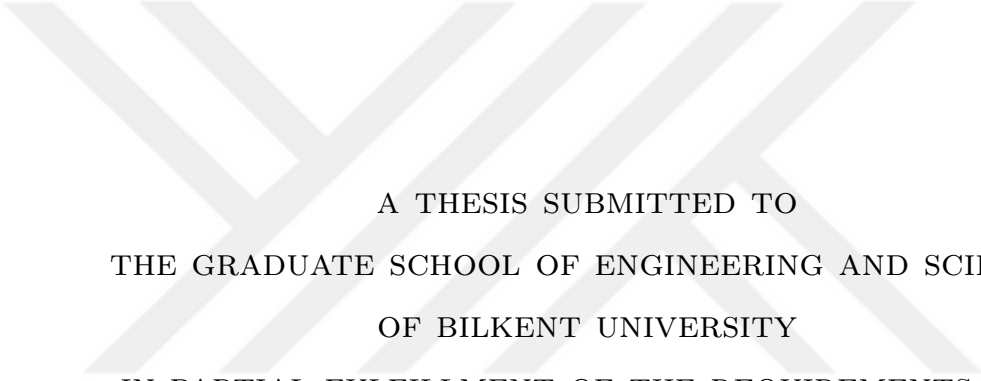


SIMPLIFICATION OF THE DATA-DRIVEN HIPPOCAMPAL CA1 MICROCIRCUIT



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By
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Simplification of the data-driven Hippocampal CA1 Microcircuit

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March 2021

We certify that we have read this thesis and that in our opinion it is fully adequate,
in scope and in quality, as a thesis for the degree of Master of Science.



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ABSTRACT

SIMPLIFICATION OF THE DATA-DRIVEN HIPPOCAMPAL CA1 MICROCIRCUIT

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Biophysically realistic neuron models provide emergent neural and circuit behaviors due to their data-driven approach and high sensitivity in representing the ionic currents. These models comprise multiple compartments for representing dendrites, which allows getting high accuracy during dendrosomatic and somato-dendritic signals. An average pyramidal cell model having around 170 compartments and 1000 synapses makes up a significant cost in computational time and memory load. When a high number of cells are considered, an ordinary computer becomes unable to simulate such circuits. With the recent developments in neuron simplification algorithms, the voltage deflection timings at the soma can be captured by preserving the transfer impedance of excitatory & inhibitory synapses to soma. It has been shown that the simplified cortical neuron models can get a high spike-synchrony with up to 250x faster simulation time.

Despite its performance at single cell level, the application of neuron reduce algorithm to circuit level analysis has not been shown yet. This work extends the use cases of the algorithm by applying it to various hippocampal morphologies and shows its performance in both single cell and network level simulations. The validations include total neuron activation rates by morphology, inter-spike intervals of the circuits, raster plots and average firing rates throughout the circuit in experiments including somatic current injection, miniature post synaptic potentials, external innervation from Schaffer Collaterals and LFP simulations. We show the successfully replicated emergent behaviors and the limitations of the simplification algorithm on neurons firing in broad frequency regimes and further present optimization techniques for those that perform sub-optimally with the simplification alone.

Keywords: Hippocampus, CA1, simplification, in-silico neuroscience, simulation.



ÖZET

VERİ TABANLI HIPPOKAMPAL CA₁ DEVRESİNİN BASİTLEŞTİRİLMESİ

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Malzeme Bilimi ve Nanoteknoloji, Yüksek Lisans

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Biyofiziksel olarak gerçekçi nöron modelleri, veriye dayalı yaklaşımları ve iyonik akımları temsil etmede yüksek hassasiyetleri nedeniyle ortaya çıkan nöral ve devre davranışları sergilemektedirler. Bu modeller, dendritleri temsil etmek için birden fazla bölme içerir, bu da dendrozomatik ve somatodendritik sinyaller sırasında yüksek doğruluk elde edilmesini sağlar. 170 bölme ve yaklaşık 1000 sinaps içeren ortalama bir piramidal nöron modeli, hesaplama süresi ve bellek yükünde önemli bir maliyet oluşturur. Çok sayıda hücre düşünüldüğünde, sıradan bir bilgisayar bu tür devreleri simüle edemez hale gelir. Nöron sadeleştirme algoritmalarındaki son gelişmelerle, nöron gövdesindeki voltaj sapma zamanlamaları, uyarıcı ve inhibitör sinapsların soma'ya transfer empedansını koruyarak yakalanabilir. Basitleştirilmiş kortikal nöron modelleri ile 250 kata kadar daha hızlı simülasyon süresi yakalamakla birlikte yüksek bir atım senkronizasyonu skoru da elde edebileceği önceki çalışmalarda gösterilmiştir. Buradaki hızlandırma, iki basitleştirme tekniğinin birleştirilmesiyle elde edilir. İlk olarak, nöron modellerinin karmaşık morfolojilerini, Rall'ın kablo modeline benzer şekilde birkaç silindirik kabloya basitleştirilir. Sonrasında, aynı özelliklere sahip sinapslar, örneğin yükselme ve alçalma zaman sabitleri aynı olanlar, tek noktalı bir süreçte birleştirilebilir. Böylece her bir bölme, biri tüm uyarıcı sinapsları ve biri tüm inhibe edici olanları temsil eden 2 sinapsa sahip olur. Bu iki yöntemi birleştirerek simülasyon hızında doğrusal olmayan bir artış elde edilebilir.

Ancak, bu algoritma devre seviyesine henüz uyarlanmış değildir. Bu çalışma, “nöron azaltma (neuron_reduce)” algoritmasını çeşitli hipokampal morfolojilere uygulayarak genişletip, algoritmanın performansını hem tek hücreli hem de ağ

düzeyinde simülasyonlarda göstermektedir. Doğrulamalar, somatik akım enjeksiyonu, Schaffer Kollaterallerini de içeren çeşitli minyatür post sinaptik aktivasyonları, ve harici nöronal innervasyon girişleri de dahil olmak üzere çeşitli deneyler ile test edilmiştir. Bu deneylerde ağların toplam nöron aktivasyon oranları, devrelerin atım arası aralıkları, raster dağılımları ve devre boyunca ortalama ateşleme oranları incelenmiştir. Bu yöntemlerle, başarılı ve başarısızlıkla yinelenen davranışlar incelenip, algoritmanın düşük seviyede atım senkronizasyonu gösterdiği nöron tipleri için de çeşitli optimizasyon teknikleri sunulmuştur.

Anahtar sözcükler: Hippocampus, CA1, basitleştirme, silikoda sinirbilim, simülasyon.

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Glossary

internal minis Spontaneous miniature post synaptic potential activations coming from internal connections.

minis Spontaneous miniature post synaptic potential activations coming from both internal and external projections.

proj minis Spontaneous miniature post synaptic potential activations coming from external projections.

Acronyms

AA Axoaxonic.

AP Action Potential.

BOLD Blood Oxygen Level Dependent (Signal).

BP Backprojecting.

BS Bistratified.

CCKBC Cholecystokinin Positive Basket Cell.

E-type Electrophysiological Type.

G-type Genetic Type.

In-Silico Silicon Based.

LFP Local Field Potential.

LTD Long Term Depression.

LTP Long Term Potentiation.

M-type Morphological Type.

ME-type Morphoelectrophysiological Type.

MF Mossy Fibers.

OLM Oriens-lacunosum/molecular.

PC Pyramidal Cell.

PP Perforant Pathway.

PPA Perforant path-associated.

PSD Power Spectral Density.

PVBC Parvalbumin Positive Basket Cell.

S-type Synaptic Type.

SC Schaffer Collateral.

SCA Schaffer Collateral Associated.

SLM Striatum Locunosum-Molecular.

SO Striatum Oriens.

SONATA Scalable Open Network Architecture Template.

SP Striatum Pyramidale.

SR Striatum Radiatum.

Tri Trilaminar.

Chapter 1

Introduction

Building realistic models of neurons has been a long pursuit since the dawn of computational neuroscience [1]. Representation of large amount of ion channel types that contribute to the intra and extracellular voltages makes these models catch more of emergent properties at the expense of additional computational burden. The more an individual cell gets non-linear differential equations due to different channel physiology, the more expensive the simulation gets [2]. That is why point neuron models emerged as a counter measure for multi-compartmental network models [3, 4]. Such simplified models range from representing only the passive properties to building much successful models that catches the attractor dynamics of individual cell type [3]. The latter, however achieves this feat in efficiency and success in physiological replication by trading off vast number of individual ion currents with several simplified equations, and therefore losing the insights that can be obtained from these channel kinetics such as their behavior in pathological conditions and individual contributions to overall electrophysiology. In this respect, point neuron models are generally used for the investigation of the network activity by utilizing neuron connectivity and topology instead of focusing on single nonlinear neural computations. Researchers using this method try to implement these simple yet efficient neuron models to create a network models of desired function such as building a hierarchical network models in robotical applications or try to utilize them to understand the basics of the connectivity

patterns of biological systems [5, 6, 7] although recent studies start to implement dendritic computations using these models [8].

In order to cope up with the computational burden as well as retain biological plausibility to greater extend, several algorithms have been proposed in recent years [9, 10]. Some of these methods try to maintain somatic voltage traces and retain dendritic tree up to a degree, therefore try to maintain and protect spatio-temporal computations within dendritic tufts [9], whereas others try to map all synapses to the soma after correcting them with several mathematical operations [10].

In this work, the recent simplification algorithm called Neuron Reduce [9] is utilized to simplify large scale data-driven network models of rat hippocampal CA1 circuit as can be seen in Figure 1.1. With the reduction's ability to speed-up the simulation process up to 200x, it is hoped that its circuit implementation can provide a useful tool for the scientific community at a fraction of computational cost meanwhile preserve as much information as possible.

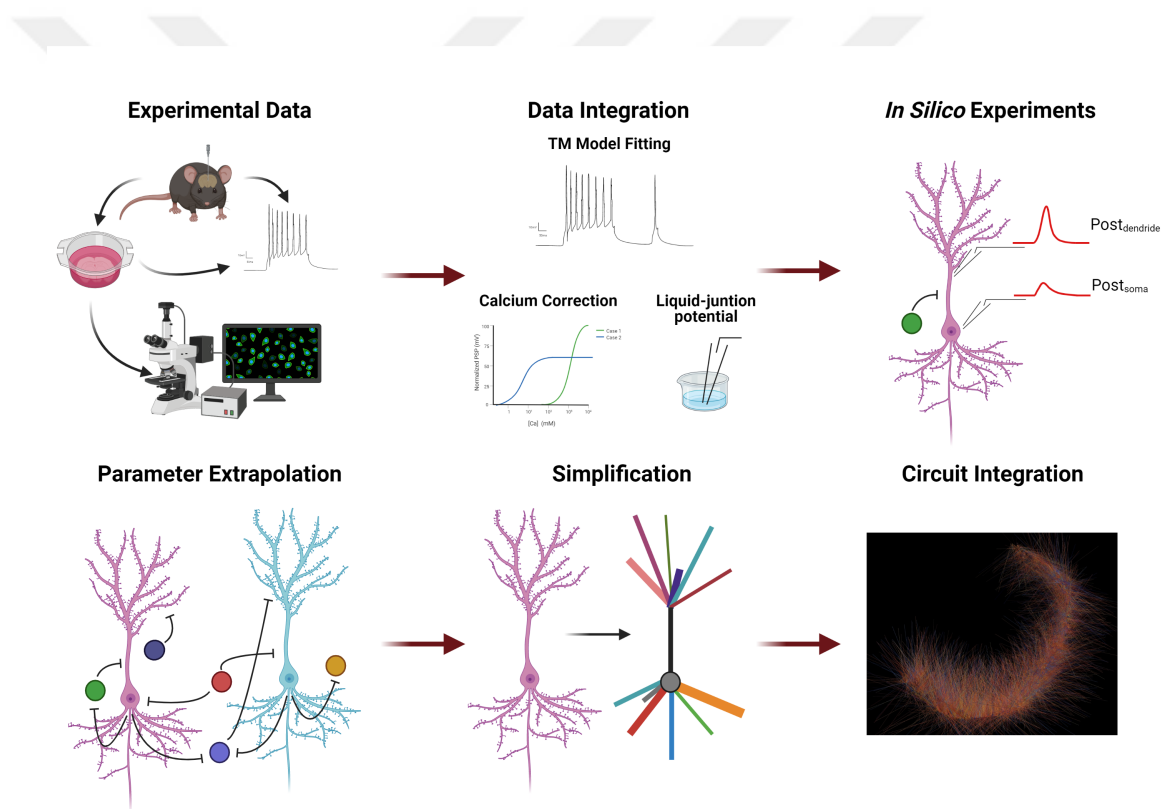


Figure 1.1: The pipeline for the circuit building and the simplification processes.

Chapter 2

Background and Theory

As the famous Nobel laureate Francis Crick once said, “There is no scientific study more vital to man than the study of his own brain. Our entire view of the universe depends on it”. The need to understand the function of the brain and its inner workings has long been a question dwelling in the minds of humankind and mostly, neuroscientists. So far, neuroscientists have studied the brain on many levels ranging from mapping its ultra-structure motifs via serial electron microscopy to investigate electrical oscillations in extracellular domain via novel methods like Neuropixels, to assessing Blood Oxygen Level Dependent (Signal) (BOLD) signals using functional magnetic resonance imaging (fMRI) and other techniques. Although this gives us a variety of information on many levels, we still have not understood fully why and how consciousness has emerged, where and how a certain memory is stored or why many pathophysiological diseases develop. Therefore, we need a fine-detailed brain model not only to understand ourselves but also to correct the problems we have experienced throughout our lives.

A complete model of the brain would help us understand the basis of almost all neurological diseases while enabling us to investigate possible ways to cure or stop the progression of them without any harm to the host. The applications of research are endless at this point of development, not only for neuroscientists

but also for artificial intelligence community to investigate its dynamics. Coupling brain model with the state-of-the-art techniques like optogenetics, designer receptors activated by designer drugs (DREADD), synthetic biology, and latest brain computer interfaces, it is theoretically possible to edit our own mind and perhaps even store it in silicon based systems.

All speculations aside, we are still at the stage where we need to find the best way for our model to correctly mimic what is going on sub-cellular levels so the system won't diverge over the long term. Techniques like reaction diffusion modeling enable us to model individual molecules, and through their random and non-random movements, we can enable molecular interactions with other proteins, and the DNA and various receptors residing inside and outside of our cells. This is the long-term goal and is limited to our current technology, as processors have not developed enough to calculate such operations. However, with data-driven approach, it is possible to start from one or two levels above, mainly modeling channel kinetics, receptor dynamics, morphological patterns, over genetically different cell models, and start modeling the brain until it is possible to model finer detailed systems.

2.1 Neuroanatomy of Hippocampus

The adult human brain consists of 6 main regions. Telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon. Hippocampus resides in limbic lobe of cerebral cortex in telencephalon [11]. Along with septal regions and amygdala, the hippocampal formation forms the major components of the limbic system. These regions are involved in emotional regulation, navigational mechanisms, generation of long term memory, motivational and hormonal mechanisms. Although the complete functional mechanism is unknown, hippocampus is one of the most studied brain regions in rodents, partly because this region and especially the dorsal part of it is easily accessible for physiological and pharmacological research. [12, 13].



Figure 2.1: A coronal section of the left hemisphere of the human hippocampus shown with purple color. Image credit: Allen Institute [11].

Figure 2.2: A coronal section of the mouse brain in which HF is depicted in green. Left, the NISSL stain of a coronal section of the brain. Right, parcelled version, obtained from the histological section. Image credit: Allen Institute, Mouse, P56, Coronal Section [14].

Although relative sizes and the finer structures can vary, different species within the same sub-phylum “Vertebrata” have conserved similar brain regions. These structures have evolved following the needs of the species, and one small structure such as olfactory bulb in humans can have a much larger allocated proportion in size and resources in dogs [15]. Recent open source atlases with high resolution 3D brain parcellation of the human and rodent brains provide a fine tool for comparative anatomical studies in these mammalian bodies (see Figures 2.1, and 2.2 [11, 14]).

Hippocampus is one of the structures we can utilize in rodents in order to understand our brain region. Simulation neuroscientists utilize rodent brain atlases, their cell models, morphologies, and other important parameters [16, 17, 18] to correctly model the brain of that species which can later be used to estimate parameters required to build a viable human brain model. What is not suitable with human experimentation could be obtained from rodent experiments in an easier way. This allows researchers a room for further and faster development of brain models until it is time to pass on to the next step, the human brain.

Hippocampus (HC) is a convolved structure that is reminiscent of sea-horse from which it gained its name. The structure belongs to a wider region called The Hippocampal Formation (HF) which includes two more regions, namely Dendate Gyrus and Subiculum. Pre- and para-subicular areas are not categorized inside this formation, but along with subiculum itself, they are called subicular complex [19]. Therefore, different groups can involve the same region within their boundaries.

All this extra parts to hippocampi makes the hippocampus definition vague. Therefore, some scientist use the term “The Hippocampus Proper” to stress the primal region of interest. Within the hippocampus proper, there are four fields called CA1, CA2, CA3, and CA4, deriving its name from Cornu Ammonis (CA), the horn of the ancient Egyptian God Amun, see Figure 2.3. However sometimes CA4 is omitted in any of this classifications [19]

The CA regions are further broken down to layer types such as Stratum (Str.)

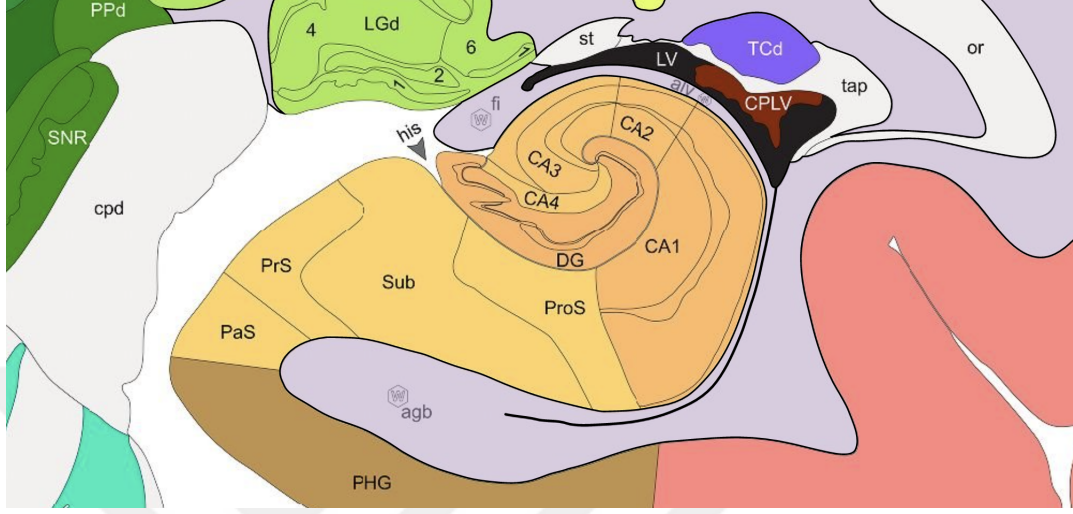


Figure 2.3: A magnified version of a coronal section of the human brain, focusing on the hippocampal formation. Image credit: Allen Institute [11].

Oriens, Str. Pyramidale (SP), Str. Radiatum (SR), Str. Locunosum-Moleculare (SLM). These regions sometimes diverge and fuse or new layers form depending on the anatomical region and slice. For instance, the aforementioned layers are present in CA1, but in CA3 there is another region called Str. lucidum (see Figure 2.4).

Since HC has become a convolved structure over the course of evolution, the basis of axes is defined on the given species. As rat and human brains differ in shape and size, the HC shape also differs. See Figure 2.5 to grasp the shape of the rat and human Hippocampal regions, respectively.

The normal coordinate system used for representing positions in the brain, such as Dorso-Ventral, Latero-Medial, Antero-Posterial axes are sometimes switched with more hippocampus-oriented axes. As in linear algebra, change of basis, sometimes allows us to better represent the information, The hippocampus is divided into 3 axes which are basically non-linear transformation of the default cartesian coordiate system (see Figure 2.5).

The long axis of the Hippocampus is known as septo-temporal (dorso-ventral (DV) or antero-posterior (AP) in humans) shown in Figure 2.6. The second axis is along brain regions, mainly from DG-CA3-CA1-Sub, is called the transverse

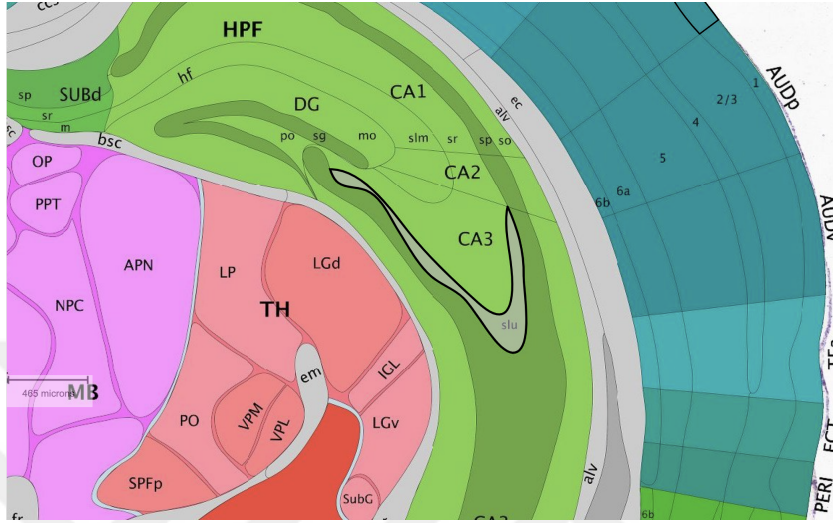


Figure 2.4: A coronal slice of the mouse brain showing hippocampal region in green. Image credit: Allen Institute, Mouse, P56, Coronal Section [14].

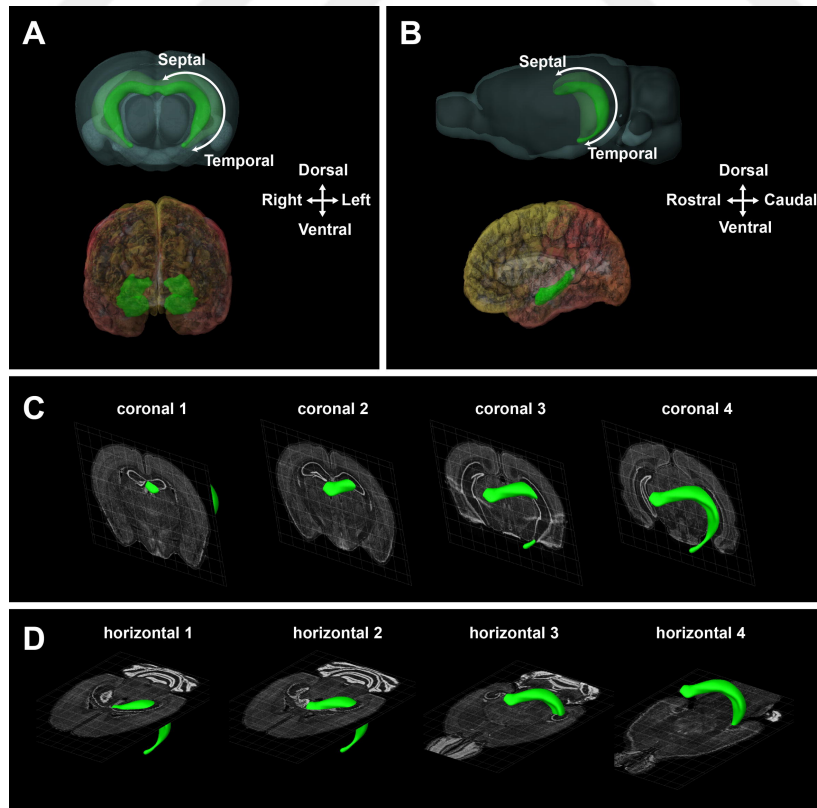


Figure 2.5: The Rat and Human Hippocampus. Obtained from Tanti et. al., 2014 [20].

or sagittal axis. The final axis that span the third dimension is the vertical axis which goes from Str. Oriens (SO) to Str. Locunosum-Molecularare (SLM) in the order of SO-SP-SR-SLM in CA1. Other layers can emerge or disappear in proximal brain regions in HF like DG has a granular layer consisting of the granular cells.

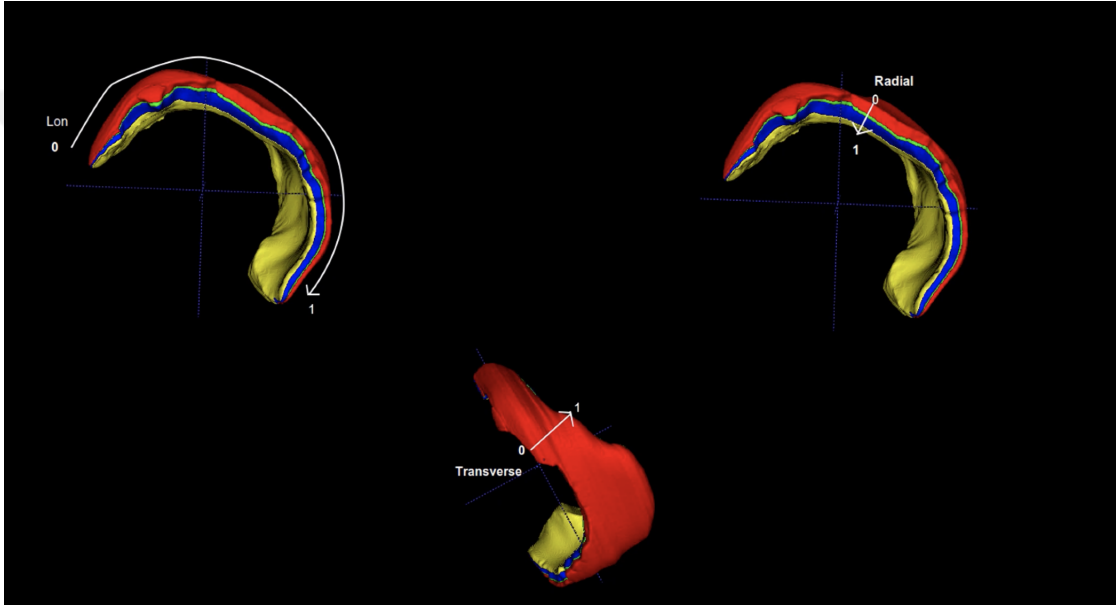


Figure 2.6: The Rat CA1 Model with its axes. Credits: Blue Brain Project, EPFL.

2.1.1 Connectome

Schaffer Collaterals (SC)

These connections emerge from CA3 region to CA1 of Hippocampus in a topological manner as shown in Figure 2.7. Axons of CA3 afferents innervate distal dendrites of pyramidal cells and play role in place-field dependent theta oscillatory input [13]. Along with the Perforant pathway, CA1 efferents play role in navigational mechanisms and episodic memory related neural activities.

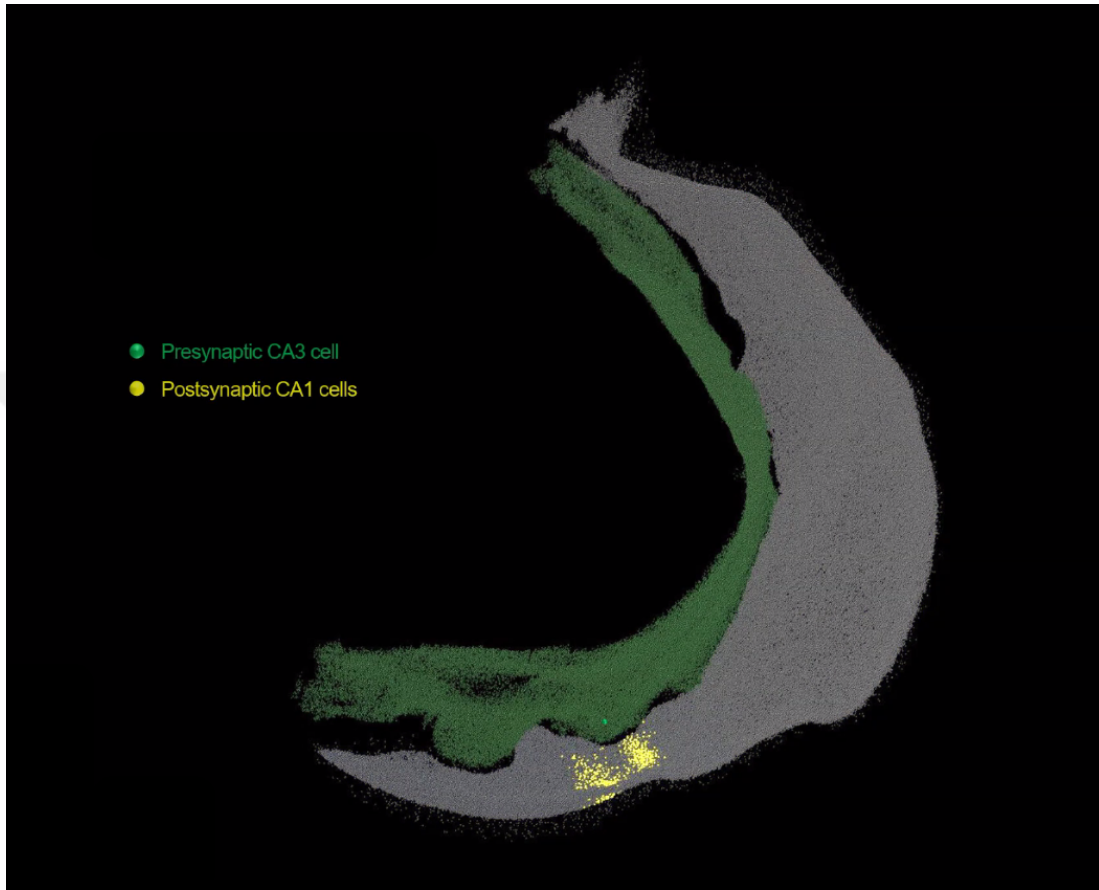


Figure 2.7: An example of a presynaptic CA3 cell (in bright green) with its post-synaptic CA1 efferents (shown in yellow) along with CA3 and CA1 regions (dark green and gray, respectively). Credits: Davide Bella, Blue Brain Project, EPFL.

