ROLE OF SHORT-TERM DYNAMICS OF SYNPSES BETWEEN DENTATE GYRUS INTERNEURONS IN SHAPING EXCITABILITY IN NORMAL AND EPILEPTIC CIRCUITS

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A Thesis submitted to the Graduate School of Biomedical Sciences, Rutgers, The State University of New Jersey in partial fulfillment of the requirements for the MS Degree

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July 2016
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This work was supported by the Santhakumar Laboratory and Rutgers Graduate School of Biomedical Sciences. I would specifically like to thank my mentor, Dr. Viji Santhakumar, for always being so generous with her time and advice, and for her in-depth comments and explanations. I would also like to thank my Thesis Advisory Committee, Dr. Catherine Myers and Dr. Josh Berlin, for sharing their expertise throughout this process. Additional thanks to Archana Proddutur for her help in developing this project, and to the entire Santhakumar Laboratory for their support and guidance.
ABSTRACT

Temporal lobe epilepsy (TLE) is a relatively common form of epilepsy that is difficult to manage and is characterized by recurrent unprovoked seizures originating in the temporal lobe of the brain. Seizures in TLE often start in the hippocampus, and are associated with structural and functional changes in the dentate gyrus (DG), a region within the hippocampus. Seizure activity can lead to physiologic changes that can underlie or worsen the severity of epilepsy. In order to elucidate the mechanisms underlying TLE, it is important to develop a detailed understanding of the specific physiological changes and their effects on network activity patterns.

The main projection neuron in the DG is the granule cell (GC), an excitatory neuron. However, most of the other cell types in the DG are inhibitory interneurons. Two of these inhibitory interneurons are parvalbumin-expressing, fast-spiking basket cells (fsBCs), and accommodating cells (ACs). Recent research has shown that the synapses between ACs and fsBCs show a functional reduction in reliability of synaptic transmission after experimental seizure induction. Previous studies identified that this change affects oscillatory coupling in simulated networks including fsBCS and ACs. Similar network oscillation disruptions in the DG have been linked to complications of epilepsy. In addition to baseline characteristics of synaptic release, synapses show activity-dependent changes in synaptic properties. Of particular relevance, synapses from fsBCs undergo short-term depression and synapses from ACs undergo short-term facilitation. However, the impact of such short-term synaptic dynamics on large-scale circuit activity patterns is not commonly modeled.

This study used computational modeling to examine how the short term dynamics of synapses between ACs and fsBCs modify network excitability and oscillations in networks with normal and epileptic synaptic characteristics. A model of the facilitation-depression synapse was successfully implemented in the NEURON
programming environment and applied to a network of DG excitatory and inhibitory neurons. Cell-type specific short term synaptic dynamics were constrained based on published experimental data in specific cell types. Excitability was compared between models of a control network of DG neurons and a post-seizure network of DG neurons. The post-seizure network was modeled to mimic the functional reduction in reliability between ACs and fsBCs seen in experimental seizure induction by decreasing the probability of synaptic release in response to firing. Implementation of the seizure-induced decrease in AC to fsBC synaptic release probability failed to alter average granule cell firing frequency and duration in response to synchronous afferent activation. Excitability was also compared between networks incorporating synapse specific short term synaptic dynamics and networks that did not. Inclusion of short term synaptic dynamics led to modest increases in excitability which were not statistically significant. In contrast to the limited change in excitability, comparison of oscillatory behavior between control and post-seizure networks revealed an increase in coherence and a change in frequency power spectra. Addition of short term synaptic dynamics resulted in decreased coherence and a change in frequency power spectra. Overall, it was shown that a decrease in functional reliability in AC to fsBC synapses, when modeled with biologically realistic facilitation-depression synapses, has little effect on network excitability, but significant effects on network oscillatory behavior.
INTRODUCTION

Temporal Lobe Epilepsy and the Hippocampus

Epileptic seizures are defined as a transient occurrence of hypersynchronous or hyper-active neuronal firing in the brain that manifests in a wide array of clinical features, such as affecting sensory function, motor function, consciousness, and memory (Fisher, et al. 2005). Epilepsy is a neurological disorder characterized by unprovoked seizures and leads to a predisposition to further epileptic seizures, along with other enduring symptoms (Fisher, et al. 2005).

Temporal lobe epilepsy (TLE) is a form of epilepsy where seizures originate in the temporal lobe. TLE is the most common form of epilepsy, and one of the most difficult to control; as a result, it is the type of epilepsy with the greatest incidence of surgical intervention (Wiebe 2000).

Seizures in TLE propagate from the temporal lobe, but often start specifically within the hippocampus. The hippocampus is an important part of the limbic circuit, and has been shown to be critical to memory, learning, and higher level cognition (Kesner 2007). As a result, patients who suffer from TLE often exhibit symptoms such as spatial memory deficits (Chauviere, et al. 2009) and personal episodic memory deficits (Viskontas, McAndrews and Moscovitch 2000), indicating altered hippocampal function, in addition to affective disorders (Perini, et al. 1996).

The hippocampus is divided into two main regions—the dentate gyrus (DG), and Ammon’s horn, or cornu Ammonis (CA). The CA is further divided into several sections, the most important of which are CA1 and CA3 (see figure 1.1). Input to the hippocampus comes from the entorhinal cortex via the perforant path (PP) to the DG, where it then goes to CA3, and then CA1; this makes up the hippocampal trisynaptic circuit. The DG has been identified as being critical to the etiology and pathology of
TLE, and therefore has become an important focus of research in this area (R. Sloviter 1994).

**Dentate Gyrus: Structure and Role in Epilepsy**

The dentate gyrus is a trilaminar structure with the main inputs located in the molecular layer. The major projection neurons of the DG, the granule cells (GC), reside in the granule cell layer. Granule cell axons, the mossy fibers, project through the polymorphic hilus to CA3. GCs are excitatory neurons that use glutamate as their neurotransmitter and stimulate the pyramidal neurons of the CA3 region of the hippocampus (Sloviter, et al. 1996). CA3 pyramidal neurons then stimulate, via Schaffer collaterals, CA1 pyramidal neurons. Both of these pyramidal neurons are excitatory, utilize glutamine as a neurotransmitter, and act as the main projection neuron for their respective region (Yeckel and Berger 1990).

![Figure 1.1: Schematic of the hippocampus showing DG, CA1, and CA3 regions, adapted from (Ramon Y Cajal 1911).](image)

There is extensive inhibition of hippocampal and DG projection neurons via many types of interneurons found in the CA and DG (Yeckel and Berger 1990). These interneurons use gamma-amino butyric acid (GABA) as a neurotransmitter and each have their own characteristics including layer specific projections,
biophysical properties, excitation patterns, synaptic release, and kinetics. Two significant inhibitory interneurons found in the DG include parvalbumin (pv) expressing, fast-spiking basket cells (fsBCs) and cholecystokinin (cck) producing, accommodating cells (ACs). A schematic showing the various cell types of the DG is shown in figure 1.2.

