A THEORETICAL INVESTIGATION OF
THE GENERATION OF A SPONTANEOUS
SLOW RHYTHM IN HIPPOCAMPUS CA1

by

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A thesis submitted in conformity with the requirements
for the degree of Master of Science
Graduate Department of Physiology
University of Toronto

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Abstract

Different rhythmic activities in CA1 characterize the neuronal correlates of several behavioral states. Recently, in an in vitro preparation of the whole hippocampus, spontaneous slow rhythms (< 4 Hz) similar to the hippocampal EEG seen in behaving animals, have been recorded. Based on the experimental data and by using numerical simulations, we suggest a mechanism in which feedback from populations of synchronized interneurons entrains an increasing and/or more synchronized activity in a spatially dynamic pyramidal cell population. In this scenario, two network properties, i.e. the number of the excitatory cells and the excitability of the interneurons, determine the frequency and robustness of these slow rhythms. Furthermore, using a stochastic phenomenological model, we show that in the face of a stochastic basal activity, these two properties enable the network to differentially amplify/suppress the modal structure of the emergent rhythmic activity, hence, act as a dynamically tunable resonant network.
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Finally I would like to acknowledge and thank NSERC of Canada for financial support.
Glossary of Symbols

$E - cell$  Model of excitatory cell
$I - cell$  Model of inhibitory cell
$t$  Time
$V$  Membrane voltage
$C$  Total membrane capacitance
$\tau_{m}$  Passive membrane time constant
$x$  Any of the gating variables ($m, h, n$)
$m$  Sodium activation variable
$h$  Sodium inactivation variable
$n$  Potassium activation variable
$\alpha_{z}(V)$  Forward rate constant for gating variable $x$
$\alpha_{m}(V)$  Forward rate constant for sodium activation
$\alpha_{h}(V)$  Forward rate constant for sodium inactivation
$\alpha_{n}(V)$  Forward rate constant for potassium activation
$\beta_{z}(V)$  Backward rate constant for gating variable $x$
$\beta_{m}(V)$  Backward rate constant for sodium activation
$\beta_{h}(V)$  Backward rate constant for sodium inactivation
$\beta_{n}(V)$  Backward rate constant for potassium activation
$\tau_{z}(V)$  Time constant of gating variable $x$
$\tau_{m}(V)$  Time constant of sodium activation
$\tau_{h}(V)$  Time constant of sodium inactivation
$\tau_{n}(V)$  Time constant of potassium activation
$x_{\infty}(V)$  Steady state of gating variable $x$
$m_{\infty}(V)$  Steady state of sodium activation
$h_{\infty}(V)$  Steady state of sodium inactivation
Steady state of potassium activation
Same as \( m_{\infty}(V) \)
Same as \( h_{\infty}(V) \)
Same as \( n_{\infty}(V) \)
Normalization factor
Inward sodium ionic current
Outward potassium ionic current
Leakage ionic current
Maximal sodium conductance
Maximal potassium conductance
Maximal leakage conductance
Sodium equilibrium (reversal) potential
Potassium equilibrium (reversal) potential
Leakage equilibrium (reversal) potential
Nonspecific background synaptic current (bias current)
Gaussian distribution
Mean of bias current; Gaussian distribution
Mean of bias current at 4.3\( \mu \)A.cm\(^{-2} \) (central value); Gaussian distribution
STD of bias current; Gaussian distribution
STD of bias current at 0.2\( \mu \)A.cm\(^{-2} \) (central value); Gaussian distribution
Uniform distribution
Mean of bias current; Uniform distribution
Mean of bias current at 4.3\( \mu \)A.cm\(^{-2} \) (central value); Uniform distribution
STD of bias current; Uniform distribution
STD of bias current at 0.2\( \mu \)A.cm\(^{-2} \) (central value); Uniform distribution
Synaptic current
Forward rate constant for receptor channel activation
Backward rate constant for receptor channel activation
Receptor channel activation
Maximal synaptic-induced conductance
Synaptic equilibrium (reversal) potential
Neurotransmitter concentration (released in synaptic cleft)
Voltage of presynaptic cell
\( F(V) \) Sigmoidal transfer function

\( \Delta \) Steepness of sigmoidal transfer function

\( V_0 \) Half activation of sigmoidal transfer function

\( i_{AMPA} \) Maximal conductance of \( AMPA \) synaptic current

\( i_{GABA_A^{\text{fast}}} \) Fast \( GABA_A \) synaptic current

\( i_{GABA_A^{\text{slow}}} \) Slow \( GABA_A \) synaptic current

\( g_{AMPA} \) Maximal conductance of \( AMPA \)

\( g_{GABA_A^{\text{fast}}} \) Maximal conductance of fast \( GABA_A \)

\( g_{GABA_A^{\text{slow}}} \) Maximal conductance of slow \( GABA_A \)

\( E_{AMPA} \) Equilibrium (reversal) potential of \( AMPA \)

\( E_{GABA_A^{\text{fast}}} \) Equilibrium (reversal) potential of fast \( GABA_A \)

\( E_{GABA_A^{\text{slow}}} \) Equilibrium (reversal) potential of slow \( GABA_A \)

\( s_{AMPA} \) Activation of \( AMPA \) receptor channel

\( s_{GABA_A^{\text{fast}}} \) Activation of fast \( GABA_A \) receptor channel

\( s_{GABA_A^{\text{slow}}} \) Activation of slow \( GABA_A \) receptor channel

\( N \) Total number of E-cells in the network

\( n \) Minimum number of E-cells required to excite the I-cell

\( T \) Network period; numerical model

\( P_{ISI} \) Inter-spike interval probability distribution function

\( ISI_{\text{mean}} \) Mean of inter-spike interval (network period)

\( ISI_{\text{std}} \) STD of inter-spike interval (network period)

\( g_{GABA_A^{\text{fast}}}^{\text{centr}} \) Central value of \( g_{GABA_A^{\text{fast}}} \)

\( g_{GABA_A^{\text{slow}}}^{\text{centr}} \) Central value of \( g_{GABA_A^{\text{slow}}} \)

\( \mu_{\text{bias}}^{\text{centr}} \) Central value of \( \mu_{\text{bias}} \)

\( \sigma_{\text{bias}}^{\text{centr}} \) Central value of \( \sigma_{\text{bias}} \)

\( g_{Na}^{\text{central}} \) Central value of \( g_{Na} \)

\( g_{K}^{\text{central}} \) Central value of \( g_{K} \)

\( g_{\text{exc}}^{\text{AMPA}} \) Maximal conductance of \( AMPA \); E-cell to E-cell connection

\( g_{\text{inh}}^{\text{AMPA}} \) Maximal conductance of \( AMPA \); E-cell to I-cell connection

\( T \) Network Period; phenomenological model

\( P_{1,1}(T) \) Probability distribution function of the firing time of each E-cell

\( P_{N,n}(T) \) Probability distribution function of the network period

\( \mu_{ISI}(N,n) \) Mean of network period
$\sigma_{SI}(N,n)$  
$\sigma^2_{SI}(N,n)$  

$R_0$: Network with no interconnection between E-cells  
$R_1$: Small-scale network with first-order connectivity for E-cells  
$R_2$: Small-scale network with second-order connectivity for E-cells  

STD of network period  
Variance of network period
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Chapter 1

Introduction

In the realm of science, the study of the constituents of macroscale phenomena has often led to mechanistic descriptions of various aspects of the observable universe. This reductionist point of view has long been a prevalent conceptual tool in all branches of science.

Our psychophysical life is a macroscale phenomenon, and at this stage in the evolution of neuroscience it is postulated that psychophysical phenomena are in fact physical processes in the brain. To understand the nature of these processes using a reductionistic approach, one should reduce the problem to multiple levels of organization within the brain. These organizational levels would be spatiotemporal constituents of the original process and as such, should be able to concert to maintain the identity of each and every unique psychophysical experience. Understanding the organizational principles that govern these constituents, is one of the major endeavors in neuroscience.

To further advance along the reductionist ladder, one can look at the local neuronal ensembles in specific brain structures. The activity of single cells within these ensembles calls for parallel organizational principles that can harmonize their behavior. Oscillations in neural circuitry can give a temporal reference to the activity of individual neurons and therefore serve as one such organizational principle. Although it is not clear whether these oscillations are one of the causal principles of neural processing or just concurrent epiphenomena, yet, it is hypothesized that they can provide temporal coordination for spatially separated parts and as such, play an active role in neural processing. Furthermore, studying the biophysical properties that underlie these neural oscillations has been central in providing a mechanistic view of the generation and propagation of such behaviors in both normal and pathological brains.

In the current study, using both theoretical and modeling approaches, a dynamical feedback mechanism that may account for the generation of a slow rhythmic activity in the neuronal networks of the CA1 region in the mammalian hippocampus is investigated.

In our modeling approach, we consider a simplified architecture of the neuronal networks in CA1. Using kinetic models in conjunction with data obtained from several previous experimental studies, a math-
ematical description of the dynamical principles that govern the behavior of the network is developed. This mathematical description which comprises a system of nonlinear differential equations is then numerically solved to simulate the activity of the neurons in CA1.

The solution to these differential equations show that the simplified model is able to generate a slow rhythmic activity in the neuronal networks of CA1. In the model, the rhythmic behavior is due to the interaction of the inhibitory and excitatory cells. In each cycle, the activity of a spatially dynamic population of excitatory cells heightens to the point where it induces a strong synchronous inhibitory signal in the inhibitory population. Subsequently, this inhibitory signal feeds back onto the excitatory cells and resets their activity. This mechanism is what we will refer to as the Dynamical Feedback Mechanism. Moreover, the results of several simulations show that the network size as well as the excitability of the inhibitory cells can control the frequency and the robustness of the rhythm.

In our theoretical approach, we devise a phenomenological model of the dynamical feedback mechanism studied in our simulations. In this model, a statistical description of the numerical results is used to investigate the modal structure of the slow rhythmic activity. The results from our theoretical approach show that the recurrent activity in the excitatory/inhibitory network is able to shape a non-modal stochastic input into a multimodal rhythmic behavior. Furthermore, the dynamics of the network is able to differentially amplify the modal structure of the rhythm to extract certain preferred frequencies while suppressing others.

1.1 Background

1.1.1 Rhythmic Activity in the Hippocampus

Different population rhythms, as reflected by spontaneous field potentials, are present in all brain structures. In vivo studies in animal models have shown that these rhythms correlate with certain behavioral states and as such, their mechanism has been the subject of intense investigation. It is not clear if these rhythms are playing an active role in neural processing or they are emerging phenomena while some other underlying processing is taking place, yet, studying these rhythms is believed to help reveal the cellular mechanisms that are responsible for various behavioral states.

Hippocampus, part of the hippocampal formation in the mammalian limbic system, is believed to play an important role in memory consolidation since both human studies and animal models have been able to show that damage confined to the hippocampal formation produces severe memory impairments.

This structure, similar to other brain structures, exhibits several different rhythmic activities that correlate with specific behavioral states. For example, EEG recordings show a 5-10 Hz theta oscillation when animals are exploring their environment [17]. When animals stop and are in a period of quiet wakefulness, the theta activity ceases and is replaced by sharp waves consisting of large amplitude irregularly occurring waveforms. Gamma oscillations (20-60 Hz) are another type of population activity that can occur as transient phenomena [80] or in other conditions like limbic seizures [11]. Slow rhythmic activity in the delta band ( < 4
Hz) has also been recorded which correlates with certain stages of sleep as well as some epileptiform activities [5]. For each of these rhythmic activities various mechanisms have been proposed. Two main sources have been studied extensively: One is the pacemaker activity of the septum which may be entraining hippocampal networks via rhythmic cholinergic and/or GABAergic inputs and the other is the resonant intrinsic and network properties of the hippocampal principal cells as well as interneurons [58, 7, 19, 37, 25, 42].

The literature on various proposed mechanisms for the induction and propagation of these rhythms is vast and beyond the scope of this introductory overview. However, since the major focus of the current work is on the slow delta activity, several mechanisms that may account for the generation and control of this particular rhythm will be further discussed. For the unfamiliar reader, a more detailed description of the hippocampus, its structure, anatomy, cell types, physiology, neuronal circuitry and function is provided in Appendix A.

1.1.2 Delta Rhythm

Recent studies have disclosed several oscillations all within the frequency range of the classical delta band (0.5-4Hz). Only within the thalamocortical structures, during resting sleep, at least three different mechanisms have been identified [5]; a slow (<1 Hz) cortically generated oscillation, a 'clock-like' thalamic oscillation (1-4 Hz) and a cortical oscillation (1-4 Hz) [5]. These studies that are either based on whole-night EEG recordings from humans or field recordings from anesthetized animals, show that the delta band, originally recorded in pathological brains due to cerebral tumors [87], can correlate with various brain conditions.

Furthermore, electrophysiological studies have unveiled several distinct activational substrates in the frequency range below 4 Hz and as such, the rhythmic activities within this range can reflect several phenomena with different mechanisms. For instance, the slow oscillations of the cortical neurons are believed to be correlated with the K-Complex (KC) at the EEG level and is associated with cyclic recurrence of synchronous synaptic activity followed by silenced periods in the cortical networks (disfacilitation) [4, 75, 74, 20]. On the other hand, the thalamic 'clock-like' delta oscillations are associated with individual neurons that are able to produce oscillations in the delta frequency band [46]. There are also pathological delta rhythms that may have different underlying mechanisms yet to be discovered.

In vivo recordings have been useful in identifying these oscillatory behaviors in their native state, however, these studies are limited in their ability to directly assess cellular activity and for various reasons pharmacological manipulations are difficult. To better understand the mechanisms underlying various processes responsible for the generation of the delta rhythm, several studies have directed their attention towards in vitro preparations to provide a mechanistic description of these rhythmic behaviors.

In the next section we will briefly review some of the in vitro studies that have been able to record the slow delta activity in the mammalian hippocampus.
**Delta Rhythm in Hippocampus**

In vitro studies of the mammalian hippocampus has shown that this structure under several pharmacological conditions, is able to exhibit delta rhythm. For instance, in guinea pig hippocampal slices, using low concentrations of penicillin, activities principally in the 2-4 Hz range have been recorded [62]. Similarly, with the perfusion of low millimole CsCl, rat CA1 pyramidal cells have been shown to elicit slow oscillations (less than 1 Hz) which seems to be $GABA_A$ mediated [91].

In other studies, intracellular recordings obtained from neurons in tissue taken from human epileptic temporal lobe and normal monkey hippocampus, using in vitro slice preparation, have shown the spontaneous generation of the so-called spontaneous rhythmic synchronous events (SRSEs), which falls within the frequency range of the delta band [64]. The results of these studies suggest that there is a normal circuitry, particularly in structures such as hippocampus, which can mediate these SRSEs [64]. It is important however, to note that the slices studied in these experiments were relatively thick (600μm as opposed to the usual 300 - 500μm) which suggests that the circuitry required for the induction of these slow events might be interrupted in thinner slices [64].

Recently an intact in vitro hippocampal preparation was forwarded [36]. Using this isolated preparation of the whole hippocampus, spontaneous delta rhythm in the CA1 region has been reported and its cellular and synaptic mechanisms have been investigated [90]. In this in vitro study, the frequency of the recorded field potentials, closely resembles specific hippocampal EEG recordings as well as some other slow rhythmic activities previously observed. The mechanism for the generation of this spontaneous slow rhythmic activity is thus far unknown, however, because of its similarity to some in vivo oscillations, it may correspond to certain behavioral states. Furthermore, since the rhythm is being spontaneously generated, understanding its neural mechanisms may reveal some important aspects of the CA1 neural circuitry.

The site of origin of this rhythm was determined to be the densely packed CA1 pyramidal layer [90]. Moreover, it was suggested that the ionic events originating from the perisomatic area of CA1 pyramidal cells are likely mediators of this slow rhythm [90].

Simultaneous extra- and intracellular whole-cell patch-clamp recording from both pyramidal cells and interneurons in the CA1 region showed that there is a significant level of coherency between the onset of the field rhythm, the firing of the GABAergic cells and the hyperpolarization of the pyramidal neurons. Furthermore, various pharmacological and electrophysiological studies have confirmed that both $AMPA$ and $GABA_A$ currents are necessary for the induction of this rhythm [90].

Fig 1.1 shows the coherence between the hyperpolarizations in a recorded pyramidal cell (top traces) and the field rhythm (bottom traces). Similarly Fig 1.2 shows the simultaneous recordings from an O/A interneuron and the extracellular potential. The coherence suggests a synchronous activity within both the pyramidal cell and interneuronal populations.

Looking at the phase relationship between the firing time of both pyramidal cells and interneurons and the simultaneously recorded field potential, suggests a particular cycle of events (Fig 1.3). The interneurons
Figure 1.1: Intracellular correlate of slow field rhythms. A, recordings from CA1 pyramidal neurons at different membrane potentials (top traces) and nearby perisomatic field potential (bottom traces) during the slow rhythmic activity. The cross-correlation (top right) is generated for when CA1 pyramidal cell is at the resting membrane potential (from Wu et al. [90] with permission).

Figure 1.2: Rhythmic activities of a recorded interneuron in CA1 region during the slow rhythmic activity. The intracellular recording from the O/A interneuron (top trace) exhibits strong correlation to the recorded field rhythm (bottom trace) (from Wu et al. [90] with permission).
have a spread phase relationship with respect to the field rhythm, yet a large percentage of them seem to be in an average of 15 degrees lead to the peak of the field potential. On the other hand, pyramidal cells are in general in less than 5 degrees lead to the rhythm. These results suggest that in each cycle, the onset of the field potential is preceded by a synchronous firing of the interneuronal population followed by a population inhibition of the pyramidal cells.

These phase relationships, the synchronous firing of the recorded interneurons, the importance of the $GABA_A$ current, the strong hyperpolarizations in pyramidal neurons and their correlation with the field onset, all suggest that the rhythm is mediated by the cyclic hyperpolarization of several pyramidal neurons that are strongly inhibited by a synchronous GABAergic network.

Given that the rhythm is generated in the CA1 region, which is still to be consolidated, and given that the current evidence towards the above mentioned cycle of events is true to the generation of the observed delta rhythm, it is still not clear why and how the neural circuitry within the CA1 region is able to generate this rhythm. The mechanisms that control the synchronization of individual interneurons is not known. The interaction between the interneuronal population and the pyramidal neurons, while engaged in this rhythmic activity, is not well-defined, the role of the AMPA current in the cycle is ambiguous and the key players in stabilizing the rhythm are not identified.

In this work, to better understand some of the possible mechanisms by which this rhythm is being mediated, a theoretical/modeling approach has been adopted. The model does not intend to answer all these questions, yet it is utilized to test whether this rhythm can be mediated by the dynamical interaction of the excitatory and inhibitory populations present in the neural circuitry of the CA1 region. Moreover, the model is used to investigate some of the important factors in controlling the frequency and the robustness of the rhythm in a network situation. Some of the important aspects of the model will now be discussed.

1.1.3 The Model

Hippocampus is divided into three subdivisions designated CA1 to CA3 that are known to have different anatomical and physiological and hence synchronizational properties. Despite their postulated distinct roles in computation, few studies have examined the specifics of the neuronal activity of each of these regions in behaving animals. In most studies recordings from CA1 to CA3 fields are reported to have grossly similar behavioral correlates and have been analyzed together as a single group [54]. Furthermore, in the multisynaptic hippocampal circuit [2], processing of information occurs during macroscopic oscillations [18] which is the natural result of the dynamical interaction of a multitude of neurons in all three regions. These all impose difficulties in understanding the dynamical properties of the neuronal networks within each subdivision.

Theoretical approaches in general and modeling techniques in particular have been useful in providing neuroscientists with a platform where they can study the spatiotemporal behavior of local neuronal networks in specifically identified brain structures and therefore have proven fruitful in understanding the dynamical
Figure 1.3: Phase relationship between the activity of individual neurons and the field rhythm. Histograms are generated from analyzing simultaneous recordings of pyramidal IPSP (A) and interneuronal EPSP (B) with respect to the field potential (from Wu et al. [90] with permission).
aspects of the behavior of neuronal populations.

The conductance-based models with synaptic connections seem like an appropriate choice for studying rhythmogenesis. Typically, the model attempts to map an interconnected network of excitatory and inhibitory cells (which is still too complicated for a direct experimental assay) into a number of differential equations in order to predict their dynamical behavior. These models, on one hand, are not overly detailed to introduce high structural instabilities and on the other hand, are based on physiological observations; therefore they can make predictions that are impossible through experimentation or even brute force modeling.

In the following sections, with the assumption that the reader is familiar with the basics of the Hodgkin-Huxley conductance-based dynamical models, we will confine our focus to the specifics of the model with regard to the generation of the slow rhythmic activity within the circuitry of the CA1. An introduction to the basics of the conductance-based models with a critical assessment of their usefulness in modeling neuronal activity is provided in Appendix B.

**Model Considerations: Interneurons**

Within the inhibitory circuits of the CA1 subregion, two types of activity have been identified: the feedback (recurrent) and the feedforward [72, 8]. These terms are solely to describe the timing of inhibitory events relative to the excitatory activity in pyramidal cells with the feedback signal occurring after the pyramidal activation. With regard to the spontaneous slow rhythmic activity in CA1 [90], the differential roles of these two distinct synaptic mechanisms have not yet been identified. However, the importance of the AMPA current suggests that the inhibitory response might be a feedback to the excitatory drive, although current evidence does not rule out the possibility of an excitatory drive from the Schaffer collaterals. Our model focuses on the feedback activity of the interneuronal population. It is important to note that the role of these two systems with regard to various different neural activities is still not known.

Looking at the results of the experimental data, the cyclic and slow recurring hyperpolarizations of the pyramidal cells suggest that the inhibitory postsynaptic potentials (IPSPs) induced by the synchronous activity of certain populations of interneurons, might be mediated through activation of GABAergic currents on different time scales. This is in agreement with the observation that electrical stimulation in the hippocampus evokes biphasic inhibitory responses [53].

The early component of this inhibitory signal is mediated by the fast $GABA_A$ response. With regard to the slow component, there are two relatively slow inhibitory currents that are known to be present in CA1 region; $GABA_B$ and $GABA_{A,slow}$. The results from the antidromic versus orthodromic stimulation of the pyramidal cells show that the feedback mechanism is unlikely to activate $GABA_B$ signals which are mostly observed following orthodromic stimulation [52]. Furthermore, single cell stimulation of the interneurons located within stratum pyramidale and in the stratum oriens-aleveus region has been consistently shown to be mediated solely by $GABA_A$ synaptic mechanisms [47, 15, 55]. Considering these lines of evidence, we
have implemented the $GABA_{A_{slow}}$ signalling pathway for the mediation of the slow component of the IPSP. It is however, important to note that at this stage, the alternative mechanism which takes into account the active role of feedforward inhibition coupled with $GABA_B$ current as the slow component remains a possibility.

