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Towards blueprints for network architecture, biophysical dynamics and signal transduction

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We review mathematical aspects of *biophysical dynamics*, *signal transduction* and *network architecture* that have been used to uncover functionally significant relations between the dynamics of single neurons and the networks they compose. We focus on examples that combine insights from these three areas to expand our understanding of systems neuroscience. These range from single neuron coding to models of decision making and electrosensory discrimination by networks and populations and also coincidence detection in pairs of dendrites and dynamics of large networks of excitable dendritic spines. We conclude by describing some of the challenges that lie ahead as the applied mathematics community seeks to provide the tools which will ultimately underpin systems neuroscience.

Keywords: neural signal processing; coupled oscillators; biological neural networks; information theory; stochastic neuroscience

1. Introduction

McCullough & Pitts (1943) demonstrated the computational power that emerges from highly simplified interacting binary neuron-like units, foreshadowing an explosion of research into information processing by such 'artificial' neural networks. In this framework, the strength of interactions fully determines how incoming signals are processed, as the spiking dynamics of individual neurons are not modelled. Meanwhile, complex biophysical models based on Hodgkin & Huxley's (1952) formalism have revealed how single isolated neurons exploit a wide array of dynamical mechanisms to produce diverse temporal patterns of voltage spikes. Surprisingly, these research frameworks have remained largely distinct. This motivates the main question we address: how do critical features of the nonlinear spiking dynamics of single neurons combine with network architecture to determine a mechanistic 'blueprint' for the principles of signal processing in the nervous system?

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One contribution of 23 to a Triennial Issue 'Mathematics and physics'.

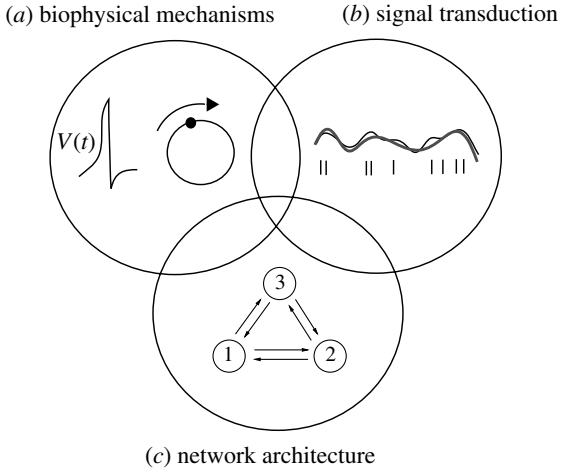

Figure 1. The mathematical neuroscience community has achieved substantial success in the analysis of single-cell biophysical mechanisms (here represented by the reduction of Hodgkin–Huxley type models to phase variables), neural signal transduction (e.g. the reconstruction of incoming signals from spike trains) and the general theory of networks of coupled dynamical systems (e.g. rings of cells as shown here). We focus on the overlap of these traditionally rather separate paths of research.

2. Three fundamental areas of mathematical neuroscience

(*a*) *Area 1: single cell mechanisms*

The area of single cell dynamics is arguably the best developed area of mathematical neuroscience. Many of the models presently in use can be viewed as refinements or reductions of Hodgkin–Huxley type nonlinear ODE models (Hodgkin & Huxley 1952), which represent the neuron as a nonlinear circuit producing temporal spikes (action potentials) in transmembrane voltage $V(t)$ (see figure 1*a*). Indeed, the parameter values and the formulae that describe the dynamics of membrane conductances have been successfully fit to experimental data for a stunning variety of cell types. The resulting differential equations are typically far too complex to be studied analytically, but techniques including time-scale separation and averaging yield more tractable models. A typical example is that of Pinsky & Rinzel (1994), who reduce the biophysically detailed multicompartment model of a hippocampal neuron by Traub *et al.* (1991) to a system containing just two compartments and a minimal set of currents. Phase (Kopell & Ermentrout 1984; Brown *et al.* 2004) or integrate-and-fire reductions go further by describing neurons in terms of single variables, with consequences that we will revisit in §3*a*.

Reduced models illuminate the fundamental mechanisms underlying the dynamics of spiking cells. Furthermore, reduced versions of a range of Hodgkin–Huxley type models often share the same characteristics and can be categorized as dynamically equivalent. Each such category is typified by a reduced 'canonical model' exhibiting the dynamical features typical of the entire cell class (Izhikevich 2000). Similarly, the mathematical mechanisms that underlie rhythmic behaviour, such as tonic spiking and bursting can be

categorized using normal forms that describe typical transitions (bifurcations) between quiescent and oscillatory dynamics (Rinzel 1987; Izhikevich 2000; Golubitsky *et al.* 2001). A complementary approach, perhaps most relevant for the present article, is to categorize neural models based on their response to external inputs, for instance, by defining phase-response curves determining spike timing or firing rate versus input current (f–I) functions determining spike frequency (Rinzel & Ermentrout 1998).