![Schematic of cell types in DG](image)

**Figure 1.2**: Schematic of cell types in DG. Adapted from (Santhakumar and Soltesz 2004).

FsBCs play a major role in the DG by providing perisomatic inhibition of GCs (Freund and Buzsaki 1996). This function allows fsBCs to modulate gamma-frequency oscillations (Bartos, et al. 2002), an important, interneuron-regulated property of the DG (Bragin, Jando, et al. 1995). ACs (also referred to as hilar commissural-associational pathway (HICAP) cells) also have a major role in the DG, partly through their inhibition of fsBCs. Inhibition of fsBCs by ACs has the potential to contribute to theta and gamma network rhythms (White, et al. 2000), and synapses between ACs and fsBCs are altered during epilepsy, which causes changes in
gamma oscillations (Yu, Proddutur and Swietek, et al. 2015). This is significant because these oscillations are the foundation of temporal encoding in the DG (Pernia-Andrade and Jonas 2014). Morphological reconstruction, firing pattern, and immunostaining of fsBCs and ACs are shown in figure 1.3.

**Figure1.3:** Physiology of fsBCs and ACs. (A) Morphology of fsBCs showing axons (in red) in the GC layer (GCL). Fast-spiking firing pattern is shown below (in red) and the inset shows immunostaining of fsBCs with biocytin (left) pv (middle) and the merged image (right). (B) Morphology of HICAP (a subset of ACs) showing axons distributed outside the GCL. Accommodating firing pattern is shown below (in black) and the inset shows immunostaining with biocytin (left), cck (middle) and the merged image (right). Adapted from (Yu, Proddutur and Elgammal, et al. 2013)

The hippocampus in general is a key structure for memory encoding of spatial and contextual information (Jarrard 1993). The DG in particular has been shown to be important in contributing to working memory (Friedman and Goldman-Rakic 1988) and in keeping distinct memories isolated, or pattern separation, in conjunction with the CA3 (Bakker, et al. 2008). Another important characteristic of the DG is that it has been shown to undergo neurogenesis, with new GCs being
produced into adulthood (Altman and Das 1965), (Ming and Song 2005). This neurogenesis is important to memory formation (Aimone, Wiles and Gage 2009), and newly created GCs are preferentially integrated into networks supporting spatial memory (Kee, et al. 2007).

During seizure activity, several major changes occur in the DG. Some of these changes occur at the receptor level, such as a change in GABA receptor expression in GCs (Brooks-Kayal, et al. 1998). Other changes include neuron loss and axon reorganization (Buckmaster and Dudek 1997), changes to neurogenesis (Scott, Wojtowicz and Burnham 2000), and, significantly, mossy fiber sprouting and reorganization (Sutula, et al. 1989), (Wuarin and Dudek 1996) (Zhang and Houser 1999). Changes in the DG during seizure activity are known to increase susceptibility to future seizures (R. Sloviter 1994), and mossy fiber sprouting in particular has been shown to provide a major contribution to network excitability (Santhakumar, Aradi and Soltesz 2005). Mossy fibers, the excitatory axons from GCs, do not normally synapse with other DG GCs; however, in mossy fiber sprouting after TLE, these axons synapse with other GCs. This is modeled as the addition of GC to GC synaptic connections (Santhakumar, Aradi and Soltesz 2005).

**Short Term Synaptic Dynamics**

Synaptic transmission between inhibitory interneurons and from inhibitory neurons to GCs follows a predictable pattern of short-term, rapid plasticity which can be either facilitation or depression, followed by recovery (Savanthrapadian, et al. 2014). Repeated action potentials from the pre-synaptic cell create an increasing (for facilitation) or decreasing (for depression) post-synaptic response in the target cell; however, once the pre-synaptic action potentials are stopped, the post-synaptic response slowly recovers to the original response (see figure 1.4). This behavior is
seen in many types of neurons, including those of the DG. Specifically, synapses from ACs have been shown to exhibit facilitation, while synapses from fsBCs have been shown to exhibit depression (Savanthrapadian, et al. 2014).

Short-term plasticity is functionally important in determining inhibitory efficacy and in shaping network excitability and input processing. For example, fsBCs are important for rapid feed-forward or feedback inhibition; however, during seizure activity, fsBCs may not be able to sustain prolonged inhibition due to excessive depression. Additionally, because ACs undergo facilitation, they may be crucial for sustained inhibition during seizure activity. Despite the importance of short-term plasticity in network behavior, it is mostly excluded from large scale network models (Santhakumar, Aradi and Soltesz 2005) (Yu, Proddutur and Elgammal, et al. 2013) (Proddutur, et al. 2013).

Computational Modeling to Understand Altered Network Activity Patterns in Epilepsy

Simulations of neuronal networks using a computational model allow for a greater level of control over the network than in a biological experimental setup. Using computational modeling, a set number of cells with specific properties can be connected into a randomly or experimentally constrained connected network, and each variable can be changed individually to determine its effect on activity patterns in the whole network.
Figure 1.4: Electrophysiologic recordings from interneurons of the DG demonstrating depression then recovery (A), and facilitation then recovery (B), adapted from (Savanthrapadian, et al. 2014).

NEURON is a software package designed to accurately model both single neurons and a network of many neurons (Carnevale and Hines 2006). This software allows for the specification of many properties, and its functionality can be augmented by NMODL. NMODL is a programming language that can be introduced into NEURON to modify parameters of a particular cell that affect its firing or synaptic pattern, and can be applied to many synapses in a network. These tools have been used in many studies to determine network activity in physiologic and pathologic conditions (Proddutur, et al. 2013) (Borgers, Epstein and Kopell 2005) (Vida, Bartos and Jonas 2006). However, these studies do not include a mechanism to account for the effects of short-term synaptic dynamics. Using computational modeling allows for further exploration into both baseline activity patterns of networks, and the effects and significance of biologically determined changes in epilepsy.

Significance
While there are many physiologic changes that occur as a result of epilepsy, one that has been recently identified is the decrease in functional reliability of AC to fsBC synaptic transmission (Yu, Proddutur and Swietek, et al. 2015). This is associated with disruptions in the oscillations of these neuronal networks, as demonstrated by computational modeling (Yu, Proddutur and Swietek, et al. 2015). Disruptions in network oscillations of the DG can be linked to memory deficits associated with epilepsy (Bragin, Wilson, et al. 2004) (Montgomery and Buzsaki 2007) (Jutras, Fried and Buffalo 2009).

Although it is known that short-term synaptic dynamics shape inhibitory efficacy, their role in oscillations and epileptic circuits has not been examined. There are currently models for synapses that include short term plasticity; however, these models do not include a mechanism for recovery from activity-dependent changes (NEURON ModelDB Accession number 3264 based on short-term synaptic plasticity described in (Varela, et al. 1997). This lack of recovery mechanism precludes their use in network activity patterns that include episodic and periodic changes in activity levels.