Perforant Pathway (PP)

Perforant pathway emerges from Lateral and Medial Entorhinal Cortices, namely MEC and LEC, and provide input to a couple of downstream regions. Layer 2 & 6 EC neurons innervate Dentate Gyrus and CA3 distal dendrites, whereas L5 and mostly L3 neurons innervate CA1 and subiculum.

Signals coming from LEC originate from Perirhinal Cortex and contain mostly unimodal neocortical inputs which is also referred to as “What Pathway”, whereas MEC inputs coming from parahippocampal regions are multimodal, mainly visual

and visuospatial, and is included in “where pathway” [12].

This model of hippocampus has Perforant Pathway projections under development which will be implemented in the reduced circuit in the later stages of development.

Mossy Fibers (MF)

These are formed by efferents of Dentate Gyrus that connects to CA3 neurons. Along with the Perforant Pathway and Schaffer Collaterals, these connections form the well known trisynaptic pathway of the hippocampus [21].

2.1.2 Neuron Classifications

Neuron models are classified with respect to their morphology, electrophysiology or to their genotype. These are called m- e- and g- types respectively. The g-type is a relatively new concept which is not included in this thesis but in the later stages of simulation, it has a potential to redefine neurons from their gene expression patterns. So instead of referring all SP_PC as pyramidal cells, we can give an array of genes to represent differences within previously defined population. M- and E- types can also be combined to represent ME-types as not all combinations of morphology and electrophysiology are possible. There are currently 107 ME types discovered (see Figure 2.9)

2.2 Data-driven Brain Modeling

This section is a short summary of what is being conducted in Blue Brain Project, one of the biggest institutions dedicated to the brain modeling, the other one being the Allen Institute. These two institutes and also other teams worldwide collaborate in modeling different parts of the brain, such as somatosensory cortex,

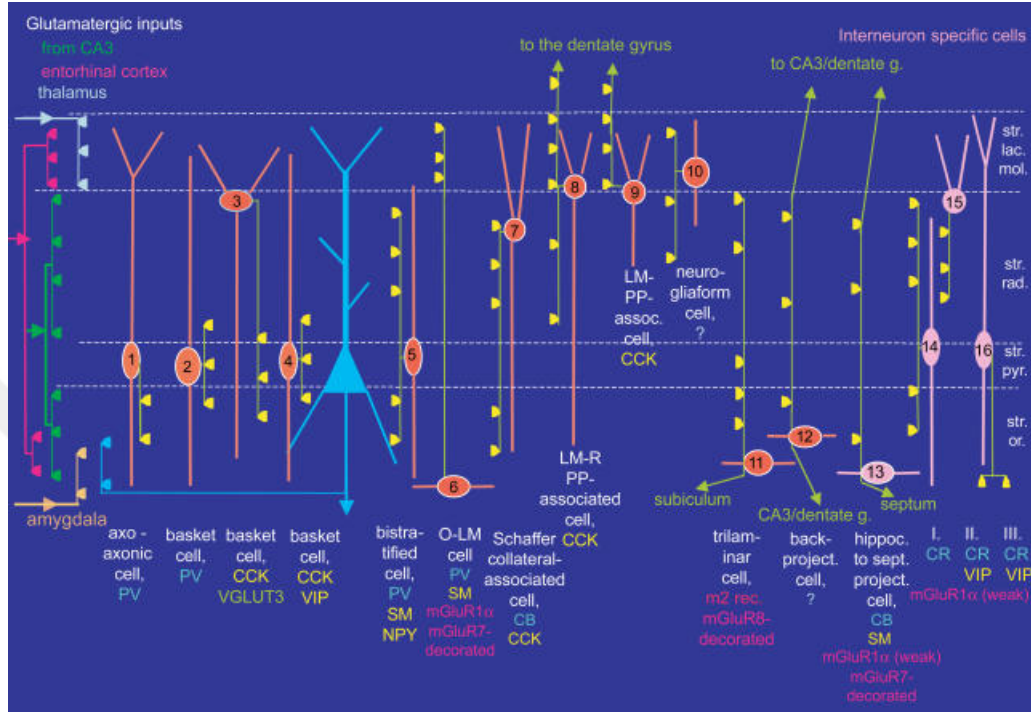


Figure 2.8: Neuron types observed in the CA1 region of the Hippocampus. Obtained from Somogyi and Klausberger et al. 2004 [22]

thalamus and hippocampus in BBP and visual cortex in Allen Brain Institute. The latter also provides new tools for invasive neuroimaging studies like NeuroPixels which is the state-of-the-art electrophysiological recording system [23].

The tools used in the neuron simulation are based on the NEURON software by Richard Hines (2006) [24], whose team created a toolbox for modeling individual neurons in-silico. Later on, the software is improved by Blue Brain Project team for the sake of parallel computing in supercomputers, hence a new version of the platform has been formed (CORENEURON) [25].

Neurons developed in-silico requires experimental constraints to generate further realistic emergent properties. The purpose here is that one can collect as many and diverse data as possible and create a circuit model from scratch but not specifically try to achieve the emergent properties. Only when the system is adequately designed, these properties can emerge. Therefore, neuron morphologies and electrophysiologies, their synaptic anatomies and physiology, layer-wise

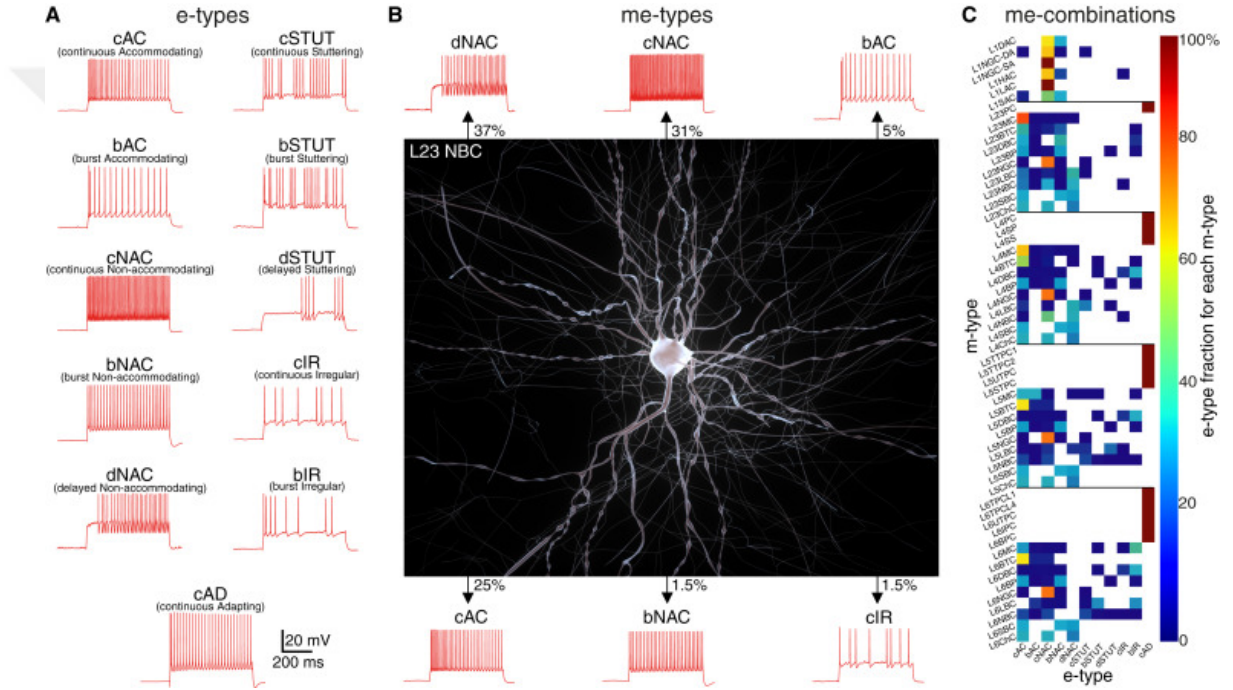


Figure 2.9: “Table of Morpho-Electrical Neuron Types. (A) e-types. Diverse firing patterns in response to depolarizing step current injections in neocortical neurons. c, continuous; d, delayed; b, bursting. AC, accommodating; NAC, non-accommodating; STUT, stuttering, IR, irregular; AD, adapting. (B) An exemplar neuron (L23NBC) with a diversity of e-types. Percentages indicate the relative frequency of e-type occurrence. (C) Fractions of e-types (11 e-types) recorded experimentally in each of the 55 m-types, making up 207 me-types. Solid lines indicate layer boundaries. See Table 1 for relation of e-types to other classifications in the literature.” Obtained from Markram et al. 2015 [17].

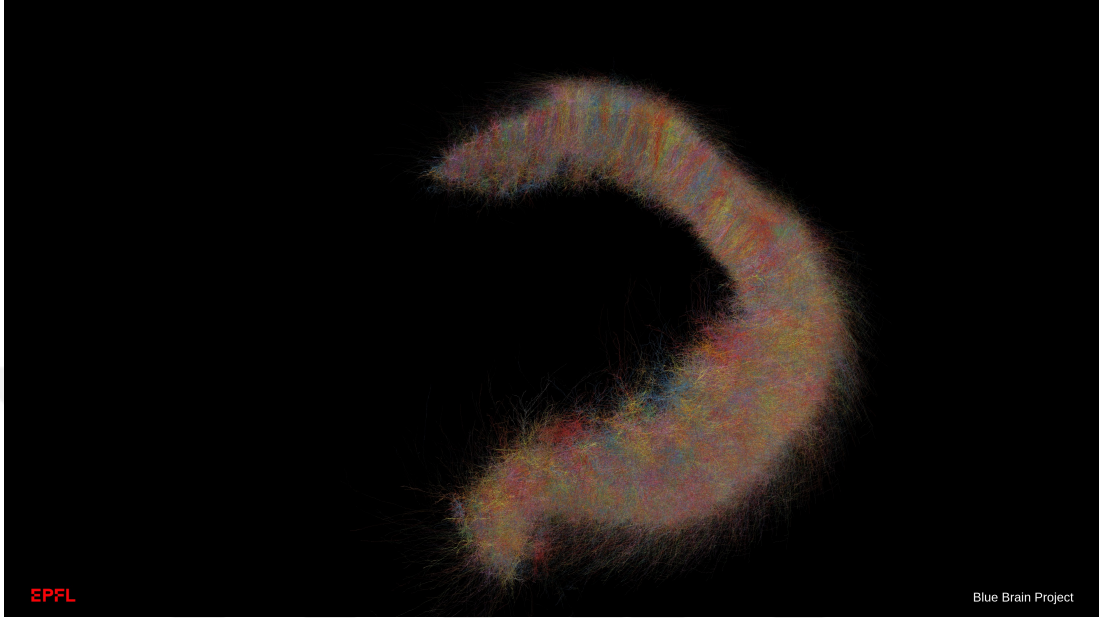


Figure 2.10: The detailed model of hippocampal CA1 circuit. Credits: Blue Brain Project, EPFL (Romani et al., 2021, unpublished).

cell numbers, inter-regional connectivity and topology and much more details are combined to create a viable circuit [17, 26, 27, 28, 29]. A resulting circuit can be seen in Figures 2.10, and 2.11.

2.2.1 Synapse models

In our circuits, an updated version of Tsodyks-Markram (TM) Model is used [29]. The model contains Long-term Potentiation (LTP) and depression (LTD) dynamics, along with multivesicular release support and corrections for calcium ion concentrations, temperature and liquid junction potential [18]. Respective equations for TM Model, STP/STD dynamics, multivesicular release model and correction measures are given in the Section 3.

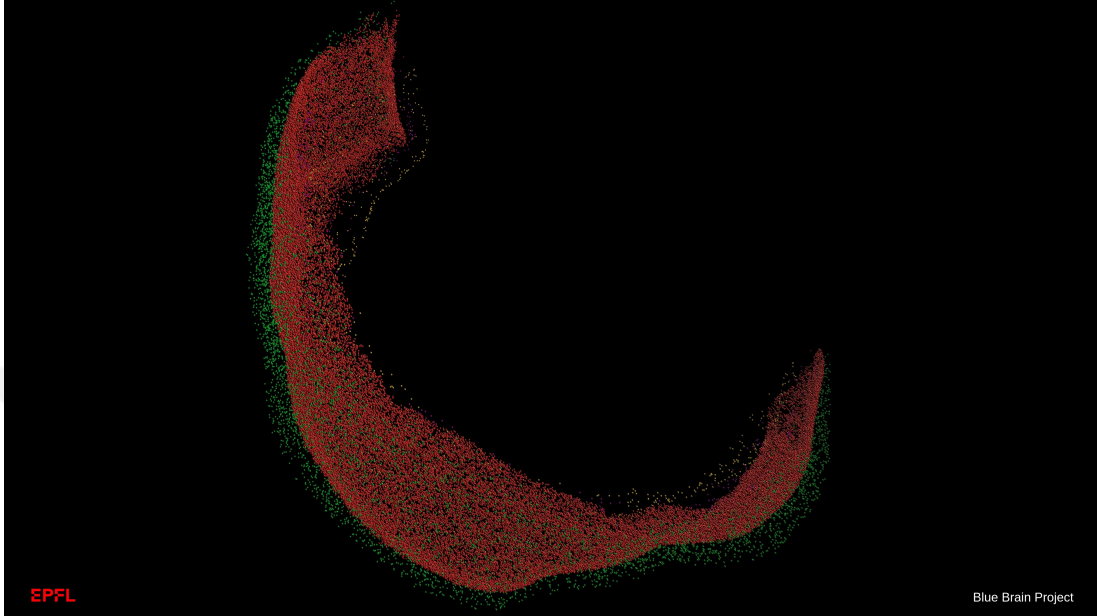


Figure 2.11: Layer profile of the Rat Hippocampus Model. For simplicity, cells are shown with single spheres. Green: Str. Oriens, Red: Str. Pyramidale, Purple: Str. Radiatum, Yellow: Str. Locunosum-Moleculare. Credits: Blue Brain Project, EPFL (Romani et al., 2021, unpublished).

2.3 Neuron Reduce Algorithm

Neuron Reduce is an algorithm that follows the Rall’s “equivalent cylinder” model to simplify a given detailed multi-compartmental neuron. It reduces the amount of computation required to simulate the model by reducing number of sections meanwhile maintaining the input/output relationship as far as possible. The synapses in the full model are then mapped to the reduced version such that the transfer impedance to the soma are kept the same, meaning that the given synaptic input from any region in the reduced neuron reaches to the soma at the same time with respect to the original one [9]. Amsalem et al. investigated the performance of this model with a variety of neuron models mainly from cortical regions, and some in cerebellum and hippocampus [9].

To validate the model accuracy, they have used a number of techniques to measure voltage dynamics, firing rate properties and correlation measure. One such method which is called SPIKE-Synchrony

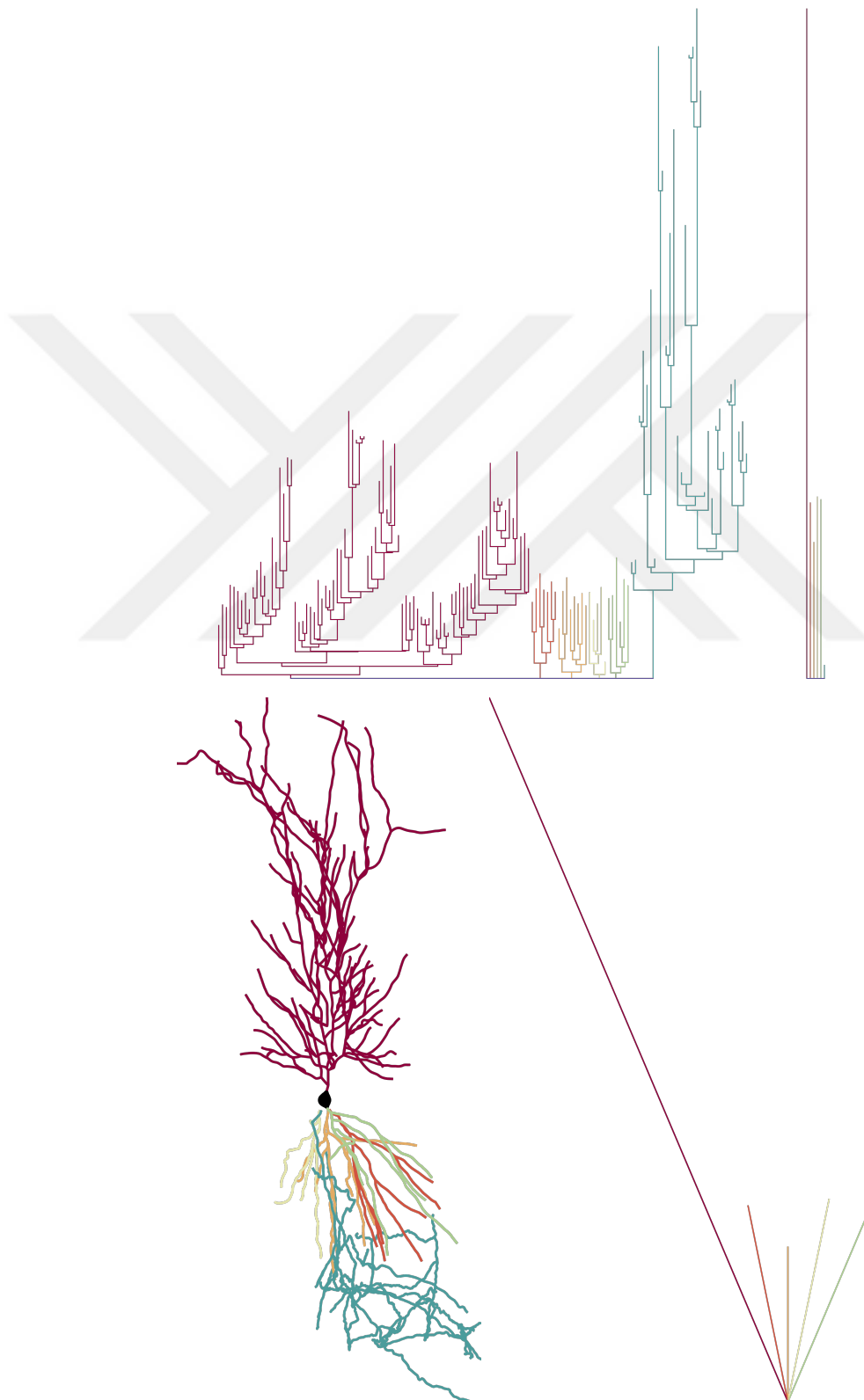


Figure 2.12: The dendrogram (top) and morphology (bottom) of a given a neuron and its reduced version in CA1 of the hippocampus, simplified with the neuron reduce algorithm.

2.4 Representing Neuronal Networks: SONATA format

The SONATA data format [30] is an open-sourced Data Format developed by multiple research institutes, including Blue Brain Project and Allen Institute for Brain Sciences. Its primary use is to represent in-silico neuronal networks such as point neuron models, virtual cells, and biophysically detailed ones, some of which are used in this thesis. The data format uses a graph-based approach such that neurons are represented as nodes and synapses and junctions are represented as edges. With the increasing complexity of the synthetic brain models and the variety of institutions building their own custom data formats, it would be difficult to collaborate and reproduce experiments on different platforms without the help of the SONATA format. Therefore, it provides a scalable and reliable archiving procedure for researchers interested in utilizing any data generated in outside of their labs but are interested to experiment on them. The format itself is vast, therefore only the relevant parts will be mentioned in this thesis. Further information can be obtained from the SONATA paper and Allen Institute SONATA GitHub page [30].

In our network models, we need 4 key elements to represent a circuit, along with a circuit configuration file that refers to these elements (`circuit_config.json`). These elements are broken down into two categories at first, namely components and networks. The components consist of biophysical neuron models and morphologies. The former basically includes NEURON HOC files [24] which provide the functional properties to a neuron using a structure i.e. its morphology. It also refers to the mod files, each of which representing a different ion channel and its kinetics, and distributes these channels over a different section of the neuron model, i.e. soma, dendrite, AIS. Different parameters like passive ion leakiness (`g_pas`), restoring voltage values for sodium and potassium channels (`Ek`, `ENa`), their rising and decaying time constants (`tau_cacum`) can also be tuned for the generation of a desired cell type. These values are primarily obtained from in-vitro and in-vivo experiments, and the ones that cannot be got are tuned with a multi-objective

genetic algorithm platform called BluePyPpt [31].

Morphology files can comprise several file formats, but mainly SWC format is used for the SONATA circuits. A given neuron's morphology is extracted with staining techniques via in-vitro techniques and using softwares like Neurolucida [32] to create 3D models in computers. Later on, cells are repaired for any broken sections or for other modeling errors. The repaired morphologies are represented in a data-format of choice, e.g. asc,swc,hdf5 and each morphology is saved in the morphologies folder. In the CA1 circuit, we have a total of 39 HOC files compared to the 2973 morphology files in the full scale CA1 circuit. This is because a given SWC file is cloned into different copies by scaling its size, rotation of its dendritic branches, or combining different dendrite and axonal trees. Note that some parts of the axons are not fully modeled in this circuit yet (e.g.. myelinated regions) but axon initial segment (AIS) is modeled as we are moving towards better models and most of the voltage-gated Na channels are located at the AIS.

The second part of the components is the networks, which include nodes and edges in hdf5 format. Nodes.h5 provide information on individual neurons like their m-type if the cell is biophysically detailed model, types of neurons included (virtual CA3 cells, biophysical CA1 cells), their model templates (HOC files) and contains many positional parameters like afferent/efferent, their surface coordinates in x, y, z dimensions.

Edges.h5 include information about the circuit population structure, the naming of each connection between node population blocks as from CA3 to CA1 or CA1 to CA1, and their synapse type. Examples for CA1 circuit's nodes and edges are given in Figures 2.13 and 2.14.

2.5 SONATA Network Reduction

This section is dedicated to the software for the Neuron Reduce simplification of SONATA circuits [9]. As the neuron reduce algorithm does not yet apply to

```

- nodes
  - hippocampus_neurons
    - 0
      - @library
        - etype
        - model_type
        - morph_class
        - morphology
        - mtype
        - synapse_class
      - dynamics_params
        - holding_current
        - threshold_current
      - etype
      - layer
      - model_template
      - model_type
      - morph_class
      - morphology
      - mtype
      - region
      - rotation_angle_xaxis
      - rotation_angle_yaxis
      - rotation_angle_zaxis
      - synapse_class
      - x
      - y
      - z
    - node_type_id
  - hippocampus_projections
    - 0
      - @library
        - model_type
      - dynamics_params
      - model_template
      - model_type
    - node_type_id

```

Figure 2.13: Tree structure of CA1 population nodes in SONATA format including virtual CA3 projections

```

- edges
- hippocampus_neurons__hippocampus_neurons__chemical
  - 0
    - afferent_center_x
    - afferent_center_y
    - afferent_center_z
    - afferent_section_id
    - afferent_section_pos
    - afferent_section_pos_orig
    - afferent_section_type
    - afferent_segment_id
    - afferent_segment_offset
    - conductance
    - decay_time
    - delay
    - depression_time
    - efferent_section_id
    - efferent_section_pos
    - efferent_section_pos_orig
    - efferent_section_type
    - efferent_segment_id
    - efferent_segment_offset
    - efferent_surface_x
    - efferent_surface_y
    - efferent_surface_z
    - facilitation_time
    - n_rrp_vesicles
    - spine_length
    - syn_type_id
    - synapse_type_id
    - u_syn
  - edge_type_id
  - indices
    - source_to_target
      - node_id_to_ranges
      - range_to_edge_id
    - target_to_source
      - node_id_to_ranges
      - range_to_edge_id
  - source_node_id
    - node_population
  - target_node_id
    - node_population
- hippocampus_projections__hippocampus_neurons__chemical
  - 0
    - afferent_center_x
    - afferent_center_y
    - afferent_center_z
    - afferent_section_id
    - afferent_section_pos
    - afferent_segment_id
    - afferent_segment_offset
    - conductance
    - decay_time
    - delay
    - depression_time
    - facilitation_time
    - n_rrp_vesicles
    - syn_type_id
    - u_syn
  - edge_type_id
  - indices
    - source_to_target
      - node_id_to_ranges
      - range_to_edge_id
    - target_to_source
      - node_id_to_ranges
      - range_to_edge_id
  - source_node_id
    - node_population
  - target_node_id
    - node_population

```

Figure 2.14: Tree structure of CA1 population edges in SONATA format including virtual CA3 projections

network levels, it is integrated to a circuit reduction pipeline in a new tool in which the circuit itself is validated for SONATA compatibility and nodes and edges are reduced accordingly. The tool will be available to the scientific community upon paper submission. For other circuit portals such as Allen Institute’s BMTK [30], the tool might not work 100 percent as it uses Blue Brain Project (BBP) software to access and change the circuitry.

To reduce a model, 4 folders are necessary under a specific folder as of version 0.1.2. First, a `circuit_config.json` file for the specification of the circuit to be reduced. This folder is actually a SONATA circuit configuration folder so any SONATA circuit in theory, given a standalone circuit, should be reduced without a problem as long as it is BBP compatible.

The required folders are components and networks where the latter includes the node and edge files in hdf5 format. The components consist of morphology sub-folder which contains all the morphologies used in the circuit and the biophysical neural models folder that includes NEURON HOC files of individual cells [24]. The reduction does not work on multiple nodes in supercomputer clusters yet, therefore a circuit with 400000 neurons can be reduced between 4-6 days on a single node.

Chapter 3

Materials and Methods

The simulations are run within Blue Brain Clusters in Swiss National Supercomputing Centre, which is tuned for NEURON processes using a sub-version that is more scalable and efficient called CORENEURON [25]. Note that the debugging and the non-production rate simulations are mostly performed with NEURON to get a better understanding of underlying errors, and it is also used in benchmark comparison with CORENEURON.

Node allocations for each job are tailored according to the simulation needs, as 1 second of simulation with 2274 neurons (CA1.O1 full circuit) can be run easily with 6 nodes, 36 jobs-per-node within 2145 seconds. The reduced counterpart, however, takes 645 seconds to be completed, which introduces 3.33 times simulation speed-up with only morphological reduction (see appendix A). Combined with synaptic merging where synapses with similar rise and decay time constants are merged in a single NEURON process, it is possible to increase this by 40 to 200 fold, on a single cell level. However, the current version of SONATA Network Reduction does not include the latter step.

The neuron models are adapted from Migliore et al. [16] and Blue Brain Project hippocampal neuron models, some of which are available in modelDB webpage [hines2016].

3.1 Post-synaptic conductance model

The post-synaptic conductances are calculated according to the Equation 3.1 where $\hat{g}$ is the peak synaptic conductance and τ_{rise} τ_{decay} are the rise and decay time constants. A is the normalization constant which enables synapses to reach their maximal value at $t_p = (\tau_{rise}\tau_{decay})/(\tau_{decay} - \tau_{rise})\log(\tau_{decay}/\tau_{rise})$ (ms).

$$g(t) = \hat{g}A(e^{\frac{t}{\tau_{decay}}} - e^{\frac{t}{\tau_{rise}}}) \quad (3.1)$$

AMPA and GABAR synaptic currents are implemented by modifying Equation 3.1 to 3.2.

$$I(t) = g(t)(V_m(t) - E_{rev}) \quad (3.2)$$

Where V_m is the membrane potential in millivolts, and E_{rev} is the reversal potential for the synapse of interest. The model is also built to be affected by the Magnesium concentration in the vicinity. This allows NMDA Receptor activities to be modified as expected (Equation 3.4).

$$I_{NMDA}(t) = g(t)mg(V_m(t))(V_m(t) - E_{rev}) \quad (3.3)$$

where $mg(V_m)$ is corrected for liquid junction potential via exploiting the works of Jahr-Stevens [33] in which short NMDA currents are reproduced by 3-4 state models.

$$mg(V_m) = \frac{1}{1 + e^{c_1 V_m}(C_{Mg^{2+}}/c_2)} \quad (3.4)$$

In Eq. 3.4, C represents the extracellular concentration, in this case for the Magnesium, and c_1 and c_2 are the constants obtained from the fitting, 0.062 (1/mV) and 2.62 mM, respectively. [18, 33].

