Modelling phase-locking in electrically-coupled networks of inhibitory cortical interneurons

Hugh Robinson[1], Kunichika Tsumoto[2], Nathan Gouwens[1], Takashi Tateno[1,3] and Kazuyuki Aihara[2,4]

[1] Department of Physiology, University of Cambridge, CB2 3EG, U.K.
[2] Aihara Complexity Modelling Project, ERATO, JST, Shibuya-ku, Tokyo, 151-0065 Japan
[3] Graduate School of Engineering Science, Osaka University, 560-8531, Japan.
[4] Institute of Industrial Science, The University of Tokyo, 153-8505, Japan.
E-mail: hpcr@cam.ac.uk, tsumoto@aihara.jst.go.jp, ng268@cam.ac.uk,
t-tateno@bpe.es.osaka-u.ac.jp, aihara@sat.t.u-tokyo.ac.jp

Abstract—Networks of fast-spiking inhibitory interneurons in the neocortex, coupled by both excitatory and inhibitory connections, are implicated in the synchronization of cortical firing at high frequencies (30-100 Hz). We have fitted physiological phase response curves of fast-spiking interneurons with a piecewise linear model, with added intrinsic noise. To describe entrainment of cell firing to that of coupled neighbours, we analysed the deterministic and stochastic bifurcations of the model, deriving conditions for phase-locking amongst neurons and characterizing its sensitivity to the parameters of synaptic connection strength and to noise.

1. Introduction

Rhythmic oscillations of concerted electrical activity can occur in the neocortex at gamma frequencies (30-80 Hz), and are thought to be associated with various cognitive tasks including sensory processing, motor control, and feature binding [1]. The synchronized firing of interneurons has been implicated in generating these rhythms [2], and models of interneuron activity suggest that network oscillations depend on mutually inhibitory synaptic conductances. However, in heterogeneous network models, coherent activity can be fragile and dependent on parameter balancing [3, 4]. Intriguingly, it has recently been found that fast-spiking (FS) interneurons are coupled by mutually excitatory electrical synapses in addition to mutual inhibitory synapses [5, 6]. Recently, using the technique of conductance injection [7] (dynamic clamp) we have experimentally measured the effect of firing in coupled presynaptic cells on the phase of periodic firing in fast-spiking interneurons [8]. This was used to construct a model of the physiological phase response relationship of fast-spiking neurons. The aim was to provide an accurate quantitative description of the dynamics of synchronization, with parameters which reflect the strength of synaptic connections. Here, we describe the bifurcations of fundamental periodic points of the deterministic, piecewise-linear phase response model. We then describe a stochastic extension of the model which takes into account intrinsic noise of cell firing, and we analyse its stochastic bifurcations.
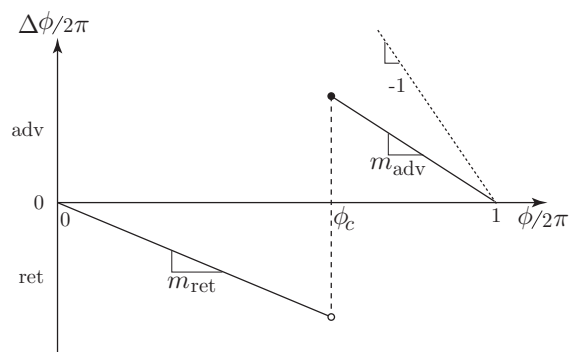

Figure 1: Schematic diagram of the phase response curve.

2. Definition of the phase response curve of FS neurons for unitary presynaptic input

Figure 1 shows a schematic diagram of an experimentally-determined phase response curve, which is given by the following piecewise linear function:

$$\Delta\phi(\phi) = \begin{cases} -m_{\text{ret}}\ \phi & (0 \leq \phi < \phi_c) \\ -m_{\text{adv}}\ \phi + m_{\text{adv}} & (\phi_c \leq \phi < 1) \end{cases} \quad (1)$$

where m_{ret} and m_{adv} are parameters which describe the slopes of phase retarding and advancing regions of the relationship, respectively, determined predominantly by the strength of GABA inhibitory connections and electrical connections, respectively, and ϕ_c represents the transition point between the regions.