Including the synaptic dynamics is crucial to understanding network activity in epilepsy particularly because epilepsy is a disorder of dynamical network function. Indeed, the same network structure leads to episodic spontaneous increases in excitability pointing to a critical role for activity dependent changes in the generation of seizures. Since short term plasticity of inhibition is a major factor in shaping inhibition, it stands to reason that it may contribute to seizure initiation. Differences in AC and fsBC synaptic dynamics are potentially important, yet understudied components in understanding how network activity is altered in TLE. Therefore, this study seeks to develop a recovery mechanism for an existing model of short-term
synaptic plasticity, and incorporate it into an existing model of the DG. This updated model will then be used to determine the effect of experimental seizure induced changes to the AC→fsBC synapse on network activity.
RATIONALE

Earlier studies have shown that AC→fsBC synapses are altered in experimental epilepsy, and that these changes disrupt network oscillations (Yu, Proddutur and Swietek, et al. 2015). However, whether or not these changes cause the hyperexcitable state, characteristic of epilepsy, in the neuronal network remains to be examined. It has also been shown that fsBC synapses show short term depression and AC synapses show synaptic facilitation. However, how the cell-specific differences in synaptic dynamics influence excitability and activity of the normal and epileptic dentate gyrus remains to be examined. This thesis extends existing models of short-term synaptic dynamics to included recovery from short term plasticity, and implements synapses constrained by cell-type specific dynamics from experimental literature, to test the hypothesis that short-term plasticity of fsBC and AC interneuron synapses coupled with post-seizure changes in AC→fsBC synapses promote a hyperexcitable state and altered rhythmogenesis within the dentate gyrus neuronal network.

Specific Aim 1: Develop a computational model for biologically realistic facilitation/depression synapses between neurons of the DG. Constrain simulated synapses to reliably reproduce the distinct cell-type specific facilitation, depression and recovery characteristics of biological fsBC→fsBC, AC→AC and AC→fsBC synapses measured in electrophysiological studies.

Specific Aim 2: Model a “control” dentate network incorporating GCs, fsBCs and ACs including the synaptic dynamics developed in Aim 1 to determine the effect of short term synaptic dynamics on activity patterns in the simulated control dentate network model. The simulation results will be used to compare excitability and
oscillatory behavior with previous implementations of the network model without short-term plasticity.

Specific Aim 3: Simulate “experimental” networks with a post-seizure synaptic dynamics between inhibitory neurons, and determine if it exhibits a hyperexcitable state or altered oscillatory dynamics, indicating its contribution in seizure activity, pathology and the progression of epilepsy. This post-seizure network will be different from the control network by reducing the reliability in synaptic transmission across the AC→fsBC synapse, a change that has recently been discovered to occur after seizure activity (Yu, Proddutur and Swietek, et al. 2015).
MATERIALS AND METHODS

Existing Synaptic Models

The NEURON programming environment comes equipped with several built-in mechanisms for modeling synapses. The Exp2Syn model is a point process that models synaptic transmission as a relatively quick exponential rise in synaptic conductivity (described by the time constant $\tau_1$) followed by a relatively slower exponential decay in synaptic conductivity (described by the time constant $\tau_2$). This function can summate multiple presynaptic inputs over time and from multiple different sources. However, this function does not account for synaptic plasticity.

This function has previously been expanded into the FDSExp2Syn function (NEURON ModelDB accession number 3264) to account for facilitation and depression as described by (Varela, et al. 1997). The facilitation and depression synapses (FDS) function by modifying by a gain factor that affects the standard maximum post-synaptic membrane conductance ($G$) after an action potential, increasing or decreasing it, respectively. This allows for the increased or decreased post-synaptic response with each repeated action potential. While this new function accounts for short-term synaptic plasticity, it does not allow for synaptic behavior to recover to baseline post-synaptic response.

Mathematically, the FDSExp2Syn function relates membrane conductance of the post-synaptic cell ($G$) to the amount of facilitation ($F$) or amount of depression ($D$) by the relations $G \sim G + (p \cdot k \cdot F)$ and $G \sim G + (p \cdot k \cdot D)$ for the facilitation and depression synapses, respectively; $p$ represents the probability of an action potential leading to a post-synaptic response (probability factor $p$ is based on a modification of FDSExp2Syn in (Yu, Proddutur and Elgammal, et al. 2013)), $k$ is a factor that represents the standard post-synaptic response for the cell type and synapse...
location, and F and D both equal 1 in the absence of facilitation or depression. Note
that D was broken into two separate factors, D_1 and D_2, so that depression could
occur at two different time courses. Each successive action potential increased F
and decreased D_{1,2} by the factors (f) and (d_{1,2}), such that after each action potential
F=F+f, D_1=D_1*d_1, and D_2=D_2*d_2 where 0<f<1 and 0<d<1. The effect of D_1 and D_2 was
combined mathematically in the program, so they will be grouped together here as
well.

F and D were also modulated based on how much time passed between
successive action potentials by the equations:

\[
F = 1 + (F - 1) \times e^{-\frac{(t_2 - t_1)}{\tau_f}} \\
D = 1 - (1 - D) \times e^{-\frac{(t_2 - t_1)}{\tau_d}}
\]

where \(\tau_f\) and \(\tau_d\) represent time factors that can be adjusted to modulate the amount
of facilitation and depression over time, \(t_2\) is the time of the current action potential,
and \(t_1\) is the time of the last action potential. This ensures that action potentials that
occur in closer proximity lead to more facilitation or depression than would occur if
they were timed farther apart.

**Implementation of Recovery in Facilitation Depression Synapses**

In order to incorporate facilitation and depression into the model network,
computational synapses were implemented that could account for this phenomenon
along with a recovery mechanism. These computational synapses were developed
from the FDSExp2Syn function mentioned above, and are synapse specific; only the
specific synapse that fires shows facilitation or depression.

The FDSExp2Syn function was modified to have physiologically based
characteristics assigned such that the post-synaptic response during an action
potential train matched electrophysiological data observed from cell pairs in previous
studies (Savanthrapadian, et al. 2014). This included adjusting values of $\tau_f$, $\tau_d$, $f$, $d_1$, and $d_2$. Additionally, to modify synaptic kinetics to match physiological data, $D_2$ was changed to $D_2 = D_2 - d_2$ with a minimum value put on $D_2$ to prevent depression from exceeding physiologically observed depression. Finally, FDSEp2Syn was updated to incorporate a recovery mechanism such that in the absence of action potentials for a certain duration, the synapse begins to “recover.” Recovery decreased the amount of change that facilitation or depression causes exponentially with time. This feature was not included in earlier versions of the synapse model and was implemented here by resetting the gain factor at a recovery time course. The threshold for the amount of time that needs to pass with an absence of action potentials before recovery begins was set to 30 ms. This threshold was chosen because this is approximately the minimum amount of time that is required to pass before any recovery becomes noticeable, based on interpolating results from (Savanthrapadian, et al. 2014).

