

STOCHASTIC MODELING AND ANALYSIS
OF NOISE IN NEURONAL CIRCUITS

by

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OF NOISE IN NEURONAL CIRCUITS

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*Dedicated to my parents,
Zeynep & Aziz*

ABSTRACT

The brain is extremely energy efficient and remarkably robust in what it does despite the considerable variability and noise arising from the inherently stochastic mechanisms that exist in the neurons and the synapses. For example, these noise sources can significantly degrade spike timing precision, which is believed to be a key factor in sensory information encoding and computations performed by the neurons and neuronal circuits. Computational modeling is a powerful tool that can help us gain insight into neuronal mechanisms utilized by the nervous system. In addition, a deep understanding and computational design tools can help develop robust neuromorphic electronic circuits and hybrid neuroelectronic systems. In this thesis, we present a general modeling framework for biological neuronal circuits that systematically captures the nonstationary stochastic behavior of ion channels and synaptic processes. In this framework, fine-grained, discrete-state, continuous-time Markov Chain (MC) models of both ion channels and synaptic processes are treated in a unified manner. Our modeling framework features a mechanism for the automatic generation of the corresponding coarse-grained, continuous-state, continuous-time Stochastic Differential Equation (SDE) models for neuronal variability and noise. Furthermore, we repurpose non Monte Carlo noise analysis techniques, which were previously developed for analog electronic circuits, for the stochastic characterization of neuronal circuits both in time and frequency domain. These techniques, which are orders of magnitude faster than traditional Monte Carlo type simulations, can be used to directly compute the spike timing jitter variance, power spectral densities, correlation functions, and other stochastic characterizations of neuronal circuit operation. We verify that the fast non Monte Carlo analysis methods produce results with the same accuracy as computationally expensive Monte Carlo simulations. We have implemented the proposed techniques in a prototype simulator where both biological neuronal and analog electronic circuits can be simulated together in a coupled manner. By using this simulator, we investigate several distinct neuronal circuit motifs

and mechanisms such as synaptic feedback inhibition, synaptic integration, and synaptic coupling. First, we show that both the spike timing precision and the energy efficiency of a spiking neuron are improved with feedback inhibition. We unveil the underlying mechanism through which this is achieved. Second, we demonstrate that a neuron can improve on the timing precision of its synaptic inputs, coming from multiple sources, via synaptic integration: The phase of the output spikes of the integrator neuron has the same variance as that of the sample average of the phases of its inputs. Finally, we reveal that weak synaptic coupling among neurons, in a fully connected network, enables them to behave like a single neuron with a larger membrane area, resulting in an improvement in the timing precision through cooperation.



Ö Z E T Ç E

Beyin enerji kullanımı konusunda son derece verimli bir organdır. Nöronlarda ve sinapslarda doğal olarak var olan stokastik mekanizmalardan kaynaklanan yüksek değişkenlik ve gürültüye rağmen beyin yaptığı işlemler konusunda oldukça güvenilirdir. Örneğin bu gürültü kaynakları nöronlar ve nöronal devreler tarafından gerçekleştirilen duyuşsal bilgi kodlama ve hesaplamalarında anahtar bir faktör olduđuna inanılan sinir uyarıtlarının zamanlama hassasiyetini önemli ölçüde düşürebilir. Hesaplamalı modelleme, sinir sistemi tarafından kullanılan nöronal mekanizmaları kavramamıza yardımcı olabilecek güçlü bir araçtır. Buna ek olarak, derinlemesine bir kavrayış ve hesaplamalı tasarım araçları, verimli nöromorfik elektronik devreler ve hibrit nöroelektronik sistemler geliştirmemize yardımcı olabilir. Bu tezde, biyolojik nöronal devreler için iyon kanallarının ve sinaptik işlemlerin durağan olmayan stokastik davranışlarını sistematik olarak koruyan genel bir modelleme sistemi sunuyoruz. Bu sistemde, hem iyon kanallarının hem de sinaptik işlemlerin ince taneli, ayrık durumlu, sürekli zamanlı Markov Zinciri (MC) modelleri birleşik bir şekilde ele alıyoruz. Modelleme çerçevemiz, nöronal değişkenlik ve gürültü için ilgili kaba taneli, sürekli durumlu, sürekli zamanlı Stokastik Diferansiyel Denklem (SDE) modellerinin otomatik olarak üretilmesi için bir mekanizmaya sahiptir. Ayrıca daha önce analog elektronik devreler için geliştirilmiş olan Monte Carlo olmayan gürültü analizi tekniklerini, nöronal devrelerin hem zaman hem de frekans alanındaki stokastik karakterizasyonu için yeniden tasarlıyoruz. Geleneksel Monte Carlo tipi simülasyonlardan birkaç mertebe daha hızlı olan bu teknikleri, sinir uyarıtlarının zamanlama titreşimi varyansını, güç spektral yoğunluklarını, korelasyon fonksiyonlarını ve nöronal devre operasyonunun diğer stokastik karakteristiklerini doğrudan hesaplamak için kullanıyoruz. Bu çok hızlı Monte Carlo olmayan analiz yöntemlerinin hesaplama açısından daha çok işlem gerektiren Monte Carlo simülasyonlarıyla aynı doğrulukta sonuçlar ürettiğini doğruluyoruz. Bu yeni teknikleri hem biyolojik nöron devrelerinin hem de analog elektronik devrelerinin birlikte bağlanmış bir şekilde simüle edilebildiği

bir prototip simülatörde uyguladık. Bu simülatörü kullanarak sinaptik geri besleme inhibisyonu, sinaptik entegrasyon ve sinaptik bağlanma gibi birkaç farklı nöronal devre motifini ve mekanizmasını araştırdık. İlk olarak, sinir uyartıları üreten bir nöronun hem sinir uyartılarının zamanlama hassasiyetinin hem de enerji verimliliğinin geri besleme inhibisyonu ile arttığını gösterdik. Bir nöronun bunu başarmasını sağlayan temel mekanizmayı açığa çıkardık. İkinci olarak, bir nöronun çoklu kaynaklardan gelen sinaptik girdilerindeki sinir uyartılarının zamanlama hassasiyetinin entegrasyon yoluyla gelişebileceğini kanıtladık: Entegratör nöronun çıkış sinir uyartılarının fazının, girdi sinir uyartılarının fazların ortalamasıyla aynı varyansa sahip olduğunu gösterdik. Son olarak, tamamen bağlı bir ağda, nöronlar arasındaki zayıf sinaptik bağlanmanın, daha büyük bir nöron zarı alanına sahip tek bir nöron gibi davranmalarını sağlayarak, sinir uyartılarının zamanlama hassasiyetini işbirliği yaparak geliştirdiklerini ortaya koyduk.

PUBLICATIONS

Contents of this thesis have previously appeared in the following publications:

- [1] D. Kilinc and A. Demir, “Spike timing precision of neuronal circuits,” *Journal of Computational Neuroscience*, vol. 44, no. 3, pp. 341–362, 2018.
- [2] D. Kilinc and A. Demir, “Noise in neuronal and electronic circuits: A general modeling framework and Non-Monte Carlo simulation techniques,” *IEEE Transactions on Biomedical Circuits and Systems*, vol. 11, no. 4, pp. 958–974, 2017.
- [3] D. Kilinc and A. Demir, “Simulation of noise in neurons and neuronal circuits,” in *Proceedings of the IEEE/ACM International Conference on Computer-Aided Design (ICCAD)*, IEEE, Austin, TX, USA, 2015, pp. 589–596.

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CONTENTS

I BACKGROUND

1	INTRODUCTION	2
1.1	Neuronal Circuits & Analog Electronics: Synergies	2
1.2	Spike Timing Precision of Neuronal Circuits	3
1.3	Previous Work: Neuronal Circuit Modeling	4
1.4	Contributions of the Thesis	6
1.5	Outline of the Thesis	9
2	BACKGROUND ON NEURONS AND NEURONAL NETWORK	11
2.1	Neurons and Neuronal Circuits	11
2.2	Markov Chain Models of Voltage-Gated Ion Channels	12
2.3	Markov Chain Models of Ligand-Gated Ion Channels	15
2.4	Stochastic Chemical Reaction Model of Neurotransmitter Release	18
3	BACKGROUND ON MARKOV CHAINS AND STOCHASTIC CHEM- ICAL KINETICS FORMALISM	20
3.1	Reduction of Markov Chain Models based on Lumpability . . .	21
3.2	Representation of Lumped MC Models as Stochastic Chemical Reactions	23

II UNIFIED MODELING & SIMULATION FRAMEWORK

4	UNIFIED FRAMEWORK FOR STOCHASTIC ANALYSIS OF NEU- RONAL CIRCUITS	26
4.1	Mapping HYB-MC-CR Model to HYB-CR Model	27
4.2	Mapping HYB-CR Model to NLSDE Model	29
5	NUMERICAL METHODS FOR MONTE CARLO SIMULATION OF NEURONAL CIRCUITS	33
5.1	Stochastic Simulation based on HYB-CR Model	33
5.2	Stochastic Simulation based on NLSDE Model	35
6	ANALYSIS-BASED, NON MONTE CARLO, NUMERICAL NOISE CHARACTERIZATION OF NEURONAL CIRCUITS	38

6.1	Time-Domain Non Monte Carlo Method	41
6.2	Frequency-Domain Non Monte Carlo Method	42
6.3	Non Monte Carlo Stochastic Characterization of Autonomously Oscillating Neuronal Circuits	44
6.4	Summary of Unified Modeling Methodology: Transformations & Approximations	48
6.4.1	HYB-MC-CR Model to HYB-CR Model	50
6.4.2	HYB-CR Model to NLSDE Model to NLSDE-SD Model	50
6.4.3	NLSDE-SD Model to LSDE-SD Model	53
6.5	Alternative Derivation Methodology	54
7	VERIFICATION OF METHODS VIA NUMERICAL SIMULATIONS	56
7.1	Verification of NLSDE-SD Model Approximation of HYB-CR Model via Monte Carlo Simulations	57
7.1.1	Neuron with a Constant Above-Threshold Stimulus . . .	57
7.1.2	Neuronal Circuit with Reconvergence	58
7.2	Verification of non Monte Carlo Methods via Monte Carlo Simulations	61
7.2.1	Neuron with Transient Above Threshold Pulse Stimulus	63
7.2.2	Neuron with Periodic Pulsed Stimulus	64
7.2.3	Neuron with a Constant Above-Threshold Stimulus . . .	66
7.2.4	Two Neurons Connected with an Excitatory Synapse . .	69
7.2.5	Five-Neuron Ring Oscillator	70
 III RESULTS		
8	AUTONOMOUSLY OSCILLATING NEURONAL CIRCUITS: EN- ERGY CONSUMPTION VS. TIMING JITTER	74
8.1	Effect of Membrane Area on Single Neuron Oscillator	76
8.2	Effect of Excitation on Single Neuron Oscillator	77
8.3	Single Neuron Vs. Five-Neuron Ring Oscillators	77
9	FEEDBACK INHIBITION	80
9.1	Spike Timing Precision Vs. Feedback Inhibition	80
9.2	Spike Timing Precision Vs. Synaptic Channel Noise	86
9.3	Energy Consumption Vs. Feedback Inhibition	89
9.4	Membrane Voltage Variance Vs. Feedback Inhibition	92

10 SYNAPTIC INTEGRATION	94
11 SYNAPTIC COUPLING	99
11.1 Synchronization Time Vs. Synaptic Coupling Strength	102
11.2 Spike Timing Precision and Spiking Period Vs. Synaptic Cou- pling Strength	104
11.3 Spike Timing Precision of Weakly Coupled Heterogeneous Neu- ronal Networks	110
12 SUMMARY AND CONCLUSION	113
 BIBLIOGRAPHY	 117



LIST OF FIGURES

Figure 1	(a) A simplified illustration of presynaptic and postsynaptic neurons, VG and LG ion channels, synapse, and neurotransmitter release mechanism. (b) A schematic representation of the interactions between the neuronal circuit components shown in (a).	13
Figure 2	MC models for (a) K^+ and (b) Na^+ ion channels. . . .	14
Figure 3	MC models for (a) excitatory AMPA/kainate receptor, and (b) inhibitory $GABA_A$ receptor ion channels. . . .	16
Figure 4	The system of chemical reactions for neurotransmitter release.	19
Figure 5	a) A generic micro MC model, where S_i 's and r_i 's are states and transition rates. b) The macro MC model constructed by composing two independent micro MCs, where superscript index of each S_i indicates the sequence number of the micro MC that is in state S_i . c) The lumped MC model of the macro MC. d) Representation as a chemical reaction system, where C_i 's and r_i 's are the chemical species and the reaction rate constants.	22
Figure 6	a) The unified modeling and simulation framework for neuronal circuits. b) The mapping methodology used in our framework, where solid arrows indicate exact mapping while dashed arrows are used if any approximation is involved in the mapping. c) An alternative mapping methodology.	27

Figure 7	a) The histogram of ISIs and b) the phase jitter variance for a single neuron where an external DC current is injected is shown for both HyB-CR and NLSDE-SD models. c) A snippet from 20 action potentials generated by our simulations, drawn on top of each other.	59
Figure 8	a) The neuronal circuit simulated for correlated excitatory and inhibitory synaptic inputs where an external DC current is injected to neuron N1. b) The neuronal circuit simulated for uncorrelated excitatory and inhibitory synaptic inputs where independent external DC currents are injected to neuron N1 and N5. c) The histogram of ISIs of neuron N4 is shown for both correlated and uncorrelated excitatory and inhibitory synaptic inputs.	60
Figure 9	a) Transient behavior of a neuron with a single above-threshold pulse excitation. The time-varying b) mean and c) variance of the membrane voltage.	65
Figure 10	a) Neuron excited with periodic above-threshold current pulses. b) Time-averaged spectral density and c) variance of the membrane voltage.	66
Figure 11	a) Neuron under tonic spiking conditions with a constant, above-threshold current stimulus. b) Time-averaged power spectral density of the membrane voltage. c) The phase jitter variance of the output action potentials.	67
Figure 12	Two neurons connected with an excitatory synapse. a) The first neuron is excited by periodic, above-threshold pulsed stimulus. b) Time-averaged power spectral density of the membrane voltage of the second neuron in (a) . c) The first neuron is under tonic spiking conditions. d) Time-averaged power spectral density of the membrane voltage of the second neuron in (c)	68
Figure 13	a) Five-neuron ring oscillator. b) Time-averaged power spectral density of the membrane voltage of neuron N1.	71

Figure 14	a) Average action potential energy consumption E_{AP} and b) Timing jitter variance slope c plotted with respect to the membrane area A_m	75
Figure 15	a) Average action potential energy consumption E_{AP} and firing frequency f_c , b) timing jitter variance slope c plotted with respect to the amplitude of the constant current injection I_{ext}	76
Figure 16	Feedback inhibition of neuron $\mathcal{N}_1$ by neuron $\mathcal{N}_2$. Neuron $\mathcal{N}_1$ is under tonic spiking conditions with a constant, suprathreshold current stimulus.	81
Figure 17	20 sample paths, generated for the membrane voltage of neuron $\mathcal{N}_1$ in Figure 16, are drawn on top of each other. The timing jitters $\alpha(T_c)$ and $\alpha(2T_c)$ are indicated for the first two output action potentials, where increasing timing jitter variance can be easily observed.	81
Figure 18	The timing jitter variance of the output spikes of neuron $\mathcal{N}_1$ in Figure 16. The amplitude of the external suprathreshold current input to neuron $\mathcal{N}_1$ is held constant at $I_{ext} = 0.25$ A/m ² . The membrane area of each neuron in Figure 16 is fixed at $A_m = 1000$ μ m ² . The numbers of receptor ion channels in the synapses between $\mathcal{N}_1$ and $\mathcal{N}_2$ are $N_{ext} = 3 \times 10^4$ excitatory AMPA/kainate receptor channels (in $\mathcal{N}_2$) and $N_{inh} = 1 \times 10^4$ inhibitory GABA _A receptor channels (in $\mathcal{N}_1$). The timing jitter variance increases linearly with time as expected.	82
Figure 19	The timing jitter variance slope of neuron $\mathcal{N}_1$ in Figure 16 with respect to the number of the inhibitory synaptic channels (in $\mathcal{N}_1$) for $I_{ext} = 0.25$ A/m ² , $A_m = 1000$ μ m ² , and $N_{ext} = 3 \times 10^4$ AMPA/kainate receptor channels (in $\mathcal{N}_2$).	83

Figure 20	The spiking period of neuron $\mathcal{N}_1$ in Figure 16 with respect to the number of the inhibitory synaptic channels (in $\mathcal{N}_1$) for $I_{\text{ext}} = 0.25 \text{ A/m}^2$, $A_m = 1000 \text{ } \mu\text{m}^2$, and $N_{\text{ext}} = 3 \times 10^4$ AMPA/kainate receptor channels (in $\mathcal{N}_2$). 84
Figure 21	The spike timing information content of the output action potentials of neuron $\mathcal{N}_1$ in Figure 16 with respect to the number of the inhibitory synaptic channels (in $\mathcal{N}_1$) for $I_{\text{ext}} = 0.25 \text{ A/m}^2$, $A_m = 1000 \text{ } \mu\text{m}^2$, and $N_{\text{ext}} = 3 \times 10^4$ AMPA/kainate receptor channels (in $\mathcal{N}_2$). . . . 84
Figure 22	The timing jitter variance slope of the output action potentials of neuron $\mathcal{N}_1$ in Figure 16 for constant $N_{\text{inh}} \cdot g_{\text{GABA}_A} = 2 \times 10^5 \text{ pS}$ is plotted with red dashed curve (square markers) with respect to the number of the inhibitory synaptic channels (in $\mathcal{N}_1$) on the lower x -axis and the conductance of a single inhibitory synaptic channel (in $\mathcal{N}_1$) on the upper x -axis. The blue solid curve (circle markers) is the same curve as the one in Figure 19, which shows the timing jitter variance slope of the output action potentials of neuron $\mathcal{N}_1$ for constant $g_{\text{GABA}_A} = 20 \text{ pS}$ with respect to the number of the inhibitory synaptic channels (in $\mathcal{N}_1$) on the lower x -axis. For both cases, the amplitude of the external suprathreshold current input to neuron $\mathcal{N}_1$ is $I_{\text{ext}} = 0.25 \text{ A/m}^2$, the membrane area of each neuron is $A_m = 1000 \text{ } \mu\text{m}^2$, and the number of excitatory AMPA/kainate receptor channels is $N_{\text{ext}} = 3 \times 10^4$ channels (in $\mathcal{N}_2$). The product $N_{\text{inh}} \cdot g_{\text{GABA}_A}$ is kept constant at each point of the red dashed curve (square markers). Thus, as the number of inhibitory synaptic channels is increased, although the mean inhibitory synaptic current does not change, the inhibitory synaptic current noise decreases. As the noise level decreases, the timing jitter variance first decreases and then becomes constant. 87

Figure 23	Feedback inhibition of neuron $\mathcal{N}_1$ by neuron $\mathcal{N}_2$. Neuron $\mathcal{N}_1$ is stimulated by a single suprathreshold current pulse with a duration of 2 msec.	91
Figure 24	The mean membrane voltages of the neurons $\mathcal{N}_1$ and $\mathcal{N}_2$ shown in Figure 23, where $\mathcal{N}_1$ (with membrane area $A_m = 1000 \mu\text{m}^2$) is stimulated by a single suprathreshold current pulse with an amplitude $I_{\text{ext}} = 0.25 \text{ A/m}^2$ and a duration of 2 msec. The numbers of the receptor ion channels in the synapses between $\mathcal{N}_1$ and $\mathcal{N}_2$ are $N_{\text{ext}} = 3 \times 10^4$ excitatory AMPA/kainate receptor channels (in $\mathcal{N}_2$), and $N_{\text{inh}} = 2 \times 10^4$ inhibitory GABA _A receptor channels (in $\mathcal{N}_1$).	91
Figure 25	The variance of the membrane voltage of neuron $\mathcal{N}_1$ shown in Figure 23 evaluated for varying number of inhibitory synaptic channels N_{inh} (in $\mathcal{N}_1$). Feedback inhibition significantly decreases the membrane voltage variance during the refractory period. The membrane voltage fluctuations become depressed for a longer duration, which prevents the excessive accumulation of timing jitter until the next spike.	92
Figure 26	The synaptic integration of excitatory inputs. Each input neuron is under tonic spiking conditions with a constant, suprathreshold current stimulus and has an excitatory synaptic connection to the output neuron. .	95
Figure 27	The timing jitter variance slope of the action potentials of the output neuron shown in Figure 26 with respect to the number of input neurons. Each input neuron is excited by a suprathreshold current stimulus with an amplitude $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$. The output neuron includes 2×10^4 excitatory AMPA/kainate receptor channels per synapse. The timing jitter variance of the output neuron $c_{ss,\text{out}}$ is the same as the timing jitter variance of a single input neuron $\bar{c}_{ss}$ scaled by $1/M_{\text{input}}$. .	97

Figure 28	Fully connected neuronal oscillator circuit with five neurons. Each neuron is under tonic spiking conditions with a constant, suprathreshold current stimulus. . . . 100
Figure 29	The timing jitter variance of the output action potentials of a neuron in the five-neuron E network in Figure 28, for $N_{\text{ex}} = 750$ and 3000 excitatory AMPA/kainate receptor channels per synapse. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$ and the membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$. The timing jitter variance of a standalone neuron excited by the same suprathreshold current stimulus $I_{\text{ext}} = 0.25 \text{ A/m}^2$, with a membrane area $A_m = 1000 \mu\text{m}^2$, is also shown. The synchronization times $T_{\text{sync},1}$ (for $N_{\text{ex}} = 3000$) and $T_{\text{sync},2}$ (for $N_{\text{ex}} = 750$) for the E networks are indicated on the graph. 100
Figure 30	The synchronization times of the five-neuron E, I, and EI networks as a function of the number of receptor channels per synapse. The amplitude of the total external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$. For the EI network, N indicates the total number of excitatory ($N/2$) and inhibitory ($N/2$) channels per synapse. For the E and I networks, N is the number of excitatory and inhibitory channels per synapse, respectively. 101

Figure 31	The timing jitter variance slope of a neuron in the five-neuron E, I, and EI networks in Figure 28 as a function of the number of receptor channels per synapse. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$. For the EI network, N is the total number of excitatory ($N/2$) and inhibitory ($N/2$) channels per synapse. For E and I networks, N is the number of excitatory and inhibitory channels per synapse, respectively. The timing jitter variance slopes of single, standalone neurons with membrane areas $A_m = 1000 \mu\text{m}^2$ and $5A_m = 5000 \mu\text{m}^2$, excited by the same suprathreshold current stimulus $I_{\text{ext}} = 0.25 \text{ A/m}^2$, are also shown. If the number of synaptic receptor channels is lower than a certain value, the timing jitter variances of the five-neuron E, I, and EI networks are the same as that of an autonomously oscillating standalone neuron with a membrane area of $5A_m$ excited by the same constant suprathreshold current stimulus.	106
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Figure 32	The spiking period of a neuron in the five-neuron E, I, and EI networks in Figure 28 as a function of the number of receptor channels per synapse. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \text{ } \mu\text{m}^2$. For the EI network, N is the total number of excitatory ($N/2$) and inhibitory ($N/2$) channels per synapse. For E and I networks, N is the number of excitatory and inhibitory channels per synapse, respectively. The spiking period for a single, standalone neuron (with membrane area $A_m = 1000 \text{ } \mu\text{m}^2$ or $5A_m = 5000 \text{ } \mu\text{m}^2$, the period is the same) excited by the same suprathreshold current stimulus $I_{\text{ext}} = 0.25 \text{ A/m}^2$ is also presented. If the number of synaptic receptor channels is lower than a certain value, the spiking periods of the five-neuron E, I, and EI networks are the same as that of an autonomously oscillating standalone neuron excited by the same constant suprathreshold current stimulus. We note that the spiking period of a standalone neuron is independent of its membrane area if the current stimulus density is kept constant. The reason for the gaps in the data (due to instability of the circuit) is explained in the main text.	107
Figure 33	A sample path for the membrane voltages of the neurons in the EI network in Figure 28. The EI network is stable and synchronized with cooperation for $N_{\text{ex}} = 2$ and $N_{\text{in}} = 2$ channels per synapse. All of the neurons in the network generate spikes periodically. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \text{ } \mu\text{m}^2$	108

Figure 34	A sample path for the membrane voltages of the neurons in the EI network in Figure 28. The EI network exhibits unstable behavior. Initially, the network behavior is dominated by neuron $\mathcal{N}_3$. However, after a perturbation due to noise in the neuronal circuit, neuron $\mathcal{N}_4$ starts to dominate the network behavior and the spiking neuron $\mathcal{N}_3$ is inhibited. We note that neuron $\mathcal{N}_5$ also tries to spike but cannot maintain its spiking state. The numbers of excitatory and inhibitory receptor channels per synapse are $N_{\text{ex}} = 2000$ and $N_{\text{in}} = 2000$, respectively. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$	109
Figure 35	A sample path for the membrane voltages of the neurons in the EI network in Figure 28. The EI network is stable and desynchronized with the domination of neuron $\mathcal{N}_4$ in the network for $N_{\text{ex}} = 20000$ and $N_{\text{in}} = 20000$ channels per synapse. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$	109

LIST OF TABLES

Table 1	Summary of the results obtained for various neuronal circuit architectures.	49
Table 2	Summary of simulation setups used for the verification of non Monte Carlo methods	63
Table 3	Spike timing precision and energy consumption analysis of neuronal circuits with and without feedback inhibition. The presence of feedback inhibition improves both the timing precision and the energy efficiency of the neuronal circuit.	90
Table 4	Spike timing precision and energy consumption analysis of neuronal circuits with feedback inhibition. As the strength of feedback inhibition is enhanced, both the timing precision and the energy efficiency of the neuronal circuit are improved.	90

ACRONYMS

ATP	Adenosine Triphosphate
DAE	Differential-Algebraic Equation
DFT	Discrete Fourier Transform
HH	Hodgkin and Huxley
HYB-CR	Hybrid Chemical Reaction
HYB-MC-CR	Hybrid Markov Chain & Chemical Reaction
ISI	Interspike Interval
LG	Ligand-Gated
LMC	Lumped Markov Chain
LPTV	Linear Periodically Time Varying
LSDE-SD	Linear Stochastic Differential Equations with Smooth Diffusion
LTV	Linear Time Varying
MC	Markov Chain
NLSDE	Nonlinear Stochastic Differential Equations
NLSDE-SD	Nonlinear Stochastic Differential Equations with Smooth Diffusion
ODE	Ordinary Differential Equation
PPV	Perturbation Projection Vector
PRC	Phase Response Curve
SCN	Suprachiasmatic Nucleus
SDE	Stochastic Differential Equation
SNR	Signal-to-Noise Ratio
SSA	Stochastic Simulation Algorithm
VG	Voltage-Gated

Part I

BACKGROUND



INTRODUCTION

1.1 NEURONAL CIRCUITS & ANALOG ELECTRONICS: SYNERGIES

The brain is extremely energy efficient and very robust in processing sensory data and in the other computations it performs [1]–[3]. On the other hand, the neurons and synapses exhibit considerable variability and noise due to the inherent stochastic behavior of ion channels and neurotransmitter release processes. This makes them noisy, arguably unreliable analog devices processing electrochemical signals [4], [5]. However, neuronal circuits in the brain, composed of neurons interconnected via synapses, can robustly perform complex computations [1], [6]. This is very similar to the challenge one faces in the design of nano-electronic systems. Shrinking the dimensions of the transistors makes them faster and more energy efficient, however, at the same time, they become less reliable and more noisy.

Over the past several decades, engineers have been trying to devise artificial devices having similar capabilities to those of the brain [7]–[9]. In line with this aim, the concept of neuromorphic engineering was proposed where both analog and digital electronic circuits are designed to emulate biological neuronal circuits present in the nervous system [10], [11]. For example, in [12], bio-inspired neuron and synapse integrated circuits are presented. In [13], a silicon model of neuron membrane dynamics based on detailed ion channel kinetics is introduced. In [14], a single transistor synapse device which exhibits plasticity, i.e., reconfigurability, is presented. Furthermore, digital circuit implementations of neurons [15] and synapses [16] have been realized. Nevertheless, in order to successfully mimic the features of the brain, its functional mechanisms need to be deeply understood, which has not been completely achieved yet.

Neuromorphic engineering emphasizes understanding and mimicking the intricate architectural mechanisms in biological neuronal circuits in order to design both analog and digital electronic circuits with similar properties.

On the other hand, analog circuit design and analysis is a deep discipline where sophisticated circuit architectures and computational techniques have been developed over the past fifty years. It makes most sense to augment the synergy between these two domains also in the reverse direction by adapting and using techniques from analog circuit analysis for a modeling and simulation framework that can treat neuronal and analog electronic circuits in a unified manner. Such a unified perspective may greatly facilitate the analysis and understanding of biological neuronal circuits. In [17], a similar unified view for analog electronic circuits and synthetic biological cellular circuits is proposed. Similarities between electronic and biological circuits are pointed out in [18] so that insights and techniques from electronics can be utilized to understand cellular mechanisms and in order to design synthetic biological circuits [19].

In this thesis, we advocate that the techniques used for electronic circuit analysis can be put to use in trying to understand the mechanisms in neuronal circuits and the functioning of a brain, as a reverse but complementary direction to neuromorphic engineering. We use a synergistic, interdisciplinary approach where we bring together concepts and techniques from analog electronic circuit analysis, computational neuroscience, and stochastic chemical kinetics. We present a unified stochastic modeling and simulation framework for neuronal circuits. We have recently utilized a similar synergistic approach in addressing a previously unsolved problem in electronic circuit analysis: In [20]–[22], we have adapted and used techniques from computational neuroscience and stochastic chemical kinetics in solving a problem that relates to the modeling and simulation of low frequency noise in nano-sized transistors and electronic circuits that do not operate in the small-signal regime.

1.2 SPIKE TIMING PRECISION OF NEURONAL CIRCUITS

A sensory neuron transmits information to multiple neurons via its axon terminals. The sensory information is ultimately delivered to the cortical neurons and integrated via their dendrites. The spike timing precision of the neurons in the cerebral cortex receiving multiple synaptic inputs is a key factor for accurate sensory data encoding, especially for the auditory

and visual systems [23]–[25]. Experimental studies have revealed that cortical neuronal circuits possess several mechanisms that enable them to modulate and improve their spike timing precision. For example, the results presented in [23], [26] show that neocortical neurons generate spikes with better timing precision when they receive a fluctuating stimulus as opposed to an unnatural constant input. The spiking mechanism in neurons is naturally designed to respond more reliably to fluctuating inputs. Another phenomenon observed in [27], [28] is that the timing reliability of neocortical spiking neurons is improved when they receive feedback inhibition via recurrent networks of local GABAergic (GABA-releasing) inhibitory neurons. Feedforward inhibition is another mechanism utilized in the cortex in order to enhance spike timing reliability of neurons [29], [30]. However, the underlying mechanisms for these phenomena have not been completely deciphered yet.

The rhythmic spiking of neuronal circuits in the neocortex has been observed experimentally [31], [32]. Neurons are synchronized with each other due to the synaptic inputs from the other neurons so that the neuronal circuit overall generates robust rhythmic oscillations. In [33], the authors show that the synaptic coupling delay between the neurons plays a crucial role in the transition between the synchronous and asynchronous states of a neuronal circuit. The spike timing precision of the neurons may play an important role in the synchronization of the neuronal circuits that generate persistent rhythms in the brain, which has not been investigated yet.

1.3 PREVIOUS WORK: NEURONAL CIRCUIT MODELING

Considerable research effort is being expended to unveil the mechanisms behind the brain function. To this end, the first step was to decipher the functional principles of the basic element of the brain, i.e., the neuron. After the discovery of action potentials (neuron membrane voltage spikes), their role in information representation and processing in the brain was partially understood. Since action potentials are generated by the activity of ion channels located in the neuron membrane, they were identified as key components of a neuron [34]. The first quantitative description of the behavior of ion channels was presented

in the seminal study of Hodgkin and Huxley [35], which was a huge step towards understanding the neuron and hence the mechanisms in the brain.

The original Hodgkin and Huxley (HH) model captures only the deterministic, mean behavior of ion channels [36]. Subsequently, single-channel recording experiments revealed the stochastic nature of ion channels [37]. These experiments have shown that ion channels open and close in a random manner, which results in an intrinsic noise known as *channel noise* in neurons [4]. In addition, the stochastic processes in the synapses, which play a key role in information propagation and processing between neurons, result in another type of noise called *synaptic noise* [5]. There were numerous studies investigating these basic noise processes, e.g., [38], [39], which have shown that they may significantly affect the information representation and processing mechanisms of neurons and hence the functioning of a brain. Although, at first thought, noise may be considered to have a degrading effect, recent studies revealed that noise correlations and noise interacting with nonlinearities may improve the reliability of computations in the brain [40], [41]. One can gain insight into this important aspect of brain mechanism via computational modeling and simulation.

The first computer-aided simulation of a neuron was presented in [42]. For the modeling of the complex morphology of neurons and neuronal circuits and the analysis of their dynamical behavior, more advanced simulation tools, such as NEURON [43] and GENESIS [44], were developed in parallel with advances in computer technology. However, these simulation tools are based on either the deterministic HH model or integrate-and-fire neuron models. Hence, they can reproduce only the deterministic, mean behavior of neuronal circuits. Although a stochastic simulation tool named Modigliani was introduced in [45], it can only perform Monte Carlo type simulations of the stochastic behavior of a single neuron. Almost all of the work in the literature has so far concentrated on the stochastic simulation of voltage-gated ion channels and single neurons. In order to simulate the stochastic behavior of a neuronal circuit, one also needs to take synaptic connections into account by considering ligand-gated ion channels and the synaptic chemical processes. A comprehensive simulator for the nonstationary stochastic behavior of both single neurons but also neuronal circuits with models also for synaptic connections seems to be missing.

The most general and accurate models that were proposed for capturing the stochastic behavior of ion channels are based on *fine-grained, discrete-state, continuous-time, inhomogeneous Markov Chains (MCs)*, where the states of an MC directly correspond to the distinct forms of these special protein molecules [36], [46], [47]. The chemical processes that take place in synaptic connections are also modeled by Markovian kinetic schemes [48]. The simulation of the membrane voltages of neurons in a neuronal circuit can be performed by solving the membrane current-balance equations coupled with the MC models of ion channels and synapses [49], [50]. In this modeling paradigm, the noise sources are represented in an implicit manner, in the sense that the dynamics of noise generation is coupled to the dynamics of the neuronal circuit in an intertwined manner. As a result, the use of special stochastic simulation techniques of the Monte Carlo type that involve random number generators is required. This type of Monte Carlo simulation can become computationally prohibitive when neurons with a large number of ion channels or a neuronal circuit with a large number of interconnected neurons are considered. To overcome this difficulty, approximate models for the stochastic behavior of ion channels based on *coarse-grained, continuous-state, continuous-time Stochastic Differential Equations (SDEs)*, i.e., Langevin equations, have been proposed [51]–[53]. These approximate models can provide considerable computational cost reduction in the analysis of a large scale neuronal circuit when it is necessary to take into account the detailed stochastic and nonlinear dynamics of each and every neuron [54].

1.4 CONTRIBUTIONS OF THE THESIS

Computational modeling and simulation is a powerful tool that can help us gain insight into mechanisms utilized by neuronal circuits in the brain. For instance, we can investigate neuronal mechanisms that make neurons extremely energy efficient in information processing and extremely precise in information transmission. Then, these mechanisms can be used as bio-inspired solutions for electronic devices. In addition, a deep understanding and computational models can help in the investigation, diagnosis and treatment

of nervous system diseases arising from the deficient control and modulation of spike timing precision. In our recent work [55], [56], we have developed a general modeling framework for biological neuronal circuits that systematically captures the nonstationary stochastic behavior of the ion channels and the synaptic processes. In this framework, fine-grained, discrete-state, continuous-time MC models of both ion channels and synaptic processes are employed in a unified manner. Our modeling framework can automatically generate the corresponding coarse-grained, continuous-state, continuous-time SDE models. In the computational neuroscience literature, both MC and SDE models have been used only in Monte Carlo type stochastic simulations for noise analysis, where an ensemble of sample paths are generated by simulating the neuronal circuit many times. This makes Monte Carlo based simulation techniques computationally expensive.

