Lectures at INRIA 2014 (Paul C. Bressloff, University of Utah)

[1] Molecular motor-based models of random intermittent search.

Abstract: Random search strategies occur throughout nature as a means of efficiently searching large areas for one or more targets of unknown location, which can only be detected when the searcher is within a certain range. Examples include animals foraging for food or shelter, the motor-driven transport and delivery of macromolecules to particular compartments within cells, and a promoter protein searching for a specific target site on DNA. One particular class of model, which can be applied both to foraging animals and active transport in cells, treats a random searcher as a particle that switches between a slow motion (diffusive) or stationary phase in which target detection can occur and a fast motion "ballistic" phase; transitions between bulk movement states and searching states are governed by a Markov process.

In this talk we review recent work on the analysis of molecular motor-based models of random intermittent search. The stochastic search process is modeled in terms of a system of Chapman-Kolmogorov equations, which are reduced to a scalar Fokker-Planck equation using perturbation methods. The reduced FP equation is used to compute various quantities that characterize the efficiency of the search process, including the mean first passage time (MFPT) to target detection. We then consider a number of applications. First, we analyze a biophysical model of bidirectional transport, in which opposing motors compete in a "tug-of-war," and use this to explore how local signaling mechanisms could regulate the delivery of molecular cargo to subcellular targets such as synapses. We then consider a higher-dimensional version of the model applied to an active transport model of cell polarization.

P. C. Bressloff and Jay Newby. Quasi-steady state analysis of motor-driven transport on a two-dimensional microtubular network. *Phys. Rev. E*. **83** 061139 (2011).

J. Newby and P. C. Bressloff. Local synaptic signalling enhances motor-driven transport in neurons. *Phys. Biol.* **7** 036004 (2010).

[2] Breakdown of fast-slow analysis in an excitable neuron with channel noise

Abstract: We consider a stochastic version of an excitable system based on the Morris-Lecar model of a neuron, in which the noise originates from the stochastic opening and closing of Na and K ion channels. It is well known that in the deterministic limit, neural excitability can be analyzed using a separation of time scales involving a fast voltage variable and a slow recovery variable, which represents the fraction of open K channels. Using large deviation theory and

WKB methods, we show that when the number of K channels is finite, fluctuations in the opening and closing of these channels leads to a breakdown in the standard fast-slow analysis, and the level of spontaneous spiking activity cannot be estimated using standard Kramer's rate theory. We also show that an exit time problem for spontaneous action potentials can be formulated by considering maximum likelihood trajectories of the stochastic process.

P. C. Bresslof and J. M. Newby. Stochastic hybrid model of spontaneous dendritic NMDA spikes. *Phys. Biol.* **11**, 016006 (13pp) (2014)

J. M. Newby, P. C. Bressloff and J. P. Keeener. The effect of Potassium channels on spontaneous action potential initiation by stochastic ion channels. *Phys. Rev. Lett.* **111**, 128101 (2013)

[3] Path integrals and large deviations in stochastic hybrid systems

Abstract: We construct a path-integral representation of solutions to a stochastic hybrid system, consisting of one or more continuous variables evolving according to a piecewise-deterministic dynamics. The differential equations for the continuous variables are coupled to a set of discrete variables that satisfy a continuous-time Markov process, which means that the differential equations are only valid between jumps in the discrete variables. Examples of stochastic hybrid systems arise in biophysical models of stochastic ion channels, motor-driven intracellular transport, gene networks, and stochastic neural networks. We use the path-integral representation to derive a large deviation action principle for a stochastic hybrid system. Minimizing the associated action functional with respect to the set of all trajectories emanating from a metastable state (assuming that such a minimization scheme exists) then determines the most probable paths of escape. Moreover, evaluating the action functional along a most probable path generates the so-called *quasi-potential* used in the calculation of mean first passage times based on WKB methods.

P. C. Bressloff and J. M. Newby. Path-integrals and large deviations in stochastic hybrid systems. *Phys. Rev. E* . In press (2014).