The FDSEp2Syn function was then modified so that once the absence of action potentials lasted beyond the 30 ms threshold, the amount of facilitation and depression became modified by the equations:

\[
F = 1 + (F - 1) * e^{-\beta_f(t_2-t_1)} \\
D = 1 - (1 - D) * e^{-\beta_d(t_2-t_1)}
\]

where $\beta_f$ and $\beta_d$ represent factors that can be adjusted to modulate how quickly or slowly recovery occurs. This recovery mechanism will continue to function in successive resets; that is, even after recovering from short-term plasticity, the affected synapse will demonstrate plasticity, and be able to recover from that plasticity, for an indefinite number of repetitions. The NMODL code for the updated FDSEp2Syn synapse function can be found in appendix A, formatted for clarity on how it was changed.
Assessment of Synaptic Function

The facilitation/depression and recovery dynamics were assessed to ensure they mimic biological synapses. To measure these properties, a computational setup was designed with a two-cell sample network: one pre-synaptic and one post-synaptic. A train of 10 action potentials at 50 Hz (to mimic the setup from biological recordings in (Savanthrapadian, et al. 2014) from the pre-synaptic cell evoked synaptic responses the post-synaptic cell through the facilitation or depression synapse, and the post-synaptic response over time was recorded. After the 10th action potential, the pre-synaptic cell rested for a variable period of time to allow the post-synaptic cell to recover to its original response. After the variable recovery period, a final pre-synaptic action potential stimulated the post-synaptic cell, and the post-synaptic response was recorded. This test was performed with 11 different recovery periods for the facilitation synapse (0.05, 0.1, 0.2, 0.4, 0.8, 1.2, 1.5, 2, 3, 5, and 8 seconds) and 12 different recovery periods for the depression synapse (0.05, 0.1, 0.2, 0.4, 0.6, 0.8, 1.2, 1.6, 2, 3, 6, and 9 seconds). This test was repeated for both the Exp2Syn and FDSExp2Syn synapses to compare their function, with a recovery period of 0.2 seconds.

Model Networks

The model for the DG neuronal network used here was adapted from (Santhakumar, Aradi and Soltesz 2005), and modified as detailed in (Proddutur, et al. 2013) and (Yu, Proddutur and Swietek, et al. 2015). The network model included 1000 GCs, 200 ACs, and 200 fsBCs. Homotypic inhibitory neurons were arranged in concentric rings, with connections randomly generated between cell types as pictured in figure 2.1. Synaptic parameters and number of connections for specific cell types are displayed in table 2.1. Additionally, intrinsic firing properties for fsBCs
are pictured in figure 2.2. The two interneurons (ACs and fsBCs) provide significant inhibitory signals to the network, and in biological systems exhibit short-term facilitation or depression inhibitory postsynaptic potential (IPSP) amplitude in response to repeated action potentials. Individual IPSP kinetics was based on cell-type specific data (Santhakumar, Aradi and Soltesz 2005). Facilitation and depression have not previously been included in large-scale computational models of this network.

Figure 2.1: Network Schematic of control (a) and post-seizure (b) networks showing network connections between GCs, ACs, and fsBCs, and a theta-frequency current injection. Decreased firing probability from AC to fsBCs in post-seizure network is displayed as a dotted line in (b). While this network schematic describes the setup when testing the oscillatory behavior of the network, note that for excitability simulations the theta-frequency injection current was replaced by stimulation simulating PP input. Additionally, sprouting (addition of GC to GC synapses) is not pictured. Adapted from (Yu, Proddutur and Elgammal, et al. 2013).

For simulations testing the oscillatory nature of the network, a current injection was used to stimulate the neurons. A base current of 200 pA (for GCs and ACs) and 500 pA (for fsBCs) was modulated by a sinusoidal current of 50 pA at various frequencies within the theta range (4, 6, 8, 10, and 12 Hz) and injected into each cell (Proddutur, et al. 2013).
<table>
<thead>
<tr>
<th></th>
<th>AC</th>
<th>fsBC</th>
<th>GC</th>
</tr>
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</table>

*Sprouting*

**Table 2.1:** Synaptic properties of modeled cells, showing rise time constant, decay time constant, and number of connections. Note there are no fsBC to AC connections, and the number of GC to GC connections vary from 0 to 75 based on sprouting level. (Santhakumar, Aradi and Soltesz, Role of Mossy Fiber Sprouting and Mossy Cell Loss in Hyperexcitability: A Network Model of the Dentate Gyrus Incorporating Cell Types and Axonal Topography 2005).

For simulations testing the excitability of the network, performant-path input to the DG was simulated in a subset of each cell type. Additionally, mossy fiber sprouting was simulated in the network by adding synapses from GCs to the proximal dendrites of other GCs (Santhakumar, Aradi and Soltesz 2005). Three sprouting levels were chosen for the simulations—25%, 50%, and 75%—in addition to a 0% sprouting level to serve as a control. These sprouting levels assume that 100% sprouting corresponds to an addition of 100 new synapses.
Figure 2.2: Intrinsic firing properties of fsBCs. (A) Membrane potential trace from biological fsBC. (B) Membrane potential trace from computer model of fsBC. (C) Firing frequency of fsBCs in response to different injection currents. Adapted from (Proddutur, et al. 2013).

Excitability Simulations

The model network was then set up both with and without the FDS to allow for comparison so that their effect on the model’s predictive ability could be assessed; networks that utilized FDS are marked as FDS, while networks that did not utilize FDS are designated nFDS. Additionally, control and experimental network configurations were set up, with the probability of an action potential evoking a postsynaptic response in the AC to fsBC synapse ($P_{AC-fsBC}$) set to 0.8 in the control network, and 0.3 in the experimental network (Yu, Proddutur and Swietek, et al. 2015).
To measure excitability, networks stimulated as described above were activated with performant path input (an artificial cell in NEURON) serving as stimulation for the network. Control and experimental networks were defined based on the probability of synaptic release at AC→fsBC synapses and set to control ($P_{AC-fsBC}=0.8$) and experimental ($P_{AC-fsBC}=0.3$) as identified in experimental studies (Yu, Proddutur and Swietek, et al. 2015). In both control and experimental networks mossy fiber sprouting progressively increased from 0%, 25%, 50%, and 75% to determine the effect of changes in inhibition at progressive increases in sprouting. These networks were run with both the FDS and nFDS configuration to determine the effect of short-term synaptic dynamics on network excitability. In total, with four sprouting levels, each in control and experimental networks, and nFDS and FDS synaptic configurations, there were 16 network setups; each setup was run with five different random seeds (allowing for five different trials) giving a total of 80 network simulations. Inter-spike-interval (ISI) of granule cell firing was used as a measure of excitability, with an increase in ISI corresponding to a decrease in excitability.

**Oscillation Simulations**

To determine the oscillatory behavior of the control and experimental networks, simulations were set up as described above. In agreement with the presence of theta modulated PP input to the DG (Pernia-Andrade and Jonas 2014) and as detailed in earlier studies (Proddutur, et al. 2013) (Yu, Proddutur and Swietek, et al. 2015) all cells were activated with a current injection modulated at five different theta-range frequencies. Staggering the time of current injection to individual neurons allowed for variability in firing. Simulations at each theta frequency input were run using both nFDS and FDS in control and experimental networks with
no sprouting, with five different random seeds, allowing for 100 total network simulations.

