5 Modeling Long Term Plasticity

Long term synaptic plasticity refers to the modification of synaptic strength lasting longer than hours or days. It is generally accepted as the principal mechanism underlying learning and memory. Thus, its abnormality is suspected to cause dementia, and other memory-related neurological diseases. Bistable biomolecular switches have been proposed as the prerequisite conditions for inducing long lasting neuronal connectivity. We have developed a calcium entrapment model that includes the interacting dynamics of NMDA receptors, calmodulin kinase, and protein phosphotase. The model was sufficient to explain the induction of long term plasticity by tetanus stimuli without incorporating any bistability component. In addition, spike timing dependent and frequency dependent plasticity can be explained by the elevated level of calcium concentration in postsynaptic compartment.

Long term potentiation (LTP) and depression (LTD) are generally regarded as the principal mechanism underlying learning and memory. Most synapses show LTP or LTD which can last for more than hours after tetanus stimuli are applied and removed. They involve multiple pathways with different time scales so more complexity is added to the postsynaptic reaction schemes as shown in Fig. 2.

5.1 Current understanding of long term plasticity

There are hypotheses explaining the long lasting change in synaptic strength after high frequency stimuli. Most of these studies suggested that bistable switch is a necessary mechanism to long lasting change [1, 9, 11]. The reaction schemes proposed usually involve MAPK (mitogen-activated protein kinase) and PKC (protein kinase C) pathways. The bistable switches require precise tuning of the species concentrations. There exist only two levels of steady state response: one at the initial concentration and the other at an elevated level corresponding to another steady state. Yet this kind of response does not reflect the fact that many responses of the long term potentiation are graded.

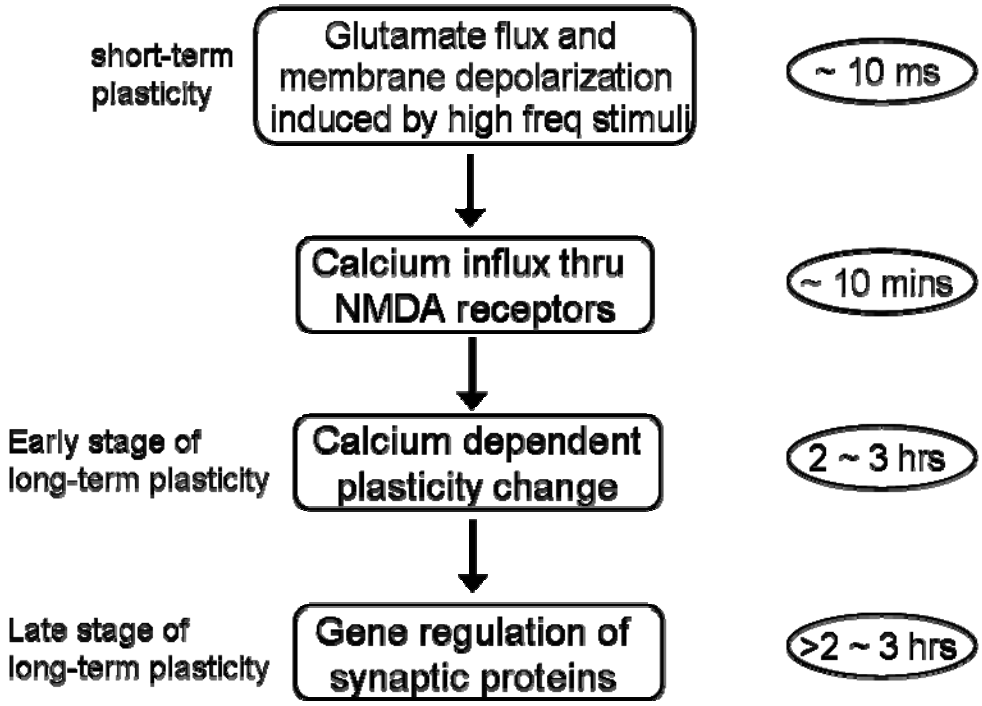

Figure 5-1 The overview diagram of short-term and long-term plasticity

5.2 Brief review on bistable models

Bistability in general indicates a phenomenon that something can rest stably in one of the two equilibrium states. An example graphical representation is shown in Figure 5-2A generated from a quadratic function. At steady state, an object will be located in either one of the two concaves.

5.2.1 Bistability in mathematics

Mathematically a function is bistable if there exist two stable states (minimum points) separated by the energy barriers (saddle points). The general formula of ordinary differential equations is $\underline{x}' = \underline{f}(\underline{x})$ on which steady state analysis can be performed to determine the stability. The initial conditions are crucial to determine the final resting state of the system. Also both the duration and amplitude of stimuli need to be considered in predicting the equilibrium state.

