Modeling calcium-dependent synaptic plasticity and its role in sleep-dependent memory consolidation

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Modeling calcium-dependent synaptic plasticity and its role in sleep-dependent memory consolidation

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Abstract

It has been shown that a single neuron can encounter different firing rates during the sleep and the awake states. Those rhythms directly have an impact on the synaptic weight between the neurons. Moreover, recent evidence shows that spindle oscillations encountered during sleep influence the calcium levels in the post-synaptic spine that trigger synaptic plasticity changes.

There exists a large number of synaptic plasticity rules. In particular, this thesis focuses on calcium-induced synaptic plasticity. However, the little number of calcium-based models do not take into account the calcium dynamics in much detail. Indeed, to reproduce protocols and obtain results that are consistent with experimental data, a great number of simplifications are often considered.

A review of the existing calcium-based models is made in order to categorize those models in a systematic way: 'How do they implement the calcium flow into the neuron?', 'What is the equation governing synaptic plasticity depending on the calcium concentration?', *etc.*

The thesis focuses on the calcium-dependent synaptic plasticity model developed by Graupner et al. (2016). This model has made simplifications to implement the calcium dynamics while being consistent with data obtained experimentally. The contribution of this thesis is first to integrate this abstract model into a conductance-based model which allows switching from a tonic pattern to a bursting pattern, encountered during the switch to the sleep state. This allows observing what are the consequences of this switch on the calcium-dependent synaptic plasticity.

The second main contribution of the thesis is to integrate a more detailed calcium dynamics into the abstract calcium dynamics model from Graupner et al. (2016).

The key message is the fact that integrating a detailed calcium dynamics into an abstract one represents a major challenge to tackle because of the large number of assumptions that have been made to construct this abstract model. This leads to the prospect that starting from a more physiological calcium dynamics then integrating a calcium-dependent synaptic plasticity rule to this model may be a more suitable way of doing.

