RESEARCH STATEMENT

Alla R. Borisyuk

My primary research efforts focus on mathematical analysis of neuronal models. The motivation for these studies comes from striving to understand information processing in the brain and to supplement experimental approaches in neuroscience. I am particularly interested in how dynamics of neural activity and computations performed by the nervous system are shaped by low-level processes such as single cell properties, network architecture, plasticity of connections between cells, etc.

Another important component of my work is to develop mathematical and computational tools for analyzing the biophysical models, which generally consist of a large number of nonlinear differential equations. I use a broad spectrum of mathematical techniques from dynamical systems theory, integro-differential equations, geometric theory of singular perturbations, stochastic processes, etc. I also supplement them with numerical simulations, using existing software and original codes in Matlab, C, XPP.

As you can see from the description of my research projects below, my work is interdisciplinary in its nature. I strongly believe that application of mathematical tools in biology enables us to address questions that are beyond means of experimental approaches. I also believe that many interesting mathematical questions arise from consideration of biological problems.

1 Responses to dynamic stimuli in the auditory midbrain

Sound waves from a point source reach the two ears at slightly different times. Mammals (including humans) use this interaural time difference (ITD) as a principal cue for azimuthal localization of low frequency sounds. Experiments show that neurons in the auditory midbrain are tuned differently to static (constant) and dynamic (time-varying) ITDs. This is in contrast to neurons in lower level structures, whose dynamic responses trace their static tuning curves.

The goal of my dissertation research, conducted under supervision of Professor J. Rinzel (Courant Institute and Center for Neural Science, NYU) and in collaboration with the experimental lab of Professor M.N. Semple (Center for Neural Science, NYU), was to develop mathematical models to explain the emergence of dynamic stimulus sensitivity.

To achieve this goal, I developed new mathematical models formulated as systems of nonlinear differential equations with slowly varying forcing [3, 4]. We showed with a combination of analytical and computational methods that most properties of auditory midbrain responses to dynamic stimuli can be explained by the convergence of the excitatory and inhibitory inputs, and the presence of cellular mechanisms of firing rate adaptation and post-inhibitory rebound. These results allowed to understand diverse data from several experimental groups within a unified framework. It also enabled us to make experimentally testable predictions.

In another part of this project, we studied the performance of our firing-rate and averaged-voltage models in comparison to a generic spiking model. The issue of a relation between these classes of models is central in the theoretical neuroscience. Firing rate models are usually easier to analyze, but they are often harder to relate directly to the biological system. We derived a reduced formulation from an integrate-and-fire model with adaptation, using the assumptions of slowly varying input and slow adaptation dynamics to perform perturbation analysis of the system. The behavior of the resulting quasi-steady-state averaged model approximates the behavior of the integrate-and-fire cell and is also closely related to the behavior of our averaged-voltage formulation. The same method can also be used to reduce more detailed spiking models.

2 Odor representation and learning in the olfactory system

A prominent conjecture in the field of olfaction is that the behavioral phenomena are in some way based on the representations of odors and on learning-induced changes to these representations in the olfactory bulb (antennal lobe for insects). Before this conjecture is tested electrophysiologically, it is necessary to investigate what types of odor-related activity patterns would be consistent with it. I am working with the experimental group of B.H. Smith (Dept. of Entomology, Ohio State University) to address this question with mathematical models. Our results demonstrate what neuronal mechanisms could underlie various known behavioral phenomena.

My initial work in this field has focused on spatial aspect of odor representations in the honeybee antennal lobe [5, 6]. We employ two types of models: a more biophysically-detailed network of spiking cells, and a more abstract model in the form of an integro-differential equation.

In the network model (as suggested by experiments) the cells are connected with all-to-all fast inhibition and with a local footprint of slow inhibition. To represent learning, we proposed that co-presentation of reinforcement with an odor modifies mutual excitatory connections between network cells and an associative neuron (AN), following the Hebbian learning rule. The AN is the model analogue of a neuron VUMmx1 in honeybees, whose activity is correlated with the presence or expectation of a reward.

