Analysis of Modification in Synaptic Plasticity
STDP (Spike Timing Dependent Plasticity) Model by Changing Intracellular Calcium Concentration

Sheila Aisyah Diva, Anis Yuniati*

Physics Department, Faculty of Science and Technology Sunan Kalijaga State Islamic University Yogyakarta
Correspondency email*: anis.yuniati@uin-suka.ac.id

Abstract
Synapses are a junction between neurons that have a plastic property. Synaptic plasticity can be in the form of long-term potentiation (LTP) and long-term depression (LTD). The changes in intracellular calcium concentration can trigger LTP and LTD. Spike Timing Dependent Plasticity (STDP) is a modification of synapses that depend on the spike timing of pre-synapses and post-synapses neuron. In this study, we analyze the effects of intracellular calcium on the STDP phenomena based on Badoual's model using mechanisms involving parameters such as calcium pumping, AMPA receptors, NMDA receptors, LTP enzymes, and LTD enzymes. In this model, a high calcium concentration will activate the LTP enzyme, while a low calcium concentration will activate the LTD enzyme, each of which will trigger the occurrence of LTP and LTD. The existence of LTP and LTD is the basis for the formation of the STDP. In this model, the parameters can be adjusted to obtain the STDP corresponding to experimental results where LTP is observed in the range between 0 < ∆t < 50ms, while LTD is observed at wider intervals between −150ms < ∆t <0. These parameters are related to the decay time of the NMDA receptor.

Keywords: intracellular calcium; LTD; LTP; STDP; synaptic plasticity

Introduction
Calcium signaling plays a role in many neuron cell processes (Perea et al., 2016) related to protein kinases (Kurniawan et al., 2018), intracellular messenger IP₃, SERCA pumps, AMPA and NMDA agonists (Kurniawan, 2015a), affected the synaptic plasticity in the form of LTD (Kurniawan, 2015b). Changes in synaptic plasticity that are influenced by neurotransmitters, glutamate, and AMPA are associated with seizures and epilepsy (Barker-Haliski & Steve White, 2015; Bonansco & Fuenzalida, 2016; Göl et al., 2019; Guli et al., 2016; Han et al., 2016; Husna & Kurniawan, 2018; Jarero-Basulto et al., 2018; Kryukov et al., 2016; Plasticity et al., 2017; T. Yu Postnikova et al., 2017; T Y Postnikova et al., 2017; Zubareva et al., 2018).

Epilepsy is one of a subject that is still being developed that involves the explanation of the mechanism (Kubena, 1994; Meric-Bernstam & Mills, 2004), treatment techniques (Kurniawan et al., 2018; Pramestii et al., 2017; Spannow, 1998; Zahra et al., 2019), and diagnoses (Approach et al., 2014; Kesahihan & Keandalan, 2015; Lestari et al., 2017; Of et al., 2015; Parameswaran et al., 2019). The study of synaptic plasticity is importantly related to several diseases, especially epilepsy.

Spike timing plasticity is a plastic property that occurs because of synaptic activity between neurons, which allows them to communicate with each other and work to control the effectiveness of communication between two or more neurons. The strength of synaptic plasticity is never static but always experiences strengthening or weakening, which is called long-term potentiation (LTP) or long-term depression (LTD) (Badoual et al., 2006). LTP is a form of synaptic plasticity that is influenced by changes in calcium concentration in the intracellular mechanism (Badoual et al., 2006; J. Lisman, 1989; John Lisman, 1985; Lynch et al., 1983; Malenka et al., 1988). Similarly, LTD has been shown to have a close relationship with the mechanism of intracellular calcium (Badoual et al., 2006; Cooper & Thakur, 2013; Cummings et al., 1996; Hines & Carnevale, 1997).

