



# Reliability, discriminability and stochastic synchronization of olfactory neurons

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## Abstract

Combining computer simulations and electrophysiological experiments we have studied the effect of noise on the responses of olfactory neurons. In particular, we first investigated the reliability of mitral cell responses and found, as previously observed in other neural systems, that, in the presence of background noise, mitral cells reliably respond to fast fluctuating inputs but not to constant stimuli. We then investigated a related property, input discriminability and a closely related phenomenon, stochastic synchronization that may account for the synchronous firing of mitral cells leading to network oscillations in the beta/gamma frequency range. We argue that these phenomena: reliability, discriminability and stochastic synchronization are not exclusive to neurons but are rather common to all devices with a resetting threshold. Therefore we suggest that an artificial nose with a hardware implementation of such devices may optimally operate with low signal-to-noise ratios.

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## 1. Introduction

Sensory systems, both natural and artificial, must reliably respond to stimuli in different and variable environments. Stimulus transduction and coding of sensory information must therefore operate in low signal-to-noise regimes. The understanding of the biophysical mechanisms for reliable neural coding and information processing in real sensory systems may inspire the design of artificial sensor technologies that operate optimally even with high levels of background noise. Combining computer simulations of neurons and electrophysiological experiments we have first studied the effect of noise on the fidelity of neural responses in the olfactory system. Then we have studied the ability of a given neuron to discriminate between similar fluctuating inputs in the presence of noise. Finally we have studied how different neurons can synchronize their electric discharges, even when they are not synaptically coupled, by their response to fluctuating, partially correlated input currents. We call this

mechanism for neural entrainment *stochastic synchrony*. We propose that it underlies the generation of gamma oscillations in the olfactory system and provide convincing evidence that mitral cells that are not synaptically coupled in the olfactory system can still synchronize their discharges by receiving common inhibitory barrages from the interneurons to which they are synaptically connected. The synchronization of mitral cells that are activated by an odor can enhance the neural representation of that odor and therefore facilitate its detection by a downstream olfactory network, as recently proposed [1].

## 2. Methods

For the electrophysiological experiments on mitral cells we used standard electrophysiological procedures as described in detail by Urban and Sakmann [2]. Briefly, acute brain slices of the olfactory bulb of mice were prepared. Then mitral cells in the slice were pharmacologically isolated from the network by blocking synaptic transmission. This permitted us to study the response of single neurons to controlled input currents plus added noise with whole-cell patch-clamp techniques. For the computer simulations we used the neural model proposed by

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Izhikevich [3], which captures many dynamical features of biological neurons with a few parameters (see below).

### 2.1. Computational modeling

All computer simulations were implemented in Matlab using the simple neural model proposed recently by Izhikevich [3], which produces voltage traces reminiscent of many different neurons in the central nervous system:

$$\begin{cases} \frac{dv}{dt} = 0.04v^2 + 5v + 140 - u + I(t) \\ \frac{du}{dt} = a(bv - u) \\ \text{threshold condition : if } v > 30 \\ \text{then } v = c, u = u + d \end{cases}$$

with  $v$  as the membrane potential and  $u$  as the recovery variable. In all simulations shown the parameters had the following values:  $a=0.02$ ,  $b=0.2$ ,  $c=-65$ ,  $d=2$ . This parameter choice corresponds to a neuron showing subthreshold resonance, and displaying class II excitability [4,5]. We chose this dynamical regime because type II excitability accounts for four properties of mitral cells: onset of repetitive firing at a finite frequency [6], post-inhibitory spikes [6], subthreshold oscillations [6] and partially negative phase-resetting curves [7]. Nevertheless, stochastic synchrony was also observed in this model for type I excitability (parameter choice  $a=0.02$ ,  $b=0.05$ ,  $c=-65$ ,  $d=2$ ). The simulated mitral cells were not directly coupled to each other but rather received partially common inhibitory inputs from granule cells, which modeled granule-cell-mediated inhibition. The granule cells were not explicitly modeled, but rather the stochastic currents they provide to the mitral cells, as described below.

The total input current to the cells  $I(t)$  had three components: (1) steady state depolarizing current modeling input from olfactory receptor neurons, the amplitude of which was varied between 3.6 and 6 (arbitrary units) in different simulations to generate sustained firing at the desired frequency; (2) the (correlated) inhibitory input from granule cells, which typically had an amplitude of one or smaller; (3) white-noise uncorrelated inputs, the amplitude of which was varied between 0 and 20% of the peak synaptic current, describing background noise.

