Role of Ryanodine Receptors in Modulating Plasticity at the Hippocampal CA1 Dendritic Spine

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Background

The calcium-dependent plasticity driven by NMDA receptors brings about long-term changes in synaptic efficacies – thought to be the basis of information storage in the brain. Recent studies have shown that intracellular Ca^{2+} release from endoplasmic reticulum (ER) via inositol-1,4,5-triphosphate receptors (IP_3Rs) produces long-term depression (LTD) in potentiated CA1 spines. The ER at CA1 dendritic spines also show presence of ryanodine receptors (RyRs) which are Ca^{2+} release channels having distinct biophysical properties than the IP_3Rs – thus, likely contributing differentially to Ca^{2+} dynamics resulting into synaptic plasticity. RyRs have also been implicated in the Alzheimer's Disease (AD) and other disorders. In this study, we explore the functional role of RyRs in modulating the synaptic plasticity at the CA1 dendritic spines.

Methods

We constructed a biophysical model of ER bearing CA1 dendritic spine. We used a single compartment, deterministic, ODE-based model. The calcium-dependent plasticity model from *Shouval et al., 2002* was used as a framework for bidirectional plasticity. The calcium-dependent plasticity was modified to calcium-bound calmodulin (aCaM) based plasticity, as aCaM levels are determined by calmodulin (CaM) in the spine – that give bounded elevation for sustained activity. We incorporated realistic ER Ca^{2+} dynamics by introducing reversible refilling of ER stores – a feature missing in previous studies. We performed the rate-based plasticity protocol to study the contribution of RyRs to plasticity at the CA1 spines.

Results

The model predicts crucial role of reversible ER store depletion to regulate the cytosolic calcium levels by restricting the flux through RyRs. We also find that RyRs can potentially enhance LTD when NMDAR conductance is high – a condition prevalent in potentiated spines – and induce LTP at frequencies lower than 15Hz in the rate-dependent plasticity (RDP) protocol. The leftward shift of LTP is more pronounced in spines having smaller NMDAR conductance. Thus, RyRs tune the plasticity depending on the NMDAR contribution.

Future Scope

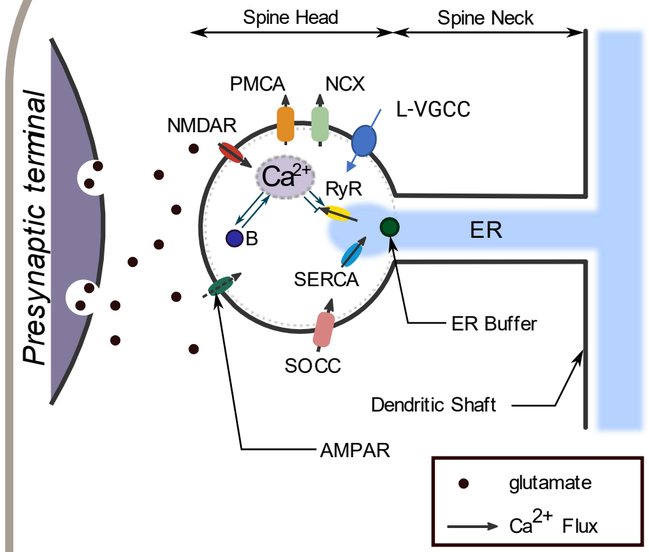
We plan to construct a biophysical model of plasticity by incorporating the dynamics of CaMKII and calcineurin, that are known to bring about plasticity at the hippocampal synapses by protein trafficking and phosphorylation. We also plan to study the effect of adding calcium-dependent potassium channels to the spine to predict the aberrational signalling previously implicated in AD synapses due to elevated cytosolic Ca^{2+} levels. Furthermore, we plan to consolidate the CA1 spine model by incorporating IP_3 receptors in the present model.

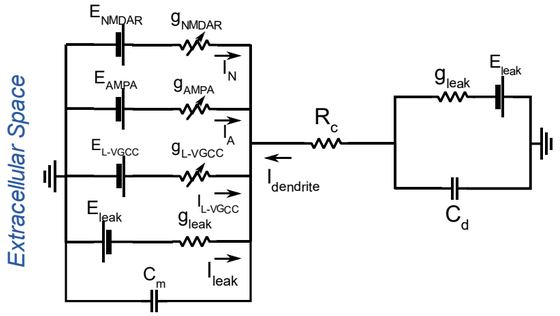
Acknowledgements

We wish to acknowledge the funding from Wellcome Trust/DBT India Alliance for the research. We also thank Indian Institute of Science Education and Research, Pune and College of Engineering, Pune.

