The importance of stochastic signaling processes in the induction of long-term synaptic plasticity

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ABSTRACT

A stochastic model of the signaling network responsible for the induction of long-term depression (LTD) at the parallel fiber to Purkinje cell synapse is described. The model includes a PKC-ERK-cPLA$_2$ positive feedback loop and mechanisms of AMPA receptor trafficking. It was tuned to replicate calcium uncaging experiments that cause LTD. The ultrasensitive activation of ERK makes the signaling network activity bistable, causing either LTD or not. Therefore, in single synapses only two discrete stable states (LTD and non-LTD) can be expressed. The stochastic properties of the signaling network causes threshold dithering and probabilistic expression of LTD, which allows at the macroscopic level for many different and stable mean magnitudes of depression. When the volume of a single spine is simulated no thresholds for the calcium input signal are present. Such thresholds appear only when the volume of simulation is increased by a factor 100 or more and the model output is then bistable. Similarly, deterministic solutions of the same model show only bistable behavior. LTD induction requires activation of the PKC-ERK-cPLA$_2$ positive feedback loop but this activity is not constant: the activities of ERK and of cPLA$_2$ fluctuate strongly. This is much less the case for PKC which is more constantly activated and thereby promotes a stable output of the pathway.

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1. Introduction

Long-term forms of synaptic plasticity play an important role in most forms of learning (Feldman, 2009). Many processes involved in any form of synaptic transmission and plasticity are known to be stochastic, including neurotransmitter release, opening and closing of ionic channels, receptors and second messengers diffusion, activation and interaction of signaling molecules (Ribault, Sekimoto, & Triller, 2011). Nevertheless, stochastic aspects of synaptic function are ignored in most models of synapses and of their plasticity (Roth & van Rossum, 2009) or of the signaling pathways involved (Kotaleski & Blackwell, 2010). The few studies where stochastic effects were included in models of induction of cerebellar long-term depression (LTD) (Tanaka et al., 2007) or of long-term potentiation (LTP) in pyramidal neurons (Graupner & Brunel, 2007) assumed that the calcium signal triggering the induction of plasticity was the main source of noise.

In this review paper we examine the stochastic properties of the signaling pathways that cause cerebellar LTD (Ito, 2001, 2002). This form of plasticity is expressed at parallel fiber synapses onto spines on the Purkinje cell. The volume of these spines is about 0.12 $\mu m^3$ (Harris & Stevens, 1988) and the number of molecules of any species in such a tiny volume is very small. For example, at rest only few ions of calcium will be present in a spine. Therefore the reaction involving calcium are expected to be very stochastic and, as we will see, the same applies for all components of the signaling pathways involved in cerebellar LTD. This stochasticity has functional consequences. For example, when LTD is induced using the ‘physiological’ co-activation of climbing fiber and parallel fiber inputs, the amount of LTD induced varies tremendously (e.g. 5%–40%; Coe smans, Weber, De Zeeuw, & Hansel, 2004) and sometimes even fails completely (De Schutter, 1995). Considering that the LTD measured in typical electrophysiological experiments reflects the mean changes at hundreds of parallel fiber synapses, this suggests a strong variability of LTD expression at the level of single synapses.

In this modeling study we focused mostly on simulating a simpler protocol, the LTD induced by a rise of calcium concentration, because the properties of this system have been quantified in great detail experimentally (Tanaka et al., 2007) and allow for a systematic analysis.

2. Model

2.1. Positive feedback loop

Most forms of long-term synaptic plasticity are initiated by a short duration calcium signal in the spine which activates a
number of signaling pathways, leading to a much slower change in the postsynaptic number of AMPA receptors (AMPAR) (Feldman, 2009; Ito, 2002). In cerebellar LTD it was demonstrated with calcium uncaging methods that a 0.5 s rise of the calcium concentration is sufficient to induce LTD, which then takes 10–20 min to reach its maximum level of depression (Fig. 1(B)) (Tanaka et al., 2007). Bhalla and co-authors proposed that this mismatch in the duration of the input signal and the expression of synaptic plasticity can be explained by a positive feedback loop that is activated by the calcium signal, specifically the activation of a mitogen-activated protein kinase (MAPK) pathway based feedback loop (Bhalla & Iyengar, 1999; Bhalla, Ram, & Iyengar, 2002). The essential components of the corresponding feedback loop (Bhalla & Iyengar, 1999; Bhalla, Mikawa, & Hirai, 1999) which leads to their removal from the postsynaptic density (see Section 2.2) and the expression of LTD. But PKC also activates the MAPK feedback loop. Fig. 1(A) shows a highly simplified version of this feedback loop with many intermediary reactions removed for clarity. In Purkinje cells the relevant member of the MAPK family of enzymes involved with induction of LTD is called the extracellular signal-regulated kinase (ERK) (Ito-Ishida, Kakegawa, & Yuzaki, 2006). So PKC indirectly activates ERK, which in turn activates cPLA$_2$. cPLA$_2$ completes the feedback loop by producing arachidonic acid (AA), an activator of PKC. The PKC–ERK–cPLA$_2$ feedback loop has been extensively investigated in Purkinje cells, confirming its essential involvement in the initial induction of cerebellar LTD (Tanaka & Augustine, 2008). A detailed description of the PKC–ERK–cPLA$_2$ feedback loop in the model can be found in Antunes and De Schutter (2012).