The $GABA_{A_{slow}}$ has been shown to be a slow, synaptically originating, inhibitory current [10]. Several studies indicate that the fast and slow $GABA_A$ arise from distinct pools of interneurons [57, 10], although the other option of having multiple axonal projections from the same interneuron is not precluded. In our study, we have assumed that from a dynamical perspective, during the generation of the field rhythm, the two inhibitory components are synchronized. In other words, either the same interneuron is responsible for eliciting both currents or the two distinct pools are dynamically entrained and both currents, although from different sources, are evoked synchronously. Our assumption is based on the fact that the experimental data suggest a high level of synchrony in the activity of interneurons. As a result, in our approach, the synchronized population of interneurons is modeled as a single interneuron which after excitation, through both fast and slow GABAergic currents induces biphasic IPSPs on the pyramidal cells. Our model therefore, does not investigate the mechanisms that underlie the interaction of these synchronous interneurons.

Model Considerations: Pyramidal cells

One of the key points in understanding the mechanism for the induction of the experimentally observed delta rhythm is to determine whether CA1 is only a substrate for the propagation of the rhythm or the actual center for its generation. The distinction between the two is crucial since one characterizes the recorded rhythm as a wave and the other as an oscillation.

If CA1 is solely a substrate for the propagation of the delta activity (synonymous with the wave hypothesis), then it is important to look for its generation elsewhere. In such a paradigm, the circuitry in CA1, would not have a delta component in its intrinsic spectral content, yet it has the properties of a passive filter for the passage of this rhythmic activity. Furthermore, the generation of the rhythm should take place in a neuronal ensemble upstream of CA1 in which case, the input to the CA1 would have a delta component which is passively conducted through CA1.

The other hypothesis, is to see whether the CA1 circuitry, irrespective of the presence of a delta component at its input, is able to generate the rhythm on its own. At this point, due to the undiscriminated nature of these two phenomena, i.e. waves and oscillations, it is difficult to definitively prefer one over the other. However, the study of the possible mechanisms and their implications may help in clarifying the source of this neural activity. In our model, we focus on the second mechanism: the generation of the rhythm within the CA1 circuitry from a non-modal synaptic input, i.e. a stochastic, spectrally nonspecific background input from the CA3 region. This input would drive the pyramidal cells in the CA1 region through the Schäffer collaterals which are the major excitatory pathway to these cells [68]. Another input to these pyramidal cells would be the feedback inhibitory signal from the synchronized basket cells and O/A interneurons within the
CA1 region [38], which in our approach are modeled as one single unit.

Stochastic neural modeling in its simplest form, i.e. one-dimensional Markov process, goes back to 1960s, when the deterministic models of motoneurons were just being established. In the last two decades a considerable effort has been put into studying solutions of the linear stochastic partial differential equations (that resulted from the stochastic cable theory) [85] and the importance of stochastic versions of nonlinear systems of equations such as those of Hodgkin and Huxley, has more recently been appreciated [82, 83, 84, 39].

In our numerical approach, we investigate the CA1 circuitry in conjunction with a nonspecific synaptic input to the pyramidal cells that are engaged in a feedback loop by their connection to basket cells and O/A interneurons. In a strict mathematical sense, we numerically analyze the space-clamped version of the nonlinear Hodgkin-Huxley differential equations using an additive Gaussian (or Uniform) white noise, which will make a standard four-dimensional temporally homogeneous Markov process.

The results of this numerical analysis is statistically analyzed and incorporated in our phenomenological model to investigate the probability distribution function of the period of the network while engaged in the slow rhythmic activity.

1.2 Conspectus

In the first chapter after giving an overview of the delta rhythm and its relation to both normal and pathological brain states, some of the neuronal substrates that may account for the generation of this rhythm in hippocampus were introduced. The dynamical feedback mechanism as a possible neuronal substrate for the generation of the slow rhythmic activity in the CA1 region was outlined and the modeling considerations for studying this mechanism in our numerical as well as phenomenological model were discussed.

In chapter two a detailed description of the methods used to carry out the simulations will be given. This will include: network architecture, individual cell models, synaptic connections, dynamics of the network and specifics of the numerical simulations. Finally the methods that were adopted to perform the sensitivity analysis -in order to examine the stability of the network behavior- will be presented.

Chapter three will be dedicated to the presentation of the simulation results and a brief analysis of the network behavior in its stable regime. The results of the sensitivity analysis will also be a part of this chapter.

The logic behind the stochastic phenomenological model, its assumptions and its relevance will be the focus of chapter four. In this chapter in addition to constructing the phenomenological model, its results will be reported. The predictions of this model for the behavior of larger networks will also be discussed.

Finally chapter five will be an effort to discuss various interpretations of the results both from the numerical simulations and the stochastic phenomenological model. Our conclusions will be stated and some of the possible avenues for further research in this direction will be highlighted.
Chapter 2

Methods: Model Architecture

With regard to the generation of the slow rhythmic activity, the dynamics of a relatively small network of several excitatory cells and one inhibitory cell is explored. Using a conductance-based formalism, each cell is modeled as a single-compartment unit. Intrinsic and synaptic dynamics are modeled using multiple differential equations and the network connectivity is inspired by the neuroanatomical studies of the CA1. In the following, the details of the model are reported.

2.1 Network Architecture

2.1.1 Network Connectivity

The network is composed of a single inhibitory cell (I-cell) and multiple (a total of $N \geq 1$) excitatory cells (E-cells). Unless one is interested in the dynamics of interconnected interneuronal networks, synchronized interneurons can in general, be modeled by a single inhibitory cell that represents the activity of the population. This approach is adopted in our model where a single I-cell represents the activity of a synchronized population of interneurons (Fig 2.1).

The excitatory synaptic connections between the pyramidal cells of the CA1, except for the nearby interconnections, are known to be sparse. Due to their proximity, the nearby pyramidal cells are approximately sensing a similar synaptic input, therefore it is further assumed that during delta activity, each group of these nearby pyramidal cells can be modeled by a single E-cell. On the other hand, since the connections between distant pyramidal cells are sparse, the model assumes no excitatory connection between individual E-cells in the model. This model will be referred to as the large-scale model (Fig 2.2).

In addition to the large-scale model, a second model is also investigated where individual pyramidal cells are represented by separate E-cells that are reciprocally coupled and is called the small-scale model (Fig 2.3).

In both models, each E-cell is reciprocally connected to the I-cell (Fig 2.2,2.3). The excitatory
connections model the excitatory drive from local pyramidal cells to the interneurons and the inhibitory synaptic connection represents the inhibitory drive from the synchronized interneuronal population to the pyramidal cells. The inhibitory effect of the I-cell, as was discussed in chapter two, is assumed to have both fast and slow components.

The main focus of our work is on the behavior of the large-scale model, which assumes no connection between individual E-cells. As will be shown in chapter four, the essence of the behavior of this model can be captured by using a simplified phenomenological model that highlights the key parameters in the induction and control of the slow rhythmic activity.

2.1.2 Individual Cell Models

Each neuron is modeled as a point process where all the distributed ionic channels are lumped into a single-compartment conductance-based unit. The cell is therefore assumed to be equipotential vis-a-vis the whole-cell patch-clamp technique in an experimental setup.

The E-cells are modeled as dynamical systems with four state variables, activation and inactivation of the sodium channel, activation of potassium channel and the membrane voltage. The activation and inactivation variables are gating variables that describe the macroscopic behavior of individual channels. Gating variables are assumed to be independent of one another and they all follow a two state kinetic model.
as depicted mathematically in the following differential equations:

\[
\begin{align*}
\frac{dm}{dt} &= \alpha_m(V)(1 - m) - \beta_m(V)m \\
\frac{dh}{dt} &= \alpha_h(V)(1 - h) - \beta_h(V)h \\
\frac{dn}{dt} &= \alpha_n(V)(1 - n) - \beta_n(V)n
\end{align*}
\] (2.1, 2.2, 2.3)

The parameters \( \alpha \) and \( \beta \) in all the three equations represent the forward and backward rate constants as shown in Fig 2.4. These equations can be written in a slightly modified form, which will have less biophysical, yet more functional meaning:

\[
\tau_z(V)\frac{dx}{dt} = x_\infty(V) - x
\] (2.4)

where \( x \) can be any of the gating variables (\( m, h \) or \( n \)). Comparing the two forms, it can be shown that:

\[
\begin{align*}
\tau_z(V) &= \frac{1}{\alpha_z(V) + \beta_z(V)} \\
x_\infty(V) &= \frac{\alpha_z(V)}{\alpha_z(V) + \beta_z(V)}
\end{align*}
\] (2.5, 2.6)
In these equations, $\tau_x(V)$ and $x_\infty(V)$ have a clear functional meaning. $x_\infty(V)$ is the asymptotic value that variable $x$ approaches exponentially with time constant $\tau_x(V)$.

Each E-cell, in addition to its sodium and potassium currents, has a passive leakage current. Using Ohm's law, each of these three currents (leakage, sodium and potassium) can be written as a conductance multiplied by an appropriate potential difference. The effective conductance, according to the Hodgkin-Huxley formalism, is quantified by the maximal conductance of a particular channel type, gated by its appropriate gating variables, and the potential difference is the driving force across that channel type, i.e. the difference between the membrane voltage and the channel's reversal potential (equilibrium potential).

$$i_{Na} = g_{Na} m^3 h (V - E_{Na}) \quad \text{(2.7)}$$
$$i_K = g_K n^4 (V - E_K) \quad \text{(2.8)}$$
$$i_{leak} = g_{leak} (V - E_{leak}) \quad \text{(2.9)}$$

$g_{Na}, g_K, g_{leak}$: maximal conductance for sodium, potassium and the leakage currents
$E_{Na}, E_K, E_{leak}$: reversal potential for sodium, potassium and the leakage conductances
The rate of change of the cell membrane voltage is determined by the incoming currents, $i_{Na}$, $i_K$, $i_{leak}$ and the synaptic current $i_{syn}$.

$$C \frac{dV}{dt} = -i_{Na} - i_K - i_{leak} - i_{syn}$$  \hspace{1cm} (2.10)

$C$: The membrane capacitance

Table 2.1 lists the parameters and equations that are used to model each E-cell:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{Na}$</td>
<td>-55mV</td>
<td>$\alpha_m(V) = \frac{1.1(V + 45)}{1 - \exp\left(\frac{V + 45}{20}\right)}$</td>
</tr>
<tr>
<td>$E_K$</td>
<td>-90mV</td>
<td>$\beta_m(V) = \frac{23(V + 50)}{1 - \exp\left(\frac{V + 50}{25}\right)}$</td>
</tr>
<tr>
<td>$E_{leak}$</td>
<td>-60mV</td>
<td>$h_\infty(V) = \frac{1}{1 + \exp\left(\frac{V - 40}{20}\right)}$</td>
</tr>
<tr>
<td>$g_{Na}$</td>
<td>35mS.cm$^{-2}$</td>
<td>$\tau_h(V) = \frac{72}{(1 + \exp\left(-\frac{V - 70}{10}\right)) \cdot (1 + \exp\left(V - 40\right))}$</td>
</tr>
<tr>
<td>$g_K$</td>
<td>9mS.cm$^{-2}$</td>
<td>$n_\infty(V) = \frac{1}{1 + \exp\left(-\frac{V - 10}{10}\right)}$</td>
</tr>
<tr>
<td>$g_{leak}$</td>
<td>0.1mS.cm$^{-2}$</td>
<td>$\tau_n(V) = \frac{9.4}{(1 + \exp\left(-\frac{V - 70}{10}\right)) \cdot (1 + \exp\left(V - 40\right))}$</td>
</tr>
<tr>
<td>$C$</td>
<td></td>
<td>$1 \mu F.cm^{-2}$</td>
</tr>
</tbody>
</table>

The model for the I-cell is taken from the work by Wang and Buzsaki [88] which in principle is similar to the model of the E-cell. The differences are as follows:

1. The activation of the sodium channels is fast; the $m$ variable is replaced by its steady state value:

$$i_{Na} = g_{Na}m^3_{\infty}h(V - E_{Na})$$  \hspace{1cm} (2.11)

2. A normalization factor, $\phi$ has been incorporated in the $h$ and $n$ rate constants, which will effectively change the time constant of these gating variables and is typically used to model the temperature dependence of these rate constants:

$$1/\phi \frac{dh}{dt} = \alpha_h(V).(1 - h) - \beta_h(V).h$$  \hspace{1cm} (2.12)

$$1/\phi \frac{dn}{dt} = \alpha_n(V).(1 - n) - \beta_n(V).n$$  \hspace{1cm} (2.13)
Figure 2.5: Steady-state curves of the gating variables for the E-cell model (a), and for the I-cell model (b), as a function of the membrane potential $V$ for sodium activation, $m_{ss}$ (same as $m_{\infty}$; in blue) and inactivation $h_{ss}$ (same as $h_{\infty}$; in green) and potassium activation $n_{ss}$, (same as $n_{\infty}$; in red).

The other differential equations that characterize the I-cell are similar to those of the E-cells and are used in conjunction with the following equations/parameters:

<table>
<thead>
<tr>
<th>Equation/Parameter</th>
<th>Value/Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{Na}$</td>
<td>$-55mV$</td>
</tr>
<tr>
<td>$E_{K}$</td>
<td>$-90mV$</td>
</tr>
<tr>
<td>$g_{Na}$</td>
<td>$35mS.cm^{-2}$</td>
</tr>
<tr>
<td>$g_{K}$</td>
<td>$9mS.cm^{-2}$</td>
</tr>
<tr>
<td>$g_{leak}$</td>
<td>$0.1mS.cm^{-2}$</td>
</tr>
<tr>
<td>$C$</td>
<td>$1\mu F.cm^{-2}$</td>
</tr>
</tbody>
</table>

The activation/inactivation steady state responses for both the E-cell and the I-cell model are shown in Fig 2.5.

The dynamics of the synaptic connections will be described in the next section, but before that, it is important to characterize the response of the isolated model neurons to an artificial injected current. For
this purpose, in our model, an artificial current, $i_{bias}$, is injected into the model neuron:

$$C \frac{dV}{dt} = i_{bias} - i_{Na} - i_K - i_{leak}$$

(2.14)

$i_{Na}$, $i_K$ and $i_{leak}$ are replaced by Equ 2.7, 2.8 and 2.9 respectively and the system of four differential equations (with $m$, $n$, $h$ and the cell voltage, $V$ as the four dynamical variables) are numerically solved.

When constant current is injected into the E-cell model, upto $i_{bias} = 2.40 \mu A.cm^{-2}$, the cell does not fire. At the threshold value of $i_{bias} = 2.40 \mu A.cm^{-2}$, the cell undergoes a Hopf bifurcation and starts to generate action potentials at a frequency of 44.55 Hz. Increasing the bias current beyond this threshold value increases the firing frequency (Fig 2.6a). The frequency of firing can go well above 100 Hz.

Fig 2.6b shows the same frequency versus bias current ($f - I$) curve for the I-cell model where the current threshold is approximately $0.20 \mu A.cm^{-2}$. The $f - I$ curve for the I-cell shows that the model can fire up to frequencies as high as 400 Hz and that it has a high sensitivity to near-threshold currents.

### 2.1.3 Synaptic Connections

In modeling small network of interconnected cells, the overall synaptic current is generally divided between two components. First is the input current that is due to the nonspecific background activity,
Figure 2.7: Two state kinetic model of the receptor ionic channels with $\alpha_{\text{rec}}$ and $\beta_{\text{rec}}$ as the forward and backward rate constants. The channel is assumed to be in either of the open or closed states. $nT$ represents $n$ molecules of the neurotransmitter $T$, that transiently bind to the channel and lead to its opening.

i.e. bias current. If we assume that individual synaptic terminals are activated by time-independent Poisson processes with spikes rates that are low relative to the membrane time constant, $\tau_m$, and also that the number of independent spikes arriving at different synapses are high relative to $\tau_m$, then we can approximate this bias current with a Gaussian distribution $[3]$, $\mathcal{G}$, with the appropriate mean, $\mu_{\text{bias}}$, and standard deviation, $\sigma_{\text{bias}}$:

$$i_{\text{bias}} \sim \mathcal{G}(\mu_{\text{bias}}, \sigma_{\text{bias}})$$  \hspace{1cm} (2.15)

In the model, all the E-cells experience a stochastic nonspecific background synaptic input (both Gaussian and Uniform stochastic input currents have been examined); therefore, their firing frequency is a stochastic variable that depends on the stochastic nature of this nonspecific bias current.

The second component of the synaptic input is due to the local synaptic interactions between the cells in the network. As illustrated in Fig 2.2 (and 2.3), the synaptic communication in the local network includes an excitatory input from each E-cell to the I-cell and an inhibitory input from the I-cell to all the E-cells (and also an excitatory input from each E-cell to other nearby E-cells in the small-scale model).

These synaptic currents are governed by rate constants that describe the opening and closing of the receptor channels. The simplest approximation to the behavior of these ionic channels is the two-state kinetic model of Fig 2.7, where $\alpha_{\text{rec}}$ and $\beta_{\text{rec}}$ are voltage-independent forward and backward rate constants.

$s$ is defined as the fraction of the receptors in the open state and is described by the following first-order kinetic equation:

$$\frac{ds}{dt} = \alpha_{\text{rec}}[T](1 - s) - \beta_{\text{rec}}s$$ \hspace{1cm} (2.16)

where $[T]$ is the concentration of the neurotransmitter in the synaptic cleft. This concentration in general, depends on the probability of release of the neurotransmitter at the presynaptic site. This release probability is a function of the presynaptic voltage (through the presynaptic release mechanisms). A sigmoidal function is one of the several equations that can approximate the relation between the neurotransmitter concentration $[T]$, and the presynaptic voltage $V_{\text{pre}}$ ($\Delta$ and $\Theta$ control the steepness and the
half-activation of the sigmoidal function respectively).

\[
[T] = F(V_{pre}) = \frac{1}{1 + e^{\frac{V_{pre} - V_{th}}{\Delta}}}
\]  

(2.17)

Using Ohm's law, the postsynaptic current \(i_{syn}\), can be written as:

\[
i_{syn} = g_{syn} \cdot \delta(V - E_{syn})
\]  

(2.18)

where \(g_{syn}\) is the macroscopic representative of the maximal conductance, \(E_{syn}\) the reversal potential, and \(V\) the postsynaptic membrane potential.

In the model, the EPSPs are mediated by fast AMPA receptors and the IPSPs are mediated by two types of GABA receptors, the \(GABA_{A,fast}\) and the \(GABA_{A,slow}\).

Each E-cell receives two types of synaptic input, the nonspecific background activity \(i_{bias}\) and the local fast and slow GABAergic inputs from the I-cell (for the E-cell \(i_{syn}\) is composed of \(i_{GABA_{A,fast}}\) and \(i_{GABA_{A,slow}}\)). The I-cell receives excitatory inputs from all the E-cells in the network (for I-cell, \(i_{syn}\) is the same as \(i_{AMPA}\)). Furthermore, the total synaptic current for both E-cells and the I-cell is the linear summation of individual postsynaptic currents:

For the \(j\)-th E-cell:

\[
i_{syn}^{j} = i_{GABA_{A,fast}}^{j} + i_{GABA_{A,slow}}^{j}
\]  

(2.19)

\[
i_{GABA_{A,fast}}^{j} = g_{GABA_{A,fast}}^{j} \cdot s_{GABA_{A,fast}}^{j} \cdot (V_{j} - E_{GABA_{A,fast}})
\]  

(2.20)

\[
i_{GABA_{A,slow}}^{j} = g_{GABA_{A,slow}}^{j} \cdot s_{GABA_{A,slow}}^{j} \cdot (V_{j} - E_{GABA_{A,slow}})
\]  

(2.21)

where

\(s_{GABA_{A,fast}}^{j}\) fraction of the \(GABA_{A,fast}\) receptor channels on the \(j\)-th E-cell in the open state

\(s_{GABA_{A,slow}}^{j}\) fraction of the \(GABA_{A,slow}\) receptor channels on the \(j\)-th E-cell in the open state

\(V_{j}\) membrane voltage of the \(j\)-th E-cell

and for the I-cell:

\[
i_{syn} = \sum_{k=1}^{N} i_{AMPA}^{k}
\]  

(2.22)

\[
i_{AMPA}^{k} = g_{AMPA} \cdot s_{AMPA}^{k} \cdot (V_{I-cell} - E_{AMPA})
\]  

(2.23)

where

\(s_{AMPA}^{k}\) fraction of the AMPA connections from the \(k\)-th E-cell to the I-cell in the open state

\(V_{I-cell}\) membrane voltage of the I-cell

The following are the parameters that characterize these local synaptic connections (the properties of the \(GABA_{A,fast}\) and the \(GABA_{A,slow}\) currents are taken from the measurements of Banks and Pearce [10]):

<table>
<thead>
<tr>
<th>Table 2.3: Parameters for the local synaptic connections</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
</tr>
</tbody>
</table>
For ail presynaptic sites $V = \text{OrnV}$ and $A = 2\text{mV}

<table>
<thead>
<tr>
<th>$g_{\text{AMPA}}$</th>
<th>0mV</th>
<th>$E_{\text{GABA_{A,fast}}}$</th>
<th>$-75\text{mV}$</th>
<th>$E_{\text{GABA_{A,slow}}}$</th>
<th>$-75\text{mV}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{\text{AMPA}}$</td>
<td>&gt; 2\mu S.cm$^{-2}$</td>
<td>2mA.cm$^{-2}$</td>
<td>$-75\text{mS.cm}^{-2}$</td>
<td>1mA.cm$^{-2}$</td>
<td>$-75\text{mS.cm}^{-2}$</td>
</tr>
<tr>
<td>$\alpha_{\text{AMPA}}$</td>
<td>12ms$^{-1}$</td>
<td>2.5ms$^{-1}$</td>
<td>$0.2\text{ms}^{-1}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_{\text{AMPA}}$</td>
<td>0.3ms$^{-1}$</td>
<td>0.1ms$^{-1}$</td>
<td>$0.025\text{ms}^{-1}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For all presynaptic sites $V_s = 0\text{mV}$ and $\Delta = 2\text{mV}$

2.2 Setting Up The Model

The complete model is composed of $N$ E-cells and one I-cell. For the network to generate a rhythmic behavior two conditions should be realized. First, the summed EPSPs on the I-cell should be strong enough to drive the I-cell beyond its spiking threshold so that the I-cell would fire. Second, the firing of the I-cell should inhibit all the E-cells in the network.

