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The Center for the Study of Rhythmic Processes began operation in the academic year 1986–1989 and was supported as a Center of Excellence through June 1990. The Center gathered together mathematicians and biologists to work on problems involving neural control of rhythmic motor behavior. There were two main problems addresses during this time. One was the structure and function of the intersegmental coordinating system of the vertebrate spinal cord, using the lamprey as the prototypic example. A broadly applicable mathematical framework was developed and applied. The major research Centers of the country working on this preparation were consolidated under the auspices of the Center. The new collaborations led to the design and performance of new experiments based on the mathematics. The second problem was the structure and function of small neural networks, such as the crustacean stomatogastric ganglion. Work was performed on tasks ranging from the biophysics of individual cells to emergent properties of the network.

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Table of Contents

<u>Center for the Study of Rhythmic Processes</u>

Personnel, 1986–1990

1. Nancy Kopell, Department of Mathematics, Boston University, P.I.
   Steven Strogatz, Postdoctoral Fellow
   Stephane Laederich, Graduate Student

2. G. Bard Ermentrout, Department of Mathematics, University of Pittsburgh

3. Eve Marder, Department of Biology, Brandeis University
   Pierre Meyrand, Postdoctoral Fellow
   Robert Zarum, Undergraduate
   James Weimann, Graduate Student
   Patsy Dickenson, Visitor

4. Avis Cohen, Neurobiology and Behavior, Cornell University
   Nicholis Mellen, Graduate Student
   Tamara Dobrof, Graduate Student
   Margaret Baker, Technician and Collaborator
   Timothy Kiemel, Graduate Student
   Peter Brodfuehrer, Collaborator

5. Karen Sigvardt, Department of Neurology, University of California, Davis
   Michael Remler, Collaborator

6. Thelma Williams, St. Georges Hospital Medical School (London)
   Simon Alford, Graduate Student

7. James Buchanan, Marquette University Department of Biology

8. Grahame Bowtell, Open University of London, Department of Mathematics

7. Irving Epstein, Department of Chemistry, Brandeis University

<u>Adjunct Members</u>

1. Carl Rovainen, Department of Physiology and Biophysics, Washington University Medical School

2. Simon Giszter, Bizzi Laboratory, Brain and Cognitive Sciences, MIT

3. Andrew McClellan, Department of Physiology and Biophysics, University of Iowa

<u>Consultants</u>

1. Lawrence Cohen, Dept. of Physiology, Yale University

2. Humberto Maturana, Department of Biology, University of Chile

I Significance

Oscillatory behavior is found in many parts of the nervous system and in both vertebrates and invertebrates. Nevertheless, it is not understood how networks which make use of dynamically complicated components are constructed so as to be able to carry out their appropriate tasks. The aim of the work of the Center is to develop a body of technique relevant to addressing such questions, and to use this technique to further the understanding of some particular neural networks.

Central pattern generators are thought to govern a range of stereotypic motions, including such rhythmic activities as walking, running, swimming, chewing and breathing. they contain neurons or neural subnetworks that, in the appropriate physiological conditions, are capable of producing oscillatory activity. The two neural networks we have concentrated on are the lamprey locomotor network and the crustacean stomatogastric ganglion (STG).

<u>The lamprey central pattern generator for locomotion</u>

The central pattern generators chosen for this study are ideal neural networks for a collaboration between mathematicians and biologists because they are relatively simple, experimentally accessible, and govern behavior that is observable. The lamprey is particularly useful because it is possible to dissect out the spinal cord, and work <u>in vitro</u> ; the neural activity of the isolated cord is essentially identical to that of the intact behaving animal. Furthermore, working with a vertebrate brings to the fore methodological challenges that cannot be ignored: unlike invertebrate preparations, it is not likely that one will learn every relevant cell and most of the connections in any reasonable amount of time. It is therefore of great importance to develop a methodology that will allow experimenters to draw conclusions about the behavior of the network from the kinds of phenomenological observations that can presently be made.

