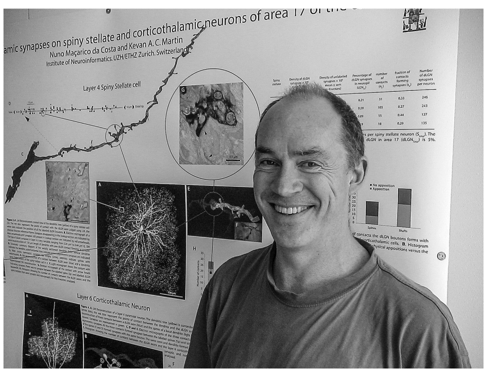
KAC Martin


synapses on spiny stellate and corticothalamic neurons of area 17 of the
Nuno Maçarico da Costa and Kevan A. C. Martin
Institute of Neuroinformatics, UZH/ETHZ Zurich, Switzerland
Layer 4 Spiny Stellate cell
Layer 6 Corticothalamic Neuron

Kevan A. C. Martin

Born:

Cape Town, South Africa
May 22, 1952

Education:

University of Cape Town, BSc (1973)
University of Cape Town, BSc Honors (1974)
University of Cape Town, MSc (1975)
Wolfson College, Oxford, DPhil (1978)

Appointments:

Weir Junior Research Fellowship, University College, Oxford (1979)
Junior Dean, University College, Oxford (1979)
Salverson Junior Research Fellowship, University College, Oxford (1982)
E. P. Abrahams Cephalosporin Junior Research Fellowship, Linacre College, Oxford (1984)
Ovenstone Senior Research Fellow, University College, Oxford (1985)
Senior Scientist, Medical Research Council Unit, Oxford (1985)
Foreign Associate of the Royal Society of South Africa (1990)
Old Members Trust Senior Research Fellow, University College Oxford (1990)
Henry Head Research Fellow of the Royal Society London (1990)
Senior Treasurer of the Amalgamated Clubs, University College, Oxford (1993)
Double Professor of Systems Neurophysiology and Director of the Institute of Neuroinformatics, University of Zurich and Swiss Federal Institute of Technology (ETH; 1995–2019)

Kevan A. C. Martin forged an interdisciplinary, multilevel approach to analyze and describe the structures and functions of the local and long-distance circuits in the neocortex in multiple species. His work has been highly influential in establishing general principles of structure, function, and computation in neocortical circuits. With Rodney Douglas, he founded the Institute of Neuroinformatics in Zurich, whose mission is to discover key principles by which brains work and implement these in artificial systems that interact intelligently with the real world. His experimental research is characterized by detailed quantitative analyses of the physiology and morphology of identified neurons and their synaptic connections and synthesizing these results in computational models that can be realized in software and in novel analogue 'very large scale integrated' (VLSI) silicon circuits. One key result of this synthesis was a "Canonical Circuit" for neocortex that, while originating from studies of the cat's visual cortex, provides an operational description of local cortical processing in species from mouse to man. Formulated at a mesopic scale, the Canonical Circuit forms the critical bridge between the microscopic synaptic and single neuron levels and the macroscopic levels of systems and behavior.

Kevan A. C. Martin

Nature or Nurture?

Any autobiography immediately raises in its author questions of free will and determinism. To what extent is their history simply a random walk determined by chance encounters, and to what extent is their history tightly constrained by circumstances? Perhaps one's personal history can be read either as a pinball's path of chance encounters and lucky breaks, or a predetermined journey along a well-constrained path. A neuroscientist's knowledge of both genetic inheritance and neuroplasticity assures us that we can never free ourselves of the influences that shape us; indeed, our own biology ensures that we can never have a truly original thought. Having spent most of my academic life studying central processing in the visual system, what significance do you give to the fact that my earliest years were spent at a blind school, or that my father founded a school for children with cerebral palsy?

With a long look in the rearview mirror, I see that structure is an abiding interest of mine. Was this because my paternal grandmother, whom I never knew, had left us boxes of microscope slides she had prepared for her biology students? There is evidently a strong aesthetic element too, for magnified views of nature I find beguiling. And then there is the pull of understanding how things might be built and work. Was this a consequence of being around my father who was forever repairing cars, building boats, and recycling and repurposing what my mother called "junk," and why I still ride (and maintain) his 1936 Ariel Square Four motorcycle? "Nothing knowingly thrown away" could have been his motto; hence, the fascinating museum of flotsam and jetsam I grew up with, which included my grandmother's histology collection. What looms largest in the mirror are the people I encountered and worked with, but two most especially: David Whitteridge, who introduced me to the visual cortex and with whom I shared a lab and office for 17 years until his death, and Rodney Douglas, my scientific partner on a voyage of discovery that is now in its fourth decade. The longevity of these scientific relationships is a pertinent fact, as is the presence of a penumbra of colleagues who have accompanied me for long periods of my scientific life. But the rearview mirror also reveals that my greatest joy is being with people who know a lot more than I do about all kinds of things.

Author note: My chapter does not include a bibliography, but the papers cited are readily available and easy to find online.

Out of Africa

I was born on the southern tip of Africa, the middle of three sons. We lived in a bungalow in the grounds of The Athlone School for the Blind, a school for black children, which was surrounded by indigenous bush on the Cape Flats, a sandy plain between Table Mountain and the Helderberg Mountains. My father had been appointed vice principal at the ripe age of 23, more on the basis of his three degrees than on any expertise in special education. He majored in physics for his BSc, English for his BA, and education for his BEd—a graduate degree. He had entered the University of Cape Town (UCT) at age 16, propelled by his parents, both of whom were émigrés from the East End of London. His mother had earned a BSc in biology from Bedford College, which was founded in 1849 as the first higher education college for women in the United Kingdom and became one of the University of London's colleges in 1900. He was musically gifted and immensely practical, no challenge seemed to faze him. Years later I came across a pupil's braille essay about the visit of Helen Keller to the school in 1951, which my father had read and transcribed between the lines in his neat longhand. One of my earliest memories is of blind children on a terrace, weaving baskets from long canes and grasses. The school still exists, and its chapel records that my grandfather was a benefactor.