In [56], for the stochastic characterization of neuronal variability and noise, we have adapted and repurposed semi-analytical analysis techniques that work both in time and frequency domains. These non Monte Carlo techniques are adapted from previously developed schemes for the noise analysis of analog circuits and repurposed for neuronal circuits, as a concrete manifestation of the synergistic approach we advocate in our work. With the non Monte Carlo techniques, averages that are needed for stochastic characterizations are computed in a semi-analytical manner. In other words, in these semi-analytical noise evaluation schemes, (differential) equations that directly govern probabilistic characterizations in the form of correlation functions (time domain) or spectral densities (frequency domain) are first derived analytically, starting from the SDEs that model the noisy dynamics of the system. However, these derived equations for the probabilistic characteristics still need to be solved numerically. This numerical computation directly produces the stochastic characterizations needed, without the use of random number generators, and without the need to compute ensemble averages or perform spectral estimation from time series data as in Monte Carlo techniques. Therefore, these semi-analytical methods are regarded as *non Monte Carlo* analysis techniques, which are orders of magnitude faster than Monte Carlo type simulations. Frequency-domain non Monte Carlo schemes can be used for neuronal circuits that are in quasi-periodic steady-state operation, e.g., for tonic firing conditions [57], [58]. On

the other hand, time-domain non Monte Carlo methods are not restricted to neuronal circuits operating in some sort of steady-state, in fact they can be applied to neurons with arbitrary time-varying behavior, e.g., for transient bursting conditions.

In [56], we have verified that these semi-analytical noise analysis techniques correctly and accurately capture the second order statistics (mean, variance, autocorrelation, and power spectral density) of the underlying neuronal processes as compared with Monte Carlo simulations. In addition, the spike timing jitter of noisy, spiking neuronal circuits can be accurately characterized based on these semi-analytical methods [56], [59]. To sum up, these non Monte Carlo methods can produce a consistent, repeatable and detailed characterization of the neuronal circuit. Thus, we can avoid costly repeated and long duration simulations of neuronal circuits in a Monte Carlo manner. In this thesis, we utilize these efficient and robust techniques in order to investigate the timing reliability of various neuronal circuit architectures.

We have implemented the techniques proposed in this thesis for the stochastic modeling and simulation of neuronal circuits in a MATLAB[®][60] based simulator, which was originally developed for the simulation of noise in analog electronic circuits [20], [61]. With the extensions to the simulator described in this thesis, the stochastic and noisy behavior of both neuronal and electronic circuits can be simulated together in a coupled manner. This neuronal circuit simulator enables the simulation of both fine-grained, discrete-state MC models and coarse-grained, continuous-state SDE models of a neuronal circuit in a unified manner. The simulator contains specialized numerical algorithms for the Monte Carlo simulation of these models. Furthermore, it employs non Monte Carlo noise analysis techniques presented in this thesis for large-scale analysis of noise in the nervous system. The simulator has a flexible and modular architecture, enabling easy development of new neuron and synapse models and prototyping of new analysis paradigms and algorithms. By using this simulator, we investigate several different neuronal circuit motifs and mechanisms such as ring oscillator, feedback inhibition, synaptic integration, and synaptic coupling. We unveil underlying mechanisms of these motifs that

¹ MATLAB[®] is a registered trademark of The MathWorks, Inc.

help neurons to be extremely energy efficient in information processing with utmost timing precision in information propagation.

1.5 OUTLINE OF THE THESIS

The thesis is organized as follows. In Chapter 2, we provide a brief background on neurons and neuronal circuits and summarize the models used for the ion channels and synapses. In Chapter 3, we review the stochastic chemical kinetics formalism and describe its relationship to MCs. We describe the so-called *lumpability* concept for MCs and discuss how it can be employed to obtain reduced, simpler MC models. Then, we present a key idea on representing generic/abstract MCs as a set of chemical reactions based on these reduced MC models.

In Chapter 4, we present our unified modeling and simulation framework. We review the essential steps for our unified framework leading to the facilitation of non Monte Carlo techniques. In Chapter 5, we describe the numerical methods utilized for stochastic, Monte Carlo numerical simulations of neuronal circuits based on MC and SDE models. In Chapter 6, we present how SDE models can be incorporated into analysis-based, non Monte Carlo noise evaluation methods. These non Monte Carlo methods enable stochastic characterization of neuronal circuits orders of magnitude faster than brute-force Monte Carlo simulations. In Chapter 7, we first verify that our unified SDE model correctly captures the properties of MC models of neuronal circuits via Monte Carlo simulations. Then, we present simulation results on neuronal circuits in various configurations in order to verify that the results computed with the proposed methods schemes match the ones obtained via laborious Monte Carlo type stochastic simulations.

After verifying non Monte Carlo methods, we utilized them in order to gain insight into several motifs observed in the nervous system. In Chapter 8, we use the non Monte Carlo Methods in order to characterize autonomously oscillating neuronal circuits with respect to energy consumption and timing reliability metrics. In Chapter 9, we consider a spiking neuron with feedback inhibition. We use the timing jitter variance of the neuron in order to quantify

its spike timing precision. We quantitatively investigate the effect of feedback inhibition on the energy efficiency and the spike timing precision of a neuron. We elucidate the underlying mechanism through which feedback inhibition improves spike timing precision. In Chapter 10, we consider a neuron with multiple excitatory synaptic inputs coming from spiking neurons. We analyze the effect of the integration of multiple afferent synaptic inputs, originating from the same sensory source, on the timing precision of the output neuron. In Chapter 11, we consider fully connected neuronal circuits where neurons are coupled with each other via synapses. We investigate the effect of the excitatory and inhibitory synapses on the synchronization time and the timing precision of the neuronal circuit.



BACKGROUND ON NEURONS AND NEURONAL NETWORKS

2.1 NEURONS AND NEURONAL CIRCUITS

In a neuronal circuit, information is represented by firing sequences of membrane potential spikes, i.e., action potentials, of neurons in various temporal patterns [36]. Ion channels located in the membrane of a neuron play a fundamental role in the generation and propagation of action potentials. Ion channels are formed by specialized proteins that function as dynamic openings in the cell membrane, allowing or inhibiting the passage of ions such as potassium (K^+) or sodium (Na^+) between the inter and extra cellular media [36]. There are two main types of ion channels, Voltage-Gated (VG) and Ligand-Gated (LG), where the former open and close with rates that are functions of the membrane potential $V(t)$, e.g., K^+ and Na^+ channels, the latter open and close with rates depending on the concentration of the ligand molecules $[L(t)]$, e.g., AMPA/kainate and $GABA_A$ synaptic receptor channels [36]. Synapses between neurons, on the other hand, enables information processing and transmission between neurons by means of *chemical processes*, where released neurotransmitters by a *presynaptic neuron* play a role in the generation of an action potential in the *postsynaptic neuron* [48], [62]. A simplified illustration of action potential propagation through a synapse is shown in Figure 1.

The membrane of a neuron behaves essentially as a capacitor and the potential difference across the membrane, $V(t)$, satisfies the following current-balance equation

$$\begin{aligned} C \frac{dV(t)}{dt} &= - \sum_i I_{ion,i} + I_{ext}(t) \\ &= - \sum_i G_{ion,i} [V(t) - E_{ion,i}] + I_{ext}(t) \end{aligned} \tag{1}$$

where C is the membrane capacitance, $I_{ion,i}$, $G_{ion,i}$, and $E_{ion,i}$ are the total channel current, the total channel conductance, and the reversal potential of the collection of i th type ion channels, respectively, and $I_{ext}(t)$ is an externally applied current [36]. The conductance of a single ion channel is a measure of how easily ions can pass through it when it is open. The ion channels in the membrane can be considered as parallel current paths in a single-compartmental neuron model [63]. As such, the total ion channel conductances are given by

$$G_{ion,i} = g_{ion,i} N_{ion,i}^O, \quad (2)$$

where $g_{ion,i}$ is the conductance of a single i th type channel, and $N_{ion,i}^O$ is the number of i th type channels in the open state. Eqn. (1) is complemented with the kinetics of ion channels and the synaptic processes, which will be described next.

2.2 MARKOV CHAIN MODELS OF VOLTAGE-GATED ION CHANNELS

VG ion channels in the neuron membrane possess internal gates which randomly open and close. The states of the gates determine the state of the ion channel, i.e., an ion channel is open when all of its internal gates are open [63]. For instance, a K^+ channel has four internal activation gates denoted by n and a Na^+ channel has three activation gates denoted by m , and one inactivation gate, denoted by h . An internal gate of a VG ion channel opens and closes in a random manner with rates that are functions of the membrane voltage $V(t)$ [63]. This causes variability and noise in the ion channel conductance and hence the membrane voltage $V(t)$. Since $V(t)$ naturally varies with time in neuronal computing, the opening and closure rates of ion channels are also time-varying.

The kinetics of an internal gate of generic type x for an ion channel can be modeled by a 2-state *Markov Chain (MC)* shown by

$$\textcircled{C} \xrightleftharpoons[\beta_x(V(t))]{\alpha_x(V(t))} \textcircled{O} \quad (3)$$

where C and O are the closed and open states of the x gate, respectively, which undergoes the transition ‘open $\rightarrow$ closed’ with a voltage-dependent rate

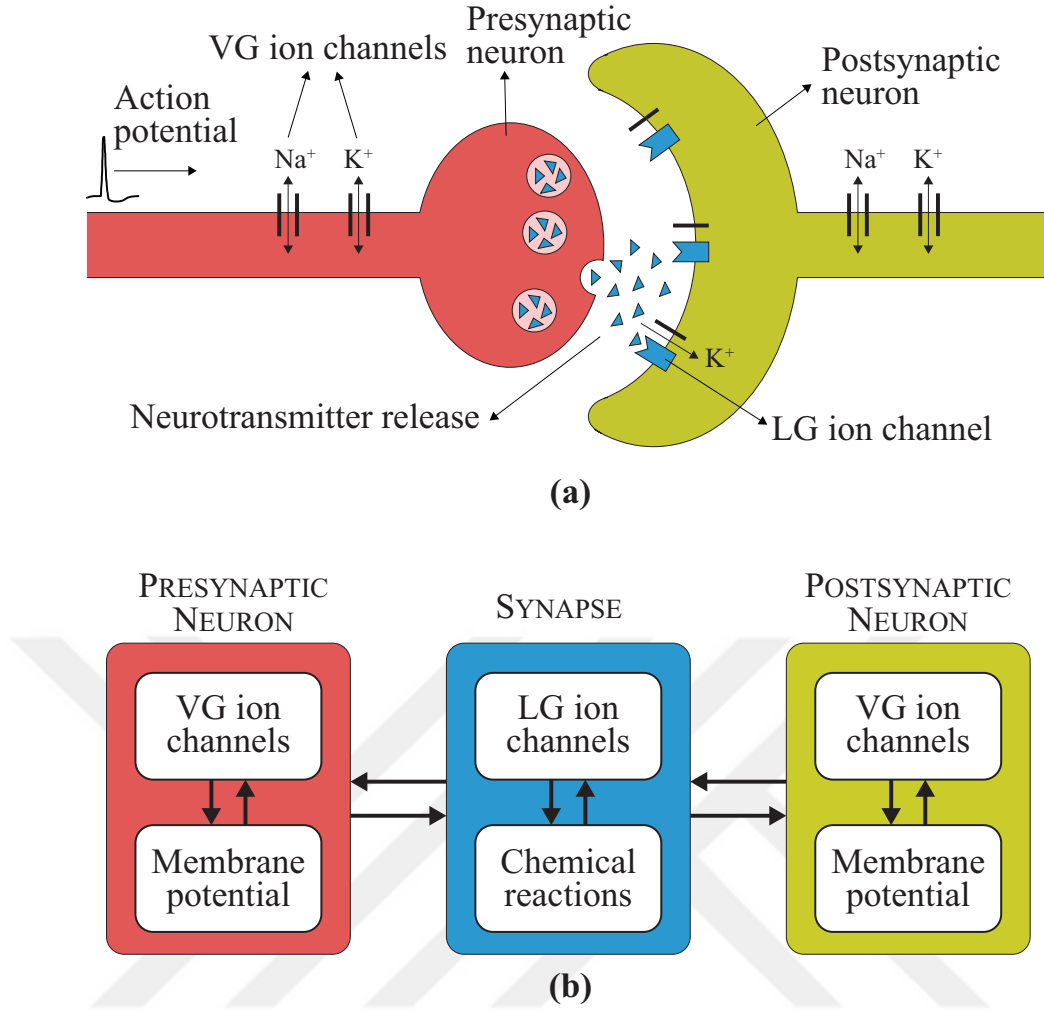
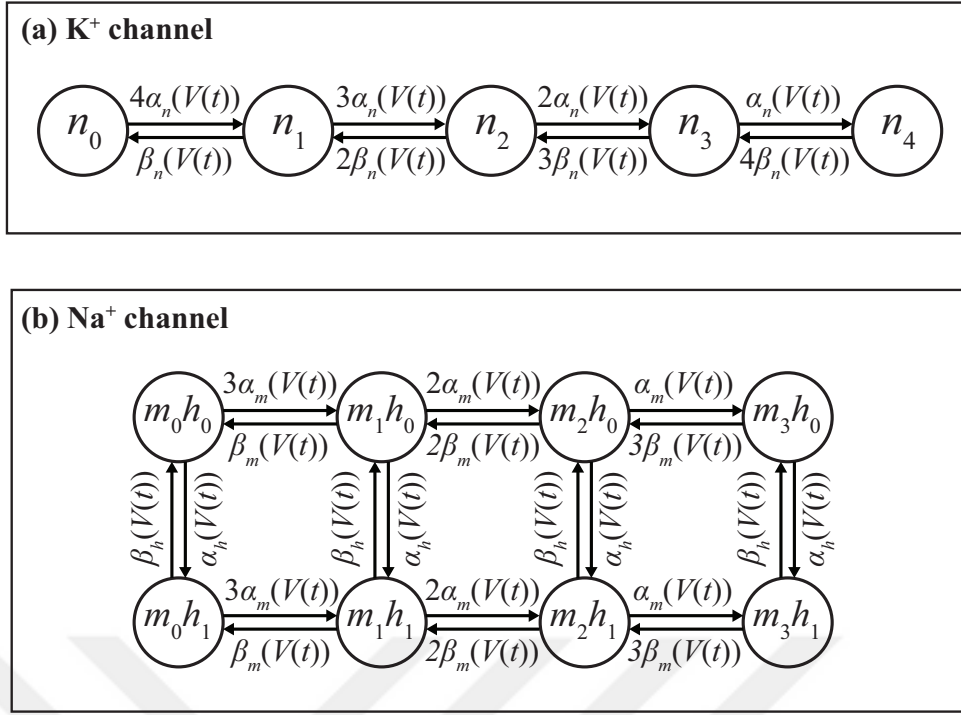


Figure 1: **(a)** A simplified illustration of presynaptic and postsynaptic neurons, VG and LG ion channels, synapse, and neurotransmitter release mechanism. **(b)** A schematic representation of the interactions between the neuronal circuit components shown in **(a)**.

$\beta_x(V(t))$ and the reverse transition ‘closed $\rightarrow$ open’ with a rate $\alpha_x(V(t))$. Thus, the kinetics of an ion channel having N gates can be described by an MC with 2^N states, formed as a composition of the N 2-state chains of the gates. With the following assumptions, stochastic models of VG ion channels become simpler:

- The internal channel gates possess the Markov (memoryless) property, i.e., the next state of the gate can be probabilistically determined given its current state, being independent of the previous history. In this case, the kinetics of a single gate x can be modeled by a 2-state MC and the

Figure 2: MC models for (a) K⁺ and (b) Na⁺ ion channels.

kinetics of an ion channel having N gates can be modeled by a 2^N -state MC.

- The gates in an ion channel are stochastically independent. This makes the composition of 2-state MCs for the gates in obtaining the 2^N -state MC for the channel with N gates quite simple, i.e., the transition rate matrix for the channel MC can be formed by computing the Kronecker sums of the matrices for the individual gate MCs.
- The gates of the same type in an ion channel, even though stochastically independent of each other, have identical transition rates determined by the same function of the membrane voltage.

With the three assumptions above, the states of the 2^N -state MC model of an ion channel having N gates can be *lumped* to obtain an MC model with reduced state-space [63], [64]. For example, the 2^4 -state MC model of a single K⁺ channel having four independent and identical n gates can be lumped to a 5-state MC as shown in Figure 2.a, where the subscript of the states indicates the count of open gates, and $\alpha_n(V(t))$ and $\beta_n(V(t))$ are the opening and closure rates of a single n gate, respectively. Similarly, the 2^4 -state MC

model of a single Na^+ channel having three independent and identical m gates and single h gate can be lumped to a 8-state MC as shown in Figure 2.b. Lumpability was used in this manner in [63], in forming a simplified MC model of a single ion channel including multiple independent and identical gates modeled by 2-state MCs. We will re-visit lumpability in Chapter 3 in the description of our unified modeling framework.

The transition rates we use for the kinetic models of K^+ and Na^+ channels are given by

$$\begin{aligned}\alpha_n(V(t)) &= \frac{0.01(V(t) + 55)}{1 - \exp[-(V(t) + 55)/10]}, \\ \beta_n(V(t)) &= 0.125 \exp[-(V(t) + 65)/80], \\ \alpha_m(V(t)) &= \frac{0.1(V(t) + 40)}{1 - \exp[-(V(t) + 40)/10]}, \\ \beta_m(V(t)) &= 4 \exp[-(V(t) + 65)/18], \\ \alpha_h(V(t)) &= 0.07 \exp[-(V(t) + 65)/20], \\ \beta_h(V(t)) &= \frac{1}{1 + \exp[-(V(t) + 35)/10]},\end{aligned}\tag{4}$$

where $V(t)$ is the membrane potential of the neuron as described by (1) and expressed in mV, α_i 's and β_i 's are expressed in msec^{-1} [36]. The ionic K^+ and Na^+ currents are given by

$$\begin{aligned}I_{\text{K}^+} &= g_{\text{K}^+} N_{n^4} [V(t) - E_{\text{K}^+}], \\ I_{\text{Na}^+} &= g_{\text{Na}^+} N_{m^3 h^1} [V(t) - E_{\text{Na}^+}],\end{aligned}\tag{5}$$

where $g_{\text{K}^+} = g_{\text{Na}^+} = 20$ pS, $E_{\text{K}^+} = -77$ mV, $E_{\text{Na}^+} = 50$ mV, N_{n^4} and $N_{m^3 h^1}$ are the total number of open K^+ and Na^+ channels, respectively [36].

2.3 MARKOV CHAIN MODELS OF LIGAND-GATED ION CHANNELS

LG ion channels in the neuron membrane contain one or more receptor sites which enable gating of these channels in response to specific types of ligands. LG channels are activated directly by neurotransmitters [48], [62]. More specifically, when ligand (neurotransmitter) molecules run into the free receptor sites of an LG channel, they probabilistically bind to these sites, causing the channel to move to one of the bound states. This happens at a rate that is a function of the concentration of ligand molecules $[L(t)]$. This is called *ligand-receptor binding*

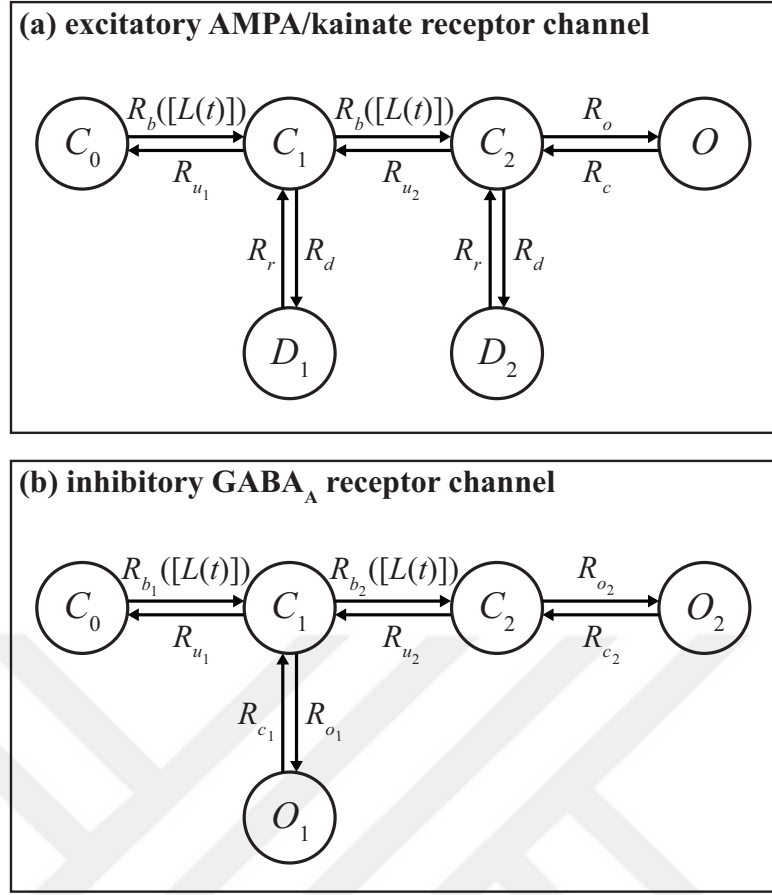


Figure 3: MC models for **(a)** excitatory AMPA/kainate receptor, and **(b)** inhibitory GABA_A receptor ion channels.

kinetic [48]. Similar to the binding, ligand molecules can be released from the bound receptor sites with a constant rate. This is known as *ligand-receptor unbinding kinetic* [48]. After bound by ligand molecules, an LG channel might enter a so-called desensitized state when it is in one of the bound states, known as desensitization. For it to move to another bound state or to move to the open state, it has to be re-sensitized first. At desensitized state, the ligand molecules remain bound but the LG ion channel is closed; and an LG ion channel at desensitized state might enter the initial bound state back, i.e., resensitization. If all receptor sites of the channel are bound and the channel is not desensitized, it may move into the open state. In summary, an LG channel can be modeled by a stochastic chain capturing all of the (un)binding, de/re-sensitization and opening/closure stochastic channel kinetics.

Similar assumptions stated for VG ion channels can be utilized in considerably simplifying stochastic modeling of LG ion channels:

- It is typically assumed that the receptor sites possess the Markov (memoryless) property, i.e., the next reaction of the receptor can be probabilistically determined from its current state, independent of the previous history of reactions.
- It is also generally assumed that the receptor sites in an LG ion channel are stochastically independent so that the transition rate matrix for the MC for an LG channel can be constructed by using Kronecker sums of the matrices derived for the receptor sites MCs.
- Sites of the same type receptor in an LG ion channel are assumed to have identical reaction rates determined by the same function of the ligand molecule concentration.

Under those assumptions, the kinetics of an excitatory AMPA/kainate synaptic receptor channel can be modeled by an MC whose *lumped* state transition diagram is shown in Figure 3.a, where C_0 is the unbound form of the receptor, C_1 and C_2 are the singly- and doubly-bound forms of the receptor, D_1 and D_2 are the corresponding desensitized states, and O is the open state for the channel [62]. Similarly, the kinetics of an inhibitory GABA_A synaptic receptor channel can be modeled by an MC whose *lumped* state transition diagram is shown in Figure 3.b, where C_0 is the unbound form of the receptor, C_1 and C_2 are the singly- and doubly-bound forms of the receptor, O_1 and O_2 are the open states for the channel [62].

The nominal values for the transition rates in the kinetic model of the AMPA/kainate receptor channel, i.e., $R_b([L(t)]) = 1.3 \times 10^7 [L(t)]$, $R_{u_1} = 5.9 \times 10^0$, $R_{u_2} = 8.6 \times 10^4$, $R_r = 6.4 \times 10^1$, $R_d = 9.0 \times 10^2$, $R_c = 2.0 \times 10^2$, and $R_o = 2.7 \times 10^3$ (all in units of s^{-1}), are given in [62].¹

¹ The results presented in Chapter 10 were obtained based on these transition rates for the AMPA/kainate receptor channel. With these values, the synaptic delay is approximately 1 msec. In order to increase the synaptic delay (between the spikes generated in the presynaptic and postsynaptic neuron connected via an excitatory synapse) by ~ 1 msec to 2 msec, we also use updated transition rates for the AMPA/kainate receptor channels, given by $R_b([L(t)]) = 1.0 \times 10^6 [L(t)]$, $R_{u_1} = 3.0 \times 10^1$, $R_{u_2} = 1.6 \times 10^5$, $R_r = 3.4 \times 10^1$, $R_d = 8.4 \times 10^2$, $R_c = 3.7 \times 10^2$, and $R_o = 0.9 \times 10^3$ (all in units of s^{-1}). The results presented in Chapter 9 and Chapter 11 were obtained based on these updated transition rates for the AMPA/kainate receptor channel. These updated values are justified based on

The nominal transition rates in the kinetic model of the GABA_A receptor channel are set to $R_{b_1}([L(t)]) = 2.0 \times 10^7 [L(t)]$, $R_{b_2}([L(t)]) = 1.0 \times 10^7 [L(t)]$, $R_{u_1} = 4.6 \times 10^3$, $R_{u_2} = 9.2 \times 10^3$, $R_{c_1} = 9.8 \times 10^3$, $R_{c_2} = 4.1 \times 10^2$, $R_{o_1} = 3.3 \times 10^3$, and $R_{o_2} = 1.1 \times 10^4$ (all in units of s⁻¹), as given in [62].

The ionic AMPA and GABA_A currents are given by

$$\begin{aligned} I_{\text{AMPA}} &= g_{\text{AMPA}} N_O [V(t) - E_{\text{AMPA}}], \\ I_{\text{GABA}_A} &= g_{\text{GABA}_A} [N_{O_1} + N_{O_2}] [V(t) - E_{\text{GABA}_A}], \end{aligned} \tag{6}$$

where $g_{\text{AMPA}} = g_{\text{GABA}} = 20$ pS, $E_{\text{AMPA}} = 0$ mV, $E_{\text{GABA}_A} = -70$ mV, N_O and $N_{O_1} + N_{O_2}$ are the total number of open AMPA and GABA_A receptor channels, respectively [62].

2.4 STOCHASTIC CHEMICAL REACTION MODEL OF NEUROTRANSMITTER RELEASE

Neurotransmitters are chemicals that are used to transmit signals from one source neuron (presynaptic) to a target neuron (postsynaptic) across a synapse. Neurotransmitters are stored in the synaptic vesicles of the presynaptic neuron and released into the synaptic cleft upon arrival of an action potential. Subsequently, they are captured by the receptors located on the postsynaptic neuron [36]. The neurotransmitter release process is governed by the following mechanisms [48], [62]. First, after the arrival of an action potential, Ca²⁺ enters the presynaptic terminal due to open Ca²⁺ channels in the neuron membrane. Then, Ca²⁺ activates a calcium-binding protein, as captured by the first chemical reaction in Figure 4, where X and X^* are unactivated and activated calcium-binding proteins, respectively. Next, activated calcium-binding protein reversibly binds and activates neurotransmitter-containing vesicles. Activated vesicles irreversibly release n molecules of neurotransmitter L into the synaptic

the diversity of activation and desensitization properties of AMPA/kainate receptor channels that is described in [65], [66]. For neurons that are reciprocally connected by excitatory and inhibitory synapses, a synaptic delay that is shorter than the depolarization duration of an action potential would result in a premature inhibition of the action potential. Thus, a ~ 1 msec increase in the synaptic delay makes the neuronal dynamics more physiologically meaningful. Prolonged synaptic delays can alternatively be modeled via distributed multi-compartment synapse or neuron models.

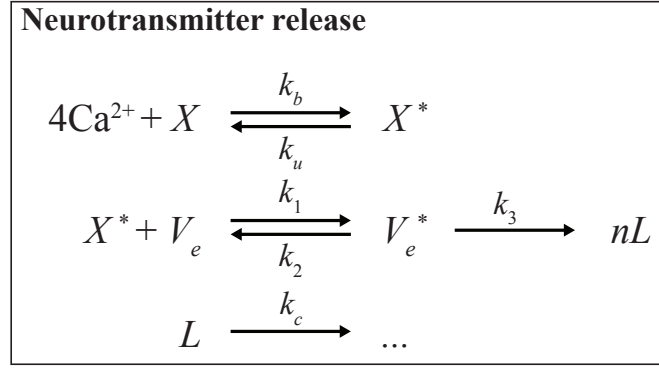


Figure 4: The system of chemical reactions for neurotransmitter release.

cleft using an exocytosis mechanism, as captured by the second chemical reaction in Figure 4, where V_e and V_e^* are unactivated and activated vesicles, respectively. The concentration of the emitted neurotransmitter molecules in the synaptic cleft is assumed to be uniform and declines due to diffusion, uptake or degradation, which is modeled by the last chemical reaction in Figure 4. The chemical reaction system in Figure 4 forms a compact representation for the MC model of the neurotransmitter release and capture process [48].

$[L(t)]$ is the concentration of neurotransmitter molecules in the synaptic cleft, which can be well approximated by

$$[L(t)] = \frac{L_{\max}}{1 + \exp[-(V_{\text{pre}}(t) - V_p)/K_p]} \quad (7)$$

where $L_{\max} = 2.84 \times 10^{-3}$ M is the maximal concentration, $V_{\text{pre}}(t)$ is the membrane potential of the presynaptic neuron expressed in mV, $K_p = 5$ mV is the steepness parameter and $V_p = 2$ mV determines the value at which the concentration is half of the maximum value [48].

BACKGROUND ON MARKOV CHAINS AND STOCHASTIC CHEMICAL KINETICS FORMALISM

In the stochastic chemical kinetics formalism, chemical reaction systems are modeled by continuous-time, discrete-state MCs that are compactly described by a set of *chemical reactions* among a number of *chemical species*. Most often, a *well-stirred* system is assumed so that concentration of molecules of each type is uniform over the entire spatial domain [67]. Thus, instead of tracking the spatial positions of each and every molecule in the system, the system state is compactly represented by a vector containing the number of molecules of each type [50]. Then, the states of the MC model of a chemical reaction system correspond to an enumeration of all the possible values of the state vector of the system can assume. The transitions between these states are compactly represented by a set of reactions among the molecular species. Most typically, the number of chemical species and reactions are much smaller than the number of possible states and transitions between these states. That is, in the stochastic chemical kinetics formalism, both the sparsity of possible transitions between the states, and more importantly, the special structure of these transitions caused by a small set of reactions, are exploited to arrive at a very compact representation for an MC that may be otherwise very unwieldy to deal with. In summary, in the stochastic chemical kinetics formalism, there is a precise map from a chemical reaction system to an MC. In our modeling framework, we utilize the *reverse* of this map in order to represent the MC models of ion channels as a set of abstract chemical reactions among a set of abstract species, which we describe next.

Next, we describe a key idea on representing generic/abstract MCs as a set of chemical reactions. As we presented in Chapter 2, not all ion channels and synaptic processes in neuronal circuit modeling are constructed based on the stochastic chemical kinetics formalism. However, starting with a generic MC model, we can still utilize a formalism analogous to stochastic chemical

kinetics by considering the abstract states and state transitions of the MC as analogous to chemical species and reactions, respectively, and arrive at a compact representation. Nevertheless, if the generic MC neither has a sparse state transition diagram nor possesses any special structure, using such a formalism does not result in a more compact representation compared with the state transition diagram. That is, for a generic MC with no special structure, the required number of abstract species and reactions will be equal to the number of states and transitions. However, the use of the stochastic chemical kinetics formalism for abstract/generic MCs greatly simplifies the mapping of the MC models of neurons and neuronal circuits to corresponding SDE models by using techniques developed for stochastic chemical kinetics [50], [68]. As such, both neurotransmitter release processes modeled naturally in the chemical kinetics formalism and abstract MC models for ion channels can be mapped to SDEs in a unified manner.

3.1 REDUCTION OF MARKOV CHAIN MODELS BASED ON LUMPABILITY

A many-to-one function on the state-space of a finite MC defines a stochastic process that takes values in a smaller state-space. This derived process is called the *lumped process*, since each of its states correspond to multiple (and hence a *lumping* of) states of the original MC through the many-to-one map. If the lumped process also has the Markov property, the original MC is said to be *lumpable* and the lumped process becomes a Lumped Markov Chain (LMC) [64]. The necessary and sufficient condition for continuous-time MCs to be lumpable [64] is given as follows. r states of the MC are partitioned into s disjoint subsets of states, denoted by $B = \{b_1, b_2, \dots, b_s\}$, through a many-to-one map. The MC is said to be lumpable with respect to the partition B if and only if the following equality holds for any subsets b_i and b_j in the partition, and for any states n, n' in the subset b_i :

$$\sum_{m \in b_j} [A]_{nm} = \sum_{m \in b_j} [A]_{n'm} \quad (8)$$

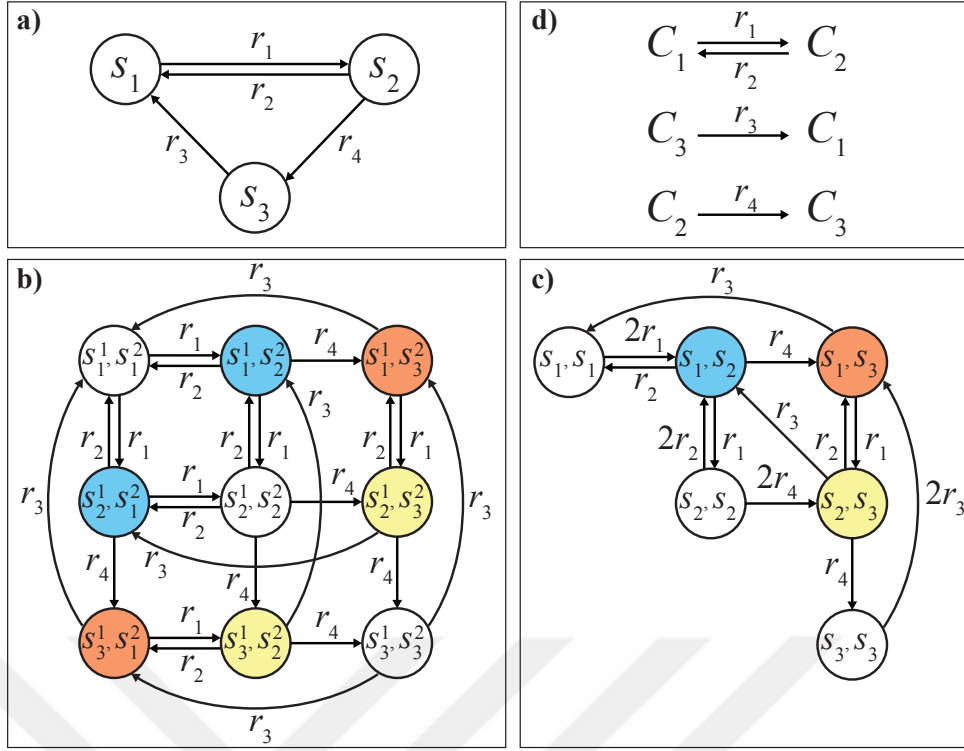


Figure 5: **a)** A generic micro MC model, where S_i 's and r_i 's are states and transition rates. **b)** The macro MC model constructed by composing two independent micro MCs, where superscript index of each S_i indicates the sequence number of the micro MC that is in state S_i . **c)** The lumped MC model of the macro MC. **d)** Representation as a chemical reaction system, where C_i 's and r_i 's are the chemical species and the reaction rate constants.

where A is the transition rate matrix [64], i.e., $[A]_{nm}$ is the transition rate from state n to state m . We should note that the lumping process here does not incur any approximations.

We utilize lumpability in a restricted setting, in order to considerably reduce the states of an MC model of a system constructed by composing *multiple independent* $\mathcal{E}$ *identical* subsystems that are each modeled by a *micro* MC. The kinetics of the complete system can be modeled by a *macro* MC, for which the transition rate matrix can be constructed as the Kronecker sum of the rate matrices for the subsystems. Using, (8), it can be shown that this macro MC is lumpable [64], with lumped states that are uniquely defined by the *count* of subsystems that are at each state of the micro MC model of a single subsystem. Here, if a macro MC consists of N micro MCs and a micro MC has m states, the number of states of the macro MC can be reduced from m^N (exponential in

N) to $\binom{m+N-1}{N} \approx N^{m-1}$ (polynomial in N) through lumping, where typically $m \ll N$.

