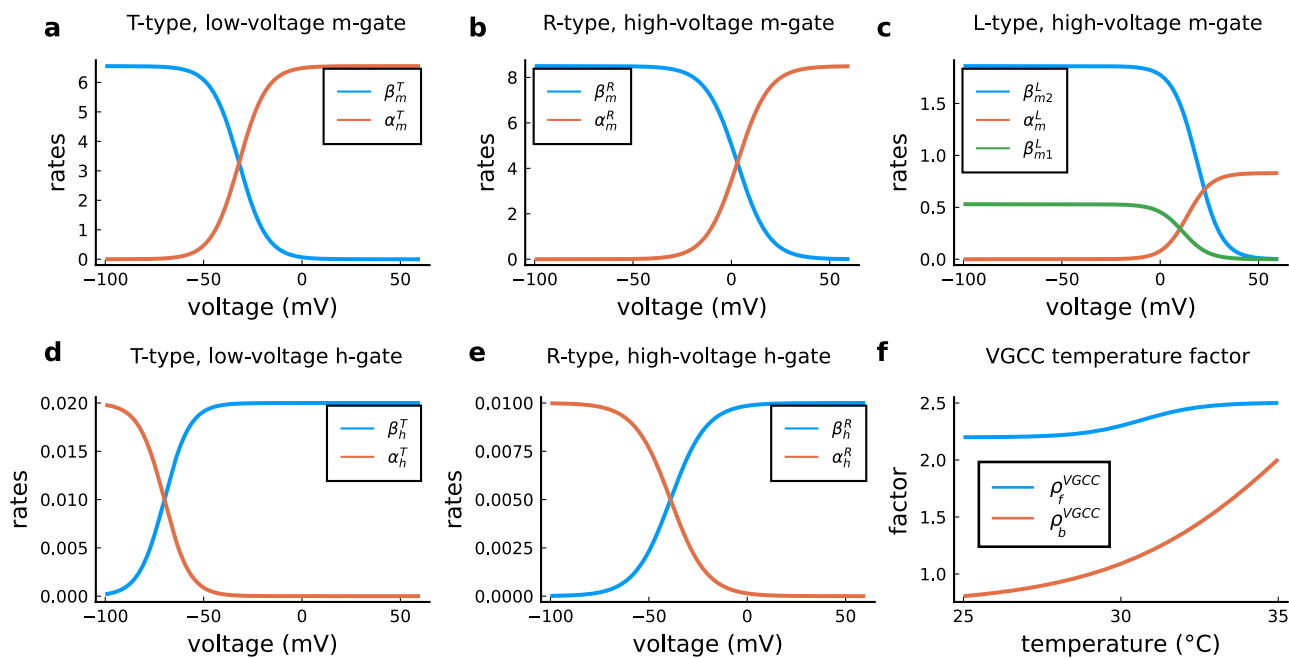
The VGCC currents are integrated to the dendritic spine and estimated using the GHK *Equation 14*, as follows:

$$I_T = \gamma_T \cdot \Phi_{Ca} \cdot O_T \quad (16)$$

$$I_R = \gamma_R \cdot \Phi_{Ca} \cdot O_R \quad (17)$$

$$I_L = \gamma_L \cdot \Phi_{Ca} \cdot (O_{L1} + O_{L2}) \quad (18)$$

980 *Table 10* presents the parameters to model the VGCC channels. VGCC rates and temperature fac-  
 981 tors are shown in *Figure 17*.



**Figure 17. | VGCC rates and temperature factors.** **a**, Activation ( $\alpha_m(V_{sp})$ ) and deactivation rates ( $\beta_m(V_{sp})$ ) for the T-type m-gate. **b**, Activation ( $\alpha_m(V_{sp})$ ) and deactivation rates ( $\beta_m$ ) for the R-type m-gate. **c**, Activation ( $\alpha_m(V_{sp})$ ) and both deactivation rates ( $\beta_2^L(V_{sp})$  and  $\beta_1^L(V_{sp})$ ) for the L-type VGCC. **d**, Activation ( $\alpha_h(V_{sp})$ ) and deactivation rates ( $\beta_h(V_{sp})$ ) for the T-type h-gate. **e**, Activation ( $\alpha_h(V_{sp})$ ) and deactivation rates ( $\beta_h(V_{sp})$ ) for the R-type h-gate. **f**, Temperature factor applied to all the rates, forward change ( $\rho_f^{VGCC}$ ) for the  $\alpha$  rates and backward change ( $\rho_b^{VGCC}$ ) for the  $\beta$  rates.

### 982 SK channel

The small potassium (SK) channel produces hyperpolarizing currents which are enhanced in the presence of intracellular calcium elevations. We included SK channels to incorporate a key negative feedback loop between spine calcium and voltage due to the tight coupling that exists between SK channels to NMDAR function (*Adelman et al., 2012; Griffith et al., 2016*). Although SK channels can additionally be regulated by metabotropic glutamate receptors and muscarinic receptors (*Tigaret et al., 2016*), we did not include these regulatory steps in the model. The SK channel current was

based on the description from *Griffith et al. (2016)* as follows:

$$\frac{dm_{sk}}{dt} = \frac{r(Ca) \cdot \rho_f^{SK} - m_{sk}}{\tau_{SK} \cdot \rho_b^{SK}}$$

$$r(Ca) = \frac{Ca^\sigma}{Ca^\sigma + h_{SK}^\sigma}$$

$$I_{SK} = \gamma_{SK} \cdot (E_{rev}^{SK} - V_{sp}) \cdot m_{sk} \cdot N_{SK}.$$

983 There is little information on how temperature effects SK channel function, but *Van Herck et al.*  
 984 *(2018)* suggests a left-ward shift in the SK half-activation when changing from 37°C ( $h_{SK} = 0.38 \pm$   
 985  $0.02 \mu M$ ) to 25°C ( $h_{SK} = 0.23 \pm 0.01 \mu M$ ); that is a 65% decrease. Thus, to mimic temperature  
 986 dependence of SK, we decided to decrease the decay time of the SK hyperpolarizing current by a  
 987 factor of two when passing from physiological to room temperature.

988

$$\rho_b^{SK} = 149.37 - \frac{147.61}{1 + e^{0.093 \cdot (T - 98.85C)}}, \quad \rho_f^{SK} = 0.005 + \frac{2.205}{1 + e^{-0.334 \cdot (T + 25.59C)}}$$

989 **Table 11** presents the parameters to model the SK channel.

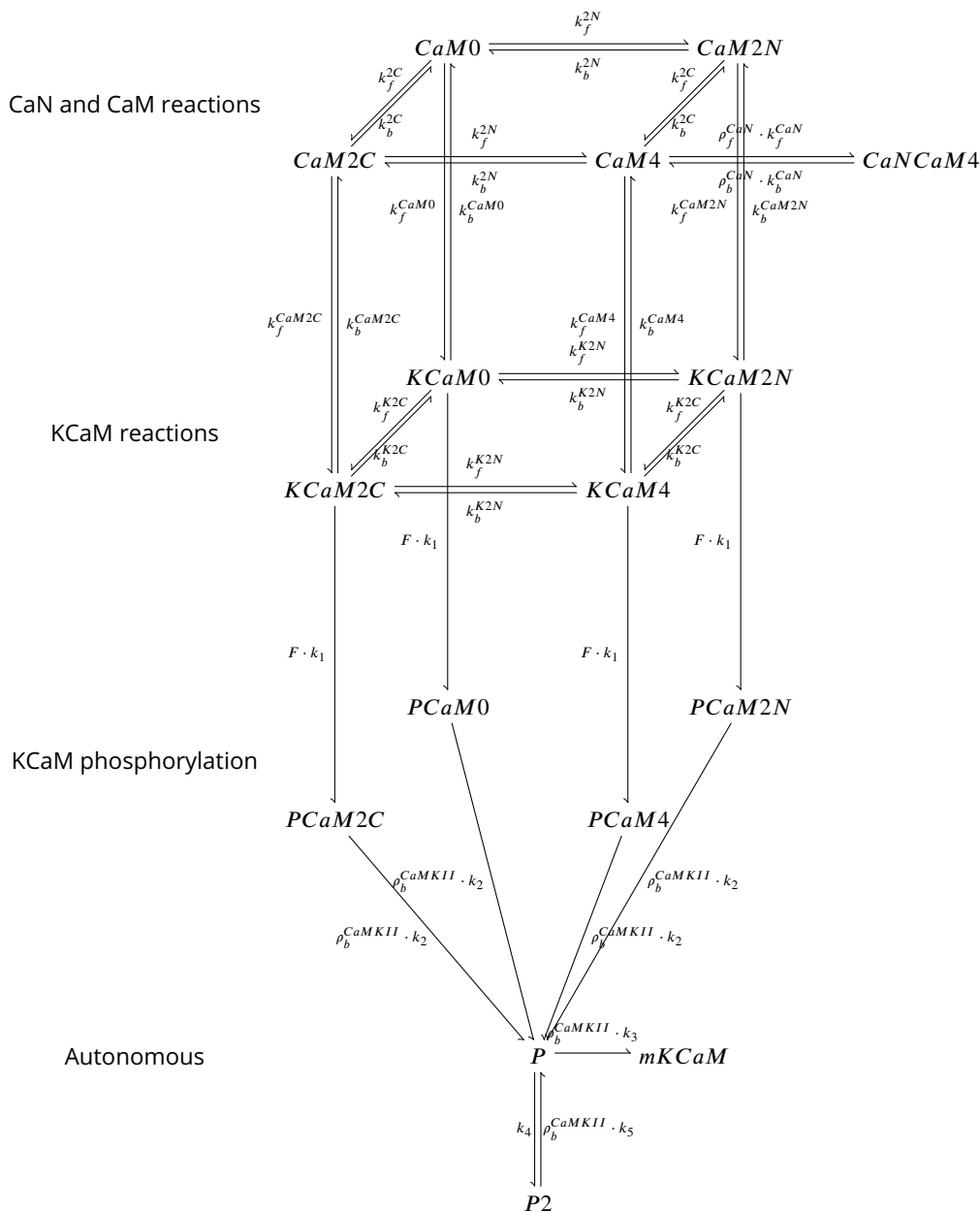
**Table 11.** SK channel parameters.

Name	Value	Reference
<b>SK channel</b>		
number of SK channels	$N_{SK} = 15$	10–200 ( <i>Bock et al., 2019</i> )
SK conductance	$\gamma_{SK} = 10$ pS	<i>Maylie et al. (2004)</i>
SK reversal potential	$E_{rev}^{SK} = -90$ mV	<i>Griffith et al. (2016)</i>
SK half-activation	$h_{SK} = 0.333$ $\mu M$	<i>Griffith et al. (2016)</i>
SK half-activation slope	$\sigma = 6$	4 ( <i>Griffith et al., 2016</i> )
SK time constant	$\tau_{SK} = 6.3$ ms	<i>Griffith et al. (2016)</i>

## 990 Enzymes - CaM, CaN and CaMKII

991 To model the enzymes dynamics, we adapted a monomeric CaM-CaMKII Markov chain from *Chang*  
 992 *et al. (2019)* which was built on the model by *Pepke et al. (2010)*. Our adaptation incorporates a  
 993 simplified CaN reaction which only binds to fully saturated CaM. That is, CaM bound to four calcium  
 994 ions on N and C terminals (see Markov chain in the *Figure 18*). A consequence of the Pepke coarse-  
 995 grained model is that calcium binds and unbinds simultaneously from the CaM terminals (N,C).  
 996 We assumed a lack of dephosphorylation reaction between CaMKII and CaN since *Otmakhov et al.*  
 997 *(2015)* experimentally suggested that no known phosphatase affects CaMKII decay time which is  
 998 probably caused only by CaM untrapping (*Otmakhov et al., 2015*). This was previously theorized in  
 999 the Michalski's model *Michalski (2013)*, and it is reflected in Chang data (*Chang et al., 2019, 2017*).  
 1000 The structure of the corresponding Markov chain is shown in *Figure 18*.