The lamprey project is now a mature collaboration, with joint papers and much useful interaction between theory and experiments [1–7, 24]. The collaboration of Kopell, Ermentrout, Sigvardt and Williams has been especially fruitful. The work of this team has attracted many invitations in the last year. Williams has given invited talks in the Neurology Dept., U.C. Davis, Department of Neurobiology, U.C. San Diego, Neuroscience Division, U.C. Berkeley. She was also an invited speaker at the U.C. Berkeley Symposium on Analysis and Modeling of Neural Systems, and at a workshop on "Realistic simulation of neuronal networks" in association with the annual meeting of European Neuroscience Association in Stockholm. Sigvardt was invited to speak in a workshop on the "Cellular Basis of Behavior" at the Nobel Institute of Neurophysiology , Karolinska Institute, Stockholm. Among the mathematics talks given by Kopell or Ermentrout discussing this work was a plenary talk given by Kopell at the annual meeting of the Society for Industrial and Applied Mathematics.

<u>Small neural networks</u>

Small neural networks provide examples that help focus questions and keep the investigations directed in biologically useful ways. The crustacean stomatogastric ganglion is particularly useful because the number of neurons is small (14 in the pyloric part of the network) and the system is well studied. Furthermore there are modulatory substances which produce interesting changes in the output of the network.

The work that we are doing is guided by the STG, but not restricted to it. We are interested more generally in how the neurons with known properties, such as the ability to burst under some conditions, or the ability to have plateau potentials, can be used as building blocks within small neural networks. Of special interest are mechanisms for regulating such quantities as the phase differences between the firing of neurons within the network, and the frequency of the network when it is oscillatory. The ultimate aim is to understand how networks can be constructed to be both flexible in their outputs under a variety of modulatory influences, yet still able to regulate those quantities which must be preserved for the appropriate functioning of the network. For this, it is central to understand the dynamics of interacting neurons having various properties. These questions are best addressed in the context of small networks. We expect that the lessons learned from thinking about the properties of small networks will help us to understand possible physiological substrates for the phenomenological characterizations used in the lamprey project.

In the previous reports, we have described in detail the work we have been doing. Much of the work has come to fruition in papers that have been submitted with this or previous reports. Hence, in this final report, we shall restrict ourselves to a brief overview of the main accomplishments of the group, and a brief description of current work and future results we expect to come out of our efforts.

II. Mathematics done by Kopell, Ermentrout, Williams, Kiemel and Laederich

A. Papers completed

A series of papers was written developing a framework for the investigation of chains of oscillators, motivated by questions about the structure and function of the lamprey central pattern generator for locomotion [1–5]. The latter was used as a prototypic example of a vertebrate spinal cord network. The original work was done based on old data, but it led to the design of new experiments intended to both corroborate the initial work and provide more detail to guide future work. Some of that work is described in published papers [5–7]. Three expository papers [8–10] were also written. The most recent work is described in more detail below.

Other mathematical work done by Kopell and Ermentrout with Air Force support includes a paper with D. Aronson on the interaction of oscillators that are modelled to have amplitude as a degree of freedom as well as phase [11]. This work has given us valuable intuition for more sophisticated modelling in networks. Also, S. Laederich, a graduate student supported by the grant, has written four papers [12–15]. The first two are related to his thesis. This thesis initially came out of attempts to relate the neural activity of the lamprey to its mechanical consequences, and effort that is being carried on by Williams and Bowtell (See Section IV). We decided that the hypotheses of our models did not hold well enough for locomotion, but the new mathematics developed to pursue the ideas were interesting. Of the two papers with M. Levi, one [15] is about a similar theme, and the other on an independent topic from mathematical physics [14].

B. Work in progress:

1. Long–range interactions.

The experimental work described above is motivated by theory that describes short range (though not necessarily just nearest neighbor) interactions. The decision to restrict initially to that class of equations was based on data showing that short pieces of the cord have phase lags per segment approximately the same as in longer pieces; this shows that long–range interactions, which are not present in the smaller pieces, cannot be necessary for the production of appropriate lags.

However, long range interactions are thought to exist, based on old split bath experiments in which the activity is suppressed over portions of the cord and coordination is measured between pieces on either side of the suppressed portion This motivated initial work by T. Kiemel (Thesis, Cornell University, 1989.) looking at some special cases of long–range interaction. His work shows that such connections can be very powerful, indeed can swamp out entirely the effects of the shorter range interactions. Furthermore, as discussed in Section IV, such interactions are relevant to problems of inappropriate regeneration. Thus, it is important to understand such connections and how they can operate in conjunction with the short–range interactions.

