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A Kinetic Model Unifying Presynaptic Short-Term Facilitation and Depression

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Abstract

Short-term facilitation and depression refer to the increase and decrease of synaptic strength under repetitive stimuli within a timescale of milliseconds to seconds. This phenomenon has been attributed to primarily presynaptic mechanisms such as calcium-dependent transmitter release and presynaptic vesicle depletion. Previous modeling studies that aimed to integrate the complex short-term facilitation and short-term depression data derived from varying synapses have relied on computer simulation or abstract mathematical approaches. Here, we propose a unified theory of synaptic short-term plasticity based on realistic yet tractable and testable model descriptions of the underlying intracellular biochemical processes. Analysis of the model equations leads to a closed-form solution of the resonance frequency, a function of several critical biophysical parameters, as the single key indicator of the propensity for synaptic facilitation or depression under repetitive stimuli. This integrative model is supported by a broad range of transient and frequency response experimental data including those from facilitating, depressing or mixed-mode synapses. Specifically, the theory predicts that high calcium initial concentration and large gain of calcium action result in low resonance frequency and hence depressing behavior. In contrast, for synapses that are less sensitive to calcium or have higher recovery rate, resonance frequency becomes higher and thus facilitation prevails. The notion of resonance frequency therefore allows valuable quantitative parametric assessment of the contributions of various presynaptic mechanisms to the directionality of synaptic short-term plasticity. Thus, the model provides the reasons behind the switching behavior between facilitation and depression observed in experiments. New experiments are also suggested to control the short-term synaptic signal processing through adjusting the resonance frequency and bandwidth.

Keywords

short-term depression/facilitation; transmitter release; frequency response; resonance frequency

Introduction

Homosynaptic short-term plasticity (facilitation or depression) which operates within the timescale of several seconds (Zucker and Regehr, 2002) is fundamental to some primary forms of nonassociative learning such as habituation and sensitization in invertebrates and in mammals (Byrne, 1982; Byrne and Kandel, 1996; Simons-Weidenmaier et al., 2006). These stimulus frequency-dependent synaptic processes have been linked to certain brain calculus or

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dynamic filtering computations that underlie a variety of brain functions and abnormalities (Fortune and Rose, 2001; Poon and Young, 2006). In cortical neurons, short-term plasticity provides a dynamic gain control mechanism for specific input firing rate to achieve the optimal synaptic transmission (Abbott et al., 1997; Tsodyks and Markram, 1997). Recently it has also been proposed as the underlying mechanism of working memory in neocortical networks (Mongillo et al., 2008).

Synapses at different locations may demonstrate distinct short-term plasticity responses appropriate for specific functional roles (Blitz et al., 2004). Also, parallel inputs to a target may express a balanced mixture of synaptic facilitation and depression such that a linear input-output relationship is maintained regardless of the input firing rate (Macleod et al., 2007). The relative balance between short-term facilitation and depression in some neural pathways may undergo developmental changes that alter the signal transfer characteristics of these pathways (Dekay et al., 2006). In some brain regions, neurons innervated by the same nerve bundle may express distinct short-term or long-term plasticity that is specific to the afferent inputs (Zhou et al., 1997).

Although both pre- and postsynaptic mechanisms may contribute to short-term plasticity, the preponderance of evidence indicates that postsynaptic effects are typically minor compared to presynaptic ones (Atluri and Regehr, 1996; Hashimoto and Kano, 1998; Zucker and Regehr, 2002). In particular, presynaptic vesicle trafficking is generally considered crucial in explaining short-term plasticity. For instance, the classic presynaptic vesicle depletion model is often used to follow depression dynamics (Thies, 1965; von Gersdorff et al., 1997; Wu and Betz, 1998) whereas calcium-dependent transmitter release is usually invoked to model facilitation (Yamada and Zucker, 1992; Bertram et al., 1996). These early studies considered facilitation and depression separately without integrating the common pathways they share. Yet more recent experimental data point out that these two phenomena are not completely independent (Stevens and Wang, 1995; Markram et al., 1998; Dittman et al., 2000).

Recently, there have been increasing efforts to develop integrative models that can unify the synaptic depression and facilitation data (Markram et al., 1998; Dittman et al., 2000). Markram et al. (1998) introduced a phenomenological model in which they describe the effects of action potentials on the utilization of synaptic efficacy and the subsequent recovery. Both depressing and facilitating responses can be explained by their model. Although mathematically simple, most of the model's abstract parameters such as absolute synaptic efficacy and utilization of synaptic efficacy are not experimentally measurable or physiologically well-defined. Dittman et al. (2000) proposed a comprehensive depression-facilitation model which incorporated detailed descriptions of the calcium dynamics involved in the transmitter release process. Yet the overall model complexity makes it difficult to interpret the effect of each model parameter on the excitatory response. Therefore, without extensive sensitivity analysis of model parameters, it is not straightforward to use the model to predict changes in short-term plasticity in new experiments.

Here, we present a general mathematical framework for presynaptic facilitation and depression based on first principles and established experimental data, with a view to pinpointing how specific biochemical parameters may contribute to the up- or down-regulation of synaptic strength. The proposed unified theory leads to a closed-form formula that parsimoniously predicts various forms of short-term synaptic plasticity with facilitation, depression, or mixed effects.

Model Development

Higher structure of the kinetic model

Figure 1A illustrates the principal biochemical pathways for excitatory neurotransmission at a glutamatergic synapse. Correspondingly, Figure 1B summarizes the model structure consisting of three parts: calcium buffering, vesicle trafficking, and postsynaptic first order delay. At first, presynaptic stimuli modulate calcium concentration through calcium buffering, which is represented by a first-order linear differential equation. Then neurotransmitter vesicle trafficking triggered by the surge of calcium concentration is modeled by a set of chemical kinetics nonlinear differential equations. Finally, a linear first-order delay equation is adopted to convert transmitter release to postsynaptic response. Corresponding model equations are presented in the following sections. All model equations and stimuli were implemented on Matlab® and Simulink® (The Mathworks, Natick, MA). Table 1 defines the nomenclature of symbols used.

Presynaptic calcium buffering

A classic mechanism of short-term facilitation is the buildup of presynaptic residual calcium and the resultant increase in neurotransmitter release (Katz and Miledi, 1968; Gingrich and Byrne, 1985; Atluri and Regehr, 1996). A first-order decay model is commonly used to relate calcium current I_{Ca} with intracellular calcium concentration Ca_i (Neher and Augustine, 1992; Dittman and Regehr, 1998):

$$\tau_{Cai}\frac{dCa_i(t)}{dt} = (-Ca_i + Ca_{i0}) + K_{Ca}I_{Ca} \approx (-Ca_i + Ca_{i0}) + K_{Ca}\sum_{k=1}^{N_p}\delta(t - t_k) \tag{1}$$

The intracellular calcium concentration starts at Ca_{i0} and is raised incrementally by each stimulus impulse, approximated herein by a Dirac Delta function δ(t) (Dittman et al., 2000; Richardson et al., 2005). The impact of each stimulus impulse to the intracellular calcium concentration is equal to the product of calcium gain and unit calcium current caused by action potential ($K_{Ca}I_{Ca}$). The calcium gain (K_{Ca}) is to convert the time series of spikes to the unit of concentration. Once the stimulus sequence ($k = 1, 2, \ldots, N_p$) ends, Ca_i decays with time constant τ_{Cai} toward Cai_0.

