Multi-Scale Simulation of Synaptic Plasticity Induced by Repetitive Magnetic Stimulation

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This paper presents a concise summary of previously published work describing a multi-scale model of location- and frequency-dependent synaptic plasticity induced by repetitive magnetic stimulation (Hananeia a spol., 2025).

Abstract

Repetitive transcranial magnetic stimulation (rTMS) induces long-term synaptic changes, but the mechanisms underlying these effects remain unclear. We developed a biophysically realistic modelling framework that integrates a voltage-dependent plasticity model with neuronal compartment models and electric field simulations to predict repetitive magnetic stimulation (rMS)-induced excitatory synaptic plasticity.

The framework reproduced experimentally observed LTP-like plasticity in hippocampal CA1 pyramidal neurons following 10 Hz repetitive magnetic stimulation, including strong distance dependence and localisation to proximal synapses. Simulations also predicted reduced plasticity at lower stimulation frequencies (5 Hz and 1 Hz). In addition, the model replicated distal synaptic plasticity induced by local electrical theta-burst stimulation and predicted both proximal and distal plasticity during magnetic theta-burst protocols. These responses were strongly facilitated by dendritic spikes and showed limited sensitivity to inhibitory suppression.

This framework enables high-resolution simulation of rMS-induced synaptic plasticity and may improve parameter screening and the design of more effective plasticity-inducing stimulation protocols.

1 Introduction

Transcranial magnetic stimulation has been used clinically for decades, yet its cellular mechanism remains elusive.

TMS induces strong electric fields in the brain tissue beneath the stimulation coil. These fields primarily excite axonal compartments rather than somatic or dendritic membranes, generating action potentials that propagate to the soma and dendrites. The clinical effect is thought to arise from its modulation of neuroplasticity; however, the relationship between the electric fields and long-term synaptic plasticity (long-term potentiation (LTP) and long-term depression (LTD)) remains incompletely understood.

We developed a modelling framework that allows simulation of realistic magnetic stimulation in morphologically complex cells with high spatiotemporal resolution. This allows modelling of plasticity arising from both global (direct electric field induced extracellular voltage) and local (events such as NMDA spikes and large postsynaptic potentials) effects.

Studies (Lenz a spol., 2015) have found strong distance dependence in the response of synapses to magnetic stimulation, wherein proximal synapses are potentiated far more strongly than distal ones by a 10 Hz magnetic stimulation protocol.

Using a reduced morphology model of the CA1 pyramidal cell, we were able to reproduce the distance-dependent pattern of magnetic stimulation induced LTP. Additionally, we predict frequency-dependent potentiation, with higher frequencies producing stronger effects. Finally, we found that high-frequency theta-burst magnetic stimulation of 100 Hz can induce potentiation in distal tuft synapses.

2 Methods

All simulations were implemented in NEURON using the NeMo-TMS toolbox (Shirinpour a spol., 2021) with a biophysically detailed but morphologically reduced CA1 pyramidal cell model (Tomko a spol., 2021). This reduced model has many of the morphological features typical of a CA1 pyramidal cell, but is far less complex than a complete reconstruction. It has two basal dendrites that each have two branches, as well as a single apical dendrite with a thickened trunk that branches into two thin tufts. Additionally, it has three oblique branches connecting directly to the apical dendrite (Fig. 1).

Because magnetic stimulation initiates action potentials in axonal locations, an explicit axon was included in the model. This consisted of an initial segment, an unmyelinated terminal segment, and myelinated internodal segments. Myelinated internodes were included to enable reliable magnetic-stimulation-induced firing; rMS-initiated action potentials do not occur without myelination.

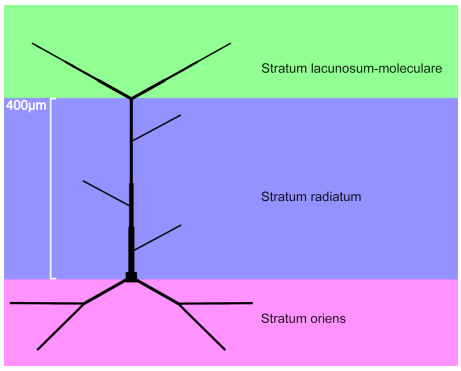

Fig. 1: Schematic of reduced model of CA1 pyramidal cell with layers highlighted.