Let us consider the dynamics of a system where a periodic stimulation (a presynaptic action potential) is

applied every $T_s = 1/\omega$ time units to an FS cell which has unperturbed firing frequency Ω ($T = 1/\Omega$). The phase $\phi_n = t_n/T$ denotes the phase right before the time of the n-th stimulus. Then we have the following piecewise linear map for FS cell model from $[0, 1)$ onto itself:

$$\phi_{n+1} = \phi_n + \Delta\phi(\phi_n) + \theta \quad (\text{mod } 1) \equiv F(\phi_n, \theta) \quad (2)$$

where $\theta = T_s/T$ is the amount of detuning of the firing phase from stimulus phase which occurs during each stimulus period. Fixed points of this map represent phase-locking or synchronization of firing with stimulus (postsynaptic cell with presynaptic cell). We have analyzed bifurcations of fixed points of periods 1, 2 and 3 for this deterministic map, and computed the Arnold tongue structure of synchronized regions for parameters m_{ret}, m_{adv} and ϕ_c.
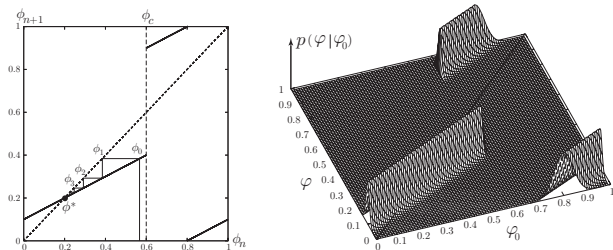
1 : 1 phase-locking response.($\omega = 72.73$)
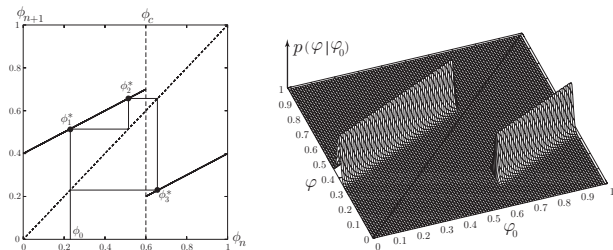
4 : 3 phase-locking response.($\omega = 57.14$)

Figure 2: (*Left*) Deterministic map $F(\phi, \theta_M)$ and its orbits $\{\phi_n\}$, (*Right*) Corresponding stochastic kernel function $p(\varphi|\varphi_0)$. Parameters $m_{\text{ret}} = 0.5, m_{\text{adv}} = 0.5, \phi_c = 0.6, \Omega = 80$. The phase sequence $\phi_0, \phi_1, \cdots$ asymptotically converges to a fixed or a periodic point which corresponds to $M : N$ phase-locking. Each stochastic kernel function $p(\varphi|\varphi_0)$ is calculated for fixed noise intensity $\sigma = 0.02$.

3. Extending to the stochastic case

However, a fixed period T for the natural oscillation of cells is an unsatisfactory idealization. In reality, individual FS neurons show random variations in firing period of 10% or more. This intrinsic noise has a major impact on the rate and extent of synchronization. Therefore, we extend the deterministic map to the case with noise. Let us consider the 1D discrete-time dynamical system in Eq.(2) defined on an interval $S = [0, 1)$ in the presence of additive noise:

$$\phi_{n+1} = F(\phi_n, \theta_M) + \xi_n, \qquad \varphi_n \in S \quad n = 0, 1, 2, \cdots, \quad (3)$$

where $\{\xi_n\}$ are independent random perturbations. More precisely, assuming that ξ is a Gaussian random variable, its density function is given by

$$p(\xi) = \frac{1}{\sqrt{2\pi}\sigma} \exp\left[-\frac{\xi^2}{2\sigma^2}\right] \quad (4)$$

where σ is a standard deviation. Numerical simulation of this map accurately reproduced the rate and extent of experimentally-measured synchronization.

First, we define a kernel function p. Let $p(\varphi|\varphi_0)d\varphi$ denote the probability for the phase to be within $(\varphi, \varphi + d\varphi)$ on the condition that the initial phase was φ_0. According to a general definition of distribution functions, we can define a kernel function $p(\varphi|\varphi_0)$ using a conditional distribution function under Eq.(3):

$$p(\varphi|\varphi_0)d\varphi = \text{Prob}\{\varphi \leq \Phi \leq \varphi + d\varphi | \Phi_0 = \varphi_0\} \quad (5)$$

The stochastic kernel $p(\varphi|\varphi_0)$ is a transition probability density function (PDF), and the relation gives a Markov operator.

Next, we consider a linear operator $\mathcal{P}$ in the presence of noise. Using the kernel function p, the linear operator $\mathcal{P}$ is defined as follows[9]:

$$\mathcal{P}h(\varphi) = \int_S p(\varphi|\varphi_0)h(\varphi_0)d\varphi_0, \qquad h \in \mathcal{D} \quad (6)$$

where $\mathcal{D}$ is the set of absolutely integrable non-negative functions with a unit L^1 norm on S and $h(\varphi)$ denotes a PDF on R. The linear operator $\mathcal{P}$ is called the Markov operator with the stochastic kernel $p(\varphi|\varphi_0)$, or the Frobenius-Perron operator[9]. The sequence $\{h_n(\varphi)\}$ produced by the operator $\mathcal{P}$ always approaches a unique invariant density asymptotically as $n \to \infty$. Figure 2 shows examples of deterministic maps and corresponding stochastic kernel functions for 1:1 and 4:3 phase-locking responses.