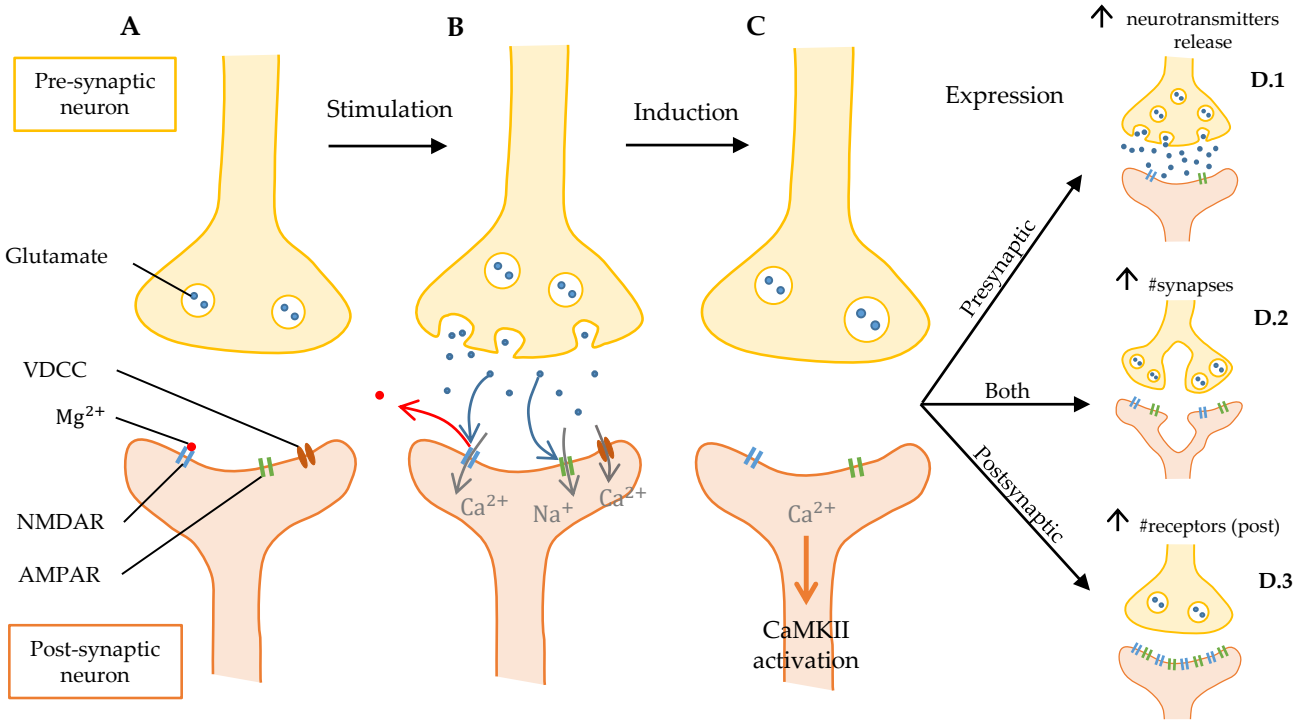


Figure 1: Molecular mechanism of LTP. **A.** The pre-synaptic neuron (yellow) is ready to release the neurotransmitters (glutamate) contained in synaptic vesicles once it receives a stimulus. The post-synaptic neuron (orange) contains NMDARs, AMPARs and VDCCs. The NMDARs are blocked are by the Mg^{2+} and no ions can pass through them. **B.** When the pre-synaptic neuron is stimulated, glutamate is released from synaptic vesicles and binds to AMPARs and NMDARs, which activates those receptors. The activation of NMDARs leads to the influx of Na^{+} ions into the post-synaptic neuron, which leads to the depolarization of the post-synaptic neuron. This removes the Mg^{2+} blockage on NMDARs and Ca^{2+} ions can enter in the post-synaptic neuron. **C.** Ca^{2+} ions trigger the activation of CaMKII. **D.** LTP has different forms of expression: an increase in the neurotransmitters release from the pre-synaptic neuron (**D.1**), an increase of the synaptic surface between the neurons (**D.2**) and an increase in the number of post-synaptic receptors (**D.3**). Adapted from (Vandewalle and Leprince, 2019).

