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AN INTRODUCTION TO THE MATHEMATICS OF NEURONS
SECOND EDITION

Modeling in the frequency domain

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This book is dedicated to Leslie, Charles, Matthew, Sarah, Robin and Sam

Contents

Preface

. . . to such discontented pendulums as we are.
Ralph Waldo Emerson

Neurons, or nerve cells, control most biological rhythms through various timing mechanisms. Among these rhythms are body temperature and rest/activity behavior, but there is also significant modulation of timers due to external physical cues such as light/dark cycles and variations in ambient temperatures. Biological timers act on time scales ranging from milliseconds to months, and experiments on them range in size from microelectrode recordings to observations in underground laboratories that are used to study daily human rhythms over periods of months.

This book introduces some modeling techniques that are useful for studying rhythms and timing from the level of neurons to higher levels in the brain, and it focuses on the behavior of neurons and networks of them in the *frequency domain*. Although much of this material is based on the earlier work of many people who studied biological rhythms, including the first edition of this book published in 1986, much of it is new, reflecting knowledge about the brain that has been created in the past ten years [2,3]. For example, the study of networks has matured during this period, and we include new material on large networks. In addition, increases in knowledge about the brain and its subsystems make it possible to include here some special studies of attention, vision, and audition.

This second edition keeps to the same format as in the first, and it continues to focus on modeling in the frequency domain through the use of a particular model, the VCON (Voltage Controlled Oscillator Neuron) model. The VCON model was originally derived as being a good model for teaching and studying the phenomenon of phase locking in biological systems, but the mathematical model for it is quite similar to models that have proved to be useful in other

settings:

- It appears as the canonical model for a general network near a multiple saddle-node on a limit cycle (SNLC) bifurcation.
- It occurs in describing emergence patterns of periodical cicadas [66].
- It arises as the model for a mechanical pendulum operating in an oscillatory or random environment [116, 135].
- It is used to describe nonlinear phenomena in power systems [73, 115].
- It arises as the model of a basic circuit used in communications theory (the phase-locked loop) [94].
- It is used to describe quantum mechanical aspects of superconductors, for example, Josephson junctions [91, 44].

In each of these cases, a mathematical model of a physical phenomenon is converted into phase and amplitude coordinates, and the model is analyzed using frequency-based methods of Fourier analysis and averaging.

Our goal here is to study the frequency and timing of neuron firing and how these can interact in networks to carry information and to control biological systems. We study the flow of information in large networks using methods similar to those used to study the flow of information in large telecommunications networks and the flow of alternating current electricity in power systems.

To study problems in the frequency domain, we work with angle (or phase) variables, and a common stumbling block for people entering this area is the question "What does the phase represent?" The following example might help get around this. Consider a one-handed stopwatch. Time is described by the hand's location, say whose tip has coordinates $(\cos 2\pi t/60, \sin 2\pi t/60)$ and t is usual time measured in seconds, relative to markings on the circumference. We can describe this timer by writing the location of the tip of the hand as being

$$(\cos\theta(t), \sin\theta(t))$$

and describing how the phase variable θ changes with t. In this case, θ is the solution of the differential equation

$$\dot{\theta} = \frac{2\pi}{60}.$$

In this way, we have moved the problem from the domain of physical variables (the position of the hand in this case) to the frequency domain ($\dot{\theta}$). Not much has apparently been gained by doing this. However, now consider a more complicated stopwatch where the markings around the edge are uneven to reflect systematic or random errors in the timer. This can be described using the

original model but now the equation for θ must account for uneven progress of time on this clock, say

$$\dot{\theta} = \frac{2\pi}{60} + f(\theta),$$

where $f(\theta) > 0$ describes when the stopwatch time is moving faster than real time and $f(\theta) < 0$ describes when it moves slower than real time. Thus, the timing is modulated, and the modulation is conveniently described using a single equation for θ.