In 1954, my father was invited to found "The Cape School for Cerebral Palsied Children." My mother, who read avidly and had the most extraordinary memory for names and faces, which she retained well into her 90s, took care of her sons' schoolwork while my father set up the new school in a Victorian villa in a suburb of Cape Town. There were no African models for the school, but from the outset, my father understood that these children would need not just teachers with special skills, but the support of a multidisciplinary team including parents; physio-, speech, and occupational therapists; psychologists; social workers; and nurses and doctors. This holistic care meant that children with brain damage, mainly due to birth trauma and many wheelchair-bound, could now be educated at a school, a hugely positive step for both pupils and parents. It was successful and a bespoke new school complex was built and named "Vista Nova." As young children, we met children with conditions that are never seen now, mainly because of the huge improvements in perinatal care and attention to genetic disorders, like phenylketonuria. Athetoid, ataxic, and spastic cerebral palsy were common. Before ventricular shunts were used, we saw hydrocephalic children with huge heads, and before seatbelts were compulsory, we saw the consequences of head injuries from car accidents.

Despite my mother's best efforts, I was an indifferent pupil, but, like her, I was an avid reader. My academic progress was not helped by being at an eminent school for white boys. The school's main interest seemed to be in its sporting achievements—rugby, field hockey, cricket, athletics, swimming, and tennis—not academic excellence. I developed a preference for gymnastics, which was a minor sport, so I trained at a local club. Throughout my high school years, I represented the Cape Province at the National Championships, and in my final year of school, I represented South Africa as a junior. This competence attracted an invitation for me to join a flying trapeze troupe to tour Europe. It was tempting, but at age 17, it seemed premature to make such a flying leap.

National service was compulsory for all white men, so January 1970 found me starting basic training as a rifleman in the 1st South African Infantry Battalion, which had its camp outside the semi-desert town of Oudtshoorn, famous for its ostrich farms and the Cango Caves. All South Africans were officially segregated by race, but whites were further divided by language and culture. All the teaching at my high school was in the English medium, so although Afrikaans, the language of the ruling Nationalist Party, was a compulsory subject, I could not speak it, nor then had any interest in doing so, for Afrikaners were generally regarded by English-speaking whites as nationalistic, unsophisticated, and racist. For a year, I lived in an Afrikaner community and heard (and spoke) little else than Afrikaans. To escape the discipline of the army, I would disappear from camp on Friday evening and hitchhike hundreds of miles, returning late Sunday evening, hoping my absence hadn't been noticed by those in charge. The motorists who gave me a lift were invariably rural Afrikaners, who warmed when hearing my improving Afrikaans, and this resulted in many enlightening conversations and more often than not, they would invite me back to their homes. In the face of their spontaneous kindness and generosity, it was impossible for me to sustain my English-speaker's negative caricature of Afrikaners.

Undergraduate Times

Discharged from the army, I joined a bank, but apart from learning the joys of double bookkeeping, it became rapidly clear that banks embodied the same divisions of rank as the army, so an escape to "higher education" at UCT beckoned. But what to study? Some years after establishing Vista Nova, my father had completed a psychology major by correspondence. I found his textbooks fascinating reading, so psychology went on the list of my major subjects along with logic and metaphysics as well as physiology. As first-year preparatory subjects, I read chemistry 1, physics 1, and zoology 1.

The first semester of zoology was taught by the head of department, Professor John H. Day, a marine biologist and invertebrate specialist. He took us on a tour of the animal kingdom, and despite complete ignorance of biology, and Latin, I was instantly entranced by his lectures. I couldn't believe how much was known about obscure (to me a least) animals with Latin names. Why would anyone want to measure the pH of the fluid in the nephron of an Amazonian beetle, for example? Similarly, psychology 1, which initially seemed to be dominated by lectures on learning theory and statistics, was no less gripping. At my secondary school, we had done precious little practical work, so the afternoon practical classes were exciting. There was one exception: I discovered from the physics practical notebooks of my father, which he had kept, that ours were pretty much identical to those he had worked through 30-plus years earlier, so this greatly dented my enthusiasm for experimental physics. Nonetheless, after just a month at UCT, the uncomfortable question arose: how was it possible that my secondary school teachers, all of whom had university degrees, had not been able to convey one jot or iota of the intellectual delights I was experiencing?

With four lectures each morning and four afternoons of lab practicals, there was little opportunity for any outside activities, but I squeezed in flamenco guitar lessons with the Cape Town doyen, Pablo Navarro. As I progressed, I joined Pablo to accompany student flamenco dancers at Hazel Acosta's studio in Cape Town. Academically, I hung on by my fingertips and no one was more surprised than I was when I managed to pass all my end-of-first-year exams.

I came from a frugal family and despite my brief encounter with banking, I never wanted to be in debt, so cash flow was always a problem. During the long vacation at the end of my first year, I managed to get a job with Jeffares and Green, a civil engineering firm that specialized in road design. As rank junior (temporary) I was assigned with the vital task of interpolating levels from the field notebooks that arrived back from the land surveyors, which I did with the help of a Facit mechanical calculator. There was a large pile of notebooks and my three months were spent working in the corner of the office of one of the design engineers, so I learned a lot about road design by osmosis. The highlight of the day, however, was hearing the tea trolley rattling slowly down the corridor to our door.