1001 *Chang et al. (2019)* data provides a high-temporal resolution fluorescence measurements for  
 1002 CaMKII in dendritic spines of rat CA1 pyramidal neurons and advances the description of CaMKII  
 1003 self-phosphorylation (at room temperature). We modified Chang's model of CaMKII unbinding  
 1004 rates  $k_2, k_3, k_4, k_5$  to fit CaMKII dynamics at room/physiological temperature as shown by *Chang*  
 1005 *et al. (2017)* supplemental files. Previous modelling of CaMKII (*Chang et al., 2019; Pepke et al.,*  
 1006 *2010*) used a stereotyped waveform with no adaptation to model calcium. Our contribution to  
 1007 CaMKII modelling was to use calcium dynamics sensitive to the experimental conditions to re-  
 1008 produce CaMKII data, therefore, allowing us to capture physiological temperature measurements  
 1009 from *Chang et al. (2017)*. Note that the CaMKII dynamic has two time scales and we capture only  
 1010 the fastest timescale which ends after stimulation ceases (at 60 s). The slowest dynamic occurs at  
 1011 the end of the stimulus, close to the maximum (*Figure 19a*). This can be caused by the transient



**Figure 18. | Coarse-grained model of CaM, CaMKII and CaN adapted from Chang et al. (2019) and Pepke et al. (2010).** Reaction from the CaM-Ca reactions (first layer) are attributed to 2Ca release and binding from different CaM saturation states CaM2C (2Ca bound to terminal C), CaM2N (2Ca bound to terminal N), CaM0 (no calcium bound), CaM4 (Ca bound to both C and N terminal). Note that CaN is allowed to bind only to fully saturated CaM. Activated CaN is represented by the state CaNCaM4. Reactions between the first (CaM-Ca reactions) and the second layer (KCaM-Ca reactions) represent the binding of free/monomeric CaMKII (mKCaM) (Pepke et al., 2010) to different saturation levels of CaM. Reactions within the layer KCaM-Ca represent the binding of calcium to Calmodulin bound to CaMKII (KCaM0, KCaM2C, KCaM2N, KCaM4). Transition of layer KCaM-Ca reactions to layer KCaM-phosphorylation represents CaMKII bound to CaM that became phosphorylated (PCaM states) (Pepke et al., 2010; Chang et al., 2017, 2019). PCaM can become self-phosphorylated (Autonomous layer with P and P<sup>2</sup>) and release CaM. Once the KCaM deactivates from autonomous states, it returns to free monomeric CaMKII (mKCaM). The CaMKII activity in this work represent the states (KCaM + PCaM + P + P<sup>2</sup>). See Chang et al. (2019) for further explanation on this system. CaNCaM4 represents the CaN activity.

1012 volume increase in the spine as measured by Chang et al. (2017). Table 12 shows the concentra-  
 1013 tion of the enzymes and Table 13 shows the parameters to model enzymes reactions in shown in  
 1014 Figure 18.

1015 The CaN concentration was chosen as the total concentration used in a previous model (Stefan  
 1016 et al., 2008) (1.6 μM) scaled by a factor of 12 due to a higher CaN concentration in dendritic spines  
 1017 (Goto et al., 1986; Baumgärtel and Mansuy, 2012) and taking into account the discrepancy between  
 1018 different CaN concentration studies (Kuno et al., 1992; Goto et al., 1986); Kuno et al. (1992) pro-  
 1019 poses 9.6 μg/mg (7.0 + 2.6 μg/mg for Aα and Aβ isoforms) for the catalytic subunit A of CaN (CaNA)  
 1020 in the hippocampus, while Goto et al. (1986) proposes 1.45 μg/mg (presumably for both isoforms).  
 1021 There is therefore a lack of consensus on CaN concentration in neurons, which seems to range  
 1022 between 1 and 10 μg/mg. However, models of CaN in spines (Stefan et al., 2008) use low values of  
 1023 CaN concentration (eg. 1.6 μM) not specific to dendritic spines without considering that these val-  
 1024 ues are taken from the whole neuropil. There is little information on CaN concentration in spines,



1025 but *Kuno et al. (1992)* note that the concentration of CaN is 50% to 84% higher in synaptosomes  
 1026 than in neuronal nuclei. With this information in mind, we set CaN spine concentration 20  $\mu\text{M}$  in  
 1027 our model. CaN was entirely activated through CaM for the following reason: CaNA is activated  
 1028 by calcium-CaM in a highly cooperative manner (Hill coefficient 2.8-3), whereas the activation of  
 1029 CaN by calcium (via CaNB) is at most 10% of that achieved with CaM (*Stemmer and Klee, 1994*). In  
 1030 other words, CaNA affinity for CaM is 16 nM to 26 pM (*Creamer, 2020*), while CaNB affinity for  
 1031 calcium ranges from 15  $\mu\text{M}$  to 24 nM (*Kakalis et al., 1995*). CaN decay time was modeled using  
 1032 experimental spine CaN activity dynamics measured in *Fujii et al. (2013)*.

**Table 12.** Concentration of each enzyme.

Name	Value	Reference
<b>Enzyme concentrations</b>		
free CaM concentration (spine)	$CaM_{con} = 30 \mu\text{M}$	<i>Kakiuchi et al. (1982)</i>
free KCaM concentration (spine)	$mKCaM_{con} = 70 \mu\text{M}$	<i>Feng et al. (2011); Lee et al. (2009)</i>
free CaN spine concentration (spine)	$mCaN_{con} = 20 \mu\text{M}$ >10 $\mu\text{M}$ (estimation from <i>Kuno et al. (1992)</i> )	

### 1033 The lack of reactions between CaN and CaMKII

1034 The protein phosphatases responsible for CaMKII dephosphorylation have not been established  
 1035 unequivocally (*Lisman, 1989*). Our model of CaMKII is based directly on a quantitative model fit  
 1036 to FRET imaging data (*Chang et al., 2017, 2019*), which implicitly account for the effects of any  
 1037 ‘hidden’ phosphatases, absorbing their contribution into the decay rates of the CaMKII activity. As  
 1038 pointed out by *Otmakhov et al. (2015)*, FRET sensor imaging of CaMKII activity unfortunately does  
 1039 not capture the identity of the phosphatases involved in the dephosphorylation of CaMKII. More  
 1040 specifically, *Otmakhov et al. (2015)* observed no significant changes in the decay constant of their  
 1041 CaMKII FRET sensor when selectively inhibiting PP1 and PP2A. Given that these two phosphatases  
 1042 are widely used in models to determine plasticity, we believe that our model is more aligned with  
 1043 data of CaMKII activity *in vivo*.

1044 Yet, our decision to include CaN in the model was determined by the evidence supporting CaN  
 1045 as the strongest candidate for calcium-sensitive protein phosphatase in the brain (*Baumgärtel and*  
 1046 *Mansuy, 2012*). Furthermore, the central role of CaN in synaptic plasticity has been demonstrated  
 1047 both pharmacologically and with genetic manipulation (*Onuma et al., 1998; Malleret et al., 2001*).

### 1048 Temperature effects on enzymatic activity

1049 We included temperature factors in the coarse-grained model using Chang’s data (*Chang et al.,*  
 1050 *2019*), as shown in *Figure 19*. For CaMKII, we fit the modified dissociation rates of the phosphoryla-  
 1051 tion states  $k_2$ ,  $k_3$  and  $k_5$  to match the data on relative amplitude and decay time using the following  
 1052 logistic function:

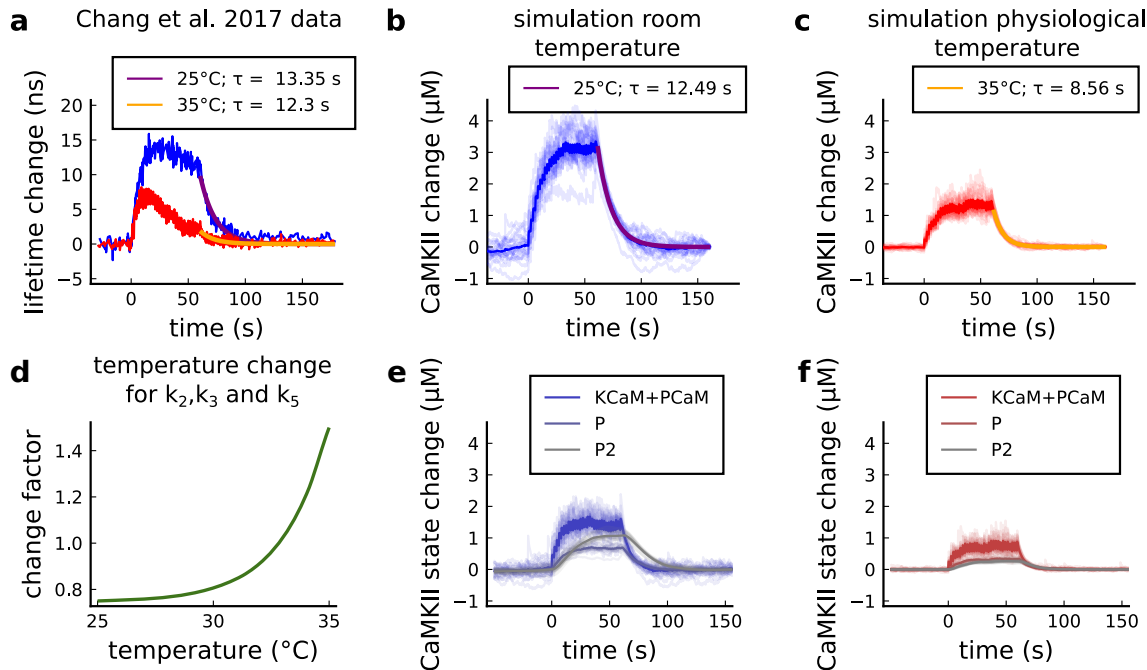
$$\rho_b^{CaMKII} = 162.171 - \frac{161.426}{1 + e^{0.511(T-45.475^\circ\text{C})}}$$

1053 For CaN, we fit the *Fujii et al. (2013)* data at 25°C as seen in *Figure 20a*. However, since CaN-  
 1054 CaM dissociation rates at physiological temperatures were not reported, we set the temperature  
 1055 factor to CaN that fits the outcomes of the protocols we proposed to reproduce. A reference value  
 1056 from the CaN-AKAP79 complex (*Li et al., 2012*) showed a  $Q_{10} = 4.46 = (2.19 \text{ s}^{-1}/9.78 \text{ s}^{-1})$  which  
 1057 is nearly the temperature factor used in our model for CaN. Therefore, both the association and  
 1058 dissociation rates are modified using the following logistic functions:

$$\rho_f^{CaN} = 2.503 - \frac{0.304}{1 + e^{1.048(T-30.668^\circ\text{C})}}$$

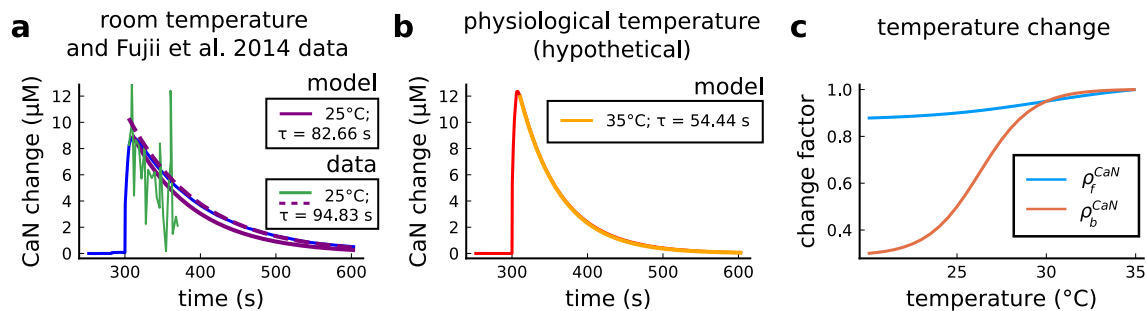
$$\rho_b^{CaN} = 0.729 + \frac{3.225}{1 + e^{-0.330(T-36.279^\circ\text{C})}}$$

1Pre, 30 at 0.49 Hz (Glu uncaging) 1 mM Ca, 2 mM Mg, P4-7 (mouse hip.)