Based on an earlier model of the MAPK feedback loop in hippocampal LTP (Bhalla & Iyengar, 1999), Kuroda, Schweighofer, and Kawato (2001) developed a model of cerebellar LTD that formed the basis of this study (Antunes & De Schutter, 2012). The new model was extensively updated and expanded to match more recent experimental data (Antunes & De Schutter, 2012).

2.2. AMPA receptor trafficking

The model explicitly simulates the trafficking of AMPAR that was not included in previous models (Bhalla & Iyengar, 1999; Kuroda et al., 2001). This allows to quantitatively match the model output with the experimental data that is expressed as a change of the AMPAR mediated synaptic current (Fig. 1(B)–(C)) (Antunes & De Schutter, 2012; Tanaka et al., 2007).

The phosphorylation of AMPAR by PKC leads to a reduction of their affinity for the glutamate receptor interacting protein (GRIP) in the postsynaptic density (Dong et al., 1997). This results in the unbinding of some of the phosphorylated AMPARs from GRIP and their diffusion out of the postsynaptic density into the spine and on into the dendritic shaft, where they are endocytosed (Wang & Linden, 2000). The model output is the change in the number of synaptic AMPAR, notice that this never drops to zero because a large fraction of AMPAR remains bound to GRIP.

2.3. Model implementation

The model is a large kinetic model of the signaling and trafficking network involved in the induction of cerebellar LTD. It contains 17 proteins plus calcium and AA in the volume of a Purkinje cell spine (Harris & Stevens, 1988) and simulates a total of 207 different reactions. Because of the small volume of spines the number of protein molecules simulated varies from 5 (for Raf, involved in activation of ERK) to 120 (for AMPAR). A complete description of all elements of the model was published previously (Antunes & De Schutter, 2012).

Many of the reaction parameters could be obtained from the literature (Antunes & De Schutter, 2012), but about one third of the parameters were not exactly known and had to be searched. The stochastic model was tuned to replicate in detail the quantitative relation between calcium inputs of different amplitudes and durations and the amount of induced LTD that was obtained in calcium uncaging experiments (Fig. 1(C)) (Tanaka et al., 2007). Matching these quantitative measurements, which are unique in the synaptic plasticity literature, together with the requirement that no spontaneous LTD occurs in the absence of calcium influx, imposed strong constraints on the stochastic model.

The AMPAR trafficking was implemented as a four compartmental model with diffusion simulated as a first order reaction (Antunes & De Schutter, 2012; Earnshaw & Bressloff, 2008).

A more complex model was constructed to simulate induction of LTD by co-activation of climbing and parallel fibers. This...
Fig. 2. LTD induced in the model when mathematically solved in different ways. A. Using the standard stochastic solution (Gillespie, 1977), the model produces graded LTD when the results of 156 simulation runs are averaged. Increasing the Ca$^{2+}$ concentration used to induce LTD leads to higher levels of stable LTD (color scale at the bottom). Increasing the duration of the Ca$^{2+}$ signal (from top to bottom panel as indicated) shifts this response curve so that lower [Ca$^{2+}$] induces LTD and maximal levels of LTD are reached faster. These features of the model accurately match quantitative measurements based on Ca$^{2+}$ uncaging experiments (Tanaka et al., 2007). B. Solving the same model deterministically (as a set of coupled ordinary differential equations) results in a very different outcome. The system behaves in a bistable manner: the Ca$^{2+}$ signal produces only non-LTD or maximal LTD, no stable intermediary levels of depression are obtained.