For instance, the following quadratic function demonstrates bistable behavior. $V(x)$ is the potential function and varies with position variable x as depicted in Figure 5-2B.

$$V(x) = -\frac{a}{2}x^2 + \frac{b}{4}x^4 \tag{1.1}$$

We can perform the steady state analysis by taking the derivative of Eq. (1.1) and factorizing the function. The location of the minimum points x_{min} can be found at $+\sqrt{a/b}$ and $-\sqrt{a/b}$ with the corresponding amplitude of the barrier ΔV equal to $a^2/4b$.

$$V'(x) = bx^3 - ax = b \cdot x \cdot \left(x^2 - \frac{a}{b} \right) = b \cdot x \cdot \left(x + \sqrt{\frac{a}{b}} \right) \cdot \left(x - \sqrt{\frac{a}{b}} \right) \tag{1.2}$$

A B

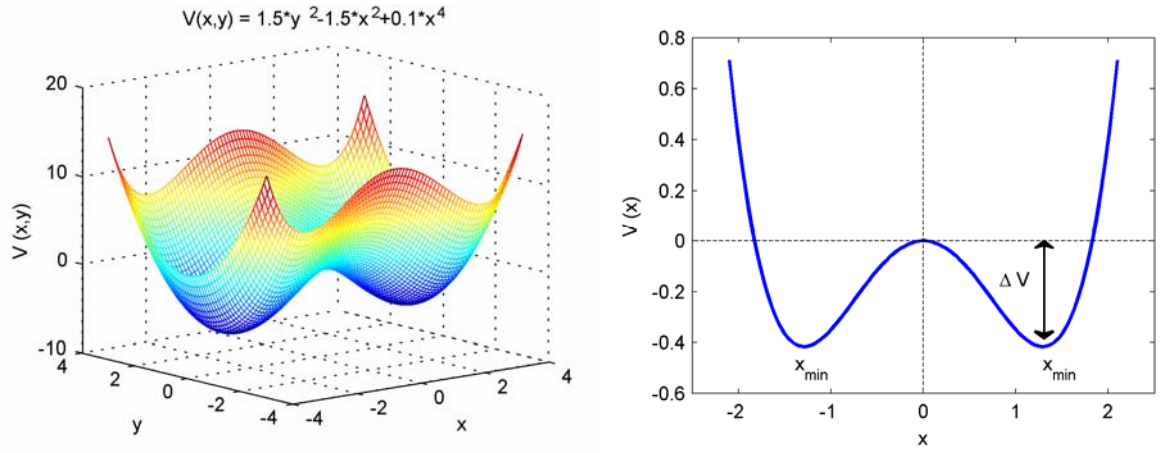

Figure 5-2 Potential responses of generic bistable functions. (A) The 3-D plot of a quadratic bistable function. (B) The 2-D plot of the function.

5.2.2 Bistability in biology

The bistable switch has been found in several biological systems and in most cases, positive feedback is the necessary condition. In this section, we include two example systems: one involves gene translation regulated by a DNA binding protein acting as activator [5] and the other is an example of signal transduction [11]. Yet the model expressions of these two systems eventually boil down to very similar mathematical formulation. First, as shown in Eq. (1.3) and Figure 5-3A, the activator is stimulated linearly by signal S and is degraded following first order reaction. Also it activates the gene translation through second order Hill equation where K_A is ligand concentration producing half occupation. The fixed values of parameters used in their research were: $k_1 = 1$, $k_2 = 1$, $k_3 = 1$, $n = 2$, $K_A = 1$, and $k_{inact} = 0.01$. With the differential equation defined and values of parameters fixed, can be integrated and analyzed later to get the bistable responses.

$$\frac{d[activator]}{dt} = k_1 S - k_2[activator] + \frac{k_3[activator]^n}{K_A{}^n + [activator]^n} \tag{1.3}$$

A B

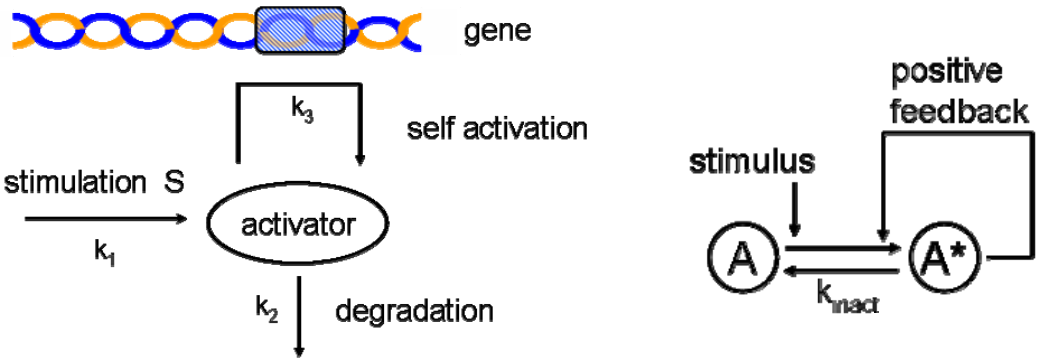

Figure 5-3 Examples of bistable systems in biology. (A) The system of gene translation. (B) The system of molecular signaling.

