The History of Neuroscience in Autobiography
Volume 10

Edited by Thomas D. Albright and Larry R. Squire
Published by Society for Neuroscience
ISBN: 978-0-916110-10-9

Eve Marder

pp. 420–455

https://www.doi.org/10.1523/hon.010010

Eve Marder

Born:

New York City, New York
May 30, 1948

Education:

Brandeis University, Waltham, Massachusetts, AB (1969)
UCSD, La Jolla California, PhD (1974)

Appointments:

Assistant Professor, Biology Department, Brandeis University (1978–1984)
Associate Professor, Biology Department, Brandeis University (1984–1990
Professor, Biology Department and Volen Center, Brandeis University (1990–present)
Cornelius Wiersma Visiting Professor of Biology, Caltech (1994–1994)
Victor and Gwendolyn Beinfield Professor of Neuroscience, Brandeis University (1994)
Chair, Biology, Brandeis University (1996–1997; 1998–1999)
Head, Division of Science, Brandeis University (2010–2014)
Senior Fellow, Janelia Research Campus, (2015–present)

Honors and Awards (Selected):

Fellow of the American Association for the Advancement of Science
Elected American Academy of Arts and Sciences (2001)
Miriam Salpeter Lifetime Achievement Award, Women in Neuroscience (2002)
W. F. Gerard Prize, Society for Neuroscience (2005)
Elected National Academy of Sciences (2007)
Fellow of the Biophysical Society (2008)
President, Society for Neuroscience (2007–2008)
Honorary Doctor of Science, Bowdoin College (2010)
George A. Miller Prize, Cognitive Neuroscience Society (2012)
Karl Spenser Lashley Prize, American Philosophical Society (2012)
Gruber Prize in Neuroscience (2013)
Elected National Academy of Medicine (2013)
Fellow of the International Society for Neuroethology (2014)
Education Award, Society for Neuroscience (2014)
Inaugural Fellow of the American Physiological Society (2015)
Kavli Prize in Neuroscience (2016)
Member, Norwegian Academy of Sciences (2016–present)
Honorary Degree, Tel Aviv University (2017)

Marder studies the dynamics of small neuronal networks, and her work was instrumental in demonstrating that neuronal circuits are not "hard-wired" but can be reconfigured by neuromodulatory neurons and substances to produce a variety of outputs. For the past 25 years, Marder's lab has combined experimental work with insights from modeling and theoretical studies. Together with Larry Abbott, her lab developed the programmable dynamic clamp, now used widely in laboratories around the world. Her lab pioneered studies of homeostatic regulation of intrinsic membrane properties, and stimulated work on the mechanisms by which brains remain stable while allowing for change during development and learning. Marder is now studying the extent to which similar network performance can arise from different sets of underlying network parameters, opening up rigorous studies of the variations in the individual brains of normal healthy animals.

Eve Marder

Introduction

Initially, I set out to write a chronological account of my development as a neuroscientist, weaving together my personal and professional development and, hopefully, maturation. I realized that sadly, I do not have the space to write about the beautiful work of all of the 27 PhD students, 46 postdocs, and many undergraduates who have worked in my lab since 1978. I apologize that I have not had the space to do justice to all of your beautiful work and to the myriad contributions of all of our collaborators. I have focused more on my early years because when I travel around the world, I meet many young people who are curious how I got started and what the world was like at the beginning of my career. Moreover, there are my writings and online lectures from my later years, but none of that existed when I was beginning my career.

Many of my previous trainees have remained in academic science, and many have moved into a variety of other careers in which their discipline, intellectual integrity, and sense of humor have allowed them to shine. I am proud of them all. I learned much from every member of my laboratory and thank you all for your time, intelligence and thoughtfulness. Indeed, perhaps the single and most important message one learns as the head of a laboratory is that no matter how smart or intuitive any one of us is, the collective intelligence of a laboratory is always richer and more insightful than any one person can be. I can trace most of the best science with which I have been associated to my willingness to listen to what people of my laboratory were saying. I suppose it has helped that I have always attracted interesting and adventuresome people, so all I had to do was to make sure that they looked carefully at their data.

As I started writing, I realized that I have made many professional choices for reasons that were not overtly scientific. Some of these choices were determined by personal ethics as related to science, community, and publication processes. It has become a truism that all science is done by community. Nonetheless, many of our present practices create conflicts between what is best for the individuals who are actually generating data and what is best for lab heads. Likewise, many of our attitudes toward publication create dynamics that are potentially wasteful of both human capital and funds that are used to generate data. And, although we collectively embrace a commitment to diversity in our professional lives and institutions, I continue to encounter situations that show the commitment to diversity does not extend to action. As a female scientist, soon to be 70 years old, I could not move through our

profession without watching and listening carefully, and then deciding what to emulate and what to ignore. Those of us women who became "successes" from those years had to be either profoundly clueless (a very useful strategy, if one can pull it off) or very good at listening and watching. So, intermingled into this autobiography are some of the lessons I learned about our scientific culture as I moved through my career.

Beginnings

I was born on May 30, 1948, at the Columbia Presbyterian Hospital at 168th Street in Manhattan. My father was just 23 and my mother was 21. My father was born in Vienna and came to New York when he was 14. My father went to City College, along with many of his generation of Viennese immigrants. My mother was born in the Bronx. Sadly, her mother died from a childbirth infection associated with my mother's birth, and she spent the first four years of her life in an orphan asylum. Her father eventually remarried and took her to live with him, her older sister, and his new wife. My mother left home at 17, as she wished to go to college, and her father wanted her to get a job. My mother was one of the first women to enter City College, where she met my father. She dropped out of school when she became pregnant, but eventually she returned to school to earn her bachelor's degree when she was in her 60s.

My earliest memories come from the days we lived on Manhattan's Upper West Side, on 84th Street between Columbus and Amsterdam Avenues. It was walking on Central Park West that my mother taught me that north was uptown, south was downtown, west was the Hudson River, and east was Central Park. As a three-year-old, I had a flawless sense of direction, given a universe on a grid, and somehow, being so carefully taught the four directions of the compass has stayed with me much of my life.

My parents were poor in those early years. We lived in a walk-up on a high floor (the slum building was later torn down to build Brandeis High School). My parents didn't have enough money to pay for a nursery school, but my mother managed to get me a scholarship to a nursery school because "I played well with others." I remember my mother carrying groceries and my stroller up many flights of stairs when she was pregnant with my brother, who was born in October of 1951.

The first scientific experiment that I remember carrying out was in the 86th Street Central Park playground. The Central Park playgrounds have vertical bar railings, and at the ripe age of three or so, I was curious if my head would fit through the railings. So, I did my experiment and put my head through the railing and promptly got stuck. This was a life-defining moment for me, because as I sat there with my head between the rails I felt unbelievably stupid, as I realized I could have used my hands to measure the relevant distance. Indeed, I date this as my first self-conscious awareness of myself as a critical decision-making person.

As all the mothers at the playground started panicking, my mother calmly walked over, picked me up, twisted my body sidewise, and pushed me through the railing, saying that babies were born head first, and she figured that my head was more important than a few scrapes on my arms or legs. I never doubted that my mother would "save me," but I remember being incredibly proud and comforted by her commonsense problem-solving intelligence.

When I was four and a half, we moved to Ridgefield, New Jersey, just across the Hudson River. We lived in a small garden apartment in a modest suburb. My parents made no particular attempt to teach me to read before I started school, and in first grade, we were taught to memorize words with the now-infamous "Dick, Jane, Spot" books. After a month of first grade, my father asked me if I could read, and I said I could read the words I had been taught. He said either I could read or I couldn't, and he handed me the *New York Times* and said "read." Thus, I discovered that I knew how to read. My mother took me to get a card at the small public library next to the elementary school, and over the next few years, I systematically read every book in the children's section of the library. One day as I happened to be reading a science book, my aunt asked me what I wanted to be when I grew up, and I answered, "a scientist." She nodded happily, and from then on whenever grownups asked me that question, I said "scientist" because it deflected all further conversation.

I was 10 years old when we moved to Irvington, New York, a small town on the Hudson River, a 45-minute train ride from Grand Central Station. My father took the train to work, and I entered the fifth grade. I discovered that I loved stringing words together in essays. Unusually, I had a young male teacher. He taught us "math" by organizing the class into teams for "math races," which made us fast and accurate at adding up long strings of numbers and at doing complex long divisions on the blackboard. In fifth grade, I realized that I could remember my textbooks almost verbatim, by imaging the pages in my head and rereading those stored images for names and dates. Only much later did I learn that this kind of eidetic memory is relatively rare, and usually goes away as children mature. In me, it persisted to a greater or lesser degree throughout high school, and this made it easy for me to remember names and dates of kings and queens of European countries, or for that matter, the Krebs cycle. Sadly, by the time I reached organic chemistry, it had mostly deserted me. It remained to some extent, as for many years I remembered the authors, years, and journals of the scientific papers I had read by visualizing the front page of the article.

In 1960, I was 12, my sister was born, and my father started a market research firm. My sixth-grade teacher let us work on our own, and she spent most of her time with the students who needed help. A few of us raced to finish our sixth-grade math workbooks and did so in a few months. She then gave us eighth-grade math books. In the spring, when I had finished eighth-grade math, she came back with an algebra book. A few days before the end of the school year, I went up to my teacher and told her I wasn't going to do

eighth-grade math again, because I had done it. I don't know what impelled me to be so brazen, but I just couldn't face redoing endless problems about percentages and interest rates. My teacher looked at me, and said, "Oh." On the last day of class, I was promoted into the eighth grade and was placed in ninth-grade algebra, with students two years older.

I only realized much later how good Irvington High School was in the early 1960s. I learned grammar, algebra, geometry, calculus, chemistry, and physics. I learned the amendments to the U.S. constitution (quite relevant today). In advanced biology, I studied respiration and photosynthesis and first learned about action potentials and synaptic potentials from *Scientific American* articles. But most important, I wrote long and detailed term papers, several of them 100 pages in the days before word processors. In 10th grade, I did an analysis of how black history was treated in the American history textbooks used in high schools. To do this, I read W. E. B. Du Bois, and other African American scholars and discovered, not surprisingly, that the history books used in our schools told a very different story than that depicted by the scholars of the civil war and later. In 11th grade, I did a term paper on Karl Marx. In 12th grade, I wrote a 100-page paper on Walt Whitman's poetry. To do the research for these papers, on Saturdays, I would take the train to New York City and go to the reading room of the New York Public Library, which was a magical place. At that time in my life, I didn't have a particularly favorite subject, probably because it was all new, and therefore interesting. My wonderful biology teacher, Bernice Essenfeld, gave me an advanced biology textbook when I announced I wanted to take the Biology SAT at the end of my sophomore year. So I read the entire book from cover-to-cover on the subway and trains on my trips to NYC, and I remembered enough to score an 800, which my teacher promptly told me wasn't as difficult as getting a 100 on the NY State Regents exam, because you could miss a question on the SAT and still score an 800!