The maximal excitatory conductance, $g_{\text{AMPA}}$ directly effects individual EPSPs and therefore the summated EPSP. If a network with a total of $N$ E-cells is assumed, for the I-cell to fire, the lowest value for $g_{\text{AMPA}}$ would correspond to the case when all E-cells are firing and the summation of all $N$ EPSPs is just strong enough to actuate the I-cell. If $g_{\text{AMPA}}$ is decreased beyond this lower limit, the summated EPSP could not make the I-cell fire. On the other hand, increasing $g_{\text{AMPA}}$ would increase individual EPSPs and would allow for smaller number of EPSPs (smaller than $N$) to actuate the I-cell. By the same token, with higher $g_{\text{AMPA}}$, sub-populations of $n < N$ E-cells would be able to drive the I-cell to fire. The relationship between $g_{\text{AMPA}}$ and $n$ will be analyzed in subsequent chapters.

For the second condition to be satisfied, the maximal conductance of the inhibitory synaptic input is adjusted such that when the I-cell fires, it hyperpolarizes all the E-cells in the network. After the inhibitory effect wears off, a stochastic input current drives individual E-cells and initiates a new cycle.

To generate the stochastic background input current, a random number generator is used. For the Uniform distribution, $U(\eta_{\text{bias}}, \omega_{\text{bias}})$, the output of the random number generator is linearly mapped onto the target range of input currents. For the case of the Gaussian distribution, $\mathcal{N}(\mu_{\text{bias}}, \sigma_{\text{bias}})$, the output of the random number generator is channeled through the polar form of the Box-Muller algorithm, and then used to generate the appropriate Gaussian distribution. Fig 2.8 shows the distribution of 100,000 samples in a 200-binned normalized histogram (equivalent to 1 second of the simulation time; integration time step 0.01 msec.).

Various simulations are performed using different $N$s and $g_{\text{AMPA}}$. In all cases, there are $N$ E-cells and one I-cell. All E-cells as well as the single I-cell are each described by four dynamical variables, the sodium activation and inactivation, the potassium activation and the membrane voltage. These add up to $4N + 4$ differential equations. Furthermore, there are $N$ excitatory synapses ($AMPA$ connections from each E-cell to the I-cell) and 2 inhibitory synapses ($GABA_{A,fast}$ and $GABA_{A,slow}$) from the I-cell to each of the $N$ E-cells. Adding these numbers, a total of $4N + 4 + 3N = 7N + 4$ differential equations characterize

\footnote{Note that for both Gaussian and Uniform distributions, at each time step, $i_{\text{bias}}$ is not the same.}

20
the dynamics of the whole network (for the small-scale model the number of equations increases due to the E-cell/E-cell synaptic connections).

These differential equations were solved using the NNET package [41], which utilizes the C-VODE numerical integration recipe to solve Hodgkin-Huxley type differential equations. The accuracy of the results was assured by reducing either the tolerance or the time step of the numerical integration for the solution to converge.

The statistical analysis of these numerical results was performed using various relevant toolboxes in the MATLAB software package.

In the case of the small-scale model, in addition to the reciprocal connections between E-cells and the I-cell, there are local connections between nearby E-cells which model the excitatory-excitatory connections in the CA1 local networks. The behavior of these local networks will be discussed in the next chapter.

2.3 Sensitivity Analysis: Methods

The simulations are carried out using specific parameters, however both the number of state variables and the number of independent parameters that are used to characterize the network are high, hence, from a dynamical perspective, the system may well be exposed to structural instabilities; acute sensitivities to the parameters used. To make sure that the network, while in the desired state, is not exposed to such instabilities, one should investigate the behavior of the network in a parameter space around the specific
parameters used to carry out the simulations; i.e. central values.

The important parameters in the mediation of the delta rhythm, are the ones that directly effect the spike generation mechanism of individual E-cells and the inhibitory rebound from the I-cell back onto the E-cells. To perform a sensitivity analysis, we have investigated the behavior of the network in the parameter subspace characterized by these principal parameters. The sodium and potassium maximal conductance, $g_{Na}$ and $g_K$, and the average nonspecific background activity $\mu_{bias}$, are the important parameters that control the firing of the E-cells. After the E-cells fire, the maximal excitatory synaptic conductance, $g_{AMPA}$, is the principal parameter in controlling the effectiveness of the EPSP. The strength of the inhibitory rebound is controlled by the maximal conductance of the inhibitory synaptic currents, $g_{GABA_{A_{fast}}}$ and $g_{GABA_{A_{slow}}}$.

The effect of $g_{AMPA}$ is studied in conjunction with $N$, the total number of E-cells in the network, and is shown to be important in controlling the robustness of the rhythm. The five dimensional parameter subspace characterized by the remaining five parameters, $g_{Na}$, $g_K$, $\mu_{bias}$, $g_{GABA_{A_{fast}}}$ and $g_{GABA_{A_{slow}}}$ is 7-binned to 90%, 95%, 98%, 100%, 102%, 105% and 110% of the central values and the network behavior is investigated by running a total of $7^5$ simulations on these points within the parameter subspace.
Chapter 3

Simulation Results

The experimental data suggests that the slow field rhythm recorded in the extracellular region of CA1 might be due to synchronized and cyclic inhibition of multiple pyramidal cells in the vicinity of the recording site. However, fast glutamate transmission via AMPA receptors is also necessary for the induction of this rhythm.

In this chapter, using a modeling approach, we report a network behavior in CA1 that can account for the stable generation of this slow rhythmic activity. It will be shown that the mechanism for the induction of this rhythm depends on the feedforward/feedback connections within the CA1 circuitry; i.e. the connections between pyramidal cells and interneurons. Furthermore, some of the characteristics of this rhythmic activity with regard to its frequency and its variability will be discussed.

3.1 Model Behavior: Reset signal

In the network model, firing of the I-cell induces a strong inhibitory signal that synchronously hyperpolarizes all the E-cells in the network and manifests itself as a peak in the extracellular field potential. After the hyperpolarizing effect of the GABAergic currents wears off, the repolarization of the E-cells brings the field potential back to its basal level. Subsequently, the synaptic input to the E-cells gradually increases their membrane potential to the point where they start firing. The firing of the E-cells first depolarizes and then excites the I-cell. The firing of the I-cell initiates a new cycle in the network (Fig 3.1).

In the sections to follow, the results of the simulations in the face of two different modes of synaptic activity, i.e. stochastic and deterministic, will be presented. Particularly, the effects of the number of the E-cells in the network in conjunction with the excitability of the I-cell will be discussed.

3.2 Deterministic mode

In the deterministic mode, the nonspecific background synaptic activity (the bias current) is assumed
Figure 3.1: A schematic diagram illustrating the recurring cycle of events in the network model while engaged in the rhythm behavior. Each turn around the loop corresponds to one cycle of the rhythm; the field onset coincides with (slightly lags) the hyperpolarisation of the E-cells.

to have a constant deterministic value. In this scheme, due to a strong enough synaptic bias current, the E-cells are able to restart firing after each round of inhibition. Furthermore, the homogeneity of the E-cells, i.e. exact similar intrinsic and synaptic properties, guarantees a perfect synchronous behavior where all the E-cells fire together. The network period is governed by the time it takes for the E-cells to fire after inhibition. As will be shown, in this mode, as long as the I-cell fires, the size of the network has no effect on the network period; the frequency is constant and there is no variability in the rhythm.

3.2.1 Two-Cell Network

The two-cell model is composed of one E-cell and one I-cell, reciprocally connected. Parameters used are those that were presented in the previous chapter. An epoch of the network behavior with $g_{AMPA} = 0.02 mS.cm^{-2}$ and $i_{bias} = 4.30 \mu A.cm^{-2}$ is illustrated in Fig 3.2. In this case the frequency of the network is approximately $1.88 Hz$.

Above a certain lower limit (current threshold), increasing $i_{bias}$ increases the network frequency. Fig 3.3 (solid line) illustrates the relationship between the frequency of the two-cell network and the input bias current to the E-cell. At $i_{bias} \approx 4.18 \mu A.cm^{-2}$ the network undergoes a qualitative dynamical change where the behavior changes from quiescent to an oscillatory mode with a frequency slightly lower than $0.1 Hz$. The frequency of these oscillations increases with increasing $i_{bias}$ such that the network frequency can range from low delta to theta band.

Comparing the two-cell network behavior with the $f-I$ response of a single E-cell, the importance
of the feedback mechanism becomes evident. An E-cell model (without the reciprocal I-cell connection) undergoes a Hopf-bifurcation at $i_{\text{bias}} \approx 2.40 \mu A.cm^{-2}$ where it starts to fire at frequencies above $40 Hz$ (Fig 3.3 dashed line). In contrast, the two-cell model starts to oscillate at $i_{\text{bias}} \approx 4.18 \mu A.cm^{-2}$ and the initial frequency of the rhythm is in the slow delta band. The dynamical effect of the inhibitory feedback signal from the I-cell is essential for the induction of this slow rhythm.

To analyze the behavior of larger networks, it is important to note that the single E-cell in this two-cell combination is able to drive the I-cell above threshold only if the maximal conductance of the excitatory synapse, $g_{\text{AMPa}}$, is strong enough to generate the appropriate EPSP. For the parameters used in the model, the lower limit for $g_{\text{AMPa}}$ is approximately $0.011 mS.cm^{-2}$. Increasing $g_{\text{AMPa}}$ beyond this limiting threshold has no effect on the network behavior, except for a slight change in the frequency (Fig 3.4).

In a regime close to the threshold of $g_{\text{AMPa}}$, the E-cell generates multiple action potentials before driving the I-cell and the duration of this burst-like activity changes with the value of $g_{\text{AMPa}}$. Fig 3.5 shows that the burst duration decreases when $g_{\text{AMPa}}$ is increased. This burst-like activity might have implications for strengthening/weakening of the synaptic connections, however, the study of such effects are beyond the scope of the current work.
Figure 3.3: $f - I$ characteristics of a single E-cell (dashed line) and an E-cell reciprocally connected to the I-cell; i.e. two cell network (solid line) for a range of input bias currents. Both single E-cell and two-cell networks undergo Hopf-bifurcation and change their behavior from silent non-firing to oscillatory. In the two-cell configuration, the current threshold is 4.18 $\mu A.cm^{-2}$ and the oscillations are in the delta and theta range (starting at 0.09 Hz), whereas for the single E-cell the threshold is 2.40 $\mu A.cm^{-2}$ and the oscillations start at much higher frequencies (44.55 Hz). The response of the two-cell network is only illustrated for input currents $\leq 6\mu A.cm^{-2}$.

3.2.2 $N$ Cell Network

In the deterministic mode, the effect of increasing the number of E-cells would only be to increase the summed EPSP on the postsynaptic site; i.e. the I-cell. However, for the I-cell, the $f - I$ relationship is very steep near threshold (Fig 2.6b) and the I-cell has a relatively short latency. Taking these two factors into account, it can be concluded that as long as the summed EPSP can drive the I-cell to fire, the number of individual EPSPs has little effect.

Fig 3.6 shows an epoch of the network behavior with five E-cells, $N = 5$. Compared to the behavior of the two-cell network, the frequency of the network does not change significantly (1.99 Hz vs. 1.88 for the two-cell network) and there is no variability in the behavior. By studying the behavior of larger networks ($N = 1$ to 20), it has been confirmed that, in the deterministic mode, the frequency of the rhythm is almost independent of the network size (except when $g_{AMPA}$ is close to its threshold value where the burst-like activity in the E-cell is evident).

However, there is one notable distinction. In a two-cell network there is a threshold of 0.011$mS.cm^{-2}$ for $g_{AMPA}$ (Fig 3.4). Increasing the number of E-cells (larger networks), increases the overall EPSP on the I-cell, and therefore, decreases the threshold for $g_{AMPA}$. In other words, there will be a larger range of $g_{AMPA}$s where the network can generate the slow rhythmic behavior. Fig 3.7 shows the effect of increasing $N$ on this lower limit. Due to various nonlinearities, including the effect of the burst-like activity of the
The frequency of the two-cell network vs. the maximal excitatory conductance of the I-cell, $g_{AMPA}$. The network starts to exhibit the rhythmic activity for values of $g_{AMPA} \geq 0.011mS\cdot cm^{-2}$ (lowest frequency $\approx 1.48Hz$). The frequency has its highest sensitivity to $g_{AMPA}$ that are close to threshold, above which the frequency asymptotically converges to slightly higher values (highest frequency $\approx 2.02Hz$). Dots illustrate the actual data points that were collected from simulations.

E-cell close to the limiting value of $g_{AMPA}$, this relationship is not linear.

The deterministic model gives a general understanding with regard to the generation of the delta rhythm in the model, however, the constant synaptic input to the E-cells is highly artificial. In this mode, apart from the intrinsic properties, the frequency of the network is primarily controlled by $i_{bias}$ and is almost independent of the network size $N$, and $g_{AMPA}$. On the other hand, $N$ controls the range of $g_{AMPA}$s that could maintain the rhythm in the network. The rhythm is essentially due to the dynamical feedback from the I-cell, yet the behavior is spatially static in the sense that all E-cell are synchronous and exhibit the exact same behavior. In the next section we turn our focus to the more realistic case where the synaptic background activity is nondeterministic and heterogeneous.

### 3.3 Stochastic mode

The stochastic mode, from a practical point of view, is identical to the deterministic mode except for the background synaptic component which is stochastic. This stochastic input, as mentioned in the previous chapter, reflects the nonspecific synaptic current induced by thousands of synaptic inputs. The model incorporates two types of distribution for this component, Gaussian $\mathcal{N}(\mu_{bias}, \sigma_{bias})$ and Uniform $\mathcal{U}(\eta_{bias}, \omega_{bias})$.

In the stochastic mode, after firing of the I-cell, similar to the deterministic mode, all E-cells go to a hyperpolarized state. However, after the effect of the inhibitory input wears off, the depolarization of
Individual E-cells follow the stochastic synaptic input and therefore, the time when they generate their next action potential is also stochastic. At each cycle the firing of the I-cell is preceded by the firing of a number of E-cells. For instance let us assume that there are \( N = 5 \) E-cells in the network and \( n = 3 \) of them must fire to actuate the I-cell. E-cells are driven by a heterogeneous stochastic synaptic input, therefore the firing time of individual E-cells would in general be different and independent of one another. The duration of a single cycle is determined by two consecutive firings of the I-cell which in this example is equal to the time when 3 of the E-cells start firing. However, since the E-cells all behave stochastically, the network does not exhibit a deterministic behavior and successive firing times of the I-cell changes from cycle to cycle.

The consequence of this stochasticity is twofold. First, that the network will have a variable frequency, and second, that the period of the network is dependent on both the network size and the number of E-cells that are needed to drive the I-cell. Another interesting result of this variability is that now there is a spatial dynamicity in the sense that from the total \( N \) E-cells in the network, in each cycle a different subset of E-cells can take part in the rhythm. This is what we call the Dynamical Feedback Mechanism, where temporal dynamicity is due to the inhibitory feedback and spatial dynamicity is due to the variability in the behavior of individual E-cells. In this paradigm, in each cycle, E-cells can dynamically form different active sub-populations to drive the I-cell. Moreover, the feedback signal from the I-cell can provide the whole population with an appropriate time reference; i.e. the rhythm. In chapter five, possible implications of such dynamicity will be further discussed.

A definition of the Dynamical Feedback Mechanism in the context of the present work is as follows:
Figure 3.6: The behavior of all the cells in a network of 5 E-cells reciprocally connected to the I-cell for a duration of 4 seconds using a deterministic bias current ($i_{bias} = 4.30\mu A.cm^{-2}$ and $g_{AMP} = 0.02mS.cm^{-2}$). E-cells are homogeneous and synchronized. The I-cell fires just after the firing of the E-cells. Here, the frequency of the oscillations is 1.99 Hz.

**Dynamical Feedback Mechanism**

The Dynamical Feedback Mechanism is associated with the behavior of a network where homogeneous excitatory cells are reciprocally connected to an entrained or synchronized interneuronal network. The excitatory cells, as a result of their heterogeneous stochastic input increase and/or synchronize their activity to form spatially dynamic sub-populations of firing E-cells that are able to drive the interneuronal population. Excitation of the interneuronal population generates a strong synchronous inhibitory signal that feeds back onto all the E-cells. This feedback signal acts as a reset mechanism to hyperpolarize the E-cells and therefore to provide them with a time reference from which they once again, due to their synaptic input, can form new active sub-populations. The Dynamical Feedback Mechanism is characterized by the interaction between the *dynamic excitatory sub-populations* and the *inhibitory feedback signal* which results in an emergent rhythmic behavior in the network.
Figure 3.7: The relationship between the number of E-cells in the network and the lowest $g_{AMPA}$ that could maintain the rhythmic behavior. Data points for several simulations (dots) are linearly interpolated. The result shows a nonlinear relationship between the two where the lower limit on $g_{AMPA}$ is lowered when there are more E-cells in the network. The smallest range for $g_{AMPA}$ corresponds to the case where $N = 1$ where the threshold for $g_{AMPA}$ is at its highest (0.011 mS.cm$^{-2}$).

In the following sections, $N$ would refer to the total number of E-cells in the network and $n$ would refer to the minimum number of firing E-cells that can induce the feedback signal, i.e. the firing of the I-cell.

3.3.1 Two-Cell Network, $N = 1, n = 1$

The stochastic model for the two-cell network, except for the bias current to the E-cell (which is stochastic), is similar to the deterministic two-cell model. As mentioned above, in this scheme the network frequency will also exhibit stochastic behavior. An epoch of the network behavior with $i_{bias} = \mathcal{N}(4.2, 0.2)\mu A.cm^{-2}$ and $g_{AMPA} = 0.015mS.cm^{-2}$, is illustrated in Fig 3.8. The interspike interval (ISI) is different for each cycle although rhythmicity (in the low frequency range) is observable.

To characterize this rhythmicity, a statistical approach has been adopted. The per-cycle ISI is taken as the period of the network which changes stochastically for each cycle. A large sample of per-cycle ISIs is obtained by running the simulation for a total of 2000 seconds in a series of 20 100-second runs. The normalized histogram of these samples would correspond to the probability distribution of the network period. The histogram is 26-binned and the data are further smoothed by spline (cubic) interpolation. These steps are illustrated in Fig 3.9.

The final ISI probability distribution, $P_{ISI}$ shows that in the two-cell network, the per-cycle ISI
Figure 3.8: An epoch of the E-cell (above) and the I-cell (below) behavior in a two-cell network configuration for a duration of 10 seconds with $g_{AMP} = 0.02 \text{mS.cm}^{-2}$ and $i_{bias} = 9(4.2, 0.2)\mu A.cm^{-2}$. The network exhibits an oscillatory pattern of activity with a stochastic period. The cycle is reset by the firing of the I-cell which has a mean and standard deviation of 553.24 and 78.99 msec respectively. The E-cell fires multiple action potentials to excite the I-cell. Subsequently, the firing of the I-cell hyperpolarizes the E-cell.

assumes values between 350 and 950 milliseconds which correspond to instantaneous frequencies of 1.05 to 2.85 Hz (Fig 3.10).

This probability distribution in general depends on the distribution of the input signal. The procedure described in Fig 3.9 is used to construct the $ISI$ probability distribution, $P_{ISI}$, of the network in the face of several other Gaussian distributed inputs. For this purpose, assuming a central value of $\mu_{bias} = 4.3$, $\sigma_{bias} = 0.2$, Gaussian distributions with means and standard deviations of 90%, 95%, 100%, 105%, 110% of this central value are fed into the E-cell as the nonspecific background synaptic input. Samples of the cycle period are obtained from a series of 500-second runs. The data are 13-binned, interpolated, corrected for negative values and finally normalized to generate the results presented in Fig 3.11a-o.

These results show the rich dynamics that is inherent in a simple two-cell stochastic network. The interaction between the stochastic input and the dynamical loop of the two-cell network produces a whole repertoire of different $ISI$ distributions. For input currents with a mean of either 90% or 95% of the central value, the network does not exhibit rhythmic activity. For higher means, the network engages in a rhythmic activity and the $ISI$ distribution exhibits notable characteristics. Some cases are fairly similar to a Gaussian distribution except from a slight skewness with a bias towards lower values (Fig 3.11a,c). For relatively higher mean values (110% of the central value), in most cases, the $ISI$ distribution becomes more symmetrical and except from a few minor side-bands the $ISI$ values are concentrated in a narrow bell-shaped distribution (Fig 3.11l-o). There are also situations where the distribution is clearly multimodal (Fig3.11b,d-k), from
Figure 3.9: A schematic diagram showing the steps in constructing the probability distribution function of the two-cell network period. The results of several runs of a two-cell network are used to construct the probability distribution function associated with the Inter-Spike Interval (ISI) of the I-cell, which characterizes the two-cell network period. Samples of the I-cell ISI are collected from a total of 20 distinct 100-second runs, (each with a different stochastic Gaussian input) (a), and the histogram of the samples are generated (b). The histogram is further smoothed using Matlab spline function (cubic interpolation) and normalized (to make the total area under the distribution curve equal to one) to represent the desired probability distribution function, $P_{ISI}$, of the network period in the two-cell configuration (c).
Figure 3.10: The probability distribution function of the two-cell network period calculated from the samples of the I-cell ISI. The distribution is a numerical reconstruction of the ISI data collected from several runs of the network activity. For methods refer to Fig 3.9.

marked bimodality (Fig 3.11f,g) to quadrimodality (Fig 3.11d,h). In chapter four, after the introduction of a phenomenological model, the importance of such a rich dynamical response in the face of various $N$s and $g_{AMPAs}$ will be investigated.

Table 3.1 lists the means ($\mu_{ISI}$) and the standard deviations ($\sigma_{ISI}$) of the network period for various different Gaussian input bias currents. For the range of inputs investigated, both the mean and the standard deviation of the $ISI$ are inversely related to the mean of the Gaussian distribution such that increasing $\mu_{bias}$ decreases the network period and its variability.