In the reduced model the cells form a one-dimensional continuum and their behavior at time t is described by the activation level $u(x, t)$, satisfying:

$$\frac{\partial u}{\partial t} = -u(x,t) + \int_{-\infty}^{\infty} \omega(|x-y|) f(u(y,t)) dy + I(x) + L(x).$$

The firing rate function $f(z)$ is either Heaviside, or threshold-linear, or sigmoidal. The coupling is inhibitory ($\omega \leq 0$), decreasing with distance $|x - y|$, and zero outside of a finite interval. The input $I(x)$ is odor-specific, linear or constant on each of several disjoint intervals. Pre-learning representation of an odor is the steady-state solution, $u_{ss}(x)$ with $L(x) = 0$, and it is unique. After the odor is learned, the learning term $L(x)$ is proportional to the firing rates of the network in the pre-learning steady state, i.e. to $f(u_{ss}(x))$. This model is a much reduced version of the real system; however, it captures the qualitative features of behavioral phenomena, yields analytical results, and allows for a systematic investigation of the parameter space.

Recently, I started working, with collaborators, on extending our models to analyze the *temporal* component of antennal lobe responses to odors (grant proposal [7] submitted to NIH). The issue of whether the temporal features contribute to odor-coding in the olfactory system is hotly debated in the experimental community, and is a source of many theoretical challenges. For example, it is shown experimentally that when presented with an odor, the collective activity of the antennal lobe has oscillatory features that are not present in the spike trains of individual cells. The specific mechanisms for this phenomenon are not understood and can be effectively explored with mathematical models.

3 Network of bursting cells: transitions between activity modes

Bursting is a mode of neuronal activity with relatively slow rhythmic alternations between an active phase of rapid spiking and a phase of quiescence. Many of the experimentally found examples have been successfully modeled, and different types of single cell bursting are sometimes classified based on the bifurcation structure of the corresponding mathematical models. Networks of bursting cells, however, have been characterized to a much lesser extent.

In the earlier modeling studies [9] Butera and collaborators developed complex experimentally constrained models for the brainstem region called pre-Bötzinger complex. It is believed that the inspiratory phase of the respiratory rhythm originates in this region. In the numerical simulations Butera et al. showed that (in agreement with experiments) individual cells can be silent, bursting, or tonically spiking, depending on the level of the tonic depolarizing current that the cell receives. However, when the cells are coupled, the network can burst synchronously for a much larger range of tonic current level. Moreover, the bursting range depends non-monotonically on the synaptic coupling.

In the project [1], with collaborators, we have conducted a thorough mathematical analysis of the mechanisms underlying this dependence of bursting range on parameters, as well as the role of coupling in selecting burst frequency. We have used a non-standard fast-slow dissection approach, incorporating averaging in the slow subsystem, to elucidate multi-dimensional bifurcation structure responsible for transitions from quiescence to bursting and from bursting to spiking. We have found that for a single cell in the bursting regime the active phase starts at the saddle-node bifurcation and terminates at the saddle-node of limit cycles. We have also shown that for a two-cell network it is necessary to consider the two-dimensional space of bifurcation parameters to characterize the transitions and to explain changes in burst and firing frequency.

Our results advance current mathematical understanding of transitions between activity modes in networks of bursting cells. Furthermore, our results also generate experimentally testable predictions relevant to network dynamics in the pre-Bötzinger complex.

4 Separating frequencies with excitatory-inhibitory networks

Excitatory-inhibitory networks arise in many neural systems, including visual cortex, olfactory system, models for thalamic sleep rhythm, parkinsonian tremor, etc. Even though a large number of experimental and theoretical studies have been devoted to studies of these systems, their functional role in information processing in the brain is not understood. It has been suggested that these networks may act to decorrelate signals in a sense that when the network receives inputs correlated with each other, it produces outputs with reduced correlation. To start exploring this issue theoretically, we addressed a simplified question of whether such a network can separate periodic pulse trains. This work [2] is done in collaboration with David Terman and Janet Best at the Mathematical Biosciences Institute, Ohio State University.

We have constructed an algorithm, which takes as an input a pulse train, made as a union of two periodic pulse sequences (with different frequencies). As an output, it produces two separate pulse trains, each having the frequency of one of the original sequences. We have shown that the algorithm performs correctly, with the exception of some special frequency- and phase- relations between the original sequences. Next, we have implemented this algorithm in a biologically-plausible conductance-based excitatory-inhibitory network. We have tested the performance of the network numerically and have shown that it separates over 90% of the inputs, provided their frequencies are in the “optimal” range. Outside of the optimal range the performance deteriorates slightly, but the errors can be corrected by varying phase shifts between inputs or initial conditions for the network. Also, the range of most successfully separated frequencies can be modified by changing model parameters.