[4] Beyond the neural master equation: Stochastic hybrid neural networks

Abstract: One of the major challenges in neuroscience is to determine how noise that is present at the molecular and cellular levels affects dynamics and information processing at the macroscopic level of synaptically-coupled neuronal populations. Often noise is incorporated into deterministic network models using extrinsic noise sources. An alternative approach is to assume that noise arises intrinsically as a collective population effect, which has led to a master equation formulation of stochastic neural networks. In this talk we extend the master

equation formulation by introducing a stochastic model of neural population dynamics in the form of a stochastic hybrid system. The latter has the advantage of keeping track of synaptic processing as well as spiking activity, and reduces to the neural master equation in a particular limit. We consider the particular problem of noise-induced transitions between metastable states of a stochastic network operating in a bistable regime.

P. C. Bressloff and J. Newby. Metastability in a stochastic neural network modeled as a jump velocity Markov process. *SIAM J. Appl. Math.* **12**, 1394-1435 (2013).

P. C. Bressloff. Metastable states and quasicycles in a stochastic Wilson-Cowan model of neural population dynamics. *Phys. Rev. E* **82** 051903 (2010)

P. C. Bressloff. Stochastic neural field theory and the system-size expansion. *SIAM J. Appl. Math* **70** 1488-1521 (2009).

[5] Wave propagation in heterogeneous neural media

Abstract: In this talk we consider two examples of the propgation and extinction of activity in heterogeneous neural media. [A] First, we consider the propagation of CaMKII waves along spiny dendrites; CaMKII is thought to be an important signaling molecule in long-term potentiation. There are at least two sources of heterogeneity in the spine distribution that occur on two different spatial scales. First, spines are discrete entities that are joined to a dendritic branch via a thin spine neck of submicron radius, resulting in spatial variations in spine density at the micron level. The second source of heterogeneity occurs on a much longer length scale and reflects the experimental observation that there is a slow proximal to distal variation in the density of spines. We analyze how both sources of heterogeneity modulate the speed of CaMKII translocation waves along a spiny dendrite. We adapt methods from the study of the spread of biological invasions in heterogeneous environments, including homogenization theory of pulsating fronts and Hamilton-Jacobi dynamics of sharp interfaces. [B] Second, we consider the effects of fast and slow spatial heterogeneities in the synaptic weight distributions on the propagation of waves in neural fields.

P. C. Bressloff. *Waves in Neural Media: From Single Cells to Neural Fields*, 450 pp. (Springer, 2013).

P. C. Bressloff. Propagation of CaMKII translocation waves in heterogeneous spiny dendrites. *J. Math. Biol.* **66** 1499-1525 (2013)

P. C. Bressloff. Spatiotemporal dynamics of continuum neural fields: Invited Topical review. *J. Phys. A* **45** 033001 (109pp.) (2012).

P. C. Bressloff. From invasion to extinction in heterogeneous neural fields *J. Math. Neurosci.* **2** (2012).

[6] A neural field model of binocular rivalry waves

Abstract: We analyze traveling wave solutions in a neural field model of binocular rivalry. We consider two one-dimensional excitatory networks with slow synaptic depression that mutually inhibit each other. Using a slow-fast decomposition, we show how the depression of excitatory synapses in the network corresponding to the dominant eye breaks a left-right eye exchange symmetry, allowing for the propagation of a traveling front solution. The latter is characterized by a retreating activity front in the dominant eye population and an advancing front in the suppressed eye population. We calculate how the speed of the front depends on various physiological parameters, and compare our results with recent experimental studies of binocular rivalry waves. We then analyze the effects of extrinsic noise on wave propagation in a stochastic neural field model. We end by describing recent work on rotating rivalry stimuli and direction selectivity.

S. M. Carroll and P. C. Bressloff. Binocular rivalry waves in directionally selective neural field models. *Physica D.* Submitted (2014)

M. A. Webber and P. C. Bressloff. The effects of noise on binocular rivalry waves: a stochastic neural field model: J*. Stat. Mech: Special issue on statistical physics and neuroscience.* **3** P03001 (2013)

P. C. Bressloff and M. A. Webber. Neural field model of binocular rivalry waves. *J. Comput. Neurosci.* **32** 233-252 (2012).

P. C. Bressloff and M. A. Webber. Front propagation in stochastic neural fields. *SIAM J. Appl. Dyn. Syst.* **11** 708-740 (2012)