For similar cash-strapped reasons, during the second year of psychology, I worked as a "demonstrator" (i.e., technical assistant) in practical classes for the fresher-year psychologists. One of my co-demonstrators and practical partner was Tim Jenkin, who later joined the banned African National Congress and built letter bombs for scattering leaflets. He was arrested and sentenced to imprisonment in Pretoria jail, from which he escaped by fashioning wooden keys to open all the doors. His autobiography was made into the film: *Escape from Pretoria*. The university campus was a hotbed of antigovernment protests, in which many of us participated, but it was also infiltrated with informers, so detention without trial of students was commonplace.

My second year saw my entry to logic and metaphysics. Dr. Barney Keaney had just been appointed as the senior lecturer, and he had devised a compendious two-year course, which began with Greek philosophy and logic and ended with the linguistic turn of the 20th century. It was a complete contrast to the work I was busy with on the science side of the campus. The criticism might be levelled that such a whirlwind ride through centuries of logic and philosophy was far too superficial for a major university course and that it would have been better to concentrate on one or two philosophic schools of thought. On the contrary, what the course did in effect was to provide me with a series of hand- and toe-holds up an otherwise blank cliff face that I could then use to climb whatever route I chose. It has worked as well as intended.

Physiology 1 was taught at the medical school as part of the preclinical years for the medical students. The head of department was a ruddy Scotsman, Archibald Sloan, who chain-smoked, but whose research area was exercise physiology. The most memorable lectures, however, were the laconic deliveries of Professor Leon Isaacson, a renal physiologist who had made fundamental measurements of the electrophysiology of the proximal tubule in Maurice Burgs's lab at NIH, where the preparation of the perfused isolated proximal tubule was first developed. Leon gave the most research-based lectures in the course, yet as a practicing consultant at the neighboring Groote Schuur hospital, his clinical experience was immense, so the medical students benefited hugely by getting his firsthand accounts of diseases of the kidney. Unlike most of the other lecturers, if I managed to generate one page of notes during one of Leon's lectures, it was a lot.

The physiology practical classes seemed to have been devised in the late-19th century, and apart from the histology practical, many of them used equally vintage apparatus, gleaming of brass. Spirometer recordings of respiration, or recordings of frog muscle twitches, were made using clockwork-driven smoked-drum kymographs. We made our own smoked paper using a paraffin burner, and then varnished the results before we smudged them, cutting out the relevant piece to mount in our lab notebooks. Although the practicals and the apparatus we used were antiquated, having a mechanical rather than electronic connection between organ and recording was instructive, and the necessity of adding significant details like date, time-base, and signal calibration to the smoked drum paper, made us more aware of the nature of the signals we were recording and the limitations and potential artifacts imposed by the methods of recording.

Psychology 2 demanded volumes of reading and essay writing. The problem of accessing the original literature was solved by the campus central library making multiple photocopies of papers or book chapters, which we could then reserve for an hour at a time. This was a cheap and efficient system and gave us good practice in reading comprehensively and note-taking. The contrast to the modern era could not be more profound: on most students' desks (and usually the surrounds of the printer) one now finds large piles of PDFs, which seem to act more as a comfort blanket than a desk-top reference library. Seeing these piles always reminds me of the story Sydney Brenner told of when he was director of the Molecular Biology Laboratory and wanted to photocopy an article after-hours. A graduate student had commandeered the sole photocopier and was copying multiple articles from a large pile of journals. Watching this for some minutes, Sydney could stand it no more and interrupted the student (who apparently had no idea to whom he was talking):

"Why don't you try neuroxing the articles instead of xeroxing them?"

"What is neuroxing?", the student asked, innocently.

"Well," said Sydney, "you open the journal and you scan the pages one after another with your eyes."

The ingenuity of psychology's system of short loans of critical readings also meant that the lecturers could include on our reading list otherwise-obscure or hard-to-obtain articles. In this way, I read Sigmund Freud's investigations of the histology of the nervous system where his embryonic ideas about excitation and inhibition began to be formed, and discovered German physiological psychologists like Willem Wundt, Hermann von Helmholtz, and Hermann Ebbinghaus through translations. It was the beginning of my long relationship with libraries, now a lost pleasure for most. Our reading is now corrupted by the predictive capitalism of websites with their siren call—"if you like that, you'll like this"—whereas in a library, there is always the serendipity of a book title catching your eye, or accidentally getting absorbed in a journal article whose topic is at oblique angles to the one you were intending to read. While we have acquired instant access to the world's libraries, the traps set by clickbait are too tempting, and so the accidental encounters are greatly diminished if not lost.

During my second year I met Fred Roux, a PhD student in the Department of Civil Engineering who was studying the properties of concrete at elevated temperatures to see whether it could be used for the secondary containment of nuclear reactors. He was funded by the Atomic Energy Commission and sought an assistant to help him with data analyses, and who better than I to calculate Young's modulus, plot stress-strain diagrams, and make the coffee? Fred lodged with the Hofmeyr family, and through Billy and Ursula Hofmeyr, I got to meet some of the leading artists and musicians in South Africa and, *inter alia*, learn about fine wines—something that never appeared on our Baptist table. Now with an additional income from Fred, I could contemplate buying small artworks on paper and began to frequent the gallery of Joe Wolpe, whose fine eye, prodigious memory, and a gentle humor was a delight. The first painting I ever bought was from another friend of the Hofmeyr's, Paul du Toit, the former pupil of Jean Welz, an Austrian émigré artist who happened to live around the corner from us and later drew my portrait. After Paul du Toit's early death, I wrote his biography, which was beautifully produced by the Fernwood Press.

