

Mathematical modelling of central pattern generators

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INTRODUCTION

Central pattern generators (CPGs) are neural networks that govern the stereotypic aspects of rhythmic motion, such as walking, swimming and running. Though they can be modulated by sensory feedback and higher brain structures, in many animals an isolated CPG is capable of autonomously generating spatio-temporal electrical signals similar to ones that guide the muscles in an intact animal. Thus, the question arises as to how the network self-organizes to produce the appropriate pattern of activity to the muscles. Many CPGs are thought to contain oscillating subnetworks or bursting neurones. In that case, the question becomes one of self-organization of relative phases of the oscillating subunits.

This paper reports on some of the mathematical problems that have arisen in an attempt to understand the structure and function of the swimming CPG of lamprey, an eel-like vertebrate. For more information on the biology of this preparation and the insights provided about the biological structure by the mathematics, see Kopell and Ermentrout (1988, 1989a) and the papers referenced therein. An elementary review article on modelling CPGs is given by Kopell (1988).

DESCRIPTION OF A CLASS OF MODELS

The swimming CPG of the lamprey is a neural network that lives in the spinal

cord of the animal. A crude description of the organization of this network is that of a chain of oscillators, each of which is a local neural subnetwork (Grillner, 1975; Cohen *et al.*, 1982). The details of the segmental oscillators which comprise the CPG are largely unknown, and it is unlikely that they will ever be fully known. For this reason, we have chosen to approach the modelling from a very general point of view; we try to understand, within a very general class of models, the implications of the kinds of phenomenological data that can currently be obtained.

We assume there are segmental oscillators, each capable of autonomously and stably producing periodic output. More specifically, we assume that the k th oscillator can be modelled by a differential equation with an orbitally stable periodic solution:

$$dX_k/dt = F_k(X_k) \quad (1)$$

where X_k lies in \mathbf{R}^q , $q \geq 2$. Equation (1) can be as complicated as is necessary and may model many neurones or a single neurone with many ionic channels. We will assume that oscillator k can communicate with its $2m$ nearest neighbours and that this coupling is additive. The coupled equations take the form:

$$dX_k/dt = F_k(X_k) + \sum_{j=1}^m [G_j^+(X_{k+j}, X_k) + G_j^-(X_{k-j}, X_k)] \quad k = 1, \dots, N \quad (2)$$

Equation (2) is very general, and complete analysis appears to be impossible. Nevertheless, with a few very general hypotheses, it becomes possible to understand much about the qualitative behaviour, especially if the chain is long. The first hypothesis is that the coupling is not so strong as to cause the variables X_k to depart significantly from the periodic solution $Y_k(t)$. Thus, the state of each segmental oscillator can be described by a single variable, the phase $\theta_k(t)$, that denotes the position of the variables on the periodic solution. Such a hypothesis may be justified in at least two situations:

- (i) Weak coupling; the interactions between the oscillators are small. The use of phase equations is then justified by the use of invariant manifold theory (Fenichel, 1971), which implies that the full set of equations has an invariant torus parameterized by the phases (Ermentrout and Kopell, 1984).
- (ii) Strong attraction: the local oscillators, when perturbed, are rapidly pulled back to the periodic solution. Singular perturbation calculations are used to justify the use of phase models.

In addition, there is a third situation which, we conjecture, allows for the reduction to such phase models.

- (iii) 'Distribution of effects': each local oscillator is composed of subunits

which oscillate at phases distributed around the cycle, and which interact with analogous oscillators by means of pulses distributed around the cycle. This situation, which exists in some known CPGs (Friesen *et al.*, 1978), is far less understood; we have seen in numerical simulations that such distribution of effects can allow interactions strong enough so that, if they were concentrated in a small part of the cycle, they would disrupt the rhythmicity (Ermentrout and Kopell, 1989a).