LTP arises when the pre-synaptic spike time precedes the post-synaptic spike, while LTD arises when the post-synaptic spike time precedes the time of pre-synaptic spike (Caporale & Dan, 2008). The most significant change that occurs in synaptic when there is a small-time difference between the spike of pre-synaptic and post-synaptic, which is accompanied by
a sharp transition from strengthening to weakening, is called STDP (Spike Timing Dependent Plasticity) (Song et al., 2000). STDP is a form of synaptic modification that depends on the difference in the time of pre-synaptic spike and post-synaptic spike, which is a biological process that functions to regulate the strength of connections between neurons in the brain and refers to the process of LTP and LTD (Badoual et al., 2006; Levy, 1983). Based on the calcium hypothesis, the relative similarity of STDP activity patterns that refers to LTP and LTD depends on the concentration of calcium in cells. However, the calcium hypothesis that explains the biophysical mechanisms underlying STDP is still unclear (Badoual et al., 2006; Sjöström & Gerstner, 2010).

In some previous computational models, post-synaptic calcium concentration was used as a signal to distinguish the sequence and time of spike in pre-synaptic and post-synaptic, wherein the model concluded that high post-synaptic calcium concentration would cause LTP. In contrast, low calcium concentration would cause LTD. However, the calcium hypothesis testing is based solely on observing post-synaptic spikes at calcium levels. They show that the results of experiments using the triplet spike of pre-synaptic and post-synaptic indicate that the spike of pre-synaptic that precedes the spike of post-synaptic then followed by the spike of pre-synaptic does not result in any change in the plasticity. Conversely, when a post-synaptic spike precedes a pre-synaptic spike and then followed by a pre-synaptic spike, it triggers LTP (Rubin et al., 2005). In this study, the modeling that was built to explain the biophysical mechanism in the STDP model related to the concentration of calcium in cells will be analyzed through the process of LTP and LTD based on the spike time of pre-synaptic and post-synaptic on the spine of neuronal cells. The computational modeling in this research involves parameters that include pumping of calcium which is influenced by AMPA receptors, NMDA receptors, LTP and LTD enzymes, which is based on the time pair of spikes in pre-synaptic and post-synaptic.

Methodology

The kinetic model used in this research follows the research of Mathilde Badoual et al. (Badoual et al., 2006), where each parameter is written using the NMODL (Model Description League) programming language, which is saved as a .mod file extension. The files then are inputted using the NEURON simulator. The kinetic model of each parameter is as follows:

1. **Calcium Pumping**

The calcium pumping process is carried out in the dendrite spine and dendrite, leading to the dendrite spine. Equation (1) is a comparison of pumping of calcium that occurs in the spine (Badoual et al., 2006; Sabatini et al., 2002).

\[
\frac{d[C_{\text{a}i}]}{dt} = -\frac{I_{ca}}{2\pi d^2} + \frac{(C_{\text{as}} - [C_{\text{a}i}])}{\tau_r} \tag{1}
\]

\[\left[C_{\text{a}i}\right]_n\] is the concentration of calcium in the spine, \(I_{ca}\) is the calcium current in the spine, \(F\) is the Faraday constant, \(C_{\text{as}} = 5\times10^{-7}\text{m}^3\text{C}^{-1}\) is the concentration of calcium in the spine at rest, \(\tau_r\) is decay time constant equal to 15 ms, and \(d\) is the depth of the submembrane framework used in this equation, with the value equal to 1/4 of the spine diameter. Equation (2) is the equation of pumping calcium from the dendrite to the spine.

\[-D([C_{\text{a}i}] - [C_{\text{a}d}]) = \frac{S_{\text{neck}}}{V_{\text{spine}}} \tag{2}\]

\(C_{ad}\) is the concentration of calcium in dendrites, \(S_{\text{neck}}\) is the cross section of the neck \(S_{\text{neck}} = 0.0078\text{m}^2\), while \(V_{\text{spine}}\) is the volume in the spine \((V_{\text{spine}} = 0.065\text{m}^3)\). These values are following with the morphological measurements carried out by Harris and Kater in 1994 (Harris, 1994).