The Department of Civil Engineering became my second home, for next door to Fred's concrete blocks, ovens, and testing machines was the Water Resources Laboratory, run by the formidable Professor Gerrit van Rooyen Marais. He needed someone to make figures for his reports and publications. I made myself available and was introduced to the "Leroy Lettering Instrument," Rotring pens, and many variants of stencils and French curves. Professor Marais showed me how to use a form of graphical statistics called probability paper, which I later adopted for analyzing data for my final year psychology thesis on time perception.

Without the medical students, my final-year physiology course had shrunk to a dozen or so students. The course material was top-heavy with biochemistry that required many metabolic pathways to be learned, which I found a chore, but the practicals were more interesting, having moved into the electronic age. We were taught how to use an oscilloscope, how to make pipettes to record intracellularly from the isolated heart, how to do calculations with an analogue computer, and how to measure sodium transport across frog's skin using an Ussing chamber. We also had to give two seminars on set topics in front of the faculty. I got the short straw as my first seminar was on sodium transport. I set off boldly, but was brought up short by Leon Isaacson when I cited an experiment in which they had used red blood cell ghosts: "What are red blood cell ghosts?" Leon inquired. I had to confess I had not the ghost of an idea and fell silent in acute embarrassment while Leon explained what they were. It was the best lesson ever to never stand up in front of an audience without thorough preparation and understanding of what I was talking about.

As final-year psychology students, we had a series of lectures from the head of department, Professor W. D. Radloff, for the first time. He would bring into the class a box file of reprints, which he would rifle through, pull out one that caught his attention, and give us a brief synopsis of its contents, and then go on to find another. One morning he pulled out a review published in *Nature* in 1972, with title "The Visual System and Neuronal Specificity" by R. M. Gaze and M. J. Keating. It was a critical review of Roger Sperry's "chemoaffinity hypothesis," and it concluded with the statement that there was much confusion in the field, not helped by ill-defined terms and ambiguity of the meanings of descriptions like "order," "randomness," and "specificity." Scientifically and philosophically it sounded intriguing, and the paper stuck in my mind. Little did I then know that five years later I would be sitting in a small room in Oxford defending my DPhil thesis against a sustained critique by my external examiner, the same Mike Keating.

Engineering and Electrodes

In the long vacation Professor Marais gave me a job, and so I was introduced to the kinetics of waste-water treatment in the activated sludge system. The lab was a large temperature-controlled space with rows of benches for chemical testing, side rooms with chemicals, ovens and fine balances, a cold room for storing raw sewage brought in a tanker from a local plant, and a mezzanine of small offices for the master's and PhD students, each of whom ran a lab-scale treatment plant. Taliep Lakay, the multitalented master-technician, who knew how to do everything, as well as the washing-up, taught me the battery of chemical tests used. He had pinned up a gallery of quotes he overheard from the professor: "Think until your head gets hurt," "Write it over and over until you get it right." Stalking the lab, chewing on an unlit pipe, was Professor Marais himself, who was merciless with any student he thought was not paying full attention to their experiment, like not maintaining their pumps, properly adjusting the aeration levels, or cleaning the settling tanks. A red rag was for the student to announce they couldn't be there on an evening or weekend because they were seeing their significant other or family. I soon realized that his insistence on undivided attention to the experiment in progress had a point, because the treatment plants took some weeks to reach steady-state and any shutdown meant time was lost in getting them back to steady-state. I later distilled this notion into the mantra for my own students during experiments: "constant vigilance." One day I had finished all my analyses early and was heading for the door. Professor Marais spotted me and called me back:

"Where are you going?"

"I've finished all my analyses for today," said I.

"Well go back and look at your apparatus and think harder about your experiment—if you walk out of the door you will not be thinking about your experiment at all!"

It was no nine-to-five environment: Professor Marais was first in and last to leave and expected us to follow his example.

I wanted to do a fourth honors year in ethics and physiology. Unfortunately, Archie Sloan insisted that the honors program in physiology was so demanding that there was no possibility of my completing a double honors—this despite the fact that I had just managed to graduate with a BSc degree in three major subjects. For my project, I decided to record from neurons in the preoptic area of the hypothalamus, which was an area of interest to my supervisor, the endocrinologist, Cyril Beardwood. The problem was that no-one knew how to make single-unit unit recordings. Fast-forward three months and after many failed attempts to record with insulated insect pins, I discovered an abstract by David Hubel (see Volume 1) with his recipe for a varnished tungsten electrode. Another month went by before I figured out how to straighten a coil of tungsten wire, etch it, and insulate it. Eventually, I recorded a fair number of stable single units. The real lesson learned, however, was never to reinvent the wheel—if someone already knew how to do something, go and learn it from them.

In the Civil Engineering Department, my career as a draughtsman flourished. The head of department, Professor John D. Martin, was writing a theoretical work for MIT Press, titled *Plasticity*, and he needed someone to draw the figures. He would give me a sheaf of pencil sketches of what he wanted, and it was my job to turn them into an annotated pen-and-ink drawing of publication quality. I never got to see the published tome until decades later and the wonder was that I had found the time to do so many drawings.