**Figure 19. | CaMKII temperature changes in the model caused by 1Pre, 30 at 0.49 Hz with glutamate uncaging (no failures allowed), 1mM Ca, 2mM Mg, P4-7 organotypic slices from mouse hippocampus.** **a**, CaMKII fluorescent probe lifetime change measured by *Chang et al. (2017)* for 25°C (blue) and 35°C (red). The decay time ( $\tau$ ) was estimated by fitting the decay after the stimulation (30 pulses at 0.49Hz) using a single exponential decay,  $y = a \cdot e^{-t/b}$ ;  $\tau = 1/b$ . **b**, Simulation of the CaMKII concentration change (with respect to the baseline) at 25°C in response to same protocol applied in the panel **a**. The simulations on the panels **b**, **c**, **e**, **f** show the mean of 20 samples. **c**, Same as in panel **b** but for 35°C. **d**, Estimated temperature change factor for the dissociation rates  $k_2$ ,  $k_3$  and  $k_5$  in the Markov chain in *Figure 18*. **e**, Change in the concentration of the CaMKII states (25°C) which are summed to compose CaMKII change in the panel **b**. **f**, Same as in panel **e** for 35°C with reference to the panel **c**.

1Pre, 100 at 20 Hz, (Glu uncaging) 2 mM Ca, Mg-Free, DIV11-13 (rat cultured hip. neurons)



**Figure 20. | CaN temperature changes in our model caused by 1Pre, 100 at 20 Hz with glutamate uncaging (no failures allowed), 2mM Ca, Mg-free, 11-13 days in vitro.** **a**, Simulated CaN change (blue solid line) in response to the same stimuli of the CaN measurement from *Fujii et al. (2013)* RY-CaN fluorescent probe (green solid line). The decay time ( $\tau$ ) estimated from data ( $y = a \cdot e^{-t/b}$ ) is 94.83 s (dashed purple line) and 82.66 s for our model (solid purple line). **b**, Simulated CaN change for physiological temperature with decay time of 54.44 s. **c**, Temperature change,  $\rho_f^{CaN}$  and  $\rho_b^{CaN}$ , applied to CaN association and dissociation rates.

**Table 13.** Parameters for the coarse-grained model published in *Pepke et al. (2010)* and adapted by *Chang et al. (2019)* and this work. *Pepke et al. (2010)* rate adaptation for the coarse-grained model  $adapt(a, b, c, d, Ca) = \frac{a \cdot b}{c + d \cdot Ca}$ . Refer to *Figure 18f* for definition of variables.

REACTIONS	Value	Reference
<b>Coarse-grained model, CaM-Ca reactions</b>		
CaM0 + 2Ca $\Rightarrow$ CaM2C	$k_f^{2C} = adapt(k_{on}^{1C}, k_{on}^{2C}, k_{off}^{1C}, k_{on}^{2C}, Ca)$	<i>Pepke et al. (2010)</i>
CaM2N + 2Ca $\Rightarrow$ CaM4		
CaM0 + 2Ca $\Rightarrow$ CaM2N	$k_f^{2N} = adapt(k_{on}^{1N}, k_{on}^{2N}, k_{off}^{1N}, k_{on}^{2N}, Ca)$	<i>Pepke et al. (2010)</i>
CaM2C + 2Ca $\Rightarrow$ CaM4		
CaM2C $\Rightarrow$ CaM0 + 2Ca	$k_b^{2C} = adapt(k_{off}^{1C}, k_{off}^{2C}, k_{off}^{1C}, k_{off}^{2C}, Ca)$	<i>Pepke et al. (2010)</i>
CaM4 $\Rightarrow$ CaM2N + 2Ca		
CaM2N $\Rightarrow$ CaM0 + 2Ca	$k_b^{2N} = adapt(k_{off}^{1N}, k_{off}^{2N}, k_{off}^{1N}, k_{off}^{2N}, Ca)$	<i>Pepke et al. (2010)</i>
CaM4 $\Rightarrow$ CaM2C + 2Ca		
	$k_{on}^{1C} = 5 \cdot 10^6 M^{-1} s^{-1}$	1.2 to $9.6 \cdot 10^6 M^{-1} s^{-1}$ ( <i>Pepke et al., 2010</i> )
	$k_{on}^{2C} = 10 \cdot 10^6 M^{-1} s^{-1}$	5 to $35 \cdot 10^6 M^{-1} s^{-1}$ ( <i>Pepke et al., 2010</i> )
	$k_{on}^{1N} = 100 \cdot 10^6 M^{-1} s^{-1}$	25 to $260 \cdot 10^6 M^{-1} s^{-1}$ ( <i>Pepke et al., 2010</i> )
	$k_{on}^{2N} = 200 \cdot 10^6 M^{-1} s^{-1}$	50 to $300 \cdot 10^6 M^{-1} s^{-1}$ ( <i>Pepke et al., 2010</i> )
	$k_{off}^{1C} = 50 s^{-1}$	10 to $70 s^{-1}$ ( <i>Pepke et al., 2010</i> )
	$k_{off}^{2C} = 10 s^{-1}$	8.5 to $10 s^{-1}$ ( <i>Pepke et al., 2010</i> )
	$k_{off}^{1N} = 2000 s^{-1}$	$1 \cdot 10^3$ to $4 \cdot 10^3 s^{-1}$ ( <i>Pepke et al., 2010</i> )
	$k_{off}^{2N} = 500 s^{-1}$	$0.5 \cdot 10^3$ to $> 1 \cdot 10^3 s^{-1}$ ( <i>Pepke et al., 2010</i> )
<b>Coarse-grained model, KCaM-Ca reactions</b>		
KCaM0 + 2Ca $\Rightarrow$ KCaM2C	$k_f^{K2C} = adapt(k_{on}^{K1C}, k_{on}^{K2C}, k_{off}^{K1C}, k_{on}^{K2C}, Ca)$	<i>Pepke et al. (2010)</i>
KCaM2N + 2Ca $\Rightarrow$ KCaM4		
KCaM0 + 2Ca $\Rightarrow$ KCaM2N	$k_f^{K2N} = adapt(k_{on}^{K1N}, k_{on}^{K2N}, k_{off}^{K1N}, k_{on}^{K2N}, Ca)$	<i>Pepke et al. (2010)</i>
KCaM2C + 2Ca $\Rightarrow$ KCaM4		
KCaM2C $\Rightarrow$ KCaM0 + 2Ca	$k_b^{K2C} = adapt(k_{off}^{K1C}, k_{off}^{K2C}, k_{off}^{K1C}, k_{off}^{K2C}, Ca)$	<i>Pepke et al. (2010)</i>
KCaM4 $\Rightarrow$ KCaM2N + 2Ca		
KCaM2N $\Rightarrow$ KCaM0 + 2Ca	$k_b^{K2N} = adapt(k_{off}^{K1N}, k_{off}^{K2N}, k_{off}^{K1N}, k_{off}^{K2N}, Ca)$	<i>Pepke et al. (2010)</i>
KCaM4 $\Rightarrow$ KCaM2C + 2Ca		
	$k_{on}^{K1C} = 44 \cdot 10^6 M^{-1} s^{-1}$	<i>Pepke et al. (2010)</i>
	$k_{on}^{K2C} = 44 \cdot 10^6 M^{-1} s^{-1}$	<i>Pepke et al. (2010)</i>
	$k_{on}^{K1N} = 76 \cdot 10^6 M^{-1} s^{-1}$	<i>Pepke et al. (2010)</i>
	$k_{on}^{K2N} = 76 \cdot 10^6 M^{-1} s^{-1}$	<i>Pepke et al. (2010)</i>
	$k_{off}^{K1C} = 33 s^{-1}$	<i>Pepke et al. (2010)</i>
	$k_{off}^{K2C} = 0.8 s^{-1}$	0.49 to $4.9 s^{-1}$ ( <i>Pepke et al., 2010</i> )
	$k_{off}^{K1N} = 300 s^{-1}$	<i>Pepke et al. (2010)</i>
	$k_{off}^{K2N} = 20 s^{-1}$	6 to $60 s^{-1}$ ( <i>Pepke et al., 2010</i> )
<b>Coarse-grained model, CaM-mKCaM reactions</b>		
CaM0 + mKCaM $\Rightarrow$ mKCaM0	$k_f^{CaM0} = 3.8 \cdot 10^3 M^{-1} s^{-1}$	<i>Pepke et al. (2010)</i>
CaM2C + mKCaM $\Rightarrow$ mKCaM2C	$k_f^{CaM2C} = 0.92 \cdot 10^6 M^{-1} s^{-1}$	<i>Pepke et al. (2010)</i>
CaM2N + mKCaM $\Rightarrow$ mKCaM2N	$k_f^{CaM2N} = 0.12 \cdot 10^6 M^{-1} s^{-1}$	<i>Pepke et al. (2010)</i>
CaM4 + mKCaM $\Rightarrow$ mKCaM4	$k_f^{CaM4} = 30 \cdot 10^6 M^{-1} s^{-1}$	14 to $60 \cdot 10^6 M^{-1} s^{-1}$ ( <i>Pepke et al., 2010</i> )
mKCaM0 $\Rightarrow$ CaM0 + mKCaM	$k_b^{CaM0} = 5.5 s^{-1}$	<i>Pepke et al. (2010)</i>
mKCaM2C $\Rightarrow$ CaM2C + mKCaM	$k_b^{CaM2C} = 6.8 s^{-1}$	<i>Pepke et al. (2010)</i>
mKCaM2N $\Rightarrow$ CaM2N + mKCaM	$k_b^{CaM2N} = 1.7 s^{-1}$	<i>Pepke et al. (2010)</i>
mKCaM4 $\Rightarrow$ CaM0 + mKCaM	$k_b^{CaM4} = 1.5 s^{-1}$	1.1 to $2.3 s^{-1}$ ( <i>Pepke et al., 2010</i> )
<b>Coarse-grained model, self-phosphorylation reactions</b>		
KCaM0 $\Rightarrow$ PCaM0		
KCaM2N $\Rightarrow$ PCaM2N	$k_1 = 12.6 s^{-1}$	<i>Chang et al. (2019)</i>
KCaM2C $\Rightarrow$ PCaM2C		
KCaM4 $\Rightarrow$ PCaM4		
Fraction of activated CaMKII	$F = CaMKII / mKCaM_{con}$	see <i>Equation 19</i> ( <i>Chang et al., 2019</i> )
PCaM0 $\Rightarrow$ P+CaM0		
PCaM2N $\Rightarrow$ P+CaM2N	$k_2 = 0.33 s^{-1}$	$0.33 s^{-1}$ ; adapted from ( <i>Chang et al., 2019</i> )
PCaM2C $\Rightarrow$ P+CaM2C		
PCaM4 $\Rightarrow$ P+CaM4		
P $\Rightarrow$ mKCaM	$k_3 = 4 \cdot 0.17 s^{-1}$	$0.17 s^{-1}$ adapted from ( <i>Chang et al., 2019</i> )
P $\Rightarrow$ P2	$k_4 = 4 \cdot 0.041 s^{-1}$	$0.041 s^{-1}$ adapted from ( <i>Chang et al., 2019</i> )
P2 $\Rightarrow$ P	$k_5 = 8 \cdot 0.017 s^{-1}$	$0.017 s^{-1}$ adapted from ( <i>Chang et al., 2019</i> )
<b>Calcineurin model, CaM-CaM4 reactions</b>		
CaM4+mCaN $\Rightarrow$ mCaN+CaM4	$k_f^{CaN} = 10.75 \cdot 10^6 M^{-1} s^{-1}$	$46 \cdot 10^6 M^{-1} s^{-1}$ ( <i>Quintana et al., 2005</i> )
mCaN+CaM4 $\Rightarrow$ CaM4+mCaN	$k_b^{CaN} = 0.02 s^{-1}$	fit from Fujii et al. 2014 ( <i>Fujii et al., 2013</i> ) see <i>Figure 20</i>