Presynaptic calcium-dependent vesicle trafficking

A vesicle depletion model with recovery has been variously proposed to describe the synaptic short-term depression process (Betz, 1970; Dittman and Regehr, 1998). According to this model, the active zone for transmitter release is either occupied by releasable vesicles (N_{rel}) or empty (N_{empty}):

$$\begin{aligned} &\text{Exocytosis:} \quad N_{rel} \xrightarrow{P_{rel}I_{Ca}} N_{\text{empty}} + n \cdot Glu \\ &\text{Recovery:} \quad N_{\text{empty}} \xrightarrow{k_{recov}} N_{rel} \end{aligned} \tag{2}$$

Upon stimulation, releasable vesicles discharge transmitters such as glutamate (*Glu*) and become empty after exocytosis. The occurrence of calcium current (I_{Ca}) triggers swift and sharp increase of local calcium concentration which is necessary for inducing exocytosis. Therefore, exocytosis is assumed to occur only during each stimulus impulse with release probability P_{rel} (Korn et al., 1984; Dittman et al., 2000; Thomson, 2000). The exocytosis process involves docking and priming of synaptic vesicle as well as fusion between the vesicle and membrane (Weimer and Jorgensen, 2003). Several presynaptic protein molecules such as

Munc13, Rab3, synaptotagmin, and kainate, have been suggested to mediate the calcium-dependent transmitter release (Fernández-Chacón et al., 2001; Rosenmund et al., 2002; Schlüter et al., 2006; Sun and Dobrunz, 2006). Meanwhile, empty vesicles are recycled and recover with rate constant k_{recov} (Betz, 1970; Matveev and Wang, 2000). Synaptotagmin has also been found to facilitate vesicle recycling (Weimer and Jorgensen, 2003).

The flux of glutamate release ($Flux_{Glu}$) is equal to the stoichiometric coefficient (n) times the reaction flux of exocytosis. The latter is equal to the number of releasable vesicles (N_{rel}) multiplied by exocytosis rate constant ($P_{rel}I_{Ca}$). Furthermore, N_{rel} is the product of two factors: the dimensionless ratio of releasable vesicles (R_{rel}) and the sum of empty and releasable vesicles (N_{total}). Hence,

$$\mathrm{Flux}_{Glu}=\frac{dGlu\,(t)}{dt}=nN_{rel}P_{rel}I_{Ca}=nN_{\mathrm{total}}R_{rel}P_{rel}I_{Ca} \tag{3}$$

Since N_{total} remains roughly constant within the timeframe of a few seconds (Kandel et al., 2000), Eq. (3) shows that $Flux_{Glu}$ is determined by two key variables: R_{rel} and P_{rel}. Initially, R_{rel} = 1 under the assumption that all vesicles are fully refilled at first. From Eq. (2), the time course of R_{rel} during stimulation depends on the difference between the recovery and exocytosis rates. The former term is equal to the fraction of empty vesicles (1-R_{rel}) multiplied by k_{recov} while the latter is the ratio of releasable vesicles (R_{rel}) times the exocytosis rate constant. Thus, the rate of change in R_{rel} can be expressed as:

$$\frac{dR_{rel}\,(t)}{dt}=k_{recov}\,(1-R_{rel})-P_{rel}I_{Ca}R_{rel} \tag{4}$$

As shown in Fig. 2B, R_{rel} starting from an initial value of unity decreases with time because of vesicle depletion caused by repetitive stimuli. It continues to fall until reaching the level where consumption is balanced by recovery.

The other variable, release probability P_{rel}, is dependent upon intracellular calcium concentration (Augustine, 2001). Evidence suggests that the binding of calcium ion to its sensor, synaptotagmin-1, is cooperative and obeys the Hill equation (Dodge Jr and Rahamimoff, 1967; Parnas and Segel, 1981):

$$P_{rel}=P_{rel,max}\frac{Ca_i^{n_{\mathrm{Hill}}}}{Ca_i^{n_{\mathrm{Hill}}}+K_{rel,1/2}^{n_{\mathrm{Hill}}}} \tag{5}$$-a

The value of Hill coefficient (n_{Hill}) was reported to be four on average which coincides with the number of binding sites of calcium on calmodulin (Katz and Miledi, 1968; Rozov et al., 2001). The parameter $P_{rel,max}$ denotes maximum release probability while $K_{rel,1/2}$ is the [Ca_i] that results into half regular release probability.

In addition, asynchronous release has been reported to occur at certain types of synapses such as the calyx of Held (Sun et al., 2007) and the cultured hippocampal neurons (Goda and Stevens, 1994; Otsu et al., 2004) as another mode of transmitter release. It is the persistent and miniature vesicle release in response to residual calcium after high-frequency stimulation. Compared to regular (or phasic) release, the amplitude of asynchronous release is smaller but decays slower. Also asynchronous release is low in its cooperativity to calcium and therefore, becomes relatively apparent at low calcium concentration. To account for this phenomenon, Eq. (5)-a

can be modified by adding an asynchronous release term, P_{asyn}, to the regular release probability (Otsu et al., 2004). The parameter $P_{asyn,max}$ denotes maximum asynchronous release probability while $K_{asyn,1/2}$ is the corresponding calcium sensitivity. The hyperbolic function and power order n_{asyn} for asynchronous release are used in instead of the Hill equation to reflect the low cooperativity to calcium.

$$P_{asyn}=P_{asyn,max}\left(\frac{Ca_i}{Ca_i+K_{asyn,1/2}}\right)^{n_{asyn}} \quad (5)\text{–b}$$

Repetitive stimulation of presynaptic neurons was found to elicit steady-state excitatory postsynaptic current (EPSC) larger than those expected from the above depletion model (Kusano and Landau, 1975; Byrne, 1982; von Gersdorff et al., 1997). To rectify this discrepancy, the idea of calcium-dependent recovery was proposed (Dittman et al., 2000). The simple hyperbolic function and ligand binding kinetics are used here to describe the dependence of recovery rate constant on residual calcium. As shown in Eq. (6), the value of rate constant k_{recov} drops to k_{recov0} when Ca_i is small, and approaches $k_{recov,max}$ when Ca_i greatly exceeds the affinity constant $K_{recov,1/2}$. Recent findings showed that recovery rate dependence on intracellular calcium can be highly nonlinear. In that case, it would be required to apply a Hill equation in which the Hill coefficient needs to be determined by experimental data (Matveev and Wang, 2000; Hosoi et al., 2007).

$$k_{recov}=k_{recov0}+(k_{recov,max}-k_{recov0})\frac{Ca_i}{Ca_i+K_{recov,1/2}} \quad (6)$$

Postsynaptic response

EPSC responses to presynaptic transmitter release are commonly modeled by a first-order decay equation (Destexhe et al., 1994; Dittman et al., 2000) below. In Eq. (7), K_{Glu} is the gain of EPSC per unit glutamate flux and τ_{EPSC} is the EPSC decay time constant.

$$\tau_{EPSC}\frac{dEPSC(t)}{dt}=-EPSC-K_{Glu}\mathrm{Flux}_{Glu} \quad (7)$$

So far we have formulated the end response, EPSC, as a function of time in a set of ordinary differential equations (ODEs). To get the transient response of EPSC under the influence of presynaptic stimuli, either the analytical solution (Dittman et al., 2000) or ODE solver can be used. The later is chosen because it is easier to implement without compromising in accuracy. This way we can focus more on deriving the analytical solution for the frequency response in the following section.

Results

Based on the above dynamic model of synaptic transmission, we derived an analytical solution to predict the postsynaptic plasticity response with respect to varying frequency of stimulation. The experimental data for model validation came from the calyx of Held in brainstem, parallel fibers to cerebellar Purkinje cells, and neocortical pyramidal cells.

Analytical Solution of Stimulation Frequency-Dependent Plasticity

Stimulation frequency-dependent synaptic plasticity has long been recognized (Thies, 1965; Zucker, 1989). Previous modeling studies have used physiologically complete but

mathematically less intuitive expressions to describe this phenomenon (Dittman et al., 2000). A more tractable approach is to consider the impulse-by-impulse moving time-averaged (instead of instantaneous) values of all state variables and solve for the resultant steady-state EPSC as a function of stimulation frequency. This simplification allowed our derivation of a closed-form solution that clearly delineates the key determinants of short-term synaptic plasticity.