At age 16, when I was applying to college, I knew that there were many people smarter than I. I was rejected by Radcliffe College (the women's branch of Harvard) after an interviewer told me that they didn't know how to evaluate my grades because they had never before seen an application from Irvington High School. When I told her that I thought the whole purpose of the SAT exams was to provide more objective criteria (all of my SATs were very good), she said, "Well, I guess you are academically strong enough, but we are looking for young women who belong here." I understood that was code for saying that I was a smart Jewish girl from Westchester County but not special enough for them to overlook that I was a smart Jewish girl from Westchester County. When I started college in the fall of 1965 at the recently established Brandeis University, I knew that I would get an excellent education and not be part of the "in-group" provided by an elite institution. The same was true four years later when I started graduate school at the even younger University of California, San Diego (UCSD).

College Years

I was at Brandeis from 1965–1969, at the peak of the 1960s. Brandeis was center-stage for much of the civil rights and antiwar foment, and it had attracted a large number of interesting and quirky students. Many of my friends were politically active, and they studied (or not) philosophy, art, sociology, comparative literature, math, and everything in between. My favorite freshman year courses were humanities and politics, in which we read the greats of political theory and classics of literature. I thought about being an English major, but became a politics major, because at the time, I wanted to become a civil rights lawyer. I struggled with my math course, which was an introduction to formal analysis. I went through the motions and worked hard, but I knew it was over my head (I don't know whose brilliant idea it was to teach freshmen analysis rather than calculus or linear algebra). I enrolled in biology and honors chemistry my sophomore year because I reasoned it would be easier to go to graduate school in English with a biology major than to graduate school in biology with an English major. I was horribly bored by my sophomore biology course because it largely repeated what I had learned in high school. I detested my course on the politics of post–World War II Europe. It seemed to consist primarily of learning the names and policies of endless political parties, all of which had alphabetic acronyms that defied understanding in terms of what their politics actually were. I switched my major to biology.

My favorite course that year was Yeats and Joyce, taught by the poet Allen Grossman. Grossman spoke in a remarkably rich and redolent prose that used the whole of the English language, and I was fascinated that he spoke language that I had only ever seen written. To this day, I remember some of his lectures, as they addressed some of the deepest and most subtle issues of how humans make flawed and heroic decisions. It wasn't until my junior year that I hit the biology courses that spoke to me as deeply as reading Joyce, Faulkner, or Virginia Woolf. First semester, I took genetics, with Chan Fulton, who taught with classic original papers. Also that semester, I took a course in abnormal psychology. The professor made a comment suggesting that schizophrenia might arise from deficient inhibition in the brain. I had never heard about inhibition in the brain, so I did a term paper to discover whether it is possible that deficient inhibition could account for schizophrenia. I went to the science library and read everything I could find about inhibition in the brain. This was 1967, and it was still possible to read a fair bit of what was known about inhibition in the brain. But, more important, in so doing, I decided I was going to be a neuroscientist.

The next semester, I took Andrew Szent-Gyorgyi's course on nerve and muscle, and a course on schizophrenic language. The latter was really an introduction into what today would be cognitive neuroscience, and the former led to my senior year thesis in Szent-Gyorgyi's lab, doing experiments on muscle protein polymerization, as there were no neuroscientists

then at Brandeis. I kept reading neuroscience and turned all the papers I wrote for other biology courses into neuroscience topics. I was fascinated by the work being done on denervation supersensitivity, as well as the early work on the specificity of connections in the retinal-tectal pathways. I was drawn to functional questions that eventually would be addressed with cellular or molecular approaches.

When it came time to apply to PhD programs, I wanted to go to the West Coast. So I applied to the University of Oregon, Berkeley, Stanford, and UCSD. Additionally, I applied to the Neurobiology Department at Harvard because Szent-Gyorgyi was a close friend of Steve Kuffler's, and he said it was the best place in the world to do neurobiology. I had strong grades, albeit not spectacular ones, having been perpetually unable to get A's in courses that bored me, and had (I know now) outstanding GRE scores. I knew it unlikely that I would get into Stanford biology because they were widely said to have a quota on women (2 out of 12). Additionally, Stanford would take only one student from any undergraduate institution, and one of my classmates already had been offered admission. I was offered admission by UCSD, Berkeley, and the University of Oregon, but I was waiting to hear from Harvard.

In 1968, it was unusual for departments to interview applicants, but Harvard Neurobiology invited three of us for a whole day interview in the department. That day was the beginning of a career-long friendship with Ron Calabrese, who eventually went to Stanford, and now is an eminent neuroscientist at Emory University. The third interviewee, Bruce Wallace did enter the Harvard program. I waited until April without word from Harvard, until I called to find out that I hadn't been offered admission, cried for 20 minutes and decided that fate was sending me west.

At the time, UCSD biology had no neuroscience faculty, but the Brandeis faculty advised me to learn modern molecular biology and then "specialize" in neuroscience. I decided against Oregon because I was told it rained all the time. Someone from Berkeley called to tell me I was the strongest applicant in their pool, so declined their offer, as I wanted to be with people smarter than I was. UCSD was on the beach, and I had fantasies of putting an experiment into the ultracentrifuge for two hours, going to the beach, and coming back to work.

I accepted the UCSD offer, graduated from college, and headed off for a summer of hitchhiking all over Europe, with *Europe on $5/day*. At the end of the summer, I hitched from Italy back to London in two days, alone. These were the days before the Internet or cell phones, but I sent my parents and sister daily postcards.

That summer, I saw lot of museums and monuments, but most notably, I walked many miles as I was happiest just exploring the streets and watching people. I loved Rome, although I realized years later that I was there in August and most of the Romans were gone, and the only people on the streets were tourists. It rained for five days when I was in Paris, and it

was years later that I saw Paris's beauty. In those days, you could tell the nationality of someone from his or her clothes and shoes. I came home from Europe, strong, tan, and the thinnest I had been since graduating from high school. In thinking back to that summer, I see that I was adventure-seeking but with extraordinary caution.

UCSD

When I flew off to southern California to start at UCSD, a brand-new institution with an extraordinary faculty, I felt it only fitting, to once again find myself at an institution just building itself, with excellence but no track-record. UCSD, as Brandeis before, gave me the freedom to find my own voice.

Allen Selverston joined the faculty in biology at UCSD the same year I started in the PhD program. In retrospect, I could not have had a better thesis supervisor. Al knew how to do things, to build things, and how to make things work. He had, even at the beginning of his career, outstanding biological intuition, and the work in his laboratory presaged much of what is happening today in circuit analysis and connectomics. Indeed, Al articulated quite clearly in the 1970s what many working in circuits today are only beginning to understand. Most important for me, he provided an environment and space that allowed me to make my own mistakes and my own discoveries. So when I completed my PhD, I knew that I had done the work independently, and I credit him, to his day, with understanding that independence was the best gift a thesis supervisor could have given to the student I was at that time.

It was only many years later that I realized that 1969 was a watershed moment for the entrance of women into life sciences PhD programs in the United States. The year before, the draft laws were changed and PhD programs were no longer eligible for draft deferments. Consequently, many young men went into MD programs (which were still draft deferrable) and into a number of new MD and PhD programs. Others left the country, were drafted, or became conscientious objectors, and ended up working jobs that delayed their entrance into PhD programs. So the entering pool of male PhD applicants dropped. Thus, while in 1968 and the prior years there were 2 women in a class of 30 at UCSD, my class had 13 women in a class of 30. Over the next few years, entrance into life sciences PhD programs became virtually 50:50 across the country. By the end of the Vietnam War, and its associated draft, the barriers for admission to PhD programs in life sciences were mostly gone. When we arrived that fall of 1969, the faculty were wondering what they would do with all of us. By May, when we were settling into labs, everyone had forgotten it was an issue. What I find most astonishing, looking back at this time, is how normal and acceptable the quotas on female admission to graduate programs were.

While we put up with incidents that would be actionable harassment in today's world, we mostly rolled our eyes when the guys said preposterous and overtly sexist things. One of my rotation supervisors kept telling me to

quit graduate school and get married and have six babies. After five weeks of this, I got so annoyed that I told him I was going to spend the last two weeks of the rotation in the library. He smiled and said he thought that was a great idea. Eventually, my rotation class figured out that this faculty member didn't want any PhD students, but was obliged to take rotation students. He therefore designed a different torture for each rotation student, and none of it was personal. He and I eventually became tennis friends.

The women of my peer group found excellent advisors, and many of them went on to successful careers, despite the fact that there were few female faculty, and certainly no one with whom I could identify. This was a world before "mentoring" and "professional development," but the young and forward-thinking faculty of UCSD had among them enough reasonable people to allow the female students to find advisors. I believe that the men and women students succeeded approximately equally.

Selverston and many of his generation came from PhD programs in which graduate students were supposed to earn their PhDs by demonstrating their ability to do independent work. When I started in Al's lab, he gave me a pile of brand-new equipment (which thankfully had manuals written in English), and told me, "Go play for a couple of months and then tell me what you want to do for your thesis."

I had become fascinated with transmitters and receptors as an undergraduate. Therefore, it was no accident that my PhD thesis project was to determine the identity of the transmitters used in the stomatogastric ganglion (STG). Don Maynard, at the University of Oregon, had developed this preparation to use it as a model system to understand how central pattern generators (CPGs) worked. The STG was ideal because it had a small number of large neurons, all of which could be identified, and it continued to be rhythmically active when removed from the animal. Selverston went to Bermuda the summer between my first and second year in graduate school to work with Maynard. He came home with the STG preparation, and he worked exclusively on it from then on. Although the STG has only about 30 neurons, it generates two different motor rhythms. The faster pyloric rhythm is pacemaker driven and is always active. The slower gastric mill rhythm is episodic and is seen only after the animal has fed or is exposed to food. Selverston and his lab did important work on the synaptic and cellular mechanisms of the generation of both rhythms.

My goal was to determine the identity of all of the chemical signaling molecules in a complete circuit, rather than study individual transmitter molecules in isolation. Even then, I had the intuition that there were insights to be gained by trying to understand the choreography of all transmitter (and now modulator) action in functionally active circuits. To this day, my laboratory continues to work on these questions.

The early 1970s were simpler days for a graduate student. I read a considerable fraction of what was published on transmitters, receptors,

and pharmacology in invertebrates. I discovered Dick McCaman, Jimmy Schwartz, David Barker, JacSue Kehoe, Philippe Ascher, Ed Kravitz, and Hirsh Gershenfeld from the literature. Dick McCamon, Jimmy Schwartz, and Ed Kravitz had pioneered methods of single neuron transmitter identification (Otsuka et al. 1967; Giller and Schwartz 1971; McCaman et al. 1984). Most notably for me, Jimmy and Dick had worked on single neuron choline acetyltransferase assays (McCaman and Dewhurst 1970; Giller and Schwartz 1971). Dick was 120 miles up the road, in Los Angeles, so one day I got in my car and drove up to City of Hope to learn his methods. He became a great friend for years. I met Jimmy Schwartz when he came to UCSD for a seminar, and he also became a very special friend, who read and critiqued my first grant proposal several years later. David Barker was a postdoc in Ed Kravitz's lab where he identified octopamine in lobsters (Barker et al. 1972) and became interested in amine modulation. It was he who first understood the results I had obtained when I had applied every transmitter candidate known then to neuroscience on the STG. And it was the extraordinarily elegant papers of Kehoe, Ascher, and Gerschenfeld (Ascher 1972; Kehoe 1972a, 1972b, 1972c; Gerschenfeld 1973; Gerschenfeld and Paupardin-Tritsch 1974a, 1974b) that pointed the way to the kind of clean neuropharmacology that I aspired to do. It was not an accident that on finishing my thesis, I decided to spend a year in Oregon in David Barker's lab before I was able to move to Paris to work at the Ecole Normale Supérièure, in the Kehoe–Ascher–Gerschenfeld group.

