Current Topics in Biophysics (BPHS 2090)

Instructor: Prof. Christopher Bergevin (cberge@yorku.ca)

Website: http://www.yorku.ca/cberge/2090F2015.html

York University
Fall 2015 (11/24/15)

References/Acknowledgement:
→ see webpage

"Current Topic"

PNAS

Effects of confinement on models of intracellular macromolecular dynamics

Edmond Chow[a,1] **and Jeffrey Skolnick**[b]

[a]School of Computational Science and Engineering, Georgia Institute of Technology, Atlanta, GA 30332; and [b]Center for the Study of Systems Biology, School of Biology, Georgia Institute of Technology, Atlanta, GA 30332

Edited by Michael L. Klein, Temple University, Philadelphia, PA, and approved October 22, 2015 (received for review July 28, 2015)

BIOPHYSICS AND COMPUTATIONAL BIOLOGY

The motions of particles in a viscous fluid confined within a spherical cell have been simulated using Brownian and Stokesian dynamics simulations. High volume fractions mimicking the crowded interior of biological cells were used. Importantly, although confinement yields an overall slowdown in motion, the qualitative effects of motion in the interior of the cell can be effectively modeled as if the system were an infinite periodic system. However, we observe layering of particles at the cell wall due to steric interactions in the confined space. Motions of nearby particles are also strongly correlated at the cell wall, and these correlations increase when hydrodynamic interactions are modeled. Further, particles near the cell wall have a tendency to remain near the cell wall. A consequence of these effects is that the mean contact time between particles is longer at the cell wall than in the interior of the cell. These findings identify a specific way that confinement affects the interactions between particles and points to a previously unidentified mechanism that may play a role in signal transduction and other processes near the membrane of biological cells.

Significance

We use Brownian and Stokesian dynamics simulations to explore diffusion processes within an idealized biological cell. Although most studies assume processes occurring in an infinite medium, we focus on the effect that confinement within a cellular membrane may have on intracellular dynamics. One finding is that model proteins near the membrane tend to diffuse along the membrane; this may give additional time for signal transduction across the membrane to occur. We also observe more strongly correlated motions near the membrane than in the cell's interior, potentially facilitating interactions between proteins there. Finally, we find that deep in the interior of the model cell, the confining effects of the finite size of a cell on the dynamics can be neglected.

confinement | cell wall | Brownian dynamics | Stokesian dynamics | hydrodynamic interactions

www.pnas.org/cgi/doi/10.1073/pnas.1514757112

“Current Topic”

Effects of confinement on models of intracellular macromolecular dynamics

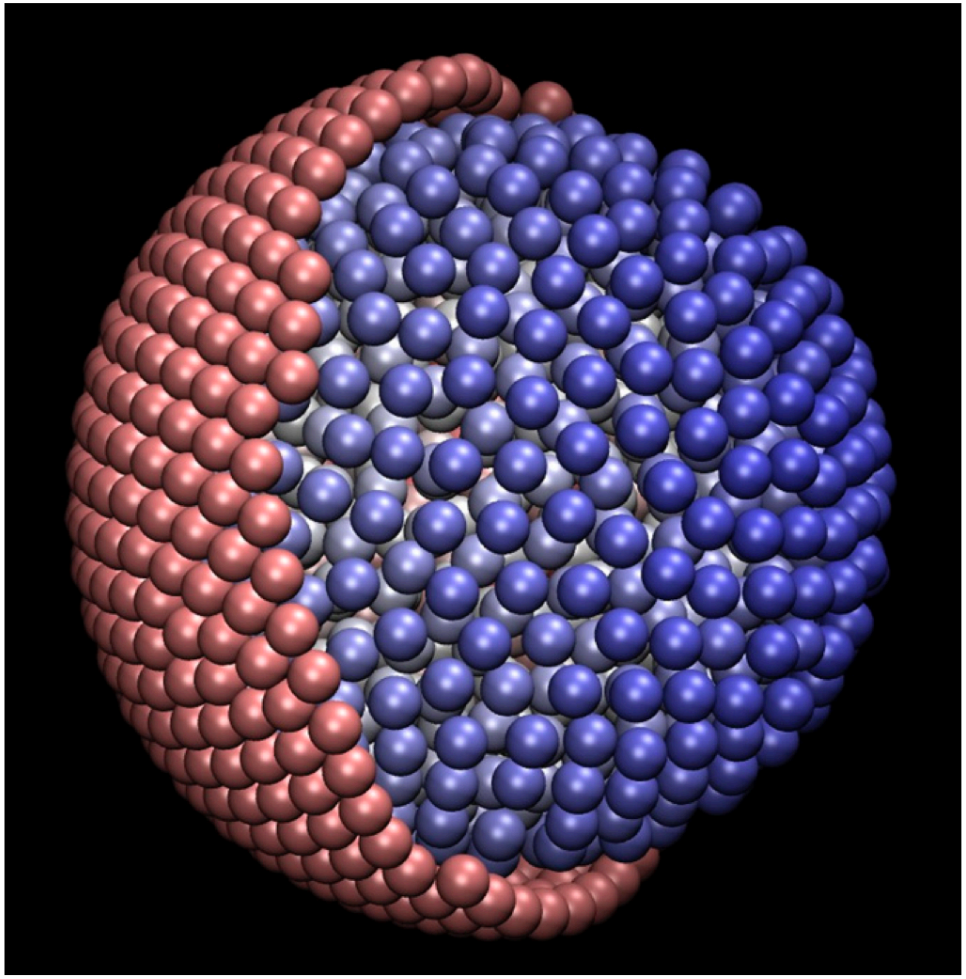
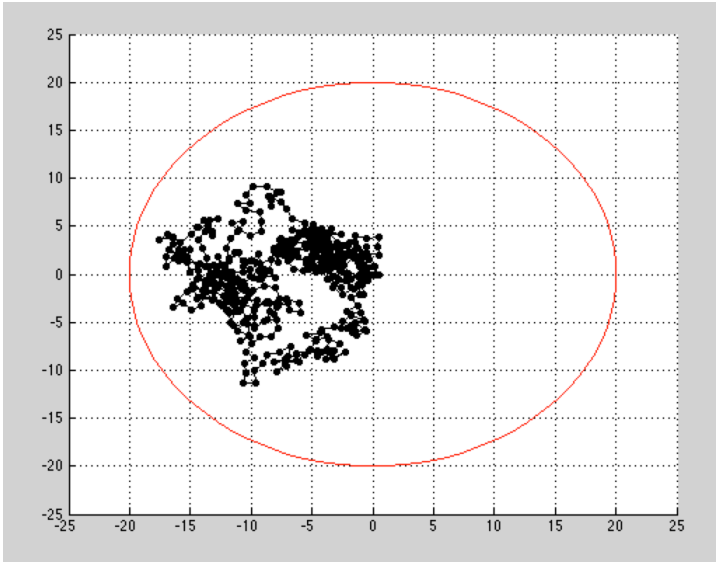


Fig. 1. Configuration for a simulation with 1,000 cytoplasm particles (in blue) and 841 wall particles (in pink). A hemisphere of the wall particles is removed to show the interior of the model.

EXwalker2D.m



www.pnas.org/cgi/doi/10.1073/pnas.1514757112

"Current Topic"

Effects of confinement on models of intracellular macromolecular dynamics

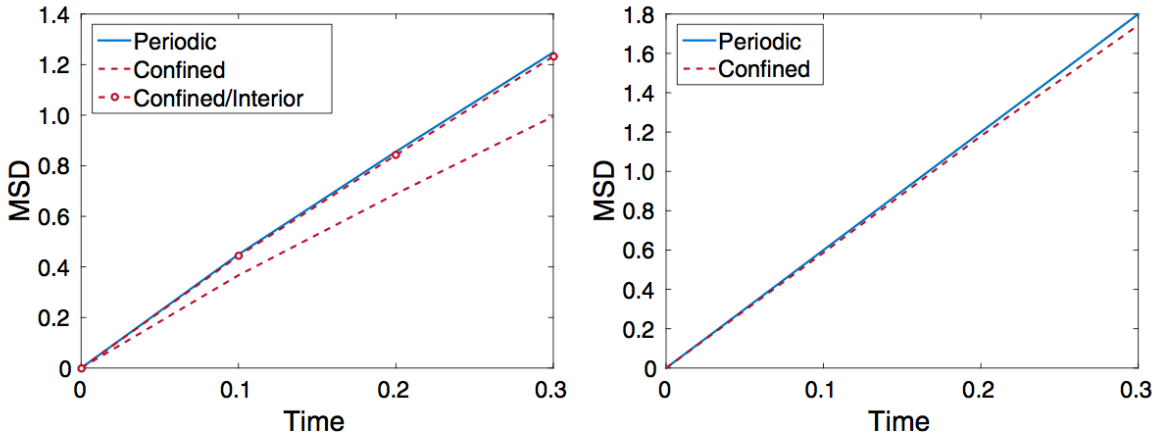


Fig. 2. MSD for 1,000 particles under periodic and confined conditions, the latter in a spherical cell of radius 14.4. (*A*) For BD with HI, there is a slowdown of particles in the confined case compared with the periodic case. This slowdown is also observed, but is very small, for particles in the interior of the cell that never encounter the boundary. (*B*) For independent but confined Brownian particles, the artificial slowdown of diffusion compared with diffusion in periodic simulations is very small over a time interval of 0.3.