Steady-state EPSC as an explicit function of stimulation frequency—Since the EPSC caused by a stimulus impulse is proportional to the corresponding glutamate flux (Eq. (3)), the steady-state *EPSC* at any stimulation frequency *r* ($EPSC_{ss}(r)$) can be rewritten as:

$$EPSC_{ss}(r) \propto \text{Flux}_{Glu,ss}(r) \quad \text{per stimulus impulse} = nN_{\text{total}} \cdot P_{rel,ss}(r) \cdot R_{rel,ss}(r) \tag{8}$$

where $P_{rel,ss}(r)$ and $R_{rel,ss}(r)$ are the steady-state values of P_{rel} and R_{rel} at stimulation frequency *r* and nN_{total} is the total quantity of releasable glutamate. Both $P_{rel,ss}$ and $R_{rel,ss}$ are functions of the steady-state time averaged intracellular calcium concentration $Ca_{i,ss}$.

Since the typical experimental method for measuring stimuli dependent frequency response is to apply regular stimuli trains to the synapse and to record the response level after it reaches the steady state, we only consider steady state values when dealing with frequency responses. Moreover, the calcium level can be viewed as the sum of two terms: "time averaged" term and "oscillatory" term. As shown in Fig. 2A, the calcium level oscillates around the "time averaged" term which is representative and relatively easy to calculate. The time average value of $Ca_{i,ss}$ is derived by setting the left hand side of Eq. (1), i.e. time derivative of Ca_i, equal to zero and solving the remaining algebraic equation. Hence, from Eq. (1) and Eq. (5) we obtain $P_{rel,ss}(r)$ as:

$$\begin{aligned} Ca_{i,ss}(r) &= \bar{I}_{Ca} \cdot K_{Ca} + Ca_{i0} = r \cdot K_{Ca} + Ca_{i0} \\ P_{rel,ss}(r) &= \frac{P_{rel,max} \cdot Ca_{i,ss}(r)^{n_{\text{Hill}}}}{Ca_{i,ss}(r)^{n_{\text{Hill}}} + K_{rel,1/2}^{n_{\text{Hill}}}} = \frac{P_{rel,max} \cdot \left(r \cdot K_{Ca} + Ca_{i0}\right)^{n_{\text{Hill}}}}{\left(r \cdot K_{Ca_i} + Ca_{i0}\right)^{n_{\text{Hill}}} + K_{rel,1/2}^{n_{\text{Hill}}}} \end{aligned} \tag{9}$$

where $\bar{I}_{Ca}$ (see Fig. 2A) is the steady-state average calcium current influx, i.e., the steady-state moving time-average of the unitary current resulting from each stimulation impulse. Then $\bar{I}_{Ca}$ can be replaced by *r* since the average value is equal to one divided by the period. Eq. (9) happens to be the first order approximation of the more rigorous expression of steady state calcium $Ca_{i,ss}(r) = Ca_{i0} + K_{Ca}\left[\tau_{Ca}\left(1 - \exp\left(-1/r\tau_{Ca}\right)\right)\right]^{-1}$ which could be derived by equating the calcium gain caused by each spike to the calcium decay over time period 1/r (Dittman et al., 2000). While the exact solution of exponential decay is applicable specifically to regular spike train, Eq. (9) is valid for estimating synaptic responses under either regular or random spike train stimulation at moderate to high frequencies.

We calculated release probability by using steady state average $Ca_{i,ss}$ which is slightly different from the minimum Ca_i before the arrival of the next spike used in the literature (Dittman et al., 2000). In terms of the value, the steady state average calcium lies between the minimum level right before the spike and the maximum level after the spike. We adopted average $Ca_{i,ss}$ instead for simplicity while keeping the algorithm physiologically reasonable. Within very narrow time windows, action potentials trigger the calcium concentration to rise steeply from its minimum level to maximum level. The calcium rising above the base level may still elicit further exocytosis, due to its fast reaction rate with the transmitter release proteins (Schneggenburger and Neher, 2000). Whether calculating the release probability by the

average or by the base calcium level would be more reasonable depends on the response time of specific transmitter release proteins to the instantaneous calcium influx.

Then the ratio of vesicles releasable at steady state, $R_{rel,ss}$, can similarly be derived from Eq. (4) by setting its left hand side equal to zero at steady state as follows:

$$\begin{aligned} & k_{recov,ss}(r)\cdot(1-R_{rel,ss})-P_{rel}R_{rel}\bar{I}_{Ca}=0 \\ \therefore \quad & R_{rel,ss}(r)=\frac{k_{recov,ss}(r)}{k_{recov,ss}(r)+P_{rel,ss}(r)\bar{I}_{Ca}}=\frac{k_{recov,ss}(r)}{k_{recov,ss}(r)+P_{rel,ss}(r)\cdot r} \end{aligned} \tag{10}$$

where $k_{recov,ss}(r)$, the steady-state value of k_{recov}, is obtained by plugging $Ca_{i,ss}(r)$ into Eq. (6). The typical time course of R_{rel} is shown in Fig. 2B with steady state value labeled according to Eq. (10).

By substituting Eqs. (9) and (10) into Eq. (8), we obtain the following closed-form expression for the steady-state EPSC as an explicit function of stimulation frequency r:

$$EPSC_{ss}(r)=\left(\frac{(r\cdot K_{Ca}+Ca_{i0})^{n_{\mathrm{Hill}}}+K_{rel,1/2}^{n_{\mathrm{Hill}}}}{P_{rel,max}\cdot(r\cdot K_{Ca}+Ca_{i0})^{n_{\mathrm{Hill}}}}+\frac{r}{k_{recov,ss}(r)}\right)^{-1} \tag{11}$$

Resonance stimulation frequency as an explicit function of physiological parameters—The steady-state EPSC is proportional to the product of $P_{rel,ss}(r)$ and $R_{rel,ss}(r)$ as suggested in Eq. (8). In general, $P_{relss}(r)$ tends to increase with stimulation frequency whereas $R_{reslss}(r)$ decreases as a result of vesicle depletion. Therefore, the steady-state EPSC should exhibit a maximum at some resonance frequency $r_{resonance}$ like a bandpass filter (Izhikevich et al., 2003). This resonance frequency can be found by taking the derivative of $EPSC_{ss}(r)$ from Eq. (11) with respect to stimulation frequency and setting the resultant equal to zero:

$$\left.\frac{\partial EPSC_{ss}(r)}{\partial r}\right|_{r_{\mathrm{resonance}}}=0 \tag{12}$$

The detailed mathematical derivation was executed by using Symbolic Toolbox of Matlab®. The resultant closed-form solution is:

$$r_{\mathrm{resonance}}=\frac{-Ca_{i0}}{K_{Ca}}+\left(\frac{n_{\mathrm{Hill}}K_{rel,1/2}^{n_{\mathrm{Hill}}}\cdot k_{recov}}{K_{Ca}^{n_{\mathrm{Hill}}}\cdot P_{rel,max}}\right)^{\frac{1}{1+n_{\mathrm{Hill}}}} \tag{13}$$

The above analytical formula is valuable in that though simple, it indicates whether a synapse tends to depress or facilitate at any stimulation frequency. The reason is that resonance frequency is the optimal stimulation frequency that elicits maximal excitatory response so a high resonance frequency indicates growing response with respect to frequency, i.e., facilitation while the opposite condition suggests depression. It also reveals the functional influences of various physiological parameters on short-term plasticity. The validity of Eqs. (11) and (13) is further tested in the following by comparison with experimental data for short-term facilitation, depression or mixed effects.

Facilitating synapses

A canonical experimental model of paired-pulse facilitation is found in the cerebellar parallel fiber (PF) connections to Purkinje cells (Atluri and Regehr, 1996). Dittman et al. (2000) applied stimuli of varying frequencies to the parallel fibers and recorded the resultant time- and frequency-dependent postsynaptic responses, both of which can be explained by our unified model.

Fig. 3A demonstrates good agreement between experimental and simulated responses in normalized EPSC as a function of stimulation frequency. Fig. 3B shows the corresponding frequency dependence of P_{rel} and R_{rel}. Note that for frequencies below 40 Hz, substantial growth in release probability with increasing residual calcium outweighs the loss of releasable vesicles as stimulation frequency is increased.