The second example is the molecular signaling with positive feedback loop as in Figure 5-3. According to the model by Xiong and Ferrell, 2002, the enzyme A is assumed to exist in two forms: active (A^*) and inactive (A) with the total concentration equal to A_{total}. The external stimulus can trigger the conversion from A to A^*; also the active form of enzyme degrades back to inactive form following first order kinetics. There is also positive feedback action by A^* to trigger more of its own production which can be modeled by n-th order Hill equation. Overall the rate of change in A^* based on material balance is shown in Eq. (1.4).

$$\frac{dA^*}{dt} = stimulus \cdot (A_{total} - A^*) + V \cdot \frac{A^{*n}}{K_A{}^n + A^{*n}} - k_{inact} A^* \qquad (1.4)$$

After the rearrangement, the ordinary differential equation becomes Eq. (1.5) which is very similar in formulation with Eq. (1.3). Therefore, we use Eq. (1.3) only in analyzing the bistability response to avoid redundancy.

$$\frac{dA^*}{dt} = stimulus \cdot A_{total} - (k_{inact} + stimulus) \cdot A^* + V \cdot \frac{A^{*n}}{K_A{}^n + A^{*n}} \qquad (1.5)$$

Two kinds of analyses are usually done to check the bistability of a given system: one is the stimulus-response analysis and the other involves checking the steady state solution. To perform the stimulus-response analysis, the signal S term in Eq. (1.3) was represented by a signal train of stimuli to potentially switch the system from one state to the other (Figure 5-4A). The steady state level of activator concentration finally reached is as high as four, and this value agrees with the results of the steady state analysis. As shown in Figure 5-4B, there are three zero crossing points representing steady state solutions of the activator concentration. Yet only two of them are stable solutions: zero and four which correspond to the two steady levels in Figure 5-4A.

A B

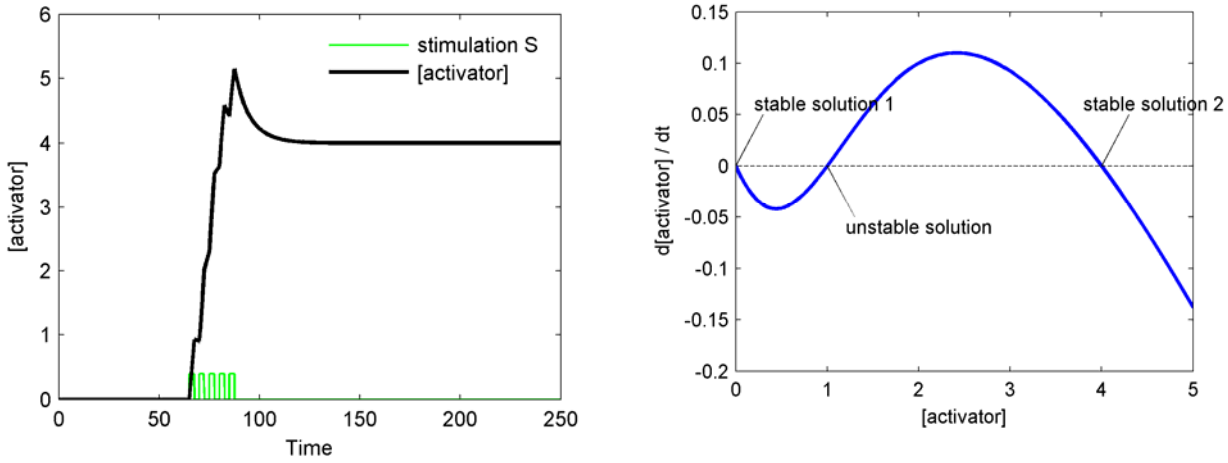

Figure 5-4 Output from a biological bistable switch. (A) The transient response of the activator concentration given a single train of stimuli. (B) The analysis plot of the system.

The special feature of bistable response is the long lasting change of response level. Given the values of parameters are tuned properly, the response can latch from one state to the other and stay there for long even after the stimuli no longer exist. Figure 5-4A does appear very similar to many long term potentiation (LTP) responses trigger by a single train of stimuli [2, 4]. It is this feather that makes bistability one of the leading hypotheses to explain long term change in synaptic plasticity.

