

Chapter 1

Integrate and fire: RC circuits to model neurons and reward monkeys

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George Gerstein and I first met in 1962 when George was transitioning from post-doctoral fellow to junior faculty at MIT and I was a graduate student in the Physics Department. We were both converts from physics to neuroscience, and understood the perspectives of a hardcore science, in which mathematical descriptions could be applied and principles derived. George was fruitfully exploring a range of sophisticated analytical strategies to capture and quantify neural dynamics. I had just had the epiphany (on LSD) that the brain was the most interesting physical system in the universe – the source of all conscious experience and behavior, and not least, where I lived. I was intrigued by the riddle of how neural activity generates all this endless experience. I thought that neural explanations of behavior would probably be like statistical mechanical explanations of thermodynamics. Of course the fatal flaw in that notion was the fact that statistical mechanics succeeded because all particles could be assumed to behave identically, whereas in the brain each neuron behaves differently.

I was looking for an appropriate advisor to guide my physics thesis and still somehow begin working on the brain. With his two physics degrees from Harvard, George was the perfect candidate. He would probably have been my dissertation advisor had he stayed at MIT rather than take off for the University of Pennsylvania. But before he left, we did collaborate on a project to describe the firing properties of a simple RC model of spiking neurons. This leaky integrator summed exponentially decaying voltage pulses representing post-synaptic potentials and generated spikes when the sum reached threshold. The resultant spike trains were grist for the statistical algorithms that George and Nelson Kiang had developed to describe the firing properties of biological neurons. The interspike- and joint interval histograms generated by the RC model resembled those seen in cerebral cortex. The results could be summarized in terms of two regimes, depending on whether the model firing threshold was above or below the mean asymptotic equilibrium level of the “mem-

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brane potential” (Figure 1.1). The model was also used to compare the dynamics produced with purely excitatory and with mixed excitatory and inhibitory pulses. These results were written up in a short Quarterly Progress Report for the Research Laboratory of Electronics (Fetz and Gerstein, 1963).

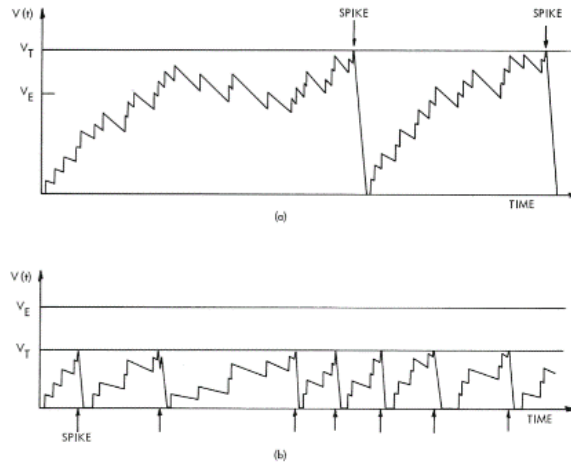


Fig. 1.1 RC neuron potential as function of time with poisson distributed EPSP inputs. Threshold (V_T) could be above (a) or below (b) equilibrium potential (V_E).

The closest that our RLE report came to being recognized in the literature was a citation in (Gerstein and Mandelbrot, 1964). That paper explored various random walk models that took discrete steps toward or away from threshold. Those crossings also generated pulse trains for analysis. In contrast, our RC model involved exponentially decaying PSPs, but the two approaches could be made to exhibit many similar properties. The random walk can also be used to model many other situations. More recently, the random walk model has proven highly fruitful in capturing the neural processes underlying decision making based on accumulating sensory evidence (e.g., Gold and Shadlen (2007)).

The last challenge that I tried to solve with George was a closed analytical expression for the interspike interval distribution of the RC neuron model in terms of model parameters. I finally abandoned this effort after George’s departure, turning to recording actual physiological neurons in the cat spinal cord in the lab of Patrick Wall, who became my thesis advisor. Pat provided a proper introduction to neurophysiology and supervised my thesis on “Pyramidal tract effects on dorsal horn interneurons”.

(When my physics graduate committee got wind of the title of my thesis, they wondered whether this was appropriate for a physics degree. They called a meeting for me to present the proposed research, and I emphasized source-sink mapping of spinal cord field potentials, using Laplacians and other Maxwellian concepts.

Afterwards, I was dismissed while they deliberated; probably thanks to Pat's input, they decided that I had just passed my thesis defense. They obviously didn't want to hear any more of it.)

After graduating, I crossed the country to do postdoctoral work at the University of Washington and learn more neurophysiology. I intended to work with Arnie Towe on pyramidal tract neurons of chloralosed cats. But being more interested in the activity of neurons in awake behaving monkeys, I joined Eric Luschei, a brilliant graduate student in Mitchell Glickstein's lab, who had developed the chronic unit recording techniques at the same time as Ed Evarts. When Mitch and Eric left Seattle for Brown University, I was free to pursue my own interests and began to investigate operant conditioning of cortical cell activity. These experiments used the RC circuit that George and I had explored, but now to reward monkeys for generating changes in cortical cell activity. The initial version was a simple leaky integrator that summed pulses from spikes of a motor cortex neuron. When the monkey increased the firing rate sufficiently to reach integrator threshold he triggered a feeder that delivered applesauce (Figure 1.2, from Fetz and Baker (1973) [this paper and others from our lab can be accessed at: <https://depts.washington.edu/fetzweb>]). A more sophisticated version integrated multiple inputs, requiring the monkey to control patterns of simultaneous cell and muscle activity to reach threshold (Fetz and Finocchio, 1975). The remarkable finding was that the monkeys could quickly generate several new and orthogonal response patterns during the course of a single session.