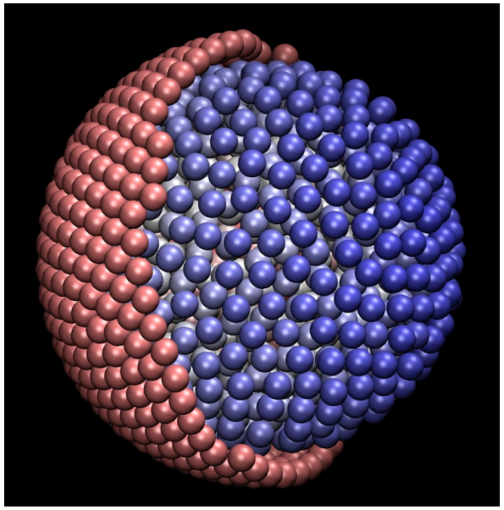
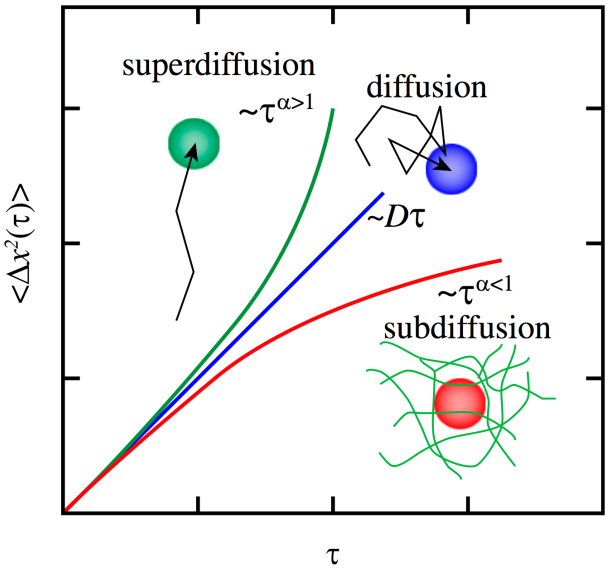


Fig. 1. Configuration for a simulation with 1,000 cytoplasm particles (in blue) and 841 wall particles (in pink). A hemisphere of the wall particles is removed to show the interior of the model.



www.pnas.org/cgi/doi/10.1073/pnas.1514757112

"Current Topic"

Effects of confinement on models of intracellular macromolecular dynamics

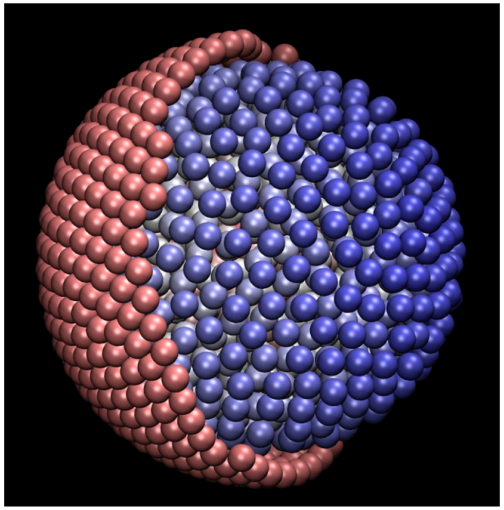


Fig. 1. Configuration for a simulation with 1,000 cytoplasm particles (in blue) and 841 wall particles (in pink). A hemisphere of the wall particles is removed to show the interior of the model.

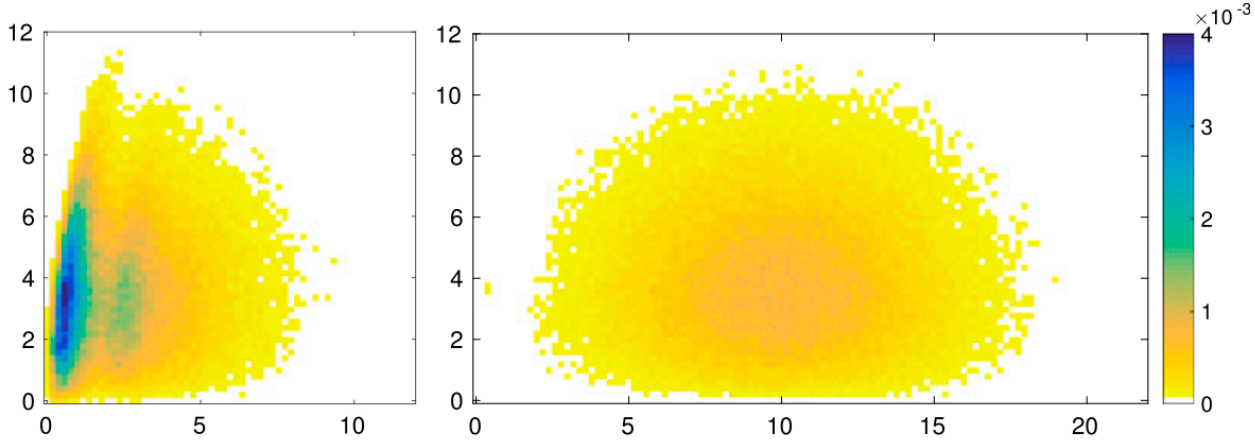
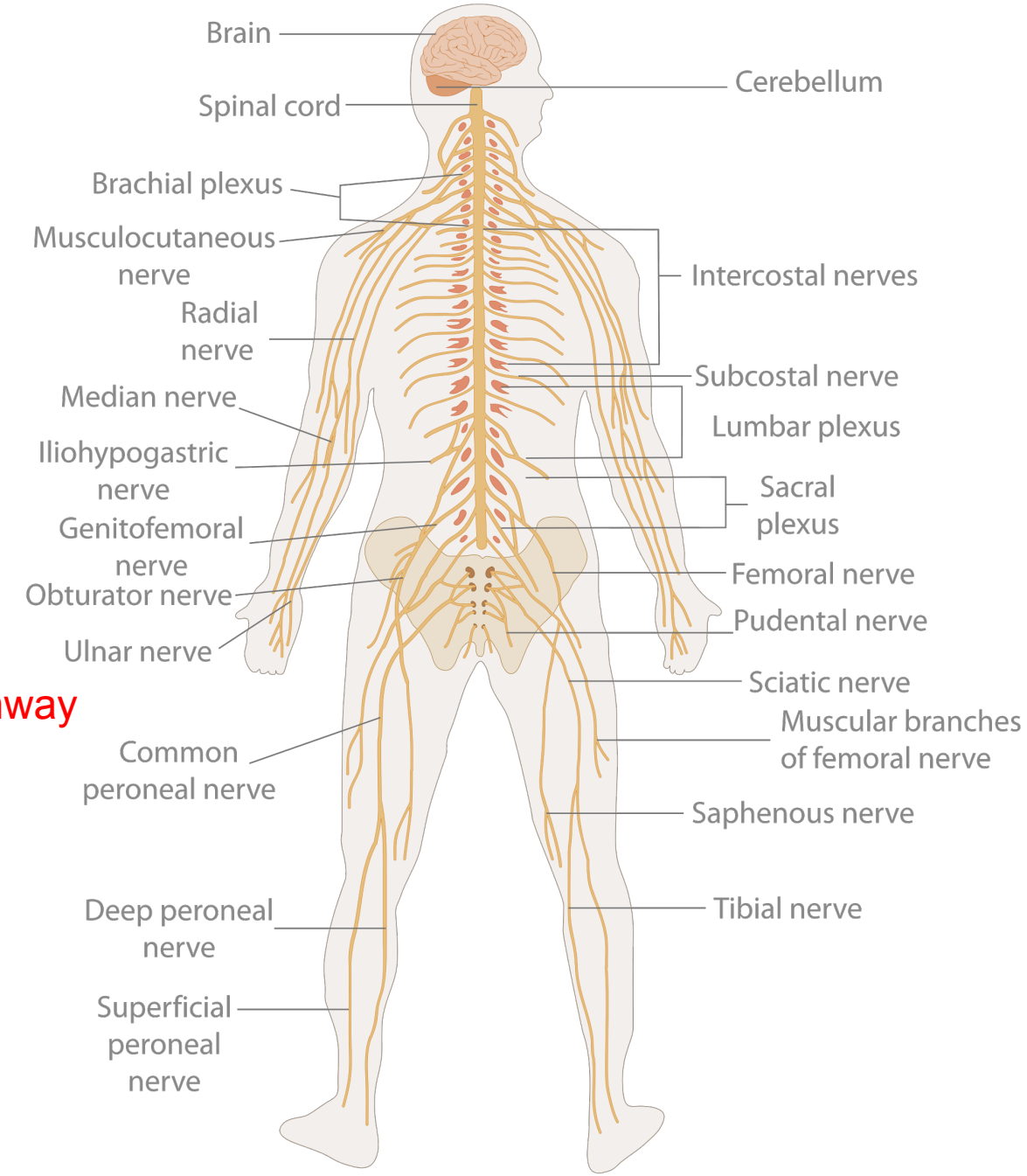