4. Calculation of stochastic bifurcations

To characterize phase-locking in this stochastic framework, and its sensitivity to the stimulus parameters, we calculated stochastic bifurcations of the phase response relationship. One "classical" definition of stochastic bifurcation, phenomenological or P-bifurcation, is based on the topological structure
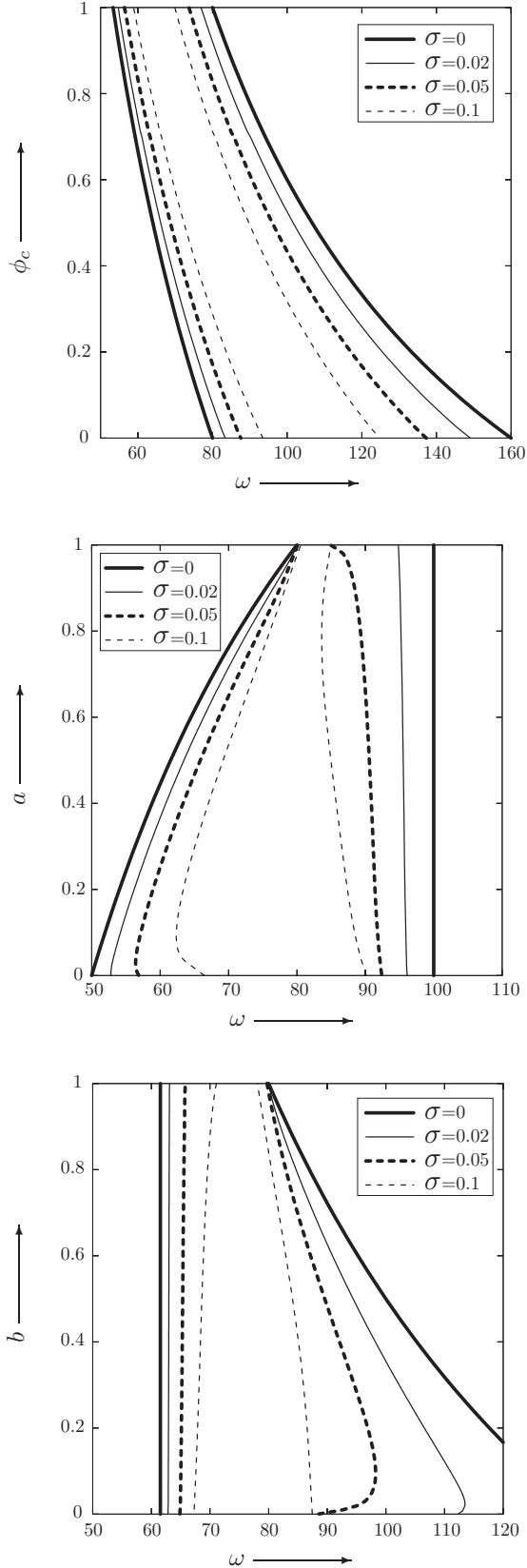
Figure 3: Bifurcation curves for the change of the intensity of the noise. Each bifurcation curves corresponds to that of 1 : 1 phase-locking responses.

of invariant densities, while another definition, the D-bifurcation, is based on analyzing the stability of multiple invariant measures[10]. However, with these definitions, it can be impossible to find bifurcations near saddle-node bifurcation points of the corresponding deterministic map as pointed out in [11, 12, 13]. For this reason, we used an alternative definition for stochastic bifurcation, based on the transitions between complex and real eigenvalues of $\mathcal{P}$ [11, 14]. In general, eigenvalues ($\mu_1 \geq \mu_2 \geq \cdots$) and corresponding eigenfunctions $\{e_i\}$ of the linear operator $\mathcal{P}$ with the kernel $p(\varphi|\varphi_0)$ can be found. The sequence $\{h_n(\varphi)\}$ of the PDF obtained by iterative application of $\mathcal{P}$ always converges to an invariant density function. In this sense, the invariant density h^*, or the eigenfunction e_1, corresponding to eigenvalue μ_1, has only static information about the operator $\mathcal{P}$, while subsequent eigenvalues determine the convergence speed of the sequence. In other words, eigenvalues μ_i and eigenfunctions e_i with $i \geq 2$ have dynamic information about $\mathcal{P}$. A stochastic bifurcation is defined by when the eigenvalues of the operator change their values from complex to real abruptly (not smoothly) at a possible stochastic bifurcation point [11, 15, 12]. In particular, we have examined the second and third eigenvalues, since the larger the modulus of the eigenvalue, the greater a factor it is in determining the dynamics or evolution.