<table>
<thead>
<tr>
<th>$\mu_{bias}$ (%)</th>
<th>$\sigma_{bias}$ (%)</th>
<th>90</th>
<th>95</th>
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<th>105</th>
<th>110</th>
</tr>
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<tbody>
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<td>90, 95</td>
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<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{ISI}$</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>100</td>
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<td>325.85</td>
<td>371.89</td>
<td>319.95</td>
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<tr>
<td></td>
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</tr>
<tr>
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<td>14.31</td>
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</tbody>
</table>
Figure 3.11: The ISI probability distribution $P_{ISI}$ of the two-cell network in the face of several different Gaussian distributed input bias currents: Mean values change from $\mu_{bias_0} = 4.3\mu A.cm^{-2}$ in the first column (a-e) to 105% and 110% of $\mu_{bias_0}$ in second (f-j) and third column (k-o). Each row corresponds to a particular value for the standard deviation of the input current: 90% (of the central value, $\sigma_{bias_0}$) for the first row (a,f,k), 95% for the second row (b,g,i) and 100%, 105% and 110% for the third (c,h,m), fourth (d,i,n) and fifth row (e,j,o) in that order ($\sigma_{bias_0} = 0.2\mu A.cm^{-2}$). Depending on the input, the distributions have either unimodal or multimodal characteristics.
The same analysis has been performed when the input bias current is taken from a Uniform distribution \( U(\mu_{bias}, \sigma_{bias}) \), the results of which are reported in Appendix C. From the results of both distributions (Gaussian and Uniform), it is evident that the generation of the rhythm in the two-cell network in general, does not depend on the distribution of the bias current whereas its modal structure does.

The two-cell network shows some of the important properties of the rhythm in the stochastic mode but because there is only one E-cell in the network the possibility of formations of dynamical E-cell sub-populations is absent. Moreover, the relationships between the network size, the mean period and the robustness of the rhythm can only be explored in the analysis of larger networks.

### 3.3.2 N Cell Network, \( N > 1, n < N \)

When there are more than one E-cell in the network, the firing E-cells in the network can vary from one cycle to the other. For instance, when there are 2 E-cells, each of them can independently drive the I-cell. An example of this is illustrated in Fig 3.12a, where the network has 5 E-cells and \( g_{AMPA} \) is chosen so that any of the E-cells can actuate the I-cell; i.e. \( n = 1 \) (\( g_{AMPA} = 0.02\text{mS.cm}^{-2} \)).

In the stochastic mode however, changing the value of the \( g_{AMPA} \) affects the network behavior. Fig 3.12b shows the same network of 5 E-cells, but with a weaker \( g_{AMPA} \) (\( g_{AMPA} = 0.008\text{mS.cm}^{-2} \)). In this case, at least two of the E-cells should start firing before the feedback signal is induced, i.e. \( n = 2 \). Unlike the deterministic mode, the firing time of the second E-cell, in general, would be different from the first one, hence the network period will be different for \( n = 2 \).

Decreasing \( g_{AMPA} \) would increase \( n \) to 3, 4 and 5 E-cells, however, there is a lower limit for \( g_{AMPA} \) beyond which the network will lose its ability to generate rhythmic behavior. This is due to the fact that \( g_{AMPA} \) modulates the amplitude of the EPSPs and lowering it below a certain value, would result in EPSPs that are too weak to drive the I-cell membrane potential to its spiking threshold, even when all E-cells are firing. This lower limit on the excitatory maximal conductance, similar to the deterministic mode, is dependent on the number E-cells in the network, \( N \). The lower the conductance, the larger the number of E-cells needed in the network to generate the rhythmic activity. Fig 3.13 shows the relationship between \( g_{AMPA} \) and the minimum \( N \) (predicted by the results of the deterministic mode (Fig 3.7)). It is important to note that \( g_{AMPA} \) does not specify the number of firing E-cells in each cycle but puts a lower limit on it. In other words, in each cycle, the number of firing E-cells can be anything from this minimum to the total number of E-cells, \( N \). Furthermore, the edge points are only approximations since the results are inferred from the non-stochastic data.

To further study the effect of \( g_{AMPA} \) and \( N \) on the network period, various simulations have been
Figure 3.12: An epoch of the network behavior with five E-cells and one I-cell. In (a), \( g_{AMPA} \) is chosen so that any of the E-cells can drive the I-cell to fire; i.e. \( n = 1 \) \( (g_{AMPA} = 0.02mS.cm^{-2}) \) whereas in (b) \( g_{AMPA} = 0.008mS.cm^{-2} \) and \( n = 2 \). The input current is stochastic with a Gaussian distribution \( (\mu_{bias} = 4.3 \text{ and } \sigma_{bias} = 0.2\mu A.cm^{-2}) \). The rhythm has a stochastic period with a mean/STD of 326.84/20.82 msec. in (a) and 368.92/26.05 msec. in (b).

carried out. As illustrated in Fig 3.14 and Fig 3.15, changing either \( g_{AMPA} \) or \( N \), would change both the mean and the standard deviation of the network period. In Fig 3.14, as an example, \( g_{AMPA} \) is tuned so that only 2 E-cells would be enough to drive the I-cell to fire, i.e. \( n = 2 \). Increasing the number of E-cells in this network, decreases both the mean and the standard deviation (shown as errorbars) of the network period (Increasing \( N \) from 2 to 10, decreases \( \mu_{ISI} \) from 791.42 to 575.53 and \( \sigma_{ISI} \) from 243.48 to 52.47 milliseconds). Since increasing \( N \), decreases the \( ISI \) variability, it can be interpreted as a network property that can control the robustness of the rhythm.

Fig 3.15 illustrates the dependence of the network period on \( g_{AMPA} \). In this case the network consists of \( N = 10 \) E-cells and the network period is shown as a function of \( g_{AMPA} \). As shown in the figure, increasing \( g_{AMPA} \) tenfold from 0.002 to 0.020 mS.cm\(^{-2} \), decreases \( \mu_{ISI} \) from 849.03 to 499.66 and \( \sigma_{ISI} \) from 85.41 to 67.20 milliseconds.

Another effect of small changes in \( g_{AMPA} \) is in controlling the duration of the burst-like activity of the sub-populations of E-cells that fire in each cycle. This quality was demonstrated in the non-stochastic model as well.
Figure 3.13: Minimum number of firing E-cells, n, that could excite the I-cell vs. the maximal excitatory conductance of the I-cell, $g_{\text{AMPA}}$. Increasing $g_{\text{AMPA}}$ would decrease the number of E-cells that are needed to make the I-cell fire; i.e. maintain the rhythm. The edge points are based on the results of a network with deterministic input current.

In general, all the characteristics of the two-cell network are directly applicable to the case of larger networks, however, for networks with $N > 1$, there is a larger dynamical range of $g_{\text{AMPA}}$ where the slow delta rhythm can be maintained. In the model, higher $g_{\text{AMPA}}$ would strengthen the effective EPSP and would therefore facilitate the excitation of the I-cell. On the other hand, $g_{\text{AMPA}}$ determines the minimum number of firing E-cells, n, that can actuate the I-cell and as such, either n or $g_{\text{AMPA}}$ can be interpreted as a measure of the excitation of the I-cell; lower (higher) ns correspond to higher (lower) levels of excitability in the I-cell (Fig 3.13).

Using this alternative interpretation, we can recapitulate our results for a network with $N > 1$ as follows: Changes in the number of E-cells that participate in the generation of the network rhythm, $N$, and/or changes in the excitability of the interneuronal population, n, can control the statistical properties of the network period. Moreover, in larger networks, rhythmic behavior emerges as long as different groups of more than n E-cells can form active subpopulations to induce the inhibitory feedback signal.

Several numerical simulations have been carried out to identify the properties of the network behavior as related to these two parameters, $N$ and n. For all simulations, a Gaussian input with $\mu_{\text{bias}} = 4.2$ and $\sigma_{\text{bias}} = 0.2 \mu A.cm^{-2}$ has been used and the simulations have run for a duration of 50 seconds. A summary of the results is illustrated in Fig 3.16 and 3.17.
Figure 3.14: The ISI of the I-cell (the network period) vs. the total number of E-cells $N$, in the network for when a minimum of two firing E-cells could drive the I-cell to threshold and maintain the rhythm; i.e. $n = 2$ ($g_{AMPA} = 0.008\, mS/cm^{2}$, refer to Fig 3.13). ISI mean and standard deviation (errorbars) both decrease with increasing $N$. The data show the result of several simulations with $N = 2, 3, ..., 10$ where each E-cell is driven by a stochastic bias current with a Gaussian distribution ($\mu_{bias} = 4.2$, $\sigma_{bias} = 0.2\, \mu A/cm^{2}$).

For different values of $n$, increasing $N$ has a unimodal effect on both the network period and its variability. As illustrated in Fig 3.16, as the number of E-cells that take part in the rhythm increases, the network period, $\mu_{ISI}$, slightly decreases and also the rhythm becomes more robust (the variability in the network period, $\sigma_{ISI}$, decreases). On the other hand, having a fixed number of E-cells in the network, increasing $n$ (making the I-cell less excitable by decreasing $g_{AMPA}$), increases the network period and its variability (Fig 3.17). In other words, in networks with a fixed number of E-cells, the rhythm can lose its robustness when the I-cell lowers its excitability.

However, in a more general view, neither the number of E-cells nor the interneuronal excitability is fixed. In such a dynamical framework, both the interneuronal excitability and the number of E-cells that are recruited in the feedback mechanism can control the statistical properties of the rhythm. In the Dynamical Feedback Mechanism, lower levels of excitability in the I-cell can be compensated by larger networks (more E-cells), which would also result in more robust rhythms. This effect is shown in the pathway in Fig 3.18, which is a reconstruction of Fig 3.16, without the errorbars. At point A, network period is approximately
Figure 3.15: The ISI of the I-cell (the network period) vs. the maximal conductance of the I-cell $g_{AMPA}$, in the network of ten E-cells reciprocally connected to the I-cell. The mean ISI decreases whereas the standard deviation (errorbars) first decreases and then increases with increasing $g_{AMPA}$. The data show the results of several simulations with $g_{AMPA} = 0.002$ to $0.02 mS.cm^{-2}$ where each E-cell is driven by a stochastic bias current with a Gaussian distribution ($\mu_{bias} = 4.2, \sigma_{bias} = 0.2 \mu A.cm^{-2}$).

650 msec., and the variability in the rhythm is relatively high (due to a large standard deviation). A decrease in the excitability of the I-cell followed by an increase in the number of E-cells ($N$) would move point A to B and then further to C. At point C, the network period is back to its original 650 msec., however the rhythm has become more robust (lower standard deviation). Repeating the same process by a decrease in the I-cell excitability, followed by an increase in the number of E-cells, would move the activity from C to D and then to point E. At this point once again, the network is exhibiting rhythmic activity with a mean period of 650 msec. but with a much lower variability (for variabilities refer to errorbars in Fig 3.16). The mechanism described in this hypothetical pathway may account for the emergence of robust rhythms from an otherwise broad distribution of network periods.

In chapter four, we devise a phenomenological model to investigate the effects of these two parameters, $N$ and $n$, on the network rhythmicity, but before that, it is imperative to test the stability of these results within the parameter space or rather, the sensitivity of the network behavior to the particular parameters used for the simulations.
Figure 3.16: The ISI of the I-cell (also the network period) vs. the number of E-cells, \( N \), in the network for when a minimum of \( n = 1 \) (black), \( n = 2 \) (blue), \( n = 3 \) (red) and \( n = 5 \) (green) firing E-cells could drive the I-cell to threshold and maintain the rhythm. For \( n = 1, 2, 3 \) and 5, \( E_{AMPA} \) was chosen to be 0.015, 0.008, 0.005 and 0.003 mS cm\(^{-2} \) respectively (refer to Fig3.13). The mean ISI as well as its standard deviation (error bars; note that for visualisation purposes, only the positive half of the error bars are shown) decreases with increasing \( N \). The data show the results of several simulations with \( N = n, n + 1, \ldots, \text{etc.} \). In all runs, each E-cell was driven by a stochastic bias current with a Gaussian distribution (\( \mu_{\text{bias}} = 4.2 \) and \( \sigma_{\text{bias}} = 0.2 \mu \text{A} \text{cm}^{-2} \)).
Figure 3.17: The ISI of the I-cell (also the network period) vs. the minimum number of E-cells that can maintain the rhythm, n, in the network with a total of $N = 5$ (blue), $N = 7$ (red) and $N = 12$ (green) E-cells. The data points correspond to $n = 1, 2, 3$ and 5 where $\theta_{AMP} = 0.015, 0.008, 0.005$ and 0.003mS.cm$^{-2}$ respectively (refer to Fig3.13). The mean ISI as well as its standard deviation (errorbars; as in Fig 3.16, only the positive half of the errorbars are shown) increases with increasing n. In all simulations each E-cell was driven by a stochastic bias current with a Gaussian distribution ($\mu_{bias} = 4.2$ and $\sigma_{bias} = 0.2\mu A.cm^{-2}$).
Figure 3.18: The figure shows the network period (also the ISI of the I-cell) vs. the total number of E-cells, N, in the network for three cases where either 2, 3 or 5 E-cells can drive the I-cell to fire. The pathway from A to E, depicts a hypothetical pathway through which the network can extract a relatively robust rhythm (point E), from a highly variable rhythmic activity (point A). The move from A to B and C to D correspond to a decrease in the excitability of the I-cell whereas B to C and D to E, illustrate increases in the number of E-cells that are mediating the rhythm. Through this hypothetical pathway, without any change in the network period, the system can reach a more robust rhythmic behavior (refer to Fig 3.16 for a comparison of the standard deviations at point A and point E).
Dynamical Feedback Mechanism

Stochastic Synaptic Bias Current

\[ \mu_{\text{bias}} \]

\[ g_{\text{Na}} \quad g_{K} \]

Spatially Dynamic
Active Excitatory Subpopulations

Biphasic
GABAergic
inhibitory signal

\[ g_{\text{GABA}_{\text{fast}}} \]
\[ g_{\text{GABA}_{\text{slow}}} \]
\[ g_{\text{AMPA}} \]

Inhibitory Feedback from
Synchronous Interneuronal Network

Figure 3.19: A schematic description of the Dynamical Feedback Mechanism showing the various important parameters in the mediation of the slow rhythm. The essential components are \( \mu_{\text{bias}}, g_{\text{Na}}, g_{K}, g_{\text{AMPA}}, g_{\text{GABA}_{\text{fast}}}, \) and \( g_{\text{GABA}_{\text{slow}}} \).

3.4 Sensitivity Analysis: Results

The results of the simulations show that the important factors for the mediation of the delta rhythm are the spiking mechanism of individual E-cells, the strength of the excitatory pathway to the I-cell, firing of the I-cell and the dynamics of the inhibitory rebound (Fig 3.19). In the previous sections, the strength of the excitatory synaptic connection, \( g_{\text{AMPA}} \), was investigated and its relation to the size of the network was explored. The other important parameters are the principal parameters that control the firing of the E-cells and the strength of the inhibitory rebound. The firing of the E-cells is primarily related to the dynamics of the sodium and potassium currents as well as the input bias current. The inhibitory rebound on the other hand, is characterized through the dynamics of the inhibitory GABAergic currents.

To study the sensitivity of the rhythm to these components, the network behavior is studied in a parameter subspace that is characterized by these five parameters: maximal conductance of the sodium and potassium currents on each E-cell \( (g_{\text{Na}} \) and \( g_{K} \) for E-cells), the mean nonspecific background bias current \( (\mu_{\text{bias}}) \) and the maximal conductance of the GABAergic synaptic currents \( (g_{\text{GABA}_{\text{fast}}} \) and \( g_{\text{GABA}_{\text{slow}}} \)). For
the purpose of our sensitivity analysis, these five parameters will be referred to as the 'five crucial parameters', and their values (that were used in the original simulations) will be referred to as the 'central values'.

We know that if a two-cell network is able to generate the rhythm, then larger networks will also be able to generate the rhythm with the same period. This would require a lower excitability in the interneuronal population (lower $g_{AMPA}$) and the only difference in the rhythm would be a decrease in the variability of the network period, $\sigma_{ISI}$, in the larger network. On the other hand, in the two-cell network, if the intrinsic properties of the E-cell are such that after inhibition the E-cell could not fire, then we can conclude that in larger networks the situation would be the same and none of the E-cells would be able to fire. In other words, the rhythmicity in the two-cell network guarantees the rhythmicity in larger networks and vice versa, only with a difference in the variability of the network period. Therefore, we confine the sensitivity analysis to the behavior of the two-cell network.

To perform the sensitivity analysis on the two-cell network, each of the five crucial parameters is changed to 90%, 95%, 98%, 100%, 102%, 105% and 110% of its central value and for each case, the behavior of the network is examined. These values are summarized in Table 3.2. For a total of $7^5$ different possibilities (considering all combinations), the behavior of the network is numerically simulated (for a duration of 10 seconds). Based on the results of these simulations, the mean and the standard deviation of the network period ($ISI$) is computed.

### Table 3.2: Parameters used for the sensitivity analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>90%</th>
<th>95%</th>
<th>98%</th>
<th>100%</th>
<th>102%</th>
<th>105%</th>
<th>110%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{Na}$ [mS.cm$^{-2}$]</td>
<td>31.5</td>
<td>33.25</td>
<td>34.3</td>
<td>35</td>
<td>35.7</td>
<td>36.75</td>
<td>38.5</td>
</tr>
<tr>
<td>$g_{K}$ [mS.cm$^{-2}$]</td>
<td>8.1</td>
<td>8.55</td>
<td>8.82</td>
<td>9</td>
<td>9.18</td>
<td>9.45</td>
<td>9.9</td>
</tr>
<tr>
<td>$\mu_{bias}$ [$\mu A.cm^{-2}$]</td>
<td>3.87</td>
<td>4.085</td>
<td>4.214</td>
<td>4.3</td>
<td>4.386</td>
<td>4.515</td>
<td>4.73</td>
</tr>
<tr>
<td>$g_{GABA_{fast}}$ [mS.cm$^{-2}$]</td>
<td>1.80</td>
<td>1.90</td>
<td>1.96</td>
<td>2.0</td>
<td>2.04</td>
<td>2.10</td>
<td>2.20</td>
</tr>
<tr>
<td>$g_{GABA_{slow}}$ [mS.cm$^{-2}$]</td>
<td>0.90</td>
<td>0.95</td>
<td>0.98</td>
<td>1.0</td>
<td>1.02</td>
<td>1.05</td>
<td>1.10</td>
</tr>
</tbody>
</table>

$\psi$ : $i_{bias} = \phi(\mu_{bias}, \sigma_{bias})$ ; $\sigma_{bias} = 0.2 \mu A.cm^{-2}$

All possible combinations are analyzed, but since it is impossible to visualize the results in a unified five dimensional space, we look at the network period and its variability with respect to only one or two of the parameters while the other parameters are held constant.

#### 3.4.1 $ISI$ vs. $g_{GABA_{fast}}$ and $g_{GABA_{slow}}$

The sensitivity of the network behavior to the two GABAergic maximal conductances are shown separately. Fig 3.20a-i shows the network $ISI$ with respect to $g_{GABA_{fast}}$. In three of the nine cases (Fig 3.20b,c,f) the network does not engage in a rhythmic behavior. This is due to the fact that in these cases
$g_K$ is relatively high and the E-cell can not produce spikes. The higher values of $g_K$, which represents high potassium conductance does not allow the input current $\mu_{bias}$ to produce an action potential. To overcome the dominant effect of higher $g_K$s, either the input current or the depolarizing sodium current which is in part controlled by $g_{Na}$ should increase. Fig 3.21a,b shows how increasing either $g_{Na}$ or $\mu_{bias}$ to 110% of its central value could result in the re-emergence of the rhythm. In all other cases in Fig 3.20, the rhythm is generated with different means and standard deviations.

In all cases where the network is able to produce the rhythmic behavior (Fig 3.21 a,d,e,g,h,i), the effect of changing $g_{\text{GABA}_{fast}}$ from 90% to 110% of its central value, while all other parameters are held constant, is only to slightly change the mean and/or the standard deviation of the network period. In other words, although the exact value of the network period depends on $g_{\text{GABA}_{fast}}$, the generation of the rhythm through the Dynamical Feedback Mechanism is not critically dependent on the value of $g_{\text{GABA}_{fast}}$, therefore, $g_{\text{GABA}_{fast}}$ does not introduce a structural instability.

The same analysis shows that the network behavior does not critically depend on the value of $g_{\text{GABA}_{slow}}$ as long as the rest of the parameters are kept constant (Fig 3.22a-i).

The results show that when other parameters are held constant, the generation of the rhythm is independent of the values of $g_{\text{GABA}_{fast}}$ and $g_{\text{GABA}_{slow}}$. Furthermore, the effect of changing these two parameters on the exact network period is only marginal ($\mu_{ISI}$ and $\sigma_{ISI}$ do not change significantly along these two dimensions).

These results simplify the sensitivity analysis, since now we can confine our attention to the effect of the remaining three parameters, $g_{Na}$, $g_K$ and $\mu_{bias}$ on the network behavior. In the following sections, we will investigate the network behavior by changing these three parameters while $g_{\text{GABA}_{fast}}$ and $g_{\text{GABA}_{slow}}$ are kept constant at their central values.

### 3.4.2 ISI vs. $i_{bias}$, $g_{Na}$ and $g_K$

To perform the sensitivity analysis, the network behavior is examined in a series of 10-second runs where in each run, $i_{bias}$, $g_{Na}$ and $g_K$, each take a percentage (90%, 95%, 98%, 100%, 102%, 105%, 110%) of its central value. In each run, either the network engages in a rhythmic activity with a particular $ISI$ or the rhythmicity is lost. In all cases where the network is unable to generate the rhythm, it is due to the relatively high $g_K$ which hampers the ability of the $i_{bias}$ to initiate an action potential in the E-cell. In these situations, increasing either the mean synaptic input or the sodium maximal conductance can restore the rhythmic behavior.

