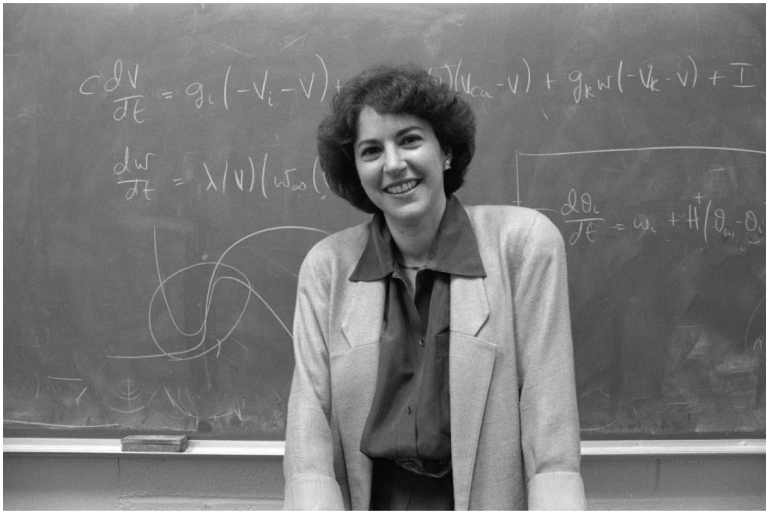
Nancy Kopell



Nancy Kopell

Born:

New York City, New York
November 8, 1942

Education:

Cornell University, Ithaca, NY, BA (1963)
University of California, Berkeley, MA (1965)
University of California, Berkeley, PhD (1967)

Appointments:

C.L.E. Moore Instructor of Mathematics, M.I.T. (1967–1969)
Assistant Professor of Mathematics, Northeastern University (1969–1972)
Associate Professor of Mathematics, Northeastern University (1972–1978)
Professor of Mathematics, Northeastern University (1978–1986)
Professor of Mathematics, Boston University (1986–present)
William Goodwin Aurelio Professor of Mathematics and Science, Boston University (2000–2009)
William Fairfield Warren Distinguished Professor, Boston University (2009–present)

Honors and Award (Selected):

Mathematical Neuroscience Prize, Israel Brain Technologies, 2015
Moser Prize Lecture, SIAM Annual Meeting, Snowbird, 2013
Elected to Honorary Membership of London Mathematical Society (one or two such awarded worldwide each year), 2011
SIAM Fellow, 2009
Massachusetts Academy of Sciences, Fellow, 2008
Von Neumann Prize/Lecture, SIAM Annual Meeting, Zurich, 2007
Weldon Memorial Prize, Oxford University, 2006
Honorary Doctorate, New Jersey Institute of Technology, May 2006
H. Dudley Wright Prize, Harvey Mudd College, 2001
Josiah Willard Gibbs Lecturer, Annual Meeting of the AMS, San Antonio, 1999
Elected to National Academy of Sciences, 1996
Elected to American Academy of Arts and Sciences, 1996
John D. and Catherine T. MacArthur Fellow, 1990–1995
J. S. Guggenheim Fellowship, 1984–1985
Alfred P. Sloan Fellow, 1975–1977

Nancy Kopell has been a pioneer in the analysis of networks of oscillators and applications to areas of chemistry and biology. Trained in pure mathematics, she switched to applied math shortly after receiving her degree and has focused mainly on neuroscience for the last three decades. She has made significant contributions to the understanding of synchronization and phase-locking of oscillators, both in abstract settings and in the context of brain rhythms. In neuroscience, she first applied her knowledge to the study of central pattern generators, especially lamprey swimming and the crustacean stomatogastric ganglion. She then began an ongoing series of papers on the physiological origins of the various brain rhythms in various parts of the neocortex as well as hippocampus, thalamus and striatum. The detailed study of the mechanism of rhythms led her to projects on the effects of rhythms in both normal cognition and disease. She has investigated how changes in rhythms due to anesthesia leads to loss of consciousness, and how pathologies of rhythms in Parkinson's disease and schizophrenia lead to abnormal coordination and cognition. She has also studied how rhythms affect gating and routing of signals in the context of normal cognition, including attention.

Nancy Kopell

Beginner Mind: A Scientific Autobiography

It seems that I've always been a beginner. Almost none of the things I've done professionally have been built on material I studied formally. Almost every major interest led to other interests about which I started off clueless, and there were many times I asked myself "am I really doing this?" As someone who did not formally train to be a neuroscientist, and spent much of her career as a mathematician, I'm especially honored to be included in this series.

Early Years

I was born in 1942. My earliest years were not promising. According to family lore, I spent much of my first years drooling, and my parents were convinced that I was developmentally delayed (then known as "retarded"). This started changing when I was about five years old. An eye test revealed that I needed glasses and eye exercises (both provided), and I started picking out tunes on our home piano, all of which added to my interaction with the world. Another probe, some form of IQ testing, revealed that I was not, indeed, mentally challenged.

Early school years went better. I grew up in a part of the Bronx known as Pelham Parkway. It was then a solidly middle-class neighborhood; I once saw it described in a newspaper as "the last of the old-time Jewish ghettos." As I grew up, I got used to all the old people sitting on the stoops of the low-rise apartment buildings, and I joined the bands of kids that played in the street. Bronx Park was near enough to walk to, and I spent a lot of time with friends playing there. I also became a voracious reader—anything with print, including the backs of cereal boxes, was fair game. We did not have an extensive home library (ours consisted mostly of Reader's Digest condensed books), so I was a regular at the public library. My father was an accountant and mother did not work outside the house, though she volunteered for many things and helped my father with his accounting work. I walked to school by myself from an early age, as did my classmates; this was a simpler time when kids had less supervision, and needed it less. We did not have a television until I was a teenager, though we bought one for my grandmother, who lived for many years in a small apartment near us. The family gathered to watch Milton Berle, (known in a Yiddish accent as Milton Boyle). I studied piano for about five years.

By the time I got to junior high school, I was considered smart. I was part of a program known as Rapid Advance, which allowed selected kids to do three years of junior high school (grades seven to nine) in two, and then enter high school as a sophomore. (As I understand it, this program was formed because schools were overcrowded. My older (by three years) sister had been part of this program, and also an earlier program allowing her to skip second grade, so she was under 16 when she graduated high school.) I don't remember learning much in junior high school besides the sociology of early teenage interactions; I vividly remember which kids were cool (not me) and which were picked on (not me either), and one boy I admired who bravely stood up for the most bullied girl. Whatever we learned seemed very easy to me, especially math, and I remember talking to one of my teachers about arithmetic mod 2, which I had rediscovered for myself. The school wasn't walking distance from my house, and it was then that I became a regular subway-goer.

For high school (grades 10–12), there was a choice. I took and passed the entrance exam to the Bronx High School of Science, but my parents were opposed to my attending there. The issue was not the distance, since I was used to being a straphanger. My parents thought that Bronx Science would be too competitive for me. Later, it became clear to me that their decision was based more on the personality of my older sister, but I didn't protest it. Ever after, I've had to correct people who simply assumed that I went there. In the end, this may have been a good choice: I seem to thrive more when the motivation is mostly internal, rather than competition or trying to live up to other people's expectation.

Though the neighborhood school (Christopher Columbus High School) didn't teach very much (every semester in English class, we started with the definition of a noun, and never got much beyond that), there were a lot of smart kids from the neighborhood, and I didn't feel bored or out of place. I think I just never expected very much from school. I did have an outstanding math teacher (Mrs. Chad, who became very well known, and moved to Bronx Science sometime after I graduated). She was my first mentor and active supporter, and I didn't mind the reputation of "teacher's pet."

My vivid memories of high school were less about intellectual matters than about interactions with people. Chemistry class provided the most adventures. The labs were an hour or under, which made it impossible to complete anything, and the exercises were designed to be carried out over several classes. One such involved heating something and having whatever came off as vapor to be cooled and collected. For this, we needed to set up the glassware, including the corks that connected the tubes to the glassware and the sinks that provided the cold water. Unfortunately, the corks were rarely of the right size, and I had to go to the teacher several times to replace a cork that was too small to hold or too large to fit in, a

task I found embarrassing. After a few iterations, I got a cork that was just slightly too large and I wedged it in. It held just until the teacher came around to look at the setups and then blew out, drenching him head to toe. In another unforgettable incident, we were playing with aqua regia, a potent combination of nitric acid and hydrochloric acid, known to be able to dissolve almost anything, including gold. It was safely held in test-tubes, until one boy in the class poked a bit too strongly and the liquid fell in his lap. The other boys in the class immediately formed a circle around him and his damaged clothes, and march-stepped him to the boys' room. It was never talked about if the damage went beyond his clothes. The classroom was also engaging: All the glassware was marked with what it would cost if we broke it, and some of the more elaborate pieces were marked "you can't afford it."

During that time, I continued to read prolifically, with no particular theme. I recall that I did read some math and science books, beyond the curriculum. At one point, I attempted to help my sister, then in college, with a take-home algebra exam. Unfortunately, I hadn't read the relevant book, and "we" got a C. I spent Saturdays or Sundays ice skating in Central Park with a friend or going to museums in Manhattan. The trip was an hour in each direction and we were young, but this was considerably before those trains became active sites of mugging, and kids weren't chauffeured around; in fact, my family didn't have a car until my late teenage years. We played stickball and catch in the street, and a game that involved aiming a Spaulding rubber ball at a brick that extended out from the wall and getting the ball to pop up. It was not the purpose of the game, but when done exactly right, the ball would go directly into my first-floor bedroom window. I had the largest collection of these balls in the neighborhood, and also an occasional visit from a neighborhood kid trying to climb through the window to retrieve his property. I went to a full-summer sleep-away camp every summer (starting from the time I was under three) and liked athletics, which I played in after-school programs.

There was one intellectually stimulating experience that I remember from my high school days. Columbia University had a program for high school kids from schools all over the city, with classes taught by Columbia professors. I took a class in population genetics from the eminent geneticist Theodosius Dobzhansky. It had a lab component, which was to breed generations of fruit flies to have more (or less) bristles on their backs. I understood quickly the hazards of working with experimental animals: To transfer the flies from the breeding jars to the place where they could be examined under a microscope, the animals were anesthetized, but not too much or they would die and not be available to breed. However, too little and the flies would wake up while being counted and fly off. Several of my prize specimens joined the outside world instead of breeding for science. I don't know how that affected the statistics of the class experiment.

College Years

When it came time for college, it was at first expected that I would go to a New York city school and live at home, as had my sister. In fact the city schools were then very good, and graduated people who became highly successful. Like many in their generation, my parents felt that it was a waste to spend money on the college education of a girl (who would get married and have children and not make use of it), but they were persuaded by family (and perhaps my teachers) to let me go away to college. Since I had a small but significant scholarship from New York State, I ended up at Cornell. My parents hoped I would join one of the free land-grant schools within Cornell (such as Agriculture), but it was not possible to major in math in those schools, so I was permitted to go to Arts and Sciences. We had a family tradition of math: Both my mother and sister majored in math, though both were happy to drop it instantly at the end of college, and I believe that was expected of me as well.

At Cornell, I toyed with becoming a chemistry major. However, I had been placed in an honors class in which the major difference was that we got pop quizzes much harder than those in the regular classes. I associated chemistry with anxiety, and stuck with math. After one semester of beginning calculus, I got placed in a math honors program. The half-dozen or so in this program were given standard textbooks for the next three semesters of calculus and told to learn it on our own. Meanwhile, our classes were on much more advanced, graduate-level material. There was far too much to cram into the class hours, so the classes were scheduled before a lunch hour and went far into the latter; I associate those classes with growling stomachs. Another notable feature were our tests, which started after dinner and went on until my curfew time (as the only woman, I was the only one with a curfew). The pressure was intense, but not over grades, and there was more bonding than competition. Some of the bonding was over bad behavior: I recall that before one of the tests, we threw many of the classroom chairs out the second-floor window, for reasons I can't remember, but which likely involved tension. After three semesters of this program, most of my classes were graduate classes, and I was hanging out with the graduate students.

At that time, Cornell considered itself *in loco parentis*, especially for the women. There were separate dorms for the sexes, and a formal atmosphere: At every Sunday lunch, we dressed in our best, sat down to tables with cloths, and began the ritual with the singing of the campus alma mater. Women wore girdles, skirts, and heels; pantyhose were just beginning to be in style, but were considered expensive, since you had to replace the entire garment if one leg had a tear. Knee-length boots were beginning to be adopted, much better adapted to the cold and snow of Ithaca. All of us got a lot of exercise walking around the many hills of the campus; it was said that

you could tell what year a coed (aka female student) was in by looking at the size of her calves (which were indeed much looked at). I joined a sorority and several singing groups (singing alto in one and soprano in another) and had the usual college experiences. I remember my classes as excellent; a professor who I later knew as a friend described the years I was at Cornell as its golden age.

I took the differences in policy for men and women for granted except for one incident. In my junior year, all the undergraduate math majors were sent a letter from IBM inviting them to interview for a summer job. I put on my girdle and heels and suitably tight skirt and hobbled my way up the hill for my appointment. My interviewer displayed great embarrassment when he saw me; it appeared that the job in question was only for men. Since it was very clear that I was not going to be offered the job, I decided to have some fun with the interview. For example, I asked why the jobs at IBM were categorized according to gender. His answer, with a straight face, was that the women preferred it that way. I must have impressed him, since they offered me another summer position, which I declined.

Instead of working at IBM, I accepted a summer fellowship in Illinois to learn to work with computers. Those were early days for computing. The machine we kids had access to was an early ILLIAC (Illinois Automatic Computer)—not the most current one, which was being used by grownups who presumably knew what they were doing, but the previous model that was then considered somewhat obsolete. It filled an entire large room and was programmed in machine language using paper tape; if a mistake was made, the tape had to be punched again from the beginning. Luckily, there was a machine that would copy the tape up to before the mistake. Later I remember working with decks of punch cards. These were more forgiving about mistakes, since individual cards could be replaced. But if the deck was accidentally dropped and fell out of order, the game was up. We spent most of our time in that room, since it was the only air-conditioned space and the summer was hot. I helped produce a program on "spin glasses" that was used by local physicists, and I was very proud. However, I stayed away from computers after that, doing all my computing through a human interface. In retrospect, this is astonishing for a computational neuroscientist. But by the time I got to the point where computers were essential, my students and postdocs were better prepared than I was, and had much more time. In general, my collaborators, students, and postdocs have been much earlier adopters of technology than I have been. I recall a lecture I gave in California, invited by David Kleinfeld. In his introduction, he told students to pay careful attention to my talk. I expected him to then tell the students why the work was important. Instead, he told them that this was perhaps the first and last time they would see a talk given with transparencies on an overhead projector. That embarrassed me enough to overcome my fear of PowerPoint and start using it. Thanks, David!

Graduate School

I had not entered college thinking about going to graduate school. But when my senior year arrived, I was not married and had nothing specific I wanted to do, so graduate school seemed like a good option. With some parental pressure to stay close to home, I applied to excellent schools up and down the east coast, and was admitted to almost all of them. But near the last minute, I got some seductive advice from a Cornell math grad student: Wherever you come from, go far away. I had an NSF Fellowship that was applicable to any school, so I applied and was admitted to Berkeley. There was more than a little parental upset when I decided to accept that offer. When I now work with students to decide about graduate schools, I'm aghast at my memory of how little thought I gave to what I would find there. I knew almost nothing about the faculty, which wouldn't have helped anyway, since I didn't have a clear idea of what I would specialize in. At Cornell, I was generally trained in pure mathematics and had thoughts of being an algebraist, the most pure of the mathematical disciplines. I also thought I might do geometry or topology, other fairly pure subjects. Other possibilities, like applied math, were never even on the radar screen.

Berkeley at that time was a huge and confusing macrocosm. In the math department, it was said that it was not known to within a hundred how many grad students there were; many graduate students had stopped taking courses or otherwise participating in the mathematical life of the mind, but were still officially on the rolls. There were very few women students, and (I recall) no women faculty. For better or worse, I stood out. I stood out more when I did well in my classes and then passed the oral qualifying exam with honors. (In spite of studying hard, I was asked questions I didn't know, but I was very good at thinking on my feet.) This led one professor to woo me to work with him in algebraic topology, and I immediately accepted; at Berkeley, with all the grad students, finding a thesis advisor was not said to be routine. Unfortunately, he turned out to be not very interested in the question he started me on, and I saw him rarely, mostly at parties. This was, to say the least, anxiety provoking. But I had other ways to fill my time: I dated, learned to play the guitar, did folk-dancing, went on hikes—and stayed intensely anxious.

There were other distractions as well: This was the era of the free speech movement, a student-led uprising stemming originally from Freedom Summer, the months that many students rode buses in the south as part of the civil rights movement. The free speech movement (FSM) was triggered when the Berkeley Admin refused to let returning students set up information tables in Sproul Plaza, the center of campus life. The FSM essentially took over the campus for a year or more, and politicized much of the student body, leading into the Berkeley protests over the war in Vietnam. I took part, but did not put myself in a position to be arrested, as did many of my friends.

This was also the first time I was really aware of sexism in the sciences. The kind of sexism I experienced from graduate school through my early career was not harassment (though there was sometimes intense sexual tension, not acted on). Rather, it was the unspoken but very widespread assumption that women in math were like dancing bears—perhaps they could do it, but not very well, and the attempt was an amusing spectacle. I was young and reasonably attractive, so I got a fair share of attention, especially in situations in which women other than administrative assistants were barely visible. I was already highly insecure about my ability (in spite of lots of encouragement from teachers from junior high school on), and any encouragement I got in grad school could easily be interpreted, at least by me, as sexual rather than scientific interest. Thus, though I had the reputation for being among the best students of my class, I did not have any of the confidence to match. Of course, this is now an old story that many institutions have since tried to remedy, with mixed success. At the time, nobody recognized it as a problem, and I was not about to tell.

My period of mathematical limbo lasted more than a year. I was rescued by another professor, Steven Smale, near the end of my third year. As he passed me in the hall, he would suggest other problems I might work on (as I said, I was known, for better or worse). All of them were far from anything I knew, and I let him know that. Luckily for me, Steve was known for being tenacious, as well as very smart (in the next year or two, he was given the Fields medal, the math equivalent of the Nobel prize). After a number of such iterations, I agreed to work on a problem that appeared very elementary. It was both elementary and hard for the same reason: There were apparently no tools that were relevant to solve it. The good news was that there was not very much to learn before I could attack it. I worked away at it for a while, mostly by myself, but at least getting somewhere. Steve was away most of the time (he was visiting at Princeton), but he had other students who were very close and who included me in the group. The main two were Mike Shub and Jacob Palis. They welcomed me graciously and proceeded to teach me the field in which I was supposed to be an expert. We formed a close-knit band, asking each other almost every day about results since the last conversation. I had found an intellectual home, and loved it. Ironically, during this time, my first advisor changed his field and joined our group. There were also other faculty members loosely affiliated. Though Steve was famous, he had moved around enough that Mike, Jacob, and I were his first students.

The field that I joined was called "dynamical systems." It was the study of the properties of differential equations. Smale had begun to revolutionize this field by introducing ways to classify the geometric properties of the equations, and he introduced methods for studying how robust those properties were to perturbations. The solutions to differential equations provide a set of transformations of the underlying space, one for each time point.

I was tasked with showing that, under some conditions, almost any transformation of the space comes from a differential equation. I got my first results very quickly, over the first summer. I showed that this hypothesis was in fact completely wrong; almost all transformations do not come from differential equations, and the ones that do can easily be perturbed so that they don't. I showed it in the context of equations on a very simple space, a one-dimensional interval. This surprised a lot of people, including those in a field I didn't even know about called foliation theory; that hypothesis was assumed by the field to be correct, and many other results were implicitly built on it.

The following fall I visited Steve at Princeton and showed him my results. He said something like, "Well, you have a thesis!" Since the proof of my first result was somewhat under three pages (and later got shorter), I was dubious. But he was convinced it would now grow quickly and planned my graduation for the next spring. So there I was, with an unfinished thesis in a field (dynamical systems) I didn't yet know, and a deadline not that many months away. I remember some all-nighters, but by the end, I had a thesis written up with more results and a respectable number of pages. I was less than 25 when I got my PhD degree. I've never since been able to do math (or science) at that intensity; I look back on that year with wonder and gratitude.

The year was not easy going. I remember one time being in despair about whether I could finish my thesis, and slumped into the office of a faculty friend, Bernard Kripke. I told him that I couldn't stand it and was going to quit. While I was there, his new wife Margaret, a grad student in biology, called him and said, essentially, "I can't stand it, I'm going to quit." Ber had an instant inspiration: He took me back to his house, mixed up a large batch of margaritas, and sat back while she and I drank and commiserated. The next day, she went back to her thesis and I to mine, and both of us got through very well.

MIT and Depression

Though I was quite successful throughout school, I had been struggling with large emotional ups and downs, partly due to family issues and likely partly due to chemical imbalances. Neither of those was acknowledged within my family, and kept as repressed as I could manage. After graduate school, these struggles caught up with me. My thesis was good enough (and my thesis advisor famous enough) to win for me a C.L.E. Moore Instructorship at MIT. This was a nontenured but fancy position for which I was the first woman. The position had very little teaching, a huge amount of freedom, and no mentoring. In spite of the academic success I enjoyed up till that point, I was very shy and highly insecure, and those years were extremely hard for me. I had chosen MIT over other options partly because I sensed a

depression coming on, and preferred to be at a place in which no one would notice. (I think I was mostly right about MIT and this.) I had gone from a position in which I had a collegial nest to one in which the doors were wide open and I had no idea where I wanted to go. There were plenty of good problems that had arisen from my thesis (and which other people followed up). But I found myself not wanting to work on any of them. Indeed, during my two years at MIT, I didn't even publish the work from my thesis, which later went into a conference volume in honor of my thesis advisor; he told me later I could have published it in the *Annals of Mathematics*, one of the most prestigious math journals.