(*b*) *Area 2: signal transduction*

Neural circuitry, from single synapses to large-scale networks, encodes and transmits incoming signals. We express this operation as $y=K(x)$, where x represents the incoming signal; $K(\cdot)$ represents a (possibly nonlinear) transfer function; and y represents the system output. The definition of the latter depends on the system at hand; often it takes the form of a temporal sequence of action potentials (a spike train) or a firing rate. Spike trains are typically stochastic, yet correlated with the input x to a cell. Perkel & Bullock (1968) began a program that sought the neural code, which would relate a specific spike train pattern to a given input, with the neural dynamics viewed as a 'black box' filter K. In this approach to systems neuroscience, information theory and pattern classification methods are used to formalize the correlations between the spike times of sensory neurons and stimuli (Rieke *et al.* 1997; Borst & Theunissen 1999; Dayan & Abbott 2001). Significant progress has been made in fly vision, where the analysis of spike-triggered stimulus ensembles reveals strong correlations between spike patterns and low-dimensional projections from a high-dimensional stimulus space (Rieke *et al.* 1997; Brenner *et al.* 2000). The relationship between natural scene statistics and optimal stimulus encoding (Barlow 1961) remains an active area of investigation. A popular approach is to derive models of neural processing (the transfer functions K) by requiring that they optimally encode those stimuli with spatio-temporal statistics which match those of naturally occurring sensory inputs (reviewed in Simoncelli & Olshausen 2001).

Another present research area is *temporal decision making*, involving neural integration of information over hundreds of milliseconds to seconds followed by an explicit behavioural choice (Wong & Wang 2006). Here, K characterizes the computations that transform competing sensory evidence for several possible alternatives into the behavioural output corresponding to the most likely alternative. Empirical studies are probing the extent to which the brain implements the algorithm of Wald's sequential probability ratio test (SPRT), which enables decisions with the *optimal* combination of speed and accuracy (reviewed in Gold & Shadlen 2002).

(*c*) *Area 3: network architecture*

The statistical analysis of connectivity patterns in complex networks is a blossoming field (Albert & Barabási 2002). However, the question of how these connectivity patterns impact network dynamics is not well explored. Coupled cell theory (Stewart *et al.* 2003) provides a start. While it applies directly to systems of Hodgkin–Huxley type, it does not address the quantitative behaviour of individual cells covered in §2*a*, but rather focuses on general patterns in the network dynamics. A coupled cell system can be described by a graph that identifies which cells are

coupled to which, and which cells and couplings are of equal type. The evolution of such a network is described by a system of ODEs. Identical 'node' symbols for individual cells imply identical internal dynamics and identical arrow types imply identical coupling. Based on architecture alone, we can identify: (i) invariant 'synchronized' subspaces on which the coordinates of certain cells are equal, (ii) non-generic bifurcations, and (iii) 'spatio-temporally symmetric' periodic solutions with well-defined frequency and phase relations between cells. Some consequences of (i) and (iii) will be explored in §3*a* and we refer the reader to the references for the fascinating consequences of (ii).

3. Links between the fundamental areas

(*a*) *Combining areas 1 and 3: single-cell dynamics and network architecture*

In this section, we describe results about biological network dynamics that follow from additional assumptions on the dynamics of individual cells and their interactions. We first assume that each cell possesses a strongly attracting limit cycle and can be described by a single phase variable $\theta_j \in \mathbb{S}^1$. In this case, the invariant 'synchronized' subspaces that arise from network architecture imply strong restrictions on the dynamics of coupled cell systems (Golubitsky *et al.* 2005, 2006). Similar conclusions hold for integrate and fire neurons with excitatory or gap junction coupling. As an example, consider the network of two identical, identically coupled phase oscillators with $\theta_1' = f(\theta_1, \theta_2)$ and similarly for the evolution of θ_2 under the replacement $1 \leftrightarrow 2$. (In a neural context, the interaction function f often has the form $R(\theta_i)I(\theta_j,t)$, where R characterizes the phase sensitivity of a neuron and I characterizes a synaptic input that depends explicitly on the presynaptic firing phase.) The structure of this oscillator network immediately implies that the diagonal $\Delta_{1,2} = \{\theta_1 = \theta_2\}$ is flow invariant (i.e. if $\theta_1(t') = \theta_2(t')$ for a specific time t', then it must be that $\theta_1(t) = \theta_2(t)$ for all time t). As a consequence, if one thinks of the two-phase oscillators as moving beads on a hoop, then the beads cannot pass one another. This simple observation has important consequences: (i) the frequencies of the two cells in this network must be equal and (ii) the two cells modelled by the oscillators are either perfectly synchronous or spike in alternation (crossing a distinguished phase value $\theta_s \in \mathbb{S}^1$ is interpreted as a spike). Furthermore, the relations (i) and (ii) hold for any pair of coevolving cells (Golubitsky *et al.* 2005, 2006). In a network of more than two cells, coupled cell theory implies that a pair of cells, i and j, coevolves if and only if every other cell in the network connects to both cells, i and j, with the same number (which may be zero) of arrows of each type, and the arrows from i to j are the same in number and type as those from j to i. Therefore, in the network (*c*) of figure 2 only the pair (1, 2) coevolves, while in networks (*a*) and (*b*) all pairs of cells coevolve.