Fig 3.23a-g uses a series of three-dimensional histograms to summarize these results. Each part illustrates the network mean period $\mu_{ISI}$ versus $g_{Na}$ and $g_K$ for a different value of mean bias current, $\mu_{bias}$. At lower values of $\mu_{bias}$ (90% to 95% of its central value), as illustrated in Fig 3.23a,b, the network behavior is rhythmic only for a limited range of relatively large $g_{Na}s$ and small $g_K$s (the elevated units in the histogram). By increasing $\mu_{bias}$, this range expands to include both smaller $g_{Na}s$ and larger $g_K$s (Fig
Figure 3.20: The ISI (in msec.) of the I-cell (also the network period) vs. 20% change in \(g_{\text{GABA}_A_{fast}}\) around its central value of \(g_{\text{GABA}_A_{fast}}^{\text{central}} = 2mS/cm^2\) (\(G_j\)% is the percentage of this central value) while all the other parameters are held constant. (a) to (i) correspond to several different values of \(g_{\text{Na}}\) and \(g_K\); each going from 95% of their central values (a) to 105% of their central values (i), as shown at the bottom of each figure. For three of the cases (b,c,f) there is no rhythmic behavior and for the rest, the rhythmic behavior is only marginally dependent on the changes in \(g_{\text{GABA}_A_{fast}}\). For a complete list of the central values, refer to parameter listing in chapter 2.
Figure 3.21: The ISI (in msec.) of the I-cell (also the network period) vs. 20% change in $g_{\text{GABA}_A_{\text{fast}}}$ around its central value of $g_{\text{GABA}_A_{\text{fast}}}=2mS/cm^2$ ($G_f\%$ is the percentage of this central value) while all the other parameters are held constant. For cases where due to an elevated maximal potassium current (105% of its central value), the network can not exhibit rhythmic behavior, increasing either the sodium maximal conductance $g_Na$ (a), or $\mu_{\text{bias}}$ (b) to 110% of its central value can result in the re-emergence of the rhythm (compare with Fig 3.21c,f).

A closer examination of these histograms reveals that the frequencies can range from less than 1Hz at its lowest to approximately 10Hz. These two ends are by no means limiting since we are only examining a small subspace around the central values, however, it shows that in the vicinity of the central values, the network exhibits rhythmic behavior from low delta to theta frequencies. The lowest frequencies correspond to elevated potassium conductances while $g_{\text{Na}}$ and $\mu_{\text{bias}}$ are high enough to maintain the rhythm. Furthermore, the frequency of the rhythm increases with increasing either $g_{\text{Na}}$ or $\mu_{\text{bias}}$ as long as $g_K$ does not suppress the rhythm altogether.

To make sure that the rhythm is actually robust, we should examine the variability of the network period, $\sigma_{\text{ISI}}$, as well. Since the effect of $g_{\text{GABA}_A_{\text{fast}}}$ and $g_{\text{GABA}_A_{\text{slow}}}$ was shown to be relatively insignificant, these two parameters are set at their central values. Each part in Fig 3.24a-g shows the dependence of $\mu_{\text{ISI}}$ and $\sigma_{\text{ISI}}$ on the input current $\mu_{\text{bias}}$, for different values of $g_{\text{Na}}$ while $g_K$ is held at its central value.

For all the cases where the network has a rhythmic activity, increasing $\mu_{\text{bias}}$ slightly decreases the mean period $\mu_{\text{ISI}}$, and also increases the robustness of the rhythm (decreases variability $\sigma_{\text{ISI}}$). When $\mu_{\text{bias}}$ is just high enough to generate the rhythm (point A on all figures), the variability (errorbars) is at its highest and drops when $\mu_{\text{bias}}$ is increased by a small percentage.
Figure 3.22: The ISI (in msec) of the I-cell (also the network period) vs. 20% change in $g_{\text{GABA}_{\text{slow}}}$ around its central value $g_{\text{GABA}_{\text{central}}}' = 1mS.cm^{-2}$ ($G_3\%$ is the percentage of this central value) while all the other parameters are held constant. (a) to (i) correspond to several different values of $g_{Na}$ and $g_{K}$; each going from 95% of their central values (a) to 105% of their central values (i), as shown at the bottom of each figure. For three of the cases (b,c,f) there is no rhythmic behavior and for the rest, the rhythmic behavior is only marginally dependent on the changes in $g_{\text{GABA}_{\text{slow}}}$. For a complete list of the central values, refer to parameter listing in chapter 2.
Figure 3.23: An estimate of the network frequency (defined as $f = 1/\tau_{MST}$) vs. changes in $g_{Na}$ and $g_K$. In each figure $g_{Na}$ and $g_K$ assume 90%, 95%, 98%, 100%, 102%, 105% and 110% of their central values (illustrated as 1, 2, 3, 4, 5, 6 and 7 on the horizontal axes) and the bars show the frequency of the network. As shown, going from (a) to (g), the mean bias current $\mu_{bias}$ changes from 90% of its central value to 110% ($\mu_{bias,\text{central}} = 4.3 \mu A.cm^{-2}$ while for all cases $\sigma_{bias,\text{central}} = 0.2 \mu A.cm^{-2}$). In all cases, non-elevated bars represent cases where the network does not exhibit rhythmic behavior. Frequencies range from less than 1 Hz to more than 10 Hz. In most cases, increasing $g_{Na}$, decreasing $g_K$ and increasing $\mu_{bias}$ increases the frequency and vice versa.
Figure 3.24: The ISI (in msec.) of the I-cell (also the network period) vs. 20% change in $\mu_{bias}$ around its central value ($\mu_{bias0} = 4.3$ and for all cases $\sigma_{bias} = 0.2 \mu A.cm^{-2}$; 1% is the percentage of the mean central value, $\mu_{bias0}$), while all the other parameters are held constant. (a) to (g) correspond to several different values of $g_{Na}$ as shown on top of each figure (going from 90% to 110% of its central value). For $g_{Na} = 90\% g_{Na}^{central}$ (a), the network does not exhibit rhythmic behavior whereas for all other cases (b-g), the network, depending on the strength of the input bias current, exhibits rhythmic behavior. The threshold for the bias current (point A on all figures) decreases for higher $g_{Na}$s.
On the other hand, going from Fig 3.24a to 3.24g the sodium maximal conductance $g_{Na}$ increases from 90% to 110% of its central value. As can be seen from the results, increasing $g_{Na}$ has three different yet interrelated effects. First it decreases the minimum $\mu_{bias}$ which can generate the rhythm (point A on figure). Second it decreases the mean period $\mu_{SI}$, and third it increases robustness (decreases $\sigma_{SI}$).

Fig 3.25a-g and 3.25a-d show the same results for two other values of $g_K$. Fig 3.25a-g shows the results for when $g_K$ is decreased to 90% of its central value. In this case, the hampering effect of the potassium conductance for the generation of action potential in the E-cell is lowered, therefore the network is able to generate the rhythm even for lower levels of $g_{Na}$ and $\mu_{bias}$. Furthermore, the rhythm is faster and more robust (both $\mu_{SI}$ and $\sigma_{SI}$ decreased).

Fig 3.26a-d shows the same results for the case where $g_K$ is increased to 110% of its central value. The results are the opposite of what is seen for the lowered $g_K$ values.

These results confirm that the rhythm is not structurally unstable and that there is a continuum in the parameter space where this behavior is stably generated. It is however important to note that within the framework of this mechanism, the robustness of the rhythm increases with the mean frequency. In other words, even within the delta band, it is predicted that slower rhythms should be more variable than faster ones.

### 3.5 Small-Scale Model

The model that has thus far been discussed does not assume any connection between individual E-cells. This assumption is largely based on the anatomical connections of the CA1 region in the mammalian hippocampus. However, for three main reasons it is important to investigate the effects of excitatory connections between individual E-cells. One is because of the the local excitatory connections between the nearby pyramidal cells of the CA1 region, which is also the reason for the name 'Small-Scale Model'. Second is to test whether these nearby connections can play any role in synchronizing the nearby pyramidal cells and therefore provide a temporal association between these cells. Third is to see whether various other brain structures that have significant amounts of recurrent excitatory connections can generate the slow rhythmic activity through the dynamical feedback mechanism. The potential mechanism discussed so far, is not necessarily bound to the anatomy of the CA1 field. For instance, CA3, which has a high degree of recurrent excitation, may be the locus for the generation of the delta rhythm which then, by way of the Schaffer collaterals, is propagated to the CA1 field.

To study the effect of these excitatory connections, a model of the network has been constructed where each E-cell has a limited number of connections to other nearby E-cells (Fig 3.27). The network is configured as a ring of E-cells reciprocally connected to a single I-cell. Two patterns of recurrent connection have been assumed. In the first case each E-cell is only connected to its two nearest neighbors and there are no connections beyond this first-order connectivity. In the second scheme, each E-cell has a second-order of
Figure 3.25: The ISI (in msec.) of the I-cell (also the network period) vs. 20% change in $\mu_{\text{bias}}$ around its central value ($\mu_{\text{bias}_0} = 4.3$ and for all cases $\sigma_{\text{bias}} = 0.2 \mu A.cm^{-2}$; as in Fig 3.24, 1% is the percentage of the mean central value, $\mu_{\text{bias}_0}$), while all the other parameters are held constant at their central values except $g_K$ which is held at 90% of its central value. Other conditions are similar to Fig 3.24. For all different values of $g_{Na}$, depending on the input bias current, the network can exhibit rhythmic activity. As compared to the results of Fig 3.24, in all cases due to a weakened $g_K$ the threshold for the bias current (point A) is decreased.
connectivity where each E-cell is connected to its four nearest E-cells. In all cases the connection is assumed to be AMPA mediated and therefore, fast and excitatory, with a maximal conductance of 0.02 mS.cm\(^{-2}\) which is comparable to the \(g_{\text{AMPA}}\) on the I-cell. Furthermore, for both patterns of connectivity, three network sizes with 5, 10 or 15 E-cells in the network have been studied. For clarity purposes, from this point on, the following notations will be adopted:

- \(g_{\text{AMPA}}^{\text{exc}}\) : E-cell to E-cell excitatory maximal conductance
- \(g_{\text{AMPA}}^{\text{inh}}\) : E-cell to I-cell excitatory maximal conductance
- \(R1\) : Network connectivity of order one (two nearest neighbors)
- \(R2\) : Network connectivity of order two (four nearest neighbors)

All combinations are analyzed for three different values of \(g_{\text{AMPA}}^{\text{inh}}\); i.e. 0.010, 0.015 and 0.020 mS.cm\(^{-2}\) while \(g_{\text{AMPA}}^{\text{exc}}\) is kept constant at 0.020 mS.cm\(^{-2}\).

### 3.5.1 5-Cell Network: \(R1\) and \(R2\)

The network behavior is simulated for a period of 5 seconds. Fig 3.28 and Fig 3.29 show the results of the simulations for \(R1\) and \(R2\) respectively. In each figure, three columns represent the results for the three different values of \(g_{\text{AMPA}}^{\text{inh}}\). For each case, several important characteristics are observable. First is the fact that similar to the behavior of the large-scale model, increasing \(g_{\text{AMPA}}^{\text{inh}}\) decreases the network period, i.e. the
Figure 3.27: A schematic diagram showing the pattern of connectivity between the E-cells and the I-cell in the small-scale model. All E-cells are reciprocally connected to the I-cell whereas within their own population, each E-cell is only connected to two (R1: first-order connectivity) or four (R2: second-order connectivity) of its nearest E-cells (the figure only has second-order connectivities).
rhythm becomes faster whereas the standard deviation increases, i.e. rhythm becomes more variable (except for $g_{AMP_A}^{inh} = 0.020 \text{ mS.cm}^{-2}$ in R2 connectivity). It is however important to note that the simulations are run for a duration of 5 seconds which provides a total of less than 20 samples of $ISI$, which depending on the actual $ISI$ distribution, might be insufficient to estimate an accurate mean and standard deviation for the network period.

For R1 (Fig 3.28), as $g_{AMP_A}^{inh}$ increases, the firing of the E-cell population becomes more sporadic. In other words, here the E-cell to I-cell excitatory drive can indirectly (through the rhythm), control the firing rate of the E-cells. The rhythm therefore, provides a substrate to control the firing rate of the E-cells. This could also change the spatial dynamicity of the E-cells. For lower values of $g_{AMP_A}^{inh}$, in almost every cycle, all the E-cells fire whereas in second and third column of Fig 3.28 where $g_{AMP_A}^{inh}$ is increased, at each cycle, only a sub-group of E-cells fire which allows for several combinations of such sub-groupings to take place.

Another observation is that most of the E-cells that fire in a given cycle are entrained. In other words, contrary to the large-scale model where individual E-cells fired independently (see Fig 3.12), here, the E-cells that fire are often synaptically coupled and therefore are temporally correlated.

There are notable differences in the behavior of the network when the order of connectivity changes from one to two. Fig 3.29 shows the same results for R2. Comparing the mean period with the R1 case, it is evident that for all three values of $g_{AMP_A}^{inh}$, the network becomes slightly slower (mean period increases) and becomes more variable. This is somewhat counterintuitive since due to a higher connectivity between the E-cells, one might expect a higher excitatory drive to the I-cell and therefore, a faster rhythm.

A closer look at the behavior of each E-cell explains this effect. When an E-cell fires, the opening of the potassium channels results in a stronger hyperpolarization which delays the next round of firing in that E-cell. Looking at the behavior of the 5-cell configuration with R2 connectivity, one can see that in each cycle, most of the E-cells tend to fire which delays their next round of firing and makes the rhythm slower. This effect is characteristic of relatively small networks where at each cycle most of the E-cells tend to fire. In the next section it will be shown that for larger networks (with 10 and 15 E-cells), since in each cycle, only a fraction of E-cells would fire, this situation will be reversed.

Comparison between the large-scale ($R0$) and small-scale ($R1$ and $R2$) model shows that higher connectivity between the E-cells, in most cases, decreases the network period. Table 3.3 lists the mean and the standard deviation of the network period for a 5-cell configuration with different orders of connectivity.

Table 3.3: $ISI$ mean and standard deviation (in msec.) for different orders of connectivity (small-scale model $N = 5$)

<table>
<thead>
<tr>
<th>Connectivity</th>
<th>$g_{AMP_A}^{inh}$ [mS.cm$^{-2}$]</th>
<th>0.010</th>
<th>0.015</th>
<th>0.020</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R0$ ($no$ recurrent excitation)</td>
<td>$\mu_{ISI}$</td>
<td>350.42</td>
<td>336.21</td>
<td>323.41</td>
</tr>
<tr>
<td></td>
<td>$\sigma_{ISI}$</td>
<td>27.35</td>
<td>16.52</td>
<td>21.34</td>
</tr>
</tbody>
</table>
Figure 3.28: The behavior of the small-scale model with 5 E-cells, each reciprocally connected to the I-cell as well as to the two nearest E-cells (R1: first-order connectivity) for a duration of five seconds. Each column corresponds to a different maximal excitatory conductance for the I-cell as shown on top of each column \( g_{\text{AMPA}}^{\text{inh}} \). In each column, E1 to E5 (rows 1 to 5) show the voltage trace of the five E-cells and the 6th row shows the response of the I-cell. The mean and standard deviation of the network period are shown on top of the I-cell voltage trace (mean, STD). In all cases, \( g_{\text{AMPA}}^{\text{inh}} = 0.020 \text{mS.cm}^{-2} \) and \( i_{\text{bias}} \) is Gaussian with \( \mu_{\text{bias}} = 4.3 \) and \( \sigma_{\text{bias}} = 0.2 \mu\text{A.cm}^{-2} \).
Figure 3.29: The behavior of the small-scale model with 5 E-cells, each reciprocally connected to the I-cell as well as to the four nearest E-cells (R2: second-order connectivity) for a duration of five seconds. All other specifications are similar to those of Fig 3.28.
3.5.2 10-Cell and 15-Cell Networks: R1 and R2

Most of the results that were discussed for the 5-cell network can be generalized to the 10 and 15-cell networks. Typically, the rhythm becomes faster and more variable with increasing $g_{AMPA}^{inh}$. The E-cells that fire in a given cycle, are temporally entrained. Furthermore, in larger networks, stronger E-cell to I-cell connection changes the population behavior of the E-cells so that in each cycle, a smaller group of E-cells would fire. The study of the spatial dynamicity is beyond the scope of this work, however, it is important to note that for a network of size $N$, the number of distinct groups will be maximized when on average, each group has $N/2$ members. This gives a range for $g_{AMPA}^{inh}$ which would provide the maximum spatial dynamicity. This argument does not take into account several other means through which groupings can take place.

To visualize the results of the simulations for the 10-cell network, the spike times are monitored on a spike-time raster plot (Fig 3.30,3.31). The results show that the E-cells are temporally entrained and also that the groupings tend to associate nearby E-cells. This is expected because the connectivity schemes are such that E-cells are synaptically coupled to their neighboring E-cells.

Moving from R1 to R2, the firings become less sporadic, i.e. more E-cells are likely to fire in each cycle and for all values of $g_{AMPA}^{inh}$, the rhythm in the R2 configuration is faster (Fig 3.31a-c). In general, except for relatively small networks, higher connectivity increases the overall excitatory drive to the I-cell and results in faster rhythms.

Going from R1 to R2, the standard deviation of the network period either decreases (for $g_{AMPA}^{inh} = 0.010mS.cm^{-2}$) or increases (for $g_{AMPA}^{inh} = 0.015$ and $0.020mS.cm^{-2}$). The mechanisms by which the robustness of the rhythm is controlled is more complicated and perhaps differentially dependent on both connectivity and $g_{AMPA}^{inh}$ so that a simple examination of the standard deviation is not adequate to characterize this dependence.

The following is a list of the means and standard deviations for the 10-cell network for R0 (no recurrent excitation), R1 and R2.

Table 3.4: ISI mean and standard deviation (in msec.) for different orders of connectivity (small-scale model $N = 10$)
Figure 3.30: The spike-time raster plot of the firing peaks of the cells in a small-scale model of 10 E-cells and one I-cell for a duration of 5 seconds. The top row shows the spiking times of the I-cell and the ten bottom rows correspond to the spiking times of the 10 E-cells. Three different maximal conductances for the I-cell has been tested as shown on top of each figure (a,b,c). All firing E-cells and the I-cell are entrained and for higher $g_{AMPA}^{inh}$, the number of E-cells that fire in each cycle is reduced. The results correspond to a first-order connectivity, R1; other parameters are the same as those used in Fig 3.28.
Figure 3.31: The spike-time raster plot of the firing peaks of the cells in a small-scale model of 10 E-cells and one I-cell for a duration of 5 seconds. The top row shows the spiking times of the I-cell and the ten bottom rows correspond to the spiking times of the 10 E-cells. Three different maximal conductances for the I-cell has been tested as shown on top of each figure (a,b,c). All firing E-cells and the I-cell are entrained and for higher $g_{AMPA}^{inh}$, the number of E-cells that fire in each cycle is reduced. The results correspond to a second-order connectivity, $R2$; other parameters are the same as those used in Fig 3.29.
The behavior of the 15-cell network is depicted in the spike-time raster plots of Fig 3.32a-c and 3.33a-c. The results agree with most of the observations in the 10-cell network, however, a precise analysis of the mechanisms that control the network period is only possible through examination of the actual probability distributions. The means and standard deviations for the 15-cell network are as follows:

Table 3.5: ISI mean and standard deviation (in msec.) for different orders of connectivity (small-scale model $N = 15$)

<table>
<thead>
<tr>
<th>$g_{AMPA}^{inh}$ [mS.cm$^{-2}$]</th>
<th>0.010</th>
<th>0.015</th>
<th>0.020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connectivity</td>
<td>$\mu_{ISI}$</td>
<td>$\sigma_{ISI}$</td>
<td>$\mu_{ISI}$</td>
</tr>
<tr>
<td>R0</td>
<td>316.24</td>
<td>310.51</td>
<td>307.23</td>
</tr>
<tr>
<td>R1</td>
<td>297.51</td>
<td>305.27</td>
<td>295.28</td>
</tr>
<tr>
<td>R2</td>
<td>310.61</td>
<td>273.77</td>
<td>260.79</td>
</tr>
</tbody>
</table>

In general the same two prominent characteristics are evident: individual E-cells are temporally entrained and at each cycle there are sub-groupings that mostly associate nearby E-cells. To visualize these two qualities, Fig 3.34 shows the cross-correlation between the firing times of all the E-cells in a 15-cell configuration (with respect to the 9th E-cell). It is evident that the correlation drops when cells are further apart, but to quantify these results, simulations for larger networks and longer run times are required.
Figure 3.32: The spike-time raster plot of the firing peaks of the cells in a small-scale model of 15 E-cells and one I-cell for a duration of 5 seconds. The top row shows the spiking times of the I-cell and the bottom rows correspond to the spiking times of the 15 E-cells. Three different maximal conductances for the I-cell has been tested as shown on top of each figure (a,b,c). All firing E-cells and the I-cell are entrained and for higher $g_{AMPA}^{inh}$, the number of E-cells that fire in each cycle is reduced. The results correspond to a first-order connectivity, R1; other parameters are the same as those used in Fig 3.28.
Figure 3.33: The spike-time raster plot of the firing peaks of the cells in a small-scale model of 15 E-cells and one I-cell for a duration of 5 seconds. The top row shows the spiking times of the I-cell and the bottom rows correspond to the spiking times of the 15 E-cells. Three different maximal conductances for the I-cell has been tested as shown on top of each figure (a,b,c). All firing E-cells and the I-cell are entrained and for higher $g_{\text{AMPAn}}$, the number of E-cells that fire in each cycle is reduced. The results correspond to a second-order connectivity, $R2$; other parameters are the same as those used in Fig 3.29.
Figure 3.34: Cross-correlogram showing the cross-correlation between the firings of all the E-cells with respect to the 9th E-cell in a small-scale model (R1: first-order connectivity) with a total of 15 E-cells ($\rho_{MPA}^{M} = 0.020 \text{mS cm}^{-2}$). The cross-correlation drops for cells that are further apart, however due to the connectivity, a significant correlation is evident between the 9th E-cell and its nearest neighbors (E8 and E10).
Chapter 4

Stochastic Phenomenological Model

4.1 Methodology

The behavior of the network in the stochastic model is essentially dependent on two factors. One is the firing of individual E-cells after inhibition which is achieved by the nonspecific background synaptic activity and the other, is the excitation of the I-cell due to the firing of the E-cells. It was noted in chapter three that there is a continuum within the parameter space where the network could generate rhythmic activity. In this chapter we want to turn our focus to the behavior of the network in this stable rhythmic regime.

The results from our numerical simulations showed that the rhythmic behavior is due to the interplay between a number of sporadically firing E-cells and a strong inhibitory rebound from the I-cell. It was further discussed that $\text{gAMP}_A$ can be interpreted as a measure for the excitability of the I-cell. However, close inspection of the behavior revealed that the reason why this parameter could control the frequency is the implicit fact that by changing $\text{gAMP}_A$ the number of E-cells that can drive the I-cell to fire, $n$, changes. Lower $\text{gAMP}_A$s correspond to a larger number of firing E-cells and vice versa. We take this implicit parameter, $n$, in conjunction with the total number of E-cells in the network, $N$, to build a stochastic phenomenological model to investigate the effect of these two parameters on the network behavior.