## 1059 Geometrical Readout

We describe here the geometrical readout mechanism which allows for plasticity outcome assignment. First, we define the following variables which are representative of "active CaMKII" and "active CaN":

Active CaN

$$CaN = CaN4$$

Active CaMKII

$$KCaM = KCaM0 + KCaM2C + KCaM2N + KCaM4$$

$$PCaM = PCaM0 + PCaM2C + PCaM2N + PCaM4$$

$$CaMKII = KCaM + PCaM + P + P2. \quad (19)$$

Calcium entry in the spine initiates a cascade of events that ultimately leads to long term plasticity changes. Specific concentrations of CaMKII and CaN trigger activation functions  $act_D$  and  $act_P$  when they belong to one of the two polygonal regions (P and D), termed plasticity regions in the main text:

$$\begin{aligned} \dot{act}_D &= a_D \cdot \mathbb{1}_D - b_D \cdot (1 - \mathbb{1}_D) \cdot act_D \\ \dot{act}_P &= a_P \cdot \mathbb{1}_P - b_P \cdot (1 - \mathbb{1}_P) \cdot act_P. \end{aligned}$$

1060 The variables  $act_D$  and  $act_P$  act as low pass filters of CaMKII and CaN activities with some memory  
1061 of previous passages in the respective plasticity regions. To specify the LTP/LTD rates, termed  $D_{rate}$   
1062 and  $P_{rate}$ , we use the activation functions,  $act_D$  and  $act_P$ , as follows:

$$\begin{aligned} P_{rate}(act_P) &= t_P^{-1} \frac{act_P^2}{act_P^2 + K_P^2} \\ D_{rate}(act_D) &= t_D^{-1} \frac{act_D^2}{act_D^2 + K_D^2}. \end{aligned}$$

1063 The Markov plasticity chain (see **Figure 21**) starts with initial conditions  $NC = 100$ ,  $LTD = 0$  and  
1064  $LTP = 0$ . **Figure 22** shows how the readout works to predict plasticity for a single orbit. **Figure 22a**  
1065 shows the enzyme's activity alone which is combined to form an orbit as shown in **Figure 22b**. The  
1066 region indicator of the respective orbit is shown in **Figure 22c**. Simultaneously, **Figure 22d** depicts  
1067 the leaky activation  $act_P$  and  $act_D$ , which will define the rate of plasticity induction in **Figure 22e**  
1068 **and f**. The rates in the plasticity Markov chain will not reset to 0 if the orbit leaves the readout.  
1069 The plasticity Markov chain is shown in **Figure 22g** with the prediction outcome represented as a  
1070 weight change (%). **Figure 22h** shows the rate,  $P_{rate}$  and  $D_{rate}$  activation profile. The LTP activation  
1071 rate is steep, meaning that orbits do not need to spend a long time inside the readout to promote  
1072 LTP induction, while the LTD region requires five-fold longer activation times. **Table 14** shows the  
1073 parameters that define the polygons of the plasticity regions (see **Figure 22b**).

$$LTD \xrightleftharpoons[D_{rate}(act_D)]{P_{rate}(act_P)} NC \xrightleftharpoons[D_{rate}(act_D)]{P_{rate}(act_P)} LTP$$

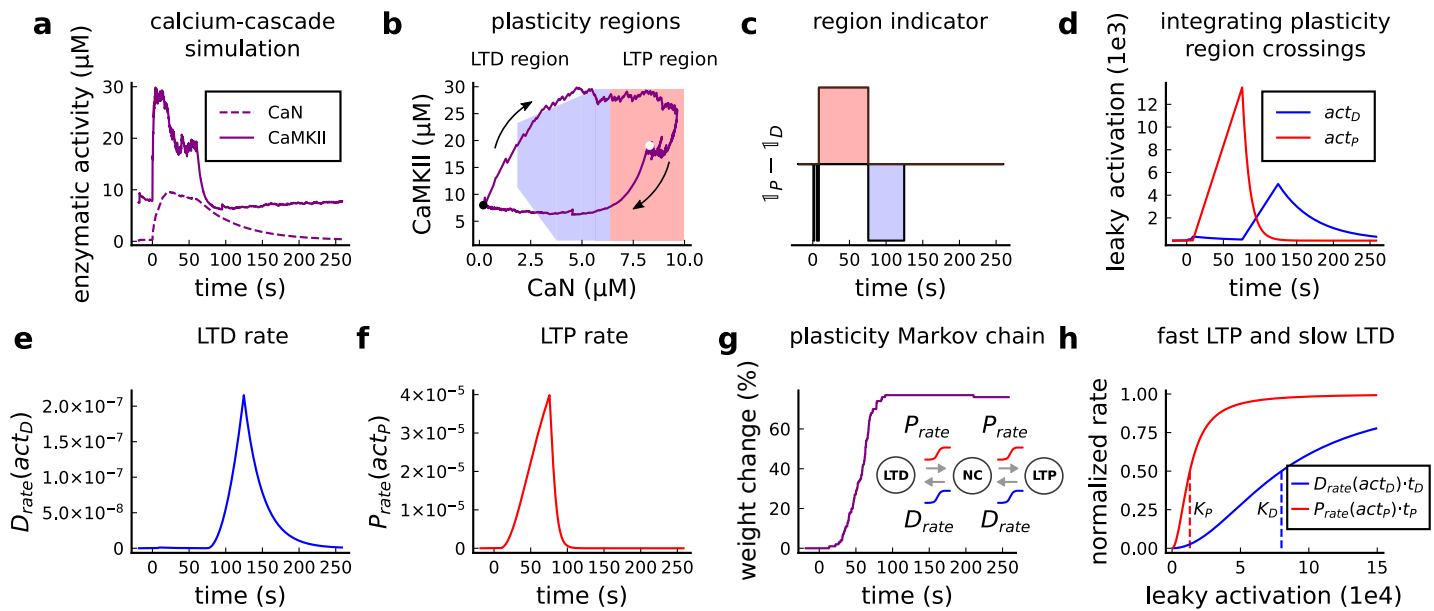
**Figure 21. | Plasticity Markov Chain.**

## 1074 Positioning of the boundaries of the plasticity regions

1075 The tuning of the plasticity region boundaries was based on four different experiments. The LTP  
1076 region was defined using Tigaret (**Figure 3**). The refinement of the LTD region was made using  
1077 the simulated dynamics from *Inglebert et al. (2020)* (**Figure 6d**, top part of the LTD boundary) and  
1078 Dudek and *Dudek and Bear (1992, 1993)* (**Figure 4d** and **Figure 5f**, bottom-left part of the LTD  
1079 boundary).

**Table 14.** Parameters to define the plasticity readout.

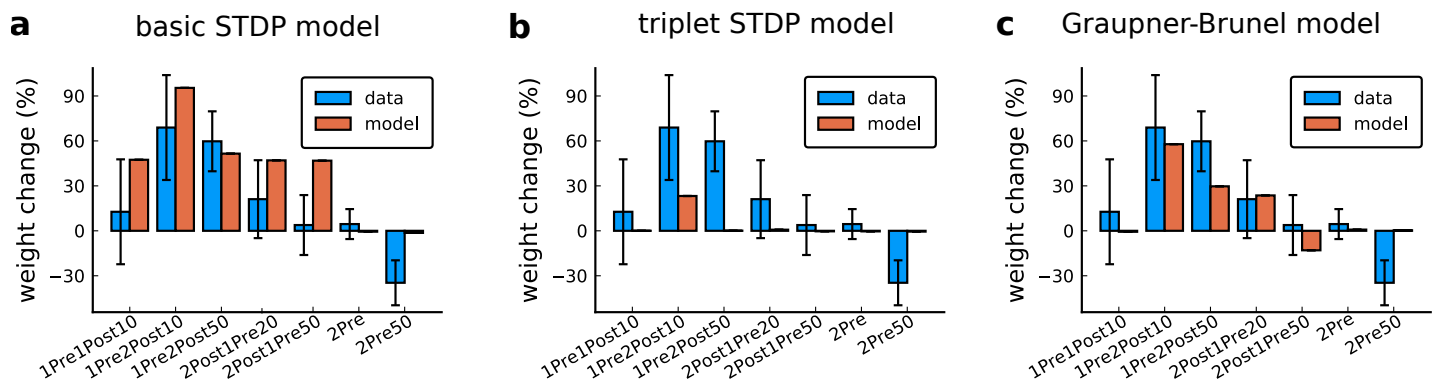
Name	Value	Reference
<b>Leaking variable (a.u.)</b>		
rise constant inside the LTD region	$a_D = 0.1 \text{ a.u.} \cdot \text{ms}^{-1}$	fitted to cover all protocols in <i>Table 1</i>
rise constant inside the LTP region	$a_P = 0.2 \text{ a.u.} \cdot \text{ms}^{-1}$	fitted to cover all protocols in <i>Table 1</i>
decay constant outside the LTD region	$b_D = 2 \cdot 10^{-5} \text{ a.u.} \cdot \text{ms}^{-1}$	fitted to cover all protocols in <i>Table 1</i>
decay constant outside the LTP region	$b_P = 1 \cdot 10^{-4} \text{ a.u.} \cdot \text{ms}^{-1}$	fitted to cover all protocols in <i>Table 1</i>
<b>Plasticity Markov chain</b>		
LTD rate time constant	$t_D = 1.8 \cdot 10^4 \text{ ms}$	fitted to cover all protocols in <i>Table 1</i>
LTP rate time constant	$t_P = 1.3 \cdot 10^4 \text{ ms}$	fitted to cover all protocols in <i>Table 1</i>
half occupation LTP	$K_P = 1.3 \cdot 10^4 \text{ a.u.}$	fitted to cover all protocols in <i>Table 1</i>
half occupation LTD	$K_D = 8 \cdot 10^4 \text{ a.u.}$	fitted to cover all protocols in <i>Table 1</i>
<b>Plasticity regions (vertices determining the polygons)</b>		
LTP region (CaN,CaMKII)	[6.35,1.4],[10,1.4],[6.35,29.5],[10,29.5]	fitted to cover all protocols in <i>Table 1</i>
LTD region (CaN,CaMKII)	[6.35,1.4],[6.35,23.25],[6.35,29.5],[1.85,11.32]	fitted to cover all protocols in <i>Table 1</i>
	[1.85,23.25],[3.76,1.4],[5.65,29.5]	fitted to cover all protocols in <i>Table 1</i>