**Analysis and Statistics**

The power of fsBC and GC firing at different frequencies in the theta and gamma ranges was measured, and coherence was calculated based on (Wang and Buzsaki 1996). Cross-frequency coupling (CFC) was calculated based on (Tort, et al. 2010) using MATLAB code developed and provided by Tort, et al. CFC calculations measure how much the amplitude of a signal at one frequency (the amplitude-frequencies) is affected by the phase of another frequency (the phase-frequencies). Amplitude-frequencies examined were in the gamma range, and phase frequencies examined were in the theta range. Data are presented as mean±sem. Data were analyzed using three-way ANOVA followed by post hoc pairwise comparison by Tukey’s test. Significance was set to p< 0.05. All simulations were run on a PC with Linux-Elementary OS in the NEURON 7.3 environment, augmented by NMODL. Statistical analysis was performed on a PC with Windows 7 using MATLAB r2011.
EXPERIMENTAL RESULTS

Implementation and validation of synapses with short-term plasticity and recovery

The facilitation and depression synapses were tested in a two-cell model network with properties matching the interneurons of the full network. The pre-synaptic cell was activated by brief current injections of 400 pA to evoke repeated action potentials that stimulated the post-synaptic cell at 50 Hz for 200 milliseconds, and the post-synaptic response was recorded. After a variable recovery period, the pre-synaptic cell released a final action potential so that the post-synaptic “recovered” response could be assessed. The amplitude of the post-synaptic response to a test action potential delivered at varying intervals after end of stimulus train (after the recovery period) was compared to the amplitude of the first post-synaptic response (before facilitation or depression occurred) and a ratio was calculated to determine relative recovery: \( \frac{\text{Amplitude}_{\text{Final}}}{\text{Amplitude}_{\text{Initial}}} = \frac{A_F}{A_I} \).

The functionality of the FDS with recovery was compared to synapses lacking recovery (just showing short-term plasticity) and the built in Exp2Syn NEURON function. For comparison, a trace of the membrane potentials of presynaptic and post synaptic cells using the Exp2Syn and short-term plasticity synapses are shown in figure 3.1 A and B, respectively. The depression synapse function was then tested with 11 trials, each with a different recovery period. To determine the behavior of the recovery function over physiologically important time intervals, the variable recovery periods were set to 0.05, 0.1, 0.2, 0.4, 0.8, 1.2, 1.5, 2, 3, 5, and 8 seconds. Figure 3.2 shows a trace of the membrane potential for both the pre-synaptic and post-synaptic cells for three of the 11 recovery periods in the depression synapse. From figure 3.2, it is clear that a longer recovery period leads to a closer return to the
baseline post-synaptic response. This effect is then quantified in figure 3.3, where the relative recovery ($A_F/A_I$) for all 11 response periods is plotted against the duration of recovery. This figure is compared to data from an electrophysiology study (Savanthrapadian, et al. 2014) whose setup is mimicked here computationally. This shows similar behavior between the physiological depression synapse and the computational depression synapse that was developed for this study. In both synapses, the time until recovery was about 2 seconds.

**Figure 3.1**: Membrane potentials of a presynaptic (red) and post-synaptic (black) cell showing the function of the Exp2Syn function built into NEURON (A) and then the function modified to include short-term plasticity, but no recovery (B).
Figure 3.2: Membrane potentials of a two-cell depression then recovery setup with a 0.05 (A), 1.200 (B), and 3 (C) second recovery period. The top (red) trace is the presynaptic cell, and the bottom (black) trace is the corresponding post-synaptic cell. The dotted line highlights the recovery interval, and the solid line emphasizes the difference in amplitude between the first response and final, recovered response.
Figure 3.3: Quantification of recovery over time. Relative recovery is measured as $A_f/A_i$ and is plotted against the length of the recovery period. Inset is the relative recovery amount plotted against length of recovery period taken from physiological data in (Savanthrapadian, et al. 2014). Notice that in both curves, recovery is complete at about 2 seconds.

The facilitation synapse was tested next, using the same two-cell setup but replacing the depression synapse with the facilitation synapse. Twelve biologically relevant recovery periods were selected to test the facilitation function: 0.05, 0.1, 0.2, 0.4, 0.6, 0.8, 1.2, 1.6, 2, 3, 6, and 9 seconds. Similar to the depression function, $A_f/A_i$ was used to quantify the relative recovery amounts over time. A sample of three of these traces is graphed in figure 3.4, and the recovery curve (along with the physiological recovery curve for comparison) is displayed in figure 3.5. Notice in both curves the recovery is about complete at approximately 6 seconds.
Membrane Potentials of Two-Cell Facilitation-Recovery Setup

Figure 3.4: Membrane potentials of two-cell facilitation then recovery setup with 0.05 (A), 2 (B), and 6 (C) second recovery periods. The top (red) trace is the presynaptic cell, and the bottom (black) trace is the corresponding post-synaptic cell. The dotted line highlights the recovery interval, and the solid line emphasizes the difference in amplitude between the first response and final, recovered response.
Figure 3.5: Quantification of recovery over time. Relative recovery is measured as $A_f/A_i$ and is plotted against the length of the recovery period. Inset is the relative recovery amount plotted against length of recovery period taken from physiological data in (Savanthrapadian, et al. 2014). Notice that in both curves, recovery is complete at about 6 s.

Network setup to examine effect of inhibitory synaptic short term plasticity on activity levels

Using the newly developed FDS, two networks (“Control” and “Experimental”) were set up matching properties of (Santhakumar, Aradi and Soltesz 2005), (Proddutur, et al. 2013), and (Yu, Proddutur and Swietek, et al. 2015), as described in the methods section. Both networks had 200 fsBCs, 200 ACs, and 1000 GCs. The experimental network was set up to have a decreased functional reliability of AC to fsBC synapses, with $P_{AC-fsBC}$ set to 0.8 in the control network and $P_{AC-fsBC}$ set to 0.3 in the experimental network as observed in previous studies (Yu, Proddutur and Swietek, et al. 2015). The activity evoked by focal synchronous afferent stimulation
of these two networks was compared to elucidate the effect of the decreased functional reliability of AC→fsBC synapses on network excitability. To determine the effect of short term plasticity of inhibitory synapses in network excitability, these two networks were modeled both with and without synapses implementing short term dynamics. Therefore, networks modeled were either Control (Con) or Experimental (Exp), and either utilized facilitation depression synapses (FDS) or had no facilitation depression synapses (nFDS). Each of these networks was run with 0%, 25%, 50%, and 75% sprouting. Each combination was then run with 5 different random seeds which determined randomization of network connectivity within set constraints and thus generated 5 distinct networks. In total, there were 80 trials run, each for 1.5 seconds.

The networks were activated by a focal synchronous input to 10% of GCs to simulate afferent excitation in slice physiology studies and output was plotted as spike time rasters. A sample of spike rasters in figure 3.6 shows the spike raster for trial 1, using FDS, with control and experimental networks, for all four levels of sprouting. This is a typical example of a trial, with recurrent firing of a subset of GCs that travels around the ring and is sustained throughout the entire duration of simulation not occurring until the 50% sprouting level and continuing at 75% sprouting. Additionally, it qualitatively appears that there is more firing in the experimental group than the control group. For comparison, figure 3.7 shows the nFDS model for structurally identical networks derived using the same seed.