Our second hypothesis is that the interaction terms depend only on the differences of the phases, i.e. the equations have the form

$$d\theta_k/dt = \omega_k + \sum_{j=1}^m [H_j^+(\theta_{k+j} - \theta_k) + H_j^-(\theta_{k-j} - \theta_k)] \quad k = 1, \dots, N \quad (3)$$

The functions H_j^\pm are 2π -periodic functions of their arguments. In case (i), it can be shown by standard averaging theory (Ermentrout and Kopell, 1989a) that new coordinates can be chosen on the invariant torus so that the coupling terms depend, to lowest order in the strength, only on the differences of the phases. The functions H_j^\pm can be explicitly computed from the original eqn (2) by averaging (Ermentrout and Kopell, 1984, 1989a). Even with stronger coupling, equations of the form (3) can result, for example in phase models for which the interaction is dispersed around the cycle as in case (iii) (Ermentrout and Kopell, 1989b).

The final general hypothesis is motivated by an important property of the coupling of neural oscillators via chemical synapses. We shall say that a function G in eqn (2) is of diffusive type if, on the average over a cycle, $G(X, X)$ vanishes. Otherwise we shall say that it is synaptic (Kopell and Ermentrout, 1986; Kopell, 1988). Diffusive coupling arises from gap junctions and passive electrical coupling of tissue, as well as diffusion among chemical oscillators. Synaptic coupling may occur when there are chemical synapses or direct interactions between cells that do not depend on the difference between the two states. For diffusively coupled cells, it can be shown that the functions H in eqn (3) satisfy $H(0) = 0$; for synaptic coupling, $H(0) \neq 0$. Our third general hypothesis is that all of the functions H of eqn (3) satisfy $H(0) \neq 0$. We shall see that synaptic coupling forces the chain of oscillators to have non-zero phase-differences, which in turn allows the lamprey to swim in an undulating manner.

For most of the rest of the chapter, we will restrict our attention to the case of nearest-neighbour coupling, $m = 1$.

NEAREST-NEIGHBOUR COUPLING

We now describe three mathematical problems associated with eqn (3) with

$m = 1$. In each case, we give a brief description of the biological origin of the question.

Normal 'fictive swimming'

Lamprey and many other fish and fish-like animals swim by undulating through the water, with motion created by waves of muscular contraction that pass axially down the animal. These waves are governed by waves of electrical activity in the central pattern generator. The spinal cord of a lamprey, isolated from the rest of the animal, may be made to produce this electrical activity (Cohen and Wallén, 1980), and the behaviour of this activity in the isolated cord, called 'fictive swimming', is essentially the same as in an intact animal swimming in a stereotypic manner (Wallén and Williams, 1984). Recordings from the ventral roots, where processes from the motoneurons leave the spinal cord, show periodic bursts of activity. The periods of this activity are uniform throughout the cord, but phase-shifted. The intersegmental phase-lags are close to constant at about 1% per segment; in a lamprey, which has about 100 segments, this results in a travelling wave with a wave-number of about one body length. The adult can also be made to swim backwards; in that case, the phase-lags are similar but of opposite sign. Remarkably, the lags remain constant over a range of frequencies, which corresponds to a range of swimming speeds. Thus, these waves are not dispersive as are, for example, chemical waves, where the phase-lag is a function of the velocity of the wave.

The mathematical problem is to understand if the above behaviour can be modelled by the solutions of eqn (3), and under what hypotheses on the frequencies ω_k and the coupling functions.

Consider eqn (3) with nearest-neighbour coupling. We are interested in 'phase-locked' solutions, i.e. periodic solutions of eqn (3). It is easy to show that in this case, $d\theta_j/dt$ is a constant Ω , independent of j and t . Let $\varphi_j = \theta_{j+1} - \theta_j$. Suppose now that N is large. As $N \rightarrow \infty$, it can be shown that if $\omega_j \rightarrow \omega(x)$, where $x = j/N$, then eqn (3) tends to the following boundary value problem:

$$\Omega = \omega(x) + 2f(\varphi(x)) + \frac{1}{N}g(\varphi(x))_x \quad 0 < x < 1 \quad (4)$$

$$\Omega = \omega(0) + H^+(\varphi(0)) \quad (5)$$

$$\Omega = \omega(1) + H^-(\varphi(1)) \quad (6)$$

Here $2f(\varphi) = H^+(\varphi) + H^-(\varphi)$ and $2g(\varphi) = H^+(\varphi) - H^-(\varphi)$. This boundary value problem is complicated by the fact that the parameter Ω is unknown and determines the boundary conditions. Elsewhere (Kopell and Ermen-

trout, 1986, 1989b) we show that if $\omega(x)$ is not too far from constant, there is a unique formal solution to eqns (4)–(6) that selects the correct value of Ω , the phase-locked frequency. Furthermore, for each formal solution to eqns (4)–(6) there is an actual solution to eqn (3).