### 2.2. Generation of correlated inhibitory currents

The inputs from granule cells into real or simulated mitral cells were generated either as miniature inhibitory postsynaptic currents (IPSC) or as white noise convolved with an alpha function (alpha noise). The IPSC-like inputs were generated in three steps: (1) for each correlation level ( $C_{in}$ ), an independent Poisson train was generated for each neuron ( $P_1, P_2, \dots, P_n$ ), plus an additional template Poisson train ( $P_0$ ). (2) For each input Poisson train ( $P_1, P_2, \dots, P_n$ ), every event had a probability  $C_{in}$  of being removed and every event of the template train had the same probability of being inserted in the input train. By proceeding this way, every input train shared on average a fraction  $C_{in}$  of events

with the template. (3) These correlated Poisson trains were then convolved with a negative alpha function ( $\alpha(t) = -t/\alpha e^{-t/\alpha}$ , time-to-peak  $\alpha = 3$  ms) to produce synaptic-like current traces ( $T_0, T_2, \dots, T_n$ ) that were used as input to mitral cells.

Alpha-noise correlated inputs were produced in three steps: (i) uncorrelated white noise inputs of unitary variance were generated. (ii) These signals were linearly mixed by multiplying them with the Cholesky factor of a symmetric, positive-definite matrix with unitary diagonal elements. The off-diagonal elements of this matrix were randomly chosen from a uniform distribution between  $C_{in} - 0.1$  and  $C_{in} + 0.1$ , where  $C_{in}$  is the desired mean correlation value. The matrix generated this way is an estimator of the correlation matrix of the mixed signals. (iii) The mixed (i.e. correlated) signals were convolved with an alpha function ( $\alpha = 3$  ms) that models synaptic filtering.

### 2.3. Analysis of reliable/correlated responses

Two standard data-analysis techniques (Matlab, signal processing toolbox) were applied to estimate the degree of reliability/synchrony induced by correlated input fluctuations in real and simulated neurons: cross-correlation analysis and spectral analysis. The cross-correlations between neural responses were calculated in three steps: (i) the membrane potential traces were replaced by binary spike trains (1 = spike, 0 = no spike). (ii) The spike trains were convolved with Gaussians of half-width sigma. For sigma > 4 ms the following calculations did not differ substantially (see Figs. 3 and 4), so we concluded that setting sigma to 5 ms was a reasonable choice to allow tolerance for jitter without influencing the estimation of synchrony (Figs. 1 and 2). (iii) The correlation matrix of the resulting traces was calculated and the off-diagonal elements averaged. Depending on our focus, this provided us with a scalar measure of the reliability of a single neuron's response to successive trials or with a scalar measure of the degree of synchrony between different neurons.

In addition, to compare the relative synchrony resulting from various kinds of inputs delivered to small numbers of real or modeled neurons an estimate of the local field potential (LFP) was calculated. This estimate was the average of the low pass filtered (six pole butterworth filter, 100 Hz cutoff) membrane potentials recorded in multiple cells, or in some cases across multiple responses in the same cell. The estimated LFP was inverted for display purposes to match LFPs that are recorded extracellularly in vitro and in vivo. Calculating the power spectrum of this estimated LFP gave us a means by which to compare the fraction of neurons responding at a given time to a particular stimulus and also allowed us to compare the degree to which cells were activated at the same time by different stimuli. The power spectrum was calculated with the Welch method (i.e. averaging the spectra estimated over smaller, overlapping windows; total signal length: 10 000 ms; window size: 1024 ms; overlap: 512 ms).

## 3. Results

First, we studied neural reliability, i.e. how reproducible the response of the neuron is to several trials with the same stimulus.