2. **AMPA receptor**

Calculation of AMPA receptor conductance values is shown in equation (3) as follows (Badoual et al., 2006; A Destexhe et al., 1994)

\[
\frac{dm}{dt} = \alpha m (1 - m) - \beta m \tag{3}
\]

\(m\) represents the receptor fraction in the open state, \(\alpha\) and \(\beta\) are forward and backward rate constants, \(T\) is the concentration of glutamate in the synaptic cleft. Conductance value is given by \(g_{\text{AMPA}} = g_{\text{AMPA}} m\), where \(g_{\text{AMPA}} = 0.5\text{nS}\) is the maximum conductance value of synapses.

3. **NMDA receptor**

Calculation of the value of calcium current at the NMDA receptor is shown in equation (4) below (Badoual et al., 2006; Alain Destexhe et al., 1998; Gardette et al., 1985; Goldman, 1943).

\[I_{ca} = P_{ca} B(V) m G(V, [C_{\text{a}i}], [C_{\text{a}d}]) \tag{4}\]

\(P_{ca} = 4.6925\text{cm}^2\text{mV/Cb}\) is the permeability of calcium, \(m\) represents the fraction when the receptor is open, and \(B(V)\) describes the voltage value that depends on the NMDA receptor current. Calculation of \(B(V)\) is shown in equation (5) below (Badoual et al., 2006; Jahr & Stevens, 1990)

\[B(V) = \frac{1}{1 + \exp(-0.062V)[M_{\theta}]/3.57} \tag{5}\]
\[ M_o = 1 \text{mM} \] is the external calcium concentration, 
\[ G(V, [C_a]_o, [C_i]) \] is linear function of voltage and ion concentration with the value is shown in equation (6) below

\[ G(V, [C_a]_o, [C_i]) = \frac{Z^2 F^2 V}{RT} \frac{[C_a]_o \exp \left( \frac{Z F V}{RT} \right)}{1-\exp\left(\frac{-Z F V}{RT}\right)} \] (6)

\( Z = 2 \) is the valence of calcium ions, \( F \) is the Faraday constant, \( R \) is the gas constant, \( T \) is the temperature in Kelvin units, \([C_a]_o\) dan \([C_i]_o = 1.5\text{mM}\) is the value of intracellular and extracellular calcium concentrations, \( g_{NMDA} = 0.3\text{nS} \) is the NMDA receptor current value.

4. LTP Enzyme
The activation of the LTP enzyme during the kinetic scheme shown in equation (7) follows (Badoual et al., 2006)

\[ K + 4C_a^{2+} \xrightarrow{a_k} K^* \] (7)

\( K \) is the non-activated LTP enzyme form and \( K^* \) is the activated LTP enzyme form. The value of \( a_k \) and \( b_k \) is constant.

5. LTD Enzyme
The enzyme activation of LTD during the kinetic scheme shown in equation (8) - (10) follows (Badoual et al., 2006)

\[ m + C_a^{2+} \xrightarrow{a_m} m^* \] (8)

\[ h + T \xrightarrow{a_h} h^* \] (9)

\[ m^* + h^* + P_h \rightarrow P_h^* \] (10)

\( m \) is an enzyme activated by calcium, \( h \) is an enzyme activated by glutamate, \( m^* \) and \( h^* \) are forms of activation used to activate the LTD enzyme, whereas \( P_h, a_m, b_m, a_h, \) and \( b_h \) are constant.

Results and Discussion
1. The relation of LTP, LTD and intracellular calcium concentration
Long Term Potentiation/LTP is triggered by activation of calcium autophosphorylation or protein-dependent calmodulin (CaMKII). Activation of protein kinase-dependent CaMKII involves four calcium ions for each calmodulin molecule in the LTP enzyme. The LTP enzyme will be activated when the concentration of calcium in the cell is high, or the peak of the LTP enzyme will also be high. However, when the concentration of calcium in cells is low, the LTP enzyme will not be activated, or the LTP enzyme peak is low. The calcium concentration for positive value of tpost-tpre (tpost-tpre = 130 ms) is shown in Figure 1. The figure shows the calcium concentration is high at the time 300 ms, indicated by sharp peak with the value of calcium concentration equal to 0.012 μM.