Fig. 3C shows the transient EPSC caused by 10 presynaptic spikes delivered at 50 Hz as found experimentally and closely matched by the model. The growing EPSC amplitude is explained by the simulated P_{rel} and R_{rel} vs. time in Fig. 3D. Specifically, rising calcium concentration during stimulation leads to increasing release probability, hence presynaptic facilitation. The upward trend continues until around 120 ms where this is offset by a concomitant decrease in releasable vesicles, and the EPSC levels off.

A single set of parameter values used for generating facilitation responses (Fig. 3A-Fig. 3D) are included in Table 2. The values of parameters were estimated by minimizing the sum of squared errors between the model and data. The parameter values are the minima of the feasible region defined as the response space reachable by positive parameter values. The initial recovery rate constant (2.2×10^{-2} ms^{-1}) and initial calcium concentration (4.7 μM) for Fig. 3 are in the same order of magnitude as those reported in the literature (Dittman et al., 2000;Augustine, 2001). The predicted low initial release probability (0.06) and high recovery rate contribute to the presynaptic facilitation of Purkinje cells under repeated stimuli.

Depressing synapses

The calyx of Held has been widely used for studying short-term depression (Augustine, 2001). In contrast to early experiments on neuromuscular junctions (Del Castillo and Katz, 1954), calyx of Held synapses in rat brainstem slices showed higher steady-state EPSC responses than predicted by simple depletion models (von Gersdorff et al., 1997) — a phenomenon which has been attributed to calcium-dependent recovery (Dittman et al., 2000). With our unified model, the set of parameter values listed in the [depression] column in Table 2 was used to generate the transient and frequency responses at the Calyx of Held by using Eq (3) – Eq. (7) and Eq (8) – Eq. (11), respectively.

In Fig. 4A, the steady-state EPSC decreases with frequency due to significant depletion of the pool of releasable vesicles with high-frequency stimuli, as demonstrated in Fig. 4B. Even though the release probability grows with frequency, it is not significant enough to counteract the loss of releasable vesicles. In conclusion, the high initial release probability of the vesicle pool (0.46) and its slow recovery (1.0×10^{-4} ms^{-1}) contribute to the depression behavior in calyx of Held. Fig. 4C shows the temporal synaptic depression of the calyx of Held from experiment and simulation for 30 impulses of 10 Hz. The temporal depression can be explained by Fig. 4D where the releasable pool is seen to decrease dramatically (from 1.0 to 0.2) during stimulation with little corresponding increases in release probability (from 0.44 to 0.57). The relatively high initial release probability reflects the high sensitivity of calcium sensor in the calyx of Held. Our estimated value of $K_{rel,1/2}$ is as low as 4 μM which is close to the value (10 μM) reported previously (Südhof, 2004).

While depletion of vesicle pools is considered as the principal mechanism, short-term depression at the calyx of Held may be attributed to other reasons as well. According to the review of the calyx of Held, other mechanisms include the inactivation of presynaptic calcium current and changes in action potential waveform (von Gersdorff and Borst, 2002). The model proposed here can accommodate these mechanisms as well. For instance, the calcium currents triggered by each stimulus in Eq. (3) and (4) have been considered constant. Yet it is possible to model time-varying calcium influx to take into account the waveform change in action potential. Also the dependence of release probability on calcium current can be modified into a time-dependent function as suggested in previous studies (Xu and Wu, 2005).

Synapses with mixed facilitation-depression effects

The dendrites of neocortical pyramidal neurons receive excitatory and inhibitory synaptic inputs and play an important role in integrating the input signals selectively (Ulrich, 2002). Many of these excitatory synapses demonstrate maximal excitatory postsynaptic potential (EPSP) at varying frequency ranges. Thus, each synapse of a single neuron behaves like a bandpass filter with its own natural resonance frequency so that presynaptic spikes of the same frequency may result in differing amplitude modulation via different synapses (Izhikevich et al., 2003). The mechanism underlying such a resonance effect may be related to frequency-dependent transition between facilitation and depression (Markram et al., 1998). For this reason, pyramidal cells provide an excellent model system for studying mixed synaptic effects and signal filtering (Holmgren et al., 2003).

The experiment data were derived from sagittal slices containing pyramidal neurons in the somatosensory cortex of Wistar rats (Markram et al., 1998). The experimental transient response (Fig. 5C) and frequency response data (Fig. 5A) at pyramidal neurons were fit with the parameter values listed in the [mixed] column in Table 2, using Eq. (3) – Eq. (7) and Eq. (8) – Eq. (11), respectively. The corresponding releasable vesicle ratio (R_{rel}) and release probability (P_{rel}) are shown in Fig. 5B and Fig. 5D, respectively. The transient response demonstrates facilitation under stimulus frequency of 30Hz because of growing release probability shown in Fig. 5D. Some parameter values listed in Table 2 such as the recovery rate constant and resonance frequency are in agreement with experimental values. First, the recovery rate constant k_{recov0} (7.5×10^{-3} ms^{-1}) is fairly close to the value of 7.7×10^{-3} ms^{-1} obtained by taking the inversion of recovery time constant of 130 ms reported by Markram et al. (Markram et al., 1998).

The corresponding frequency response of both experimental and simulated steady-state EPSP (Fig. 5A) shows a resonance frequency peak at ~25 Hz, in close agreement with that predicted by Eq. (13). The resonance effect is due to the opposing trends of the amount of available vesicles and the release probability with varying stimulation frequency. In addition to the resonance frequency, the bandwidth is another metric that characterizes synapses as filters. The commonly used half-power (or −3dB) bandwidth is defined as the range of stimulation frequency where the EPSP amplitude is at least 71% of the maximum. Below this pass band, stimuli of low frequency do not cause sufficient calcium ion influx to maintain the initial release of neurotransmitters. At the high-frequency end, the repetitive stimuli further drain the vesicle pools without sufficiently enhancing release probability such that the EPSP amplitude decreases with stimulation frequency. The bandwidth may vary with respect to several biophysical parameters. These potential phenomena are further discussed in the “Previous experimental results explained and new experiments suggested” section.

Discussion

Determinants of short-term plasticity

We have presented a unifying model that summarizes how some presynaptic factors independently and collectively influence the directionality of short-term plasticity. The resonance frequency, a function of several critical biophysical parameters, is the single key indicator of the propensity for synaptic facilitation or depression under repetitive stimuli. Since it is the optimal stimulation frequency that elicits maximal excitatory response, a high resonance frequency indicates facilitation whereas a low resonance frequency suggests depression in the normal range of stimulation frequencies as labeled in Fig. 6. Thus, our analytical solution of resonance frequency as shown in Eq. (13) is valuable in assessing the contributions of specific or multiple biophysical parameters to short-term synaptic plasticity.

The parameters influencing resonance frequency include initial calcium concentration (Ca_{i0}), gain of calcium (K_{Ca}), recovery rate constant (k_{recov}), and calcium sensitivity for release ($K_{rel,1/2}$). From Eq. (13), the resonance frequency decreases monotonically with Ca_{i0} and grows with $K_{rel,1/2}$ and k_{recov}. To better visualize the independent effect of each parameter on the resonance frequency, two 2-D perturbation plots are made by varying one independent variable at a time around the condition given in Fig. 5. To demonstrate the combined effects of model parameters on the resonance frequency, two 3-D multivariate perturbation plots were also obtained by varying two parameters simultaneously. As shown in Fig. 6A and 6B, high Ca_{i0} and high K_{Ca} result in low resonance frequency and a tendency for depression. The reason is that both these factors contribute to high initial release probability (P_{rel0}). This is consistent with the general consensus that high initial release probability predisposes to depletion of vesicles and depression (Betz, 1970;Schneggenburger et al., 2002). The causal relationship between utilization of synaptic efficacy (i.e., high basal release probability) and depression was also suggested by Markram et al., 1998. Fig. 6C and 6D shows that facilitation prevails as the value of k_{recov} gets larger. Synapses with higher recovery rate constants are less likely to get depressed because their releasable vesicles are recycled quickly after stimuli. This coincides with the hypothesis that smaller recovery time constants lead to higher resonance frequency and thus, facilitation (Markram et al., 1998). On the other hand, based on Fig. 6B, depression arises at the low half occupancy concentration, $K_{rel,1/2}$, which indicates high calcium sensitivity of transmitter release. That is, synapses with releasable vesicles very sensitive to calcium tend to experience saturation of P_{rel}. Since further calcium inflow cannot elicit stronger transmitter release, they get depressed easily. The predicted trend agrees with previous finding that the depressing calyx of Held is fairly sensitive to intracellular calcium (Augustine, 2001).