Sir Bryan Matthews—inventor of the oscillograph, differential amplifier, and other physiological instruments, and rare collaborator of E. D. Adrian—visited South Africa in 1974 as part of a Royal Society-British Council educational tour. His lecture in the Physiology Department included a demonstration of the activity of a muscle endplate, which he recorded from himself with an electrode fashioned from a hypodermic needle. Seeing an action potential firing under conscious control made a huge impact on me. In the lab, he tried to show us honors students how to record from the optic tectum of a frog, but our pipettes were inadequate. The most significant part of his visit, however, was giving me advice about which neurophysiologist I might approach in England about the possibility of doing a doctorate. He suggested I write to Professor Charles Phillips, a distinguished motor cortex physiologist in Oxford. I duly posted off a hand-written blue aerogramme and waited. Some weeks later I had a reply: Professor Phillips had recently been appointed head of the Department of Human Anatomy following the untimely death of Geoffrey Harris, discoverer of the portal system of the hypothalamus, which delivers releasing factors to the anterior pituitary. Although he was not in a position to take on a student, he had asked around the department and had found that someone called Tim Horder might be interested. In those pre-internet days, there was not much I could discover in the library about what research topic Tim actually pursued. Still, I wrote to him explaining that I was particularly interested in the work of Gaze and Keating on the retinotectal system and Sperry's theory of chemospecificity. It was a bull's-eye, for Mike Gaze had been Tim's PhD supervisor at Edinburgh University. A slow exchange of blue aerogrammes followed about my science, my unusual academic trajectory, funding, and choice of college. Tim typed all his letters, but was obviously not a touch typist as the letters bounced up and down and there were many *xxxx* crossings-out.

Mastering Wastewater

With the increasing likelihood that I could go to Oxford, whose term started in October, I needed to save some money to supplement the small bursary I had been awarded from UCT for postgraduate study. I asked Professor Marais if he had a lab job for me for nine months after I finished my BSc (Honors) in December. He made the unexpected suggestion that I enroll for a master's degree in civil engineering. Thus, in addition to the long days running my experiments on the biological removal of phosphorus from wastewater, which was a new topic in the lab, I found myself sitting with card-carrying civil engineers in night courses in aquatic chemistry, kinetic modeling, and plant design. I already knew how do the chemical analyses and maintain the reactors, so I was quickly up and running, but the theory was a longer haul and I needed a lot of handholding from one of the PhD students, George Ekama. Professor Marais's kinetic equations showed that only a small amount of phosphorus was removed by the practice of routinely extracting a fixed fraction of the liquor in order to maintain a constant "sludge age." The fraction of phosphorus taken up by the active organisms could be significantly increased, however, by subjecting the sludge to a short anoxic phase, which could evoke something called "luxury uptake" of phosphorus—that is, uptake more than is needed for building cells. I realized that Professor Marais's kinetic equations predicted that under luxury uptake significant amounts of phosphorus would be removed if the sludge age was kept sufficiently short. When I took my reasoning to him, I expected the worst, but he saw the significance immediately, and we devised a series of experiments to test the quantitative predictions.

Six months later, and a lot of intensive work, a good fit of experimental data to the theoretical curve had emerged. It was my first experience of having a significant insight and testing it experimentally—hugely encouraging. By then I was reasonably experienced at writing up experiments and, unlike Professor Marais, who was an Afrikaner, my mother tongue was English. I gave him the first draft of my research report. Some days later, he stalked in to the lab and gave me my typescript back without any annotations or corrections, and simply said, "write it over." I was livid, but I had forgotten that he was an avid reader of English prose and poetry, and that the essayist, Lord Macaulay was one of his favorite authors. Indeed, Professor Marais wrote succinct and limpid prose, and no one could set out the derivation of an equation more elegantly than he. Some 15 drafts later, we called it quits. My study was preliminary, and there were years of theory and experiments by others ahead, but what my work had done was to embed the problem of phosphorus removal in the familiar kinetic language of the lab so that what could be predicted and what had to be measured was defined. Much later, I discovered the Zen concept of *Shoshin* (the beginner's mind), in which there are many possibilities, unlike the expert's mind, in which there are few. A beginner's mind certainly applied to mine. The rare opportunity I had been given was to plant the seed for what became a major research area of the lab.

The Dreaming Spires

I wrote my theory exams, submitted my thesis, and left for Oxford in September 1975 with one suitcase, my guitar, and clutching a blue aerogramme from Tim Horder saying he had accepted me as a DPhil student.

Tim's unconventional typing style made for an interesting conversation with the U.K. immigration officer, who reluctantly let me in, but with the injunction to register immediately at the Oxford police station. Out of the train window, I caught my first glimpse of the dreaming spires of Oxford, which was to be my home for the next two decades.

Tim had secured a place for me at a new graduate college, Wolfson College. Its founding principal, Sir Isaiah Berlin, had decreed that it would not follow the traditional college hierarchy of Junior (undergraduate), Middle (graduate), and Senior (Fellow) Common Rooms and it would have no "high table" for Fellows in the dining hall, and would be mixed, with families in residence. This was an ideal choice for me as I had not the faintest clue of the subtle mores of Oxbridge college life. Even then, the competitive nature of the intellectual conversations in the Wolfson common room was like nothing I had ever experienced, and it had a strange psychological consequence: after about six months I realized that people were finishing my sentences, so tentative had I become about uttering anything. But, understanding that most of these graduates had been training in this clever repartee for years, I consciously remedied my speech impediment. What was most exciting was to go to lectures by people whose work I had studied, particularly the philosophers, like Gilbert Ryle and Peter Strawson, and to repair my deficient knowledge of classic films through the Oxford University Film Club. At the end of the year, good news arrived from Cape Town: I had been awarded an MSc in civil engineering *cum laude*. I felt an imposter, but because I was on another track, no card-carrying engineer need be too offended.