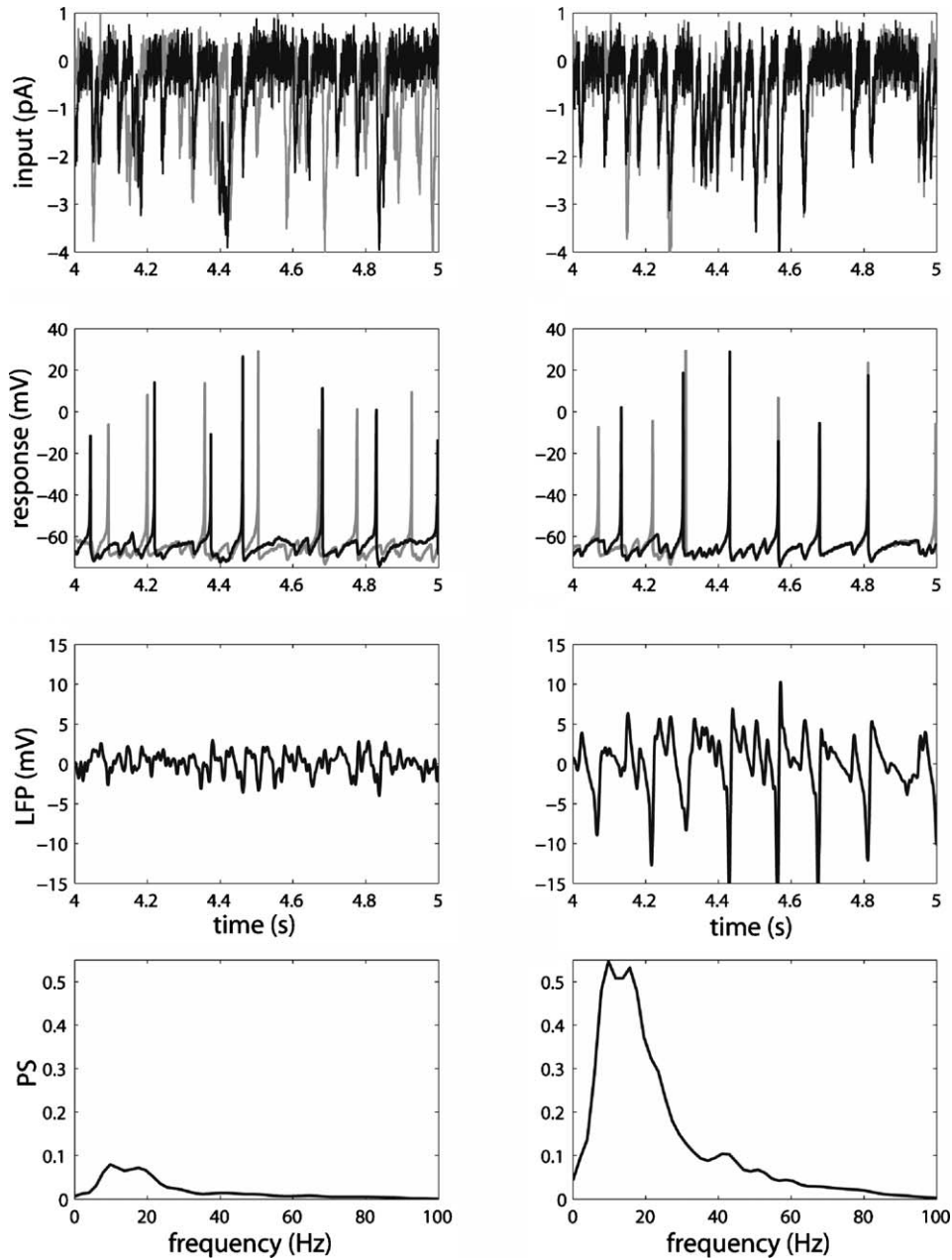


Fig. 1. Results of computer simulations. The figure has two interpretations. One as an example of mitral cell reliability, and two as an example of stochastic synchronization across mitral cells. (1) Mitral cell reliability: a single mitral cell responds to two successive different fluctuating currents (left) and to two successive similar ones (right) in the presence of background noise. The neuron responses become increasingly similar as the input currents are more similar. (2) Stochastic synchrony across mitral cells: several mitral cells (only two are shown) receive uncorrelated, fluctuating input currents and correlated ones in the presence of background noise. As a result the local field potential (LFP) indicates a large network oscillation in the later case (right) but not in the former (left). The power spectrum (PS) of the LFP clearly reveals coherent network activity in the band enclosing the firing rates of the mitral cells.

The stimuli consisted either of step currents or of fast fluctuating signals (low-pass filtered white noise or synaptic-like currents) that were unchanged across trials (frozen fluctuating inputs; see Section 2). Then, different amounts of perturbing white noise were added in different experiments (background noise was typically 20% of the signal amplitude). As previously found in other neural systems [8–10], we observed that in the presence of moderate levels of background noise olfactory neurons respond reliably only to fast fluctuating inputs in both, computer models (Fig. 1) and patch-clamp experiments (Fig. 2). In partic-

ular, the inhibitory input pulses tend to reset the voltage traces to similar values, so that if the pulses are reliable across trials, the response of the neuron will be reliable as well. Analogously, if input pulses are shared across several neurons, these neurons are likely to synchronize their activity, as we explain below.