My days at UCSD were happy. Soon after I joined the lab, Brian Mulloney came as a postdoc, and he was a source of daily encouragement and much knowledge. Largely inspired by the work on denervation supersensitivity, I was fascinated by the question of how a neuron that received synaptic inputs from many different neurons would regulate the number and distribution of its receptors. I had the notion that answering this question in the STG would provide critical insight into what central nervous system neurons might be doing. This was before slice preparations, so it was easy to see the allure of asking this question with the STG. To that end, I learned the STG preparation, and I tried all of the agonists I could buy on the STG. I discovered that every putative transmitter I applied to the STG changed the pyloric rhythm in a different way. I decided that this wasn't going to tell me very much about the transmitters used by the STG neurons, but this observation was the first indication of the extent of neuromodulation that eventually would be one of the major foci of my scientific work.

I turned to trying biochemical methods for transmitter identification. I spent a while developing micro-dansyl chloride chromatograms, which told me that there was a lot of taurine in the STG. Eventually, I visited Dick McCaman and learned his method of single-neuron dissection after ethylene glycol freeze substitution. When it was clear that this was going to work on single-STG neurons, Dick told me that Dave Schubert at the Salk Institute was also doing choline acetyltransferase assays, and I should talk to him.

When I went over to see Schubert at the Salk, Schubert invited me to do the choline acetyltransferase assays in their lab—so that is what I did. At the time, the Salk group in which I worked included Dave Schubert, Jim Patrick, Yoshi Kidokoru, and Steve Heineman. They were young, were extraordinarily patient and kind with me, and became an endless fount of relevant expertise, both with regard to biochemistry and cellular electrophysiology. It was Kidokoru and Heineman who gave me advice on ACh iontophoresis.

My routine was to physiologically identify the STG neurons, dissect them into tiny individual glass test tubes, and freeze them on dry ice and to put the ice bucket into the freezer for a day or two until I had enough identified neurons. At that point, I took the ice bucket to Salk for the choline acetyltransferase assays. Statistics weren't part of our training, but I was concerned that the single-neuron enzyme signal was small. I ran as many blanks as neurons in each assay (usually 10–15 in each run) and used a cut-off for what I called "signal" that was 5–10 cpm higher than the highest of the blanks. My logic was that the range of the blanks, if I ran enough of them, would allow me to sample the random error in the assay. In retrospect, I realize I had created an experimental p-value.

The choline acetyltransferase assays showed strong positive signals in several classes of identified neurons and were consistently negative in other classes of neurons. Most of the STG neurons are motor neurons that make excitatory synapses on specific stomach muscles and inhibitory synapses on other neurons in the STG neuropil. I quickly figured out that the muscle targets of these neurons provided an easy place to assess the possible transmitter candidates. Among the choline acetyltransferase–positive neurons were the pyloric dilator (PD) neurons that innervate four sets of extrinsic stomach muscles. Using these muscles, I determined that the muscles contracted in response to ACh and carbachol, that iontophoretic applications of ACh produced muscle depolarizations, and that curare blocked the synaptic potentials in the muscles evoked by nerve stimulation. The muscles innervated by the neurons that did not have choline acetyltransferase contracted in response to glutamate, which we now know is the transmitter used by those neurons, both at their excitatory neuromuscular junctions and at their inhibitory junctions in the STG neuropil. At the end of my PhD, I had a tentative transmitter candidate for each of the identified motor neurons in the STG (Marder 1974, 1976).

Postdoc Years

After a year at the University of Oregon in David Barker's lab where I did iontophoresis onto STG neurons and discovered that they responded to amines and amino acids, I packed up to move for a postdoc in the Kehoe–Ascher–Gerschenfeld and colleagues group at the Ecole Normale Supérieure under the auspices of a Helen Hay Whitney Fellowship.

Because I had worked entirely independently as a graduate student and had dealt successfully with Selverston's version of benign hands off advising, I assumed I would have no problem adapting to the Paris lab. But moving to Paris presented unexpected challenges.

I had studied French in high school and college, but I had never spoken it, or really heard it. Nine years after my last French class, I arrived in Paris and did not understand a word. Everyone in the lab spoke English, but all lab conversations were uncompromisingly in French, except those that were one-on-one with me. I learned French for the second time; this time it wasn't the conjugation of the future subjunctive, but it was lab and Parisian slang. While in Paris, I had the frustrating sensation that there was a wall between the part of my brain that had studied French from books when I was in school and the part of my brain that became reasonably fluent in conversational French. I never lost my American accent and was reminded of that whenever a Parisian cab driver willfully refused to understand the way I pronounced "Rue Descartes."

I had come from a laboratory at UCSD that was part of the "simple systems, circuit cracking" field (doing then with electrophysiology and dye-fills what people today are doing genetic lines, optogenetics, and so on in flies, worms, and mice), and I was entering the world of channel biophysics. Consequently, I had to learn French and biophysics at the same time, just to follow the conversations at the lunch canteen. My new French colleagues were friendly and supportive, but when I arrived, I was woefully ignorant of quantitative membrane biophysics. Philippe Ascher, whom I eventually grew to love dearly, terrified me, as I had the impression that stupid things fell out of my mouth whenever I talked to him. JacSue Kehoe was unbelievably generous; she fed me dinner multiple times every month, made sure I was okay and introduced me to people she thought I might like. JacSue had more energy than anyone I had ever met before: She did extraordinary experiments, raised her young sons, and adopted any number of stray foreigners. When I first arrived, she asked me to make a preparation so that she could replicate some of my experiments (which she did). She taught me to make microforge hand-pulled electrodes, and then she left me to get on to do what I wished, which was to characterize the receptors on STG neurons.

At UCSD, I had worked with *Panulirus interruptus*, the Pacific spiny lobster. In Paris, lobsters were *trop cher* (too expensive), so I went to the local fish market at Rue Mouffetard in search of a cheaper large marine crustacean. I found *Cancer pagurus*, the local crab, and much to the amusement of the fishmongers, used to go to the market in search of crabs that were *bien vivant* for experiments. When I first brought the crabs back to the lab, I had to find the STG, only to discover that although the pyloric rhythms of crabs and lobsters were similar, the different body architectures resulted in appreciable differences in the gross morphologies of the stomach and the STGs. One of the problems I had not anticipated is that the crab

STG is very flat and translucent, so optics that were adequate for *Panulirus* or *Aplysia* were less than ideal for the crab STG.

I was extremely fortunate in my time at the Ecole Normale that Danièle Paupardin-Tritsch agreed to work with me. Danièle and I conversed in a strange mélange of French and English: She spoke French to me, I tried to answer in French and then flipped into English whenever I needed to. Somehow, even early on, Danièle understood me. Danièle had just finished her PhD thesis with Gerschenfeld on serotonin actions in *Aplysia* (Gerschenfeld and Paupardin-Tritsch 1974a, 1974b) and wanted a change of pace, so we worked on ACh, glutamate, and GABA responses on STG neurons and muscles (Marder and Paupardin-Tritsch 1978, 1980). The work we did then set the stage for the characterization of transmitter responses that my lab did years later.

During those Parisian years, I became friends with a number of other remarkable people, including Alain Marty, Anne Feltz, and Paul Adams, all of whom were outstanding receptor and synaptic biophysicists. There were incessant discussions of science, films, and politics in the lab, and it was the first time I felt that everyone around me was smarter than I was. Alain knew a number of cheap, good restaurants, and we went to a lot of films. I loved walking the streets of Paris, despite the inevitable "draggeurs" who followed and harassed American women in the streets. I got into the habit of walking in the middle of the street to avoid the inevitable dog excrement on the sidewalks and to make sure no one could jump out of bushes to attack me when I was walking alone at midnight coming back from a movie or dinner. But Paris was magic and the 4th, 5th, and 6th Arrondissements where I mostly traveled were very beautiful.

Home Again as an Assistant Professor

When I left for my foreign postdoc, "they" (the same "they" who tell my undergraduates that two majors are better than one) told me I would never find a job in the United States while abroad. But I had two offers for good faculty positions, and I returned to the United States in the fall of 1978 to start as an assistant professor at Brandeis. In retrospect, I realized that those offers came precisely because I had followed my own instincts, thus differentiating myself from many of the other very talented people who were also on the job market that year. When I left in 1975 to move to Europe, I wasn't sure I would ever want to return, as this was at the end of the Vietnam War, and I wasn't proud to be American. Three years later, I had come to understand that as distasteful some features of American politics and culture were (and are today), I was at the end of the day, American.

Having lived in the 4th and 5th Arrondissments in Paris, upon my return to the United States, I immediately looked for places to live in the most urban environment I could find and afford (walking distance to films, coffee houses,

and book stores). After a month of desperate looking for a rental, I ended up buying a tiny place in the heart of Harvard Square with wood floors, fire place, white walls, a minimal kitchen, and a sketchy bathroom. It had big bow windows, and a southern exposure. Given that I had no furniture, the fact that it was tiny was an asset, as after all, I was returning from microscopic Parisian apartments. I had no money and ended up with two mortgages. By today's standards the $27,500 price tag was almost nothing, but my salary was $16,000/year, and there were months that I would have to put together quarters and pennies to buy coffee or milk. But I loved that little apartment and being three blocks from the middle of Harvard Square. I also explored the rest of Boston and wistfully looked at the beautiful buildings in the Back Bay (where we later lived for 20 years). I went to the Italian section of town (the North End) when I missed France and Italy. We still go to the Café Vittoria, which I discovered in 1978 had the best cappuccino in Boston.

It was eerie to return as a faculty member to the place I had left as an undergraduate nine years previously. In some ways, the Brandeis campus was much the same; in other ways, it was totally changed, and not for the better. I returned to the consequences of nine years of deferred maintenance. Buildings that had been new when I left in 1969 had leaking roofs and were unpainted in 1978. I had left a campus of 1,800 undergraduates and came back to one whose enrollments had been expanded to cover budget deficits. Happily, the senior faculty members who remembered me were wise enough to leave me to find my own way.

When I arrived in my new lab, it was filled with years of departmental detritus. I started at Brandeis only a few weeks after Ron Calabrese started his new lab at the Harvard Biolabs. Ron was incredibly helpful, as he shared advice about amplifiers, recordings, coffee shops, and restaurants. Also important was a friendship I early established with Kalpana White, a fly developmental geneticist, who started a year ahead of me at Brandeis. Kalpana was then (and remains so now) unusually wise, and her friendship was critical to me as I tried to maneuver through the rocky times of starting a lab.