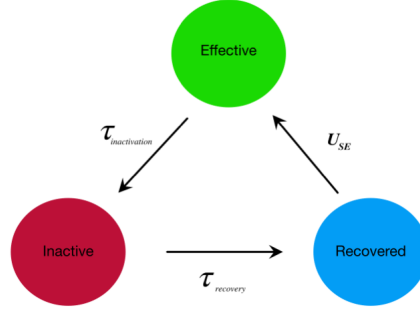


Figure 3.1: The schematics for synaptic pool dynamics and their relationship with the U_{se} parameter.

3.2 Short-Term Potentiation

The short term potentiation and depression dynamics in this model are represented with Equations 3.5, and 3.6 which is a refined version of TM Model [29]. The dynamics between the different synaptic pools are represented in the schematic in figure 3.1 where the sum of the pool fractions add up to 1.

$$\frac{dR(t)}{dt} = \frac{1 - R(t)}{D} - U(t)R(t)\delta(t - t_{spike}) \quad (3.5)$$

$$\frac{dU(t)}{dt} = \frac{U_{SE} - U(t)}{F} + U_{SE}(1 - U(t))\delta(t - t_{spike}) \quad (3.6)$$

Here, the available neurotransmitter resources R , are released with probability U , which is dependent on the absolute release probability U_{SE} , the current value of U , facilitation time constant F , and the Dirac Delta function of the presynaptic spike time $\delta(t - t_{spike})$. The rise and decay time constants, and U_{SE} in the model are fit to the experimental values as well as A_{SE} which is the absolute synaptic efficacy where $PSPamplitude = A_{SE}U(t_{spike})R(t_{spike})$. [18, 31, 34, 35].

3.3 Stochastic Tskodyks-Markram Model with multivesicular release

Multi-vesicular release of the TM model is obtained by a quantal model [36] and 2-state Markov Process shown in Equations 3.7 to 3.10 where 0 means the vesicle is unavailable and 1 means available for release and the arrows represent the transition between the states. The value of a given vesicle's state of unavailability decays with the time constant D and the transition $1 \rightarrow 0$ is dependent on the probability of U ($U(t)$).

$$P_{1 \Rightarrow 0} = U(t) \quad (3.7)$$

$$P_{1 \Rightarrow 1} = 1 - P_{1 \Rightarrow 0} \quad (3.8)$$

$$P_{0 \Rightarrow 0} = e^{-(t-t_{spike})/D} \quad (3.9)$$

$$P_{0 \Rightarrow 1} = 1 - P_{0 \Rightarrow 0} \quad (3.10)$$

This stochasticity makes the model different from the traditional TM Model and introduces variability in the post-synaptic voltages in which the amplitude of the voltage deflection is dependent on the number of readily releasable pool size (N_{RRP}) [17, 18, 26, 37, 38, 39]

With the stochasticity, TM model shown previously becomes Equations 3.11, 3.12, 3.13

$$g(t) = \hat{g}A(d(t) - r(t)) \quad (3.11)$$

$$\frac{dd(t)}{dt} = -\frac{d(t)}{\tau_{decay}} + A\frac{N_r}{N_{RRP}}\delta(t - t_{spike}) \quad (3.12)$$

$$\frac{dr(t)}{dt} = -\frac{r(t)}{\tau_{rise}} + A\frac{N_r}{N_{RRP}}\delta(t - t_{spike}) \quad (3.13)$$

where N_r is the current miniature post-synaptic potential which is upper bound to N_{RRP} .

3.4 Correcting measures

The model is corrected for calcium concentration and temperature with Hill isotherm Q10 scaling factors in Equations 3.14 and 3.15, respectively [40, 17, 18]:

$$U_{SE} = \frac{[Ca^{2+}]_0^4}{K_{1/2}^4 + [Ca^{2+}]_0^4} \quad (3.14)$$

$$\tau_{sim} = \tau_{exp}/Q10^{(T_{sim}-T_{exp})/10} \quad (3.15)$$

where U_{SEmax} is the maximum value of U_{SE} at high levels of calcium concentrations, and K is the calcium concentration at which $U_{SE} = 1.5U_{SEmax}$ that is obtained from Rozov et al. [41]. This allows nonlinear synaptic release patterns depending on the calcium concentration [18]. For the temperature correction Q10 scaling factor is experimentally obtained value for each receptor where $T = 34$ Celcius is used in these simulations. Finally, holding and steady-state potentials are corrected by the theoretical Liquid Junction Potentials as in Ecker et. al. [18, 42]

3.5 In-house and other tools utilized

3.5.1 Bluepy / BluepySNAP

Bluepy is a python toolbox for basic circuit level analyses and importing procedures. It is an in-house toolbox but uses a backend of an open-sourced version of it called BluePySnap which can also handle these procedures. Before SONATA collaboration, Bluepy had been used with custom circuit and reporting format exclusive to BBP researchers. Currently, both tools are useful in loading the circuit used in this thesis. However, one should note that multiple population support is still under development as of Feb 2020. That is why several toolboxes that requires bluepy backend cannot be used with SONATA circuits. The most prominent examples are PSP-validation and BGLibPy.

3.5.2 CoreNEURON

CoreNEURON [25] is the supercomputer friendly version of NEURON [24] which lowers the simulation time an order of magnitude via utilization of new hardware capabilities in the large-scale simulations. In the hippocampal o1 microcircuit an 8.36 times increase in speed is observed (1 second of simulation with SC, 2374 vs 568 seconds, 64 nodes each).

3.5.3 Emsim

This is a library used for Local Field Potential (LFP) generation after simulating the circuit. It uses a distance-based algorithm to calculate the voltages in specified locations as if there are electrodes recording the signals there from surrounding neuron dendrites.

3.5.4 Psp-validation

This library is used to optimize PSP amplitudes between pairs of neurons given a reference data. It uses a BluePy backend therefore cannot be used with the SONATA circuits with multiple populations yet but as a workaround, full CA1 circuit without a second population was used to tune the m-type pairs in this work.

$$\hat{g}_{scaled} = \hat{g} \frac{PSP_{full}(1 - PSP_{red}/df)}{PSP_{red}(1 - PSP_{full}/df)} \quad (3.16)$$

The Equation 3.16 shows how the PSP validation scaling is calculated where PSP_{full} (mV) and $PSP_{reduced}$ (mV) are the full and the reduced circuit PSP amplitudes respectively. $df = |E_{rev} - V_{ss}|(mV)$ is the driving force [43] and g , $\hat{g}$, $\hat{g}_{scaled}$ represent synaptic, peak synaptic and scaled peak synaptic conductances, respectively.

3.5.5 BGLibPy

BGLibPy is a simulation tool used for detailed study of small numbers of neurons in simulations defined by BlueConfig. BlueConfig is the configuration file for simulations in which circuit path, node and edges paths, target files, stimulation and reporting blocks and all other required values are given. BGLibPy gets necessary parameters for simulation from BlueConfig and without the need to send the simulation as a job via slurm, it allows scientists to simulate neuron or small neuron groups within the boundaries of a python environment i.e. Jupyter Notebook.

3.5.6 Sonata network reduction

Sonata Network Reduction is the circuit level adaptation of the neuron reduce algorithm which uses bglibpy and several other tools in its backend. The network, as the name suggest, should comply with the SONATA standards such that legacy circuits and its elements need to be converted to SONATA readable format. These processes take some time and expertise to be completed which took almost half of this master thesis project. However, with the updated version of the Sonata Network Reduction, several circuits including ones in somatosensory cortex was reduced but it is out of the boundaries of this work. It is worth to note that the current version of the Sonata Network Reduction reduces only the morphologies instead of doing that and merging synapses with the same attributes as shown in the Neuron Reduce paper (Sup Table 1 [9]).

3.5.7 Neuromorphovis

This toolbox is used to visualize single or several neurons which uses Blender in its backend. Most of the single cell images in 3D were obtained with Neuromorphovis tool.

3.5.8 Efel

Efel or “Electrophys Feature Extraction Library” is an open-sourced python library used to extract features from voltage recordings of a given neuron. It is used to calculate spike synchrony measures, firing rates and peak synaptic amplitude calculations.

3.6 External toolboxes

3.6.1 Python toolboxes

A number of python toolboxes were used to access, rearrange and plot the neuronal data (numpy, matplotlib, seaborn, pypike). All of which are accessible in PyPI and are well documented. Most of these libraries are included in the well defined anaconda packages but we preferred python virtual machines to create the necessary libraries [44].

3.6.2 Slurm System and Cluster Utilization

Slurm is a workload manager program used to send specific jobs to the Blue Brain clusters. [45]. One can define the amount of nodes, jobs-per-node, ntasks-per-job, cpu constraints, time limit and reporting and notification features in an sbatch file. Once sent, the manager puts the job in queue and depending on the priority and the amount of nodes and time required.

3.7 Benchmarking

It is important to do benchmarking tests in a controlled fashion on both the original and the simplified circuits. To achieve this, two CA1 microcircuits, aka CA1.O0 (2274 cells) and CA1.O1 circuit (18,198 cells), and the full scale CA1 (440k cells) are used. The microcircuit consists of hexagonal structure (see Figure 3.2 for O1 circuit), similar to the Markram 2015 paper [17], instead of the actual C shaped rat hippocampus.

Although total simulation times are comparable in full and reduced circuits on multi-node process, time taken to instantiate cells are 43 times lower in the reduced circuit (49.45s vs 1.15s) for 18198 cells with CORENEURON Version :

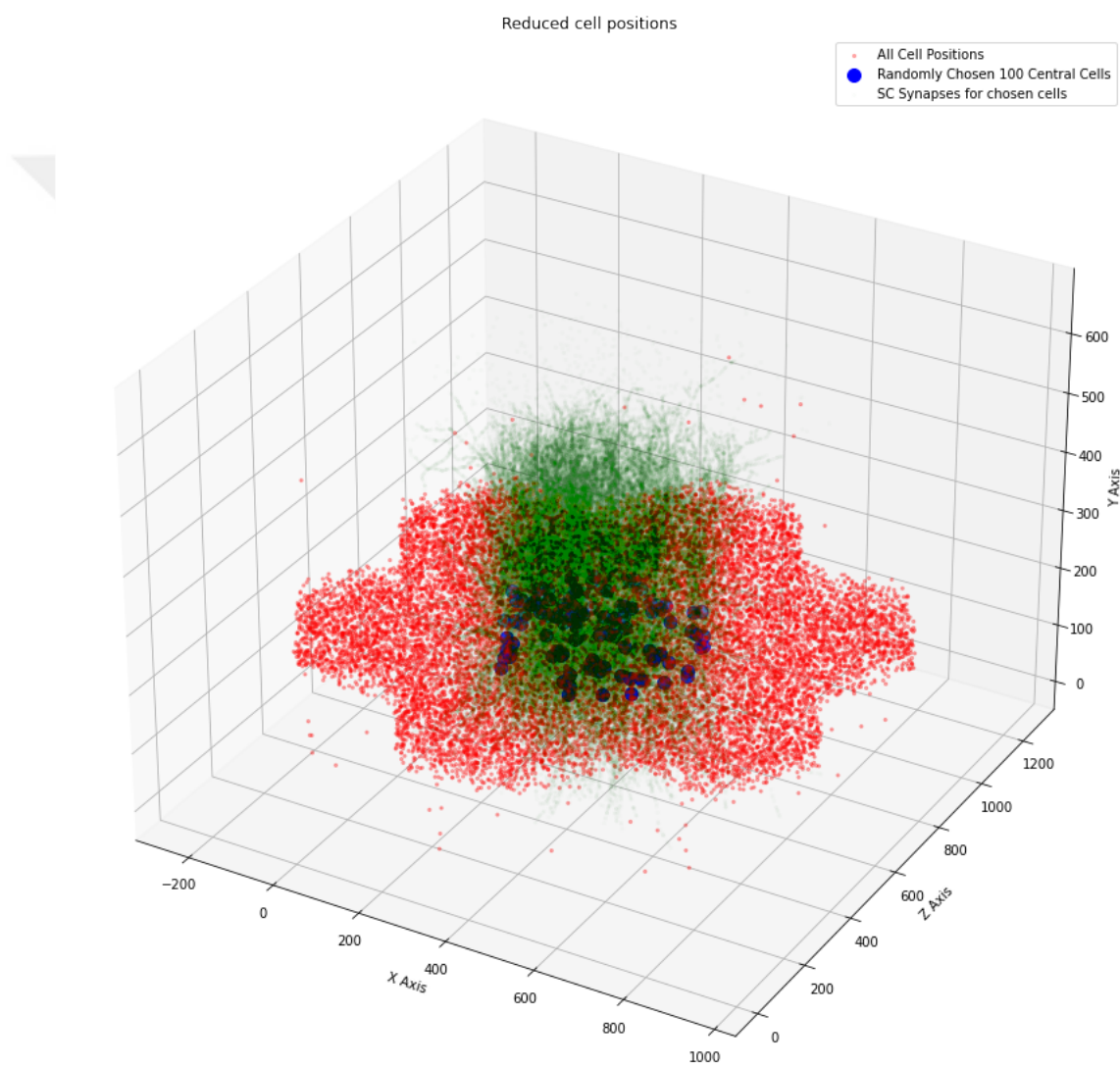


Figure 3.2: CA1.O1 circuit with 100 randomly selected cells with their afferent CA3 Connections.

0.21.0 483f9d9.

The simulation times were compared in these three circuits where we observed an increase in speed-up ratios as the circuit size gets bigger. Figure 3.3 shows the how circuit size has a positive effect in network reduction performance.

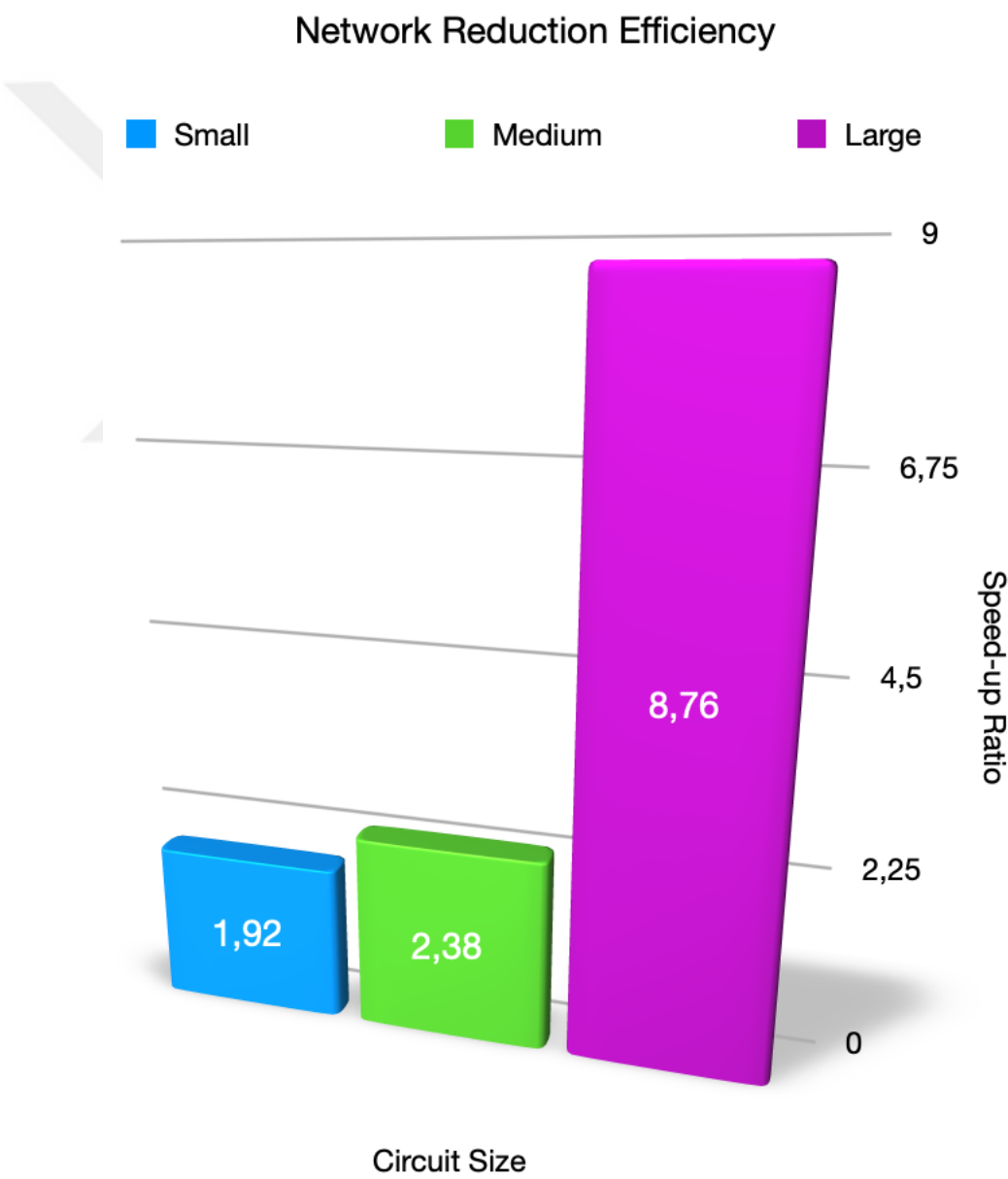


Figure 3.3: Comparison of simulation times of 3 hippocampal circuits at different sizes. The performance of the algorithm scales up with the circuit size

As the circuit gets bigger, the circuit build time also gets bigger. With the same node allocation, simplified circuit built time was 1.03 s compared to 49.45s of the full one (corresponding to 2% of the original). Instantiating synapses are also another heavy process which takes 34.87 s for full versus 37.19 s for the reduced one.

Of course running jobs on multiple clusters introduces delay in assessing the neuron parameters which would not be a case in running the job on a single core. That is why, a simplistic approach was taken to compare the simulation run times on 1 node and 1 job-per-node in each node where there are 36 cores per node. To make a balanced loading of neurons to each core, 100 most central pyramidal cells were used as simulation target and the benchmark testing was conducted accordingly.

On minimal node allocation (1 node, 1 job-per-node) it takes 22.04 seconds to simulate a full circuit with CORENEURON (69.12 s with NEURON) whereas for the reduced circuit it takes 9.04 seconds (18.58 s for NEURON) for 10 ms of circuit simulation. This difference for 10 ms of simulation introduces from 58.9 to 73.1 percent reduction in real time for different simulator choices.

The relative efficiency observed in neuron-reduce algorithm which may be up to 200x depends on the combination of both morphological reduction as well as synaptic merging. The latter technique was unfortunately not available in the current version of the SONATA Network Reduction. However, a significant reduction in simulation time can still be observed with morphological reduction alone as shown in 3.3. A further increase in simulation speed can also be achieved with down-sampling rate of the segments whereby less number of segment swill increase the efficiency but at the expense of simulation accuracy. To achieve the best result, we have followed the guidelines of the author of neuron reduce paper and chose `-total-segments-manual` to 0.1 i.e. 10% of the original number of segments was taken.

Chapter 4

Node Reduction

4.1 Single Cell Reduction of Individual Hippocampal Cells as a Control

As a simplistic approach, a number of artificial synapses were added (10k) to a given complex cell to assess the reduction procedure in single neuron basis [9]. With 8500 excitatory and 1500 inhibitory synapses with respective parameters given in Table 4.1, complex cell simulations are created and shown in *Figure 4.1*.

Table 4.1: Synaptic Parameters used in Single Cell Reduction of Hippocampal Neurons.

Single Cell Simulation Synaptic Parameters					
Synapse Type	e_syn	tau1	tau2	spike_interval	syn_weight
EXC Synapses	0	0.3	1.8	1000/2.5	0.0016
INH Synapses	-86	1	8	1000/15	0.0008

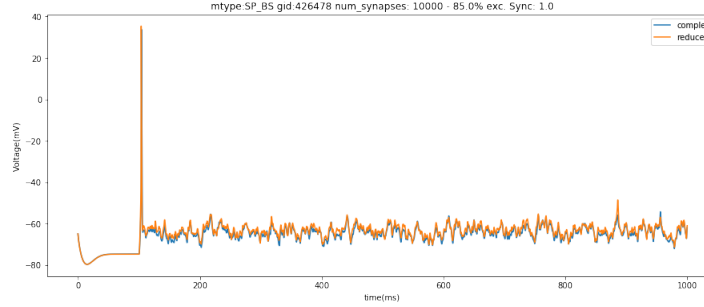


Figure 4.1: Single Cell Reduction of SP_BS neuron with 850 excitatory and 150 inhibitory synapses. See Table 4.1 for synaptic parameters

Table 4.2: Synaptic Parameters used in Single Cell Reduction of Hippocampal Neurons with more inhibitory inter-spike interval.

Single Cell Simulation Synaptic Parameters					
Synapse Type	e_syn	tau1	tau2	spike_interval	syn_weight
EXC Synapses	0	0.3	1.8	1000/2.5	0.0016
INH Synapses	-86	1	8	1000/5	0.0008

If the reduced cell gets a good spike synchronization score, then it will be deemed useful in the circuit. For this, neurons from each morphology was taken and simulated. Then, cells are reduced and simulated again for voltage trace comparison and spike-synchrony calculation with a python toolbox “PySpike” [44]. By repeating this protocol for all m-types, spike-synchronization scores were obtained. As can be seen in Table 4.3, most of the m-types have a reasonable score except for SP_PC (one example trace is given in Figure 4.4). In the circuit level simulation, this behavior is also observed as all m-types had a similar total firing rates except for pyramidal cells (Figure 5.11).

To overcome this problem, the synaptic parameters were investigated to see if the reduced pyramidal cell activities can match the original ones, not only in rate-based manner but also temporally. The SPIKE-Synchrony measure was therefore used as a metric to investigate the spike time dynamics and to find the working interval of synaptic parameters. Since the simplification amount is traded off with the accuracy, we have to find where the simplification starts to fail and reduce the

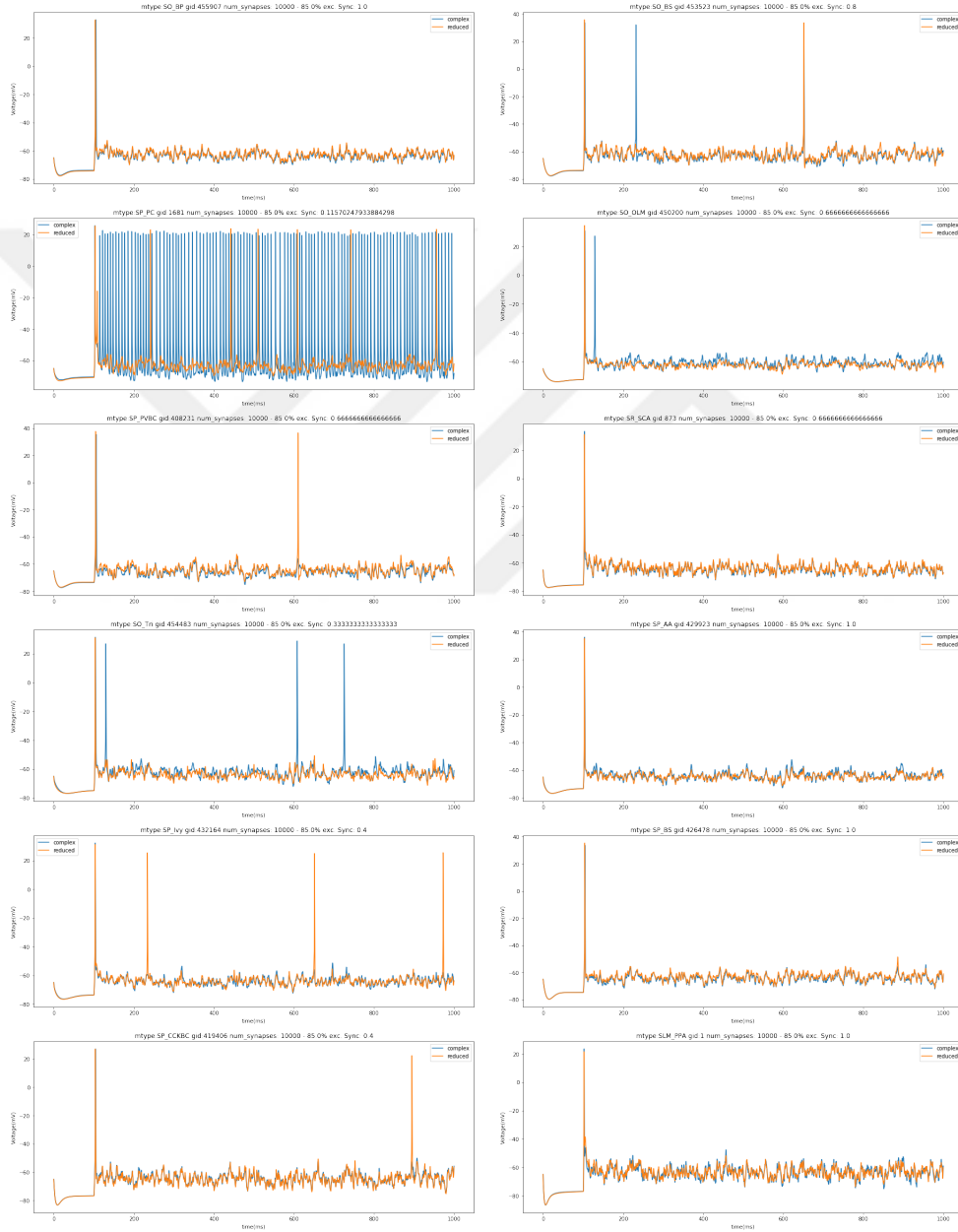


Figure 4.2: Single Cell Reduction for neurons from each m-type with 850 excitatory and 150 inhibitory synapses. See Table 4.1 for synaptic parameters

Table 4.3: M-type wise full and reduced cell simulation times, and their respective spike synchrony scores with synaptic parameters in Table 4.1

Single Cell Simulations				
M-type	Full(secs)	Reduced(Secs)	Spike_Sync	Ratio
SP_Ivy	70,55	2,90	0,40	24,33
SP_AA	67,95	1,66	1,00	40,93
SP_PVBC	94,68	14,20	0,66	6,67
SP_BS	89,64	6,30	1,00	14,23
SR_SCA	69,57	7,41	0,67	9,39
SO_BP	69,99	3,80	1,00	18,42
SO_Tri	69,19	1,97	0,34	35,12
SP_PC	97,41	3,88	0,12	25,11
SO_OLM	95,38	0,95	0,67	100,40
SO_BS	59,19	3,12	0,8	18,97
SP_CCKBC	63,41	11,12	0,40	5,70
SLM_PPA	57,61	6,02	1,00	9,57

models up to that point. Table 4.2 and Figure 4.5 show an example case where the frequency of the inhibitory synapses were decreased to 1/3rd of the original in all m-types. Of course, this is not the best way of solving the problem, but a mere technique to investigate the successful working range of simplified neurons in-silico. More sophisticated measures would use scaling techniques that looks for peak post-synaptic potentials given m-type pairs and tune the weights in the reduced circuit accordingly, see psp-validation technique in the methods section and later stages of this section for synaptic conductance correction of individual morphologies.

It should be also stressed that in previous studies, cells that fire at low frequency regimes tend to have problems with simplification algorithm [9]. That is why experiments with spontaneous activity in this study had problems in getting spikes for the low firing ME types. Therefore, hippocampal cells with no external stimulation may not be a good substrate for this simplification algorithm. Instead, experiments with a rhythmic theta input bearing long-distance connections as explained in Buzsaki 2002 [13] may be used to validate the full hippocampal model. Alternatively, higher activity showing regions like cerebellum could benefit from this reduction pipeline.