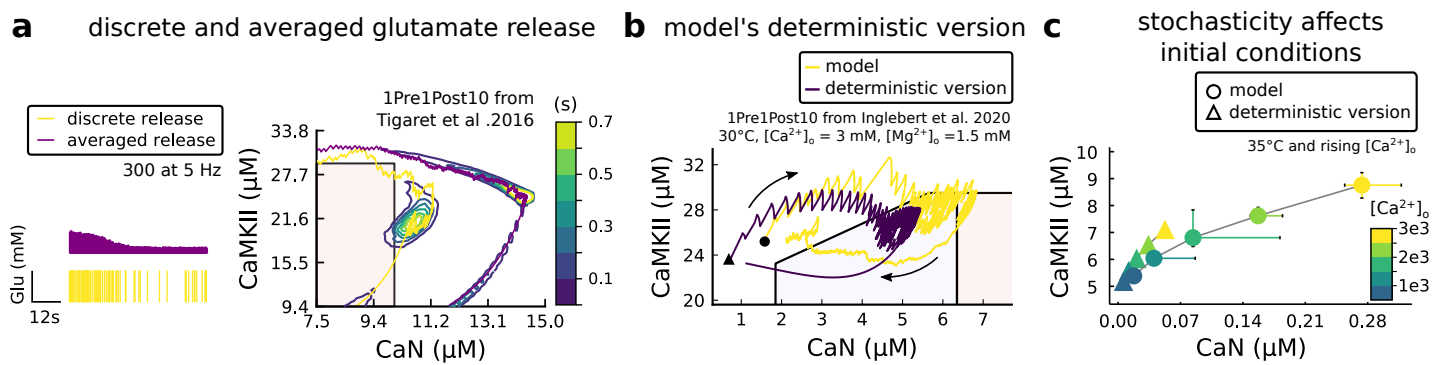
**Figure 22.** | Plasticity readout for the protocol 1Pre2Post10, 300 at 5Hz, from *Tigaret et al. (2016)*. **a**, CaMKII and CaN activity in response to protocol 1Pre2Post10. **b**, Enzymatic joint activity in the 2D plane showing LTP and LTD's plasticity regions. The black point marks the beginning of the stimulation, and the white point shows the end of the stimulation after 60 s. **c**, Region indicator illustrating how the joint activity crosses the LTP and the LTD regions. **d**, The leaky activation functions are used as input to the LTP and LTD, rates respectively. The activation function has a constant rise when the joint-activity is inside the region, and exponential decay when it is out. **e**, The LTD rate in response to the leaky activation function,  $act_D$ , in panel **d**. Note that this rate profile occurs after the stimulation is finished (60 s). The joint-activity is returning to the resting concentration in panel **a**. **f**, The LTP rate in response to the leaky activation function,  $act_P$ , in panel **d**. **g**, Outcome of the plasticity Markov chain in response to the LTD and LTP rates. The EPSP change (%) is estimated by the difference between the number of processes in the states LTP and LTD,  $LTP - LTD$ . **h**, Normalized LTP and LTD rates (multiplied to their respective time constant,  $t_D$ ,  $t_P$ ) sigmoids. The dashed line represents the half-activation curve for the LTP and LTD rates. Note in panel **d** that the leaky activation function reaches the half-activation  $K_P = 1.3e4$ .

## 1080 Supplemental files

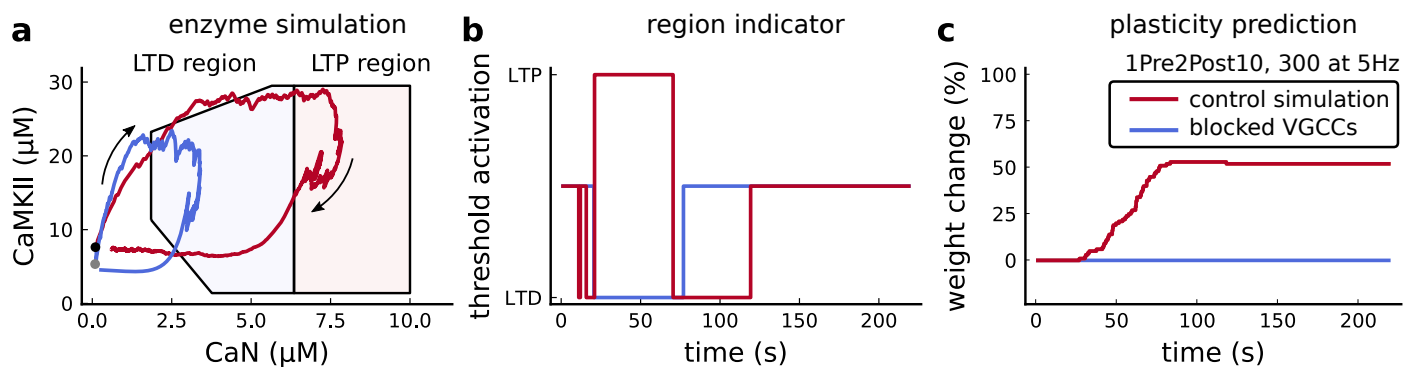
1081 **Figure 3-Figure Supplement 1** shows best fit to the *Tigaret et al. (2016)* data from seven spike-  
 1082 timing dependent plasticity protocols, for three leading STDP models in the field: classic pairwise  
 1083 STDP (*Song et al., 2000*), triplet STDP (*Pfister and Gerstner, 2006*), and calcium-based Graupner-  
 1084 Brunel STDP (*Graupner and Brunel, 2012*) models. Parameters for each model that mimized the  
 1085 mean-squared error with the data were discovered using Bayesian optimization using the Bayesian  
 1086 Optimization package in the Julia programming language. **Figure 4-Figure Supplement 1** shows vari-  
 1087 ations of *Dudek and Bear (1992)* parameters for  $[Ca^{2+}]_o$ ,  $[Mg^{2+}]_o$ , temperature and dendritic spine  
 1088 distance from the soma. Also, it shows the Poisson spike train protocol (as in *Figure 7g,h.*) for  
 1089 temperature and age parameters obtained from an estimation of the body temperature regula-  
 1090 tion during development (or thermoregulation maturation, also called maturation of temperature  
 1091 homeostasis, estimated in *Figure 3-Figure Supplement 1g*). **Figure 5-Figure Supplement 1** expands  
 1092 the presynaptic burst strategy hypothesized to recover the LTD in adult slices (*Figure 5c*) for 900  
 1093 pairing repetitions. Also, **Figure 5-Figure Supplement 1** tries to isolate the contribution of each  
 1094 age-dependent mechanism (NMDAR, GABA<sub>A</sub>, BaP efficiency switches) for 3 and 5 Hz predictions  
 1095 in *Dudek and Bear (1993)* experiment. We fixed each of the three mechanisms coding for age in  
 1096 our model at P5 and P50, to observe how they shape the plasticity. Note the experiment in *Fig-*  
 1097 *ure 6-Figure Supplement 1d-i* is only to theoretically show how each age mechanism contributes to  
 1098 plasticity in *Figure 5*. Also we compare predictions between different STDP experiments across age.  
 1099 **Figure 3-Figure Supplement 4** presents modifications of *Inglebert et al. (2020)* STDP experiment  
 1100 and the reproduction of *Mizuno et al. (2001)* data. **Figure 6-Figure Supplement 2** shows multiple  
 1101 aspects related to temperature in STDP experiments and the temperature and age choices for the  
 1102 publications described in *Table 1* compared to physiological conditions. We estimate how the rat's  
 1103 body temperature physiologically evolves in function of age using *McCauley et al. (2020)* and *Wood*  
 1104 *et al. (2016)* data.



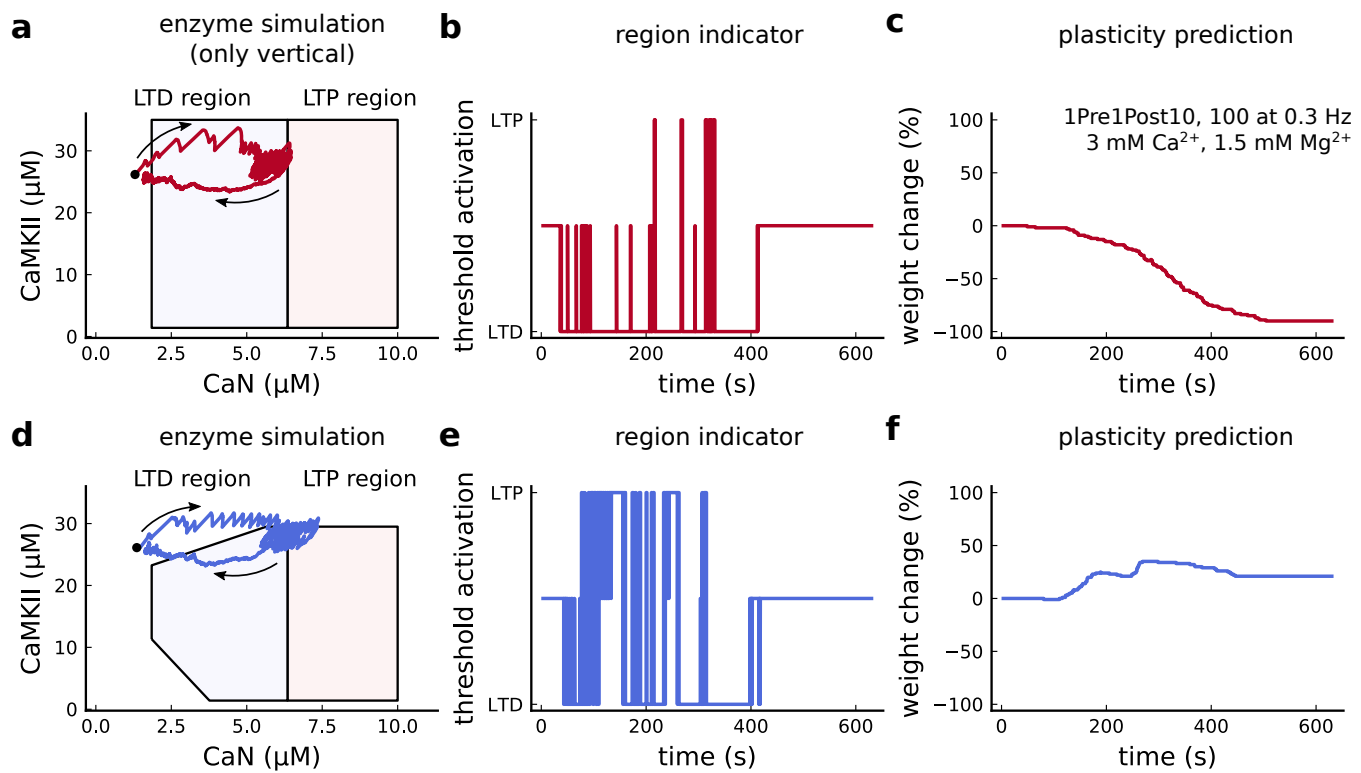
**Figure 3 - Supplement 1. | Standard models for predicting plasticity fail to account for the data from *Tigaret et al. (2016)*.** a-c, Mean weight change for the *Tigaret's* data (blue), error bars denote  $\pm 1$  s.d. Plasticity protocols indicated by labels on x-axis. Green bars show mean plasticity predicted for the same protocols by classic STDP (*Song et al., 2000*) (panel a), triplet STDP (*Pfister and Gerstner, 2006*) (panel b), or Graupner-Brunel calcium-based STDP (*Graupner and Brunel, 2012*) model (panel c).



**Figure 3 - Supplement 2. | Comparison showing different roles of stochasticity in the model.** **a**, Left, Glutamate concentration from a single realization of the model (yellow) and averaged Glutamate concentration (purple) from 100 repetitions of the model for 300 pulses train at 5 Hz. Right, 1Pre1Post10 from Tigaret *et al.* (2016) using the model (yellow) and a version of the model (purple) in which the glutamate concentration is the average one (as in Left panel). The time spent (s) is shown for the different glutamate release modes (stochastic and averaged) with an example trajectory (purple and solid yellow lines). There are no failures in averaged release; therefore, enzymes are over-activated. **b**, A comparison between our model and a fully deterministic version for the 1Pre1Post10 from Inglebert *et al.* 2020 (Inglebert *et al.*, 2020). Note the significant mismatch, which does not allow the deterministic model to reach the LTP region that determines the plasticity outcome. This effect is mainly caused by the stochastic calcium sources, which the deterministic model fails to reproduce. The black triangle (circle) marks the initial conditions of the deterministic version (model). This initial condition is reached by letting the model evolve with no input. **c** The initial conditions are increasingly different when comparing the model and its deterministic version for rising concentrations of external calcium concentrations.



