Abstract

The nervous system displays a variety of rhythms in both waking and sleep. These rhythms have been closely associated with different behavioral and cognitive states, but it is still unknown how the nervous system makes use of these rhythms to perform functionally important tasks. To address those questions, it is first useful to understood in a mechanistic way the origin of the rhythms, their interactions, the signals which create the transitions among rhythms, and the ways in which rhythms filter the signals to a network of neurons.

This talk discusses how dynamical systems have been used to investigate the origin, properties and interactions of rhythms in the nervous system. It focuses on how the underlying physiology of the cells and synapses of the networks shape the dynamics of the network in different contexts, allowing the variety of dynamical behaviors to be displayed by the same network. The work is presented using a series of related case studies on different rhythms. These case studies are chosen to highlight mathematical issues, and suggest further mathematical work to be done. The topics include: different roles of excitation and inhibition in creating synchronous assemblies of cells, different kinds of building blocks for neural oscillations, and transitions among rhythms. The mathematical issues include reduction of large networks to low dimensional maps, role of noise, global bifurcations, use of probabilistic formulations.

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1. Introduction

The nervous system creates many different rhythms, each associated with a range of behaviors and cognitive states. The rhythms were first discovered from scalp recordings of humans, and the names by which they are known still come mainly from the electroencephalograph (EEG) literature, which pays attention to
the frequency and behavioral context of those rhythms, but not to their mechanistic origins. The rhythmic patterns include the alpha (9-11 Hz), beta (12-30 Hz), gamma (30-80 Hz), theta (4-8 Hz), delta (2-4) Hz and slow wave (.5-2 Hz) rhythms. The boundaries of these ranges are rough. More will be said about the circumstances in which some of these rhythms are displayed.

It is now possible to get far more information about the mechanisms behind the dynamics of the nervous system from other techniques, including electrophysiology. The revolutions in experimental techniques, data acquisition and analysis, and fast computation have opened up a broad and deep avenue for mathematical analysis. The general question addressed by those interested in rhythms is: how does the brain make use of these rhythms in sensory processing, sensory-motor coordination and cognition? The mathematical strategy, to be discussed below, is to investigate the “dynamical structure” of the different rhythms to get clues to function. Most of this talk is about dynamical structure, and the mathematical issues surrounding its investigation. I’ll return at the end to issues of function.

2. Neuromath

The mathematical framework for the study of brain dynamics are the Hodgkin-Huxley (HH) equations. These are partial differential equations describing the propagation of action potentials in neurons (cells of the nervous system). The equations, which play the same role in neural dynamics that Navier-Stokes does in fluid dynamics, are an elaborate analogy to a distributed electrical circuit. The central equation,

\[ Cv' = \sum I_{ion} + \nabla^2 v + \sum I_{syn} + I_{ext} \]

describes conservation of current across a piece of a cell membrane; \( v \) is the cross-membrane voltage and the left hand side is the capacitive current. The first sum on the right-hand side represents the intrinsically generated ionic currents across the membrane. The term \( \nabla^2 v \) represents the spatial diffusion, and \( I_{ext} \) the current fed into the cell. \( \sum I_{syn} \) represents the currents introduced by coupling from other cells. Thus, these equations can also be used to model networks of interacting neurons, the focus of this talk.

Each of the intrinsic currents \( I_{ion} \) is described by Ohm’s law: \( I_{ion} \) is electromotive force divided by resistance. In this context, one usually uses the concept of “conductance”, which is the reciprocal of resistance. The electromotive force depends on the type of charged ion (e.g., Na, K, Ca, Cl) and the voltage of the cell; it has the form \([v - V_{ion}]\), where \( V_{ion} \) is the so-called “reversal potential” of that ion.