For illustrative purposes, let us consider $N = 2$ independent micro MCs with $m = 3$ states as shown in Figure 5.a. The macro MC has $3^2 = 9$ states whose transition diagram is in Figure 5.b, where superscript indices indicate the sequence number of the micro MC. According to the lumpability condition, if different states of the macro MC correspond to the same count of micro MCs in the same state, e.g., states with the same color in Figure 5.b, then they can be lumped into a single state. For two micro MCs case, (S_i^1, S_j^2) and (S_j^1, S_i^2) states can be lumped into a single state (S_i, S_j) . For the LMC model of the macro MC, the ordering of the micro MCs is immaterial. The state transition diagram of the LMC model with $\binom{3+2-1}{2} = 6$ states is shown in Figure 5.c.

3.2 REPRESENTATION OF LUMPED MC MODELS AS STOCHASTIC CHEMICAL REACTIONS

An important special case, in which using a formalism analogous to stochastic chemical kinetics is significantly advantageous, is the MC model of a system constructed by composing multiple independent and identical subsystems as discussed in Section 3.1. The state transition diagram of the macro MC model for such a system has a sparse and special structure that is revealed through lumpability. In this case, a state vector whose i th entry indicates the count of micro MCs at the i th state and a set of transitions same as the transitions of a micro MC are sufficient to describe the states and transitions of the LMC model of the macro MC model. The LMC model can be compactly represented, in the stochastic chemical kinetics formalism, where chemical species (reactions) are analogous to the states (transitions) of the micro MC and the “molecule” count of each species is analogous to the count of subsystems that are at each state of a micro MC. This count is an entry of the state vector. The analogous chemical reaction system of an MC model is a mathematically exact representation. In the rest of the thesis, these unified Markovian models will be referred to as MC models, whether they originate from actual chemical reaction systems as

in synaptic processes, or from MC models of ion channels represented as a set of abstract chemical reactions.

As an example, we again consider the system constructed by composing multiple independent and identical subsystems where each subsystem is modeled by a 3-state MC with a state transition diagram as shown in Figure 5.a. The macro MC model of the entire system can be compactly represented with a state vector of length three and the set of reactions shown in Figure 5.d, *no matter how many identical subsystems are composed*. The state vector, denoted by $\mathbf{N}_t^d$, can be shown as

$$\mathbf{N}_t^d = \begin{bmatrix} N_{t,1}^d \\ N_{t,2}^d \\ N_{t,3}^d \end{bmatrix}, \quad (9)$$

where $\mathbf{N}_t^d \in \mathbb{R}^3$ is the state vector whose i th entry, i.e., $N_{t,i}^d$, is the discrete-state count of the molecule species of type C_i at time t . The subscript t and the superscript d are used to signify that $\mathbf{N}_t^d$ is a continuous-time and discrete-state stochastic process, respectively. To sum up, since a micro MC has three states (four transitions), a state vector with three elements whose i th entry indicates the number of micro MCs at the i th state (a set of transitions with four elements same as the transitions of a micro MC) is sufficient to describe the states (transitions) of the LMC model of the macro MC. Although the number of states in the macro MC (lumped macro MC) model has exponential (polynomial) growth with the number of composed subsystems, in the analogous reaction system formalism, the size of the state vector, i.e., the number of chemical species, remains the same at three. In this case, all of the state transitions are compactly described by the set of reactions shown in Figure 5.d again independent of how many subsystems are composed.

Part II

UNIFIED MODELING & SIMULATION FRAMEWORK

UNIFIED FRAMEWORK FOR STOCHASTIC ANALYSIS OF NEURONAL CIRCUITS

Stochastic behavior of ion channels is directly modeled by MCs. On the other hand, stochastic synaptic processes are represented with chemical reactions and modeled by Markovian kinetic schemes as described in Chapter 2. These models are used for the most general and accurate description of the stochastic behavior of neuronal circuits. Nevertheless, in order to simulate the nonstationary behavior of neuronal circuits with a number of interconnected neurons, a unified modeling framework that considers both ion channels and synaptic processes is required. In Figure 6.a, our proposed modeling framework for neuronal circuits is represented as a block diagram. In Figure 6.a, we use a neuronal circuit with two neurons, depicted on the left, as an illustrative and simple example in order to describe and present the flow of the framework. The presynaptic and postsynaptic neurons are modeled foremost with their corresponding current-balance equations. These equations are coupled with the MC models of VG ion channels. On the other hand, for the synapse, a chemical reaction system that models the neurotransmitter release process is coupled with the MC models of LG ion channels. All of these models are also coupled with each other due to the synaptic connection between the two neurons. These models constitute the *Hybrid Markov Chain & Chemical Reaction* (**HYB-MC-CR**) model shown in Figure 6.a. Here, we use the term *hybrid* to emphasize the coupled discrete-continuous nature of the model: **(i)** Discrete-state MCs and chemical reactions, **(ii)** Continuous-state membrane voltages and currents. Next, we present the details of the approximations and transformations performed in our unified modeling methodology, which is summarized in Figure 6.b. An alternative mapping methodology will also be discussed in Chapter 6.

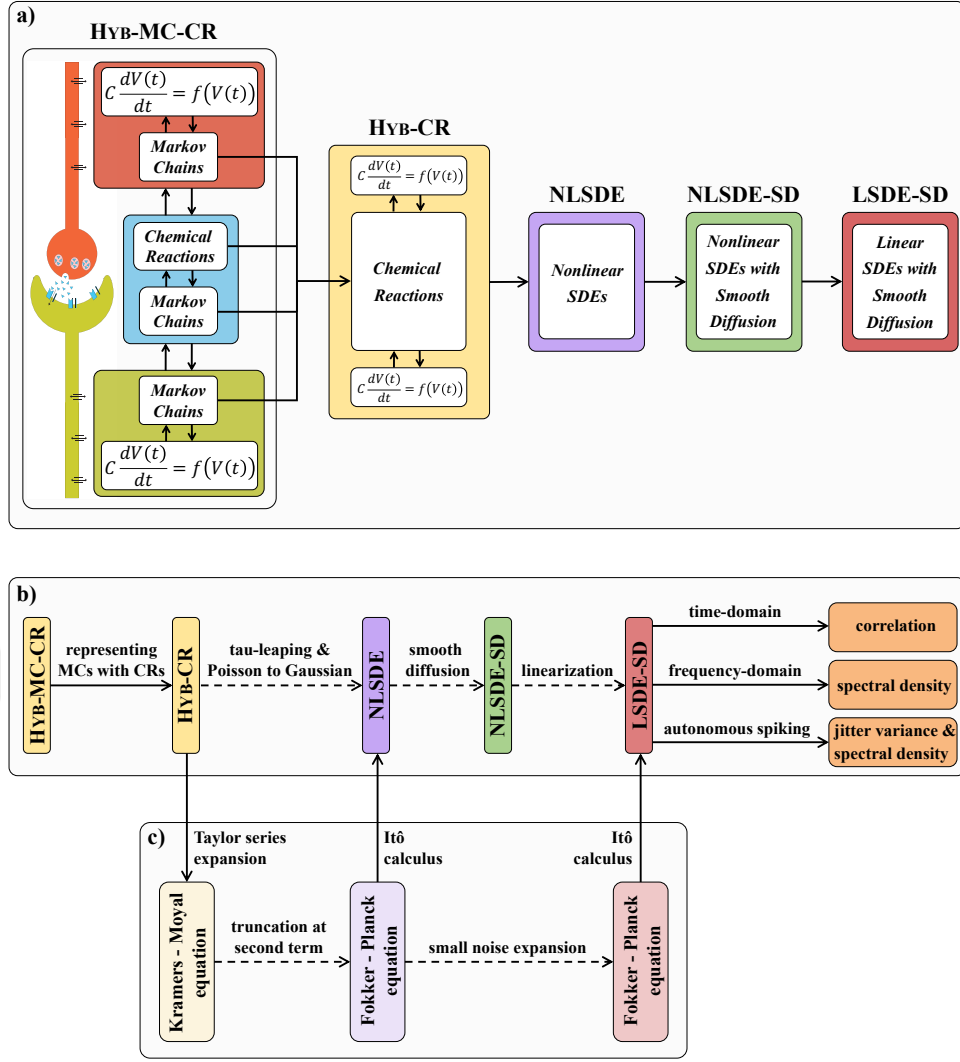


Figure 6: **a)** The unified modeling and simulation framework for neuronal circuits. **b)** The mapping methodology used in our framework, where solid arrows indicate exact mapping while dashed arrows are used if any approximation is involved in the mapping. **c)** An alternative mapping methodology.

4.1 MAPPING HYB-MC-CR MODEL TO HYB-CR MODEL

The unified, discrete-state, MC based model depicted by the *Hybrid Chemical Reaction* (**HYB-CR**) model in Figure 6.a is based on representing the MC models in the **HYB-MC-CR** model with analogous chemical reaction systems. Here, we utilize the stochastic chemical kinetics formalism, where chemical reaction systems are modeled by continuous-time, discrete-state MCs. In our modeling framework, we assume that ion channels located in the membrane of a neuron are *stochastically independent*, even though there is a sort of coupling

among them due to the fact that they are controlled by the same membrane voltage. We also assume that, over a small patch of the neuron membrane, all VG channels are subject to the same membrane voltage $V(t)$. Similarly, we assume that the LG channels in a synapse area are exposed to the same neurotransmitter molecule concentration $[L(t)]$. As a result, MCs for the same type of ion channels in the same patch of the membrane (or synapse area) become stochastically independent & identical, even though they are physically distinct.

Now, we can obtain a unified model for the ion channels and the synaptic processes after mapping all of the MC models to an analogous chemical reaction system. The analogous chemical reaction system is combined with the chemical reaction systems of the synaptic processes in order to arrive at a single, unified chemical reaction system indicated in the HYB-CR model in Figure 6.a. We use the vector $\mathbf{N}_t^d \in \mathbb{R}^P$ to represent the concatenated state vectors of the ion channels and the synaptic processes, where P is the number of species in the entire chemical reaction system formalism. The subscript t and the superscript d are used to signify that $\mathbf{N}_t^d$ is a continuous-time and discrete-state stochastic process, respectively.

Next, we gather the current-balance equations for the membranes of the neurons. The collection of current-balance equations, given in (1), can be represented as a system of Differential-Algebraic Equations (DAEs) as follows

$$\frac{\partial}{\partial t} \mathbf{q}(\mathbf{v}(t), \mathbf{N}_t^d) + \mathbf{f}(\mathbf{v}(t), \mathbf{N}_t^d) + \mathbf{b}(t) = 0 \quad (10)$$

where $\mathbf{v} \in \mathbb{R}^M$ is the vector of membrane voltages of M neurons, the nonlinear vector functions $\mathbf{q}$ and $\mathbf{f} \in \mathbb{R}^M$ represent the neuron membrane capacitances and ion channel currents, respectively, $\mathbf{b}(t) \in \mathbb{R}^M$ captures any external stimulus applied to the neuronal circuit. That is,

$$\begin{aligned} \mathbf{v}(t) &= \begin{bmatrix} V_1(t) \\ \vdots \\ V_M(t) \end{bmatrix}, \quad \mathbf{q}(\mathbf{v}(t), \mathbf{N}_t^d) = \begin{bmatrix} C_{m,1}V_1(t) \\ \vdots \\ C_{m,M}V_M(t) \end{bmatrix}, \\ \mathbf{f}(\mathbf{v}(t), \mathbf{N}_t^d) &= \begin{bmatrix} -\sum_i G_{\text{ion},i}[V_1(t) - E_{\text{ion},i,1}] \\ \vdots \\ -\sum_i G_{\text{ion},i}[V_M(t) - E_{\text{ion},i,M}] \end{bmatrix}, \quad \mathbf{b}(t) = \begin{bmatrix} I_{\text{ext},1}(t) \\ \vdots \\ I_{\text{ext},M}(t) \end{bmatrix}, \end{aligned} \quad (11)$$

where the current balance equations of the neurons defined by (1) are concatenated. We note that both $\mathbf{q}$ and $\mathbf{f}$ depend on the integer valued state vector $\mathbf{N}_t^d$, since the conductances and hence other electrical characteristics of the neurons depend on the states of the MCs. The current-balance equations of the neurons in a circuit described by (1) are coupled with each other through synapses. That is, a presynaptic neuron releases neurotransmitter molecules according to its membrane potential. The released neurotransmitter molecules bind to the LG ion channels located in the membrane of a postsynaptic neuron. Then, the LG ion channels open and lead to a change in the membrane potential of the postsynaptic neuron. Furthermore, Eqn. (10) coupled with the aggregated chemical reaction system constitutes the unified model for the hybrid discrete-continuous HYB-CR model in Figure 6.a.

4.2 MAPPING HYB-CR MODEL TO NLSDE MODEL

We present the automated mapping of the HYB-CR model to the unified, continuous-state, SDE based stochastic model captured by the system of *Nonlinear Stochastic Differential Equations* (NLSDE) model in Figure 6.a. The SDEs, also known as Langevin equations [54], constitute a coarse-grained and approximate but still nonstationary model for a neuronal circuit. Simulations based on SDEs incur considerably less computational cost. The use of the analogous chemical reaction system representation for MCs greatly simplifies the mapping of the MC models of neuronal circuits to corresponding SDE models based on techniques previously developed for stochastic chemical kinetics [50], [68]. As such, both neurotransmitter release processes modeled naturally in the chemical kinetics formalism and abstract MC models for ion channels can be mapped to SDEs in a unified manner.

We can compactly represent a macro MC that corresponds to a number of independent & identical channels as an abstract and analogous chemical reaction system, as described in Chapter 3. The neurotransmitter release process is already described by a set of chemical reactions, as described in Chapter 2. Hence, all of the neuronal machinery is now modeled with a set of aggregated chemical reactions that compactly describe their corresponding

MC models. Now, we can employ techniques devised for stochastic chemical kinetics [50], [67], [69] in mapping the MC models of a neuronal circuit to a set of SDEs. These techniques are based on the so-called *tau-leaping assumption* followed by *Gaussian approximations of Poisson distributions* [50], [67], [69]. Here, we skip the derivation of the mapping technique, which is described in detail in [50], [55], [67]. We note that in order to satisfy the tau-leaping condition while ensuring the validation of Gaussian approximations of Poisson distributions, a large number of ion channels or molecules need to be present. Otherwise, the SDE approximation of the MC models might become inaccurate.

We can approximate $\mathbf{N}_t^d$, i.e., the state vector of the aggregated chemical reaction system in HYB-CR, with a continuous-time, continuous-state process $\mathbf{N}_t^c$ satisfying the following system of nonlinear Itô SDEs

$$d\mathbf{N}_t^c = \boldsymbol{\mu}(\mathbf{v}(t), \mathbf{N}_t^c)dt + \boldsymbol{\sigma}(\mathbf{v}(t), \mathbf{N}_t^c) d\mathbf{W}_t \quad (12)$$

where $\mathbf{N}_t^c \in \mathbb{R}^P$ is the state vector whose i th entry, i.e., $N_{t,i}^c$, is either the (fractional) count of ion channels that are at state S_i or the (fractional) count of molecule species of type C_i at time t . $\mathbf{W}_t \in \mathbb{R}^T$ is a vector of independent Wiener processes, P and T are the number of the states and the transitions in the analogous chemical reaction system. The functions $\boldsymbol{\mu}(\mathbf{v}(t), \mathbf{N}_t^c)$ and $\boldsymbol{\sigma}(\mathbf{v}(t), \mathbf{N}_t^c)$ are the *drift* and *diffusion* parts of the SDE, respectively, obtained from the MC models of the ion channels, as described in Chapter 2 and in [56]. In this model, the drift component captures the mean, deterministic, but time-varying behavior of the ion channels and the synaptic processes while the diffusion component arises from the random effects.

For the analogous chemical reaction system based on the MC models of ion channels, the nonlinear vector function $\boldsymbol{\mu}(\mathbf{v}(t), \mathbf{N}_t^c)$ can be expressed as the product of a nonlinear matrix function and a vector as $\boldsymbol{\mu}(\mathbf{v}(t), \mathbf{N}_t^c) = \mathbf{A}(\mathbf{v}(t), \mathbf{N}_t^c) \mathbf{N}_t^c$, where the entries of $\mathbf{A}(\mathbf{v}(t), \mathbf{N}_t^c)$ are

$$A_{i,j} = \begin{cases} r_{ji}(\mathbf{v}(t), \mathbf{N}_t^c) & \text{if } i \neq j \\ -\sum_{i, i \neq j} r_{ji}(\mathbf{v}(t), \mathbf{N}_t^c) & \text{if } i = j \end{cases} \quad (13)$$

where r_{ji} is the transition rate from state j to i in the micro MC model. These rates depend on the membrane voltages of the neurons $\mathbf{v}(t)$ for the VG ion

channels and the concentration of the neurotransmitter molecules $[L(t)]$ in the synaptic clefts for the LG ion channels. The entries of $\sigma(\mathbf{v}(t), \mathbf{N}_t^c)$ are

$$\sigma_{i,k} = \begin{cases} \sqrt{r^k(\mathbf{v}(t), \mathbf{N}_t^c) N_{t,i}^c} & \text{if } k^{\text{th}} \text{ transition is "to" } i^{\text{th}} \text{ state} \\ -\sqrt{r^k(\mathbf{v}(t), \mathbf{N}_t^c) N_{t,i}^c} & \text{if } k^{\text{th}} \text{ transition is "from" } i^{\text{th}} \text{ state} \end{cases} \quad (14)$$

where r^k is the rate of the k th transition. The index k for a transition is determined by arbitrarily enumerating all of the transitions in the micro MC model.

Let us consider the example in Figure 5.a, with the corresponding chemical reaction system in Figure 5.d, for which we can obtain the following SDE

$$\begin{aligned} \begin{bmatrix} dN_{t,1}^c \\ dN_{t,2}^c \\ dN_{t,3}^c \end{bmatrix} &= \begin{bmatrix} -r_1 & r_2 & r_3 \\ r_1 & -r_2 - r_4 & 0 \\ 0 & r_4 & -r_3 \end{bmatrix} \begin{bmatrix} N_{t,1}^c \\ N_{t,2}^c \\ N_{t,3}^c \end{bmatrix} dt \\ &+ \begin{bmatrix} -\sqrt{r_1 N_{t,1}^c} & \sqrt{r_2 N_{t,2}^c} & \sqrt{r_3 N_{t,3}^c} & 0 \\ \sqrt{r_1 N_{t,1}^c} & -\sqrt{r_2 N_{t,2}^c} & 0 & -\sqrt{r_4 N_{t,2}^c} \\ 0 & 0 & -\sqrt{r_3 N_{t,3}^c} & \sqrt{r_4 N_{t,2}^c} \end{bmatrix} \begin{bmatrix} dW_{t,1} \\ dW_{t,2} \\ dW_{t,3} \\ dW_{t,4} \end{bmatrix}. \end{aligned} \quad (15)$$

The above is a system of only three SDEs (involving four Wiener processes), same as the number of states (transitions) of the micro MC model of an ion channel. Hence, it represents a significant reduction in model complexity, from a macro MC that has an exponentially (in the number of channels) growing state-space to three differential equations. However, even if we have used matrix-vector product notation in the above equation in order to reveal its structure, it represents a set of *nonlinear* equations, since the transition rates depend on the state vector, which is not shown explicitly for notational simplicity. A compact system of SDEs as in (12) can be easily derived from any type of MC model of multiple ion channels. We note that the procedure outlined above for deriving $\mu(\mathbf{v}(t), \mathbf{N}_t^c)$ and $\sigma(\mathbf{v}(t), \mathbf{N}_t^c)$ is valid only for the analogous chemical reaction system obtained for the MC models of ion channels. For chemical reactions that involve two or more molecules (of the same or different species), the procedure described in [50], [67] can be used to obtain $\mu(\mathbf{v}(t), \mathbf{N}_t^c)$ and $\sigma(\mathbf{v}(t), \mathbf{N}_t^c)$. Then, these systems of nonlinear SDEs for the ion

channels and the synapses are combined to arrive at a single set of equations in the form given in (12).

After approximating discrete valued $\mathbf{N}_t^d$ with continuous valued $\mathbf{N}_t^c$, the system of equations in (10) becomes

$$\frac{\partial}{\partial t} \mathbf{q}(\mathbf{v}(t), \mathbf{N}_t^c) + \mathbf{f}(\mathbf{v}(t), \mathbf{N}_t^c) + \mathbf{b}(t) = 0. \quad (16)$$

Now, we can combine the two coupled equations (12) and (16) as a single set of nonlinear Itô SDEs given by

$$\frac{\partial}{\partial t} \mathcal{Q}(\mathbf{x}(t)) + \mathcal{F}(\mathbf{x}(t)) + \mathcal{B}(t) + \mathcal{D}(\mathbf{x}(t)) \boldsymbol{\eta}_t = 0 \quad (17)$$

where $\mathbf{x}(t) = [\mathbf{v}(t), \mathbf{N}_t^c]^T$, and $\mathcal{Q}, \mathcal{F}, \mathcal{B} \in \mathbb{R}^{M+P}$ and $\mathcal{D} \in \mathbb{R}^{(M+P) \times T}$ with entries given by

$$\begin{aligned} \mathcal{Q}(\mathbf{x}(t)) &= \begin{bmatrix} \mathbf{q}(\mathbf{v}(t), \mathbf{N}_t^c) \\ \mathbf{N}_t^c \end{bmatrix}, \quad \mathcal{F}(\mathbf{x}(t)) = \begin{bmatrix} \mathbf{f}(\mathbf{v}(t), \mathbf{N}_t^c) \\ -\boldsymbol{\mu}(\mathbf{v}(t), \mathbf{N}_t^c) \end{bmatrix}, \\ \mathcal{B}(t) &= \begin{bmatrix} \mathbf{b}(t) \\ \mathbf{0}_R \end{bmatrix}, \quad \mathcal{D}(\mathbf{x}(t)) = \begin{bmatrix} \mathbf{0}_{M \times T} \\ -\boldsymbol{\sigma}(\mathbf{v}(t), \mathbf{N}_t^c) \end{bmatrix}, \end{aligned} \quad (18)$$

and $\boldsymbol{\eta}_t$ is a column vector of T independent standard white Gaussian noise processes. Eqn. (17) is the continuous-state, SDE based model represented by NLSDE in Figure 6.a.

In the next chapter, we will describe how the HYB-CR and the NLSDE models are used in stochastic, Monte Carlo type simulations.

NUMERICAL METHODS FOR MONTE CARLO SIMULATION OF NEURONAL CIRCUITS

For the stochastic simulation of neuronal circuits, MC and SDE based models need to be properly interfaced with the current-balance equations of neurons [55]. Here, we describe Monte Carlo type numerical techniques based on both MC and SDE models for stochastic simulation. Monte Carlo techniques are computationally expensive, however, we use them in order to verify the accuracy of the non Monte Carlo techniques that will be subsequently presented.

5.1 STOCHASTIC SIMULATION BASED ON HYB-CR MODEL

The stochastic simulation of neuronal circuits based on HYB-CR model is performed by utilizing a generalized version of the *Stochastic Simulation Algorithm (SSA)* [50]. The system of DAEs in (10) is numerically integrated [70] while the aggregated chemical reaction system for the neuronal circuit is stochastically simulated in a coupled manner [49]. Due to the coupling between the continuous valued membrane voltages and the discrete-state chemical reaction system, the numerical integration and the discrete event simulation of the reaction system need to be properly interfaced with each other. The simulation of discrete-state MCs produces a number of events in time causing jumps in the ion channel conductances and the neurotransmitter concentrations, and hence in the membrane voltages according to (10). On the other hand, the transition rates of these MCs depend on the membrane voltages that are being computed with the DAE solver. Thus, **(i)** the jump event times with which the DAE solver needs to be synchronized are not known ahead of time, and **(ii)** the rates of the jump events depend on the outcome of the DAE solver itself.

Here, we employ a technique that was described in [20], [21] for simulating low-frequency noise in electronic circuits. In this technique, a useful property

of continuous-time MCs, called *uniformization* [71], [72], is utilized so that the state transition event times, i.e, the reaction times of the chemical reaction system, can be generated ahead of time. Using the uniformization technique, a homogeneous Poisson process with a known, constant rate is used to generate a number of potential jump event times for the inhomogeneous MCs with time-varying transition rates that model the ion channels and synaptic processes. Then, these events are selected randomly and partitioned among the transitions of the MCs. As a result, the iterative computation of the timing of the implicit state transition events by the DAE solver is not needed. However, the DAE integrator needs to place a time step at all discrete event times. The constant rate of the homogeneous Poisson process, known as the majorizing event rate, needs to be chosen such that it is not exceeded by the total event rate during the simulation [21]. A similar technique that we describe here was proposed for the simulation of stochastic chemical reactions with mixed differential equation and MCs in [73], and for the simulation of noise in digital circuits in [74]. For the simulation of a neuronal circuit under nonstationary conditions, using SSA without the uniformization algorithm yields inaccurate results as pointed out in [20], [21], [75].

A more efficient simulation method based on *adaptive uniformization* was investigated in [21] in the context of the simulation of noise in electronic circuits. In the adaptive uniformization technique, the majorizing event rate is dynamically updated, i.e, adapted, during the simulation, as opposed being set to a constant value at the start [76]. This potentially results in reduced computational complexity, and also relaxes the requirement that all of the simulation history be discarded if the majorizing event rate was not set high enough at the start. However, it was shown in [21] that the adaptive uniformization technique causes stochastic bias and yields inaccurate results when it is used to simulate an electronic circuit under nonstationary conditions, and the only way to fix it is to revert to the standard uniformization technique with an upfront chosen constant majorizing event rate. Similarly, the adaptive uniformization technique is not suitable for the simulation of nonstationary neuronal circuits.

Note that using HYB-CR for the simulation of a neuronal circuit may result in very small integration time-steps in the DAE solver since the density (in

time) of the discrete events increases with the number of ion channels and synapses. Thus, the computational cost of HYB-CR is very high. Next, we focus on how the approximate, low-cost NLSDE model is used in stochastic, Monte Carlo type simulations.

5.2 STOCHASTIC SIMULATION BASED ON NLSDE MODEL

For the stochastic simulation of neuronal circuits based on SDE models, the collection of current-balance equations need to be solved along with the system of SDEs generated from the MC based models in a coupled manner as described by the NLSDE model in (17). In NLSDE, discrete MC states $\mathbf{N}_t^d$ are mapped into continuous variables $\mathbf{N}_t^c$ defined by (12). When solving NLSDE in (17) numerically, a continuous variable in $\mathbf{N}_t^c$ may wander out of the interval it should be confined to and cause the expressions that appear in the square roots in the diffusion part of (17), $\mathcal{D}(\mathbf{x}(t))$, to become negative. In order to address this “square root contingency” problem, we use a technique that was proposed in [21]. This technique is based on the fact that the drift part of the NLSDE model in (17) describes the deterministic but time-varying mean trend of the membrane voltages of the neurons, the ion channels, and the neurotransmitter release processes, whereas the diffusion part captures the nonstationary fluctuations around this time-varying mean. In this technique, which is called *Smooth Diffusion* [21], the diffusion part of the SDE based model is determined by a smooth process $\mathbf{x}_s(t)$ as follows

$$\frac{\partial}{\partial t} \mathcal{Q}(\mathbf{x}(t)) + \mathcal{F}(\mathbf{x}(t)) + \mathcal{B}(t) + \mathcal{D}(\mathbf{x}_s(t)) \boldsymbol{\eta}_t = 0 \quad (19)$$

where $\mathbf{x}_s(t)$ is obtained by removing the diffusion part of the original NLSDE model in (17) as below [21], [55]

$$\frac{\partial}{\partial t} \mathcal{Q}(\mathbf{x}_s(t)) + \mathcal{F}(\mathbf{x}_s(t)) + \mathcal{B}(t) = 0. \quad (20)$$

In order to compute $\mathbf{x}_s(t)$ by solving (20), well-established numerical methods developed for DAEs can be used. The “noiseless” $\mathbf{x}_s(t)$ is deterministic but still captures the mean but time-varying behavior of the ion channels and the synapses. Hence, it is similar to the deterministic HH equations even though the correspondence is not exact.

It is important to note that the nonlinear structure of the drift part of the NLSDE model in (17) is maintained in (19). Eqn. (19) constitutes the system of *Nonlinear Stochastic Differential Equations with Smooth Diffusion* (NLSDE-SD) model shown in Figure 6.a. In this model, the stochasticity is introduced by the independent standard white Gaussian noise processes, i.e., $\boldsymbol{\eta}_t$, in (19). Here, by using the smooth process $\mathbf{x}_s(t)$ in the diffusion part of the NLSDE in (17) instead of the actual stochastic process $\mathbf{x}(t)$, we ignore *modulation of noise by noise*, which is a small, higher order effect, as in the case of noise analysis for electronic circuits [21]. In [77], a simulation algorithm similar to the Smooth Diffusion technique is mentioned, which assures the existence of the square roots of matrices that need to be computed in order to obtain the diffusion parts of the SDE models presented in [77]. Nevertheless, for our NLSDE-SD model, matrix square root computation is not required.

Our preliminary results, presented in [55], showed that the first and second-order statistics obtained via the approximate NLSDE-SD model are quite accurate, when compared with those obtained via HYB-CR, based on Monte Carlo simulations. We have also verified the accuracy of the approximate NLSDE-SD model when it is used in another completely different domain, namely for low-frequency noise in electronic circuits [20], [21]. Furthermore, in the literature, there are several studies showing that, when the SDE models are obtained in a correct manner, they represent quite accurate diffusion approximations for the discrete MC models [51], [68].

In the simulation techniques summarized above, HYB-CR and NLSDE-SD are used in Monte Carlo type stochastic simulations for nonstationary noise characterizations, where an ensemble of sample paths is generated by simulating the neuronal circuit many times. Then, the stochastic characteristics relevant for neuronal circuit operation such as time-varying variances, correlation functions and power spectral densities are estimated by computing sample averages over the obtained ensemble. On the other hand, the duration of each of the simulated sample paths needs to be long enough in order to obtain power spectral density estimations with a desired frequency resolution. The large number and the long duration of the sample paths that need to be generated make Monte Carlo simulation inefficient. However, NLSDE-SD, as opposed to HYB-CR, is not restricted to Monte Carlo based noise analysis. Next, we

show how the special mathematical structure of NLSDE-SD enables us to use semi-analytical noise evaluation methods.



ANALYSIS-BASED, NON MONTE CARLO, NUMERICAL NOISE CHARACTERIZATION OF NEURONAL CIRCUITS

The HYB-CR model is the most general and accurate description of the stochastic behavior of neuronal circuits since it models the kinetics of the ion channels and the synaptic processes true to their discrete nature. However, HYB-CR owes this accuracy to its complex mathematical structure with coupled discrete random events due to state transitions of the MCs and chemical reactions and continuous variables such as membrane voltages and currents. This hybrid (continuous-discrete) nature of HYB-CR precludes any kind of straightforward analytical treatment. In HYB-CR, the noise sources are represented in an implicit manner. Their effects are hidden in the jump events in the membrane voltages of the neurons occurring at random times. These jumps then affect the transition rates of the aggregated chemical reaction system describing the behavior of the ion channels and the synapses, which eventually determine the random jump times of the subsequent events. As a result, the dynamics of noise generation cannot be separated from the mean dynamics of the neuronal circuit itself.

The special mathematical structure of the NLSDE-SD model enables the separation of the random effects generated by the ion channels and the synaptic processes from the mean, deterministic behavior of the neurons. The stochasticity appears as additive components. However, these components are modulated by the behavior of the rest of the neuronal circuit. As a result, the NLSDE-SD model can capture the internal nonstationary dynamics of the individual noise generating mechanisms. The deterministic drift part along with the stochastic diffusion part of the NLSDE-SD model can capture the intricate and nonstationary dynamics of the ion channels and the synaptic processes.

With the semi-analytical (non Monte Carlo) techniques presented in [56], stochastic characterizations of neuronal circuits can be directly computed, without the need to generate a large ensemble of simulated sample paths for the membrane voltages. Even though these techniques still require carefully devised numerical computations, they do not require computationally expensive, repeated simulations using random number generators. A consistent, reproducible and detailed stochastic characterization of neuronal circuits can be obtained efficiently. In this thesis, we utilize these semi-analytical methods in order to compute nonstationary stochastic characterizations, which are then processed and distilled in order to arrive at succinct conclusions regarding the timing precision of spiking neuronal circuits.

The non Monte Carlo, numerical noise characterization techniques we describe next are based on a version of NLSDE-SD model obtained through linearization. We can express the solution of NLSDE-SD in (19), $\mathbf{x}(t)$, as

$$\mathbf{x}(t) = \mathbf{x}_s(t) + \mathbf{x}_n(t) \quad (21)$$

where $\mathbf{x}_n(t)$ is the deviation from $\mathbf{x}_s(t)$ caused by the stochasticity in (19) and $\mathbf{x}_s(t)$ is the solution of NLSDE-SD without the stochastic diffusion component, as previously defined by (20). We now assume that the magnitude of $\mathbf{x}_n(t)$ is small compared to $\mathbf{x}_s(t)$, i.e., the stochastic components in (19) cause small perturbations around $\mathbf{x}_s(t)$. This is commonly assumed for semi-analytical noise analysis techniques [57], [78], [79]. Thus, we can now linearize the drift component of NLSDE-SD in (19) around $\mathbf{x}_s(t)$ to obtain

$$\frac{d}{dt}(\mathbf{C}(t)\mathbf{x}_n(t)) + \mathbf{G}(t)\mathbf{x}_n(t) + \mathbf{H}(t)\boldsymbol{\eta}_t = 0 \quad (22)$$

where $\mathbf{H}(t) = \mathcal{D}(\mathbf{x}_s(t))$ (as in the smooth diffusion technique in (19)) and the Jacobian matrices $\mathbf{C}, \mathbf{G} \in \mathbb{R}^{(M+P) \times (M+P)}$ have the block forms given by

$$\mathbf{C}(t) = \left. \frac{\partial}{\partial \mathbf{x}} \mathcal{Q}(\mathbf{x}) \right|_{\mathbf{x}=\mathbf{x}_s(t)} = \begin{bmatrix} \frac{\partial \mathbf{q}}{\partial \mathbf{v}} & \frac{\partial \mathbf{q}}{\partial \mathbf{N}_t^c} \\ \mathbf{0}_{P \times M} & \mathbf{I}_P \end{bmatrix}_{\mathbf{x}=\mathbf{x}_s(t)}, \quad (23)$$

$$\mathbf{G}(t) = \left. \frac{\partial}{\partial \mathbf{x}} \mathcal{F}(\mathbf{x}) \right|_{\mathbf{x}=\mathbf{x}_s(t)} = \begin{bmatrix} \frac{\partial \mathbf{f}}{\partial \mathbf{v}} & \frac{\partial \mathbf{f}}{\partial \mathbf{N}_t^c} \\ -\frac{\partial \boldsymbol{\mu}}{\partial \mathbf{v}} & -\frac{\partial \boldsymbol{\mu}}{\partial \mathbf{N}_t^c} \end{bmatrix}_{\mathbf{x}=\mathbf{x}_s(t)}, \quad (24)$$

where $\mathbf{0}_{P \times M}$ is the $P \times M$ matrix with all zero entries and $\mathbf{I}_P$ is the $P \times P$ identity matrix. Eqn. (22) is the system of *Linear Stochastic Differential Equations with Smooth Diffusion* (**LSDE-SD**) shown in Figure 6.a. In LSDE-SD, the simulation of the “noiseless” solution $\mathbf{x}_s(t)$ via (20) and the simulation of noise $\mathbf{x}_n(t)$ via (22) are separated. However, $\mathbf{x}_s(t)$ needs to be computed first, or concurrently with $\mathbf{x}_n(t)$, since the Jacobian and the diffusion matrices in (22) depend on it.

It is important to note that even though LSDE-SD represents a linear set of SDEs, the matrices involved are time-varying as dictated by the time-varying nature of $\mathbf{x}_s(t)$. Thus, LSDE-SD can capture frequency translation¹ and nonstationary effects. At the same time, due its linear nature, LSDE-SD is amenable to semi-analytical treatment enabling non Monte Carlo schemes. A technique that is also based on a linear noise approximation was described in [80] for the evaluation of fluctuations in biochemical networks. However, they have considered only the stationary, time-invariant case.