3. Probabilistic induction at bistable synapses

3.1. Stochastic and deterministic solutions of the model are different

Fig. 2(A) shows how the stochastic model replicates the calcium uncaging data of Tanaka et al. (2007) as summarized in Fig. 1(C). These plots show the mean response of the stochastic model, averaged over 156 runs. Each panel shows LTD induced by different amplitudes of the calcium input given for different signal durations that increase from top to bottom. One can observe a graded response to different amplitudes for all signal durations, but as the duration increases more amplitudes of calcium input lead to maximal LTD. This shift in the response curve was described by Tanaka et al. (2007) as a leaky integration of the calcium signal. Overall the model matches the graded response curves and time course of LTD induction quite accurately (Antunes & De Schutter, 2012).

In Fig. 2(B) we show the response of the same model for the same input conditions when it is solved deterministically. As mentioned in Section 1 this corresponds to how most models of synaptic plasticity are solved. Notice that the response of the model is now completely different and no longer matches experimental data. The deterministic response is bistable: either no LTD is induced – though a transient reduction of the number of AMPAR is often observed – or maximal LTD is induced. The graded response is no longer present, but there is still a shift in response of the model depending on calcium signal duration. In Section 3.4 the cause of these differences will be examined.

This strong difference between stochastic and deterministic solutions was unexpected and confirms the importance of solving signaling network models with a small number of molecules stochastically. These stochastic solutions should already be used during the model fitting phase, as was the case in this study.

3.2. In single spines the model response is bistable

In most experiments LTD is induced in many spines simultaneously, e.g. Tanaka et al. (2007) estimate that the uncaging stimulus activates hundreds of spines. A single run of the stochastic model can be considered to correspond to events in a single spine, assuming no interaction occurs between spines. When such single runs are analyzed (Fig. 3) a completely different picture emerges compared to the mean responses shown in Fig. 2. Fig. 3(A) shows in each panel multiple single run responses of the model to the same calcium signal, with increasing signal amplitude from panel to panel; it can be compared with the top panel of Fig. 2(A) which shows the mean response of the model to the same duration signal. As for the mean responses, low amplitude stimuli cause no LTD and all model responses are noisy fluctuations around the baseline number of AMPARs (top row of Fig. 3(A)). When the calcium signal amplitude increases a second type of response appears where full, maximal LTD develops (bottom row). Notice that for single runs there are only two types of responses – no LTD or maximal LTD – and either can occur for the stronger stimuli. The model therefore included, in addition to the above, voltage-gated calcium influx and Inositol 1, 4, 5-trisphosphate mediate calcium release from internal stores based on Doi, Kuroda, Michikawa, and Kawato (2005). The model was run using the STEPS simulator (Hepburn, Chen, Wils, & De Schutter, 2012) that implements the Stochastic Simulation Algorithm (Gillespie, 1977), but also allows for a deterministic solution of the same model. The model scripts and a table listing all reactions and parameters is available at ModelDB (http://senselab.med.yale.edu/ModelDB/ShowModel.asp?model=141270).
predicts that in single spines LTD induction is bistable as suggested previously (Tanaka et al., 2007): all or none, without any graded responses.

A similar bistable behavior is shown in Fig. 3(B): here the signal amplitude is constant over all panels but signal duration increases. Note also that, especially for large amplitude or long duration signals, failure of LTD is sometimes not immediate: in several runs the number of AMPARs initially declines moderately, but then returns to the baseline. Once LTD is induced, it is stable as observed in very long runs of the model lasting several simulated hours.

Figs. 2 and 3 show simulated responses to a brief cytoplasmic calcium stimulus, mimicking uncaging experiments (Tanaka et al., 2007). This raises the question whether the model shows similar behavior when synaptic stimulation is used instead. Fig. 4 shows the response to a standard LTD induction protocol consisting of repetitive joint activation of climbing fiber and parallel fiber synapses. Induction of LTD is slower but again the single run responses are bistable: LTD or no LTD.

