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This dissertation entitled

COMPUTATIONAL STUDY OF STIMULUS-INDUCED SYNCHRONY IN THE CAT RETINA

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Synchronization of neuronal responses across two or more neurons is ubiquitous in the visual system. Including other species, it has been observed in the retina (Mastronarde, 1989), the lateral geniculate nucleus (Alonso et al., 1996), and the visual cortex (Engel et al., 1991a) of the cat. Although a robust phenomenon, the role of synchronization is poorly understood.

This dissertation investigates stimulus-induced synchrony in the cat retinal ganglion cells. For this purpose two modeling approaches are employed. First, a two-layered feed-forward neural network model of a circuit that connects photoreceptor cells to X type ganglion cells in cat retina is presented. The first layer simulates the behavior of photoreceptor and bipolar cells, and its spatial response is modeled descriptively using a difference of gaussians function. The second layer simulates the behavior of ganglion cells and is modeled mechanistically using a noisy, leaky integrate and fire model. The model is constrained by the experimental data, and is used to study correlated spiking activity between the neighboring ganglion cells under uniform illumination. The model shows that common input only to the ganglion cells does not account for the experimentally observed correlations on the time scale of 2–10 ms between X type neighboring ganglion cells. However, a gap junction (electrical coupling) of conductance 0.02 mS/cm$^2$ between the ganglion cells gives rise to the observed correlations between their spike trains.

Second, the neural circuitry underlying the receptive fields of the retinal ganglion cells is neglected, and the ganglion cells are modeled by a more realistic conductance-based
mathematical model. For Ornstein-Uhlenbeck noise as stimulus, the firing characteristics of a single model neuron are explored as the parameters of the stimulus are varied. Moreover, the responses of the uncoupled neurons to common Ornstein-Uhlenbeck noise with respect to the stimulus-induced phase synchronization are studied. The dependence of phase synchronization on the noise variance and frequency contents is explored. It is shown that optimal phase synchronization is achieved for a certain cut off frequency of the common noise source. For physiologically relevant stimuli, however, it is found that a gap junction coupling is required between the pair of neurons to realize tight synchrony.

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Chapter 1

Introduction

How is the distributed neuronal activity of visual cortical neurons integrated to give rise to unified perception? Even after decades of research, this question is unresolved. Although much has been learned about the nervous system at the cellular and molecular level by the single cell studies, our understanding of how functions (perception, behavior etc.) derive from these basic building blocks is poor. In general, the integrative functions of the central nervous system that give rise to unified perception and behavior are poorly understood.

In the visual system, for example, signals related to different features of a visual object, such as motion, color and form, are distributed and processed, in parallel, in specialized modules of the visual cortex (Zeki, 1993). This leads to a highly fragmented representation of objects in the visual field, and is caused by the columnar organization of the visual cortex. All the cells in one column respond only to a stimulus edge of the same direction, and cells in the different column respond to different orientation of the stimulus. Due to this behavior, cortical neurons are called feature-detectors. These parallel pathways and the highly fragmentary nature of sensory representation in the cortex pose a problem to the brain known as the binding problem: To perceive the world of integrated objects, the brain
has to link different features of the same object together. Moreover, these parallel pathways
do not converge to a single center which can integrate the information distributed across
neuronal population to generate coherent percepts.

A solution to the binding problem had been proposed based on single cell responses
(Barlow, 1972). According to this proposal, individual neurons that are tuned to particular
constellations of input activity form the explicit neuronal representations of a distinct per-
ceptual object that is characterized by a unique collection of elementary features. These
neurons, with highly specific response properties, receive converging inputs from the pri-
mary visual stages, and are assumed to be located at the final stages of the visual processing.
Although this approach offers an explanation for a restricted set of functions it fails to pro-
vide a general solution to the binding problem (Crick, 1984). One of the drawbacks of
this model is the number of neurons required to represent virtually infinite combinations of
features of the real-world objects, referred to as ‘combinatorial explosion’. Moreover, this
model of integration performed by the brain lacks experimental support.

This prompted the development of alternate concepts that emphasize distributed dy-
namical processes that rely on self-organization. The underlying idea for these concepts
is derived from the work of Hebb (1949), and is based on the assumption that the distinct
perceptual objects are represented by the assemblies of interconnected neurons rather than
single cells. Participating neurons of these cell assemblies are assumed to encode only the
elementary features of the perceptual object. In Hebb’s model, concurrently enhanced fir-
ing rate of the participating neurons responding to features of a particular object binds them
together into an assembly. This model offers several distinct advantages. For example, it
resolves the problem of the ‘combinatorial explosion’ as at different times, a given neu-
ron can be a part of a different assembly representing a different object thereby reducing
the number of cells required. But, a major drawback of this model, recognized only recently (von del Malsburg, 1981), is its assumption that in a particular region of the cortex, at a given time only single assembly is activated, whereas other assemblies are suppressed. This leads to a problem for peripheral stages of signal processing of feature-rich natural scenes where coactivation of several assemblies is required.

Further improvement to Hebb’s model was proposed by von del Malsburg (1981) which preserves the advantages of Hebb’s model and provides a different scheme, based on temporal coding, to tag the participating neurons of one assembly. According to this proposal, cortical neurons can be tagged through the precise synchronization of their firing activity, instead of enhanced firing rate. In this model, feature-detecting neurons of the visual cortex spike in synchrony when they are encoding features of the same object, whereas their responses become uncorrelated when responding to different objects. In addition to other advantages, this model overcomes the problem posed by Hebb’s model. That is, it allows for the existence of coactivating assemblies in the cortex, since the members of different assemblies are tagged by their correlated activity. Furthermore, the neuronal assemblies become highly dynamic entities, and the participating neurons can now modify their membership by changing the temporal pattern of their firing activity. Thus, assembly coding along with the tagging based on the synchronous activity of neurons appears to be an attractive candidate for the solution of the binding problem.

In recent years, evidence has accumulated that synchrony may be playing the role of establishing relationship among distributed responses. It has been shown that neurons in the cat primary visual cortex exhibit stimulus-induced oscillatory responses in the frequency range of 40–60 Hz (Eckhorn et al., 1988; Gray and Singer, 1989). Furthermore, it has also been shown that, based on the global stimulus properties, these oscillatory responses
can be synchronized across separate columns (Gray et al., 1989), across different areas (Engel et al., 1991a), and even across different hemispheres (Engel et al., 1991b). Thus, it has been suggested that the synchronized activity—whether oscillatory or not—of neurons provides a mechanism for linking individual neurons to form dynamical assemblies.

As the output neurons of the retina, ganglion cell responses represent the final integrated visual signals conveyed to the visual areas of the cortex via the lateral geniculate nucleus (LGN).

A number of classic studies have shown that the spiking activity of retinal ganglion cells, both in vertebrates and invertebrates, display oscillatory patterns. In later studies, both spontaneous and stimulus-induced oscillatory activity has been described in the retina of cats (Kuffler, 1953; Rodieck, 1967; Castelo-Branco et al., 1998; Neuenschwander et al., 1999).

Neuenschwander and Singer (1996), using simultaneous multi-electrode recordings from the cat retina and LGN, showed that the stimulus-induced oscillatory responses of the retina become synchronized over spatially segregated ganglion cells. Also, the temporal patterning in the retina induced synchronized responses in the LGN neurons. They observed that the synchronized activity in the retina depends on the global properties of the stimulus such as size and continuity. This, as the authors note, can be utilized to convey information to the higher visual areas for linking neurons responding to the same visual objects. A recent study has shown that synchronized LGN responses effectively influence activity in the cortical cells (Alonso et al., 1996). Thus, it has been suggested that the oscillatory responses of the retina and the LGN (Doty and Kimura, 1963; Laufer and Verzeano, 1967; Neuenschwander and Singer, 1996) play an important role in the modulation and synchronization of the oscillatory responses of the cortex. Castelo-Branco et al. (1998), using si-
multaneous multi-unit recordings from different visual areas as well as the LGN and the retina of cat, provided evidence in the support of this hypothesis. Their study confirms the existence of feedforward synchronization in the cortex caused by the high-frequency oscillations.

It is often assumed that the ganglion cells encode information independent of each other. Each ganglion cell responds to the stimulus, by modulating its firing frequency, within its receptive field and then transmits that information to the next visual stage independent of other ganglion cells. This simplifying assumption is being challenged by recent studies based on multielectrode recordings from many species, including goldfish (Arnett, 1978; Johnsen and Levine, 1983), salamander (Meister et al., 1995) and cat (Mastronarde, 1989). All of these investigations report that nearby ganglion cells do not act independently, but they tend to fire together in synchrony over different time scales.

Pairwise recordings from cat retinal ganglion cells (Mastronarde, 1983a), under a high uniform illumination, showed that nearby ganglion cells exhibit tendency to fire together. Ganglion cell pairs with overlapping receptive fields showed either positive correlation (when both cells were of the same functional type) or negative correlation (when both cells were of a different functional type). No such effect was observed for ganglion cells with non-overlapping receptive fields. It was speculated that this synchronization effect is due to the shared input from the spiking amacrine cells. The time course of this correlation was brief and was found to be 2–10 msec. A similar study of cat retinal ganglion cells (Mastronarde, 1983b), under very low uniform illumination and darkness, reported two basic modes of synchronous firing of nearby ganglion cells. Correlations at a time scale of 2–10 msec and rather slow correlations at a time scale of 40–50 msec were observed. Single quantal events in the rods were argued to be the source of this correlation. Another study
on cat retinal ganglion cells (Mastronarde, 1983c), using electric stimulation of the optic tract, showed that ganglion cells can affect each other. It was found that neighboring cells of the same polarity tend to synchronize over a very short time scale (0.5–1 msec). The study argued that the mechanism responsible for this effect is the gap junctions between ganglion cells.

The functional role of synchronized activity in information processing in brain is still a matter of debate. In addition to its perceptual consequences, it has been shown to carry more information, and is found to be particularly more effective in transmitting information to the subsequent processing stages. A study on salamander retina concluded that synchronized spike trains of two ganglion cells encoded more information than the information available by treating them independently (Meister et al., 1995). It is yet to be shown that higher visual areas really take advantage of this extra information.

However, it is known that the spiking activity in the retinal afferents is highly effective in driving the target LGN cells. Usrey et al. (1998), during their in vivo study of the cat retina and the LGN, found that when the interspike interval between two spikes from the same ganglion cell is less than 30 msec, the probability of the second spike to illicit a geniculate spike is higher than the first, and that this effect enhances the firing frequency of the target LGN cells. A similar effect was reported by Rowe and Fischer (2001). In addition, they found that the effect of nearby spikes on the transmission was much higher in the presence of structured visual stimulation than its absence. They proposed that this enhanced transmission is caused by the synchronized responses of the parallel ganglion afferents.

Many stimuli can synchronize neuronal responses across two or more neurons in several ways. Although true stimulus-induced synchrony is independent of the underlying neural
circuitry, neuronal populations also show stimulus-induced synchrony due to anatomical convergence (common input) (Sillito et al., 1994) and emergent synchrony (coherent oscillations discussed above). An indirect evidence for the true stimulus-induced synchrony in the visual system is accumulating in the recent years. It has been shown that when the neurons are repeatedly stimulated with a stereotyped input, their responses are reproducible on a time scale of several milliseconds. If neuronal responses are temporally precise for repeated stimuli then, assuming homogeneous neuronal assembly, these neurons could also be synchronized at the same time scale by the stimulus exciting the population simultaneously. In addition to other species, precise responses to repeated stimuli have been demonstrated for the cat retina and LGN (Reich et al., 1997). Furthermore, this form of synchrony is known to be reproduced reliably from one level to the next.

This dissertation investigates stimulus-induced synchronization in the cat retina, and is organized as follows. A review of basic anatomy and physiology of the early visual system, retina and LGN, is presented in Ch. 2. Ch. 3 describes a model of the cat early visual system and explores the stimulus-induced correlations among neighboring ganglion cells. Stimulus-induced phase synchronization in a conductance-based mathematical model for cat retinal ganglion cells is explored in Ch. 4. Finally, Ch. 5 presents summary of this thesis.
Chapter 2

Early visual system

In this chapter, a review of basic anatomy and physiology of the early visual stages, retina and lateral geniculate, is presented. The following discussion is confined almost exclusively to cat early visual stages.