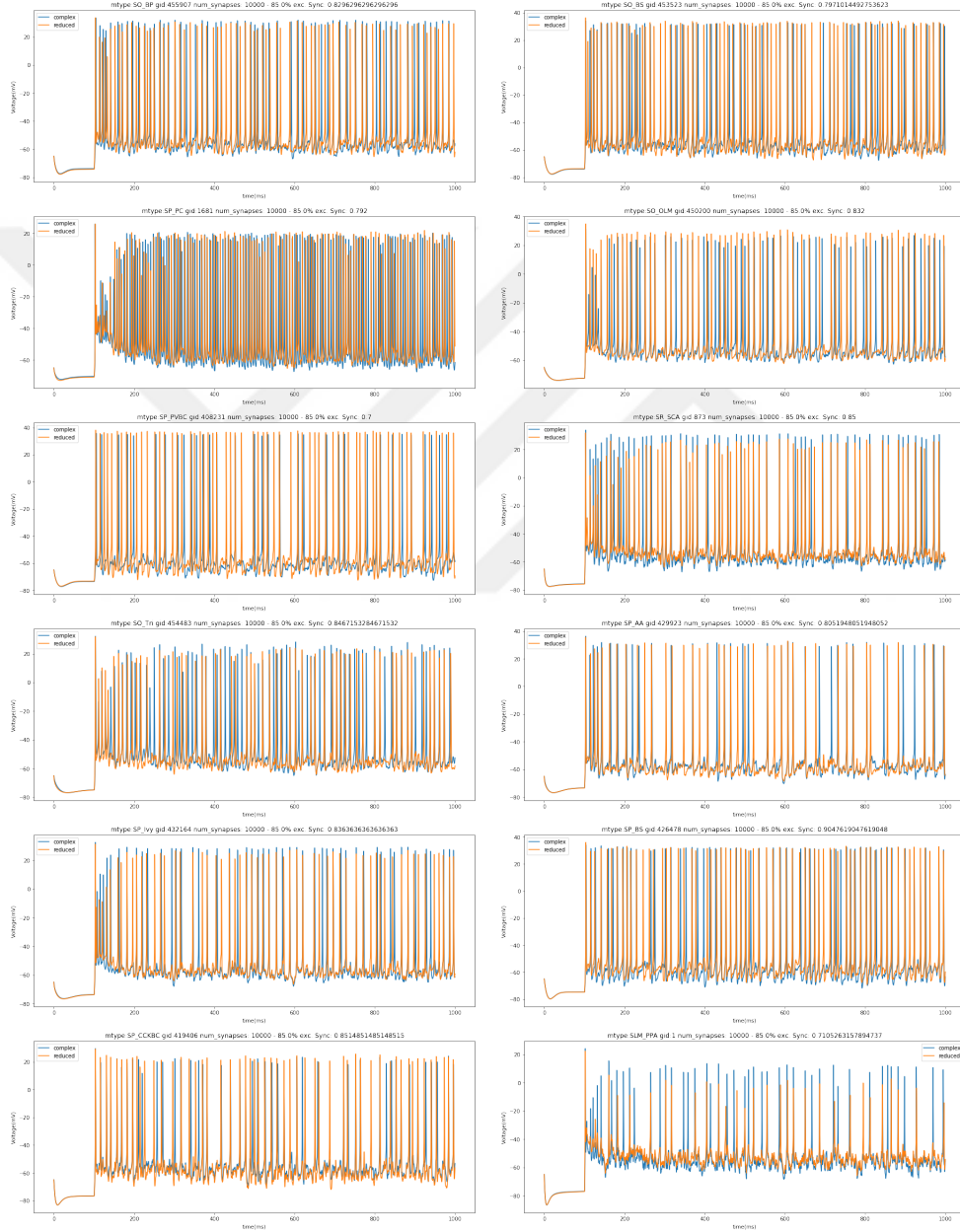


Figure 4.3: Single Cell Reduction for neurons from each m-type with 850 excitatory and 150 inhibitory synapses. See Table 4.2 for synaptic parameters

Table 4.4: M-type wise full and reduced cell simulation times, and their respective SPIKE-Synchronization scores with synaptic parameters in Table 4.2

Single Cell Simulations				
M-type	Full(secs)	Reduced(SeCS)	Spike_Sync	Ratio
SP_Ivy	67,44	2,9	0,84	23,26
SP_AA	66,63	1,64	0,81	40,63
SP_PVBC	94,42	14,16	0,7	6,67
SP_BS	88,94	6,26	0,9	14,21
SR_SCA	68,88	7,38	0,85	9,33
SO_BP	69,32	3,8	0,83	18,24
SO_Tri	68,59	1,96	0,85	34,99
SP_PC	96,75	3,85	0,79	25,13
SO_OLM	94,95	0,93	0,83	102,1
SO_BS	58,74	3,09	0,8	19,01
SP_CCKBC	62,89	11,08	0,85	5,68
SLM_PPA	56,28	5,99	0,71	9,40

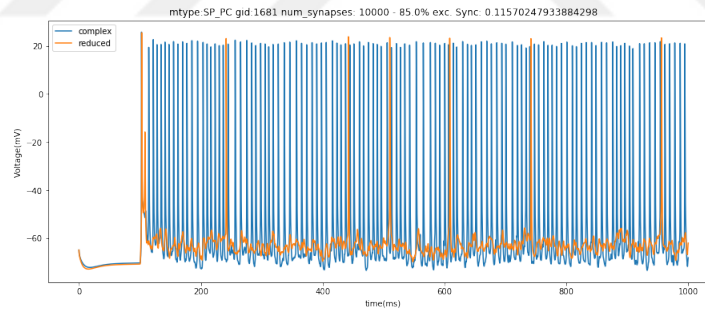


Figure 4.4: Single Cell Reduction of SP Pyramidal Cell with 850 excitatory and 150 inhibitory synapses with synaptic parameters given in Table 4.1

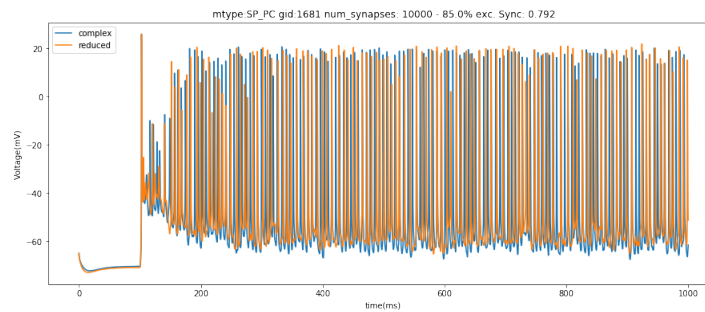


Figure 4.5: Single Cell Reduction of a pyramidal cell with 850 excitatory and 150 inhibitory synapses and 1/3rd less of inhibitory synaptic activation, see Table 4.2 for more detail.

There are several ways to deal with this error. One can perform psp-validation on the reduced circuit and compare the `g_syn` value of the reduced cell to match with the full one after obtaining the scale factor. We will discuss this technique later on in psp-validation chapter. Another method, to understand the underlying reason of this discrepancy, is to play with synapse parameters in a methodological fashion so that we obtain a good spike synchronization. Ideally, we would not have to utilize to these optimizations, but since the reduction pipeline does not promise the action potential amplitudes to be the same, we needed to apply them. Also, since the most of the CA1 circuit comprises SP PCs, it is essential that they work nicely. Note that in the normal circuit building pipeline, full models of the neurons are also tuned to match the in-vitro experiments. With increasing toolbox developments, we could move from the hand-tuned synapses to psp-validated scaling factors to match with the correct psp amplitudes.

4.1.1 Dealing with Pyramidal Cells

With the current model of SP PC cells, the reduction itself is unable to cope with the cellular activity levels of their original counterparts. As this can be seen in network level simulations, the first and the foremost from raster plots, and also from the single cell simulations i.e. Figure 4.4.

The investigation of the FI curved (F: Firing Rate, I: Current Injected) [46, 47] in Figures 4.6, 4.7, 4.8, which is a technique that injects current to soma of the neuron and checks for the response patterns with increasing current strength, show that the full and reduced pyramidal cells spike at similar rates, although in some cases delayed activation is observed. This eliminates the problem that some SP PCs cannot spike at all and instead focuses the problem to either synaptic processes or AP thresholding at the soma or axon initial segment. In our model, unless specified otherwise, the voltages are thresholded at the soma.

Through extensive debugging of synaptic parameters such as varying inhibitory and excitatory inter-spike intervals, and synaptic weights on a random SP PC cell with numbers ranging from 1k to 10k, it is found that decreasing the inhibitory

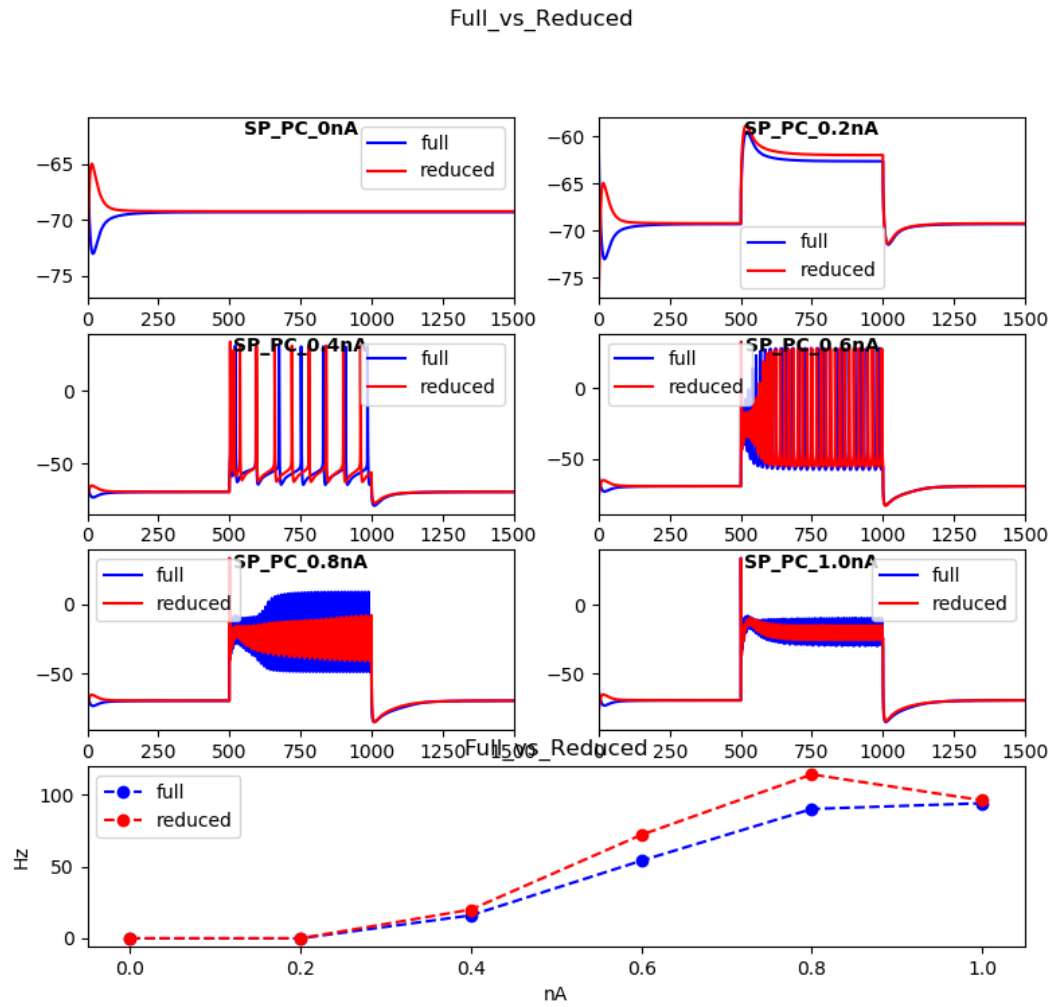


Figure 4.6: An FI curve for a SP_PC neuron

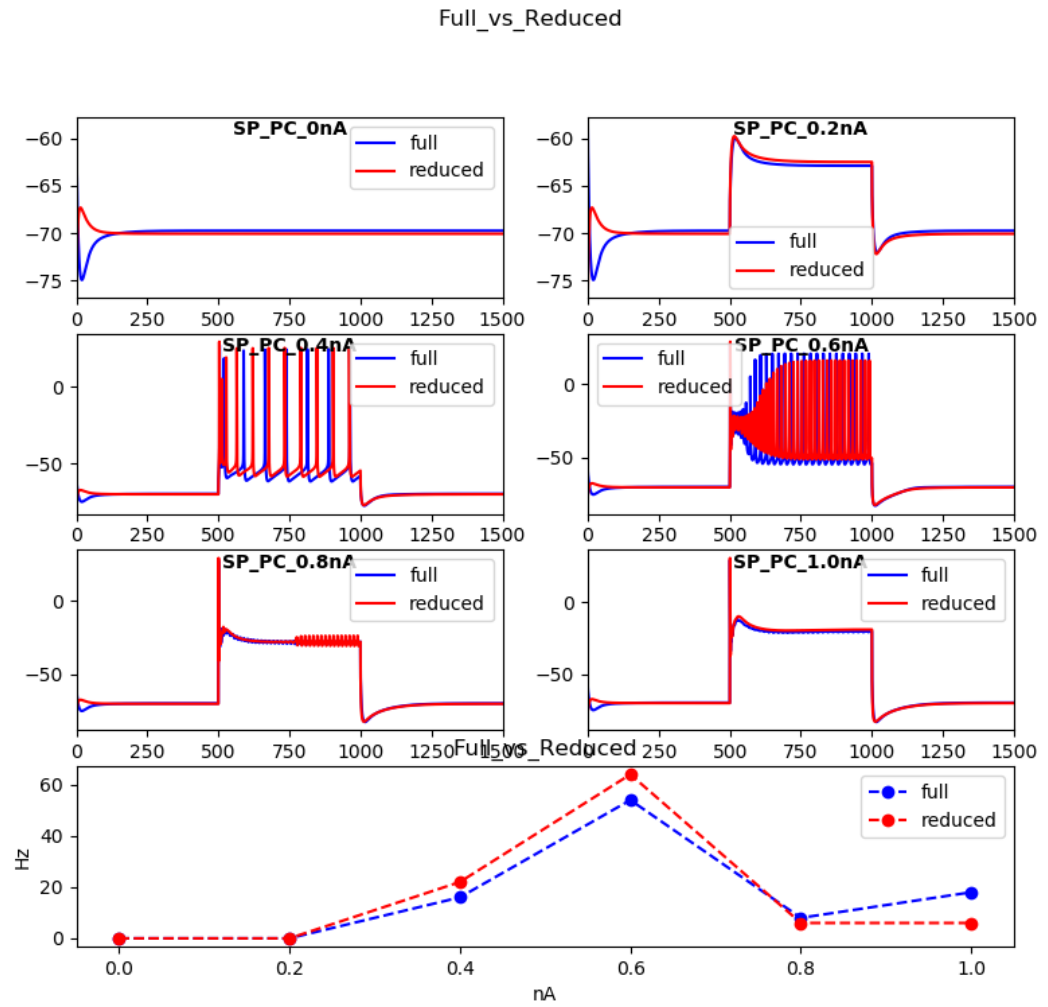


Figure 4.7: An FI curve for a SP_PC neuron.

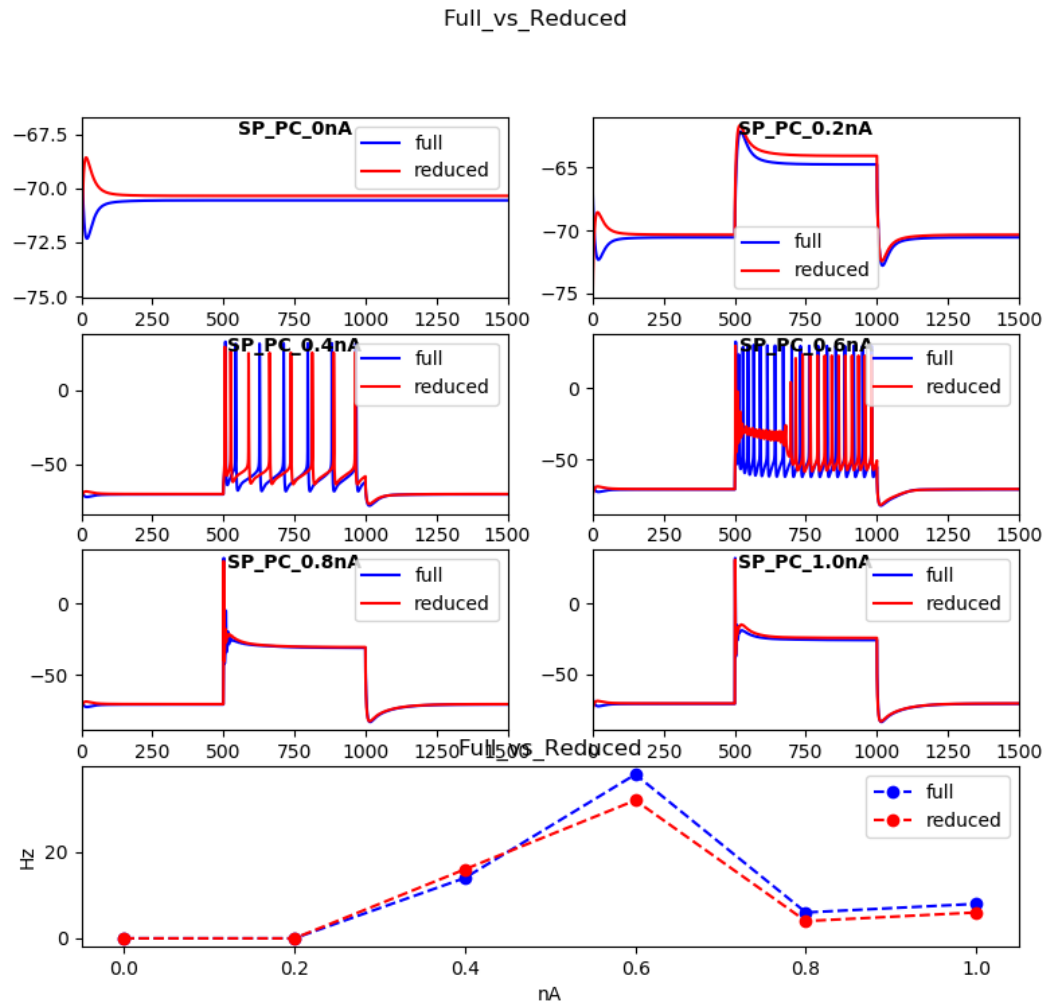


Figure 4.8: An FI curve for a SP_PC neuron.

synaptic intervals or increasing excitatory ones as well as increasing excitatory synaptic strengths increases the spike synchronization scores (see Figure 4.9 for the effects of the excitatory or inhibitory synapse weights on a given cell, and Figure 4.10 for the voltage traces of the former case). To validate this further, longer simulations were executed e.g. 30 s and the spike synchronies, and shorter simulations were validated with them. This supports the notion that the simplification works better with neurons in higher activity regimes.

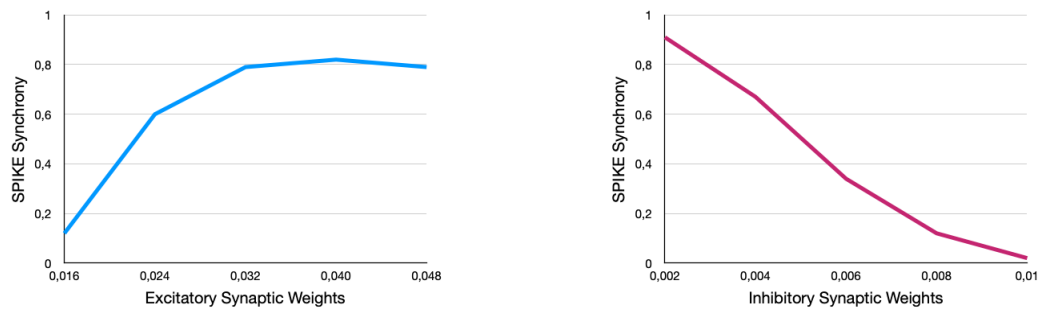


Figure 4.9: Effects of excitatory and inhibitory weights on SPIKE-Synchronization on a given pyramidal cell.

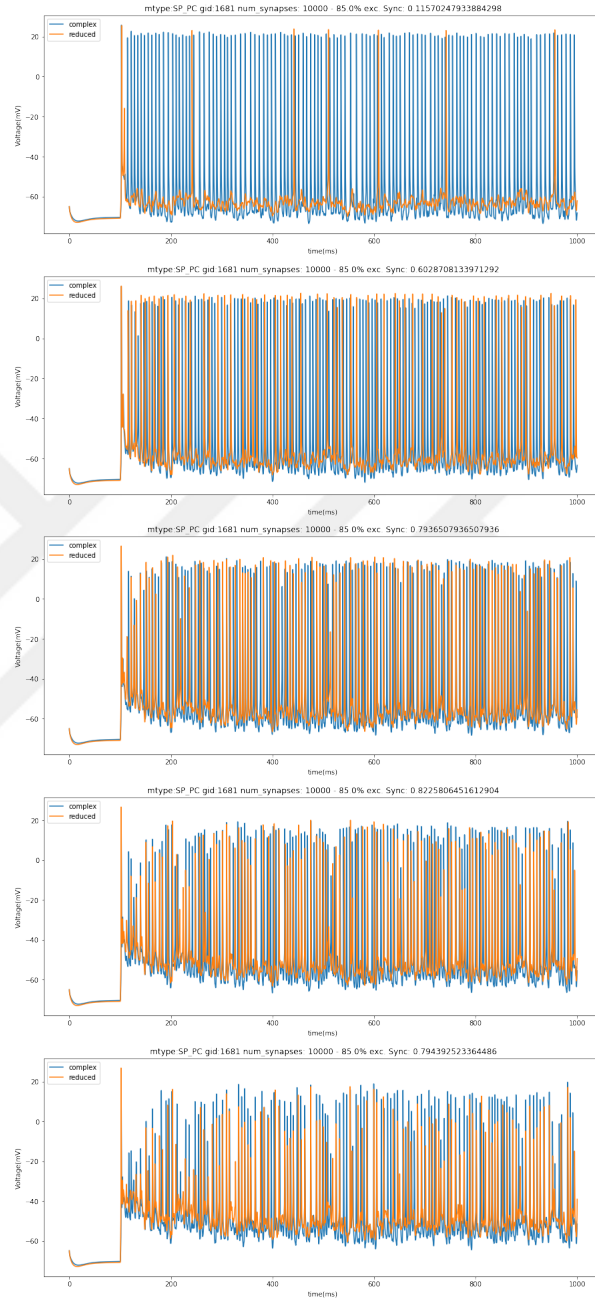


Figure 4.10: Increasing the weights on the SP_PC neurons have a positive effect on the spike synchrony

4.1.2 PSP-validation Correction

As a more sophisticated approach, neurons from each morphology in the full and the reduced circuit ($n=50$) are simulated where m-type - m-type pairs were generated and simulated for 1 second with a repetition of 35 times. The peak post synaptic amplitudes were then recorded for full circuit and compared with the reduced one (see Figure 4.11). Then, scaling factors were obtained from the equation 3.16 which are shown in Figure 4.12. These scaling are then applied to the respective BlueConfig files (or can be applied to the edges.h5 files) as a conductance parameter update. The results of this optimization are given in the following chapter.

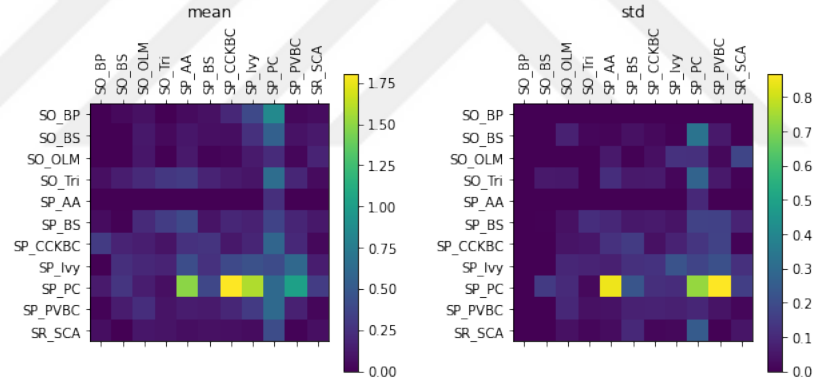


Figure 4.11: Mean and standard deviation PSP-validation amplitudes for the morphological types of the original neurons. For each square, 50 cells were averaged with 35 repetitions

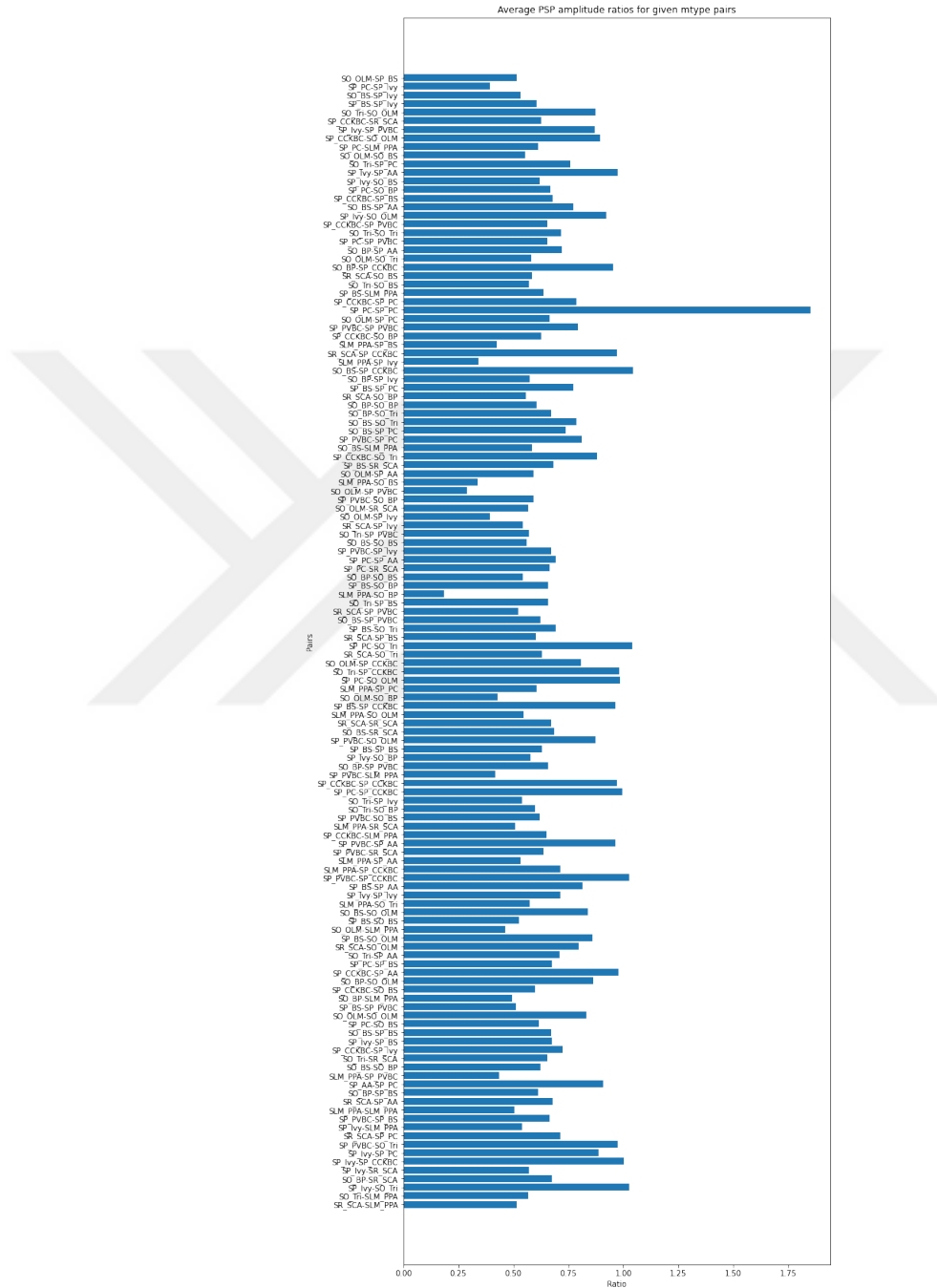


Figure 4.12: The scaling parameters obtained from the original version of the CA1 circuit using psp-validation algorithm.

Since the neuron reduce algorithm does not promise to keep the same post synaptic amplitudes but just the voltage deflection timings (i.e transfer impedance to

the soma), we hypothesized that complex cells with basal and apical dendrites like pyramidal cells have issues with this amount of reduction rate i.e. 0.1 percent of total number of segments in the full circuit. However, performing this has not increased the Spike Synchrony and also increased the simulation time significantly. Therefore, highly nonlinear neuron models may not be of best use for morphological reduction but for synapse merging processes. As stated in Amsalem et. al., these two methods together can speed up the simulation time around 40x but one of the two techniques alone can also be used instead of both in these circumstances.

Although not included in this thesis, future works will focus on synapse merging for those which have similar rise and decay time constants (see neuron reduce github repository and the paper for more detail) [9].

Chapter 5

Circuit Reduction

5.1 CA1.O1 Reduction

The majority of the reduction validation as well as experiments in the circuit level were conducted in CA1 microcircuit due to copy right limitations on the full scale realistic CA1 circuit. The micro-circuit is also a test environment for development of new tools and substrate for initial experiments pre-production rate. The hexagonal structure of the microcircuit, shown in figures 5.1 and 5.2, is a reminiscent of the one in Markram 2015 paper [17] in which the neocortical circuit was created with a hexagonal lattice pattern. Similarly, the CA1 circuit is created with a very similar pipeline [18] which consists of 4 layers previously explained in section 2.