Bistability of plasticity at single synapses has been reported in experimental studies of hippocampal LTP (O’Connor, Wittenberg, & Wang, 2005; Petersen, Malenka, Nicoll, & Hopfield, 1998) but, to our knowledge, not in cerebellar LTD. The model results shown in Figs. 3 and 4 demonstrate why it could be useful for LTD to be bistable: the number of AMPARs in the postsynaptic density is extremely noisy. This noise would make the distinct graded responses present in averages of hundreds of synapses indistinguishable at the level of a single spine. We propose that bistable synapses provide a more reliable detection of the presence of LTD at single synapses when the Purkinje cell integrates over many inputs. Note that the bistable synapses in our model differ considerably from the binary Purkinje cell synapses proposed by Brunel, Hakim, Isole, Nadal, and Barbour (2004), because bistable synapses never go to

**Fig. 3.** Single-run results of the model demonstrate that cerebellar LTD always happens as an all-or-none process. The properties of the input can only modulate the probability of LTD induction. Each color represents a different single run of the stochastic model. A. Effect of increasing amplitude of the Ca\(^{2+}\) signal used to induce LTD (indicated on each panel) for a constant duration of 1 s. B. Effect of increasing duration of the Ca\(^{2+}\) signal used to induce LTD (indicated on each panel) for a constant peak amplitude of 1.5 µM.
Fig. 4. Synaptic induction of LTD in the model. Single runs of the model when LTD is induced with a standard protocol (300 pairings of CF and PF stimulation at 1 Hz; Karachot et al., 1994). Similar to induction by elevating $[\text{Ca}^{2+}]$, the single run responses of the model are bistable: non-LTD or maximal LTD. When averaged over many runs classic LTD curves are produced (not shown).

zero, the number of AMPARs in the postsynaptic density jumps from about 120 to about 84.

3.3. Probabilistic induction of LTD

We have emphasized the bistability of responses in single synapses, but Fig. 3 shows another important property of the model: the induction of LTD is probabilistic. For a given calcium signal it is impossible to predict whether LTD will be induced or not in a single synapse, the amplitude and duration of the calcium signal only modulate the probability of maximal induction. When responses are averaged over many synapses the response amplitude will be proportional to this probability of induction (Antunes & De Schutter, 2012).

Fig. 5(A) shows another consequence of the probabilistic induction: there is no threshold of the (integrated) calcium concentration for LTD induction. One observes two clouds of points in this plot: the lower one corresponds to a failure of LTD, the higher one to successful LTD induction. Although these two clouds have slightly different ranges of calcium concentration, they mostly overlap horizontally and no threshold can be discerned. The lack of a calcium threshold for LTD induction has important consequences for imaging experiments: one cannot use single spine calcium imaging (Higley & Sabatini, 2008) to infer the induction of synaptic plasticity with certainty.

3.4. Model size influences stochasticity

The absence of a defined threshold for calcium is an example of threshold dithering. Threshold dithering is the consequence of noise that obscures the threshold in a bistable dynamical system (Gammanito, 1995) and has been observed frequently in noisy biological systems (Arkin, Ross, & McAdams, 1998; Simpson et al., 2009). One way to investigate this phenomenon is to reduce the noise in the model, which is most easily achieved by increasing the Biochemical Population Size (BPS) (Bhalla, 2004). Increasing BPS corresponds to making the simulated volume larger and thereby increasing the number of molecules in the model. As can be seen in Fig. 5, increasing from BPS₁ (the volume of a spine, Fig. 5(A)) to BPS₈ (8 times larger, Fig. 5(D)) causes a clear reduction of the noise in the responses and diminishes the overlap between calcium concentrations corresponding to the two states of the bistable system. Further increases of the BPS enhance these effects and by BPS₆₄ (Fig. 5(G)) an absolute threshold has emerged that separates the two states completely. To summarize, Fig. 5 demonstrates that there is an inherent relation between noise and the absence of a clear threshold, which is typical for threshold dithering in stochastic systems.

The phenomenon of threshold dithering also explains the difference between graded and bistable responses observed respectively for the stochastic and deterministic solutions of the model (Fig. 2). Mean responses of the model with BPS₆₄ or larger look very

Fig. 5. Single-run results showing the occurrence and failure of LTD in systems containing different biochemical population sizes (BPS₁–BPS₁₂₈) in response to different $\text{Ca}^{2+}$ signals (varying from 0 to 3.5 µM and from 0.5 to 30 s). LTD was measured as the percentage of AMPARs removed from the postsynaptic membrane. $\text{Ca}^{2+}$ signals were integrated over the duration of the signal to reduce noise. Systems containing small population sizes have a wide overlap between the integrated $\text{Ca}^{2+}$ signals that fail or succeed to induce LTD (BPS₁–BPS₈). Increasing the population size causes a narrowing of this overlap, but a defined threshold appears only when the population is enlarged more than 100 times its original size.
similar to the deterministic solutions shown in Fig. 2 (Antunes & De Schutter, 2012). The large noise affecting reactions in the volume of a single spine causes threshold dithering and makes the bistable system probabilistic, resulting in graded responses when averaged over many spines. Conversely, in a deterministic simulation the noise is absent and the responses reflect the underlying bistable nature of the system.