Next, we describe how the Linear Time Varying (LTV) representation in LSDE-SD can be employed in both time and frequency domain non Monte Carlo schemes for efficient and robust noise and fluctuation characterization. With these time and frequency domain techniques adapted from techniques previously developed for analog electronic circuits, one can avoid costly repeated and long duration simulations of the neuronal circuit in a Monte Carlo manner. We refer to these non Monte Carlo methods as semi-analytical noise evaluation schemes, since (differential) equations that involve probabilistic characterizations in the form of correlation functions or spectral densities are first derived analytically, but these equations still need to be solved numerically. As such, the stochastic characterizations are computed directly, without the use of random number generators, without the need to compute ensemble averages or perform spectral estimation from time series data as in Monte Carlo techniques.

¹ In linear but time-varying systems, perturbations at a given input frequency can cause fluctuations at other frequencies as well as the input frequency.

6.1 TIME-DOMAIN NON MONTE CARLO METHOD²

The transient, time-domain analysis technique [57] to be outlined next is not restricted to neuronal circuits operating in some sort of steady-state (e.g., tonic firing). It can be applied in more general time-varying scenarios, e.g., for transient bursting conditions. In this technique, differential equations for the auto- and cross-correlation functions of the noisy neuronal circuit are first derived analytically and then solved with specialized numerical methods. More specifically, the solution of the system of linear SDEs in (22), i.e., $\mathbf{x}_n(t)$, is known as a multivariate Ornstein-Uhlenbeck process, which in fact is a nonstationary, multivariate Gaussian process [54], [57]. Since $\mathbf{x}_n(t)$ is Gaussian, it can be completely characterized by its mean and correlation function. The mean of $\mathbf{x}_n(t)$ is given by $E[\mathbf{x}_n(t)] = 0$. The correlation matrix of the components of $\mathbf{x}_n(t)$ as a function of t is defined by

$$\mathbf{K}(t) = E[\mathbf{x}_n(t)\mathbf{x}_n(t)^T] \quad (25)$$

where $\mathbf{K} \in \mathbb{R}^{(M+P) \times (M+P)}$. In [57], it was shown that $\mathbf{K}(t)$ satisfies the following system of Ordinary Differential Equations (ODEs)

$$\frac{d}{dt}\mathbf{K}(t) = \mathbf{E}(t)\mathbf{K}(t) + \mathbf{K}(t)\mathbf{E}(t)^T + \mathbf{F}(t)\mathbf{F}(t)^T \quad (26)$$

where

$$\begin{aligned} \mathbf{E}(t) &= -\mathbf{C}(t)^{-1} \left[\frac{d}{dt}\mathbf{C}(t) + \mathbf{G}(t) \right] \\ \mathbf{F}(t) &= -\mathbf{C}(t)^{-1}\mathbf{H}(t). \end{aligned} \quad (27)$$

$\mathbf{E}(t)$ and $\mathbf{F}(t)$ are computed by using $\mathbf{x}_s(t)$, which is the solution of (20). Eqn. (26) is known as the differential Lyapunov matrix equation [81]. In order to compute $\mathbf{K}(t)$, we solve (26) by using a specialized numerical method [82]. $\mathbf{K}(t)$ represents the noise correlation matrix of the neuronal circuit variables as a function of time. The time-varying noise variances of the neuronal circuit variables, or the noise correlations between these variables at a given time point are captured by $\mathbf{K}(t)$.

² The technique outlined in this section is based on a previously proposed technique for electronic circuits, described in [57].

Using the results in [57], we can also compute the noise correlations of the neuronal circuit variables at different time points, which is defined as

$$\mathbf{K}(t_{\text{ref}}, t) = \mathbb{E}[\mathbf{x}_n(t_{\text{ref}})\mathbf{x}_n(t)^T] \quad (28)$$

where $\mathbf{K}(t_{\text{ref}}, t)$ satisfies the following system of ODEs

$$\frac{\partial}{\partial t}\mathbf{K}(t_{\text{ref}}, t) = \mathbf{K}(t_{\text{ref}}, t)\mathbf{E}(t)^T \quad (29)$$

and t_{ref} is a fixed reference time point such that $t \geq t_{\text{ref}}$.

This technique can be applied to any neuronal circuit with any kind of excitation to produce the noise variances and covariances of neuronal circuit variables, e.g., membrane voltages, ion channel conductances and currents, as a function of time. This method needs to be implemented in a specialized manner when a neuronal circuit is under tonic spiking conditions. Indeed, a neuron with a constant above-threshold current stimulus spikes regularly [36], and it can be considered as an autonomous oscillator. Autonomously oscillating neurons exhibit phase fluctuations, or spike timing jitter, with an increasing variance [20], [57], [59]. The time-domain non Monte Carlo technique described above can be used to compute spike timing jitter variance of such oscillating neurons as described in [57]. In Section 6.3, we will describe how the stochasticity in autonomously oscillating neurons can be further characterized also in the frequency domain using another specialized non Monte Carlo scheme.

6.2 FREQUENCY-DOMAIN NON MONTE CARLO METHOD³

Neurons and neuronal circuits exhibit rich and complex behavior depending on the nature of the excitations and their internal dynamics. For instance, a neuron with a periodic excitation at frequency f_i can generate a periodic output, spiking or not, at the same frequency. On the other hand, a neuron with a time-invariant, above threshold current excitation can generate a periodic output, i.e., tonic spiking, at a frequency f_o that is autonomously determined by its internal dynamics. In a more intricate case, a neuron with an above

³ The technique outlined in this section is based on previously proposed techniques for electronic circuits, described in [58], [78], [83], [84].

threshold periodic excitation at frequency f_i can generate a multi-frequency (or quasi-periodic) output determined by two fundamental frequencies, namely the input frequency f_i and the autonomously determined frequency f_o . In the most general case, a neuronal circuit with a multi-frequency excitation will generate a multi-frequency output. In this case, the fundamental frequencies that determine the output will be the union of the fundamental frequencies present in the input excitation and a set of frequencies autonomously generated by the internal dynamics of the neurons. In all of these cases, the neuronal circuit variables become cyclostationary or quasi-cyclostationary. The frequency domain technique we outline next can handle the cases summarized above and is based on techniques previously proposed for analyzing noise in electronic circuits [58], [78], [83], [84].

For simplicity of notation and clarity of exposition, we consider below only the simple case where the excitation is periodic with a single frequency, and assume that no additional autonomous frequencies are generated by the internal dynamics of the neuronal circuit. In this case, the LTV system in (22) becomes Linear Periodically Time Varying (LPTV) where the fundamental frequency is known as dictated by the excitation.

We assume that the excitation and the response are both characterized by the fundamental frequency f_c and the corresponding period $T_c = \frac{1}{f_c}$. First, we compute the deterministic, periodic steady-state solution $\mathbf{x}_s(t)$ by solving (20) using a pseudospectral technique known as *harmonic balance* [85]. We discretize (20) by uniformly spaced L points in time over one period T_c , and transform the equation into frequency-domain. We compute the truncated Fourier series coefficients for $\mathbf{x}_s(t)$ from the $(-K)$ th harmonic up to the K th one given by $\mathbf{X}_s = [X_s^{(-K)}, \dots, X_s^{(K)}]^T$ where $L = 2K + 1$ [58]. Here, since $R = M + P$ neuronal circuit variables are discretized in time with L collocation points, we need to solve a non-linear system of equations for $R \times L$ unknowns to find the truncated Fourier series representations of all neuronal circuit variables.

In order to obtain the harmonic transfer functions between the noise sources and the neuronal circuit variables for the LPTV system in (22), we transform (22) into frequency-domain and compute the matrix transfer function

$$H(f) = -[G + j2\pi fC]^{-1}D \quad (30)$$

where $G = \mathbf{\Omega}_R \mathbf{\Gamma}_R \mathbf{C}_L \mathbf{\Gamma}_R^* + \mathbf{\Gamma}_R \mathbf{G}_L \mathbf{\Gamma}_R^*$, $C = \mathbf{\Gamma}_R \mathbf{C}_L \mathbf{\Gamma}_R^*$, and $D = \mathbf{\Gamma}_R \mathbf{H}_L \mathbf{\Gamma}_T^*$. Here, $\mathbf{\Omega}_R$ is the $RL \times RL$ diagonal frequency-domain differentiation matrix and $\mathbf{\Gamma}_R$ is the $RL \times RL$ Discrete Fourier Transform (DFT) matrix for R variables. $\mathbf{C}_L$, $\mathbf{G}_L$, and $\mathbf{H}_L$ are block-diagonal matrices with $C(t_i)$, $G(t_i)$, and $H(t_i)$ for $i = 1, \dots, L$ on the diagonals. These transfer functions are then used to compute the so-called harmonic power spectral densities as a probabilistic characterization of the cyclo-stationary neuronal circuit variables [58].

In LSDE-SD, the noise sources in $\boldsymbol{\eta}_t$ are independent white noise processes, hence, their spectral correlation matrix is the identity matrix, i.e., $S_{\boldsymbol{\eta}}(f) = \mathbf{I}_T$. Then, the spectral correlation matrix of the stochastic processes $\mathbf{x}_n(t)$ is given by

$$S_{\mathbf{X}}(f) = H(f)S_{\boldsymbol{\eta}}(f)H(f)^* = H(f)H(f)^*. \quad (31)$$

Since $\mathbf{x}_n(t)$ is a cyclostationary process, there is non-zero correlation between its different spectral components that are separated from each other by an integer multiple of the fundamental frequency f_c . In the multi-frequency case mentioned above, the correlation structure of the spectral components is more complex, but they can be treated with a more general version of the frequency domain technique outlined in this section. In the most general, arbitrarily time-varying, nonstationary case, there is nonzero correlation between all spectral components. This case can be treated with the time domain technique described in Section 6.1 above.

6.3 NON MONTE CARLO STOCHASTIC CHARACTERIZATION OF AUTONOMOUSLY OSCILLATING NEURONAL CIRCUITS ⁴

We now describe a specialized time and frequency domain technique for the probabilistic characterization of neuronal circuits under autonomous tonic spiking conditions. The simpler version of the technique we outline next is applicable to a single neuron with an above threshold constant input, or

⁴ The technique outlined in this section is based on a previously proposed technique for electronic circuits, described in [59].

a group of interconnected neurons that are frequency locked to each other, spiking at a constant single frequency or tone. With this technique, one can directly compute the spike timing jitter variance with respect to a reference and the corresponding spectral density of the fluctuations in the membrane voltage.

This method relies on a mathematical description of the phase of the oscillating neurons, known as a phase equation [59], [84], [86], [87]. Phase equations represent radically reduced dimension models for the dynamical behavior of neurons and are tremendously useful in directly characterizing phase fluctuations and spike timing jitter. Phase equations for oscillators has been used in mathematical biology to study coupled oscillating neurons [87], [88], and in electronics for the analysis of phase noise in oscillators [59], [89].

In order to capture spike timing jitter in the noise analysis of autonomously oscillating neurons, we express the solution of (19) by modifying (21) as [59]

$$\mathbf{x}(t) = \mathbf{x}_s(t + \alpha(t)) + \mathbf{x}_n(t). \quad (32)$$

In (32), $\alpha(t)$ is the stochastic timing jitter (phase deviation) in $\mathbf{x}_s(t)$, and $\mathbf{x}_n(t)$ represents the stochastic amplitude deviation added to $\mathbf{x}_s(t + \alpha(t))$, both arising from noise. Since $\mathbf{x}_s(t)$ is periodic with a period T_c , it defines a limit cycle (a closed orbit that is parametrized by t) in the state-space of the neuronal variables. $\mathbf{x}_s(t + \alpha(t))$ traces exactly the same limit cycle (orbit) that corresponds to $\mathbf{x}_s(t)$, but with a random time deviation. On the other hand, $\mathbf{x}_n(t)$ represents an orbital deviation, i.e., an additive noise component. That is, the trajectory traced by $\mathbf{x}_s(t + \alpha(t)) + \mathbf{x}_n(t)$ (in the state-space of the neuronal variables) deviates from the limit cycle defined by $\mathbf{x}_s(t)$ or $\mathbf{x}_s(t + \alpha(t))$, due to the additive noise component $\mathbf{x}_n(t)$ [59]. To sum up, $\alpha(t)$ represents the *timing noise* or timing jitter for a spiking neuronal circuit, whereas, $\mathbf{x}_n(t)$ captures the additive *amplitude noise* in the neuronal circuit response. The decomposition of the noisy neuronal circuit variable into the time-shifted $\mathbf{x}_s(t + \alpha(t))$ and the additive $\mathbf{x}_n(t)$ is performed in such a way so that $\mathbf{x}_n(t)$ stays small and bounded, whereas the time deviation $\alpha(t)$ may grow large [59], to values possibly exceeding the spiking period T_c .

Autonomously oscillating systems, that determine their own rhythm based on their internal dynamics, possess a timing noise $\alpha(t)$ that freely diffuses due

to lack of a perfect timing reference. This behavior is unlike that of systems that are forced to oscillate at a frequency imposed by an external periodic stimulus. Thus, the variance of $\alpha(t)$, in general, increases with time even if the noise sources, $\boldsymbol{\eta}_t$, in (19) are always small. On the other hand, the orbital deviation $\mathbf{x}_n(t)$ remains small as compared to $\mathbf{x}_s(t+\alpha(t))$. In [59], the stochastic characterization of the timing jitter (noise) $\alpha(t)$ was rigorously derived. It was shown that, asymptotically with time, $\alpha(t)$ becomes a Gaussian random process with zero-mean and a variance given by $\text{Var}[\alpha(t)] = \text{E}[\alpha(t)^2] = c_{ss} t$. The asymptotic (steady-state) slope of the timing jitter variance is constant and represented by c_{ss} . It is important to note that $\alpha(t)$ represents the total accumulated timing noise of the noisy output $\mathbf{x}_s(t+\alpha(t))$ at time t with respect to the noiseless output $\mathbf{x}_s(t)$. That is, $\text{Var}[\alpha(kT_c)]$ is the timing jitter variance of the k th spike, where T_c is the spiking period, with respect to a trigger (reference) set at the first spike. On the other hand, spike-to-spike accumulated jitter (for the timing of the $k+1$ th spike, with the trigger set at the previous k th spike) is constant and given by $c_{ss} T_c$, that is, it is independent of k . Therefore, the slope of the timing jitter variance c_{ss} and the spiking period T_c are two important parameters that can be used to characterize the timing precision of a spiking neuronal circuit. The period T_c and the noiseless response $\mathbf{x}_s(t)$ for an autonomously oscillating neuronal circuit can be computed by finding the periodic steady-state solution of (20) via well-established numerical methods, e.g., time-domain shooting methods and frequency-domain Fourier spectral collocation based methods [90]. Then, the asymptotic timing jitter variance slope c_{ss} can be directly computed based on a specialized perturbation analysis. On the other hand, the time it takes for the timing jitter variance to settle to its asymptotic linear form, i.e., $\text{Var}[\alpha(t)] = c_{ss} t$, is also an important parameter in characterizing the timing noise performance of oscillatory systems. We next review both a direct (steady-state) technique [59] that produces the asymptotic timing jitter variance slope, as well as a transient, time-domain technique [57] which enables also the computation of the settling time.

The spike timing jitter variance of noisy neurons at spike times kT_c (coinciding with the rising or falling edge of the k th action potential where the slope is the highest) can be directly computed by

$$\text{Var}[\alpha(kT_c)] = \frac{\mathbf{K}_{ii}(kT_c)}{\left(\frac{d\mathbf{x}_{s,i}(t)}{dt} \right)^2 \bigg|_{t=kT_c}} \quad (33)$$

as discussed in [57], where i selects the membrane voltage of one of the spiking neurons in the circuit. It was shown in [57] that $\text{Var}[\alpha(kT_c)]$ is the same for all of the neurons in the circuit if they oscillate in a locked manner. By computing $\text{Var}[\alpha(kT_c)]$ via (26) and (33), one can reveal its transient behavior before and as it settles to the asymptotic linear form given by $\text{Var}[\alpha(kT_c)] = c_{ss} kT_c$.

The steady-state method, to be reviewed next, can be used for neuronal circuits that are in periodic steady-state operation, e.g., for tonic firing conditions [56], [58], [59]. In this case, the slope c_{ss} of the asymptotic form of the timing jitter variance, i.e., $\text{Var}[\alpha(t)] = c_{ss} t$, can be computed directly with a very efficient numerical technique. It was shown in [59] that

$$c_{ss} = \frac{1}{T_c} \int_0^{T_c} \mathbf{v}^T(\tau) \mathbf{H}(\tau) \mathbf{H}^T(\tau) \mathbf{v}(\tau) d\tau \quad (34)$$

where $\mathbf{v}(t)$ is the periodic steady-state solution of the so-called adjoint equation given below

$$\mathbf{C}^T(t) \frac{d}{dt} \mathbf{v}(t) - \mathbf{G}^T(t) \mathbf{v}(t) = 0 \quad (35)$$

with the following normalization condition

$$\mathbf{v}^T(t) \mathbf{C}^T(t) \frac{d}{dt} \mathbf{x}_s(t) = 1 \quad (36)$$

$\mathbf{v}(t)$ and the integral in (34) can be computed with efficient numerical techniques [86], [91]. $\mathbf{v}(t)$ is known as the *Perturbation Projection Vectors (PPVs)* [91], entries of which are the infinitesimal *Phase Response Curves (PRCs)* [88]. Phase models for oscillators have been studied extensively in several disciplines, such as electronics [59], mathematical biology [92] and neuroscience [87], [88]. A review on the topic, encompassing several disciplines, can be found in [93], [94].

The timing jitter variance slope c can be computed using the technique described in [59]. Then, the power spectral density of oscillating neuronal circuit variables with timing jitter, i.e., $\mathbf{x}_s(t + \alpha(t))$, is given by

$$S(f) = \sum_{i=-K}^K X_s^{(i)} X_s^{(i)*} \frac{f_c^2 i^2 c}{\pi^2 f_c^4 i^4 c^2 + (f + i f_c)^2} \quad (37)$$

where $X_s^{(i)}$ is the i th Fourier series coefficient of $\mathbf{x}_s(t)$ computed via the pseudospectral harmonic balance method [59]. The power spectral density of the neuronal circuit variables without phase deviations, i.e., $\mathbf{x}_s(t)$, consists of Dirac Delta, δ , functions located at integer multiples of the fundamental frequency f_c . The stochastic phase deviation process $\alpha(t)$ spreads the power of the δ functions according to (37) [59].

The technique described above, applicable to tonic spiking cases, is significantly faster than the frequency-domain non Monte Carlo method described in Section 6.2. There is a generalization of this technique for neuronal circuits autonomously oscillating at multiple frequencies which are all determined by their internal dynamics [84].

In this thesis, we use the semi-analytical noise analysis techniques outlined above, via our unified modeling framework, in order to investigate the timing reliability of various neuronal circuit structures. We have verified and confirmed all of the results presented in this thesis, that were obtained with the semi-analytical techniques described above, against straightforward Monte Carlo simulations of the SDEs of the neuronal circuits. The verification of our semi-analytical, non Monte Carlo methods in this thesis has been carried out in detail in the next chapter. A summary of the results presented in this thesis is given in Table 1. In the subsequent chapters, we discuss the details of these findings.

6.4 SUMMARY OF UNIFIED MODELING METHODOLOGY: TRANSFORMATIONS & APPROXIMATIONS

Our unified modeling methodology enables analysis-based, non Monte Carlo noise characterization techniques. In deriving these techniques, our starting point was the HYB-MC-CR model, which is considered to be the golden model

Table 1: Summary of the results obtained for various neuronal circuit architectures.

Neuronal circuit architecture	Results
Single, standalone neuron excited by a constant suprathreshold current stimulus.	⇒ Timing jitter variance is inversely proportional to membrane area and amplitude of stimulus current [Section 8.1 and 8.2] [56]. ⇒ Average action potential energy is proportional to membrane area and inversely proportional to amplitude of stimulus current [Section 8.1 and 8.2] [56].
Multiple neurons connected with excitatory synapses in a ring structure, where the neuronal circuit is autonomously spiking without an external stimulus.	⇒ For a given energy budget, multiple small neurons in a ring configuration have better spike timing precision compared with a single large neuron [Section 8.3] [56].
Feedback inhibition of a spiking neuron.	⇒ Timing jitter variance is a monotonically decreasing function of the number of synaptic receptor channels in the inhibitory feedback synapse [Section 9.1] [55]. ⇒ As the channel noise of the inhibitory feedback synaptic receptors decreases, the timing jitter variance first decreases then becomes constant [Section 9.2] [55]. ⇒ Energy efficiency is improved as the number of synaptic receptor channels in the inhibitory feedback synapse is increased [Section 9.3] [55].
A neuron integrating excitatory synaptic inputs from multiple spiking neurons.	⇒ Timing jitter variance is inversely proportional to the number of excitatory inputs [Chapter 10] [55]. ⇒ Phase of the output spikes of the integrator neuron has the same variance as the sample average of the phases of the input spikes [Chapter 10] [55].
Fully connected neuronal networks, where each neuron is connected to the other neurons via synapses and excited by a constant suprathreshold current stimulus. The synapses are excitatory, inhibitory, or balanced excitatory and inhibitory, corresponding to E, I, and EI networks.	⇒ Synchronization time is a monotonically decreasing function of the number of synaptic receptor channels per synapse [Section 11.1] [55]. ⇒ The inhibitory synapses in the fully connected networks speed up the synchronization of the network [Section 11.1] [55]. ⇒ For relatively weak synaptic coupling (i.e., for 100 or less synaptic receptor channels per synapse), timing jitter variances and spiking periods of M_{sync}-neuron fully connected networks are the same as those of a single neuron with a membrane area equal to $M_{\text{sync}}A_{HM}$, where A_{HM} is the harmonic mean of the membrane areas of the neurons in the network [Section 11.2 and Section 11.3] [55].

in this work since it is directly based on the physical behavior of ion channels and synapses. Then, we derived several other modeling paradigms based on a number of transformations and approximations, as described in Chapter 4, Chapter 5, and Chapter 6. The various models and the relationships between them are shown in Figure 6.b, where a solid arrow indicates that the mapping between the models corresponds to a transformation that does not involve any

approximations, whereas a dashed arrow means approximations were employed. In this section, we elaborate on the implications of the transformations and approximations used, and compare the stochastic characteristics of the models considered in our framework. Furthermore, we present an alternative view of the mappings between the models, as illustrated in Figure 6.c.

We now provide the details of the approximations and transformations performed in our unified modeling methodology in the following subsections.

6.4.1 HYB-MC-CR *Model to* HYB-CR *Model*

For the transformation of HYB-MC-CR to HYB-CR, we represent MC models of ion channels with analogous chemical reactions. This mapping is exact and does not involve any approximation. Here, we utilize the fact that chemical reaction systems can be used as compact representations of MCs with a certain state transition structure. By mapping MCs to chemical reactions, only a semantic modification is performed on the model. Thus, HYB-MC-CR and HYB-CR are mathematically equivalent.

6.4.2 HYB-CR *Model to* NLSDE *Model to* NLSDE-SD *Model*

HYB-CR is first mapped to NLSDE. Then, NLSDE-SD is obtained from NLSDE. This is done in three stages as described below:

- The first step is to use the *tau-leaping assumption*, where a time interval $[t, t + \tau)$ is considered and the rate with which a reaction/transition in synapses/ion channels takes place in this time interval is assumed to be constant [50], [67], [69]. With this assumption, a multiple number of reaction/transition events are allowed to take place in $[t, t + \tau)$. Thus, the number of occurrences of the reactions/transitions in the aggregated chemical reaction system becomes independent Poisson random variables. This is an approximation: In actuality, the rates of reactions/transitions need to be updated after every event. With the tau-leaping assumption, multiple events are allowed to occur before rates are updated.

- In the second step, *Gaussian approximations of Poisson distributions* are performed, assuming that every reaction/transition occurs a number of times in $[t, t + \tau)$ [50], [67]. This approximation is based on a standard result from probability theory, which relates to the fact that a Poisson random variable with large mean can be well approximated by a Gaussian random variable with the same mean and variance. After carrying out this step, NLSDE is obtained.
- NLSDE is transformed to NLSDE-SD in order to enable reliable stochastic simulations of neuronal circuits based on SDE models. In this transformation, we use the Smooth Diffusion technique presented in [21] for the analysis of noise in electronic circuits. The smooth process $\mathbf{x}_s(t)$, which is the solution of (20), is used in the diffusion part of NLSDE in (19) instead of the actual stochastic process $\mathbf{x}(t)$. This approximation corresponds to ignoring *modulation of noise by noise*, which is a small, higher order effect [21].

Now, we compare the stochastic characteristics of the approximate NLSDE-SD model with H_{YB-CR} . The system variables in both of these models are stochastic. The first two moments⁵ of these variables are their mean, variance and correlations, that together constitute a second-order probabilistic characterization. For most practical purposes, this kind of a stochastic characterization is adequate. For comparison, we consider the first two moment equations that one can derive for H_{YB-CR} and NLSDE-SD. These moment equations are not *closed* in general [57], [95]. That is, the implicit equation that describes the time evolution of a moment of certain order involves one or more higher-order moments. In order to compute the moments for these models, one has to solve an infinite hierarchy of moment equations. Therefore, one can not directly compute and compare the moments from H_{YB-CR} and NLSDE-SD. However, in a restricted setting that will be spelled out below, the first two moment equations for H_{YB-CR} and NLSDE-SD become closed. Moreover, in this special case, one can show that the first and second moment equations for H_{YB-CR} [95] are the same as those obtained from NLSDE-SD [96]. In order for the above to hold, the reaction/transition rates in H_{YB-CR} need to be linear functions

⁵ The n th moment of a random variable is the expected value of its n th power.

of the system variables, i.e., the membrane voltages, the number of ion channels at different states, and the molecule count of chemical species [95]–[97]. More specifically, for the chemical reaction systems in the synapses, all of the reactions have to be at most first-order, i.e., have at most one reactant, and the reaction rate constants must not depend on the system variables. For the ion channels, on the other hand, all of the reactions in the corresponding analogous chemical reaction system are always first-order by construction. Thus, only the transition rate constants need to be independent of the system variables. We note that, in this restricted setting, NLSDE-SD becomes a system of linear SDEs. In general, in neuronal circuit models we consider, we encounter second or higher-order reactions in synaptic processes. Also, the transition rate constants of the VG and LG ion channels do depend on the system variables, namely, the membrane voltages and the ligand concentrations. Therefore, this special case does not hold in general for a neuronal circuit.

Although the first and second-order moment equations of HYB-CR and NLSDE-SD are not closed and cannot be directly obtained for neuronal circuits, one can still compute these moments by ensemble averaging via Monte Carlo simulations. If the tau-leaping assumption and Gaussian approximations mentioned above are justified, then NLSDE-SD can accurately approximate the first and second-order stochastic characterization of a neuronal circuit as captured by HYB-CR. The theoretical basis for this claim is loosely based on the fact that Poisson distributions are approximated with Gaussian distributions with the *same* mean and variance. More specifically, if there are a large number of ion channels or molecules present, we can choose a “small enough” τ to satisfy the tau-leaping condition while ensuring a “large enough” mean for the Poisson random variables that validates the Gaussian approximations [50], [68]. However, the somewhat imprecise arguments above need to be supported by empirical evidence that can be gathered by running stochastic Monte Carlo simulations. We have indeed done so by comparing the second-order stochastic characterizations obtained by Monte Carlo simulations of both HYB-CR and NLSDE-SD. Our preliminary results, presented in [55], showed that the first and second-order statistics obtained via the approximate NLSDE-SD model are quite accurate, when compared with those obtained via HYB-CR. Furthermore, in the literature, there are several studies showing that, when the SDE models

are obtained in a correct manner, they represent quite accurate diffusion approximations for the discrete MC models of the ion channels [51]–[53]. Similarly, SDE models of chemical reaction systems, i.e., Langevin equations, can be used to accurately analyze their stochastic time evolution [50], [68]. We have also verified the accuracy of the approximate NLSDE-SD model when it is used in another completely different domain, namely for low-frequency noise in electronic circuits [20], [21].

6.4.3 NLSDE-SD *Model to* LSDE-SD *Model*

NLSDE-SD is mapped to LSDE-SD by linearizing NLSDE-SD around the “noiseless” solution $\mathbf{x}_s(t)$. Here, the linearization enables *moment closure* for NLSDE-SD, i.e., the first and second-order probabilistic moments based on LSDE-SD can be computed without involving higher-order moments. The non Monte Carlo noise analysis techniques described in Section 6.1, Section 6.2, and Section 6.3 essentially relate to the direct computation of first and second-order moments in both the time and frequency domains, i.e., auto-correlation functions and spectral densities. It is important to note that, even though LSDE-SD enables moment closure, it is by no means equivalent to assuming that the restricted, simple case spelled out above holds. The more general nature of LSDE-SD stems from the fact that the linearization is performed around a “noiseless” solution of the NLSDE-SD with stochasticity removed. This noiseless solution is not a simple fixed point, in fact, it is time-varying. In other words, even though LSDE-SD represents a set of linear SDEs that is obtained via linearization, it is not equivalent to restricting the model to be linear upfront by construction.

The derivation of LSDE-SD in (22) is based on several approximations starting from the hybrid HYB-CR model as detailed above. However, one can reveal the direct relation between these two models in order to attain a better understanding of the accuracy of LSDE-SD. In [95], it is shown that if the first and second moment equations for a discrete MC based model of a chemical reaction systems are derived after the reaction/transition rates are linearized, they will become closed. In fact, the moment equations derived

as such are the same as the ones provided in [96] for a linear SDE model of chemical reaction system. We note that in the restricted setting described in the previous subsection, the reaction/transition rates are already linear functions of the system variables. In that case, NLSDE-SD becomes a linear system of SDEs. As a result, only for that restricted setting, the first two moments of HYB-CR and LSDE-SD are exactly the same. Since the conditions of the special case does not hold in general, the moment correspondence between HYB-CR and LSDE-SD is not exact. However, the first and second-order moments of HYB-CR are well approximated by LSDE-SD for a neuronal circuit, based on the same arguments and empirical observations mentioned when we compared NLSDE-SD with HYB-CR .

LSDE-SD forms the basis for the non Monte Carlo noise analysis methods covered in this chapter. If it is treated in the time-domain, the correlation matrix of the system variables can be obtained as presented in Section 6.1. A frequency-domain treatment of LSDE-SD produces the spectral correlation matrix of the system variables as shown in Section 6.2. For autonomously oscillating neurons, a specialized nonlinear perturbation technique can be used to compute timing jitter and spectral densities as discussed in Section 6.3.

6.5 ALTERNATIVE DERIVATION METHODOLOGY

In order to clarify the accuracy of LSDE-SD and further reveal its relation to HYB-CR , we present an alternative view of the model mapping process. In this approach, LSDE-SD can be derived from HYB-CR as summarized in Figure 6.c.

- First, the *Kramers-Moyal equation* of the aggregated chemical reaction system in HYB-CR is derived by expanding its master equation in a Taylor series [54], [68], [98]. The Kramers-Moyal expansion is another mathematical representation for HYB-CR without any approximations, provided that the expansion is carried out to infinite order.
- Kramers-Moyal expansion is truncated at two terms and a *Fokker-Planck equation* is obtained [54]. A Fokker-Planck equation is a partial differential equation describing the time evolution of the probability density function for a system of SDEs. It can be shown, by using Itô calculus, that the

system of SDEs corresponding to the Fokker-Planck equation obtained in this step is the same as the NLSDE [54], [68].

- Finally, the *small noise expansion* technique is applied to the Fokker-Planck equation to obtain LSDE-SD. In this technique, a “small parameter” is introduced as a multiplying factor in the term that describes the noise sources [54]. Then, the solution of the equation is written as a functional power series in terms of the introduced small parameter. Finally, an infinite set of partial differential equations is obtained from the coefficients of this power series. The first equation in this set is the Fokker-Planck equation that corresponds to LSDE-SD [54], [68]. We note that the small noise expansion technique in effect is equivalent to the combination of the smooth diffusion and linearization approximations we have used in deriving LSDE-SD.

This alternative methodology to derive LSDE-SD is considerably more complex than the one we have utilized in our framework. It is not straightforward to use this alternative flow in an automated manner. The unified modeling methodology we have presented enables automatic derivation of each model so that we can easily implement it in a simulation framework. On the other hand, the mathematical correspondence of the models is more apparent in this alternative view.

VERIFICATION OF METHODS VIA NUMERICAL SIMULATIONS

We employ numerical analysis and simulation techniques that were previously developed for low-frequency noise in electronic circuits as implemented in a new neuron circuit simulator, which enables the simulation of both discrete and continuous models of a neuronal circuit in a unified manner. Our simulator automatically maps the MC models of ion channels and synapses to their corresponding SDE models and contains specialized numerical algorithms for the Monte Carlo simulation of either fine-grained, discrete-state MC models of neurons and synapses to better capture the stochastic behavior, or their coarse-grained, continuous-state SDE models to significantly decrease the computation time, all in a unified framework. It can be easily used to construct a complete SDE model that captures both the ion channel and synaptic noise for a circuit of neurons connected with synapses. Furthermore, one can employ non Monte Carlo noise analysis techniques for large-scale analysis of noise in the nervous system based on non Monte Carlo methods devised for electronic circuits. The simulator has a flexible and modular architecture, enabling easy development of new neuron and synapse models and prototyping of new analysis paradigms and algorithms. Our neuron circuit simulator is available for public download under the ModelDB section (with accession number 239146) of the Senselab database (<http://senselab.med.yale.edu>).

Our simulation framework is currently based on a single-compartment neuron model. Multi-compartment neuron models can also be implemented in our framework provided that each compartment includes sufficient number of ion channels so that the continuous NLSDE-SD model is justified. However, our modeling and analysis framework is mainly intended for analyzing the complex dynamics of moderate scale neuronal circuits with a lumped, i.e., single-compartment, neuron model. We think that our framework fills a niche between the simulation of large scale neuronal networks based on very simple,

integrate-and-fire type neuron models on one extreme, and the distributed, detailed modeling of the complex 3D morphology of a single neuron or small scale neuronal circuits on the other. This is actually very similar to the situation in the simulation landscape for electronic circuits. There is, on one extreme, large scale simulation of digital and mixed-signal circuits based on very simple transistor models that do not capture intrinsic device noise. On the other hand, there is distributed semiconductor device simulation based on solving drift-diffusion equations in 3D. Then, in the middle of this simulation hierarchy, there are specialized analog/RF circuit simulation techniques intended for the detailed analysis of moderate size analog building blocks such as mixers and oscillators.

Next, we first present the verification of NLSDE-SD model approximation of HYB-CR model via Monte Carlo simulations. Then, we verify the accuracy of non Monte Carlo methods via Monte Carlo simulations.

7.1 VERIFICATION OF NLSDE-SD MODEL APPROXIMATION OF HYB-CR MODEL VIA MONTE CARLO SIMULATIONS

Neurons used in our numerical analyses include 18 K^+ channels/ μm^2 and 60 Na^+ VG channels/ μm^2 [36]. In analyzing various neuronal architectures, the number of excitatory and inhibitory synaptic receptor LG channels per synapse are varied, in accordance with the physiologically plausible values for the receptor channel densities, the number of synapses, and the membrane areas of the neurons [99], [100]. We utilize well established kinetic schemes for K^+ and Na^+ channels, as shown in Figure 2.a and Figure 2.b [36]. Excitatory synapses include AMPA/kainate receptor channels with a kinetic scheme shown in Figure 2.a [62]. Inhibitory synapses include GABA_A receptor channels having a kinetic scheme illustrated in Figure 2.b [62].

7.1.1 *Neuron with a Constant Above-Threshold Stimulus*

We have simulated the membrane voltage of a single neuron with $10\mu\text{m}^2$ area including 600 Na^+ and 180 K^+ channels, where an external 2.5 pA DC current

is injected. We have simulated the neuron with both the MC-based HYB-CR and SDE-based NLSDE-SD models for a duration of 300 ms with our simulator. We report results on the statistics of Interspike Intervals (ISIs) and phase jitter of the periodic spiking output based on 1500 membrane voltage sample paths obtained with both the HYB-CR and NLSDE-SD models. The simulation time of the HYB-CR model is 25 times longer than that of the NLSDE-SD model.

The histogram of ISIs and the variance of phase jitter for the spiking neuron membrane are shown in Figure 7.a and Figure 7.b, respectively. According to the results, the HYB-CR and NLSDE-SD models produce quite similar histograms. However, the mean of ISIs for the NLSDE-SD model is slightly higher than that for the HYB-CR model. Similar results were obtained in [51], [53].