In the last year, Ermentrout and Kopell have done considerable work on more special cases of long–range coupling, and a manuscript is now in preparation. Our work started out motivated by the question of why the wave–length of the wave of activity is approximately one body length; we conjecture that the long–range interactions are important for that. We were also led to inquire if this wave length is a consequence of events that occur dring development, which led us further to look at reported behavioral sequences in early development of vertebrates, including lampreys. The paper investigates two kinds of interactions: 1) long fibers to or from points near the ends of a piece of cord to points near the center and 2) "translation invariant" coupling in which every point is connected to the point a half wave–length away. The mathematics shows that as some parameters are varied, the system can go through a sequence that could be seen behaviorally as "C–coils", "S–waves" and travelling waves, the sequence observed (roughly) in developing vertebrates with undulatory locomotion. Furthermore the travelling waves have wave–length equal to one body length.

<u>2. Relaxation oscillators</u>

One theme we have explored is the difference between relaxation oscillators, which have different time scales built into them and oscillators whose periodic motions have only one time scale. This may be significant, since neural oscillators are mainly of relaxation type, and there has been far less work on such systems. With a student, Kopell has done numerical work coupling relaxation oscillators or non–relaxation oscillators in various ways, including all–all coupling and a linear geometry. One notable outcome is that with relaxation oscillation, the transients before locking occurs are much shorter relative to the period of the oscillation; indeed a set of 40 oscillators in a chain could essentially lock within two cycles, far less than what is seen with non–relaxation oscillators in a chain. Another conclusion is that strong coupling can be less disruptive to neural oscillators in a relaxation regime than to those in a more sinusoidal regime. In particular, many models of neural oscillators, strongly coupled, undergo "oscillator death", in which the rhythm stops. Models of neural oscillators (Hodgkin–huxley like equations) were shown to permit much stronger mutual coupling before the onset of oscillator death than similar equations with parameters for which the oscillators were not of relaxation type. A paper is currently in preparation. Ermentrout, Kopell and L. Abbott have also explored how the use of relaxation oscillations may help solve the problem of how a system of coupled oscillators such as the lamprey CPG can buffer physiologically important phase lags against changes in local oscillator frequency

3. <u>Small networks and more detailed modelling</u>.

One set of questions, currently considered by Kopell and a student, are motivated by neurons in the crustacean stomatogastric ganglion (STG). We are numerically investigating the behavior of equation modelling a neural oscillator coupled in various manners (two way electrotonic and/or one–way inhibitory) to an equation modelling an excitable but not oscillatory neuron. We are especially interested in the phenomena we are seeing involving "frequency demultiplication", in which the excitable cell fires once for each n spikes (or bursts) of the oscillator. Some of the cells for which this is relevant in the STG have inputs from both pyloric and gastric subnetworks; since the gastric subnetwork has a period roughly 5 times as long, we are exploring whether the phenomena we are seeing might be useful in coordinating the outputs of the two subnetworks.

Another set of questions is currently being investigated by Williams, Ermentrout and Kopell. These concern levels of detail in modelling. The earlier work of Kopell and Ermentrout showed that under very broad hypotheses, some behavior of systems of is well represented by simpler systems characterized only by the phase of the oscillators and the phase–dependent coupling functions. We could then characterize the output of the system by the properties of the coupling functions. The current work is directed to understanding how to derive the coupling functions from more detailed descriptions of small networks. We are especially interested in understanding how to reduce the lamprey models of Buchanan and Grillner to this more abstract level.

III. Work of Sigvardt and Williams

A. Collaboration with Kopell and Ermentrout

Sigvardt and Williams have provided experimental data that has been used both to corroborate the mathematical theory and to constrain the future development. There are two kinds of experiments using the isolated, in vitro lamprey spinal cord that Sigvardt and Williams have developed so far, with many variations. The first kind are the "split bath" experiments. In these, different parts of the cord are exposed to different concentrations of the excitatory amino acid D–glutamate. In preparations exposed to uniform concentrations of D–glutamate, the concentration affects the frequencies. The hypothesis behind the work is that the local oscillators are affected directly by the concentrations at their respective positions, but also indirectly through the coupling of the oscillators. The mathematical framework then makes predictions about what might be seen when the concentrations are varied in different parts of the cord. In particular, it discusses how phase lags among the oscillators respond to changes in frequencies along the cord. It should be emphasized that the expected changes turn out to depend on some of the properties of the oscillators and the coupling. Hence, some of the data is used to determine the relevant properties, which in turn helps to make the predictions more specific.