Simply stated, the directionality of short-term plasticity depends on the amount of vesicle release caused by each action potential relative to the vesicle recovery rate. As a result, high initial release probability (P_{rel0}) and low recovery rate (k_{recov}) cause depression; opposite conditions may bring facilitation. The initial release probability itself is influenced by calcium concentration and calcium release sensitivity. The estimated parameter values (Table 2) from various depressing and facilitating synapses support the concept. First, comparing the initial release probability (P_{rel0}) indicates how rapidly vesicles are consumed. Depressing synapses (calyx of Held) have a much higher value (0.46) than facilitating synapses (PF to Purkinje). In addition, facilitating synapses with recovery rate constants as high as $0.022 ms^{-1}$, refill their vesicle pools faster than depressing ones. For synapses demonstrating clear-cut short-term tendencies, this kind of direct comparison is straightforward. However, for synapses that are more ambivalent or those that express mixed-mode facilitation-depression depending on the stimulation frequency, integrative models incorporating critical biophysical parameters such as presently proposed are needed to quantitatively predict the tendency of synaptic plasticity.

Previous experimental results explained and new experiments suggested

It is theoretically possible to alter tendency of short-term plasticity by adjusting the parameter values in the kinetic model. Recent studies have validated the possibility of reversing short-term facilitation and depression by manipulating the expression of some presynaptic proteins. For instance, Han et al. (2006) compared the expression of hippocampal short-term plasticity in RGS2 (regulator of G protein signaling 2) knockout and wild-type mice. Since RGS2 downregulates presynaptic Ca^{2+} channel inhibition, RGS2 deprivation would leave less calcium flowing into the presynaptic terminal after each impulse, i.e., smaller K_{Ca}. Our model predicts that synapses with smaller K_{Ca} tend to facilitate (Fig. 6A), which coincides with the experimental trend (Han et al., 2006). Similarly, Sippy et al. (Sippy et al., 2003) switched rat hippocampal synapses from pair-pulse depression to facilitation by increasing expression of neuronal calcium sensor-1 (NCS-1). Since more calcium sensors means that a higher calcium concentration is required to saturate the calcium binding proteins, i.e., higher $K_{rel,1/2}$, our model predicts that the latter should lead to facilitation (Fig. 6B), which matches the experimental findings.

In addition to changing resonance frequency, we hypothesize that the bandwidth of the frequency response can be altered by adjusting the values of biophysical parameters. New experiments can be performed to confirm this hypothesis. Based on Eq. (11), the frequency response depends on several parameters governing calcium-dependent release. To explore this relationship, perturbation analysis was performed around the condition of Fig. 5A to obtain parameter dependent frequency response surfaces with resonance frequency and bandwidth labeled (Fig. 7A and Fig. 7B). The result of Fig. 7A suggests the sharpening effects of higher intracellular calcium concentration gain per action potential (K_{Ca}) on the bandwidth of frequency response. Thus, a byproduct of intracellular calcium regulation may be the modulation of selectivity in short-term synaptic signal processing. Fig. 7B demonstrates the broadening effects of higher recovery rate constant (k_{recov0}) on the frequency response. That is, fast recovery rate would expand the bandwidth and increase synaptic transmission efficacy. If these hypotheses are validated by new experiments in which K_{Ca} and k_{recov0} can be manipulated to reproduce Fig. 7, Eq. (11) and Eq. (13) can serve as the working equations for controlling and designing the desired properties of short-term synaptic signal processing.

The time averaged expressions of intracellular calcium concentration and release probability as functions of stimulation frequencies in Eq. (9) are applicable to either regular or random spike train at medium-to-high frequencies. On the other hand, the exact solution of frequency dependent synaptic response in previous study (Dittman et al., 2000) was developed specifically for regular spike trains. Under physiological conditions, neuronal activities and spiking events tend to be stochastic rather than regular. Therefore, the time averaged expressions in this study are especially useful for exploring consequences of irregular simulation. For instance, it has been proposed that special temporal patterns beside the rate of stimulation are influential to the efficacy of synaptic signal transmission (Markram et al., 1998;Fuhrmann et al., 2002). Moreover, stochastic resonance, the phenomenon of enhanced signal transmission by noise addition can be another direction of short-term plasticity research. New experiments can be performed to confirm whether the existence of noise would shift resonance frequency value suggested in Eq. (13) or elevate the optimal amplitude of the synaptic response in Eq. (11).

Comparison with previous models

Table 3 summarizes the attributes of this kinetic model in comparison with previous ones. In early studies (listed in the bottom two rows of the table), the classic presynaptic vesicle depletion model was used to follow depression dynamics (Thies, 1965;Wu and Betz, 1998) while calcium-dependent transmitter release was considered to model facilitation (Yamada and

Zucker, 1992;Bertram et al., 1996). Since these models treated facilitation and depression separately, the number of experimental data that can be fit by each model was limited and an expression of resonance frequency could not be derived.

Models capable of describing both facilitation and depression are listed in the second category of Table 3. The reduced form of our resonance frequency model matches the results obtained in the theoretical model by Markram et al., 1998. Since their model did not take into account the nonlinear relationship between release probability and calcium concentration, the Hill coefficient is approximately one. Given a Hill coefficient equal to one and initial calcium concentration negligible compared to calcium inflow caused by stimulation ($Ca_{i0} << K_{Ca}$), the reduced form of Eq. (13) becomes $r_{\text{resonance}} = \sqrt{K_{rel,1/2} k_{recov} / K_{Ca} P_{rel,max}}$. The resonance frequency expression proposed was $r_{\text{resonance}} = \sqrt{1/U \cdot \tau_{facil} \cdot \tau_{rec}}$ in which U was utilization of synaptic efficacy, τ_{facil} and τ_{rec} are the time constant of facilitation and recovery from depression, respectively. They considered U partly or completely determined by the probability of release which is P_{rel} in this model. The recovery rate constant (τ_{rec}) corresponds to the inverse of k_{recov} in this model.

In addition to the agreement, three important features distinguish our kinetic model from the other two facilitation-depression models (Markram et al., 1998; Dittman et al., 2000). First, our model is based on biophysical descriptions with measurable physiologic parameters, as opposed to the phenomenological efficacy utilization model. Biophysical models like ours are experimentally testable and can direct future experiments for controlling short term plasticity. Second, a systematic approach was taken to describe the underlying biochemical reactions in order to explain a broad range of experimental data. By combining previous work with new physiological insights, we were able to integrate more sets of experimental data (in both frequency and time domains of three different synapses) than any previous models. Third, mathematical simplicity was maintained throughout model development to keep the model tractable. The simple and tractable model description makes possible a comprehensive closed-form mathematical solution of the resonance frequency that allows multivariate prediction of short-term plasticity and its dependence on several key biophysical parameters.

In conclusion, compared to previous phenomenological and biophysical models that attempted to integrate experimental data of facilitation and depression, our model is based on essential physiological reaction schemes with closed-form mathematical expressions. The overall model is more tractable than complex computer simulations while being more physiology-based and predictive than abstract phenomenological descriptions.

Limitations of the model

Model applicability is limited by several simplifying assumptions made. First, the model is deterministic and does not include the stochastic nature of the process. That is, the average profiles of the biochemical species are modeled instead of individual molecules. Since most of the species considered exist in large amount, this assumption is justified. Yet the downside of simple deterministic approach is that the probabilistic distribution of possible outcomes cannot be calculated. In order to estimate the range of possible responses, especially in cases with only small number of molecules, stochastic modeling is necessary.