Figure 2.1 illustrates the visual pathways from the retina to the visual cortex. The retinal ganglion cells are the output neurons of the retina, whose axons form the optic nerve. The optic nerve carries discharge patterns of the ganglion cells to cells of a relay station (lateral geniculate nucleus). Lateral geniculate nucleus in turn, through the optic radiation, projects onto the visual cortex. As shown in Fig. 2.1, left (right) half of each retina receives information from the right (left) half of the visual field. The retinal input from each retina then divides in two at the optic chasim such that the right visual field projects to the left side of the brain and the left visual field projects to the right side of the brain.
Figure 2.1: Visual pathways from the retina to the visual cortex in primates. (From Dowling, 1987.)
2.1 Retina

Vertebrate retinas share a common organization and process retinal signals in a fundamentally similar way with a relatively few cell types (Dowling, 1987). Figure 2.2 shows the organization of retina with five major cell types arranged in layers. Photoreceptor cells, rods and cones, in the outer nuclear layer are sensitive to light and are concerned with night and daytime vision, respectively. These cells make connections to the bipolar cells in the inner nuclear layer, which in turn project onto the ganglion cells in the ganglion cell layer. The axons of ganglion cells form the optic nerve which transmits information to higher visual areas. Besides these feedforward connections, there are lateral connections which transmit information laterally in the retina. These connections are formed by the horizontal and amacrine cells. There are many cell types, with different structure, connections, and function, within each major class of cell types.

2.1.1 Photoreceptor cells

Photoreceptor cells convert light into electrical signal which marks the start of vision. The absorption of light gives rise to a cascade of events that modifies the ionic fluxes across the plasma membrane of these cells (for a review see McBee et al., 2001). This change in ionic fluxes causes changes in the membrane potential.

There are two types of photoreceptor cells in cat retina: rods and cones. Rods are responsible for night vision, whereas cones mediate day vision, and provide better spatial and temporal resolution.

One of the two reasons for better spatial resolution of cones is that they are concentrated in the fovea, one region of the retina, where the visual image is least distorted. The second reason is that to detect dim light, signals from rods are pooled in the interneuron (bipolar
Figure 2.2: Organization of retina. Five major cell types are arranged in layers. (From http://www.webvision.med.utah.edu.)
cell) to enhance the signal. This improves the ability of rods to transmit a signal generated by dim light to the higher order neurons. On the downside, this limits the ability of the rod system to detect spatial variations in the image, due to the pooling at the interneuron.

Responses of rods are somewhat slower due to which they can detect a small amount of light. However, this deteriorates their temporal resolution. On the other hand, responses of cones are brisker which helps them provide better temporal resolution of the visual image.

Photoreceptors, unlike typical neurons, respond in graded potentials to visual stimuli. When illuminated, these cells respond with an hyperpolarization, that is, inside of the cell becomes more negative relative to its external environment. The size of the hyperpolarized response is graded with the light intensity. Not all photoreceptors hyperpolarize to light, however. The majority of invertebrate photoreceptors, studied so far, depolarize to light. Figure 2.3 shows hyperpolarizing responses of mudpuppy rods and cones. Notice the slower responses of the rods and relatively longer time to recovery to the base or resting level. Penn and Hagins (1972) reported that in darkness, there is a steady influx of depolarizing current at the outer segment of the rat rods which keeps them depolarized. Light suppresses this ”dark current”, thereby hyperpolarizing the cell. The exact waveform of the photoreceptors response depends on a feedback from the horizontal cells or the gating of voltage dependent channels in the inner segment membrane or both (Baylor et al., 1971, 1979; Fain et al., 1978; Atwell and Wilson, 1980; Bader et al., 1982).

2.1.2 Horizontal cells

Horizontal cells are a class of second-order neurons which receive synaptic inputs from many photoreceptor cells. They are responsible for the lateral transmission of information in the outer retina.
Figure 2.3: Hyperpolarizing responses of rods and cones of mudpuppy. Responses of rods are slower and longer lasting. The number to the left of each response gives the equivalent intensity of the light flash used to evoke the response in log quanta/cm$^2$-flash. (From Dowling, 1987.)
All mammalian retinas contain two types of horizontal cells. Horizontal cells of cats have been studied extensively, and the two types are called A-type and B-type (Dowling et al., 1966). These two types have different morphology and make different contacts with rods and cones. Type A cells do not have axons, whereas type B cells have fine axons. It has been shown in a Golgi-stained study of the horizontal cells that the processes of type A cells and the dendritic processes of type B cells connect exclusively with cone terminals, whereas the axon terminal of type B cells contacts only rods.

The receptive fields of horizontal cells are larger than those of bipolar or ganglion cells because they receive inputs from receptors over a large area of the retina. Additionally, horizontal cells are connected to each other through junctions allowing the flow of current through. This coupling increases the size of their receptive fields even further.

Horizontal cells, like photoreceptor cells, respond in a maintained graded potential, when the retina is stimulated with light. The nature of their responses depends upon the wavelength of the impinging light. One type of horizontal cell responds with hyperpolarization to light of all wavelengths, while another type hyperpolarize to some wavelengths and depolarize to other wavelengths. The cats retina, however, only has the former type (Nelson et al., 1976).

It has been shown that for a wide range of contrasts\(^1\) (up to 0.6), cat horizontal cells can be regarded as linear (Molenaar et al., 1983). But for higher contrasts (0.7-0.9), the response nonlinearities are expressed. On the basis of their transfer properties, cat horizontal cells can be classified into three classes based on their frequency cutoffs and latencies: \(H_n\) (‘narrow’)-type, \(H_m\) (‘medium’)-type, and \(H_w\) (‘wide’)-type. Figure 2.4 shows responses of these three types of horizontal cells for squarewave modulated white light stimuli. \(H_n\)

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\(^1\)Contrast is defined as: \((I_{\text{max}} - I_{\text{min}})/(I_{\text{max}} + I_{\text{min}})\), where \(I_{\text{max}}\) and \(I_{\text{min}}\) are the peak and trough intensities.
(‘narrow’) -type responses display a latency of 45-55 ms and a frequency cutoff of 25-40 Hz, H_m (‘medium’) -type responses display a latency of 20-30 ms and a frequency cutoff of 55-70 Hz, and H_w (‘wide’) -type display a frequency cutoff of 95-110 Hz (Fig. 2.5).

2.1.3 Bipolar cells

Information from the outer retina to the inner retina is passed through the bipolar cell pathways. Bipolar cells receive synapses from the photoreceptor cells and provide excitatory inputs to amacrine and ganglion cells. These cells have receptive fields that show antagonistic center-surround arrangement. The center-surround organization of the bipolar cell receptive field arises by the combined effect of direct input from photoreceptor cells from a small region of space and antagonistic signals pooled over a wider region of space by the horizontal cells. Moreover, like ganglion cells, they express ON and OFF centers.

Bipolar cells, like photoreceptors and horizontal cells, respond with a maintained graded potential when the retina is illuminated. On the basis of their responses to light, bipolar cells are divided into two classes. These two classes segregate the visual signal from receptors into two separate pathways: ON pathway and OFF pathway. ON-bipolar cells depolarize whereas OFF-bipolar cells hyperpolarize in response to illumination. This dichotomous response to a single neurotransmitter, glutamate, released by photoreceptor cells is achieved through different kinds of receptors expressed by these cells. ON-bipolar cells express inhibitory metabotropic glutamate (mGluR6) receptors (de la Villa et al., 1995) whereas OFF-bipolar cells express excitatory AMPA/kainate receptors (Sasaki and Kaneko, 1996).

Morphologically, bipolar cells of cat retina are classified into nine different classes. One class makes synaptic contacts exclusively with rods (rb) and the rest (cb1-cb8) with cones. However, recently a population of bipolar cells in the cat retina has been identified which
Figure 2.4: Response of three different types of cat horizontal cells to squarewave modulated white light stimuli. (From Foerster et al., 1977.)
Figure 2.5: Transfer functions of three different types of cat horizontal cells. Symbols represent experimental data, whereas continuous curves denote model predictions based on parallel and simple circuit elements. (From Foerster et al., 1977.)
makes contacts with both cones and rods (Fyk-Kolodziej et al., 2003). Rod bipolar axon terminals end in the inner two third of the inner plexiform layer (sublamina b) where they interact with amacrine cells. These cells hyperpolarize to illumination of their receptive field centers (Fig. 2.6(a)).

Cat retinal cone bipolar cells, on the basis of their contacts with the cones, are classified into two groups: invaginating bipolar cells and flat bipolar cells. Invaginating bipolar cone axon terminals end in sublamina b and depolarize to illumination of their receptive field centers, whereas flat bipolar cone axon terminals end in outer third of the inner plexiform layer (sublamina a) and hyperpolarize to illumination of their receptive field centers. Figure 2.6(b) shows responses of a cone bipolar (cb2) cell.

2.1.4 Amacrine cells

Amacrine cells, located in the inner plexiform layer, act as a pathway for mutual interactions between bipolar cells and modulate the visual message transmitted from bipolar cells to ganglion cells. Based on their morphology and morphology of their processes in the inner plexiform layer, amacrine cells in the cat retina have been classified into at least 22 types.

Although a number of functional roles have been proposed for these cells, the functional significance of these neurons is not yet completely understood.

On the bases of their responses amacrine cells, in most retinas, can be divided in two classes: transient amacrine cells and sustained amacrine cells. Transient cells always respond by depolarization, and generally do not show center-surround antagonistic receptive field organization. In cat retina, the best characterized transient amacrine cell is the AII. The AII amacrine cell is one of the rod amacrine cells through which rod bipolar cells con-
Figure 2.6: Intracellular responses of cat bipolar cells. (a): Intracellular responses of rod bipolar cell when stimulated with slit stimuli at different distances from the receptive fields center; distances are indicated in μm to the left of each trace. (b): Intracellular responses of cone bipolar (cb2) cell when stimulated with slit stimuli at different distances from the receptive fields center; distances are indicated in μm to the left of each trace. (From Nelson and Kolb, 1983.)
tact retinal ganglion cells. These cells make small gap junctions among themselves and large gap junctions with the axons of invaginating cone bipolar cells.

The AIIs response to light is a transient depolarization followed by a decay toward the base level (Fig. 2.7). In some other species, however, transient cells show depolarizations at both the onset and cessation of the stimulus. The majority of these cells show a center depolarizing receptive field mechanism, but there are few cells that show center-surround antagonistic receptive field organization (Nelson, 1982).

### 2.1.5 Ganglion cells

Ganglion cells are the output neurons of the retina whose axons carry information to the higher visual areas through the optic nerve. Their visual responses have been studied extensively. Each ganglion cell responds to light directed on a restricted region of the retina. This region is called the receptive field of the cell. The receptive field of neighboring ganglion cells overlap and is organized into two concentric, mutually antagonistic regions. On the bases of their receptive field properties ganglion cells can be divided into two groups: ON-center cells and OFF-center cells. Figure 2.8 shows response patterns generated by ON- and OFF-center cells for different stimulus conditions. ON-center cells increase their firing rate when light is shone onto the center of their receptive field and show inhibition when the surround of their receptive field is illuminated. Whereas, OFF-center cells are inhibited when the center of their receptive field is illuminated and fire strongly when the surround of their receptive field is illuminated. Both ON and OFF cells show a weak response when both center and surround are illuminated simultaneously. This shows that the ganglion cells are sensitive to the contrast in the visual input and it is this characteristic of the visual scene that is reported to the higher visual areas of the brain (Kandel et al., 1991). ON
Figure 2.7: Responses of AII amacrine cell. Stimulus is a broad field, 400 nm of about 0.5 s duration. Numbers to the left of each trace indicate the strength of the stimulus in log quanta $\mu m^{-2}s^{-1}$. (From Nelson, 1982.)
and OFF-center ganglion cells of the cat retina, on the basis of their responses to external stimuli, can be classified into two major classes: X and Y cells (Enroth-Cugell and Robson, 1966). When their respective receptive fields are illuminated, X cells respond in a sustained fashion, and display fairly linear spatial summation, whereas Y cells respond in a transient fashion, and display nonlinear spatial summation.

Typically, linear spatial summation is tested by measuring the response of ganglion cells to a counterphased or drifting sine-wave gratings at various relative grating positions or spatial phases. Enroth-Cugell and Robson (1966), observed that when the grating is positioned so that the transition from light to dark passes directly through the center of the receptive field, X cell firing rate shows no modulation. This is known as a null response, and is regarded as a linear summation performed by the X cell, that is the excitation caused by the bright bar is balanced by the inhibition due to the dark bar. On the other hand, for Y cells, no such grating phase can be found, and their firing rate increases to both the introduction and removal of grating. These nonlinear responses of Y cells are attributed to small, nonlinear subunits scattered throughout their receptive fields (Shapley and Victor, 1976). In cat retina, X cells account for 55 percent of the ganglion cell population, whereas Y cells make up just 4 percent (Wässle et al., 1981a,b).

Due to the difference in the response properties of X and Y ganglion cells, it has been hypothesized that the underlying retinal circuitry of these two cell classes is different. Based on summation properties of these cells, Hochstein and Shapley (1976) proposed two distinct models for X and Y cells. The X cell model is simpler and consists of a linear center region and a linear surround region. The Y cell model, in addition to a linear center region and a linear surround, includes several small nonlinear subunits. The existence of

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2Counterphased gratings are obtained by gradually making the brighter areas darker and vice versa sinusoidally.
Figure 2.8: Responses of ON- and OFF-center ganglion cells to five different stimuli in their receptive fields; the bar shows the duration of the stimulation. (From Kandel et al., 1991.) A: ON-center cells respond best to a spot of light shone on the central part of their receptive fields (stimulus 3). Light shone onto the surround of OFF-center cell causes reduction in the activity which resumes as the light is turned off. B: The spontaneous activity in OFF-center is reduced with the illumination of the central part of their field and accelerates when the stimulus is turned off.
the nonlinear subunits is assumed based on the sensitivity of the Y cells to higher spatial frequencies independent of the grating’s relative spatial phase.