Fig. 6. Particle distribution after a time interval of 10 for the case of 20,000 cytoplasm particles in BD simulations with HI. Results are plotted on a portion of a semicircular disk of radius 40 and centered on the plane at (40,0). (*A*) When the particle is initially at the wall, the particle has a tendency to stay near the wall. (*B*) For a particle initially away from the wall, at (10,0), the particle has a tendency to diffuse relatively uniformly.

www.pnas.org/cgi/doi/10.1073/pnas.1514757112

Moving on: Nervous system

Neurons = Information highway



Wikipedia (nervous system)

Neurons

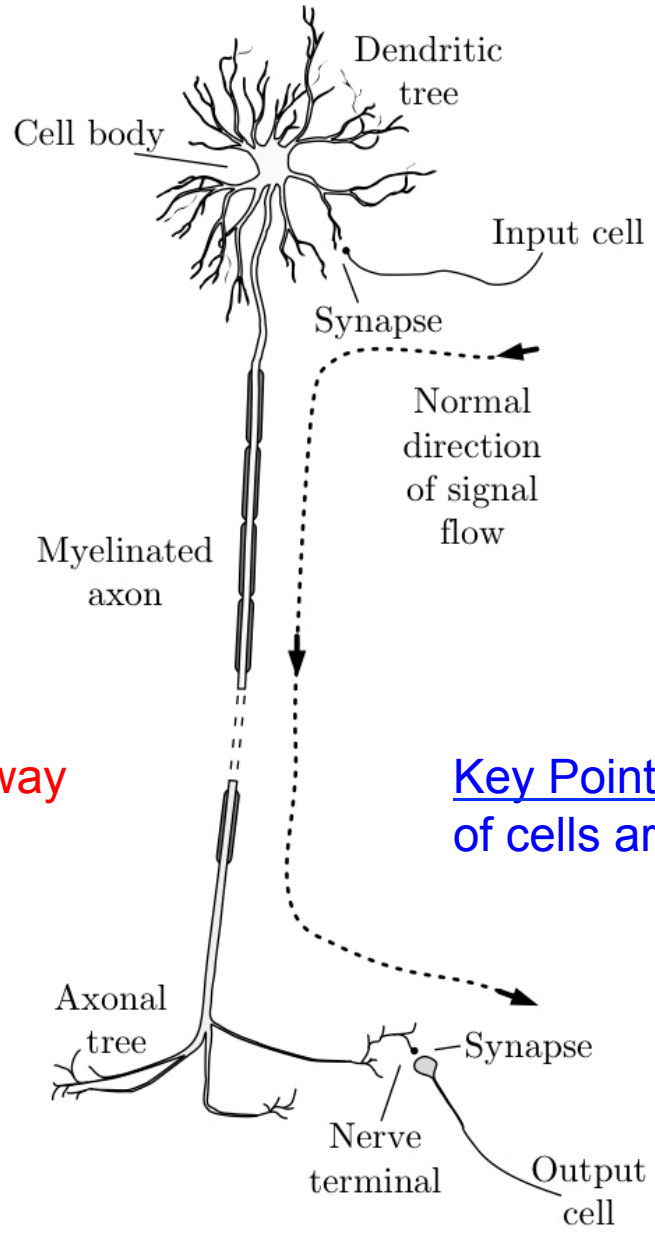


Figure 1.22

Neurons = Information highway

Key Point: Electrical properties of cells are important

Weiss (1996)

Neurons

Human brain contains ~10^{11} (100 billion) neurons!
(with 100 trillion+ connections inbetween)