Second, the assumption of spatially homogeneous intracellular calcium is a simplification. In fact there are many intracellular organelles such as mitochondria and endoplasmic reticulum that can store and release calcium. In addition, the calcium concentration is highly localized and there can be significant calcium concentration gradients within the cytoplasm (Augustine, 2001; Rizzuto and Pozzan, 2006). The first-order delay equation used to model calcium buffering effects only takes into account the loss of total calcium by diffusion and pumping.

Therefore, its validity is limited to the intracellular calcium near release sites within a short period of time. In order to extend the model to address pre- or post-synaptic long-term potentiation and depression, a detailed description of the spatiotemporal effects of calcium signal transduction would be necessary. Multiple resonance frequencies might arise because of different calcium binding rate constants.

Finally, we have mainly considered presynaptic vesicle depletion and residual calcium (Xu et al., 2007) yet postsynaptic reactions may also influence short-term plasticity. For instance, the desensitization of postsynaptic receptors causes depression (Trussell et al., 1993) and activation of postsynaptic calcium channels might increase synaptic strength (Akopian and Walsh, 2002). To distinguish the pre- and postsynaptic effects, in addition to tracking EPSCs and EPSPs, measuring the dynamic response of neurotransmitter release may be necessary.

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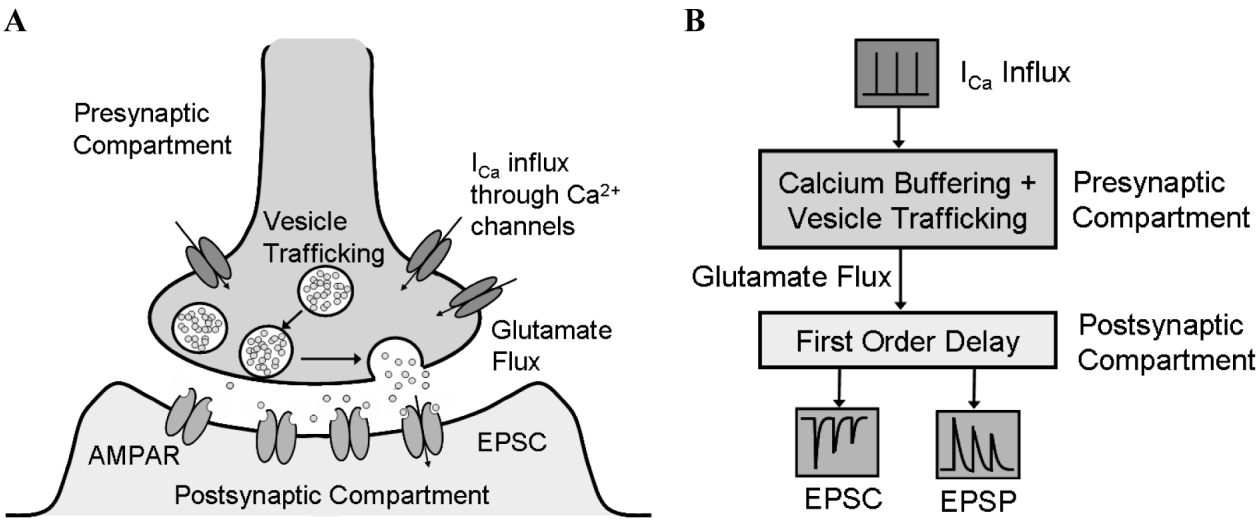

Figure 1.

A, The simplified structure of generic synaptic junctions and signal transmission pathways involved. AMPAR stands for α-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid receptor; EPSC is excitatory postsynaptic current. B, The summary of the model structure with signal transduction from presynaptic compartment to postsynaptic compartment in series.

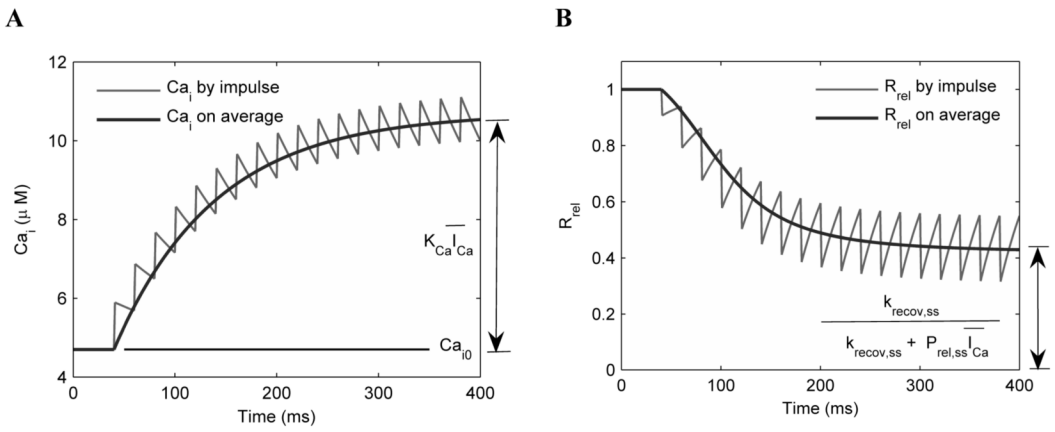

Figure 2.

The instantaneous time courses of key biophysical variables caused by impulses (zigzag lines). Also the average time courses are represented by the smooth curves. A, An example of intracellular calcium concentration (Ca_i) time course. B, an example of releasable vesicle ration (R_{rel}) time course.

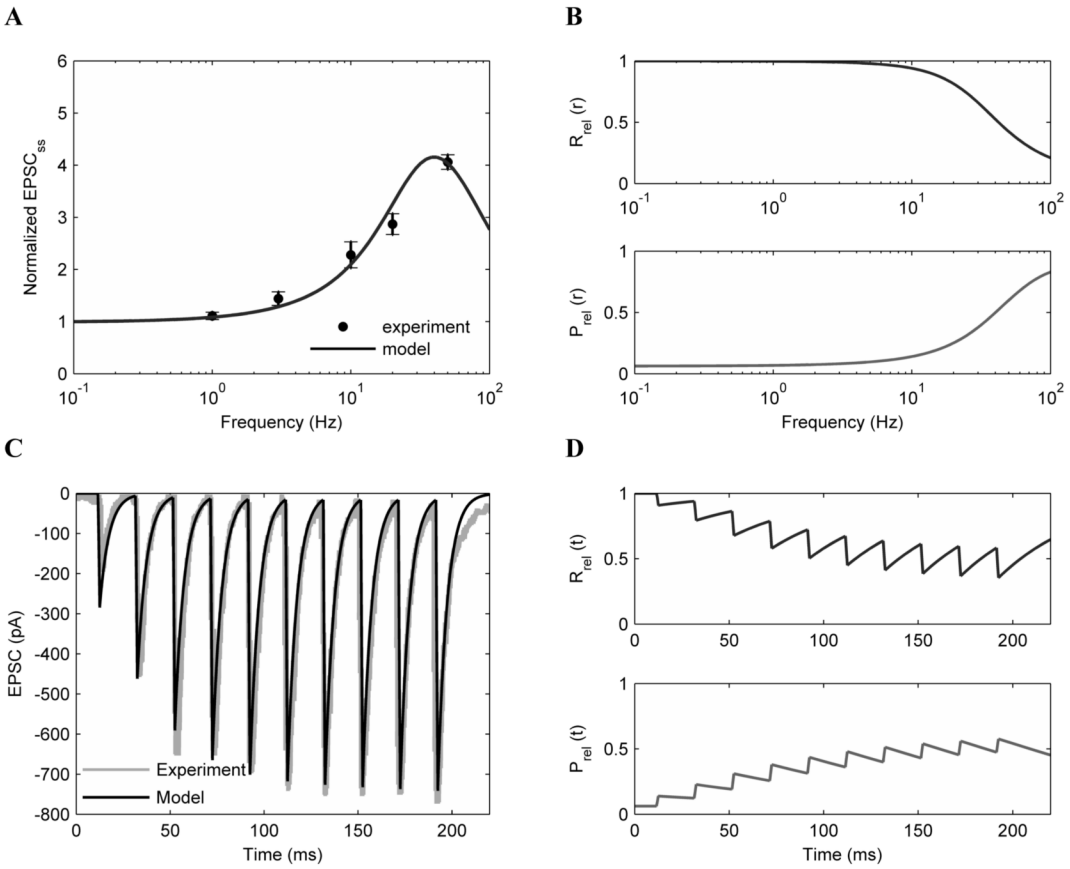

Figure 3.