MIT was both welcoming and a center for the kind of unexamined sexism that was almost universal at that time. I vividly remember one time in the math common room in which some math graduate student asked me, "Why aren't there any good women in mathematics?" (He did not say "present company excluded.") So now I was supposed not only to succeed on my own, but also defend the successes of my scientific sisters. As I recall, I was not up to it, and fled. I did a lot of hiding during those two years. My colleagues from dynamical systems continued to invite me to many conferences and workshops, and I attended some of them. They did their best to encourage me and get me to start working again and were all very kind. But I knew that I didn't want to stay in that field and was unsure about mathematics as well. I knew I could love doing it, as I loved doing my thesis. But math can be very narrow as well as very deep, and as I looked forward, the idea of doing similar things in 10 or 20 years was claustrophobic. I knew I had to change fields and had no idea how.

During that time, I was not entirely inert. I was reading lots of theoretical literature about self-organization, hoping it would be relevant to issues of pattern formation (development) in biology. There were two then-fashionable gurus that I tried to follow. One was Ilya Prigogine, who had developed a theory of "dissipative structures," or self-organization far from equilibrium. This became the body of work that developed my allergy to "theories of everything": abstract declamations that didn't quite illuminate anything, though they could be said to apply to many things. I read and read and couldn't find what I considered content. This experience helped shape my understanding about the politics of prizes: Prigogine got a Nobel prize for that work (and one of his colleagues, on being asked to comment, said, "It was only to be expected").

The second major guru I tried to understand was Rene Thom, a very distinguished mathematician who had developed a mathematical body of work known as catastrophe theory. This work was an extension of what is called bifurcation theory, a study of how the qualitative properties of systems can change dramatically when some parameters of the system are changed just a bit. Thom focused on systems of a particular kind (so-called "gradient systems") and classified the bifurcations within them. The work was justly

praised for its elegance and depth, but it was being marketed as relevant to understanding changes in the world. Unfortunately, no one could come up with a convincing example that followed his theory. There were several of us from the Boston area who were interested in learning the mathematics (including Gabe Stolzenberg, who much later became my husband), and we had an ongoing working group. We became experts, which turned out to be highly important for my career, but not in a straightforward manner (more below).

My First Faculty Job: Northeastern University

My position at MIT was not tenure track, and I certainly had not distinguished myself there. What to do next? There were several things that helped. First, the times were much more forgiving than now. I suspect that someone with no publications in the two years after graduation would now not be able to get any faculty positions. Second, my (then still unpublished) thesis was a kind of underground classic, and that made me desirable, even if somewhat damaged. I had several possibilities, none at the level (or close) to MIT. I took the offer at Northeastern, partly so I wouldn't have to move. (The depression was still with me.)

The math department at Northeastern was totally different from MIT, in ways that turned out to be very good for me at that time. At MIT, common room conversation was often about ranking living mathematicians: who was the best, the second best etc. As can be imagined, I did not find this conducive to happiness. I also didn't want to compete according to the standard rules: Mathematics is very hierarchical, and problems are often considered interesting because X, who is very famous, pronounces that it is. There was a clear notion of what is math and what isn't, and the things I was starting to get interested in were not on the radar of my MIT pure-math colleagues. The Northeastern math department, by contrast, was then an intellectual free-for-all. People were not competing with one another, and their interests varied widely. The expectations about publishing were low, so all pressure was internal. Since I'm very good at generating internal pressure, and not so comfortable with rigid external pressure, this was a good situation for me. I could breathe out and try to find out who I wanted to be when I grew up.

The sexism that was endemic in math was not absent from Northeastern, but it had a different flavor. There were then a fair number of quite strange people in that department and an acceptance of this state of affairs. So, in that department, a dancing bear did not stand out that much, even if she was experimenting with topics that would not be welcomed in most traditional math departments (and most math departments are still traditional). If I was going to be eccentric, at least I had company. However, the lack of women was perceived to allow bad behavior: Once, in a later meeting of

full professors, administrative people (female, of course) were brought in to maintain a civilizing effect on the discourse.

Within the Boston and more general math community, I still had to cope with attention of the wrong kind. There were many incidents that fell short of what can be called harassment but still set a tone about interactions. In one, I gave an invited talk at Brandeis, at which some audience member continually asked pointedly pointless questions; I finally assigned him a quota, and kept hash marks on the board for each. At an invited talk at a Midwestern school, the entire hiring committee showed up, though I hadn't applied; at the colloquium party later that evening, a well-lubricated faculty member confessed to me that the department had had to fill out a form about how many women they intended to hire in the next five years, and he proudly reported: 0,0,0,0,0. At one point after I was tenured, I got a letter from a faculty member at Berkeley inviting me to apply for an assistant professor position, though I was already an associate professor. I wrote back inviting him to apply for a similar position at Northeastern. That letter was posted on the door of many people at Berkeley, becoming part of my publication oeuvre. I grew to have a thicker skin, something that was invaluable when I found myself in similar outsider positions for scientific, rather than gender, reasons.

One story I love is less about me than about my husband, and beautifully illustrates the atmosphere of the time. Gabe had given a Boston area-wide math colloquium at Harvard and was being taken out to dinner, as was the custom. I came along as significant other. There were four of us in a car, the other two being famous Harvard mathematicians. With Gabe and me in the back seat, the others had an animated discussion of why there were no women in the world good enough to be at Harvard, oblivious to the potential reactions of the young woman mathematician in the back seat. "Well," said one (roughly), "maybe there is someone, but she is in a remote part of the Soviet Union and we can't get her." After a long and uncomfortable time, Gabe piped up and said, "George, according to your criteria, many of the people currently in your department don't deserve to be there." George thought about this and then allowed that this might be so. "Well," said Gabe, "so why aren't any of those people women?" George later had a talented daughter, and changed his attitude.

During that time, I also started my career as a serial hobbyist. Northeastern had an excellent early music group, and I joined it, playing recorders and krummhorns, capped-reed instruments that buzz. We had access to instruments from the New England Conservatory and were given the use of instruments, provided we agreed to play them in the next concert (free at Northeastern, not at the conservatory). I agreed to learn the racket, a precursor to a bassoon that looked like a coffee can with a pig's tail. I did, barely, manage to get out a simple base line for the next concert, which was difficult since the finger holes did not match my fingers (a friend created a pinky extension for me).

My other hobby was various versions of art. My partner in crime was Harriet Fell, who was a grad student at MIT when I was an instructor. We did some photography together, and took a class in pottery at MIT. She made small beautiful things and I made large "interesting" ones. One of the things I tried to do was produce a good pyramid, using slabs of clay. Unfortunately, I couldn't get the slabs to stay upright for the pyramid, and it was quite sorry looking. Harriet confiscated my work in progress and transformed it: She cut a hole on the back slab which we later corked, and added a very large nose on the front two angled slabs. There was also a very large tongue emerging from another hole. We glazed it a Pepto-Bismol pink (except for the tongue, which was rough and red instead of smooth and pink) and named it The Nose. Now what to do with it? MIT had a glass case with a lot of models of mathematical objects, including spheres and pyramids. We decided that would be a perfect place for The Nose and presented it to the then chair of the math dept. He accepted it with perfect solemnity and promised it would be put on a rotating stand to best exhibit its fine features. Shortly thereafter, some administrative assistant with less of a sense of humor disappeared it, and it has never since been seen. Harriet and I also hung around at a lab at MIT that had previously produced submarines for the Korean War and now ran courses with names like "metal sculpting for students." We were by then no longer at MIT, but we were female, and that was enough to get us the privilege of hanging out after hours and on weekends. I learned just enough about welding to not kill myself or others. That avocation stopped abruptly when someone at MIT did kill himself by walking into a laser that had not been properly shielded; a subsequent safety crackdown throughout the Institute made it very uncomfortable for the head of that lab to allow noninsured people to play with dangerous toys. Many years later, I ran into him, and he invited me to come back. I tried, but never found the same communication with metal that had been effortless before. My mind had moved on. I also entertained myself during that time with sailing and rowing on the Charles River.

Oscillating Chemical Reactions

I'm not finding it easy to make a clear date-based story of my career, and part of the reason is that, usually, many things were happening at once. My interest in catastrophe theory continued into the Northeastern days, and I was known as a local expert. One day I got a visit from a graduate student in chemistry who was concerned with what would later become famous as the Belousov-Zhabotinsky (BZ) reaction. This was a chemical reaction that turned red and blue about every second if continually stirred. If left in a thin sheet and covered (to prevent fluid motion via convection), it formed complex patterns of interacting rings. The student was sure that catastrophe theory could explain this. So we had many sessions in which we went

through catastrophe theory (and some of the Prigogine work), trying to see the relevance to the BZ patterns. Finally, I told him that I thought that catastrophe theory would not be of any use. Disappointed, he dropped the project in my lap (metaphorically speaking: a main ingredient was sulfuric acid) and went off to work with Prigogine.

Once I saw that system, and weaned myself from the expectation that the tools to understand it were available, I realized that this provided a concrete example of the kind of self-organization I wanted to study. But how to do it? It occurred to me that, though there was no fluid motion involved, the theory of pattern formation in fluid dynamics would give me some clues to the relevant mathematics I could use. So I set out to learn about patterns in fluids. This, of course, was pre-Web days; you found things out from painful days in the library and/or finding the right people to guide you. MIT was then (and still is) an active leader in fluid dynamics, so I walked across the river from my apartment in Boston and knocked on the door of one well-known expert. I regard it as one of the luckiest events of my life that he wasn't there, because then I walked down a few more doors and knocked at the door of Lou Howard, another renowned fluids expert, who was also well-known for his wide-ranging intellectual curiosity. It appeared that I arrived at the right time for Lou. For whatever reasons in his life, he was ready for something new, and after questioning me closely about the reasons for my interest and the BZ system, he mostly dropped his fluids work and became my collaborator for the next seven or eight years. This did not make me popular with his other collaborators!

Those were my real postdoc days. It was during this time that I turned myself (with his help) into an applied mathematician. Though I had worked in dynamical systems, which involve differential equations, my work had not required me to actually learn to solve them. (I did that for the first time teaching an elementary version of the topic at MIT.) Applied math has a large number of computational techniques that tend not to get taught in pure math classes, partly because they don't necessarily end up with a proof of something. But those techniques are extremely valuable in getting intuition, and that's when I started to learn them. By computation, I don't mean computers—these were the days of pads and pencils and many scrawled pages of formulae trying to lead to a comprehensible formula for something. There could be bugs, but the software was the human brain, not a code.

The patterns formed in the BZ system were very complex and never the same from experiment to experiment. But they had common features: Bright blue spots appeared in the deep red medium, propagating outward in a ring, and then another spot would appear in the center of the ring. This created locally a set of concentric rings we called a "target pattern" (not unlike the logo of Target, but with more rings). Adjacent target patterns crashed into one another in a manner reminiscent of abrupt shocks. Applied mathemati-

cians work in a similar way to experimental scientists: They focus on some repeatable aspects of behavior and try to explain them. Lou and I started by looking at a thin radial strip within a target pattern, in which the behavior was essentially that of a periodic traveling wave: a pattern that would be stationary if the observer ran alongside at the appropriate speed. We were interested in the mechanistic origin of those traveling waves. There are many ways of describing what a "mechanism" is, a lesson that was very useful to me as a neuroscientist. A standard applied math method would be to create a fairly complex model of the chemistry that displayed the periodic changes in color while stirred, add in the spatial interactions (via diffusion), and then see if that model displayed traveling waves. I had a different idea: Perhaps (almost) any system that produced an oscillation when stirred would produce these patterns when ions were allowed to diffuse without gross fluid motion. My abstract math background allowed me to formulate and prove such a result, and Lou's background enabled us to see appropriate simplifications and produce helpful calculations. The generalization, and others we were able to make, was highly useful because it made strong predictions. Any system that could oscillate, and had a couple of other properties, should produce these patterns. Later, Irv Epstein of the Brandeis chemistry department was able to construct families of oscillating reactions, and they did indeed form these patterns.

One of the papers we did was an attempt at explaining the origin of the interaction among the target patterns, with something like shocks between adjacent target patterns. We came up with a simple ("caricature") mathematical model in which we could reproduce those shocks and understand (within that system) what caused them to form. A question that always arises (or should arise) when using a highly simplified description of some phenomenon is whether the results will be the same in more realistic versions of the system with many more details; that is, does the simplification merely allow us to see the essence of a phenomenon more clearly, or do the results of the study depend on removing the complexities? To answer this in the shock case, Lou and I made a stab at the problem in the general setting of reaction-diffusion equations (Howard and Kopell 1977). We used some classic applied math techniques, which were calculations known in some cases to yield good approximations to answers that were hard to compute. But we used them in what was regarded as a very weird way: In a coordinate system corresponding to running along a traveling wave, we looked at how phases at a given spatial point affected the phases nearby in space, something that was wholly uncausal. The computations we did showed how the general case mimicked the much simpler case, but there was no way to prove that the computations were anywhere near correct. In the current publishing climate, this likely would have remained in a drawer. But then, though we got some teasing for this strange work, we were able to publish it in an MIT-run journal. Recently, I learned that the work was a precursor to a now-hot field in math

known as spatial dynamics, in which the work is far more rigorous, but in the same spirit as our early computations.

The work we did revealed principles that went beyond the BZ system that we were studying. These included pure math papers on general observations (theorems) about bifurcations that were useful in the application to the BZ patterns. So, in the end, I was indeed doing things related to catastrophe theory. I laughed when, long after my episode learning about catastrophe theory, I got a note from Rene Thom saying that my BZ work would help to extend catastrophe theory. Throughout my career there has been a tension between abstraction and detail. I sometimes refer to this tension as finding "which differences make a difference." My mathematical background leads me to try to explain phenomena in a very general way, but as I later got deeper into biology, the specificity of various phenomena stared me in the face and changed some of my working methods. More of this is described below.

Throughout the series of papers that we wrote together on many aspects of the patterns, Lou and I had highly different styles of working: He grabbed a pad and starting computing, while I sat on what he called my three-legged stool and stared out into the distance. I tend to work by visualizing the geometry of the solutions and then trying to get down on paper the results of the visualization (which does involve some calculation); he worked entirely by calculating. At the end of a session, we would compare notes. They were usually in the same direction. But after one session, we diverged, and I insisted I was right; he later found an error in a 15-page calculation. That never happened again, but I was very proud for one day, since Lou almost never made mistakes, and I had found that there was an error without actually looking at the calculation. Though we worked differently and separately, we found it helpful to do the work together in some unused room that MIT let us use. It had a fridge that was stocked with Lou's favorites: oranges and pickles, consumed with a lot of bad coffee.

The working atmosphere was very different from current times in multiple ways, one of which concerned time frames and expectations about productivity. This was an unavoidable consequence of differences in technology. There were no word processors, so multiple drafts were retyped multiple times, or written out in long-hand multiple times. Manuscripts could not be e-mailed to colleagues or put on a Web site. If you wanted your colleagues to see your work in less than the year or so it would take for publication, you sent out preprints. The papers I wrote with Lou tended to be generous in length. I vividly remember a day in the 1970s in which I had about 100 copies of some long paper reproduced at a local printer, page by page separately, and then spent hours collating the copies and stapling. Then there was collecting a list of recipients, stuffing large envelopes, and addressing them. Of course, sending out 100 copies was a form of hubris,

but the hope was that a significant subset of recipients would at least read the abstract or perhaps save the paper in a file cabinet.

In addition to the mathematical work we did, we had an experimental component. We played with the patterns in a tiny lab in the MIT basement that used to be part of a men's room before it became part of the fluid dynamics lab, and then ours. Our first paper described patterns that formed when the concentrated sulfuric acid was poured gently into a test tube in which the other ingredients were well mixed (Kopell and Howard 1973). The patterns were waves of blue propagating upward in a red medium, but not at uniform speeds or distances. We came up with a reason for it that did not involve any fluid motion. To test this idea, Lou created a camera that could take space-time pictures of a vertical slit of the test tube by moving the camera slowly across the test tube as the pattern unfolded. It proved our hypothesis. We later built a demonstration using compound pendula, showing the same space-time behavior due to a gradient in frequency rather than any actual coupling. We built it out of wooden rods, cut-up lengths of metal rods, straight pins to pivot on and shrink wrap, and displayed it many places. The math for that (unlike for the complex target patterns) was very simple and earned me some disapproval from someone who had a more restricted view of what math was (or was for). But it got into *Science*, my first and only research paper in that journal. We also produced various versions of the target patterns and related spiral patterns, used mainly for demonstrations in talks; it was still possible at that time to take concentrated sulfuric acid on a plane and keep it under the seat. I was not a very careful experimentalist, and small drops of the acid too often met my attire. One time after a stint in the lab, my fortune cookie at a Chinese restaurant announced "you will get new clothes."

In addition to working together at MIT, I visited Lou in the summer when he was a part of the computational fluids course at Woods Hole Oceanographic Institute. I was not a student in that course, though I was included in the annual picture the years I was around at the right moment. In other years, I was included in a head shot mounted on a picture of the cover of a garbage can. I stayed with him and his family at a small cottage on Crooked Pond. The property had a "little house" (barely big enough for a bunk bed) that I occupied for the few days I visited. The "big house" was sufficiently small that his four kids all slept on the porch; none of them wanted to bunk with the many spiders that inhabited the little house. Crooked Pond was wonderful to swim in except that its shores had many snakes, to be avoided while entering and leaving. This was nature, if not red in tooth and claw.

Continuing to be a (Pure) Mathematician

During this time and continuing thru the next decades, I was also working on questions that were purely mathematical. In general, I'm attracted to

questions that have a strong geometric component, where I can visualize what the mathematical behavior might be. Many such systems are *singular*: This means that there are multiple time scales and, in a limit in which the ratio of these scales is infinite (or zero), the system has fewer variables. Almost all models describing neural systems have such multiple time scales associated with the multiple kinetics of intrinsic and synaptic currents.

One of the first of these papers I did on singular systems (Kopell 1979) was about "resonance," used in a different way than matching frequencies of input and a target. As a parameter in a system is varied, there is a sequence of discrete values at which there is a solution to the problem. Looked at in the right coordinates, I could see that the solution corresponded to a pair of surfaces being rotated with respect to one another as the parameter varied. I used this to describe (and prove) what this form of resonance was (Kopell 1979). I emphasize the sole authorship because of one of the reviews I got when I used this to apply for an NSF math grant. The review said, approximately, "She has never done anything before working with Lou Howard and will not do anything after." Both statements, of course, were untrue, and ignored by NSF: I got the grant. I later visited Caltech, where some people had done related work using very different ideas. When I got there, I was greeted by someone who told me (the first minute he saw me): "X tells me I don't have to read your paper, since he can prove this in a much easier way." A scientific boxing match was then set up, in which we hurled questions at each other in the presence of a completely male audience clearly rooting for the home team. I was happy enough with my performance; I definitely held my own, especially considering I had no time for preparation. At the end, I chided the audience for the unregulated level of testosterone and hostility in the room, and after that they were nicer to me, maybe because I had survived the hazing initiation and could now be considered one of the boys. This was one more incident leading to a thicker skin.

In general, singularly perturbed systems display invariant manifolds (potentially higher dimensional surfaces with the property that a trajectory starting on such a surface stays there). Much of the behavior of the full system can be understood from the geometry of the invariant manifolds. Thus, being able to track invariant manifolds from a set of initial conditions is a highly useful tool. With Chris Jones, I invented a new technique for doing this (Jones and Kopell 1994). It used what is known as differential forms, a set of ideas from differential geometry (which I had never formally studied). Instead of following individual trajectories, one could follow whole surfaces by following the planes tangent to them. We used this to understand and bring some mathematical rigor to trajectories near singular solutions, which often make sharp angles at points in the trajectory. Methods following one trajectory at a time could not handle this, but methods looking for intersecting surfaces, such as the use of differential forms, could do so. This method was picked up by others as well and used widely.

The methods I used for my mathematical work were *constructive*, meaning roughly that any item I claimed to exist was conjured up using an explicit construction, rather than a double negative. ("Suppose not. Then there is a contradiction.") Gabe was a standard-bearer of the constructive school of mathematical thought, which was not (then or now) in ascendency. One mathematical friend remarked he thought that I used this approach "to keep peace in the family." In fact, I used it because it made much more sense to me than the mystery of mathematical objects that couldn't *not* exist but were wholly undefined. In general, I tend to question most things I come in contact with; another mathematical friend said that the sentence he most associates with me is "Why?"