Yet there is discrepancy between experimental results of LTP and modeling output of bistable systems in the case of multiple trains of stimuli [6]. As shown in Figure 5-5, two trains of stimuli are applied to the system. After the first train, the level of activator concentration latches to four, one of the stable equilibrium states. Yet even with the application of the second stimuli train, the final concentration level remains the same. This is another feature of the bistable system as its name implies. The number of stable steady states is just two. Therefore, even if the further stimulation is applied, the system still returns to the same steady state level. This feature, however, contradicts with many experimental results of LTP which show continuous and graded responses after application of multiple stimuli trains [6]. This discrepany will be discussed further in the later section of model development. There we consider calcium entrapment at postsynapse to better explain the physiology of long term potentiation and the measured responses triggered by multiple trains of stimuli.

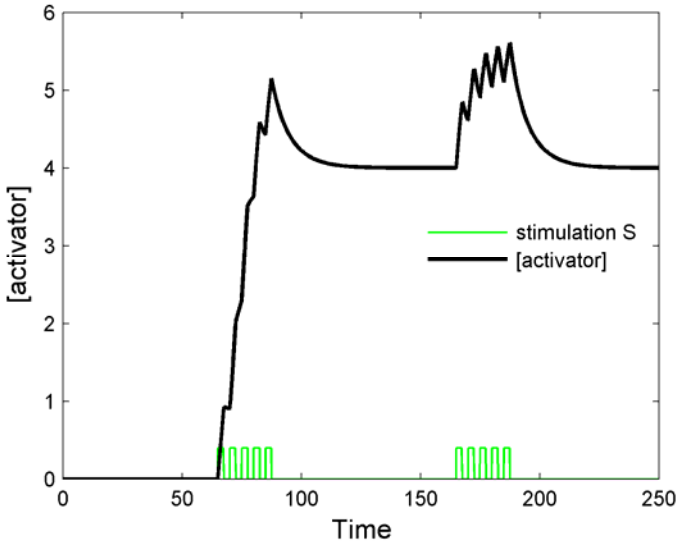

Figure 5-5 The transient response of the activator concentration triggered by two stimuli trains shows only one nonzero steady state level, according to the bistable switch model.

5.2.3 Bistability in other systems

There are other systems that demonstrate bistability. The most recognized one is the bistable switch built from electrical circuits [10] and the one well known in chemical reaction engineering is the bistable behavior of exothermic reactions in mixed flow reactors [8]. Bistable switches, also called flip-flop and latches and are the basic memory units. Two inverter gates and OR gates are needed respectively to construct a simple bistable switch. Positive feedback is the key component for setting up the bistable circuit. There are two stable states that the system can take on and the exact final resting state depends on the history of the activities [10]. As for the chemical reactor systems, the operation conditions are determined by the analysis results of mass balance and energy balance. For exothermic reactions in mixed flow reactors, the material balance curve may appear S-shaped while the energy balance is a straight line on a conversion versus temperature plot. If there are three crossing points or solutions of mass and energy balances, bistable behavior will show. The three crossing points are called the unreacted state, the reacted state, and the ignition point. Under such circumstance, a small turbulence in feed condition may cause the reactor to jump between the two stable states [8]. Even though bistable behaviors appear in a number of systems, they share the same attribute which is the existence of two stable states. This attribute, however, does not match the response of long term plasticity well. Therefore, alternative reaction schemes need to be developed to resolve the discrepancy between experiments and models.

5.3 Model development of long term plasticity

To resolve the disagreement, we decided to reexamine the relevant reaction pathways at synapse. The systems of interest consist of presynaptic and postsynaptic

compartments. Even though a few studies have found some contribution to LTP by presynapse, the mechanism of long term plasticity is generally attributed to postsynaptic reactions. Since NMDA receptors gating calcium inflow at postsynaptic membranes can only be activated through substantial depolarization, we suspected calcium signaling is the most important factor in causing LTP. There were also studies suggesting intracellular calcium is sufficient and necessary to induce change in long term plasticity [3, 12]. Hence, we developed a calcium entrapment model to simulate the change in excitatory response after stimulation. The systematic model consists of equivalent electrical circuits as well as ligand- and voltage-gated NMDA receptors. This built model is supported by a broad range of experimental measurements. According to the result of model differentiation, we confirmed that calcium entrapment model explains graded response of synaptic LTP better than biostability mechanism.