Coevolution of more than two cells allows one to group cells into *ordered collections*, within which frequencies are identical, the ordering of phases is dynamically invariant and the sequence of spikes is fixed. This restricts the type of solutions that a phase-reduced network can support. The networks in figure 2*a*,*b* are symmetric under interchange of cells 1 and 2. Moreover, all the three cells coevolve and hence no solutions in which cells fire at different frequencies are possible. On the other hand, the three-cell network in figure 2*c*

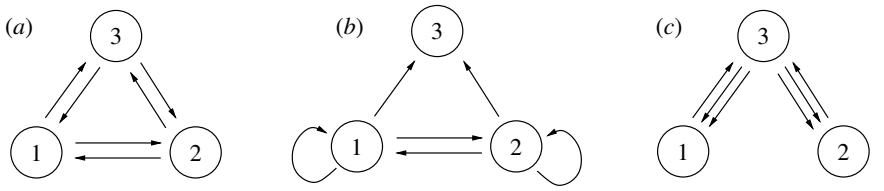

Figure 2. (*a*,*b*) Examples of three-cell networks in which all cells coevolve: assuming one-dimensional cell dynamics, they cannot support multifrequency oscillations. (*c*) A network in which cell 3 can robustly oscillate at twice the frequency of cells 1 and 2, as only cells 1 and 2 coevolve.

has the same symmetry, but cell 3 does not coevolve with cells 1 and 2, and there are no restrictions on its frequency. Using group theoretical methods, one can see that the symmetry of this network implies that the solutions in which cells 1 and 2 are one-half period out of phase and cell 3 oscillates at twice their frequency can be supported, in fact by open sets of ODEs with this architecture. This type of network was analysed by Pervouchine *et al.* (2005) in the context of theta rhythms in the hippocampus and entorhinal cortex, and similar multifrequency solutions were central in explaining the behaviour observed in experiments.

(*b*) *Combining areas 2 and 3: signal transduction and network architecture*

In this section, we discuss an example of how neural signal transduction has been studied in structured networks without incorporating the underlying single-cell dynamics. Rather, simple first-order kinetics are assumed to govern a network of neural ensembles, each of which is characterized by a firing rate versus input or 'f–I' function. Such networks have classically been used to model pattern identification and classification (reviewed in Cowan 2004), and more recently, the temporal dynamics of decision making (Usher & McClelland 2001), which we now discuss. The underlying models take the form of simplified, stochastic Wilson–Cowan equations (Wilson & Cowan 1973)

$$\dot{y}_j = -y_j + f\left(\sum_i K_{ij} y_i + x_j\right) + \xi_j, \tag{3.1}$$

where f is the 'f–I' function; y_j is the firing rate of ensemble j; the x_j are 'input' rates representing evidence for the various alternatives; and the final noise term ξ_j represents internal and incoming fluctuations. The weights K_{ij} determine network architecture and interactions. If f is piecewise linear, then the K_{ij} may be chosen so that noisy incoming signals are processed via the optimal SPRT (discussed in §2*b*), illustrating the interplay between neural architecture and processing of noisy signals in the discrimination between two alternatives (Brown *et al.* 2005; Bogacz *et al.* in press). The requisite conditions on the K_{ij} are precisely those found by Seung (1996) to give a *line attractor*: a neutral direction in which the system's intrinsic dynamics vanish, allowing direct integration of inputs x_j over time (see figure 3).

(*c*) *Combining areas 1 and 2: signal transduction and single-cell mechanisms*

In *temporal* neural codes, the precise timing of action potentials reflects specific features of a dynamic stimulus; but how does single-cell dynamics, characterized by diverse and nonlinear membrane conductances and the spatial

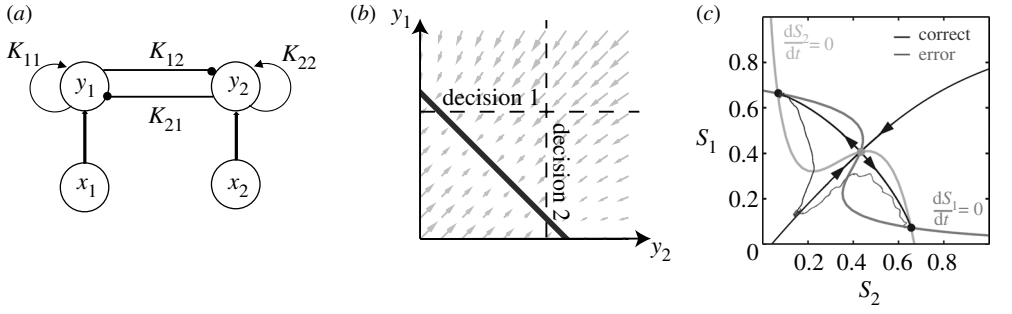

Figure 3. Under certain conditions, the network (*a*) implements the SPRT algorithm. This requires a line attractor for the firing rates y_j (bold line in (*b*)) for the 'intrinsic' dynamics (i.e. absent inputs x_j). Following arrival of inputs, a decision corresponding to input j is made when firing rate y_j crosses its threshold (dotted lines). (*c*) The spiking neuron model presented in Wong & Wang (2006; from which figure is adapted) implements similar dynamics, but with certain deviations from 'pure' line attractor dynamics (and hence the SPRT) consistent with features of empirical data (see references therein).