**Figure 3 - Supplement 3. | Effects of blocking VGCCs.** **a**, Combined enzyme activity of the experiment 1Pre2Post10, 300 at 5 Hz described in Tigaret *et al.* (2016) with and without VGCCs (legend in panel **c**). The arrows indicate time flow, and the grey and black dots represent the initial conditions. Note the effect of VGCC blocking on the initial conditions. **b**, Region indicator associated to panel **a**. **c** Plasticity prediction for the simulated experiment with and without VGCCs. Note that when VGCCs are blocked LTP cannot be induced, in agreement with Tigaret *et al.* (2016) experimental data.

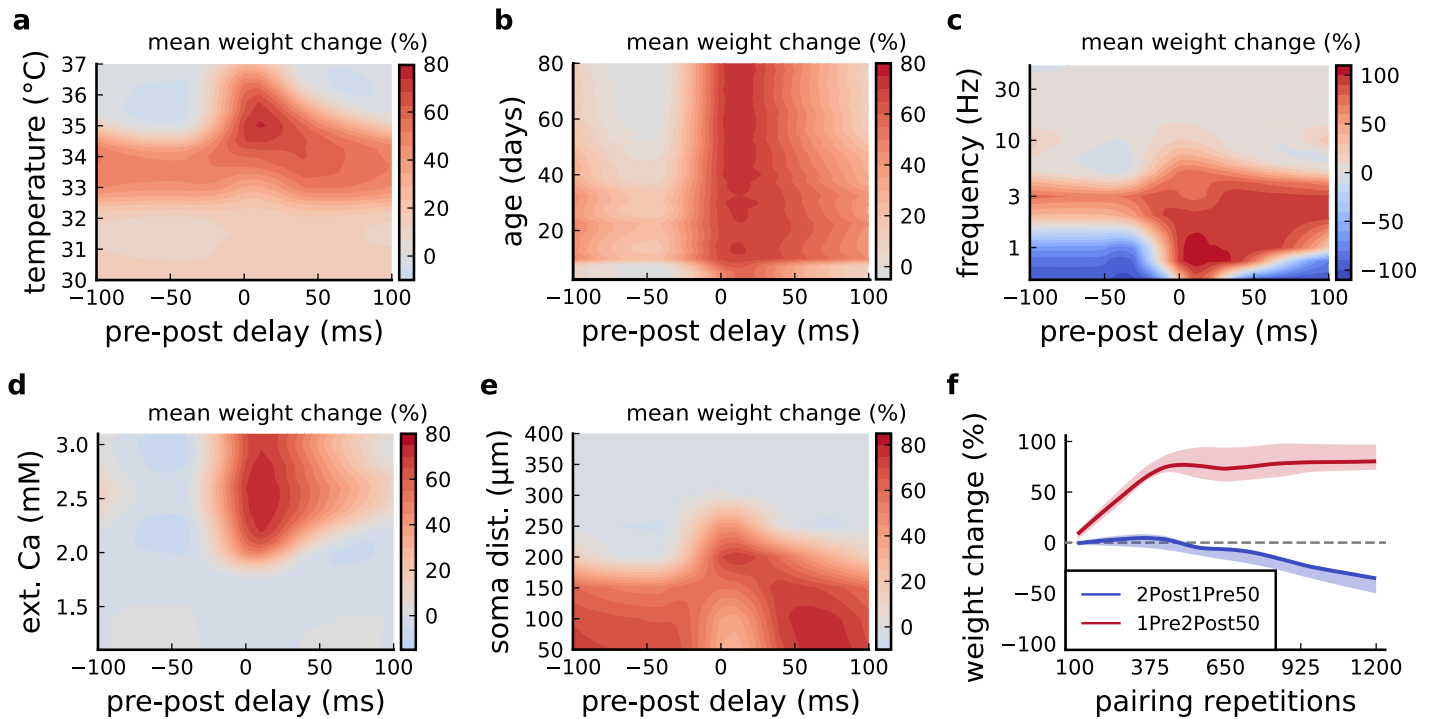


**Figure 3 - Supplement 4. | Exclusively setting vertical boundaries (no CaMKII selectivity) fails to capture the correct plasticity outcome.**

**a** Combined activity of the protocol 1Pre1Post10, 100 at 0.3 Hz with experimental conditions as in *Figure 6c* considering the polygonal regions responding only to CaN thresholds. Note that most of the activity resides in the LTD region. The arrows indicate time flow and black dot represents the initial condition. **b**, Region indicator related to panel **a**. **c**, Plasticity prediction shows LTD, instead of LTP. **d**, Same as **a** but considering the plasticity regions sensitivity both to CaMKII and CaN. **e**, Region indicator related to panel **d**. **f**, Plasticity prediction for panel **d** showing LTP agreeing with data described in *Figure 6c*.

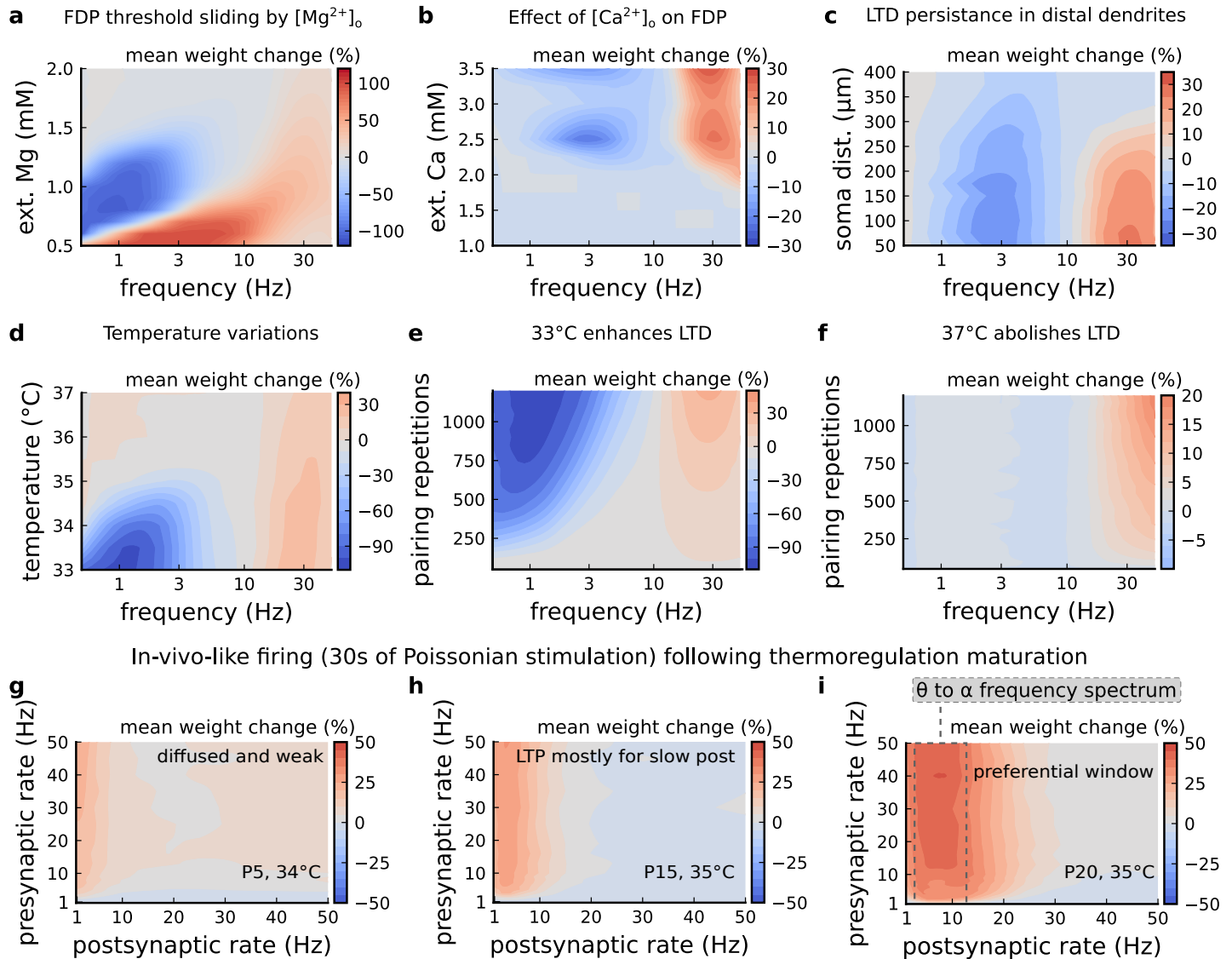


### Varying experimental parameters in Tigaret et al. 2016 - 1Pre2Post(delay)

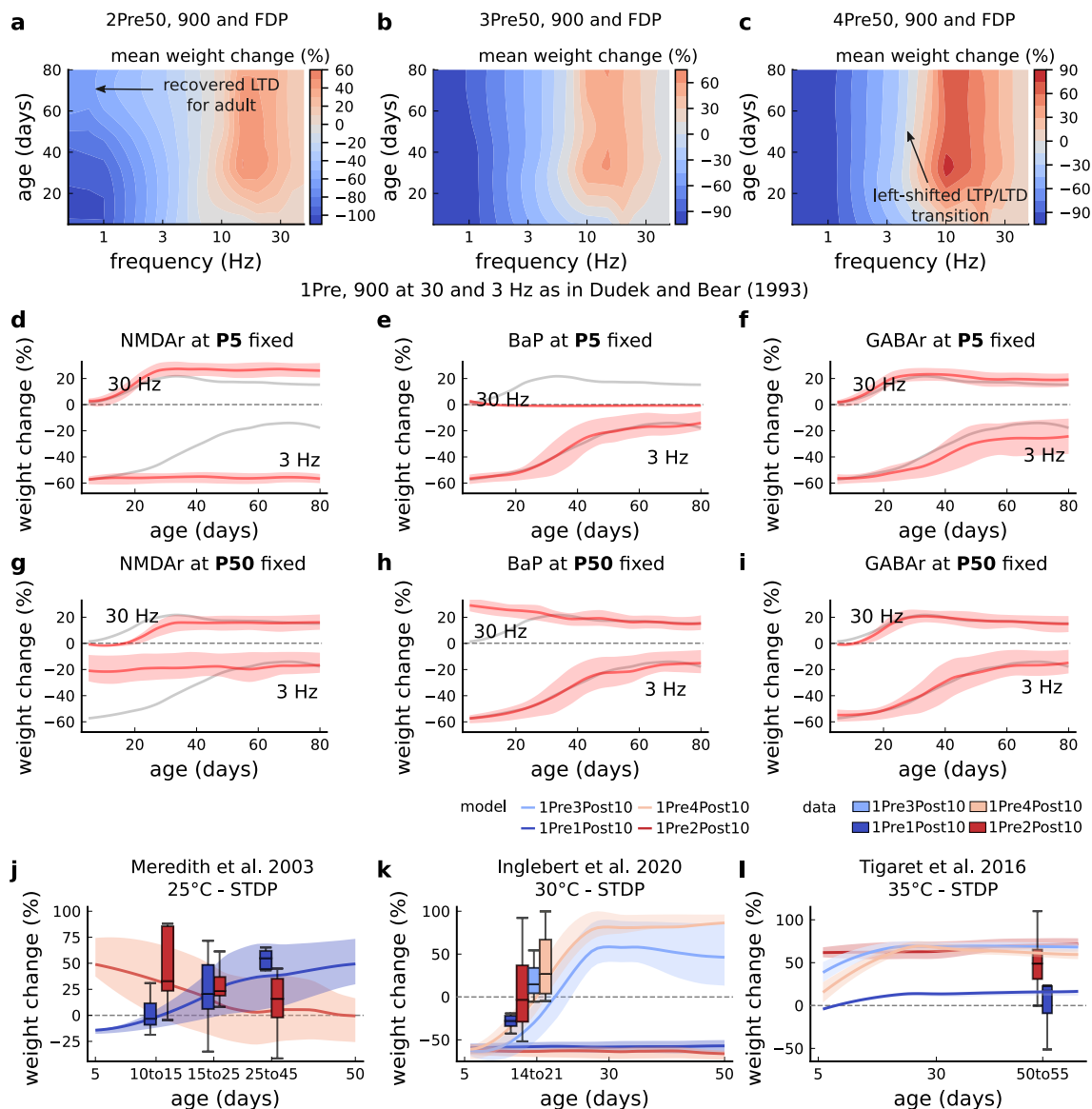


**Figure 3 - Supplement 5. | Varying Tigaret et al. (2016) experimental parameters.** **a**, Mean synaptic weight change for 1Pre2Post(delay) varying the temperature. **b**, Mean synaptic weight change for 1Pre2Post(delay) varying the age. **c**, Mean synaptic weight change for 1Pre2Post(delay) varying the frequency. **d**, Mean synaptic weight change for 1Pre2Post(delay) varying the  $[Ca^{2+}]_o$ . **e**, Mean synaptic weight change for 1Pre2Post(delay) varying the distance from the soma. A similar trend in distal spines was previously found in *Ebner et al. (2019)*. **f**, Mean synaptic weight change of 1Pre2Post50 and 2Post1Pre50 when number of pulses increases or decreases. Note the similarity with *Mizuno et al. (2001)* in *Figure 161c*.