4. Stochastic network fluctuations are not uniform

4.1. The signaling network shows strong fluctuations

Till now we have focused on the stochastic relation between the triggering calcium signal and the amount of LTD induced. Next we analyze the activation of the three main components of the PKC-ERK-cPLA$_2$ feedback loop during LTD induction. In Fig. 6 four different runs of the model for the same input conditions are shown: in the upper panels LTD induction failed, while in the lower ones it was successful. When LTD fails a transient peak of PKC activation is present but it does not successfully activate the feedback loop, resulting in low ERK and cPLA$_2$ activities. This reflects the probabilistic activation described in Section 3 and it is clear that the amplitude of initial PKC activation is a poor predictor of LTD induction: initial peak activity of PKC is higher for both examples of LTD failure than for the ones where it succeeds (this is not systematically so: see Fig. 4(A) in Antunes & De Schutter, 2012 for the opposite relation). The differences in outcome are explained by microscopic differences of the chemical state of the model at the time of the calcium signal, which are being explored in more detail.

When LTD is induced the feedback loop becomes activated, but notice that this activation is not constant: the activity of all components fluctuates strongly. These fluctuations affect ERK and cPLA$_2$ much more than PKC. While the activation of PKC generally stays above 40%, those of ERK and cPLA$_2$ often drop close to zero and then rebound. The strong fluctuations of ERK and cPLA$_2$ are also strongly correlated with each other, but not with those of PKC (Antunes & De Schutter, 2012). Despite these strong fluctuations the activation of the feedback loop is persistent over time. This can be explained by the slow deactivation kinetics of PKC, sufficient PKC activation remains to restart the feedback loop if necessary.

4.2. LTD can be triggered by different stimuli

Experimentally, LTD can be induced by directly activating the PKC-ERK-cPLA$_2$ feedback loop, without raising the calcium concentration (Tanaka & Augustine, 2008). The signaling network model has similar properties. Fig. 7 shows the activation of the feedback loop by activated ERK (A) and by activated cPLA$_2$ (B), the inset shows the resulting LTD. The main difference with Fig. 6 is that the initial peak activation of PKC is now absent but otherwise the results look very similar, with ERK and cPLA$_2$ showing much stronger stochastic fluctuations than PKC.

When using activated components of the feedback loop to induce LTD no thresholds exists for the integrated signal, similar to the lack of a calcium threshold (Fig. 5) (Antunes & De Schutter, 2012). This finding indicates that the variability of the calcium signal is not the most important source of noise in the signaling pathway as suggested previously (Graupner & Brunel, 2007; Tanaka et al., 2007), but that the stochasticity is distributed over the whole pathway.

4.3. Stochastic fluctuations of ERK and cPLA$_2$ activity

Do the differences in the propensity for stochastic fluctuation observed in Figs. 6 and 7 play a functional role in the probabilistic induction of LTD? We have investigated this question using two different approaches. Here we show the coefficient of variability (CV, measured over 156 simulations during the entire time window after the stimulus) for the three components studied and how it relates to BPS (Fig. 7(C)). For the normal volume of BPS, the CVs of ERK and cPLA$_2$ are similarly high and much larger than that of PKC, as can be expected from their different fluctuations properties. As expected the CV decreases when BPS increases, but it does so much faster for PKC, which reaches a third of its original value at BPS$_{23}$, than for ERK and cPLA$_2$, where this happens only at BPS$_{32}$. The fact that the CV for ERK and cPLA$_2$ reaches low values only for BPS$_{64}$ where a real threshold appears in the model (Fig. 5), strongly suggests that their stochastic fluctuations play a major role in LTD induction.

Fig. 6. Temporal course of PKC, ERK and cPLA$_2$ activation during the induction of LTD. In the two upper panels LTD induction failed, while in the lower ones it was successful. The components of the signaling network present very distinct patterns of activation: large magnitude fluctuations in ERK and cPLA$_2$ sustain the activation of the network while PKC activation is more constant. LTD was induced by Ca$^{2+}$ pulses of 4 s and 2.0 µmol L$^{-1}$, applied at 10 min.
role in establishing the threshold dithering and the probabilistic induction of LTD.

