My work is on the nonlinear dynamics of neurons, neural networks, and neural populations. These dynamics are beautiful, and are richly varied from setting to setting – at times governed by mechanisms we can distill and explain and at times eluding our best analytical tools. Beyond explaining the emergent dynamics of neural circuits, we want to understand how they encode and make decisions about the sensory world. Making progress on these twin problems requires a range of perspectives and methods. I delight in collaboration with fellow theorists of many different backgrounds, and with cognitive neuroscientists, clinicians, and neurophysiologists. Our methods blend data analysis, dynamical systems, stochastic processes, and information theory – and treat neural dynamics occurring on a number of spatial and temporal scales.

Noise and spike generation in single cells:

We begin at the smallest scale, with fluctuations in the ion channel molecules that drive spikes in single neurons. Traditionally, this *channel noise* is described by piecewise-determinstic Markov processes that are time-consuming to simulate and difficult to analyze. Despite more than a decade of research, it remained unclear what the options are for incorporating channel noise in the model that forms a touchstone for neuroscience: equations of Hodgkin-Huxley (HH) type for the neural spike. We have shown that reformulating the HH system into stochastic differential equations (SDEs) can accurately and efficiently capture channel noise [*Phys. Rev. E,* 2011*, PLOS Comp. Biol.* 2011]. Importantly, the resulting SDEs can be separated so that channel noise becomes a separate stochastic source *added* to the classical HH equations. The result is greater efficiency in computational simulation, and new connections between ion channel kinetics and celebrated mathematical results for the HH system.

Noisy coding and neural prosthetics:

Channel noise is a central issue in the function of *cochlear implant prostheses* for deafness and profound hearing loss. Indeed, this noise source can both limit and shape the information that the implants' electrical stimuli transfer to auditory nerve fibers. In collaboration with Jay Rubinstein (UW Bioengineering / Otolaryngology), we seek to quantify and optimize this encoded information. The key idea is to use reduced point process models from mathematical statistics to capture noisy spiking dynamics [*J. Comp. Neurosci.* 2010; and *J. Neurophys.*, 2012]. The advantage is twofold. First, if very carefully designed, these models can be fit to experimental data with a (provably) one-to-one correspondence between model parameters and key empirical statistics. Second, the models allow for explicit calculations of encoded information, saving orders of magnitude in simulation time and identifying features of spike train responses that correlate with human perception. This advances us toward a computational testbed for novel stimulation patterns that will maximize transmitted information.

Chaos and limits on precise spike patterns:

Stochastic fluctuations are not the only mechanism that can limit spike time precision. With Lai-Sang Young (NYU Mathematics) and Kevin Lin (Arizona Mathematics), we have shown that feedback connections in neural circuits often come with an unexpected price: they can diminish the precision of spike times in single cells by creating dynamical instabilities [*J. Nonlinear Science, 2009; J. Comp. Neurosci., 2009*]. Based on geometrical reasoning and computations of Lyapunov exponents, we identify a novel role for phase-locked oscillations in driving the transition to chaos. We show that such chaos can easily occur in circuits with as few as two cells, and that it occurs even more readily in large circuits.

The structure of these network responses has a highly surprising feature that we believe could strongly impact neural coding. Despite the fact that the chaotic instabilities are very strong (i.e., large Lyapunov exponents), only a small fraction of the cells in a network are impacted at any one time. This "spares" the majority of the network, enabling it to produce precise spike patterns despite the network chaos [*Phys Rev E, 2013*].

Taken together, our results advance a predictive theory of network-generated limitations on spike time reliability and hence temporal encoding of sensory information.

Beyond single cells – the *collective* nature of the neural code:

In the simplest framework for neural coding, neurons are assumed to work as independent transmitters of sensory signals, and the total information is (literally) the sum of the individual parts. While this is appropriate in, for example, the cochlear implant application above, the independence assumption is often invalid: collective effects occur via spike-spike correlations among neurons. Why study these correlations? Their presence can dramatically boost *or* diminish levels of encoded information across a network, but which of these occurs depends subtly on the precise structure of how correlations occur.

The structure of correlations, in turn, depends on the circuit mechanisms that create them. Perhaps the most ubiquitous such mechanism is overlapping, or *convergent*, connectivity across layers, followed by spike-generating nonlinearities at each downstream cell. In principle, this could produce an exceedingly complicated collective response across a neural population. However, with Alex Reyes (NYU Neural Science), Jaime de la Rocha (Barcelona Neuroscience), Brent Doiron (Pittsburgh Mathematics), and Kresimir Josic (Houston Mathematics), we find that the opposite is the case: convergence followed by spike-generation often yields highly systematic correlation structures between pairs of neurons [*Nature*, 2007; *Phys. Rev. Lett.*, 2008; *Phys. Rev. E*, 2010; *J. Neurophys.* 2012]. These structures, in turn, strongly increase or decrease encoded information in ways that we can quantify and understand via information theory [*Neural Comp.*, 2009; *ArXiv, 2013*] – and that we can link to similarities and differences in spiking dynamics for distinct types of neurons. Intriguingly, fundamental aspects of the correlation structure are determined by the Hopf vs. saddle-node normal forms of the underlying neurons.