![Figure 1. Calcium concentration for tpost-tpre 130 ms.](image1)

LTP enzyme signals represented by \( \%K^* \) in Figure 2. Comparing with the result shown in Figure 1, when the calcium concentration is high, the LTP enzyme will be activated. Meanwhile, when the calcium concentration is low, the value of LTP enzyme also low. As shown by a sharp peak in Figure 2 at the time close to 300 ms, the value of LTP enzyme is 0.04 μM.

![Figure 2. LTP enzyme for tpost-tpre 130 ms.](image2)

The strengthening of the calcium signal in the biophysical mechanism in the STDP model depends on the interaction of Backpropagating Action Potential (BAP) and Excitatory Postsynaptic Potential (EPSP) which increases the calcium permeability that is affected by NMDA receptors and is voltage-dependent. BAP is a phenomenon when the action potential makes a voltage spike at the end of the axon and returns to the dendrite. The interaction between BAP
and EPSP can cause many things (Caporale & Dan, 2008), for example, that it can strengthen the calcium signal when the NMDA receptors are opened with three to four times larger in the dendrite (Magee & Johnston, 1997).

EPSP can cause changes in the conductance values in dendrites which cause BAP to return to dendrites, whereas an increase in BAP can cause calcium influx to flow through calcium channels that depend on voltage to increase LTP without any contribution from Ca2+ induced Ca2+ release (CICR). Calcium is mediated by pumping calcium ATPases to the endoplasmic reticulum (SERCA pumps) and by exchanging Na+ -Ca2+ on the plasma membrane or Ca2+ -ATPase plasma membrane (Caporale & Dan, 2008; Holthoff & Tsay, 2002). This process can be simplified and represented by the value of the decay time constant \( \tau_c \) in the calcium pumping equation. A value of \( \tau_c \) of 15 ms initiated by a current pulse in the initial segment section, while EPSP in the spine is triggered by the action potential in the cells of pre-synaptic. Increased calcium permeability will cause calcium signals to strengthen. The voltage-dependent NMDA receptor in this mechanism is represented by the value of \( B(V) \) in the calcium current equation. The value of \( B(V) \) in this mechanism plays a role in opening or closing the magnesium block channel contained in the NMDA receptor.

![](image)

**Figure 3**. The enzyme activated by calcium \( m^* \) and the enzyme activated by glutamate \( h^* \) for tpost-tpre 130 ms.

Long Term Depression/LTD is triggered by the activation of protein phosphatase. Activation of protein phosphatase involves the neurotransmitter (glutamate) and also the concentration of calcium in cells. Glutamate will be released to the AMPA receptor when there is an action potential in pre-synaptic cells. The LTD enzyme will not be activated when the calcium concentration in the cell is high, or the LTD enzyme peak is low. Still, when the concentration of calcium in the cell is low, the LTD enzyme will be activated, or the peak enzyme LTD is high. The enzyme activated by calcium \( m^* \) and the enzyme activated by glutamate \( h^* \), are shown in Figure 3. The sharp peak at the time close to 300 ms indicate that \( m^* \) is high, as the consequence that calcium concentration reach the highest concentration at the same time as shown in Figure 1. The enzyme activated by glutamate \( h^* \) is high at the time close to 150 ms as the result that the calcium concentration is start to produce at the same time, as shown in Figure 1. The LTD enzyme is represented by \% \( Ph^* \) in Figure 4. The sharp peak is shown at the time close to 150 ms, as the consequence that the mechanism for activating LTD enzyme is occur when \( m^* \) is low and \( h^* \) is high.