The following sections will be based on different activation levels, some of which are synaptic and others are with current injection. The spontaneous miniature post synaptic potentials (aka minis) within CA1 circuit and microcircuit neurons are referred as internal minis, whereas minis coming from Schaffer Collaterals are called as proj-minis. If both minis are available in the simulation, it is called as all-minis. Sometimes, additional inputs are given in the simulation configuration file such as an external 0.1 Hz stimulus from SC or any other target. This is

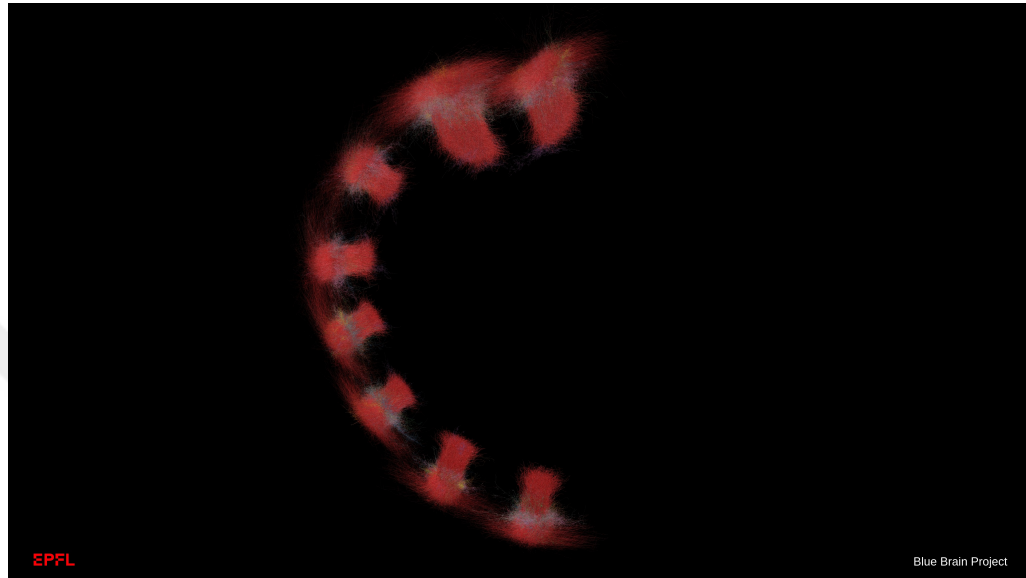


Figure 5.1: An example of 8 microcircuits obtained from the complete CA1 circuit.

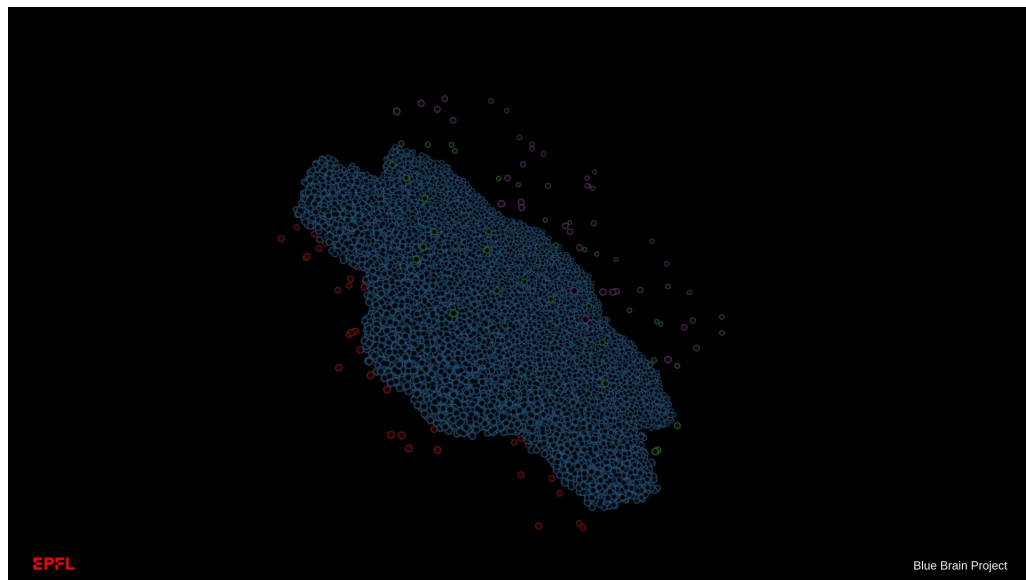


Figure 5.2: The hexagonal structure of the CA1 microcircuit. Neurons are represented as spheres for simplicity. Neurons within the same layer are colored the same.

called Synapse Replay as cell gids with given time are considered as fired outside the scope of the simulation but its post-synaptic neurons are activated in their respective dendritic/somatic sections. In our replay models, we have SC replay with 0.1 Hz Poisson Firing Rate and internal replay with 1 & 5 Hz firing rates.

5.1.1 Current Injection

This section investigates the reduced circuit dynamics via current injection techniques. Currently, only current injection from soma has been performed. Figures 5.3, 5.4, 5.5 show the firing rate histograms of 4 seconds of simulation for different reduced circuits. Figure 5.3 shows that the full and the reduced circuit having a clear difference in their PSTHs mainly because of over-inhibition by inhibitory neurons coupled with independent lower activation rates of pyramidal cells. This behavior is eliminated when PSP validation scaling was conducted by an amounts of those shown in figure 4.12. The hand-tuned PC-PC weights shown in figure 5.5 has a better PSTH amplitude compared to the psp-validation scaled simulation but their phases are uncoupled as can be seen in the figure 5.6.

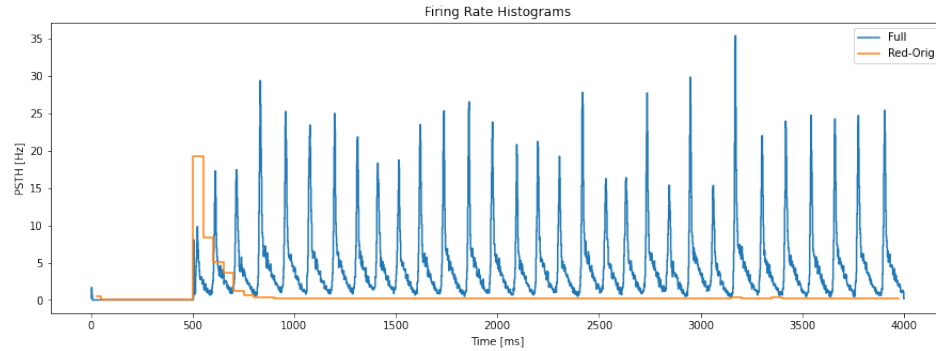


Figure 5.3: PSTHs of full and reduced (original) microcircuits for the current injection to the soma experiment (120 percent of threshold depolarization).

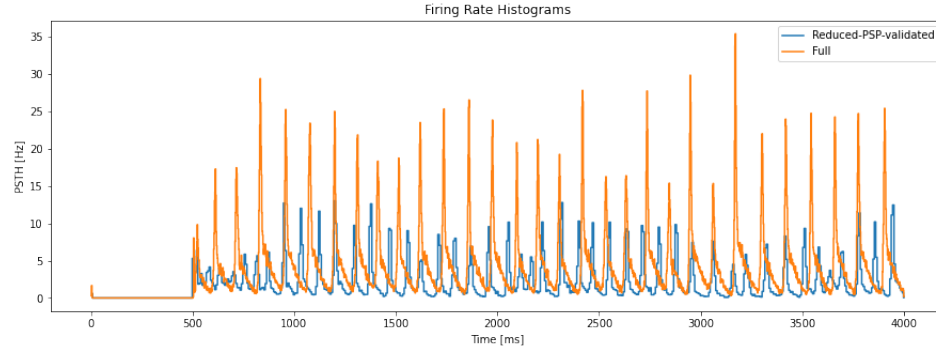


Figure 5.4: PSTHs of full and reduced (psp-validation fixed) microcircuits for the current injection to the soma experiment (120 percent of threshold depolarization).

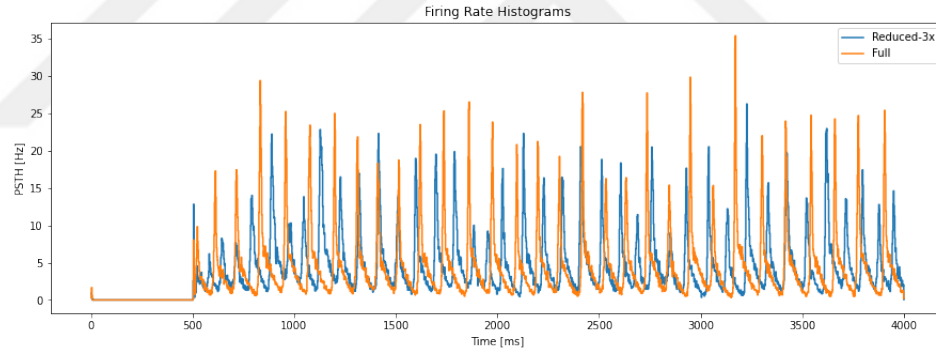


Figure 5.5: PSTHs of full and reduced (hand-tuned) microcircuits for the current injection to the soma experiment (120 percent of threshold depolarization).

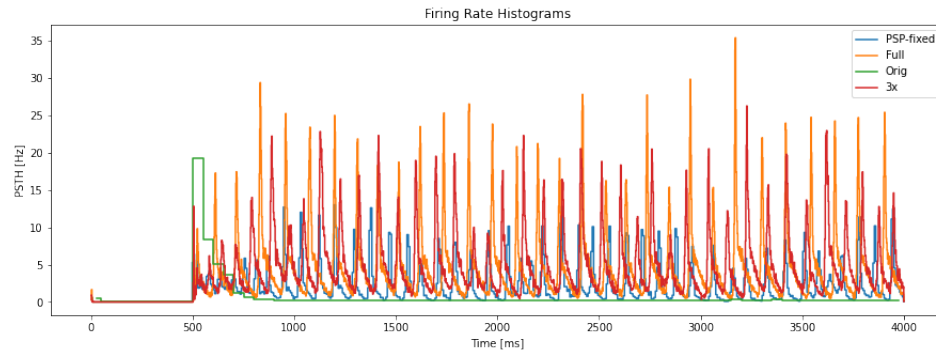


Figure 5.6: Comparison of different simulations in figures 5.3 5.4, 5.5

Simulation Reports are shown in figures 5.7, 5.8 5.9 where although the original or raw reduction has a firing rate of SP PCs quite low, the mean frequencies of all the circuit is much higher than the original microcircuit. This is because this value is a measuring technique for the activated neurons and cells that do not fire are not included. This allows overactive interneurons to dominate the frequency of the overall distribution. However, in the raster plots, it is clearly visible that the pyramidal cells do not fire after 700th ms (500th ms is the onset of the current injection). The same measure in the first rows are more reliable in the psp-validation fixed and the hand tuned experiments as pyramidal cells start to dominate the measure.

ISI plots are somewhat similar in full and raw reduced circuits as relative refractory periods and later on Poisson firing probability can be observed but with a slight difference in slope. The initial peak in ISIs cannot be seen in the original reduced circuit but can be in the following corrections.

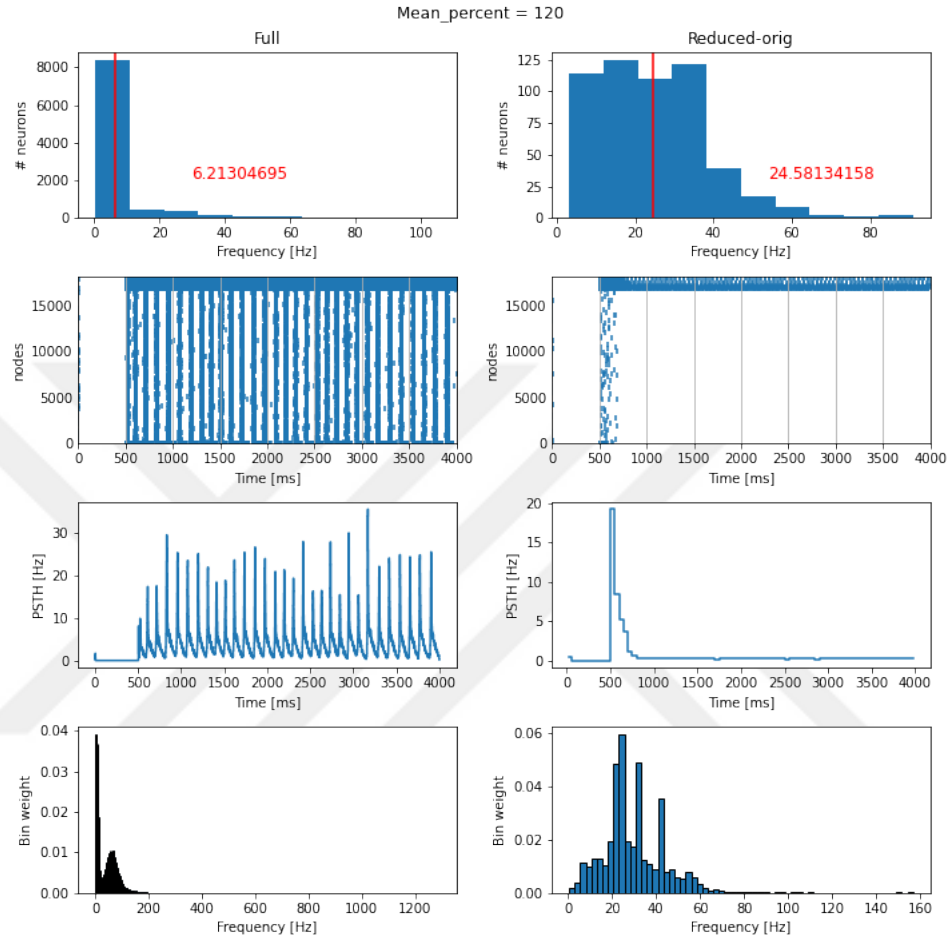


Figure 5.7: Simulation reports for full vs. reduced(original) CA1 microcircuits for current injection experiment.

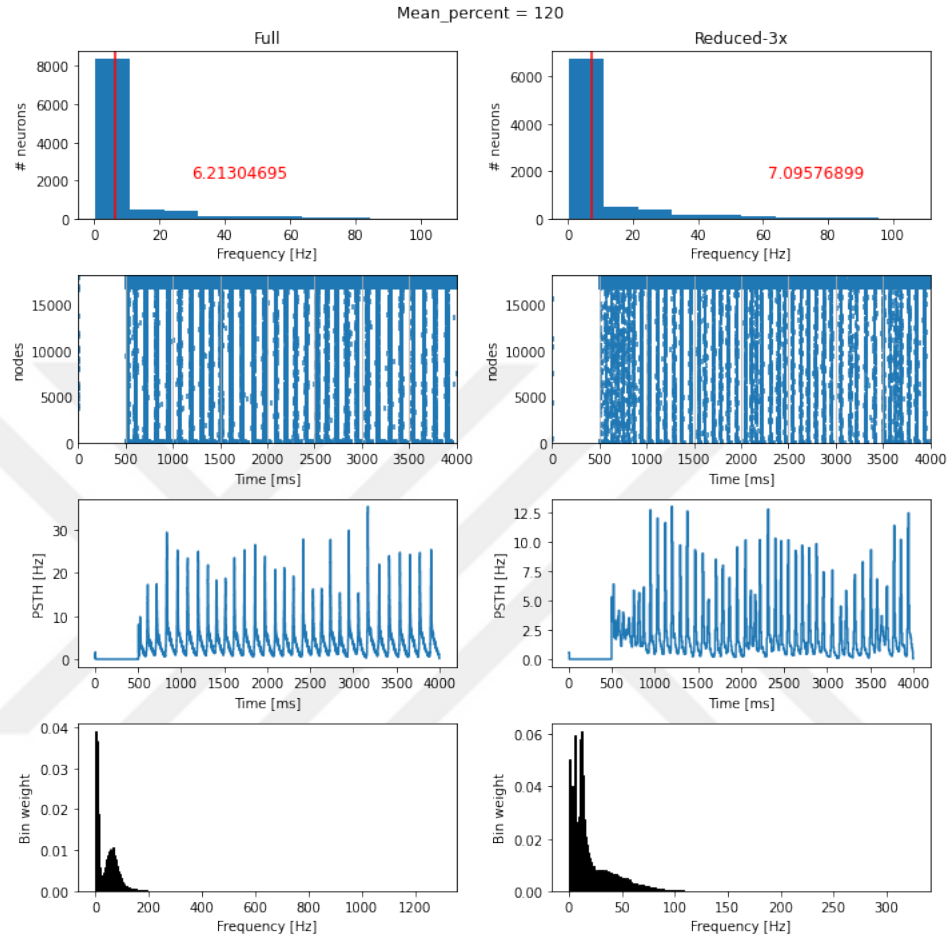


Figure 5.8: Simulation reports for full vs. reduced(hand-tuned) CA1 microcircuits for current injection experiment.

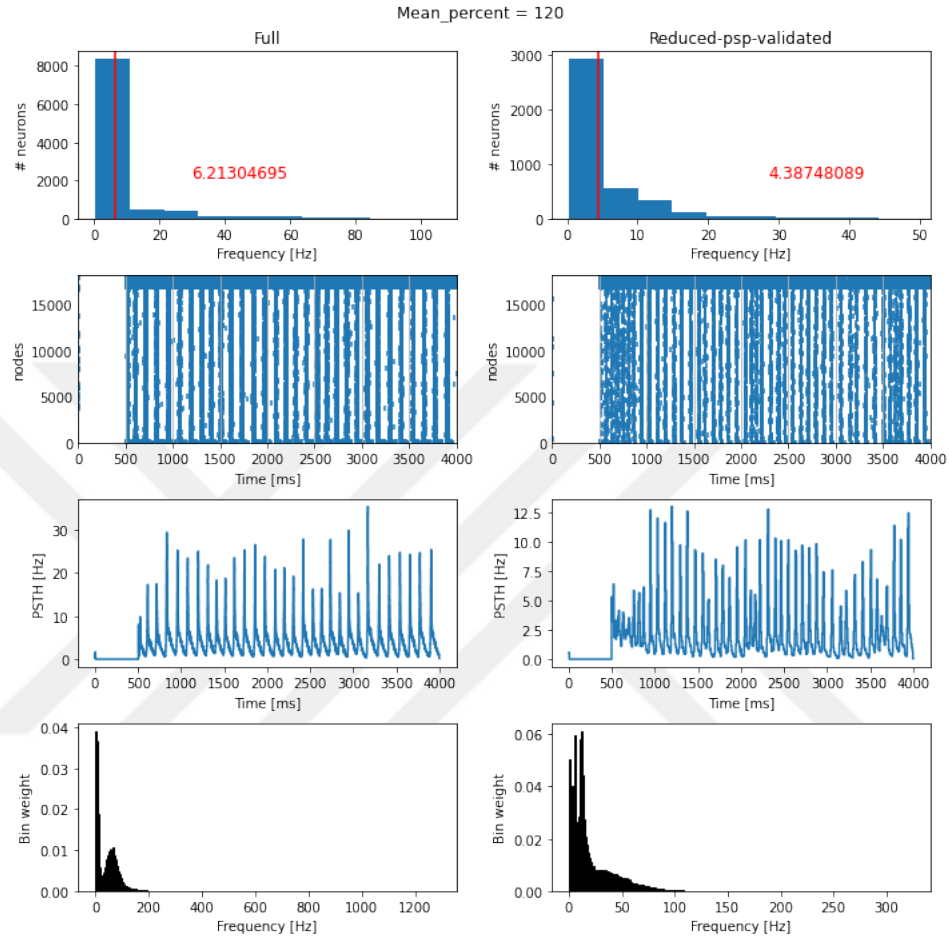


Figure 5.9: Simulation reports for full vs. reduced(psp-validation corrected) CA1 microcircuits for current injection experiment.

The total m-type wise activation rates shown in Figures 5.10 show a vast difference of activation in full and original reduced circuit from the aforementioned reasons. Here, we can see that not only SP PCs but also other cell types struggle to catch up with the full rates. Then, the corrected measures somewhat fine tune almost all m-types in hand-tuned circuit (see Figure 5.11) but for the psp-validated one, the cells still under represent themselves (Figure 5.12). To investigate the voltage dynamics, 5 randomly chosen cells are given for full and the reduced circuit which are then compared within the same timeline in Figure 5.13.

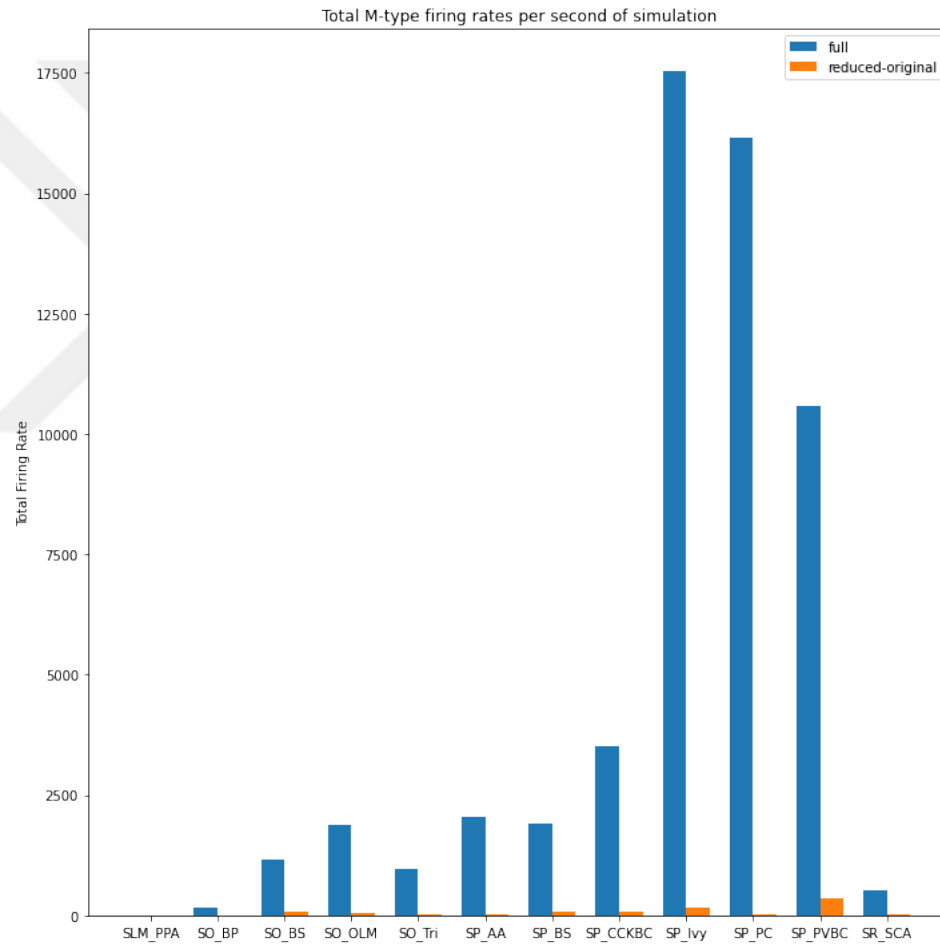


Figure 5.10: Total m-type activation rates comparison for full vs. reduced(original) CA1 microcircuits for current injection experiment.

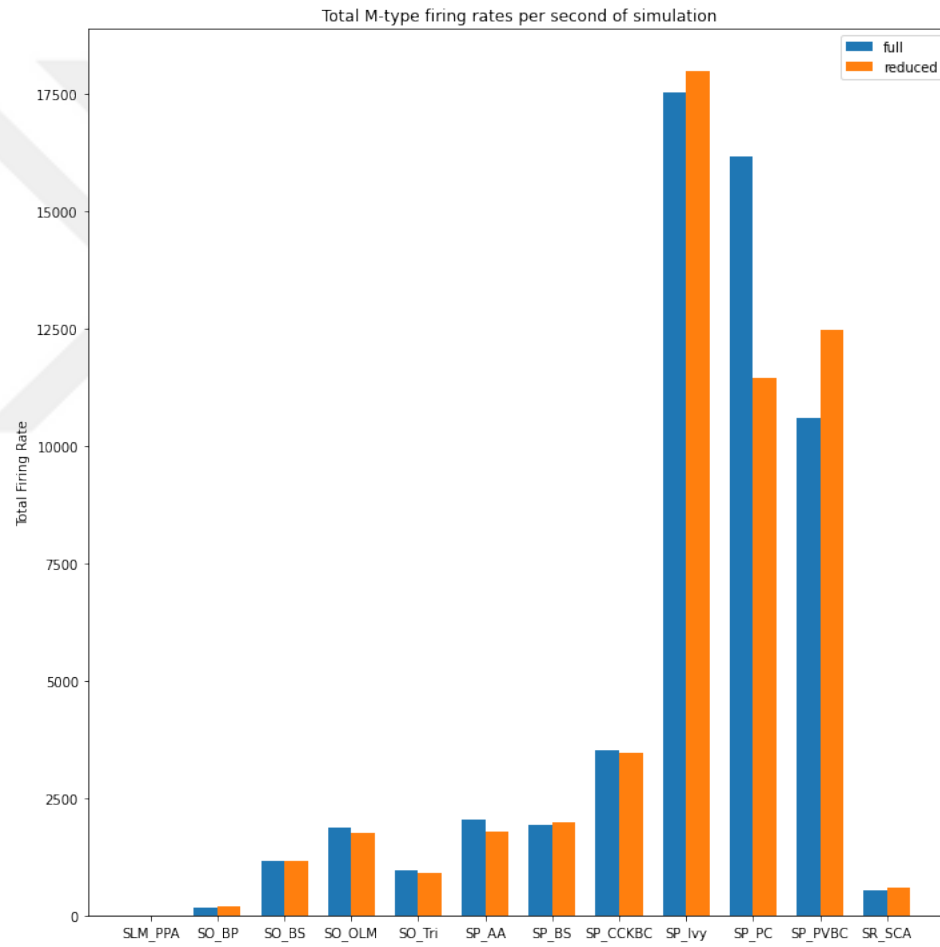


Figure 5.11: Total m-type activation rates comparison for full vs. reduced(hand-tuned) CA1 microcircuits for current injection experiment.

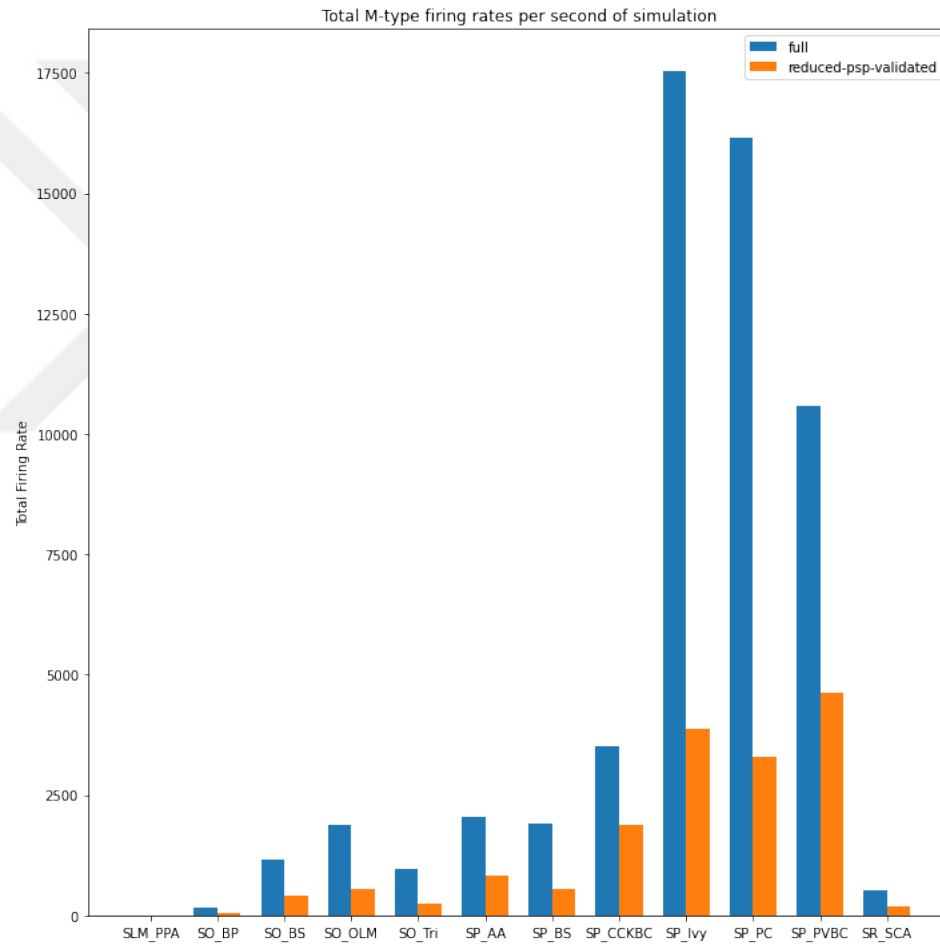


Figure 5.12: Total m-type activation rates comparison for full vs. reduced(ppsp-validation corrected) CA1 microcircuits for current injection experiment.