Axons of X cells conduct more slowly than those of Y cells, and X cells tend to have smaller receptive fields as compared to Y cells. X cells respond better to the high spatial frequencies and the spatial resolution of X cells is better than that of Y cells. But if the nonlinear responses of Y cells, due to the nonlinear subunits which are capable of responding to higher spatial frequencies, are taken into account, spatial resolution of Y cells is comparable to that of X cells. In cats, it is generally believed that X cells are concerned with the spatial aspect of the image whereas Y cells are concerned with the temporal aspects of the image.

In addition to the two major classes, X and Y, of ganglion cells discussed above, there exists another group called W cells (Stone and Fukuda, 1974). W cells constitute approximately half of the retinal ganglion cell population in cats. Their receptive fields exhibit a variety of responses with some having X-like response characteristics whereas some having Y-like response characteristics. Axons of W cells conduct slower than both X and Y cells, and their receptive field centers are comparable in size to Y cells receptive field centers.

2.2 Lateral geniculate nucleus

Lateral geniculate nucleus (LGN), with its laminar arrangement, is the target of most of the retinal ganglion cells, and is the principal subcortical region that processes visual information for visual perception. Relay cells of the LGN project to the primary visual cortex (area 17 in cat). LGN receives most of its synapses from other than retina (feedback from visual cortex etc.)
Relay cells of the LGN receive their primary input from a single ganglion cell or very few of the same functional type. Consequently, the basic spatial and temporal characteristics of the relay cells are very similar to their retinal afferents. Like their retinal afferents, relay cells show ON- or OFF-center characteristics and display center-surround antagonistic receptive field organization. Apart from few subtle differences, the X, Y and W classification discussed above holds true, as a first approximation, for relay cells.
Chapter 3

Modeling of cat early visual system

Vertebrate retinas share a common organization and process retinal signals in a fundamentally similar way (Dowling, 1987). Photoreceptor cells convert light into electric signals which are then processed by horizontal, bipolar, amacrine and ganglion cells. The discharge patterns of ganglion cells, the output neurons of retina, are then transmitted to the visual areas of the brain through optic nerve.

Ganglion cells exhibit complex dynamics and interactions. Depending on the type of presynaptic inputs, they integrate presynaptic inputs differently. Furthermore, numerous experimental studies in a variety of species have shown that spiking activity in the neighboring ganglion cells can be highly correlated (Arnett and Spraker, 1981; Johnsen and Levine, 1983; Mastronarde, 1983a,b,c; Meister, 1996). These correlations exhibit various time scales, and their role in retinal signaling is still an open question. Depending upon the time scale of the synchronous firing, various schemes of the underlying circuitry have been proposed (Mastronarde, 1989; Brivanlou et al., 1998). The aim of this chapter is to create a model that will serve as a foundation for more complex models of nonlinear dynamics of ganglion cells and to explore the intraretinal connectivity that can explain the reported correlations.
Based on their responses to external stimuli, ganglion cells of the cat retina can be classified into three major classes: X, Y, and W cells (Rowe and Stone, 1977). These cells are the beginnings of independent, parallel visual pathways. X cells are characterized by their linear response in the sense that they compute local temporal contrast by summing excitatory and inhibitory signals over both center and surround regions of the receptive fields (Barlow, 1953; Kuffler, 1953). They receive input from both bipolar and amacrine cells (McGuire et al., 1986), although bipolar inputs predominate.

In this chapter, I model the circuit that connects photoreceptor cells to X cells and compare model responses to experimental results. The model is then used to explore the underlying mechanism of correlations on the time scale of 2-10 ms in the spiking activity of the neighboring ganglion cells. I show that neighboring ganglion cells in the model display these correlations, indicated by a peak in cross-correlation histogram, provided they are coupled through gap junctions, and estimate the conductance of the gap junction required to exhibit such correlations.

This chapter is organized as follows. In Sec. 3.1 I describe the model of the circuit that connects photoreceptor cells to X cells. The experimental methods to obtain data are mentioned briefly and data analysis methods used are described in Sec. 3.2. In Sec. 3.3 the main results are presented, and the findings of this chapter are discussed and summarized in Sec. 3.4.

### 3.1 The model

The model used for this study consists of a feedforward network of two layers of neurons (Fig. 3.1(a)). Neurons of each layer are arranged on a cartesian grid. Cells of the first
Figure 3.1: Illustration of the model. (a) shows two layers of neurons with feedforward connections where cells of L1 simulate photoreceptor cells (PC) and bipolar cells (BC) and cells of L2 simulate the retinal ganglion cells (GC). (b) shows signal processing in the network where the input signal undergoes spatiotemporal filtering, caused by the retinal bipolar cells, before it is processed by the spike generators, the retinal ganglion cells.
layer (L1) receive input signals, filter them, and feed them to the cells of the second layer (L2) (Fig. 3.1(b)). Cells in L1 produce only graded responses; cells in L2 produce spikes. Because $b_1$ type bipolar cells account for most of synapses on X cells, we use $b_1$ cell properties to describe cells of L1. Receptive fields of $b_1$ cell are known to have a center-surround structure (Nelson and Kolb, 1983). Therefore their spatial responses, $S(x, y)$, are modeled using a difference of gaussians (DOG) function, originally introduced as a description for the responses of cat ganglion cells (Rodieck, 1965):

$$S(x, y) = \frac{K_c}{\pi r_c^2} \exp\left(-\frac{x^2 + y^2}{r_c^2}\right) - \frac{K_s}{\pi r_s^2} \exp\left(-\frac{x^2 + y^2}{r_s^2}\right),$$

(3.1)

where $K_c$ and $K_s$ are the center and surround sensitivities, respectively, and $r_c$ and $r_s$ specify the corresponding widths.

The temporal response of each cell in L1, $G(t)$, is modeled by a cascade of $N_L$ low-pass filters each with a time constant of $\tau_L$, similar to that employed by Victor (Victor, 1987):

$$G(t) = \begin{cases} \frac{t^{N_L-1}}{(N_L-1)!\tau_L^{N_L}} \exp\left(-\frac{t}{\tau_L}\right) & , \quad t \geq 0 \\ 0 & , \quad t < 0 \end{cases}.$$

(3.2)

Treating the layer of bipolar cells as linear, shift invariant system we can transform the light signal $s(x, y, t)$, falling onto the retina, into an electric signal $s_i(x, y, t)$ by convoluting $s(x, y, t)$ with the kernel $S(x, y)G(t)$:

$$s_i(x, y, t) = \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} \int_{0}^{t} s(x', y', t') S(x - x', y - y') G(t - t') \, dx' \, dy' \, dt'. \quad (3.3)$$

Integrate-and-fire models have been extensively used for the computational studies of
networks of neurons (Hopfield and Herz, 1995; Campbell et al., 1999). In these models, a variable representing the membrane potential changes continuously until it reaches a firing threshold, $V_{th}$. In order to accommodate the spontaneous activity of cat ganglion cells (Barlow, 1953), we chose to use a noisy variation of the leaky integrate-and-fire model (NLIFM) for the ganglion cells. A recent study (Reich et al., 1998) compared the firing statistics of NLIFM with that of the cat retinal ganglion cells and showed that the NLIFM can be used to describe spike-generating mechanism of cat retinal ganglion cells. A NLIFM of a ganglion cell is given by

$$C \frac{dV_i(t)}{dt} = -\frac{V_i(t) - V_{rest}}{R} + \beta \sum_{k=1}^{N} w_k s_k(t) + \xi_i(t), \quad (3.4)$$

where $R$ is membrane resistance, $C$ is membrane capacitance, $V_i$ is the membrane potential of cell $i$, $V_{rest}$ is the resting value of the membrane potential, $\beta$ is a scaling factor, $N$ is the total number of excitatory synapses, $w_k$ is the weight and $s_k(t)$ is the output of the $k$-th bipolar cell that synapses on the ganglion cell, and $\xi_i(t)$ are white noise sources (random input current to the ganglion cell) with $<\xi_i(t)> = 0$, $<\xi_i(t)\xi_j(t')> = 2D \delta(t - t') \delta_{ij}$, where $D$ is the noise strength, common to all ganglion cells.

It is known that immediately after a neuron fires an action potential the membrane goes into a refractory state for a few milliseconds (Katz, 1966). To incorporate this into the model, the firing threshold is treated as a dynamic variable. For simplicity we define the firing threshold of neuron $i$ as $V_i^{th}(t) = \theta_i(t) + V_{rest}$, where $\theta_i(t)$ evolves in time according to

$$\frac{d\theta_i(t)}{dt} = -\frac{(\theta_i(t) - \theta_0)}{\gamma}. \quad (3.5)$$
Each time a neuron fires, that is when \( V_i(t) = V_i^{th}(t) \), \( \theta_i \) is increased by a constant \( \alpha \), and it decays back to its original value, \( \theta_0 \), with time constant, \( \gamma \).

Coupling between the cells of the two layers is excitatory and local: only a few cells of L1 excite a given cell in L2. The strength of this constant coupling between cell i of L1 (presynaptic cell) and cell j of L2 (postsynaptic cell) is of Gaussian form:

\[ w_{ij} = a \exp\left[-\frac{d_{ij}^2}{2\sigma^2}\right], \tag{3.6} \]

where \( d_{ij} \) is the lateral distance between cells i (presynaptic) and j (postsynaptic) when parallel to plane of the layers and \( \sigma \) is the standard deviation, which corresponds approximately to the distribution of bipolar synaptic contacts on ganglion cell dendrites (Cohen and Sterling, 1991). There are no connections within a layer.

For numerical computations Eqs. 3.4 and 3.5 are discretized in first order as:

\[ V_i(t_{n+1}) = V_i(t_n)(1 - \frac{\Delta t}{\tau}) + V_{rest} \frac{\Delta t}{\tau} + \frac{\beta s_i(t)}{C} \Delta t + \sqrt{2D\Delta t} \frac{Y}{C} \tag{3.7} \]

and

\[ \theta_i(t_{n+1}) = \theta_i(t_n)(1 - \frac{\Delta t}{\gamma}) + \frac{\theta_0}{\gamma} \Delta t, \tag{3.8} \]

where \( \tau = RC \) is a membrane time constant, \( \Delta t = t_{n+1} - t_n \) is a time step, \( s_i(t) \) is the net signal received from afferent cells of L1 and Y is a uniformly distributed gaussian random variable with an average zero and standard deviation one.

Figure 3.2 shows traces of the membrane potential and dynamic firing threshold of the model ganglion cell. The model is stimulated with a weak constant illumination. After every spike the firing threshold is increased by a constant amount and between the spikes it decays to a fixed value. The variable nature of the firing potential threshold endows the ganglion cells with there lativere fractory period.
Figure 3.2: A trace of the membrane potential and dynamic action potential firing threshold of the model ganglion cell. A weak uniform illumination is used to excite the model cells. Smooth line represents membrane potential and dashed line (red color) denotes variable firing threshold. Notice increase in the firing threshold as the cell fires an action potential and decay between two successive spikes. This scheme implements relative refractory period in the ganglion cell. Model parameters are the same as given in Table 3.1.
3.2 Experimental methods and data analysis

Data from retinal ganglion cells were obtained from recordings in cat retina by my collaborator. Recording methods used are described in detail elsewhere (Rowe and Palmer, 1995). Briefly, animals were anesthetized by continuous intravenous infusion of Nembutal (1.5 mg/kg/hr), paralyzed by continuous intravenous infusion of Flaxedil (8 mg/kg/hr), and artificially respirated. Rectal temperature was maintained at 37.5°C throughout the experiment by a homeostatically controlled electric blanket. Expired CO₂ was continuously monitored and respiratory rate and/or volume adjusted so as to maintain it close to 4%.

Glass micropipettes filled with 1M NaCl and having impedances between 10 and 20 Megohms were used to isolate the spike activity of single retinal ganglion cells. All visual stimuli were generated by a Picasso Image Generator and presented on a CRT screen (Tektronix 608) at a distance of 57 cm from the posterior nodal point of the eye. Spectacle lenses were used to focus the eye on the CRT screen. The mean luminance of this screen was 3 cd m⁻².