A similar picture arises when the frequency ranges of the stochastic fluctuations are analyzed: ERK and cPLA$_2$ undergo systematically faster frequency stochastic fluctuations than PKC when the feedback loop is activated (Antunes & De Schutter, 2012). This suggests that feedback activation is robust for strong ERK and cPLA$_2$ fluctuations but not for similar sized PKC fluctuations. We investigated this with simulated perturbation experiments (Fig. 8). The simulation starts with successful activation of the feedback loop and induction of LTD but 10 min after the stimulus we impose a fast fluctuation of PKC, by repeatedly reducing its activation to zero for a brief time (black arrows). This PKC fluctuation shuts the feedback loop down and LTD fails (top panel). In the following three panels we investigate whether the feedback loop can be restarted by applying a short fluctuation in the activity of PKC, ERK or cPLA$_2$ (colored arrows). As predicted the network reacts very differently: a positive fast fluctuation of PKC activity cannot restart the feedback loop while a similar manipulation of ERK or cPLA$_2$ does result in LTD induction.

4.4. PKC and ERK are activated differently

In this section we have observed that ERK has quite different properties compared to PKC and suggested that this has a functional role in the signaling network that induces LTD. This cannot be explained by different number of molecules affecting their respective stochasticity because these are very similar in the model: 48 PKC molecules and 49 ERK molecules. But it can be explained by differences in their biochemical properties.

A critical property of ERK is the ultrasensitivity of its activation, which requires dual phosphorylation happening in a two-collision mechanism (Huang & Ferrell, 1996), causing it to respond strongly to suprathreshold inputs (Ferrell, 2002). Conversely, in the feedback loop PKC is activated by AA by a classic second-order reaction (O’Flaherty, 2001) which will reduce fluctuations (Antunes & De Schutter, 2012) and its deactivation is quite slow.

5. Conclusions

In this modeling study we firmly demonstrate that the stochasticity of signaling networks involved in synaptic plasticity is an essential property of these systems. Not only do stochastic and deterministic solutions of the same model behave very different (Fig. 2), but we have argued that the LTD expression at single synapses has to be bistable – which is an emergent property of the model – to compensate for the strong noise levels of the synaptic current (Fig. 3). Finally, the stochastic fluctuations in the signaling network (Fig. 6) generate threshold dithering (Fig. 5), which enables the system to reliably express graded LTD at the macroscopic level (averaged over many spines).
Based on manipulating the size of the system by changing the BPS we demonstrated that there is only a narrow window of spine sizes for which this network shows reliable graded LTD (about a factor 4 either way: Antunes & De Schutter, 2012), Decreasing size too much leads to a monostable system with always spontaneous LTD, while increasing it too much leads to bistable induction. Interestingly, spine sizes in Purkinje cells are quite constrained (Harris & Stevens, 1988) compared to those in pyramidial neurons (Harris & Stevens, 1989). One interpretation has been that this reflects the role of increased spine size in the induction of LTD in pyramidal neurons (Matsuzaki, Honkura, Ellis-Davies, & Kasai, 2004), compared to the absence of changes in spine size when cerebellar LTD is induced (Srdula & Linden, 2007). But here we give a different interpretation to the constrained spine size: it is necessary to ensure proper probabilistic functioning of the signaling network underlying LTD induction.

The probabilistic induction is supported by the structure of the network: the positive feedback loop and ultrasensitivity of ERK signaling network underlining LTD induction. The probabilistic induction is supported by the structure of the network: the positive feedback loop and ultrasensitivity of ERK signaling network underlining LTD induction. The probabilistic induction is supported by the structure of the network: the positive feedback loop and ultrasensitivity of ERK signaling network underlining LTD induction. The probabilistic induction is supported by the structure of the network: the positive feedback loop and ultrasensitivity of ERK signaling network underlining LTD induction. The probabilistic induction is supported by the structure of the network: the positive feedback loop and ultrasensitivity of ERK signaling network underlining LTD induction. The probabilistic induction is supported by the structure of the network: the positive feedback loop and ultrasensitivity of ERK signaling network underlining LTD induction. The probabilistic induction is supported by the structure of the network: the positive feedback loop and ultrasensitivity of ERK signaling network underlining LTD induction. The probabilistic induction is supported by the structure of the network: the positive feedback loop and ultrasensitivity of ERK signaling network underlining LTD induction.

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