While this does display a typical pattern, it was not the only pattern that occurred. Figure 3.8 shows the spike rasters for trial 2 using the FDS model network. Notice that synchronous firing begins at the 50% sprouting level, but at the 75% sprouting level in the experimental group, firing engulfs the entire network and then
stops, never reaching the synchronous firing pattern. For comparison, figure 3.9 shows spike rasters for a structurally identical network but with the nFDS model network. Here, the 75% sprouting level in the experimental group does not spread to the full network but instead leads to recurrent GC firing sustained throughout the duration of simulation. This expansion to the full network firing occurred in several trials with no apparent pattern, at either the 50% or 75% sprouting levels, regardless of whether control or experimental networks were implemented with or without FDS.
Spike Rasters for Trial 1 Using FDS

Figure 3.6: Spike rasters for trial 1 using the FDS model. Left column is for the control network, right column is for the experimental network. Four levels of sprouting were tested: 0% (A), 25% (B), 50% (C), and 75% (D).
Figure 3.7: Spike rasters for trial 1 using the nFDS model. Left column is for the control network, right column is for the experimental network. Four levels of sprouting were tested: 0% (A), 25% (B), 50% (C), and 75% (D).
Figure 3.8: Spike rasters for trial 2 using the FDS model. Left column is for the control network, right column is for the experimental network. Four levels of sprouting were tested: 0% (A), 25% (B), 50% (C), and 75% (D). Notice that the right column on D has an erratic pattern, and firing stops at 250 ms, never reaching a synchronous firing pattern, despite 50% sprouting having synchronous firing.
Figure 3.9: Spike rasters for trial 2 using the nFDS model. Left column is for the control network, right column is for the experimental network. Four levels of sprouting were tested: 0% (A), 25% (B), 50% (C), and 75% (D). Notice that the right column on D does not have an erratic pattern, the way 3.7D does.
As is evident from the spike rasters (figures 3.6-3.9), 0% sprouting did not produce much cellular firing. Because the same GC (cells 401-1400) never fired twice within the 0% sprouting networks, they were not included in subsequent excitability analysis.

In the remaining networks, excitability was measured using a MATLAB code that calculated inter-spike interval (ISI). ISI was used as a measure of excitability, with a lower ISI corresponding to increased excitability. Figure 3.10 shows the average ISI over 5 trials for each network type (25-75% sprouting, FDS or nFDS networks) in order to compare the control and experimental networks. In these comparisons, the only significant difference between control and experimental networks is in the 75% sprouting networks using FDS. Unexpectedly, there was a decrease in firing (increase in ISI) of the experimental network. This can also be seen in figure 3.11, which displays percent change from control to experimental networks for both FDS and nFDS networks. Although the variability was high, networks with nFDS synapses enhanced excitability with decrease in AC→fsBC synaptic release, when networks included FDS synapses networks tended to decrease excitability.
Figure 3.10: Excitability of 6 different network types, each with control and experimental network parameters, for a total of 12 network setups. Data are show as mean±sem. (*) indicates p<0.05.

**Percent Change of ISI from Con to Exp**

Figure 3.11: Percent change in ISI from control to experimental networks. A positive percent change corresponds to an increase in ISI, which corresponds to a decrease in excitability. The only significant percent change from con to exp is in the FDS network with 75% sprouting, (*) indicates p<0.05.
To determine the effect of using the FDS model on network excitability, ISI was then compared between FDS and nFDS networks. As shown in Figure 3.12 including short term plasticity invariably reduced ISI/increased excitability within each network type with this effect being significant at lower levels of sprouting. These differences are then calculated as a percent change, and separated by type of network (con or exp) in figure 3.13.

**Figure 3.12:** Excitability of 6 different network types, each with and without FDS, for a total of 12 network setups. Mean and standard error are pictured, n=5. The (*) for con 25% and exp 25% signifies p<0.05 between nFDS and FDS. All other differences were not significant (p>0.05).
Overall, only several network configurations were able to show a significant difference between control and experimental networks, or between nFDS and FDS. Three-way ANOVA analysis similarly reveals no significant differences between nFDS and FDS, control and experimental networks, and different sprouting levels; additionally, there were no significant interactions between these factors (p>0.05).

**Examination of the effect of inhibitory synaptic short term plasticity on network oscillations**

Oscillatory dynamics of the FDS networks were then examined. A network of 200 fsBCs, 200 ACs, and 1000 GCs, was injected with a sinusoidal current to determine the oscillatory effects of the control and experimental networks. The current injections were varied within the theta frequency range, with injections at 4, 6, 8, 10, and 12 Hz. A sample of the spike rasters from the control and experimental networks with a 4 Hz current injection is shown in figure 3.14. Five trials were performed of each network (control and experimental) for each injection current, and with nFDS or FSD, for a total of 100 trials.
Figure 3.14: Spike Rasters for control (A and B), and experimental (C and D) networks with a 4 Hz injection current. A displays con GCs, B is con, fsBCs and ACs, C is exp GCs and D is exp fsBCs and ACs.
First, coherence in the networks was looked at. Coherence increased from control to experimental networks and decreased from nFDS to FDS networks as shown in figure 3.15. Three-way ANOVA analysis indicated that these differences are significant (p<0.05), in addition to the effect of injection current being significant. Additionally, all three interactions (the interaction of nFDS/FDS with con/exp, the interaction of nFDS/FDS with injection current, and the interaction of con/exp with injection current) were all significant (p<0.05).

**Figure 3.15:** Percent increase in coherence from nFDS to FDS (A) and from control network to experimental network (B). Data displayed as mean and standard error of 5 trials.
Next, power spectra were taken across theta and gamma frequencies and compared between control and experimental networks, and nFDS and FDS networks. Figure 3.16 shows the power spectra for networks with all five injection currents averaged over 5 trials, comparing control and experimental networks. Figure 3.17 shows power spectra over all five injection currents comparing nFDS and FDS networks. These figures reveal a frequency shift in where the peak power is located.

Lastly, cross frequency coupling (CFC) was examined. Using MATLAB code from (Tort, et al. 2010), CFC was calculated as modulation index (MI). As the phase of low frequency signals further affects the amplitude of high frequency signals, MI increases. The lower frequency signals are therefore referred to as phase frequencies, and the higher frequency signals referred to as amplitude frequencies. Figure 3.18 shows comodulograms of four different network configurations, which show the MI for different phase frequencies and amplitude frequencies. In this figure, ACs were used as an example; see appendix B for the other comodulograms. Finally, figure 3.19 shows the percent change in maximum MI from nFDS to FDS, and from control to experimental networks. ANOVA analysis revealed a significant decrease in MI from nFDS to FDS. While there was a decrease in MI from control to experimental (which compares favorably with (Yu, Proddutur and Elgammal, et al. 2013)), it was not significant.
**Figure 3.16**: Average power spectra for networks with injection currents at 4 (A), 6 (B), 8 (C), 10 (D), and 12(E) Hz. Power spectra are shown for delta (inset) and gamma frequency ranges and compared between con and exp networks.
Figure 3.17: Average power spectra for networks with injection currents at 4 (A), 6 (B), 8 (C), 10 (D), and 12(E) Hz. Power spectra are shown for delta (inset) and gamma frequency ranges and compared between nFDS and FDS networks.
Figure 3.18: Comodulograms showing MI over different phase frequencies and amplitude frequencies for ACs averaged over 5 injection currents and 5 trials. Networks configurations were control/nFDS (A), control/FDS (B), experimental/nFDS (C), and experimental/FDS (D).