The dynamics of the conductances are what make the equations so mathematically interesting and rich. In a simple description of the conductance, each ionic current has up to two “gates”, which open or close at rates that are dependent on the voltage of the cell. For each such gate, there is then a first order equation of the form

\[ x' = [x_{\infty}(v) - x]/\tau_x(v) \]
where $x$ denotes the fraction of channels of that type that are open at any given time, $x_\infty(v)$ is the steady state value of $x$ for a fixed voltage, and $\tau_x(v)$ is the rate constant of that gating variable. For example, the standard Na current has the form $I_{Na} = \mathcal{E} m^3 h |v - V_{Na}|$, where $\mathcal{E}$ is the maximal conductance, and $m$ and $h$ are gating variables satisfying the above equation for $x$. The dynamics for $m$ and $h$ differ because $m_\infty(v)$ is an increasing function of $v$, while $h_\infty(v)$ is a decreasing function; also $\tau_m(v)$ is much smaller than $\tau_h(v)$. The (chemical) synaptic currents have the same form as the intrinsic ones, with the difference that the dependence of the driving force on voltage uses that of the post-synaptic cell, while the conductance depends on the pre-synaptic voltage. That is, $I_{syn}$ has the form $\mathcal{E} \tilde{x} |v - V_{syn}|$, where $\tilde{x}$ satisfies the equation for $x$ above, with $v$ replaced by $\tilde{v}$, the voltage of the cell sending the signal, and $V_{syn}$ is the reversal potential of the synapse. The coupling is said to be excitatory if the current is inward (increases voltage toward the threshold for firing an action potential) or inhibitory if the current is outward (moves voltage away from threshold for firing.)

For a simple version of the HH equations, there are three ionic currents; one of these (Na) creates an inward current leading to an action potential, one (K) an outward current helping to end the action potential, and a leak current (mainly Cl) with no gating variable. The HH equations are not one single set of equations, but a general (and generalizable) form for a family of equations, corresponding to different sets of intrinsic currents (which can depend on position on the neuron), different neuron geometries, and different networks created by interactions of neurons, which may themselves be highly inhomogeneous. Numerical computation has become highly important for observing the behavior of these equations, but does not suffice to understand the behavior, especially to get insight into what the specific ionic currents contribute; this is where the analysis, including simplification, comes in. For an introduction to HH equations, some analysis and some of its uses in models, see [1].

### 2.1. Some mathematical issues associated with rhythms

It is not possible to analyze the full class of equations in all generality. Our strategy is to look for mathematical structures underlying some classes of behavior observed experimentally; the emphasis is on the role of dynamical systems, as opposed to statistics, though probabilistic ideas enter the analysis.

Our central scientific question here is how rhythms emerge from the “wetware”, as modeled by the HH equations. As we will see, different rhythms can be based on different sets of intrinsic currents, different classes of neurons, and different ways of hooking up those cells. There are some behaviors we can see by looking at small networks, and others that do not appear until the networks are large and somewhat heterogeneous. Even in the small networks, there are a multiplicity of different building blocks for the rhythms, with excitation and inhibition playing different roles. Noise appears, and plays different roles from heterogeneity.

Investigators often use simplifications of the HH equations. For example, this talk deals only with “space clamped” cells in which the spatial distribution of each cell is ignored, and the equations become ODEs. (There are circumstances under
which this can be a bad approximation, as in [2]). Under some circumstances, the 4-dimensional simplest space-clamped HH equations (one current equation, three gating variables) can be reduced to a one-dimensional equation; thus, networks of neurons can be described by a fraction of the equations that one needs for the full HH network equations. Another kind of reduction replaces the full HH ODEs by maps that follow the times of the spikes. In both cases, there are at least heuristic explanations for why these reductions are often very successful, and hints about how and why the simplifications can be expected to break down.

3. Mathematics and small networks of neurons

3.1. Centrality of inhibition in rhythms

Some kinds of cells coupled by inhibition like to form rhythms and synchronize [3-5]. This is unintuitive, because inhibition to cells can temporarily keep the latter from firing (see below for important exceptions), but mutual inhibition can encourage cells to fire simultaneously.

There are various ways to see this, with methods that are valid in different contexts. For weak coupling, it can be shown rigorously that the full equations reduce to interactions between phases of the oscillators [6]; the particular coupling associated with inhibition can then be shown to be synchronizing (though over many cycles) [7]. If the equations can be reduced to one-dimensional “integrate and fire” models, one can use “spike-response methods” to see the synchronizing effect of inhibitory synapses on timing of spikes. Both of these are described in [6] along with more references.