My work pattern also had to adapt to Oxford life. In the first weeks, I would arrive too early at the Department of Human Anatomy and have to wait for someone to unlock the front door. Unlike Professor Marais, Tim did not stalk the lab or berate his students. Instead, he would appear at random intervals, have a quick chat, and then rapidly disappear again to the library or to his heavy tutorial load in Jesus College. He was a decided iconoclast, which made for interesting conversations on embryology and pattern formation, about which I knew nothing. Tim spent one afternoon initiating me into the techniques of anesthetizing a goldfish, preparing it for recording from the optic tectum, and mapping multiunit receptive fields using an Aimark perimeter he had loaned from the University Laboratory of Physiology where he had been a Demonstrator. Being able to wave a wand around in the visual field and find the small area where the neurons responded is a wonder that has never left me. The electrodes and amplifiers Tim used were decidedly primitive, even compared to what I had used in Cape Town, so as soon as I acquired a license from the Home Office to do animal experiments on my own, I asked Professor Phillips if he had any more modern equipment to spare, whereupon he lent me one of his valve cathode followers, powered by a 110-volt battery, and some Tektronix valve

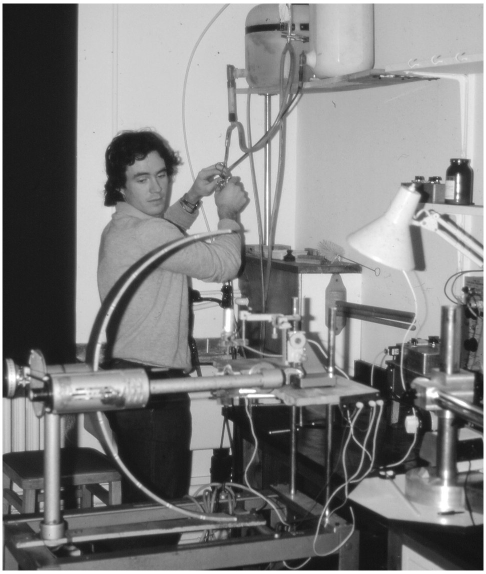


Figure 1. Preparing to map the optic tectum of an anesthetized goldfish using an Aimark perimeter. Photo credit: Stuart M. Bunt.

amplifiers. Not quite solid-state technology, but nonetheless, it all worked flawlessly. I also secured three glass-insulated tungsten electrodes from Alan Ainsworth, Colin Blakemore's technician in Cambridge. They were top-of-the-range and I managed to make them last the entire two years of my DPhil experiments. I had two projects, the first was to extend Mike Gaze's work on the plasticity of retinotectal connections, the second was to explore further the phenomena first observed by Mike Keating that binocular receptive fields on the optic tectum of frogs remained congruent throughout post-metamorphic development despite large shifts in the relative positions of the two eyes.

Anatomical Matters

As I was in the Department of Human Anatomy, I thought it would be a good opportunity to learn some human neuroanatomy, so I asked the Reader who ran the class, Tom Powell, if I could watch the medical students' dissections.

"Oh," he said. "I'm short of a Demonstrator, would you be interested?" Of course, I would! Every week, I took my *Cunningham's Manual of Practical Anatomy* and sat down with a fixed brain and learned how to do the week's dissection. Having crammed the necessary knowledge, I thought I was sufficiently well-prepared for the class, but I had not anticipated the cleverness of the Oxford medical student, who needed no dissection guide, just a gesture in the direction of which part of the brain to cut into very small pieces. Ten minutes into a three-hour class, I would be called over to a group clustered at a dissection table, given a handful of brain fragments and interrogated:

"Where is the fifth nerve nucleus?"

"Show us the corticobulbar tract."

I would then have to reconstruct the three-dimensional (3D) jigsaw, not always possible, and resection the assemblage along the textbook dissection planes hoping there was still something left to see. I had not the confidence to tick them off, or the 3D knowledge to identify structures from odd planes of section, so it was all acutely embarrassing. I did learn neuroanatomy, however.

Tom Powell had a reputation for not suffering fools gladly, but he made an exception in my case and allowed me to use his histology facilities for my anatomical studies. His technician, Ron Brooks, taught me the newly introduced method of horseradish peroxidase (HRP) for tracing fibers from tectum to retina and to use tritiated proline to trace projections from retina to tectum. Powell's group always took their "elevenses" in the lab, so while they drank tea, I cut and reacted sections and had free tutorials on the work they were doing on the macaque brain. Tom Powell is best known for his studies with Vernon Mountcastle on the columnar organization of the somatosensory cortex in the cat and monkey and of promoting the idea of the uniformity of the neocortex, but he made significant contributions to all the major systems of the brain. He was mentor to a stellar list of medically qualified doctoral students and postdoctoral colleagues, one of whom was Ted Jones—certainly the most scholarly and erudite neuroscientist I ever met. Many years later, I started some physiology experiments with Ted at UC Irvine, but the first Gulf War burst upon the TV screens, and we found it too distracting to continue.

In Tim's lab, I was analyzing the phenomenon of "compression" in the retinotectal system of goldfish. The entire visual field of one eye is represented on the optic tectum and Mike Gaze and colleagues had shown that following removal of half the tectum, a complete retinal representation would reform on the remaining half, whether or not the optic nerve was cut. If the nerve was left intact, they occasionally found that the original projection did not compress and that the regenerating projection then formed an orderly map on the same piece of tectum, with the result that one location in the tectum received input from two quite different locations of the retina. I discovered how to induce "duplication" reliably and then found that, in a minority of cases, the duplicate projection was reversed in polarity compared with the remaining intact projection. This had never been seen and it led to another series of experiments to show that the ordering across the mediolateral axis could similarly be reversed reliably. I presented preliminary results on the duplication and polarity reversal at a meeting of the Society for Experimental Biology. The raw data seemed too complicated to show in a short talk, so I made schematics of the essential results, which may have sufficed for the non-cognoscenti, but unfortunately for me, Mike Gaze was in the audience. His comment was cutting: “Might have been interesting, but I needed to see the data.” Point taken!