The second class of experiments are mechanical forcing experiments. In these, the in vitro cord is pinned down, except for a few end segments that are attached to a small motor. The motor moves the end segments back and forth at a speed regulated by the investigator, in a range comparable to that of natural motion. The movement is transduced into electrical activity by mechanoreceptors in the spinal cord, notably the edge cells. The direct effects of the bending are thought to be local, but the coupling of the local oscillators causes more global effects. The observable quantities include the range of frequencies at which the cord can be entrained and the phase lags along the cord.

The published joint papers from the collaboration of Kopell, Ermentrout, Sigvardt and Williams [6–7,] all concern our first set of experiments using the mechanical forcing paradigm. These papers focused on information that can be obtained about the nature of the coupling system from data about the range of frequencies that yield entrainment under mechanical forcing. The mathematics predicts the following, almost independent of the details of the oscillators and the coupling: When the forcing is at one end of a piece of the cord, the range of entrainment should include frequencies both higher and lower than the unforced frequency of the ensemble; when the forcing is at the other end, the range includes frequencies either higher or lower than the ensemble frequency. Furthermore, the mathematical theory says that the coupling going in the direction from the former end to the latter is responsible for setting the phase lags along the cord, ie. "dominates" the intersegmental coupling going in the other direction. The general prediction was found to be correct in the data, which could then be used to make the further prediction that the caudal–rostral coupling dominates the coupling in the opposite direction.

The latter prediction cannot at present be directly tested. However, it turns out the the mathematical theory is rich enough to allow the same question to be tested in a completely different indirect way. That is, the mathematics relevant to the split bath paradigm [2] says that the outcome of the split bath experiments also depends on dominance. Two kinds of split–bath experiments have been carried out by Sigvardt and recently been partially analyzed. In these, there are two or three compartments with different concentrations of D–glutamate. The phase lags within and between compartments are measured. In the paradigm with two compartments, the phase–lags are measured when the concentration is uniform at higher and lower control concentrations , and when the rostral and caudal halves have different concentration. In the paradigm with three compartments, the concentration in the center may be either higher or lower than those of the ends. The mathematics in [2] predicts qualitative features of the phase lags for each of these cases. The predictions depend on exactly the features that are given by the forcing data: which direction coupling is dominant, and whether the range of entrainment for forcing at the non–dominant end is above or below the ensemble frequency. The data that has so far been analyzed confirms the hypothesis that the caudal–rostral coupling is dominant. A paper describing this work is in preparation.

Not all the work described in the rest of this section was not supported directly by the AFOSR Grant. However, it is part of the overall program of the Center, and is closely connected to work that was supported, so we include a brief description. The cited work was supported.

B. Cellular analysis of the lamprey locomotor CPG

This is the major focus of Dr. Sigvardt's work separate from the collaborative efforts. This work provides information about how the network oscillation is produced. As the theoretical work progresses toward deeper levels of analysis, the cellular work summarized below, as well as her future cellular experiments, will provide the constraints on which the future theoretical work of the collaboration can be based. Some of the work is described in an expository paper [16].

Agonists of excitatory amino acid transmitters are potent in eliciting fictive locomotion and activation of one of the excitatory amino acid receptors, the NMDA receptor, induces bistable membrane properties in some of the neurons of the lamprey spinal cord. From this, she hypothesized that the NMDA–induced TTX–insensitive membrane properties are important for the operation of the spinal network generating locomotion. It had also been hypothesized that inhibitory glycinergic transmission plays an important role in he generation of rhythmicity providing the inhibitory phase of the membrane potential oscillations in lamprey ventral horn neurons. However, using brainstem or tailfin–activated fictive locomotion, Alford and Williams demonstrated that spinal cord networks can produce a robust rhythmic output when glycinergic transmission is blocked by strychine and hypothesized that burst transmission is the result of voltage–dependent processes inherent to neurons within the network. Alford and Sigvardt [17] studied these membrane potential oscillations using single–electrode voltage clamp during tailfin–activated locomotion in the presence of strychnine and found that peak inward current during each burst of rhythmic activity is voltage dependent. This voltage–dependence is blocked by the specific NMDA–receptor blocker APV and by removal of magnesium ions from the bathing solution. This study provided the first evidence that rhythmic activity in ventral horn neurons during naturally evoked locomotory activity depends on the activation of voltage–dependent properties induced by EAA–mediated neurotransmission. Furthermore, as has been previously suggested, it provided evidence that rhythm generation in the locomotor network is not necessarily dependent on glycine–mediated inhibitory neurotransmission, since both the depolarization and the repolarization phase of the oscillatory activity can be accounted for by currents linked to NMDA–receptor activation. Alford, Sigvardt and Williams then continued an investigation of the ionic mechanisms underlying this long–lasting outward current and found that the repolarization phase of the NMDA–activated oscillation is due to a calcium–activated potassium and chloride conductance, confirming the original hypothesis.