As another example, a voltage pulse might be described by a quite complicated function of time, say

$$V(t),$$

describing an action potential at a site on a nerve membrane. The voltage V lies in some interval, say

$$V_{\min} \leq V(t) \leq V_{\max}.$$

Such a function can frequently be described by a fixed (simpler) wave form having a variable phase. In these cases, a phase variable θ can be defined by

$$\cos\theta(t) = (V(t) - \bar{V})/\sigma,$$

where $\bar{V}$ is the mean of V:

$$\bar{V} = \frac{V_{\max} + V_{\min}}{2},$$

and σ measures its range:

$$\sigma = \frac{V_{\max} - V_{\min}}{2}.$$

The variable θ is a phase variable in the sense that it measures the extent of development of the signal, V. Typically, θ satisfies a differential equation that can be derived from the one for the physical variable V.

Phase variables in our applications eventually converge to the form

$$\theta \to \omega t + \phi,$$

where we call ω the *frequency* and ϕ the *phase deviation* of the signal. We will find that as in FM-radio, ω is like an address (on the radio dial) and ϕ carries timing information. Both ω and ϕ carry information. In high-dimensional cases (where ω, ϕ, etc. are vectors) such solutions form knots on a high-dimensional torus that phase locking shows will persist in the presence of noise [54].

Another important point of view presented and used here is that of bifurcations. Bifurcations often occur in systems and are observable in experiments.

These are circumstances where slight changes in data or state can result in dramatic changes in system behavior.

If a system is operating in a hyperbolic manner (there are no imaginary eigenvalues for relevant linearizations), then small changes in the system should not cause major disruptions in its behavior. In contrast, if some eigenvalues are near the imaginary axis, then a small change in the system's state or in the parameters describing it can result in dramatic changes in a network's behavior. Bifurcations can occur in many ways, but one of the more complicated elementary bifurcations to study is the fold bifurcation since it requires one to have nonlocal knowledge of the system. VCON models are quite useful for studying systems near such bifurcations since they are constructed on the basis of a saddle-node bifurcation near a limit cycle; consequently, they simultaneously capture a fold bifurcation and tractable nonlocal behavior. For example, consider the equation

$$\dot{\theta} = \omega + \cos\theta.$$

When $0 \leq \omega \leq 1, \theta \to \cos^{-1}\omega$ as $t \to \infty$. But, if $\omega > 1, \theta \to \infty$. If we are reading output of the system as a periodic function of θ, then the output stabilizes in the first case, and it oscillates in the second. This switch in the system's behavior from stable to oscillatory results from the saddle-node bifurcation that occurs when ω increases through the value $\omega = 1$.

Phase locking is important in electrical and mechanical systems [135]. It enables a system to provide a stable output even in the presence of significant levels of noise. Phase locking has also been found to occur in neural tissue [43, 46, 49, 5, 59, 60, 92, 87], and descriptions and analysis of phase locking are done in the frequency domain.

The emphasis here is placed on frequency and phase-deviation information of neurons. This is done by deriving a model in the frequency domain for the hillock region of a nerve cell where voltage pulses (action potentials) are triggered. Time delays in propagation of signals along membranes, across synapses, through dendritic trees and in cell bodies are modeled by including appropriate filters in the circuits. It is intriguing that frequency and timing of action potentials can result in the storage of information and in physiological and psychological responses of the system, and there remain many interesting and untouched aspects of this kind of information storage and retrieval and processing by neural networks.

How general is this approach using VCONs? Any model of a neuron or a network of them using dynamical systems will have the form

$$\dot{x}_i = \mathcal{F}_i(x), \tag{0.1}$$

where $i \in \overline{1, N}$ (where N is a large number) describes the addresses of all

elements in the network, and the vectors $x_i, \mathcal{F}_i \in E^{m_i}$ describe the dynamics of each circuit element and the impact of all other elements on it.