Facilitation in the rat parallel fiber to Purkinje cell synapse. A, The frequency response of EPSC. Data are shown as mean ± standard error of the mean (SEM). B, The frequency response of vesicle ratio and release probability by model. C, The transient EPSC caused by stimuli at 50 Hz. D, The corresponding transient releasable vesicle ratio and release probability by model. Data source: (Dittman et al., 2000).

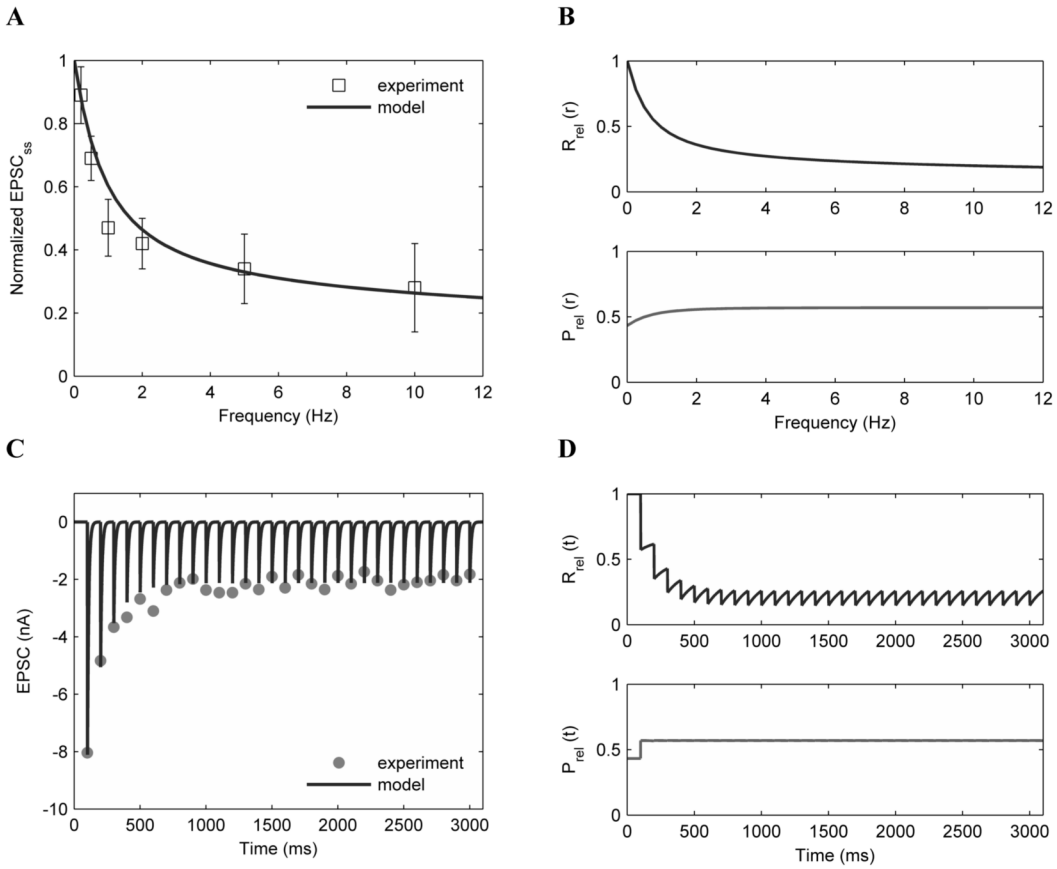

Figure 4.

Responses of depressing synapses. A, The frequency response of EPSC in the rat calyx of Held synapse. Data are shown as mean ± standard error of the mean (SEM). B, The frequency response of vesicle ratio and release probability by model. C, The transient EPSC caused by stimuli at 10 Hz in the rat calyx of Held synapse. D, The corresponding transient releasable vesicle ratio and release probability by model. Data sources: (von Gersdorff et al., 1997).

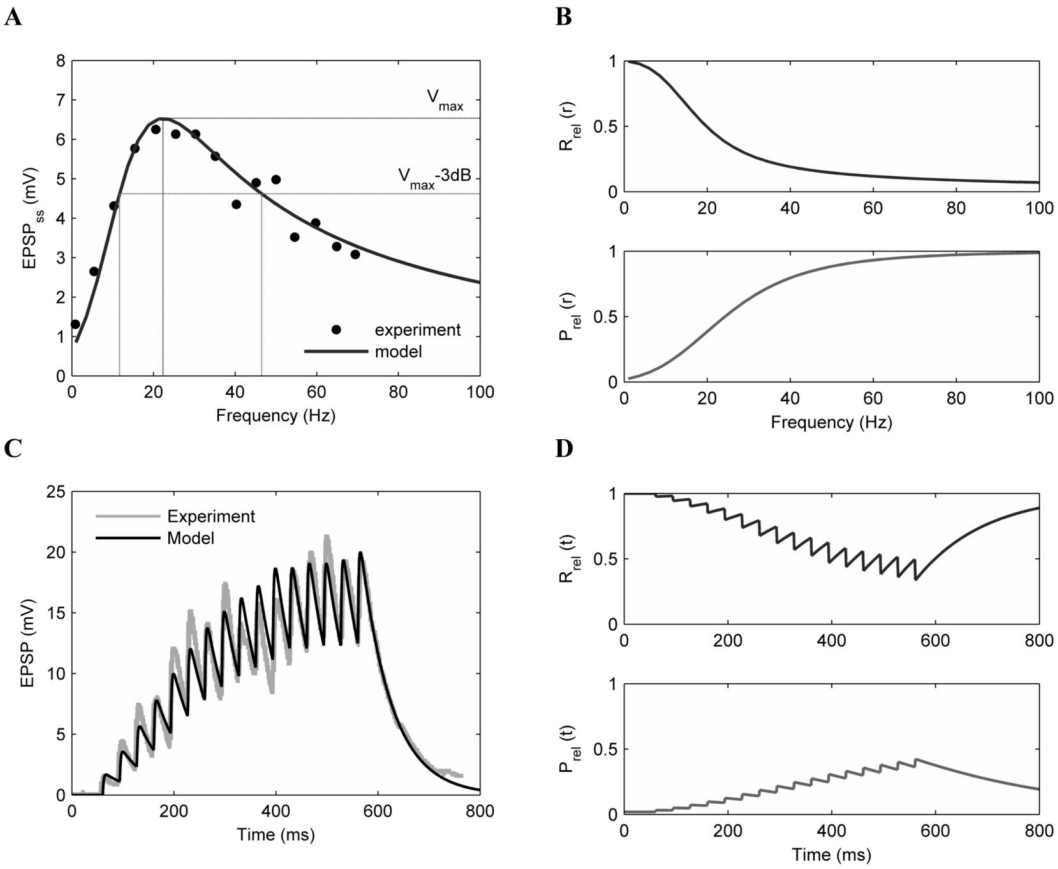

Figure 5.

Synaptic plasticity in rat pyramidal neurons under mixed effects. A, The EPSP as a function of frequency, with maximum and bandwidth labeled. B, The frequency response of releasable vesicle ratio and release probability by model. C, The transient EPSP caused by stimuli at 30 Hz. D, The corresponding transient releasable vesicle ratio and release probability by model. Data source: (Markram et al., 1998).