Fictive locomotion induced by bath application of excitatory amino acids does not appear to be affected by the GABA–A blocker bicuculline. However, since the action of one inhibitory mechanism may be masked by activity in another, Alford, Sigvardt and Williams [18] investigated the effects of GABA and bicuculline on burst generation after blocking inhibitory glycinergic transmission with strychnine. They found that in the presence of strychnine, bicuculline increases the initial frequency of rhythmic activity and increases the mean duration of an episode of bursting, demonstrating that there must be some GABA–mediated inhibition involved in controlling the frequency of the network oscillation. They went on to demonstrate that GABA inhibition plays a role in the repolarization phase of the rhythmic activity, but that the effects of GABA on the rhythmic activity must be presynaptic to the ventral horn neurons being studied.

C. Neural activity, mechanics and hydrodynamics

An expository paper [19] crediting support of the A.F. was written by Williams on the relationship between the neural activity and the mechanical activity it induces. Some of the work on which that is based, and current work, is described below.

1. Timing studies

The relative timing between neural activation and body curvature is controlled in the lamprey by powerful movement–generated feedback. Sigvardt and Williams did a series of forcing experiments in which the phase delays between applied movement and the ventral–root activity nearest the point of maximal bending were measured from pieces of spinal cord taken from different points along the body length. They found that along most of the body, the phase delay between the movement and the ventral root activity near the point of maximal bending is approximately 0.5. This is approximately the value seen during swimming in the caudal half of the the animal. Since this timing is disadvantageous in terms of energy consumption, they concluded that this timimg must be important for the hydrodynamics of swimming. Tesing this hypothesis requires 1) knowledge of the time delays between motorneuron activation and the development of tension and 2) mathematical analysis of the hydrodynamics of the swimming lamprey, to show where tension is required along the body for the development of forward propulsion. Work on these topics is being carried out by Williams and her colleagues.

2. Properties of muscle fibers

The arrangement of muscle fibers and connective tissue elements within the body of the lamprey is such that activation of the myofilaments within one myosegment produces tension tending to develop a local curvature concave to the active side. Development of this curvature is opposed by the inertial, viscous and elastic properties of the notochord, the skin, and the muscle itself and by the surrounding water. The time–dependent relation between the motoneuronal activation and tension within the body wall is being investigated with the aid of a mechanical model of the lamprey body developed by Williams and Bowtell, incorporating viscoelastic and inertial elements. Experiments with excised lamprey tissue by Curtin and Williams are being used to investige the relationships between muscle length, velocity and tension, and these data are being incorporated into the model.

3. Fluid mechanics and swimming

The question of how changes in body shape interact with the water to propel the animal forward lies within the realm of fluid mechanics. The equations of fluid mechanics combine the Newton's laws of motion for fluid particles with a consideration of the forces due to viscosity. Lampreys are anguilliform (eel–like) swimmers, which means that significant swimming movements are produces over most of the body length. To explain this type of swimming, one needs to show that the distribution of pressure along the boundaries of the fish result in a net forward force. Current research by Carling and Williams is attempting a full description of the hydrodynamics of anguilliform swimming by numerically solving the equations of fluid mechanics in the presence of a moving boundary (the swimming lamprey), using a super–computer. The final link in the description of how the observed time course of activation of motorneurons in the lamprey leads to forward movement will be examined by putting the model of the lamprey body into the hydrodynamic equations.