National Geographic

Action potentials

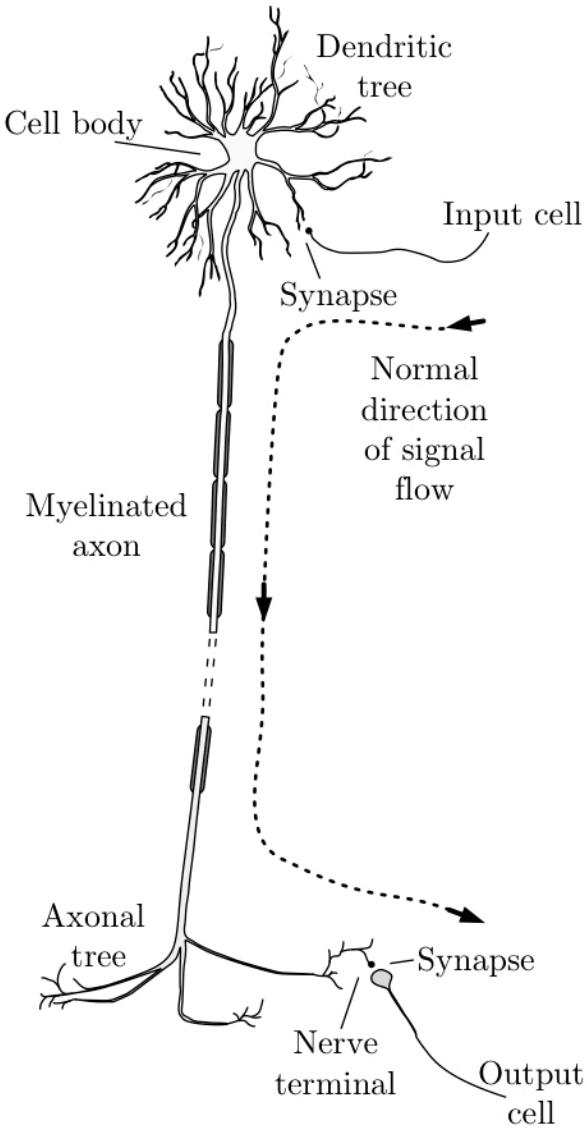


Figure 1.22

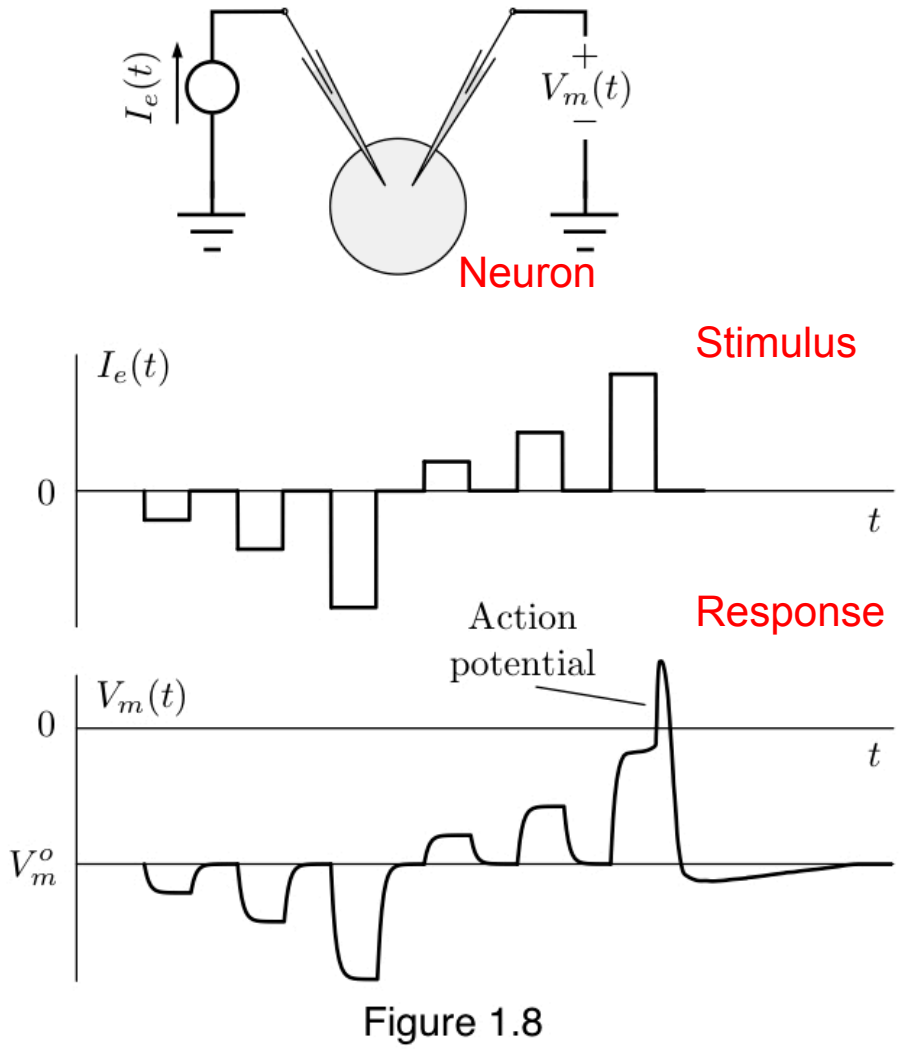
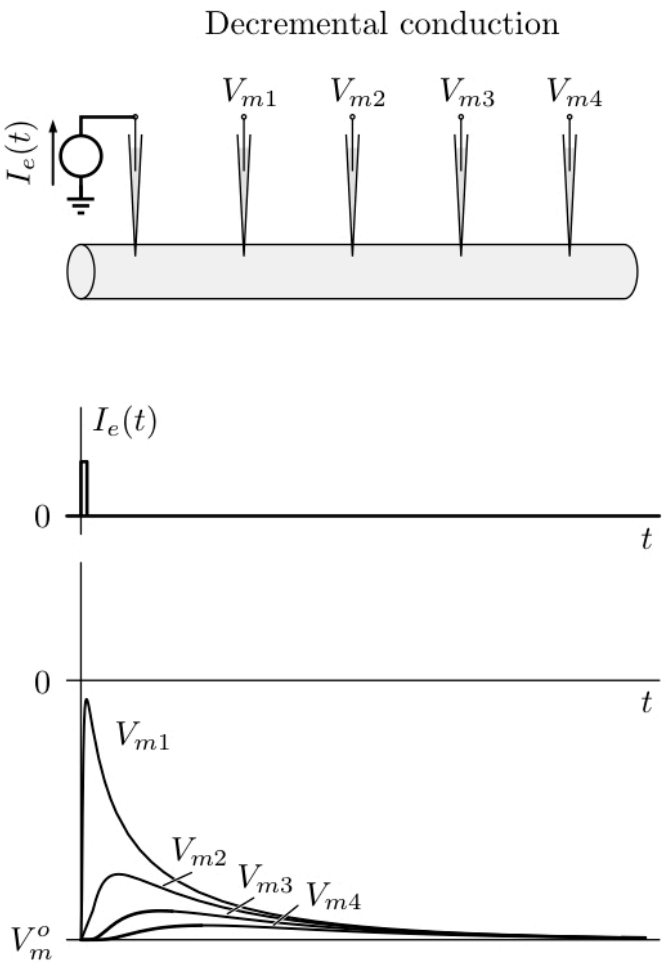


Figure 1.8

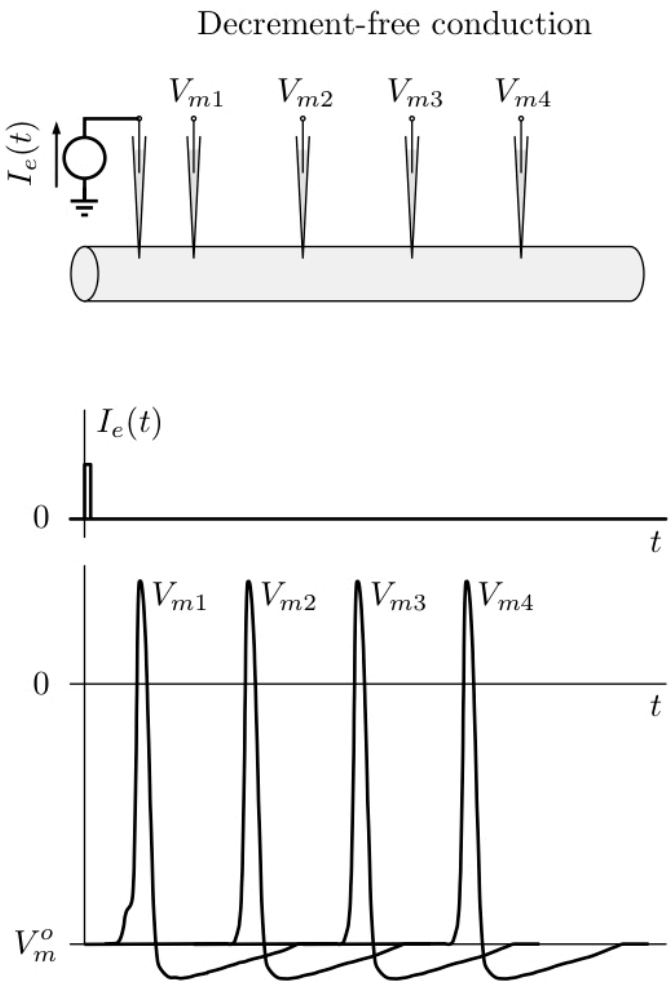
- Spikes!
- Key property here is transmembrane potential

Weiss (1996)