We next extend our mathematical analysis to capture correlations in networks that add structured patterns of recurrent, or feedback, interactions. We show that a linearly coupled point process representation both (1) accurately predicts recurrent spiking dynamics driven by nonlinear SDEs, and (2) admits an exact series solution that exposes the contribution of successively more-complex network features to correlated spiking [*PLOS Comp. Biol.*, 2011]. We then apply our results to the problem of predicting network-wide levels of correlation in neural networks with random connectivity profiles. Here, we base our prediction of correlations on low order statistics of the graphs: specifically, the prevalence of diverging connectivity motifs, in which one cell provides input to two others, and chain motifs, in which two cells are connected via a third intermediary cell. Together with overall connection probability, we find that these two aspects alone are sufficient to predict network-wide correlation. The result does not depend on a simple truncation of network interactions at paths of a particular length, but instead composes effects of short paths into long ones in a systematic, closed-form manner [*J. Stat. Mech 2013; PRE, 2014*].

The scale of collective dynamics in neural populations:

Emerging multielectrode recording and imaging techniques are yielding simultaneous access to neural populations on unprecedented scales. A fundamental question is whether these populations can be fully described by pairwise correlations, or whether further *higher-order correlations* (among triplets of cells, etc.) also occur. Much hangs in the balance. If higher-order correlations do occur, then neural signal encoding and processing could involve a combinatorial explosion of spike patterns, posing a truly formidable challenge for statistical and dynamical models.

What network mechanisms will determine scale of correlations in neural circuits? With Fred Rieke (UW Physiology / Biophysics), we use dynamical and statistical modeling, together with asymptotics, to identify a key factor. While network responses to bimodal input signals shared by all circuit elements deviate substantially from maximum entropy predictions, responses to unimodal inputs, regardless of connectivity, do not. Our simulations, constrained by intracellular recordings, suggest that this result applies to certain retinal networks across a broad range of light inputs, explaining a number of empirical results and making strong predictions for further experiments [*Frontiers*, 2014; *ArXiV*, 2012, 2013].

Collective spiking and synchrony:

The results above are on the origin of collective spiking for networks driven by strong fluctuations, as typifies many neural circuits. Thus, the key results are based on tools for stochastic processes. In circuits

with less noise, dynamical systems methods reveal the resulting spike patterns as synchrony among subgroups of cells. Our work starts with the simplest, globally-coupled architectures, and phase models of neurons (i.e., coupled flows on the torus). With Phil Holmes (Princeton Applied Mathematics) and Jeff Moehlis (UCSB Engineering), we contribute new results on how the form of their coupling determines the existence and stability of phase-locked states [in *Perspectives and Probs. in Nonlin. Sci.*, 2003]. With Marty Golubitsky (OSU Mathematics) and Josic, we then treat networks with more general coupling architectures. For phase or integrate-and-fire (i.e., one dimensional) models, we find different classes of synchronized, partially synchronized, and spatio-temporally symmetric (i.e., phase-shifted) solutions that are forced to exist by the coupling architecture. The invariance of these solutions restricts and organizes the collective spiking patterns that the network can produce [*J. Nonlinear Science*, 2006].

Beyond coupling interactions, collective spiking can also be driven by common input signals. With Holmes and Moehlis, we show how both type of, and distance from, four typical transitions (bifurcations) to periodic firing determine a neuron's phase response curve, and hence the timing of its spikes in response to coupling currents and external inputs [*Neural Comp.*, 2004, *J. Comp. Nsci.* 2004]. In particular, we find new scaling relationships between "resting" spike frequencies and the amplitude of signal-evoked transients. Moreover, working with Herschel Rabitz (Princeton Chemistry) we show that *optimal* inputs to perturb spikes have the same form and a related scaling to the underlying phase response curves [*J. Comp. Nonlin. Dyn*., 2006]. These results connect the nonlinear dynamics of single neurons with a fundamental aspect of how they process incoming signals.

Restoring collective activity through neural prosthetics:

If connectivity parameters are *mistuned* from normal operating values, as in, e.g., Parkinson's disease, pathological oscillations develop that interfere with network function. In clinical therapy, the network receives global input from a prosthetic device with a stimulating electrode. Typical stimulus patterns overwhelm pathological oscillations with strong, fast impulses. Our work with Rabitz uses complex biophysical models suggest an alternative: if designed with network dynamics in mind, different, weaker waveforms can create instabilities that strongly diminish pathological synchrony [*J. Neuroengineering*, 2007; *J. Comp. Neurosci.*, 2007].