The temporal dynamics of retinal ganglion cells were determined using a sum of sinusoid temporal modulation signal as a probe (Victor and Shapely, 1980). The stimulus was a spatial sine wave grating with a spatial frequency of 0.2-0.3 cycles per degree, centered on the receptive field so that modulation of the contrast of the grating produced maximum linear responses. The contrast is modulated in time by a signal which is the sum of eight sinusoids whose frequencies are 0.3165, 0.678, 1.4012, 2.8476, 5.7404, 11.526, 23.0972 and 46.2396 Hz (Fig. 3.3). These are all odd integer multiples (7, 15, 31, 64, 127, 255, 511, 1023, 2047, 4095, 8191, 16384, 32768, 65536, 131072, 262144, 524288, 1048576).

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¹Dr. M. H. Rowe, Department of Biological Sciences, Ohio University, Athens
Figure 3.3: Temporal modulation of contrast of a spatial sine wave used to calculate temporal tuning curves of real and model ganglion cells.
511 and 1023, respectively) of a common fundamental frequency (.0452 Hz), resulting in a periodic ensemble whose period is that of the common fundamental, 22.1184 seconds. This periodicity is important because it allows the cell’s response to the stimulus to be accurately measured within a finite period of time. The duration of each stimulus episode was 22.1184 seconds. During each presentation, all component sinusoids are of equal contrast. Contrast values were set at .125, .1, .075, and .05 per sinusoid. The spike train of the cell during each presentation is recorded in the form of a histogram containing 4096 bins of 5.4 ms each. The amplitude and phase of the ganglion cell’s response at each input frequency is extracted from the histogram by Fourier analysis. Data from the model were analyzed in a similar way. The response amplitudes at input frequencies, both from the model and experimental data, are plotted.

To measure contrast sensitivity, a measure of the ability to distinguish signal and noise, of the model neurons, sinusoidal gratings of various spatial frequencies, with drift frequency of 1 Hz, were used. Figure 3.4 illustrates the sinusoidal grating drifting over the receptive field of a bipolar cell; for simplicity only one receptive field is shown. A post-stimulus time histogram was accumulated as the 50 cycles of the stimulus were presented to the model neurons, and the fundamental Fourier component of the histogram was calculated using the formula (Linsenmeier et al., 1982)

\[
\frac{4}{N} \left\{ \left[ \sum_{i=1}^{N} x_i \cos\left( \frac{2\pi i}{N} \right) \right]^2 + \left[ \sum_{i=1}^{N} x_i \sin\left( \frac{2\pi i}{N} \right) \right]^2 \right\},
\]

(3.9)

where \( N \) is the number of bins in the histogram and \( x_i \) is the firing rate during the \( i \)th bin. For each spatial frequency, the reciprocal of the contrast value that elicited a fundamental Fourier response of 10 spikes/sec (Linsenmeier et al., 1982) was used as a measure of
Figure 3.4: Visual stimulus, drifting sinusoidal grating, used to calculate spatial tuning curves of the model ganglion cells. For simplicity, the receptive field of only one bipolar cell is shown.
Figure 3.5: Illustration of the construction of the cross-correlation histogram for two spike trains. P is a reference cell whereas Q is a target cell.

Cross-correlation histograms are typically used to assess interactions between pairs of neurons (Rodieck, 1967). It describes the firing rate of one neuron as a function of time before and after the spike in second neuron. Figure (3.5) illustrates construction of cross-correlogram: each spike in the reference cell (P) is assumed to occur at time zero and a histogram of the spikes in the target cell (Q) is accumulated for a specified time lag, both backward and forward. The histogram is then scaled by dividing the number of spikes in a given bin by the bin width (in seconds) and by the number of spikes from P. The cross-correlation histogram has a complex structure, and rules to infer interactions between the neurons from the cross-correlation histogram have been elucidated (Moore et al., 1970). If there is a sharp peak around zero delay, the two neurons tend to fire synchronously, and the width of the peak describes the time scale of the synchronous activity. On the other hand, a flat curve indicates that the two neurons are firing independently. To construct cross-correlograms for our model neurons, we used a bin size of 1 ms, and a base-line level, given by the flat region of the cross-correlogram, is calculated by averaging the bins from 50 to 100 ms from the center of correlogram.
Table 3.1: Parameters for spatiotemporal model

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<td>$\mu$A/cm$^2$</td>
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<tr>
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<td>ms</td>
<td>$\sigma$</td>
<td>10</td>
<td>$\mu$m</td>
</tr>
</tbody>
</table>

Figure 3.6: Temporal frequency tuning curves of X ganglion cell measured with sum of sinusoid temporal modulation signals at several contrast levels per sinusoid, (a) 12.5% contrast, (b) 10% contrast, (c) 7.5% contrast, (d) 0.5% contrast. Note that the model responses agree very well with the experimental data.
I chose model parameters (shown in Table 3.1) based on experimental and theoretical data available in the literature and by fitting the frequency tuning curves (see Fig. 3.6) of the model with those of the experimental data.

### 3.3 Results

Figure 3.6 shows temporal frequency responses obtained from the model ganglion cell and an X cell when stimulated with standing gratings temporally modulated with a sum-of-sinusoids. It is clear that the model data matches very well with the experimental data. Shown in Fig. 3.7 are the spatial frequency responses of the model ganglion cell, when stimulated with drifting gratings, compared with the fit to unpublished experimental data from my collaborator’s laboratory for an X ganglion cell. Note that the model data is in agreement with the responses obtained from the experiments.

With the model tuned, I consider two nearby ganglion cells stimulated with a weak uniform illumination. The two ganglion cells receive common input from two afferents of L1. Only with feedforward connections, the cross-correlogram (Fig. 3.8(a)), constructed from their spike trains, is flat indicating that the two cells spike independently. Next I introduce gap junction between the two ganglion cells of L2, that is, a term $I_{\text{gap}} = -g_{\text{gap}}(V_i - V_{\text{pre}})$, where $g_{\text{gap}}$ is the gap junction conductance and $V_{\text{pre}}$ is the presynaptic membrane potential, is added to Eq. (3.4) of the model. For $g_{\text{gap}} = 0.02 \text{ mS/cm}^2$, the cross-correlogram (Fig. 3.8(b)), in agreement with the experimental findings (Mastronarde, 1983a), shows a peak centered at zero lag. The width of the peak, at the base level, is 11 ms. The peak becomes more pronounced and sharp as the conductance of the gap junction is increased (data not shown). Thus in the model correlations arise only in the presence of gap junctions.
Figure 3.7: Spatial frequency tuning curves of X ganglion cell measured with a drifting grating. Smooth line is a fit to unpublished experimental data from our laboratory for an X ganglion cell whereas empty symbols designates the responses from the model. Note that the model responses compare reasonably well with the experimental data.
Figure 3.8: Cross-correlation histograms for two adjacent model ganglion cells responding to uniform illumination. (a): The Cross-correlogram is flat in the absence of gap junction. (b): The Cross-correlogram shows a peak when the gap junction conductance of 0.02 mS/cm$^2$ is introduced between the ganglion cells. Base line (dashed line) denotes the flat region of the correlogram.
between the ganglion cells and cannot be explained on the basis of shared inputs from the afferents.

### 3.4 Discussion

This model does not include amacrine cells which are known to provide 30% of the inputs to the X-cells. With such an input, amacrine cells should contribute to the receptive field properties of their target X cells. In fact, amacrine cells have been proposed to give rise to the X cell surround receptive field (McGuire et al., 1986). The model can be readily extended to include amacrine cells, but as the simulations indicate, the modeled circuitry is a good approximation to the underlying circuitry of the X-cell’s receptive field. It is not implied that the role of amacrine is not important in shaping the responses of the X cells. Further, the model includes only on-X pathway, neglecting off-X pathway. This approach is justified as the information in cat retina is mainly processed independently in parallel pathways (Enroth-Cugell and Robson, 1966).

The present model can be easily extended to explore underlying circuitry of the nonlinear receptive fields expressed by Y and W cells in cat retina (Hochstein and Shapley, 1976; Rowe and Cox, 1993). Although X cells are generally regarded as linear cells, even they express the nonlinear behavior (Barlow et al., 1977). This nonlinear behavior in the ganglion cells is realized as they sum signals from independent regions called subunits whose response characteristics are strongly nonlinear. These subunits can be included in the model and the functional organization of the receptive fields can be investigated. Thus the model provides a skeleton on the top of which more complex and physiologically relevant circuitry can be built.
In this chapter, I have presented a two-layered feedforward network model of the early on-X pathway in cat retina which is able to reproduce experimentally observed spatial tuning and linear temporal dynamics of retinal ganglion cells. This model provides a simple framework for the study of more complex aspects of the temporal structure of retinal ganglion responses, as well as the basis of correlated activity between ganglion cells. Furthermore, it provides a foundation for investigating the influence of additional neural circuitry on more complex ganglion cell receptive field properties. Responses from this model can also be used as inputs to models of higher visual areas such as the lateral geniculate nucleus.
Chapter 4

Phase synchronization in cat model ganglion cells

Neighboring ganglion cells in the vertebrate retina, due to the overlap in their receptive fields, receive the same signal. A number of studies in a variety of species have reported that these cells show spike synchronization in their stimulus-induced responses (Arnett and Spraker, 1981; Johnsen and Levine, 1983; Mastronarde, 1983a,b,c). This synchronization exhibits various time scales and its role in visual information processing is an unresolved issue in brain research.

Synchronization, first described by Christiaan Huygens (1673), of two or more weakly interacting systems is understood as a mutual adjustment of their inherent time scales to a single rhythm (for a recent modern review on synchronization see Pikovsky et al. (2001)). It is ubiquitous in nature and is known to play an important role in the self-organization of nonlinear oscillatory systems (Kuramoto, 2003). Mutual synchronization is exhibited by a range of biological oscillators including, electrosensitive cells in the paddlefish (Neiman et al., 1999a), pacemaker cells of the heart (Wilders and Jongsma, 1993), loco-
motion and breathing in running mammals (Bramble and Carrier, 1983) and human heart and respiratory system (Schäfer et al., 1998). In biological systems synchronization can be a signature of either the normal functioning of a system, such as performance of a pacemaker, or pathological dynamics, such as abnormal synchronization of ensembles of neurons in Parkinsonian or epileptic patients (Glass, 2001; Tass, 1999). In neuroscience, synchronization is considered to be an important mechanism of stimulus encoding which is based on the precise timing of neurons firing rather than simply on modulation of their firing rates (Mainen and Sejnowski, 1995; Singer, 1999).

The phenomenon of synchronization, first introduced for deterministic self-sustained oscillators, was extended to two other classes of systems. First, synchronization was shown to occur in chaotic systems (Pecora and Carroll, 1990; Rosenblum et al., 1996) which are still deterministic systems with complicated, random-like dynamics. Noise is inevitably present in any dissipative system and thus studies of noise influence on synchronization are of great importance. Pioneered by R.L. Stratonovich (Stratonovich, 1963), synchronization of stochastic systems has attracted attention of researchers in different areas of natural sciences (Strogatz, 2003; Pikovsky et al., 2001). In weakly nonlinear oscillators, such as van der Pol oscillator, noise always plays against synchronization (Stratonovich, 1963). However, in excitable or in bistable system which exhibit the phenomenon of stochastic resonance (Gammaitoni et al., 1998) synchronization can be greatly enhanced by noise (Lindner et al., 2004).

A phenomenon closely related to synchronization occurs when an ensemble of nearly identical non-coupled oscillators are subjected to a common noise field (Pikovsky, 1984). Jensen et al. (1998) studied synchronization of deterministic Hodgkin-Huxley neurons due to common noise and related the observed synchronization to the reliability of neural re-
sponses (Mainen and Sejnowski, 1995). Similar results were obtained for other popular models of neurons including, Fitzhugh-Nagumo, Morris-Lecar, and Hindmarsh-Rose. It was proposed that this synchronization underlies the reliability of neuronal responses reported in a variety of neural systems including cat retinal ganglion and lateral geniculate nucleus cells (Reich et al., 1997). Synchronization of non-identical sensory neurons due to common noise was recently demonstrated experimentally on paddlefish electroreceptors (Neiman and Russell, 2002).

The encoding scheme used by neurons to represent and transmit information about the external stimuli is an unresolved issue of systems neuroscience. Classically, it is thought that neurons use their average firing rate to encode the external stimuli (Adrian, 1928). Despite the fact that it has been argued (Gautrais and Thorpe, 1998) that the rate coding is inefficient, it still enjoys wide acceptance. This scheme is being challenged by temporal coding (Reich et al., 2001), which uses precise temporal structure of the neuronal spike train to transmit information. One line of evidence in favor of the temporal coding scheme is recently accumulated experimental evidence that certain neuronal systems are capable of reproducing spike trains, when stimulated with fluctuating stimuli, on millisecond scale which can serve as a useful substrate for temporal coding. Examples include rat neocortical neurons (Mainen and Sejnowski, 1995), cortex of awake monkey (Bair and Koch, 1996), ferret visual cortex (Nowak et al., 1997), H1 neurons of fly visual system (de Ruyter van Steveninck et al., 1997), tiger salamander and rabbit retinal ganglion cells (Berry et al., 1997) and cat retinal ganglion and lateral geniculate nucleus cells (Reich et al., 1997).