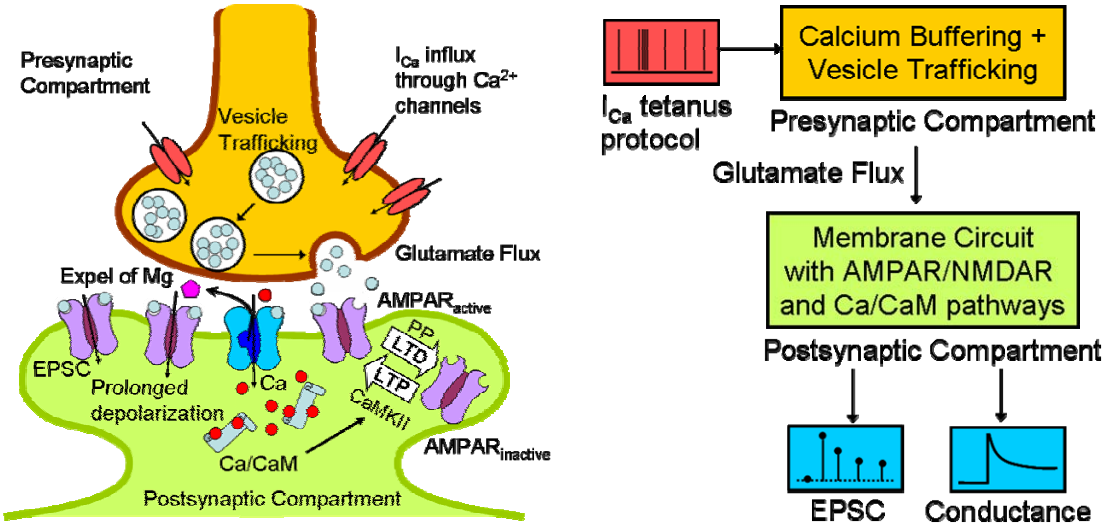

Figure 5-6 (A) The signal transmission pathways of long-term plasticity at synapses. (B) The summary of corresponding systems and signals in our study.

5.3.1 Dual regulation of NMDA receptors by membrane potential and glutamate

Activities of NMDA receptors influence long term plasticity change through regulation of calcium inflow. The conductance of NMDA receptors (g_{NAMDAR}) depends not only on glutamate concentration (Glu) but also on membrane voltage (V_{dent}). The voltage dependence results into selective signal transmission and has been modeled with the logistic function as shown in Eq. (1.6) (Jahr, 1990) [7]. The voltage dependent activity function rises to a maximum ($g_{NMDARmax}$) following a sigmoidal curve with half way voltage equal to $V_{1/2}$ and slope as large as $0.5k_{NMDA}$ at that point. Then ligand-receptor model with association constant K_{Glu} is adopted to describe glutamate dependence. Glutamate concentration can be related back to the presynaptic stimuli (I_{pre}) by a simple two compartment model; the details are described in supplemental materials. Finally, the expression of g_{NMDAR} (V_{dent}, Glu) can be inserted into equivalent circuits to calculate EPSP.

$$g_{NMDAR}\left(V_{dent}, Glu\right) = \frac{g_{NMDARmax}}{1+e^{-k_{NMDA}\left(V_{dent}-V_{1/2}\right)}} \cdot \frac{Glu}{Glu+K_{Glu}} \tag{1.6}$$

The total amount of calcium (CaT) flowing into postsynapse is proportional to the integration of current flow through NMDA receptors over the time of stimuli. Based on Ohm's Law, I_{NMDAR} can also be expressed as the product of conductance (g_{NMDAR}) and dendrite membrane potential (V_{dent}). Furthermore, depending on the total amount, calcium inflow may either up- or down-regulate signal transduction pathways and lead to synaptic plasticity change.

$$CaT \propto \int_{t_{stimuli}} I_{NMDAR} dt = \int_{t_{stimuli}} g_{NMDAR} V_{dent} dt \tag{1.7}$$

5.3.2 Calcium dependent plasticity regulated by kinase and phosphatase

We assume that most calcium ions entering postsynapse through NMDAR binds with calmodulin and tend not to leak out during typical experimental time of hundreds of minutes. In fact, the change in steady state level is likely to be due to the entrapment of intracellular calcium. Afterwards, the cooperative combination of calmodulin kinase (K) with calcium (Ca) activates the enzyme. The calcium dependent protein kinase (Ca_4K) once being activated can also phosphorylate other proteins. Meanwhile, binding to calcium activates protein phosphatase, which may dephosphorylate downstream enzymes (Malenka, 1999). Both Ca_4K and Ca_4P are assumed to be in equilibrium with their downstream reservoirs, termed Ca_4K_{rev} and Ca_4P_{rev}, respectively.