1V. Work of Cohen laboratory

A. Regeneration.

This laboratory has been working on regeneration in the lamprey, both in ammocoetes (the larval stage) and in adults. The major result [20] is that functional recovery is not limited to the larval stage, but can be seen in adult animals as well. The key control experiment was done, i.e. testing monotoneuron behavior in the presence of curare to remove the effects of twitches or residual muscle fibers [21]. However, this "functional recovery" could better be described as "dysfunction" [23]; the measured phase lags were definitely abnormal as compared with usual fictive or in vitro swimming measurements. One hypothesis advanced to explain these results is that some long fibers may regenerate and to inappropriate segments [23]. Indeed, modelling results by T. Kiemel show that such inappropriate regeneration may lead inappropriate electrical activity. This hypothesis is further corroborated by experiments that show that, upon removal of distal segments (and, presumably, some of the longer fibers), the cord behaved better. These experiments reinforce the need to study the effects of long fibers in the cord. As reported above, such beginning investigations have been made by both Kiemel and Kopell, Ermentrout.

B. Development.

It is of interest to understand the differences in electrical activity between the larval (ammocoete) lamprey and the adult as one of the steps in understanding developmental changes that occur in the transition between the stages. The adult in–vitro isolated spinal cord has stable behavior easy to characterize. This is not true of the ammocoete. In the latter, the bursting pattern takes a long time to stabilize and is less stable than that of the adult, with phase differences switching and drifting around the appropriate values. The instability is seen in short pieces as well as long ones. Through transformation (to the adult stage) the pattern begins to stabilize and be less variable. In the late transformers, the patterns are similar to those of adults. Anatomically, one difference is that ammocoetes seem to lack some of the medial coordinating fibers.

3. Normal coordinating system.

One question raised about the normal coordinating system was how much variation it had to cope with; this is important in understanding how regulation could be done. One kind of variation is in the frequencies of the local oscillators along the cord. Further experiments were done to show that frequency differencies along pieces of the cord are maintained for hours, i.e. are not just related to the acute trauma of cutting.

4. Optics.

The optical equipment was purchased in the hope that the voltage dependent dyes that could be monitored by this equipment would be sensitive enough to allow the mapping of connections. This equipment was set up (a considerable amount of work) and preliminary work was done to test dyes. Signals were obtained, but the ration of signal to noise is not yet sufficient to produce the desired results.

It is planned that the equipment will be used in an alternative manner. Cohen is preparing to work with M. O'Donovan on chick spinal cords, and use the setup to measure voltage changes during chick fictive locomotion an movements during early development.

V Work of Marder and collaborators on STG

A. Single cell oscillators (Epstein, Bucholtz, Golowasch, Meyrand, Marder)

In collaboration with Dr. I.Epstein, Dr. F. Bucholtz and Mr. J. Golowasch are writing mathematical models that describe the behavior of isolated LP neurons from the crab stomatogastric ganglion (STG). These data are described in [30, 31, 34–36]

Dr. P. Meyrand studied the activation of the myogenic rhthms of a shrimp muscle by FMRFamide–like peptides. He found that these peptides can transform a passive muscle and a neurogenic muscular system into an oscillatory one that acts myogenically . These data are in [32].

B. Network Oscillators – experimental (Marder, Dickenson, Meyrand, Weimann

Dickenson has recently found that two peptides, RPCH and proctolin can reliable activate rhythmic cardiac sac behavior. Under some conditions the cardiac sac rhythm is transformed from a one–phase rhythm in the presence of RPCH. These data are described in [27].

Dr. Meyrand and Mr.Weimann have been describing neurons that can "move" from one pattern generating circuit to another [29,33]. This is a different view of how neural networks are organized and will be the subject of Mr. Weimann's Ph.D thesis.

Publications [26] and [28] are overviews.

C. Related work on small networks

More investigators have joined to work on issues related to the modelling of crustacean neural networks, and a spinoff group from the Center has been formed, directed by Marder. The group includes Kopell, Epstein and two new people, L. Abbott of the Brandeis Physics Dept., and T. Kepler, a Ph.D. student of Abbott who is now doing a post–doc in the Marder lab. This work is not supported directly by the Center grant, but has been inspired by the Center, and has contributed directly to the thinking of Center personnel, such as Kopell. Abbott produced a mechanism to explain how the phase lag between an oscillator and and excitable neuron might remain constant under changes of frequency in the oscillator; the mechanism is very robust and should work for a large class of relaxation oscillators, including standard models of neurons. This method has led to current work of Kopell on a lamprey–related problem for the regulation of phase lags between a pair of oscillators as the frequency is changed. Marder, Abbott and Kepler have produced a paper on "The effect of the electrical coupling on the frequency of a neuronal ocscillator, with the anti–intuitive answer that the coupling can lead to either an increase or a decrease in the network frequency. This work is motivated by a subnetwork of the STG consisting of an inherent oscillator and a follower cell with electrical coupling. With consultations from this group, Kopell is working with a student on a two cell network modelled on a subnetwork of the STG, with one of the two cells an oscillator. (This work was described above in Section II).