This system can change from static to oscillatory behavior in two simple (codimension = 1) ways: Either through a saddle-node on a limit cycle (SNLC) bifurcation or through a Hopf bifurcation. Both of these are observed in neuroscience experiments. There are many other ways that this can happen, but they involve more constraints (higher codimension) and in that sense are less likely [58]. In the SNLC case, there is an invariant limit cycle that is homeomorphic to a circle, say $x = C(s)$ where $s \in \overline{0, 2\pi}$ such that $|C'(s)|^2 > 0$ for all s, $\mathcal{G}(s) \equiv C'(s) \cdot \mathcal{F}(C(s))/|C'(s)|^2$ satisfies $\mathcal{G}(0) = \mathcal{G}'(0) = 0$, $\mathcal{G}''(0) > 0$ and $\mathcal{G}(s) > 0$ for $0 < s < 2\pi$. In addition, $N - 1$ of the eigenvalues of $\mathcal{F}_x(C(s))$ have nonzero real parts for each $s \in \overline{0, 2\pi}$. Then the system restricted to C is simply $\dot{s} = \mathcal{G}(s)$, and its canonical model is $\dot{\theta} = \omega + \cos\theta$ for ω near 1 in the sense that there is a smooth invertible function $h : S^1 \to S^1$ such that for any solution for s, there is a solution for θ such that $s(t) \equiv h(\theta(t))$. The equation for θ here is the core of the VCON models.

The Hopf bifurcation case is studied elsewhere. It is not studied in depth here because phase locking methods for it require more technical mathematics to derive than our approach here.

We focus here on VCONs and networks of them to gain insight to how such systems, in particular ones that encounter saddle-node bifurcations, can process information.

The first chapter introduces elementary circuit theory and some of its mathematics. Particularly important in this chapter is the introduction of voltage-controlled oscillators (VCOs) and some elementary circuits that use them. VCOs are the central devices in our frequency-based neuron theory developed in later chapters.

Chapter 2 discusses some mathematical aspects of clocks. In particular, it is shown that VCO circuits are quite similar to *simple clocks*, which have helped our understanding of biological rhythms. Phase-resetting experiments are also described in Chapter 2. Finally, it is shown how simple clocks are related to neurons. This chapter is intended to introduce ideas of modeling and analysis in the frequency domain.

The third chapter describes the physiology of neurons and some electrical circuit analogs of them. Among the latter are the Hodgkin–Huxley model, the FitzHugh–Nagumo model, and some simplifications of them. These represent the traditional approach to neuron modeling. The VCON is also introduced in Chapter 3.

The VCON model is quite similar to relaxation oscillation models of neuron behavior but, unlike relaxation oscillators, it is surprisingly simple to study since it accurately models phase aspects of the circuit while avoiding technical

asymptotic approximations. For example, the most sophisticated model of neurons to date involves variables that account for ionic currents and the opening and closing of channels for them, but these are derived in terms of physical quantities of voltage, current, and chemical concentrations. Study of such models for phase locking requires conversion of these variables, using mathematical methods, to phase and amplitude variables, which may not be possible. On the other hand, the model of a VCO is posed in phase variables from the start, by design of some brilliant electrical engineers, to facilitate direct study without use of technical mathematical transformations.

Chapter 4 deals with signal processing in phase-locked feedback circuits, and it sets the scene for our later treatment of signal processing in neural networks. Phase-locked loops (PLLs) are analyzed by using the rotation vector method. It is shown in Chapter 4 that the VCON is a PLL, and the rotation vector method is then applied to describing the stable response of a VCON to external oscillatory forcing. This approach shows how to construct an energy-like function, the minima of which correspond to the stable responses of the VCON.

Several examples of small neural networks are modeled and analyzed in Chapter 5. Among these are a simple bursting pattern generator (the Atoll model), the control of respiration during exercise, and the mechanisms of rhythm splitting in crepuscular mammal activity. Numerical simulations and the rotation vector method are used to determine phase-locking behavior within these small networks.