Following invariant surfaces turns out to be a powerful method for applications to specific equations. After the work on tracking invariant manifolds (early 1990s), I was drawn to see if such ideas could be applied to a well-known and open problem of "blow-up," or the focusing singularity of the nonlinear Schrodinger equation. The problem had been much investigated by standard tools of applied math, including "matching asymptotic expansions," in which calculations are made separately for regions governed by different times scales, and then these are somehow put together in ways that constrain the individual calculations. Everyone agreed that this was likely to give correct intuition, but there were holes in the argument that kept the calculation from being considered a proof of the existence of the desired solution. I had a sense that combining the calculations with geometry could produce a proof, and this problem, acknowledged to be very hard, could be a proof of principle about the importance of geometry. The role of the calculations was to suggest the right variables in which to look for the geometry, and then dynamical systems methods using invariant manifolds could be used. To make it work, I needed a collaborator who knew the asymptotics of this set of equations. I approached one such well-known person, who did not have time, but he recommended Michael Landman, a younger investigator who was in Australia. This was way before Skype. I had never met him (and met him briefly only once in Paris, when we were almost done with the paper). Nevertheless, it was possible to send ideas back and forth by e-mail and solve the problem. This time I managed to please those working in different ways: The project showed that both applied math techniques and pure math techniques could be combined to do something that neither had been able to accomplish (Kopell and Landman 1995). It might have been a coincidence, but shortly thereafter I was elected to the National Academy of Sciences (1996) in both pure math and applied math. At that point, I was deep into trying to understand neuroscience, so I signed up for the neuroscience section.

Even when my primary interest has been neuroscience, as it has been for the past decades, I've been continuing to make occasional forays into purely mathematical questions that arise from the neuroscience. One such

set of papers I did with Horacio Rotstein and others was on "canards." These are sets of solutions that arise in the transition from a subthreshold oscillation to a full "relaxation oscillator," a system of equations with a periodic trajectory that has slowly changing plateaus and fast transitions among them; canards are important in neuroscience in understanding so-called "mixed mode" oscillations, in which full spiking or bursting alternates with subthreshold behavior (Rotstein et al. 2008). In general, I think that almost all simulations give rise to interesting mathematical issues, but I haven't had the time to follow up any but a few. But trying to understand why simulations behave the way they do can lead to new mathematics (Kramer et al. 2008). Currently, I'm most interested in interactions of rhythms, or effects of temporally structured input to networks that have multiple time scales; these areas are still mathematically almost virgin.

Introduction to Mathematical Biology: Oscillators and Bard Ermentrout

The work I did with Lou on pattern formation in chemistry was inspired by pattern formation in biology and extended by others in that direction. It was not about biology, but it was close enough that I got invited to the Gordon Research Theoretical Biology Conferences. This was in the 1970s, the early days of the field of mathematical biology (not counting a much earlier era that had not left much of a mark on biology). There were few enough people in this field that we could all go to the same conference, whose talks (in each conference) ranged from ecology to genetics to immunology to all forms of physiology and any kinds of mathematics that might be relevant to any of the above. The conferences, which started in the early 1970s, were the place to go to network with others and find out the general state of the art. Compared to now, that state was pretty primitive and not accorded much respect; we went as much for comfort and fellowship as for the science. Over time, that yearly conference went to every two years, and eventually ended. As mathematical biology got more and more tied to cutting-edge biology, people wanted to go to the relevant biology conferences, not ones that were only "theoretical." But in the 1970s, the conference served an important purpose of creating a community that has remained and encouraging many collaborations.

My first such Gordon conference was in July, and my talk was on the Fourth of July. Lou and I prepared carefully for that talk. We made a filter for a slide machine that was red except for a vertical bright blue stripe in the middle. We shined this edge-on to the contraption that had the swinging pendula: Every time a pendulum swung through the middle, it turned blue, and the rest of the time, it was red. Thus, we mimicked the red stripes propagating through a blue medium in a test tube. It was a big success with the crowd. It seems to me that it was easier to have fun with science way back then; science has gotten a lot more competitive and that makes it harder to enjoy it in simple ways.

Mathematical biology in the 1970s and 1980s was more mathematical than biology. I didn't start considering myself working in this field until the 1980s, and then with much more of a focus on mathematics. My collaboration with Bard Ermentrout started with intestines and peristalsis, a very Bardish topic. Bard had initially corresponded with me about some simulations done with Lou in the late 1970s. In the early 1980s, he initiated an interaction by calling me about a paper he was working on concerning traveling waves associated with peristalsis. In the simulations he was doing, the waves did not travel down the entire length of the model intestine; instead, they broke up into apparently decoupled waves, though there was no break in the coupling. Bard had computations suggesting that this was to be expected, but no clear intuition for why. I was a reasonable person to contact, since the work I had done with Lou included analysis of traveling waves in a locally periodic environment, and I had geometric tools with which to think about his question; this complemented his expertise on computation and linear algebra. He recalls that I said it should be easy—and then called back a week later to say it wasn't easy (see below).

Bard and I were an odd couple: We met in person for the first time in Washington when he was a postdoc working with John Rinzel and I had come for a NSF review panel. I was dressed as I thought a panelist should present herself, in a skirt and heels and neat grooming. Bard walked into my hotel lobby in cutoffs and a t-shirt with holes. He suggested we go to a bar, where he gave what I learned was his standard opening with a new person: a description of why he had only pieces of various fingers (answer: an explosion when he was trying to make bombs to give to the Black Panthers, who didn't want them; explanation of the explosion: not enough cornstarch). In later years, every time he introduced me, he claimed that he had picked me up at a bar.

At this point, Lou and I both felt that we had done what we wanted with the BZ reaction, and he went back to fluids, while I was back to (mainly) pure math. In spite of the obvious personality differences, the collaboration with Bard lasted over two decades and produced over 25 papers, most of them in pre-Internet days, and so with work carried out by handwritten letters and telephone calls. Much of the work that Bard and I did was on oscillators that were coupled to one another with weak signals. For such coupling, it turned out that there is a general theory that could be developed that is not dependent much on the details of the oscillator or the coupling, and there was a way to condense the effects of each oscillator on the other in a function we called "the H-function," from our notation (Kopell and Ermentrout 2002). A version of such a theory had been previously published in Russian and had been unknown to us; we developed a more geometric and intuitive version, and later showed the equivalence of the theories. The theory allowed us to make many inferences about interactions of networks of such oscillators from just one computation about each. That is, any changes in physiology

that made a difference to how neural oscillators would synchronize or lock with a nonzero phase lag showed up as a change in the H-function. This was very similar in spirit to the work I had done about patterns in reaction-diffusion equations, in which the details of the reactions were shown to (mostly) not matter to the outcome. I learned this lesson very well, and then had to partly unlearn it.

The early work that Bard and I did was mostly about chains of oscillators, not all relevant to intestines. It was necessary to produce new mathematical tools, since almost all the voluminous literature about oscillators dealt with linear oscillators. In biology (and in the BZ reaction), the relevant systems are nonlinear oscillators that have a single periodic solution to which other solutions approach in time. These are called limit cycle oscillators. The first significant paper we did was motivated by intestines, in which the length of gut could be conceptualized as a chain of oscillators with a gradient in frequency along the chain, producing peristaltic waves. This was the problem Bard had called me about. We showed that the waves were a consequence of a frequency gradient (Ermentrout and Kopell 1984). We worked with weakly coupled oscillators, so (as in the BZ study), we did not have to specify the details of the oscillators. Our work showed that when the gradient is too steep to allow phaselocking at a single frequency (with a single wave), there are "frequency plateaus," or sequences of oscillators having the same frequency, with a jump in frequency from one plateau to another. The work showed unexpected geometry in the solutions; we rediscovered, in the context of networks of oscillators, a kind of "bifurcation" (qualitative change of behavior do to a small change in some parameter). The work has been cited many hundreds of times, though I doubt by any biologists.

Bard and I went on to do other papers as well about chains of oscillators, some of which were related to our later work on lamprey, though we were motivated at that time just by the mathematics. In Kopell and Ermentrout (1986), we looked at chains of oscillators that may or may not have a frequency gradient, and asked what produced synchrony or waves or any other dynamical behavior. Again, with weak coupling, the setting was very general. If a finite chain of identical oscillators is connected in a way mathematically equivalent to diffusion (e.g., with coupling from gap junctions), they tend to synchronize. The central insight of the new work was a mathematical generalization of properties of chemical synapses: They do not behave like diffusion, and because of that, even if the oscillators are identical, they can speed each other up or slow one another down. (Cells connected by standard gap junctions ignore one another if they have the same voltage.) This speeding up or slowing down could give rise to waves along the chain. Such waves were very different from those associated with a frequency gradient, as in peristalsis. It was that insight that later got us started on lamprey swimming. We also extended the work in many ways,

including looking at behavior as the number of oscillators increased without bound (Kopell and Ermentrout 1990). This connected us with a community of physicists, including David Ruelle, who were looking at large ensembles of particles, again in the limit of numbers of particles. I went to some conferences and wrote some papers because of this, but it was not a lasting interest.

Another early paper of ours made a big splash for something we thought was a minor point in the paper. We were investigating a kind of "bursting" pattern in which there are multiple spikes within a longer time period, and the spikes are faster in the middle of the burst. This was again a subject that Bard started and brought to me. He had shown, using Lou-type standard applied math calculations, how the solutions are forced to behave. However, the calculations did not satisfy the reviewers, who didn't believe the results at all. With geometric methods that were very different from the standard calculations, we were able to reframe the questions, using a change of variables that amounted to a different perspective (Ermentrout and Kopell 1986). In this new perspective, we had a simpler model that was easy to analyze. The most noticed point was our proof that anything in a large class of models could be turned into this simple one by a change of coordinates. In general, simple models may be easy to analyze, but their relationship to ones of interest may be unknown. By establishing this relationship, we could know when our analyses applied to much more complex models. The simple model has been called "the theta model," after the notation we used, and is now showing up all over in work on mathematical neuroscience.

Bard and I also worked on many other questions associated with oscillators, including how interactions could change amplitude of the oscillations (Aronson et al. 1990; Ermentrout and Kopell 1990). We also wrote many reviews on oscillators, some of which appeared in dark places, but which seem to have been found by interested readers (Kopell and Ermentrout 2002).

In 1990, I was awarded a prestigious MacArthur ("genius") Fellowship. Though they never identify the basis for the award (and the use is unrestricted), it seemed likely that the work with Bard was involved. I had remembered it as connected with work on lampreys (below), but the first paper on that came out in 1990.

Going to Boston University

In 1986, I moved to the Boston University (BU) Mathematics Department. Northeastern has since become a very good and very popular school, but in the mid-1980s the department was in turmoil. I had appreciated the wild-west atmosphere of the Northeastern Math Department, but it had gotten out of hand, and I was ready for more stability. When BU approached me, I was very receptive. The fact that I could continue to live in the same place

and just take a different subway was certainly a plus. This has turned out to be a wonderful decision for me. I often refer to my department as the most collegial and functional group I've ever had the pleasure to work with (I was very familiar with dysfunction). We have made hard decisions together without recriminations and supported each other's attempts to both develop a top group in pure mathematics but also to connect mathematics to the rest of the university and the rest of science.

The department is now a combined math–stat group, something that has fostered important collaborations. It has been very easy within BU to form collaborations in multiple departments. Within the BU Biomedical Engineering Department, I worked with Jim Collins on genetic oscillators and John White on networks of neural oscillators (more below). I now work with Xue Han (also with biomedical engineering) on pharmacological and optogenetic projects associated with basal ganglia and Parkinson's disease (PD; below), as well as Tim Gardner (biology) on oscillations in songbirds and Howard Eichenbaum and Mike Hasselmo (psychology) on hippocampal rhythms. There are also others, such as Barb Shinn-Cunningham and Helen Barbas, who share mentoring of students with me. I have had and still have collaborators in the math department (Tasso Kaper, Uri Eden, Mark Kramer), but don't feel pressure to restrict interactions to that group. Indeed, BU has strongly encouraged interdisciplinary outreach. BU has also been very generous to me. In 2000 I was given a chair (William Goodwin Aurelio Professor of Mathematics and Science), upgraded in 2009 to another (William Fairfield Warren Distinguished Professor). These positions came with a huge amount of freedom, which I gratefully took advantage of. The freedom, including much less formal teaching (but much informal teaching and mentoring, which I love), allowed me to do lots of community building, described below.

Lampreys

Most of the things in which I became interested showed up in my life by accident. I met Avis Cohen for the first time in the late 1970s when she was a grad student and I was a young professor. She had invited me to speak at a conference in honor of Eric Lenneberg, a mentor of hers who had recently committed suicide. The eclectic group of invitees, who included Ursula Bellugi and Noam Chomsky and my future husband Gabe, consisted of those who had been on the mind of Lenneberg, and I was apparently among them. The work with Bard, plus the earlier work with Lou, earned me a reputation as "the oscillator lady." That meant that I was fair game for those who had questions about anything periodic. Within neuroscience, the most obvious and accessible networks involving things periodic were central pattern generators (CPGs), networks of neurons involved in periodic motor activity. Much later, Avis, who was working on lamprey locomotion,

recruited me to write a pedagogical chapter (Kopell 1988) about oscillators for a book she was editing on central pattern generators.

There is a huge amount that can be said about oscillators, and many books have been written. The chapter had to be much more specific: What do people who work on CPGs need to know about this topic? Unfortunately, though I knew a lot about oscillators, at the time, I knew almost nothing about how CPGs might involve and use oscillators. I had a Sloan Fellowship at the time, which relieved me from teaching, so I decided to dig into this. This was (again) before PubMed, so I clearly needed help and guidance. Avis sent me a large box of reprints (yes, people made reprints then), and I went through all of them, at first understanding a small subset of the words. She very patiently put up with all my extremely naïve questions. And then she sent me a second large box of reprints to absorb. My paper was only a book chapter, and most of the other participants could knock off their contributions in a short time. Mine took almost a year as I learned a field, figured out what people in that field needed to know, figured out what I could say that would be useful to them, and learned to write it in a way that would be accessible. I recall the chapter was about 60 typed pages, done before word processors, and Avis made me rewrite it six times. Each time, I learned something about communication with people who collect data and think about them in a way that was very foreign to me. Avis was more scientifically junior than me, but she was an essential mentor in allowing me to transition from thinking about abstract oscillators to thinking about important biological examples.

Avis also invited me to give a poster at a conference in Stockholm (home of Sten Grillner, then the most well-known scientist working on lamprey locomotion). I realized that previous work with Bard (Kopell and Ermentrout 1986) gave us a central insight into what might produce the traveling wave of electrical activity that is the basis for swimming in various kinds of fish and other vertebrates, such as lampreys. This was one of the few vertebrate preparations that were being explored, and the electrical behavior could be reproduced in an isolated spinal cord ("fictive swimming"), making it especially attractive as an experimental preparation. As described above, the fact that chemical synapses could speed up or slow down oscillations could give rise to waves in a chain of oscillators, such as a lamprey spinal cord. I discussed this work in a poster.

I remember vividly how strange it was to present a poster (mathy people rarely did that at the time). What do I put for materials and methods? (Answer: pencil and paper, the method of thinking.) This was a smallish conference, in which everyone seemed to know almost everyone else, and I knew only Avis. Of course, people went first to the posters of their friends, and I stood around feeling very much the wallflower. After a while Karen Sigvardt and Thelma Williams appeared at my poster, and sniffed around suspiciously. But they engaged with this strange interloper, and after a while, even got

interested. This was the start of a multiyear, multipaper collaboration with me and Bard (and sometimes Avis). Avis hosted several lamprey meetings at Ithaca, with the small group of people actively working on this subject. It was there that I saw how these animals were kept in captivity: Many of these long, slim animals were attached by their suckers to a host fish, prompting Bard to remark about the resemblance to Rastafarian locks.

The central work that we did was related to trying to prove experimentally that the "fictive locomotion" in the lamprey spinal cord was indeed this new kind of wave, powered by chemical synapses, not diffusion or gradients in frequency. The mathematics had shown that, unless the coupling in the two directions was identical, one of the two directions was dominant in the sense that it determined the phase relationships between the neighboring oscillators, almost independently of the other coupling. However, the nondominant coupling did have an effect: It changed the phase relationships at the edge corresponding to the origin of the nondominant direction. From our work on weakly coupled oscillators, we were able to use our H-functions to figure out what properties would lead one edge or the other to be "dominant" and control the propagation; this dominant direction need not be same as the direction of the wave (Kopell et al. 1991).

It was unclear if such a description of propagation actually applied to the lamprey. My first attempts to come up with reasonable experiments were laughable. So how could we prove that the fictive locomotion was indeed guided by this new kind of wave? It occurred to us all that we could do this only by somehow demonstrating the existence of the "edge effect." Technically, this was hard to do with the whole lamprey cord. Karen came up with the idea of cutting the cord and looking at the two new edges created. But look at what? It was very hard to measure the actual phase lags near the edges to enough accuracy. Here was where the mathematics helped again. Bard and I had analyzed what happens when a chain of oscillators is "forced" with a periodic input, that is, is given periodic input at one end. The analysis showed that there is a difference in outcomes depending on whether the end receiving the periodic input was the dominant end or not. More specifically, the math showed that, with periodic input at the dominant end, the chain could be made to oscillate at frequencies above and below the natural chain frequency. But with periodic input at the nondominant end, the chain would respond only to frequencies above *or* below the natural frequency.

Karen and Thelma were game to try this out. To do this, they developed a rig in which a tiny motor was attached to one of the two newly created edges and wiggled the end of the cord, with most of the cord pinned down. Because the cord has mechanoreceptors, wiggling created a periodic signal at that edge of the cord. They then measured the range of frequencies at which the activity of the motor could entrain the whole piece of spinal cord. From a biological point of view, the experiment was very strange; as Karen liked to say, there was absolutely no biological reason apart from the

mathematics for wiggling a cord with a motor. But the experiment worked (Williams et al. 1990): It produced the effects that were predicted and taught us a few biological things we didn't know before: (1) ascending coupling sets the intersegmental phase lags, whereas descending coupling changes the frequency of the coupled oscillators; (2) there are differences in the ascending and descending coupling other than strength; and (3) coupling slows down the oscillators, suggesting it is primarily inhibition-based. I recall that Karen and Thelma presented this before publication at SfN, and I was bursting with pride. At this time, there was still not much attention paid to mathematics, and being able to make highly unintuitive predictions from mathematics was not very frequent.

The lamprey work that we did was thought to be a paradigmatic example of collaboration between experiments and theory, and so Karen and I were booked yearly at the Woods Hole course on Methods in Computational Neuroscience. This went on for a significant number of years after both Karen and I stopped working on lamprey. It was a popular gig, since we did a dog and pony show alternating back and forth in the one to two hours we had and setting up punch lines for the other. I did get tired of that talk after a while (and was released from what one course director called "fish duty"), but it was a tremendous amount of fun while it lasted. It was also wonderful to spend informal time with Karen and other scientists over multiple days. The talks we gave together were a challenge for me, since the audience was so broad and the some of the mathematics quite technical. I recall some mathematicians from the Oceanographic Institute dropping in on one of these talks and listening to me try to get the essence of the ideas across. After, one said "but surely there are hypotheses?"

Another Kind of Modeling: Turning Physiology into Mathematics

At some point around the early 1990s, the direction in which Bard and I were taking the lamprey work became less exciting to us. We had explored many nuances of how chains of oscillators give rise to patterned activity, without going into any depth about the nature of the oscillators or the nature of synaptic coupling. The questions we had asked had answers that did not depend on those details, and as I was in my mathematical mode, that made me happy. Other people continued to explore questions about swimming in vertebrates, notably Sten Grillner's group working on the structure of individual lamprey segments, and Thelma Williams and collaborators, who put together the original insights with work involving the mechanical structures of the animal that constrain movement.

This was also around the time that Bard and I got divorced (amicably) as a mathematical couple. At the beginning of our collaboration, essentially all of our papers had the other as an author. But after a decade or so, Bard said to me "I don't want to be married any more, I want to be promiscuous."

After I got over being jilted, I decided that this was a very good decision for both of us, and it started an era in which I was also scientifically promiscuous, continuing to occasionally write papers with Bard.

By this time, I had become something of an expert on a variety of central pattern generators and decided to look more closely at some of them. An obvious mentor for me was Eve Marder, who was doing very interesting work on crustacean networks (lobsters and crabs). With her encouragement, I started hanging out at Brandeis and picking up more of the culture of biological experimentation. The work she was doing was producing data showing complex patterns of activity among small networks of neurons; these patterns could be changed by application of neuromodulators. The central questions for me were: What caused these patterns to emerge? And how did the modulation change the interactions? These were clear mathematical questions.

The mathematics needed to address these questions had a very different flavor from what I had done before. In working on the lamprey and the BZ chemical reaction, it was possible to use weak coupling to abstract out most of the details behind the local behavior (such as within an individual lamprey segments), and the segments were (reasonably) treated as the same. In going from a network of networks (i.e., chains of segments) to the lobster stomatogastric ganglion (STG), more detail needed to be considered. Though each of the cells in the STG was capable of oscillating in the right circumstances, each had its own dynamical personality, its own set of intrinsic currents, and its own set of connections with other cells in the network. It was not possible to understand the network without making a detailed acquaintance with each of the network participants. Eve was an excellent mentor over that period, which included times in which she was totally baffled by my various turns of mind, some of which were not good ideas, as she let me know. Another scientist I hung out with during that time was Ed Kravitz, then working with crustaceans, and now with fighting flies. In addition to his science, Ed was known for his elaborate jokes and the great parties that he gave for students at Woods Hole.