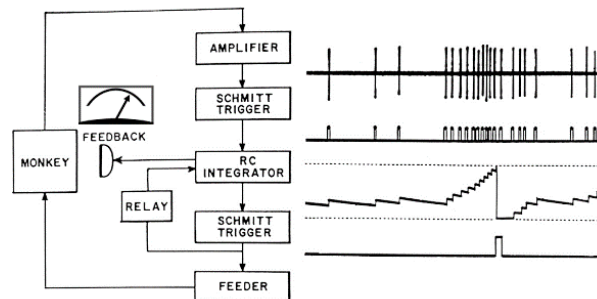


Fig. 1.2 RC integrator used to reward monkey for bursts of activity in neurons. Integrator voltage deflected neurofeedback meter arm.

In order to provide the monkey with continuous feedback about how close his neural activity was getting to reinforcement threshold the integrator voltage was displayed on a meter facing the monkey. The rightward position of the meter arm corresponded to the feeder trigger, and monkeys quickly learned to do what it took to drive that meter to the right and get applesauce. At that time, I saw this meter as a device for providing biofeedback about neural activity. Had I realized that neural control of the meter arm was a first step toward brain-controlled prosthetic arms,

my career might have been different. In retrospect it would probably have been more exciting to pursue further experiments in volitional control of neural activity to drive external devices. Instead, my physics training diverted me to focus on proving causality between premotor neurons and muscles in behaving monkeys, using spike-triggered averages of EMG activity.

The basic RC circuit that George and I initially investigated has been extended to artificial neural networks of multiple “integrate-and-fire” (IAF) units. The IAF units sum more realistically shaped post-synaptic potentials to firing threshold and affect their targets via weighted connections. The connection weights can be derived from networks of continuous units trained with back-propagation to perform particular spatiotemporal transforms (Fetz, 1993). The conversion involves replacing individual continuous units with a group of IAF units connected with the same relative weight (Maier, Shupe, and Fetz, 2003). More recently we have found that networks of IAF units endowed with spike-timing dependent plasticity can be used to simulate cortical plasticity induced with closed-loop activity-dependent stimulation (Shupe and Fetz, unpublished).

Our studies of motor cortex neurons and their relation to limb movement have provided many occasions to apply the analytic techniques pioneered by George and his colleagues. The basic principles of spike train correlations first described in Perkel, Gerstein, and Moore (1967) were fundamental to investigating synaptic interactions between cortical neurons (Fetz, Toyama, and Smith, 1991; Smith and Fetz, 2009). We also investigated the synaptic mechanisms underlying features in correlated spike trains with intracellular recordings of post-synaptic potentials (Cope, Fetz, and Matsumura, 1987; Matsumura, Chen, Sawaguchi, Kubota, and Fetz, 1996).

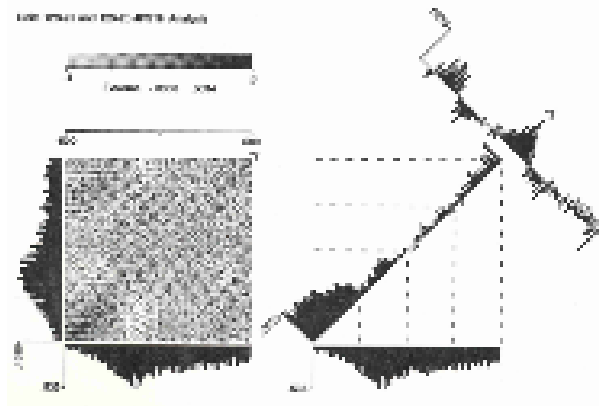


Fig. 1.3 JPSTH of two motor cortex neurons during movement task. From Smith, Doctoral Dissertation, University of Washington, 1989.

Another useful technique pioneered by George was the Joint Peri-Stimulus Time Histogram (JPSTH) analysis of Aertsen, Gerstein, Habib, and Palm (1989). We used the JPSTH to dissect the time-varying correlations between motor cortex neurons during movement. Figure 1.3 is an unpublished figure from the thesis of Wade Smith (Smith, 1989). The histograms along the x- and y-axes at left show the response averages of two simultaneously recorded neurons during performance of a ramp-and-hold wrist flexion-extension task. The overall cross-correlogram between the two neurons (upper right histogram) shows a broad central common input peak, but notably, the time resolution of the central slice plotted along the diagonal reveals that most of the above-chance common input occurs well before the maximum firing rates of the neurons.

I last saw George on the happy occasion of his retirement symposium at the University of Pennsylvania in 2003. Many of his friends and collaborators convened to look back at his full and productive life, pushing the envelope with innovative computational approaches and wide range of experimental achievements. George was still full of enthusiasm for what struck him as interesting issues, and even seemed a bit more tolerant of what he used to dismiss with “Bah, Humbug”. We are all indebted to George for his many seminal contributions and will miss his steadfast friendship.

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