$$\begin{aligned} I_{NMDAR} &\xrightarrow{K_{Ca}} Ca \underset{k_{out}}{\overset{k_{in}}{\rightleftharpoons}} Ca_{store} \\ Ca &\xrightarrow{k_{leak}} Ca_{out} \end{aligned} \tag{1.8}$$

The time derivative of calcium concentration and that at intracellular store can be represented in the following equation.

$$\frac{d}{dt}\begin{pmatrix} Ca \\ Ca_{store} \end{pmatrix} = \begin{pmatrix} -\left(k_{leak}+k_{in}\right) & k_{out} \\ k_{in} & -k_{out} \end{pmatrix} \cdot \begin{pmatrix} Ca \\ Ca_{store} \end{pmatrix} + K_{Ca}\begin{pmatrix} I_{NMDAR} \\ 0 \end{pmatrix} \tag{1.9}$$

Since calcium concentration is much larger than that of kinase and phosphatase, we can assume that the binding of calcium with these two proteins does not influence calcium concentration much.

$$\begin{aligned} 4Ca + K &\underset{k_{CaKb}}{\overset{k_{CaKf}}{\rightleftharpoons}} Ca_4K \\ 4Ca + P &\underset{k_{CaPb}}{\overset{k_{CaPf}}{\rightleftharpoons}} Ca_4P \end{aligned} \tag{1.10}$$

The dynamics of calcium, kinase, and phosphotase expressed in chemical reactions can be converted into a set of ordinary differential equations. The concepts of material balance and chemical reactions are used in conversion.

$$\begin{aligned}\frac{dCa_4K}{dt} &= k_{CaKf}\frac{Ca^4}{Ca^4 + K_{CaK}^4} - k_{CaKb}Ca_4K \\ \frac{dCa_4P}{dt} &= k_{CaPf}\frac{Ca^4}{Ca^4 + K_{CaP}^4} - k_{CaPb}Ca_4P\end{aligned} \tag{1.11}$$

The mobilization of AMPA receptors depend upon the concentrations of both activated kinase Ca_4K and protein phosphatase Ca_4P. Calcium kinase contributes to the insertion of more AMPA receptors to postsynaptic membrane, which was hypothesized as the mechanism of LTP. Other the other hand, calcium protein phosphatase may internalize AMPA receptors and cause long term depression (Bear, 1996).

$$AMPAR_{inactive} \underset{k_{AMPARb}+V_{CaP}CaP}{\overset{k_{AMPARf}+V_{CaK}CaK}{\rightleftharpoons}} AMPAR_{active} \tag{1.12}$$

5.3.3 The conceptual modeling of gene expression

The permanent change of synaptic plasticity can only be realized by protein synthesis regulated by gene expression. The protein that most directly contributes to the synaptic conductance is AMPA receptor. Yet due to the difficulty in quantifying the transcription and translation reactions, not many sets of experimental data are available that reveal step-by-step procedures of permanent plasticity formation. At this stage of research, it is known that calcium pathway, cAMP (Cyclic adenosine monophosphate) pathway, and CREB (cAMP response element-binding) are crucial in strengthening long term plasticity. Therefore, the strategy we took was to propose a general integration model. According to the model, new experiments are suggested as well. Afterwards, the validity of the model can be checked and details of it can be further expanded by the results of proposed experiments.

The following figure (Figure 5-8A) visualizes the overall reaction schemes we propose. Although two essential pathways, cAMP and calcium signaling cascades, contribute to the activation of CREB, we focus on the second one only for simplicity. In the beginning, the stimuli pass onto the calcium or calcium complex through the calcium entrapment model. Then the entrapped calcium leads to the transient increase in the concentration of CREB. At the end, the gene translation of synaptic protein, AMPA receptor, activated by CREB consolidates memory formation (Eq. (1.13)). The synthesis rate of AMPAR by translation ($AMPAR_{syn}$) is modeled by fourth order Hill equation as shown in Eq. (1.14) and Figure 5-8B.

$$I_{stimuli} \rightleftharpoons Ca \rightleftharpoons \ldots\ldots\ CREB \xrightarrow{k_{gene}} AMPAR_{syn} \tag{1.13}$$

$$\frac{dAMPAR_{syn}}{dt} = k_{gene}\frac{CREB^4}{CREB^4 + K_{Hill}^4} \tag{1.14}$$

Eventually, the total concentration of AMPAR would be equal to the original AMPAR plus the newly synthesized $AMPAR_{syn}$. The simulation results based on our proposed model are discussed in the following section.

$$AMPA_{total} = AMPA + AMPA_{syn} \tag{1.15}$$

5.4 Modeling results

The results from three protocols were modeled. The first one is applying multiple trains of high frequency tetanus stimuli and the second one is the frequency-dependent long-term plasticity. Then the third one is the prediction based on the gene expression model we proposed.