I was hired ostensibly to teach animal physiology (something I had never taken). I wasn't particularly worried about this: I obtained the undergraduate text that was considered the best. I bought two different medical school physiology textbooks and proceeded to read the medical school texts, and then the undergraduate text, staying a lecture or two ahead of the students. Although I had 90 students in physiology, by the end of the semester, I knew all of their names, something I can no longer do.

I set up our first rig, purchased with grants from the McKnight Foundation and the National Science Foundation (NSF). Unlike today, my set-up funds were more symbolic than actual, and it was necessary for me to get grant funding to buy my first electrophysiology set-up. Happily, I had submitted grants during my last postdoc year, and they were awarded by the time I was ready to set up my lab. Chris Lingle (today a world-class channel biophysicist

at Washington University), whom I had met when I was in Oregon, joined the lab as a postdoc. Shortly thereafter, I benefited from a terrible tragedy: Fred Lang, a wonderful developmental neurobiologist working at Woods Hole, was killed by a drunk driver, leaving eight graduate students, including Judith Eisen (now an eminent developmental neurobiologist at the University of Oregon), who joined my lab. Judith was already an accomplished scientist, and within a few months, we were working together as peers, colleagues, and friends. Soon afterward, I hired Michael O'Neil as a technician (several years later he wrote our first dynamic clamp program) and Scott Hooper (professor at Ohio University and University of Cologne) joined us as my second PhD student. I remember walking around the lab one evening to discover three rigs were running simultaneously, wondering how it had all happened.

One day in August 1981, I was sitting outside at the student union eating my lunch and reading the *New York Times*, when a gust of wind blew away the paper, and Art Wingfield, a professor in the psychology department, rescued it and returned it to me. In a few months, Art had moved in with me in the tiny Cambridge apartment. After 20 years of living together, we got married in 2001. When we met, Art's youngest of three children was 15, and living with his mother in England. Over the years Art's children grew up, established interesting careers, married wonderful people, and in turn had two children each, who have developed into fascinating people. Each of Art's kids lived with us for several months at different times in their lives, as did my two nieces. As they all lived with us when they were almost "grownup," I had the pleasure of spending time with them without the worries of their early years.

The work that Judith Eisen and I did was the beginning of mechanistic studies of circuit neuromodulation, and presages much of today's work in *C. elegans* and *Drosophila*. We knew from my thesis work that the PD neurons were cholinergic and suspected that the anterior burster (AB) neuron, to which the PD neurons are strongly electrically coupled, was not. Judith and I realized that the electrical coupling between the PD and AB neurons created confounds for circuit analysis, as an inhibitory postsynaptic potential (IPSP) recorded in a follower neuron, such as pyloric (PY) or lateral pyloric (LP), might come as a result of transmitter liberated from either the PD, AB neurons, or both of them. Likewise, an IPSP evoked by the LP neuron that could be recorded in both the AB and PD neurons might be direct on either or both of the neurons showing the IPSP. To disambiguate the circuit, we used Miller and Selverston's Lucifer yellow photoinactivation technique (Miller and Selverston 1979). We showed that both the PD and AB neurons inhibited the pyloric follower neurons, but that the LP neuron inhibited the PD neurons but not the AB neuron (Eisen and Marder 1982).

With this knowledge, we wanted to ask how much of the IPSP evoked by the simultaneous depolarization of the AB and PD neurons came from each of the two presynaptic neurons. To do this, we applied picrotoxin to

block the AB-evoked IPSPs. We became completely frustrated, as each time we did the experiment, we got a different answer: Sometimes the IPSP was blocked to a small extent, other times almost completely. Finally, it dawned on us that if the contribution of the two components varied under different physiological conditions, then that was exactly what should be expected!

This experience taught me an important lesson as a scientist and mentor: Often the most important new insights come from being stuck and being forced to think differently about a problem by data that at first blush seem inconsistent or unreliable. Judith realized that a neuromodulator or an input synapse that would preferentially activate or inhibit the transmitter released from the AB or PD neurons would alter the transmitter mix in the IPSP, and consequently the time course of the IPSP and the firing phase of the follower neurons (Eisen and Marder 1984). The four papers that constituted Judith's PhD thesis were arguably the first clear mechanistic description of circuit modulation, and a clear demonstration that circuits are not hard-wired, but rather are flexible.

At the same time Judith and I were working on neuromodulation in the STG, Pete Getting, working in *Tritona*, was developing the idea that circuits could be reconfigured by sensory and other inputs, so that the same circuit could produce different outputs (Getting and Dekin 1985; Getting 1989). Pete and I spent hours talking, and he was an enormous intellectual support for our initial work on neuromodulation. To this day, I miss the conversations we never had the chance to have (Marder 2015b).

In 1983 Barb Beltz, then a postdoc in Ed Kravitz's lab, published a beautiful paper on serotonin immunohistochemistry in the lobster nervous system (Beltz and Kravitz 1983). Shortly thereafter, Barb and I tried this method on the stomatogastric nervous system. One look through the microscope changed my life, as I immediately saw the bright 5-HT-stained gastropyloric receptor (GPR) neurons, the stained neuropil in the STG, and fibers and neurons in the esophageal and commissural ganglia. This taught me how much one can learn by "just seeing." That experience has always made me value discovery science and to be uncomfortable with people who dismiss new science as "only descriptive." Seeing something for the first time can often tell you in a glance something you would have no way of otherwise knowing or predicting.

In 1984, we published eight papers, most of them on neuromodulation, and I received tenure. Between 1984 and 1990, Art and I moved to a dramatic fifth-floor apartment in the middle of the Back Bay, we made important strides forward in understanding neuromodulation and circuit switching, and I started working with theorists. In 1990, I was promoted to professor.

Taking My Voice

Although I was by the standards of the day, assertive for a young woman, the signals from many of my peers and colleagues that I was too pushy were always

there, and I must have internalized many of them. Nonetheless, I was acutely aware that I was not "heard" as well as Peter Getting and some of my other male colleagues. I marveled at how well Pete was heard and knew some of it was due to his remarkable clarity. But I also knew that our message was as fundamental and important as his was. At the time, there were few female speakers at Society for Neuroscience (SfN) and other scientific meetings. In 1985, Janis Weeks and I cochaired an SfN symposium with the two of us, Ron Calabrese, and Pete Getting, to highlight some of the best work on small circuits. When Janis and I first discussed this symposium, we thought about asking only female speakers, but decided it would have been such a strong statement that it would detract from our scientific message. Janis and I decided that two women out of four speakers was revolutionary enough but couldn't be criticized. In 2008, when I was president of SfN, I invited four female speakers (I was just fed up enough by this point to not care what "they" might say, and there were so many wonderful women available). Many young women thanked me for doing it, and a number of older men grumbled behind my back (not daring to complain to my face), despite the fact that the speakers were all outstanding.

I didn't realize how unconsciously influenced I was by the attitudes around me until 1987 when Mary Kennedy, who had become a good friend, invited me to give a seminar at CalTech. I gave a talk that I thought was daring and adventuresome, in which I was trying to articulate a change in conceptual framework. Afterwards, Mary came up to me and said my talk was fine, but there was no reason for me to be so "tentative." At that moment, I realized that my internal calibration system was entirely untrustworthy, as it still reflected years of having been told I was too assertive. Learning to "take one's voice" is something that many of us have had to do, and it demands listening well, as well as on occasion being willing to insist on being heard. It required me to be willing to be viewed as shrill or a witch, and it has forced me to be willing to interrupt men who were talking through me or ignoring me. This happens less to me today, but I suspect it still happens to younger women all the time.

Neuromodulation

I had never done any anatomy, but Kalpana was an expert light microscopist and taught me a great deal. This started a profitable time in the lab, as we routinely screened any antibody that I could beg or buy that had been raised against transmitters and neuropeptides. This quickly revealed the very large number of peptide modulators in the stomatogastric nervous system. To this day, my lab continues to combine anatomical characterization of modulator and neuronal projections with electrophysiological investigations (Beltz et al. 1984; Marder et al. 1987a; Nusbaum and Marder 1988, 1989a).

One of my favorite papers is still Scott Hooper's major thesis paper on the effects of proctolin on the pyloric rhythm (Hooper and Marder 1987). Scott had previously shown that proctolin modulated the pyloric rhythm,

but he wished to account for proctolin's actions on the intact network in terms of its actions on individual target neurons. To that end, Scott isolated each identified neuron from its network inputs, and described proctolin's actions (or lack thereof) on each neuron type. Scott noticed that when he isolated the AB neuron, it went faster than it did when it was left attached to its electrically coupled neighbors, the 2 PD and 1 ventricular dilator (VD) neurons. He then designed a beautiful set of experiments that argued that the non-proctolin-sensitive neurons were effectively slowing down the pacemaker AB neuron (Hooper and Marder 1987). This was initially surprising to us, but it made sense once we had seen the data and thought about it.

I learned an important lesson from working with Scott. One day he walked into my office and started explaining his data and his thoughts about it, and I realized that I was learning from him. He had complete ownership of his data, and he had obviously thought more deeply about it and understood it better than I had. At that moment, I knew he was intellectually ready to graduate. Indeed, over and over again, I have been able to mark, almost to the day, when I knew my students were ready to graduate as they came in to show me something in their data that marked their transition to an independent scientist.

Mike Nusbaum joined the lab as a postdoc at the end of 1984, and from the very beginning, Mikey's interest was the circuitry of the descending modulatory inputs to the STG. Mikey and I spent many nights eating pizza in the lab at his desk in those halcyon days when we were allowed to have food in the lab, and he identified an important pair of modulatory proctolin neurons, the MPNs (Nusbaum and Marder 1989a, 1989b). In his own lab, at the University of Pennsylvania, Mikey has continued to work to describe the complex circuitry between the descending modulatory neurons and the STG, with a marvelous dedication to picking apart a tangle of pathways and modulator actions. To this day, we continue to collaborate on some projects.

By the end of the 1980s, we had unambiguously demonstrated that many neuromodulators influenced the STG, and each did so to reconfigure the STG in a different way (Marder et al. 1987b). At the time, we argued that this was important to provide behavioral flexibility to the animal.

A major change in the way we identified new peptide modulators in the stomatogastric nervous system benefited years later by development of new mass spectroscopy methods. Lingjun Li spent a short postdoc in the lab and has since carried out extensive identification of the neuropeptides in crustaceans. Therefore, after years of difficult purification of neuropeptides, state-of-the art chemistry has shown the presence of hundreds of neuropeptides in the stomatogastric nervous system (Christie et al. 2010; Li et al. 2003).