Large neural networks are studied in Chapters 6 and 7. Chapter 6 describes memory, phase changes, and synchronization in networks; Chapter 7 describes certain networks in and near the neocortex. These networks respond to external stimulation in a variety of interesting and complex ways. Energy surfaces have been derived by others to clarify some responses of networks of On-Off neurons, or Ising-like networks, and Chapter 6 describes some of their work. However, we consider here more realistic problems where the equations we derive are gradient-like fields for phase deviations between synchronized oscillators. This associates with stable phase deviations a memory surface, or as we say here, a *mnemonic surface*. The mnemonic surface approach allows us to interpret stable firing patterns of parts of the brain as representing its short-term memory and its behavioral response. VCON networks are very rich in stable firing patterns and, although they are not as complicated as ionic current circuits, they clearly show how firing frequencies within the network can store, recall, and process phase information. Energy-like surfaces have been used by psychologists in interesting ways: The work of Helmholtz, Freud, and Jung illustrates their impact.

Chapter 7 is largely devoted to creating and studying networks that model

parts of the neocortex and its collateral processes. We aim at the thalamic searchlight, a paradigm for focusing attention, and at pattern formation and wave propagation in the neocortex and the visual cortex.

The appendixes at the end of the book present certain methods of differential equations that I have found to be useful review for students with varying backgrounds in mathematics and a brief summary of topics from bifurcation theory that are relevant to this work. Recommended for further reading are [11, 36, 72, 92].

There have been a number of developments since publication of the first edition of this book that bear directly on the present book. In fact, they constitute the reasons for pursuing a second edition. The following list of items is now folded into the present edition:

- The emphasis of this work on the frequency domain and the signal processing methods developed here are highlighted and expressed in terminology that is closer to common usage in the engineering literature.
- Additional material is included on how noise in signals affects the models derived here. New material is included describing the works of Skorokhod, Chetaev, Kuramoto, Wentzel, and Friedlin in the context of neuroscience.
- More work is included on both chemical and electrical synapses. For the most part the analysis in the first edition was for electrical synapses only.
- New work is presented relating the approach taken in this book with the rest of the neuroscience modeling literature, much of which has emerged since the publication of the first edition. Our approach is through the frequency domain, and new material is included that describes how ionic channel models can be converted for study in the frequency domain and how variables in the frequency domain models are related to physiological variables. In particular, we formulate the VCON model in terms of activity and phase where activity is interpreted as being the firing rate of a cell and phase as having (eventually) the form $\omega t + \phi$.
- Material on bifurcations is now included. The VCON model developed and studied here turns out to be closely related to the canonical model of a fold (or saddle-node) bifurcation. This connection between VCONs and bifurcations is interesting since most bifurcation phenomena, or phase changes in a system, are detectable in experiments. Therefore, it is through connections between bifurcations in the model and predicted phase changes in a network that we can relate our model to possible experiments. Bifurcations involve dimensionless parameters that should be accessible through experiments.
- There are numerous tantalizing connections between the VCON model and models from quantum mechanics. This might be relevant to studies

of consciousness that are now ongoing [107], and some of these similarities are pointed out in the present edition.

- Several new simulations have been developed and carried out for neural circuits using VCON methodologies. These include
  - Attention networks in the thalamus–reticular complex region of the brain.
  - Shivering and flight governed by central pattern generators in moths.
  - The development of mnemonic surfaces, that is, surfaces that describe remembered states of a system.
  - The dynamics of cortical columns. We derive and study the *pencil model* in Chapter 7.
  - The development of ocular dominance in the visual cortex of newborns. This is modeled using synapse strengthening due to synchronous firing of presynaptic and postsynaptic cells.

The work presented in this book is based on courses in mathematical modeling where this material has been used. It can do no more than provide a snapshot of certain aspects of the brain in a research field that is creating masses of new and useful material every day. The focus here is on mathematical modeling, and thus this material should not be construed as being useful directly for clinical purposes.

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