Electrical excitability

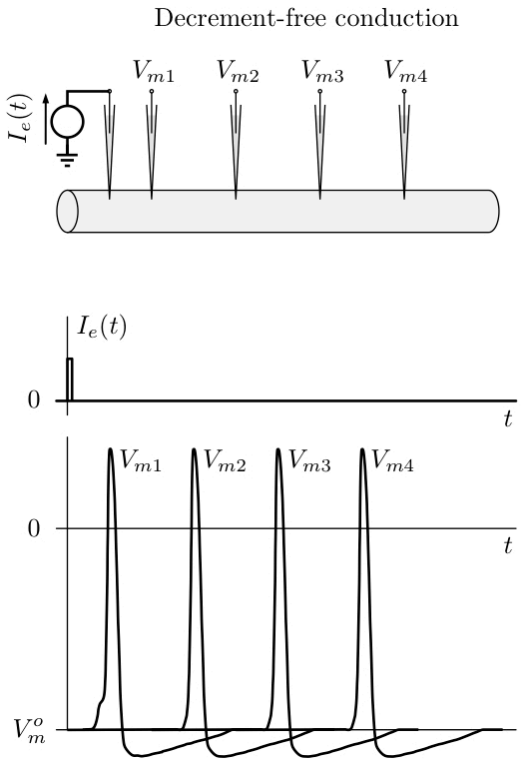


electrically inexcitable cell

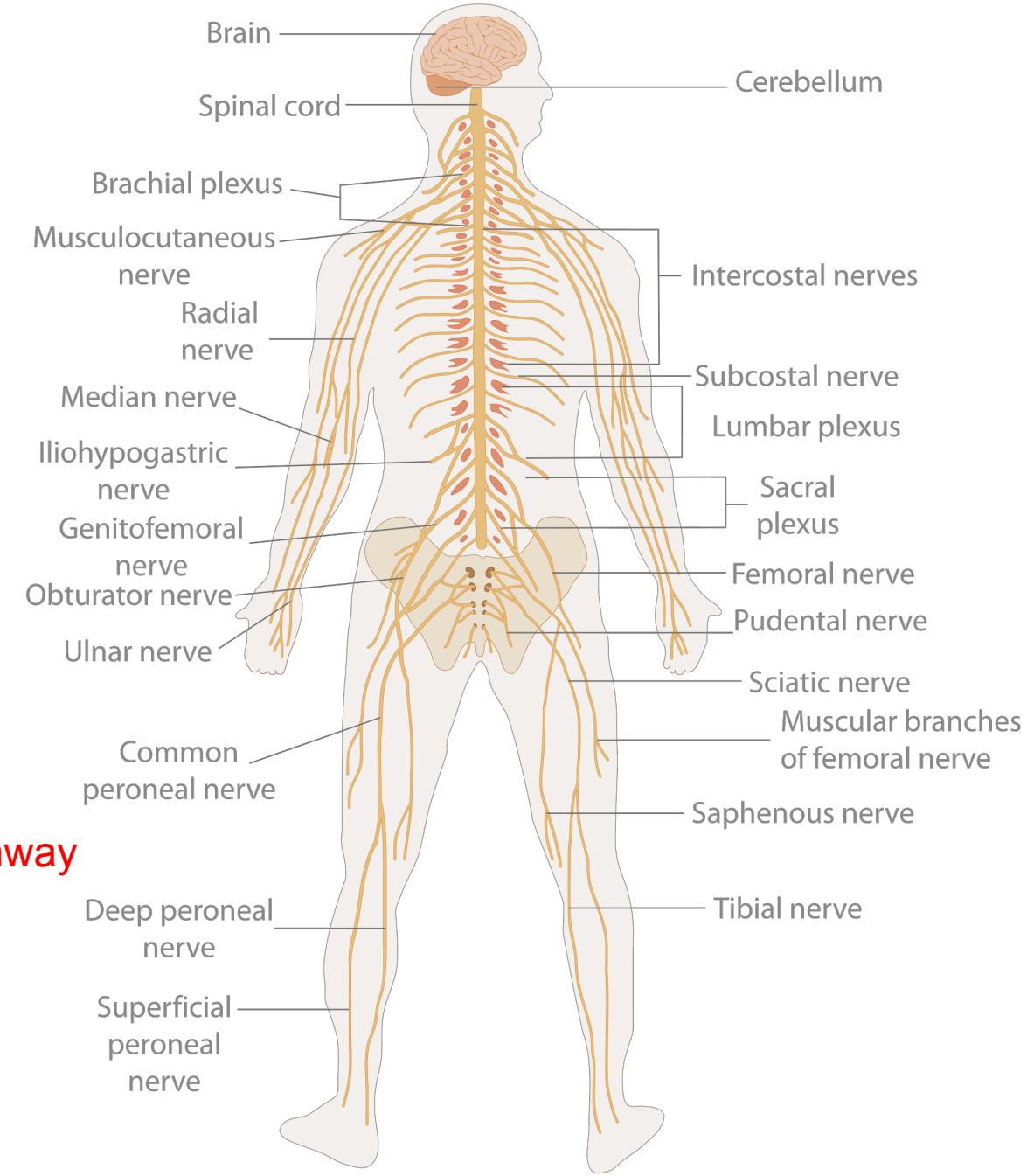


electrically excitable cell

Weiss (1996)



Neurons = Information highway



Wikipedia (nervous system)

Action potentials → Encoding

Question:
How is a stimulus (i.e., "signal") encoded in spike patterns?

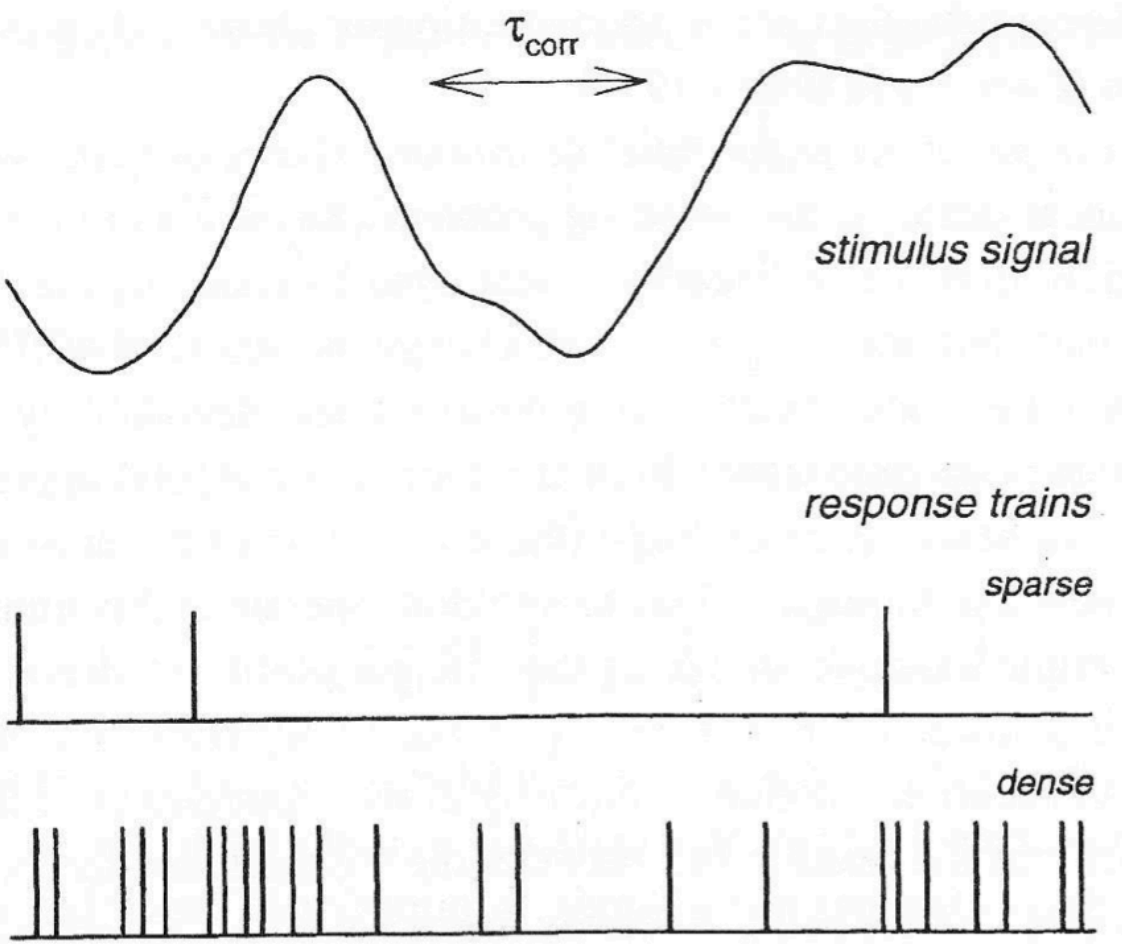
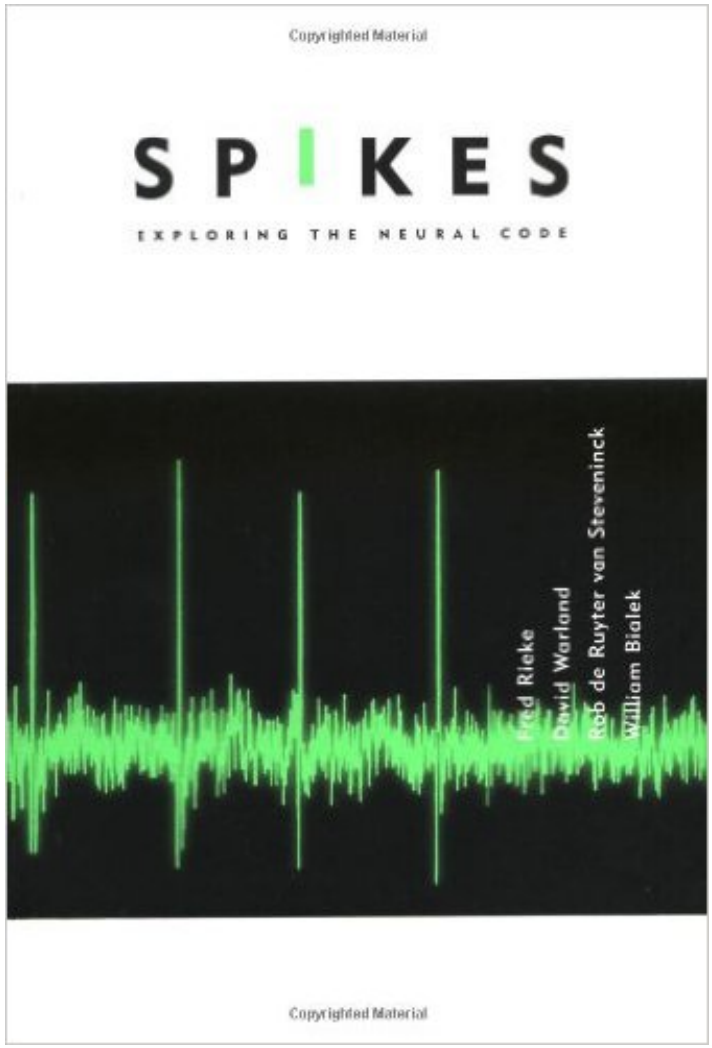
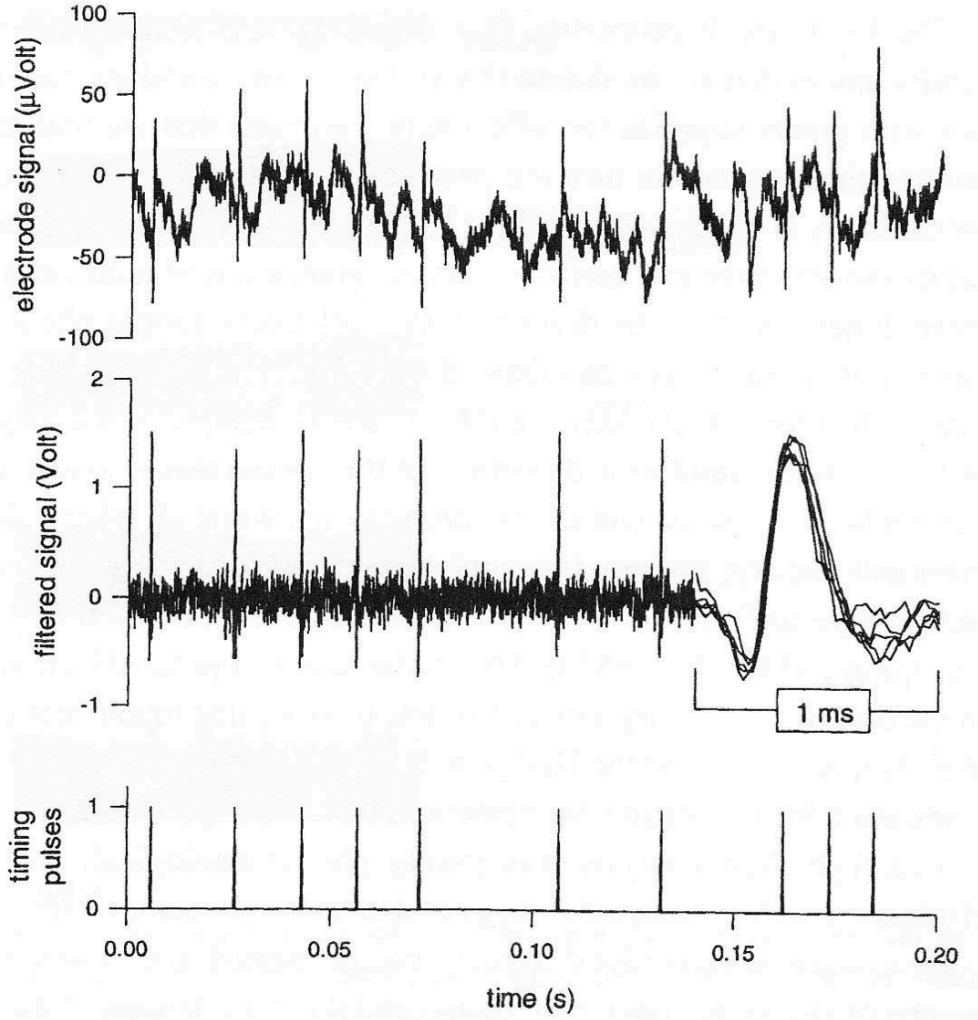