Switching

When Jim Weimann joined the lab as a PhD student, he wished to study the gastric rhythm of the crab, *Cancer borealis*. To that date, we had not

seen gastric mill rhythms in the crab. After several months of work, Jim announced to me that there were no gastric mill neurons in the crab, because all of the neurons he found appeared to be firing in time with the faster pyloric network. I told him to properly identify the somata using paired intracellular recordings from the gastric mill muscles and the STG somata. By so doing, Jim discovered that many of the gastric mill neurons fire in time with the pyloric rhythm (Weimann et al. 1991; Weimann and Marder 1994). This observation became one of the first clear examples of neurons that could switch between being part of different central pattern generating circuits. This kind of switching is seen very clearly in the crab, and in the Maine lobster *Homarus americanus* (Bucher et al. 2006), but it is less evident in *Panulirus interruptus*, the Pacific Coast spiny lobster.

At the same time, Patsy Dickinson, on sabbatical from Bowdoin College, showed that red pigment concentrating hormone (RPCH) created a conjoint rhythm from neurons of disparate circuits in *Panulirus interruptus* (Dickinson et al. 1990). These examples led to our understanding that different modulatory conditions could dramatically alter the participation of neurons in different functional circuits.

Moving to Theory

Avis Cohen at Cornell who worked on the lamprey spinal cord CPG, insisted on introducing me to Nancy Kopell, an applied mathematician (then at Northeastern University, now at Boston University), who was working on theory of coupled oscillators. Nancy and I became friends in the late 1980s, and that friendship continues today. When I first met Nancy, she was looking to neuroscience for interesting math problems, while today Nancy is using mathematics to illuminate neuroscience problems. Nancy and I published together during the 1990s on oscillator function.

Nancy was catalytic in fostering a collaboration between me and Irv Epstein, a world expert on chemical oscillators in the Brandeis chemistry department. Ron Harris-Warrick had found that oscillations in different modulators were differentially sensitive to tetrodotoxin, and he suggested that there could be different oscillation mechanisms, some preferentially dependent on sodium channels, others on calcium channels (Harris-Warrick and Flamm 1987). Irv's simulations showed that that it was possible to obtain similar-looking bursting behavior by very different sets of conductances (Epstein and Marder 1990). This was, for me, the first inkling of the extent to which degenerate cellular and circuit mechanisms play a role in neuronal and circuit activity.

When Jorge Golowasch joined the lab in the late 1980s, he wanted to characterize biophysically the voltage and time-dependent currents in STG neurons, with the goal of understanding how neuromodulators altered the intrinsic properties of their target neurons. Jorge determined that the peptide, proctolin, activated a voltage-dependence inward current that was blocked by

extracellular Ca^{2+} (Golowasch and Marder 1992). This current is ideally tuned to activate and enhance bursting, and it is of prime importance for the action of numerous peptide modulators (Swensen and Marder 2000). Jorge also used voltage-clamp methods to measure a number of different membrane currents in the LP neuron, and then together with a postdoc in Irv Epstein's lab, constructed a semirealistic model of the LP neuron (Buchholtz et al. 1992).

Although this model was no less successful than many of its era, I found its construction frustrating because it showed us that (a) the currents we couldn't measure accurately were critical for the model's performance; (b) we didn't know whether we should use our "best" or our "mean" data to model each current; and (c) the model was fragile, and juggling one conductance required juggling others to compensate. Despite its limitations, or because of its limitations, the intellectual understandings that grew from this work shaped our work profoundly for the next 25 years. Indeed, much of the work that I did with Larry Abbott, Astrid Prinz, and others had its roots in the frustrations that I experienced in this attempt to build a biophysically realistic STG model neuron.

When I met Larry Abbott in the late 1980s he was a just minted full professor of particle physics in the Brandeis Physics Department. Like others of his generation, Larry became attracted to neural network theory, and he was working with his student Tom Kepler on memory in artificial neural networks. By happenstance, Jim Weimann and Tom Kepler were recipients of a graduate fellowship that required them to go to the same lunch for the fellowship donors. Afterward, Jim invited Tom back to the lab to show him a biological circuit in operation. Tom immediately ran over to Larry's office to get him, and the rest is history. From then on, Larry set about to educate himself about neuroscience, and in so doing, taught me how to educate physicists interested in moving into neuroscience.

When Larry asked me what he should read, I handed him Kandel, Schwartz, and Jessell. Larry started at the beginning and dropped into my office almost every day with questions. After several months, he stated happily that he "was starting to see the same words over again," which gave him comfort because he was afraid that there were an infinite number of words he had to learn. Although he made a joke of this, it showed me that the biggest barrier that a physicist had to learning neuroscience was that the knowledge in neuroscience is not derivable. Instead, it requires learning a lot of cellular mechanisms with strange names or parts of the brain with even stranger names, before it is possible to understand the literature and think creatively.

Larry, like many physicists transitioning into neuroscience, found the fact that the pyloric rhythm maintained constant phase over a substantial frequency range fascinating (Abbott et al. 1991). I was equally curious to understand the way that the PD neurons influenced the frequency of the AB neuron (Kepler et al. 1990). The LP neuron model that Jorge Golowasch and Frank Buchholtz were working on posed a very difficult question. Although

each biological neuron was successful at finding a balanced set of conductances that gave rise to a reliable and characteristic set of intrinsic properties, it was shockingly difficult to tune a conductance-based model to replicate the biological neuron's behavior. This told me that we must have been missing an important principle about how electrical excitability is controlled. For the better part of a year, I badgered Larry to think about this problem. For months he said it was "too hard." Then, one day Larry came in and said he thought he had a simple solution, and it was this solution that gave rise to the notion that neurons and networks could self-tune to a desired activity state.

Homeostasis

In 1992, there was a rich tradition of ion channel biophysics. But, any self-respecting biophysicist would wish to study a single kind of channel, or voltage-gated current, in isolation, uncontaminated by all of the other conductances in the neuron. So there were experts on Na^+, K^+, and Ca^{2+} currents, but different labs usually studied these currents. Likewise, others were working on the molecular regulation of these currents. Again, it was characteristically different people working on the regulation of different currents.

In contrast, Larry realized that if the neuron used a simple negative-feedback, activity-dependent control of its activity to regulate *all* of its conductances, then the control problem no longer required that the neuron measure and match the expression of each of its conductances in the way that all of us who were fine-tuning models found so difficult. The first of these self-tuning homeostatic models was published in 1993 (LeMasson et al. 1993), followed by Gina Turrigiano's papers that provided experimental support for the idea of activity-dependent tuning of conductance densities (Turrigiano et al. 1994; Turrigiano et al. 1995). Of course, homeostatic negative feedback mechanisms are core to the regulation of many physiological processes. What was novel with these models is that they applied a well-understood principle in the context of many physiological processes to the control of all of the conductances in a neuron, rather than assuming that each type of channel was independently regulated.

In the first generation of the homoestatic models, intracellular Ca^{2+} concentrations were used to create a global target of the neuron's activity, and then to guide changes in conductance densities. This was followed by a second-generation model (Liu et al. 1998) that used three Ca^{2+} sensors. More recently, a third generation of more biologically plausible integral control models was implemented in which the rate of change of each conductance is regulated separately (O'Leary et al. 2013; O'Leary et al. 2014; O'Leary and Marder 2016). Using simple rules, these models find sets of "neurons" that capture much of what is present in the biological data.

When Gina Turrigiano moved to her own lab, she rapidly switched to studying rat neurons in culture, and very shortly thereafter, she and Sacha

Nelson published their landmark paper on synaptic scaling (Turrigiano et al. 1998). Because synaptic scaling provided a counterpoint to long-term potentiation and Hebbian plasticity, almost immediately its importance was recognized. Today, homeostasis of intrinsic excitability and activity-dependent scaling of synaptic strength have become central to our understanding of circuit development and function.

Dynamic Clamp

One of the first projects that Larry Abbott and I envisioned was to create circuits of defined connectivity by coupling cultured neurons in varying configurations that would allow us to create artificial electrical and chemical synaptic connections but give us control of the strength of these connections. My first idea was to use the membrane potential of one neuron to control the current through an iontophoretic electrode-delivering transmitter to a postsynaptic neuron. Larry immediately realized that a simple electronic circuit could provide the electrical simulation of a gap junction. Together with Andy Sharp and Michael O'Neil, we started to build these circuits (Sharp et al. 1992). Helped by an early conversation with John Rinzel during a summer course at Woods Hole, these efforts turned into the concept of a fully programmable dynamic clamp.

The dynamic clamp creates an artificial conductance, either a voltage-dependent conductance or an artificial chemical synapse (Sharp et al. 1993a, 1993b), using intracellular recordings and equations that model the applied conductance. This allows the investigator to do simulations using biological neurons. Our initial dynamic clamp program was extremely difficult to implement because of the limitations of the hardware at the time. The code was written in machine language by Michael O'Neil, because computers and boards were so slow by today's standards. A less general, but faster system was developed by Hugh Robinson (Robinson and Kawai 1993) to study Na^+ currents. Over the years, a large number of different dynamic clamp systems have been developed by investigators around the world (Butera et al. 2001; Prinz et al. 2004a), and we have used a number of different dynamic clamp programs to study the dynamics of small circuits or the actions of single voltage-dependent currents (Sharp et al. 1996; Turrigiano et al. 1996; Bartos et al. 1999; Grashow et al. 2009, 2010; Goaillard et al. 2010). Today, the dynamic clamp is routinely implemented and used by many investigators wishing to investigate the sensitivity of neuronal excitability to a particular conductance.

Multiple Solutions

In the late 1990s, Mark Goldman, then one of Larry Abbott's students and now a world-renowned professor at the University of California, Davis, wished to ask how many different sets of conductances could give rise to similar behavior.

Therefore, he constructed a population of about 5,000 model neurons, each with five voltage-dependent conductances and a leak (Goldman et al. 2001). Mark found that similar electrical behavior could result from different sets of conductance densities, and that in some cases, even small changes in conductance densities produced quite disparate intrinsic properties (Goldman et al. 2001; Golowasch et al. 2002). Measurements of K^+ currents in identified neurons were consistent with a range of conductance densities (Golowasch et al. 1999; Goldman et al. 2001). This work showed that the value of no single conductance was sufficient to predict the neuron's activity (Goldman et al. 2001) but that predicting the neuron's output required knowing the correlated values of three different conductances. This work also provided a lovely example of what we called "failure of averaging" (Golowasch et al. 2002), which can occur when averages of a population fail to represent the behavior of all of the individuals that contributed to that average.

Following on Goldman's lead, postdoc Astrid Prinz (now at Emory University) wished to find models of the pyloric rhythm. She first created a database of 1.7 million model neurons, each with eight conductances (Prinz et al. 2003), and then used some of these neurons to create a database of more than 20 million circuits, built with the architecture of the pyloric rhythm (Prinz et al. 2004b). This paper gave examples of virtually identical circuit outputs that resulted from disparate sets of underlying conductance densities (Prinz et al. 2004b). This result was an example of a computational study that completely changed the way in which we subsequently designed, implemented, and analyzed experiments. The lessons we took from this work were as follows: (a) much of the variability in measurements we saw across animals is likely biological, and not merely a result of experimental error; (b) it is important to obtain as many measurements as possible on each individual, and to look for correlations across parameters; and (c) if each animal is an individual solution, within a range of parameters, they would be differentially sensitive to perturbations.