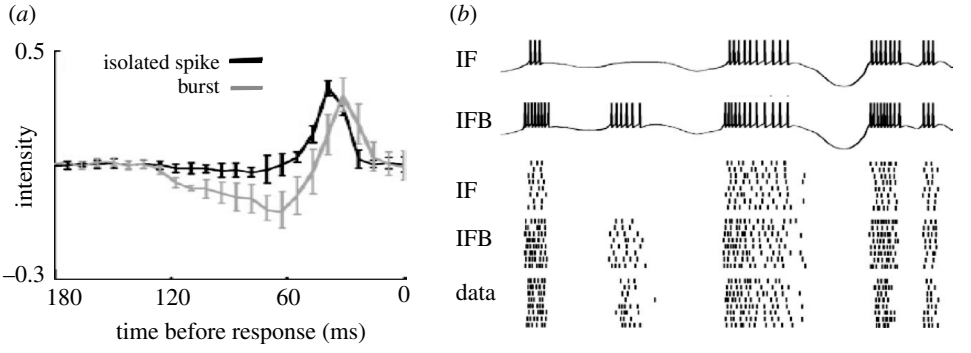

Figure 4. (*a*) Average stimulus preceding an isolated spike (black) and a burst (grey) in a thalamic relay cell in the LGN of the cat visual system. The stimulus was a clip from the movie 'Raiders of the lost ark'. (*b*) Typical voltage response of an IF and an IFB model neuron (top) and comparison of spike times over multiple trials with both models to actual data (raster plots, bottom). Figure adapted from Lesica & Stanley (2004).

extent of dendrites, determine such a code? Formalizing how distinct temporal coding schemes arise from these conductances is an emerging field of mathematical neuroscience.

(*d*) *Burst coding*

A typical patterning of action potentials is a rapid *burst* of sequential spikes (e.g. second trace in figure 4*b*; see also Coombes & Bressloff 2005), raising the question what stimulus features such bursts represent. Physiological and modelling studies of pyramidal neurons in the lateral geniculate nucleus (LGN) area, which processes visual inputs, offer a clue: in these cells, the *termination* of an extended negative current input generates a burst. A recent study has shown that certain temporally rich stimuli, such as natural scenes, contain periods of prolonged hyperpolarization that reliably elicit burst responses (Lesica & Stanley

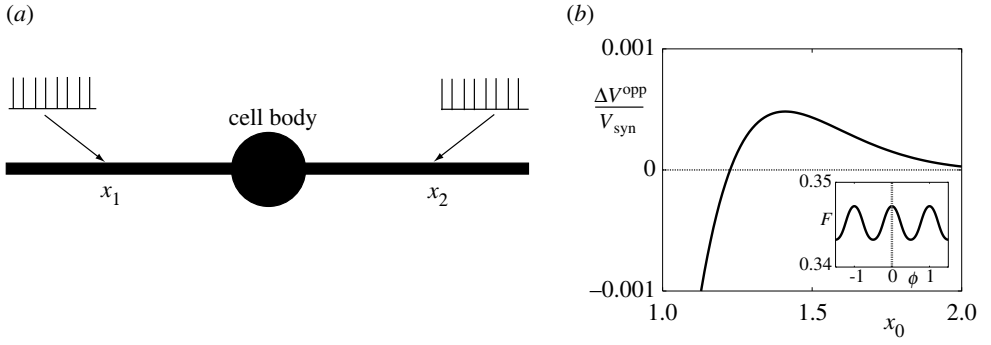

Figure 5. (*a*) A caricature of a bipolar cell with a central cell body and two dendritic branches. (*b*) A plot of the function $\Delta V^{\text{opp}}_{(2)}/V_{\text{syn}}$ with $D=\tau=\Delta=1$, showing that the largest variation in somatic response (for inputs on either side of the soma) occurs at a non-zero value of x_0 at roughly 1.41. The inset shows the corresponding plot of the function F, which is a simple measure of the large time voltage response at the soma. This would cause a corresponding periodic variation in the cell firing rate as a function of ϕ.

2004). This is observed by computing the average stimulus that elicits a burst of spikes and comparing it to the average stimulus that elicits an isolated spike (figure 4*a*). Furthermore, this selectivity for stimulus features can be captured by an integrate-and-fire-and-burst (IFB) model neuron (Smith *et al.* 2000), but not a standard integrate-and-fire (IF) model (figure 4*b*). These studies are an elegant example of how single-cell biophysical dynamics (in this case, a slow T-type calcium current which generates bursts) can shape the temporal code.

(*e*) *Coincidence detection in dendrites*

Both mammals and birds use 'coincidence-detector' neurons in the auditory brainstem, which have *bipolar* dendrites (see figure 5), to detect temporal differences in sound arrival times between ears (the interaural time difference) to an astounding accuracy of 10–100 μs; this enables localization of a sound source. Agmon-Snir *et al.* (1998) show that the bipolar cell structure, combined with the spatial segregation of inputs, enhances their performance at this task in comparison with 'point neurons' (lacking dendrites). Here, we revisit their work, showing how the interacting bipolar components (viewed as a small cellular network) interact with membrane dynamics to enable transduction of input signals (interaural time differences) into neural outputs (here, voltage at the cell body).