The model has many ion channels, and is tuned to reproduce the electrophysiological behavior of the biological cell, and its behavior is independently validated by the HippoUnit test suite (Sáray a spol., 2021).

Simulation of the rMS-induced magnetic field was done using the NeMo-TMS toolbox. The toolbox's uniform magnetic field option was chosen for simplicity as we modelled an in-vitro experiment, where complex geometry of neural tissue was not a factor. Here, the magnetic stimulation is implemented as an extracellular potential at every compartment in the model, shown in equation 1, where V_e is the extracellular voltage, E is the electric field vector, and ds is the differential over a given segment of membrane, and $E_{(x,y,z)}$ are the x, y, and z components of the electric field at location (x, y, z):

$$V_e(x,y,z) = -\int \vec{E}\cdot d\vec{s} = -\vec{E}\cdot\vec{s} = -(E_x x + E_y y + E_z z) \quad (1)$$

The temporal component is encoded in a separate timecourse which is multiplied by this uniform spatial component; the time course also contains the temporal shape (monophasic or biphasic) of the stimulus. These temporal shapes are based on recorded waveforms from real stimulators and are included in the NeMo-TMS framework.

When simulating an rMS pulse we stimulated all synapses simultaneously with the extracellular voltage application, with a delay of 1ms between the magnetic stimulus and the synaptic activation. This was chosen because rMS strongly activates axon terminals without the activation of their cell bodies, which would lead to synaptic activation.

To model synaptic plasticity, we used the synaptic plasticity model of Ebner et al. (Ebner a spol., 2019) for AMPA/NMDA synapses and the non-plastic Exp2Syn method with a negative reversal potential was used for GABA synapses.

The Ebner model is a voltage-based phenomenological plasticity model of a combined AMPA/NMDA synapse with internal variables corresponding to biophysical processes. It considers four separate pathways of plasticity: presynaptic LTP, presynaptic LTD, postsynaptic LTP, and postsynaptic LTD.

128 excitatory AMPA/NMDA synapses and 18 inhibitory GABA synapses were placed in all layers of the cell and assigned to the various layers in the model (see Fig. 1), based on relative synapse numbers in Megıas a spol. (2001).

3 Results

3.1 Validation of the synaptic plasticity model for local electrical simulation

Since our synaptic plasticity model was not tuned for the CA1 region, we used the experiments of Ikegaya et al. (Ikegaya a spol., 2002). In this experiment, the cells were directly electrically stimulated by a series of 900 pulses delivered to the Schaffer collaterals (stratum radiatum and stratum oriens targets) at a constant frequency of either 1, 10, 30, or 100 Hz. In these experiments, weight changes were measured both with inhibition present and absent.

After adjusting the parameters of our model, we found results within observed standard deviation for all conditions except for the 1 Hz and 10 Hz control cases. The change in synaptic weights was negligible at frequencies below 10 Hz (Fig. 2).

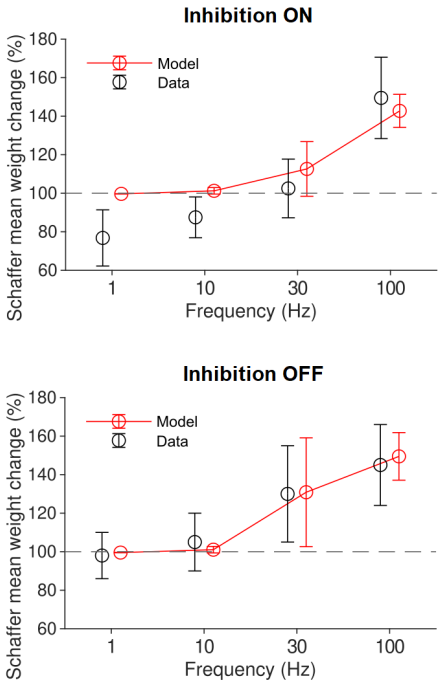

Fig. 2: Model reproduces electrical stimulation data from Ikegaya et al. for most frequencies. Top: Frequency dependence with inhibition on. Bottom: Frequency dependence with inhibition off.