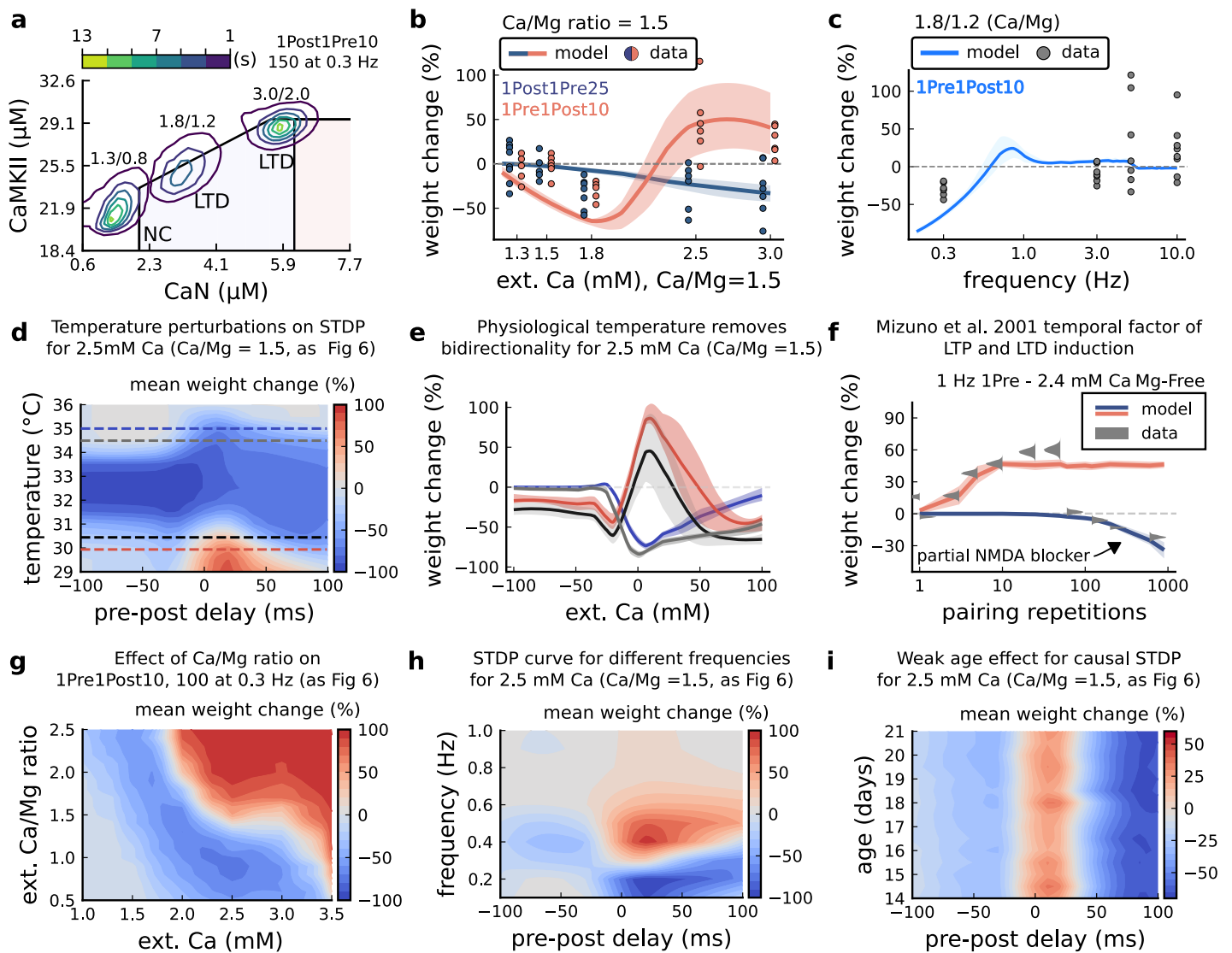
### Varying experimental parameters in Dudek and Bear 1992 FDP



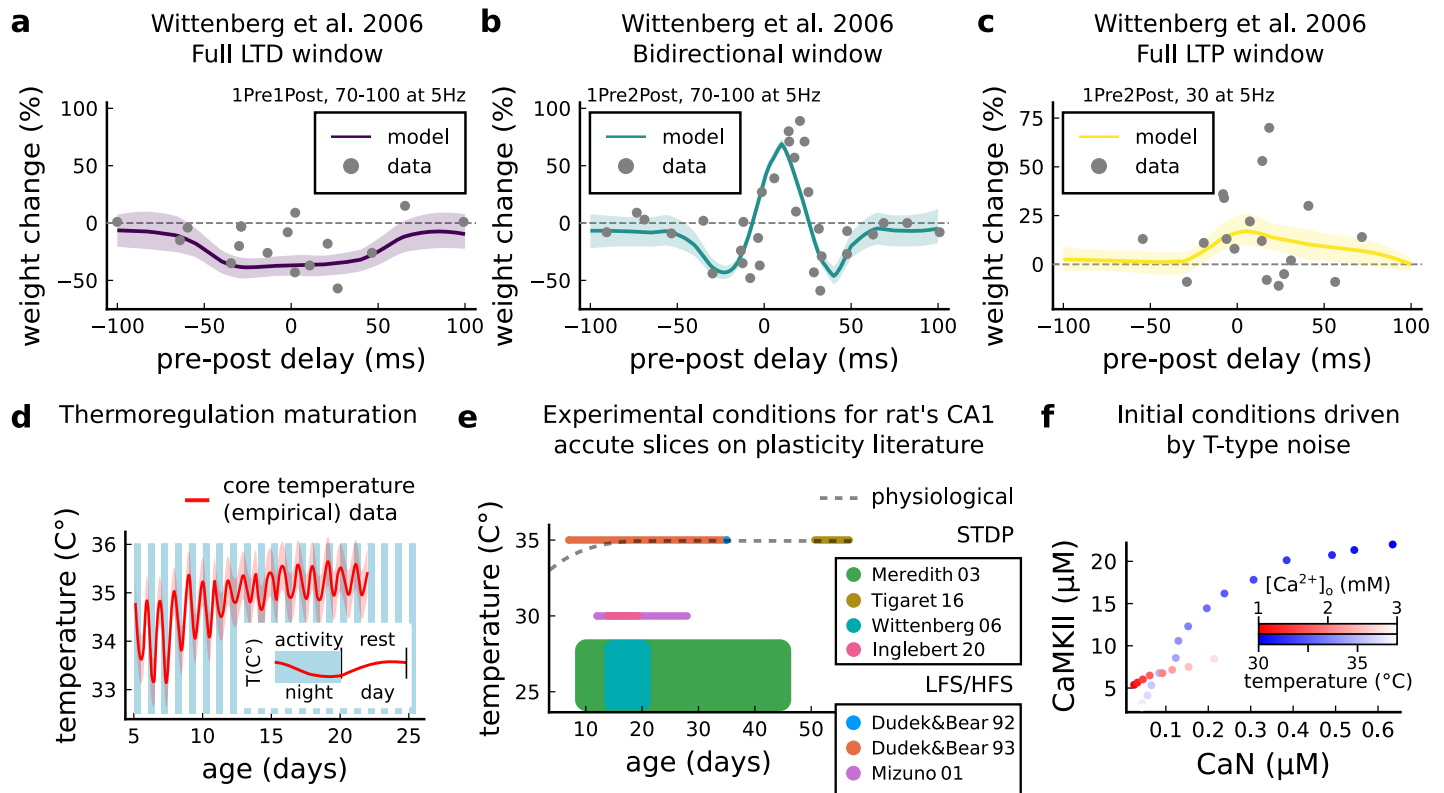
**Figure 4 - Supplement 1. | Varying experimental parameters in *Dudek and Bear (1992)* and Poisson spike train during development.** **a**, Mean synaptic weight change for the FDP experiment varying the  $[Mg^{2+}]_o$ . Original  $[Mg^{2+}]_o$  in *Dudek and Bear (1992)* is 1.5 mM (dashed grey line). **b**, Mean synaptic weight change for the FDP experiment varying the  $[Ca^{2+}]_o$ . Original  $[Ca^{2+}]_o$  in *Dudek and Bear (1992)* is 2.5 mM (dashed grey line). **c**, Mean synaptic weight change for the FDP experiment varying the distant from the soma. Original distance in *Dudek and Bear (1992)* is 200  $\mu m$  (dashed grey line). Changing the distance from the soma modifies how fast BaPs evoked by EPSP will attenuate. Note that LTD is prevalent for a spine situated far from the soma. **d**, Mean synaptic weight change for the FDP experiment varying the temperature. Original temperature in *Dudek and Bear (1992)* is 35 $^{\circ}C$  (dashed grey line). **e**, Mean synaptic weight change for the FDP experiment varying the pairing repetitions at 33 $^{\circ}C$  showing how LTD is enhanced. **f**, Mean synaptic weight change for the FDP experiment varying the pairing repetitions at 37 $^{\circ}C$  showing how LTD is abolished. **g**, Mean synaptic weight change for pre and postsynaptic Poisson spike train during 30 s for P5 and 34 $^{\circ}C$ . The panel shows that there is weak and diffused LTP. **h**, Mean synaptic weight change for pre and postsynaptic Poisson spike train during 30 s for P15 and 35 $^{\circ}C$ . The panel shows that there is a start of LTP window forming for slow postsynaptic rates (<1 Hz). **i**, Mean synaptic weight change for pre and postsynaptic Poisson spike train during 30 s for P20 and 35 $^{\circ}C$ . The panel shows that a window forms around 10 Hz postsynaptic rate similar to what is shown by *Graupner et al. (2016)* and in *Figure 7h*.