5.4.1 The two trains of high frequency stimuli

Long term potentiation by single train tetanus stimuli can be fit by both bistable switch model and our calcium entrapment model. The reason is that for single train stimuli, the resultant response only demonstrates two levels of steady states. As the name of bistable model suggests, there exists two levels of steady states, which can match the LTP response by single train stimuli.

However, the response caused by multiple trains of stimuli is graded and is applicable for model differentiation. As shown in Fig. 2, multiple train stimuli lead to further increase in the level of synaptic strength. The graded response cannot be explained by the zero or one bistable model but can be well matched by the continuous built up of residual calcium.

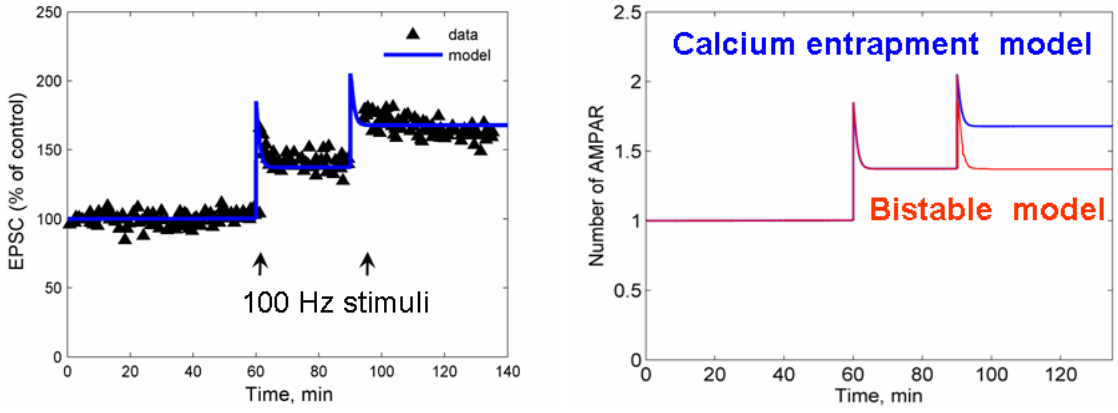

Figure 5-7 The model discrimination for long term plasticity based on graded LTP response

5.4.2 Frequency-dependent plasticity

Most research has focused upon long term potentiation since Bliss and Lomo discovered the high tetanus stimuli experimental protocol. Yet neuroscientists had been speculating the existence of long term depression. It was not until the work by Dudek et al. [4] got published in 1992 that researches realized the determining effects of stimuli frequency on the directions of long term plasticity.

The typical response of rate dependent synaptic plasticity is as shown in. If the synapses were to follow the bistability mechanism for retaining long lasting change in plasticity, the amplitude of the change in plasticity would only switch between two levels. By contrary, the experimental responses show multiple levels of steady state synaptic plasticity possible.

Yet according to calcium entrapment model, higher frequency stimuli cause more calcium influx to the postsynaptic compartment. Moreover, with the two-component model, different levels of calcium concentration can result into multiple values of post stimuli steady state synaptic plasticity.

5.4.3 Results of gene expression modeling

As shown in Figure 5-8C, the signals of upstream species tend to last shorter while those of downstream species can sustain longer. It is likely that the intermediate reactions are to maintain the traces after stimulation so that further downstream gene expression can be initiated. According to the integration model proposed, if the concentration of CREB surpasses the threshold value, synaptic proteins will be synthesized. In addition, there is no consumption term for the synthesized AMPA receptors. This is the reason for long lasting change in synaptic plasticity even after the stimuli are removed. Original AMPA receptor concentrations rise due to stimuli but decay throughout the

As for further development, we suggest two new experiments. The first one is to track the concentrations of intermediates such as calcium kinase to determine the time span of their actions. With the results of the new experiments, more information regarding the subsystems can be obtained in additional to stimuli current as the only input and synaptic conductance as the only output. The second is to decide the quantitative relationship between CREB concentration and protein synthesis rate of AMPA receptors to test the applicability of Hill equation. Finally, detect the decomposition rate of synthesized proteins to examine the hypothesis of no significant consumption.