Consider an (infinite) neural cable with membrane potential $V(x, t)$ at position $x\in\mathbb{R}$ and time $t\in\mathbb{R}^+$, and synaptic inputs at positions x_1 and x_2 governed by

$$V_t = -\frac{V}{\tau} + DV_{xx} + I_{\text{syn}}, \tag{3.2}$$

where the synaptic input $I_{\text{syn}} = I_{\text{syn}}(x, t) = \varepsilon\sum_{n=1,2}\delta(x-x_n)g(x_n, t)(V_{\text{syn}} - V(x, t))$, with $g(x_n, t) = \sum_{m\in\mathbb{Z}^+}\delta(t-(m+\phi_n)\Delta)$. This represents a postsynaptic current induced by the arrival of a train of incoming spikes, arriving periodically with a frequency $1/\Delta$ and of strength $\varepsilon>0$. The term $(V_{\text{syn}} - V(x, t))$ is an excitatory 'shunt' that pushes the membrane potential towards the reversal potential for the synapse,

$V_{\rm syn}>0$, and underlies the nonlinearity of synaptic processing. Here, we take the phases ϕ_1 and ϕ_2 to be 0 and ϕ, respectively, such that $\phi\in[0,1)$ is a measure of the phase difference between the two incoming signals. The firing rate is observed to be maximal at $\phi=0$ and varies periodically with ϕ, with a minimum at $\phi=1/2$, so that any mechanism that enhances the difference between the maximum and the minimum firing rates improves sound localization. The formal solution to equation (3.2) is

$$V(x,t)=\int_0^t {\rm d}s\int_{-\infty}^{\infty}{\rm d}yG(x-y,t-s)I_{\rm syn}(y,s), \tag{3.3}$$

where we have assumed $V(x,0)=0$ and $G(x,t)={\rm e}^{-t/\tau}{\rm e}^{-x^2/(4Dt)}/\sqrt{4\pi Dt}$ is the Green's function for the cable equation. Note that equation (3.3) only gives V in an implicit form, since $I_{\rm syn}$ also depends directly on V. However, repeated substitution of equation (3.3) into itself generates a (Neumann) series expansion that we may truncate (for sufficiently small ε) to obtain an approximate expression for V in closed form. Writing this expansion in the form $V=\varepsilon V_{(1)}+\varepsilon^2 V_{(2)}+\cdots$ we find $V_{(1)}(x,t)=V_{\rm syn}\sum_n H(x-x_n,t-\phi_n\Delta)$, with $H(x,t)=\sum_m G(x,t-m\Delta)$. At next order we have

$$V_{(2)}(x,t)=-V_{\rm syn}\sum_{n,p}H(x-x_n,t-\phi_n\Delta)H(x_n-x_p,(\phi_n-\phi_p)\Delta), \tag{3.4}$$

where the sums are over spine indices. At this level, we clearly see the effects that the shunting currents can have, as they lead to a nonlinear mixing of the inputs. Consider the cell body to be at $x=0$, so that the cell is partitioned into two dendritic branches with inputs at equal distances, x_0, from the cell body. We distinguish the two important cases: (i) where both inputs are on the same side of the soma (same branch) and (ii) where they are on the opposites sides of the soma (different branches). Denoting the response of the cell body $V(0,t)$ by $V^{\rm same}(t)$ and $V^{\rm opp}(t)$ in the two cases, one may check that $V^{\rm same}(t)$ is always less than $V^{\rm opp}(t)$. Hence, to maximize response at the cell body for *any* ϕ, it is desirable to place inputs on different branches, as it is the case biologically. Assuming that the cell firing rate, f, is a monotonically increasing function of the average somatic voltage, we may answer a related question—how these inputs should be located to maximize the variation of f with ϕ.

After taking the long time average (denoted by angle brackets), we find $\langle V_{(2)}^{\rm opp}\rangle\propto F(x_0,\Delta,\phi)$—a given periodic function of ϕ. Hence, the firing rate, f, will be similarly periodic and will vary most strongly when x_0 is chosen so that $\Delta V=\langle V\rangle|_{\phi=1/2}-\langle V\rangle|_{\phi=0}$ is maximal. Importantly, for $\Delta V^{\rm opp}$, there is an optimal choice of x_0 that can enhance the variation of f over a cycle for a given Δ (figure 5).

4. Combining all three areas

There are many fields of computational neuroscience where elements of signal transduction, single cell dynamics and network architecture have been studied in combination. In this section, we review three examples: long time-scale integration in spiking networks, dynamics of nonlinear dendritic spine networks and models of electrosensory networks. In the first of these, we will see how the biophysical details of single cell dynamics may be encapsulated by a firing rate description similar to equation (3.1); in the latter two, the details of spike timing must be retained.

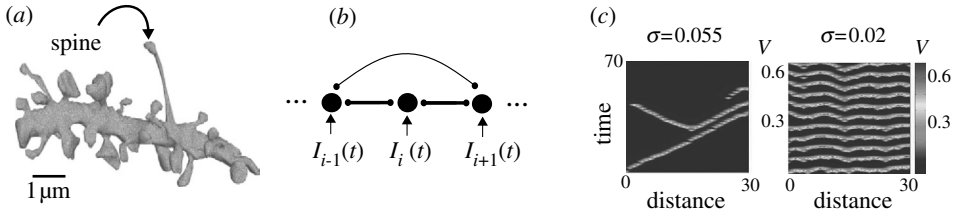

Figure 6. (*a*) A spine studded dendrite (photo from Medical College of Georgia, http://synapses.mcg.edu). (*b*) Schematic of the SDS network, the spine clusters are represented by the black circles and the 'effective' coupling between spines are the links. (*c*) Patterns of activity for weak ($\sigma=0.055$) and strong ($\sigma=0.2$) input intensities. The spine distribution is regular with 30 spines distributed over the cable, and a rectangular action potential shape with $\eta_0 6=\tau_s=1$. Prepared with the help of Yulia Timofeeva.