A neuron with a constant above-threshold current input spikes regularly [36]. It can be considered as an autonomous oscillator, hence, it exhibits phase fluctuations with an increasing variance [20]. Simulation results also reveal that the phase jitter variance increases linearly, as shown in Figure 7.b. Furthermore, the phase fluctuations with increasing variance can be easily observed on a snippet from only 20 action potentials generated by our simulations plotted on top of each other, as shown in Figure 7.c. In addition, the phase jitter variance for the HYB-CR and NLSDE-SD models closely matches under nonstationary conditions. According to the results in [53], [101], SDE model, similar to NLSDE-SD model obtained by our methodology, reveal accurate first and second order statistical behavior compared with MC models. The results reveal that the NLSDE-SD model can be used to compute the stochastic characteristics of spiking neurons that match the ones obtained by HYB-CR model rather well, with a significantly less computational cost.

7.1.2 Neuronal Circuit with Reconvergence

We now consider a simple neuronal circuit in order to investigate the effect of correlations between the excitatory and inhibitory synaptic inputs of a neuron on its output spiking behavior. We use neurons having a membrane with $10\mu\text{m}^2$ area including 600 Na^+ and 180 K^+ channels. We use 200 AMPA/kainate

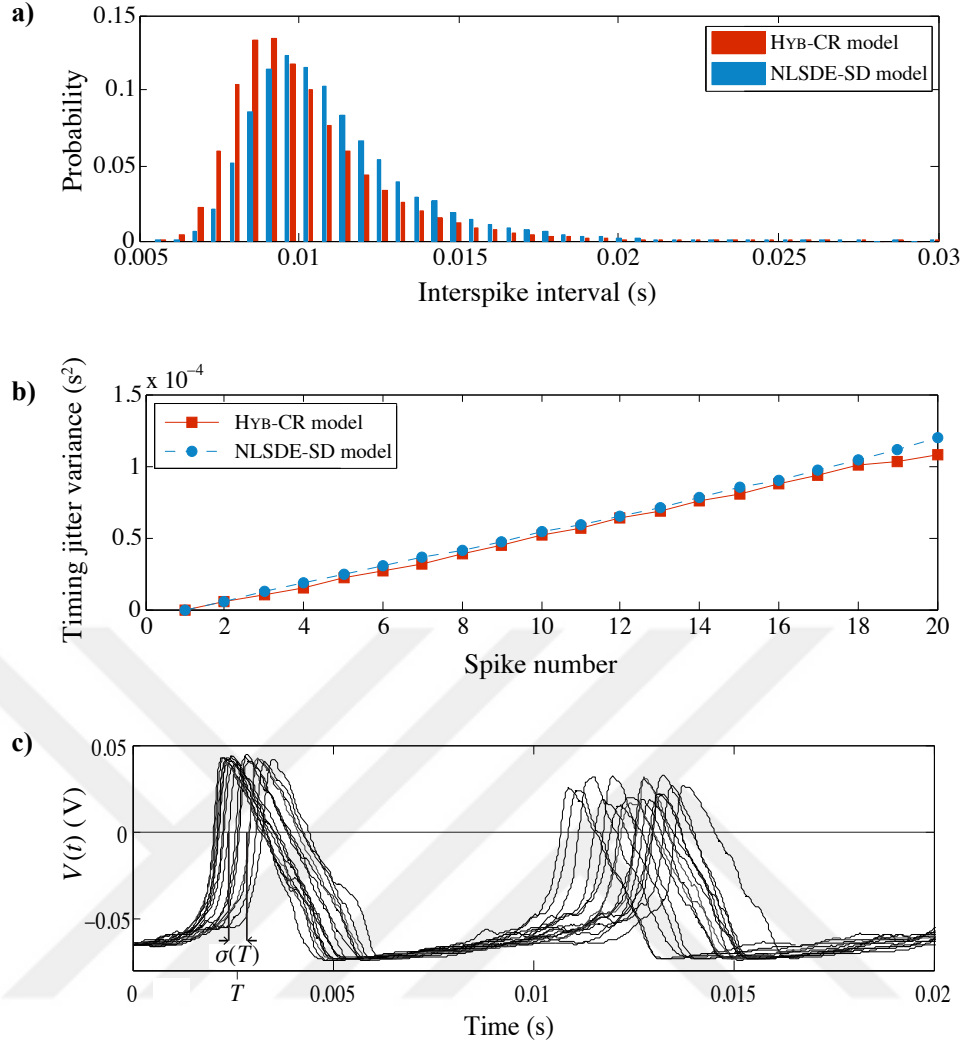


Figure 7: **a)** The histogram of ISIs and **b)** the phase jitter variance for a single neuron where an external DC current is injected is shown for both H_{YB-CR} and NLSDE-SD models. **c)** A snippet from 20 action potentials generated by our simulations, drawn on top of each other.

and $GABA_A$ receptor ion channels for excitatory and inhibitory synapses, respectively [62]. We use a 2.5 pA DC current source input.

We simulated the simple neuronal circuits shown in Figure 8.a and Figure 8.b for correlated and uncorrelated excitatory and inhibitory synaptic inputs, respectively, using NLSDE-SD model of neurons and synapses. While filled circles represent excitatory synapses, empty ones represent inhibitory synapses. For both circuit topologies, the inhibitory synaptic inputs to the neuron N4 is delayed by N2 and N3. Similar delayed feed-forward inhibition is a characteristic of many cortical neuronal circuits, e.g., in the hippocampus, the cerebellum,

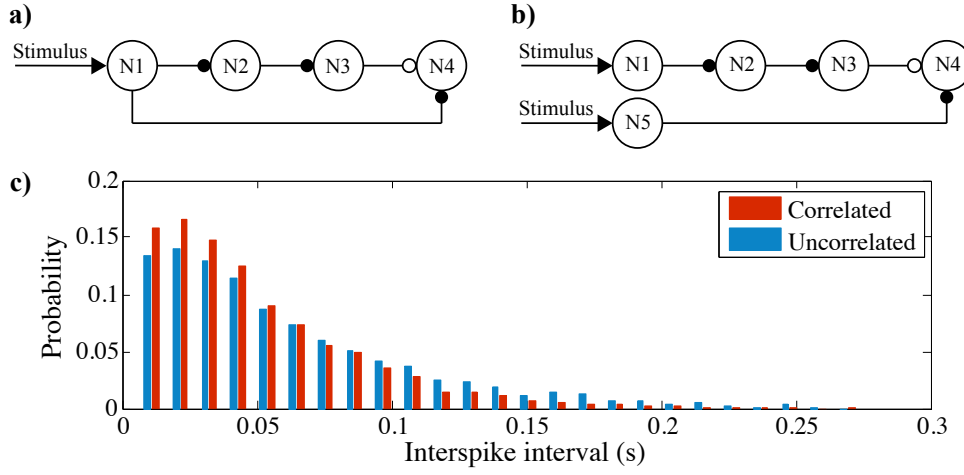


Figure 8: **a)** The neuronal circuit simulated for correlated excitatory and inhibitory synaptic inputs where an external DC current is injected to neuron N1. **b)** The neuronal circuit simulated for uncorrelated excitatory and inhibitory synaptic inputs where independent external DC currents are injected to neuron N1 and N5. **c)** The histogram of ISIs of neuron N4 is shown for both correlated and uncorrelated excitatory and inhibitory synaptic inputs.

the barrel cortex and the auditory cortex [40]. In the neuronal circuit shown in Figure 8.a, N4 receives correlated excitatory and inhibitory inputs due to re-convergence in the circuit, but in the circuit shown in Figure 8.b, these inputs to N4 do not have any correlations.

The histogram of ISIs of the output spikes for correlated and uncorrelated excitatory and inhibitory synaptic inputs are shown in Figure 8.c by using 1500 membrane voltage sample paths obtained by Monte Carlo simulations. Based on the histograms, we can conclude that the correlation between excitatory and inhibitory inputs greatly decreases the variance of ISIs. More specifically, while the variance of ISIs for correlated excitatory and inhibitory inputs is 0.0015s^2 , it becomes 0.0023s^2 for uncorrelated inputs. For the uncorrelated case, the tail of the histogram is longer than that of the histogram for the correlated case, which is not visible in Figure 8.c. Experimental studies also have shown that correlations between excitatory and inhibitory inputs can reduce the variance of ISIs and greatly enhance response fidelity and stimulus encoding [40].

7.2 VERIFICATION OF NON MONTE CARLO METHODS VIA MONTE CARLO SIMULATIONS

We now compare results obtained with the non Monte Carlo schemes and traditional Monte Carlo type stochastic simulations in order to verify the approximations (small noise assumption leading to linearization) in the derivation of the non Monte Carlo methods. For these simulations, we have developed a MATLAB[®] based simulator, which was initially devised for the simulation of noise in electronic circuits [20], [61]. The CPU times to be reported are for a machine with Intel i7-3520M CPU (2.9 GHz) and 16 GB memory. We would like to note that the absolute CPU times for our prototype, interpreted code based implementation are reported in order to indicate the speedup obtained with non Monte Carlo schemes versus Monte Carlo simulations. With a compiled code implementation and further optimizations, the non Monte Carlo schemes will actually run much faster.

It is important to note that the accuracy of the approximate NLSDE-SD model, as compared with the HYB-CR model, improves as the number of ion channels or molecules is increased. This is due to the fact that the approximations that were introduced in deriving the continuous NLSDE-SD model from the discrete-continuous HYB-CR become more accurate. With increasing number of ion channels and molecules, the fluctuations are subdued. As such, the small noise assumption used in the derivation of non Monte Carlo methods also becomes well justified. With a very small number of ion channels or molecules, stochastic simulations based on the NLSDE-SD model, as well as the non Monte Carlo schemes, may produce inaccurate results. In [55], in order to verify the SDE approximations of the MCs, we have simulated a neuron model with $10 \mu\text{m}^2$ membrane area, where the NLSDE-SD model produced accurate second order statistics when compared with those obtained via HYB-CR model. The Monte Carlo type simulations we report in this thesis are all based on the nonlinear and stochastic NLSDE-SD model.

All of the results we present next were obtained with single-compartment neuron models having $1000 \mu\text{m}^2$ membrane area and including 60000 Na^+

and 18000 K^+ channels. For excitatory synaptic connections, we used 20000 AMPA/kainate synaptic LG ion channels in the synaptic area of a neuron [62].

In the following subsections, we consider various canonical neuronal circuit scenarios in order to verify the accuracy of the non Monte Carlo methods. A summary of all of these simulation scenarios is given in Table 2. Here, I_{ext} is the amplitude of the external current injection, T_c and D are the period and the duty cycle for the periodic stimuli, respectively. In all cases, we first generate a large ensemble of sample paths for the membrane voltages via Monte Carlo simulations. Then, the stochastic characterizations are computed by ensemble averaging. We also run time- and frequency-domain non Monte Carlo analyses in order to directly compute the stochastic characterizations, i.e., variances and time-averaged¹ power spectral densities of the neuron membrane voltages. We also compute the spike timing jitter variance of the action potentials for autonomously oscillating neurons based on non Monte Carlo methods.

The stochastic characterizations presented in Figure 9, Figure 11, Figure 10, Figure 12, and Figure 13 show that the Monte Carlo simulation results (blue solid curves) and the non Monte Carlo evaluation results (red dotted curves) are almost in perfect agreement. Furthermore, the results in Table 2 demonstrate that the non Monte Carlo schemes are three orders of magnitude faster than brute-force Monte Carlo simulations. We note that, if the time-averaged power spectral density of the membrane voltage is computed using (37) as described in Section 6.3, it captures only the effect of the fluctuations due to phase diffusion. Although this method offers significant further efficiency over the more general frequency-domain technique in Section 6.2, it may not always yield accurate results as shown in Figure 11.b, Figure 12.b, Figure 12.d, and Figure 13.b (orange dashed curves).

¹ The fluctuations of the neuron membrane, in this case, is a cyclo-stationary process, where the spectral density is a function of both frequency and time with a periodic time dependence [102]. Here, we present its average over time. However, we can also compute higher-order spectra of these processes.

Table 2: Summary of simulation setups used for the verification of non Monte Carlo methods

Simulation setup	Stochastic characterization	Monte Carlo simulation	Non Monte Carlo evaluation	Results
Neuron with transient above threshold pulse stimulus $I_{ext} = 0.25 \text{ A/m}^2$ for a 1 ms duration shown in Figure 9.a	Membrane voltage variance	180 ms simulation 2000 sample paths 80 hr CPU time	Time-domain 5 min CPU time	Figure 9.c
Neuron with periodic pulsed stimulus $I_{ext} = 0.25 \text{ A/m}^2$, $T_c = 10 \text{ ms}$, $D = 20\%$ shown in Figure 10.a	Membrane voltage power spectral density	50 s simulation 50 sample paths 1375 hr CPU time	Frequency-domain 1 hr CPU time	Figure 10.b
Neuron with periodic pulsed stimulus $I_{ext} = 0.25 \text{ A/m}^2$, $T_c = 10 \text{ ms}$, $D = 20\%$ shown in Figure 10.a	Membrane voltage variance	60 ms simulation 2000 sample paths 25 hr CPU time	Time-domain 15 min CPU time	Figure 10.c
Neuron with constant above threshold stimulus $I_{ext} = 0.25 \text{ A/m}^2$ shown in Figure 11.a	Membrane voltage power spectral density	50 s simulation 50 sample paths 1250 hr CPU time	Frequency-domain 1 hr CPU time	Figure 11.b
Neuron with constant above threshold stimulus $I_{ext} = 0.25 \text{ A/m}^2$ shown in Figure 11.a	Action potential timing jitter variance	250 ms simulation 2000 sample paths 100 hr CPU time	Time-domain & frequency-domain 10 min CPU time	Figure 11.c
Two neurons connected with an excitatory synapse. First neuron with periodic pulsed stimulus, $I_{ext} = 0.25 \text{ A/m}^2$, $T_c = 10 \text{ ms}$, $D = 20\%$ shown in Figure 12.a	Membrane voltage power spectral density	50 s simulation 50 sample paths 2700 hr CPU time	Frequency-domain 2 hr CPU time	Figure 12.b
Two neurons connected with an excitatory synapse. First neuron with constant above threshold stimulus, $I_{ext} = 0.25 \text{ A/m}^2$ shown in Figure 12.c	Membrane voltage power spectral density	50 s simulation 50 sample paths 2500 hr CPU time	Frequency-domain 2 hr CPU time	Figure 12.d
Five neurons connected with excitatory synapses in a ring structure shown in Figure 13.a	Membrane voltage power spectral density	50 s simulation 50 sample paths 2500 hr CPU time	Frequency-domain 5 hr CPU time	Figure 13.b

7.2.1 Neuron with Transient Above Threshold Pulse Stimulus

We consider the setup illustrated in Figure 9.a. The external stimulus (current injected) is set to zero for the first 90 msec. Then, at $t = 90 \text{ ms}$, a current pulse with an amplitude of 0.25 A/m^2 and a duration of 1 msec is applied to the neuron. With this stimulus, a single action potential is generated in the neuron membrane. The mean membrane voltage of this action potential is shown in Figure 9.b. The duration of the action potential is around 20 msec.

The time-varying variance for the neuron membrane voltage is shown in Figure 9.c. The blue (solid) curve was obtained with Monte Carlo type simulations based on computing the variance over 2000 simulated sample paths. The red curve (round marks) was obtained with the time-domain non Monte Carlo noise analysis technique. Without an external stimulus, the neuron membrane

voltage fluctuates (with a constant variance) around its mean resting potential of -65 mV. Due to the action potential generated with the current pulse input, the membrane voltage and the rates of the ion channels undergo a fast variation. Thus, the membrane voltage variance has peaks at the rising and falling edges of the action potential, i.e., the depolarization and repolarization phases, as observed in Figure 9.c. During the refractory period, the membrane voltage reaches its minimum value around -75 mV, at which most of the ion channels are closed [36], [51]. As a result, the fluctuations in the membrane voltage become subdued. The dip value in the membrane voltage variance in Figure 9.c coincides in time with the minimum value of the membrane voltage during the refractory period, as expected. When the action potential ends, the variance of the membrane voltage returns to its steady-state value at the resting membrane potential. The results in Figure 9.c demonstrate an excellent match between Monte Carlo simulations and the proposed time-domain non Monte Carlo analysis scheme. The non Monte Carlo method is not only accurate but also efficient, since it is three orders of magnitude faster than the Monte Carlo technique.

7.2.2 Neuron with Periodic Pulsed Stimulus

We now consider a neuron with a periodic, pulsed stimulus, where the stimulus is above threshold during the pulse durations only. As such, the neuron generates an action potential for every pulse in the stimulus, with a periodic membrane voltage where the period is set by the stimulus. In this case, we use the frequency-domain non Monte Carlo scheme outlined in Section 6.2. An external stimulus current with an amplitude of 0.25 A/m² and a duration of 2 msec is injected to the neuron membrane at every 10 ms, i.e., the excitation is periodic with a frequency $f_c = 100$ Hz as shown in Figure 10.a.

The time-averaged² power spectral density of the neuron membrane voltage is shown in Figure 10.b. The blue (solid) curve was obtained via spectral

² The fluctuations of the neuron membrane, in this case, is a cyclo-stationary process, where the spectral density is a function of both frequency and time with a periodic time dependence [102]. Here, we present its average over time. However, we can also compute higher-order spectra of these processes.

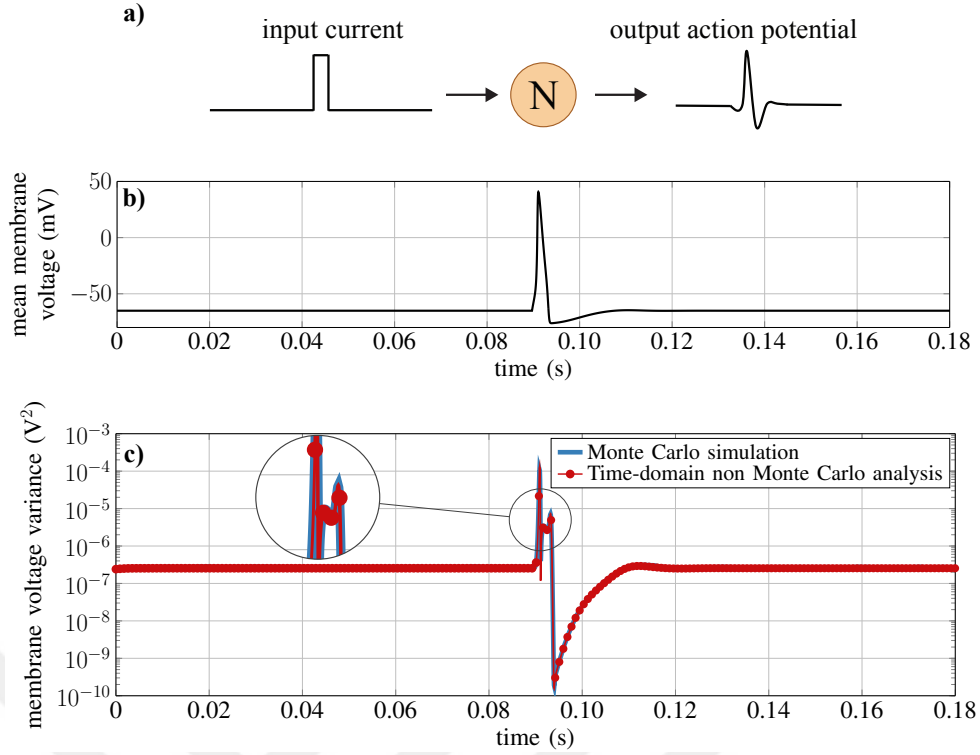


Figure 9: **a)** Transient behavior of a neuron with a single above-threshold pulse excitation. The time-varying **b)** mean and **c)** variance of the membrane voltage.

estimation on 50 membrane voltage sample paths (each with a duration of 50 secs, corresponding to 5000 cycles at $f_c = 100$ Hz) generated by Monte Carlo simulation. The spikes at multiples of $f_c = 100$ Hz are the harmonic components of the periodic action potentials and the skirts around them constitute the power spectral density of the fluctuations. The red curve (round marks) was computed by using the frequency-domain non Monte Carlo noise analysis technique, which is for only the power spectral density of the fluctuations around the deterministic, periodically time-varying mean membrane voltage. The results in Figure 10.b and the inlay of the same figure reveal that the Monte Carlo and the non Monte Carlo methods are almost in perfect agreement. The frequency-domain non Monte Carlo technique is three orders of magnitude faster than conducting Monte Carlo simulations.

The time-varying variance for the membrane voltage of the neuron with a periodic, pulsed stimulus is shown in Figure 10.c. The blue (solid) curve is the variance that was obtained via Monte Carlo type simulations based on 2000 membrane voltage sample paths. The red curve (round marks) was obtained

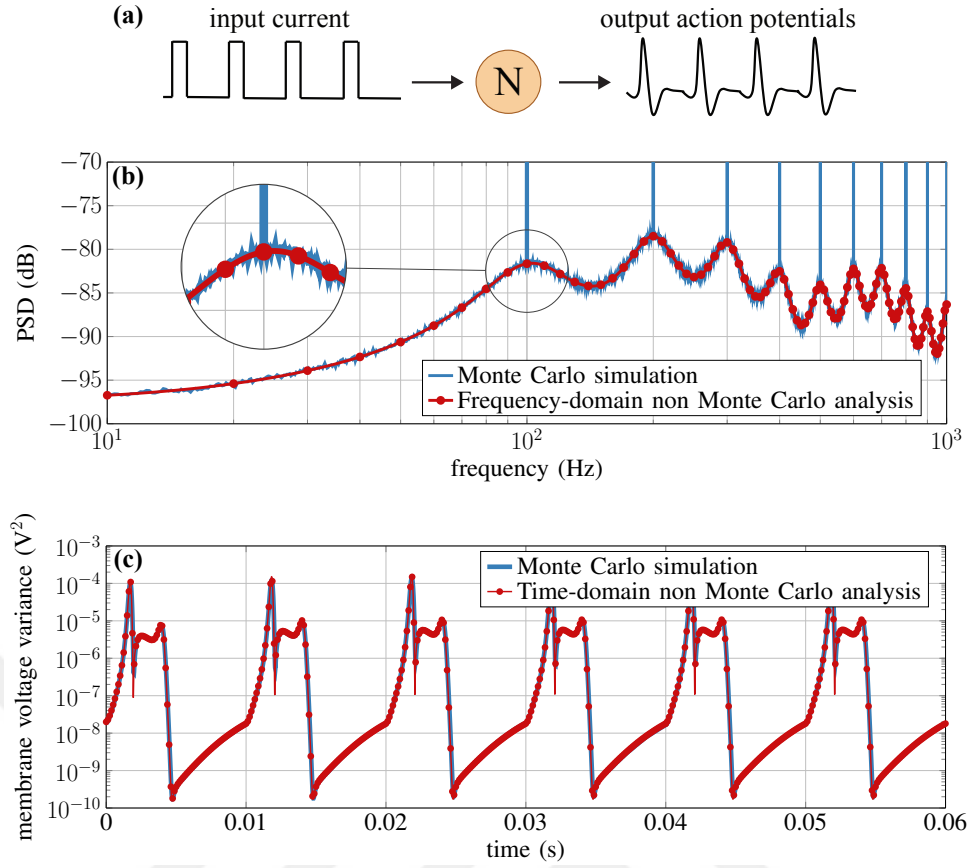


Figure 10: **a)** Neuron excited with periodic above-threshold current pulses. **b)** Time-averaged spectral density and **c)** variance of the membrane voltage.

with the time-domain non Monte Carlo noise analysis technique. The superior accuracy of the proposed time-domain non Monte Carlo method is validated with the results in Figure 10.c.

7.2.3 Neuron with a Constant Above-Threshold Stimulus

We now consider a neuron excited by a constant, above-threshold current stimulus. In this case, the neuron is autonomously oscillating, i.e., it is under tonic spiking conditions as illustrated in Figure 11.a. The amplitude of the external current stimulus is 0.25 A/m^2 and the action potentials are periodic with a frequency around $f_c = 92 \text{ Hz}$.

In Figure 11.b, the time-averaged power spectral density of the autonomously oscillating neuron membrane voltage is shown. The peaks at multiples of $f_c = 92 \text{ Hz}$ are the harmonic components of the action potentials. The tones

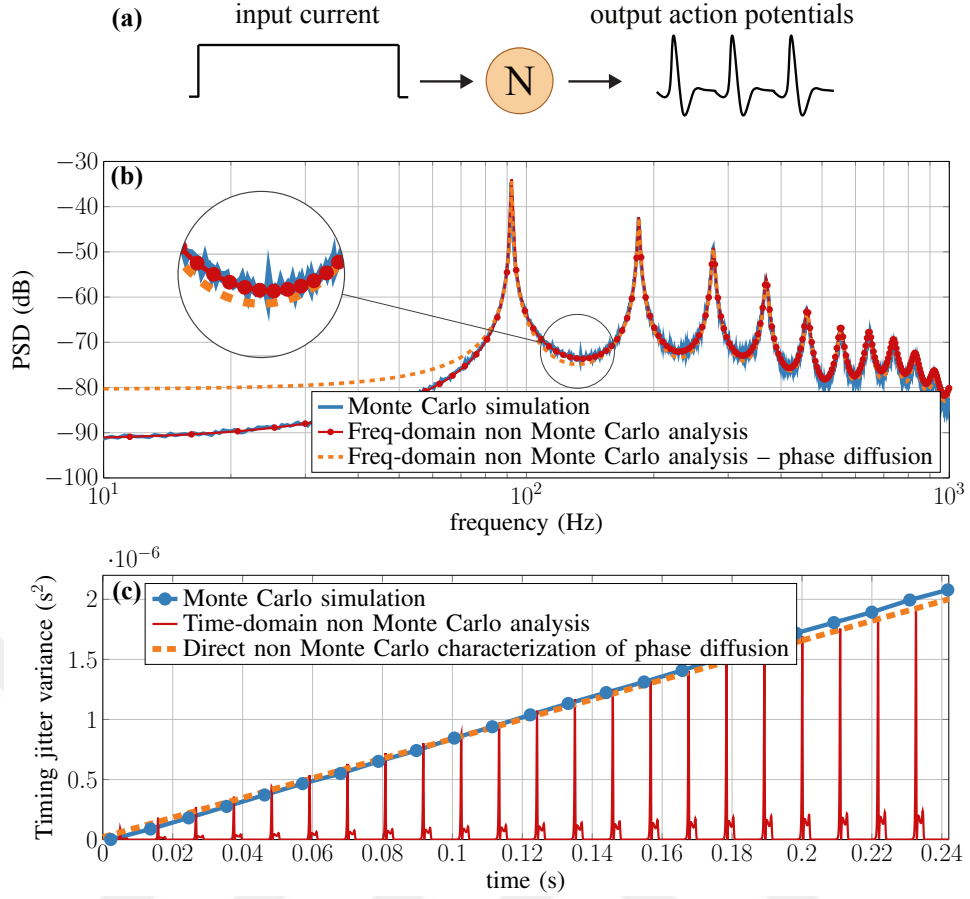


Figure 11: **a)** Neuron under tonic spiking conditions with a constant, above-threshold current stimulus. **b)** Time-averaged power spectral density of the membrane voltage. **c)** The phase jitter variance of the output action potentials.

in the spectrum are smeared due to the spectral spreading effect of noise and fluctuations in the neuron. This is unlike what can be seen in Figure 11.b for the case when the neuron was driven with a periodic stimulus, where the spiky tones at the fundamental frequency and its harmonics can be observed. Autonomous oscillators, unlike systems that are forced to oscillate at a frequency imposed by an external periodic stimulus, possess a phase that is freely diffusing. This results in spectral spreading in the frequency domain, and also timing jitter with an increasing variance in the time domain [59]. The blue (solid) curve was obtained via Monte Carlo simulations based on 50 membrane voltage sample paths of the neuron for a duration of 50 sec (4600 cycles). The red curve (round marks) was computed with the frequency-domain non Monte Carlo noise analysis technique outlined in Section 6.2. It is the full spectrum, capturing the effects of both the phase diffusion and the additive second

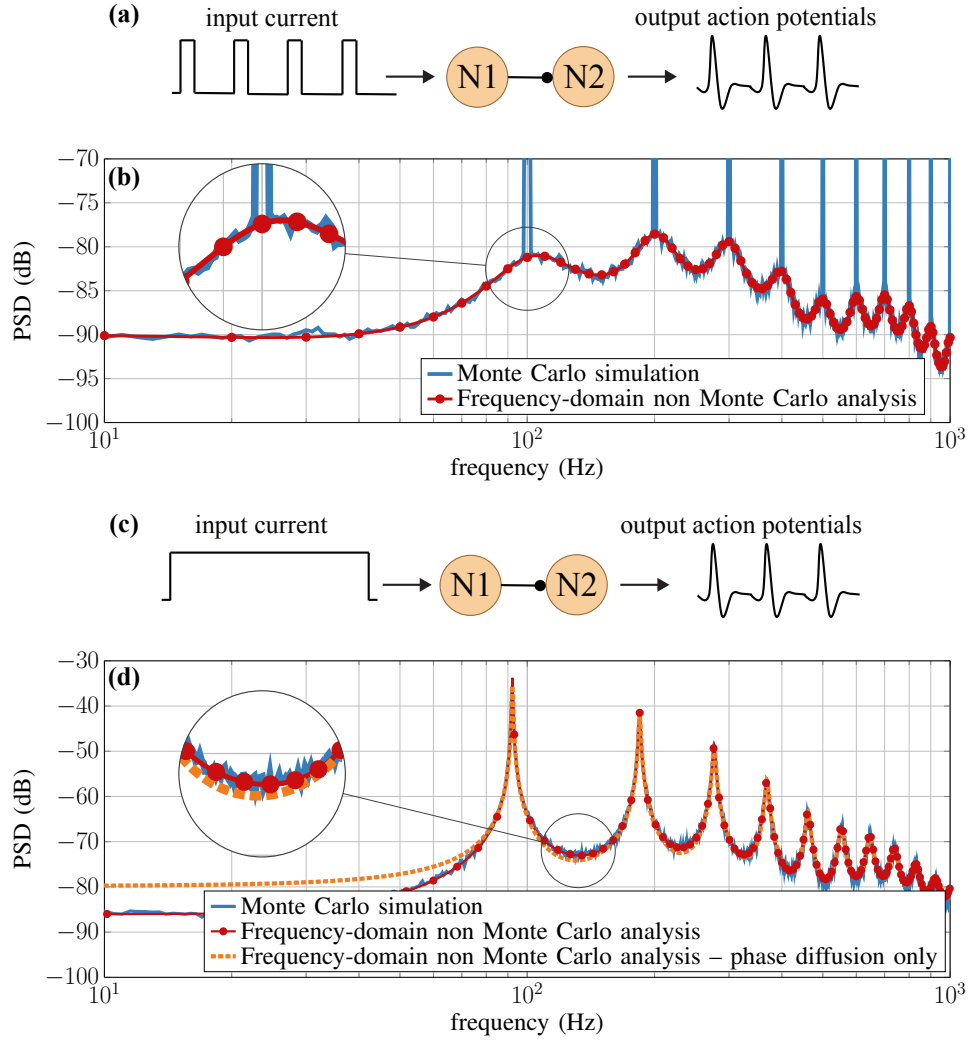


Figure 12: Two neurons connected with an excitatory synapse. **a)** The first neuron is excited by periodic, above-threshold pulsed stimulus. **b)** Time-averaged power spectral density of the membrane voltage of the second neuron in **(a)**. **c)** The first neuron is under tonic spiking conditions. **d)** Time-averaged power spectral density of the membrane voltage of the second neuron in **(c)**.

noise term in (32). The orange (dashed) curve is the time-averaged power spectral density of the membrane voltage computed using (37) as described in Section 6.3, which captures only the effect of the fluctuations due to phase diffusion.

The results in Figure 11.b reveal that the results of the Monte Carlo and the frequency-domain non Monte Carlo methods match almost perfectly, which also can be seen in the inlay of the same figure. Both of the non Monte Carlo schemes outlined in Section 6.2 and Section 6.3 are orders of magnitude faster

than Monte Carlo simulations. Furthermore, if one is interested in only the effects of phase diffusion and the equivalent spike timing jitter, the technique described in Section 6.3 offers significant further efficiency over the more general technique in Section 6.2 which can also capture the effects of additive, i.e., amplitude, noise.

In Figure 11.c, the spike timing jitter variance of the action potentials, with respect to a trigger spike, is shown. This result shows that the timing jitter variance of the action potentials increases linearly with time [57]. The blue curve (round marks) was obtained by post-processing membrane voltage sample paths obtained via Monte Carlo simulations. The orange (dashed) curve was obtained by the method presented in [59] as outlined in Section 6.3. The red (solid) curve was obtained by using the time-domain non Monte Carlo method described in Section 6.1, with a modification described in [57] that enables handling autonomous oscillators. The slope of the peaks of the red (solid) curve indicates the rate of increase for the accumulating timing jitter. All three methods for the characterization of timing jitter are in near perfect agreement.

The above results once again confirm the accuracy of the non Monte Carlo methods utilized for neuronal circuits, which are orders of magnitude faster than brute-force Monte Carlo simulations.

7.2.4 Two Neurons Connected with an Excitatory Synapse

Here, we consider two neurons connected with an excitatory synapse. The first neuron drives the second neuron which has 20000 AMPA/kainate synaptic LG ion channels in the synaptic area [62]. We consider two cases: **(i)** First neuron has a periodic, above-threshold pulsed excitation with a frequency $f_c = 100$ Hz, illustrated in Figure 12.a, and **(ii)** First neuron is excited by a constant, above-threshold stimulus, resulting in tonic firing with a frequency around $f_c = 92$ Hz, shown in Figure 12.c. The second neuron is excited via the synapse.

The time-averaged power spectral densities for the membrane voltage of the neuron N2 for the two cases above are shown in Figure 12.b and Figure 12.d,

respectively. The blue (solid) curve is the power spectral density obtained via Monte Carlo type simulations. The red curve (round marks) was computed by using the frequency-domain non Monte Carlo noise analysis technique. In Figure 12.d, the orange (dashed) curve is the time-averaged power spectral density of the membrane voltage of the neuron N2 in Figure 12.c computed as described in Section 6.3. The plots in both Figure 12.b and Figure 12.d reveal that the results obtained via Monte Carlo and the non Monte Carlo methods match almost perfectly. We also verified that the time-domain non Monte Carlo method preserves its excellent performance for multi neuron circuits with synaptic connections. We observed near perfect agreement between the result obtained via the time-domain method and Monte Carlo simulations for the time-varying variance of the membrane voltage of the neuron N2 in Figure 12.a and the spike timing jitter variance of the neuron N2 in Figure 12.c.

7.2.5 *Five-Neuron Ring Oscillator*

In the mammalian brain, the primary circadian clock for the timing of neuronal, endocrine, and behavioral rhythms is generated by the Suprachiasmatic Nucleus (SCN) within the hypothalamus [103]. In the SCN, neurons are synchronized by the synaptic inputs from other neurons so that the neuronal circuit overall generates rhythmic oscillations [103]. The frequency and amplitude of these autonomous oscillations are determined by the particular neuronal circuit organization [103].

Oscillatory neuronal circuits in the SCN can have complex organizations. Here, we consider a simple example, namely a five-neuron ring oscillator circuit where neurons are connected in a ring structure with excitatory synapses, as shown in Figure 13.a. Each neuron in the ring contains 20000 slow AMPA/kainate LG ion channels [62]. Once an action potential is generated in the membrane of one of the neurons due to a temporary external stimulus, the neuronal circuit starts exhibiting autonomous oscillations with a frequency around $f_c = 91$ Hz. As in an electronic ring-oscillator circuit, the autonomous oscillation frequency decreases as the number neurons in the ring increases, due to the additional delay introduced by the synapses.