The amplitude of the pulses used in the simulations and experiments mimics physiological values of inhibitory postsynaptic currents (<10 pA). Work in progress is addressing the robustness of reliability and stochastic synchrony with respect to variations of intrinsic cell properties as well as to the amplitude and waiting

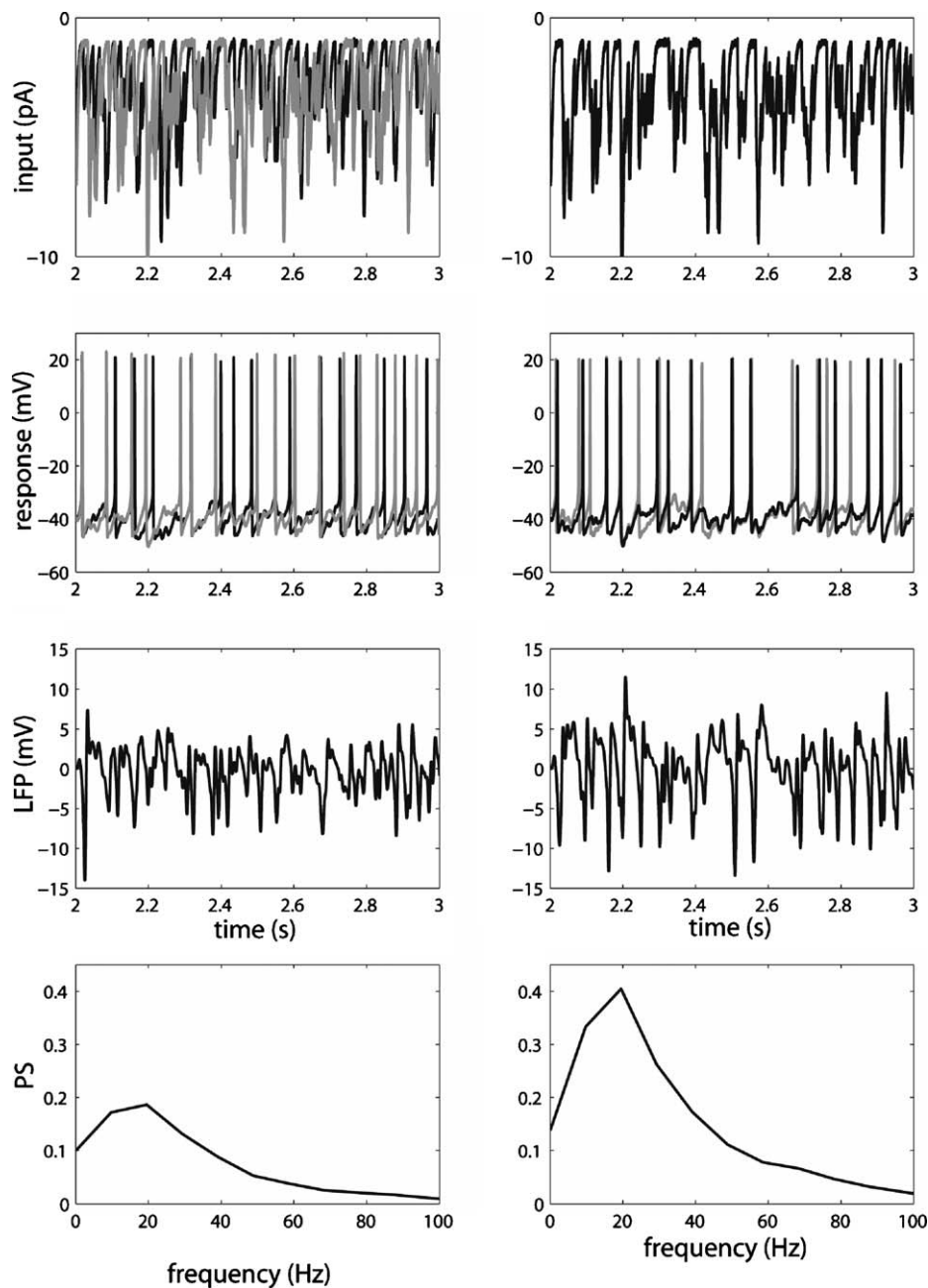


Fig. 2. Experimental results. Same analysis as in Fig. 1 but with electrophysiological data from patch-clamp recordings in mitral cells. The effects of neural reliability and stochastic synchronization are less pronounced in the experiments because of the larger background noise from intrinsic sources. In spite of this, note the qualitative agreement with the computer simulations.