![](image)

**Figure 4**. LTD enzyme for tpost-tpre 130 ms.

The glutamate found in the synapses valve will be sent to the receptors on the post-synaptic when there is an action potential in pre-synaptic cells, such as kinetics on AMPA receptors that mediate conductance. The release of glutamate or transmitter (T) through synapses activates the enzyme \( h \) to \( h^* \). Meanwhile, calcium will activate the enzyme \( m \) to \( m^* \) while the LTD enzyme activation process from \( Ph \) to \( Ph^* \) is carried out by enzymes \( m^* \) and \( h^* \). The mechanism of enzyme activation of LTD occurs when the enzyme peak \( m^* \) is low, and the enzyme peak \( h^* \) is high, when the enzyme peak \( h^* \) is high, the enzyme LTD will be activated from \( Ph \) to \( Ph^* \) and has a high peak. Conversely, when the enzyme peak \( m^* \) is high and the enzyme peak \( h^* \) is low, the LTD enzyme will still be activated but has a small value.

Simulation results with tpost-tpre has a positive value (tpost-tpre = 130 ms) shows that the LTP enzyme peak has a higher value than the LTD enzyme peak value, where the LTP enzyme peak value is 0.04 \( \mu \)M and the LTD enzyme peak value is 0.012 \( \mu \)M. We concluded based on these results that the positive value of tpost-tpre triggers the occurrence of LTP in cells because of the value of LTP> LTD. When the value of LTP is higher than the value of LTD, synapses activity will experience strengthening. LTP will play an important role in the mechanism of storing information in the brain when the value of LTP is high.

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2. The relation of STDP phenomenon and intracellular calcium concentration

Figure 5. LTP and LTD curve for $t_{post} - t_{pre}$ from -100 to 100 ms.

The synaptic plasticity of the STDP model is based on measuring synaptic weights through spike time pairs of pre-synaptic and post-synaptic, with $\Delta t$ (the time difference between the post-synaptic spike and pre-synaptic spike) < 0 will give a negative value of synaptic weight change, whereas $\Delta t > 0$ will give a value of positive synaptic weight change.

Changes in synaptic weights that are positive will cause plasticity to strengthen. Meanwhile, changes in synaptic weights that are negative will weaken plasticity. The curve of the change in synaptic weight value is described in Figure 5, where the total value of the synaptic weight change is the value of LTP-LTD. Meanwhile, in the previous analysis, it has been explained that changes in intracellular calcium concentration values can cause the onset of strengthening (LTP) and weakening (LTD). From these results, it can be concluded that the synaptic plasticity of the STDP model is related or influenced by changes in intracellular calcium concentration values. In other words, changes in intracellular calcium concentration affect the changes in this model through the mechanism of LTP and LTD. Based on the time difference between the relative pre-synaptic and post-synaptic, the curves of the STDP model, is shown in Figure 6. The STDP curve is obtained from LTP curve - LTD curve.

Figure 6. STDP curve for $t_{post} - t_{pre}$ from -100 to 100 ms.

The decay time $\tau_r = 10$ ms with $t_{post} - t_{pre}$ values at intervals of -200 ms to +150 ms gives the simulation results of realistic STDP model curve that close to the results of experiments conducted by Bi and Poo, where the LTP window is observed in the time interval $0 < \Delta t < 50$ ms, and the LTD window is observed in the time interval of $-150 < \Delta t < 0$ ms.

Conclusion

Based on the results and studies, it can be concluded that the occurrence of LTP and LTD is influenced by the large concentration of calcium in neuron cells through the mechanism of activation of the LTP and
LTD enzymes. High calcium concentration causes LTP, and low calcium concentration causes LTD. The time of pre-synaptic spike that precedes the time of post-synaptic spike (tpost-tpre is positive) gives rise to LTP, while the time of post-synaptic spike which precedes the time of pre-synaptic spike (tpost-tpre is negative) gives an LTD. The STDTP model curve based on the tpost-tpre value shows the LTP and LTD processes that are influenced by the large calcium concentration in neuron cells. The STDTP curves are consistent with experimental results where LTP is observed in the range between 0 <t <50ms, while LTD is observed at wider intervals between -150ms <t <0. In the future study, the parameters need to be varied to be compared with the results from experimental research in various organism.

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