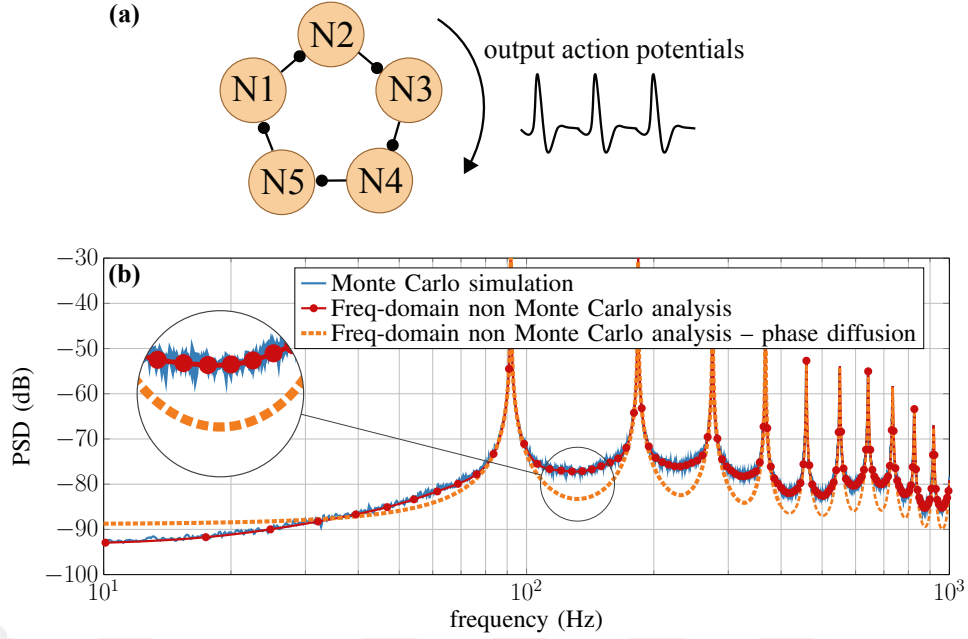


Figure 13: **a)** Five-neuron ring oscillator. **b)** Time-averaged power spectral density of the membrane voltage of neuron N1.

A constant current injection is required for a single, standalone neuron to autonomously oscillate, i.e., for tonic spiking. However, in order for the five-neuron ring oscillator to maintain its autonomous oscillation, an external, constant stimulus is not required. Here, it is important to note that the energy loss in a neuron is compensated by ion pumps. Ion pumps are transmembrane proteins which consume energy to expel ions through the membrane against their concentration gradient [36]. The energy is supplied to the ion pumps by Adenosine Triphosphate (ATP) molecules. Ion pumps keep the ion concentration difference between the inside and the outside of the neuron at a certain value so that the neuron can maintain its activity. The ion concentration differences maintained by the ion pumps are captured by the constant reversal potentials $E_{ion,i}$ in (1) as voltage sources connected in series to the ion channels.

In Figure 13.b, the time-averaged power spectral density of the membrane voltage of neuron N1 is shown. The blue (solid) curve was obtained via Monte Carlo simulations based on 20 membrane voltage sample paths of neuron N1 for a duration of 50 sec (4550 cycles). The red curve (round marks) was computed with the frequency-domain non Monte Carlo noise analysis technique. The perfect agreement between these results again verifies the accuracy of the non

Monte Carlo method for a complex neuronal circuit. The orange (dashed) curve is the time-averaged power spectral density of the membrane voltage computed only for the effect of the fluctuations due to phase diffusion. For the five-neuron ring oscillator, considering only the phase diffusion does not yield an accurate result unlike for the case of an autonomously oscillating single neuron presented in Section 7.2.3. The reason for this mismatch is the slower dynamics of the LG ion channels in the excitatory synapses compared with the VG ion channels. In this case, the effect of the additive second noise term in (32) becomes significant in addition to the fluctuations caused by phase diffusion.



Part III

RESULTS



AUTONOMOUSLY OSCILLATING NEURONAL CIRCUITS: ENERGY CONSUMPTION VS. TIMING JITTER

In the mammalian brain, the primary circadian clock for the timing of neuronal, endocrine, and behavioral rhythms is generated by the Suprachiasmatic Nucleus (SCN) within the hypothalamus [103]. In the SCN, neurons are synchronized by the synaptic inputs from other neurons so that the neuronal circuit overall generates rhythmic oscillations. The frequency, amplitude, and the timing accuracy of these autonomous oscillations are determined by the particular neuronal circuit organization.

In order to gain some insight into the mechanisms, energy efficiency and timing reliability of autonomous neuronal oscillators, we consider two neuronal circuits: **(i)** An autonomously oscillating neuron excited by a constant, above-threshold current stimulus as shown in Figure 11.a, **(ii)** An autonomously oscillating five-neuron circuit where neurons are connected in a ring structure with excitatory synapses as shown in Figure 13.a. In order to investigate the mechanisms of circadian oscillators in the SCN, similar ring network topologies with various connection scenarios have been previously considered in the literature [33], [104]. In a ring network, once an action potential is generated in the membrane of one of the neurons due to a temporary external stimulus, the neuronal circuit starts exhibiting autonomous oscillations if the synaptic delays are sufficiently large. As in an electronic ring-oscillator circuit, the autonomous oscillation frequency decreases as the number neurons in the ring increases, due to the additional delay introduced by the synapses.

Autonomous oscillators, unlike systems that are forced to oscillate at a frequency imposed by an external periodic stimulus, possess a phase that is freely diffusing [59]. This results in spike timing jitter with an increasing variance in the time domain. This behavior has actually been observed in experimental studies [23]. We run frequency-domain non Monte Carlo analyses

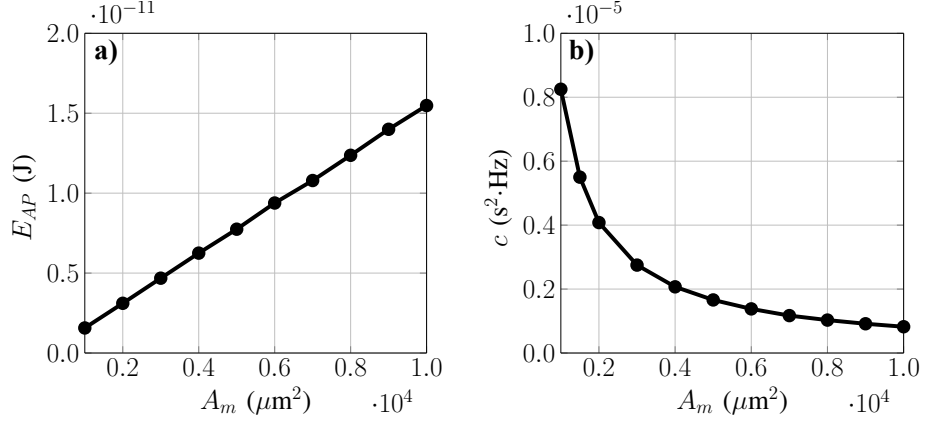


Figure 14: **a)** Average action potential energy consumption E_{AP} and **b)** Timing jitter variance slope c plotted with respect to the membrane area A_m .

in order to compute the slope of the timing jitter variance c where $E[\alpha(t)^2] = ct$, as described in Section 6.3.

We consider the current balance equation of the neuron membrane in (1) for the energy consumption analysis. The power, i.e., energy consumption rate, of a neuron due to the ion currents passing through its membrane and the power supplied by an external stimulus are given by

$$\begin{aligned} P_{\text{ion}}(t) &= \sum_i G_{\text{ion},i} [V(t) - E_{\text{ion},i}]^2, \\ P_{\text{ext}}(t) &= V(t) I_{\text{ext}}(t). \end{aligned} \quad (38)$$

The energy consumption for an action potential can be computed by integrating $P_{\text{ion}}(t)$ and $P_{\text{ext}}(t)$ over the duration of the action potential [105]. In neurons, energy is consumed by ion pumps, which are transmembrane proteins. Ion pumps expel ions through the membrane against their concentration gradient by consuming energy in the form of ATP molecules [36]. Hence, ion pumps play a fundamental role in keeping the ion concentration difference between the inside and the outside of the neuron at a certain value so that the neuron can maintain its activity after an action potential. The ion concentration differences maintained by the ion pumps are captured by the constant reversal potentials $E_{\text{ion},i}$ in (1), as voltage sources connected in series to the ion channel conductances. The total energy consumed in order for a neuronal circuit to spike is computed as the sum of the energy consumed by the ion pumps and the energy supplied by the external current injection. In order for a neuronal ring oscillator to maintain its autonomous oscillation, an external, constant

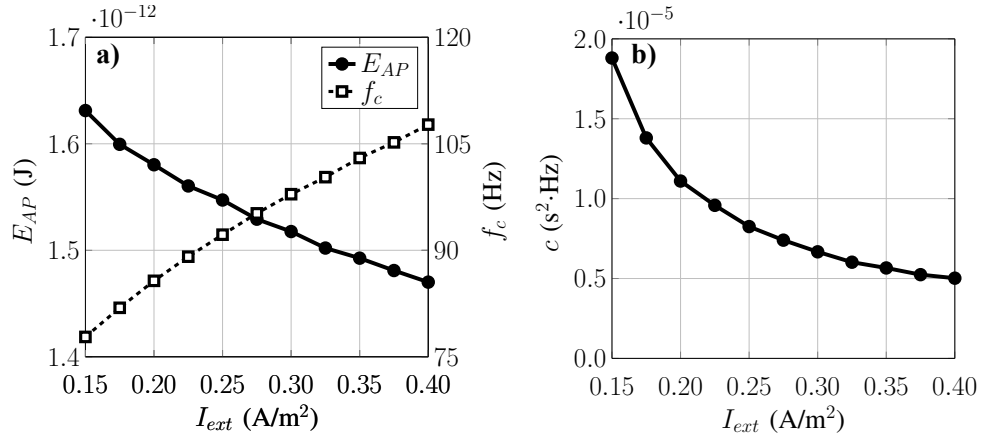


Figure 15: **a)** Average action potential energy consumption E_{AP} and firing frequency f_c , **b)** timing jitter variance slope c plotted with respect to the amplitude of the constant current injection I_{ext} .

stimulus is not required. The total energy consumption is determined by only the activity of the ion pumps. In both cases, we compute the average energy consumed by a neuronal circuit in generating an action potential, denoted by E_{AP} , by averaging over 100 action potential cycles.

8.1 EFFECT OF MEMBRANE AREA ON SINGLE NEURON OSCILLATOR

We first consider an autonomously oscillating standalone neuron stimulated by a constant current. We consider neurons with varying membrane areas while keeping the external current input and the densities of ion channels in the membrane constant at $I_{ext} = 0.25$ A/m², 60 Na⁺ channels/ μm^2 , and 18 K⁺ channels/ μm^2 , respectively. In this case, the firing frequency of the neuron is $f_c = 92$ Hz, independent of the membrane area A_m [36]. The dependence of average action potential energy E_{AP} on the membrane area A_m of the neuron is depicted in Figure 14.a, which shows that E_{AP} increases as A_m is increased. This is expected, since the number of ion channels and hence the total channel conductance, $G_{ion,i}$, are directly proportional to the membrane area A_m . In Figure 14.b, the effect of the membrane area A_m on the slope of the timing jitter variance c is shown. As the membrane area is increased, the fluctuations in the neuron are subdued, that results in a reduction in the timing jitter

variance. More specifically, the results in Figure 14.b show that the timing jitter variance slope c is inversely proportional to the membrane area A_m .

8.2 EFFECT OF EXCITATION AMPLITUDE ON SINGLE NEURON OSCILLATOR

We now consider an autonomously oscillating standalone neuron stimulated by a constant current with varying values, while keeping the membrane area fixed at $A_m = 1000 \mu\text{m}^2$, with the ion channel densities equal to 60 Na^+ channels/ μm^2 and 18 K^+ channels/ μm^2 . The firing frequency of the neuron does depend on the value I_{ext} of the external current injection [36]. In particular, an increase in I_{ext} results in an increase in the oscillation frequency f_c , as shown in Figure 15.a (dashed curve with square marks). Since larger f_c corresponds to shorter durations for the action potentials, the average action potential energy decreases, as shown in Figure 15.a (solid curve with round marks). An approximately linear relation can be observed between E_{AP} and I_{ext} . Moreover, Figure 15.b shows that an autonomously oscillating standalone neuron with higher injection currents has a lower timing jitter. Similar observations were also reported in [52]. According to the results in Figure 15.b, we can roughly assess the relationship between the timing jitter variance slope and injection current as $c \sim 1/I_{ext}$.

8.3 SINGLE NEURON OSCILLATOR VS. FIVE-NEURON RING OSCILLATOR

We next compare the performance of a standalone neuron oscillator with that of a five-neuron ring oscillator from a timing jitter and energy consumption perspective. The membrane area of each neuron in the ring oscillator is chosen as $A_m = 1000 \mu\text{m}^2$ with the ion channel densities equal to 60 Na^+ channels/ μm^2 , 18 K^+ channels/ μm^2 , and 20 slow AMPA/kainate synaptic receptor channels/ μm^2 . The additional energy consumption due to the excitatory synapses between the neurons in the ring oscillator is computed based on the current passing through the AMPA/kainate synaptic receptor channels. The

firing frequency is $f_c = 91.8$ Hz. For the five-neuron ring oscillator, the average action potential energy consumption is $E_{AP} = 8.58 \times 10^{-12}$ J and the timing jitter variance slope is $c = 7.26 \times 10^{-7} \text{s}^2 \cdot \text{Hz}$. In order to match the energy consumption and the firing frequency of the five-neuron ring oscillator with the standalone neuron oscillator, we set $I_{ext} = 0.25 \text{ A/m}^2$ and $A_m = 5500 \mu\text{m}^2$ for the single neuron oscillator. In this case, the timing jitter variance slope of the single neuron oscillator is computed as $c = 1.51 \times 10^{-6} \text{s}^2 \cdot \text{Hz}$, which is roughly twice the one obtained for five-neuron ring oscillator. Similarly, in order to match the timing jitter slope of the five-neuron ring oscillator with a single neuron, we set $I_{ext} = 0.25 \text{ A/m}^2$ and $A_m = 11350 \mu\text{m}^2$. In this case, the energy consumption of the single neuron becomes roughly twice that of the ring oscillator. To summarize, given an energy (or membrane area) budget, it is better, from a timing reliability perspective, to have five small neurons in a ring configuration as opposed to a single large neuron that has about five times the membrane area. It is interesting that, the existence of synaptic connections between the neurons in the ring architecture case results in an improvement in the timing reliability and energy efficiency of the circuit. This is despite the fact that the synaptic processes themselves introduce stochasticity that is expected to have a detrimental effect on timing reliability. We obtained similar results for a seven-neuron ring architecture.

The above results suggest that if neurons are excited by synaptic currents, their output action potentials have better timing reliability. This reveals the preference of neurons for particularly shaped waveform excitations, i.e., excitatory synaptic currents that are produced by presynaptic neurons. These results are consistent with experimental studies which have shown that the spike timing precision of neurons can be improved when a neuron is stimulated with a fluctuating current resembling synaptic currents as opposed to a constant, above-threshold current stimuli [23]. In addition, our results show that forming synaptic connections between smaller neurons is a more energy efficient and effective mechanism than increasing the size of a neuron for achieving better spike timing precision. Finally, the following question naturally arises: What sort of synaptic connections and neuronal configurations yield improved timing reliability and energy-efficiency? We have looked into only simple ring

configurations. Further investigation into more elaborate configurations is part of future work.



FEEDBACK INHIBITION

Experimental findings suggest that the timing precision of the firing of neurons is an important factor in accurate sensory information representation, especially for the auditory and visual systems [23]–[25]. It has been observed experimentally that the timing reliability of spiking neurons is improved when they receive feedback inhibition [27], [28]. In the literature, there are numerous experimental studies investigating feedback inhibition from this perspective [29], [106]. However, the underlying mechanisms have not been completely unveiled yet. We investigate this phenomenon from a computational modeling and simulation perspective based on the framework summarized in Chapter 4, via the methods presented in Chapter 6.

9.1 SPIKE TIMING PRECISION VS. FEEDBACK INHIBITION

We use the setup shown in Figure 16 in order to investigate the effects of feedback inhibition on the spike timing precision and try to gain some insight into the underlying mechanism. A constant suprathreshold current stimulus is injected into neuron $\mathcal{N}_1$. In this case, the neuron $\mathcal{N}_1$ is oscillating, i.e., it is under tonic spiking conditions. The neurons $\mathcal{N}_1$ and $\mathcal{N}_2$ are connected via synapses, where filled and empty circles represent excitatory and inhibitory synapses, respectively. More specifically, $\mathcal{N}_1$ makes an excitatory synapse on $\mathcal{N}_2$, whereas $\mathcal{N}_2$ makes an inhibitory synapse on $\mathcal{N}_1$. Therefore, each spike generated by $\mathcal{N}_1$ initiates another spike in the membrane of $\mathcal{N}_2$, which eventually inhibits $\mathcal{N}_1$. This constitutes feedback inhibition for $\mathcal{N}_1$.

The phase fluctuations with an increasing variance can be easily observed in Figure 17, where only 20 membrane voltage waveforms (for neuron $\mathcal{N}_1$) generated by Monte Carlo simulations are plotted on top of each other. At steady-state, the timing jitter variance evaluated at each multiple of the oscillation period T_c is given by $\text{Var}[\alpha(kT_c)] = c_{ss}kT_c$. If we normalize $\text{Var}[\alpha(kT_c)]$

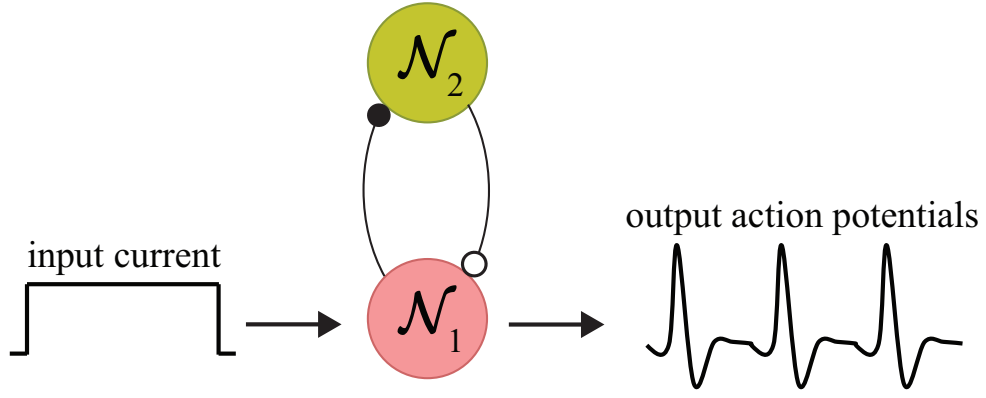


Figure 16: Feedback inhibition of neuron $\mathcal{N}_1$ by neuron $\mathcal{N}_2$. Neuron $\mathcal{N}_1$ is under tonic spiking conditions with a constant, suprathreshold current stimulus.

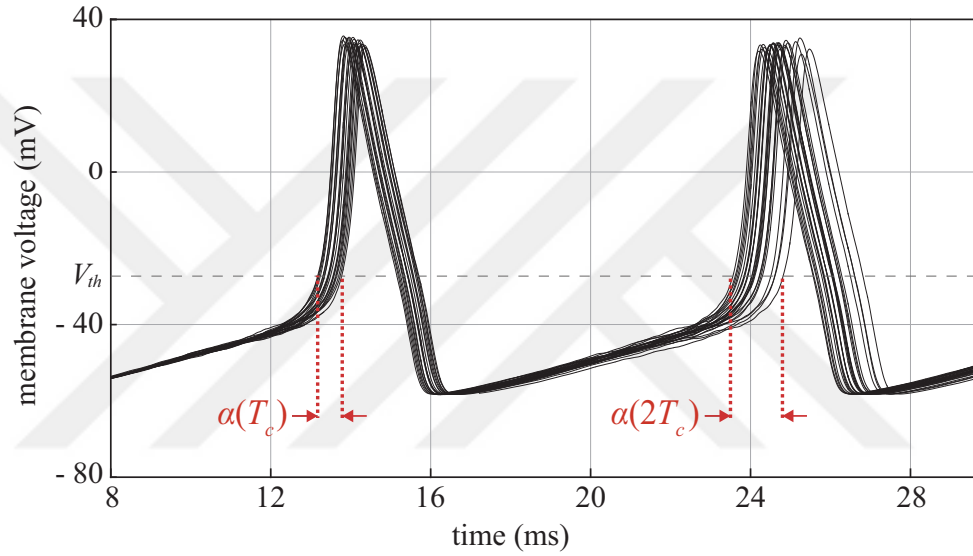


Figure 17: 20 sample paths, generated for the membrane voltage of neuron $\mathcal{N}_1$ in Figure 16, are drawn on top of each other. The timing jitters $\alpha(T_c)$ and $\alpha(2T_c)$ are indicated for the first two output action potentials, where increasing timing jitter variance can be easily observed.

with kT_c , we get the slope c_{ss} , which is the accumulation rate of the timing jitter variance. We use the timing jitter variance slope c_{ss} of a spiking neuron to quantify its spike timing precision. Hence, we can compare the timing precision performance of spiking neurons with different spiking periods at the end of a given duration.

For the analysis in this chapter, the amplitude of the external suprathreshold current input to neuron $\mathcal{N}_1$ is held constant at $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is fixed at $A_m = 1000 \text{ } \mu\text{m}^2$ with the VG ion

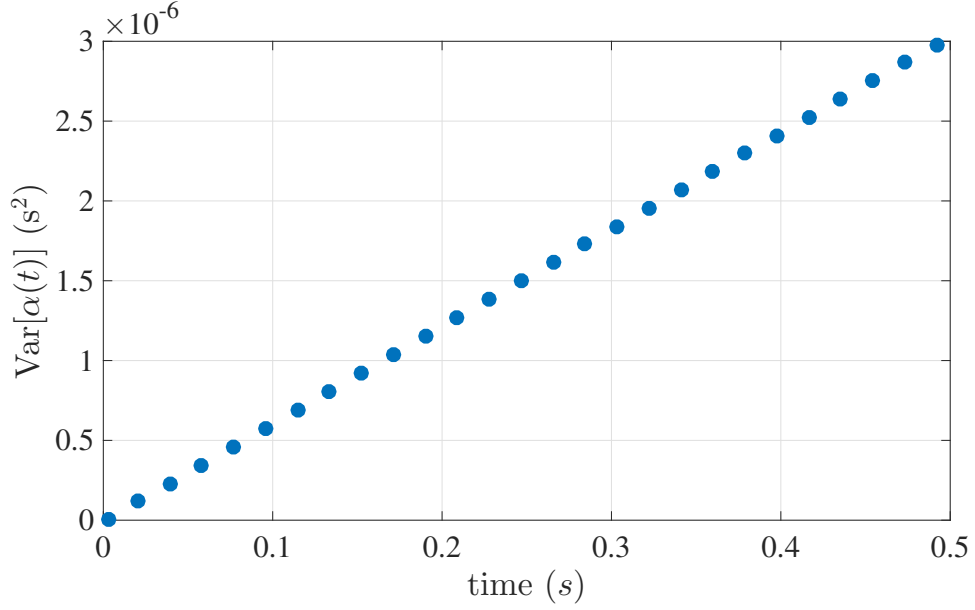


Figure 18: The timing jitter variance of the output spikes of neuron $\mathcal{N}_1$ in Figure 16.

The amplitude of the external suprathreshold current input to neuron $\mathcal{N}_1$ is held constant at $I_{\text{ext}} = 0.25$ A/m². The membrane area of each neuron in Figure 16 is fixed at $A_m = 1000$ μm². The numbers of receptor ion channels in the synapses between $\mathcal{N}_1$ and $\mathcal{N}_2$ are $N_{\text{ext}} = 3 \times 10^4$ excitatory AMPA/kainate receptor channels (in $\mathcal{N}_2$) and $N_{\text{inh}} = 1 \times 10^4$ inhibitory GABA_A receptor channels (in $\mathcal{N}_1$). The timing jitter variance increases linearly with time as expected.

channel densities equal to 60 Na⁺ channels/μm² and 18 K⁺ channels/μm². The number of the excitatory receptor ion channels in the synapse between $\mathcal{N}_1$ and (on) $\mathcal{N}_2$ is also kept constant at 3×10^4 AMPA/kainate receptor channels. In Figure 18, the timing jitter variance, $\text{Var}[\alpha(t)]$, for $N_{\text{inh}} = 1 \times 10^4$ inhibitory GABA_A receptor ion channels (for the synapse from $\mathcal{N}_2$ to $\mathcal{N}_1$), is shown. For each point in Figure 18, the timing jitter variance at a multiple of the oscillation period T_c , i.e., $\text{Var}[\alpha(kT_c)]$, was computed using the transient semi-analytical method reviewed in Chapter 6. The timing jitter variance increases linearly with time as expected, without any transient settling behavior in this case.

In order to assess the effect of the inhibitory feedback synapse, the number of the inhibitory GABA_A receptor ion channels N_{inh} in the membrane of $\mathcal{N}_1$ is varied. For each value of N_{inh} , the asymptotic timing jitter variance slope of the neuronal circuit in Figure 16 is computed via the steady-state

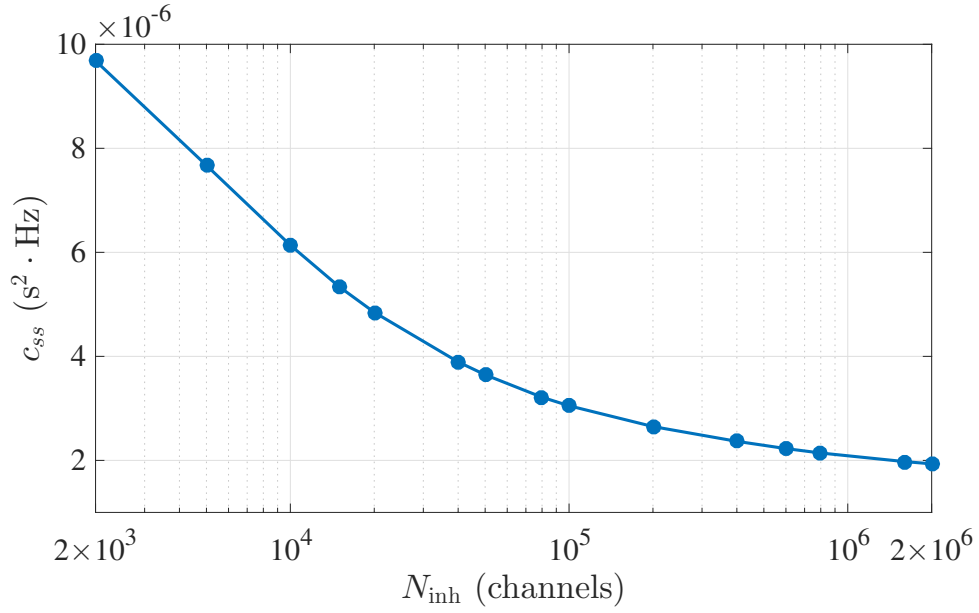


Figure 19: The timing jitter variance slope of neuron $\mathcal{N}_1$ in Figure 16 with respect to the number of the inhibitory synaptic channels (in $\mathcal{N}_1$) for $I_{\text{ext}} = 0.25 \text{ A/m}^2$, $A_m = 1000 \mu\text{m}^2$, and $N_{\text{ext}} = 3 \times 10^4$ AMPA/kainate receptor channels (in $\mathcal{N}_2$).

semi-analytical method reviewed in Chapter 6. The results in Figure 19 show that as the feedback inhibition strength is increased, the timing jitter variance decreases. These results are consistent with experimental findings which have shown that the spike timing precision of neurons is improved when they receive feedback inhibition [28]. In addition, an increase in the feedback inhibition strength results in an increase in the spiking period, as shown in Figure 20. This behavior suggests that feedback inhibition prolongs the refractory period of neuron $\mathcal{N}_1$.

In order to more clearly elucidate the spike timing precision improvement brought about by feedback inhibition, we consider the amount of information that can be coded by the timing of a spike. Given the timing of the k th spike, the timing of the $(k+1)$ th spike is a Gaussian random variable with a variance of $c_{ss}T_c$, which indicates an uncertainty in the timing of the $(k+1)$ th spike. Due to this uncertainty, the amount of information that can be encoded by the timing of the $(k+1)$ th spike within one oscillation period T_c is limited. More precisely, the timing of the $(k+1)$ th spike within one period T_c cannot be determined with a resolution that is better (less) than the standard deviation

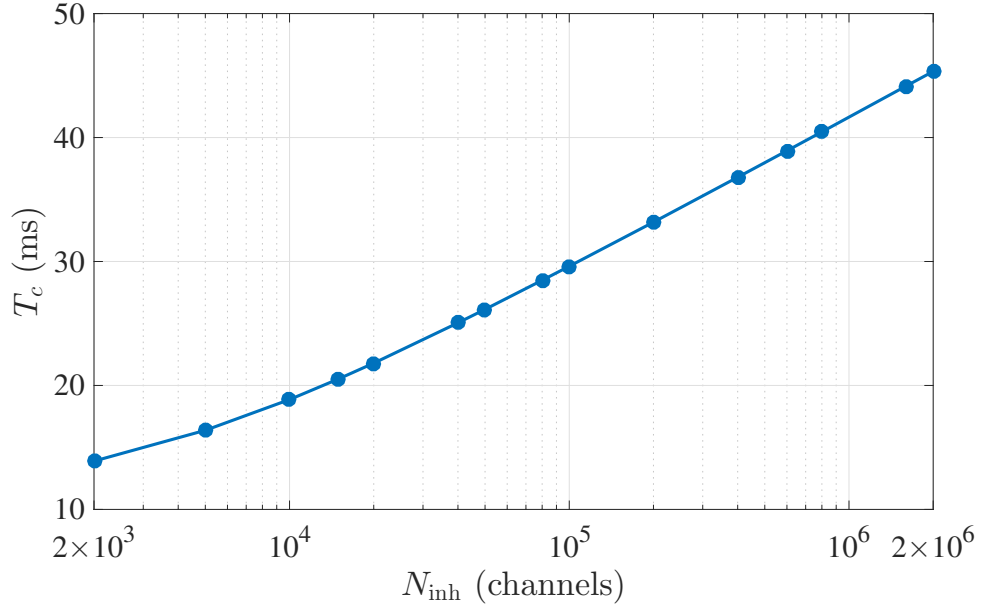


Figure 20: The spiking period of neuron $\mathcal{N}_1$ in Figure 16 with respect to the number of the inhibitory synaptic channels (in $\mathcal{N}_1$) for $I_{\text{ext}} = 0.25 \text{ A/m}^2$, $A_m = 1000 \mu\text{m}^2$, and $N_{\text{ext}} = 3 \times 10^4$ AMPA/kainate receptor channels (in $\mathcal{N}_2$).

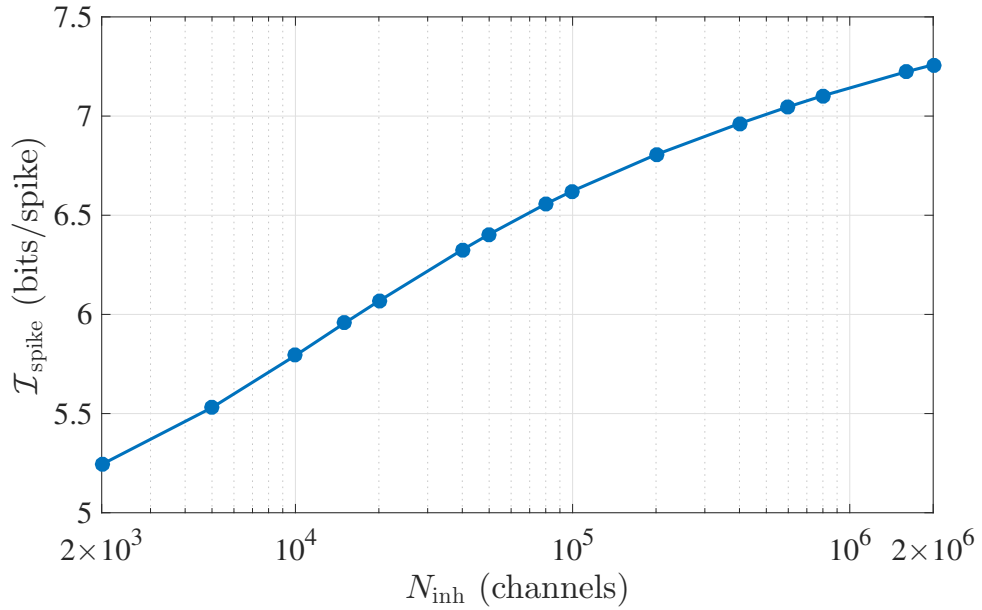


Figure 21: The spike timing information content of the output action potentials of neuron $\mathcal{N}_1$ in Figure 16 with respect to the number of the inhibitory synaptic channels (in $\mathcal{N}_1$) for $I_{\text{ext}} = 0.25 \text{ A/m}^2$, $A_m = 1000 \mu\text{m}^2$, and $N_{\text{ext}} = 3 \times 10^4$ AMPA/kainate receptor channels (in $\mathcal{N}_2$).

of timing jitter, i.e., $\sqrt{c_{ss}T_c}$. The information encoded by the spike can be reliably decoded only when the timing needs to be resolved within $\sqrt{c_{ss}T_c}$.

If the amount of information encoded dictates a finer resolution requirement for reliable detection, then the information may be lost as a result of the uncertainty due to timing jitter. Thus, the count of possible timing intervals that can be resolved and used to encode information by the $(k + 1)$ th spike is limited and given by

$$\mathcal{L}_{\text{spike}} = \frac{T_c}{\sqrt{c_{ss} T_c}} = \sqrt{\frac{T_c}{c_{ss}}}. \quad (39)$$

The information content, $\mathcal{I}_{\text{spike}}$, per spike measured as the number of binary bits that can be represented by the timing of the spike is then given by

$$\mathcal{I}_{\text{spike}} = \log_2 (\mathcal{L}_{\text{spike}}) = \frac{1}{2} \log_2 \left(\frac{T_c}{c_{ss}} \right), \quad (40)$$

where T_c/c_{ss} can be considered as the Signal-to-Noise Ratio (SNR). In particular, as T_c is increased or c_{ss} is decreased, the SNR increases, which results in an increase in the spike timing information content. The information content for the two-neuron circuit in Figure 16 is shown in Figure 21 as a function of the number of inhibitory synaptic channels (in neuron $\mathcal{N}_1$), which indicates that feedback inhibition improves the information content that can be encoded in the spike timings.

The justification and basis for the discussion and derivation above originate in well established concepts and results in information theory. The information content relation in (40) is very similar to the information capacity of an additive white Gaussian communication channel [107].

With zero jitter, the spikes are separated from each other with exactly T_c . In this case, other than being a perfect time reference, the spike timings do not indeed contain any information. This may suggest that it would be better if the spike timings were completely randomized from an information content point of view. However, this situation will change when the frequency/period of spiking is modulated, for instance, with signals from sensory receptors. In this case, the spike timings will not be separated from each other with a fixed T_c , but with a time-varying $T_c(t)$ that encodes sensory information. Then, lower jitter in spike timings will allow the detection and determination of the spike timings with a higher resolution, resulting in a higher information content that can be encoded in the timings.

9.2 SPIKE TIMING PRECISION VS. SYNAPTIC CHANNEL NOISE

The results above on feedback inhibition were obtained with SDE models of the ion channels and the synapses. The noise (diffusion) part of these SDE models depend on the noiseless mean (drift) component. The diffusion parts were not added to the model in a phenomenological manner. Their form is directly linked to the noiseless drift component and are both derived from the Markovian models of the ion channels [56]. Thus, with an SDE model, when the number of the synaptic LG channels is varied, both the mean synaptic current and also the synaptic channel noise levels change. This is indeed what happens in a real neuron. In order to dig deeper into this, we observe that the noise, *relative to the mean*, contributed by the synaptic channels decreases with increasing number of LG receptor channels. This is so because the drift (mean) component of the SDE that governs channel behavior is proportional to the number of channels, whereas the diffusion (noise) component is proportional to the *square root* of the number of channels. Then, the following question may arise: Is the spike timing precision improvement observed with increasing number of feedback inhibitory synaptic channels due to (i) increased mean inhibitory feedback current, i.e., stronger feedback inhibition, or (ii) reduced synaptic current noise relative to the mean? In order to shed light onto this matter, we need to separately analyze the effects of the mean and noise of the synaptic current. For this, we keep the mean inhibitory synaptic current entering into neuron $\mathcal{N}_1$ fixed by keeping the total maximal receptor channel conductance constant, given by the product $N_{\text{inh}} \cdot g_{\text{GABA}_A}$, where g_{GABA_A} is the conductance of a single inhibitory GABA_A receptor channel. That is, as N_{inh} is varied, we also vary g_{GABA_A} accordingly in order to keep their product constant. Although doing this does not have a physiological basis, it can help answer the question posed above. When the number of inhibitory synaptic channels is increased in this setup, the noise contributed by the synaptic channels decreases while the mean synaptic current is held constant. This is so because while both the drift and diffusion components of the SDE that governs the synaptic current are proportional to g_{GABA_A} , the drift part is proportional to N_{inh} and the diffusion part is proportional to $\sqrt{N_{\text{inh}}}$.