time of the pulses. Preliminary results reveal the robustness of neural reliability and stochastic synchronization with respect to intrinsic variability of cell parameters in both, simulations and experiments.

Our detailed study of the computer models revealed that a resetting threshold and synaptic (input low-pass) filtering are sufficient for a neuron to respond reliably to fluctuating inputs in the presence of background noise. Indeed, both elements together constitute a minimalist model of a neuron, so that any neuron can in principle respond reliably to fluctuating signals in a noisy environment. However, a quantitative improvement

(50%) of this effect is obtained when the neuron behaves as a subthreshold resonator (band-pass filter) rather than a subthreshold integrator (low-pass filter; data not shown). Interestingly, many neuronal types can be cast in one of these two categories [4,5] and in particular, recent work by the authors shows that mitral cells in the olfactory system behave as resonators [7].

We then investigated the reliability of the neural response, not to several repetitions of the same stimulus but to several trials of less and less similar stimuli. Thus, we studied the discriminability of inputs by mitral cells. We found that mitral cells trigger similar spike trains when stimulated with similar random

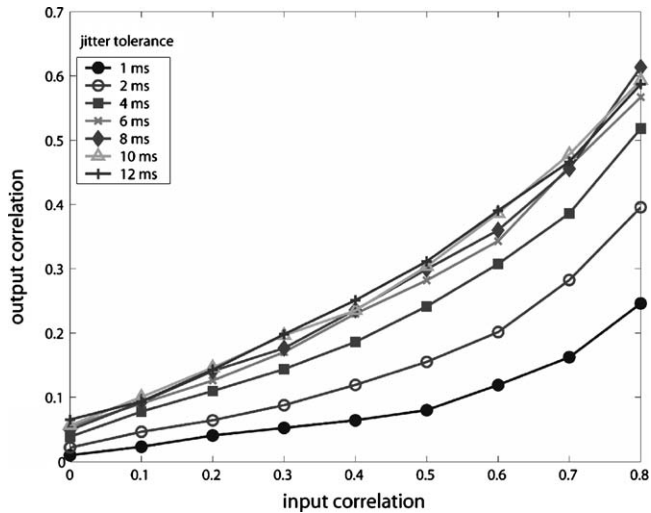


Fig. 3. Input–output relationship in computer simulations. The figure has two interpretations. One in terms of single mitral cell discriminability, and two showing the monotonous increase of average synchrony (correlation) across mitral cells with increasing average correlation of the inputs. (1) Mitral cell discriminability: the responses of a single mitral cell to successive fluctuating inputs are the more similar the more similar the inputs. (2) The synchrony (cross-correlation) across mitral cells becomes more apparent with increasing average correlation across input currents. The correlation of the outputs is calculated as the correlation coefficient of the spike trains of mitral cells (see Fig. 1, second row) convolved with a Gaussian of width  $2\sigma$ . Spikes that occur in different cells within a time window of  $2\sigma$  (jitter tolerance) are regarded as synchronous and contribute to the output correlation. The results show that correlated fluctuating inputs trigger synchronous spikes in different cells within a time window of 4 ms.

inputs. Moreover, the similarity (correlation) of the responses was a monotonic increasing function of the similarity of the stimuli (Figs. 3 and 4). This property applies to any device with a resetting threshold, like neurons: whereas the first order statistics of the inputs (mean) determines the number of spikes fired within a given time window, the second order statistics (fluctua-