Figure 2.19
Estimation in sparse and dense spike trains. An important factor determining the success of the estimation process of Fig. 2.18 is the mean interval between spikes relative to the correlation time of the input signal. If the spikes are sparse, as in the top spike train, the stimulus correlation time divided by the mean interval between spikes provides a small parameter which can be used to construct a systematic approach to estimation, as described in more detail in the text. If, as in the lower response train, the number of spikes per correlation time becomes of order one, or bigger, this condition is not fulfilled and a perturbative approach to reconstruction is not feasible.

Rieke et al (1996)

Action potentials





Rieke et al (1996)

Action potentials

→ One needs a bit of care when measuring APs (i.e., spikes)

Note: APs can be measured intra- and extra-cellularly

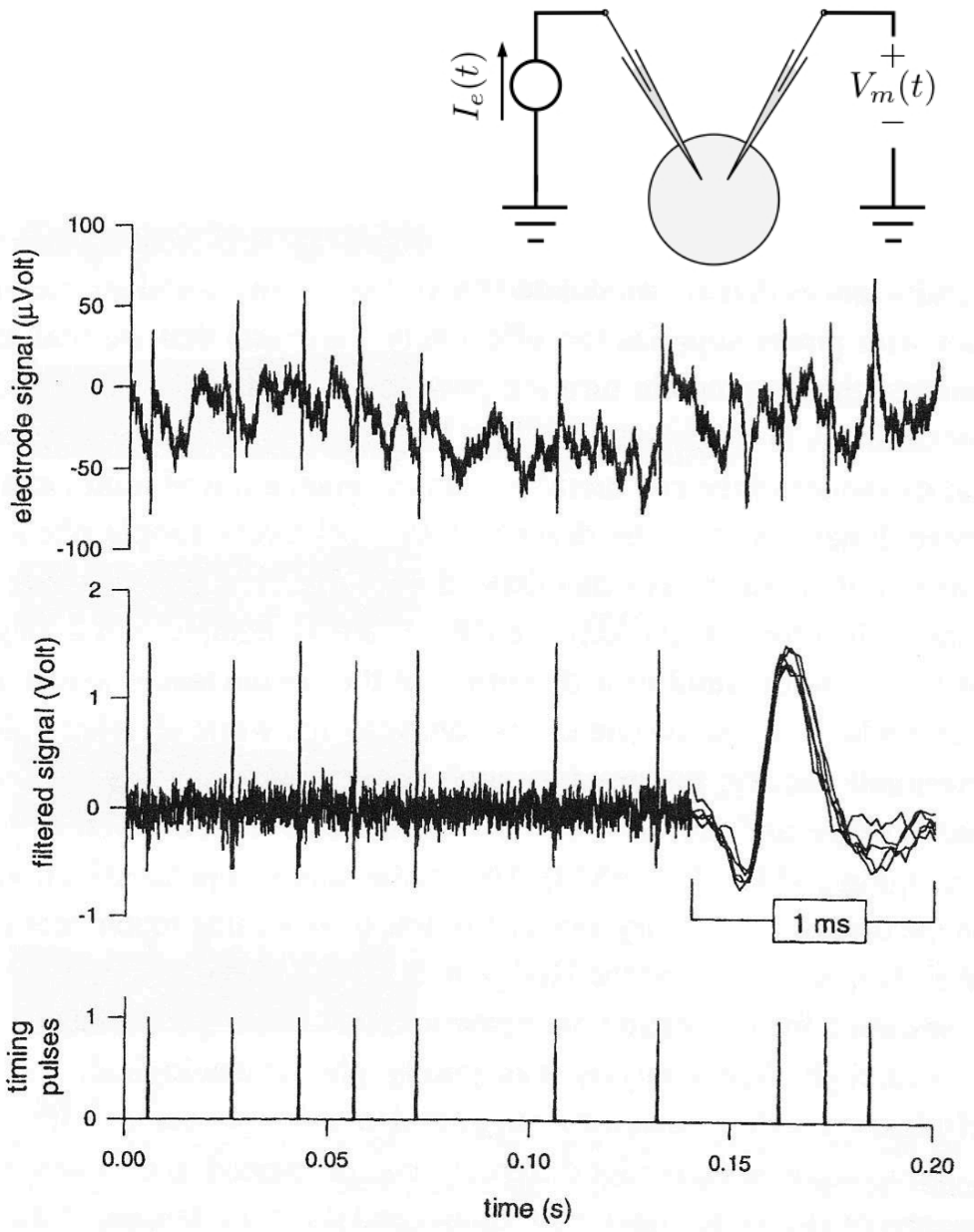
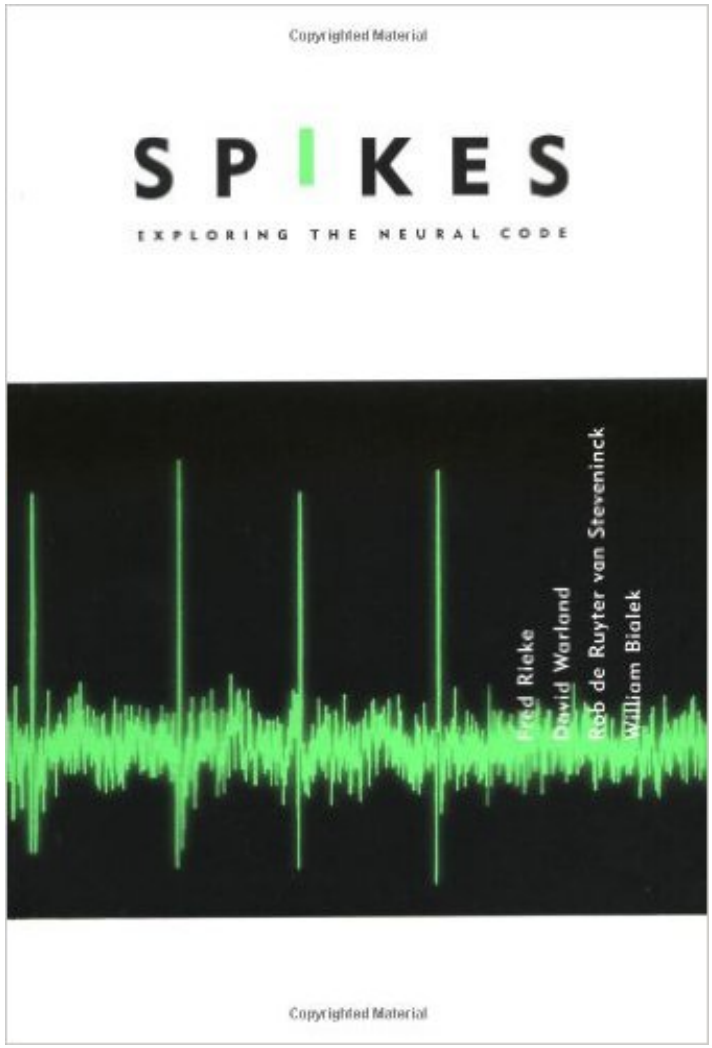