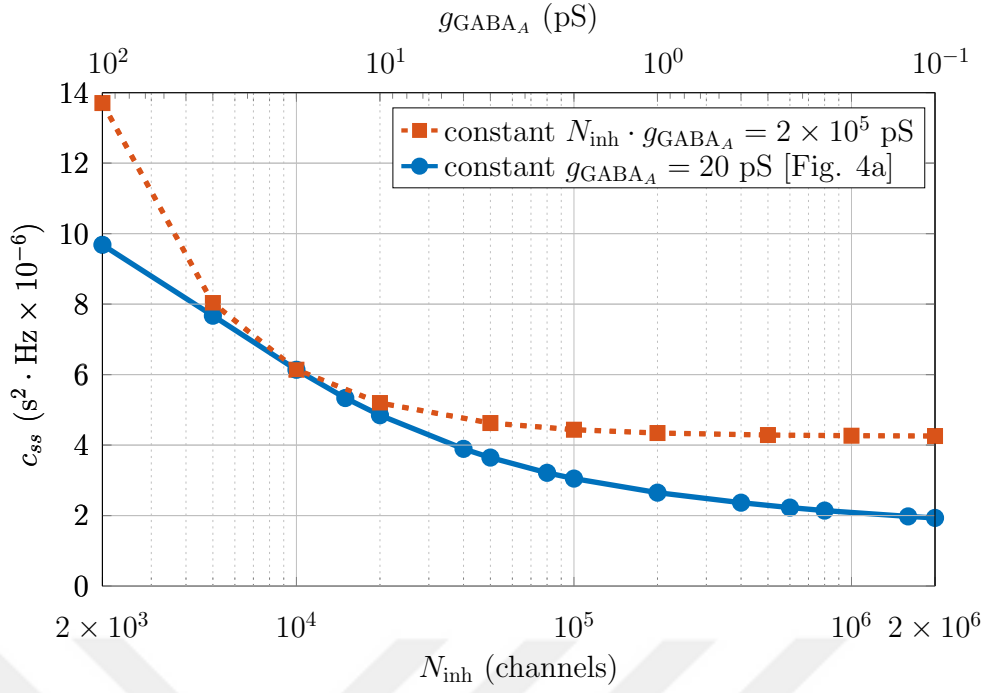


Figure 22: The timing jitter variance slope of the output action potentials of neuron $\mathcal{N}_1$ in Figure 16 for constant $N_{\text{inh}} \cdot g_{\text{GABA}_A} = 2 \times 10^5$ pS is plotted with red dashed curve (square markers) with respect to the number of the inhibitory synaptic channels (in $\mathcal{N}_1$) on the lower x -axis and the conductance of a single inhibitory synaptic channel (in $\mathcal{N}_1$) on the upper x -axis. The blue solid curve (circle markers) is the same curve as the one in Figure 19, which shows the timing jitter variance slope of the output action potentials of neuron $\mathcal{N}_1$ for constant $g_{\text{GABA}_A} = 20$ pS with respect to the number of the inhibitory synaptic channels (in $\mathcal{N}_1$) on the lower x -axis. For both cases, the amplitude of the external suprathreshold current input to neuron $\mathcal{N}_1$ is $I_{\text{ext}} = 0.25$ A/m², the membrane area of each neuron is $A_m = 1000$ μm^2 , and the number of excitatory AMPA/kainate receptor channels is $N_{\text{ext}} = 3 \times 10^4$ channels (in $\mathcal{N}_2$). The product $N_{\text{inh}} \cdot g_{\text{GABA}_A}$ is kept constant at each point of the red dashed curve (square markers). Thus, as the number of inhibitory synaptic channels is increased, although the mean inhibitory synaptic current does not change, the inhibitory synaptic current noise decreases. As the noise level decreases, the timing jitter variance first decreases and then becomes constant.

In Figure 22, the timing jitter variance slope of the output action potentials of neuron $\mathcal{N}_1$ in Figure 16 for constant mean synaptic current (i.e., for constant $N_{\text{inh}} \cdot g_{\text{GABA}_A} = 2 \times 10^5$ pS) is shown with red dashed curve (square markers) for varying values of N_{inh} (on lower x -axis) and g_{GABA_A} (on upper x -axis).

The curve in Figure 19 is also included in Figure 22 with a blue solid curve (circle markers), which shows the timing jitter variance slope of the output action potentials of neuron $\mathcal{N}_1$ for constant $g_{\text{GABA}_A} = 20$ pS with respect to the number of the inhibitory synaptic channels (in $\mathcal{N}_1$) (on lower x -axis).

As the number of inhibitory synaptic LG channels is increased while the mean inhibitory synaptic current is held constant as discussed above, the channel noise of these inhibitory LG channels decreases and eventually becomes negligible compared with the channel noise of the VG ion channels in neuron $\mathcal{N}_1$. Since the number of VG ion channels, as well as the mean inhibitory current, is constant in this scenario, the contribution of the VG channels to noise and timing jitter does not change. Thus, as the number of inhibitory synaptic channels is increased, the timing jitter variance of neuron $\mathcal{N}_1$ first decreases due to the reduction in LG channel noise, but then becomes constant mainly arising from VG channel noise. This behavior can be clearly observed on the red dashed curve (square markers) in Figure 22. On the other hand, as the number of inhibitory synaptic LG channels is reduced while the mean inhibitory synaptic current is held constant, the channel noise of the inhibitory LG ion channels becomes more prominent and eventually becomes comparable to the noise of the VG ion channels in neuron $\mathcal{N}_1$. Hence, the increase in LG channel noise results in an increased timing jitter variance.

In Figure 22, the two curves intersect at the point where g_{GABA_A} is set to its nominal value of 20 pS with $N_{\text{inh}} = 10^4$ for the red dashed curve (square markers) with constant $N_{\text{inh}} \cdot g_{\text{GABA}_A}$, i.e., with constant mean inhibitory synaptic current. The points on the blue solid curve (circle markers) with constant $g_{\text{GABA}_A} = 20$ pS correspond to larger mean inhibitory synaptic currents compared with the points on red dashed curve (square markers) for $g_{\text{GABA}_A} < 20$ pS, i.e., to the right of the intersection point, with the difference increasing as one moves further right from the intersection point. Furthermore, for both curves, the inhibitory synaptic channel noise relative to the mean synaptic current decreases with increasing N_{inh} . In particular, for $N_{\text{inh}} > 10^5$, the noise of the inhibitory LG channels is negligible in both scenarios. That is why, the curve with constant mean inhibitory synaptic current (red dashed curve, square markers) is flat. However, in the case with constant g_{GABA_A} (blue solid curve, circle markers), the timing jitter is *further* reduced with

increasing mean synaptic current for $N_{\text{inh}} > 10^5$, where the dominant noise sources are the VG ion channels whose count is held constant. This shows that the improvement of timing precision with increased inhibitory synaptic strength (and hence with stronger feedback inhibition) can not be attributed to only the reduction of the relative synaptic noise due to larger number of synaptic channels. Thus, the answer to the question posed above is as follows: The spike timing precision improvement observed with increasing number of feedback inhibitory synaptic channels is due to a combined effect of both stronger feedback inhibition and also reduced synaptic current noise relative to the mean.

The behavior to the left of the intersection point in Figure 22 also requires a comment. For $N_{\text{inh}} < 5 \times 10^3$, the noise of the inhibitory LG channels dominates when compared with the noise from the VG channels. This results in worse spike timing precision in both cases. On the other hand, for the curve with constant $N_{\text{inh}} \cdot g_{\text{GABA}_A}$ (red dashed curve, square markers), LG channel noise level is even higher due to larger g_{GABA_A} values as N_{inh} is further reduced. This results in worse timing precision when compared with the case (blue solid curve, circle markers) with constant g_{GABA_A} , even though the mean synaptic current is higher in the former.

9.3 ENERGY CONSUMPTION VS. FEEDBACK INHIBITION

The total energy consumed by a neuronal circuit per action potential, denoted by E_{AP} , is computed by using Eqn. (38) as described in detail in Chapter 8. We present mean energy consumption per action potential values of a neuronal circuit, which are evaluated over 100 action potential cycles.

In order to assess the effect of feedback inhibition from a timing jitter and energy consumption perspective, we consider a standalone neuron excited by a constant suprathreshold current stimulus, I_{ext} , and compare its jitter, c_{ss} , and energy consumption, E_{AP} , to that of the neuronal circuit with feedback inhibition in Figure 16. We set the parameters of the standalone neuron circuit in such a way so that its firing frequency, $f_c = 1/T_c$, is the same as that of the one with feedback inhibition. If the standalone neuron has the

Table 3: Spike timing precision and energy consumption analysis of neuronal circuits with and without feedback inhibition. The presence of feedback inhibition improves both the timing precision and the energy efficiency of the neuronal circuit.

Simulation setup	N_{inh}	I_{ext}	A_m	f_c	E_{AP}	c_{ss}
Standalone neuron	0 ch	0.09 A/m ²	2150 μm^2	64.2 Hz	3.58×10^{-12} J	$4.20 \times 10^{-5}\text{s}^2\cdot\text{Hz}$
Standalone neuron	0 ch	0.09 A/m ²	4600 μm^2	64.2 Hz	7.61×10^{-12} J	$1.93 \times 10^{-5}\text{s}^2\cdot\text{Hz}$
Neuron with feedback inhibition	0.2×10^4 ch	0.17 A/m ²	1000 μm^2	64.1 Hz	3.56×10^{-12} J	$1.93 \times 10^{-5}\text{s}^2\cdot\text{Hz}$

Table 4: Spike timing precision and energy consumption analysis of neuronal circuits with feedback inhibition. As the strength of feedback inhibition is enhanced, both the timing precision and the energy efficiency of the neuronal circuit are improved.

Simulation setup	N_{inh}	I_{ext}	A_m	f_c	E_{AP}	c_{ss}
Neuron with feedback inhibition	0.2×10^4 ch	0.17 A/m ²	1000 μm^2	64.1 Hz	3.56×10^{-12} J	$1.93 \times 10^{-5}\text{s}^2\cdot\text{Hz}$
Neuron with feedback inhibition	0.2×10^4 ch	0.17 A/m ²	3600 μm^2	64.1 Hz	12.32×10^{-12} J	$0.54 \times 10^{-5}\text{s}^2\cdot\text{Hz}$
Neuron with feedback inhibition	2.0×10^4 ch	1.25 A/m ²	750 μm^2	64.4 Hz	3.52×10^{-12} J	$0.54 \times 10^{-5}\text{s}^2\cdot\text{Hz}$

same *energy consumption per spike (timing jitter variance slope)* as that of the neuronal circuit with feedback inhibition, its *timing jitter variance slope (energy consumption)* is roughly twice the one obtained for the neuronal circuit with feedback inhibition. Thus, feedback inhibition of a spiking neuron improves its energy efficiency for a given spike timing precision, or alternatively, feedback inhibition yields better spike timing precision for a given energy consumption, as summarized and quantified in Table 3.

We next consider the neuron with feedback inhibition in Figure 16 with a larger inhibition strength, obtained by increasing the number of the inhibitory GABA_A receptor ion channels (in $\mathcal{N}_1$) tenfold, and compare its performance to the case with weaker feedback inhibition. We again make sure that the firing frequencies of the two cases are the same by choosing the relevant parameters appropriately. If the *energy consumption (timing jitter variance slope)* of the high inhibition strength case is the same as that of the low inhibition case, its

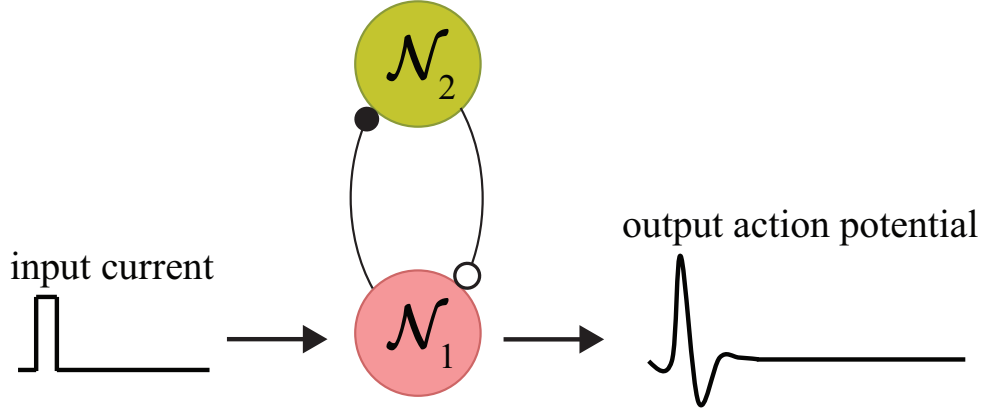


Figure 23: Feedback inhibition of neuron $\mathcal{N}_1$ by neuron $\mathcal{N}_2$. Neuron $\mathcal{N}_1$ is stimulated by a single suprathreshold current pulse with a duration of 2 msec.

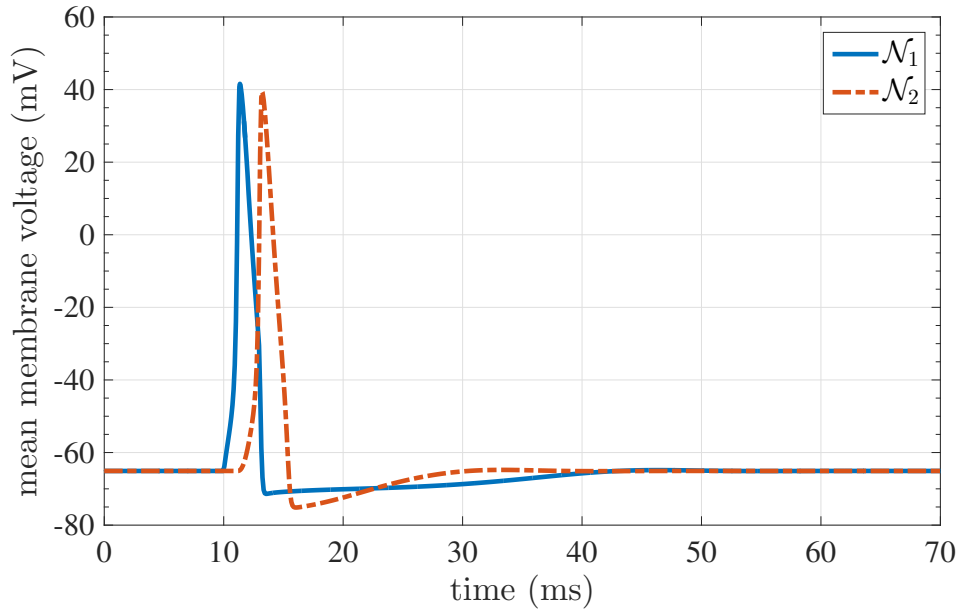


Figure 24: The mean membrane voltages of the neurons $\mathcal{N}_1$ and $\mathcal{N}_2$ shown in Figure 23, where $\mathcal{N}_1$ (with membrane area $A_m = 1000 \mu\text{m}^2$) is stimulated by a single suprathreshold current pulse with an amplitude $I_{\text{ext}} = 0.25 \text{ A/m}^2$ and a duration of 2 msec. The numbers of the receptor ion channels in the synapses between $\mathcal{N}_1$ and $\mathcal{N}_2$ are $N_{\text{ext}} = 3 \times 10^4$ excitatory AMPA/kainate receptor channels (in $\mathcal{N}_2$), and $N_{\text{inh}} = 2 \times 10^4$ inhibitory GABA_A receptor channels (in $\mathcal{N}_1$).

timing jitter variance slope (energy consumption) is approximately 3.5 times better. Thus, as the strength of feedback inhibition is enhanced, both the timing precision and the energy efficiency of the neuronal circuit are improved, as summarized and quantified in Table 4.

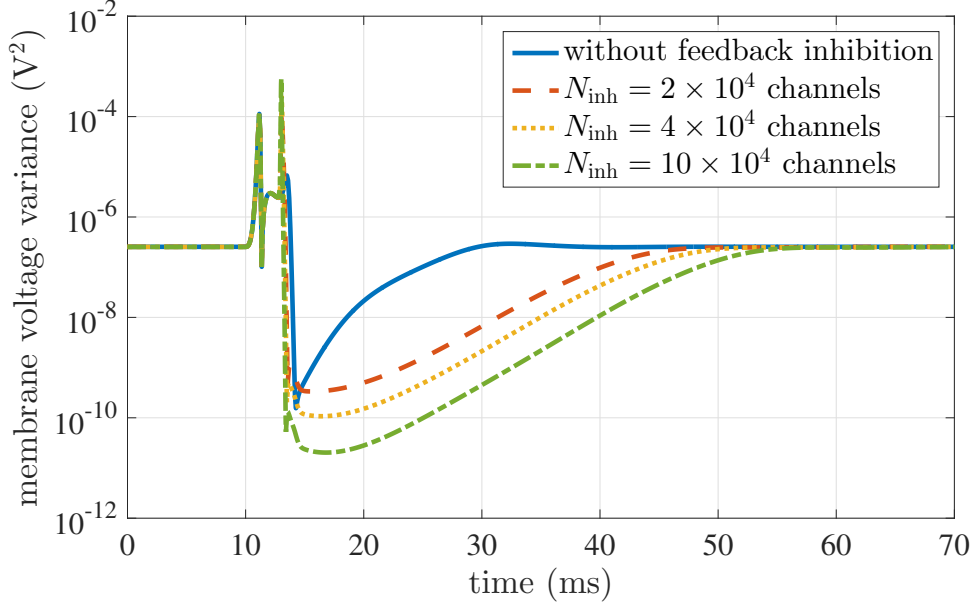


Figure 25: The variance of the membrane voltage of neuron $\mathcal{N}_1$ shown in Figure 23 evaluated for varying number of inhibitory synaptic channels N_{inh} (in $\mathcal{N}_1$). Feedback inhibition significantly decreases the membrane voltage variance during the refractory period. The membrane voltage fluctuations become depressed for a longer duration, which prevents the excessive accumulation of timing jitter until the next spike.

9.4 MEMBRANE VOLTAGE VARIANCE VS. FEEDBACK INHIBITION

We next analyze the transient dynamics of feedback inhibition. We use the same setup described above. However, in this case, at $t = 10$ msec, a transient suprathreshold current stimulus with an amplitude $I_{\text{ext}} = 0.25$ A/m² and a duration of 2 msec is injected into neuron $\mathcal{N}_1$, as opposed to a constant current stimulus. The updated setup is shown in Figure 23. With the transient stimulus applied to $\mathcal{N}_1$, a single action potential is generated in its membrane, which initiates another action potential in the membrane of $\mathcal{N}_2$ as shown in Figure 24. We compute the membrane voltage variance of $\mathcal{N}_1$ via the transient semi-analytical method summarized in Chapter 6. In our previous work [56], we have shown that the second order stochastic characterization of neuronal circuits can be accurately computed by using this technique.

The membrane voltage variance of $\mathcal{N}_1$ for varying feedback inhibition strengths can be seen in Figure 25. Let us first consider the case without

feedback inhibition. Without an external stimulus, the neuron membrane voltage fluctuates, with a constant variance around its mean resting potential of -65 mV, until $t = 10$ msec. Due to the action potential generated with the injection of the current pulse at $t = 10$ msec, the membrane voltage and hence the transition rates of the ion channels undergo a fast variation. Thus, the membrane voltage noise variance exhibits peaks at the rising and falling edges of the action potential, i.e., during the depolarization and repolarization phases, as observed in Figure 25. During the refractory period, the membrane voltage reaches its minimum value, which is around -75 mV. At this point, most of the ion channels are closed [36], [51]. As a result, the fluctuations in the membrane voltage become subdued. The dip value in the membrane voltage variance in Figure 25 coincides in time with the minimum value of the mean membrane voltage of $\mathcal{N}_1$ shown in Figure 24, in the beginning of the refractory period, as expected. When the refractory period ends, the variance of the membrane voltage returns to its steady-state value, corresponding to the resting membrane potential.

According to the results in Figure 25, feedback inhibition results in a significant reduction in the membrane voltage variance during the refractory period. The inhibition of $\mathcal{N}_1$ by $\mathcal{N}_2$ prolongs the refractory period of neuron $\mathcal{N}_1$, during which most of the ion channels remain closed. As a result, the membrane voltage fluctuations become depressed for a longer duration, which prevents the excessive accumulation of timing jitter until the next spike. This may be the key mechanism through which feedback inhibition enhances spike timing precision.

SYNAPTIC INTEGRATION

In the mammalian brain, the sensory information is transmitted to the neocortex, where it is processed for behavioral and cognitive functions [108], [109]. The processing in the cortical neurons involves the integration of their synaptic inputs and the generation of trains of action potentials in various temporal patterns. For a cortical neuron receiving multiple synaptic inputs, its spike timing precision is important in producing a coherent output in response to sensory stimuli.

A sensory neuron transmits information to multiple neurons with an axonal divergence of its output. On the other hand, a neuron can receive multiple synaptic inputs through dendritic convergence. These motifs are prevalent in the nervous system. For example, cortical neurons receive multiple afferent synaptic inputs originating from sensory sources [110]. For example, the information about head and body motion is transmitted to the vestibular system through multiple sensory pathways [111].

We consider dendritic convergence in a neuron, which receives multiple excitatory synaptic inputs from spiking neurons, as shown in Figure 26. We analyze the effect of the synaptic inputs on the timing precision of the output neuron. Each input neuron is excited by a constant suprathreshold current stimulus with an amplitude $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron in the setup is fixed at $A_m = 1000 \text{ } \mu\text{m}^2$ with the VG ion channel densities set to $60 \text{ Na}^+ \text{ channels}/\mu\text{m}^2$ and $18 \text{ K}^+ \text{ channels}/\mu\text{m}^2$. The output neuron includes 2×10^4 excitatory AMPA/kainate receptor channels per synapse. Each input neuron is spiking at the same frequency due to the same constant suprathreshold current excitation, while the output neuron generates an action potential upon the arrival of an excitatory synaptic input. The strength of a single excitatory synapse is sufficient to induce an action potential in the membrane of the output neuron. In the absence of variability and noise, the input neurons generate spikes at the same time, even though

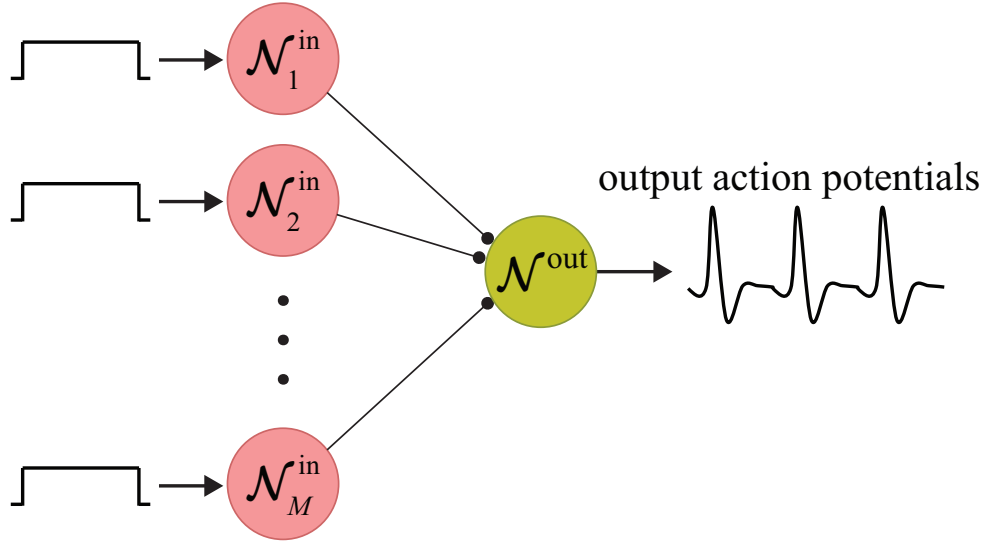


Figure 26: The synaptic integration of excitatory inputs. Each input neuron is under tonic spiking conditions with a constant, suprathreshold current stimulus and has an excitatory synaptic connection to the output neuron.

they are not coupled with each other. This setup, in a simplistic manner, represents the situation in which the sensory information relayed by each of the input neurons comes from the same source.

We use the transient semi-analytical method in order to compute the asymptotic timing jitter variance slope of the output neuron shown in Figure 26. The results in Figure 27 reveal that as the number of excitatory synaptic inputs M_{input} is increased, the timing precision of the output neuron is improved. It is indeed interesting to note that the timing jitter variance of the output neuron, $c_{ss,\text{out}}$, is equal to that of a single input neuron, $\bar{c}_{ss}$, scaled by $1/M_{\text{input}}$. That is, the timing jitter variance of the output neuron is $\bar{c}_{ss} t/M_{\text{input}}$.

We next consider multiple independent spiking input neurons with different membrane areas. Hence, each input neuron has a distinct timing jitter variance $\bar{c}_{ss,i}$. Since the excitation current per unit membrane area, $I_{\text{ext}} = 0.25 \text{ A/m}^2$, is set to the same value for all of the input neurons, their spiking frequencies are all equal. Based on running extensive analyses using the transient semi-analytical technique, we arrive at the following result: The timing jitter variance slope of the output neuron is given by

$$c_{ss,\text{out}} = \frac{1}{M_{\text{input}}^2} \sum_{i=1}^{M_{\text{input}}} \bar{c}_{ss,i}. \quad (41)$$

The above result is consistent with the one we have obtained for the case of input neurons with identical membrane areas. It can be explained as follows: The output neuron is in effect estimating the unperturbed timing of the input spikes denoted by t (which represents the same sensory information encoded by the spike timings of all of the input neurons), given M_{input} independent sample observations for their perturbed timings, i.e., $t + \alpha_i(t)$, corresponding to the spikes of the input neurons with a timing uncertainty. The timing deviation of the i th input neuron is $\alpha_i(t)$ and becomes an additive Gaussian random variable $\mathcal{N}(0, \bar{c}_{ss,i} t)$ asymptotically with time, as discussed in Chapter 6. Furthermore, $\alpha_i(t)$'s are independent since they arise from independent noise sources contained in different neurons. The estimate for the timing, denoted by t_{estimate} , can be computed by the sample average of the M_{input} observations, i.e.,

$$t_{\text{estimate}} = \frac{1}{M_{\text{input}}} \sum_{i=1}^{M_{\text{input}}} (t + \alpha_i(t)). \quad (42)$$

Then, the variance of the timing estimate (spike timing uncertainty at the output) is given by

$$\text{Var}[t_{\text{estimate}}] = \frac{1}{M_{\text{input}}^2} \sum_{i=1}^{M_{\text{input}}} \bar{c}_{ss,i} t \quad (43)$$

where the slope of the variance is the same as the timing jitter variance slope in (41) that was distilled from the simulation data. Thus, the sample average operation above is effectively implemented by the synaptic integration of the input spikes.

Our results suggest that the synaptic integration of multiple afferent synaptic inputs originating from the same sensory source may be an important mechanism that is utilized by the cortical neurons in regulating spike timing precision. The sensory data is first transmitted to multiple neurons via axonal divergence of the sensory neuron. The information is transmitted through different neural pathways. Finally, dendritic convergence in an intermediate or a cortical neuron improves spike timing precision and hence the reliability of the information received.

Feedforward inhibition is considered to be another mechanism utilized in the cortex in order to enhance the spike timing reliability of neurons [29],

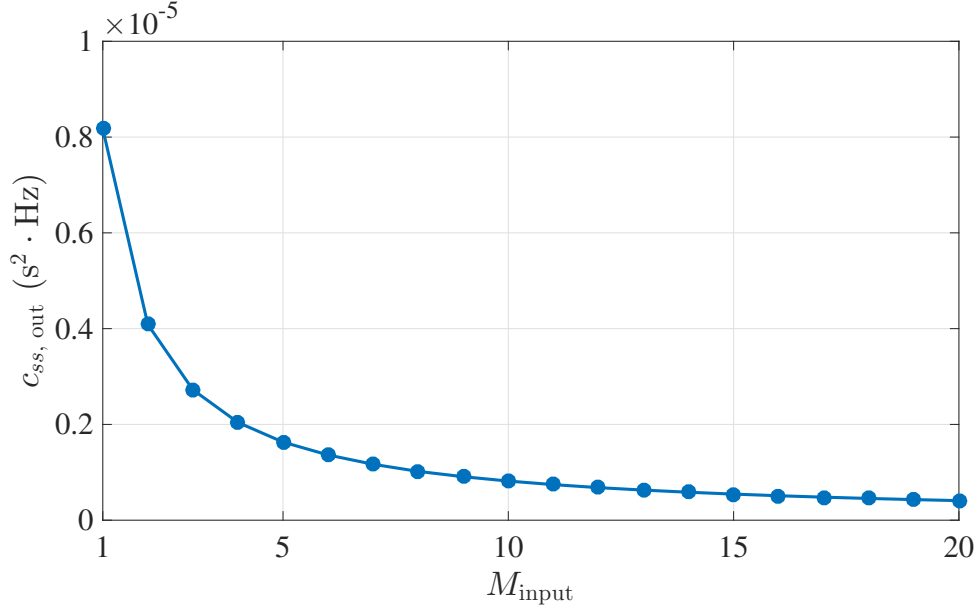


Figure 27: The timing jitter variance slope of the action potentials of the output neuron shown in Figure 26 with respect to the number of input neurons. Each input neuron is excited by a suprathreshold current stimulus with an amplitude $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \text{ } \mu\text{m}^2$. The output neuron includes 2×10^4 excitatory AMPA/kainate receptor channels per synapse. The timing jitter variance of the output neuron $c_{ss, \text{out}}$ is the same as the timing jitter variance of a single input neuron $\bar{c}_{ss}$ scaled by $1/M_{\text{input}}$.

[30]. For example, feedforward inhibition of $\mathcal{N}^{\text{out}}$ in Figure 26 would narrow its integration window, which reduces the effective number of the received input spikes. However, according to our results, integrating more inputs from multiple neurons enhances spike timing precision. At first thought, this seems to contradict with the enhancement of timing reliability via feedforward inhibition. However, there is in fact no contradiction. Feedforward inhibition acts so as to establish coincidence detection for the received spikes in $\mathcal{N}^{\text{out}}$, which can reduce the jitter due to the spontaneous spikes generated by the input neurons without any sensory cause [29], [30]. That is, with feedforward inhibition, a spontaneous action potential generated in an input neuron is prevented from inducing a subsequent action potential in $\mathcal{N}^{\text{out}}$, unless other input neurons fire at the same time. Feedforward inhibition ensures that $\mathcal{N}^{\text{out}}$ fires if it receives multiple input spikes with coincident timing. On the other hand, in the scenario we have considered above, all of the input neurons

receive the same sensory stimulus and generate spikes that are coincident within a deviation due to noise. Furthermore, an action potential generated in an input neuron is able to induce another action potential in $\mathcal{N}^{\text{out}}$ on its own. In summary, these two motifs, i.e., **(i)** feedforward inhibition that effectively subdues spontaneous spikes with no sensory cause, and **(ii)** synaptic integration of multiple inputs that encode the same sensory stimulus, may represent different mechanisms utilized by the neurons in the cortex in order to enhance spike timing reliability.



SYNAPTIC COUPLING

Rhythmic collective oscillations are commonly seen in the operation of neural circuits. The neurons in these circuits are synchronized with each other through their synaptic connections so that the circuit overall spikes in a robust manner. The nature of these rhythmic oscillations are determined by the particular neuronal circuit organization. In [33], the authors argue that the synaptic coupling delay between the neurons determines the transition between synchronous and asynchronous states of a neuronal circuit. The spike timing precision of the neurons directly relates to the synaptic delay between them, and may be an important factor in the synchronization of the neuronal circuits that generate robust rhythms in the brain.

The synchronization of coupled oscillators is ubiquitous, e.g., synchronized pendulum clocks that are placed on the same wall and the synchronous flashing of fireflies [112]. The synchronization in these systems is facilitated mainly through a mechanism called *injection locking* [113]. The timing jitter variance of autonomously oscillating electrical circuits can be reduced by injection locking [114]. A similar mechanism is possibly exploited by the circuits in the brain in order to reduce the timing noise and enhance the timing reliability of the generated spikes. Next, we investigate the effect of the nature and the strength of the synaptic coupling among neurons on the timing precision of a neural circuit. Here, we define the *synaptic coupling strength* to be synonymous to the number of LG synaptic receptor channels per synapse.

Oscillatory neuronal circuits in the brain can have complex organizations. For simplicity, we consider fully connected neuronal circuits. That is, each neuron is connected to all of the other neurons in the circuit via synapses, as shown in Figure 28 for a five-neuron network. Similar network topologies with various connection scenarios have been considered in the literature [33], [104] in order to investigate the mechanisms of synchronous oscillations in the brain.

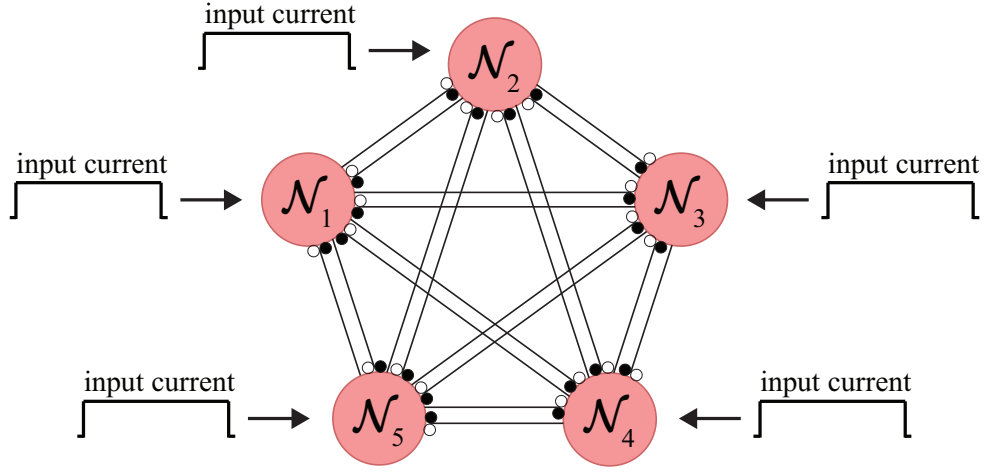


Figure 28: Fully connected neuronal oscillator circuit with five neurons. Each neuron is under tonic spiking conditions with a constant, suprathreshold current stimulus.

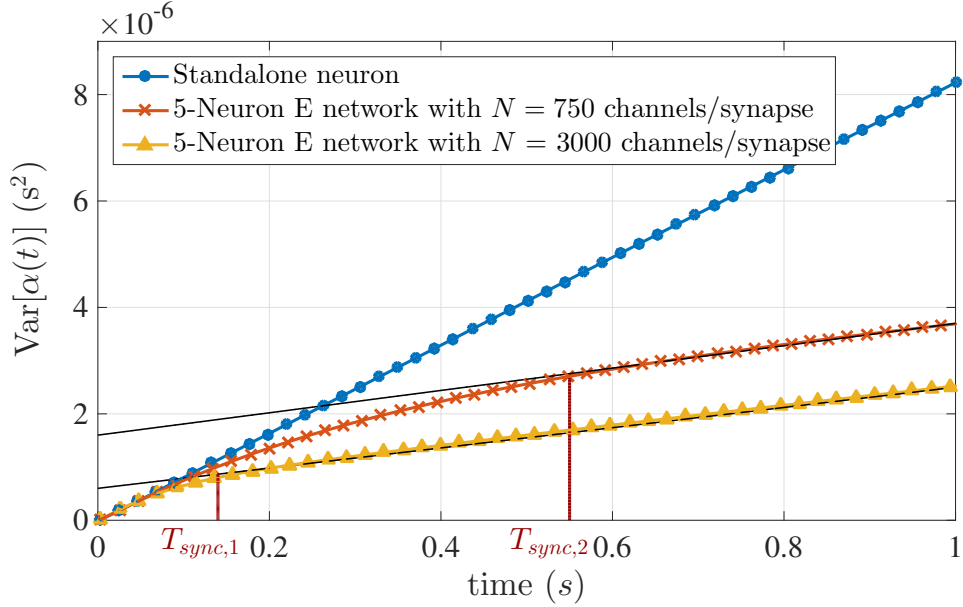


Figure 29: The timing jitter variance of the output action potentials of a neuron in the five-neuron E network in Figure 28, for $N_{\text{ex}} = 750$ and 3000 excitatory AMPA/kainate receptor channels per synapse. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$ and the membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$. The timing jitter variance of a standalone neuron excited by the same suprathreshold current stimulus $I_{\text{ext}} = 0.25 \text{ A/m}^2$, with a membrane area $A_m = 1000 \mu\text{m}^2$, is also shown. The synchronization times $T_{\text{sync},1}$ (for $N_{\text{ex}} = 3000$) and $T_{\text{sync},2}$ (for $N_{\text{ex}} = 750$) for the E networks are indicated on the graph.