In practice, since the operator $\mathcal{P}$ is of infinite dimension, we estimated approximate values for these eigenvalues of $\mathcal{P}$ by replacing $\mathcal{P}$ with a finite dimensional square matrix obtained by discretizing the phase φ_0 and φ [11, 15], with criteria for sufficient resolution to ensure accuracy. In these numerical calculations, the stochastic kernel $p(\varphi|\varphi_0)$ corresponds to the stochastic (transition probability) matrix denoted by a real $N_a \times N_a$ square matrix A. The advantage of this method is its relative simplicity together with the fact that it replaces $\mathcal{P}$ with a stochastic matrix whose properties are well known. To investigate the characteristic of the kernel, we apply spectral analysis to the stochastic matrix. As an example of this, Figure 3 shows 1:1 stochastic phase-locking regions (Arnold tongues) calculated in this way, for parameters ϕ_c, m_{ret} and m_{adv} at various noise intensities.

5. Conclusions

We have analysed the bifurcations of a realistic model of the physiological phase response relationship of fast-spiking interneurons, which are believed to play a central role in binding together episodes of synchronized oscillation in the cortex. Intrinsic noise of neurons was included in the model, and we characterized its stochastic bifurcations according to a definition which is sensitive to dynamics of the stochastic

map, in addition to the invariant density of the phase. This model may serve as a component of large-scale network models of spatial synchronization of periodic activity in the cortex.

Acknowledgments

References

[1] G. Buzsaki and A. Draguhn "Neuronal oscillations in cortical networks", Science 304:1926-1929, 2004.

[2] M.A. Whittington and R.D. Traub, "Inhibitory interneurons and network oscillations in vitro", Trends Neurosci. 26:676-682.

[3] J.A. White et al. " Synchronization and oscillatory dynamics in heterogeneous, mutually inhibited neurons", J. Comput. Neurosci. 5:5-16, 1998.

[4] J.A. White et al. "Networks of interneurons with fast and slow gamma-aminobutyric acid type A (GABAA) kinetics provide substrate for mixed gamma-theta rhythm", PNAS 97:8128-8133, 2000.

[5] M. Galarreta and S. Hestrin "A network of fast-spiking cells in the neocortex connected by electrical synapses", Nature 402:72-75, 1999.

[6] J.R. Gibson, M. Beierlein and B.W. Connors "Two networks of electrically coupled inhibitory neurons in neocortex", Nature 402:75-79, 1999.

[7] H.P.C. Robinson and N. Kawai, "Injection of digitally synthesized synaptic conductance transients to measure the integrative properties of neurons", J. Neurosci. Methods 49:157-165, 1991.

[8] N.W. Gouwens and H.P.C. Robinson, "Phase-resetting by combined gap-junctional and inhibitory coupling amongst fast-spiking cortical interneurons", Society for Neuroscience meeting, San Diego, 2004.

[9] A. Lasota, M.C. Mackey, "*Chaos, Fractals and Noise*: Stochastic aspects of dynamics," 2nd ed. Springer-Verlag New York Inc., 1994.

[10] L. Arnold, "*Random Dynamical Systems*" Springer, Berlin, 1998.

[11] S. Doi, J. Inoue, and S. Kumagai, "Spectral Analysis of stochastic phase lockings and stochastic bifurcations in the sinusoidally forced van der Pol oscillator with additive noise," J. Stat. Phys. 90:1107–1127, 1998.

[12] T. Tateno and Y. Jimbo, "Stochastic mode-locking for a noisy integrate-and-fire oscillator," Phys. Lett. A 271:227–236, 2000.

[13] T. Tateno, "Noise-induced effects on period-doubling bifurcation for integrate-and fire oscillators," Phys. Rev. E 65:021901, pp.1–10, 2002.

[14] J. Inoue, S. Doi, and S. Kumagai, "Numerical analysis of spectra of the Frobenius-Perron operator of a noisy one-dimensional mapping: Toward a theory of stochastic bifurcations," Phys. Rev. E 64:056219, pp.1–7, 2001.

[15] T. Tateno, "Characterization of stochastic bifurcations in a simple biological oscillator," J. Stat. Phys., 92:675–705, 1998.