In a more recent study, Gabrielle Gutierrez and Tim O'Leary studied five-cell networks of coupled oscillators. They showed that changes in network performance that look identical at the network level can result from changes in three different synapses (Gutierrez et al. 2013). This work shows that degenerate solutions to circuit performance arise easily from parallel pathways resulting from electrical coupling. The implications of this work are obvious: Without a connectome that reveals where parallel pathways in circuits are likely to be found, pharmacological or optogenetic approaches may lead to incomplete or misleading results, by finding only one of several circuit mechanisms that could be responsible for a change in circuit output.

Animal-to-Animal Variability

In response to Astrid's 2004 paper, we set out to determine how much variability is biologically present across individuals in the parameters that

determine intrinsic excitability and synaptic strength. We did this by combining single-cell polymerase chain reaction measurements of the mRNA copy numbers for single ion channel genes with voltage-clamp measurements of synaptic strengths and voltage-dependent conductances (Schulz et al. 2006, 2007; Goaillard et al. 2009; Tobin et al. 2009). These studies showed an approximately two- to sixfold variability in the same parameter in the same identified neuron across animals, and also revealed interesting sets of correlations in the expression of ion channel genes and conductances (Schulz et al. 2006, 2007; Goaillard et al. 2009; Tobin et al. 2009). This highlights the importance of plotting all of the data points in a study, and not only reporting means and standard errors. We were very encouraged that similar data were soon forthcoming from Ron Calabrese's work on leech (Roffman et al. 2012) and can be seen in studies of vertebrate systems (Swensen and Bean 2005; Sobie 2009).

As a follow-up to these initial experiments, Rachel Grashow used the dynamic clamp to make artificial networks by coupling single neurons of various cell types to the same oscillator model (Grashow et al. 2010). These experiments provided direct evidence for compensation of one set of variable properties with another variable process.

Interestingly, not only are the intrinsic and synaptic currents in the pyloric cells and circuit variable, but neurons of the same cell type are also morphologically variable (Bucher et al. 2007; Otopalik et al. 2017a), but this may not be important for the operation of the STG because the neurons are electronically compact (Otopalik et al. 2017b).

Animal-to-animal variability arises automatically in Tim O'Leary's integral control models as they self-assemble (O'Leary et al. 2014). Taken at face value, we have learned that many solutions produce similar behavior, but these nonetheless represent a small fraction of solutions that would arise with randomly varying parameters. My personal take on all of these data is that the molecular machinery of real neurons can achieve a two to six range of many parameters (synaptic strengths, channel number) in the same identified neurons across the population, but these neurons would be hard-pressed to achieve a 5 percent precision of those same parameters. Likewise, maintaining a target activity profile means restricting values to a certain part of parameter space, and this is the space that biology has found.

Perturbations

If each individual animal or person has a different set of underlying parameters, then there should be a range of perturbations that all healthy individuals can deal with or withstand. But if a perturbation is more extreme, one might expect that some individuals would be more successful than others (Marder et al. 2015). To test the predictions of these premises, we have been studying the effects of temperature on the STG motor patterns

(Tang et al. 2010; Tang et al. 2012 Rinberg et al. 2013; Caplan et al. 2014; Soofi et al. 2014; O'Leary and Marder 2016). Modest changes in temperature produce robust and reliable responses across preparations. But as the temperature is increased to extreme levels, close to or outside of the range that the animals would routinely encounter in their natural habitats, preparations crash (i.e., they lose their characteristic functional outputs). Each animal crashes with unique and diverse sets of dynamics, as expected if each individual starts with a different set of intrinsic and synaptic properties. This work is instructive for thinking about how individual humans respond differentially to stresses of all kinds. More recently, we have started to study other global perturbations, including changes in pH and K^+ concentrations, to determine whether individual animals differ in their robustness to several perturbations.

Time Sharing and Interruptions

My office has always adjoined my lab, and my door is open except in the unusual case that someone wants to talk confidentially. In my last office, I could hear many of the conversations that took place as people worked. My present office is further from the dissection bays so I hear fewer routine conversations unless I wander down to the back of the lab. I worked at the bench myself until after I was a full professor, and of course during those years, I knew a lot more about the status of the freezers and daily lab dramas than I do today.

Because my office door is always open, there are days and weeks that I am interrupted almost continuously during normal work hours. I unconsciously developed strategies to deal with these interruptions. I have always been good at switching back and forth between tasks. I learned that if I leave documents open where I was working, that the page cues me back into the mind-set of where I was. I routinely work between 5 p.m. and 8 p.m., when the day has quieted down, and I am less distracted. Of course, clever members of my lab have also figured out that if they wish my undivided attention, those are good hours. I often work Sunday afternoons, and again this allows me quieter times.

More than 20 years ago, after one particularly disrupted day when I was trying desperately to get a manuscript or a grant finished, I realized that many of my colleagues restrict their availability and time much more than I do, and this perhaps translated into greater productivity. I decided then that I couldn't give up being who I was, even if it meant I wouldn't rise to the top of our profession because I might publish one or two fewer papers each year. In retrospect, who knows whether I might have published more papers had I not allowed these interruptions, but I also know it would have made me a much unhappier person to close my door. And, I have received more than my fair due of honors and accolades.

The Larger Scene

I have spent and continue to spend considerable time and energy working on the national and international level. I was first asked to serve on a study section when I was still an assistant professor, as there were so few women that we were roped in when we were still young and inexperienced. Since that first study section, I have served on a series of study sections or review panels for the National Institutes of Health (NIH) and NSF. I was on the Board of Scientific Counselors for the National Institute of Neurological Disorders and Stroke (NINDS) Intramural Program, I served on the NINDS Council, the Working Group for the Brain Initiative, and now serve on the Brain Advisory Council. I also serve on the Council of the National Academy of Sciences, as well as on scientific advisory boards for various institutions around the world.

At the onset of my career, there were immediate positive dividends from national engagement. It was interesting, and I met investigators from other institutions, who were working on a variety of problems. Of course, the negatives were that all of these activities took me away from my own work. On balance, for many years, I was able to balance effectively my engagements off-campus with my work on-campus. I read and write quickly (or at least do so when I am pushed by deadlines), so some tasks that are time-consuming for some people are less so for me. That said, as I have gotten older, I find traveling increasingly unpleasant. This is partly because traveling has become vastly more unpleasant and because I have a learned aversion to airplanes.

So why do I continue to say yes to as many of these activities? Especially to those that require riding on airplanes? If I am honest, I think I continue to serve because I feel an obligation to be an advocate for small laboratories, for people working on unconventional species, for women, for young people, and for people working at nonelite institutions. A very strong part of me is concerned by the concentration of power and resources in the hands of few. As science increasingly demands expensive technologies, this has become a major problem. I believe deeply that the strength of American science has always been its distributed and random nature: Someone in Wyoming, Oklahoma, or Puerto Rico can do wonderful experiments that could change the way we think about some important biological process. I worry that unless strong voices remind us that we have to treasure our scientific diversity and innovation across the myriad institutions that make up American science, we risk the foundational premises on which American science rests. I don't enjoy having to remind my colleagues that they should think before knee-jerking to award favors to our most elite institutions, no matter how deserving their scientists, but I continue doing so. The positional information of where we work is as important in the progress of science as it is in the development of an organism.

I was editor in chief of the *Journal of Neurophysiology* from 2002 to 2008. I changed the gender balance of the editorial board, but I tried to

maintain the journal's position as an excellent venue for the publication of substantial and thorough reports of systems and cellular neuroscience. At the *Journal of Neurophysiology*, I prided myself in trying to ensure that reviews were fair and that papers were improved by the review process.

I joined the editorial board of *eLife* as a senior editor at its inception, and now I am one of its deputy editors. *eLife* takes a good deal of my time, and my husband periodically urges that I quit *eLife* as its duties follow me daily and around the world. I was attracted to *eLife* because I hoped we would publish important and outstanding science while allowing manuscripts to retain the personality and flavor that their authors wished. Unlike many of the most prestigious journals, *eLife* has no length or word limitations, and instead employs many features that allow authors to present complete stories, with appropriate controls in the body of the paper. Importantly, *eLife* uses a consultative review process that is designed to remove conflicting reviews before an author has to try to make sense of inconsistent or inaccurate reviews. And, importantly, *eLife* tries to avoid reviewers and authors "upping the ante" on authors by asking for more and more experiments.

eLife has become a very well-respected journal and has published many important papers in all areas of biology. I always felt that my support for *eLife* was one way to make our postdocs believe that excellence could triumph over the stranglehold represented by the most elite journals. In some ways, *eLife's* commitment to excellence, and therefore its selectivity, is both its strength and its weakness, as we also make decisions partially on the basis of our assessments of novelty and significance. But, on balance, I continue to believe in *eLife's* mission to improve the transparency and immediacy of scientific publication. Nonetheless, *eLife* does not function in a vacuum, and our authors, reviewers, and editors are influenced strongly by today's culture of scientific publication. I keep trying to remind our editors and reviewers that our job is to publish the science that our authors have done and that our job is not to create arbitrary hurdles and publication delays. It is a real editorial challenge to strive for rigor and innovation without letting reviewers and editors destroy author autonomy. Interestingly, the most common complaint that reviewers and editors make about the papers we review is that the authors are trying to "oversell" the novelty and significance of their work. Thus, we all recognize the deleterious consequence for our science of the dominance of elite publications, but most of us have learned to sell and oversell our work.

I have served the SfN (and other scientific societies as well) in many capacities, including on the Program Committee, Publication Committee, Committee on Committees, and Council. In 2007—2008, I was SfN president. Because the SfN staff is so professional and expert, my time as SfN president was considerably less onerous than I had feared, and it was an interesting challenge to help steer SfN in ways that helped the international community of neuroscientists. I found it fascinating to watch an

organization that needs to remain flexible enough to respond to changes in our world and stable enough to resist whims of an ever-changing leadership. In some ways, SfN as an organization parallels the adult nervous system: It must be both plastic and robust, and this is a never-ending challenge both for the permanent staff and its scientific leadership.

Over the years, I have written and published many scientific review articles, some of which have been influential (Harris-Warrick and Marder 1991; Marder and Calabrese 1996; Marder and Goaillard 2006; Marder and Bucher 2007; Marder 2012). One of the reasons I continue to write and publish reviews is because I am fully aware that the idiosyncrasies of the stomatogastric nervous system make it difficult for an outsider to find the important take-home messages embedded in the literature on this preparation. I am also aware that many experimentalists find the theory literature difficult, so sometimes reviews that capture messages from theory are helpful (Marder and Taylor 2011; Marder et al. 2014; Marder et al. 2017). This is also why I continue to ride on airplanes more than I would like, as I know that the messages of our work are more readily accessible when the logic of many papers is presented in a 50-minute talk than it ever could be in the individual papers.