Our results demonstrate that excitatory-inhibitory networks are capable of separating frequencies contained in the input. Note that each element in our network is “biophysical”, the cells do not have a preferred frequency, the network does not tune itself to specific frequencies, and the performance is robust to jitter in the incoming pulse trains. We also suggest that such a network may theoretically be used in the brain as an efficient object identifier, if different possible object attributes are coded by different frequencies.

As a next stage of this project we are using stochastic input trains with a fixed correlation structure and study the dependence of the output correlation on the network parameters.

5 Spiking models with adaptation as diffusion processes

In some neurobiological contexts it is important to consider a neuron as embedded in a large network of similar cells or receiving stochastic background input from surrounding tissue. In these cases the voltage evolution is described by stochastic differential equations. For example, a generalized integrate-and-fire neuron with firing rate adaptation can be described by

$$\begin{aligned} dV_t &= (f(V_t) - A_t g(V_t) + I(t))dt + \sigma d\beta_t, \\ dA_t &= -cA_t dt, \end{aligned} \tag{1}$$

with the following condition: when V_t reaches the threshold value b, it is reset to the value $a < b$. At the same time, A_t is increased by an amount, dependent on the value of A_t at the time of the jump.

In these equations, often, $f(v) = -v$ (leaky integrate-and-fire) or $f(v) = v^2$ (quadratic integrate-and-fire). The function $g(v) > 0$, $0 < c \ll 1$ and A_t is the adaptation variable. Our goal in this project (which is in its early stages and is in collaboration with Firas Rassoul-Agha, Mathematical Biosciences Institute, OSU) is to study the behavior of this model for $I(t) = I_0 + I_1 \cos(\omega t)$.

To start, mathematical theory due to Feller [10] allows to consider a one-dimensional version of process (1) (with $A_t \equiv 0$) in the context of rigorously defined stochastic processes. While general multidimensional extensions of this theory do not exist, we believe it can be extended to include full model (1). Earlier work in theoretical neuroscience focused on the adaptation-free case ($A_t \equiv 0$) and either did not include noise [11] or considered $I_1 \ll I_0$ [8] and did not rely on the full strength of stochastic analysis methods.

References

[1] J. Best, A. Borisyuk, J. Rubin, D. Terman, M. Wechselberger. The dynamic range of bursting in a model respiratory pacemaker network, *in preparation*

[2] J. Best, A. Borisyuk, D. Terman. Decorrelation in neuronal systems: separating frequencies, *in preparation*

[3] A. Borisyuk, M. N. Semple, J. Rinzel. Computational model for the dynamic aspects of sound processing in the auditory midbrain. *Neurocomputing* 38: 1127-1134, 2001

[4] A. Borisyuk, M. N. Semple, J. Rinzel. Adaptation and inhibition underlie responses to time-varying interaural phase cues in a model of inferior colliculus neurons. *J. Neurophysiol.* 88: 2134-2146, 2002

[5] A. Borisyuk, B. H. Smith. Odor interactions and learning in a model of the insect antennal lobe. *Neurocomputing* 58-60: 1041-1047, 2004

[6] A. Borisyuk, B. H. Smith. Model antennal lobe: odor interactions in binary mixtures, *in preparation*

[7] A. Borisyuk, B. H. Smith, D. Terman, G. Wright. NIH R01: Importance of temporal information for olfactory codes, *proposal submitted to NIH in October 2004*

[8] N. Brunel, V. Hakim. Fast global oscillations in networks of integrate-and-fire neurons with low firing rates. *Neural Comput.* 11: 1621-1671, 1999

[9] R. J. Butera, J. Rinzel, and J. C. Smith. Models of respiratory rhythm generation in the pre-Botzinger complex: I. Bursting pacemaker neurons, *J. Neurophys.* 82: 382-397, 1999

[10] W. Feller. The parabolic differential equations and the associated semi-groups of transformations. *Ann. of Math. Ser. II.* 55: 468-519, 1952

[11] J. P. Keener, F. C. Hoppensteadt, J. Rinzel. Integrate-and-fire models of nerve membrane response to oscillatory input. *SIAM J. Appl. Math.* 41: 503-517, 1981