Methods

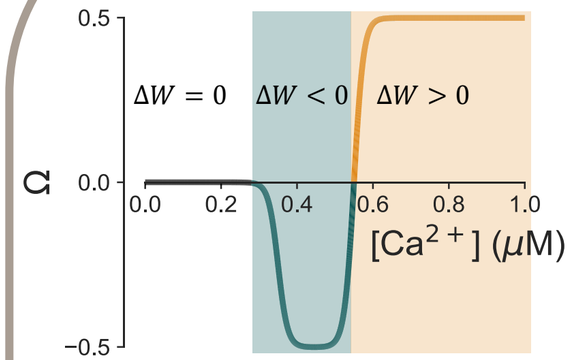
CA1 Spine Model

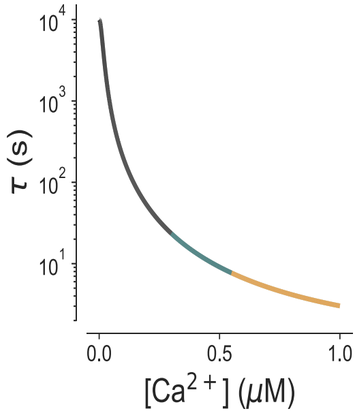




- Spine head is modelled as a sphere of volume $0.06\ \mu m^3$.
- Presynaptic glutamate binds to AMPA and NMDA receptors and causes depolarization of membrane, that activates NMDA receptors to open and bring extracellular calcium in the cytosol.
- Elevated cytosolic Ca^{2+} triggers intracellular Ca^{2+} release from the RyRs.
- SERCAs pump the cytosolic free Ca^{2+} into the ER, whereas PMCA and NCX pump it into the extracellular space. These drive Ca^{2+} against the gradient and are active pumps.
- Ca^{2+} buffers – calbindin and calreticulin present in cytosol and ER respectively – rapidly bind free Ca^{2+} and regulate Ca^{2+} levels.
- The dendritic membrane voltage dynamics are modelled as Hodgkin-Huxley-style equations as described in *Mahajan and Nadkarni 2019.*

Calcium Dependent Plasticity Model

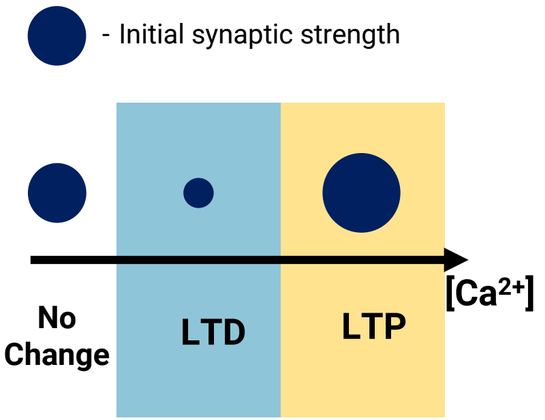




$$\tau(x)\frac{dW}{dt} = -W + \Omega(x)$$

$x =$ Ca^{2+} or aCaM

Calcium Hypothesis:



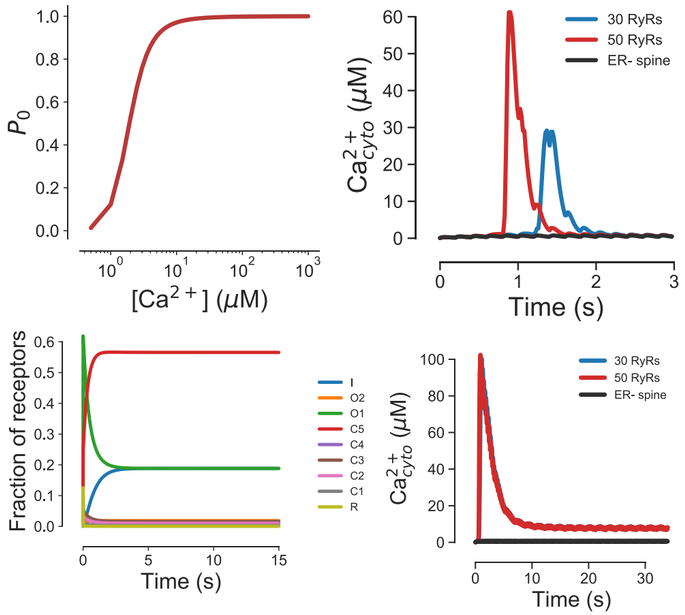
$\Omega(x)$ captures the calcium hypothesis for a given induction variable x – we used aCaM.