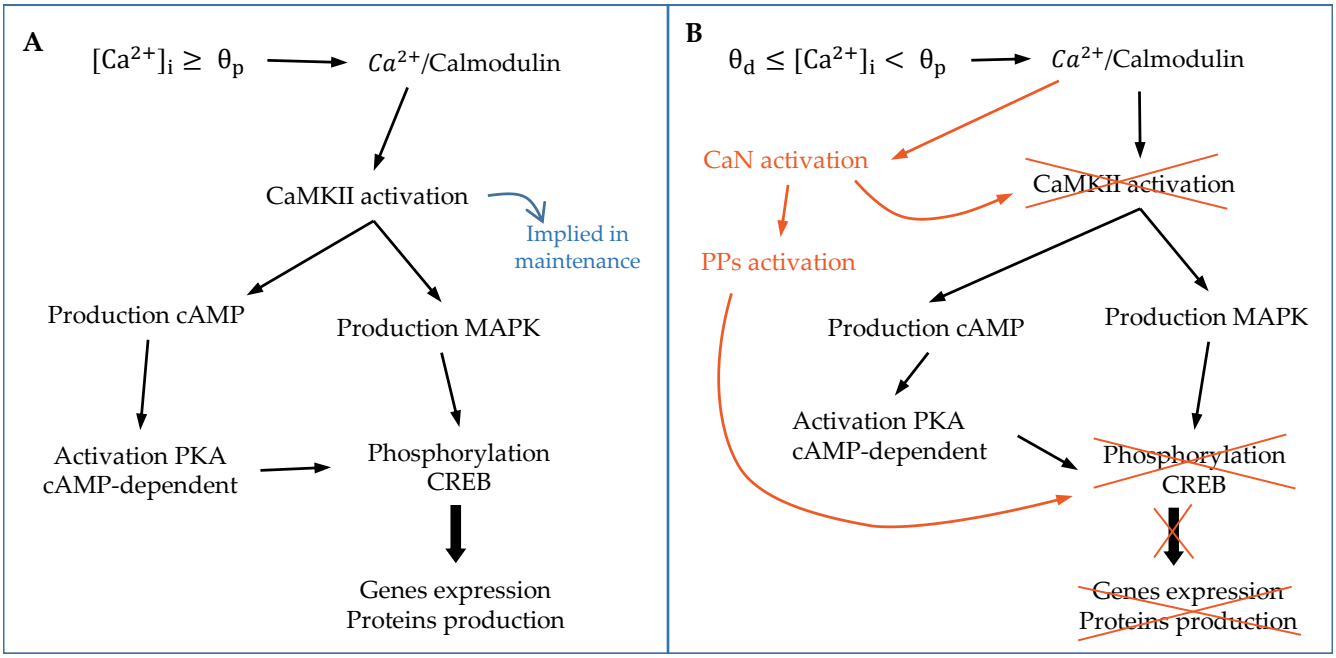


Figure 2: Cascade pathways of LTP and LTD induction. θ_p is the threshold to exceed to get a potentiation and θ_d is the depression threshold. **A.** LTP induction. High levels of calcium concentration ($[Ca^{2+}]_i \geq \theta_p$) allow the activation of the CaMKII which finally results in the CREB protein phosphorylation. This phosphorylation leads to genes expression and proteins production. CaMKII also has the ability of autophosphorylation so this protein kinase also has a role of synaptic plasticity maintenance. **B.** LTD induction. Lower levels of calcium ($\theta_d \leq [Ca^{2+}]_i < \theta_p$) activate the calcineurin phosphatase (CaN) which, in turn, activates protein phosphatases (PPs) and prevents the CREB phosphorylation. Inspired from (Vandewalle and Leprince (2019), Golbert et al. (2017)).