This model should incorporate the two important factors that generate the rhythm: the stochastic firing of the E-cells and the excitability of the I-cell. To satisfy the latter, it is necessary and sufficient to have an $n$ that is less than or equal to the total number of E-cells in the network, $N$. This means that in the model, the I-cell would fire when $n = 1, 2, 3, ..., \leq N$ of the E-cells start firing. Furthermore, the model assumes that all $N$ E-cells reset after this event.

The first condition, i.e. stochastic firing of the E-cells after inhibition, calls for a probability distribution that can describe the stochastic firing of individual E-cells in the network. The question of what distribution to use is not a trivial one, however, the results of the numerical simulations are used as the
primary clue. The network scheme that has been considered throughout (except for the small-scale model), assumes no connection between individual E-cells. Furthermore, it assumes that the negative feedback signal from the I-cell has the same effect on all E-cells. Taking these two points into account, it can be concluded that as far as the activity of individual E-cells is concerned, between successive inhibitions, the activity of different E-cells is essentially independent. In other words, in the time window just after one inhibition and before the next firing of the I-cell, the network of \( N \) E-cells and one I-cell acts as \( N \) disjoint networks of each, one E-cell and one I-cell. Within this framework, between successive inhibitions, the firing times of each E-cell in the network is stochastically similar to a network with only one E-cell; i.e. \( N = 1 \) and \( n = 1 \) (Fig 4.1).

By using this idea, we can now focus on the results that were collected from the numerical simulation of the two-cell network. In the two-cell network, each time the E-cell starts firing, it drives the I-cell to fire and the firing of the I-cell determines the cycles of the rhythm; therefore, the firing times of the E-cell can be
accurately approximated with the probability distribution of the network period. This distribution, which was numerically constructed in section 3.3.1, will be used in this section as the distribution of the firing times of all E-cells after inhibition. This probability distribution which will be referred to as \( P_{N=1, n=1}(T) \) is re-illustrated here in Fig 4.2 (Fig 3.10).

![Figure 4.2](image-url)

**Figure 4.2**: The probability distribution function of the two-cell network period calculated from the ISI distribution of the I-cell. The distribution is a numerical reconstruction of the ISI data collected from several runs of the network activity and is representative of the firing times of each E-cell after inhibition (explained in the text, section 4.1).

### 4.2 Setting up the Model

Now we have all the elements we need to set up the phenomenological model. A network of \( N \) E-cells are connected to a single I-cell which is representative of a synchronized equipotential interneuronal population. When the I-cell fires, it inhibits all the E-cells in the network. Following inhibition, each E-cell after a time interval \( T \), starts firing. The firing time for each E-cell is an independent stochastic variable that is in general, different for different E-cells. At each cycle and for each E-cell, \( T \) is taken from the probability distribution \( P_{1,1}(T) \). When \( n \) of the E-cells (from the total \( N \) E-cells) fire, they excite the I-cell which repeats the cycle of events anew.

In this model, unlike the numerical model, we have only a few of parameters, \( N \), \( n \) and \( P_{1,1}(T) \). It is important however to note that the foundation of this model is built upon the results of the numerical simulations. Moreover, one of the critical parameters in the phenomenological model, \( P_{1,1}(T) \), is directly obtained from the results of the numerical simulations of the two-cell network. This parameter is the product
of the interaction between the Gaussian stochastic input and the intrinsic/synaptic properties and as such, features the inherent qualities of the network that are relevant to the generation of this rhythmic behavior.

Using this model, given \( N \) and \( n \), we want to find the period of the network. The question can be rephrased as follows:

**Given \( P_{1,1}(\mathcal{T}) \) as the probability distribution of the firing times of each E-cell after inhibition, what is the probability distribution of the network period, \( P_{N,n}(\mathcal{T}) \), when there are a total of \( N \) E-cells from which a subset of \( n \) are necessary and sufficient to drive the I-cell to fire.**

The cycle starts with an inhibition from the I-cell. Following inhibition, at time intervals \( \mathcal{T}_1, \mathcal{T}_2, \mathcal{T}_3, ... \), the first, second, third, ..., \( i \)th E-cell starts firing. The cycle is completed just after the firing of the \( n \)th E-cell when the I-cell, once again inhibits all the E-cells. In other words, the period of the network is characterized by the time when the \( n \)th E-cell starts firing. Since the firing times of all E-cells at each cycle is stochastic, the network period which is the same as the firing time of the \( n \)th E-cell would also be a stochastic variable.

To find the probability distribution of \( P_{N,n}(\mathcal{T}) \), in each cycle, E-cells are enumerated according to the order which they fire, from \( E_1 \) to \( E_N \). Any of the \( N \) E-cells in the network can be the \( n \)th E-cell to fire and therefore there are \( N \) different possible choices for \( E_n \). From the remaining \( N - 1 \) E-cells, \( n - 1 \) of them should fire before \( E_n \) which gives \( n - 1 \) combinations of an \( N - 1 \) set or mathematically, \( \binom{N-1}{n-1} \) permutations. The remaining \( N - n \) E-cells should all fire after \( E_n \). Taking all these combinations into account, \( P_{N,n}(\mathcal{T}) \) will be:

\[
P_{N,n}(\mathcal{T}) = P_{1,1}(\mathcal{T}).P_{1,1}(\tau \leq \mathcal{T})^{(n-1)}.P_{1,1}(\tau \geq \mathcal{T})^{(N-n)} \frac{N!}{(N-n)!(n-1)!} \tag{4.1}
\]

where:

\[
P_{1,1}(\mathcal{T}) \quad PDF \ of \ the \ firing \ time, \ \mathcal{T}, \ of \ each \ E-cell \tag{4.2}
\]

\[
P_{1,1}(\tau \leq \mathcal{T})^{(n-1)} = \left[ \int_0^{\mathcal{T}} P_{1,1}(\tau)d\tau \right]^{(n-1)} \quad \text{prob. of (n-1) E-cells firing before } \mathcal{T} \tag{4.3}
\]

\[
P_{1,1}(\tau \geq \mathcal{T})^{(N-n)} = \left[ \int_{\mathcal{T}}^{\infty} P_{1,1}(\tau)d\tau \right]^{(N-n)} \quad \text{prob. of (N-n) E-cells firing after } \mathcal{T} \tag{4.4}
\]

\(^1\)By checking whether \( P_{N,n}(\mathcal{T}) \) is normalized or not, one can make sure that the number of permutations is calculated correctly. In our phenomenological model, irrespective of the specific values of \( N \) and \( n \), \( P_{N,n}(\mathcal{T}) \) is normalized, therefore, the number of permutations is correct.

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The mean and the variance of this distribution can be calculated as follows:

\[
\mu_{SI}(N, n) = \mathcal{E}(T) = \int_0^\infty \tau \cdot \mathcal{P}_{N,n}(\tau) d\tau
\]

\[
\sigma_{SI}^2(N, n) = \mathcal{E}(T^2) - \mathcal{E}(T)^2 = \left[ \int_0^\infty \tau^2 \cdot \mathcal{P}_{N,n}(\tau) d\tau \right] - \mu_{SI}^2(N, n)
\]

The phenomenological model enables us to capture the essence of the dynamical feedback mechanism using only a small number of parameters (\(N\), \(n\) and \(\mathcal{P}_{1,1}(\mathcal{T})\)). Apart from the fact that this simplified model does not introduce structural instabilities (inherent in more detailed models), it provides a very fast alternative for studying the behavior of the circuit. With the previous numerical method, the study of the behavior of large networks (tens of E-cells) can take up to several months whereas with the phenomenological model the same study can be carried out in one day.

As mentioned, \(\mathcal{P}_{1,1}(\mathcal{T})\) is directly taken from the numerical results and is used in equations 4.1 to 4.7 (in conjunction with \(N\) and \(n\)) to model the behavior of larger networks. The calculations are all carried out using the MATLAB software package. In this regard, the relevant script files are reported in Appendix E.

### 4.3 Phenomenological Model: Results

Considering several networks with different number of E-cells (\(N\)) and different I-cell excitabilities (\(n\)), we have calculated the mean and the standard deviation of the network period (Equ 4.6, 4.7). Fig 4.3 summarizes some of these results. Similar to our numerical results, the mean period (\(\mu_{SI}(N, n)\)) and its variability (\(\sigma_{SI}(N, n)\)) both depend on the network size and unimodally decrease with increasing \(N\). In other words, as the number of E-cells increases the rhythm becomes faster and more robust. As an example, in a network where \(n = 10\) E-cells are necessary to make the I-cell fire, the network should have a minimum of \(N = n = 10\) E-cells. As the total number of E-cells increases from 10 to 150, both the mean and the standard deviation of the network period decrease (from 667.28 and 58.98 msec. to 454.21 and 8.55 msec. respectively).

The same results when drawn with respect to \(n\) (Fig 4.4), show that the rhythm can lose its robustness as the I-cell becomes less excitable (\(n\) increases). In other words, to have a robust rhythm for a decreased level of excitability, the total number of E-cells should increase. For example, when \(N = 50\), the network loses its robustness for values of \(n\) that are close to 50, however, for the same level of excitability, the rhythm becomes robust (low variability) when \(N\) goes up to 75.
Figure 4.3: The figure shows the network period vs. the total number of E-cells, $N$, in the network for several cases where either $n = 2, 10, 25, 50, 75$ or $100$ firing E-cells can drive the I-cell to fire and maintain the rhythm. The mean network period as well as its standard deviation (errorbars) decreases with increasing $N$. For each curve, the data show the results of several network sizes from $N = n$ to $N = 150$.

Using equation 4.1, we can calculate the actual probability distribution of the network period for different values of $N$ and $n$. Fig 4.5 and Fig 4.6 show the probability distribution of the network period for different network sizes with different excitabilities. In Fig 4.5, the curve in blue shows the distribution for the two-cell network ($N = 1$ and $n = 1$). As the number of E-cells increases, the whole distribution shifts towards lower values; i.e. the network period decreases. Moreover, the distribution contracts which accounts for less variability in the rhythm.

Fig 4.6 demonstrates the distribution of the network period for cases where both $N$ and $n$ increase (larger network with lower excitability in I-cell). The shape of the distribution changes such that the peak and the spread of the distribution move to higher values which corresponds to an increase in the mean network period, i.e. slower rhythms, however, it is difficult to interpret this data with regard to the variability of the network period.

Close inspection of these distributions reveals an important quality of the network. Looking at the initial probability distribution on a linear-log scale, it becomes evident that this distribution has seven identifiable bumps which are labeled $P_1$ through $P_7$ (Fig 4.7). One at $T \approx 545$ msec., which is the first and the strongest peak of the distribution ($P_1$). $P_2$ to $P_7$ are located at 610, 665, 700, 750, 805 and 855.
Figure 4.4: The network period vs. the minimum number of E-cells that can maintain the rhythm \( n \), in the network with a total of \( N = 50, 75, 100, 125 \) and \( 150 \) E-cells. For all network sizes, the mean network period as well as its standard deviation (errorbars) increases with increasing \( n \).

milliseconds in that order.

In the case of the two-cell network, the first peak \( P_1 \), is the strongest and the other peaks are essentially suppressed. However, in larger networks where both \( N \) and \( n \) are increased, the peak of the probability distribution moves to the right; i.e. larger values. The results of Fig 4.6, when drawn on a log-linear scale (Fig 4.8), show that these larger networks, depending on the value of \( N \) and \( n \), amplify one or several bumps that were originally found in \( P_{1,1} (\mathcal{J}) \). As shown in Fig 4.6, \( N = n = 5 \) amplifies \( P_2 \) and weakens \( P_1 \) whereas \( N = n = 20 \) strengthens \( P_3, P_4 \) and \( P_5 \), effectively suppresses \( P_1 \) and weakens \( P_2 \). This trend continues so that for the case of \( N = n = 100 \), the last four bumps, i.e. \( P_4 \) to \( P_7 \), are the major peaks of the distribution.

In the dynamical feedback mechanism, according to the results from the phenomenological model, the network has the quality of strengthening or weakening different peaks that are in the probability distribution. In other words, by setting different network sizes in conjunction with the appropriate I-cell excitability, networks can have several rhythms with different periods. This means that with regard to the period of the rhythmic behavior, the network is potentially multimodal with the ability to extract certain periodic behaviors that are inherent in the dynamics. The multimodality of the rhythm is readily depicted in Fig 4.9 where several distributions of the network period (for all values of \( 1 \leq N = n \leq 200 \)) are superimposed.

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Figure 4.5: The probability distribution of the network period. Each curve shows the distribution for a different network size with a total of $N = 1$ (blue), $N = 2$ (green), $N = 3$ (red), $N = 6$ (magenta) and $N = 10$ (black) E-cells from which one E-cell is enough to maintain the rhythm ($n = 1$). As the number of E-cells increases, the distribution of the network period, $P_{N,1}(T)$, moves toward lower values and becomes narrower, i.e. the rhythm becomes faster and more robust.

It is important to note that in the original probability distribution, the existence of seven different bumps, $P1$ to $P7$, was due to the interaction of the Gaussian stochastic input with the intrinsic properties of the E-cell and the I-cell. Any alteration in the stochastic nature of the input bias current, or the intrinsic properties of the E-cell will in general, change the shape of the probability distribution for the two-cell network, $P_{1,1}(T)$, which will consequently alter the distribution of the period for larger networks. The phenomenological model only focuses on the effects of $N$ and $n$, but since the original distribution for $N = n = 1$ depends on both the intrinsic properties and the bias current, the aforementioned multimodality is in fact dependent on the synaptic currents, intrinsic properties and network dynamics.

Changing the distribution of the input bias current in a two-cell configuration ($N = n = 1$), affects the distribution of the network period as was shown in chapter three. In the following sections, using several different stochastic bias currents, the distribution of the network period for various $Ns$ and $ns$ will be investigated.
Figure 4.6: The probability distribution of the network period. Each curve shows the distribution for a different network size with the lowest possible I-cell excitability; i.e. \( n = N \), where there are a total of \( N = 1 \) (blue), \( N = 5 \) (green), \( N = 20 \) (red) and \( N = 100 \) (black) E-cells from which all are needed to maintain the rhythm \( (n = N) \). With increases in \( N \) and \( n \), the distribution of the network period, \( P_{N,n}(T) \), moves toward higher values, i.e. slower rhythms. However, with respect to the robustness of the rhythm, no clear increase or decrease in the variability is observable.

### 4.3.1 Results: Gaussian Bias Input

In chapter three, several different Gaussian distributions were used to construct the \( ISI \) probability distribution of the two-cell network \( (N = 1, n = 1) \). Here, using our phenomenological model, we analyze the effect of larger networks (larger \( N \)s) and/or lower excitabilities (larger \( n \)s) on the network period.

According to the logic of the phenomenological model, we can use the \( ISI \) distribution of the two-cell network \( (P_{ISI}) \) for the firing time of each E-cell after inhibition, \( P_{1,1}(T) \). This distribution is used in equation 4.1 to calculate the probability distribution of larger networks, \( P_{N,n}(T) \), with a total of \( N \) E-cells from which a subset of \( n \) are necessary and sufficient to drive the I-cell to fire.

Using Gaussian input bias currents with three different means, and five different standard deviations, a total of 15 \( ISI \) distributions for the two-cell network have been constructed. They have been used as \( P_{1,1}(T) \) in equation 4.1 and the network distribution for \( 1 \leq n \leq 200 \) and \( n \leq N \leq 200 \) has been calculated accordingly.

Some of these results are summarized in Fig 4.10 where the input current is Gaussian with a mean of
Figure 4.7: The probability distribution function of the two-cell network period (Fig 4.2) on a linear-log scale. The distribution has seven identifiable bumps that are labeled P1 to P7 which are located at $T \approx 545, 610, 665, 700, 750, 805$ and $855 \text{msec.}$ respectively.

$\mu_{\text{HiCo}} = 4.3 \mu \text{A.cm}^{-2}$ and five different standard deviations which are 90%, 95%, 100%, 105% and 110% of a central value of 0.2 $\mu \text{A.cm}^{-2}$ (rows a-e). The column on the left (a1-e1) shows the original distribution of the two-cell network. The middle column (a2-e2) shows the distribution of the network period for several values of $N$ while $n = 10$ and the third column (a3-e3) shows the same distribution for various $n$s while $N = 100$.

Looking at the results in the center column, it is evident that for larger networks (larger $N$s), the distributions move towards lower values which means that the rhythm becomes faster. Furthermore, the distribution becomes narrower which corresponds to a more robust rhythm. However, due to the existence of sidebands within the distribution, the standard deviation of the network period does not monotonically decrease.

In cases where the original distribution (left column) is multimodal, the effect of changing $N$ is to move the peak of the network distribution close to one of the preferred modes. In other words, the original distribution provides the network with several modes (preferred periods) and the network, depending on its size and the excitability of the I-cell, can amplify specific modes while suppressing the others.

The right column shows cases where $N = 100$ is held constant (the network size does not change), and the I-cell excitability, $n$, changes between 20, 50 and 100. The distribution moves towards higher periods (slower rhythms) as $n$ increases. Moreover, for all cases, the distribution is in accordance with the original
Figure 4.8: The probability distribution of the network period on a linear log scale. Each curve shows the distribution for a different network size while $n = N$. With increases in $N = n$, the distribution of the network period, $P_{N,n}(T)$, moves toward higher values by suppressing the lower bumps while amplifying the higher ones. For $N = n = 1$ (blue), the distribution has its peak at the lowest bump, $P_1$. In network with $N = n = 5$ (green) the peak has moved to $P_2$. $N = n = 20$ (red) has $P_3$ and $P_4$ as well as a strong component in $P_5$. For $N = n = 100$ (black), the first three bumps ($P_1 - P_3$) are suppressed whereas $P_4 - P_7$ are strongly amplified.
Figure 4.9: The probability distribution of the network period. The distribution of all the networks with $N = 1, 2, 3, ..., 200$ E-cells from which all are needed to maintain the rhythm ($n = N$), are superimposed. Irrespective of the network size, the distribution embodies seven identifiable peaks. According to the specific ranges of $N = n$, these seven peaks are differentially amplified/attenuated.
Figure 4.10: The distribution of the network period for several different values of \(N\) and \(n\) and also different Gaussian inputs. The left column (a1-e1) shows the original distribution of a two-cell network, \(P_{1,1}(T)\). The middle column (a2-e2) shows the distribution of the network period for \(N = 10\) (blue), \(N = 20\) (green) and \(N = 100\) (red) with \(n = 10\) (\(P_{10,10}(T)\), \(P_{20,10}(T)\) and \(P_{100,10}(T)\)). The right column (a3-e3) shows the distribution of the network period for \(n = 20\) (blue), \(n = 50\) (green) and \(n = 100\) (red) with \(N = 100\) (\(P_{100,20}(T)\), \(P_{100,50}(T)\) and \(P_{100,100}(T)\)). In all three columns, rows a,b,c,d and e correspond to five different Gaussian inputs with the same mean \((\mu_{bias} = \mu_{bias0})\) and standard deviations that are 90\%, 95\%, 100\%, 105\% and 110\% of the central value \((\sigma_{bias0} = 0.2\mu A.cm^{-2})\) respectively. The results show that increasing \(N\) with \(n\) constant (a2-e2), amplifies the lower peaks whereas, increasing \(n\) with \(N\) constant (a3-e3), suppresses lower peaks and amplifies higher peaks.
multimodal envelope provided by the distribution of the two-cell network period.

Appendix D summarizes the results for cases where both the mean and the standard deviation of the Gaussian input bias current are changing.

4.3.2 Results: Uniform Bias Input

The same type of analysis has been performed for the case where the input bias current is Uniform, the results of which are summarized in Appendix D.

Although the distribution of the network period is strongly dependent on the stochastic nature of the input current, the same behavioral qualities seem to persist; increasing $N$ moves the distribution towards faster rhythms (decreases the period) whereas increasing $n$ does the opposite. Moreover, the distribution of the network period is a modal amplification of the distribution of the firing times of the E-cells.

These results show that the final distribution depends on various factors: the stochastic nature of the input bias current, the intrinsic and synaptic characteristics of the cells, the excitability of the interneuronal population and the number of E-cells that are mediating the rhythm. The interaction between the stochastic bias current with the dynamics of individual cells generates a multimodal distribution from which depending on the interneuronal excitability as well as the network size, certain modes are extracted and amplified. Although any of these factors can drastically change the shape of the final distribution, within the framework of the Dynamical Feedback Mechanism, the principles that govern the interplay of these factors do not change.
Chapter 5

Conclusions and Future Directions

5.1 Discussion

The original motivation for this work was to understand the mechanisms that underlie the generation of a spontaneous slow rhythm in the CA1 region of the mammalian hippocampus. After formulating the question and performing a preliminary analysis of the experimental data, various possible neuronal mechanisms were hypothesized. These mechanisms were further investigated and confronted with the experimental data. As a result of these investigations, a dynamical feedback mechanism was preferred and further delved into. Thenceforth, the focus of this work has been to study various characteristics of the neuronal networks in the CA1 region that can generate this slow rhythmic behavior.

The experimental data suggests that the slow field rhythm recorded in the extracellular region of CA1, is due to the synchronized and cyclic inhibition of multiple pyramidal cells in the vicinity of the recording site. The underlying mechanism described here hypothesizes that an entrained/synchronized population of interneurons (I-population) might be responsible for the generation of this cyclic inhibition. Moreover, it is assumed that this inhibitory feedback signal is evoked by a heightened excitatory drive which is due to an increased and/or more synchronized activity in the pyramidal cell population.

The structure of this behavior is due to a recurrent loop of excitation and inhibition, where heightened excitation, evokes a (negative) inhibitory feedback signal which suppresses the excitatory activity. However, due to a nonspecific background synaptic input, after the effect of the inhibition wears off, the excitatory activity builds up anew, and a new cycle begins.

In each cycle, different groups of pyramidal cells can synchronize or heighten their activity to drive the interneurons. This quality provides the rhythm with a spatial dynamicity where different sub-populations can be activated at different cycles of the rhythm, hence the name dynamical feedback mechanism.

One of the important factors about this study, is its consideration for a stochastic synaptic input, which practically has a flat frequency response and as such has no frequency preference. The study shows that the
network is able to produce a robust rhythmic behavior in specific frequency ranges despite the nonspecificity of the synaptic input. Furthermore, the recurrent excitatory/inhibitory loop, uses this stochastic input to shape a multimodal inter-spike interval distribution, $P_{ISI}$, as was discussed in chapter four. This distribution therefore depends on both the synaptic input and the intrinsic properties of the cells in the network. This multimodal distribution has several preferred frequencies that can then be further extracted and amplified by the dynamics of the network. The results from the phenomenological model shows that extraction of one of the several modes inherent in the $ISI$ distribution, can now be achieved by tuning the number of E-cells that mediate the rhythm and/or the excitability of the I-population. In other words, the network can act as a filter with different resonance frequencies depending on these two properties.