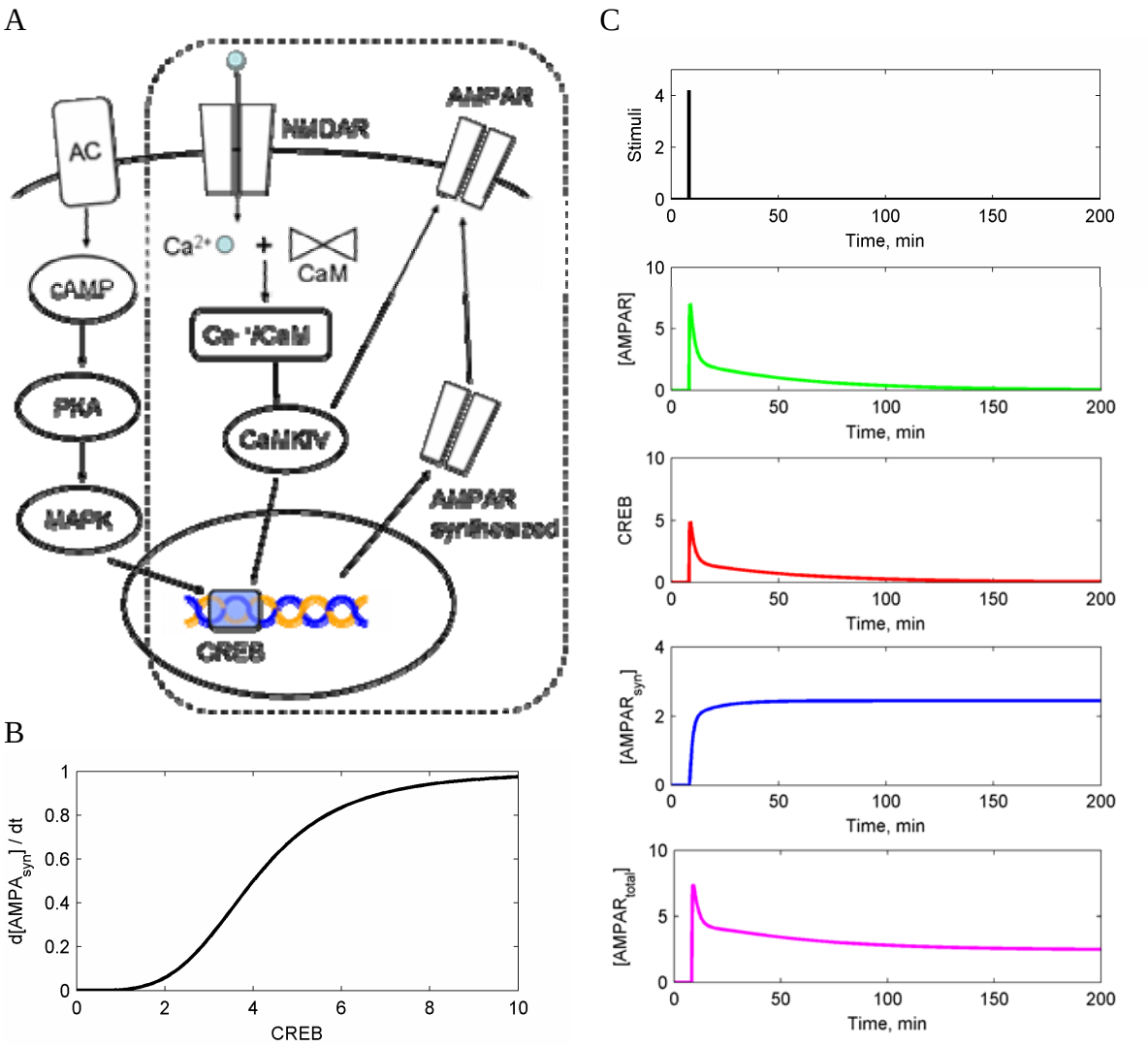

Figure 5-8 The conceptual reaction scheme and example responses of intermediates that lead to translation of synaptic protein. (A) cAMP and calcium signaling pathways are the two major contributors to synaptic protein synthesis. We focus on calcium signaling pathway which is enclosed in dash line. CaMKIV: calmodulin kinase IV. AC: adenylate cyclase. PKA: protein kinase A. MAPK: mitogen-activated protein kinase. (B) The dependence of protein translation rate on CREB modeled by Hill equation. (C) The concentrations of intermediates belonging to calcium signaling pathways. Note that downstream intermediates tend to last longer.

5.5 Conclusion of long term plasticity

The induction of long term potentiation by tetanus stimuli involves several subsystems interacting with one another. The frequency dependence is the result of cumulative calcium and calcium dependent synaptic plasticity. Even thought bistable models have been proven useful in explaining cell fate decision or cell differentiation, the

memory formation process is unlikely to follow such mechanism. The main reason is bistable systems demonstrate discrete instead of continuous behavior which is contradictory to common memorization processes. The strength of macroscopic memory or microscopic synaptic plasticity varies with respect to the intensity and frequency of external stimuli. It is very likely that the final equilibrium state of biological memory can rest on continuous levels instead of just zero and one as bistable models suggest.

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