How does this occur, and how general are the underlying mechanisms? We suggest that "elliptic bursting" dynamics in single cells could be responsible for the key desynchronizing effects [*SIAM J. App. Dyn. Sys.*, 2011]. We compute *circle maps* that describe the response to pulsatile stimulation, and trace discontinuities and expansive regions in these maps to separatrices and dynamical slow passage effects. Our result is that this discontinuity and expansion in single cells leads to desynchrony among many.

Neural architectures that compute over time:

How does the brain assess noisy streams of sensory input and decide when enough evidence has accumulated to act? At the core of such decision making must lie neural networks that integrate signals over time. We study the stochastic dynamics of such *neural integrator* circuits. With Holmes, Jonathan Cohen (Princeton Neuroscience), and collaborators, we start by showing that the dynamics of simple circuits of this type can be projected onto slow manifolds, and that the resulting models of drift-diffusion processes crossing thresholds can implement statistically optimal algorithms for decision making [*Stoch. Dyn.*, 2001, *Int. J. Bifn Chaos,* 2005; *Psych. Rev.*, 2006]. This connection between network dynamics and optimal signal processing provides a benchmark for parameterizing and interpreting neural models of decisions. The hypothesis that neural networks in the brain indeed implement these optimal algorithms makes strong and testable predictions for both firing patterns of neural groups and statistical patterns of behavioral performance [*Trans. IEICE*, 2005; *Psych. Rev.*, 2006].

One of these predictions is that decision algorithms require time dependent modulation of the sensitivity (gain) of neural integrators as task-relevant stimuli occur. A hypothesis is that the brainstem area locus coeruleus (LC) is responsible for this modulation, via its release of the neurotransmitter norepinephrine. We compare data on LC firing patterns with predictions under optimality, and find a surprisingly good match [*Int. J. Bifn. Chaos*, 2005, *Neural Comp., 2008*]. This supports a role for the LC in dynamically facilitating decisions – for example, by implementing filters matched to the time course of

incoming sensory information.

A long-standing puzzle is that decision making occurs on timescales substantially longer than those of individual neurons and synapses. These long timescales presumably require network-level mechanisms – such as precisely balanced feedback – that actively sustains constant levels of neural activity. Importantly, *robust* network architectures have been discovered that achieve this balance without implausibly-fine tuning of parameters. The underlying mechanism, however, exacts a price for the sensitivity it provides: robust networks become less sensitive to their inputs. Faced with this tradeoff between sensitivity and robustness, are robust networks plausible candidates for the central cognitive task of *decision making*?

In collaboration with Michael Shadlen (Columbia Neuroscience), we first analyze the impact of lost sensitivity on performance in decision making tasks. To our surprise, we find almost *no* performance degradation in a wide range of robust networks. We explain this via sequential analysis tools from statistics. Next, we show that model predictions match a rigorous battery of experimental constraints from physiology and behavior [*J. Neurophys.*, 2013]. These novel results suggest viability of the robust network mechanism, which could be a widespread solution to the problem of neural decision making over time.

Beyond decision making, neural integrator circuits may also underlie our ability to estimate elapsed time – and explain how this ability is degraded in disease. With John Rinzel (NYU Mathematics / Neural Science), Chara Malapani (Columbia Psychiatry), and collaborators, we use highly idealized integrator models to describe behavioral data from Parkinsonian subjects both on and off dopamine therapy, and find that basic circuit parameters predict highly non-intuitive features of Parkinsonian timing data [*Brain Res.*, 2006]. We investigate the neural dynamics of timing on a finer scale in collaboration with Rinzel and Matthew Matell (Villanova Psychology). Here, we analyze multiunit neuronal data from the cortices of rats performing timing tasks, and find strongly heterogeneous dynamical patterns from cell to cell – a finding that our allied theoretical work suggests can lead to optimally informative codes [*Behav. Neurosci.*, 2011].

Expository writing:

Beyond review articles targeted to colleagues [*Curr. Opinion 2012a, 2012b*], I share the joy and challenge of mathematical neuroscience in articles aimed at three levels of the general science and applied mathematics community. First, targeting our peers in other fields, we discuss the thrill of a new confluence of theoretical approaches to neuroscience in the publications [*Proc. Royal Soc.*, 2006; *SIAM Rev.,* 2011]. Second, targeting students and beginning scholars, we write three co-authored, multimedia articles in the peer-reviewed Scholarpedia (online) to provide accessible overviews of underlying topics in dynamical systems. Finally, we share the beauty and excitement of the field at the advanced high school / beginning college level through our multimedia site `Hodgkin and Huxley and the Mathematics of the Spike,' which was invited as one of the first features of the Society for Industrial and Applied Mathematics' *WhyDoMath* initiative.