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Figure 3.19: Percent change in maximum MI for different cell types averaged over 5 injection currents and 5 trials each.
DISCUSSION

Seizure activity that is characteristic of TLE has been shown to cause changes within the neuronal circuitry that it affects, causing changes to patients’ abilities in memory, learning, and higher-level thinking (Viskontas, McAndrews and Moscovitch 2000) (Kesner 2007). Seizure activity has also been shown to worsen the severity and progression of epilepsy, leading to an important question: Are these changes simply caused by epilepsy, or are they also contributing to it? Answering this question for various physiological changes caused by TLE can allow for proper targeting in future studies of potential interventions for TLE. It is in this context that this study aims to determine how a functional decrease in AC-fsBC synaptic reliability affects neuronal network rhythms and excitability. Utilizing an established model of the DG (Santhakumar, Aradi and Soltesz 2005), this study incorporates a facilitation-depression synapse to increase modeling accuracy and determine if this AC-fsBC synaptic change is significant in the progression of TLE.

Using the NEURON programming environment, with augmented capabilities provided by NMODL, facilitation-depression synapses were developed that could accurately replicate the physiologic behavior of synapses in the DG. Measuring the facilitation-recovery and depression-recovery dynamics of these computational synapses within a two-cell model network allowed for validation of their function. This testing demonstrated that the computational synapse successfully matched physiological data from (Savanthrapadian, et al. 2014). It is important to note, however, that experimental data for all of the synapses is not available, and this limitation potentially introduces inaccuracies into the model. Additionally, facilitation and depression kinetics may change with frequency, and this potential effect was not simulated.
Short-term synaptic plasticity in the DG is important in modulating inhibition and in signal processing, and is therefore an important process to potentially add accuracy to the model. In experimental models of TLE, it is particularly useful to add this phenomenon because many effects of TLE manifest as changes in synaptic properties that could be affected by short-term synaptic plasticity.

Implementing this synapse to the established DG network showed some changes in network excitability. In particular, excitability of the network increased when modeled with the facilitation-depression synapses at both the 25% and 50% sprouting level. There was no difference in excitability at 75% sprouting; however, looking closer at the spike rasters for these networks reveals a more complicated picture. Several of these networks never began firing in a synchronous pattern the way most of the other networks did. The erratic firing pattern that they showed is dissimilar to the expected synchronous firing, and perhaps disallowed an accurate representation of the excitability of these networks. Another possible explanation of this phenomenon is that, at lower levels of sprouting, the addition of short-term synaptic plasticity meant that depression of fsBC to GC synapses decreased inhibition in the network significantly; at higher levels of sprouting, however, the effects of sprouting dominated over the effects of depressing fsBC to GC synapses.

Once it was established that the addition of facilitation-depression synapses had an effect of network excitability, testing began to determine if the decreased firing probability of AC-fsBC synapses had an effect on the network. This decreased firing probability was shown in a previous study to affect network oscillations (Yu, Proddutur and Swietek, et al. 2015), but was not shown to affect network excitability. Additionally, this change was never modeled with the potential increased accuracy afforded by the addition of facilitation-depression synapses. Comparisons between
control and experimental networks showed that in most cases (nFDS 25-75% sprouting, FDS 25-50% sprouting), there was a non-significant increase in excitability. However, the FDS 75% sprouting network had a significant decrease in excitability from control to experimental networks. It is possible that this change did not affect network excitability much, and it is also possible that a larger sample size is needed to further elucidate the effects of this change. It is also possible that this effect occurred because the AC to fsBC synapses facilitate; therefore, introducing short-term plasticity increased inhibition on fsBCs. The functional reduction in AC to fsBC synaptic transmission seen in experimental TLE may be a compensatory mechanism to disinhibit fsBCs, allowing further inhibition of GCs.

Network oscillations were also examined in several different ways. The first way oscillatory behavior was looked at was through power spectra of the firing frequency of each cell type. From this analysis, it is clear that the experimental network has greatest power at a higher firing frequency than the control network. Additionally, coherence was measured based on (Wang and Buzsaki 1996) and compared between control and experimental networks using facilitation-depression synapses. Previous studies (Proddutur, et al. 2013) have shown that the control and experimental networks have changes in coherence, and this study is able to replicate that result. Coherence increased significantly from the control network to the experimental network for all 4, 6, 8, 10, and 12 Hz input frequency.

These changes in oscillatory behavior are important to the progression of TLE because changes in network rhythms have a real effect on cognitive processes (Bragin, Wilson, et al. 2004) (Montgomery and Buzsaki 2007) (Jutras, Fried and Buffalo 2009). Showing that this synaptic change has the ability to affect oscillations
can, therefore, show that it also potentially has an effect on the progression of symptoms associated with TLE.

Lastly, cross-frequency coupling was looked at between control and experimental networks for each trial. From the resulting comodulograms, it is clear that this network exhibits significant cross-frequency coupling when looking at phase frequencies in the low theta range, and amplitude frequencies in the high gamma range. This finding is consistent with expectations for cross-frequency coupling in the DG. However, there does not appear to be any real changes in CFC from the control to the experimental networks. When comparing maximum MI between control and experimental networks, and between nFDS and FDS networks, the only significant change was a decrease in MI from nFDS to FDS. It is unclear why this effect occurred.
SUMMARY AND CONCLUSIONS

This current study seeks to improve an established model network of the DG by incorporating short-term plasticity of interneuronal synapses into the network, and to use the model to study the effects of a decreased functional reliability of AC-fsBC synapses associated with TLE. The resulting network successfully incorporates physiologically realistic facilitation-depression synapses and shows some differences in the excitability of networks modeled with these synapses. Using this updated model, the decreased reliability of AC-fsBC synapses was shown to affect network oscillations. However, using this updated model was not able to show that a decrease in functional reliability of AC-fsBC synapses had a consistent effect on network excitability.

From this study, it can be concluded that biologically realistic facilitation-depression synapses are able to change the output of the established DG model, potentially increasing its accuracy. It can also be concluded that using this new model, a decreased functional reliability in AC-fsBC synapses has an effect on network oscillations, but not necessarily an effect on network excitability.