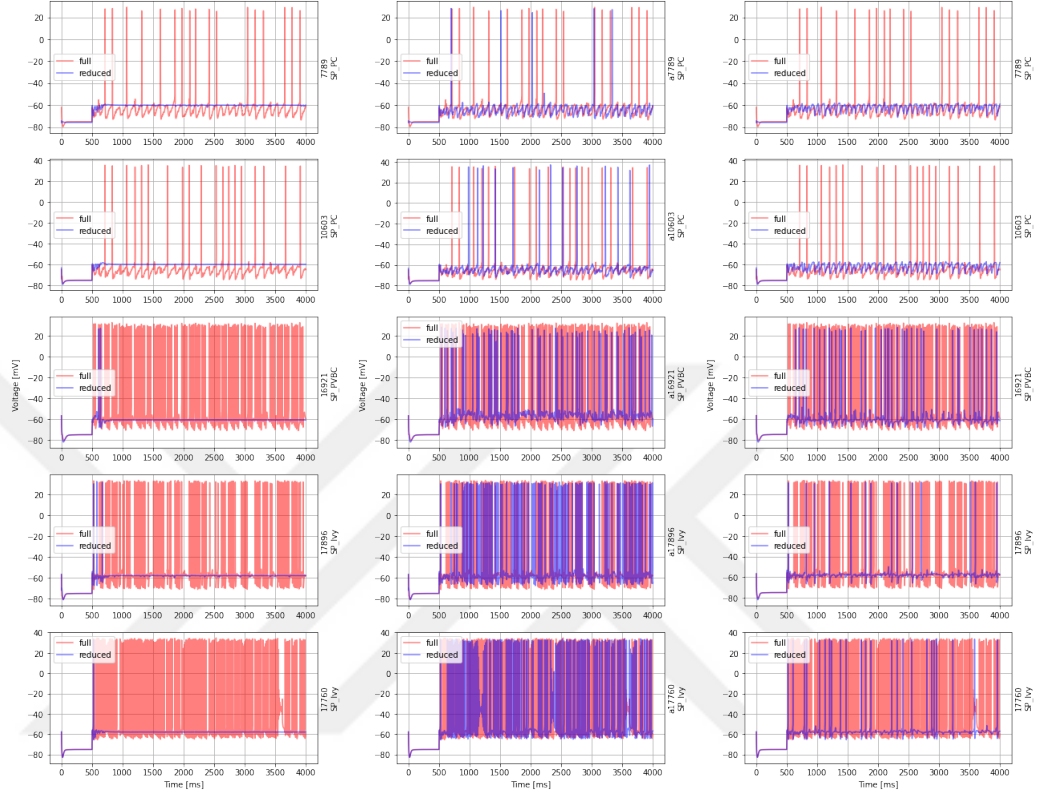


Figure 5.13: Voltage traces of 5 randomly chosen cells from each simulation. Columns: Reduced:Original, Reduced:Hand-tuned (3x PCPC weight) , Reduced:PSP-validation fixed

5.1.2 Internal Minis

The simulation with the internal minis are the weakest type of synaptic activation with respect to further analyses. The minis rate from each neuron to another from now on is set to $\lambda = 0.1$ from the Poisson distribution. The simulation reports for the full and the reduced microcircuits are given in 5.14 and 5.15. As can be seen from the raster plots, even the full circuit has a low activation rate of individual m-types. Similar to other raster plots, SP PCs are located at the bottom of the raster Figures due to an excessive number of cells.

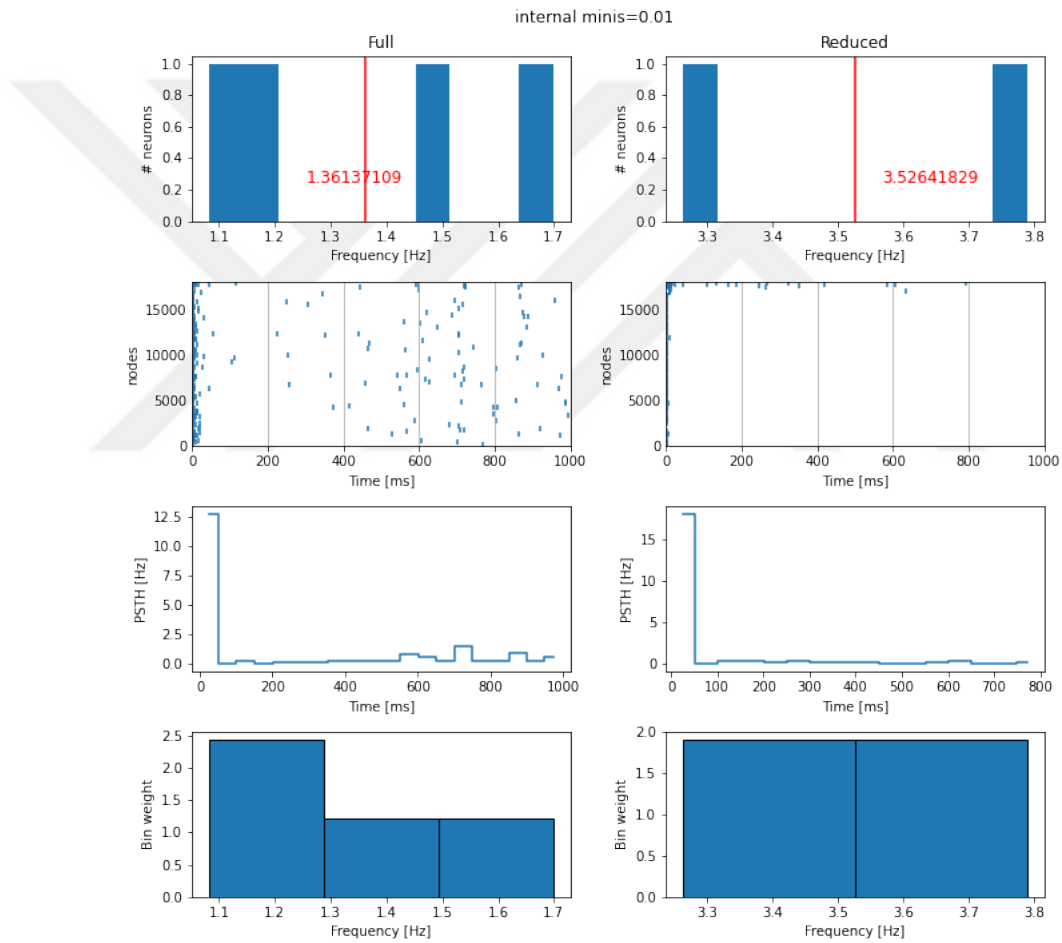


Figure 5.14: Simulation Report comparison (internal minis) for Full vs. Reduced CA1 microcircuits. From top to bottom: Mean activation frequencies, Raster plots, Firing rate histograms, Inter-Spike Intervals.

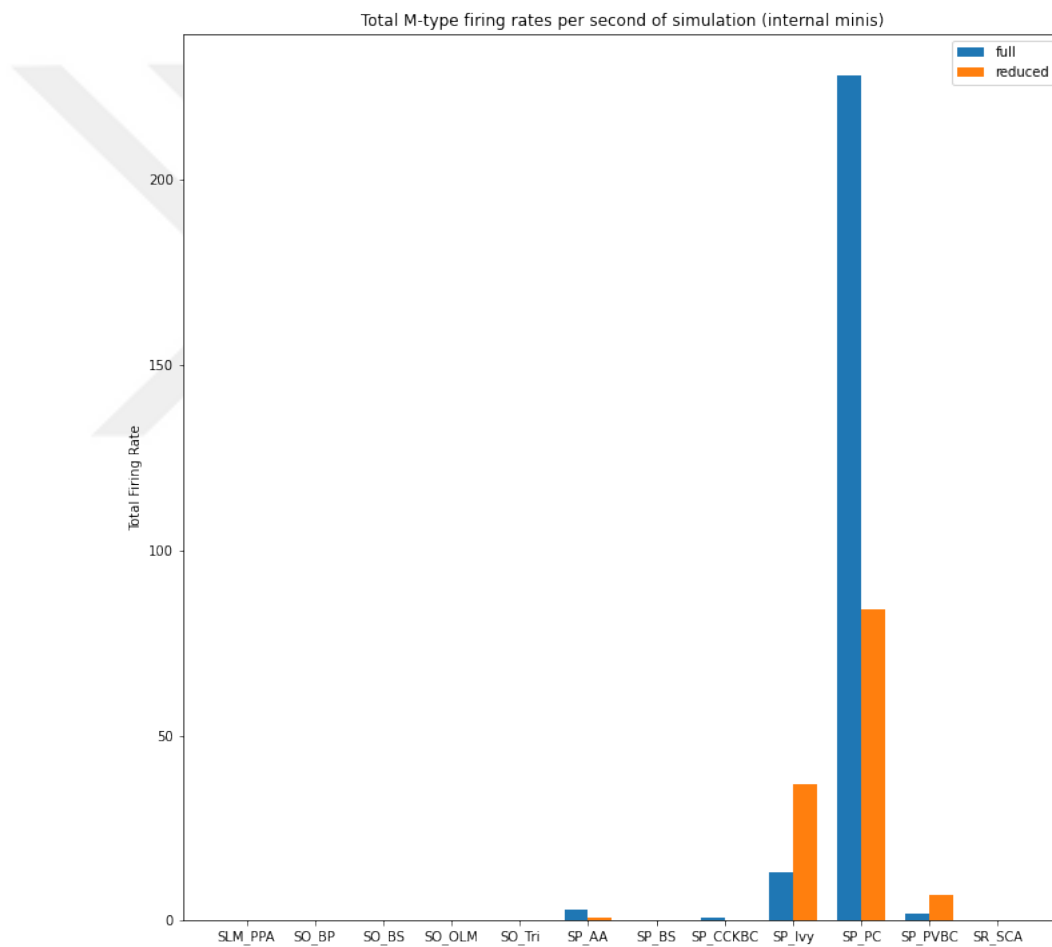


Figure 5.15: Total m-type activation rates comparison for full vs. reduced CA1 microcircuits.

5.1.3 Projection Minis

In this thesis, external projections only CA3 efferents aka Schaffer Collaterals (SC) which are not topologically constrained although still created with experimental constraints with respect to layer-wise connections and number of afferents. There are 1,384,032 CA3 virtual nodes with 7,980,953,382 afferents in SC for the 456,491 cells in the CA1 circuit. This number scales down in the CA1 microcircuit as the number of CA1 nodes are down-sampled to 10% of the original. Below are the simulations of the reduced and full CA1 microcircuit. Unfortunately, SC synapses cannot be tuned yet with PSP-validation due to experimental limitations, as SONATA circuits cannot be used with PSP-validation where there are external connections. This is a limitation of the current model, which is under last stages of development as of writing of this thesis.

Total activation rates indicates that SC connections with minis rate of 0.01 initiates only the pyramidal cells in the full circuit but are enough to excite some inhibitory cell types in the reduced ones. This behavior of over-activated reduced cells are shown in Amsalem et al. for the reduced neocortical cell types [9]. Similarly, certain highly active hippocampal interneurons, when reduced, can be prematurely excited. Unfortunately, PSP-validation could not be performed on the projections as the current state of the simulator and SONATA format.

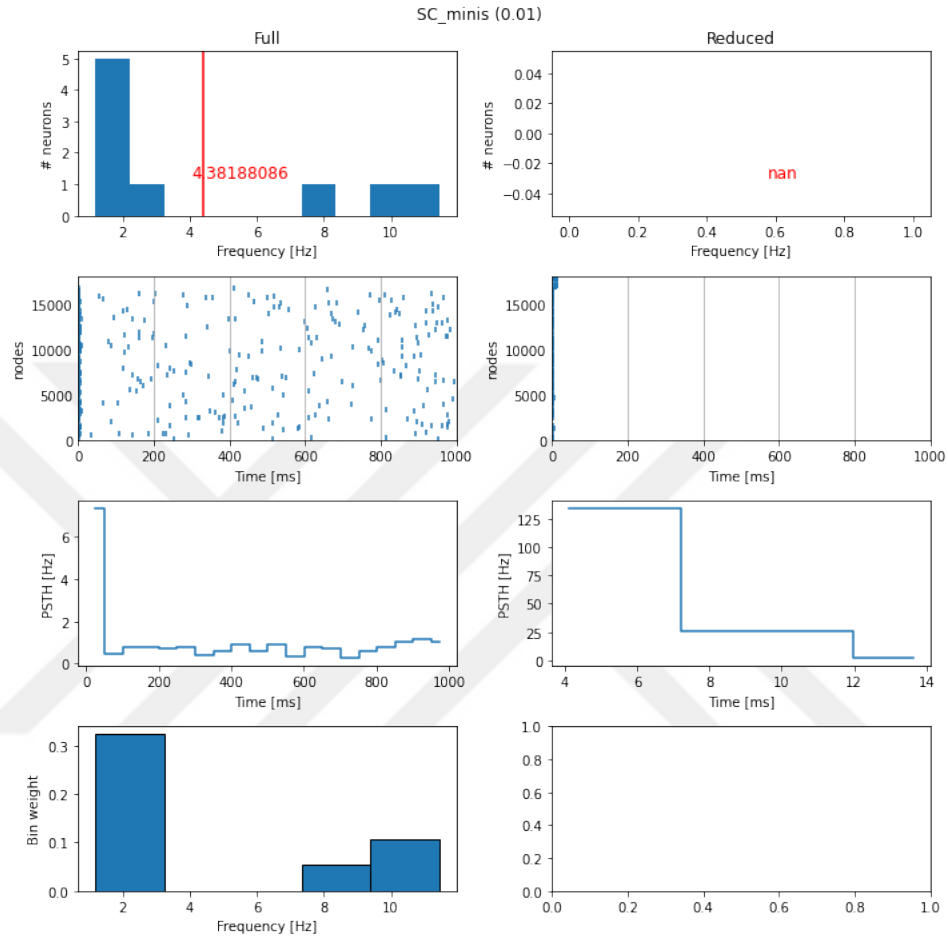


Figure 5.16: Simulation Report comparison (projection minis) for Full vs. Reduced CA1 microcircuits. From top to bottom: Mean activation frequencies, Raster plots, Firing rate histograms, Inter-Spike Intervals. Note that there are not enough spikes to create some plots for the reduced circuit.

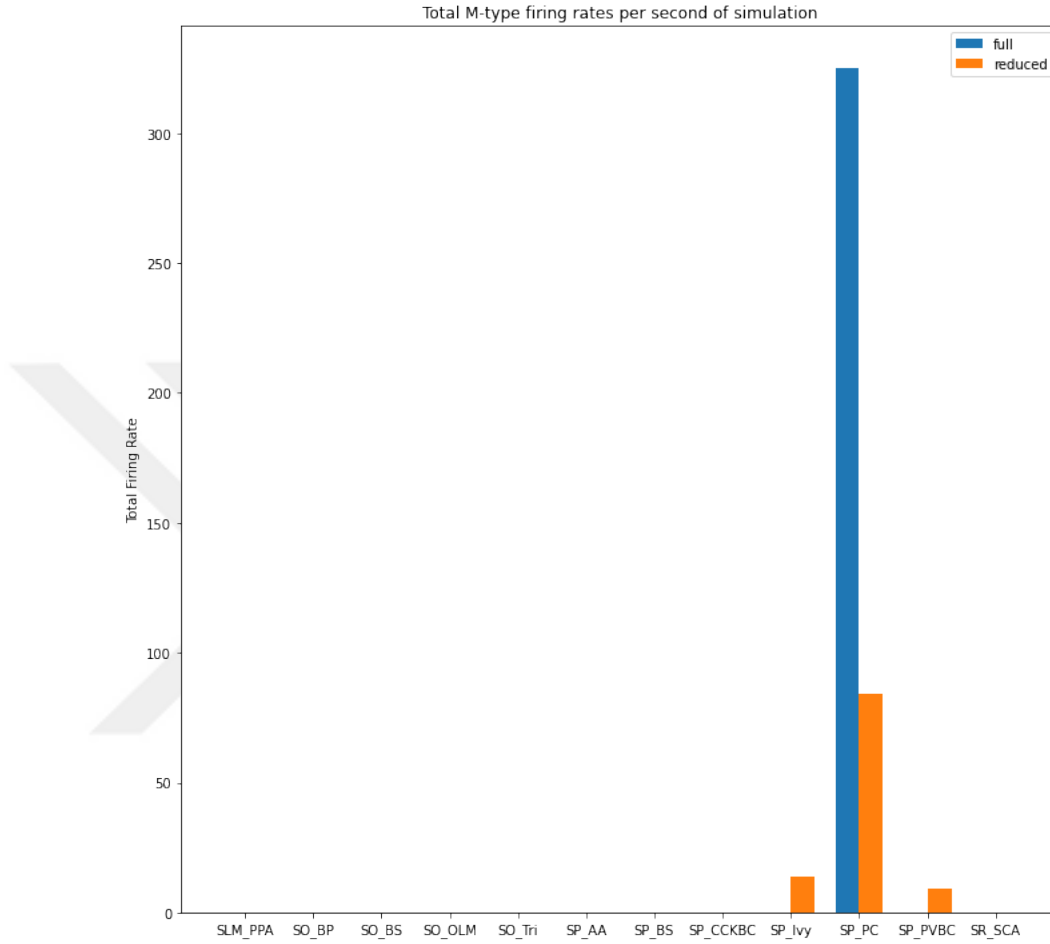


Figure 5.17: Normalized Activation rates (per second) for each m-type in CA1 microcircuit simulation from projections only.

5.1.4 All Minis

When internal and projection minis are combined, we expect to see a higher activation rate in the circuit for both full and the reduced versions. It is indeed visible by comparing the mean frequency plots on the first rows of simulation reports. The reduced circuit, however, could not be activated enough with the CA3 activation, but a comparison can be made by total activation rates. This section of simulation does not have psp-tuned or hand-tuned versions

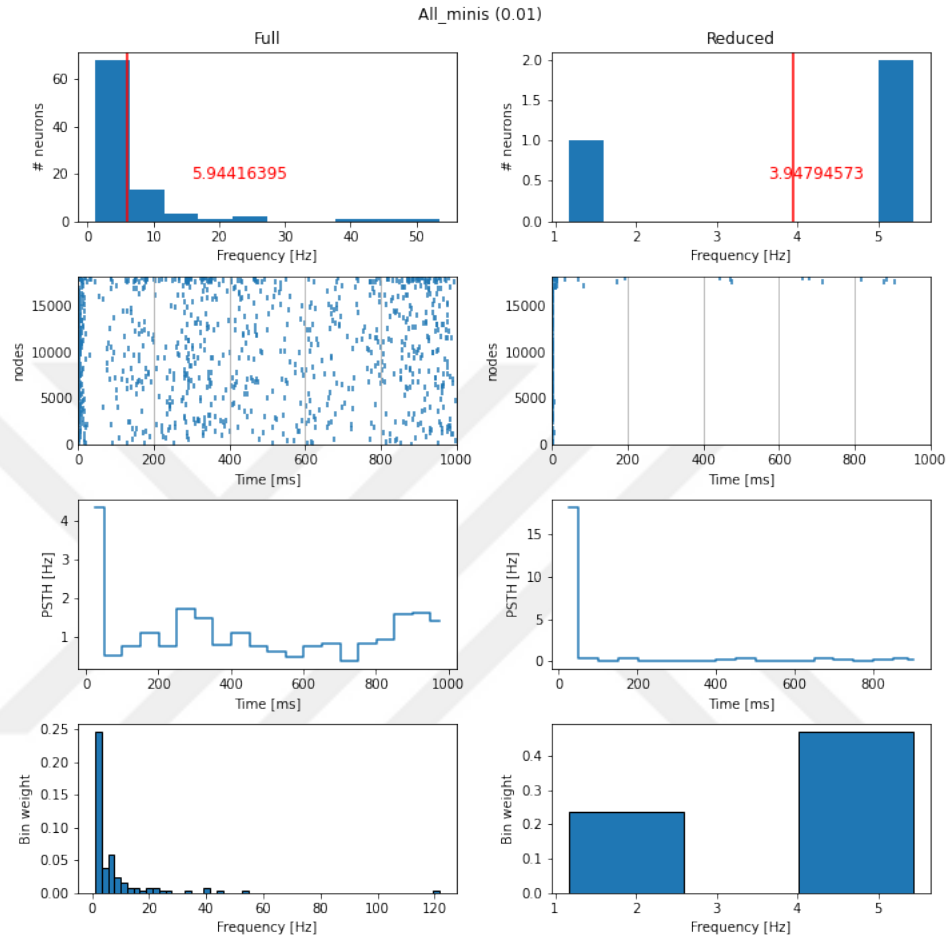


Figure 5.18: Simulation Report comparison (all minis) for Full vs. Reduced CA1 microcircuits. From top to bottom: Mean activation frequencies, Raster plots, Firing rate histograms, Inter-Spike Intervals. Note that there are not enough spikes to create some plots for the reduced circuit.

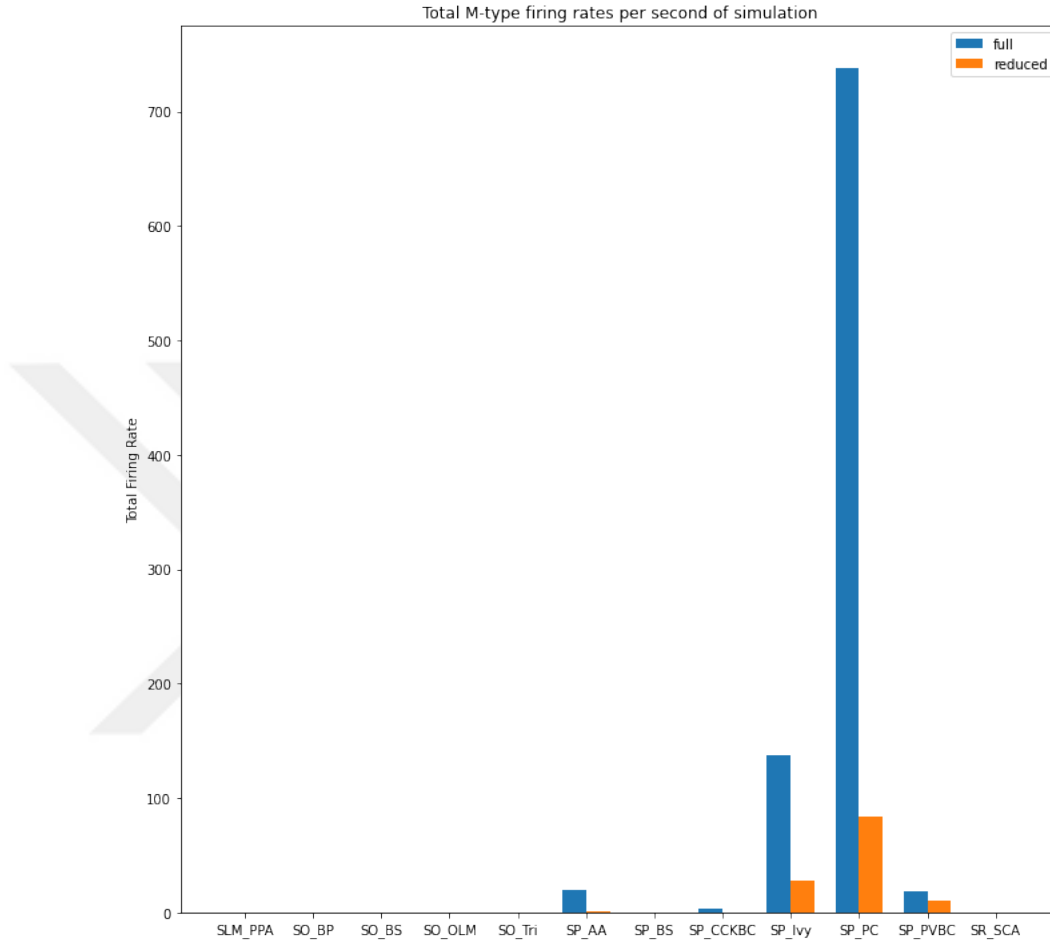


Figure 5.19: Normalized Activation rates (per second) for each m-type in CA1 microcircuit simulation for all minis.

5.1.5 All Minis and Synapse Replays

On top of all minis, an additional synaptic input with a predetermined frequency was provided to the circuit. In this case, 0.1 Hz SC input was given starting from 200th ms until 1500th ms in a 2 second simulation. Figure 5.23 shows the comparison of Full, Reduced, and the Hand-tuned circuits. Rate based coding has been shown in Figures 5.20, 5.21, and 5.22.

Similar to the proj_minis, reduced SP_Ivy, SP_AA, SP_PVBC firing rates have

somewhat higher activation rates than the original circuit. In contrast, SP_PC cells in the full circuit are again activated much more than the reduced circuit. This implies that CA3 to excitatory cells are under-represented in the reduced circuit whereas CA3 to Inhibitory cells are over-represented. A future scaling of CA3 to CA1 peak synaptic conductances may have a beneficial effect on the rate based tuning of the system. Finally, in Figure 5.24, we can see a cumulative representation of ISI and PSTH graphs shown in Figure 5.23 for better comparison. The original and hand-tuned versions of the reduced circuit have a quite similar PSTH peak values, whereas full and psp-tuned reduced circuits are closer and have a lower peak PSTH plateau than the former two simulations. This implies that although the total activation rates are not caught with the psp-validation scaling of peak synaptic conductances, the intrinsic features of the model are restored with respect to the original CA1 microcircuit.

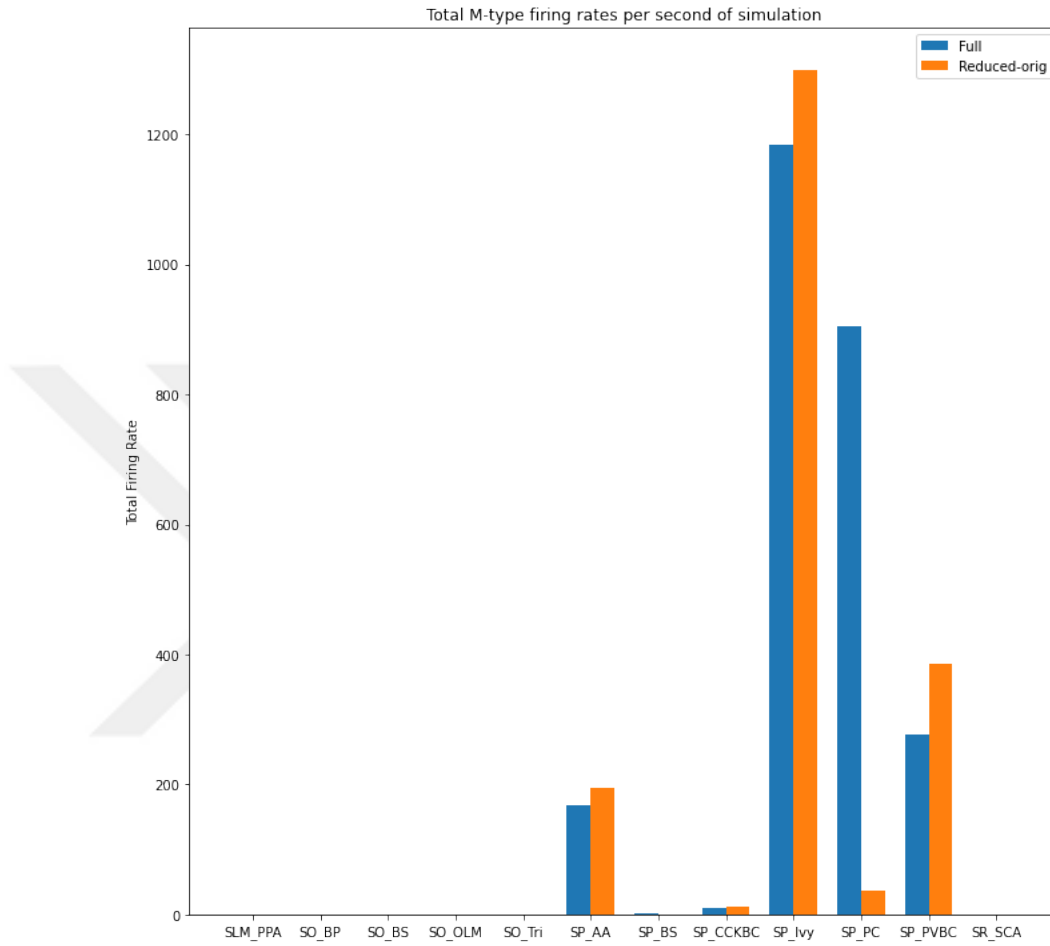


Figure 5.20: Normalized Activation rates (per second) for each m-type in CA1 microcircuit simulation (original reduction).

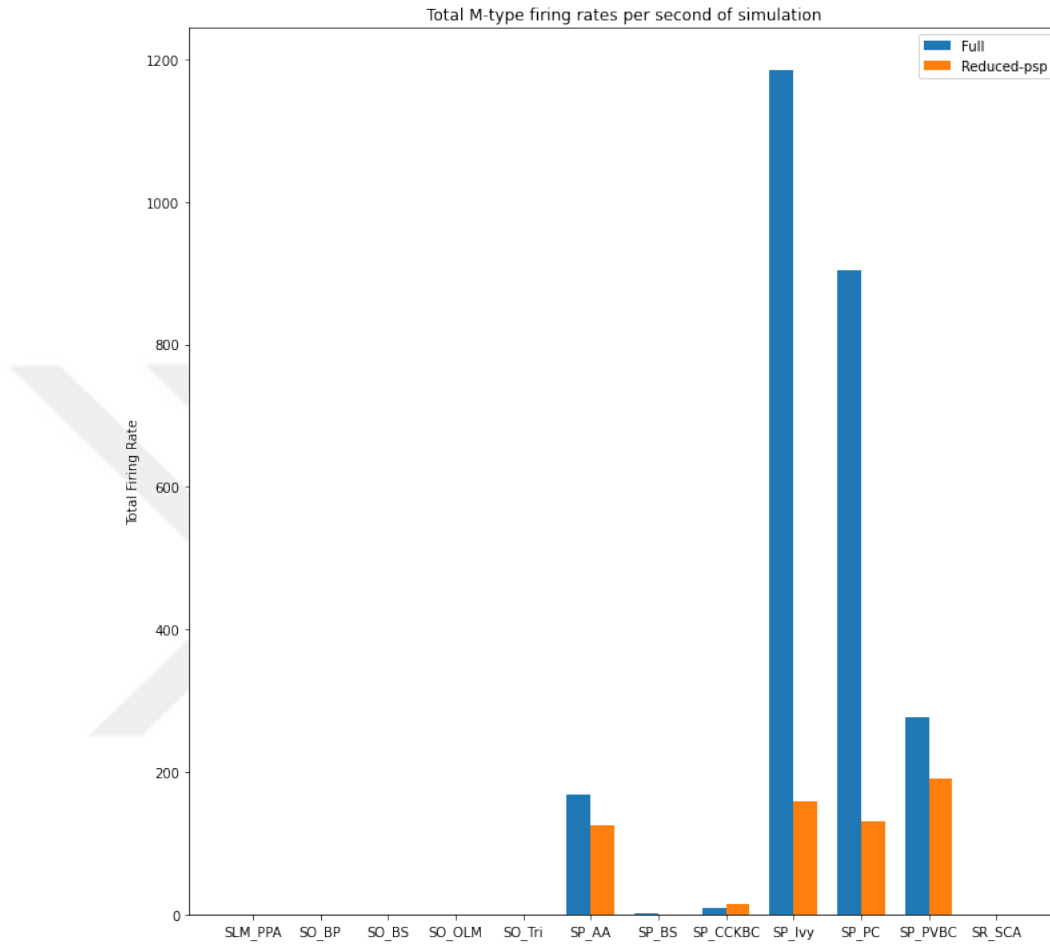


Figure 5.21: Normalized Activation rates (per second) for each m-type in CA1 microcircuit simulation (psp-corrected).