3.2 Proximal LTP induction by repetitive magnetic stimulation

To determine whether our plasticity model would be applicable to a realistic rMS protocol, we simulated the experiments of Lenz et al. (Lenz a spol., 2015). In this study, an rMS of 900 pulses at 10 Hz was applied to hippocampal slice cultures. We modeled this with a train of 900 monophasic pulses with an amplitude of 275 V/m, which is above the cell's firing threshold.

As a result, the mean Schaffer collateral weight increased by 30%, with the LTP induction strongly localized in the proximal dendrites, consistent with what was observed in Lenz. Considering only the proximal dendrites of the stratum radiatum, we observed an average weight increase of 65% above baseline, whereas the distal synapses on the apical dendrite showed no LTP.

To predict the frequency dependence of synaptic plasticity induced by this rMS protocol, we also delivered 900 stimuli at lower frequencies of 1, 5, 6, 8, and 9 Hz. Proximal LTP was induced, with the amount of potentiation much less at lower frequencies (Fig. 3).

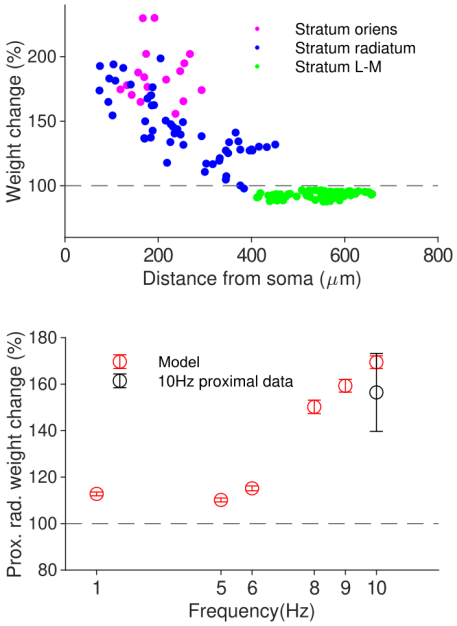

Fig. 3: Potentiation from 10 Hz magnetic stimulation is much stronger in the proximal dendrites than distal, and is stronger with higher frequencies. Top: Distance dependence of weight change in response to 10 Hz 900 pulse stimulus. Bottom: Frequency dependence of average weight change in proximal (<200 μm) synapses.

Consistent with data, our simulations showed that rMS induced LTP at much lower frequencies (10 Hz vs 30-100 for classical protocols) than commonly used plasticity inducing protocols.

3.3 Distal LTP induction by theta-burst stimulation protocols

To determine what conditions could show LTP elicitation at greater distances, we implemented a simulation of a theta-burst stimulation protocol.

Induction of LTP in these distal synapses has been shown to require the presence of dendritic spikes (Kim a spol., 2015). Since our plasticity model is capable of generating responses to subthreshold local events, we investigated if our model could reproduce this.

We applied a local electrical stimulation protocol of 15 bursts of 5 pulses at 100 Hz, applied only to the synapses in the distal tuft. We repeated the same protocol both with and without inhibition present, since in the study of Kim et al. (Kim a spol., 2015), inhibition was blocked to facilitate dendritic spikes.

As a comparison to these local electrical stimuli, we investigated the effect of rMS applied in a similar theta-burst fashion. In these cases, the rMS-like stimulus was a biphasic pulse delivered at 275 V/m. Because this was modelling magnetic stimulation, all synapses were activated simultaneously with the magnetic pulse, similarly to in Section 3.2.

We compared the LTP/LTD distance profiles of all four cases - local electric stimulation and magnetic stimulation both with and without inhibition. With purely electric TBS and no inhibition, LTP was observed in the distal tuft, along with the presence of dendritic spikes. With inhibition present, the dendritic spikes were abolished, and LTP greatly reduced (Fig. 4).