In this chapter I study phase synchronization in non-coupled, noisy Hodgkin-Huxley-type models of cat retinal ganglion cells. I show that these model neurons exhibit phase
synchronization when stimulated with random stimuli of appropriate strength. The quality
of synchronization on stimulus parameters is also investigated. Furthermore, influence
of gap junction coupling between the model cells on the quality of synchronization, for
physiologically relevant stimuli, is studied.

The chapter is organized as follows. In Sec. 4.1, the neuronal model studied is in-
roduced. In Sec. 4.2 I describe the stimulus protocol used and discuss its relevance for
physiological systems. Measures used for assessing responses of the model are introduced
in Sec. 4.3. In Sec. 4.4, first I describe the bifurcations found in the deterministic version
of the model. Second, I investigate the dependence of firing characteristics of the model
neuron on the stimulus parameters. Finally, I investigate the effect of gap junction coupling
between two model cells on the quality of synchronization. The findings of this chapter are
discussed and summarized in Sec. 4.5.

4.1 Single-compartment model

Based on an earlier study on tiger salamander retina (Fohlmeister et al., 1990),
Przybyszewski et al. (1996) proposed Hodgkin-Huxley-type neuron model for cat retinal
ganglion cells. Their model included four voltage-gated currents: Na\(^+\) current (\(I_{Na}\)), Ca\(^{2+}\)
current(\(I_{Ca}\)), delayed rectifier (non-inactivating) K\(^+\) current (\(I_{K}\)), A-type (inactivating)
K\(^+\) current (\(I_{A}\)), and one Ca\(^{2+}\)-activated K\(^+\) current (\(I_{KCa}\)).

\(I_{Na}\) is sensitive to tetrodotoxin (TTX) and shows rapid inactivation which is thought
to underlie action potential generation. \(I_{K}\) is sensitive to tetraethylammonium (TEA)
with conductance characteristics similar to the delayed rectifier of the original Hodgkin-
Huxley model. \(I_{A}\) is sensitive to 4-aminopyridine (4-AP) and shows transient inactivation.
\(I_{KCa}\) is sensitive to increases in free intracellular Ca\(^{2+}\) and is a primary cause of after-
hyperpolarization in cat ganglion cells. $I_K$ determines the width of the action potential, whereas spike frequency is mainly controlled by both $I_{KCa}$ and $I_K$ (Fohlmeister et al., 1990).

Cat retinal ganglion cells exhibit characteristic spontaneous activity. In order to account for this fact, current balance equation of the original model is modified by including a Gaussian white noise term $\xi(t)$ that mimics the ion channel fluctuations and other sources of neuronal noise (Schneidman et al., 1998; Manwani and Koch, 1999; White et al., 2000). Furthermore, a nonspecific leak current, $I_L$, is included in our model as illustrated in Fig. 4.1. The modified model reads

$$C \frac{dV}{dt} = -(I_{Na} + I_K + I_{Ca} + I_A + I_{KCa} + I_L) + I(t) + \xi(t), \quad (4.1)$$

where $C$ is the membrane capacitance, $V$ is the membrane potential, $I(t)$ is the input current to the cell, and $\xi(t)$ satisfies $\langle \xi(t) \rangle = 0, \langle \xi(t)\xi(t') \rangle = 2\epsilon\delta(t-t')$, where $\epsilon$ is the noise strength. And the ionic currents are

$$I_{Na} = \bar{g}_{Na}h_m^3(V - V_{Na}), \quad (4.2a)$$
$$I_K = \bar{g}_Kn^4(V - V_K), \quad (4.2b)$$
$$I_{Ca} = \bar{g}_{Ca}c^3(V - V_{Ca}), \quad (4.2c)$$
$$I_A = \bar{g}_Aa^3h_A(V - V_{K}), \quad (4.2d)$$
$$I_{KCa} = \bar{g}_{KCa}(V - V_{K}), \quad (4.2e)$$
$$I_L = g_L(V - V_L), \quad (4.2f)$$
Figure 4.1: Equivalent electric circuit of our model. $C$ represents membrane capacitance, $g_{Na}$, $g_{K}$, $g_{A}$, and $g_{Ca}$ are voltage gated Na$^{+}$, non-inactivating K$^{+}$, inactivating K$^{+}$, and Ca$^{2+}$ conductances respectively, $g_{L}$ is the nonspecific leak conductance, and $g_{KCa}$ is Ca$^{2+}$ gated K$^{+}$ conductance; $\xi$ represents neuronal noise.
where \( \bar{g}_j \) and \( V_j \) are the maximal conductance and the reversal potential for ion \( j \) respectively, \( g_L \) is the leak conductance, and \( g_{KCa} \) is the calcium gated potassium conductance written as

\[
g_{KCa} = \bar{g}_{KCa} \frac{[Ca^{2+}]_i}{1 + [Ca^{2+}]_i} (V - V_K).
\]

Here \([Ca^{2+}]_i\) is intracellular calcium concentration and \( \bar{g}_{KCa} \) is the maximal conductance.

The reversal potentials for all the ions except for \( Ca^{2+} \) were kept fixed, whereas \( Ca^{2+} \) reversal potential, \( V_{Ca} \), was updated dynamically according to the Nernst equation

\[
V_{Ca} = \frac{RT}{2F} \log \frac{[Ca^{2+}]_e}{[Ca^{2+}]_i}.
\]

Here \( R \) is the gas constant, \( T \) is the absolute temperature, and \( F = 9.648 \times 10^4 \) col/mol is the Faraday’s constant. The calcium dynamics is governed by

\[
\frac{d[Ca^{2+}]_i}{dt} = -0.000015I_{Ca} - 0.02([Ca^{2+}]_i - 0.0001), \tag{4.3}
\]

and the gating variables (m, h, c, n, A, and \( h_A \)) satisfy the ordinary differential equations:

\[
dx/dt = -(\alpha_x(V) + \beta_x(V))x + \alpha_x(V), \tag{4.4}
\]
where $\alpha_x(V)$ and $\beta_x(V)$ are the rate constants for a gating variable $x = m, h, c, n, A, h_A$, respectively, and are given by

\[
\begin{align*}
\alpha_m & = \frac{-0.05(V + 30)}{\exp(-0.1(V + 30)) - 1}q_{10}, \\
\beta_m & = 0.5 \exp(-(V + 55)/18)q_{10}, \\
\alpha_h & = 0.0182 \exp(-(V + 50)/20)q_{10}, \\
\beta_h & = \frac{0.35}{\exp(-0.1(V + 20)) + 1}q_{10}, \\
\alpha_n & = \frac{-0.004(V + 40)}{\exp(-0.1(V + 40)) - 1}q_{10}, \\
\beta_n & = 0.025 \exp(-(V + 50)/80)q_{10}, \\
\alpha_c & = \frac{-0.003(V + 13)}{\exp(-0.1(V + 13)) - 1}q_{10}, \\
\beta_c & = 0.0467 \exp(-(V + 38)/18)q_{10}, \\
\alpha_A & = \frac{-0.0011(V + 90)}{\exp(-0.1(V + 90)) - 1}q_{10}, \\
\beta_A & = 0.00667 \exp(-(V + 30)/10)q_{10}, \\
\alpha_{h_A} & = 0.105 \exp(-(V + 70)/20)q_{10}, \\
\beta_{h_A} & = \frac{0.1}{\exp(-0.1(V + 40)) + 1}q_{10}.
\end{align*}
\]

Here $q_{10}$ is the temperature compensating factor.

The parameter values used in the simulation are: $C = 1.0 \mu F/cm^2$, $g_{Na} = 60.0$ mS/cm$^2$, $g_{Ca} = 2.0$ mS/cm$^2$, $g_K = 12.0$ mS/cm$^2$, $g_A = 36.0$ mS/cm$^2$, $g_{KCa} = 0.05$ mS/cm$^2$, $g_L = 0.2$ mS/cm$^2$, $V_{Na} = 35.0$ mV, $V_K = -75.0$ mV, $V_L = -60.0$ mV, and $\epsilon = 5.0 \mu A^2/cm^4$.

Figure 4.2(a) shows a train of action potentials from the deterministic model-ganglion cell ($\epsilon = 0$). The cell fires repetitively in response to a depolarizing current pulse of 10 $\mu A/cm^2$. During action potentials, the internal calcium concentration increases (4.2(b))
Figure 4.2: Simulated response of the deterministic ganglion cell model when stimulated with a depolarizing current pulse. (a): Trace of the membrane potential (continuous line) and depolarizing current pulse (dashed line). (b): Changes in the intracellular calcium concentration due to the $I_{Ca}$. (c): Ionic currents during a single action potential. Negative currents ($I_{Na}$ and $I_{Ca}$) flow into the cell and positive currents ($I_{K}$, $I_{A}$, and $I_{KCa}$) flow out of the cell.
which in turn gates the calcium dependent potassium current ($I_{KCa}$). In Fig. 4.2(c), flow of currents included in the model during a single action potential are shown: $I_{Na}$ and $I_{Ca}$ flow into the cell causes the depolarization of the cell membrane, and $I_{K}$, $I_{A}$, and $I_{KCa}$ flow out of the cell repolarizes the membrane. Note the relatively small magnitude of $I_{Ca}$ and $I_{KCa}$.

Numerical integration of the Eqs. (4.1), (4.3), and (4.4), referred to as the model hereafter, has been performed using Euler method with integration time step $\Delta t = 10^{-5}$ ms. The simulations were run for 5 minutes, and the membrane potential was recorded at a resolution of 0.1 ms. The firing threshold was set at -20 mV, and the spikes times $\{t_i\}$ were recorded every time membrane potential crossed firing threshold with positive slope.

### 4.2 Stimulation

The model neurons are driven with stimulus of the form $I(t) = I_0 + y(t)$, where $I_0$ is a constant background current and $y(t)$ is an Ornstein-Uhlenbeck (OU) noise. This form of current may represent an approximation to that resulting from the stochastic gating of ion channels present in neuronal membrane or to randomly occurring synaptic input currents with exponential decay. The OU noise was generated by low-pass filtering white Gaussian noise $\eta(t)$ as

$$\frac{dy(t)}{dt} = -\frac{1}{\tau} y(t) + \sqrt{\frac{2D}{\tau}} \eta(t), \quad (4.6)$$
where $\tau$ is the correlation time and $D$ is the variance of the OU noise respectively, and $\eta(t)$ satisfies

\begin{align*}
\langle \eta(t) \rangle &= 0, \quad (4.7) \\
\langle \eta(t)\eta(t') \rangle &= \delta(t-t').
\end{align*}

The OU noise, $y(t)$, obeys time correlation function:

\begin{equation}
\langle y(t)y(t') \rangle = D \exp(-\frac{|t-t'|}{\tau}). \quad (4.8)
\end{equation}

The power spectrum of $y(t)$ is given by the Fourier transform of the correlation function,

\begin{equation}
S(\omega) = \int_{-\infty}^{+\infty} \langle y(t)y(0) \rangle \exp(-i\omega t)dt = \frac{2D\tau}{(1 + \omega^2\tau^2)}. \quad (4.9)
\end{equation}

Note that for a given variance, $D$, $S(\omega)$ vanishes both for $\omega = 0$ and $\tau \to +\infty$.

For this choice of OU process, the variance is independent of correlation time. It is, therefore, possible to keep the variance constant and investigate dependence of responses of the model cells on the frequency contents of the input signal as the correlation time is varied. Figure 4.3 shows the power spectrum of OU noise for different correlation times with a fixed value of $D = 30 \, \mu \text{A}^2/\text{cm}^4$. The area under the spectral density function $S(\omega)$, total power, remains constant as the correlation time varies.

Numerical simulation of Eq. (4.6) is performed by using the method of Fox et al. (1988) as:

\begin{equation}
y(t + \Delta t) = y(t) \exp(-\frac{\Delta t}{\tau}) + \sqrt{D(1 - \exp(-\frac{2\Delta t}{\tau}))}, \quad (4.10)
\end{equation}
Figure 4.3: Power spectrum of OU noise for different correlation times $\tau$ with a fixed value of $D = 30 \, \mu A^2/cm^4$. Notice the change in power spectrum, but the area under the curve is constant.
Figure 4.4: Sample paths of OU process for different correlation times with variance $D = 30 \mu A^2/cm^4$. (a): $\tau = 0.01$ ms. (b): $\tau = 2.0$ ms. (c): $\tau = 200.0$ ms.
where $\Delta t$ is the integration time step and $Y$ is a uniformly distributed gaussian random variable with an average zero and standard deviation one. Figure 4.4 shows sample paths of OU process for different correlation times with variance $D = 30 \mu A^2/cm^4$. For small value of $\tau$, the OU noise shows rapid fluctuations. The fluctuations become slow as the correlation time increases.