The 1990s was a transitional time for mathematical biology. There was still not very much work being doing on networks of real neurons, as opposed to "neural networks," which were artificial networks whose connectivity could be changed by an artificial plasticity to "learn" certain behaviors, but whose connection to biology was still being gingerly investigated. In 1984, John Hopfield had published a very influential paper on what came to be called "Hopfield networks." These were abstract networks of nodes that were connected by symmetrical weights. Such networks, started at random initial conditions, would converge to an "attractor" and could be "trained" to learn specific attractors, which was conceived as a model of associative memory, and later (with David Tank) as a way to do fast "neural" computations. There were a lot of interesting math/physics questions that could be

investigated about these networks, and physicists flocked in droves. People who picked up that thread and carried it far included Haim Sompolinsky and Larry Abbott. The study of these networks, which could be done analytically, was the starting point for much speculation about cognitive function that could be conceptualized as network properties. It was also the beginnings of a different kind of thread, one that focused more on physiology and the dynamics properties of single cells. John Rinzel and his colleagues were pioneers of this direction, producing many modeling papers on ionic currents (Sherman and Rinzel 1992; Wang and Rinzel 1993), cable properties (based on earlier work of Wilfred Rall), and effects of electrical coupling. Those two threads in computational neuroscience stayed mostly apart for many decades; I believe that much more than the current overlap is going to be needed to understand cognition. One continuing gulf between those communities is about what constitutes an "explanation." In writing this mini-bio, I came upon a chapter I wrote in the 1970s (Kopell 1978) before I was working in neuroscience and found that, even then, I was preoccupied by how differently people thought about intellectual issues and what they find satisfying.

Of course, the 1990s was also a time when computer simulation became available, and the study of more complex problems became possible. The number of people interested in computational neuroscience grew and new journals appeared: *Neural Network* in 1988, *Neural Computation* in 1989, and *Journal of Computational Neuroscience* in 1994. Around this time, many groups were starting to work on biophysical oscillators, not necessarily neural. There was work on respiratory oscillators (Butera et al. 1999). Mathematical work, such as that of Eugene Izhikevich on bursting (Izhikevich 2000), was getting a lot of attention. X. J. Wang, with Gyorgi Buzsaki and others, were working on synchronization (see below). My work with Eve and her group fit well with the zeitgeist.

This was also a transitional period for me, in which I was still very focused on mathematical structure and how one could understand interactions of network participants by using abstractions of cells. (I did not publish in a biology journal until 1990.) For example, a bursting cell was described by a relaxation oscillator. Some of the cells were "bistable," with ability to remain stably at a fixed low or high voltage. I became interested in how elements with these mathematical properties could interact, and whether such a study could give insights into the workings of CPGs, especially the crustacean STG. The experiments in Eve's lab provided many projects for me and introduced me to intrinsic conductances, such as the hyperpolarization-activated inward conductance h-current, which provided a slow time constant and which opposed both excitation and inhibition, shaping the interactions of cells having those conductances. I turned these physiological properties into mathematical ones that I could play with. Izhikevich later wrote a book on dynamical systems and properties of intrinsic and

synaptic currents, taking this very useful theme much further (Izhikevich 2007). During this time, I was also much influenced by the work of John Rinzel. John and collaborators were studying a variety of specific biophysical systems, notably thalamocortical networks (Wang et al. 1995), as was Alain Destexhe (Destexhe 1998). John was working in a more biophysical way, while I tried to use abstractions of the biophysical properties. His work was also a big influence on me as I later turned to more biophysical descriptions and simulations, going even farther away from the abstractions of Hopfield networks.

The crustacean STG network has a small number of cells, most of which are not intrinsic oscillators. Though the interaction of oscillators was well-studied (especially if the coupling was weak and the oscillators were not of relaxation type), the interaction among periodically bursting cells and nonperiodic cells was not well understood. With my students (Tom LoFaro and Christina Soto-Trevino) and members of Eve's extended group (Larry Abbott, then doing a lot of joint work with Eve; Farzan Nadim, a former student of mine; and Yair Manor, Gwen LeMasson, Scott Hooper, and others), I wrote a series of papers on subsets of the STG network, and how the multiple time scales associated with intrinsic and synaptic currents could give rise to oscillating networks (Skinner et al. 1994; Marder et al. 1998). Some of the behavior was complicated, such as subharmonic coordination, in which one cell could participate on a fraction of the cycles of the other (LoFaro et al. 1994). Others were unintuitive: for example, how electrical coupling between a bistable element and a burster could create a network oscillator (Kopell et al. 1998). Farzan had done a very theoretical thesis for his math PhD, which had nothing to do with oscillators or physiology, and then did a postdoc with Ron Calabrese. He was the first of my students and postdocs to turn themselves into experimentalists. I recall telephoning Ron (over some holiday) and discussing the possibility that Farzan might join him to get a bit of experimental experience. Ron said "why not a full postdoc"—and a career was born. This was a time when it was rare for people with theoretical backgrounds to be welcomed into labs (and supported!), and I was happy at Ron's prescience in seeing the possibilities. And I was delighted to be able to work with Farzan again in Eve's lab over very different questions.

The cells of the STG that oscillate are bursters, which can be described, as above, as relaxation oscillators. One theme I explored with another student, David Somers, was the differences between coupled relaxation oscillators and coupled nonrelaxation oscillators. These projects were inspired by Eve's work, but not directly connected to them. I had not fully taken in how different the network outcomes could be, and David had to work hard to convince me. One of our papers, on chains of relaxation oscillators, showed why such chains could synchronize much faster than chains of nonrelaxation ones. The work (Somers and Kopell 1993), in the end analytical, started with

a huge amount of simulations. Now I take it for granted that doing large quantities of simulations is likely to be an important precursor to seeing interesting results, but then I was computationally naïve and not at all used to working that way. Another major insight that came out of David's work was that phase relationships among coupled relaxation oscillators are generally much more rigid than among nonrelaxation oscillators: They like to synchronize or antisynchronize and don't like anything in between. Two relaxation oscillators, coupled by excitation, can synchronize in antiphase (Kopell and Somers 1995), depending on the duty cycle of the oscillator. The rigidity of the phases was a big surprise, and I've continued to use that insight in thinking about very complex networks in which the phase relationships seem rigid.

One of the themes I've been interested in, starting from the days in Eve's lab, has been ways in which small changes in some parameters in a network can make very large differences. This is closely related to bifurcation theory, except that the bifurcations, or switches, were not ones that had previously been described and were "global" rather than local. By global, I mean that one couldn't understand the switching behavior by looking in a small range of the variables, since it depends on the large ranges of the variables. There are many slow variables that can trigger a switch, and synaptic depression or facilitation is among them; the STG network provides examples of these and one of the papers I did with Farzan and Eve's group was on switches due to synaptic depression (Nadim et al. 1999). Large switches in network behavior occur in large mammalian networks as well. But because of the general complexity, it is harder to find them, and even harder to analyze. One early foray into this was a paper I did with David Terman and Amit Bose on transitions between spindling and delta sleep rhythms (Terman et al. 1996). These ideas are now reappearing as I try to understand interacting rhythms that appear with various kinds of anesthesia (see below).

Synchronization of Neuronal Oscillators

In the 1990s, studying synchronization of neural oscillators was an industry. The circumstances under which even a pair of neuronal oscillators would synchronize were not at all understood. Bard and I had done a lot of work on this using our "weak coupling" methods. Other people, notably Carmen Canavier (Achuthan and Canavier 2009) and going back to work by Art Winfree, had produced and exploited methods called "phase response curves" (PRC), which are applicable to larger coupling among elements. These are mathematical descriptions of how much an external input to an oscillator changes the phase of that oscillator. Such PRCs can be used to predict when two oscillators will synchronize or lock in antiphase or some other phase relationship, or not lock at all. It can also be used to understand

if an oscillator will entrain to a periodic external input. The PRC depends on the specific input and the details of the oscillator, but it can be computed once and used to understand interactions in multiple circumstances. New technology, such as the dynamic clamp pioneered by Eve's group (Sharp et al. 1993), made it possible to measure PRCs for specific neurons with inputs that were designed to represent specific, and measured, synaptic currents. This helped to make the study of synchronization a more experimental quantitative study.

Synchronization can be achieved in many ways; even for a pair of cells, the coupling can be excitatory, inhibitory, or electrical (gap junctions), as well as mixtures. It seems to have been assumed that excitation would be good for synchronization, so it came as a surprise when people started showing that mutual inhibition could also synchronize. Some of this interest came from physiological networks that were entirely inhibitory, such as the thalamic reticular nucleus; other interest came from the suspicion that oscillating networks of neurons that contained both excitatory (E) and inhibitory (I) cells were paced by the inhibitory components. X. J. Wang and John Rinzel (Wang and Rinzel 1993) were among the early contributors to this industry, showing numerically, for a biophysically based model of spindles in the reticular nucleus, that inhibition with a long enough decay time could synchronize cells. This whetted the appetites of the theoretically minded to try to understand how this could happen. Bard, Larry Abbott, and Carl van Vreeswijk (Van Vreeswijk et al. 1994) wrote a very influential paper about inhibition and synchronization. In their hands (i.e., for their models and techniques), a conclusion was that decay time of the inhibition had to be longer than a spike to get stable synchronization. It seemed to some of us that this was not the whole story (Gerstner et al. 1996), and I was involved in various papers trying to tease this out (Kopell and Ermentrout 2002).

Inhibition between cells, especially relaxation oscillators (bursting cells) could produce also antiphase behavior. John Rinzel and collaborators had pointed out two mechanisms by which this could occur, which they called "release and "escape." In the first, one cell is held down until the other stops firing and releases it from inhibition, while in the latter, a cell starts to burst on its own time scale and inhibits its partner. With Frances Skinner, then of Eve's group, I explored mutually inhibitory relaxation oscillators. We looked deeper into the mathematics and saw how the mechanisms affect the overall frequency of the network (Skinner et al. 1994). The issue of what controls the frequency of neural oscillators was also a large theme then, studied mostly in connection with small networks (e.g., two cells; Kopell and Ermentrout 2002), and is still open for large networks. In general, everything turned out to be more complicated than it seemed. Other papers showed that excitatory coupling might or might not produce synchronization (Bose et al. 2000). Even gap junction coupling, assumed by almost everyone to be synchroniz-

ing, provided some surprises: At least for a pair of cells, the shape of the spike and the after-hyperpolarization helped determine if the cells would synchronize or go into antiphase or something else (Chow and Kopell 2000).

There was also work on networks with larger numbers of cells. John White was a major experimental collaborator I had on issues involving synchronization. John worked on slices of hippocampus using the dynamic clamp invented in the Marder lab; he was interested in theoretical ideas as well as direct experimental verification of such ideas. The first paper we did together, with Carson Chow and students Jason Ritt and Christina Soto-Trevino (White et al. 1998) concerned a model of a mildly heterogeneous inhibitory network. Synchrony in wholly inhibitory networks can be very fragile in the absence of gap junctions. This paper showed that the ways in which synchrony can break depends on the parameter regimes, including strong vs. weak drive and long vs. shorter decay time of inhibition. In some regimes, the more strongly driven cells suppress their neighbors while staying coherent with one another; in other regimes, the cells become more free running with respect to their network partners. In a follow-up paper, we looked at frequency control in reduced models and showed that only in the portion of the phase space associated with suppression and coherence of the remaining cells is the frequency of the network determined by the decay time of the inhibition (Chow et al. 1998). This work connected the behavior of the network in the presence of heterogeneity to the mechanisms that control the frequency of the network. Though the paper was analytical and computational, we were able to replot data of Whittington and his group (Whittington et al. 1996) concerning inhibitory gamma rhythms (30–90 Hz) to support our conclusions.

Though both inhibition and gap junctional coupling could provide synchronization, work with Bard on larger networks showed that they do this in different ways (Kopell and Ermentrout 2004). The inhibitory synapses act to eliminate the effects of different initial conditions, whereas the electrical synapses mitigate suppression of firing due to heterogeneity in the network. A single pulse of inhibition to a homogeneous group of cells can synchronize them by preventing them from spiking until the inhibition wears off for all of them. But when there is heterogeneity, a pulse of inhibition will not do that, and even a small amount of electrical coupling can overcome the tendency to become asynchronous.

Just when the community was beginning to get good intuitions about the mechanisms of synchronization in fairly simple cells (caricatures of standard Hodgkin–Huxley equations or relaxation oscillators), it began to be understood that adding nonspiking intrinsic currents to the description of the cells could completely change their synchronization behavior. The currents most associated with this anti-intuitive (given our then-current intuition) behavior were the M-current and h-current, which Eugene Izhikevich calls “resonant currents” for their involvement in some kinds

of oscillations. Each of these currents opposes the inputs that give rise to them. An M-current turns on with excitation and then provides a hyperpolarizing current, while the h-current turns on with inhibition and then provides a depolarizing current. With these currents in cells, the effects of inhibition or excitation could be reversed (Crook et al. 1998; Ermentrout et al. 2001; Acker et al. 2003).

A paper with John White's group (Netoff et al. 2005) and experimental involvement from Matt Banks tested some of these ideas about synchronization, using O-LM cells in the hippocampus, which interact via inhibition, but which have an h-current. Tay Netoff measured both the PRC and the synchronization in hybrid networks associated with one real cell and one cell "in silico." The synchronization results matched the theory from the PRCs and showed that these O-LM cells would not synchronize with their natural transmitter, GABA, but would synchronize with excitation. The explanation for this behavior came from the above intrinsic currents whose effect could be seen in the PRC. The study produced many insights into synchronization with inhibition or excitation, but they were complex enough that even I got a headache thinking about them. Eventually, the goal of getting a definitive answer to exactly when inhibition or excitation could synchronize was apparently dropped by the community.

Inhibition could not always synchronize inhibitory cells (O-LM) yet those cells participate in rhythms in which they do synchronize; this raises the question of how such synchronization comes about. That was a fairly clear mathematical question, but the intuition for an answer came from looking at the actual physiological networks involving multiple simultaneous rhythms (see Gamma/ Theta below). Other questions, such as effects of noise on synchronization, continued to be studied by others, notably Bard (Ermentrout et al. 2008). There was also a cadre of mathematicians, including Steve Strogatz (formerly a postdoc of mine), who were investigating synchronization in more abstract networks of oscillators. Much of the abstract work was done on networks (sometimes called Kuromoto systems) that had special properties allowing the use of various tools for analysis. Unfortunately, many of the results (not just the methods) depended critically on the simplifications; they would disappear with small perturbation to the systems and were therefore not relevant to most applications. Awareness of this phenomenon increased my sensitivity to the issues surrounding making reduced models.

Gamma, Beta, Hippocampus, Traub, and Whittington

In the late 1990s, my perspective started to shift, and I found myself at least as interested in the physiological phenomena as the mathematics problems that they generated. I didn't stop thinking mathematically, but problems interested me less if I didn't see the relevance to specific biological networks. This shift was likely associated with two collaborations. One

was with John White of the Biomedical Engineering department of BU, the other with Roger Traub and Miles Whittington. In general, the networks I started to focus on were larger, more heterogeneous and altogether more messy. It was clear that pencil and paper were no longer going to be the only—and perhaps not even the primary—tools of the trade.

I had met Roger decades earlier (around 1967) when I was an instructor at MIT, and he did his first and only year of graduate school in math. (He then went to medical school.) He attended a course I taught in differential topology, and for many years into our collaboration (and maybe still), he referred to me as a topologist. It was not until 1997–1998 that we met again at a conference in Minnesota, in the dead of winter in an unusually cold year. This time we connected over biology and modeling, rather than pure math. Roger talked about his work on "doublets" (Traub et al. 1996), a pair of spikes in a fast-spiking (FS) interneuron. Roger had shown experiments and simulations demonstrating that two areas of a hippocampal slice between which there was a conduction delay could synchronize with no phase difference if the interneurons involved in the gamma produced doublets.

Roger has a completely different style of modeling than I do, one I often refer to as "traubian." He works with extremely large and detailed models, needing supercomputers before the rest of us. This style works for him since he is very careful and self-critical; he wouldn't believe a result of a simulation until he had tried every way he could think of to break it and failed. With the level of complexity he used, he could reproduce fine details and make very strong predictions. Among them is the still controversial statement that axo-axonic gap junctions among pyramidal cells are critical to the formation of some brain rhythms, including the gamma rhythm (30–90 Hz); Roger has amassed a large amount of evidence in favor of this hypothesis. Later on, I was asked to do a short piece on Roger's massive model of a thalamocortical column (Traub et al. 2005), and I called it "Does it have to be this complicated?" My answer was that, at least in Roger's hands, it does, to get the unexpected and game-changing hypotheses that he could produce.

I recall that Roger suggested to me that there might be an interesting mathematical project associated with the doublets. (It was clearly different from any of the other mechanisms for synchrony that Bard and I had investigated.) The obvious question was: How does it work to produce the zero-phase lag? In general, traubian models could reproduce experimental details in ways that were impossible for more pared-down models. However, the downside of this ability was that the great complexity of the models made it very hard to understand how the model did what it did. I felt commissioned to try to find out how doublets produce synchronization, and recruited Bard to help me with it. The model we came up with was simple and surprising (Ermentrout and Kopell 1998). We considered a pair of E/I circuits, connected with conduction delays; each cell was described by a basic Hodgkin–Huxley model, but the actual analysis abstracted the details of the

voltage and gating variables to times of cells firing. A doublet was the consequence of the inhibitory cells getting excitation from both its own pair and the other pair; because of the conduction delay, the inputs are separated. We calculated the timing of the spikes of the cells of both pairs, and how they influenced one another, and showed that if the E-cells start off unsynchronized, it affected the timing within the doublets, which then pushed the pair toward stable synchrony. I liked that paper because it showed how thinking conceptually could provide insight into very messy simulations. I was also involved in a paper (Fuchs et al. 2001) from Hannah Monyer's group, which used genetically engineered mice to break the doublets and destroy synchrony. The model had predicted that the time course of the AMPA-mediated excitation onto inhibitory cells had to be significantly faster than that of the decay of inhibition. Fuchs and colleagues slowed down this excitation in mutant mice; though the gamma oscillations remained, the synchrony among distant areas was disrupted.

Roger introduced me to Miles, who was his closest experimental collaborator; they had a long-standing collaboration relating to work on epilepsy. Later, when I did work with Miles without Roger, I experienced this as an act of great generosity by Roger: When Miles worked with me, he had less time for Roger. But there were lots papers that we did together, along with various collaborators. The first papers, including the doublets paper, were all set in the hippocampus. Miles was focusing there because, around that time, that's where the action was in brain rhythms (though mostly about theta, which is still true for most hippocampal researchers). Miles had been heavily influenced by some of the Hungarian researchers who had/have cornered much of the important field of interneuron research, especially in the hippocampus. Notably, Gyorgy Buzsaki, with collaborators such as Csicsvari, had seeded the interest of many people in hippocampal rhythms in the mid-1980s. Miles was partnering with Eberhard Buhl (who died tragically of a chronic disease in 2003 at the age of 43) to do in vitro physiology of hippocampal slices; together they pioneered methodology to make slices behave like in vivo rhythms under a variety of different modulatory conditions. Miles told me that his partial pivot from epilepsy to brain rhythms dates to a talk he heard from Rudolfo Llinas in the early 1990s on sleep rhythms; he and Roger Traub each was reminded of data (experimental and unrelated simulations) which had the signature of gamma oscillations, leading to their famous 1995 *Nature* paper with John Jefferys on gamma in interneuronal networks (Whittington et al. 1995), which came to be called ING (interneuronal network gamma).

Miles and Roger, with other collaborators, together produced and simulated multiple different rhythms. In another seminal paper (Traub et al. 1996), they investigated gamma rhythms in networks for which the excitatory to inhibitory connections were intact (unlike the 1995 paper), and they originated what has come to be called pyramidal interneuron network

gamma (PING). In addition to the hippocampal gamma rhythm, they discovered a rhythm in the beta frequency range that we came to call "beat-skipping beta": There was an underlying gamma rhythm, sustained by the FS interneurons, but pyramidal cells fired on every other cycle, and more cells fired in one cycle than the other (Traub et al. 1999). The beta rhythm made use of slow potassium conductances, and this was not just a slowed-down version of gamma. One of the first papers I did with Miles and Roger concerned the different synchronization properties of gamma rhythms and beta rhythms, building on the doublet ideas in both the massive simulations and simplified models. As we were to find out later, there are many (!) different mechanisms that produce beta rhythms (12–30 Hz). In the hippocampal beta, the doublets work predicted that the conduction delay must be bounded (e.g., by 8–10 ms) for the doublets mechanism to work. The new work, with Bard (Kopell et al. 2000), used that paradigm to show why the slower rhythm could tolerate longer conduction delays and still produce synchrony. Though the work was motivated by the hippocampal beta, our aim was to suggest why beta oscillations would be good for synchronization between regions of the neocortex. I still believe the title of that paper ("Gamma Rhythms and Beta Rhythms Have Different Synchronization Properties"), but the methods by which this happens in the neocortex now seem unlikely to be the same as in a hippocampal slice. This gang, along with Eberhard Buhl, also did a review paper on inhibition-based rhythms, including gamma and this beta (Whittington et al. 2000).