The excitability of the I-population partly depends on the intrinsic characteristics of the interneurons. Given the diversity of interneurons known to be present in hippocampus and other cortical regions, it is conceivable to speculate that a functional outcome of this heterogeneity may be to dynamically control different network frequencies. However, it remains an experimental challenge to quantify the excitability of synchronous interneuronal populations and to relate it to the generation and/or control of different network frequencies.

The diversity of interneurons coupled with the spatial dynamicity of E-cells provided by the dynamical feedback mechanism, raises the possibility of having different concurrent rhythms. In this respect, we would like to speculate that the interaction of the E-cells with several synchronous I-populations may be taking place at different temporal and spatial levels so that the network would produce multiple nested rhythmic activities simultaneously. The activity of small local active groups of E-cells may excite highly excitable local interneuronal populations (due to somatic and/or proximal dendritic inputs) to produce local rhythmic activities on certain frequencies. However, the activity of these E-cells when coupled with many other distant groups may be able to excite other larger, yet less excitable interneuronal populations (through distal dendritic regions) and generate rhythmic behaviors on larger scales, hence the co-existence of nested rhythms.

It is important to note that in our discussion, excitability is by no means an explicit property that we assign to an interneuron or a predefined interneuronal population. A single interneuron when coupled with other interneurons may potentially act as part of different excitable populations, and as such, both the active E-cells and I-populations are highly dynamic with regard to their spatial specificity. In other words, different morphologies, different synaptic and intrinsic properties of one single interneuron may associate it with different I-populations. It is therefore the dynamics of the network that assign a particular interneuron to one or more I-populations.

The same qualitative properties are hypothesized for E-cells. The axonal arborization of different E-cells potentially associate them with different networks, however, the state of the network assigns the E-cell to a specific sub-population. In such a paradigm, a single cell, either excitatory or inhibitory may engage in different rhythms with different temporal structures and at different spatial scales.
5.2 Future Directions

There are many avenues by which the results of this work can be further refined and/or enriched. The following are some immediate directions that are conceivable:

5.2.1 Model Enhancement

Incorporating Details

In order to carry out numerical simulations of the network behavior, individual cells were described as single compartment Hodgkin-Huxley conductance-based units with first order kinetics describing all their intrinsic and synaptic processes. However, using more realistic models for individual neurons, including multicompartmental units with more accurate synaptic and intrinsic properties, could refine these results. This can provide a better understanding of the neural activity at the cell level, which then make the results more amenable to physiological testing. The dynamics of the slow delta rhythm, may be due to interaction of various factors, including several slow intrinsic dynamics, i.e. slow activating potassium currents, or slow synaptic communications, i.e. GABA\textsubscript{B}, which are all ignored in this study in order to focus on the network properties. Similarly, the current model uses a simplified pattern of connectivity that is known to be present in the CA1. This can also be improved.

Mutual Inhibition

Various other assumptions in the numerical model should be further investigated in the light of a more detailed cellular model. For instance it is assumed that a population of synchronized interneurons is responsible for the synchronous inhibition recorded in pyramidal cells. Although the experimental data is in favor of this hypothesis, the mechanism for entraining/synchronizing individual interneurons is not well understood. Several studies have investigated the possible mechanisms for the generation of synchronous firing in reciprocally interconnected interneurons. It would be important to expand the architecture used in the current study to incorporate models of interconnected interneurons to see if they are compatible with the Dynamical Feedback Mechanism proposed here.

Spectral content of the Stochastic Input

Many other improvements at the cellular level would depend on the availability of the experimental data. The assumption for the stochastic input, as the nonspecific background activity impinging on all E-cells, represents our lack of knowledge on any specificity in this input signal. Both Gaussian and Uniform distribution used here are non-modal (practically flat in the frequency domain), which is not necessarily an accurate representative of this input. Further work can enrich the results of this study by investigating stochastic inputs that have stronger components in certain frequency bands. At this stage, we can not rule
out the possibility of a strong delta component in this nonspecific input. In fact, it is important to note that the rhythm that has been recorded in the CA1 field may actually depend on the activity of other regions of hippocampus. For instance, the highly recurrent network of pyramidal cells in CA3 may be responsible for the generation of this rhythm, in which case, the synaptic input would arguably have a strong delta component and the model then should incorporate this component into its synaptic structure. Extracellular recording from the Schaffer collaterals might shed some light on the nature of this input signal, both in time and frequency domains.

5.2.2 Other Implications

Other Rhythmic Activities

The mechanism proposed by the phenomenological model could potentially correspond to rhythmic behaviors in various other frequency ranges. The model essentially shows that the network can extract specific modes of a potentially multimodal distribution depending on the number of E-cells and the excitability of the I-population. In general, this does not restrict the behavior of the network to the delta band. Several other distributions in other frequency ranges (particularly theta) could be utilized to investigate the possibility of the emergence of other rhythmic activities through the Dynamical Feedback Mechanism.

Nested Oscillations

An important generalization would be to use the phenomenological model with several I-cells with different excitabilities to study the possibility of having coexisting rhythms (with different frequencies) in the network. It is especially important since in the experimental setup, in several cases, simultaneous delta and theta rhythms have been recorded. Furthermore, this approach might be useful in understanding the effects of these interactions on modulating the frequency of the field rhythmic activity.

Population Coding

Due to the spatial dynamicity of the E-cells, at each cycle a different sub-population of E-cells may become activated. From an information coding perspective, these sub-populations may contain different neuronal messages. Although the existence of such population codes is highly speculative, it would be interesting to confront the results of the current phenomenological model with other models of population coding to investigate the Dynamical Feedback Mechanism as a vehicle to code information. In the current model, the spatial dynamicity coupled with the emergent rhythmicity provides a potential substrate for spatiotemporal coding.
Appendix A

Hippocampus

A.1 Anatomy: Structure and Cell Types

The sea horse-shaped hippocampus has a readily identifiable structure at both gross and histological levels; both the cell bodies and the zones of connectivity are arranged in orderly layers. As part of the limbic system, the hippocampus together with the dentate gyrus, subiculum, presubiculum, parasubiculum and entorhinal cortex, constitute what is collectively referred to as the hippocampal formation.

The hippocampal formation appears to have a long C-shaped axis that extends from the septal nuclei rostrally, over and behind the diencephalon, into the temporal lobe caudally and ventrally. The long and the orthogonal axes of the hippocampus are typically called the septotemporal and the transverse axes respectively (Fig A.1).

Hippocampus consists of a distinct principal cellular layer called the pyramidal cell layer. The cell bodies of pyramidal neurons are arranged, three to six cells deep within this layer. These neurons have elaborate dendritic trees extending to the regions above and below the pyramidal cell layer. The apical portion of the dendrites is longer than the basal portion and extends from the apex of the soma towards the center of the hippocampus, i.e., towards the dentate gyrus. Both the apical and the basal dendrites go into a number of strata where they make different types of synaptic contacts. The basal portion extends to the stratum oriens and the apical part traverses three strata: stratum lucidum, strata radiatum and stratum lacunosum-moleculare (Fig A.2).

Within the principal cell layer of the hippocampus, based on the size and appearance of the neurons, three fields designated CA1, CA2 and CA3 have been identified [21]. CA2 has been a matter of some controversy but the other two fields exhibit clear anatomical and physiological characteristics and also seem to have distinct roles in the flow of signals within the hippocampus.

From an anatomical perspective, the mammalian CA3 field shows a layer of well-formed and regularly oriented pyramids. The hallmark of these cells, their long micro-dendrites, cover confined portions of both
Figure A.1: Line drawing of a lateral cut-away view of the rat brain. The hippocampus is a banana-shaped structure that extends from the septal nuclei rostrally to the temporal cortex, caudally. The long axis is called the septotemporal axis and the orthogonal, the transverse axis (TRANS). Above left, is a slice cut perpendicular to the long axis. The figure shows several fields of the hippocampal formation and some of the typical intrinsic connections (from Shepherd G.M. [68]).

apical and basal dendrites and mainly contact the mossy fibers of the dentate gyrus.

The CA1 region, the other main region of the hippocampus, has been shown to expand markedly with phylogenetic advance, and has undergone by far the greatest morphological changes from insectivores to higher primates. In humans, this subregion is particularly prominent. The pyramidal layer is typically arranged into a deep and a superficial stratum, each being formed of several rows of pyramids that are relatively loosely packed [21].

The delimitation of CA1 from CA2/3 can be made with considerable precision since the cells of CA1 are clearly smaller and paler than those of CA2/3. On the other hand, the delimitation between the pyramidal cells in the CA1 and the subiculum becomes considerably difficult in higher primates. The cells of CA1 tend to be more uniformly dispersed and they become darker. From an anatomical point of view, it is also notable that in cell-stained material, all of the pyramidal cells of this uniform layer seem to be of the same type; subdivision into upper and lower sections is not possible.

In all these fields, apart from the pyramidal population, there is a population of intrinsic neurons or interneurons that spreads out through the hippocampal strata and accounts for approximately 10% of the cells within these subregions [26]. While morphological identification of this small population is lacking, anatomical studies show that individual interneurons in both hippocampus and neocortex constitute a highly heterogeneous population with respect to their morphology as well as their position.

The first attempts to identify these interneurons were made by Ramon y Cajal and his pupil Lorente de No. Their observations of interneurons, or non-pyramidal cells as they called them, showed that within the hippocampal formation, these cells tend to have two important characteristics: first the laminar distribution
Figure A.2: Schematic diagram showing the morphologies (a) and the axonal/dendritic arborisation (b) of a typical pyramidal cell and several types of interneurons (from McBas C.J. and Fisahn A. [45]).

of dendritic trees which could predict differential sources of afferent inputs and second, the pattern of axonal arborization which serves as a strong footprint for target selectivity. Further investigations in this direction have been useful in classifying interneurons mostly with respect to their target selectivity. Chandelier or axo-axonic interneurons were shown to have rows of axonal terminals on the initial segments of the principal layer of both dentate gyrus and hippocampus [71]. Another identifiable population of interneurons are the basket cells, which predominantly innervate the perisomatic region of the pyramidal cells (cell bodies and most proximal dendrites), but are otherwise heterogeneous. A third group of interneurons, bistratified cells, are those that synapse on to the dendritic trees of the principal cells and show great variability in location of their soma and the pattern of their dendritic and axonal arborization. Another class of interneurons, called interneuron-selective (IS) cells, has recently been described that specializes in innervating specific subsets of other interneurons. The intrinsic capability of mutual inhibitory networks to generate rhythmic patterns of activity has lately drawn a lot of attention towards this subtype [88]. Fig A.2 is a summary diagram of various hippocampal interneurons, their morphology, their orientation and their axonal arborization.

Now that the basic anatomical correlates of individual cell types have been laid out, we can delve
more deeply into the physiological characteristics of these different cell types and their interactions.

**A.2 Physiology: Electrical Specifications**

**A.2.1 Pyramidal cells**

Although the electrophysiological behavior of different neurons in the hippocampus is variable, but within different cell types some general commonalities are evident. Similar to many other regions in the brain, major anatomical dissimilarities correlate with differences in the physiological characteristics. The pyramidal cells in the hippocampus compose an apparently homogeneous population, with a categorical distinction seen only between the large and small pyramids of CA3 and CA1 respectively, but relatively minor differences among cells within a given field.

CA1 pyramidal neurons can fire repetitively at up to several hundred Hertz [63], whereas CA3 pyramidal neurons tend to fire in short bursts of five to ten action potentials [89, 27] and are believed to be important for explaining the seizure susceptibility of the hippocampus [34, 35, 78, 81].

The actual behavior of an isolated pyramidal cell is determined both by the site and the intensity of the stimulation. Typically, when CA3 pyramidal cells are slightly depolarized by somatic current injection, rhythmic bursts of up to 4 Hz occur. Further somatic depolarization then causes the firing pattern to spike doublets and then to rhythmic action potentials. On the other hand, steady current injection into the apical dendrites could evoke bursts at frequencies of at least 8 Hz [77].

Steady injection of current into the soma of CA1 pyramidal cells, leads to spike trains that exhibit strong frequency accommodation, i.e. slowing of frequency with time [65, 43]. Current injection into the dendrites on the other hand, can generate various firing patterns from repetitive fast spikes with declining amplitude to compound burst-like spiking patterns [9].

Intracellular recording from these pyramidal cells shows distinct electrical properties that are in part related to their various sub-cellular properties. As an example, a typical CA1 pyramidal cell has an average resting potential of approximately \(-65mV\), input resistance of 25 – 30MΩ and membrane time constants averaging 12 – 15msec. The threshold for initiation of an action potential in the soma is about 10 – 15mV depolarized from the usual resting potential and the action potentials have amplitudes of 70 – 80mV [34, 35, 63]. These cells are shown to be electrically short, i.e. approximately one time constant [14, 32, 86]. It is important however, to note that these properties are primarily obtained from recordings in slice preparations and as such, might be considerably biased.

In pyramidal neurons of both CA1 and CA3, following the initiation of an action potential, the basic sequence of synaptic transmission begins which typically results in an excitatory response in the target neuron. The major excitatory neurotransmitter in the hippocampus is glutamate [60, 76] which binds both ionotrophic and metabotropic receptors. The ionotrophic glutamate receptors consist primarily of AMPA, kainate and NMDA receptors which are found in various combinations in different parts of
the hippocampus. AMPA and kainate receptors mediate fast excitatory postsynaptic potentials (EPSPs), whereas NMDA receptors mediate slower-rising and slower-decaying EPSPs. The metabotropic receptors induce their effect indirectly through G-proteins, and in many situations their effects can be more accurately referred to as neuromodulatory [33].

A whole repertoire of ionic currents have been reported on both CA1 and CA3 pyramidal cells. These channels exhibit various voltage and/or ligand dependencies. For instance, CA1 pyramidal neurons exhibit fast sodium and potassium conductances [66], calcium conductance [66, 89] as well as various other types of potassium conductances [31, 13, 12, 29].

A.2.2 Interneurons

Interneurons in the mammalian brain both in the hippocampus and in several neocortical regions have eluded most classification attempts. They seem to constitute a highly heterogeneous population. They contain different peptides and different calcium-binding proteins; they have different morphologies [26] and exhibit different membrane properties [51].

On the basis of the presently available information, as Freund and Buzsaki [26] have discussed, most -if not all- of the interneurons in both the dentate gyrus and hippocampus are most probably GABAergic and therefore predominantly inhibitory. However, apart from their GABAergic nature, hippocampal interneurons are rather diverse [26]. Even within a particular field in the hippocampus, these cells exhibit various firing patterns that partly depend on the differential expression of their voltage-gated channels. We shall confine our attention to the typical characteristics of the interneurons residing in the CA1 field, which are also more related to the subject of the current study.

Inhibitory cells in CA1, exhibit at least three distinct discharge patterns, regular, irregular and clustered (burst) [56] (Fig A.3). Although various studies have recorded slightly different electrical properties, certain characteristics seem to be prominent. Some commonalities include depolarizing after-potentials (DAP), pronounced after-hyperpolarization (AHP) amplitudes, spike accommodation and the ability to fire at frequencies of several hundred Hertz [56, 51, 15].

Dendrites, cell bodies and the axon initial segment of every principal cell in all cortical structures are innervated by inhibitory interneurons [26]. In hippocampus, stimulation of the afferent fibers elicits biphasic inhibitory postsynaptic potentials (IPSPs) in principal cells. The early phase is due to the activation of chloride (Cl\(^-\)) specific GABA\(_A\) currents which in addition to their fast inhibitory postsynaptic effect, increase the membrane conductance and shunt other excitatory and inhibitory currents [73]. The late phase is linked to the slow metabotropic GABA\(_B\) receptor; however, recent studies have proposed alternative mediators like the slow GABA\(_A\) synaptic current [10]. The mechanism for the induction of these complex IPSP patterns through different receptor sub-groups are far from clear [73, 10, 70] and needs further investigation.

Several pharmacological studies have tried to characterize the intrinsic properties of these interneurons, including their voltage and ligand gated transmembrane ionic channels. Besides the sodium
Figure A.3: Spontaneous activity of neurons with regular (A), irregular (B), and clustered (C) firing patterns. In each case a membrane potential trace is shown together with a histogram of interspike intervals constructed (using a program written in Labview, National Instruments) from data acquired during at least 3 min. (D) shows the proportion of the recorded cells in stratum lacunosum-moleculare (SLM; n = 49), stratum radiatum (SR; n = 68), and stratum oriens (SO; n = 39) discharging with these patterns (from Parra et al. [56]).
Figure A.4: Original drawing of the hippocampal formation by Ramon y Cajal, showing the laminar structure as well as several cell morphologies with their axonal/dendritic arborizations.

and potassium currents underlying fast spike generation, several other ionic currents, including $I_H$, $I_T$ and $I_D$ [56] have been identified but their kinetics and their spatial distributions are yet to be elucidated.

A.3 Circuitry: Pathways, Networks and Their Behaviors

The general direction of signal flow and the circuitry within the hippocampal formation was first described by Ramon y Cajal (Fig A.4). His studies of the morphology of the axonal and dendritic arborization, coupled with those of Lorente de No [21], suggested that the signal flow in hippocampal formation follows an intrahippocampal loop which starts from entorhinal cortex and after traversing the dentate gyrus, hippocampus and subiculum, loops back onto deeper layers of the entorhinal cortex.

Andersen and colleagues [6] later highlighted the importance of the unidirectional progression of excitatory pathways within the dentate gyrus and hippocampus and coined the term trisynaptic circuit, which constitutes a complex of three main subfields: dentate gyrus (DG), CA3 and CA1. Granule cells, the principal cells of the dentate gyrus are the major target of the entorhinal afferents which are believed to be the major carriers of the sensory information into the hippocampal formation. Mossy fibers, the axonal projections of the granule cells then innervate the principal cells of CA3, the second stage in the trisynaptic circuit. The next and last stage in this complex is the CA1 field which is the major target of
CA3 pyramidal axons, the Schaffer collaterals. The main extrinsic projections of CA1 pyramidal cells which constitute the output of the so-called trisynaptic circuit are to the subiculum and entorhinal cortex where the intrahippocampal loop is closed (Fig A.5).

The simplified picture of the signal flow within the intrahippocampal loop has motivated many hypotheses with regard to the mechanisms of signal processing in various structures involved, however, to test these hypotheses, a detailed analysis of the behavior of local networks in different fields in the hippocampus and their synaptic interactions is indispensable.

Pair recordings have shown that the pattern of connectivity between different cell types, i.e. pyramidal and inhibitory neurons, and in different regions of the hippocampus is highly variable. The connectivity between CA3 pyramidal neurons is higher than the same type of connection in CA1 [79, 22]. In the stratum pyramidale, the unitary EPSP recorded from pyramidal cells in CA3 is relatively slower and weaker than for the interneurons [49, 50, 47]. On the other hand, the unitary IPSPs exhibit various amplitudes and response times [48].

The local synaptic connections of the CA1 field has also been investigated using pair recordings [22]. The synaptic connection between pyramidal cells, although very sparse, does not appear to be random, in that nearby pyramidal cells can be interconnected [77]. Contrasted to pyramidal-pyramidal connections, a
disproportionate number of CA1 pyramidal cells synapse onto nearby interneurons (about 50%) even though interneurons form only 10% of the total population [77]. As for the reciprocal connections, about 25 basket cells innervate a CA1 pyramidal cell [15], where half of the synaptic contacts are on the soma and half on the dendrites [77]. The IPSPs involve $GABA_A$ receptors and a unitary IPSP can be larger than 2 mV. In addition to basket cells, axo-axonic cells also synapse onto pyramidal neurons. It has been estimated that one axo-axonic cell contacts 1200 pyramidal cells in-vivo [40]. Besides basket cells and axo-axonic cells, other types of interneurons are also shown to make synaptic contacts with the dendritic regions of CA1 pyramidal cells [28].

A.4 Function: Standard Depiction

Before closing our review of the hippocampus, it is imperative to make mention of some of the well-established hypotheses with regard to the function of this structure.

Perhaps the most widely accepted proposal for hippocampal function relates to its role in memory [24]. In a landmark paper by Scoville and Milner [67], the results of the studies on H.M., probably the most thoroughly studied neuropsychological patient in memory research, showed that bilateral hippocampal removal results in a permanent loss of the ability to encode new information into long-term memory. The same memory impairment has been seen in other patients with bilateral damage restricted to the hippocampus [92].

In animal models, designed memory tasks have confirmed that damage confined to the hippocampal formation produces severe memory impairments. In a standard Morris water maze task, by trial and error, rats learn to locate and swim towards a submerged platform in a small pool of milky water where they can not see the platform. Animals with lesions in the hippocampus region are practically unable to master this task.

Several hypotheses have attempted to explain the role of various macroscopic rhythms that are observed during different behavioral tasks. One theory suggests that during theta activity when the animal is engaged in an exploratory task, the underlying neural activity is responsible for acquiring novel representations of its environment and that the consolidation of these representations is then facilitated during the sharp wave activity observed between animal's successive exploratory attempts [17, 69]. It is further hypothesized that the neural activity during slow wave sleep redirects the information stored in hippocampus during daytime, back into cortex for long-term storage [16].

Understanding the relationship between single cell activity, population rhythms and their importance in behavior are some of the major goals in the study of the hippocampus.
Appendix B

Modeling

Within a cubic millimeter of cortical tissue, there are approximately one hundred thousand neurons and one million synapses mostly arising from intracortical connections [23]. Therefore, neuroscientists, even those studying sub-cellular events, find themselves working with systems with thousands of interacting components. These components are almost invariably engaged in interactions forming multiple feed-forward signals coupled with feed-back loops which quickly evade attempts to predict their behavior using simplistic intuitive approaches.

Refining hypotheses into formal models calls for platforms where actual experiments can be expanded to larger-scale simulations. Computer simulations have been used as a technique to model the nervous system at many different structural scales, including biophysical, the circuit and the system levels. One of the major reasons for using such simulations is to overcome the limitations imposed by the complexity of neural activity introduced in experimental approaches.

Single channel recording techniques [61] have shown that individual voltage-dependent ionic channels undergo rapid transitions between conducting and non-conducting states. The macroscopic population behavior of these channels can be accurately captured using kinetic models that describe these conformational transitions. The remarkably successful quantitative description of the action potential introduced by Hodgkin and Huxley [30] is an instance of this class of models which are commonly referred to as 'Markov models'.