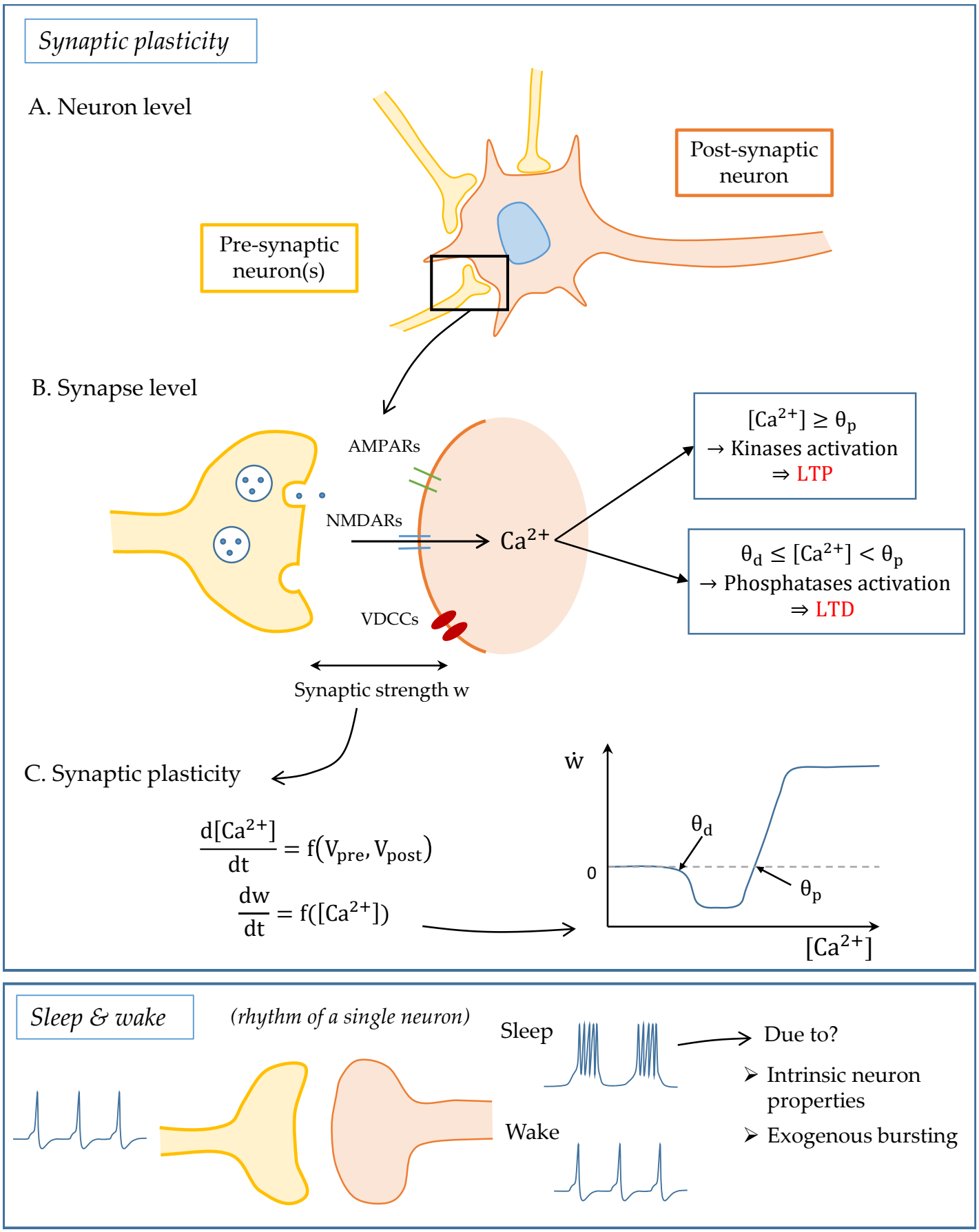


Figure 3: Summary of **Part I**.

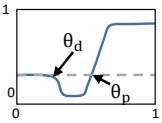
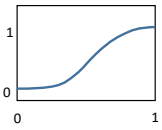
Model	Ca^{2+} source	I_{NMDA} modeling	$[Ca^{2+}]$ modeling	Definition of w	$w([Ca^{2+}])$
Graupner and Brunel, 2016	NMDARs VDCCs		Sum of exponentials	Abstract weight	$\dot{w}(c) \propto (1-w)\Theta[c-\theta_p] - w\Theta[c-\theta_d]$ θ_p: potentiation θ_d: depression
Shouval, 2002	NMDARs	$I_{NMDA} \propto P_0 G_{NMDA} H(V_{pre})$	$\frac{d[Ca]}{dt} = f(I_{NMDA}, [Ca])$	Abstract weight	$\dot{w} \propto \eta([Ca]) \cdot \Omega([Ca])$ Ω:  η: 
Standage, 2014	NMDARs	NMDAR activation: $\dot{g} = -\frac{g}{\tau} + a \cdot x \cdot (1-g)$ a: receptor saturation x: receptor opening	$\frac{dCa}{dt} = f(Ca, \tau_{Ca}, BAP, g)$	Abstract weight	If LTP: $\Delta w_p \begin{cases} \propto [Ca] \; if \; [Ca] > \Theta_p \\ = 0 \; if \; [Ca] \leq \Theta_p \end{cases}$ If LTD: $\Delta w_d \begin{cases} \propto [Ca] \; if \; [Ca] > \Theta_d \\ = 0 \; if \; [Ca] \leq \Theta_d \end{cases}$
Honnuraiah (2013) Anirudhan (2015)	NMDARs	$I_{NMDA} = I^{Na}_{NMDA} + I^{K}_{NMDA} + I^{Ca}_{NMDA}$ $I^{Ca}_{NMDA} \propto \overline{P}_{NMDA} \cdot P_{Ca} \cdot s(t) \cdot MgB(V) \cdot ([Ca]_i - [Ca]_o)$	$\frac{d[Ca]_i}{dt} = f\left(I^{Ca}_{NMDA}, ([Ca]_i - [Ca]_o)\right)$	Abstract weight	$\dot{w} \propto \eta([Ca]) \cdot \Omega([Ca])$ η, Ω: see Shouval 2002 for their functional form
Olcese, 2010	NMDARs	$I_{NMDA} = f(g_{NMDA}, V)$ $\dot{g}_{NMDA} = f(g^{peak}_{NMDA}, t)$	$[\dot{Ca}] = -\frac{[Ca]}{\tau_{Ca}} + J_{Ca} \sum \delta(t - t_i)$ J_{Ca}: calcium influx at NMDARs t_i: post-syn. spike timing	Nb. AMPARs	Plasticity direction depends on $[Ca^{2+}]$ levels

Table 1: Summary of the different calcium-based models that are explained in Chapter 5.