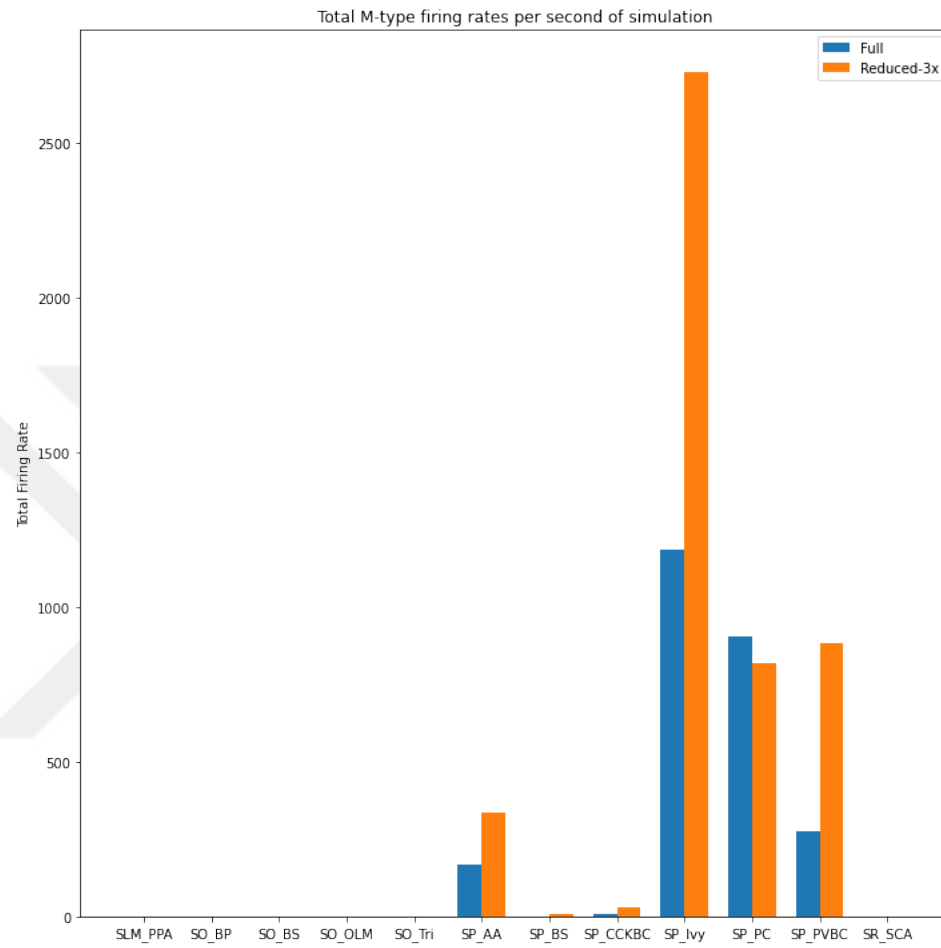


Figure 5.22: Normalized Activation rates (per second) for each m-type in CA1 microcircuit simulation (hand-tuned).

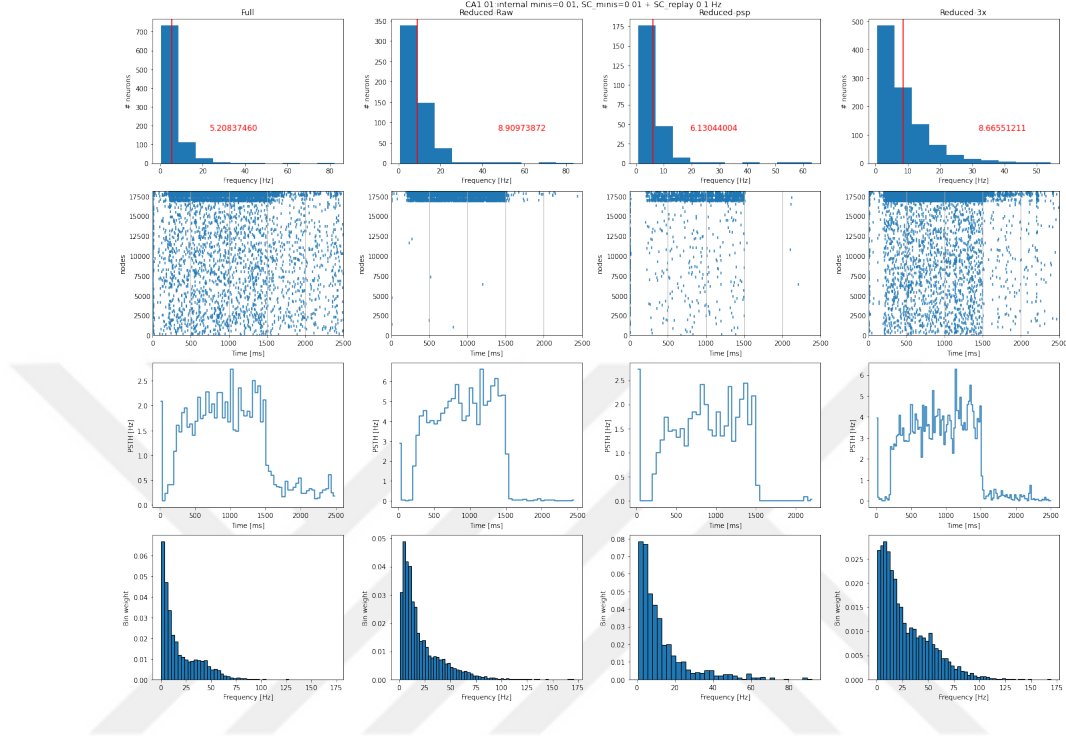


Figure 5.23: Simulation Report Comparisons for full, reduced, psp-validation-corrected and hand-tuned simulations for each m-types per second of CA1 microcircuit simulation.

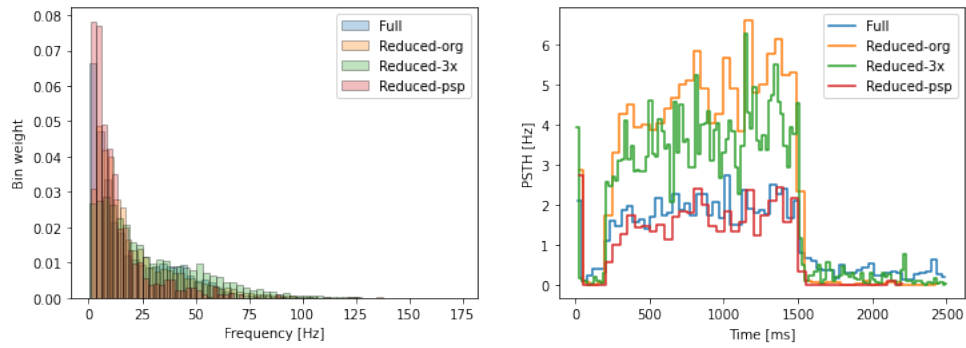


Figure 5.24: Comparison of inter-spike intervals and peri-stimulus time histograms for the experiments in a single plot

5.2 LFP Simulations

This section translates what is simulated within some of the previous simulations to in-silico extracellular recordings. The recordings were obtained via a software tool called Electro-magnetic simulation software (EMSim) which is an in-house tool used in BBP.



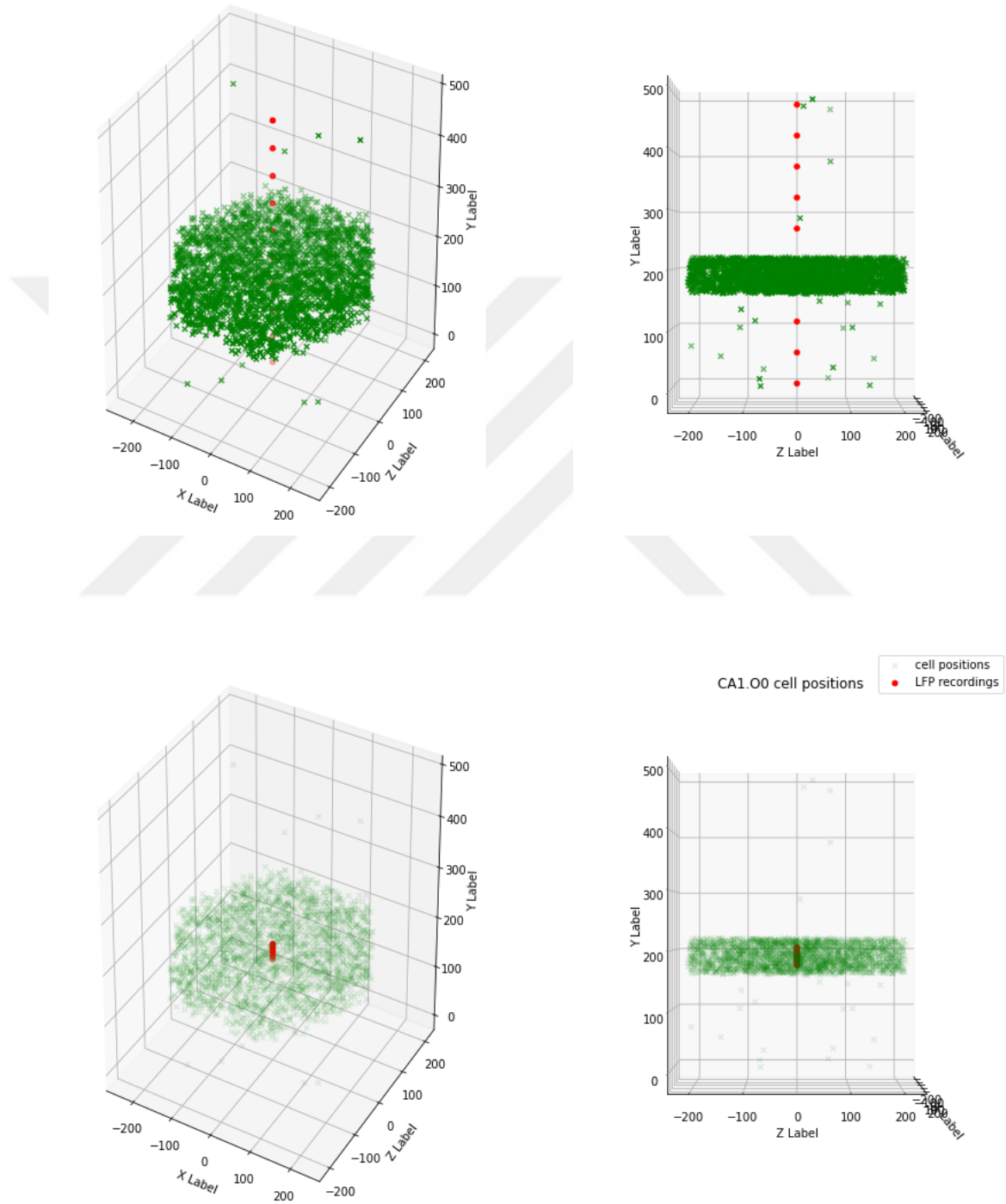


Figure 5.25: LFP electrodes with respect to the CA1 microcircuit with red dots. Green dots represent Str. Pyramidale neurons as spheres

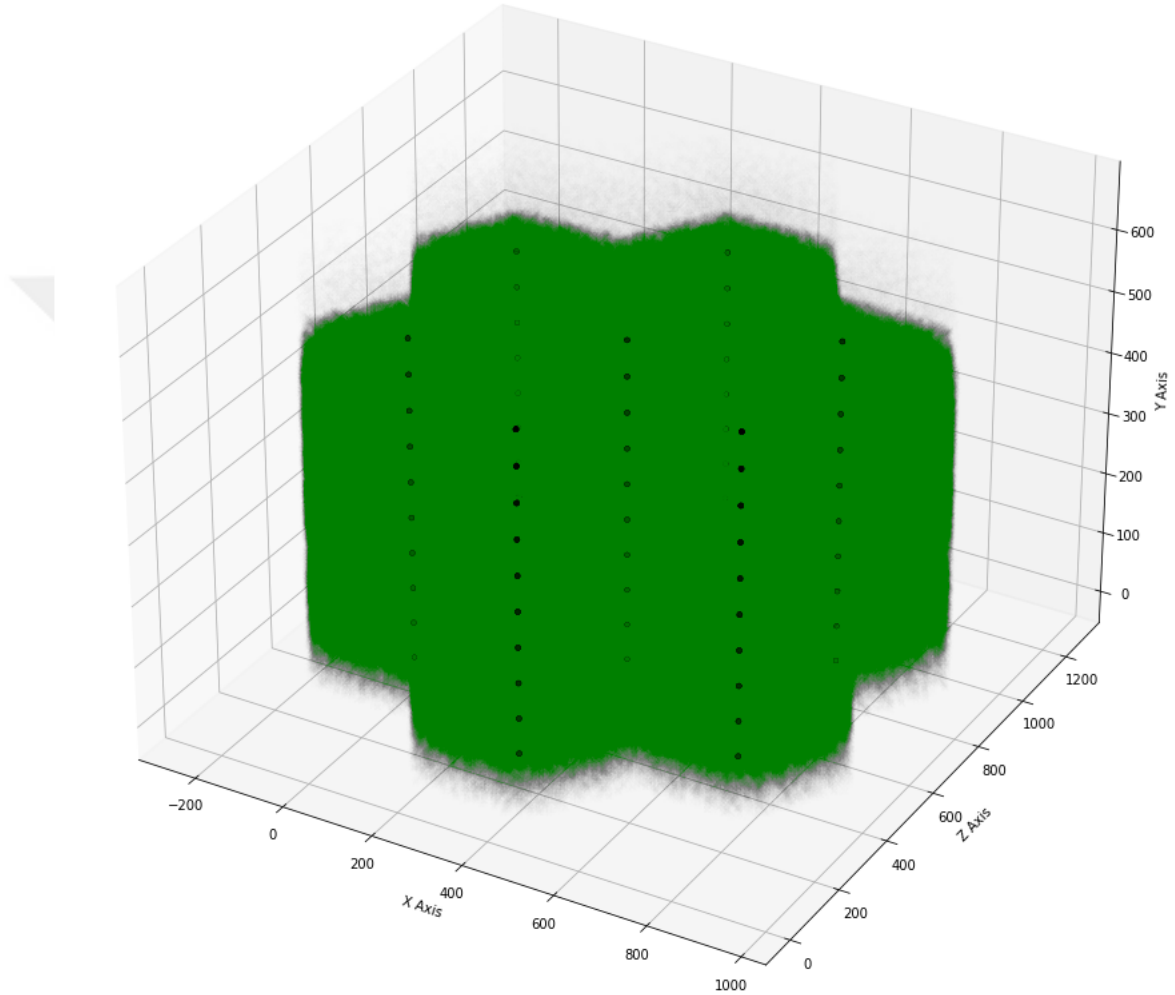


Figure 5.26: Electrodes placed on each column (7x10 recording sites). Neurons from all layers are shown with green dots.

5.2.1 All minis and Synapse Replay

The same simulation in subsection 5.1.5 is used for LFP analysis for the full and the reduced circuit. The recording sites are given in Figure 5.26 which consists of 7x10 electrodes. An easier and less dense representation can be seen in 5.25 where red dots represent the channels.

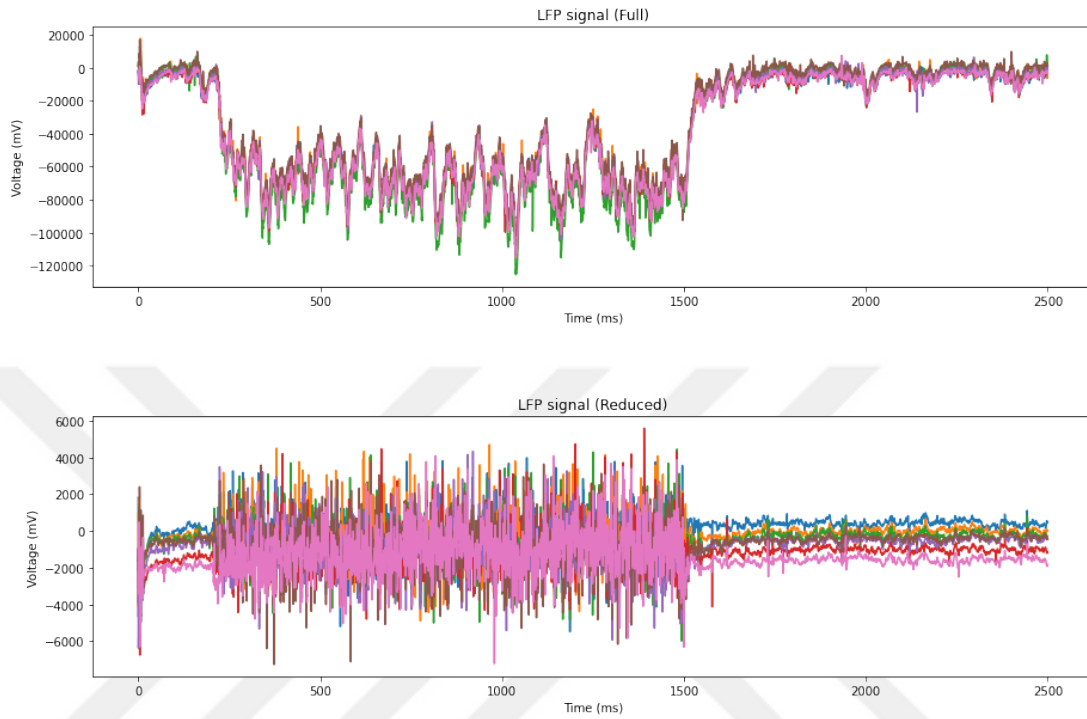


Figure 5.27: LFP voltage recordings for full and the reduced CA1 microcircuits by 2500 ms. The input starts at $t=200$ ms until $t=1500$. Only channels on top of each column are shown.

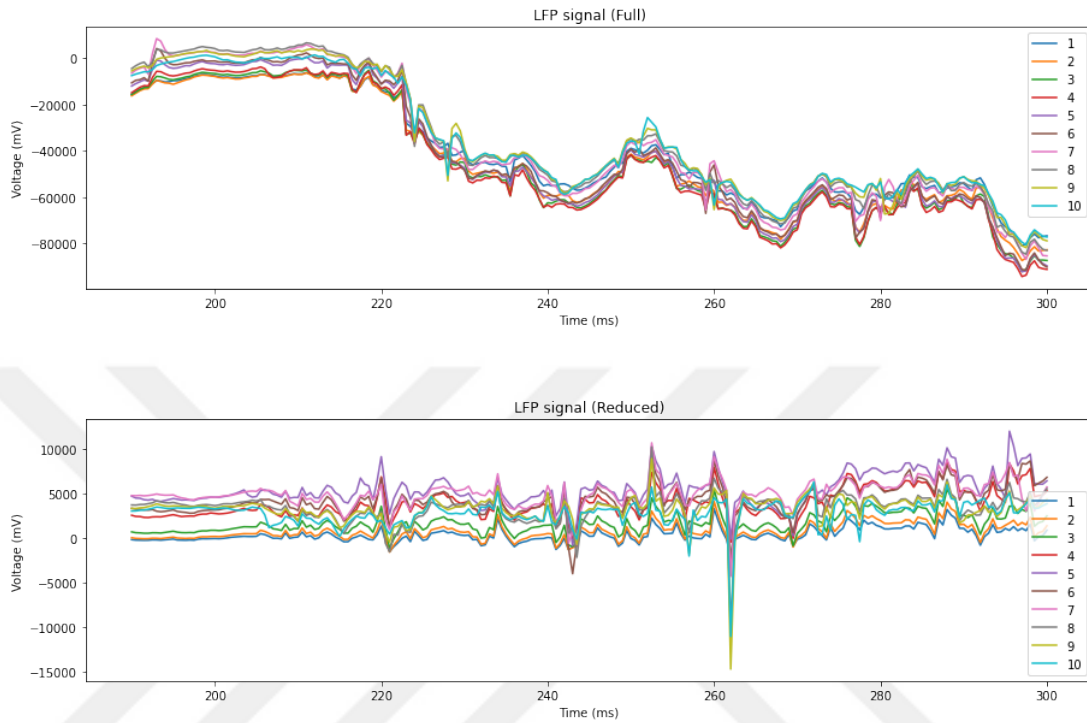


Figure 5.28: LFP signals before and after the stimulation onset for 1 column in Figure 5.26

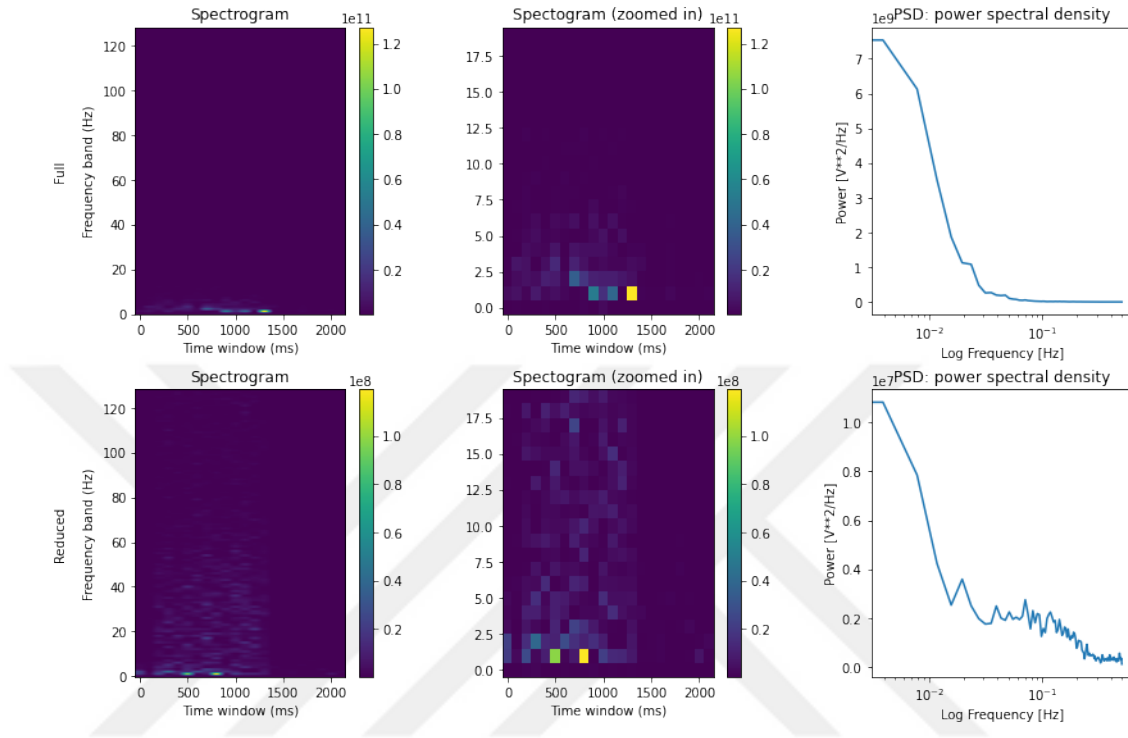


Figure 5.29: Signal Spectrogram and PSD of full and reduced simulations. Top: Full Circuit. Bottom: Reduced circuit. From left to right: Full range spectrogram showing all frequency regimes, zoomed version of the first spectrogram (0-20 Hz), PSD of the signal

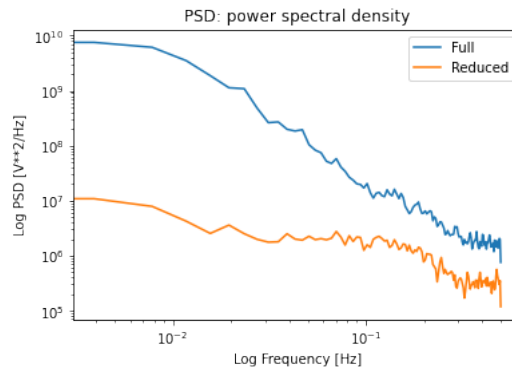


Figure 5.30: Power Spectral Density (PSD) comparison of the full and the reduced circuit in log-log plot.

5.2.2 Current Injection

Similar to the previous chapter, LFP simulations were also conducted to check the plausibility of the simplified microcircuit on current injection experiments. As can be seen from 5.31 and 5.32 different levels of approach that we used to fix the total firing rates cannot rescue the LFP oscillations observed in the full circuit. In that respect, the reduced microcircuit exhibits oscillations at higher frequencies on top of what is observed in the original microcircuit and also with a lower power in PSD plots by several orders of magnitude. This suggests that the dendritic structure plays a crucial role for the LFP analysis which cannot be fully replicated with the reduction pipeline alone even the firing rates are almost the same.

This lack of emergent property can be because of diminishing voltage disturbances over the extracellular space in which the reduced circuit has a fraction of dendritic volume spreading over the hippocampal region. This, in turn, affects what can be captured by the electrodes adversely since a high number of independent current sources coming in the full neuron model can only be transmitted from several reduced dendrites.

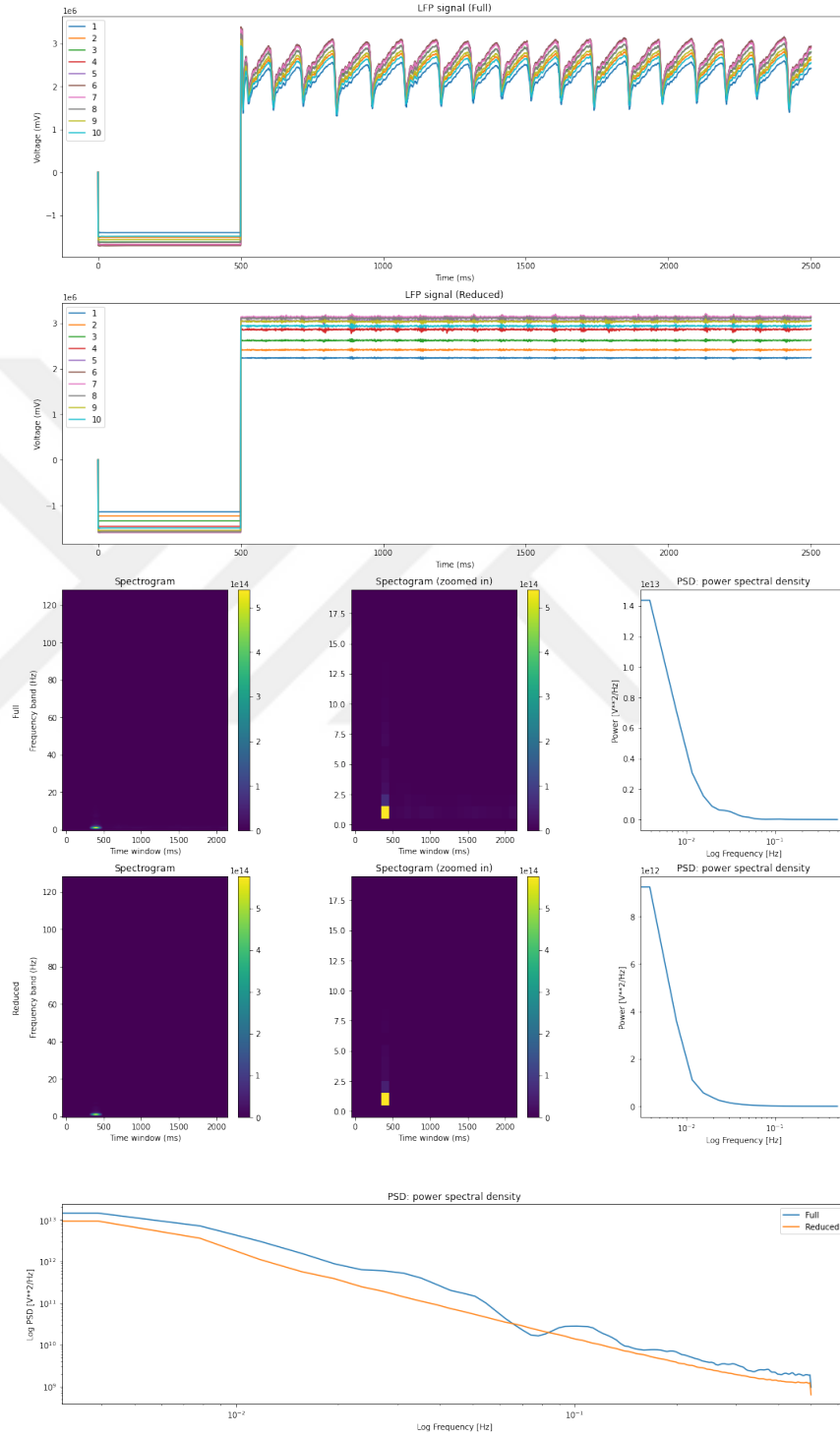


Figure 5.31: LFP analysis for the CA1 microcircuit (PC-PC = 3x) for the 120 percent depolarization experiment (simtime=2500 ms).