(*a*) *Temporal integration in spiking networks*

It is a prominent challenge to understand the neurobiological implementation of long time-scale dynamics, such as that required for optimal or temporally extended decision processing (see §3*b*) or for the maintenance of accumulated information over time (Seung 1996; Seung *et al.* 2000), in networks of biophysically based cells. Here, the relevant question is how slow manifolds emerge along which incoming information can be gradually integrated. Seung *et al.* (2000) created a spiking neuron model with this property, exploiting the method of averaging over slow network (synaptic) time-scales to derive a model of the form (3.1), which was used to identify critical parameters. Wong & Wang (2006) applied similar techniques, computing how integration time-scales in a decision task depended on network and single-cell properties. Here, the network of spiking cells is divided into two subpopulations (analogues of y_1 and y_2 in equation (3.1)) representing accumulated inputs (analogues of x_1, x_2) corresponding to the two alternatives. Following averaging, single-cell dynamics are summarized by population input–output relationships (cf. f–I functions; §3*b*), and network architecture allows for both sustained activity and competition between alternatives. The nullclines for the resulting *reduced* system (of the form (3.1)), with trajectories of the *spiking* system, are shown in figure 3*c*. We note that the robustness of integration time-scales to the precise setting of network or cellular parameters is another active area of research: Koulakov *et al.* (2002) show how bistability at the cellular level imparts such robustness to the population, again highlighting the interplay between single-cell and network dynamics and the neural information processing that they can support.

(*b*) *Nonlinear spines and noise-induced wave propagation in dendrites*

More than 100 years ago, Cajal (1998; recent translation) observed small appendages along dendritic shafts which he labelled *spines* (figure 6*a*). Spines serve as junction points between presynaptic axons and postsynaptic dendrites and hence mediate interactions between neurons. Subsequent experiments suggested that signal processing could occur in the spines, the dendrites or in their interaction (London & Hausser 2005). In this section, we consider a mathematical model of a network of interacting nonlinear spines. Despite the fact that these dynamics occur

within a single biological cell, we mathematically treat the spine network similar to a network of interacting neurons. We review how it processes signals that are encoded in the intensity of the stochastic spatially extended dendritic input by organizing the pattern of activation across the spine network.

Building on Baer & Rinzel (1991), Coombes & Bressloff (2003) introduce and analyse a tractable 'spike-diffuse-spike' (SDS) model of a dendrite bearing excitable spines. The dynamics of each spine is modelled with a reduced 'leaky integrate-and-fire' (LIF) process. Spine–spine coupling is mediated by an otherwise passive section of dendrite separating adjacent spine clusters. The cable potential is again modelled by equation (3.2) with the synaptic current replaced by a spine-stem current of the form $Dr_{\rm a}\rho(x)(\hat{V}-V)/r$, where r is the spine-stem resistance and $r_{\rm a}$ is the axial resistance per unit length of cable. Since in real neurons, spines are attached at discrete points along a dendritic branch, the spine density function $\rho(x)$ is taken as $\rho(x)=\bar{n}\sum_m\delta(x-x_m)$ with x_m, the position of the mth spine cluster, and $\bar{n}$ spines per cluster. The jth time that a spike is generated in the mth spine is denoted t_{jm} and is determined according to an LIF process for the spine potential U_m, such that $U_m(t^+)=0$ whenever $U_m(t)=U_{\rm th}$, with

$$\hat{C}\frac{\partial U_m}{\partial t}=-\frac{U_m}{\hat{r}}+\frac{V(x_m,t)-U_m}{r}+\sigma\xi_m(t), \tag{4.1}$$

where $\hat{C}$ and $\hat{r}$ are the spine head capacitance and resistance; inputs $\sigma\xi_m$ are defined below. After a spike, the spine head potential is in a refractory state for a time-period $\tau_{\rm R}$. Since the dynamics of $V(x,t)$ between two adjacent spines is given by a linear cable equation, when $\bar{n}Dr_{\rm a}/r\ll 1$, $V(x,t)$ is well approximated by

$$V(x,t)=\frac{\bar{n}Dr_{\rm a}}{r}\int_0^t\sum_k G(x-x_k,t-s)\,\hat{V}(x_k,s)\,{\rm d}s, \tag{4.2}$$

where G is Green's function of the cable. Here, $\hat{V}(x_m,t)=\sum_j\eta(t-t_{jm})$ represents the effective output of the spines ($\eta(t)$ is the shape of an action potential, here simplified as $\eta_0\Theta(t)\Theta(\tau_{\rm s}-t)$). In total, we have a network of excitable spines where the 'effective' voltage coupling between spines is determined self-consistently via the LIF mechanism (4.1) and equation (4.2). Figure 6*b* shows a schematic of the SDS model.