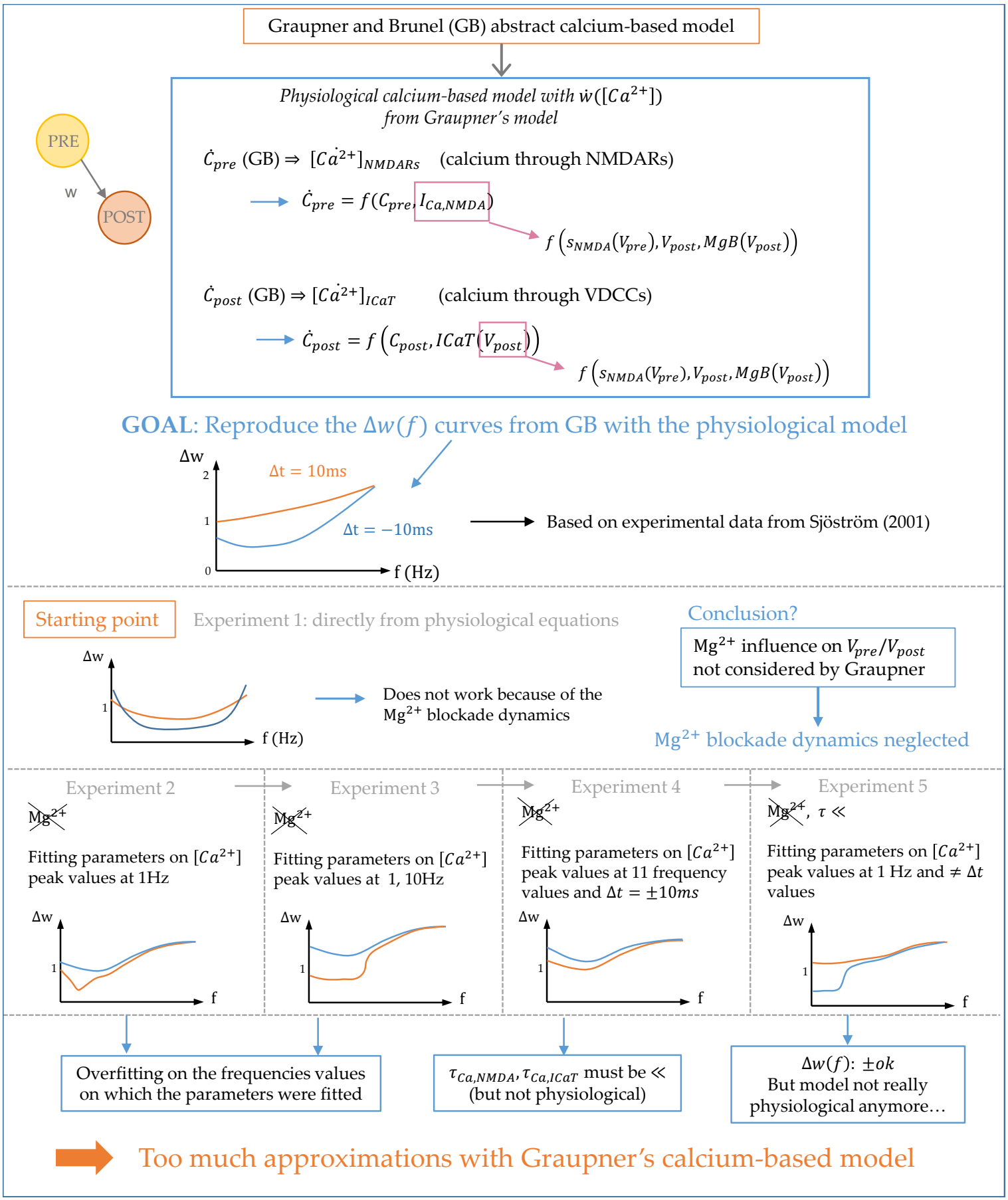


Figure 4: Summary of the methodology used to integrate a detailed physiological calcium dynamics into a simplified model.