

Improved Mathematical Modeling of Persistent Post-cortical Spreading Depression

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1. Abstract

Cortical spreading depression (CSD) is the propagation of a relatively slow wave in cortical brain tissue that is linked to some pathological conditions such as stroke and migraine. Most of the existing literature investigates the dynamics of short-term phenomena such as the depolarization and repolarization of membrane potentials or large ion shifts. Here, we focus on the clinically relevant, hour-long state of neurovascular malfunction in the wake of CSDs. This dysfunctional state involves widespread vasoconstriction and a general disruption of neurovascular coupling. We demonstrate, using a mathematical model, that the dissolution of calcium that has aggregated within the mitochondria of vascular smooth muscle cells can drive an hour-long disruption. We model the rate of calcium clearance as well as the dynamic implications on overall blood flow. Based on reaction stoichiometry, we quantify a possible impact of calcium phosphate dissolution on the maintenance of F₀F₁-ATP synthase activity.

2. Model Setup

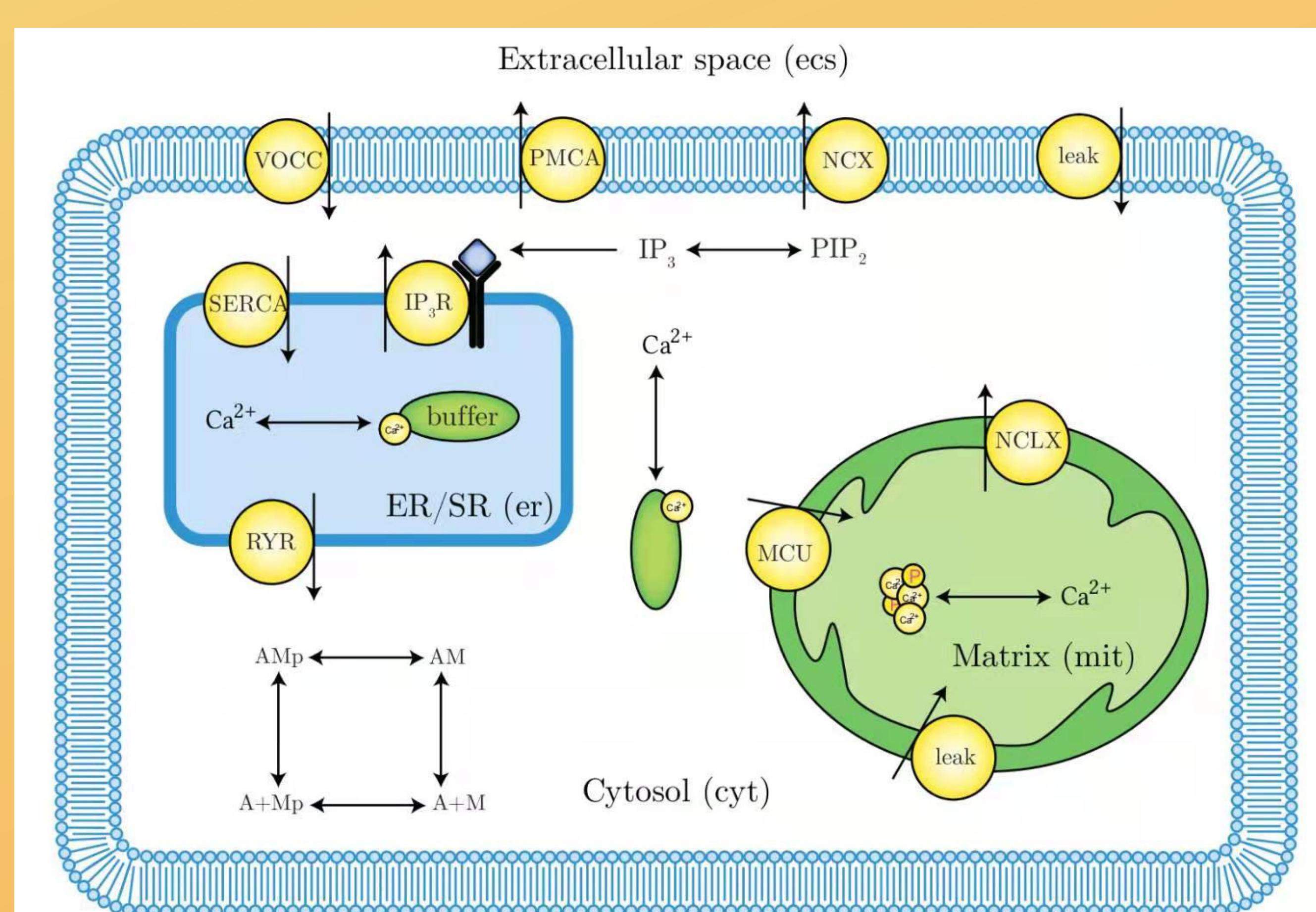


Figure 1. Schematic diagram of the model. The system consists of four compartments, i.e., cytosol, mitochondria, endo(sarco)plasmic reticulum, and extracellular space.

$$\begin{aligned} \frac{d [Ca^{2+}]_{cyt}}{dt} &= \frac{1}{b_{cyt}}(J_{er \rightarrow cyt} + J_{mit \rightarrow cyt} + J_{ecs \rightarrow cyt} + J_{cyt \rightarrow cyt}) \\ \frac{d [Ca^{2+}]_{er}}{dt} &= -\frac{r_{er}^{cyt}}{b_{er}} J_{er \rightarrow cyt} \\ \frac{d [Ca^{2+}]_{mit}}{dt} &= b_{mit}(J_{mit \rightarrow mit} - r_{mit}^{cyt} \cdot J_{mit \rightarrow cyt}) \\ J_{mit \rightarrow mit} &= -\alpha \cdot \frac{dQ}{dt} \\ \frac{dQ}{dt} &= \begin{cases} \gamma_1 \cdot \exp(-\frac{k}{[\log_{10}(\frac{[Ca^{2+}]_{mit}}{cs})]^2}) & \text{if } [Ca^{2+}]_{mit} > cs \\ \gamma_2 \cdot (cs - [Ca^{2+}]_{mit}) \cdot Q & \text{otherwise} \end{cases} \end{aligned}$$

$$J_{mit \rightarrow cyt} = J_{mcu} + J_{nclx} + J_{mit, leak}$$

3. Results and Discussion

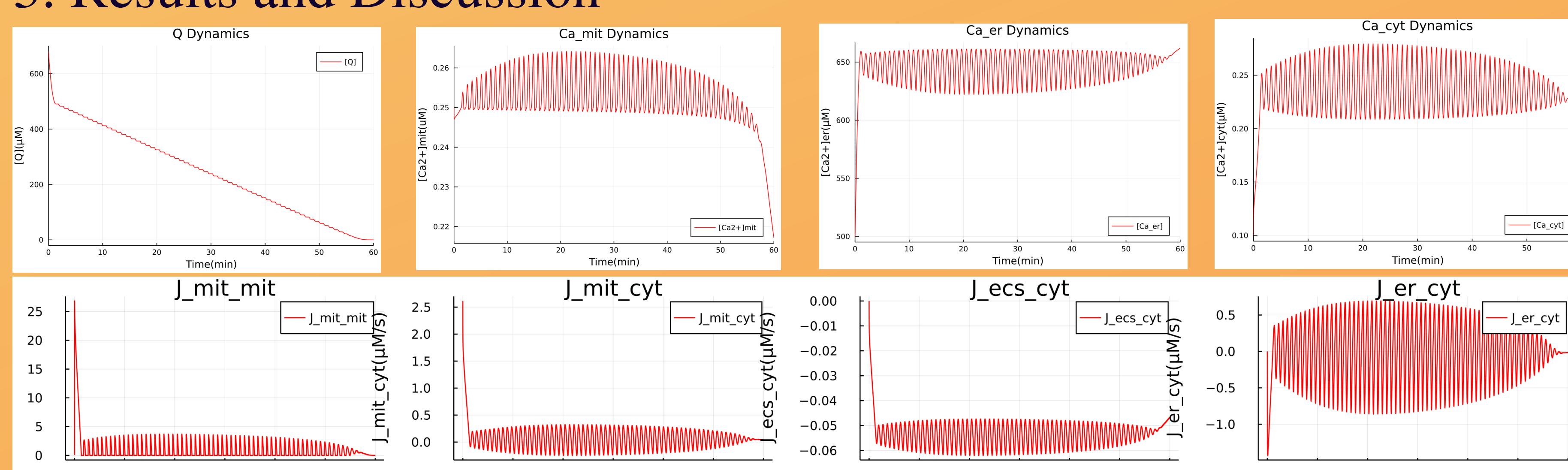


Figure 2. Model time evolution in 60 minutes when the initial value of Q is 650.