We now show the importance of chemical synaptic interactions for inducing fictive swimming in the lamprey. Suppose that there is no frequency gradient, i.e. $\omega(x) \sim \text{constant}$. If the coupling is diffusive, then the unique solution to eqns (4)–(6) is $\phi \equiv 0$. This does not correspond to swimming; the entire preparation simply oscillates synchronously. Small differences in frequency lead to phase-lags that lie around 0 and can take on either sign. On the other hand, if $H^\pm(0) \neq 0$, then $\phi = 0$ does not solve eqns (4)–(6), since the boundary conditions will be violated. Instead, there is a solution $\phi(x)$ that is constant except in a region near one of the ends of the medium. Depending on the sign of ϕ , this corresponds to forward or backward swimming. Significant variations from constant local frequency lead to non-constancy of the phase-lags as a function of k , at least for nearest-neighbour coupling.

An important observation is that the phase-lags are independent of the local frequencies of oscillation. More specifically, raising the local frequencies uniformly raises the emergent network frequency Ω by that amount without changing the phase relationships among the oscillators. Thus, one can get higher frequency (corresponding to faster swimming) while maintaining the wavelength.

In the special case that H^+ is a multiple of H^- , the two boundary conditions are of opposite signs. Then the relative strengths of the forward and backward coupling determines if the constant part of the solution is positive or negative. Since the sign of the phase-lag specifies whether the wave goes forward or backward along the chain, such a case provides a simple mechanism for switching between forward and backward ‘swimming’: one need only tune the coupling strengths.

The reader may note that many of these results occur for coupling in only one direction (Stein, 1971). However, as we describe below, it is possible to entrain the lamprey spinal cord oscillators by periodically forcing the preparation at either end; this is impossible with unidirectional coupling. Thus, bidirectional coupling is a fundamental property of the lamprey CPG.

‘Split baths’ and large changes in local frequency

It is possible to induce different local frequencies in parts of the cord by exposing different parts of the cord to baths with different ionic concentrations. One mathematical question is to find out what the consequences of such manipulations would be in equations of the form (3), and how the consequences depend on the coupling functions. This was done elsewhere (Kopell and Ermentrout, 1989b), along with other generalizations of the work (Kopell and Ermentrout, 1986) described above.

We will consider a simple example. Suppose that $\omega(x) = \omega_0 + \alpha p(x)$, where $p(x) \geq 0$ is a bump centred at a point x_0 in the interior of the medium and having a maximum value of 1. If $\alpha < 0$, then the region in the neighbourhood of x_0 has a lower frequency than the surrounding cord, while if $\alpha > 0$, the same region has a higher frequency. For α of sufficient magnitude, the solution to eqns (4)–(6) undergoes a transition in behaviour from waves propagating in one direction to waves that propagate bidirectionally. It is shown by Kopell and Ermentrout (1989b) that if $f'' > 0$, then for α large enough and positive, the centre of the cord leads the rest of the cord in phase, and so waves propagate outward from the centre. If $f'' < 0$, then if $\alpha < 0$ is of sufficient magnitude, the centre of the cord acts as a wave sink; waves originate at the ends and collide in the centre. These two behaviours are mutually exclusive; for fixed f , this transition occurs for $\alpha > 0$ or $\alpha < 0$ but not both.

The few experiments with raised or lowered frequencies that have so far been done have uncovered an anomaly in our original guesses about the operation of the network. That is, the transition phenomenon described above appears to happen both for raised frequencies *and* for lowered ones. There are at least two sources of the possible discrepancy, both of which give rise to new and challenging mathematics problems. One is that the altered composition of the bath changes the coupling as well as the frequencies. Another is that long-distance fibres, which are known to exist and which have been left out of this class of equations, are capable of changing the output of that experiment.