Another method, which I believe is most intuitive, looks at the ongoing effect of forced inhibition on the voltage of the cells, and how some of the processes are “slaved” to others. This is seen most clearly in the context of another one-dimensional reduction that has become known as the “theta” model, because of the symbols used for the phase of the oscillations [8]. The reduced equations have been shown to be a canonical reduction of equations that are near a saddle-node bifurcation on an invariant circle (limit cycle). Many versions of HH-like models (and some kinds of real neurons) have this property for parameter values near onset of periodic spiking, and they are known as “Type 1” neurons.

The “theta model” has the form

$$\theta' = (1 - \cos \theta) + I(1 + \cos \theta).$$

Here the equation for the phase $\theta$ has periodic solutions if the parameter $I$ is positive, and two fixed points (stable, saddle) if $I$ is negative. To understand the effects of forced inhibition, we replace $I$ by a time dependent inhibition given by $I - gs(t)$, where $s(t) = \exp(-t/\tau)$ for $t > 0$, and zero otherwise. With the change of variables $J(t) = 1 - g \exp(-t/\tau)$, this is a 2-D autonomous system. Figures [9] and analysis show that the system has two special orbits, known in the non-standard analysis literature as “rivers” [10], and that almost all of the trajectories feed quickly into
one of these, and are repelled from the other. The essential effect is that initial conditions become irrelevant to the outcome of the trajectories. A similar effect works for mutually coupled systems of inhibitory neurons.

The rhythm formed in this way is highly dependent on the time scale of decay of the inhibition for the frequency of the network [11, 12]. These models, and the “fast-firing” inhibitory cells that they represent, can display a large range of frequencies depending on the bias ($I_{\text{ext}}$ in HH, the parameter $I$ in the theta model); however, in the presence of a small amount of heterogeneity in parameters, the rhythm falls apart unless the frequency is in the gamma range (30-80 Hz) [4, 13]. This can be understood from spike response methods or in terms of rivers.

The above rhythm is known as ING or interneuron gamma [14, 15]. A variation on this uses networks with fast-firing inhibitory cells (interneurons or I cells) and excitatory cells (pyramidal cells or E-cells). This is called PING (pyramidal interneuron gamma) [14, 15]. Heuristically, it is easy to understand the rhythm: the inhibitory cells are set so they do not fire without input from the E-cells. When the E-cells fire, they cause the I-cells to cross firing threshold and inhibit the E-cells, which fire again when the inhibition wears off. This simple mechanism becomes much more subtle when there is heterogeneity and noise in large networks, which will be discussed later.

### 3.2. Excitation and timing maps

The fast-firing cells described above are modeled using only the ionic currents needed to create a spike. Most other neurons have channels to express many other ionic currents as well, with channel kinetics that range over a large span of time constants. These different currents change the dynamical behavior of the cells, and allow such cells to be “Type II”, which means that the onset of rhythmic spiking as bias is changed is accompanied by a Hopf bifurcation instead of a saddle node. The type of onset has important consequences for the ability of pair of such cells to synchronize. E.g., models of the fast-firing neuron, if connected by excitatory synapses, do not synchronize, as can be shown from weak coupling or other methods described above (e.g., [7]). However, if the cells are Type II, they do synchronize stably with excitation (and not with inhibition). This was shown by Gutkin and Ermentrout using weak coupling methods [16]. A more specific case study was done by Acker et al. [17], motivated by neurons in the part of the cortex that constitutes the input-output pathways to the hippocampus, a structure of the brain important to learning and recall. These cells are excitatory and of Type II (J.White, in prep.); models of these cells, based on knowledge of the currents that they express, do synchronize with excitatory synapses, and do not with inhibitory synapses.

The synchronization properties of the such cells can be understood from spike-timing functions and maps [17]. Given the HH equations for the cell, one can introduce at any time in the cycle excitation or inhibition whose time course is similar to what the synapse would provide. From this, one can compute how much the next spike is advanced or delayed by this synapse. From such a graph, one can compute a spike-time map which takes the difference in spike times in a single cycle to the difference in the next cycle.
The analysis of such a map is easy, but the process raises deeper mathematical issues. One set of issues concerns what is happening at the biophysical level that gives rise to the Type II bifurcation, which is associated with a particular shape of the spike advance function [18]. Analysis shows that the Type II is associated with slow outward currents or certain slow inward currents that (paradoxically) turn on when the cell is inhibited [16, 17]; this shows how biophysical structure is connected with mathematical structure.