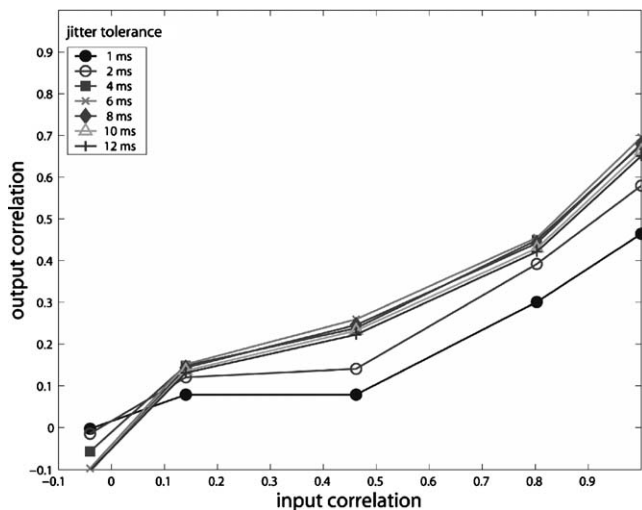


Fig. 4. Input–output relationship in mitral cells. Same analysis as in Fig. 3 but with electrophysiological data from patch-clamp recordings in mitral cells. The discriminability and the increase of stochastic synchronization with increasing average input correlation follow the same pattern as in computer simulations.

tions) determine the timing of the threshold crossings. Thus, the more similar the input fluctuations are, the more similar are the responses. We therefore concluded that devices with a resetting threshold are optimal to reliably detect and discriminate fluctuating signals even when they are contaminated by background noise.

Reliability and discriminability are single-cell properties. However, neural reliability is conceptually equivalent to a ubiquitous network property: synchrony. In effect, instead of considering a single neuron stimulated several times by the same input, one can consider an ensemble of identical cells stimulated by the same input. If one cell reliably responds to that stimulus, the neural ensemble will be synchronized. In addition, if the identical cells of the ensemble receive, not identical, but only similar (correlated) inputs the neurons will not perfectly synchronize but their firing will still be correlated. In fact they will be synchronized on average. The degree of synchronization depends on the degree of similarity between inputs. Interestingly, such a neural ensemble provides a simple but realistic model of the olfactory bulb dynamics: mitral cells have similar electrophysiological properties and are not synaptically connected to each other if they belong to different glomeruli [2,11]. Yet they are able to synchronize around their typical firing rate during *in vivo* stimulation (20–60 Hz) [12]. A possible solution of this paradox is provided by the fact that mitral cells excite local interneurons (granule cells) which in turn inhibit several mitral cells by releasing GABA neurotransmitter in a stochastic manner [13]. As a net result, mitral cells receive spatially correlated inhibitory currents that make them fire most of their spikes at the same time. In other words, the stochastic *disynaptic* inhibition between mitral cells via granule cells can effectively synchronize the mitral cells. Finally, the ensemble of synchronous mitral cells could be easily read out by a downstream neural network by a mechanism of coincidence detection, as recently proposed [1].

#### 4. Conclusions

In summary, we have shown that real and artificial neurons (devices with a resetting threshold) reliably detect and discriminate fast fluctuating signals even in the presence of background noise. In addition, similar stimuli yield similar neural responses. These single-cell properties also help elucidate the mechanisms underlying stochastic neural synchronization and in particular, in the olfactory bulb, the generation of beta/gamma oscillations.

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## Biographies

**Roberto Fernández Galán** received a masters degree in physics from the Universidad Autónoma de Madrid in 1999 and obtained his PhD in theoretical biophysics from the Humboldt Universität zu Berlin in 2003. Currently he is an associate researcher in the Department of Biological Sciences of Carnegie Mellon University in Pittsburgh, where he combines computer simulations and electrophysiological recordings to study neural dynamics in the olfactory system of mice. He is also affiliated to the Center for the Neural Basis of Cognition in Pittsburgh. His research interests focus on natural sensory coding, neural dynamics and, more generally, on topics crossing the boundaries between physics and biology.

**G. Bard Ermentrout** received his PhD from the University of Chicago in biophysics and theoretical biology. He is a professor of mathematics and neurobiology at the University of Pittsburgh where he has been on the faculty since 1982. In 2004 he was appointed as university Professor of Computational Biology. In addition to his work in theoretical biology, he is interested in gardening and exotic birds.

**Nathaniel N. Urban** obtained his PhD from the University of Pittsburgh before doing postdoctoral work in the lab of Bert Sakmann at the Max-Planck Institute for Medical Research in Heidelberg Germany. Since 2002, Urban has been an assistant professor in the department of Biological Sciences at Carnegie Mellon University in Pittsburgh, Pennsylvania. Urban is interested in the computational properties of single neurons and small circuits and specifically on mechanisms and functions of lateral inhibition in the olfactory system.