V1 Coordinating Activities of the Center

The collaborations described above have been carried out using a combination of telephone, E–mail and visits. The Center has held annual workshops, each attended by approximately 12–15 people. At these workshops, the progress of the year was reviewed and the strategies for the future were discussed. Also, at each workshop there were several attendees from outside the Center to discuss related scientific problems. In its first year, the Center ran a very well–attended seminar series on Dynamical Systems in Biology; it also hosted many visitors in that and succeeding years.

In addition to fostering research, the Center was actively concerned with the support and training of future scientists. Some of the students and post–docs are listed under personnel of the Center. Other students were also supported (e.g. three at Boston University and one at the University of Pittsburgh) to do training projects related to the work of this grant. This training work continues to grow, and students who participate can take advantage of the combined expertise of the biologists and mathematicians working closely together.

Manuscripts

* 1. G.B. Ermentrout and N.Kopell, "Oscillator death in systems of coupled neural oscillators", SIAM J. Appl. Math. 50:125–146 (1990)

* 2. N. Kopell and G.B. Ermentrout, "Phase transitions and other phenomena in chains of coupled oscillators", SIAM J. Appl. Math. 50: 1014–1052 (1990)

* 3. N. Kopell, G.B. Ermentrout and W. Zhang, "Multiple coupling in chains of oscillators", SIAM J. Math. Anal. 21: 935–953 (1990).

G.B. Ermentrout and N. Kopell, Multiple pulse interactions and averaging in systems of coupled oscillators", to appear in J. Math Biol.

* 5. N. Kopell, G.B. Ermentrout and T. Williams, "On chains of oscillators forced at one end", to appear in SIAM. J. Appl. Math.

* 6. T.L. Williams, K.A. Sigvardt, N. Kopell, G.B. Ermentrout and M.Remler, "Forcing of coupled nonlinear oscillators: Studies of intersegmental coordination in the lamprey locomotor central pattern generator", J. Neurophysiol. 64, (1990) 862–871

7. K.A. Sigvardt, T.H. Williams, N. Kopell and G.B. Ermentrout, "Forcing of non–linear oscillators: studies of intersegmental coordination in the lamprey locomotor central pattern generator" (abstract of the above), in Neural Mechanisms of Behavior, J. Erber, H. Menzel, H. Todt, eds. Stuttgart, 1989.

8. N. Kopell and G.B. Ermentrout, "Coupled oscillators and the design of central pattern generators", Math. Biosciences 90: 87–109 (1988)...

9. N. Kopell, "Toward a theory of modelling central pattern generators", in Neural Control of Rhythmic Movements of Vertebrates, Cohen, Rossignol, Grillner, eds, Wiley, N.Y. (1988)

10. N. Kopell, "Structure and function in an oscillating neural network", in Computational Neuroscience, E. Schwartz, ed., MIT Press, (1990)

* 11. D. Aronson, G.B. Ermentrout and N. Kopell, "Amplitude response of coupled oscillators", Physica D 41: 403–449 (1990).

12. S. Laederich, "Boundary value problems for partial differential equations with exponential dichotomies", Journal of Differential Equations, to appear.

13. S. Laederich, "Periodic solutions of nonlinear differential–difference equations", Zeitschrift fur Angewandte Mathematik und Physik, in press, Jan 1991.

S. Laederich and M. Levi, "Invariant curves and time–dependent potentials", Ergodic Theory and Dynamical Systems, to appear.

15. S. Laederich and M. Levi, "Qualitative dynamics of planar chains", preprint

16. K.A. Sigvardt, "Modulations of properties of neurons underlying rhythmic movements in vertebrates", Seminars in Neuroscience, 1:55–65 (1989).

17. S. Alford and K. Sigvardt, "Excitatory neurotransmission activates voltage–dependent properties in neurons in spinal motor system of lamprey", J. Neurophys. 62:334–342 (1989).