Periodic forcing

There are stretch-sensitive neurones, thought to be the so-called 'edge cells' that are synaptically coupled to some of the neurones involved in the oscillations (Grillner *et al.*, 1984). Such mechanoreceptors provide the possibility of periodically forcing the chain, using a motor to move the last few segments of the cord, while the rest of the cord is pinned and so remains motionless (McClellan and Sigvardt, 1988; Sigvardt and Williams, in preparation). The effects of this forcing are believed to be local, i.e. only the oscillators closest to the forcing are directly driven (McClellan and Sigvardt, 1988; Sigvardt and Williams, in preparation). Thus, the resulting entrainment is due to the intersegmental coupling between the oscillators. The cord can be entrained to a range of frequencies by forcing at either end. This implies that there must be coupling between oscillators in both directions. (For unidirectional coupling, there is only one end at which forcing has any effect on the phase-lags throughout the chain.)

The mathematical question here is an inverse one: what information can be obtained, at least within the context of models of the form (3), from the

phase-lags along the cord that can be measured during these entrainment experiments? To understand forcing of a single segment in a nearest-neighbour coupled chain, we return to (3) with $m=1$ and add a term for forcing (Kopell and Ermentrout, unpublished data). This term has the form $H(\omega_f t - \theta_m)$, where ω_f is the frequency of the forcing and $j=1$ or N . If the chain is phase-locked, then $d\theta_k/dt = \omega_f$ for all k and t . For simplicity of discussion and definiteness, we assume that the local frequencies are constant, say ω , and that $f'' > 0$. Suppose that we force the chain at $k=N$. Then eqn (3) gives rise to the following set of equations for the phase differences $\phi_k = \theta_{k+1} - \theta_k$:

$$\omega_f = \omega + H^+(\phi_1) \quad (7)$$

$$\omega_f = \omega + H^+(\phi_{k+1}) + H^-(\phi_k) \quad k=1, \dots, N-2 \quad (8)$$

$$\omega_f = \omega + H^-(\phi_{N-1}) + H_f(\xi) \quad (9)$$

where $\xi = \omega_f t - \theta_N$.

Equation (8) can be viewed as a discrete dynamical system: within the range in which H^+ is invertible, ϕ_{k+1} can be obtained from ϕ_k . This dynamical system can have fixed points, which must satisfy

$$\omega_f - \omega = H^+(\phi) + H^-(\phi) \equiv 2f(\phi) \quad (10)$$

f is typically parabola-shaped in the region in which H^+ is monotone, and so outside some interval of values for ω_f , there are no critical points. If there are critical points, there are typically two, one stable and one unstable. Equation (7) may be interpreted as giving the initial condition for the dynamical system (8). With knowledge of the critical points, one can then predict the 'orbit' of the phase-lags along the chain (here k and not time is the variable). Locking occurs if eqn (9) can be satisfied. The larger the amplitude of H_f , the larger the range of frequencies for which this is possible. For fixed H_f , for locking to occur, $|\omega_f - \omega - H^-(\phi_{N-1})| \equiv A(\phi_{N-1})$ must be sufficiently small. If ϕ_1 is not in the basin of attraction of the stable fixed point, ϕ_{N-1} is generally very far from the value that minimizes $A(\phi)$, making it very difficult to achieve locking unless the amplitude of H_f is very large. Furthermore, it is possible to compute the frequency values for which the initial ϕ is in the above basin of attraction, and it turns out that ω_f must satisfy $\omega_f > \Omega_L \equiv \omega + H^+(\phi_L)$, where ϕ_L is the zero of $H^-(\phi)$ near $\phi=0$. (Ω_L is one of the two possible frequencies taken by the unforced chain depending on the relative strengths of the coupling (Kopell and Ermentrout, 1986).) This provides an explicit bound on the range of possible forcing frequencies; a bound at the other end is given by the point at which eqn (9) cannot be satisfied. One also has from this a description of the trajectory for each possible ω_f . A similar analysis can be done with forcing at $k=1$, and in general this gives a different entrainment

range and set of trajectories. The qualitative properties of the trajectories turn out to depend on the sign f''' and other properties of the coupling functions, as does the range of entrainment. Thus, data on the trajectories, which can be measured (at least crudely) in the lamprey spinal cord, constrain the possible ways in which the coupling can be done. Although all but some possibly anomalous data can be accounted for in this context, we are reserving any predictions until we understand better how the introduction of long-range fibres affects the conclusions of the analysis.