Figure 1.2
All-or-none coding by action potentials. Each action potential generated by the cell has a similar shape. Thus action potentials are the elementary units of the neural code. The top panel shows the difference between the voltage recorded with a fine tungsten wire placed near a cell in the fly's brain and that recorded with a reference electrode placed in the body fluid. The middle panel shows the same voltage after band-pass filtering to separate the relatively high frequency components in the action potential from low frequency noise; after filtering, the shapes of individual action potentials are quite similar. At the right, five action potentials are shown overlaid on an expanded time scale. This gives an impression of the shape and of the reproducibility of the time course. The bottom panel shows timing pulses generated electronically by a threshold discriminator circuit.

Rieke et al (1996)

Action potentials



CENTRAL CLAIMS OF THIS BOOK

Nearly seventy years ago, Adrian summarized the first generation of experiments on neural coding (Adrian 1928). We have argued that, even today, this classic work contains a large fraction of what we know about the language of the brain. Forty years later, Perkel and Bullock (1968) provided an encyclopedic summary of the state of the field, a handbook of diverse candidate coding strategies in different systems. What can we add after all these years?

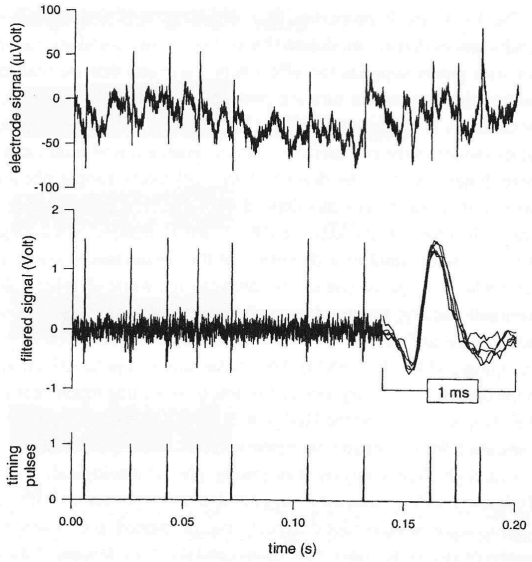
We believe that there has been substantial progress in both the formulation and the resolution of three major issues regarding coding by single neurons. These three points form the core of our presentation:

1. *Representation of time-dependent signals.* In a variety of sensory systems, single neurons produce on the order of one spike per characteristic time of stimulus variations—a sparse temporal representation. This is in direct contradiction to a simple, intuitive implementation of the rate coding idea, since the rate is an average quantity not available from a single spike. Sparse temporal codes can be decoded by simple algorithms, even when the encoding is a complex nonlinear process. Thus the problem of *decoding*—the problem solved by our homunculus—may be simpler than the classical problem of encoding.

2. *Information rates and coding efficiency.* The focus on signals with realistic time dependencies leads to the demonstration that single neurons can transmit large amounts of information, on the order of several bits per spike. In at least one case, signals with more natural temporal correlations are coded more efficiently, so that the spike train provides more information with roughly the same number of spikes. These high rates come close to saturating the fundamental physical limits to information transmission.

3. *Reliability of computation.* Understanding the reliability of the nervous system requires that we understand the code which the system uses to represent the answers to its computational problems; the study of neural coding is thus tied to much broader issues of neural computation. In several systems there is agreement between at least two of three fundamental quantities: The reliability of behavior, the reliability of single neurons, and the fundamental physical limits to reliability imposed by noise in the sense data itself. It is clear that the approach to the physical limits is closest for the more natural tasks of processing time-dependent signals.

Action potentials



How reliable/reproducible is spiking?

Reliability of Spike Timing in Neocortical Neurons

Zachary F. Mainen* and Terrence J. Sejnowski

It is not known whether the variability of neural activity in the cerebral cortex carries information or reflects noisy underlying mechanisms. In an examination of the reliability of spike generation using recordings from neurons in rat neocortical slices, the precision of spike timing was found to depend on stimulus transients. Constant stimuli led to imprecise spike trains, whereas stimuli with fluctuations resembling synaptic activity produced spike trains with timing reproducible to less than 1 millisecond. These data suggest a low intrinsic noise level in spike generation, which could allow cortical neurons to accurately transform synaptic input into spike sequences, supporting a possible role for spike timing in the processing of cortical information by the neocortex.