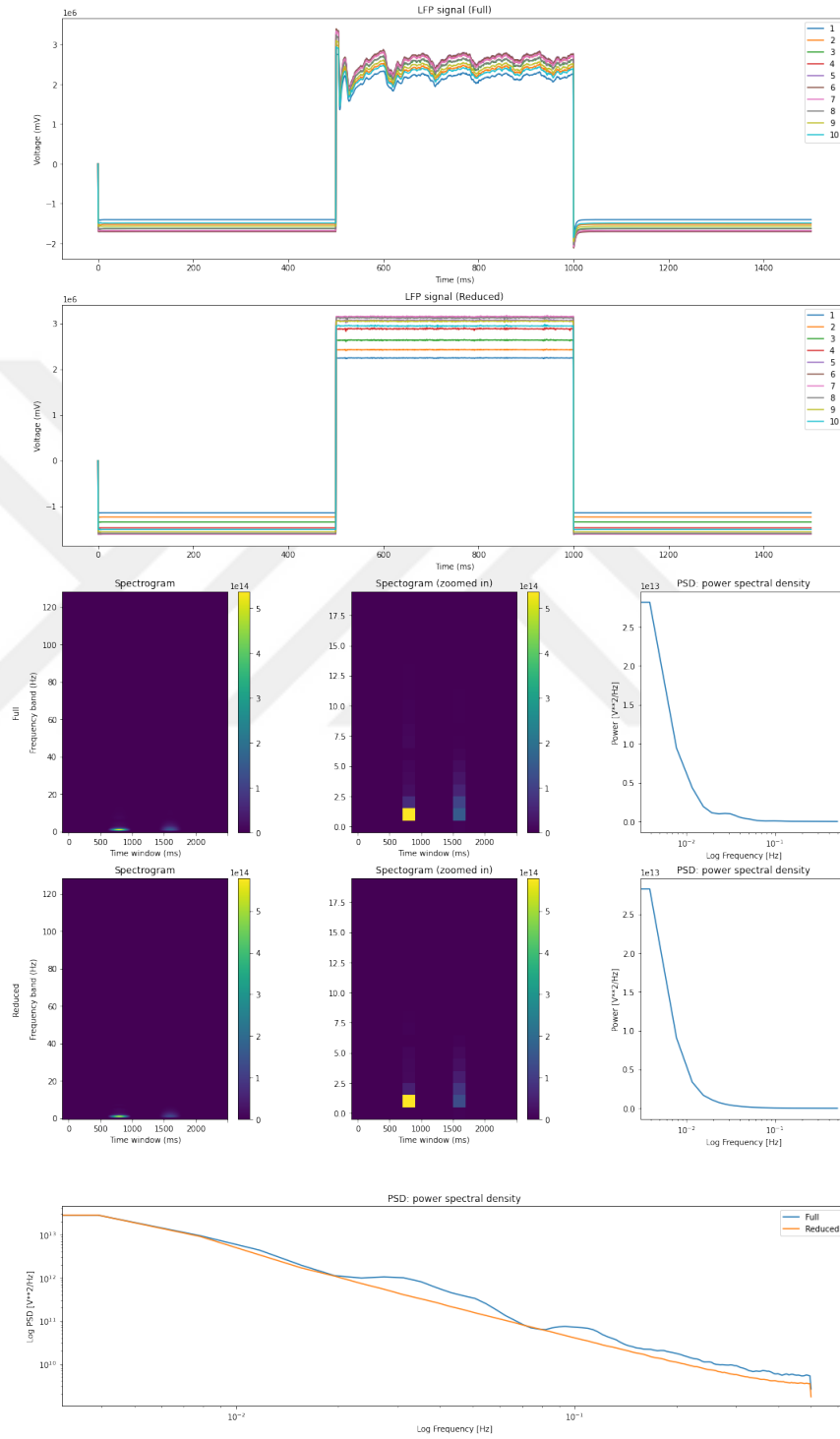


Figure 5.32: LFP analysis for the CA1 microcircuit (psp-validation corrected) for the 120 percent depolarization experiment (simtime=1500 ms).

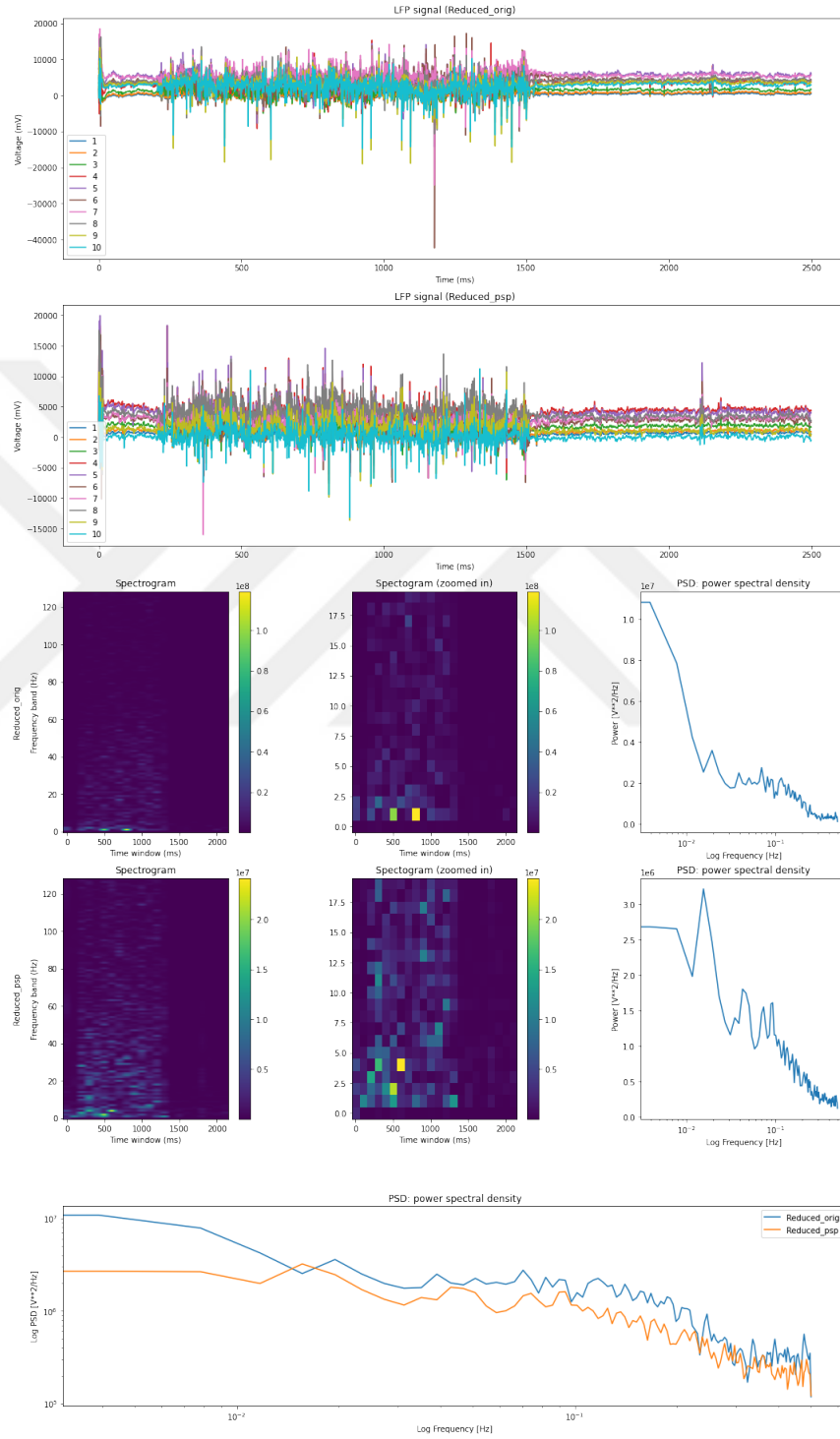


Figure 5.33: LFP analyses of the reduced psp-validation corrected and hand tuned weights were compared.

Chapter 6

Discussions, Limitations and Concluding Remarks

In this thesis, the application of “Neuron-Reduce” algorithm to the hippocampal CA1 microcircuit has been investigated. The plausibility of the algorithm on a single cell level has been shown on several neo- and thalamocortical as well as hippocampal single cell models. [16, 17, 26, 48, 49, 50, 51]. These models are validated with artificial synapses, as shown in the algorithm’s GitHub page. Their first way was to add a number of synapses (10000) to a given single cell model in which 85 percent of them were excitatory. In this study, the same approach was utilized to investigate all hippocampal single cell morphologies within BBP dataset [16]. The models are then reduced and corresponding accuracy measures such as spike-synchrony and isi-distance, were obtained [52]. Synchronization scores with synapse parameters shown in Table 4.1 is given in Table 4.3. The relatively low synchrony levels on several m-types were investigated under higher excitation (in circuit level) or lower inhibition (in single-cell level, see Table 4.4) rates. It has been observed that increasing firing rate of the original neuron has a positive effect on the SPIKE-Synchronization as also shown in Figures 2f,2g, and 7g of the foundation paper by Amsalem et al. [9] or here in Figure 6.1.

The drawback in our model is that hippocampal pyramidal cells in a circuit level

without PP, SC or any other external innervation tend to fire in very low rates, thereby reside in low SPIKE-Synchrony region. We have seen an average of 0.067 Hz for SP_PC cells in all_minis and SC stimulation at 0.1 Hz experiment (amas for short) between 200-1500th ms and 0.033 Hz after the stimulation ends (see in Figure 5.23 raster plot section). This means that the activation is reduced by 50 percent within 1 second after the end of stimulation, which will probably decay further in longer time periods unless a stable attractor is formed. The same simulation in the reduced circuit has 0.0003 Hz within the stimulation period and 0 Hz after the stimulation end, meaning that the intrinsic dynamics cannot linger in the network due to under-excitability of excitatory cells and/or over-activation of inhibitory cells. This behavior changes when fixing measures are introduced. As shown in the PSTH graph of the Figure 5.24, some form of intrinsic dynamics were recovered in the psp-validation scaled circuit but it is unable to get the correct total rate based metric 5.21. Instead, this feat was satisfied by hand-tuned circuitry for the pyramidal cells. Note that this is a crude approach to mitigate the difference in total PC activation rate hence it should not be used for emergent property search unless a very specific condition such as simulation without inhibitory morphologies was chosen as a subject of interest. Perhaps, for future studies, parameter optimization approaches like BluePyOpt [31] or Deep Learning methods can be used to fit these individual m-type activation rates to the those in the original circuit as a measure to cope up with the problem. There may be a pareto-front of solutions in getting correct levels of activation in which case the solution can be chosen in a randomized manner.

LFP simulations have revealed that first-order metrics like signal amplitude were not satisfied with the reduced circuit (see Figures 5.27, 5.28). Similarly, the frequencies of LFP rates in the time window are not in sync and reduced cells show 3 orders of magnitude lower power. However, for higher-level analyses, one can hypothesize that although the power is lower, the frequency ranges are caught in the reduced circuit in Figure 5.29 i.e. the 0-2.5 Hz interval.

In summary, the simplification algorithm has shown its effectiveness over high stimulation regime in single-cell level however this feat is not easily achieved even with peak conductance matching individual m-type rates. LFP analysis requires

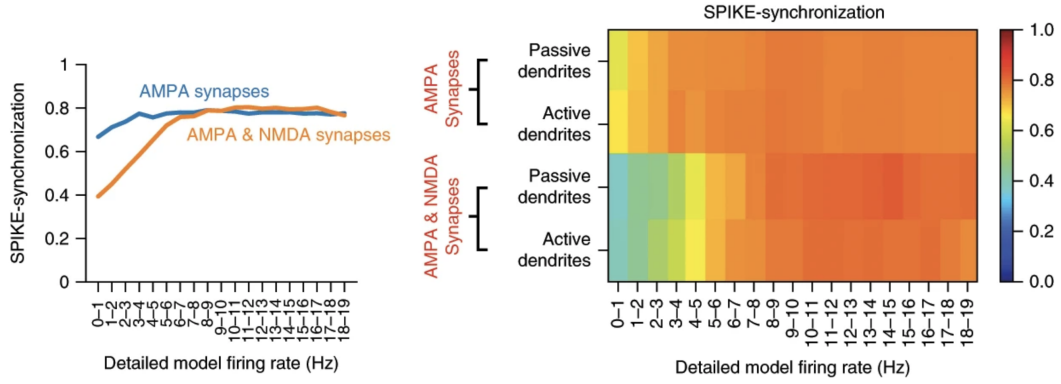


Figure 6.1: The accuracy of the reduction algorithm has been affected by the detailed model firing rate. Left, detailed model firing rate vs SPIKE-synchronization for AMPA and AMPA & NMDA synapses separately. Note that at low frequency regimes (< 7 Hz), including NMDA has an adverse effect on the reduction. Right, the same metric has been effected in NMDA, including synapses in both active and passive dendrites. Obtained from Amsalem et. al 2020 [9]

complex dendritic structure to cope up with the full scale power levels and other unobserved emergent proprieties. This implies that for certain types of electrophysiological behavior, the underlying morphological structure as well as detail models are essential. Further studies may use less dendritic reduction with more synaptic merging techniques. Limitations in this study includes the absence of synaptic merging that has been used in the original neuron reduce algorithm (see supplementary Table 1 for more detail) which hindered the simulation time reduction in the circuit level. Future versions of SONATA Network Reduction should focus more on synaptic merging to scale up the efficiency. Another limitation is that the full scale CA1 circuit shown in Figure 2.10 was unable to be used in this thesis for privacy reasons. Therefore, even in the full circuit, certain hippocampal signature oscillations like theta activity were not generated.

Future works of simplification will work on the full scale CA1 circuit in which oscillation levels, an upgraded network reduction algorithm with synaptic merging and further validations will be performed. Some of these validations include unidirectional signal propagation within the hippocampus, theta oscillations, effects of neuromodulation and extracellular calcium levels as well as further experiments in depolarization levels. Neuromodulation is especially an important

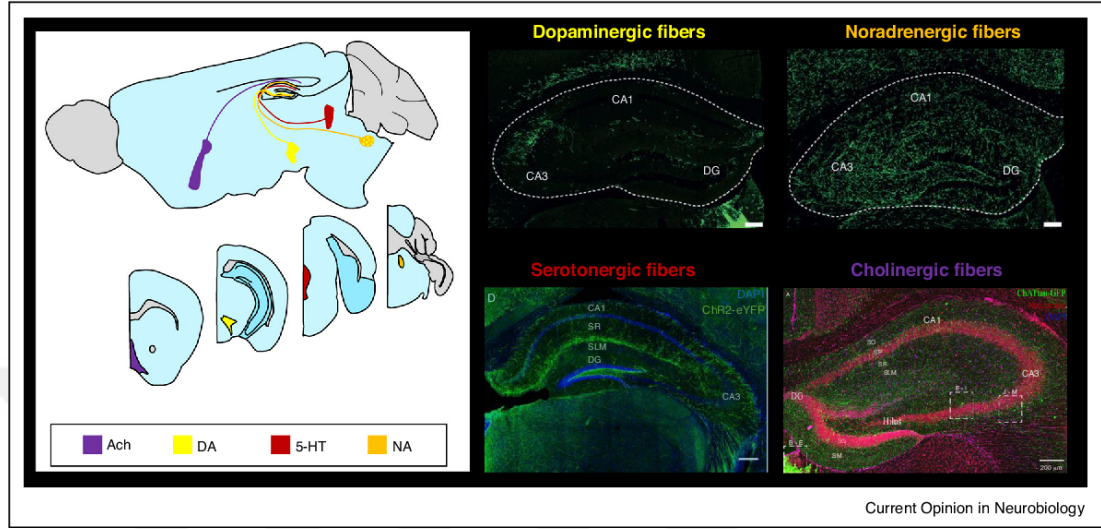


Figure 6.2: Neuromodulator pathways that project to hippocampus from different nuclei

subject in which the excitability of neurons are modulated with neurotransmitters like Acetylcholine, Dopamine or Serotonin 6.2 [53]. These molecules are generated within separate regions of the brain and transported to the end regions via projection neurons [54].

A parallel work has also been conducted for the rat somatosensory cortex model, but due to time limit and data protection measures, it was not included in this thesis. Further works will include circuit specific validations for this circuit as well as single-cell level analyses. With its time efficiency, we believe this method can be further improved and implemented in creating robotic applications that are based on biological network models and general artificial intelligence.

Appendix A

Additional Benchmark Data

Exp 1	Neuron vs CORENEURON (ratio : 8.36x)								
Neuron vs CORE	proj42 O1f - default simulator								
	(/gpfs/bbp.cscs.ch/project/proj42/circuits/CA1.O1/20191017/)								
	- 1s sim + 5s Forwardskip + SC								
	32 nodes bigjob 36 ntasks-per-node -> 2374s - 40 mins								
	reindexed CA1.O1f at proj112/scratch/reindex_again - CORENEURON								
	- 1s sim + 5s Forwardskip + SC								
	64 nodes bigjob 36 ntasks-per-node -> 568 s								
Exp 2	##### scratch -> ratio: 3.326								
mooc	mooc_f - using CORENEURON								
	/gpfs/bbp.cscs.ch/project/proj112/scratch/kurban/CA1_O1_20200424_reindexed/reindex_again/test_mooc/simulation/SC_minis								
	- 1s sim - 5s Forwardskip + SC								
	6 nodes, 36 tpn, nvme cpu -> 2145 s								
	mooc_f - CORENEURON								
	/gpfs/bbp.cscs.ch/project/proj112/scratch/kurban/CA1_O1_20200424_reindexed/reindex_again/test_mooc/reduction/reduced_sonata								
	- 1s sim + 5s Forwardskip + SC								
	6 nodes, 36 tpn, nvme cpu -> 645 s								
Exp 3	##### home -> ratio: 1.92								
o0	** no SC in O0								
	O0r - NEURON								
	gpfs/bbp.cscs.ch/project/proj112/scratch/kurban/new_reduction/simulations/minis/reduced/seed-7235								
	- 1.5 s sim + 5s Forwardskip, no SC								
	4 nodes, 16 tpn, nvme cpu -> 499 s								
	O0f - NEURON								
	/gpfs/bbp.cscs.ch/project/proj112/scratch/kurban/new_reduction/simulations/minis/full/seed-7235								
	- 2 s sim + 5s Forwardskip, no SC								

	6 nodes, 12 tpn, nvme cpu -> 856 s						
Exp 4	##### home - all minis -> ratio: 3.05						
all_minis + replay	mooc_f - CORENEURON						
	/gpfs/bbp.cscs.ch/project/proj112/home/kurban/simplify/mooc/simulation/full/all_minis_and_SC_1Hz_stim						
	- 2.5 s sim - 5s forwardskip + SC + spike replay						
	6 nodes, 36 tpn, nvme cpu -> 5495s						
	mooc_r - CORENEURON						
	/gpfs/bbp.cscs.ch/project/proj112/home/kurban/simplify/mooc/simulation/reduced/all_minis_and_SC_1Hz_stim/weights_to_sppc_to_sppc_3x						
	- 2.5 s sim - 5s forwardskip + SC + spike replay						
	6 nodes, 36 tpn, nvme cpu -> 1801s						
Exp 5	##### home -> ratio: 1.40						
mooc- internal minis	mooc_f - NEURON - internal minis						
	/gpfs/bbp.cscs.ch/project/proj112/home/kurban/simplify/mooc/simulation/full/internal_minis						
	- 1 s sim - 5s forwardskip + no SC						
	6 nodes, 36 tpn, nvme cpu -> 7793s						
	mooc_r - NEURON - internal minis						
	/gpfs/bbp.cscs.ch/project/proj112/home/kurban/simplify/mooc/simulation/internal_minis						
	- 1 s sim - 5s forwardskip + no SC						
	6 nodes, 36 tpn, nvme cpu -> 5593s						
Exp 6	##### home -> ratio: 8.76						
CA1-internal minis	CA1f - internal minis						
	/gpfs/bbp.cscs.ch/project/proj112/home/kurban/simplify/CA1/simulation/full/internal_minis						
	- 1 s sim - 5s forwardskip + no SC						
	64 nodes, 36 tpn, nvme cpu ->						
	Solver Time : 22615.1						

	Simulation Statistics						
	Number of cells: 456292						
	Number of compartments: 332801388 (14.49x of the reduced circuit)						
	Number of presyns: 8999607428						
	Number of input presyns: 1036996751						
	Number of synapses: 17998302272						
	Number of point processes: 17998486592 (11.33x)						
	Number of transfer (gap) targets: 0						
	Number of spikes: 10472						
	Number of spikes with non negative gid-s: 10472						
	CA1r - internal minis						
	/gpfs/bbp.cscs.ch/project/proj112/home/kurban/simplify/CA1/simulation/reduced/internal_minis						
	- 1 s sim - 5s forwardskip + no SC						
	64 nodes, 36 tpn, nvme cpu ->						
	Solver Time : 2581.02						
	Simulation Statistics						
	Number of cells: 456292						
	Number of compartments: 22959762						
	Number of presyns: 794015818						
	Number of input presyns: 152402145						
	Number of synapses: 1587119052						
	Number of point processes: 1587303372						
	Number of transfer (gap) targets: 0						
	Number of spikes: 21095						
	Number of spikes with non negative gid-s: 21095						

Figure A.1: Details on the circuit level simulations for various CA1 circuits (O0,O1,full)

Appendix B

Reduced 3D Neuron & Network Models

Neurons and circuits are visualized via BBP tool “Brayns” [17] with a supernode allocated to load the circuit file, neuron positions, and cell components.



Figure B.1: Detailed and Reduced morphologies for a pyramidal neuron

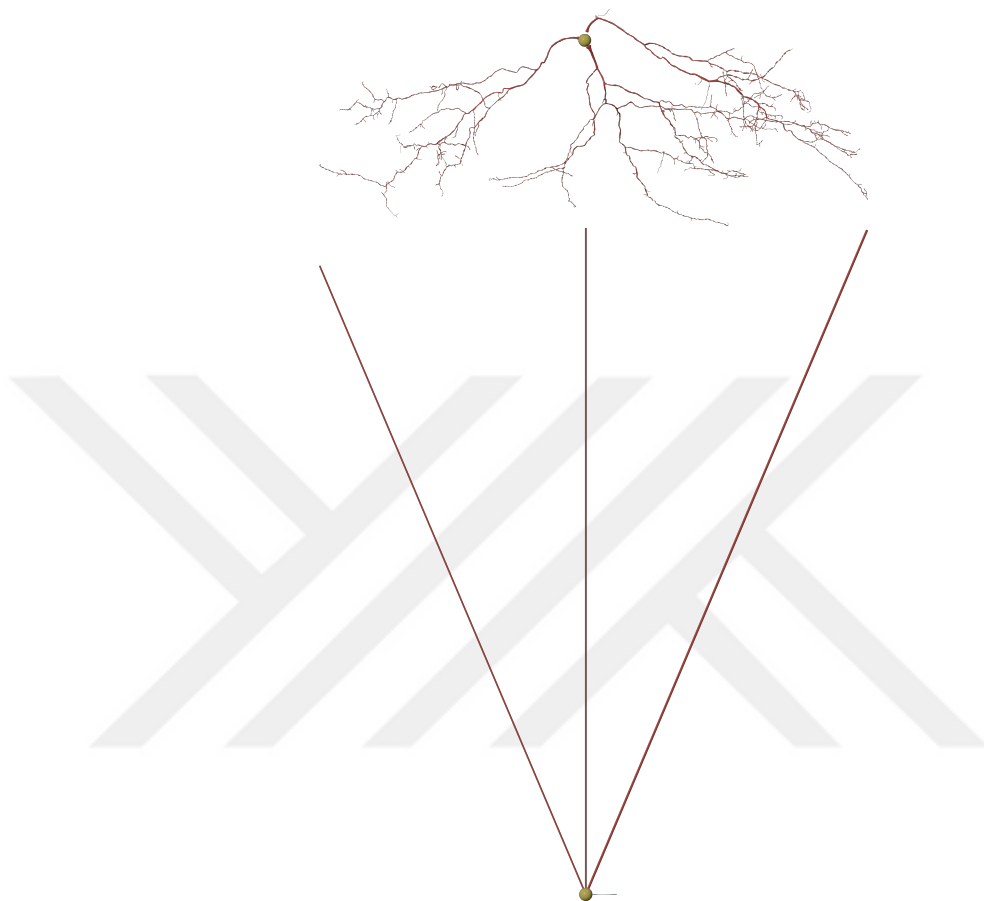


Figure B.2: Detailed and Reduced morphologies for an interneuron

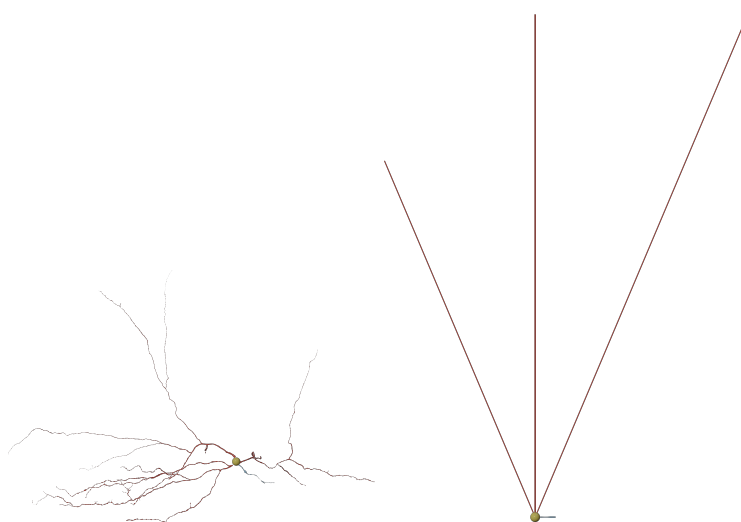


Figure B.3: Detailed and Reduced morphologies for an interneuron

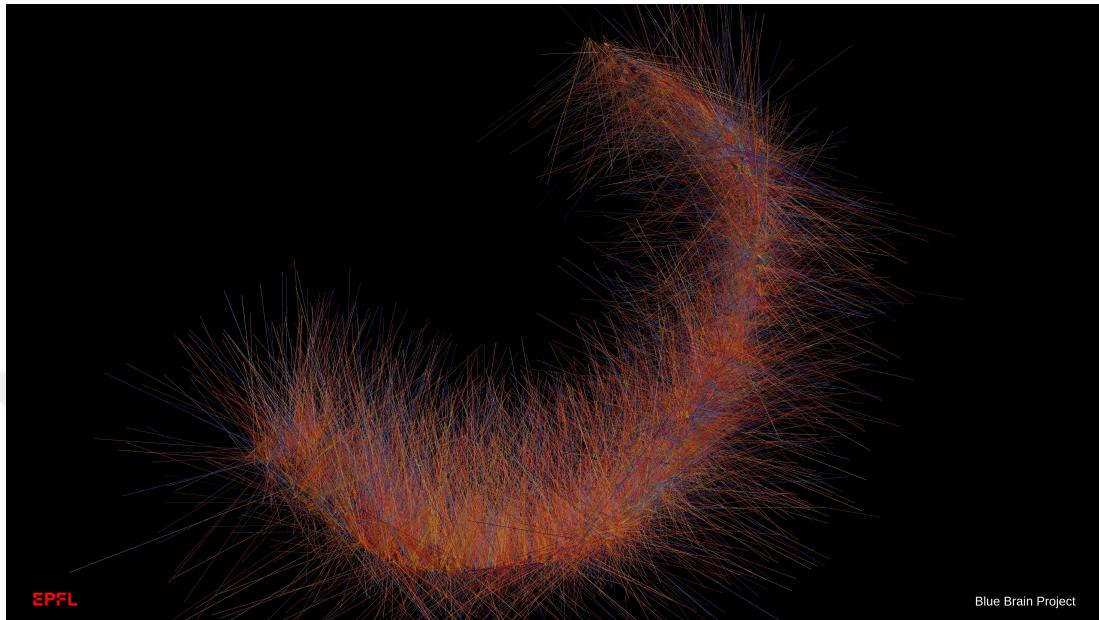


Figure B.4: Visualization of the reduced CA1 Circuit.

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