A second set of questions concerns why the high-dimensional coupled HH equations can be well approximated by a 1-D map. (In some parameter ranges, but not all, this is any excellent approximation). The mathematical issues here concern how large subsets of high-dimensional phase space collapse onto what is essentially a one-dimensional space. Ideas similar to those in Section 3.1 are relevant, but with different biophysics creating the collapse of the trajectories. In this case (and others) there are many different ionic currents, with many different time scales, so that a given current can be dominant in some portion of the trajectory and then decrease to zero while others take over; this leads to structure that is more complex than that of the traditional “fast-slow” equations, and which is not nearly as understood. Such reductions to 1-D maps have been used in other investigations of synchrony [19-21] involving multiple cells and multiple kinds of currents.

3.3. More complex building blocks: Fancier inhibitory cells

So far, I’ve talked about networks containing fast-firing neurons (inhibitory) or excitatory cells. But there are many different kinds of cells in the nervous system, with intrinsic and synaptic currents that make them dynamically very different from one another. Once there are more currents with more time scales, it is easier to create more rhythms with different frequency. That is, the differences in frequencies often (but not always) come from some time scales in the interacting currents, and cannot be scaled away.

The stellate cell of Section 3.2 is an excellent example of currents creating frequencies; in a wide range of parameters, these cells, even without coupling, form a theta rhythm. Indeed, they are believed to be one of the primary sources of that rhythm in the hippocampus, which is thought by many to use these rhythms in tasks involving learning and recall. As described above, these cells are excitatory, and synchronize when coupled by excitation.

More puzzling are inhibitory cells in the hippocampus that are capable of forming theta rhythms as isolated cells with ionic currents similar to those in the stellate cells. The puzzle is that these cells do not cohere (in models) using inhibitory coupling. (The decay time of inhibition caused by these cells is roughly four times longer than the inhibition caused by the fast-firing cells, but neither fast nor this slower decaying inhibition creates synchrony in models.) So what is providing the coherence seen in the theta rhythm? (The rhythm can be seen in small slices that do not have inputs from other parts of the brain producing theta, so in such a paradigm, the rhythm must be produced locally.)

One suggestion (Rotstein, Kopell, Whittington, in preparation) is that the inhibitory rhythms seen in slice preparations with excitation blocked pharmacolog-
ically depend on both kinds of inhibitory cells discussed, the special ones (called O-LM cells [22]) and the others. Simulations show that networks of these cells can have the O-LM cells synchronize and I-cells synchronize at a different phase, to create an inhibitory network with considerably more complexity than interacting fast-firing cells involved in ING. Again, this can be reduced to a low-dimensional map for a minimal network (two O-LM cells, one fast firing I-cell). However, the reduction now requires properties of the currents involved in the O-LM model, including the kinetics of the gating variables.

3.4. Interaction of rhythms

Another set of mathematical issues is associated with transitions among rhythms. In general, rhythms slower than gamma (e.g., beta, theta and alpha) make use of ionic currents that are active between spikes. These currents are voltage-dependent, so that changes in voltage, in the sub- and super-threshold regimes, can turn on or off these currents. Thus, neuromodulators that change the voltage range of a neuron (e.g., by changing a leak current) can change which other currents are actively expressed. In that way, they can cause a switch from one rhythm to another. For example, models of the alpha rhythm [20] suggest that this rhythm makes use the inhibition-activated “h-current”; this current is effectively off line if the voltage is increased (even below threshold level). Thus, a switch from alpha to a faster rhythm (gamma or beta) can be effected by simply making the E-cells operate in a moderately higher voltage regime.

These switches can be seen in simulations (Pinto, Jones, Kaper, Kopell, in prep.), but are still understood only heuristically. The mathematical issues are associated with reduction of dimension methods. In the regime in which the network is displaying alpha, there are many more variables that are actively changing, notably the gating variables of each of the currents that is important in this rhythm. When there is a switch to gamma and those currents go off line, the phase space becomes effectively smaller. The mathematics here involves understanding how that phase compression takes place.