SCIENCE • VOL. 268 • 9 JUNE 1995

Action potentials

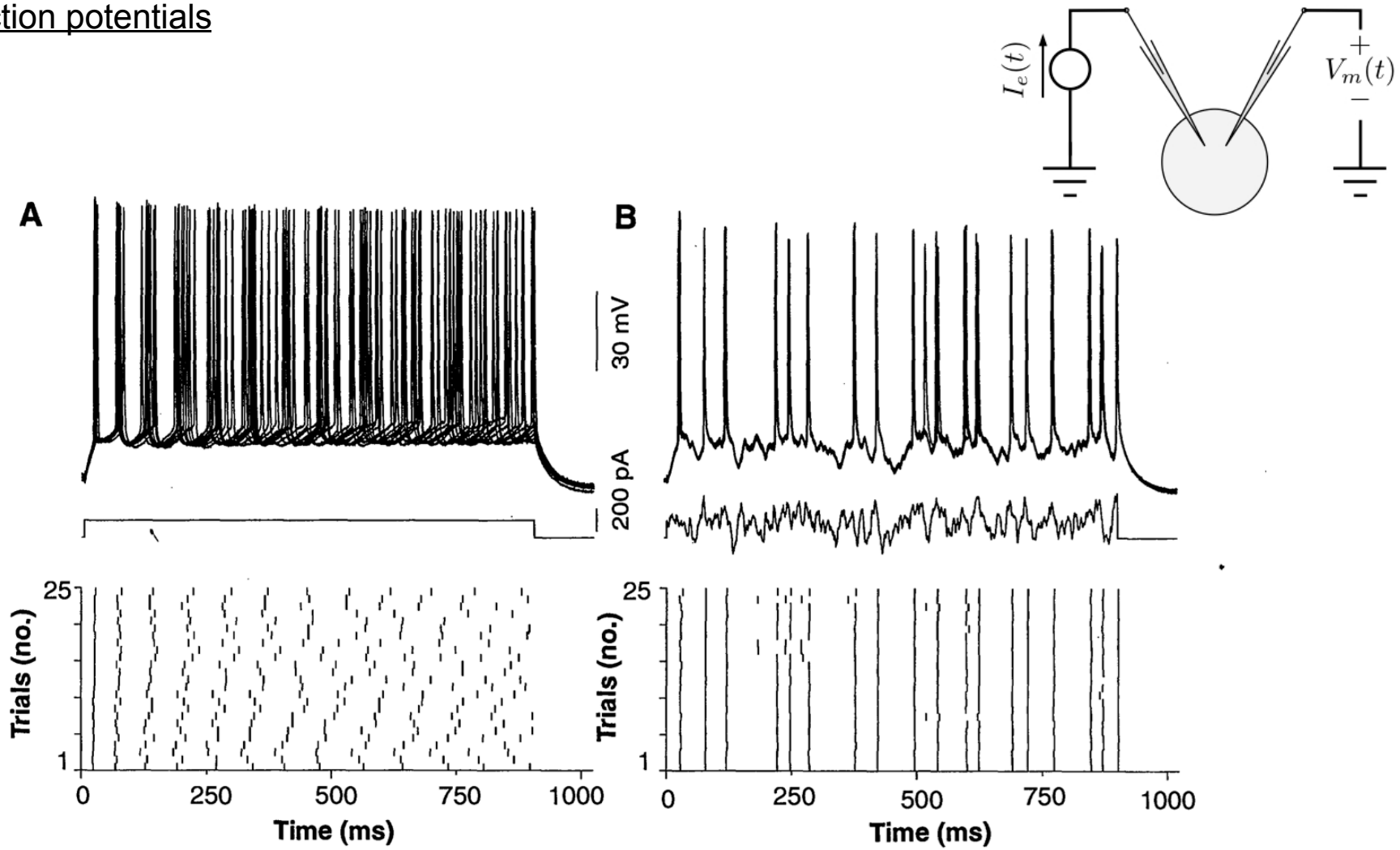
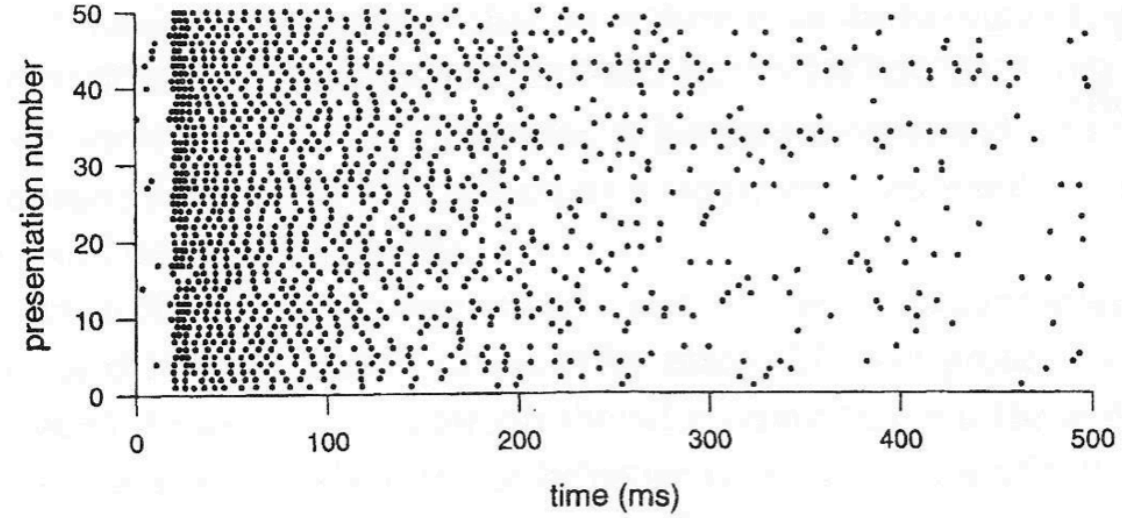


Fig. 1. Reliability of firing patterns of cortical neurons evoked by constant and fluctuating current. (**A**) In this example, a superthreshold dc current pulse (150 pA, 900 ms; middle) evoked trains of action potentials (approximately 14 Hz) in a regular-firing layer-5 neuron. Responses are shown superimposed (first 10 trials, top) and as a raster plot of spike times over spike times (25 consecutive trials, bottom). (**B**) The same cell as in (A) was again stimulated repeatedly, but this time with a fluctuating stimulus [Gaussian white noise, $\mu_s = 150$ pA, $\sigma_s = 100$ pA, $\tau_s = 3$ ms; see (*14*)].

Action potentials



Different ways of looking at the data....

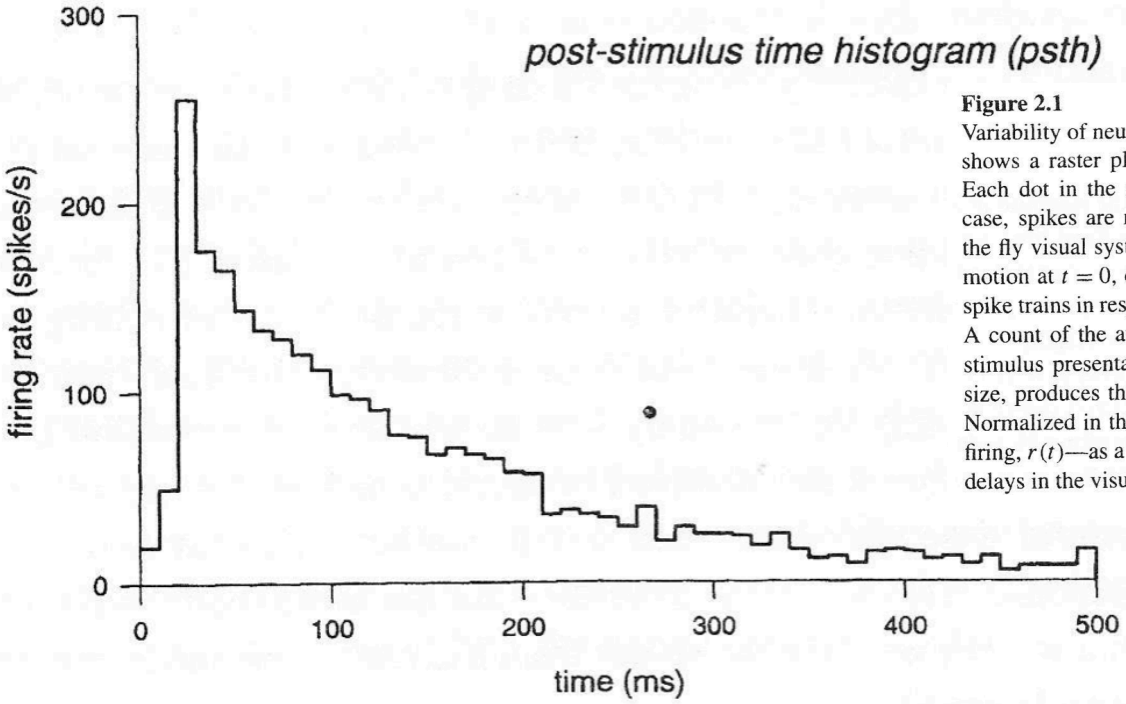


Figure 2.1
Variability of neural responses and construction of the average response. The top panel shows a raster plot of 50 individual spike trains in response to a stimulus at $t = 0$. Each dot in the raster plot marks the time of occurrence of a single spike. In this case, spikes are recorded extracellularly from the movement sensitive neuron H1 in the fly visual system, as in figure 1.2. The visual pattern seen by the fly makes a step motion at $t = 0$, creating a brief impulse of nonzero angular velocity. We see that the spike trains in response to repeated presentations of the same stimulus are not identical. A count of the average number of spikes in each bin (10 ms in this case) following stimulus presentation, and normalization to the number of presentations and the bin size, produces the post-stimulus time histogram, or psth, shown in the bottom panel. Normalized in this way, the psth gives the firing rate—or probability per unit time of firing, $r(t)$—as a function of time. The delay before the peak in the firing rate is due to delays in the visual receptors and in the synapses between the receptors and H1.

Rieke et al (1996)