Over the past 20 years I have published about 20 short opinion pieces, first in *Current Biology* and more recently in *eLife*. These pieces are usually born in frustration with aspects of our scientific and educational lives and enterprises (Marder 2000, 2015a). Some of these papers are funny in places, but they all are part of my attempt to remind myself and others of what is important in how we live our lives as scientists and educators. We all struggle to stay on a path that leads to the discovery of new knowledge and the nurturing of our trainees. But there are many dangers on those paths, and I struggle with them daily.

2018

Art and I now live on the Boston waterfront, just outside of the North End and its Italian restaurants and markets. We see glorious sunsets and watch the endless varieties of boats, large and small. In the summer, I swim in an open-air public pool, right on the water's edge two blocks from our apartment. In the winter, the cold winds blow off the harbor. We sometimes take the water taxi from our building to the airport, but usually I opt for the seven-minute drive through the tunnel from our home to the airport terminal.

This past semester I once again taught Principles of Neuroscience to 80 students. I still love the first half of this course because it starts with the fundamental principles of cellular neuroscience, and I know that most of what I cover in that part of the course will remain "true" in 10 or 20 years. I don't enjoy the second half of the course as much because it deals with problems and processes that still feel fundamentally unexplained. I feel less

comfortable with trying to explain the mechanisms underlying higher cognitive processes. That said, I enjoy watching the light go on in students' eyes as they understand a new concept. I have the sense that while my students are as smart as ever, they learn differently. I still teach on the black board with colored chalk, and still require students to write answers in their own words on exams. I know that our students are better at doing oral presentations than they were in the past, but they seem less adept at extracting the logic of a scientific argument from the literature.

I still have an open door in the laboratory, and 95 percent of the time, I stop what I am doing when someone puts their head in my door, whether they are colleagues, random undergraduates, or one of my lab members.

I have stayed at Brandeis University for 40 years. I am now the fourth oldest of the full-time faculty in my department. All of us were hired as beginning assistant professors, and we have matured in place. Among the 30 or so active research faculty in the biology and biochemistry departments, five are members of the National Academy (Jim Haber, Chris Miller, Michael Rosbash, Gina Turrigiano, and myself) and have been here since starting their labs. Michael Rosbash and Jeff Hall (who went emeritus several years back) were just awarded the Nobel Prize, and a number of us have received other prestigious international awards. Other eminent senior faculty (Jeff Gelles, Dan Oprian, Doro Kern, Liz Hedstrom, Leslie Griffith, Sue Lovett, Sacha Nelson, Bruce Goode, and Piali Sengupta) also have been here since they started as assistant professors.

Until recently, people would invite me to apply for positions as deans, provosts, chairs, and institute directors at various institutions. During the past year or two, those invitations have largely stopped, which is fine because I never applied for a job at another institution. Instead, in the last year or so, people have started asking me if I have retirement plans. I do not. I was lucky enough to get an NINDS R35 award that will provide me with good grant funding for another seven years, as long as we continue to be productive. Thus far, I am still attracting excellent postdoc and graduate students, and I have a list of 15 or so manuscripts that are 50–80 percent completed, so there is much work to be done. I have stayed at Brandeis largely because of my colleagues. They are wicked smart, compassionate, have great senses of humor, and share the belief that the creation of new knowledge is one of the most important of human endeavors.

What has changed in me is that I have far less patience, or for that matter interest, in university politics and procedures, and in other national and international activities. I have grown to abhor memos, and I really don't care the way I used to about the requirements for our degrees, or how other institutions govern themselves. Although it is important to sometimes offer advice to colleagues at other institutions about their graduate programs, it just isn't as interesting as it might have been 25 years ago. Likewise, individual students are as compelling as always, but decisions about the formal

mechanisms we use to evaluate and educate them seem increasingly pointless, as I have decided that some of them will become real scientists regardless of what we do, and others will not, regardless of what we do. We aren't good at predicting which ones will do great work and which will become discouraged. Sometimes, the right conversation is more important than all our programmatic activities. Thus, my door remains open.

When I walk back to the rig rooms and watch recordings of the rhythms of our preparations, I find myself in the same state of wonder that I first felt as a beginning graduate student. Peeking into the mysteries of life never gets old.

References

Abbott, L.F., Hooper, S.L., and Marder, E. (1991). Oscillating networks: Control of burst duration by electrically coupled neurons. *Neural Comp 3*, 487–497.

Ascher, P. (1972). Inhibitory and excitatory effects of dopamine on Aplysia neurones. *J Physiol 225*, 173–209.

Barker, D.L., Molinoff, P.B., and Kravitz, E.A. (1972). Octopamine in the lobster nervous system. *Nature New Biol 236*, 61–62.

Bartos, M., Manor, Y., Nadim, F., Marder, E., and Nusbaum, M.P. (1999). Coordination of fast and slow rhythmic neuronal circuits. *J Neurosci 19*, 6650–6660.

Beltz, B., Eisen, J.S., Flamm, R., Harris-Warrick, R.M., Hooper, S.L., and Marder, E. (1984). Serotonergic innervation and modulation of the stomatogastric ganglion of three decapod crustaceans (*Panulirus interruptus, Homarus americanus* and *Cancer irroratus*). *J Exp Biol 109*, 35–54.

Beltz, B.S., and Kravitz, E.A. (1983). Mapping of serotonin-like immunoreactivity in the lobster nervous system. *J Neurosci 3*, 585–602.

Bucher, D., Johnson, C.D., and Marder, E. (2007). Neuronal morphology and neuropil structure in the stomatogastric ganglion of the lobster, *Homarus americanus*. *J Comp Neurol 501*, 185–205.

Bucher, D., Taylor, A.L., and Marder, E. (2006). Central pattern generating neurons simultaneously express fast and slow rhythmic activities in the stomatogastric ganglion. *J Neurophysiol 95*, 3617–3632.

Buchholtz, F., Golowasch, J., Epstein, I.R., and Marder, E. (1992). Mathematical model of an identified stomatogastric ganglion neuron. *J Neurophysiol 67*, 332–340.

Butera, R.J., Wilson, C.G., DelNegro, C.A., and Smith, J.C. (2001). A methodology for achieving high-speed rates for artificial conductance injection in electrically excitable biological cells. *IEEE Trans Biomed Eng 48*, 1460–1470.

Caplan, J.S., Williams, A.H., and Marder, E. (2014). Many parameter sets in a multicompartment model oscillator are robust to temperature perturbations. *J Neurosci 34*, 4963–4975.

Christie, A.E., Stemmler, E.A., and Dickinson, P.S. (2010). Crustacean neuropeptides. *Cell Mol Life Sci 67*, 4135–4169.

Dickinson, P.S., Mecsas, C., and Marder, E. (1990). Neuropeptide fusion of two motor pattern generator circuits. *Nature 344*, 155–158.

Eisen, J.S., and Marder, E. (1982). Mechanisms underlying pattern generation in lobster stomatogastric ganglion as determined by selective inactivation of identified neurons. III. Synaptic connections of electrically coupled pyloric neurons. *J Neurophysiol 48*, 1392–1415.

Eisen, J.S., and Marder, E. (1984). A mechanism for production of phase shifts in a pattern generator. *J Neurophysiol 51*, 1375–1393.

Epstein, I.R., and Marder, E. (1990). Multiple modes of a conditional neural oscillator. *Biol Cybern 63*, 25–34.

Gerschenfeld, H.M. (1973). Chemical transmission in invertebrate central nervous systems and neuromuscular junctions. *Physiol Rev 53*, 1–119.

Gerschenfeld, H.M., and Paupardin-Tritsch, D. (1974a). Ionic mechanisms and receptor properties underlying the responses of molluscan neurones to 5-hydroxytryptamine. *J Physiol 243*, 427–456.

Gerschenfeld, H.M., and Paupardin-Tritsch, D. (1974b). On the transmitter function of 5-hydroxytryptamine at excitatory and inhibitory monosynaptic junctions. *J Physiol 243*, 457–481.

Getting, P.A. (1989). Emerging principles governing the operation of neural networks. *Annu Rev Neurosci 12*, 185–204.

Getting, P.A., and Dekin, M.S. (1985). Mechanisms of pattern generation underlying swimming in *Tritonia*. IV. Gating of central pattern generator. *J Neurophysiol 53*, 466–480.

Giller, E., Jr., and Schwartz, J.H. (1971). Choline acetyltransferase in identified neurons of abdominal ganglion of Aplysia californica. *J Neurophysiol 34*, 93–107.

Goaillard, J.M., Taylor, A.L., Pulver, S.R., and Marder, E. (2010). Slow and persistent postinhibitory rebound acts as an intrinsic short-term memory mechanism. *J Neurosci 30*, 4687–4692.

Goaillard, J.M., Taylor, A.L., Schulz, D.J., and Marder, E. (2009). Functional consequences of animal-to-animal variation in circuit parameters. *Nat Neurosci 12*, 1424–1430.

Goldman, M.S., Golowasch, J., Marder, E., and Abbott, L.F. (2001). Global structure, robustness, and modulation of neuronal models. *J Neurosci 21*, 5229–5238.

Golowasch, J., Abbott, L.F., and Marder, E. (1999). Activity-dependent regulation of potassium currents in an identified neuron of the stomatogastric ganglion of the crab *Cancer borealis*. *J Neurosci 19*, RC33.

Golowasch, J., Goldman, M.S., Abbott, L.F., and Marder, E. (2002). Failure of averaging in the construction of a conductance-based neuron model. *J Neurophysiol 87*, 1129–1131.

Golowasch, J., and Marder, E. (1992). Proctolin activates an inward current whose voltage dependence is modified by extracellular Ca^{2+}. *J Neurosci 12*, 810–817.

Grashow, R., Brookings, T., and Marder, E. (2009). Reliable neuromodulation from circuits with variable underlying structure. *Proc Natl Acad Sci USA 106*, 11742–11746.

Grashow, R., Brookings, T., and Marder, E. (2010). Compensation for variable intrinsic neuronal excitability by circuit-synaptic interactions. *J Neurosci 30*, 9145–9156.

Gutierrez, G.J., O'Leary, T., and Marder, E. (2013). Multiple mechanisms switch an electrically coupled, synaptically inhibited neuron between competing rhythmic oscillators. *Neuron 77*, 845–858.

Harris-Warrick, R.M., and Flamm, R.E. (1987). Multiple mechanisms of bursting in a conditional bursting neuron. *J Neurosci 7*, 2113–2128.

Harris-Warrick, R.M., and Marder, E. (1991). Modulation of neural networks for behavior. *Annu Rev Neurosci 14*, 39–57.

Hooper, S.L., and Marder, E. (1987). Modulation of the lobster pyloric rhythm by the peptide proctolin. *J Neurosci 7*, 2097–2112.

Kehoe, J. (1972a). Ionic mechanisms of a two-component cholinergic inhibition in Aplysia neurones. *J Physiol (Lond) 225*, 85–114.

Kehoe, J. (1972b). The physiological role of three acetylcholine receptors in synaptic transmission in Aplysia. *J Physiol (Lond) 225*, 147–172.

Kehoe, J. (1972c). Three acetylcholine receptors in *Aplysia* neurones. *J Physiol (Lond) 225*, 115–146.