Roger continued to expand my synchronization horizons by producing examples of phenomena that challenged my intuitions. In a complex model of interneuron gamma synchrony (Traub et al. 2001), he showed that gap junctions were important for synchrony in spatially distributed networks; experimental support for this work had come from Gabor Tamas. That gap junctions should enable synchrony was not surprising; the surprising thing was that the gap junctions could be very local and still create global synchrony across a chain; this was a very different mechanism from the previous work Bard and I had done on chains of oscillators. I didn't do any of the modeling in that, but I earned my authorship by musing on mechanisms that then enabled Roger to make his simulations work.

The experimental hippocampal slice work of Whittington inspired me about other questions as well. After we had shown that gamma and beta rhythms have different synchronization properties, I started thinking about gamma, beta, and cell assemblies, with postdoc Mette Olufsen. The first part of our work (Olufsen et al. 2003) looked at gamma and cell assemblies, and showed that the physiological properties of gamma (feedback inhibition, time scale determined by the decay time of inhibition), was perfect for creating cell assemblies and protecting those assemblies against distractors (whose inputs go to cells that are inhibited via lateral inhibition.) We then looked at what happens to cell assemblies in the transition from the gamma

to the beat-skipping beta, which involves a decay of excitation and an activation of a slow outward potassium current. The modeling predicted that Hebbian changes of connections among pyramidal cells occurring during the gamma rhythm help to give rise to the beta rhythm. Furthermore, two different inputs at different strengths could now create cell assemblies that fire at different times in the beta cycles (on different cycles of the underlying gamma rhythm). This was a very strong prediction, and one that Miles was able to check: By using tiny excitatory inputs to areas of a hippocampal slice close enough to share a set of interneurons, he was able to confirm the surprising prediction. We thus had a mechanism that turned a difference in magnitude in inputs into a discrete temporal difference.

In this work, as in much of the other work I've done, I was swimming against the tide (or maybe just "a" tide): The experimental work was in vitro and members of the in vivo community often discount in vitro work. Though Miles and Roger have discussed in detail why in vivo rhythms share the properties of in vitro ones (Traub et al. 1999; Traub and Whittington 2010), some members of the community continue to focus more on the undeniable differences (e.g., there are many more connections in vivo and therefore far more inputs without pharmacological intervention). The devaluation of in vitro work is a significant problem for modelers trying to connect physiology to behavior, since biophysical modeling requires a level of detail that is rarely obtainable from in vivo work. For example, it has become very clear from in vitro work that different rhythms can be associated with different layers (more below); but primate physiologists have been reluctant to accept that because it has been so difficult to be sure of layer information. Now that electrodes with the ability to measure at multiple layers are in more widespread use, there may be less reluctance to accept the insights that have come out of the in vitro work about the differences in physiology of the different layers (as well as different regions of the brain) and potential functional implications (more below). The most important lessons I've learned from the in vitro work concern how to think about the effects of signals to local regions of the brain. There is unavoidable complexity in physiology, anatomy, and the effects of neuromodulation, much of which cannot be ignored in trying to understand how incoming signals are processed. I now try to form collaborations that involve multiple experimentalists covering both in vivo and in vitro recordings.

Of course, another opposing tide has been the opposition to the idea that brain rhythms are anything more than the "exhaust fumes" of cognition. As one of the pioneers in the study of rhythms, Charlie Gray has been especially eloquent about the challenges of working in such an intellectual environment. For me, the experience of hearing such strong and (to my mind) unsupported convictions about the irrelevance of rhythms has helped to strengthen my own resolve to pay more attention to evidence and less to fashionable currents of thought. Also, there has been and continues to be

very distinguished work on both oscillators and/or in vitro preparations, so there are allies.

A Deeper Look at Gamma Rhythms

By the early 2000s, I had written many papers related to gamma rhythms. But questions about the mechanisms of gamma kept coming up. At its simplest, PING rhythms are interactions of excitatory and inhibitory cells, in which the decay time of the inhibition plus the excitability of the pyramidal cells determine the period: The excitatory cells fire and make the inhibitory cells fire; the E-cells fire again when the inhibition wears off sufficiently. But for networks having large number of cells, the circumstances under which the cells would self-organize into a rhythm, or be asynchronous, or display other dynamical behavior, was not well understood.

Parallel to the time I was working with Miles and Roger, I also started collaborating with Christoph Borgers, a mathematician interested in brain dynamics. From 2003 through 2008, we had a series of paper addressing basic properties of this rhythm and potential functional implications. The papers were influenced by the work of Roger and Miles, but also by the growing impact of the papers of Wolf Singer, including the first major paper on gamma in the neocortex with Charlie Gray in 1989 (Gray et al. 1989). Those papers hypothesized that the gamma rhythm was important for "binding" the activity of local neurons; among other consequences, such binding would make downstream effects stronger via synchronizing the input to neurons. Among the open questions was why gamma, as opposed to any other rhythm, should be associated with binding. Another major influence was the work of Bob Desimone and collaborators (especially, at that time, John Reynolds) on gamma rhythms and attention (Reynolds et al. 1999).

Our first papers addressed aspects of how a network of excitatory and inhibitory cells could synchronize, especially if the number of connections from I- to E-cells or E- to I-cells was sparse. There had previously been substantial work about oscillations in networks of excitatory and inhibitory cells, including the work of Walter Freeman in the 1970s and spike-rate models, such as the Wilson Cowan model of 1972. None of the previous models took into account the specific physiological properties of the PING gamma rhythms. We used a network of simplified "theta" model (no connection to the theta rhythm) that Bard and I had invented to see what was needed in the way of connectivity. Our main conclusion was that the connectivity could be very sparse and still get synchrony, and we explained how this worked (Borgers and Kopell 2003). A later paper (Borgers and Kopell 2005) extended our modeling to networks with noisy drive. One question was why the synchronization mechanism of the gamma rhythms, involving feedback inhibition, seemed to work well mostly in the gamma range, since it was possible to get much higher or lower frequencies in a small network of

one E- and one I-cell. We looked computationally and analytically at where synchronization failed, especially when there was noise. Although each of the cells could fire at almost any frequency, the E/I network synchronized only in the gamma range, justifying the "G" in PING. The period was determined by the decay time of the inhibition; the same mechanism could produce a slower rhythm if the inhibition had a slower decay (e.g., if it was mediated by dendrite targeting interneurons such as low-threshold spike [LTS] cells.)

We then started considering gamma in the context of cognition, especially attention, partly with Steve Epstein. Here the focus was on a different variation of gamma, called "background gamma," "sparse gamma," or "noise-driven gamma." In this rhythm, the pyramidal cells fire at a rate much lower than that of the population; the inhibitory cells fire close to the population rate. Noise is essential for this kind of gamma: Tonic excitation is not enough to push the pyramidal cells over threshold, even when the inhibition is at its lowest, but noise at the right phases can do so. Our model was a seriously simplified version of a model introduced by Roger Traub (Traub et al. 2005) to account for this kind of gamma rhythm in superficial cortical layers: In Roger's version, the noise comes from ectopic spikes in pyramidal axons, spread around by axo-axonic gap junctions; in ours, the noise is put in by hand. In this and another paper, we asked what attention was doing physiologically that could be important cognitively. In another paper (Borgers et al. 2005), we focused on inputs to networks that were either asynchronous or displayed a background gamma rhythm. We showed that the transition to rhythmicity within the target network could happen by cholinergic modulation (associated with attention) by reducing the outward M-currents in principal cells; such rhythms accompany states of preparatory attention or vigilance. Furthermore, when the target network is rhythmic, the inhibition is concentrated in some windows, leaving other windows in which weak signals could have an effect on the target, allowing detection of weaker signals in the presence of gamma rhythms than otherwise. Experimental confirmation of this idea came from recent work of Siegle and colleagues (2014).

There are other versions of sparse gamma that make use of adaptation currents, such as the M-current or the closely related hyperpolarization-activated inward h-current (Kopell and LeMasson 1994; Kilpatrick and Ermentrout 2011). Kopell and LeMasson (1994) may have been the first paper to note that the gamma rhythms enable "windows of opportunity" for excitatory cells to fire. It's still not well understood in what ways this version of low-firing rate gamma differs from noise-driven gamma, and how it might contribute to attention or other cognitively important states.

I recall (perhaps falsely), that in the mid-2000s, Wolf backed off from saying there was anything special about gamma, and what was really important was synchrony. I disagreed: Our gang thought that gamma was

special because its specific physiological bases gave it functionally important properties. Christoph, Steve and I continued to think about the relevance of gamma papers to attention (Borgers et al. 2008), inspired by work of Desimone and colleagues. Reynolds and colleagues (1999) had found that simultaneous presentation of multiple stimuli can reduce the firing rates of neurons in extrastriate visual cortex below the rate elicited by a single preferred stimulus, an effect that was corrected by attention. Our simulations showed how this effect may arise from strong excitatory drive to a substantial local population of FS inhibitory interneurons. With enough drive, the FS cells are excited enough to spike by themselves, without direction from the pyramidal cells; this can lead to a loss of coherence in that population, which in turn can be shown to raise the effectiveness of inhibition. We proposed that, in attentional states, FS interneurons may be subject to a bath of inhibition resulting from cholinergic activation of a second class of inhibitory interneurons (such as LTS cells), restoring conditions needed for gamma rhythmicity. The cholinergic modulation of other classes of interneurons became a theme that I used for later work on attention with Jung Lee (discussed below). Christoph, Steve, and I also showed that, in the context of the gamma in the target network, more input to one subset of pyramidal cells leads that subset to take over control of interneurons and suppress cells reacting to other inputs via lateral inhibition. Although lateral inhibition works in the absence of gamma rhythmicity, simulations showed that the ambient rhythms significantly increased its efficiency. One main point that I cite over and over is that, in a network displaying this kind of gamma, as long as cells share the same interneurons, multiple inputs will produce a winner-take-all outcome of a single assembly. That result is special to gamma, and later work (Kopell et al. 2011) showed a different result for one kind of beta rhythm (15 Hz in slice) because of different underlying physiology.

The final paper in that series (Borgers and Kopell 2008) focused on the rhythmicity of the input rather than the state of the target. More coherent excitatory stimuli were known to have a competitive advantage over less coherent ones (Singer 1999). We showed that this advantage is amplified greatly when the target includes inhibitory interneurons acting via GABAa-receptor-mediated synapses and the coherent input oscillates at gamma frequency: A coherent input oscillating at gamma frequency can be highly effective at preventing less coherent competing inputs from being noticed when the target network includes inhibitory interneurons acting via GABAa-receptor-mediated synapses. Two factors contribute to this effect. First, inhibition in effect raises the leakiness of the target neurons, thereby greatly amplifying the known advantage of a more coherent excitatory input over a less coherent competitor. A highly coherent stimulus can break through the inhibition generated in the target network, while less coherent competitors cannot. Second, when a gamma frequency train of excitatory input pulses

entrains a target network of excitatory and inhibitory model neurons, the timing of the inhibitory spike volleys in the target favors that train over any competing pulse train that has a different frequency or phase. That paper inspired work of Pascal Fries (Bosman et al. 2012) that corroborated our ideas. In an earlier paper (Borgers et al. 2008), we had proposed a different way in which gamma rhythmicity may play a role in stimulus selection; there we showed that gamma rhythmicity helps a strongly driven assembly suppress activity in a less strongly driven one if the two assemblies share a single interneuron network. Thus, the competition was between two assemblies in Borgers and colleagues (2008), whereas in Borgers and Kopell (2008), the competition was between two stimuli competing for control over a single assembly. Combinations of the two scenarios are possible and plausible; for instance, two different stimuli might drive two different but overlapping assemblies within a larger network. Paul Tiesinga, David Golomb, and David Hansel were doing related work around that time, and I recall closely studying their papers to see how our ideas overlapped or were complementary.

More recently, Christoph and I used the insights of our 2008 papers to think about sizes of cell assemblies in the neocortex. The work came out of a collaboration with Ed Boyden and his student Giovanni Talei Franzesi. The experiments concerned optogenetic manipulation of slices to form cell assemblies. We were especially interested in weak (sparse or noise driven) gamma vs. strong gamma. An experimental observation that surprised us was that low-power optogenetic stimulation of pyramidal cells lowers gamma power, while high-power stimulation raises it. Our guess was that low-power stimulation excites too small a number of pyramidal cells to generate strong gamma, but on the other hand disrupts background weak gamma. That led us to do modeling on whether there needs to be a minimum number of pyramidal cells (depending on other parameters) receiving drive for them to form a cell assembly displaying gamma (Borgers et al. 2012). We showed that, when the number of cells is too small, the synaptic interactions may not be strong or homogeneous enough to support the mechanisms we had previously described underlying the rhythm, especially when there is heterogeneity in the synaptic strengths. Furthermore, when there is heterogeneity, the model showed that the synchronization could not happen over many cycles (as is often the case with networks of oscillators); because of the mathematical structure associated with feedback inhibition, they were forced to synchronize in a cycle or two or not at all. The work explained aspects of the optogenetic recordings and also gave reasons why attention experiments in monkeys with very focused stimuli do not give rise to added gamma power (Chalk et al. 2010). Ed's technological inventions were also the inspiration for other work with Christoph, Giovanni and Annabelle Singer on gamma oscillations; in current work, we are using Ed's robo-patcher to do intracellular recordings in awake behaving rodents, and finding surprises about the relationship of single cell spiking to LFPs.

Gamma and Theta, Mostly Hippocampus

John White got me interested in networks that were much more complex than pairs of cells. Some work involving networks with multiple different kinds of interneurons had been done by Matt Banks and Bob Pearce (Banks et al. 1998), who showed that there were (at least) two classes of interneurons in hippocampal slices that mediate GABAa inhibition with two different time scales: fast (the usual, around 8 ms) and slow (around 50 ms). With John, Matt and Bob, I wrote a paper about a much more complex network that had multiple time scales associated with both gamma and theta (4–12 Hz) rhythms (White et al. 2000). The motivation was to understand more about the interaction of these rhythms, as often observed by multiple experimental groups, notably Buzsaki and his collaborators and students. In particular, we were interested in the different roles of intrinsic rhythms within the hippocampus vs. effects of input from extrinsic sources such as the septum, especially since the cells in the septum did not necessarily fire on the same phase. There was a very surprising result in our simulations, which used the fast inhibition to get a gamma rhythm (ING) and the slow one to mediate the theta time scale. The very surprising result concerned phase-dispersed external drive at theta frequencies to either class of interneurons; that is, different cells got input at different phases. The simulations showed that, under a broader range of conditions, including heterogeneity in drive, the networks can amplify and resynchronize phasic responses to the external drive. I was involved in doing the project, but I never really understood how that happened until a graduate student of mine (Amanda Serenevy) started to study a much simpler version that had only one class of interneurons with a theta time scale but still had phase dispersed input to a large collection of cells. She was able to prove (Serenevy and Kopell 2013) that the phase dispersion could sometimes lead to a more powerful gamma than synchronous input, and could allow a larger range of input frequencies to entrain the target network. The main idea is that the period of the drive has to be close to that of the target, and the more cells participate, the more inhibition there is and the slower the rhythms of the target network. Heterogeneity in the phase of the drive can enable the target network to dynamically select the appropriate number of neurons for participation in spiking episodes, thereby creating the right amount of inhibition in the network to facilitate locking to the period of the drive. This didn't account for all the results in the White et al. paper, but it made me a lot more comfortable with the earlier simulations.

John had another big influence in my life: especially in the first half of my career, I was highly reactive to adverse outcomes (e.g., rejected papers and grant proposals). John was far more laid-back, and I took him as my role model in learning how to roll with the punches. Of course, it helped to learn

more about grantsmanship in neuroscience and how to frame papers to be attractive to audiences.

I was also influenced by work done in the Whittington lab by Martin Gillies (Gillies et al. 2002) on atropine-resistant theta in the hippocampus. Roger had done a traubian model of experimental results in which theta was produced in response to metabotropic glutamate receptor activation under conditions of reduced AMPA receptor activation. This had far more biophysical detail than anything I was considering. It led John and me to work with Miles and others to understand in our simpler terms what was going on to produce the rhythmicity. In a paper by Horacio Rotstein (Rotstein et al. 2005), we looked at networks of O-LM cells (which produce the slower GABAa-mediated inhibition) and FS cells (no AMPAergic excitation, as in Gillies et al. 2002). Earlier work (above) had suggested that individual O-LM cells, by themselves, are capable of producing a single-cell theta-frequency firing, but coupled O-LM cells are not capable of producing a coherent population theta. By including in the model FS interneurons, which give rise to inhibitory post-synaptic potentials (IPSPs) that decay faster than those of the O-LM cells, coherent theta rhythms are produced. Reciprocal connections from the O-LM cells to the FS cells serve to parse the FS cell firing into theta bursts, which then can synchronize the O-LM cells. The model reproduces relative phases of theta frequency activity in O-LM and FS cells in the Gillies data, and the hyperpolarization-activated h-current in the O-LM cells is critical to the synchronization mechanisms. The interaction between the h-current and inhibition is at the heart of rebound from inhibition and has turned up in multiple later papers (McCarthy et al. 2006; McCarthy and Kopell 2012). The Rotstein et al. (2005) paper answered questions about how cells that don't synchronize with their natural transmitters can synchronize when other kinds of cells are in the network. In related work (Pervouchine et al. 2006), Dmitri Pervouchine showed how excitatory entorinal cortex (EC) stellate cells, which synchronize with excitation, can desynchronize in the presence of other cells types, such as FS cells.

The paper on gamma and theta that I most like to cite was done with Tengis Gloveli (Gloveli et al. 2005). I think it was Tengis who initiated this collaboration, perhaps with some encouragement from Roger and Miles, who were also involved. This was a hippocampal in vitro paper, in which the slices were cut in multiple ways: the usual transverse way (which I describe as slicing a banana for breakfast), the longitudinal way (bananas Foster), and a coronal section (Chinese stir fry). With exactly the same fluid bathing the slices, the rhythms that appeared depended on the angle of the cut. The transverse one produced gamma rhythms, the longitudinal slices produce theta rhythms, and the coronal slices produced gamma-nested theta rhythms. How could this happen? This was clearly a modeling problem, and Horacio Rotstein and I addressed it. At first, it seemed as if it was important to make a very large three-dimensional model that could accom-

modate the ability to make slices through the network. However, Horacio and I realized that the central issue was not the geometry per se but which connections were preserved by the various cuts. We made a relatively simple model with only two of each kind of cell (FS, O-LM and pyramidal), and modeled the slices as cutting some connections and preserving others. With strong connections among the pyramidal and FS cells as occurs in the transverse slice, we got gamma; when the connections from the O-LM cells were relatively strengthened, as happened in the longitudinal slice, the network switched to a theta. And intermediate parameters produced the nesting. A central new understanding was that which rhythms manifested depended on which cells controlled the activity of the FS cells. This understanding has shaped other work of mine on interacting rhythms.

A follow-up modeling paper (Tort et al. 2007) considered the interaction of gamma and theta in large networks. We were attempting to understand how the existence of the theta rhythm in a network could affect synchronization among cell assemblies that formed with the help of gamma (see above). This time the network was much larger, with lots of pyramidal cells, so we could look at cell assemblies. The modeling showed that the slower theta rhythm was able to coordinate assemblies that were displaying gamma. There could be coordination even if the members of separate assemblies had no connections to one another and were connected only via O-LM cells. An underlying idea, that coordination can be done by periodic reset at a slower frequency, has been very valuable in thinking about other situations and rhythms.

Now that our group was more comfortable with large and complex models, we did other gamma/theta models as well. A previous model by Hasselmo and colleagues (2002) suggested that some fundamental tasks are better accomplished if memories are encoded and recovered in the hippocampus during different parts of the theta cycle. This model was very influential and insightful, but it was less tightly tied to biophysics than I would have liked. So Mike, postdoc Steve Kunec, and I decided to try a more down-and-dirty model to make specific suggestions about the underlying circuitry from the physiological data that Mike had acquired. We were able to suggest networks, including pyramidal cells, FS and O-LM cells, inputs from the septum, dentate, and entorhinal cortex, that could perform the separation (Kunec et al. 2005). At the time, I was still giving lots of talks to mathematical audiences, but I was trying to give them a flavor for what real physiological networks were like, and what kinds of questions and challenges they posed. It was hopeless to try to explain this model, so I flashed it up in one slide, with the take-home message that real physiology could be very complicated.

Frances Skinner made things more complicated with different physiological models of the hippocampal O-LM cells, making use of still more biophysics than we had (Saraga et al. 2003), and followed up related results in a series of papers. I made a stab at simplifying things in the context

of understanding why frequencies of theta and nested gamma oscillations tend to change together (Malerba and Kopell 2013). Working on both small abstract models and large detailed ones was one reaction to the tension between abstraction and a more fleshed out description of the world. With my theta/gamma collaborators, I tried to review what I knew by the end of 2000s about this interaction (Kopell et al. 2010).

Sleep and Anesthesia: Work with Emery Brown

I have met a substantial number of collaborators and potential collaborators at conferences. One such collaboration that has stuck over more than a decade was with Emery Brown, who is both a PhD statistician and a card-carrying working MD anesthesiologist. We got to talking at a conference in Pucon, Chile, in 2002 on computational neuroscience. (Emery remembers that we walked around in fields full of large steers protective of their space; I remember evening drinks and intense conversation). At that time, Emery's research was mainly on statistics, rather than anesthesia, but he was interested in starting research on anesthesia. We know that anesthesia changes brain rhythms, and I was hooked; we decided to collaborate.