**Figure 5 - Supplement 1. | Duplets, triplets and quadruplets for FDP, perturbing developmental-mechanisms for LFS and HFS in *Dudek and Bear (1993)*, and age-related changes in STDP experiments (*Inglebert et al., 2020*; *Tigaret et al., 2016*; *Meredith et al., 2003*).** **a**, Mean synaptic weight change (%) for the duplet-FDP (2Pre50) experiment varying age. The panel shows showing that not only LTD is enhanced but also LTP. **b**, Mean synaptic weight change (%) for the triplet-FDP (3Pre50) experiment varying age. The panel shows that LTD magnitude is enhanced for adult rats and the LTD-LTP transition is shifted leftward. **c**, Mean synaptic weight change (%) for the quadruplet-FDP (4Pre50) experiment varying age. The panel shows a further leftward shift on the LTD-LTP transition (compared to 3Pre50). **d**, Mean synaptic weight change (%) for the 1 Pre 900 at 30 and 3 Hz with *Dudek and Bear (1993)*. Fixing NMDAR at P5 (more GluN2B than GluN2A) causes an increase of LTD and a slight increase of LTP for adult rats compared to baseline (grey solid line). **e**, Same experiment as panel **d** but fixing BaP maturation at P5 (higher BaP attenuation). LTP is abolished, but LTD is not affected. This is because AP induced by the EPSP attenuate too fast for 30 Hz and are thus not able to produce enough depolarization to activate NMDARs. **f**, Same experiment as in panel **d** but fixing GABA<sub>A</sub> maturation at P5 (excitatory GABA<sub>A</sub>) which only slightly enhances LTD (3 Hz) for adult rats. **g**, Same experiment as panel **d** but fixing NMDAR at P50 (more GluN2A than GluN2B). LTD appears with decreased magnitude for young rats compared to baseline (grey solid line). **h**, Same experiment as panel **d** but fixing BaP maturation at P50 (less BaP attenuation). LTP is enhanced for young rats because the BaP pairing with the slow closing GluN2B produces more calcium influx. **i**, Same experiment as panel **d** but fixing GABA<sub>A</sub> maturation at P50 (inhibitory GABA<sub>A</sub>) which does not affect the FDP experiment. **j**, Mean synaptic weight change (%) for *Meredith et al. (2003)* single versus burst-STDP experiment for different ages. The data from Meredith (boxplots) were pooled by the age as shown in the x-axis. The solid line represents the mean, and the shaded ribbon the 2nd and 4th quantiles simulated by the model (same for panels **a-f**). **k**, Mean synaptic weight change (%) for *Inglebert et al. (2020)* STDP experiment in which the number of postsynaptic spikes increases. The x-axis marker from 14-21 indicates that only this interval was published without further specification. We use our model to estimate age related changes to *Inglebert et al. (2020)* protocols. Note that the model does not cover the 1Pre2Post10 properly (model predicts only outcomes near the first data quantile). Notice that single and burst STDP leads to LTD, meanwhile *Meredith et al. (2003)* lead to LTP or NC. **l**, Mean synaptic weight change (%) for *Tigaret et al. (2016)* STDP experiment which compares single versus burst STDP. The x-axis marker from 50-55 indicates that only a interval was published without further specification. We use our model to estimate age related changes to *Tigaret et al. (2016)* protocols. It is noticeable that each STDP experiment has a different development.



**Figure 6 - Supplement 1. |  $[\text{Ca}^{2+}]_o$  and  $[\text{Mg}^{2+}]_o$  related modifications for *Inglebert et al. (2020)* experiment. **a**, Mean time spent for anticausal pairing, 1Post1Pre10, at different Ca/Mg concentrations. The contour plots are associated with the *Figure 6a-c*. **b**, STDP and extracellular Ca/Mg. Synaptic weight change (%) for causal (1Pre1Post10, 100 at 0.3 Hz) and anticausal (1Post1Pre10, 150 at 0.3 Hz) pairings varying  $[\text{Ca}^{2+}]_o$  from 1.0 to 3 mM (Ca/Mg ratio = 1.5). **c**, Varying frequency and extracellular Ca/Mg for the causal pairing 1Pre1Post10, 100 at 0.3 Hz. Synaptic weight change (%) for a single causal pairing protocol varying frequency from 0.1 to 10 Hz.  $[\text{Ca}^{2+}]_o$  was fixed at 1.8 mM (Ca/Mg ratio = 1.5). **d**, Mean synaptic weight change (%) for *Inglebert et al. (2020)* STDP experiment showing how temperature qualitatively modifies plasticity. The dashed lines are plotted in panel **b**. **e**, Mean synaptic weight change (%) showing effects  $0.5^\circ\text{C}$  from panel **a**. Black and grey solid lines represent the same color dashed lines in panel **a** ( $30$  and  $30.5^\circ\text{C}$ ). The bidirectional curves, black and grey lines in panel **a** (dashed) and panel **b** (solid), becoming full-LTD when temperature increases to  $34.5$  and  $35^\circ\text{C}$ , respectively yellow and purple lines in panel **a** (dashed) and panel **b** (solid). Further increase abolishes plasticity. **f**, Mean synaptic weight change (%) for *Mizuno et al. (2001)* experiment in Mg-Free ( $[\text{Mg}^{2+}]_o = 10^{-3}\text{mM}$  for best fit) showing the different time requirements to induce LTP and LTD. For LTD, to simulate the NMDAr antagonist D-AP5 which causes a NMDAr partial blocking we reduced the NMDAr conductance by 97%. Note the similarity with *Figure 3-Figure Supplement 5f*. **g**, Mean synaptic weight change (%) of *Inglebert et al. (2020)* STDP experiment changing  $[\text{Ca}^{2+}]_o$  and Ca/Mg ratio. **h**, Mean synaptic weight change (%) of *Inglebert et al. (2020)* STDP experiment changing pre-post delay time and frequency. Note the similarity with *Figure 3-Figure Supplement 5c*. **i**, Mean synaptic weight change (%) of *Inglebert et al. (2020)* STDP experiment changing pre-post delay time and age. Age has a weak effect on this experiment done at  $[\text{Ca}^{2+}]_o = 2.5\text{mM}$ .**



**Figure 6 - Supplement 2. | Temperature and age effects.** **a**, Mean synaptic weight change (%) for *Wittenberg and Wang (2006)* STDP experiment for 1Pre1Post10, 70-100 at 5 Hz (see (*Table 1*)) showing a full LTD window. Our model also reproduces the data showing that when temperature is increased to 32 – 34°C LTD is abolished (data not shown). **b**, Mean synaptic weight change (%) for *Wittenberg and Wang (2006)* STDP experiment for 1Pre2Post10, 70-100 at 5 Hz (see (*Table 1*)) showing a bidirectional window. **c**, Mean synaptic weight change (%) for *Wittenberg and Wang (2006)* STDP experiment for 1Pre2Post10, 20-30 at 5 Hz (see (*Table 1*)) showing a bidirectional window. We noticed that for *Wittenberg and Wang (2006)* experiment, done in room temperature, the temperature sensitivity was higher than for other experiments. **d**, Core temperature varying with age representing the thermoregulation maturation. This function (not shown) was fitted using rat (*Wood et al., 2016*) and mouse data (*McCauley et al., 2020*) added by 1°C to compensate species differences (*Wood et al., 2016*). The blue and white bars represent the circadian rhythm as shown in *McCauley et al. (2020)*. However, the "rest rhythm" for young rats (P5-14) may vary. **e**, Dotted grey line represents the averaged physiological temperature at different ages in the rat (estimated from mean value of panel **d**). For the papers the we fitted by the model, we depict the range of temperature and age used. Note that only few experiments were performed at near physiological conditions. **f**, Initial conditions for CaN-CaMKII resting concentration for different [Ca<sup>2+</sup>]<sub>o</sub> and temperature values. When [Ca<sup>2+</sup>]<sub>o</sub> is changed, temperature is fixed at 35°C, while when temperature is changed, [Ca<sup>2+</sup>]<sub>o</sub> is fixed at 2 mM.

**Table 1 - Supplement 1.** Comparison of recent computational models for plasticity highlighting the experimental conditions implemented and the experiments in the hippocampus and cortex they reproduce. See *Table 1-Table Supplement 2* for additional details on experimental conditions of experimental works.

Model	<i>Graupner and Brunel (2012)</i>	<i>Ebner et al. (2019)</i>	<i>Jedrziewska-Szmek et al. (2017)</i>	<i>Inglebert et al. (2020)</i>	<i>Chindemi et al. (2020)</i>	<i>Rodrigues et al. 2021</i>
model framework	extension of Shouval et al. (2002)	extension of Clopath et al. (2010) and modified from Hoy et al. (2011)	modified from Evans et al. (2013)	extension of Graupner and Brunel (2012)	extension of Graupner and Brunel (2012)	
<b>Parameter</b>						
temperature	absent	absent	temperature corrected ion channels (but not receptors)	no temperature control needed (experiments covered are at 30°C)	only in the GHK equation	temperature is selectable on the dendritic spine level for ion channels, receptor and the calcium cascade
development	absent	absent	absent	absent	absent	age is selectable and implemented by GABA <sub>A</sub> and NMDAR switch and BaP maturation and External Ca and Mg
aCSF	absent	absent	absent	phenomenological changes in pre and post amplitudes to mimic extracellular calcium effects	in vivo or in vitro changes for release probability, calcium reversal potential on NMDAR-induced calcium influx	are selectable and affect release probability, reversal potential, NMDAR and VGCCs calcium current driving force
<b>Plasticity experiments reproduced (quant. comparisons only)</b>						
	X	X			X	X
<i>Sjöström et al. (2007)</i>	X					
<i>Wittenberg and Wang (2006)</i>	X					
<i>Wang et al. (2005)</i>	X					
<i>Sjöström and Häusser (2006)</i>	X					
<i>Nevejan and Sakmann (2006)</i>	X					
<i>Letzkus et al. (2006)</i>	X					
<i>Weber et al. (2016)</i>	X					
<i>Fino et al. (2010)</i>	X		X			
<i>Pawlak and Kerr (2008)</i>	X		X			
<i>Shen et al. (2008)</i>	X		X			
<i>Inglebert et al. (2020)</i>				X		
<i>Markram et al. (1997)</i>					X	
<i>Rodriguez-Moreno and Paulsen (2008)</i>					X	
<i>Egger et al. (1999)</i>					X	
<i>Tigaret et al. (2016)</i>					X	
<i>Dudek and Bear (1992)</i>					X	
<i>Dudek and Bear (1993)</i>					X	
<i>Mizuno et al. (2001)</i>					X	
<i>Meredith et al. (2003)</i>					X	
<i>O'Connor et al. (2005)</i>					X	
(not included due to space)					X	
<i>Bittner et al. (2017)</i>					X	
(not included due to space)					X	

**Table 1 - Supplement 2.** Comparison of the experimental conditions for the different reproduced datasets in *Table 1-Table Supplement 1* covering experiments from neocortex, hippocampus and striatum

Experimental work	Age (days)	[Ca <sup>2+</sup> ] <sub>o</sub> (Mm)	[Mg <sup>2+</sup> ] <sub>o</sub> (Mm)	Temperature (°C)
<i>Sjöström et al. (2001)</i>	12-21	2.5	1	32-34
<i>Wittenberg and Wang (2006)</i>	14-21	2	1	24-30 or 30-34
<i>Wang et al. (2005)</i>	embryonic day 17-18	3	2	room
<i>Sjöström and Häusser (2006)</i>	14-21	2	1	32-35
<i>Nevian and Sakmann (2006)</i>	13-15	2	1	32-35
<i>Letzkus et al. (2006)</i>	21-42	2	1	34-35
<i>Weber et al. (2016)</i>	49-77	1.25	1.3 or 0.1	32-35
<i>Fino et al. (2010)</i>	15-21	2	1	34
<i>Pawlak and Kerr (2008)</i>	19-22	2.5	2	31-33
<i>Shen et al. (2008)</i>	19-26	2	1	room
<i>Inglebert et al. (2020)</i>	14-20	1.3-3.0	Ca/1.5	30
<i>Markram et al. (1997)</i>	14-16	2	1	32-34
<i>Rodriguez-Moreno and Paulsen (2008)</i>	9-14	2	2	room
<i>Egger et al. (1999)</i>	12-14	2	1	34-36
<i>Tigaret et al. (2016)</i>	50-55	2.5	1.3	35
<i>Dudek and Bear (1992)</i>	35	2.5	1.5	35
<i>Dudek and Bear (1993)</i>	7-35	2.5	1.5	35
<i>Mizuno et al. (2001)</i>	12-28	2.4	Mg-Free (most experiments)	30
<i>Meredith et al. (2003)</i>	9-45	2	2	24-28
<i>O'Connor et al. (2005)</i>	14-21	2	1	27.5-32
<i>Bittner et al. (2017)</i>	42-63	2	1	35

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