The temporal forcing of spine m, $\xi_m(t)$, is zero mean Gaussian white noise of intensity σ, which is uncorrelated across the spines network. This models an asynchronous presynaptic pool of neurons driving the spine ensemble. In response to weak stochastic forcing, the SDS model shows sporadic waves of activity separated by periods of quiescent dendritic activity (figure 6*c*). When the intensity of the fluctuations is increased, the noise-induced waves are coherent in time and the periods of activity are spaced at roughly the refractory time, $\tau_{\rm R}$, of the excitable spines. These noise-dependent dynamics are prototypical of a wide field of study in noise-induced transitions in nonlinear systems (see García & Sancho 1999). The noise-induced regularity of the dendritic spine network shown above could serve as a direct code for the intensity of dendritic forcing. Alternatively, as neurons typically have many dendritic branches, the activity in the single branch modelled above could modulate, or perhaps even gate, the neuron's response signals received in *other*

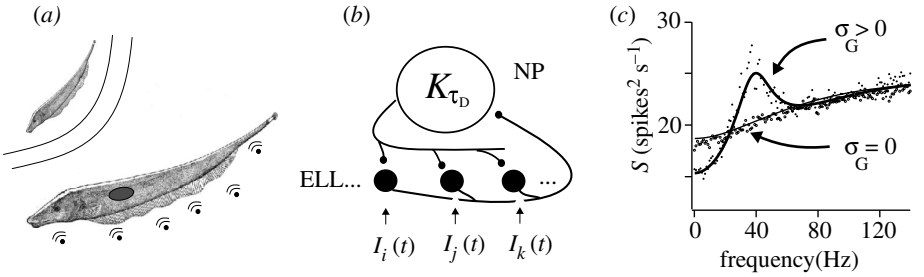

Figure 7. (*a*) An electric fish experiences *global* electrosensory inputs from a communicating fish (upper left) and *local* inputs from swarm of prey Daphnia (bottom right). The filled circle on the body is the approximate size of the receptive field of an ELL pyramidal neuron. (*b*) Schematic of the ELL pyramidal cell population and global inhibitory feedback from populations of bipolar cells in the NP nucleus. (*c*) The spike train power spectrum, S, of a representative neuron in the network when $\sigma_G = 0$ and $\sigma_L = 0.565$ or when $\sigma_G = 0.4$ and $\sigma_L = 0.4$. Simulations of the LIF system are circles and solid lines are from a linear response calculation.

branches (see Jarsky *et al.* (2005) for an example in CA1 hippocampal neurons). In either case, the distinct wave dynamics and subsequent stimulus transfer arise from a network of nonlinear spines, where the effective 'network' architecture is determined self-consistently with the dynamics that it supports.

(*c*) *Stimulus discrimination in the electrosensory system*

The neural correlates of sensory perception are being explored by experimentalists and theorists alike. A feed-forward analysis of sensory systems considers the direct path from afferents (such as photoreceptors) proceeding into the thalamus and terminating in the cortex. A puzzling observation from sensory anatomy is that a majority of the synaptic input to thalamic cells does not originate in lower centres, but rather feeds back from the cortex (Allito & Usrey 2003).

The electrosensory system of weakly electric fish is an example where feedback projections are well mapped and whose effects have been analysed mathematically (Turner *et al.* 1999; Doiron *et al.* 2003, 2004). Electrosensory images to a patch of skin are coded by electroreceptors which in turn project to a population of pyramidal neurons in the electrosensory lateral line lobe (ELL) brain area. In this section, we consider the oscillatory dynamics of the ELL pyramidal cell network in response to signals distinguished by the extent of spatial correlation among inputs to distinct pyramidal cells.

We idealize the stimuli driving the receptive field of the mth pyramidal neuron as $I_m(t) = \sigma_L \xi_m(t) + \sigma_G \xi_G(t)$. $I_m(t)$ is separated into two distinct processes: $\xi_m(t)$ is a local stochastic forcing exclusive to neuron m, modelling a prey input or an uncorrelated background scene. In contrast, $\xi_G(t)$ is a global stochastic input common across all receptive fields, representative of a communication call that drives a large portion of the skin. For simplicity, $\xi_m(t)$ and $\xi_G(t)$ are zero mean Gaussian white noise processes. These two distinct stimuli classes, which the fish must routinely distinguish, are schematically illustrated in figure 7*a*. *In vivo* spike trains from ELL pyramidal cells exhibit an oscillatory response when $\sigma_G > 0$, but not when $\sigma_G = 0$, showing distinct responses to these two categories of stimuli (Doiron *et al.* 2003).

ELL pyramidal neurons do not locally project to one another within the ELL, but they do project to higher brain centres which feedback extensively to the ELL. One centre of interest is a population of bipolar neurons in the nucleus praeminentialis (NP) that project inhibitory inputs to the ELL. To explore the mechanism behind the observed oscillatory spike response to correlated, but not uncorrelated, stochastic forcing, Doiron *et al.* (2003, 2004) modelled the ELL–NP network as a homogeneous ensemble of N LIF neurons. The membrane potential of the mth pyramidal cell $U_m(t)$ obeys

$$\frac{\mathrm{d}U_m}{\mathrm{d}t} = -U_m + \mu + \frac{g}{N}\sum_j \int_0^\infty K_{\tau_\mathrm{D}}(s) y_j(t-s)\mathrm{d}s + I_m(t). \tag{4.3}$$

Here, μ is a static bias current applied to all neurons, and the standard LIF spike-reset rules apply (see §4*b*). The spike train output for neuron j is $y_j(t) = \sum_k \delta(t - t_{jk})$ with t_{jk} as the kth threshold crossing of neuron j, and the feedback from the NP bipolar cells is modelled as a temporal convolution of spike train inputs with the filter $K_{\tau_\mathrm{D}}(t) = \mathrm{e}^{-(t-\tau_\mathrm{D})/\tau_\mathrm{S}}/\tau_\mathrm{S}^2 \Theta(t-\tau_\mathrm{D})$. The inhibition is of strength $g/N<0$, where each inhibitory pulse has a time-scale τ_s, and τ_D represents a fixed delay. A schematic of the ELL–NP network is shown in figure 7*b*.