$\tau(x)$ is reproduces the distinct time scales for LTD and LTP induction – minutes for LTD and seconds for LTP.

x dependent τ also prevents oscillations in synaptic weights.

Results

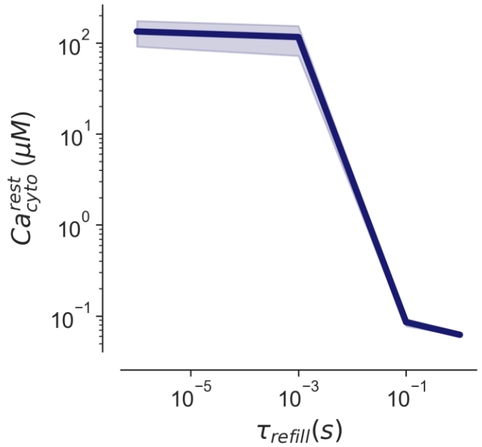
RyR dynamics



- RyR dose response shows sustained activity even at high calcium levels.
- RyRs show transient activity with a Ca^{2+} input, and quick adaptation to a lower open probability state.
- Ca^{2+} efflux from the RyRs, thus, produces a transient peak which decays rapidly.

Distinct biophysical properties of RyRs produce different Ca^{2+} dynamics at the spine

Reversible ER Ca^{2+} depletion and calcium regulation

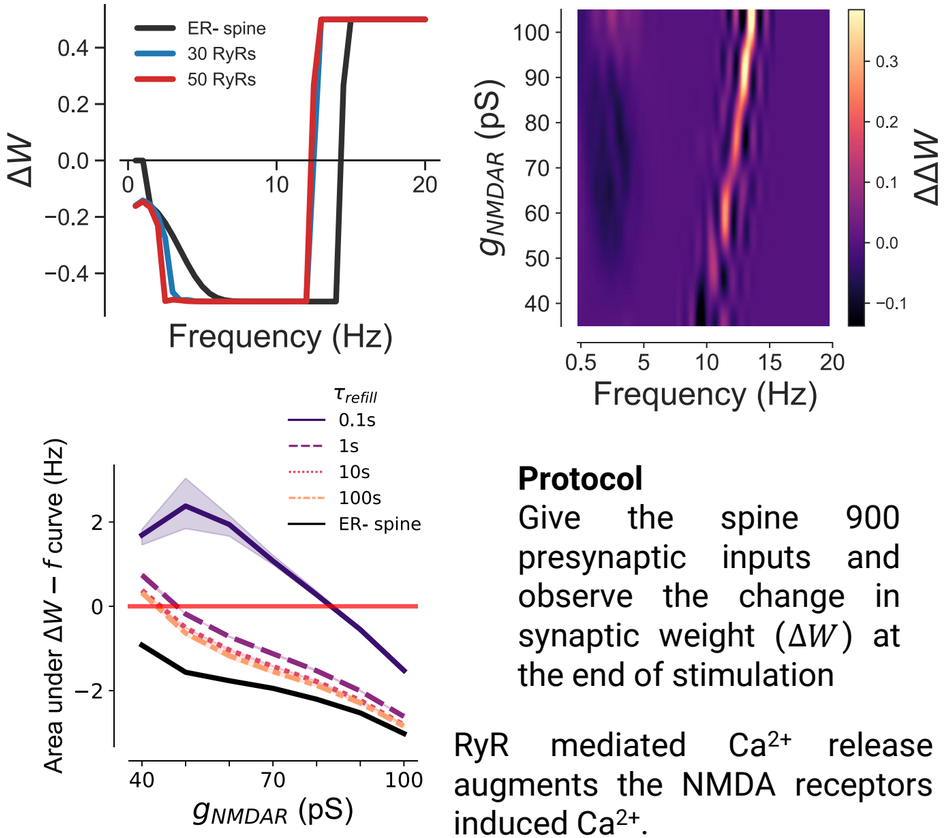


$$J_{refill} = \frac{Ca_0^{den} - Ca_{ER}(t)}{\tau_{refill}}$$

Ca_0^{den} is fixed to 250 μM.