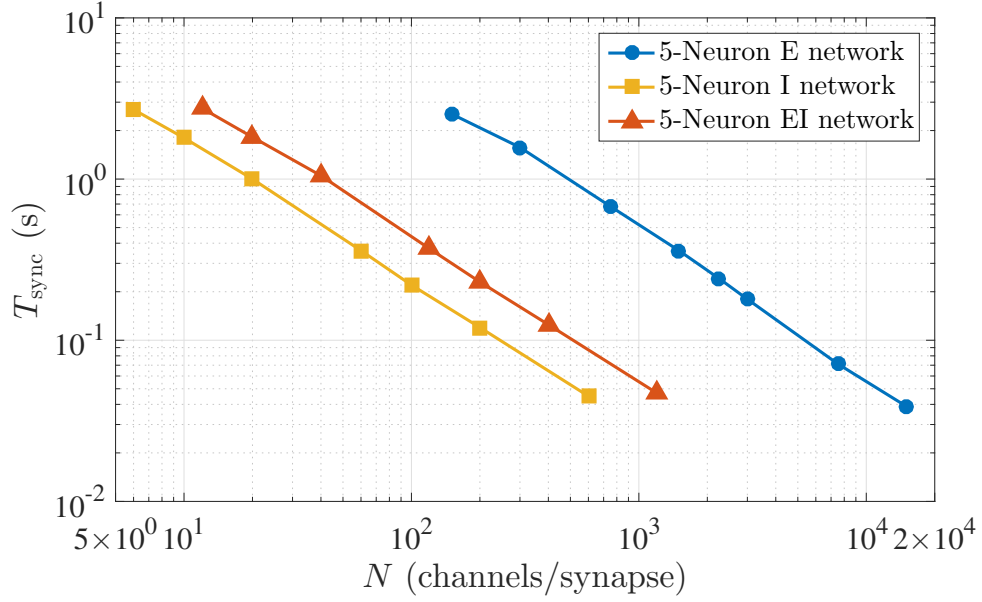


Figure 30: The synchronization times of the five-neuron E, I, and EI networks as a function of the number of receptor channels per synapse. The amplitude of the total external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$. For the EI network, N indicates the total number of excitatory ($N/2$) and inhibitory ($N/2$) channels per synapse. For the E and I networks, N is the number of excitatory and inhibitory channels per synapse, respectively.

For the five-neuron network in Figure 28, we consider three different cases: **(i)** an excitatory (E) network with only excitatory synapses, **(ii)** an inhibitory (I) network with only inhibitory synapses, and **(iii)** a balanced excitatory and inhibitory (EI) network with both excitatory and inhibitory synapses. For the EI network, the numbers of the excitatory and inhibitory synaptic receptor channels per synapse is set to the same value. We denote the total number of LG receptor channels per synapse with N . Each neuron in the network shown in Figure 28 is excited by a constant suprathreshold current stimulus with an amplitude $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is fixed at $A_m = 1000 \mu\text{m}^2$, with the VG ion channel densities equal to 60 Na^+ channels/ μm^2 and 18 K^+ channels/ μm^2 . For the three cases stated above, the numbers of the excitatory AMPA/kainate receptor channels and the inhibitory GABA_A receptor channels per synapse are varied in order to observe their effect on the timing reliability of the neuronal circuit.

11.1 SYNCHRONIZATION TIME VS. SYNAPTIC COUPLING STRENGTH

The instantaneous timing jitter variance of the output action potentials of a neuron in the five-neuron E network is shown in Figure 29, for both $N_{\text{ex}} = 750$ and 3000 excitatory channels per synapse. In addition, the timing jitter variance of a single, standalone neuron excited by the same suprathreshold current stimulus density is also shown in Figure 29. The firing rates for these three cases (i.e., (i) standalone neuron, (ii) and (iii) 5-neuron network with $N_{\text{ex}} = 750$ and 3000) are roughly the same and equal to $f_c = 1/T_c = 92.0$ Hz. The data for the plots in Figure 29 was computed via the transient semi-analytical method for the jitter variance of a number of consecutive spikes occurring at $t = kT_c$, i.e., $\text{Var}[\alpha(kT_c)]$.

The results in Figure 29 show that the timing jitter variances, for all of the cases considered, increase *linearly asymptotically with time*, as predicted by the theory presented in [59]. Although the timing jitter variance of the standalone neuron reaches its asymptotic form immediately, the five-neuron network exhibits transient behavior before settling to its asymptotic linear form. In an oscillating neuronal circuit, there are multiple oscillating units (i.e., individual neurons) coupled with each other. When these coupled oscillators reach a steady-state, they may become synchronized, i.e., they lock with each other and the whole circuit behaves as one oscillating unit. Here, synchronization is used to refer to this condition of lock. However, the fact that the oscillators are locked with each other does not mean that they become noiseless. The stochasticity that arises from the ion channels and the synapses is still there, even with synchronization. The overall neuronal circuit oscillator is still noisy and has an increasing timing jitter variance with time even after synchronization. For any oscillator (whether it is composed of a single oscillating unit, or multiple units that are locked with each other) without an embedded perfect time reference, the timing jitter variance increases asymptotically linearly with time, as shown in [59]. For oscillators composed of multiple, locked oscillating units, the asymptotic timing jitter variance may be different (usually less) than that of the individual units if they were operating alone. The jitter variance of the composite oscillator is reduced through a sort of cooperation of the

individual neurons in the network. On the other hand, the synchronization mechanism (injection locking via coupling) that eventually locks the individual units with each other has a time constant that is usually (much) larger than the oscillation period. The effect of this time constant can be observed if the timing jitter of the spikes generated by the neurons are computed with respect to the timing of an initial trigger (reference) spike [115]. In the short time scale (for the spikes that immediately follow the reference spike), the timing jitter variance slope (i.e., jitter accumulation rate) observed is equal to the slope one would obtain if the neuron under consideration was operating alone as an independent unit. In the longer time scale, when the observed spike and the reference spike are separated from each other by more than the synchronization time constant, the jitter variance accumulation rate becomes smaller. This behavior is very similar to the operation of phase locked loops (PLLs) used in electronic circuits, where the phase of a noisy oscillator is locked to the phase of a cleaner reference signal with more precise timing [115], [116]. The synchronization time in the case of PLLs is determined by the loop bandwidth. For neuronal circuits, we define *synchronization time* T_{sync} to be the time duration (measured from the reference spike) that is needed for the timing jitter slope to settle to its reduced, locked value from the larger value that corresponds to the standalone state of the neuron. The jitter characteristics discussed above can be observed in the results presented in Figure 29.

It is important to note that, when the neurons in the network are locked, that is, when they operate as one oscillation unit, the timing jitter variances of all of the neurons in the network are the same. In fact, the timing jitter variance that is computed for a neuronal circuit is a network property shared by all of the neurons that are locked to each other. This is also apparent in the representation of the timing jitter as a common time deviation $\alpha(t)$ in $\mathbf{x}_s(t + \alpha(t))$, that is shared by all of the membrane voltages in the state vector $\mathbf{x}_s$. The technique we use for computing the periodic $\mathbf{x}_s(t)$ (based on Fourier spectral collocation, mentioned in Chapter 6), with noise removed, reveals whether the neurons are indeed locked to each other operating as one oscillation unit, or oscillating independently.

For various number of synaptic channels per synapse, the synchronization times for the five-neuron E, I, and EI networks were computed, shown in

Figure 30. As the number of LG receptor channels per synapse is increased, the synchronization time decreases for all network types. The effect of the synaptic inputs of a neuron from other neurons in the circuit is enhanced when the coupling strength is increased due to larger number of synaptic receptor channels. As a result, the time constant of the synchronization mechanism becomes smaller. According to our results, the EI network synchronizes roughly one order of magnitude faster than the E network for the same total number of excitatory and inhibitory receptor channels per synapse, as observed in Figure 30. In addition, the synchronization time of the I network is almost half of that of the EI network. As we increase the proportion of the inhibitory channels, for a given total number of (excitatory and inhibitory) receptor channels per synapse, the synchronization time of the EI network decreases. In the light of the results obtained for the feedback inhibition mechanism in Chapter 9, the inhibitory synapses possibly help speed up the synchronization of the network by preventing the excessive accumulation of timing jitter until the next spike. In the next section, we analyze the effect of the coupling strength on the asymptotic timing jitter variance of the fully connected five-neuron networks.

11.2 SPIKE TIMING PRECISION AND SPIKING PERIOD VS. SYNAPTIC COUPLING STRENGTH

We now consider the asymptotic (beyond the synchronization time) timing jitter variance slopes and the spiking periods for the five-neuron E, I, and EI neuronal circuits. The steady-state jitter variance slopes are computed via the steady-state semi-analytical method reviewed in Chapter 6. The obtained results are presented in Figure 31 and Figure 32, which also includes results on the timing jitter variances and the spiking periods of single, standalone neurons with membrane areas A_m and $5A_m$ stimulated by the same suprathreshold stimulus current density.

The results in Figure 31 and Figure 32 show that the behaviors of the I and EI networks are substantially different from that of the E network, due to the presence of the inhibitory synapses. According to these results, the

response of the E network continuously varies as the coupling strength is increased. However, the I and EI networks exhibit a three-phase discontinuous response as a function of the coupling strength: **(i)** stable and synchronized with cooperation, **(ii)** unstable, **(iii)** stable and desynchronized with the domination of one neuron in the network. These three phases for the EI network are illustrated in Figure 33, Figure 34, and Figure 35, where sample paths for the membrane voltages of the neurons in the network are presented. We note that, in the unstable case, the timing jitter variance and the spiking period become meaningless. That is why there are gaps in the graphs for the I and EI networks in Figure 31 and Figure 32. Next, we discuss in detail the behavior of the fully connected E, I and EI networks as the coupling strength is changed.

According to the results in Figure 31, if the number of the synaptic receptor channels is lower than a certain value, i.e., with weak coupling, the asymptotic timing jitter variance slopes, c_{ss} 's, of M_{sync} -neuron E, I, and EI networks are the same as that of an autonomously oscillating standalone neuron with a membrane area of $M_{\text{sync}}A_m$, excited by the same constant suprathreshold current stimulus. In [56], we have shown that the asymptotic timing jitter variance slope for a neuron with a constant suprathreshold current is inversely proportional to its membrane area. Indeed, if a neuron with a membrane area of A_m has a timing jitter variance slope $\bar{c}_{ss}$, then for a neuron with a membrane area of $M_{\text{sync}}A_m$, the slope becomes $c_{ss} = \bar{c}_{ss}/M_{\text{sync}}$. It can be concluded that weak synaptic coupling between neurons in the E, I, and EI networks enables them to behave like a single neuron with a larger membrane area, i.e., the timing precision of these networks is improved by cooperation. In fact, we have found out that this improvement is realized even with very weak coupling, all the way down to 1 channel/synapse. This manifests itself as a reduction in the timing jitter slope beyond the synchronization time T_{sync} , when computed with the transient semi-analytical technique, albeit with larger synchronization times for weaker coupling. We note that when the synaptic connections between the neurons are completely removed, each neuron indeed operates in a standalone manner. Then, the timing jitter variances of the neurons become equal to that of a standalone neuron with membrane area A_m , without any reduction.

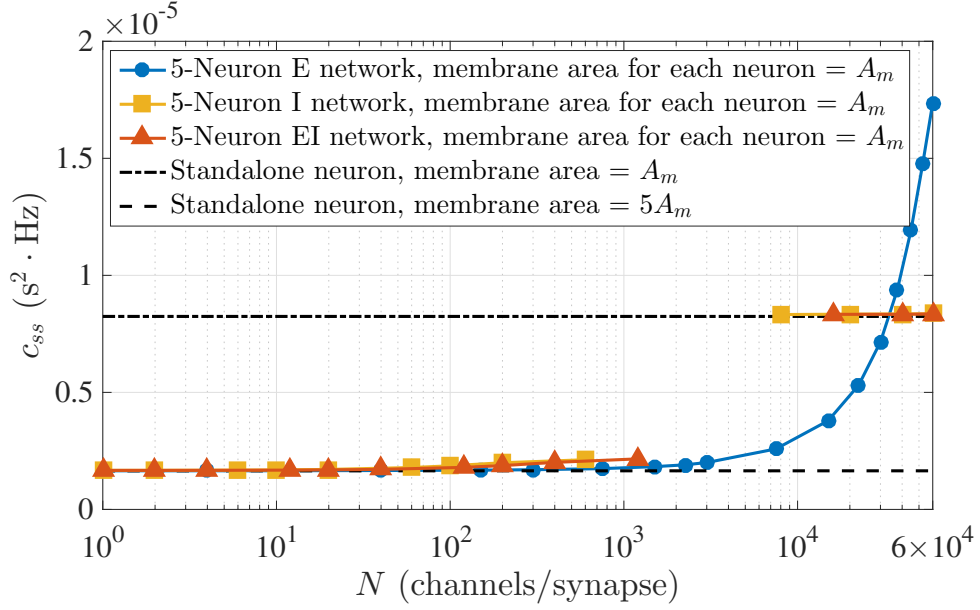


Figure 31: The timing jitter variance slope of a neuron in the five-neuron E, I, and EI networks in Figure 28 as a function of the number of receptor channels per synapse. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$. For the EI network, N is the total number of excitatory ($N/2$) and inhibitory ($N/2$) channels per synapse. For E and I networks, N is the number of excitatory and inhibitory channels per synapse, respectively. The timing jitter variance slopes of single, standalone neurons with membrane areas $A_m = 1000 \mu\text{m}^2$ and $5A_m = 5000 \mu\text{m}^2$, excited by the same suprathreshold current stimulus $I_{\text{ext}} = 0.25 \text{ A/m}^2$, are also shown. If the number of synaptic receptor channels is lower than a certain value, the timing jitter variances of the five-neuron E, I, and EI networks are the same as that of an autonomously oscillating standalone neuron with a membrane area of $5A_m$ excited by the same constant suprathreshold current stimulus.

The results in Figure 32 show that, if the number of synaptic receptor channels is lower than a certain value, the spiking period of the E, I, and EI networks are the same as that of an autonomously oscillating standalone neuron excited by the same constant suprathreshold stimulus current density. This result is consistent with the timing jitter variance of the E, I, and EI networks for weak coupling, i.e., they behave like a single neuron oscillator with a membrane area of $5A_m$.

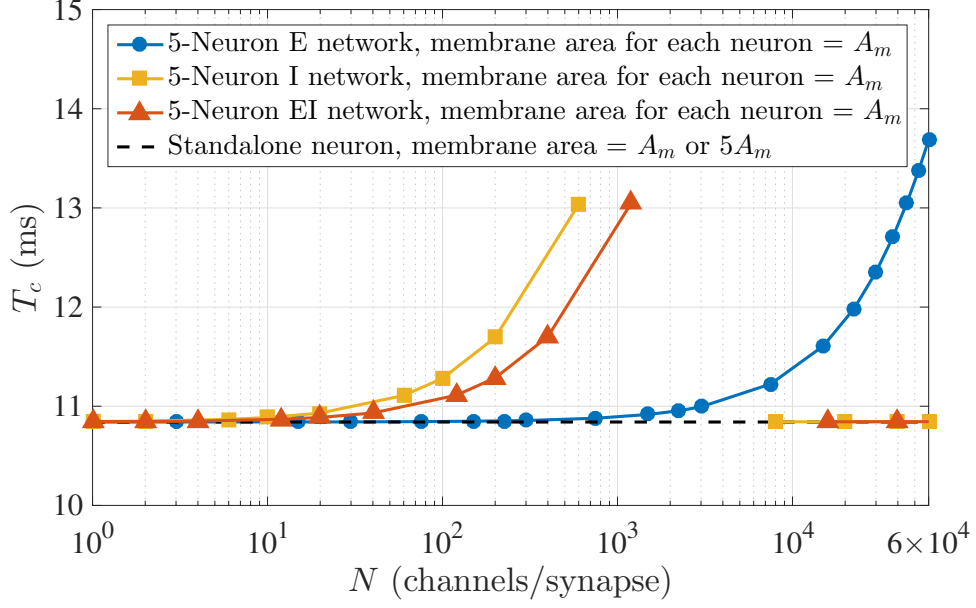


Figure 32: The spiking period of a neuron in the five-neuron E, I, and EI networks in Figure 28 as a function of the number of receptor channels per synapse. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$. For the EI network, N is the total number of excitatory ($N/2$) and inhibitory ($N/2$) channels per synapse. For E and I networks, N is the number of excitatory and inhibitory channels per synapse, respectively. The spiking period for a single, standalone neuron (with membrane area $A_m = 1000 \mu\text{m}^2$ or $5A_m = 5000 \mu\text{m}^2$, the period is the same) excited by the same suprathreshold current stimulus $I_{\text{ext}} = 0.25 \text{ A/m}^2$ is also presented. If the number of synaptic receptor channels is lower than a certain value, the spiking periods of the five-neuron E, I, and EI networks are the same as that of an autonomously oscillating standalone neuron excited by the same constant suprathreshold current stimulus. We note that the spiking period of a standalone neuron is independent of its membrane area if the current stimulus density is kept constant. The reason for the gaps in the data (due to instability of the circuit) is explained in the main text.

As we further increase the number of the synaptic receptor channels per synapse, the ion currents passing through these LG channels start to dominate the currents passing through the VG K^+ and Na^+ channels in the neuron. Thus, strong synaptic coupling among the neurons emerges as a disruption to the internal spiking dynamics. This results in an increase in both the timing

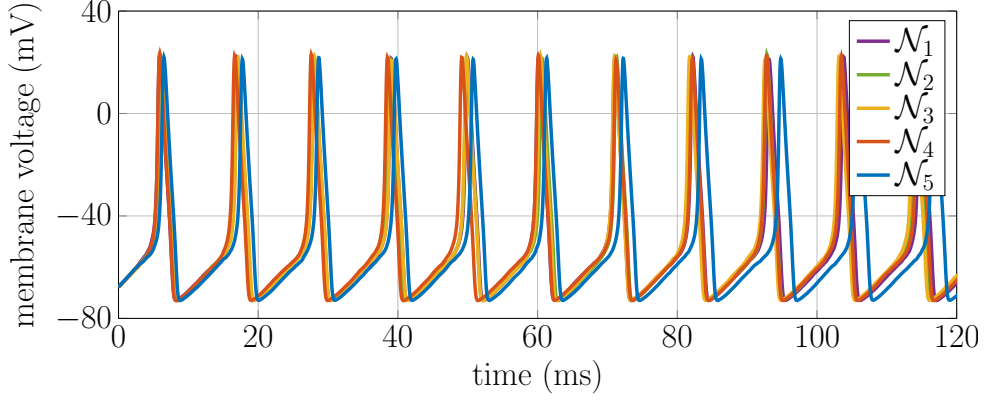


Figure 33: A sample path for the membrane voltages of the neurons in the EI network in Figure 28. The EI network is stable and synchronized with cooperation for $N_{\text{ex}} = 2$ and $N_{\text{in}} = 2$ channels per synapse. All of the neurons in the network generate spikes periodically. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$.

jitter variance slope and the spiking period as observed in Figure 31 and Figure 32, respectively. In other words, the timing reliabilities of the fully connected E, I, and EI networks start to deteriorate for coupling strengths that are above a certain value. The increase in the timing jitter slope c_{ss} of the networks may be due to the prolonged oscillation periods T_c . We have observed a similar relationship between c_{ss} and T_c for the single, standalone neuron oscillator in [56]. We also note that, as the number of receptor channels per synapse is increased, the spiking periods of the I and EI networks increase more than that of the E network. In addition, the increase in the spiking period of the I network is higher than that of the EI network. That is, as we increase the proportion of the inhibitory channels for a given total number of (excitatory and inhibitory) channels per synapse, the spiking period of the network increases. This behavior may be due to the fact that the inhibitory synapses try to depress the spiking behavior of the network, opposing the suprathreshold external current stimulus. This may then result in an increase in the spiking period, as observed in Figure 32.

If the number of the receptor channels per synapse in the I and EI networks exceed 600 and 1200 channels/synapse, respectively, these networks become unstable. The inhibitory synapses in both the I and EI networks try to shut down the spiking of the neurons. However, at the same time, each neuron is

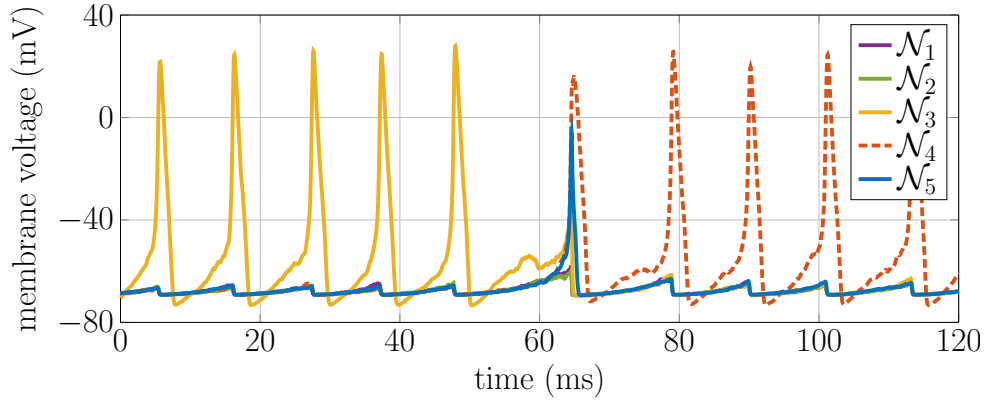


Figure 34: A sample path for the membrane voltages of the neurons in the EI network in Figure 28. The EI network exhibits unstable behavior. Initially, the network behavior is dominated by neuron $\mathcal{N}_3$. However, after a perturbation due to noise in the neuronal circuit, neuron $\mathcal{N}_4$ starts to dominate the network behavior and the spiking neuron $\mathcal{N}_3$ is inhibited. We note that neuron $\mathcal{N}_5$ also tries to spike but cannot maintain its spiking state. The numbers of excitatory and inhibitory receptor channels per synapse are $N_{\text{ex}} = 2000$ and $N_{\text{in}} = 2000$, respectively. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$.

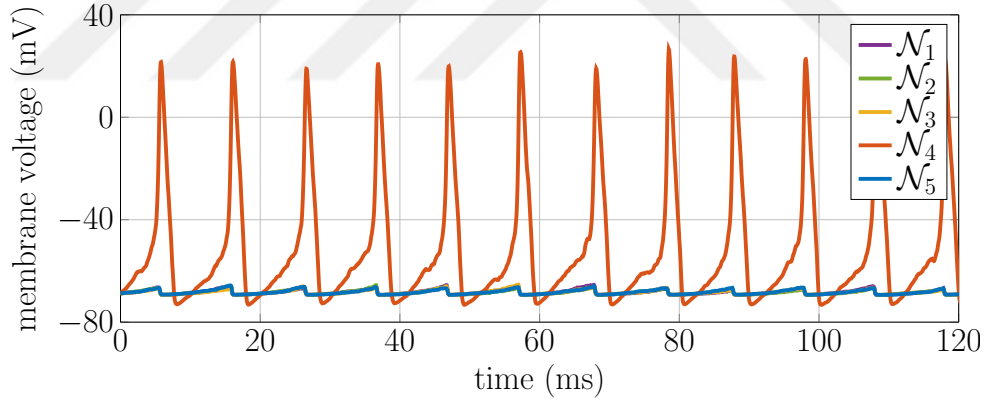


Figure 35: A sample path for the membrane voltages of the neurons in the EI network in Figure 28. The EI network is stable and desynchronized with the domination of neuron $\mathcal{N}_4$ in the network for $N_{\text{ex}} = 20000$ and $N_{\text{in}} = 20000$ channels per synapse. The amplitude of the external suprathreshold current input to each neuron is $I_{\text{ext}} = 0.25 \text{ A/m}^2$. The membrane area of each neuron is $A_m = 1000 \mu\text{m}^2$.

being forced to oscillate by the suprathreshold current stimulus, and in the EI network also by the excitatory synapses. Due to the imbalance between these

two driving forces, the behavior of the I and EI networks becomes unstable. The unstable behavior of the EI network is illustrated in Figure 34. Initially, the network behavior is dominated by a spiking neuron. However, after a perturbation due to noise in the neuronal circuit, another neuron starts to dominate the network behavior and then inhibits the initially spiking neuron. That is, the oscillation of the network is not stable, and noise causes the behavior of the network to change randomly. In contrast, the stability of the E network is maintained as the number of excitatory receptor channels per synapse is increased. In the E network, all of the driving forces, i.e., the synapses and the current stimulus, are excitatory, which do not result in instability even for stronger synaptic coupling. As the number of synaptic receptor channels in both the I and EI networks is further increased beyond 8000 and 16000 channels/synapse, respectively, one of the neurons in these networks shuts down the other neurons completely, which re-stabilizes the overall network activity as illustrated in Figure 35. That is, the inhibitory synapses of that neuron become dominant when compared with the excitatory driving forces and remains dominant even in the presence of disturbances due to noise. However, in this case, the overall neuronal circuit behaves like a single, standalone neuron with a membrane area A_m . This is the expected behavior, because the activity of the network at this point is dominated by a single neuron. That is, the spiking period and the timing jitter variance slope of the I and EI networks become same as those of a single neuron oscillator with a membrane area of A_m excited by the same stimulus current density.

11.3 SPIKE TIMING PRECISION OF WEAKLY COUPLED HETEROGENEOUS NEURONAL NETWORKS

We can conclude based on the above results is that weak synaptic coupling among the neurons in E, I, and EI networks is a key mechanism that improves the timing precision of neuronal circuits through cooperation. A weakly connected M_{sync} -neuron circuit behaves like a single neuron with a membrane area equal to the total membrane area of the neurons in the network, i.e.,

$M_{\text{sync}}A_m$, assuming that the neurons in the network have equal membrane areas.

Now, we consider a heterogeneous, fully connected network, where each neuron has a different membrane area $A_{m,i}$, but excited by the same stimulus current density $I_{\text{ext}} = 0.25 \text{ A/m}^2$. Here, we would like to clarify that heterogeneity to the network is introduced only through different membrane areas, which results in different noise levels for each neuron. We have performed extensive characterizations for the timing jitter performances of various heterogeneous, fully connected E, I, and EI neuronal circuits with varying number of neurons and varying membrane areas. By carefully analyzing these extensive set of results, we arrive at the following conclusion: The asymptotic timing jitter variance slope c_{ss} of a weakly coupled, heterogeneous network with M_{sync} neurons is the same as that of a standalone, single neuron with a membrane area of $M_{\text{sync}} A_{HM}$, excited by the same (per neuron) current density. Here, A_{HM} is the harmonic mean of the membrane areas of M_{sync} neurons, given by

$$A_{HM} = M_{\text{sync}} \left[\sum_{i=1}^{M_{\text{sync}}} \frac{1}{A_{m,i}} \right]^{-1}. \quad (44)$$

This conclusion applies to all of E, I, and EI heterogeneous networks. This result is consistent with the one for the case when the neurons in the network have equal membrane areas, i.e., $A_{HM} = A_m$ with $A_{m,i} = A_m$. Since the harmonic mean is limited by the value of the minimum element as expressed by $A_{HM} \leq M_{\text{sync}} \min\{A_{m,i}\}$, the performances of the E, I, and EI networks in terms of their timing jitter variance slopes are limited by the performance of the smallest neuron in the network. The smallest neuron has the worst timing jitter performance. Therefore, in order to improve the performance of the network, either the membrane area for the neuron with the smallest area should be increased or it should be removed from the network. We can conclude that, given a total membrane area budget, the optimal weakly coupled network (E, I or EI), with respect to the timing jitter performance, is the one where the neurons are similarly sized.

In order to investigate the main mechanism behind the above result, let standalone neurons with membrane areas of A_m and $A_{m,i}$ have timing jitter

variance slopes of $\bar{c}_{ss}$ and $\bar{c}_{ss,i}$, respectively. As mentioned previously, the asymptotic timing jitter variance slope is inversely proportional to the membrane area, i.e., $\bar{c}_{ss}A_m = \bar{c}_{ss,i}A_{m,i} = \text{constant}$. Then, for a neuron with a membrane area of $M_{\text{sync}}A_{HM}$, the jitter variance slope is given by

$$\begin{aligned} c_{ss} &= \frac{\bar{c}_{ss}A_m}{M_{\text{sync}}A_{HM}} = \frac{1}{M_{\text{sync}}^2} \sum_{i=1}^{M_{\text{sync}}} \frac{\bar{c}_{ss}A_m}{A_{m,i}} \\ &= \frac{1}{M_{\text{sync}}^2} \sum_{i=1}^{M_{\text{sync}}} \bar{c}_{ss,i}. \end{aligned} \quad (45)$$

This result is very similar to the timing jitter variance slope of a neuron integrating M_{sync} synaptic inputs from multiple independent standalone neurons with timing jitter variance slopes of $\bar{c}_{ss,i}$ and membrane areas of $A_{m,i}$, given by (43) in Chapter 10. However, in an M_{sync} -neuron fully connected network, each neuron receives synaptic inputs from the other $(M_{\text{sync}} - 1)$ neurons. We note that, in such a network, each neuron itself also behaves like an oscillating standalone neuron due to the suprathreshold current stimulus. Then, each neuron in the fully connected network integrates the timing information of M_{sync} neurons (including itself), with area $A_{m,i}$ and jitter slope $\bar{c}_{ss,i}$ for the i th neuron. Thus, the above results are indeed consistent with the results presented in Chapter 10. In conclusion, it can be said that the fully connected E, I, and EI networks also loosely implement the sample average mechanism (as in synaptic integration considered in Chapter 10) on the spike timings of the neurons in the network, provided that they are weakly coupled. If the number of the LG receptor channels are increased beyond a certain threshold value, the behaviors of the heterogeneous networks are similar to those of the homogeneous networks discussed above.

SUMMARY AND CONCLUSION

The main contributions of this thesis are three-pronged:

- A general modeling and simulation framework for neuronal circuits that captures the nonstationary stochastic behavior of the ion channels and the synapses in a unified manner is established. This framework facilitates the automatic mapping of the MC models of the ion channels and the synapses to their corresponding approximate SDE models.
- Repurposing of analysis-based, non Monte Carlo, numerical noise characterization techniques, that were previously developed for noise analysis of analog circuits, in order to compute stochastic characterizations of biological neuronal circuits. These non Monte Carlo schemes are three orders of magnitude faster than brute-force Monte Carlo type simulations that are prevalently used in computational neuroscience. We have shown that the results obtained with the non Monte Carlo methods are in near perfect agreement with the results obtained via computationally expensive Monte Carlo simulations.
- Utilization of the semi-analytical, non Monte Carlo techniques for the stochastic characterization of the timing jitter and noisy membrane voltages of spiking neuronal circuits. These semi-analytical methods helped us gain insight into common neuronal circuit motifs. Namely, we investigated three distinct neuronal circuit motifs: **(i)** feedback inhibition, **(ii)** synaptic integration, and **(iii)** excitatory and inhibitory synaptic coupling. The results helped us reveal the underlying mechanisms behind these neuronal circuit motifs.

In Chapter 2, we provided a brief background on neurons and neuronal circuits and summarized the MC models used for the ion channels and stochastic chemical kinetics models used for neurotransmitter release process in synapses.

In Chapter 3, we reviewed the stochastic chemical kinetics formalism and described its relationship to MCs. We described a key idea on representing generic/abstract MCs as a set of chemical reactions. Then, we described the

so-called *lumpability* concept for MCs and discuss how it can be employed to obtain reduced, simpler MC models. Next, we described how these reduced MC models can be represented as a set of chemical reactions.

In Chapter 4, we describe a unifying formalism for automatically deriving the corresponding SDE models, based on techniques from stochastic chemical kinetics through *lumped MC* models of ion channels and synapses and their representation as a set of chemical reactions. With this formalism, we can exploit the sparsity and special structure in the MC models and arrive at compact SDE models. We review the essential steps for our general modeling framework leading to the facilitation of non Monte Carlo techniques

In Chapter 5, we describe the numerical methods utilized for stochastic, Monte Carlo numerical simulations of neuronal circuits based on MC and SDE models. Namely, we describe numerical simulation techniques that (i) solve the problem of synchronization of the current balance equation of neurons with the MC jump events, and (ii) fix the imaginary square root term contingency in solving the SDE models. These are based on recent techniques that were developed for simulating low-frequency noise in electronic circuits.

In Chapter 6, we present how SDE models can be incorporated into analysis-based, non Monte Carlo noise evaluation methods to *directly* compute non-stationary stochastic characterizations of neuronal circuits by eliminating the need to generate a large ensemble of long, simulated sample paths for the membrane voltages. With the non Monte Carlo techniques, averages that are needed for stochastic characterizations are computed in a semi-analytical manner. Although these techniques still require carefully conceived numerical computations, they avoid costly repeated simulations that involve the use of random number generators. The non Monte Carlo schemes are orders of magnitude faster than traditional Monte Carlo simulation techniques and produce a consistent, repeatable and detailed characterization of the neuronal circuit.

In Chapter 7, we first showed that the approximate SDE models can accurately capture the nonstationary stochastic behavior of neurons and neuronal circuits by comparing NLSDE-SD model with HYB-CR model. Then, we present simulation results on neuronal circuits in various configurations in order to verify that the results computed with the proposed non Monte Carlo schemes

match the ones obtained via laborious Monte Carlo type stochastic simulations. We have shown that the results obtained with the non Monte Carlo methods are in near perfect agreement with the results obtained via computationally expensive Monte Carlo simulations.

In Chapter 8, we use the non Monte Carlo Methods in order to characterize autonomously oscillating neuronal circuits with respect to energy consumption and timing reliability metrics. Our results showed that in autonomous neuronal oscillator circuits, forming synapses between smaller neurons is a more energy efficient and effective mechanism than enlarging the membrane of a neuron in order to reduce noise and improve spike timing precision.

In Chapter 9, we consider a spiking neuron with feedback inhibition. We use the timing jitter variance of the neuron in order to quantify its spike timing precision. We quantitatively investigate the effect of feedback inhibition on the energy efficiency and the spike timing precision of a neuron. We showed that feedback inhibition improves the timing precision and energy efficiency of a spiking neuron. In addition, we have elucidated that this improvement is due to the fact that feedback inhibition prolongs the refractory period of a neuron. Since most of the ion channels remain closed in the refractory period, the membrane voltage fluctuations become subdued for a longer duration. Thus, feedback inhibition prevents the excessive accumulation of timing jitter until the next spike and enhances spike timing precision.

In Chapter 10, we consider a neuron with multiple excitatory synaptic inputs coming from spiking neurons. We analyze the effect of the integration of multiple afferent synaptic inputs, originating from the same sensory source, on the timing precision of the output neuron. We showed that a neuron can improve on the timing jitter of its inputs by synaptic integration. Furthermore, our results suggest that a neuron in effect performs a sample average of the timings of the input spikes, which improves the timing precision of its output spikes.

In Chapter 11, we consider fully connected neuronal circuits where neurons are coupled with each other via synapses. We investigate the effect of the excitatory and inhibitory synapses on the synchronization time and the timing precision of the neuronal circuit. Our results revealed that weak excitatory or inhibitory coupling among neurons in a fully connected network enables

them to behave like a single neuron with a larger membrane area in such a way so that the timing precision of the network is improved by cooperation. This improvement is maximized, with a total membrane area budget, if the neurons in the network are similarly sized.

Future work includes developing and implementing the non Monte Carlo techniques for neuronal circuits that exhibit multi-frequency oscillations as outlined in the thesis. We also aim to extend non Monte Carlo methods for distributed neuronal circuit models. The next important step in this line of work is to use the proposed analysis and modeling schemes in trying to decipher and understand the role of noise in neuronal circuits. Future work also includes the utilization of the synergistic, interdisciplinary approach advocated in this thesis for the analysis of hybrid neuroelectronic circuits where neuronal and electronic circuits are interfaced with each other.

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