A related set of mathematical questions concerns rhythms that are “nested”, one within another. For example, the theta rhythm often presents as the envelope of a series of faster gamma cycles, and the beta rhythm, at least in some manifestations, occur with the I-cells firing at a gamma rhythm and the E-cells firing at the slower beta rhythm, missing some cycles of the inhibitory rhythm. The gamma/beta switch has been understood from a physiological point of view (see [19] and its references) and has been simulated. The gamma/theta nesting is less understood, though new data and simulations are providing the physiological and heuristic basis for this [22; Rotstein, Kopell, Whittington, in prep.].

4. Large networks

Though there are many more examples of other building blocks, I’m turning
to issues that do not appear in small network analysis. I’m going to go back to a very simple building block, but now put many such together. The simple building block is one E cell, one I-cell, which together can create a gamma rhythm.

4.1. Sparse coupling

We now consider a network with N E-cells and M I-cells, with random coupling from the E-cells to the I-cells and vica versa. Suppose, for example, there is a fixed probability of connection in each direction between any pair of E and I cells. Then the number of inputs to any cell is distributed across the population, leading to heterogeneity of excitation and inhibition. Is it still possible to get coherent gamma rhythms? This can be answered with mathematical analysis using the “theta neuron” model described above [9]. To understand synchrony in E/I networks, it is helpful to understand what each pulse of inhibition does to the population of excitatory cells and vica versa. The part in which both probability and dynamical systems play a large role is the effect of a pulse of inhibition on a population. The “rivers” referred to above in Section 3.1 create synchronization if the inputs to cells have no variance, but with variation in the size of the inputs, there is a spread in the times of the outputs. This can be accurately computed using features of the dynamics and probability theory. Similarly, but with less accuracy, one can compute the the effect of variation of inputs on the spike times of the receiving population due to a pulse of excitation. The results lead to unintuitive conclusions, e.g., that increasing the strength of the inhibition (which strengthens the synchronizing effect of the rivers) does not reduce the desynchronizing effects of random connectivity. Furthermore, tight synchrony can be obtained even with extremely sparse coupling provided that variance in the size of the inputs is small.

4.2. Loss of coherence

The above analyses can be put together to understand synchrony of “PING”. However, they leave only partially answered many questions about larger networks. One such question, which is central to understanding how the assemblies of neurons are created and destroyed, is the circumstances under which the synchrony falls apart, i.e., what modulations of cells and/or synapses will lead to loss of coherence of the gamma rhythm. The above analysis shows that too large a variation in size of inputs to different cells of the same population can be fatal. Similar phenomena occur with too much variation in drive or intrinsic currents. There are less obvious constraints that are understood from working with smaller networks described above. From those, it is possible to see that ING and PING operate in different parameter regimes: the firing times of the population in ING are governed by the bias of the I-cells (as well as the decay time of the inhibition); in PING, the inhibitory cells are more passive until driven by the E-cells, and the timing comes from bias of the E-cells (as well as decay of inhibition). This means that the mechanism of coherence can switch between ING and PING by changing relative excitability of the two populations. Changing the strengths of the I-E and E-I synapses can also get
the population (large or small) out of the regime in which the E-cells synchronize the I-cells, and vice versa.

A more mysterious issue that cannot be addressed within minimal networks is how the size of the sub-populations responding on a given cycle affects the coherence on the next cycle and the numbers of cells participating, especially when there is some heterogeneity in the network. E.g., as the number of inhibitory neurons firing in a cycle changes, it changes the total inhibition to the E-cells, which changes the number of E-cells that are ready to fire when inhibition wears off, and before the next bout of inhibition. If the amount of inhibition gets too small, or inhibition gets too dispersed, the coherence can rapidly die. Without taking into account the trajectories of each of the large number of cells, it is likely that some possibly probabilistic account of the numbers of cells spiking per cycle can give some insight into the dynamical mechanisms surrounding failure of coherence.

Such a reduction has been successfully used in a different setting, involving the long-distance coherence of two populations of heterogeneous cells. In this case, if the populations are each minimal (one E/I pair) for each site, there is a 1-D map that describes the synchronization, with the variable the timing between the E and I sites [19]. For large and heterogeneous networks, the synchronization (within some parameter regimes) can be described by a 3-dimensional map, in which the first variable is the time between the first spikes of a cycle in the two E-cell populations, and the others are the fraction of I-cells firing on that cycle in each of the two I-cell populations (McMillen and Kopell, in prep.).