Kepler, T.B., Marder, E., and Abbott, L.F. (1990). The effect of electrical coupling on the frequency of model neuronal oscillators. *Science 248*, 83–85.

LeMasson, G., Marder, E., and Abbott, L.F. (1993). Activity-dependent regulation of conductances in model neurons. *Science 259*, 1915–1917.

Li, L., Kelley, W.P., Billimoria, C.P., Christie, A.E., Pulver, S.R., Sweedler, J.V., and Marder, E. (2003). Mass spectrometric investigation of the neuropeptide complement and release in the pericardial organs of the crab, *Cancer borealis*. *J Neurochem 87*, 642–656.

Liu, Z., Golowasch, J., Marder, E., and Abbott, L.F. (1998). A model neuron with activity-dependent conductances regulated by multiple calcium sensors. *J Neurosci 18*, 2309–2320.

Marder, E. (1974). Acetylcholine as an excitatory neuromuscular transmitter in the stomatogastric system of the lobster. *Nature 251*, 730–731.

Marder, E. (1976). Cholinergic motor neurones in the stomatogastric system of the lobster. *J Physiol 257*, 63–86.

Marder, E. (2000). Bitter and twisted. *Curr Biol 10*, R1.

Marder, E. (2012). Neuromodulation of neuronal circuits: Back to the future. *Neuron 76*, 1–11.

Marder, E. (2015a). Bars and medals. *eLife 4*, e05787.

Marder, E. (2015b). Lost voices. *eLife 4*, e06536.

Marder, E., and Bucher, D. (2007). Understanding circuit dynamics using the stomatogastric nervous system of lobsters and crabs. *Annu Rev Physiol 69*, 291–316.

Marder, E., and Calabrese, R.L. (1996). Principles of rhythmic motor pattern generation. *Physiol Rev 76*, 687–717.

Marder, E., Calabrese, R.L., Nusbaum, M.P., and Trimmer, B. (1987a). Distribution and partial characterization of FMRFamide-like peptides in the stomatogastric nervous systems of the rock crab, *Cancer borealis*, and the spiny lobster, *Panulirus interruptus*. *J Comp Neurol 259*, 150–163.

Marder, E., and Goaillard, J.M. (2006). Variability, compensation and homeostasis in neuron and network function. *Nat Rev Neurosci 7*, 563–574.

Marder, E., Gutierrez, G.J., and Nusbaum, M.P. (2017). Complicating connectomes: Electrical coupling creates parallel pathways and degenerate circuit mechanisms. *Dev Neurobiol 77*, 597–609.

Marder, E., Haddad, S.A., Goeritz, M.L., Rosenbaum, P., and Kispersky, T. (2015). How can motor systems retain performance over a wide temperature range? Lessons from the crustacean stomatogastric nervous system. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol 201*, 851–856.

Marder, E., Hooper, S.L., and Eisen, J.S. (1987b). Multiple neurotransmitters provide a mechanism for the production of multiple outputs from a single neuronal circuit. In *Synaptic Function*, G.M. Edelman, W.E. Gall, and M.W. Cowan, eds. (John Wiley & Sons), pp. 305–327.

Marder, E., O'Leary, T., and Shruti, S. (2014). Neuromodulation of circuits with variable parameters: Single neurons and small circuits reveal principles of state-dependent and robust neuromodulation. *Annu Rev Neurosci 37*, 329–346.

Marder, E., and Paupardin-Tritsch, D. (1978). The pharmacological properties of some crustacean neuronal acetylcholine, gamma-aminobutyric acid, and L-glutamate responses. *J Physiol 280*, 213–236.

Marder, E., and Paupardin-Tritsch, D. (1980). The pharmacological profile of the acetylcholine response of a crustacean muscle. *J Exp Biol 88*, 147–159.

Marder, E., and Taylor, A.L. (2011). Multiple models to capture the variability in biological neurons and networks. *Nat Neurosci 14*, 133–138.

McCaman, M.W., Ono, J.K., and McCaman, R.E. (1984). 5-hydroxytryptamine measurements in molluscan ganglia and neurons using a modified radioenzymatic assay. *J Neurochem 43*, 91–99.

McCaman, R.E., and Dewhurst, S.A. (1970). Choline acetyltransferase in individual neurons of Aplysia californica. *J Neurochem 17*, 1421–1426.

Miller, J.P., and Selverston, A. (1979). Rapid killing of single neurons by irradiation of intracellularly injected dye. *Science 206*, 702–704.

Nusbaum, M.P., and Marder, E. (1988). A neuronal role for a crustacean red pigment concentrating hormone-like peptide: Neuromodulation of the pyloric rhythm in the crab, *Cancer borealis*. *J Exp Biol 135*, 165–181.

Nusbaum, M.P., and Marder, E. (1989a). A modulatory proctolin-containing neuron (MPN). I. Identification and characterization. *J Neurosci 9*, 1591–1599.

Nusbaum, M.P., and Marder, E. (1989b). A modulatory proctolin-containing neuron (MPN). II. State-dependent modulation of rhythmic motor activity. *J Neurosci 9*, 1600–1607.

O'Leary, T., and Marder, E. (2016). Temperature-robust neural function from activity-dependent ion channel regulation. *Curr Biol 26*, 2935–2941.

O'Leary, T., Williams, A.H., Caplan, J.S., and Marder, E. (2013). Correlations in ion channel expression emerge from homeostatic tuning rules. *Proc Natl Acad Sci USA 110*, E2645–2654.

O'Leary, T., Williams, A.H., Franci, A., and Marder, E. (2014). Cell types, network homeostasis, and pathological compensation from a biologically plausible ion channel expression model. *Neuron 82*, 809–821.

Otopalik, A.G., Goeritz, M.L., Sutton, A.C., Brookings, T., Guerini, C., and Marder, E. (2017a). Sloppy morphological tuning in identified neurons of the crustacean stomatogastric ganglion. *eLife 6*, DOI: 10.7554/eLife.22352.

Otopalik, A.G., Sutton, A.C., Banghart, M., and Marder, E. (2017b). When complex neuronal structures may not matter. *eLife 6*, DOI: 10.7554/eLife.23508.

Otsuka, M., Kravitz, E.A., and Potter, D.D. (1967). Physiological and chemical architecture of a lobster ganglion with particular reference to GABA and glutamate. *J Neurophysiol 30*, 725–752.

Prinz, A.A., Abbott, L.F., and Marder, E. (2004a). The dynamic clamp comes of age. *Trends Neurosci 27*, 218–224.

Prinz, A.A., Billimoria, C.P., and Marder, E. (2003). Alternative to hand-tuning conductance-based models: Construction and analysis of databases of model neurons. *J Neurophysiol 90*, 3998–4015.

Prinz, A.A., Bucher, D., and Marder, E. (2004b). Similar network activity from disparate circuit parameters. *Nat Neurosci 7*, 1345–1352.

Rinberg, A., Taylor, A.L., and Marder, E. (2013). The effects of temperature on the stability of a neuronal oscillator. *PLoS Comput Biol 9*, e1002857.

Robinson, H.P., and Kawai, N. (1993). Injection of digitally synthesized synaptic conductance transients to measure the integrative properties of neurons. *J Neurosci Methods 49*, 157–165.

Roffman, R.C., Norris, B.J., and Calabrese, R.L. (2012). Animal-to-animal variability of connection strength in the leech heartbeat central pattern generator. *J Neurophysiol 107*, 1681–1693.

Schulz, D.J., Goaillard, J.M., and Marder, E. (2006). Variable channel expression in identified single and electrically coupled neurons in different animals. *Nat Neurosci 9*, 356– 362.

Schulz, D.J., Goaillard, J.M., and Marder, E.E. (2007). Quantitative expression profiling of identified neurons reveals cell-specific constraints on highly variable levels of gene expression. *Proc Natl Acad Sci USA 104*, 13187–13191.

Sharp, A.A., Abbott, L.F., and Marder, E. (1992). Artificial electrical synapses in oscillatory networks. *J Neurophysiol 67*, 1691–1694.

Sharp, A.A., O'Neil, M.B., Abbott, L.F., and Marder, E. (1993a). The dynamic clamp: Artificial conductances in biological neurons. *Trends Neurosci 16*, 389–394.

Sharp, A.A., O'Neil, M.B., Abbott, L.F., and Marder, E. (1993b). Dynamic clamp: Computer-generated conductances in real neurons. *J Neurophysiol 69*, 992–995.

Sharp, A.A., Skinner, F.K., and Marder, E. (1996). Mechanisms of oscillation in dynamic clamp constructed two-cell half-center circuits. *J Neurophysiol 76*, 867–883.

Sobie, E.A. (2009). Parameter sensitivity analysis in electrophysiological models using multivariable regression. *Biophys J 96*, 1264–1274.

Soofi, W., Goeritz, M.L., Kispersky, T.J., Prinz, A.A., Marder, E., and Stein, W. (2014). Phase maintenance in a rhythmic motor pattern during temperature changes *in vivo*. *J Neurophysiol 111*, 2603–2613.

Swensen, A.M., and Bean, B.P. (2005). Robustness of burst firing in dissociated purkinje neurons with acute or long-term reductions in sodium conductance. *J Neurosci 25*, 3509–3520.

Swensen, A.M., and Marder, E. (2000). Multiple peptides converge to activate the same voltage-dependent current in a central pattern-generating circuit. *J Neurosci 20*, 6752–6759.

Tang, L.S., Goeritz, M.L., Caplan, J.S., Taylor, A.L., Fisek, M., and Marder, E. (2010). Precise temperature compensation of phase in a rhythmic motor pattern. *PLoS Biol 8*, e1000469.

Tang, L.S., Taylor, A.L., Rinberg, A., and Marder, E. (2012). Robustness of a rhythmic circuit to short- and long-term temperature changes. *J Neurosci 32*, 10075–10085.

Tobin, A.E., Cruz-Bermudez, N.D., Marder, E., and Schulz, D.J. (2009). Correlations in ion channel mRNA in rhythmically active neurons. *PLoS ONE 4*, e6742.

Turrigiano, G., Abbott, L.F., and Marder, E. (1994). Activity-dependent changes in the intrinsic properties of cultured neurons. *Science 264*, 974–977.

Turrigiano, G.G., LeMasson, G., and Marder, E. (1995). Selective regulation of current densities underlies spontaneous changes in the activity of cultured neurons. *J Neurosci 15*, 3640–3652.

Turrigiano, G.G., Leslie, K.R., Desai, N.S., Rutherford, L.C., and Nelson, S.B. (1998). Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature 391*, 892–896.

Turrigiano, G.G., Marder, E., and Abbott, L.F. (1996). Cellular short-term memory from a slow potassium conductance. *J Neurophysiol 75*, 963–966.

Weimann, J.M., and Marder, E. (1994). Switching neurons are integral members of multiple oscillatory networks. *Curr Biol 4*, 896–902.

Weimann, J.M., Meyrand, P., and Marder, E. (1991). Neurons that form multiple pattern generators: Identification and multiple activity patterns of gastric/pyloric neurons in the crab stomatogastric system. *J Neurophysiol 65*, 111–122.