4.3 Measures of stochastic synchronization

Synchronization is defined as a phase locking or frequency entrainment of two or more periodical oscillators which is sustained in a finite range of oscillators parameter values. If we denote the instantaneous phases of two oscillators as $\Phi_{1,2}(t)$, and the phase difference $\phi(t) = \Phi_1(t) - \Phi_2(t)$, then the condition for phase locking is $|\phi(t)| < \text{const}$, meaning that the phase difference remains bounded. We note, that such definition of phase synchronization does not impose a restriction on the amplitudes of interacting oscillators. For example, in the case of synchronization of two chaotic oscillators their amplitude can be uncorrelated (Rosenblum et al., 1996).

The presence of noise leads to diffusion of the oscillator’s phases such that definition of synchronization given above is never fulfilled. The condition of phase locking can be satisfied only for limited durations (phase locking segments) which are interrupted by abrupt changes of the phase difference (phase slips). Thus, in the case of stochastic systems synchronization must be understood in a statistical sense, which leads to the concept of stochastic synchronization (Neiman et al., 1999b; Pikovsky et al., 2001). The conditions for synchronization can be established by imposing restrictions on fluctuations of phase difference or frequencies of interacting systems.
The instantaneous phase of a non-periodic signal cannot be defined uniquely. The discussion on various definitions of the instantaneous phase can be found in (Rosenblum et al., 2001). In this study we introduce the phase of a spiking neuron as following. Phase of a neuron increases by $2\pi$ every time it fires and interpolates linearly between two sequential spikes:

$$\Phi(t) = 2\pi i + 2\pi \frac{t - t_i}{t_{i+1} - t_i}, \quad t_i \leq t < t_{i+1}. \quad (4.11)$$

The probability density of the phase difference $P(\phi)$ with wrapped phase difference $\phi(t)$ defined on the interval $[0, 2\pi]$ is the simplest measure of synchronization. In the case of perfect synchronization $P(\phi)$ is given by a $\delta$-function, $P(\phi) = \delta(\phi - \phi_0)$, where $\phi_0$ is a constant phase shift. In the opposite limit of no synchronization, the probability density $P(\phi)$ is uniform. Between these limiting cases the existence of a well expressed peak in $P(\phi)$ signifies stochastic synchronization. The existence of this peak can be characterized by single numbers, called synchronization indices. We used here two indices. First is the intensity of the first Fourier mode of the probability density $P(\phi)$ defined by (Rosenblum et al., 2001):

$$\gamma^2 = \langle \cos \phi(t) \rangle^2 + \langle \sin \phi(t) \rangle^2, \quad (4.12)$$

where $\langle .. \rangle$ denotes temporal averages. The index $\gamma$ assumes values from 0 (no synchronization) to 1 (perfect phase locking for noise free case). The second index is based on the Shannon entropy of $P(\phi)$ normalized to its maximal value for the uniform distribution. This index involves additional parameter, the number of partitions $N$ of the phase difference:

$$\rho = \frac{S_{\text{max}} - S}{S_{\text{max}}}, \quad (4.13)$$
Here $S = -\sum_{k=1}^{N} p_k \ln p_k$, where $p_k$ is the probability of the phase difference in the $k$-th partition and $S_{max} = \ln N$ is the maximal value of the entropy for the uniform distribution. This definition of synchronization index depends on the number of partitions $N$ used, and are estimated as (Otnes and Enochson, 1972): $N = \exp[0.626 + 0.4 \ln(M - 1)]$, where $M$ is the number of samples of the phase difference.

### 4.4 Results

First I consider the bifurcations in the deterministic model ($\epsilon = 0$). I used AUTO software package (Doedel et al., 2001) to perform the bifurcation analysis of the model. Figure 4.5 shows the bifurcation diagram of the model for the bifurcation parameter $I(t) = I_{dc}$. The system goes through saddle-node bifurcations at points SN1, SN2, and SN3 for the approximate bifurcation parameter values of 0.2517 $\mu$A/cm$^2$, 0.2515 $\mu$A/cm$^2$, and 0.2501 $\mu$A/cm$^2$ respectively. A pair of stable and unstable periodic orbits are bifurcated through the saddle-node bifurcation of periodic orbits at point SN3. The unstable part vanishes through a subcritical Hopf bifurcation at point HB1 for $I_{dc} \approx 0.622 \mu$A/cm$^2$ making the fixed point unstable. At point HB2, the system undergoes a supercritical Hopf bifurcation and the fixed point loses its stability giving birth to a stable periodic orbit.

Figure 4.6 shows the frequency of the stable (filled circles) and unstable (empty circles) periodic solutions of the deterministic model versus input DC current. According to the classification, first proposed by Hodgkin (1948), the discontinuous nature of the F/I (frequency versus input current) curve, with oscillations arising with nonzero frequencies, indicates that the model exhibits type II dynamics. In contrast type I dynamics is characterized by continuous F/I current that shows oscillations arising at arbitrary low frequencies.
Figure 4.5: The bifurcation diagram of the deterministic model neuron shows maximal value of the membrane potential as a function of bifurcation parameter $I_{dc}$. Solid (dotted) line denotes stable (unstable) fixed points whereas filled (empty) circles denote stable (unstable) periodic orbits. SN and HB denote saddle-node and Hopf bifurcations respectively. (b) shows enlarged part of (a).
Figure 4.6: Frequency of periodic orbits of the deterministic model as a function of bifurcation parameter $I_{dc}$. Filled circles represent stable whereas empty circles represent unstable periodic orbits. (b) shows enlarged part of (a).
Next I studied firing characteristics, firing rate and coefficient of variation (CV), of the model neuron when stimulated with OU noise of different variances. CV is a measure of spike train irregularity and is defined as the standard deviation divided by the mean interspike interval,

\[ CV = \frac{\sqrt{\langle \Delta T^2 \rangle}}{\langle T \rangle} \]  

(4.14)

where \( \langle \Delta T^2 \rangle = \langle (T - \langle T \rangle)^2 \rangle \) is the variance and \( \langle T \rangle \) is the mean of interspike intervals, respectively. For a Poissonian spike train CV=1, whereas a periodic spike train leads to CV=0. For the rest of the discussion the background current \( I_0 \) is kept fixed at 0.15 \( \mu \)A/cm\(^2\) and only OU noise parameters are varied. Figure 4.7(a) shows the firing rate whereas Fig. 4.7(b) shows the CV as a function of the correlation time \( \tau \) of the stimulus; circles denote \( D = 30 \mu \)A\(^2\)/cm\(^4\) and squares denote \( D = 40 \mu \)A\(^2\)/cm\(^4\). Notice that the firing rate goes through maxima as \( \tau \) increases whereas CV increases monotonically with the increase in \( \tau \). Thus with the increase in correlation time, keeping variance of the noise fixed, the spike train becomes more irregular. Furthermore, for increasing noise variance, \( D \), the firing rate and the maxima are shifted to higher values of \( \tau \).

Inspection of Fig. 4.8(a) reveals that two non-coupled neurons in the absence of common fluctuating stimuli, driven only by a constant bias current, do not show any tendency to fire together. And their responses are mostly dominated by the internal noise in the absence of a structured stimulus. But, when they are stimulated with common OU noise of appropriate strength and frequency contents, their responses become better synchronized (Fig. 4.8(b)). Note that due to the intrinsic noise, the two cells will never become perfectly synchronized.

To investigate phase synchronization in model cells caused by common random stimuli and its dependence on the frequency contents of the input signal, two non-coupled neurons
Figure 4.7: Firing characteristics of the model neuron as a function of correlation time, $\tau$, of the OU noise for different values of noise variance $D$: circles represent $D = 30 \, \mu A^2/cm^4$ and squares represent $D = 40 \, \mu A^2/cm^4$. (a) shows firing rate versus $\tau$ and (b) shows CV versus $\tau$. 
Figure 4.8: Membrane potentials of two non-coupled model neurons. (a): In the absence of external input. (b): The cells are stimulated with common OU noise of variance $D = 40 \mu A^2/cm^4$ and correlation time $\tau = 2$ ms. Note the tendency of the cells to fire in synchrony.
Figure 4.9: Probability densities of the phase difference of the two non-coupled model neurons, stimulated with common OU noise of variance $D = 30 \mu A^2/cm^4$. (a) for $\tau = 0.01$ ms and (b) for $\tau = 2$ ms.
Figure 4.10: Synchronization indices for two non-coupled model neurons when stimulated with common OU noise for different values of the noise variance $D$: circles represent $D = 30 \mu A^2/cm^4$ and squares represent $D = 40 \mu A^2/cm^4$. (a) and (b) show synchronization indices versus correlation time of the input signal.
Figure 4.11: Cross-correlation histogram for two non-coupled model cells, stimulated with OU noise having parameters $D = 30 \mu A^2/cm^4$ and $\tau = 2$ ms. Synchronization index, $\gamma_{1,1}$, in this case is 0.53.
are stimulated with the common OU noise. For very small correlation time $\tau = 0.01$ ms the probability density of their phase differences is uniform as shown in Fig. 4.9(a), indicating lack of synchronization. But for $\tau = 2$ ms a pronounced peak can be seen in the probability density (Fig. 4.9(b)) indicating a preferred value of the phase difference. The two synchronization indices, computed as explained in 4.3, are plotted in Fig. 4.10 as a function of correlation time of the input signal; circles denote $D = 30 \mu A^2/cm^4$ and squares denote $D = 40 \mu A^2/cm^4$. Although the two indices differ quantitatively, their qualitative behavior is similar. The two non-coupled cells show almost no synchronization for small correlation times. But as the correlation time increases the cells begin to synchronize better and the cells show optimal synchronization for a critical value of correlation time. If the correlation time is increased further, the quality of synchronization decreases. We note that the maximum in synchronization indices appears at $\tau = 2$ ms, independent of the noise variance.

Typically, interactions between pairs of neurons are assessed by constructing cross-correlation histogram (CCH) (Rodieck, 1967). It describes the firing rate of one neuron as a function of time before and after the spike in second neuron. A sharp peak around zero delay in CCH reflects spike synchronization between the two cells, and width of the peak serves as a measure of time scale of these interactions. The method of construction of CCH is described in detail on page 48. Let us consider a CCH for a case when the two non-coupled model cells are stimulated with the OU noise of variance $D = 30 \mu A^2/cm^4$ and correlation time $\tau = 2$ ms. The narrow peak in Fig. 4.11 represents synchronization at a very short time scale. The synchronization index in this case is $\gamma = 0.53$. The standard deviation of the input signal to produce such a tight synchrony is large as compared to the currents received by the ganglion cells ($\approx 0.5 \mu A/cm^2$). When the model cells are driven
Figure 4.12: Synchronization index for weak common input. The stimulus is OU noise with variance $D = 0.25 \, \mu A^2/cm^4$. 
with the OU noise of standard deviation 0.5 $\mu$A/cm$^2$, their responses show no synchronization (4.12). Thus, common random stimulus of physiologically relevant strength fail to account for the tight synchrony.

Strong enough electrical coupling between pair of cells modeled by Hodgkin-Huxley equations is known to synchronize their solutions. Thus the model cells are coupled through a gap junction, that is a term $I_{\text{gap}} = -g_{\text{gap}}(V - V_{\text{pre}})$, where $g_{\text{gap}}$ is the gap junction conductance and $V_{\text{pre}}$ is the presynaptic membrane potential, is added to Eq. (4.1) of the model. Next I estimate magnitude of the gap junction conductance required for the two coupled cells to exhibit tight synchrony, when stimulated with an input signal of physiologically relevant strength. The dependence of the synchronization index $\gamma$ on the the gap junction conductance $g_{\text{gap}}$, when the two coupled model cells are stimulated with the OU noise of variance $D = 0.25 \mu$A$^2$/cm$^4$ and correlation time $\tau = 2$ ms, is shown in Fig. 4.13. For very small values of $g_{\text{gap}}$ the model cells lack synchronization, but as $g_{\text{gap}}$ is increased the cells become better synchronized. For $g_{\text{gap}} \geq 0.4 \text{ mS/cm}^2$, the cells exhibit almost perfect synchronization. From Fig. 4.13 it is clear that for the pair of model cells to synchronize on a small time scale, when the synchronization index $\gamma$ is approximately 0.53, $g_{\text{gap}} \approx 0.08 \text{ mS/cm}^2$ is required.