The model in [2] assumes that the concentration of calcium in the mitochondria remains constant so that the rate change of calcium is zero. In this improved work, we build the mitochondrial calcium dynamics model when there is an excess of calcium ions that forms calcium-phosphate clusters (shown in Fig. 1). The rate of change in cluster formation depends on the calcium concentration relative to the concentration saturation point (cs) and cluster concentration itself (Q) [1].

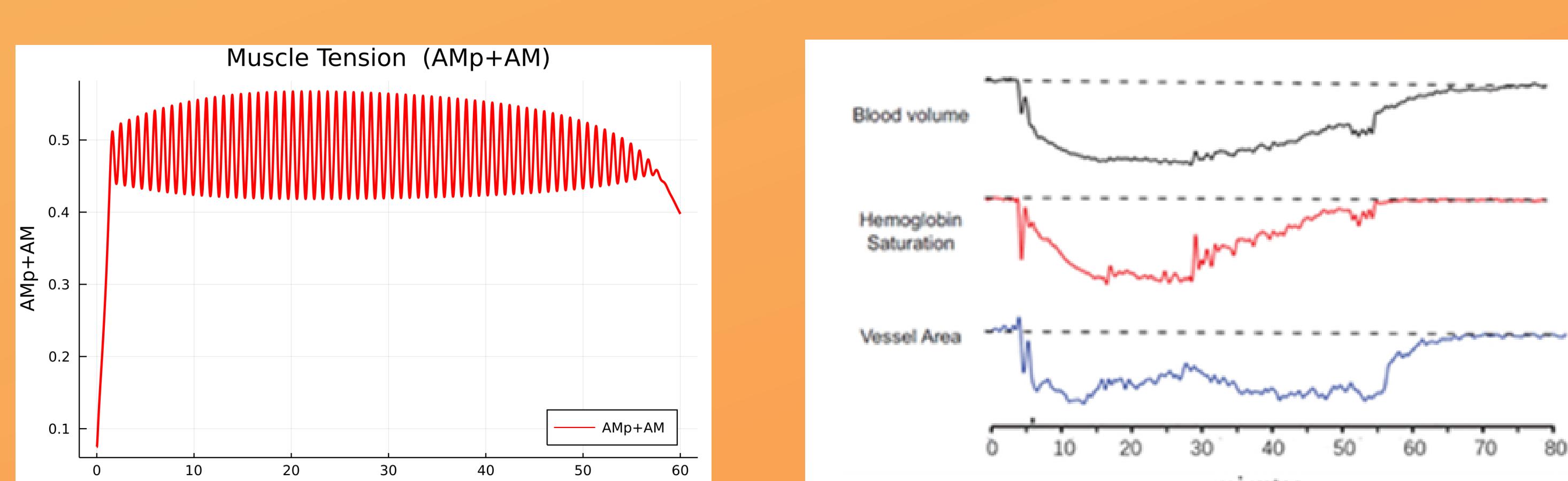


Figure 3. Muscle tension predicted by the model (left). Physiological measurements following CSD at a long time scale verify the model (right), reprinted from [2].

We have presented a model of calcium dynamics within smooth muscle vascular cells incorporating relevant endoplasmic reticulum, mitochondrial, and plasma-membrane dynamics that participate in responding to elevations in calcium concentration. We have also improved the calcium dynamics in mitochondria by considering the process of calcium crystallization from supersaturated solution (i.e., $J_{mit-mit}$) compared to the established model in [2]. Using this model, we demonstrated macroscopic vascular behavior consistent with the hour-long disruption in neuro-vascular coupling following cortical spreading depression.

References:

- [1] Solesio ME, Garcia Del Molino LC, Elustondo PA, Diao C, Chang JC, Pavlov EV. Inorganic polyphosphate is required for sustained free mitochondrial calcium elevation, following calcium uptake. *Cell Calcium*. 2020 Mar;86:102127. doi: 10.1016/j.ceca.2019.102127.
- [2] Xu S, Chang JC, Chow CC, Brennan KC, Huang H (2020) A mathematical model for persistent post-CSD vasoconstriction. *PLoS Comput Biol* 16(7): e1007996. <https://doi.org/10.1371/journal.pcbi.1007996>.