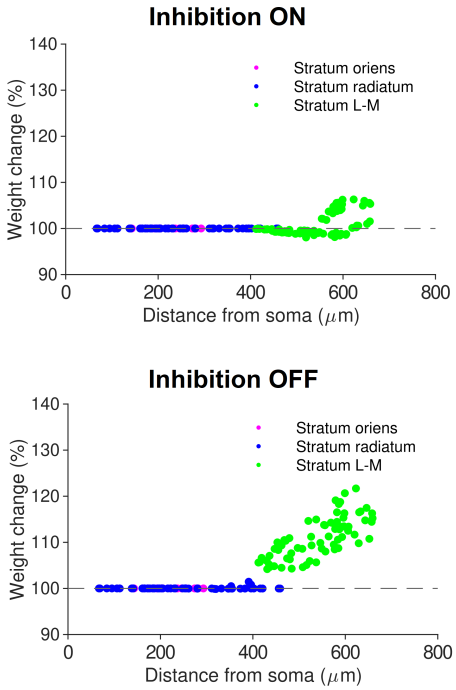

Fig. 4: Electrical theta-burst stimulation produces LTP in distal tuft when inhibition disabled. Top: Inhibition on. Bottom: Inhibition off.

With the magnetic stimulation, however, we observed LTP not only in the proximal branches, but in the distal tuft, both in the presence and absence of inhibition. In these cases, proximal LTP was of similar magnitude to distal LTP, unlike in our 10 Hz simulations (Fig. 5).

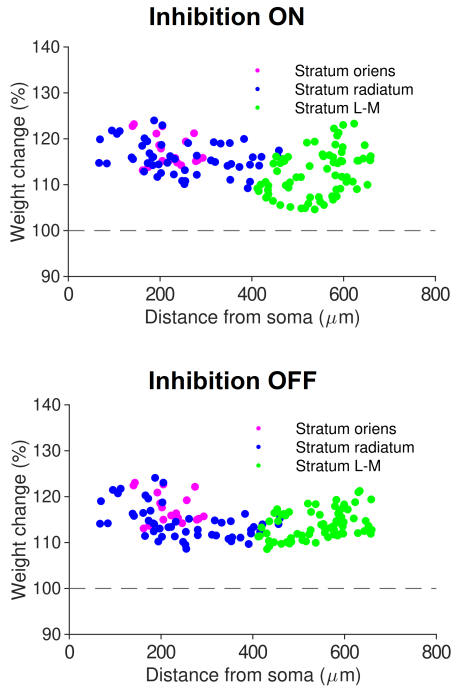

Fig. 5: Magnetic theta-burst stimulation produces LTP all over the cell both with and without inhibition. Top: Inhibition on. Bottom: Inhibition off.

4 Discussion and Conclusion

We present a modelling framework capable of reproducing experimentally observed location-dependent synaptic plasticity induced by repetitive magnetic stimulation. The model replicated the key finding of distance-dependent potentiation of proximal synapses, with decreasing synaptic change with increasing distance.

Furthermore, we predict a dependence of potentiation magnitude on stimulation frequency, with stronger synaptic potentiation at higher frequencies.

Finally, the model suggests that distal tuft synapses can be potentiated by theta-burst stimulation: locally, through dendritic spike induction, and magnetically, through a similar burst protocol.

Our voltage-dependent model explains these observations: simpler spike-dependent plasticity models would not capture attenuation of backpropagating action potentials. Inhibition can further modulate this process, as inhibitory postsynaptic potentials reduce the efficacy of backpropagating action potentials. Similarly, dendritic spikes mediated by voltage-gated sodium channels are often subthreshold but, in our model, were crucial for distal tuft potentiation under theta-burst stimulation.

Limitations of the model include the absence of metaplasticity (Abraham, 2008) and inhibitory plasticity (Lenz a spol., 2016), both of which may influence responses during prolonged stimulation. In particular, disinhibition is a known mechanism for facilitating excitability and plasticity (Lenz a Vlachos, 2016). We also employed a reduced single-cell morphology rather than a complete cell reconstruction and did not model network-level effects, which are likely relevant given the large tissue volumes stimulated by TMS. These remain important directions for future work.

Overall, this study shows that biophysically grounded modelling can reproduce known effects of repetitive magnetic stimulation while generating testable predictions for new protocols. Such approaches may help guide future experimental design and optimisation of stimulation paradigms.

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