### 4.5 Discussion

The question whether neurons receiving the same input will fire at nearly the same times is very important from the perspective of neural encoding. Because if they do, that is if the neurons are reliable, then, they can use temporal coding to transmit information to downstream neurons. Since the simulated model cells show synchronized firing (4.8), depending on the characteristics of common inputs, this suggests, in agreement with the experimental
Figure 4.13: Synchronization index for two model cells coupled through gap junction versus gap junction conductance. The stimulus is OU noise with parameters $D = 0.25 \mu A^2/cm^4$ and $\tau = 2$ ms.
findings, that these cells are reliable. The results of this chapter, thus, support the view that the synchronization underlies the reliable discharge times of the neurons. The reliability increases as the correlation time of the input increases, for strong enough input, but as the correlation time is increased further, the cells become less reliable. This shows that the reliable spiking of the cells strongly depends on the frequency contents of the input signal. It is worth mentioning that based on the model of noise used, one might observe different behavior. For instance, when the non-coupled model neurons are stimulated (data not shown) with the model of OU noise that did not conserve the total power in the signal as its correlation time was varied, they showed monotonic decrease in reliability with the increase in the correlation time. That is, neurons behave reliably when the stimulus contained more power at higher frequencies. This is the conclusion reached by many studies (Mainen and Sejnowski, 1995; Schneidman et al., 1998; Yamanobe and Pakdaman, 2002). Note that the criterion used here to assess reliability is different from other experimental and theoretical studies.

In this chapter, I investigated bifurcations in the model neurons of cat retinal ganglion cells, and studied the dependence of their firing characteristics on the parameters of OU noise. This kind of stimulus mimics the synaptic drive in the neurons, and has been used extensively in theoretical studies (Tuckwell et al., 2002; Middleton et al., 2003; Lindner, 2004; Moreno and Parga, 2004) of neuronal responses. The firing rate exhibits maxima at a critical value of the correlation time and this maxima shifts to a higher value of correlation time as the variance of OU noise increases. When stimulated with common OU noise, a pair of non-coupled model cells show phase synchronization. This synchronization in their responses is quantified with the two synchronization indices, and its dependence on the frequency contents and variance of the input signal is studied. It is observed that the model
cells synchronize better for input signals of appropriate strength, and that they display optimal synchronization for a certain cut off frequency.

The simulations show that tight spike synchrony, observed in experiments, for the model cells cannot be explained with the shared common noisy inputs. But as suggested by many experimental studies (Mastronarde, 1983a,c; DeVries, 1999; Hu and Bloomfield, 2003), it is possible to have model cells, coupled through gap junction, synchronize at a small time scale with common noisy stimuli of physiologically relevant strength. We estimated the gap junction conductance to be approximately 0.08 mS/cm$^2$ for the model cells to exhibit tight synchrony.
Chapter 5

Summary

Visual stimuli can synchronize responses of neuronal populations in several ways. In this thesis, I have used computer simulations to explore stimulus-induced synchrony in the cat retina.

A two-layered feedforward neural network model of a circuit that connects photoreceptor cells to X type ganglion cells in cat retina has been described. The first layer simulates the behavior of photoreceptor and bipolar cells, whereas the second layer simulates the behavior of ganglion cells. Using descriptive modeling approach, the spatial responses of the first layer are modeled by a difference of gaussians. Whereas the cells of the second layer are modeled mechanistically using a noisy, leaky integrate and fire model. It is shown that this simple network model is capable of reproducing experimentally measured spatial and temporal tuning curves of ganglion cells. The model is then used to explore correlated spiking activity between the neighboring ganglion cells under uniform illumination. Common input only to ganglion cells does not synchronize the X type neighboring ganglion cells on the time scale of 2–10 ms, as is observed in experimental studies. However, a gap junction between ganglion cells can synchronize their responses. It is found that a gap junction of
conductance 0.02 mS/cm² gives rise to the observed correlations between their spike trains.

Furthermore, the framework of phase synchronization is used to study stimulus-induced synchrony in a conductance-based mathematical model for cat retinal ganglion cells. The model cells include internal noise sources that are statistically independent in different neurons. For Ornstein-Uhlenbeck noise as stimulus, firing characteristics of a single model neuron as a function of the stimulus parameters are investigated. It is found that the firing rate exhibits maxima at a critical value of the correlation time and this maxima shifts to a higher value of correlation time as the variance of OU noise increases. Phase synchronization of the uncoupled neurons to common Ornstein-Uhlenbeck noise is characterized by various synchronization indices including the one that is based on the Shannon-entropy of the probability distribution of phase differences. The dependence of phase synchronization on the noise variance and frequency contents is studied. It is found that phase synchronization becomes optimal for a certain cut off frequency of the common noise source. For a pair of neurons to display tight synchrony when stimulated with common stimulus of physiologically relevant strength, a gap junction coupling is required.
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Appendix A

Thermal activation by power-limited colored noise

A.1 Introduction

Ever since the pioneering work of Smoluchowsky (Smoluchowski, 1913), scientists were fascinated by the conceptual richness and predictive power of the evolving theory of stochastic processes. Applications of such theory are ubiques and range from chemical reaction rates (for an excellent and comprehensive review, see Hänggi and Borkovec, 1990), over quantum optics and atomic optics to models of neuroscience (Kemptner et al., 1998) and cell biology (Falcke et al., 2000; Shuai and Jung, 2002).

The general subject is rooted in the study of the motion of small particles suspended in a fluid and moving under the influence of random forces that result from collisions with molecules of the fluid propelled by thermal fluctuations, or in short the phenomenon of Brownian motion (Einstein, 1905, 1926). In early studies, the fluctuations occur on a time
scale which is very much shorter than that of the Brownian particle. On the time scale of the Brownian particle, the correlation function of the random force $\xi(t)$ driving the Brownian particle can then be assumed to be a $\delta$-function, i.e.

$$\langle \xi(t) \rangle = 0$$
$$\langle \xi(t)\xi(t') \rangle = 2\delta(t - t').$$ (A.1)

This assumption considerably simplifies the problem, because it allows one to treat the stochastic dynamical motions as a Markov process for which many methods and approximation schemes are available (van Kampen, 1992; Stratonovich, 1963; Wax, 1954; Risken, 1984). Fluctuations that can be treated under this assumption are often termed white noise. The hallmark of white noise is its infinite variance. Although on a first glance this seems unphysical, it is not. It reflects the compression of the originally finite collision time $t_c$ during which the Brownian particle interacts with a molecule into an infinitesimally small time interval conserving the interaction energy.

In the physical world, the assumption that the fluctuations are fast in comparison to the relevant system time scales may not always be true. In a neuronal system, for example, fluctuations associated with the opening and closing of calcium channels are slow in comparison with those associated with the opening and closing of sodium and potassium channels. To approximate such fluctuations by noise-terms that are $\delta$-correlated would be inappropriate, and the resulting model would produce inaccurate predictions. One of the simplest examples of time-correlated noise is Gaussian noise $\varepsilon(t)$ with zero mean and an
exponential correlation function, i.e.

\[
\langle \varepsilon(t) \rangle = 0
\]
\[
\langle \varepsilon(t)\varepsilon(t') \rangle = \frac{D}{\tau} \exp \left( -|t - t'| \right),
\]
(A.2)

with variance \( \sigma^2 \equiv \langle \varepsilon^2 \rangle = D/\tau \). In the limit \( \tau \to 0 \), the correlation function approaches the \( \delta \)-function and thus \( \varepsilon(t) \) is white noise if the noise strength \( D \) is kept constant. The linear Ornstein-Uhlenbeck process (with zero mean)

\[
\dot{\varepsilon} = -\frac{1}{\tau} \varepsilon + \frac{\sqrt{D}}{\tau} \xi
\]
(A.3)

with \( \xi(t) \) being characterized by Eq. (A.1) is consistent with the correlation function in Eq. (A.2) (transients neglected) and can be used as a generator of exponentially correlated noise. Eq. (A.3) can be integrated, i.e.

\[
\varepsilon(t + \delta t) = \varepsilon(t) \exp \left( -\frac{\delta t}{\tau} \right) + \frac{\sqrt{D}}{\tau} \exp \left( -\frac{t + \delta t}{\tau} \right) \int_t^{t+\delta t} \exp \left( \frac{s}{\tau} \right) \xi(s) \, ds
\]
(A.4)

The philosophy behind the parameterization of the Ornstein-Uhlenbeck noise by the noise strength \( D \) is to preserve the ”action” of the noise on the position of a Brownian particle \( x(t) \) driven by \( \varepsilon(t) \) in the limit \( \tau \to 0 \). For example in the case of simple Brownian motion

\[
\dot{x} = \varepsilon(t),
\]
(A.5)
where \( x(t) \) is the position of the Brownian particle, we define the action of the noise \( \varepsilon(t) \) as the change of the position of the Brownian particle within the time interval \( \delta t \), i.e.

\[
\delta x = x(t + \delta t) - x(t) = \int_t^{t+\delta t} \varepsilon(s) \, ds.
\]  
(A.6)

Integrating Eq. (A.3) from \( t \) to \( t + \delta t \) one finds

\[
\varepsilon(t + \delta t) - \varepsilon(t) = -\frac{1}{\tau} \int_t^{t+\delta t} \varepsilon(s) \, ds + \frac{\sqrt{D}}{\tau} \int_t^{t+\delta t} \xi(s) \, ds
\]  
(A.7)

and thus by inserting Eqs. (A.7) and (A.4) into Eq. (A.6)

\[
\delta x = \int_t^{t+\delta t} \varepsilon(s) \, ds = -\tau \varepsilon(t) \left( \exp \left( -\frac{\delta t}{\tau} \right) - 1 \right) \\
+ \sqrt{D \left( 2\delta t - 3\tau + 4\tau \exp \left( -\frac{\delta t}{\tau} \right) - \tau \exp \left( -\frac{2\delta t}{\tau} \right) \right)} G(1)
\]  
(A.8)

where \( G(a) \) is a random number drawn from a Gaussian distribution with variance \( a \).

In the limit \( \tau \to 0 \) (at constant \( D \)), only the first term under the square root of Eq. (A.8) is nonzero, yielding the action

\[
\delta x = \sqrt{2D\delta t} \tilde{G}_1
\]  
(A.9)

consistent with the white-noise Langevin equation \( \dot{x} = \xi(t) \).

The philosophy for my approach here is different. The starting point is a system of interest, represented by the system variable \( x(t) \), is driven by a fluctuating force \( \varepsilon(t) \) with correlation time \( \tau \). The variance \( \sigma^2 \) of the noise \( \varepsilon(t) \) is considered fixed and the effects of such noise on \( x(t) \) is studied as the correlation time \( \tau \) is changed. The white-noise limit \( \tau \to 0 \) is now different from the white noise limit in the interpretation above, as the
variance of noise—like in a real physical system—does not grow to infinite. The action of such noise on a Brownian particle with position \(x(t)\), described by Eq. (A.5) vanishes in the limit \(\tau \to 0\) since \(D = \sigma^2 \tau\) vanishes in Eq. (A.8).

This kind of colored noise is best parameterized by the correlation time \(\tau\) and the variance \(\sigma^2\). The generating stochastic differential equation reads

\[
\dot{\varepsilon} = -\frac{1}{\tau} \varepsilon + \sqrt{\frac{\sigma^2}{\tau}} \xi(t).
\]  

(A.10)

where \(\xi(t)\) is characterized by Eq. (A.1). Since the equation is linear, the autocorrelation function can be easily determined as

\[
K(t - t') \equiv \langle \varepsilon(t)\varepsilon(t') \rangle = \sigma^2 \exp \left( -\frac{|t - t'|}{\tau} \right).
\]  

(A.11)

The spectral density, given through Wiener-Khintchine theorem by the Fourier transform of the autocorrelation function

\[
S(\omega) = \int_{-\infty}^{\infty} \langle \varepsilon(t)\varepsilon(0) \rangle \exp(-i\omega t) dt = 2\sigma^2 \frac{\tau}{1 + \omega^2 \tau^2},
\]  

(A.12)

vanishes for \(\tau = 0\) and for \(\tau \to \infty\) at a given value of the variance of the noise \(\sigma^2\). As \(\tau \to 0\), the spectral density becomes flat, i.e. the noise more white, but the total power, i.e. the area under the spectral density

\[
\int_{-\infty}^{\infty} S(\omega) d\omega = \int_{-\infty}^{\infty} S(\omega) \exp(i\omega t)|_{t=0} = 2\pi K(0) = 2\pi \sigma^2,
\]  

(A.13)

is finite and conserved. The spectral density is at maximum when \(\omega \tau = 1\).
A.2 Colored Noise driven bistable flow

Here I consider a one dimensional bistable flow driven by colored noise. This can be envisioned as the overdamped motion of a Brownian particle in a bistable potential $V(x)$. The position $x(t)$ of the particle obeys the differential equation

$$m\gamma \ddot{x} + V'(x) = \varepsilon(t), \quad (A.14)$$

with the potential

$$V(x) = \frac{b}{4}x^4 - \frac{a}{2}x^2, \quad (A.15)$$

where, $a$ and $b$ are positive-valued parameters. For further discussion it is useful to bring Eqs. (A.14) and (A.15) together with Eq. (A.10) in dimensionless form. With the new dimensionless variables

$$\bar{x} \equiv \frac{1}{\alpha}x \equiv \sqrt{\frac{b}{a}}x$$
$$\bar{t} \equiv \frac{1}{\beta}t \equiv \frac{a}{m\gamma}t$$
$$\bar{\varepsilon} \equiv \frac{1}{\delta}\varepsilon \equiv \frac{b}{a^3}\varepsilon$$
$$\bar{\xi}(\bar{t}) \equiv \sqrt{\beta}\xi(\beta t) = \sqrt{\frac{m\gamma}{a}}\xi\left(\frac{m\gamma}{a}t\right), \quad (A.16)$$

and parameters

$$\bar{\sigma}^2 \equiv \frac{a^3}{b}\sigma^2$$
$$\bar{\tau} = \frac{m\gamma}{a}\tau, \quad (A.17)$$
and subsequent omission of all bars in the new variables and parameters, one finds

\begin{align*}
\dot{x} &= x - x^3 + \varepsilon \\
\dot{\varepsilon} &= -\frac{1}{\tau}\varepsilon + \sqrt{\frac{\sigma^2}{\tau}} \xi(t),
\end{align*}