Shortly thereafter, two people who were excellent candidates for carrying out joint work arrived at my lab. Cecilia Diniz Behn had a master's degree in (pure) mathematics, but a strong interest in applied math, and we started her on sleep circuits. The motivation was to understand the effects of dexmedetomidine, an anesthetic that works through sleep pathways. In the end, there was a lot to learn and work on just focusing on normal sleep, and our collaboration hadn't gotten back to dex until the last year. The second person was Michelle McCarthy, an MD PhD student who had completed her MD work and wanted to do her PhD in applied math. For various personal and professional reasons, it was decided by her UCLA department to ship Michelle east and have her work with Emery, who asked me to participate. Of course I was delighted. Michelle worked on GABAa circuits, with propofol as the prototype. For the next four years, we met almost every Wednesday at BU. After that, Emery moved from the Martinos Center for Biomedical Imaging (a less accessible place) to MIT, and I became the commuter, though our meetings were less often by then.

Cecilia's work was to understand what controls switches between sleep and wake, focusing on the mouse, which has multiple such switches during each day, including brief awakenings as well as sustained sleep. When we started, I did not know anything about sleep (or anesthesia), but I did know a lot about relaxation oscillators, and our first go at this problem considered the network as coupled relaxation oscillators. The previous models of deep/slow wave sleep had not considered the microstructure represented by the brief awakenings, which were often just considered noise. However, to get at that microstructure, we needed detailed information about many parts

of the sleep network. By classifying various structures as sleep active, wake active and REM active, and using knowledge about anatomical connectivity of these structures, she was able to reproduce the microstructure (Behn et al. 2007). This, along with statistical analyses that she did, earned her a prize for the best thesis that year about circadian rhythms. Emery and I were off to a good start! (And so was Cecilia, who became an expert on circadian rhythms, later getting deeply involved in the underlying physiology and doing a postdoc with Beth Klerman and Tom Scammell.)

Michelle arrived about the same time as Cecilia, and worked on a phenomenon known as "paradoxical excitation": With low doses of the much-used anesthetic propofol, the subject is often excited rather than sedated, in a manner similar to someone who is drunk with alcohol. One important physiological correlate of paradoxical excitation was an increase in power in a broad range of beta frequencies (12–20 Hz). Michelle's project was to understand what it was about propofol that caused the increase in beta power. It took another decade (current work) until we began to understand why the increased beta rhythms might cause the motor disorientation associated with this phenomenon.

Michelle and Cecilia were the first of my students to work on projects that required them to do detailed and broad biological literature searches. As an MD–PhD student, Michelle was in a good position to do this for propofol. She determined that, though propofol is a "dirty" drug, at least at physiologically relevant doses, the main effect was on the kinetics and size of synaptic inhibition: Propofol increased both the amplitude and duration of IPSPs. Our question then was: could those physiological effects cause the increase in power in the beta frequency band? Michelle's modeling suggested that the beta power might arise from a membrane level interaction between the GABAa current and an intrinsic membrane slow potassium current (M-current). In a multicellular network, this interaction can enable a switch from baseline interneuron synchrony to propofol-induced interneuron antisynchrony (McCarthy et al. 2008). In later work, Michelle dissected the mathematical mechanism by which this can happen (McCarthy and Kopell 2012). Importantly, this mechanism for beta gave Michelle a very original idea about the origin of pathological beta in Parkinson's disease, an idea that opened up an entirely new line of research in my group, with new collaborators (more below).

As the dose of propofol is increased, a subject experiences changes in brain rhythms associated with the degree of anesthesia (Brown et al. 2011). Emery and I worked systematically through these different levels with a succession of trainees. Loss of consciousness is associated with the onset of the alpha rhythm (9–11 Hz), coexistent with a slow oscillation (1–4 Hz or even slower). ShiNung Ching, our next joint trainee, was delegated to figure out how this level of anesthesia, associated with a larger change in inhibitory kinetics, could lead to such changes in brain rhythms. ShiNung

had a background in control theory, rather than neuroscience or dynamical systems, but got into the project very quickly. He created models of thalamocortical networks, using a longer decay time for the inhibition (in both structures) than in Michelle's work. He found that the lengthening of the time scale did two things that worked together to produce a pathological alpha rhythm: It slowed down the rhythms in the cortex, and it enhanced and lengthened bouts of spindling in the thalamus via inhibitory rebound (Ching et al. 2010). The two effects together led to a pathologically ongoing alpha activity that locked the activity of the cortex. This suggested that, rather than shutting down activity, the propofol was creating activity that was dysfunctional for normal cognitive activities. This suggestion, which was later confirmed experimentally, led to the overall hypothesis of our collaboration: Changes in brain rhythms due to physiological changes by anesthetics alter the interaction of regions (and the dynamics within a region) in such a way as to prevent normal cognition. There is now a hotbed of experimental and computational activity in Emery's universe aimed at understanding the effects of multiple different kinds of anesthetics from the point of view of our system-level hypothesis. This point of view, which focuses on pathologies in brain rhythms, is relevant to a variety of neurological diseases (Cannon et al. 2014; Pittman-Polletta et al. 2015).

ShiNung also looked at still higher doses of propofol, which produce so-called "burst suppression," in which neural activity is flat-lined in between bursts of activity. The effects of the higher dose are similar to those found in the context of other conditions, such as hypothermia and coma. With Emery, we proposed a unifying mechanism for burst suppression that accounts for all of these conditions, suggesting how the features of burst suppression may arise through the interaction between neuronal dynamics and brain metabolism, including ATP-gated potassium channels (Ching et al. 2012). ShiNung went on, with Emery and others, to get a closed-loop control system for delivering anesthetics in such a way as to prevent excessive burst suppression in an ICU setting, when some deliberate burst suppression is desired (Ching et al. 2013). For his work, he was awarded a prestigious career grant from the Burroughs Wellcome Fund (BWF).

It seems to me that almost everything I've done or thought about turns up as relevant in some other project. (I recall Sidney Coleman, a friend and famous physicist, once remarking that his big breakthrough on some project was remembering something he had done decades before.) In this case, the other relevant project was with Sujith Vijayan, who was working with me on alpha oscillations associated with the awake state, rather than the spindling of falling asleep or the alpha in loss of consciousness. Using work of M. L. Lorincz, S. W. Hughes, and V. Crunelli (Lorincz et al. 2008), Sujith created a model of awake alpha. ShiNung and Sujith then worked together to explain the classic and not understood phenomenon of "anteriorization," in which the normal alpha in the occipital cortex disappears

and a frontal alpha rhythm emerges. They showed that anteriorization can be understood as a differential effect of anesthetic drugs on thalamic nuclei with disparate spatial projections, i.e., the drugs disrupt the normal, depolarized alpha in posterior-projecting thalamic nuclei while they engage a new, hyperpolarized alpha in frontothalamic nuclei (Vijayan et al. 2013). Thus, the modeling work on awake-state alpha was able to give insight into detailed phenomenology of anesthesia. Sujith was also able to use this model to understand sleep disorders related to fibromyalgia, specifically the injection of episodes of alpha rhythm during periods of slow wave (deep) sleep (Vijayan et al. 2015). Ironically, he had just started working on fibromyalgia when I was diagnosed with chronic fatigue syndrome (see below), a closely related disorder.

Among the most useful translational things done so far by our group was the work of Patrick Purdon (Purdon et al. 2013) concerning EEG signatures of loss and recovery of consciousness under propofol. This followed up on earlier work showing that loss of consciousness (LOC) is associated with the onset of alpha and slow rhythms. Patrick and gang showed that the faster alpha rhythm nests inside the delta rhythm (in the same way that gamma nests inside theta rhythms in the hippocampus). What was surprising, and extremely useful, was the observation that the way in which the alpha nests in the slow rhythm depends on the level of anesthesia: Near LOC, the alpha is found in the trough of the slow rhythm, while in deep anesthesia, it is at the peak of the slow rhythm. This gives a way to measure, online during an operation, how deep is the level of anesthesia. Since an overdose of anesthesia can lead to major postsurgical problems, especially for elderly patients, accurate measurement of the affects of anesthesia is an important clinical problem. The paradigm of Purdon and colleagues, which gives a much better way than previous methods for monitoring appropriate dosage, is currently being used clinically at Massachusetts General Hospital. Current modeling work is analyzing how the trough-peak switch comes about, with the possibility of being able to manipulate effects of the anesthetics. Emery's gang, which includes many experimentalists, is now also investigating other kinds of anesthesia, including ketamine, dex, and inhalation anesthetics (e.g., sevoflurane). They appear to have different underlying mechanisms and to change brain rhythms in different ways; all, we believe, disrupt normal interactions of regions of the brain. Lots to figure out!

Parkinson's Disease and Beta Oscillations

It was Michelle McCarthy who got me interested in PD, which is now a major part of the work of my group. After she had done the work with Emery on paradoxical excitation and beta rhythms under propofol, she had the idea that the beta oscillations in PD associated with inability to initiate movement might come about from similar mechanisms. I was skeptical. I already

knew of many mechanisms for producing rhythms in the beta frequency band (more below) and didn't see why the parkinsonian beta should have any relationship to any of the ones I already knew about. But Michelle was ahead of me; she had carefully read a huge amount of the literature about PD and had an argument: The central idea came from the fact that levels of dopamine and acetylcholine often move in opposite directions. Thus, when dopamine levels drop due to losses of dopamine-producing cells, the level of cholinergic tone can increase. (Indeed, therapy with cholinergic antagonists predated dopamine therapy.) In the modeling of the beta due to propofol, the beta frequency rhythms come from an interaction of the inhibition and the M-current, an intrinsic current that is lowered in the presence of cholinergic muscarinic agonists. Michelle started with a model of a network of the main type of striatal cells, the medium spiny neurons (MSNs), in a "normal" state in which the spiking rate was low and beta power was very low. By adding acetylcholine agonists (modeled as reducing the M-current), the firing rate went up and so did the beta power. Mechanistically, this formed a beta rhythm with antiphase behavior of the MSNs as in the propofol model.

The relationship of theory/computation and experiment is very chicken and egg. In many cases, computation comes after some experiments to explain the details of what happened in that experiment. In other cases, as in this one, the theory is motivated by a largish body of previous work, and there may be no initial experimental component. I sometimes think of those papers as bait: The hope (sometimes realized, sometimes not) is that the paper will get some experimentalist to sniff around and decide that it would really be interesting to follow the ideas. In the PD case, we were extremely lucky. We happened to talk with Xue Han, who was then a postdoc in the lab of Ed Boyden at MIT and working also with Bob Desimone. She said it would be easy (for her!) to design an experiment to look for the beta oscillations in the striatum by injecting carbachol, a cholinergic agonist, while using controls to make sure the carbachol was localized there. The very first mouse was a success, with results obvious even without statistics! The recordings from the mouse showed bouts of beautiful beta oscillations interrupted by artifacts associated with trembling (though not at the PD tremor rate). The rest of the mice followed suit, and we had our first paper (McCarthy et al. 2011).

The question of where the parkinsonian beta originates is a complicated one, since the beta oscillation traverses the entire basal ganglia loop. Our suggestion that the striatum might be a central player was controversial from the start. Indeed, the first few experimentalists that we approached were not interested in testing Michelle's model, because they didn't think it could be right (a very good reason for not spending time on something!). There were several good reasons for this skepticism. One is that the striatum is almost completely inert as a slice; it is hard to make it do anything. Even in vivo, the firing rate is low in normal animals, far from the beta

frequencies (there is evidence that it is significantly higher in a parkinsonian animal). Another is that the cells of the striatum are almost completely inhibitory, even the MSNs, the projection neurons. Though there is precedent for completely inhibitory rhythms (e.g., ING), for some, this made a striatal beta less plausible. Finally, there were other candidates for the origin of PD beta that seemed more plausible to others. One such is the motor cortex, which can produce beta rhythms in slice (Yamawaki et al. 2008), and which projects to the striatum (more or less everything projects to the striatum). The second is a pair of structures in the so-called indirect pathway, the subthalamic nucleus (STN) and external globus palladus (GPe). In vitro, the STN-GPe pair can produce oscillations (Plenz and Kitai 1999), though the published experiments did not show them at a beta frequency. There were well-established computational models of the oscillations (Terman et al. 2002) showing that STN-GPE could, with various parameter tweaks, produce a beta frequency oscillation. We found the striatal model more plausible because the striatum is among the first places to lose dopaminergic tone when dopamine cells are destroyed, because cholinergic agonists were a form of treatment before current dopaminergic treatments, and because we had a clear mechanistic account of where the beta was coming from that was tied to PD changes.

I expected that our experimental paper would have a large impact on the PD modeling community (it has had an effect on some of the experimental community, including surgeons). It was (but perhaps shouldn't be) surprising to me how strong a pushback we got. By this point in my career, I'm good at thinking for myself, listening hard to what others are saying so I can learn from it, but not swayed by either numbers or another's force of conviction. I don't find convincing any arguments I've heard against our point of view, nor the experimental evidence that is proposed to support the other points of view. Indeed, sometimes it's hard for me to understand how others *can* find those experiments convincing, even when faced with arguments against them that seem obvious to us. But science, as everyone says, is conservative, and those points of view predate ours.

We now have many more experiments, looking at motor cortex and STN and their interactions with striatum, done with both pharmacology and optogenetics. This work is slowly making its way toward publication, along with other modeling papers that I believe give deep mechanistic insight into why pathological beta oscillations are associated with inability to move. As usually happens in science, further work injected more complications in the story (though we still believe, and have more evidence for, the gist of the story). We've partnered with Sri Sarma and her group (Johns Hopkins) to think about mechanisms of deep brain stimulation (Santaniello et al. 2015), which are complementary to ones our modeling has suggested. (New experimental results, not yet published, support our ideas.) We have started a collaboration with Emad Eskandar, a neurosurgeon who does deep brain stimulation,

to test our theories about the interaction of beta and delta rhythms in the basal ganglia, and we have ongoing conversations with others with whom we may collaborate. I hope that the larger body of work will change minds.

Schizophrenia

Many of the things I now consider a core part of my interests were motivated by the interests of my students and postdocs. A student of mine, Nathan Veirling-Claassen (previously Dorea Vierling-Claassen), was very interested in neurological diseases. The disease whose connections to brain rhythms were most studied was schizophrenia (SZ). Peter Uhlhass and others had been emphasizing the importance of rhythms to brain diseases such as SZ, but there was very little modeling attempting to connect changes at a physiological level to changes in brain rhythms. Nathan's project considered work of Kwon and colleagues (1999), who looked at responses of patients with SZ and controls to 40 Hz auditory inputs; controls had the standard 40 Hz steady-state response, but patients with SZ showed a preference for 20 Hz responses. In collaboration with Peter Seikmeier and Steve Stufflebeam, who did related experimental work, we created two computational models, one large/detailed and one small/more abstract to try to understand the origin of the difference in response (Vierling-Claassen et al. 2008). The models were based on postmortem studies indicating that cortical interneurons in subjects with SZ have decreased GAT-1 (a GABA transporter) and GAD 67 (one of two enzymes responsible for GABA synthesis); these alterations change the GABA kinetics. The models transition from control to schizophrenic frequency response when an extended inhibitory decay time is introduced, as thought to happen in SZ (Lewis et al. 2005). Working simultaneously with the two models was eye-opening. We expected that we would see much more with the more complex and detailed model, but it was so complex that we had trouble understanding the basic phenomena. The smaller model enabled us to more quickly understand what was important to getting the 20 Hz responses, and that understanding constrained the larger model enough to produce the results in the larger model as well. The larger model helped us to understand the importance of cellular heterogeneity, which was hard to model with small numbers of cells. Since Nathan was working for a math PhD, the results were also used to generate a model we could study analytically, and Nathan produced new mathematics about families of excitatory/inhibitory oscillators with periodic input (Vierling-Claassen and Kopell 2009). After that, Nathan went on to become an experimentalist, working with Chris Moore and now contributing to understanding neurological disease.

That was the last paper that I published on SZ until very recently. Gyury Buzsaki invited me to do a review for Biological Psychiatry on SZ and brain rhythms (Pittman-Polletta et al. 2015). By then, I had read enough more on SZ

and rhythms (including the work of Kevin Spencer and much more from Peter Uhlhass) to realize that I had a story I wanted to tell about the subject, even if it was going to take a lot of work to dig up the evidence. Most of this literature search was done by first author, Ben Pittman-Polletta, with help from Bernat Kocsis, Sujith Vijayan, and Miles. We used the review to spell out the reasons why we thought that changes in rhythms were so important to neurological diseases. The basic picture that we sketched, using many papers for support, was this: Changes at the cellular and molecular level—especially those affecting the function of inhibitory interneurons—alter the rhythmic coordination of neuronal activity. These alterations interfere with local processing, which is mediated by rhythmic activity. Perturbations of the oscillatory structure of local processing upset large-scale coordination of neuronal activity across brain regions. Finally, distorted local processing and large-scale coordination produce altered cognition. The big (ten thousand foot) picture is very similar to the one that is guiding the work with Emery Brown and which is also (I believe) relevant to many other neurological diseases. The details are different, but in each case the framework provides ways to proceed to tease out those details.

More Neocortical Rhythms: From in Vitro Recordings to in Vivo Control of Behavior

It was always the hope that the deep understanding that can come from manipulation of slices would lead to hypotheses about cognition. Of course, everyone recognized the difficulty and perils of trying to make such a leap. In the earlier days of studying in vitro rhythms, most of the results were about single frequency bands in single regions of the brain. As the slice experiments got more sophisticated (based on earlier understanding), they were more able to reproduce the multiple rhythms found in vivo, as well as address interactions among regions. Although the rhythms in slices are cleaner and more powerful than those in vivo, they are believed (at least by some of us) to be similar in mechanism, enough for us to use these as clues to understand how rhythms might facilitate function in vivo.

Still More Betas. The beta oscillation that I had considered with Miles and Roger was the beat-skipping beta in hippocampus in vitro. Through my interest in PD and propofol, I had become aware of other mechanisms for producing beta rhythms in the brain. About this time, I started working with Miles on still more beta rhythms in vitro. With Anita Roopun and others, Miles was showing that different parts of the brain could produce rhythms of exactly the same frequency in completely different ways (Roopun et al. 2006; Roopun et al. 2010). In secondary somatosensory cortex (S2) a parietal, multimodal area, the intrinsic burster (IB) cells could produce such a 25 Hz (beta 2) rhythm in the presence of the glutamatergic agonist

kainate and the absence of any chemical synapses, communicating through gap junctions. In primary auditory cortex (A1), there was another 25 Hz rhythm, this one requiring a cholinergic agonist (carbachol) as well as synaptic interactions between IB cells and interneurons that mediate GABAa inhibition significantly slower than that of the FS cells. These slow-inhibitory interneurons, likely LTS cells, are dendrite targeting, unlike the FS cells. A very peculiar finding was that each of these betas could live happily in their respective deep layers while the superficial layers produced a standard noise-driven gamma. Indeed, the slices could be cut along layer four, and the gamma and beta rhythms would continue to exist, even a little more happy (higher power).

The most unexpected result concerned the gamma/beta 2 in S2. When the kainate was partially antagonized (mimicking the reduction of excitatory input), after some time the gamma and beta 2 rhythms switched to beta 1 (15 Hz; Roopun et al. 2008). Now the rhythms in the superficial and deep layers were dependent on one another. How that could occur, and what it might be good for, were subjects that I explored with Mark Kramer, then a postdoc in our group. Mark created a model showing that the beta 1 is a concatenation of the gamma and beta 2: Each cycle of beta 1 contains one cycle of a gamma rhythm and one of a beta 2 rhythm. (Do the math: it works to get a 15 Hz rhythm!) Each gamma cycle triggers a beta 2 cycle by rebound from inhibition and similarly for beta 2 and gamma. The model could have been right out of a Rube Goldberg construction. But it made many specific predictions that we tested, and it passed all tests. So we are comfortable using it to think about what might be implications.

This beta 1 rhythm has properties that other rhythms have not yet been shown to have. An important one is that it continues even though the excitation that initially caused the gamma and beta 2 has diminished; this happens because the rhythm is sustained by rebound from inhibition. In addition, it has another property concerning cell assemblies: In models of gamma oscillations (Borgers and Kopell 2005), multiple assemblies of cells that get feedback inhibition from the same collection of FS inhibitory cells compete with one another. The most active assembly takes control of the inhibitory neurons, and uses them to suppress other cells. By contrast, multiple streams of input to different sets of pyramidal cells have a different effect when the target network is already displaying a beta rhythm (Kopell et al. 2011); they can coexist even though they share feedback inhibition. This allows for a kind of short-term memory that can permit the manipulation and coordination of cell assemblies. We think this is especially important since it occurs in a parietal cortex, a critical area for multimodal coordination and interactions of brain regions. The special properties of the beta 1 rhythm have been motivating current work with Miles and Anne-Lise Giraud about expectations and errors of expectations (more below).