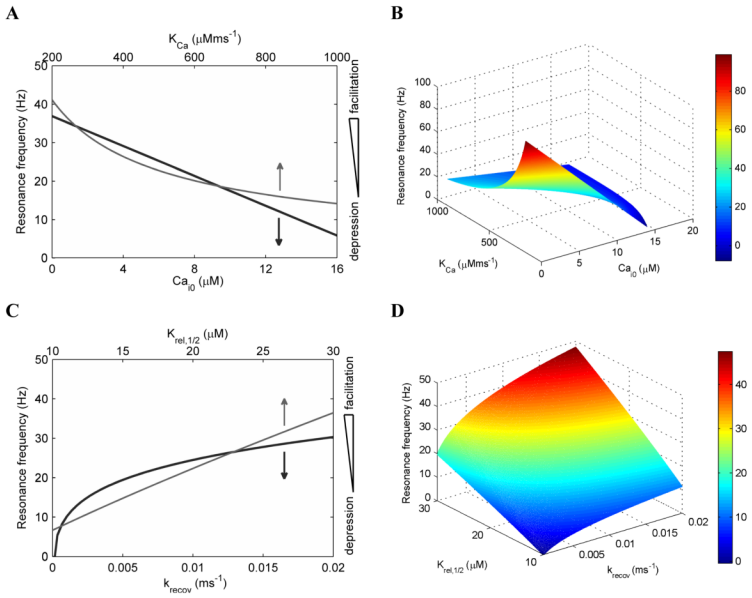

Figure 6.

Perturbation analysis of resonance frequency as a function of various physiological parameters based on Eq. (13). The vertical arrows indicate the x-axis that each curve belongs to. The color bars indicate the value of resonance frequency at the synapse. A, The 2-D plot of resonance frequency against initial calcium concentration and gain of calcium current to concentration. B, The 3-D plot of resonance frequency against initial calcium concentration and gain of calcium current to concentration. C, The 2-D plot of resonance frequency against recovery rate constant and calcium sensitivity. D, The 3-D plot of resonance frequency against recovery rate constant and calcium sensitivity.

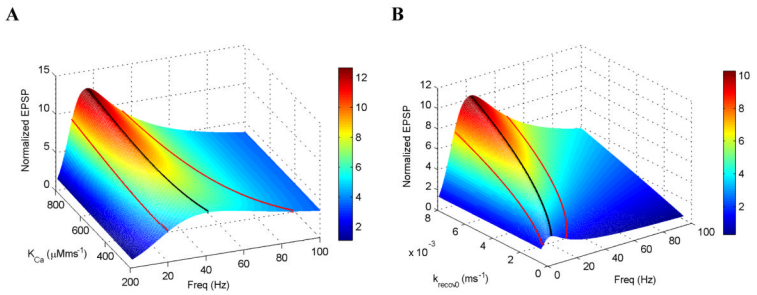

Figure 7.

Frequency response surfaces constructed by changing physiological parameters based on Eq. (11). The center line indicates the resonance frequency and the lines on the both sides label the half-power bandwidth (−3dB). A, The frequency response as a function of concentration gain per action potential (K_{Ca}). B, The frequency response as a function of initial recovery rate constant (k_{recov0}).

Table 1

Nomenclature of symbols

Symbols	Units	Definitions
Ca_i	μM	Intracellular calcium concentration
Ca_{i0}	μM	Initial intracellular calcium concentration after resting
$Flux_{Glu}$	# ms^{-1}	The flux of glutamate release
Glu	#	The number of glutamate molecules as neurotransmitter
I_{Ca}	Hz	Inflow calcium current as Dirac Delta function
$K_{asyn,1/2}$	μM	Calcium sensitivity regarding asynchronous release
k_{recov}	ms^{-1}	Recovery rate from empty to releasable state
k_{recov0}	ms^{-1}	Initial recovery rate from empty to releasable state
$k_{recov,max}$	ms^{-1}	Maximum recovery rate from empty to releasable state
$k_{recov,ss}$	ms^{-1}	Steady state recovery rate from empty to releasable state
K_{Ca}	μMs^{-1}	Intracellular calcium concentration gain per action potential
K_{Glu}	μMs^{-1}	Glutamate concentration gain caused by influx of glutamate
$K_{rel,1/2}$	μM	Calcium sensitivity regarding transmitter release
$K_{recov,1/2}$	μM	Calcium concentration giving one half recovery rate
n	#	Number of glutamate released per vesicle
n_{asyn}	-	Power coefficient of asynchornous transmitter release
n_{Hill}	-	Hill coefficient of transmitter release caused by calcium
N_p	#	Number of stimulus impulses
N_{rel}	-	Number of vesicle releasable at active terminals
N_{empty}	-	Number of empty vesicle at active terminals
N_{total}	#	Total number of vesicle per synaptic terminal
P_{asyn}	-	Probability of asynchronous release
$P_{asyn,max}$	-	Maximum probability of asynchronous release
P_{rel}	-	Probability of release
$P_{rel,0}$	-	Initial probability of release
$P_{rel,max}$	-	Maximum probability of release
$P_{rel,ss}$	-	Probability of release at steady state
r	Hz	Frequency of stimuli
$r_{resonance}$	Hz	Resonance frequency of stimuli that causes max responses
R_{rel}	-	Remaining ratio of vesicles releasable
$R_{rel,ss}$	-	Remaining ratio of vesicles releasable at steady state
τ_{Cai}	ms	Time constant of calcium buffering
τ_{EPSC}	ms	Time constant of EPSC decay

Table 2

Model parameters for different synapses. The values of parameters were estimated by minimizing the sum of squared errors between the model and data. The parameter values are the minima of the feasible region defined as the response space reachable by positive parameter values.

Parameters	Definitions	Units	PF to Purkinje (Facilitation)	Calyx of Held (Depression)	Pyramidal neurons (Mixed)
Ca_{i0}	Initial calcium concentration	μM	4.7	5.3	7.5
k_{recov0}	Initial recovery rate constant	ms^{-1}	2.2×10^{-2}	1.0×10^{-4}	7.5×10^{-3}
$k_{recov,max}$	Maximum recovery rate constant	ms^{-1}	2.2×10^{-2}	6.6×10^{-3}	7.5×10^{-3}
K_{Ca}	Gain of calcium	$\mu M ms^{-1}$	120	2130	515
$K_{rel,1/2}$	Calcium sensitivity of transmitter release	μM	9.0	4.0	20
$P_{rel,max}$	Maximum release probability	-	0.9	0.6	1
$^{\ddagger}P_{rel0}$	Initial release probability	-	0.06	0.46	0.02
$^{\dagger}r_{resonance}$	Resonance frequency	Hz	39.9	≤0	22.3

Note: other common parameters that have the same values across different types of synapses include $n_{Hill} = 4$ and $K_{recov,1/2} = 20$ μM.

$^{\ddagger}P_{rel0}$ is the initial release probability from substituting estimated parameters into Eq. (5) and

$^{\dagger}r_{resonance}$ is the resonance frequency calculated by using Eq. (13).

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Table 3

Model comparison of this kinetic model with respect to previous ones in terms of several key attributes

	Model type	Underlying Mechanism	Model complexity	Data modeled	Expression for resonance frequency
Kinetic model unifying facilitation and depression	biophysical	calcium-dependent vesicle trafficking	moderate	Six data sets of facilitation, depression & mixed plasticity in time and freq.	available
Synaptic efficacy utilization model (Markram et al., 1998)	phenomeno-logical	utilization of synaptic efficacy	simple	Two data sets of mixed short-term plasticity in time and freq.	available
Facilitation, depression, and residual calcium model(Dittman et al., 2000)	biophysical	calcium-dependent facilitation and depression	complex	Three data sets of facilitation & depression in freq.	unavailable
Facilitation model (Yamada and Zucker, 1992; Bertram et al., 1996)	biophysical	enhanced facilitation by residual calcium	simple	Several data sets of facilitation	unavailable
Depression model (Thies, 1965; von Gersdorff et al., 1997; Wu and Betz, 1998)	biophysical	vesicle depletion	simple	Several data sets of depression	unavailable