On a visit to Mike Keating and Mike Gaze at the Medical Research Council’s National Institute of Medical Research at Mill Hill, I met the theorist David Willshaw, who was doing a master’s degree with Mike Gaze. David had already produced some important results from models of pattern formation with Martin Prestige in Edinburgh and later with Christoph von der Malsburg in Göttingen. Our paths were to cross many times over the next decades. I also met Chris Kennard, a medical doctor who was doing his PhD with Mike Keating, and later, as a distinguished neurologist, gave me critical support when my father was diagnosed with an acoustic neuroma.

Reading and Writing

Tim’s favorite medium of publication was the *Proceedings of the Physiological Society*, which were the abstract of talks given at the Physiological Society meetings and refereed by those present. The author order on Physiological Society publications was then alphabetical. Philosophically and morally, this seemed right to me and it removed all the jostling and elbowing for positions in the list of authors. All publications from my lab followed this alphabetical ordering, regardless of journal. We had interesting discussions over the years about this policy and its alternatives, but there was never great resistance to it. It was impossible in our team-style of working to define exactly who first thought what and who did what, as many journals now insist. The present absurdity of identifying several “first authors” and a similar slew of “senior authors,” with the “also-helped” authors sandwiched between, was avoided. I made it a practice not to include my name on an experimental paper simply because I had suggested the experiment, but had not made any significant practical contribution.

Tim had been invited to take part in a Society for Experimental Biology symposium, and the lectures were to be published in a book. He asked me to help with his chapter. I agreed, but what I had not properly understood was that he had no intention of publishing his lecture. Instead, Tim intended to review every publication ever published on fiber ordering in the vertebrate visual system. I spent countless hours in the Radcliffe Science library and the Bodleian library reading obscure journals, as well as sifting through mountains of reprints left by Sir LeGros Clarke in the department’s library. The pithy title of our chapter said it all: “Morphogenetics as an Alternative to Chemospecificity in the Formation of Nerve Connections: A Review of the

Literature before 1978, Concerning the Control of Growth of Regenerating Optic Nerve Fibres to Specific Locations in the Optic Tectum and a New Interpretation Based on Contact Guidance." Professor Marais would have been envious of the number of drafts it went through, but at least it gave me a comprehensive knowledge of the literature and gave grateful retinotectal researchers easy access to obscure observations. Perhaps this experience is the source of my frequent despair at the lack of scholarship evident in so many contemporary publications, even reviews. Our claim that the ordering of fibers emerging from the retina mattered to their final destination prompted a number of prominent investigators—David Hubel and Otto Creutzfeldt included—to investigate the retinotopic ordering of fibers in the cat's optic nerve and tract. For me, it was a close encounter with an iconoclastic and perfectionist mind.

One benefit of my new knowledge was that Tim now let me tutor some of his students. I had little idea of what an Oxford tutorial was, but Tim explained that it involved the student reading set texts, writing an essay, and then discussing it, or "reading it," during an hour-long one-on-one tutorial. Again, I had not reckoned with the cleverness of Oxford students, for one of my first tutees was someone called Mike Fischer, who had already graduated in physics and was taking a second bachelor's degree in physiology. To describe our tutorials as "lively" is an understatement, for as experienced tutee, Mike easily anticipated all the twists and turns of my critiques of his essays and taught me more than I gave him, but it was a great experience for me.

In my third year I became 'Captain of Men's Boats' at Wolfson College and captain of the Oxford University Men's Gymnastics Team. The rowing, coxing, and coaching commitments meant that six days a week my early mornings were spent on the river—and there was that thesis to write.

The Waynflete Professor

It was time to think of where I was heading next. I wanted to continue research on the visual system, but I knew I did not want to continue working on retinotectal development and plasticity, which now needed a much more cellular-molecular approach to determine the mechanisms underlying the phenomena I had been observing. A solution was close at hand: Tim had heard that the Waynflete Professor of Physiology and head of the University Laboratory of Physiology was looking for someone to replace his postdoc, Peter Clarke, who was leaving to take up a position at the University of Lausanne. I put up my hand and was invited for an interview. It was memorable. In his vast office, I was introduced to Professor David Whitteridge, who sat in an armchair, with stockinged and sandaled feet, and proceeded with an interrogation. In addition to Tim's recommendation, I had three pluses to offer: I was from a former British Colony, I knew a huge amount about a subject dear to his heart (retinotopic maps), and as a boy, I had made a crystal radio and knew what a "cat's whisker" was and did. I got the gig. We worked together until his death 17 years later. He was the most gracious scientist I ever met, and although I wrote three different obituaries when he died, I still felt I had not given an adequate account of his life.