* 18. S. Alford, K.A. Sigvardt, T.L. Williams, "GABAergic control of rhythmic activity in the presence of strychnine in the lamprey spinal cord", Brain Research, 506: 303–306 (1990).

19. T.L. Williams, " The neuro–mechanical link in lamprey locomotion", in Neural and Sensory Mechanisms in Locomotion, D.M. Armstrong and B.M.H. Bush, eds, Studies in Neuroscience Series, Manchester University Press, 227–244 (1991).

20. A.H. Cohen, M.T. Baker and T.A. Dobrov, "Evidence for functional regeneration in the adult lamprey spinal cord following transection", Brain Research, 496: 368–372 (1989)

* 21. A.H. Cohen, "Regenerated fibers of the lamprey spinal cord can coordinate fictive swimming in the presence of curare", J. Neurobiol. 19 (1988) 193–198.

* 22. A.H. Cohen and M.T. Baker, "Functional and non–functional regeneration in the spinal cord of adult lampreys" in International Symposium on Neuronal Regeneration, P.J. Reier, R.P. Bunge and F.J. Seil, eds., A. Liss, N.Y., to appear.

23. A.H. Cohen, T.A. Dobrov, L. Guan, T. Kiemel and M.Y. Baker, "The development of the lamprey pattern generator for locomotion", J. Neurobiol., in press. (1990)

* 24. A.H. Cohen, "Studies of the lamprey central pattern generator for locomotion": A close relationship between modeling and experimentation", in Dynamic Patterns in Complex Systems", J.A.S. Kelso, A.J. Mandell and M.F. Schlesinger (eds), World Scientific Publishing, Singapore, to appear. Appendix by N. Kopell.

25. A.H. Cohen, S.A. Mackler and M.E. Selzer, "Behavioral recovery following spinal transection: Functional regeneration in the lamprey CNS", TINS 11 (1988) 227–231

26. E. Marder and P. Meyrand, "Chemical modulation of oscillatory neural circuits", in Cellular and Neuronal Oscillators, J. Jacklet, ed., Marcel Dekker N.Y. pp317–338 (1989)

27. P.S. Dickenson and E. Marder, "Peptidergic modulation of a multi–oscillator system in the lobster. I. Activation of the cardiac sac rhythm by the neuropeptides proctolin and red pigment concentrating hormone", J. Neurophysiol., 61:833–884.

28. E. Marder and M.P. Nussbaum, "Peptidergic modulation of the motor pattern generators in the stomatogastric ganglion", in Perspectives in Neural Systems and Behavior", T.C. Carew and D. Kelley, eds., Alan Liss Inc, N.Y. pp73–91 (1989).

29. J. M. Weiman, P. Meyrand and E. Marder, "Neurons that participate in several behaviors", in Frontiers in Crustacean Neurobiology, K. Weise, W–D Krenz, J. Tautz, H. Reichert and B. Malloney, eds. Birkhauser Verlag, Basel, pp 424–430, (1990)

* 30. I.R. Epstein, and E. Marder, "Modulation of a conditional neural oscillator: a model describing the action of multiple modulatory substances", Biol. Cyber., 63: 25–34 (1990)

31. J. Golowasch, W. Kumar and E. Marder, "How to modulate neuronal rhythms: from networks to biophysics", in Frontiers in Crustacean Neurobiology, K. Weise, W–D Krenz, J. Tautz, H. Reichert and B. Malloney, *eds.* *Birkhauser* Verlag, Basel, pp 417–423, (1990)

32. P. Meyrand and E. Marder, "Matching neural and muscle oscillators control by FMRFamide–like peptides". J. Neuroscience, in press (1991).

33. J. M. Weiman, P. Meyrand and E. Marder, "Neurons that form multiple pattern generators: Identification and multiple activity patterns of gastric/pyloric neurons in the crab stomatogastric system". J. Neurophysiol., in press (1991).

34. J. Golowasch and E. Marder, "Ionic currents of the Lateral Pyloric Neuron of the Stomatogastric Ganglion of the Crab", submitted (1991).

35. F. Buchholtz, J. Golowasch, I.R. Epstein and E. Marder, "A mathematical model of an identified stomatogastric ganglion neuron", submitted (1991).

36. J. Golowasch, F. Buchholtz, I.R. Epstein and E. Marder, "The contribution of individual ionic currents to the activity of a model stomatogastric ganglion neuron", submitted (1991).