The original work by Hodgkin and Huxley was not directly inspired by such kinetic models and as such, was fairly limited in its scope, however, its extensions have led to characterization of many other voltage-dependent currents including various transmembrane and synaptic channels and as such, have laid the foundation for various quantitative analyses of cellular activity. In the following, we will introduce the basics of the Hodgkin-Huxley (HH) formalism and will discuss its applications in modeling neural activity.

B.1 Conductance-Based Models: Introduction

The work of Hodgkin and Huxley [30] has developed a mathematical framework which can be used to
relate the membrane voltage of a given cell to the population behavior of its several ionic currents through their conductances. Each conductance is typically characterized by a reversal or equilibrium potential, \(E\), and a maximal conductance, \(g\), that is regulated by dynamical voltage dependent activation and inactivation parameters, \(m\) and \(h\). Together these parameters make a quantitative description of the contribution that a specific ionic current makes to the membrane voltage of the cell, \(V\).

\[
I = g m^a h^b (V - E) \tag{B.1}
\]

The activation and inactivation variables can vary between zero and one and their dynamics are described by differential equations that model the kinetics of specific channels. The essential properties of the activation/inactivation variables can be captured by a simplified kinetic model with just two states, open and closed. In such a simplified model the opening and closing of the channel can be described by rate variables \(\alpha\) and \(\beta\) which describe the dynamics with which channels change their state and are generally voltage dependent.

\[
\frac{dm}{dt} = \alpha_m(V). (1 - m) - \beta_m(V). m \tag{B.2}
\]

\[
\frac{dh}{dt} = \alpha_h(V). (1 - h) - \beta_h(V). h \tag{B.3}
\]

In a conductance-based description of a single neuron, the inhomogeneous spatial distribution of various channel types calls for a multicompartmental model where at each compartment the dynamical variables, i.e. \(g\), \(\alpha\) and \(\beta\), can accurately describe the behavior of that compartment. In such a detailed model, one should first compartmentalize the neuron to relatively homogeneous segments, identify each segment’s various conductances and other dynamical variables and then formulate the appropriate differential equations that characterize the electrical properties of that segment.

If for simplicity, it is assumed that the whole cell is homogeneous with regard to its conductances (and the intracellular domain is equipotential, \(V\)), then a single compartmental model could characterize the membrane voltage of the cell. Let us further assume that our hypothetical homogeneous cell has only sodium, potassium and leakage currents (\(i_{Na}, i_{K}\) and \(i_{leak}\) respectively), then the behavior of the cell could be explained by the following differential equations:

\[
C \frac{dV}{dt} = -g_{Na} m^3 h (V - E_{Na}) - g_{K} n^4 (V - E_{K}) - g_{leak} (V - E_{leak}) - i_{syn} \tag{B.4}
\]

\[
\frac{dm}{dt} = \alpha_m(V). (1 - m) - \beta_m(V). m \tag{B.5}
\]

\[
\frac{dh}{dt} = \alpha_h(V). (1 - h) - \beta_h(V). h \tag{B.6}
\]

\[
\frac{dn}{dt} = \alpha_n(V). (1 - n) - \beta_n(V). n \tag{B.7}
\]

In Equ B.4, the sodium conductance, \(g_{Na}\), is regulated by activation and inactivation parameters, \(m\) and \(h\); the potassium conductance, \(g_{K}\), is regulated by an activation parameter, \(n\); leakage conductance,
$g_{\text{leak}}$, in a voltage-independent non-specific cation current which is always active; $i_{\text{syn}}$ is representative of the summed postsynaptic currents and $C$ characterizes the capacitive properties of the cell membrane.

Similar to the intrinsic ionic conductances, synaptic currents are also characterized by the population response of individual channels undergoing rapid transitions between distinct conformational states. Using kinetic models to describe these transitions, one can accurately characterize the macroscopic behavior of these currents. Kinetic models are inherently flexible in their level of detail, ranging from the detailed biophysically realistic gating models to the simplified models where channels are either open or closed. Once again, if we assume that the behavior of channels can be captured using the simplified two state model and neglect heterosynaptic nonlinearities, the total synaptic current would be the sum of individual conductance-based synaptic inputs.

$$i_{\text{syn}} = \sum g_{\text{syn}}.s(V - E_{\text{syn}})$$

$$\frac{ds}{dt} = \alpha.F(V).(1 - s) - \beta.s$$

(B.8)

(B.9)

The activation variable, $s$, is simply governed by the two rate variables, $\alpha$ and $\beta$ and signifies the fraction of the ionic channels in the open state. The only difference is the function $F(V)$ which depicts the dependency of the opening rate, $\alpha$, to the the voltage of the presynaptic cell.

For the case of a multicompartmental model, each compartment will have its own dynamical properties and its own set of differential equations. Applying the appropriate boundary conditions and solving all the differential equations for all the compartments, the behavior of the whole cell can be characterized. In such a framework, the same principles would apply to all the compartments except for certain technicalities that would arise due to compartmentalization: inhomogeneities and abrupt modification of properties at the intersections.

In general, if by means of physiological and pharmacological studies, we could measure the appropriate macroscopic parameters, i.e. synaptic and intrinsic ionic dynamics, the aforementioned set of differential equations would be a complete mathematical description of the macroscopic electrical behavior of the cell. In theory, this means that the dynamical behavior of a network of cells with known physiological properties and synaptic connections could be fully realized through the numerical integration of the appropriate set of conductance-based differential equations.

Although this modeling technique provides a fairly detailed description of macroscopic processes in neural systems, there are various cases where this modeling approach is not justifiable. Depending on the question of interest, in order to avoid either oversimplification or overcomplication of the problem, one should decide what level of detail to include in the model. In the next section we will briefly assess the usefulness of the conductance-based models as well as their shortcomings.
B.2 Conductance-Based Models: Critical Assessment

In general there are two major concerns with regard to the appropriateness of the conductance-based models, its accuracy and its applicability. Studies of single ion channels have greatly expanded our understanding of membrane conductances at both microscopic and macroscopic levels. Detailed knowledge of single channel dynamics has confirmed some of the assumptions made in the simplified Hodgkin-Huxley description, but in other instances inaccuracies have been identified. For example, the sodium channel modeled so successfully were later shown to function in a different manner [1].

Almost all processes essential to electrophysiology of brain can be accurately described through kinetic models, therefore the accuracy of a conductance-based model will depend on the underlying details used to describe the biophysical gating of single channels. Some models, based on voltage clamp studies, have incorporated more than a dozen states [59]; others have utilized detailed kinetic models for the gating of receptors and intracellular second messenger systems such as calcium conductances whereas, Hodgkin and Huxley used what is perhaps the simplest form of such kinetic models with only two states, open and closed. Therefore, these biophysical inaccuracies of single cells can be alleviated by making a stronger link between the macroscopic description of a conductance with the actual channel dynamics [44].

The level of detail to use in a model is not a simple question. Even the simplest models used in small neural systems, involve a large numbers of dynamical variables and parameters that could introduce structural instabilities. This means that the behavior of such a model can change dramatically when relatively small modifications are made to its parameter values. As the model becomes biophysically more and more detailed, the number of parameters that are needed to characterize the system increases and this will typically engender larger structural instabilities. This would not be problematic if we could experimentally determine the exact value of all the relevant parameters, that is all the conductances, their dynamics and their distribution on all the cells. Unfortunately, this is rarely, if ever, the case. The extended structure of most neurons severely limits the accuracy with which parameters can be measured and therefore large instabilities in the model are inescapable.

Because of these limitations, a detailed model of a given neuron, even if it accurately matches the behavior of a biological cell under certain conditions, can not be viewed as a unique description of that cell. By using such a model in a network of interconnected neurons, it will be difficult to make general predictions of the behavior of the network and this is why it is important to understand the appropriateness of cellular models in studying neuronal networks. Ironically, the source of this problem is related to the rich dynamics that these models offer.

Conductance-based models are from one side, too simplified to accurately simulate neural systems in vivo and from the other side, are too detailed to make general predictions with regard to how the brain does computation, however they are useful in understanding how small networks of cells interact, something that would be too complicated in an experimental setup. The practice of using these models has demonstrated that they can provide insights for some of the complex nonintuitive behaviors and dynamics that small
networks embody.

The intermediate level of detail that conductance-based models provide, make them a perfect tool for the analysis of certain population behaviors that can emerge from the dynamical interaction of individual cells. They can offer mechanistic description for several network behaviors and as such, can be used as a foundation for other more abstract modeling approaches. These models are playing essential role in understanding various phenomena both at single cell and at network level. Some of the applications include the study of multistability in neuronal networks, the generation and propagation of rhythmic activity, synaptic plasticity and neuronal bursting.
Appendix C

\( \mathcal{P}_{ISI} \) for Uniform input distribution

In chapter three, to characterize the rhythmicity of the model network, a statistical approach was adopted where samples of the \( ISI \) of the I-cell were obtained, histogrammed, smoothed and normalized to generate the corresponding probability distribution of the network period, \( \mathcal{P}_{ISI} \).

The results for the Gaussian input were presented in section 3.3.1. The same analysis has been performed when the input bias current is taken from a Uniform distribution; i.e. \( i_{bias} \sim U(\eta_{bias}, \omega_{bias}) \). In this case \( \eta_{bias} \) and \( \omega_{bias} \) are the mean and the range of the inputs. The distribution of the network period is constructed from a normalized, interpolated 13-binned histogram of several samples obtained from 500-second runs, the result of which is shown in Fig C.1a-o. The central values are chosen to be \( \eta_{bias_0} = 4.3 \) and \( \omega_{bias_0} = 0.2 \mu A.cm^{-2} \). For distributions with a mean of up to 95% of the central value, the network does not exhibit any rhythmic activity. However, for larger mean values (100%, 105% and 110% of \( \eta_{bias_0} \)), the network generates slow rhythms with unimodal (Fig C.1a-e), bimodal (Fig C.1k-o) or trimodal (Fig C.1f-j) ISI distributions. The mean and the standard deviation of the network period, for the case of the Uniform distribution is listed in Table C.1.

Table C.1: \( ISI \) mean and standard deviation for different Uniform inputs (in msec.)

<table>
<thead>
<tr>
<th>( \eta_{bias} ) (%)</th>
<th>( \omega_{bias} ) (%)</th>
<th>90</th>
<th>95</th>
<th>100</th>
<th>105</th>
<th>110</th>
</tr>
</thead>
<tbody>
<tr>
<td>90,95</td>
<td>( \mu_{ISI} )</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>( \sigma_{ISI} )</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>100</td>
<td>( \mu_{ISI} )</td>
<td>438.20</td>
<td>432.36</td>
<td>426.65</td>
<td>421.67</td>
<td>417.04</td>
</tr>
<tr>
<td></td>
<td>( \sigma_{ISI} )</td>
<td>26.27</td>
<td>27.18</td>
<td>29.69</td>
<td>27.86</td>
<td>30.12</td>
</tr>
<tr>
<td>105</td>
<td>( \mu_{ISI} )</td>
<td>261.50</td>
<td>260.38</td>
<td>257.54</td>
<td>257.58</td>
<td>254.42</td>
</tr>
<tr>
<td></td>
<td>( \sigma_{ISI} )</td>
<td>10.66</td>
<td>10.88</td>
<td>11.70</td>
<td>9.31</td>
<td>12.46</td>
</tr>
<tr>
<td>110</td>
<td>( \mu_{ISI} )</td>
<td>192.79</td>
<td>192.48</td>
<td>191.94</td>
<td>190.30</td>
<td>189.65</td>
</tr>
<tr>
<td>$\sigma_{\text{ISI}}$</td>
<td>5.93</td>
<td>6.52</td>
<td>6.86</td>
<td>7.13</td>
<td>7.46</td>
<td></td>
</tr>
</tbody>
</table>

$\eta_{\text{bias}_0} = 4.3$ and $\omega_{\text{bias}_0} = 0.2 \mu A \text{ cm}^{-2}$ are the central values.
Figure C.1: The $I_{SI}$ probability distribution $P_{I_{SI}}$ of the two-cell network in the face of several different uniformly distributed input bias currents: Mean values change from $\eta_{bias_0} = 4.3 \mu A.cm^{-2}$ in the first column (a-e) to 105% and 110% of $\eta_{bias_0}$ in second (f-j) and third column (k-o). Each row corresponds to a particular value for the standard deviation of the input current: 90% (of the central value, $\omega_{bias_0}$) for the first row (a,f,k), 95% for the second row (b,g,i) and 100%, 105% and 110% for the third (c,h,m), fourth (d,j,n) and fifth row (e,l,o) in that order ($\omega_{bias_0} = 0.2 \mu A.cm^{-2}$). Depending on the input, the distributions have either unimodal or multimodal characteristics.
Appendix D

$P_{N,n}(T)$ for Gaussian & Uniform input distributions

The distribution of the two-cell ISI ($P_{ISI}$) is taken as the firing time distribution of each E-cell after inhibition, $P_{1,1}(T)$, and is applied to Eqn 4.1 to calculate the probability distribution of the network period, $P_{N,n}(T)$, for a network with a total of $N$ E-cells from which a subset of $n$ are necessary and sufficient to drive the I-cell to fire.

With three different mean values, and five different standard deviations, a total of 15 distributions were used as $P_{1,1}(T)$ and the network distribution for $1 \leq n \leq 200$ and $n \leq N \leq 200$ was calculated accordingly.

A few of the results of these analyses were summarized in Fig 4.10 with Gaussian inputs with a mean of $\mu_{bias_0} = 4.3 \mu A.cm^{-2}$ and five different standard deviations (90%, 95%, 100%, 105% and 110% of the central value, $\sigma_{bias_0} = 0.2 \mu A.cm^{-2}$). Here, we report the results for the other Gaussian as well as Uniform inputs. Fig D.1 and D.2 correspond to Gaussian inputs with a $\mu_{bias}$ of 105% and 110% of the central mean value ($\mu_{bias_0} = 4.3 \mu A.cm^{-2}$) respectively and Fig D.3 to D.5 show the results of the same analysis for a Uniform input distribution with a mean of 100%, 105% and 110% of the central mean value ($\eta_{bias_0} = 4.3 \mu A.cm^{-2}$) respectively.
Figure D.1: The distribution of the network period for several different values of $N$ and $n$ and also different Gaussian inputs. The left column (a1-e1) shows the original distribution of a two-cell network, $\mathcal{P}_{1,1}(T)$. The middle column (a2-e2) shows the distribution of the network period for $N = 10$ (blue), $N = 20$ (green) and $N = 100$ (red) with $n = 10$ ($\mathcal{P}_{10,10}(T)$, $\mathcal{P}_{20,10}(T)$ and $\mathcal{P}_{100,10}(T)$). The right column (a3-e3) shows the distribution of the network period for $n = 20$ (blue), $n = 50$ (green) and $n = 100$ (red) with $N = 100$ ($\mathcal{P}_{100,20}(T)$, $\mathcal{P}_{100,50}(T)$ and $\mathcal{P}_{100,100}(T)$). In all three columns, rows a,b,c,d and e correspond to five different Gaussian inputs with the same mean ($\mu_{\text{max}} = 105\%\mu_{\text{max},0}$) and standard deviations that are 90%, 95%, 100%, 105% and 110% of the central value ($\sigma_{\text{bias}} = 0.2\mu A\cdot cm^{-1}$) respectively. The results show that increasing $N$ with $n$ constant (a2-e2), amplifies the lower peaks whereas, increasing $n$ with $N$ constant (a3-e3), suppresses lower peaks and amplifies higher peaks.
Figure D.2: The distribution of the network period for several different values of $N$ and $n$ and also different Gaussian inputs.
The left column (a1-e1) shows the original distribution of a two-cell network, $P_{1,1}(T)$. The middle column (a2-e2) shows the distribution of the network period for $N = 10$ (blue), $N = 20$ (green) and $N = 100$ (red) with $n = 10$ ($P_{10,10}(T)$, $P_{20,10}(T)$ and $P_{100,10}(T)$). The right column (a3-e3) shows the distribution of the network period for $n = 20$ (blue), $n = 50$ (green) and $n = 100$ (red) with $N = 100$ ($P_{100,20}(T)$, $P_{100,50}(T)$ and $P_{100,100}(T)$). In all three columns, rows a, b, c, d and e correspond to five different Gaussian inputs with the same mean ($\mu_{bias} = 110\%\mu_{bias_0}$) and standard deviations that are 90%, 95%, 100%, 105% and 110% of the central value ($\sigma_{bias_0} = 0.2\mu A.cm^{-2}$) respectively. The results show that increasing $N$ with $n$ constant (a2-e2), amplifies the lower peaks whereas, increasing $n$ with $N$ constant (a3-e3), suppresses lower peaks and amplifies higher peaks.
Figure D.3: The distribution of the network period for several different values of $N$ and $n$ and also different Uniform inputs. The left column (a1-e1) shows the original distribution of a two-cell network, $P_{1,1}(T)$. The middle column (a2-e2) shows the distribution of the network period for $N = 10$ (blue), $N = 20$ (green) and $N = 100$ (red) with $n = 10$ ($P_{10,10}(T)$, $P_{20,10}(T)$ and $P_{100,10}(T)$). The right column (a3-e3) shows the distribution of the network period for $n = 20$ (blue), $n = 50$ (green) and $n = 100$ (red) with $N = 100$ ($P_{100,20}(T)$, $P_{100,50}(T)$ and $P_{100,100}(T)$). In all three columns, rows a,b,c,d and e correspond to five different Uniform inputs with the same mean ($\eta_{\text{bias}} = \eta_{\text{biasm}}$) and standard deviations that are 90%, 95%, 100%, 105% and 110% of the central value ($\omega_{\text{bias}} = 0.2\mu A.cm^{-2}$) respectively. The results show that increasing $N$ with $n$ constant (a2-e2), amplifies the lower peaks whereas, increasing $n$ with $N$ constant (a3-e3), suppresses lower peaks and amplifies higher peaks.
Figure D.4: The distribution of the network period for several different values of $N$ and $n$ and also different Uniform inputs. The left column (a1-e1) shows the original distribution of a two-cell network, $P_{1,1}(T)$. The middle column (a2-e2) shows the distribution of the network period for $N = 10$ (blue), $N = 20$ (green) and $N = 100$ (red) with $n = 10$ ($P_{10,10}(T)$, $P_{20,10}(T)$ and $P_{100,10}(T)$). The right column (a3-e3) shows the distribution of the network period for $n = 20$ (blue), $n = 50$ (green) and $n = 100$ (red) with $N = 100$ ($P_{100,20}(T)$, $P_{100,50}(T)$ and $P_{100,100}(T)$). In all three columns, rows a,b,c,d and e correspond to five different Uniform inputs with the same mean ($\eta_{bias} = 105\% \eta_{bias_0}$) and standard deviations that are 90%, 90%, 100%, 105% and 110% of the central value ($\omega_{bias_0} = 0.2 \mu A \cdot cm^{-2}$) respectively. The results show that increasing $N$ with $n$ constant (a2-e2), amplifies the lower peaks whereas, increasing $n$ with $N$ constant (a3-e3), suppresses lower peaks and amplifies higher peaks.
Figure D.5: The distribution of the network period for several different values of $N$ and $n$ and also different Uniform inputs. The left column (a1-e1) shows the original distribution of a two-cell network, $P_{1,1}(T)$. The middle column (a2-e2) shows the distribution of the network period for $N = 10$ (blue), $N = 20$ (green) and $N = 100$ (red) with $n = 10$ ($P_{10,10}(T), P_{20,10}(T)$ and $P_{100,10}(T)$). The right column (a3-e3) shows the distribution of the network period for $n = 20$ (blue), $n = 50$ (green) and $n = 100$ (red) with $N = 100$ ($P_{100,20}(T), P_{100,50}(T)$ and $P_{100,100}(T)$). In all three columns, rows a,b,c,d and e correspond to five different Uniform inputs with the same mean ($\eta_{bias} = 110\%\eta_{bias0}$) and standard deviations that are 90%, 95%, 100%, 105% and 110% of the central value ($\omega_{bias0} = 0.2\mu A.cm^{-2}$) respectively. The results show that increasing $N$ with $n$ constant (a2-e2), amplifies the lower peaks whereas, increasing $n$ with $N$ constant (a3-e3), suppresses lower peaks and amplifies higher peaks.
Appendix E

Phenomenological model: MATLAB Scripts

To calculate the probability distribution function of the network period, $P_{N,n}(T)$, from the parameters of the phenomenological model ($N$, $n$ and $P_{1,1}(T)$), we have used the following script files (m-files in MATLAB):

To construct $P_{1,1}(T)$ from the results of the numerical simulations

\[
\begin{align*}
[simu\_hist\ samples] &= \text{hist}(simu, 13); \\
s_i &= \text{min}(samples); \\
s_f &= \text{max}(samples); \\
T &= s_i : 0.1 : s_f; \\
pdf11 &= \text{spline}(samples, simu\_hist, T); \\
\text{for dummy} &= 1 : \text{length(pdf11)} \\
\quad pdf11(\text{dummy}) &= \text{max}(0, pdf11(\text{dummy})); \\
\text{end} \\
pdf11 &= pdf11/\text{trapez}(T, pdf11) \times 10^3; \\
\text{cum}_\text{pdf} &= \text{cumtrapz}(T, pdf11)/1000;
\end{align*}
\]

To construct $P_{N,n}(T)$ from $N$, $n$ and $P_{1,1}(T)$
\[ \text{permutations} = \frac{\text{factorial}(N)}{\text{factorial}(n-1) \cdot \text{factorial}(N-n)}; \]
\[ \text{pdf} \ N_n = \text{pdf11} \cdot \text{cum_pdf}(n-1) \cdot (1 - \text{cum_pdf})(N-n) \cdot \text{permutations}; \]

where:
- \( \text{simu} \) Vector containing the samples of the network period from the simulations
- \( \text{simu_hist} \) Histogram of the simulation results
- \( s_i \) Minimum sample period
- \( s_f \) Maximum sample period
- \( \text{pdf11} \) \( \mathcal{P}_{1,1}(\mathcal{T}) \)
- \( N \) Number of E-cells in the network
- \( n \) Number of E-cells needed to make the I-cell fire
- \( \text{cum_pdf} \) \( \mathcal{P}_{1,1}(\mathcal{T} \leq \mathcal{T}) \)
- \( \text{pdf} \ N_n \) \( \mathcal{P}_{N,n}(\mathcal{T}) \)
Bibliography


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