(A.18)

with

\begin{align*}
\langle \xi(t) \rangle &= 0 \\
\langle \xi(t)\xi(t') \rangle &= 2\delta(t - t').
\end{align*}

(A.19)

The solution for a not-normalized system, specified by any set of parameters \(a, b, \gamma\) and \(m\) can be obtained from the single solution of the scaled system by using the above transformation rules. For example, from escape rates \(\bar{r}(\bar{\tau}, \bar{\sigma}^2)\) obtained from the scaled system, one can obtain the specific escape rates with parameters \(a, b, \gamma, m\) by

\[
\bar{r}(a, b, m, \gamma, \tau, \sigma^2) = \frac{1}{\beta(\gamma, a, m)} \bar{r}(\bar{\tau}(\bar{\tau}, a, \gamma, m), \bar{\sigma}^2(\bar{\sigma}^2, b, a)).
\]

(A.20)

The Fokker-Planck equation for the probability density in the extended \(x - \varepsilon\) phase space is given by

\[
\frac{\partial P(x, \varepsilon, t)}{\partial t} = -\frac{\partial}{\partial x} \left( x - x^3 + \varepsilon \right) P(x, \varepsilon, t) \\
+ \frac{1}{\tau} \varepsilon P(x, \varepsilon, t) + \frac{\sigma^2}{\tau} \frac{\partial^2}{\partial \varepsilon^2} P(x, \varepsilon, t)
\]

(A.21)
A.2.1 Escape rates for small correlation times

In the limit of small correlation times, i.e. $\tau \ll 1$ (in the dimensionless variables introduced above), the variable $\varepsilon$ in the second equation of Eqs. (A.19) approaches a steady state at a rate $1/\tau$, much faster than the variable $x$. On the time scale of the variable $x$, we can thus set $\dot{\varepsilon} = 0$ thus finding $\varepsilon = \sqrt{\sigma^2 \tau} \xi(t)$ which can be inserted into the first equation of Eqs. (A.19), yielding the white-noise Langevin equation for $x$

$$
\dot{x} = x - x^3 + \sqrt{\sigma^2 \tau} \xi(t),
$$

(A.22)
equivalent to the Smoluchowski-equation for the probability density $P(x,t)$

$$
\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x} (x - x^3) P(x,t) + \sigma^2 \tau \frac{\partial^2}{\partial x^2} P(x,t).
$$

(A.23)

Following Kramer’s theory (for a review, see Hänggi and Borkovec, 1990), the activation rate out of one of the potential minima at $x = \pm 1$ (in dimensionless units) is given by

$$
r(\tau, \sigma^2) = \frac{1}{\sqrt{2\pi}} \exp \left( -\frac{1}{4\tau \sigma^2} \right).
$$

(A.24)

In the limit $\tau \to 0$, the escape rate thus vanishes exponentially (see also Fig. A.3). This is clearly a consequence of the fact that the spectral density of $\varepsilon(t)$ vanishes at $\tau = 0$. 
A.2.2 Escape rates for large correlation times

For large correlation times, i.e. $\tau \gg 1$, the variable $\varepsilon$ is much slower than the system variable $x$. Thus, the system variable $x$ approaches a quasi steady-state $x_{ss}$

$$x_{ss} - x_{ss}^3 + \varepsilon = 0 \quad (A.25)$$

within a time interval in which the auxiliary-variable $\varepsilon$ does not change. In other words, the system variable $x$ is relaxing to the minima of the potential

$$V(x, \varepsilon) = \frac{1}{4} x^4 - \frac{1}{2} x^2 - x \varepsilon \quad (A.26)$$

given by the roots of Eq. (A.25). A transition of the system variable, say from the left to the right, happens when the left potential minimum disappears (see Fig. A.1), i.e. when $\varepsilon$ exceeds the critical value

$$\varepsilon_{crit} = \frac{2}{\sqrt{2\tau}}. \quad (A.27)$$

Thus, the mean first passage-time $T_{MFPT}$ is given by the mean first passage time of the auxiliary variable $\varepsilon$, governed by Eq. (A.10) to reach the critical value $\varepsilon_{crit}$ starting out with an initial value $\varepsilon_0 = -\varepsilon_{crit}$. The solution of this problem is standard (Gardiner, 1985) and reads

$$T_{MFPT} = \frac{\tau}{\sigma^2} \int_{-\varepsilon_{crit}}^{\varepsilon_{crit}} \exp\left(\frac{y^2}{2\sigma^2}\right) dy \int_{-\infty}^{y} \exp\left(-\frac{x^2}{2\sigma^2}\right) dx. \quad (A.28)$$

Most importantly, it is obvious from Eq. (A.28) that the escape rate $r = 1/(T_{MFPT})$ decreases proportional to $\tau^{-1}$ as $\tau \to \infty$. I evaluate the integrals numerically and find that the result compares favorably with simulations (see next section) shown in Fig. A.3. The approach presented here is similar to the one put forward in (Tsironis and Grigolini, 1988;
Figure A.1: The potential $V(x, \varepsilon)$ is shown for indicated values of $\varepsilon$. 
de La Rubi et al., 1988) except that I do fully evaluate the mean first passage time without a weak-noise approximation.

Thus, the escape rate, at small $\tau$, first increases with increasing correlation time, reaches a maximum and then decreases. For $\tau \to 0$, the spectral density of the fluctuations becomes flat and decreases in magnitude all over the frequency range relevant for barrier crossing, thus leading to a decreasing escape rate. For $\tau \to \infty$, the system slows down and thus also escape events.

### A.3 Stochastic Simulations

Several numerical approaches were developed to simulate bistable systems driven by colored noise. A precise approach based on the numerical calculation of the smallest eigenvalue of the corresponding Fokker-Planck equation (A.21) (see e.g. Risken, 1984) under appropriate boundary conditions was utilized by Jung and Hänggi (Jung and Hänggi, 1988). An alternative approach based on direct numerical simulation of the Langevin equations was introduced by Fox and Roy (Fox et al., 1988) and Fox (Fox, 1991). Here I follow the latter procedure to simulate Eqs. (A.19) and determine the mean time $\langle T \rangle$ in between two subsequent escape events over the barrier. The escape rate can be obtained as $r = 1/\langle T \rangle$.

The scheme in Eq. (A.8) is exact to all orders in the time-step $\delta t$ but only valid for free Brownian motion. In the presence of a force field systematic schemes up to higher orders can be derived (Fox, 1991), but are cumbersome and not more efficient than first order schemes. Adding the force $x - x^3$ to the Langevin equation and expanding the scheme in Eq. (A.8) down to terms up to linear orders in $\delta t$ yields the first-order solver
A first-order solver of Eq. (A.18) is given by

\[
x(t + \delta t) = x(t) + \delta t \left[ x(t) - x^3(t) + \varepsilon(t) \right],
\]

\[
\varepsilon(t + \delta t) = \varepsilon(t) \left( 1 - \frac{\delta t}{\tau} \right) + \sqrt{\frac{2\delta t}{\tau}} G(1).
\] (A.29)

For a given set of parameters \((\tau, \sigma)\), Eqs. (A.29) were iterated with a time step of \(\delta t = 10^{-3}\) until \(10^4\) escape events occurred. An escape event was identified by a transition between \(x = -1\) and \(x = 1\) (see Fig. A.2). Time intervals between successive events are recorded and the average time interval, an approximation for \(\langle T \rangle\) that becomes exact for infinitely long recording times is shown in Fig A.3. As predicted by the theory above, the escape rate for small \(\tau\) increases for increasing \(\tau\), reaches a maximum, and then falls off \(\propto 1/\tau\).

The approximative results for small and large \(\tau\) presented above compare favorably with the simulations.

**A.4 Threshold crossing driven by energy-limited colored noise**

In this section I consider the effects of noise on a simple device responds with a pulse \(\delta(t - t')\) when it’s input \(\varepsilon(t)\) crosses a threshold-value, \(\varepsilon_0\), from below. The device is driven by Gaussian colored noise with constant total power. In order for the threshold crossing rate to be non-infinite due to jitter around the threshold, at least the second moment \(M_2\) of the spectral density \(S(\omega)\), i.e.

\[
M_n = \int_{-\infty}^{\infty} \omega^n S(\omega) d\omega
\] (A.30)
Figure A.2: Numerical simulation of Eqs. (A.29) for $\sigma^2 = 0.2$ and for indicated values of $\tau$. First ten escape events are shown and marked by triangles.
Figure A.3: Numerical calculation of the escape rate versus \( \tau \) for indicated values of \( \sigma^2 \). Asymptotic predictions for small \( \tau \) Eq. (A.24) and large \( \tau \) Eq. (A.28) are shown by dotted and dashed lines, respectively.
or equivalently, the second derivative of the two-point autocorrelation function has to exist (Jung and Mayer-Kress, 1995). A possible realization of such a stochastic process \( \varepsilon(t) \) is twice low-pass filtered Gaussian white noise, i.e. (Jung, 1994)

\[
\ddot{\varepsilon} = -\frac{1}{\tau_2} \varepsilon + \frac{1}{\tau_2} h \\
\dot{h} = -\frac{1}{\tau_1} h + \frac{\sqrt{\sigma^2 (\tau_1 + \tau_2)}}{\tau_1} \xi(t),
\]

(A.31)

with

\[
\langle \xi(t) \rangle = 0 \\
\langle \xi(t) \xi(t') \rangle = 2\delta(t - t').
\]

(A.32)

with \( \langle \varepsilon \rangle = 0 \) and \( \langle \varepsilon^2 \rangle = \sigma^2 \) and cut-off frequencies \( 1/\tau_1 \) and \( 1/\tau_2 \), which I assume to be equal here, i.e. \( \tau_2 = \tau_1 = \tau \). The two-point autocorrelation function and the spectral density of \( \varepsilon(t) \) can be readily obtained as

\[
\langle \varepsilon(t) \varepsilon(t') \rangle = \frac{D}{2\tau} \left( 1 + \frac{|t - t'|}{\tau} \right) \exp \left( -\frac{|t - t'|}{\tau} \right)
\]

(A.33)

and

\[
S(\omega) = \frac{2\tau \sigma^2}{(1 + \tau^2 \omega^2)^2}.
\]

(A.34)

The threshold crossing rate can be obtained readily (Jung and Mayer-Kress, 1995),

\[
r_{th} = \frac{1}{2\pi \tau} \exp \left( -\frac{\varepsilon_0^2}{2\sigma^2} \right)
\]

(A.35)
Rewriting (A.32) as
\[
\ddot{\epsilon} + \frac{2}{\tau} \dot{\epsilon} + \frac{1}{\tau^2} \epsilon = \frac{\sqrt{2\sigma^2 \tau}}{\tau^2} \xi(t)
\] (A.36)

the average energy is given by
\[
E = \frac{1}{2} \langle \dot{\epsilon}^2 \rangle + \frac{1}{2\tau^2} \langle \epsilon^2 \rangle = \frac{\sigma^2}{\tau^2}
\] (A.37)

The threshold crossing rate in terms of the correlation-time \( \tau \) and the average energy \( E \) of the noise is given by
\[
\dot{r}_{th} = \frac{1}{2\pi \tau} \exp \left( -\frac{\epsilon_0^2}{2\tau^2 E} \right).
\] (A.38)

Thus, at constant average energy \( E \), the escape rate increases with increasing correlation time for small \( \tau \), reaches a maximum at \( \tau_m = \epsilon_0 / E \).

**A.5 Summary and Discussion**

I have shown that the escape rate of a bistable system driven by colored noise with constant power exhibits a bell-shaped dependence on the correlation time of the noise. This behavior is different from previous studies where the power (or equivalently variance) of the noise decreases with increasing correlation time. There, as to be expected, the escape rate decreases monotonously with increasing correlation time of the noise (Jung and Hänggi, 1988). In the limit \( \tau \to 0 \), the escape rate vanishes since the spectral density vanishes uniformly (white noise with finite variance), while in the limit \( \tau \to \infty \) the escape slows down decreasing the escape rate. Similarly, threshold crossing rates in colored-noise driven threshold detectors also exhibit a bell-shaped dependence on the correlation time, if the average energy of the noise is kept constant.