Related work has been done from a different perspective, starting with asynchronous networks and asking how the asynchrony can lose stability [23-25]. Work using multiple time scales to address the formation of “clusters” when synchrony fails is in [26].

4.3. Noise, PING, and frequency control

One of the main differences between ING and PING is the difference in robustness. Small amounts of heterogeneity of any kind make ING coherence fall apart dramatically [4,13]. By contrast, PING is tolerant to large ranges of heterogeneity. The “ping-pong” mechanism of PING is also able to produce frequencies that cover a much wider range than the ING mechanism, which is constrained by loss of coherence to lie in the gamma range of approximately 30-80 Hz [4,13]. Since many versions of gamma seen in experiments are of the PING variety, this raises the question of what constrains the PING rhythms to stay in the gamma frequency range.

A possible answer to this comes from simulations. C. Borgers, D. McMillen and I found that heterogeneity, unless extreme, would not disrupt the PING coherence. However, a very small amount of noise (with fixed amplitude and poisson-distributed times) could entirely destroy coherence of the PING, provided the latter had a frequency below approximately 30 Hz; if the same noise is introduced when the network is in the gamma range, the behavior is only slightly perturbed. Furthermore, the ability to withstand the noise is related to adding some I-I connections, as in ING. A heuristic explanation is that, at low frequencies, the inhibition to the
I-cells (which has a time constant around 10ms) wears off before the excitation from the E-cells causes these cells to spike. Thus, those cells hang around the threshold for significant amounts of time, and are therefore vulnerable to being pushed over threshold by noise. The mathematics has yet to be understood rigorously.

5. Mathematics and clues to function

The mathematical questions are themselves interesting, but the full richness of the scientific endeavor comes from the potential for understanding how the rhythms generated by the brain might be used in sensory processing, motor coordination and cognition. We are still at the outer edges of such an investigation, but there are many clues from animal behavior, physiology and mathematics. Work done with EEGs (see, e.g., reviews [27,28]) has shown that many cognitive and motor tasks are associated with specific rhythms appearing in different parts of the tasks. Gamma is often associated with attention, awareness and perception, beta with preparation for motor activities and high-order cognitive tasks, theta with learning and recall and alpha with quiet awareness (there are several different versions of alpha in different parts of the brain and found in different circumstances). Work done in whole animals and in slice preparations are giving clues to the underlying physiology of the rhythms, and how various neuromodulators change the rhythms, e.g., [14]. Much of the math done so far has concerned how the networks produce their rhythms from their ionic currents and connectivity, and has not directly addressed function. However, the issues of function are starting to be addressed in terms of how the dynamics of networks affects the computational properties of the latter.

One of the potential functions for these rhythms is the creation of “cell assemblies”, temporary sets of neurons that fire synchronously. These assemblies are believed to be important in distributed processing; they enhance the effect of the synchronized pulses downstream, and provide a substrate for changes in synapses that help to encode experience. (“Cells that fire together wire together.”) Simulations show, and help to explain, why gamma rhythms have especially good properties for creating cells assemblies, and repressing cells with lower excitability or input [29]. Furthermore, the changes in synapses known to occur during gamma can facilitate the creation of the beta rhythm (see [19] for references), which appears in higher-order processing. Mathematical analysis shows that the beta rhythm is more effective for creating synchrony over distances where the conduction time is longer. Thus, we can understand the spontaneous gamma-beta switch seen in various circumstances (see [19] and [29]) as creating cell assemblies (during the gamma portion), using the synaptic changes to get cell assemblies encoded in the beta rhythm, and then using the beta rhythm to form highly distributed cell assemblies.

The new flood of data, plus the new insights from the mathematics, are opening up many avenues for mathematical research related to rhythms and function. A large class of such questions concerns how networks that are displaying given rhythms filter inputs with spatio-temporal structure, and how this affects the changing cell assemblies. This question is closely related to the central and controversial questions of what is the neural code and how does it operate. These questions will
likely require new techniques to combine dynamical systems and probability, new ways to reduce huge networks to ones amenable to analysis, and new ideas within dynamical systems itself, e.g., to understand switches as global bifurcations; these are large and exciting challenges to the mathematical community.

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