Multiple Gammas in the Same Slice. Miles' lab has produced many surprises. One surprise concerned two different gamma frequencies in the input and superficial layers of rodent A1 in vitro. These rhythms have totally different mechanisms and can be made to each appear by themselves (Ainsworth et al. 2011). At some levels of bath application of the glutamate agonist kainate, they are synchronous; at higher doses, they break apart with the superficial layers displaying a much higher gamma frequency. Though other groups had seen multiple gamma bands in vivo and in vitro, this was the first paper to show that the different "flavors" of gamma could manifest in different anatomical layers. Furthermore the deep layers of A1 respond to the superficial layer activity when the kainate dose is low (corresponding to input signals that are less salient) but to the input layers when the latter is producing a faster rhythm. It was not at all clear what were the underlying mechanisms for these observations and what were the functional implications. That led Shane Lee and me, working with Miles and Matt Ainsworth, to make a multilayer model of A1; I think that was my first multilayer model (Ainsworth et al. 2011). Via this model, we were able to understand in a mechanistic way what allowed the rhythms to synchronize or break apart. In conjunction with the experiments, it suggested an important functional implication: When signals are highly salient, they may not need to be processed further in the superficial layers in order to provoke a response via the output (deep) layers. When the input is not quite so salient, further interaction with other signals, taking place in the superficial layers, may be important to processing the signal for further action. Thus, the work suggested that layer-specific signals create dynamic regulation of coordination.

There was another important result about multiple gamma rhythms from the Whittington group, with modeling help from mine, this one concerning the entorhinal cortex (Middleton et al. 2008). The authors discovered what was probably a new kind of interneuron, which we named a "goblet cell" for the shape of the neuron. This cell was mostly in layer three, while the FS interneurons were more concentrated in layer two; these cells types are mutually inhibitory. The standard gamma in the usual artificial cerebral spinal fluid is formed by the interaction of FS cells and pyramidal cells, as in the rest of the neocortex. However, the FS cells of the EC require excitation mediated by NMDA currents, and in the presence of ketamine (an NMDA-receptor antagonist), the FS cells are inhibited and the goblet cells are disinhibited; this allows the formation of a gamma rhythm from the goblet cells and the pyramidal cells, a rhythm a little slower than the more standard gamma. The potential significance of this new gamma rhythm comes from the fact that the slower gamma rhythm matches that of CA3 and the faster one that of CA1. The CA3 and CA1 targets are parts of separate pathways. To the extent that the matching of frequencies facilitates communication (partially understood via modeling), the work suggested that modulation of

NMDA receptors could change the routing of signals. This came out shortly before the in vivo work of L. L. Colgin and M. B. and E. I. Moser (Colgin et al. 2009), showing routing of two bands of "gamma" rhythms (one a much higher frequency) to different parts of the hippocampus.

Top-Down Gamma, Attention, and Beta Signaling. Although bottom-up signals are believed to be mostly associated with gamma rhythms, and top-down signals with beta rhythms (Bastos et al. 2015), this is not entirely true. Even in vitro, it is possible to get top-down gamma signals. Anita Roopun of Miles' group examined a slice that contained A1, S2, and the connections between them (Roopun et al. 2010). She and colleagues showed that, without cholinergic modulation, there was top-down gamma from S2 to A1 between the superficial layers. Although S2 could produce a beta rhythm in its deep layers, A1 did not hear it; there was no Granger causality signal. When carbachol is added, the deep layers show both top-down and bottom-up signals, and there is a very strong top-down beta signal to A1. Thus, cholinergic modulation changes the direction of signaling between A1 and S2, even in slice.

At this point, there had already been a number of studies pointing to the importance of top-down beta signaling in the context of attention (Fries et al. 2001; Buschman and Miller 2007). Attention is often accompanied by cholinergic modulation, so this study motivated me and postdoc Jung Lee (no relation to Shane Lee) to try to understand the role of top-down beta in attention. To do this, we decided to reproduce the results of Fries and colleagues (Fries et al. 2001; Fries et al. 2008), in which attentional effects led to increased gamma in the superficial layers. This was not an obvious place to start, since Pascal and colleagues were mainly concerned with the increased gamma, and we were concerned with the role of the top-down beta. Our modeling results (Lee et al. 2013) showed the connection between top-down beta and increased gamma in the superficial layers (the presumed target of Pascal's recordings). Only in the presence of cholinergic modulation, the top-down beta caused the activation of a beta-frequency network in the deep layers, which included the activation of interneurons mediating slow GABAa inhibition; this inhibition, ascending to interneurons in L4 and the superficial layers and targeting inhibitory cells, changed the interaction of excitation and inhibition in those layers in such a way as to produce more activity and more gamma power in both the input and the superficial layers. So we showed how top-down activity in some frequencies to which the bottom layers are resonant could produce changes across all the layers. Since gamma is good for creating cell assemblies, it became clearer how the top-down signals could produce a gain increase that would be useful in passing signals along to the next region.

Recent work with Jung and Miles is suggesting an even more complex and interesting story; this has to do with the top-down superficial gamma

that becomes top-down and bottom-up in the presence of cholinergic modulation. Jung's modeling (Lee et al. 2015) has shown that, in the absence of cholinergic modulation, the top-down gamma, which goes primarily to the FS cells of the superficial target network, can at least partially prevent input from the thalamus from reaching the superficial layers. Adding cholinergic modulation changes the situation so bottom-up and top-down gamma can actually alternate in talking to one another. The simulations predict that top-down processes using both gamma and beta may work in concert to ensure appropriate cortical filtering during enhanced primary representation of input in attention-related tasks. The Roopun work (Roopun et al. 2010) and the subsequent modeling reveal a highly regulated system in which modulation affects interlayer and interregional interactions, and brain rhythms are critically involved in mediating these interactions. It is examples like this and the ones above that give me hope that a deep study of brain dynamics, pulling together in vivo, in vitro, and modeling work, can help to understand cognition at a more mechanistic level.

Meanwhile, slice physiology continues to throw more surprises at us. Miles' group studied a "sleeping slice" of S2 that produced a delta rhythm with other faster rhythms nested in it, and Roger produced a traubian model of it (Carracedo et al. 2013). This work is inspiring thoughts about cortical delta and its role in active sensing (Lakatos et al. 2008). Fiona LeBeau, a continuing collaborator of Miles, has been studying rodent frontal cortices and finding dynamical patterns that are very different from those found in sensory and parietal cortices. They are also finding a huge heterogeneity of cellular properties, which is likely to be closely related to the ability of frontal cortex to be very broadly tuned and participate in multiple tasks. These physiological findings are motivating a lot of modeling work in our group, notably about the nature of decisions (more below).

Wading into Data Analysis

In almost all my career, I've been working with nonlinear differential equations, using them to explore how different processes affect one another. I had no training in statistics, except for a course in probability as an undergraduate. I knew statistics were important, but I treated them as facts I was given, to contemplate and figure out how processes interact. I now realize how naïve it was to treat analyzed data as pure facts. As I hang out more and more with experimentalists, and participate in the sometimes-frustrating discussions about how to analyze the data that was so effortfully acquired, I look at the methods section of papers with a new and more probing eye. My education started at the hands of two postdocs in my group, Adriano Tort and Mark Kramer. Adriano contacted me in 2005, to ask if he could come on a Brazilian Fellowship to work with me. He had undergrad training in physics, was getting a master's degree in

math and a PhD in biochemistry related to medicine (which may have been associated with still another degree). He had a letter of recommendation from Jacob Palis, my fellow Smale-advisee from Berkeley, though Jacob did not mention the connection. I remember asking myself what I could possibly do with such a person; I realized soon after he arrived what a gift he was to me. I don't think Adriano knew that much math or statistics or computation when he arrived, but somehow he seemed able to inhale what he needed and breathe out a finished ability to work at a professional level. He wrote several papers with me I'm still very proud of, using dynamical systems modeling (mentioned above with theta oscillations). It was his idea to also start writing papers on data analysis. When Adriano left my group, it was to become a full professor in Brazil and start his own lab. (I'm not sure he had ever done any experimental work before.) I recall that the competition involved writing essays (closed book) on a very large number of subjects. He told me that he managed to write about twice as much as anyone else in the allotted time, and I wouldn't be surprised if his essays had four times as much content. Although the competition was open to all levels, Adriano got the job.

Mark, who is/was very interested in epilepsy, had a previous background working in ECoG with Bob Knight, and had come to my group to get experience modeling at a more physiological level. He was already skilled in aspects of data analysis, and teamed up with Adriano. The issue of cross-frequency coupling had come up in our work on gamma and theta rhythms. It is easy to see rhythms and interactions of rhythms when they aren't there, but appear as an artifact from filtering or other kinds of manipulation of the data. In a methods paper, Mark and Adriano described how artifacts may arise and suggested means to detect them (Kramer et al. 2008). We also worked with Ann Graybiel's group to analyze cross-frequency coupling within and between hippocampal and striatal LFP signals as rats performed a task requiring active navigation and decision making (Tort et al. 2008). The amplitudes of the high-frequency oscillations and their phase within a co-occurring theta changed in different parts of the task. Furthermore, at different times in the task, the particular subbands of frequencies engaging in the cross-frequency coupling changed in a repeatable way. This experiment displayed remarkable temporal structure in the brain, closely related to function; I thought this was pretty convincing evidence of the importance of rhythms in cognition, but minds change slowly. Adriano and I also wrote data analysis papers with the group of Howard Eichenbaum. In one of these (Tort et al. 2010), Adriano used ideas from physics to construct a new algorithm for computing cross-frequency coupling, and this method has been picked up by many others. Ever since, I've had an undeserved reputation for being an expert in data analysis. However, Mark and Adriano have had a lasting effect on my group by teaching others, who teach others etc., and attracting data analysis experts

to our group. So, in fact, our group continues to have these skills, and we have been involved in analysis of data from multiple labs.

While Mark was working with me, he was also continuing his work on epilepsy, and developing his own research program involving meso-scale network analysis (in the spirit of connectomics). Near the end of his post-doc, he applied for and got a career award from the BWF (this was before ShiNung), which paid a significant amount of his salary for the next few years. I made good use of that to get BU to hire Mark as an assistant professor. BU did not make it easy: As in many institutions, the higher administration was suspicious of someone coming from an internal group, even though there was tremendous support both within the math department and in neuroscience circles. The negotiations went up to within an hour or two of when Mark needed to reply to another offer, but eventually the administration came through. Mark has now become a mainstay of the computational part of the BU Program in Neuroscience, and it is hard to imagine that program without him. He and Uri Eden (a former student of Emery's that I also helped bring to BU) have an ongoing weekly neural data analysis "happening" in which investigators can bring their statistical questions and problems and get advice. This has been a great boon to the Boston neuroscience community.

Scientist as Amoeba

As I've moved throughout my career, I keep picking up new things. But the new things haven't been random. Almost every new interest builds on what I've done before, which determines where my head is at that point. The specifics of what I learned doing the pure, and then applied, math help to inform both the questions I ask and the methods that occur to me to start with. The image of an amoeba comes to mind: Wherever I am intellectually, I'm always extending a few pseudopods to sample the environment around me. Sometimes the latter is very tasty, and I move the bulk of my interests in that direction. In addition to the themes that I mentioned above, there were other directions I started on, and may go back to. For example, for a few years, I collaborated with Leslie Kay on rhythms in the olfaction system (Kay et al. 2009) as well as thinking about olfactory rhythms in insects (Sivan and Kopell 2004).

I'm continuing most of the major threads that I've begun in the past 15 or 20 years. I'm still interested in the physiological bases of brain rhythms, and the emerging data about this from the lab of Miles Whittington suggests a level of complexity we have yet to explore computationally. The work on PD and anesthesia continues to be very rich, and other neurological diseases are presenting important questions with significant computational components. Currently, three of my students are MD-PhDs. Our initial forays into normal cognition are showing that the insights from the study of the

physiology of rhythms, and also the changes in them in pathological states, can be useful for understanding how dynamics contribute to normal brain function. And even mathematical efforts are productively continuing: Simulations about any of the other themes almost always throw off mathematical questions concerning why the simulations behave the ways they do. These are more specific, involving more mathematical and physiological structure, than the early foundations that I and others helped lay.

It seems to me that all those threads are now converging, and the area of convergence (not a point) is an intellectual framework I call "dynomics" (Kopell et al. 2014). An extension of "connectomics," this framework goes beyond the construction of the connectome by emphasizing not only which brain regions are connected to which others, but what signals are sent along the connections and how such signals coordinate pairs of regions. It also goes beyond "functional connectomics," which deals with slowly changing networks of connected regions associated with brain activity during a particular brain state (such as attention or rest; see Bullmore and Sporns 2009).

One of the main themes I associate with dynomics is the idea of routing via fast dynamics: Signals that are given to some local network create an output that depends heavily on context, which can manifest physiologically as modulation states or other inputs to the same structure. Some signals may be filtered out (Cannon et al. 2014), and others may be enhanced (Lee et al. 2013). Thus, how a signal is carried around the brain through a network of networks depends on all these task- and state-dependent contingencies and works via ms.-precise dynamics. It is impossible to study all tasks and all states. So the construction of an all-inclusive theory that would contain all there is to know about this subject, as suggested by the *-omics* ending, is a fantasy. But I think that is also true of all the other omics, starting from the ur-omics, genomics; as people learn more, inevitably there are complications and convolutions, and separations into other intellectual pathways (proteomics, metabolomics, and so on). I start out without the fantasy that I think was/is fairly widespread about the ability of genomics, connectomics, etc. to provide a complete explanation of anything. But even without unreasonable expectations, the partial understanding provided by the study of these subjects has been extraordinary useful. So the labeling of the study of dynamics in the brain as "dynomics" is an attempt to point out that this is a valid and important area for study, one that needs to go on in parallel with the study of large- and small-scale connectivity.

This label aptly summarizes the themes I've been attempting to pursue. On the mathematical level, it is both explicit and open-ended: All signals with temporal structure arrive at a set of neurons that have a state with its own instantaneous temporal structure. How does the latter affect the processing of the former? The interaction of any two pairs of regions, with input from other regions as well, poses a question of this form that can be

translated into computational and even mathematical questions. Almost all the mathematics that I now do fits into this class of questions.

The dynome concept also provides a lens through which to view large issues of cognition. What is an expectation/prediction? How is active sensing carried out? What happens when we make a decision? Thinking in terms of dynamics makes one frame those questions differently than if one wants a kind of abstract answer. For example, though essentially all cognition involves previous history that leads to expectations, how such expectations are manifested in physiology and how they change reactions to stimuli is far from understood. The dynome concept leads me to think of predictions as dynamic "preparations" of network pathways: earlier experience sets up a network via plastic changes (and initial conditions) to have different dynamic reactions than if the earlier experience had not happened. "Prediction errors" are then anything that happens if other pathways are used and hence there are other outcomes. This kind of mechanistic thinking is very different from the well-known and much-cited theories of Karl Friston on predictive coding (Friston 2012), which often are expressed in an abstract form about changing probabilities. With Anne-Lise Giraud, I've begun to think about specific situations involving prediction errors (Arnal et al. 2011), using intuition gained from studying interactions of regions via rhythms, to work toward a more mechanistic and specific set of explanations.

Similarly, there is a large literature in modeling about decision making that has been highly successful in accounting for many results on experiments concerning decisions. For the most part, however, these theories address the phenomenology of decision making (such as accumulation of evidence) rather than the underlying biophysical mechanisms, with models that are fairly abstract, or they find biophysical mechanisms that could underlie the abstract ideas (for a review, see Wang 2012). I've started thinking about decisions (mostly rule-based decisions rather than accumulation of evidence) from a different point of view. Issues of decision making involve routing of signals in an essential way: Given the current and past stimuli in a given context (whether cued or learned from feedback), some motor activity is chosen. Thus, inputs are somehow mapped to motor outcomes. In general, this involves large fractions of the brain (especially if the task is at all complicated), and signals must be routed though all parts of the brain that take part in this mapping. Since I believe that signal routing is partially controlled through the expression of brain rhythms, the origin of a "decision" is a very attractive question for me. With some of my current group of students and postdocs, we are investigating interactions of prefrontal cortex and the basal ganglia, making use of our knowledge in rhythms in those areas to investigate such decisions.

I've started to work with Charlie Schroeder on issues of active sensing, which involves attention. The central set of questions is how the brain arranges that sensory signals manage to arrive at an optimal moment when

the brain is prepared to work with them. Ongoing low-frequency rhythms in the brain in the waking state, such as delta oscillations (Lakatos et al. 2008), are likely to be major players, and it is likely to take computational modeling (and maybe even some math) to figure out how these rhythms facilitate sensory processing. Pascal Fries and Sabine Kastner are doing experiments on attention and dynamics that are very interesting to me, posing specific questions about mechanisms of various kinds of attention. I suspect that essentially every aspect of normal and pathological cognition can be recast in terms of neural dynamics (not necessarily rhythmic) and routing of signals. Whether that will turn out to be a fruitful—and tasty—thing to do I'm eager to explore.

Onward and sideways!

On Math, Numerical Simulations, and Modeling

Creating mathematical models and testing them with numerical simulations is a completely different intellectual endeavor than pure math, which involves stating hypotheses and finding out the consequences of those hypotheses, as backed up by proofs. The latter is as close as we can get to ground truth. However, the trade-off is generally that the hypotheses have to be very constraining in order that the problem be tractable to available techniques. To apply this to any phenomena outside of math generally involves moving away from the limiting circumstances of the hypotheses under which the desired conclusion can be derived. Letting go is a very slippery slope intellectually. Sometimes, one can prove results "somewhat" away from limits (e.g., a ratio of two different time scales is very large or very small), but it has been observed many times that the calculations that hold rigorously only in some limit actually work far from this limit. So when is numerical observation a real contribution to the literature? With the advent of high-speed computers, the sociology has changed with respect to this question: In some past decades, numerical observations not backed by proofs were considered suspect; now proofs not backed by numerics are suspect.

The issues surrounding numerics get much thornier when the models are so complicated that they are nowhere near anything that can be analyzed by mathematical techniques. Though some people dismiss models with the remark that a model can be tuned to do anything, I think the state of affairs is much more nuanced, and much more like experimental science. To me, the central issue in working with numerical models, one that I grapple with in every paper that I write, is what constitutes intellectual honesty. The naysayers are correct that it often is possible to tune a model to recreate some phenomena. This may or may not give insight. If the assumptions of the model (or the parameter ranges that are chosen for the model) are wildly unphysiological or extremely implausible, the answer is probably not. The model parameters don't have to match numbers that were measured,

because all such numbers are themselves fallible—for example, measured in particular circumstances in a particular way, and might change in different preparations in different ways. But a model should include a vigorous defense of how the chosen parameters were arrived at. Even if the parameters are reasonable and the model can account for a variety of phenomena, it can be thoroughly wrong: The phenomena may be consequences of entirely different mechanisms not considered in the model.

It's a continuing puzzle, both intellectual and moral, how to operate in such an environment, and something that modelers need to be trained to face. On the one hand, the inability to create "truth" can be paralyzing for some people, and it is likely the reason that fewer mathematicians than physicists turn to neuroscience. (At least in the mathematical world, it is believed that physicists are less fastidious about dotting i's and crossing t's.) On the other hand, the knowledge that models are forced to be fallible tempts some people to grant themselves more leeway than they should honestly take, and at least some of the readers (if not the reviewers) can see this in the finished product. (I have heard some students—not mine!—say that they were told to "reproduce" some data, no matter how they get there.) I know of no method of dealing with this other than disciplined self-criticism, an open mind, and (in the end) a willingness to be wrong in print. There is also an unevenness in the quality of reviewing of computational papers for noncomputational journals (especially high-profile ones): Reviewers tend to pounce on details that are not central, or give the paper a pass on main issues regarding the correctness or relevance of a model. Since computational papers need to be read by experimentalists, this is an ongoing problem for the computational community and for any parts of the experimental community that are listening to the computational conversation. In some sense, these are problems of a growing and successful computational community; in the early days, when theoreticians talked among themselves, these problems were not relevant. But problems they are, and I hope the computational community will figure out how to address them. Of course, this is closely associated with the general pressures that all scientists are feeling now to produce results that will allow papers, grants, jobs, tenure, etc. It seems to me that the pressures, and the response to them, have gotten distinctly worse over the past decade, and I deeply hope that this will be reversed.

Though the conversation among experimentalists and theorists/modelers has gotten more extensive and deeper over the years, I sometimes wonder what we really understand about each other's knowledge base and thought processes. An incident I keep coming back to occurred when I was quite junior and Gabe was giving a talk at a small workshop that had as participants mathematicians, physicists, philosophers, and biologists. A well-known and very distinguished neuroscientist gave a talk that, implausibly, centrally involved a highly technical area of mathematics known as

tensor theory. As I looked around the audience, all the mathematicians and physicists seemed to be shaking their heads sideways in disagreement and/or disbelief. But the biologists apparently believed they had understood perfectly. I concluded that items that are fact based and subject to critique for one community are apt to be metaphorical for the other, a prime reason why interdisciplinary reviewing is so hard. Metaphors can be very useful, but not so much for understanding mechanisms.

As I near the end of my career, I've become drawn to more and more scientifically ambitious questions and more accepting of the limitations of my (and everyone else's) work. I'm now addressing questions that likely cannot be fully answered with the experimental and modeling tools that we now have. However, I'm convinced of the inadequacy of experimental tools alone, including big data approaches. Big data can supply huge amounts of information that can be queried, but what determines which questions are asked of such databases? This requires ideas and hypotheses. From where do they come? A study of a variety of experimental work can lead to ideas about how phenomena are connected and open new intellectual pathways. However, as the phenomenology gets more and more complex, it becomes harder and harder to suggest implications—too many things can happen in too many contingent situations. This is the essential reason for modeling, and also the reason why modeling is so fraught. It would be easy to dismiss the whole activity of modeling (as some do), if only there were some better alternative. More data alone won't save us.