NON-NEAREST-NEIGHBOUR COUPLING

In the lamprey spinal cord, there is anatomical evidence that neurones in each segment have processes that extend locally for at least several segments. (This is in addition to the long-distance fibres.) If the local oscillators are roughly the size of a segment, this implies that the coupling of each oscillator is to several of its neighbours. A mathematical question is then: what difference, if any, does this make in the behaviour of the network?

The analysis of eqn (3) for $m > 1$ is much more complicated than for $m = 1$. So far, we have done work corresponding to the first question in the previous section, i.e. the ability to reproduce the stereotypic 'fictive swimming'; we have not studied the effects of large changes in frequency or of mechanical forcing. Even for the first question, the results are not as complete as for $m = 1$; in particular, we can no longer explicitly determine analytically the frequency Ω of the phase-locked ensemble. Also, the existence and uniqueness of a solution has not been fully established. The problem is not completely specified until one specifies how the edges are to be dealt with, e.g. by removing all terms referring to non-existent oscillators. It can be shown (Zhang, 1988; Kopell *et al.*, 1989) that, for an open set of modifications of the end eqn (3), and away from the edges of the chain, there is a solution which approaches the solution to the algebraic equation

$$\Omega = \omega(x) + \sum_{j=1}^m (H_j^+(j\varphi) + H_j^-(-j\varphi)) \equiv \omega(x) + 2F(\varphi) \quad (11)$$

for some value of Ω . Equation (11) is analogous to the 'outer' equation for (4), e.g. the equation obtained by letting $N \rightarrow \infty$. The methods used to show that (3) behaves like a solution to (11) involves exponential dichotomies for non-autonomous discrete systems (Palmer, 1988). In (4), the 'boundary' conditions allow us to determine the value of Ω , and matching between the inner and outer equation enables us to conclude this choice of Ω is unique. We have no explicit analogous conditions for multiple coupling. Recently, we have developed an iterative scheme that allows us to find Ω independently of the form of $\omega(x)$, if $\omega(x)$ is not too far from constant. Thus, we can predict

the behaviour of the solution, at least away from the boundaries. This iterative scheme matches numerical calculations of the true solutions (and is much quicker), but it is unproven.

Using the outer eqn (11), we see that the multiple neighbour system behaves, at least away from the boundaries, like a modified version of a nearest-neighbour system, with the function $F(\phi)$ replacing $f(\phi)$ in the determination of most of the solution. One important effect is that local changes in frequency create smaller changes in phase-lags if there is multiple coupling, even if the coupling is normalized so that the total amount of the coupling is not increased; thus, the multiple coupling buffers against changes in local frequency and helps to insure that the phase-lags are constant. This can be understood by comparing the function F in eqn (11) with its analogue f in (3). For example, in the special case $f(\phi) = A \cos \phi$ for some A and $F(\phi) = \sum_j A_j \cos(j\phi)$, with A, A_j of the same sign, it can be seen from methods of trigonometric addition that $F(\phi)$ is a much thinner function with a larger derivative in the relevant region. In addition, even in the absence of frequency differences, suitably normalized multiple coupling leads to smaller phase-lags than nearest-neighbour coupling, a phenomenon that is noteworthy, since the lags in the lamprey cord are only 1% per segment. This is more subtle to see and has not been rigorously proved, though it is clear from the numerics. Our intuitive explanation of it depends on the above heuristically derived iterative scheme for the emergent frequency Ω of the locked chain, which in turn determines the lags away from the boundary according to (11) (see Zhang, 1988; Kopell *et al.*, 1989).

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