Restricting σ_G to be at most the same order as σ_L and the feedback strength g to be small, Doiron *et al.* (2004) and Lindner *et al.* (2005) used linear response techniques to analytically describe the spike train of a representative neuron of the ELL network via its power spectrum S (figure 7*c*). A clear peak in S is present when $\sigma_\mathrm{G}>0$, indicative of an oscillation in the spike train. The peak is absent when the correlated forcing is replaced with the uncorrelated forcing ($\sigma_\mathrm{G}=0$). These results match those observed in experiments for similar stimuli conditions (Doiron *et al.* 2003, 2004). Of critical importance is the delay parameter τ_D, which sets the time-scale of the oscillation: the ELL–NP model predicted that delayed inhibitory feedback from the NP to the ELL was responsible for the oscillation. This was subsequently verified by pharmacological blockade of this feedback (Doiron *et al.* 2003). In summary, the combination of the single-cell spiking dynamics (as modelled by a LIF mechanism) and a globally coupled delayed network architecture allows the electrosensory system to code spatially extended input correlations (i.e. prey versus communication style signals) with a temporal organization (i.e. oscillation) of its single neuron responses.

5. Challenges for the future

A central task is to integrate the three theoretical disciplines reviewed here: single neuron dynamics, signal transduction and network architecture. A two-pronged approach is to develop a collection of central examples, or 'neural blueprints', along with allied mathematical toolboxes that abstract the blueprints from specific biological models. Unlike, for example, normal forms and their reduction techniques in ODEs, these blueprints and their associated toolboxes must be motivated and categorized by not only their cellular dynamics and network architectures, but also the qualitative signal transduction functions that they perform.

Blueprints with one or two of the theoretical disciplines have been successfully identified; examples include the blueprint of the phase/IF models and the mathematical toolbox of multiple time-scale analysis for ODEs, the blueprints of small networks producing multifrequency oscillations and the tools of coupled cell theory, and the blueprint of low-dimensional stimulus representations identified with the toolbox of spike-triggered analysis allied with information theory and optimal statistical tests. Finally, the bipolar neuron is another such blueprint, illustrating how the spatial distribution of distinct temporal inputs can maximize a neuron's selectivity for coincident inputs, as analysed through a perturbation analysis.

Successful blueprints at the *overlap* between the three disciplines would show how network architecture and biophysical dynamics combine to enable a particular signal transduction function. The simplified Wilson–Cowan type models with slow manifolds form blueprints for long time-scale neural integration, derived through the toolbox of temporal averaging. The IF representation of the ELL network is another blueprint, here illustrating how *spatial* codes distinguishing stimuli (i.e. global versus local correlations) can be translated into *temporal* codes (i.e. oscillations). Here, the corresponding toolbox is the linear response theory for stochastic networks with feedback, which computes the temporal correlations in network spike times. The recent work on dendritic spine networks suggests a blueprint for spatially extended dynamics in single dendritic branches, derived using the toolboxes of Green's functions and cable theory.

Numerous challenges remain as theoretical neuroscientists seek to find the blueprints and mathematical frameworks that will meet the challenges posed by increasingly rich experimental studies. We list three features of this biological data, one from each of the three fundamental theoretical topics, that we anticipate will be essential in generating these blueprints. *Signal transduction*: evidence for Barlow's hypothesis (1961) that neural systems are optimized to process natural scenes, as illustrated in the thalamic bursting work of Lesica & Stanley (2004) as well as the electric fish prey/communication discrimination shown in Doiron *et al.* (2003, 2004); *network architecture*: there is increasing evidence for non-random connectivity, ranging from topographic arrangement of sensory input to small-scale clustering and structure of cortical connections (Song *et al.* 2005); *single-cell dynamics*: presence of multiple time-scales in the dynamics of single cells such as adaptation and bursting that give rise to long-term correlations in spike times.

Several emerging mathematical methodologies will be of use in developing blueprints that illustrate these and other biological features. We list three of these that we find especially promising in their potential to tie together our three fundamental topics. (i) Event-triggered statistics can be applied to *network* (rather than single cell) activity, identifying features of signals that are encoded owing to network architecture. (ii) The slowly evolving modes of neural populations can be used to build low-dimensional computational (Laing 2006) and analytical (Knight 2000) models of *stimulus-driven* networks; as above, networks with common low-dimensional dynamics could be grouped into common blueprints. (iii) Techniques for the analysis of temporal codes can be applied to deduce how network interactions, rather than membrane dynamics alone, shape selectivity for specific stimuli (Chacron *et al.* 2005; Masuda *et al.* 2005).

In our vision, the future development of neural blueprints, allied with mathematical techniques that allow for their extension and interpretation, will not only inspire the growth of new fields in applied mathematics, but also streamline the process of experimental discovery in neurobiology.

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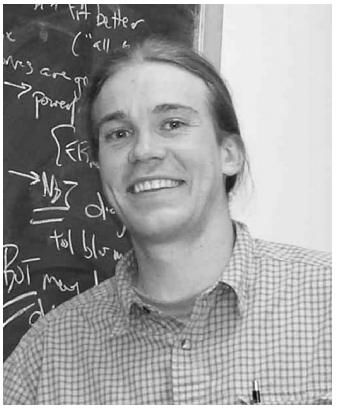

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