Herding Cats

For most of my career, I've been collaborating with a variety of people. Indeed, as a theory person, I've been highly dependent on my experimental collaborators for data. For young theorists, it is often difficult to find experimental collaborators. I've also been struck by how much students and postdocs tend to stay within their labs, and not learn from the much larger scientific community. Finally, when I was "growing up" scientifically, there were no signposts or well-trodden paths for those of us interested in things interdisciplinary. All this has motivated me to form scientific networks and to be chief cheerleader within them. I discovered that I liked to do this and was good at it. One reason may have had to do with family: I married in 1978 and have two stepchildren (and by now five grandkids), but I was rarely a custodial parent. Mentoring lots of younger colleagues, students, and postdocs tapped into my underused maternal instincts. I have been known to be fierce in defense of my mentees and, when invited, sometimes formed close personal relationships, forming part of my extended family. (My husband and I have also "adopted" various nonmentee young adults over the years, helping them in various ways.)

One of my first attempts at community-building was an Army-sponsored group of people from various institutions working on CPGs to which I gave

the unfortunate acronym CRP (Center for Rhythmic Processes). It had no home space and just a plaque outside my door; I noticed that people would dance a bit as they passed my office. That lasted through the length of an Army Research Office grant supporting it.

The second attempt (1997–2011) was called the Center for BioDynamics (CBD). It was headed up by me and Jim Collins, who had the idea to start this. Jim, who is now highly successful in the fields of synthetic biology and systems biology, was then a young professor of biomedical engineering who had worked on genetic oscillators and other topics for which dynamics were critical. The idea was to create a group of investigators within BU who were all interested in some aspects of dynamics within biology. Getting grants for groups has never been straightforward. We became aware that NSF Division of Mathematical Sciences (DMS) had a call for Group Infrastructure Grants (GIGs), and we persuaded them that human capital could indeed be infrastructure, which we were prepared to create. This grant supported eight of us from a variety of departments around BU, not for senior salary, but for the support of graduate students and postdocs. It was an NSF version of a training grant, but was sui generis, like all the other training-like grants that I've put together. Our hope was not only to support such students but to change the culture of BU so that interdepartmental interactions became easier and more widespread. In this, we were quite successful, and the later neuroscience and systems biology initiatives at BU date from our efforts. At the end of the five-year grant, we were deemed successful, but NSF no longer had GIGs. So we were invited to put in a smaller proposal for a smaller number of people under the standard program for standard grants, which we definitely weren't. This continued the NSF tradition of being able to work in a flexible way, passing the hat among potential constituencies. This got us through another five years. After that, the NSF DMS had a more formal funding opportunity called Research Training Grants (RTGs). As usual, we didn't quite fit the description of fundable RTGs, but this was overlooked. At the end of 15 years, we decided not to apply for a further grant as CBD. By then, the computational neuroscience and the systems biology parts of the CBD had both grown to be independent initiatives (the other parts of math biology were sustained but didn't grow); this was the BU version of the growth and decline of the Gordon Conference in Math Biology: Progress called for further specialization. CBD was officially decommissioned in 2011, though its Web site is still up.

Early on in the history of the CBD, I was asked to serve on an advisory board for the Burroughs Wellcome Fund (BWF). The main job of the board was to advise on institutional grants associated with the interface between the physical sciences and the mathematical sciences. After serving on that board for a couple of years, it occurred to me that I might be very good at running the kind of group project that BWF was supporting. This was also a BU endeavor, which we called the Program in Mathematical and

Computational Neuroscience (PMCN), again a kind of cross-department training grant with a mandate to do community building, but this time with a more focused scope. Howard Eichenbaum was the codirector. It was not really a program, but centers were proliferating at BU, and this was a compromise among various pressures on names. The P enabled us to have an unofficial logo of a pumpkin (try pronouncing PMCN). We nursed the five-year funding for seven years, and used it create a strong and vibrant computational community at BU.

At the end of the PMCN grant, I decided to expand the scientific community for this effort more broadly across the Boston area and still more focused as to theme. A new beginning required a new name, and I called it the Cognitive Rhythms Collaborative (CRC), a catchy name intended to suggest a rock group. The mission of the CRC was to build a scientific community around the set of questions concerned with the measurement, analysis and modeling of brain rhythms, aimed at a deeper understanding of brain function in normal and pathological situations. In other words, it was everything I was interested in, and a good excuse to get together the large number of groups in the Boston area with overlapping interests. The CRC started with informal dinner meetings open to all CRCers, sponsored by the McGovern Institute, with intense interactions rather than formal talks. (I have a reputation among collaborators for intense scientific interactions; Charlie Schroeder once referred to an informal small group meeting I had arranged as a "Vulcan mind meld.")

A year of two into this experiment, the NSF DMS got a new director who was interested in helping to create "people networks," to enhance collaborations, to mentor students and postdocs, and to move science forward at a faster pace. At the beginning of his job, he went on a listening tour to many math departments, and I was put on his schedule. I had no inkling of his new ideas, and he had none about my previous activities, but we soon realized that we had common interests: I had already created a people network. It was not what he had in mind (he was thinking more in terms of purely mathematical networks), but it was close enough. A year or so later, he invited me and one other group (headed by Chris Jones and dealing with atmospheric science) to apply for a five-year grant for the CRC. We got the grants, and our groups provided a loose template for a more general program that NSF started a year or two after.

The CRC is open to all comers, but I made sure that some of the key Boston players would be on board. Some were obvious: at MIT, Bob Desimone, Emery Brown, Earl Miller, Ann Graybiel, Chris Moore, Matt Wilson; from Martinos Imaging Center, we had Matti Hamalainen, Steph Jones, Steve Stufflebeam, Seppo Ahlfors, Sydney Cash, and Patrick Purdon; from BU, there was me and Mark Kramer, Uri Eden, Oded Ghitza, Xue Han, Howard Eichenbaum, Michael Hasselmo, Michelle McCarthy, Kamal Sen, Jason Ritt, Barbara Shinn-Cunningham, and Lucia Vaina; and there were

other people interested in brain dynamics from other institutions, including Emad Eskandar, Donald Katz, Robert Sekuler, Christoph Borgers, Bernat Kocsis, Daniel Goldin, Kevin Spencer, Ritchie Brown, Robert Stickgold, and Daniel Polley, including some from outside of Boston (e.g., Miles). Some of the members were not obvious, for example Ed Boyden, who knew a lot about many, many things, but not so much brain dynamics. He and I had our first serious discussion when we sat next to each other a McGovern dinner—possibly at the 2007 Scolnick Prize dinner. That led us to start talking about applying optogenetics to rhythms and to collaborations with Miles. I was very happy to have him be a part of the CRC; he was always the first to respond whenever I sent out broadcasts asking for input or help.

Among us, the CRCers have a very broad variety of skills, including genetics, technology development, in vivo and in vitro physiology, using techniques for human measurements (EEG/MEG/Ecog), neurosurgery, statistics, and dynamical systems modeling. Though there were subsets of people who already talked to one another, the CRC created a framework in which these interactions were much more frequent and specific, especially among the younger colleagues associated with the senior members. With funds to support a significant number of postdocs, we were able to produce working groups on a variety of topics. We also had the data analysis group run by Mark Kramer and Uri Eden; this group helps all CRC members (and anyone can become a CRC member) with data issues, as well as creating cutting-edge new analyses. There has also been a yearly retreat and a mini-symposium. We did one large meeting so far. Through these mechanisms, student, postdocs, and faculty have multiple options for intense or casual interactions throughout the year. It is the impression of many of us that the CRC has notably improved the collaborative atmosphere in this field, with happy reactions from students and postdocs, and I'm at least as pleased with this as anything I've done in science.

Having never acquired an ongoing sugar daddy for these organizational efforts (and with BU definitely not interested in finding such a donor), I had to keep reinventing my scientific networks to appeal to the next transient funder and my own evolving interests. This wasn't necessarily a bad thing (though it took continual effort). Endings that were out of my control enabled me to reformulate what the network was supposed to do and reengage only those people who were active and relevant. I was very fortunate to be able to find new opportunities as old ones melted away and be able to build on the skills and communities I had helped to create. But I do hope that we can make the CRC outlive the ending of its funding.

Meanwhile, other things were happening involving BU and neuroscience. Starting from the time I was working on the CBD, Steve Grossberg was actively running a department (Cognitive and Neural Studies, CNS) and a center (Center for Adaptive Studies). Steve's group was focused on issues of mathematical psychology and used techniques and approaches that

were more engineering based. Those I worked with were more biophysically based, and the two groups were not highly interactive. About the time that the CBD ended, the CNS department was decommissioned, and Barb Shinn-Cunningham started a center with a long name, informally called CompNet by everyone. This group was to marry the remnants of CNS with the CBD group to take better advantage of the rich range of skills at BU; I helped a bit as codirector. CompNet served a very good transitional role, and now we have still another organizing umbrella, Center for Systems Neuroscience, with a new building and leadership of Mike Hasselmo. As I attempt to keep going my scientifically focused but geographically more spread network, I'm very happy to see this developing neuroscience community at BU. For more on BU history of neuroscience, see http://www.bu.edu/neuro/graduate/computational-neuroscience/cnhistory/.

Academic Travel

One of the great perks of working in academia is the ability to travel. I've done my share of colloquium talks, conferences, and panels, but there are a few trips that stick in my mind for the unexpected experiences. The first one of these was in graduate school. Some professors I knew were associated with a summer school in L'Aquila, Italy; not enough students had applied, and I was asked if I wanted to go (fully supported). It was not my field, but I was not about to turn down this opportunity. The school was in the foothills of the Apennine mountains, and I was eager to climb some accessible route. I kept hinting throughout the time of the school that someone should organize such an outing, but no one took me up on it. So near the end, I organized this trip. The plan was to climb up a fairly easy route and then take the funicular train back down. There were a lot of us, with a multitude of mother tongues, and English was more tolerated than embraced. This made it hard to move the crowd along at the pace required to make the last train down, and we did indeed, barely, miss the last train down. A highly fit group of young Frenchmen arrived at the top when we did, and then ran down the mountain in the small amount of time before darkness fell. But we were not so fit or skilled, and found ourselves in the dark, without flashlights, trying to pick our way downward. Luckily, the moon soon arose and helped, but it was not easy or fast. As we neared the bottom, we heard a lot of dogs barking: They were part of a search team that had been sent for us by the Frenchmen. I think I will not be soon forgotten at L'Aquila!

Another unforgettable trip occurred in 1981. Out of the blue, I got a call from a woman who was executive director of Committee of Concerned Scientists, a human rights organization. She was looking for a woman scientist to accompany her to Moscow and Leningrad to visit "refuseniks" (those who had been denied permission to leave, mostly Jews) and dissidents. I had been recommended to her by a colleague, and she gave me one

hour to decide whether to go; we weren't going to leave for some weeks, but preparations needed to be made. I used the hour to check the credentials of that group, which I had not previously heard of, and then accepted. I prepared for this in the spirit of cloak and dagger: I knew that I should not have material in Cyrillic, since it would be clear that I didn't know any Russian. But we needed a list of names and addresses of those we planned to visit. So I transliterated the list into English letters and created a scientific bibliography. When we needed to hand an address to a cab driver, I transliterated it back to Cyrillic, not necessarily faithful to the original. One of those we visited claimed I had written his address with a Yiddish accent! We were aware of being trailed, though we were not stopped. I gave the last of the famous "Sunday seminars" (given on a Tuesday to evade the KGB) at the home of Irina Brailovsky, whose house was known to be bugged, and when she introduced me, she spoke right into the mike on the ceiling. So this was the only talk I've ever given that was piped straight to the KGB; I wonder what they made of the discourse on the BZ reaction. That talk was also notable to me because of the avidness with which the audience absorbed the material. Not all of them understood English, and after each sentence or two, the audience erupted in Russian, discussing the content among themselves; when they quieted down, I went back, briefly, to speaking. We also visited the wife of Andrei Sakharov and brought her some things from the states. I kept up with some of the people we visited, especially when they were later able to leave Russia. And I started being more involved in human rights work.

A later trip to the then–Soviet bloc occurred when I was invited to give a talk at an International Congress of Mathematicians, held every four years, and this time in Warsaw in 1983. It was a time when Solidarity was very active in Warsaw, and many people had been imprisoned for their political activities. I was unsure whether to go or boycott, and I called a well-known member of Solidarity who happened to be visiting at Harvard. His advice was to go and smuggle in anything I could for Solidarity. So I packed my suitcase with needed carbon paper and some embargoed books. The agents at the Warsaw airport were carefully checking, but somehow I managed to get on a line in which suitcases were not being opened, and so my contraband made its way safely inside. The Poles seem ecstatic at having so many foreigners around, with a loosened sense of political control. One said to me something like: "Everyone is here, and they are talking about everything!" There was a plan among a subgroup of speakers to dedicate their talks to some imprisoned person. I was assigned someone (whose name I could barely pronounce) and started my talk with a one-sentence dedication. The next speaker was Russian, and he was clearly very upset by this; he made movements suggesting he wanted to cut me off, but my dedication was too brief to allow this. He started his own talk by saying (with meaningful emphasis): "I'm going to be talking on a theme similar to that of the previous speaker, *but I have*

a different interpretation." I don't know how much the audience understood the veiled political allusion, which was clear to me.

There were also many memorable trips that I took with groups of MacArthur Fellows, with one or more of the fellows organizing a trip to places where they worked. I got to dig for dinosaurs in Montana with Jack Horner, spend time on Indian reservations, explore the Amazon (including a butterfly farm) and the Galapagos Islands, and travel around Madagascar. It was an extraordinary privilege to travel with these experts and get access to places not easily reachable.

In Sickness and Health

As a child I was very athletic (good genes; my mother was women's athletic director at a camp I went to). I was highly active through graduate school. A few years after that, shortly into my time at Northeastern when I was close to 30, I contracted mononucleosis (again I was a late-bloomer—people usually get this at an earlier age). Mono is believed to be viral, and for some unlucky people, it has after-effects that can linger. For me, the after-effects never went away. One of main symptoms of mono is intense fatigue, as well as swollen lymph glands, and those came back at irregular intervals for irregular periods of time. I kept working during those times, though there were moments in which I had to head for the nearest flat surface and collapse. (In my current office, there is a couch for that purpose). I recall teaching a class in which I had essentially no voice. The class was small and I gathered them around me at the blackboard (I was not contagious) and whispered my pearls of wisdom. The sequelae were especially bad for the first few years, and I kept canceling acceptances for conferences and speaking invitations. Since these were all about topics from my graduate work that I was trying hard to flee, those invitations were a mixed blessing. My husband guessed that I might be using the mono as an excuse not to go. I wasn't sure; I thought that wasn't so, but it was hard to tell.

Various versions of this have gone on through the years, with "flares" that ranged up to a few months. I continued to work, and be mostly productive, with times when reviews were months late, and classes or invitations were canceled. It was not for almost another 40 years that this illness was diagnosed: chronic fatigue immune dysfunction syndrome (CFIDS); it has a lot of other names, including systemic exertion intolerance disease, myalgic encephalomyelitis, and postviral fatigue syndrome. The mother of all flares occurred in 2009 at a SfN meeting. I had signed myself up to do too much: I was running a short course at which I was also giving a talk, I was actually standing in front of a poster (for a full four hours) and talking about it, though by that point my voice and my energy had long since parted ways with me. I was visiting the requisite number of other posters,

seeing the friends I wanted to make contact with, having meals with new potential collaborators, going to socials and other meetings, and not giving myself enough time to rest in between. I knew I was stressing myself, but I convinced myself that there was good stress and bad stress and this was all the former. Bad mistake! At the end of the poster, I went to my room, slept for about 24 hours, and then took the first plane home. I did not start to recover for about a year.

As in other flares, I dutifully went to my doctor, without much hope. I had previously been sent to the usual array of specialists who did the usual array of tests, and I passed them all. Then the flare would pass before they could come up with a diagnosis. I was lucky that they did not say to my face that they thought I was malingering (a common experience of many people with CFIDS). This time, the flare lasted a year and my primary was a bulldog; she saw I was really sick and would not give up until she figured out why. (Being able to do something about it was another thing.) This was for better or worse: better that she really cared, which was the best thing she could do for me (including muscling her way into appointments for me with booked-up specialists), and worse because none of the specialists she sent me to seemed to have a clue. Since CFIDS is not understood (and I didn't yet have a label), and it comes with a bewildering array of symptoms (neurological, muscular, cognitive ("brain fog"), immune-related, gastrointestinal etc., ad nauseum), I was thrown into the medical maw and saw at least one practitioner from essentially every department in the practice (well, maybe not dermatology). Most just expressed bafflement, as I meekly showed up for my appointments. One, a cardiologist to whom I had been sent after leaving a hospital to which I had been sent because I had trouble breathing, expressed annoyance when I went through the ritual of detailing the symptoms: Why did he have to listen to all that? What did it have to do with my heart? There was a clear implication in his manner to me that he hoped I would not darken his door again.

Eventually, after about six months of doctor-hopping, the second neurologist I saw had an idea. It seems that CFIDS is related to another mysterious illness called fibromyalgia, which is associated with pain originating at tender points. So he lay me down on the examining table, systematically poked a bunch of body parts, and counted how many times I screamed. I failed! (Use of terminology in which the patient actually gets a diagnosis from a test.) CFIDS is usually a diagnosis of exclusion, and my medical practice had done all that seemed to me possible in excluding everything else. It is commonly first triggered by mono, which was in my record. A look at my medical record now suggested to this neurologist that the previous string of undiagnosed illnesses had a common etiology. BINGO! I heard him dictating his report: "Patient accepts diagnosis." I was indeed very glad to have a label that implicated my body. The bad news came next: He told me that nobody in the practice treated this illness, and I was on my own. Indeed, as

far as I could later see, nobody in Boston treated this illness, partly because some of them didn't believe in it and partly because everyone in the medical profession seemed to know that nothing they knew would be helpful. Getting a label was helpful partly because I could now stop going to doctor appointments and concentrate on getting better.

While I had continued to dutifully show up to my baffled interlocutors, I had earlier reached a similar conclusion to that of my second neurologist about the efficacy of standard medical treatment and started looking for alternative routes to health. This included yoga (done very, very gently), herbs, acupuncture, and a lot of sleep and rest. It was helping, but nothing got me even close to where I had been before this flare started (not to speak of before the mono). One day, a year or so after I became sick, when I could barely get out of bed, my friend Amy Wong showed up and dragged me (leaning on her arm for support) to see her qi gong sifu (teacher) in Chinatown. Sifu Donald Wong (no relation) taught a version of a Chinese standing meditation technique. Perhaps because I had previously done some baby yoga, I responded very quickly to his exercises and started coming regularly (once a week). For a while, each session made me feel temporarily worse and then better than before the session; this was "detoxing." Over months, my health gradually returned, something surprising to my doctors, and not usual. I've continued the practice of dragging sick friends to Sifu Donald, with mixed results but some definite successes. Now that I've had more than five years of practice, with his encouragement, I've also begun to teach the basics of qi gong in an informal class at BU.

It occurred to me that meditation has a lot in common with doing mathematics or trying to solve a scientific puzzle by the Method of Pure Thought. Both require an intense but very relaxed concentration, to allow an awareness of many things while blocking out other things (such as shopping lists and deadlines). I recall a story that was told to me by the wife of my fellow math student Mike Shub. She said he did most of his mathematics lying down on a sofa with his eyes closed, and she couldn't tell if he was working or sleeping.

A couple of years after starting qi gong, after watching others in my Chinatown gym work out with various martial art routines, I started showing up early for the qi gong class and doing tai chi with a martial arts teacher, Sifu Larry Wong (no relation to Sifu Donald or friend Amy). This time, it was not my gender that earned me the privilege of hanging out, but my age; Sifu Larry was amused at the idea of teaching someone who was starting at age 70. And, of course, I was pleased by the opportunity to begin something entirely new and very physical at age 70. The tai chi he is training me on is a martial art, not "tai chi for grannies." Although he shows me the uses of all the moves (blocking, punching, kicking) for fighting, he is discouraging me from actually doing the latter; bones don't heal as fast at this age. But I hope to talk him into letting me at least spar.

On Recognition and Gender

Though I've experienced a fair number of incidents in which my gender was a disadvantage, I'm guessing that these have been balanced by others in which my gender was helpful. Certainly after more consciousness got raised, and perhaps even before then, being female made me stand out, and got the work I did some extra attention. How that might have played into recognition I'm not sure. I do know that I have been the beneficiary of some major privileges: fellowships (Sloan and Guggenheim) that allowed me to reduce teaching; a chair (and then a more padded chair) from Boston University, that gave me extraordinary freedom and some "play" money; and the opportunities that come with being a MacArthur Fellow and a member of the National Academy of Sciences.

About recognition itself, I'm very grateful but also ambivalent about the whole idea of prizes. Recognition has been extremely helpful in my career. Yet recognition sometimes seems to be bestowed in random (as well as political) ways. I'm very aware of many people doing excellent work with less external emotional support and recognition, and (in my opinion) many people doing not so good work who are extremely successful. I've learned to be zen about other peoples' opinions (even before doing meditation, though that helps): I enjoy (but not too much) the ones that agree with me and listen hard to other points of view (but mostly to the reasoning, not necessarily the conclusions). Mainly, I've been very grateful to be a player in an ever-changing game, with the opportunities to work with and learn from wonderful people.

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