- Previous study considers ER Ca^{2+} clamped to 250 μM.
- Sustained RyR flux and clamped ER Ca^{2+} levels maintain a constant electrochemical driving force for RyR flux, thus elevating resting Ca^{2+} levels to pathological levels.
- Realistic ER Ca^{2+} dynamics restore the Ca^{2+} regulation in the cytosol.

RyRs modulate plasticity at CA1 spine



RyRs mediated Ca^{2+} release stabilizes potentiated synapses and aids smaller synapses to potentiate.

Protocol

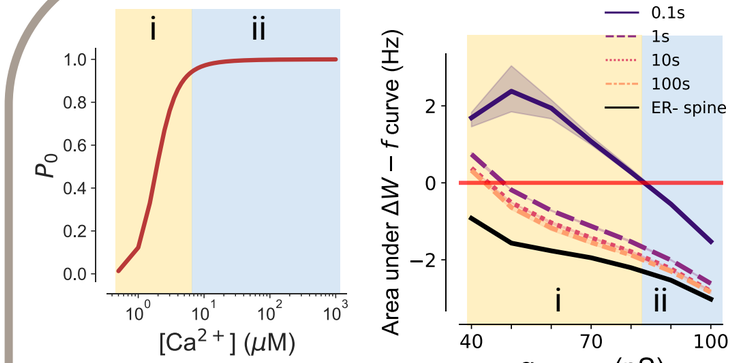
Give the spine 900 presynaptic inputs and observe the change in synaptic weight (ΔW) at the end of stimulation

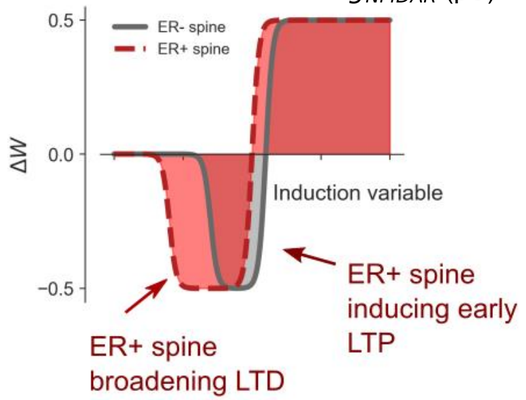
RyR mediated Ca^{2+} release augments the NMDA receptors induced Ca^{2+}.

This lead to:

- Increase in **LTD** magnitude for low NMDAR conductance.
- Induction of **LTP** at frequencies < 15 Hz for high NMDA conductance.

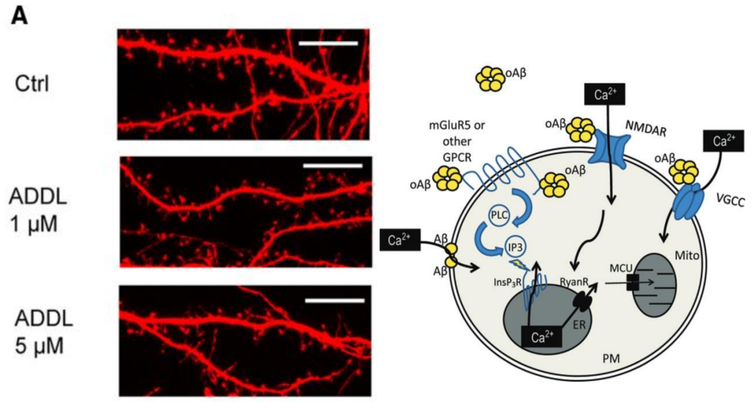
Plasticity modulation mechanism





- **In Linear Region (i)**
  - The RyRs fail to attain their maximum flux, hence, ER stores do not completely deplete out even at high frequency input.
  - This causes LTD to be induced at lower input frequencies.
- **In Saturation Region (ii):**
  - At low frequencies, high NMDA conductance brings in Ca^{2+} in $1-10\,\mu M$ range thus activating the RyRs.
  - RyRs push the Ca^{2+} beyond LTD threshold and increase it's magnitude.

Implications in Alzheimer's Disease



Zhang et al., 2015 *Popugaeva et al., 2018*

- Amyloid β (Aβ) induces loss in mushroom spines in AD synapses.
- Elevated ER and cytosolic Ca^{2+} are observed in AD spines. High Ca^{2+} sets up a positive feedback for Aβ production and also triggers BK channels and supresses firing in the network.
- We found role of RyRs in elevating cytosolic Ca^{2+} levels when ER Ca^{2+} remains fixed. We plan to incorporate BK channels and characterize plasticity modulation in a AD spine.

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