In the future, this work could be improved upon by collecting data on different types of synapses, and including short-term synaptic plasticity in these synapses as well. Additionally, the network used here was a simplified version only including several cell types; perhaps a more complete network would elucidate more conclusive results. In the future, the FDS with recovery developed here could be incorporated into a larger network. Finally, the model used here could be useful in testing other physiological changes from TLE to determine their effects on excitability and oscillatory behavior, particularly those changes that heavily rely on synaptic behavior.
BIBLIOGRAPHY


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ABBREVIATIONS

$A_F/A_i$: Amplitude$_{Final}$/Amplitude$_{Initial}$; measure of the relative post-synaptic recovery

AC: Accommodating Cell

CA: Cornu Ammonis, or Ammon’s horn

Cck: cholecystokinin

Con: Control network

CFC: Cross-Frequency Coupling

DG: Dentate Gyrus

Exp: Experimental Network

FDS: Facilitation-Depression Synapses

fsBC: Fast Spiking Basket Cell

GABA: Gamma-Amino Butyric Acid

GC: Granule Cell

HICAP: Hilar Commissural-Associational Pathway

IPSP: Inhibitory Postsynaptic Potential

ISI: Inter-Spike Interval

nFDS: Non Facilitation Depression Synapses

pv: parvalbumin

TLE: Temporal Lobe Epilepsy
APPENDIX A: Modified FDSExp2Syn Function

Changes made to add recovery function are in bold. Facilitating function:

NEURON {
    POINT_PROCESS FDSExp2SynACAC
    RANGE tau1, tau2, e, i
    NONSPECIFIC_CURRENT i
    RANGE g
    GLOBAL total, Cdur, beta
    RANGE f, tau_F, d1, tau_D1, d2, tau_D2, P, Q, new_seed, k, z
}

UNITS {
    (nA) = (nanoamp)
    (mV) = (millivolt)
    (umho) = (micromho)
}

PARAMETER {
    tau1 = 0.1 (ms) < 1e-9, 1e9 >
    tau2 = 10 (ms) < 1e-9, 1e9 >
    e = 0 (mV)
    f = 0.917 (1) < 0, 1e9 > : facilitation, 0.917
    tau_F = 94 (ms) < 1e-9, 1e9 > :94
    d1 = 0.2 (1) < 0, 1 > : fast depression, 0.2
    tau_D1 = 380 (ms) < 1e-9, 1e9 > :380
    d2 = 0.2 (1) < 0, 1 > : slow depression, 0.2
    tau_D2 = 9200 (ms) < 1e-9, 1e9 > :9200
    P = 0.8 (1) <0, 1>
    Cdur = 30 (ms)
    beta = 0.0008 (/ms)
ASSIGNED {
    v (mV)
    i (nA)
    g (umho)
    factor
    total (umho)
    k
    z
}

STATE {
    A (umho)
    B (umho)
}

PROCEDURE new_seed(seed) {
    set_seed(seed)
}

INITIAL {
    LOCAL tp
    total = 0
    if (tau1/tau2 > 0.9999) {
        tau1 = 0.9999*tau2
    }
    A = 0
    B = 0
    tp = (tau1*tau2)/(tau2 - tau1) * log(tau2/tau1)
    factor = -exp(-tp/tau1) + exp(-tp/tau2)
    factor = 1/factor
}
BREAKPOINT {
    SOLVE state METHOD cnexp
    g = B - A
    i = g*(v - e)
}

DERIVATIVE state {
    A' = -A/tau1
    B' = -B/tau2
}

NET_RECEIVE(weight (umho), F, D1, Q, D2, tsyn (ms)) {
    INITIAL {
        F = 1
        D1 = 1
        D2 = 1
        tsyn = t
        P = 0.5
        Q = 0
    }
    z = scop_random()
    k = 0
    z = z-P
    if (z>=0) {
        k = 0
    }else{
        k=1
    }else{
        k=1
    }
    if(t-tsyn>Cdur) {
        F = 1 + (F-1)*exp(-beta*(t-tsyn))
        Q = 1
    }
if(Q==0) {
    F = 1 + (F-1)*exp(-(t - tsyn)/tau_F)
}

tsyn = t
    A = A + weight*factor*F*D1*D2*k
    B = B + weight*factor*F*D1*D2*k
    total = total+weight*F*D1*D2*k
A = A + weight*factor*k
    B = B + weight*factor*k
    total = total+weight*k
F = F + f
    Q = 0
}
Depressing function:

NEURON {
    POINT_PROCESS FDSExp2SynBCBC
    RANGE tau1, tau2, e, i
    NONSPECIFIC_CURRENT i
    RANGE g
    GLOBAL total, Cdur, beta
    RANGE f, tau_F, d1, tau_D1, d2, tau_D2, P, Q, new_seed, k, z
}

UNITS {
    (nA) = (nanoamp)
    (mV) = (millivolt)
    (umho) = (micromho)
}

PARAMETER {
    tau1 = 0.1 (ms) < 1e-9, 1e9 >
    tau2 = 10 (ms) < 1e-9, 1e9 >
    e = 0 (mV)
    f = 0 (1) < 0, 1e9 > : facilitation, 0.917
    tau_F = 0 (ms) < 1e-9, 1e9 > :94
    d1 = 0.1 (1) < 0, 1 > : fast depression, 0.2
    tau_D1 = 500 (ms) < 1e-9, 1e9 > :380
    d2 = 0.8 (1) < 0, 1 > : slow depression, 0.2
    tau_D2 = 1000 (ms) < 1e-9, 1e9 > :9200
    P = 0.8 (1) <0, 1>
    Cdur = 30 (ms)
    beta = 0.0009 (/ms)
}
ASSIGNED {
    v (mV)
    i (nA)
    g (umho)
    factor
    total (umho)
    k
    z
}

STATE {
    A (umho)
    B (umho)
}

PROCEDURE new_seed(seed) {
    set_seed(seed)
}

INITIAL {
    LOCAL tp
    total = 0
    if (tau1/tau2 > 0.9999) {
        tau1 = 0.9999 * tau2
    }
    A = 0
    B = 0
    tp = (tau1 * tau2) / (tau2 - tau1) * log(tau2 / tau1)
    factor = -exp(-tp / tau1) + exp(-tp / tau2)
    factor = 1 / factor
BREAKPOINT {
    SOLVE state METHOD cnexp
    g = B - A
    i = g*(v - e)
}

DERIVATIVE state {
    A' = -A/tau1
    B' = -B/tau2
}

NET_RECEIVE(weight (umho), F, D1, Q, D2, tsyn (ms)) {
INITIAL {
    F = 1
    D1 = 1
    D2 = 1
    tsyn = t
    P = 0.5
    Q = 0
}
    z = scop_random()
    k = 0
    z = z-P
    if (z>=0) {
        k = 0
    }else{
        k=1
    }
    if(t-tsyn>Cdur) {
D1 = 1 - (1-D1)*exp(-beta*(t-tsyn))
D2 = 1 - (1-D2)*exp(-beta*(t-tsyn))
D2=1
Q = 1
}
if(Q==0) {
D1 = 1 - (1-D1)*exp(-(t - tsyn)/tau_D1)
D2 = 1 - (1-D2)*exp(-(t - tsyn)/tau_D2)
}

tsyn = t
A = A + weight*factor*F*D1*D2*k
B = B + weight*factor*F*D1*D2*k
total = total+weight*F*D1*D2*k
A = A + weight*factor*k
B = B + weight*factor*k
total = total+weight*k
D1 = D1 * d1
if(D2>-7) {
D2 = D2 - d2
}
Q = 0
}
**APPENDIX B: Comodulograms for GCs and fsBCs**

**Figure B.1:** Comodulograms showing MI over different phase frequencies and amplitude frequencies for fsBCs averaged over 5 injection currents and 5 trials. Networks configurations were control/FDS (A), control/nFDS (B), experimental/FDS (C), and experimental/nFDS (D).
Figure B.2: Comodulograms showing MI over different phase frequencies and amplitude frequencies for GCs averaged over 5 injection currents and 5 trials. Networks configurations were control/FDS (A), control/nFDS (B), experimental/FDS (C), and experimental/nFDS (D).