David Whitteridge was universally called "DW" or "Prof," even by his wife Gweneth, who was a medical historian and an expert on William Harvey, discoverer of the circulation of the blood. Prof was a product of Oxford's Medical School and had been Sir Charles Sherrington's last Demonstrator. He did his BSc (now MSc) with Jack Eccles on transmission through the ciliary ganglion, work he published in the *Journal of Physiology* in 1937. For a meeting of the Physiological Society, he renovated and demonstrated some of Sherrington's original apparatus and later wrote a *Trends in Neuroscience* article about it. I served as a subject for an experiment using Sherrington's original flicker-fusion apparatus, which Prof had resurrected. Prof was at the frontline when Jack Eccles and Henry Dale were locking horns about the nature of synaptic transmission. According to Prof, who was then an undergraduate, Sherrington told them he thought that Dale was right and synaptic transmission was chemical, not electrical, as Eccles supposed. They rushed to tell Eccles, who riposted, "The Old Man hasn't seen my latest results." By the time Prof introduced me to his erstwhile supervisor, Eccles was an old man himself, and a grand one. I had been hoping to discuss his work with Karl Popper on consciousness, but had to content myself with listening.

During World War II, Prof did research on paraplegics at Stoke Mandeville Hospital with Sir Ludwig Guttman, who pioneered paraplegic sports, which eventually became the hugely successful Paralympic Games. Together, they discovered autonomic dysreflexia, which affected the control systems for blood pressure and temperature. After the Bhopal disaster in 1984, when due to human error, poisonous gas escaped from a chemical plant, he resumed his collaboration with Autor Singh Paintal in Delhi to study the mechanism of phosgene gas poisoning, which they had last investigated in the 1950s in Edinburgh.

Although Prof was reputed to have a "high IQ and low pH," I soon discovered that he had a wicked sense of humor, a compendious knowledge of physiology, and an unlimited fund of stories about scientists, especially Sherrington. His own papers were characterized by one or two elegant summary figures and a polyglot authorship. His mother was French, so he delighted in translating key passages of Ramón y Cajals's *Histologie de Systeme Nerveaux* for us. When Peter Clarke, a devout Christian, asked Prof for advice about how he might learn French, he twinkled, "On the pillow, dear boy, on the pillow." Peter took his advice to heart and when he arrived in Lausanne, he married Stephanie, a cognitive neuroscientist from the

French-speaking part of Switzerland. Whenever Prof launched into a story with a visitor, he would often preface it with, "Kevan has probably heard this one already," but I rarely had. His best-known work on vision was with Peter Daniel of the topographic representation of primate area 17. Over five summers, they mapped the entire cortex of different old-world species and using the metric they called the "magnification factor," they developed a mathematical model that accurately predicted the 3D shape of the monkey's area 17. That the physical shape of the neocortex might be determined by the constraints of a representation of a peripheral organ was a completely novel concept, and their example remains unique.

When I joined his lab, Prof was working on the development and plasticity of binocular vision in sheep, which he chose because the precocial lambs could avoid a visual cliff on their day of birth and thus were an excellent choice for exploring questions of nature or nurture. He had a long history of working with sheep, with classic studies on eye muscle spindles with Peter Daniel and Sybil Cooper. His lab was huge—and needed to be to accommodate a lifetime's collection of antique electrophysiology equipment, along with plastic and latex rubber models of the visual cortex of cats and primate, which were frequently pulled out for impromptu tutorials. He believed that building one's own apparatus was "good for the soul and reduced the number of reported artifacts." I had to learn how to operate a series of "Jock Boxes," which were bespoke interfacing instruments designed and made by W. T. S. "Jock" Austin, Prof's erstwhile technician in Edinburgh. Calibrating blood pressure manometers and CO_2 machines was a major pre-experiment activity, as was grinding the seats of metal catheter taps using jeweler's rouge. Prof loved doing experiments and was first at the operating table when venous and arterial cannulations and tracheostomies were needed, whistling tunelessly when things were not going smoothly. His maxim: "the only thing certain in an experiment is that long pieces of tubing will be cut in to shorter pieces" was practiced diligently. He admonished clumsy experimenters (i.e., me) who caused voltage transients by touching forceps to the stereotaxic apparatus, saying, "that would have broken a galvanometer string," but when I innocently asked how many strings he had broken, he guffawed: "I'm not that old!"

Another new arrival in the lab was Henry Kennedy, who was taking a sabbatical year from an institute of the National Institute of Health and Medical Research (*Institut national de la santé et de la recherche médicale;* INSERM) at Bron, near Lyon. Henry shared with Prof the descent of a French mother and an English father. He was then collaborating with Guy Orban in Leuven and Jean Bullier in Bron, both of whom had learned their trade in Peter Bishop's (see Volume 1) department in Australia and had adopted Geoff Henry's methods and nomenclature for mapping and classifying cortical receptive fields. Our introduction got off to a bad start when Henry, an ardent devotee of traditional English pubs, suggested we meet in the King's Arm to discuss what we might do together. I replied that I never went to pubs. He has never forgotten the rebuff.

Ungulate Investigations

Prof had recently published a *Nature* paper with Peter Clarke and V. S. Ramachandran, reporting that neurons with binocular receptive field disparities were present in newborn lambs. Henry and I decided to do a more in-depth analysis of the development of receptive fields in sheep. We found that while most neurons were orientation-tuned in the newborn, other features like direction selectivity and end-inhibition were absent. Of most interest were the so-called obligate binocular cells, which would respond only to binocular simulation over a narrow range of binocular disparity. These were absent in the newborn, but constituted 15 percent of the neurons we encountered in the adult. One particular neuron lives on in memory: we were recording from a 70 kilogram adult sheep and encountered a neuron I could not drive. Henry decided that by hook-or-by-crook he would map its receptive field. He lit a cigarette, sat down at the tangent screen, and over the next 40 minutes gave me a master class in hand-plotting receptive fields. The receptive field he painstakingly teased out was not only obligate binocular cell, requiring a precise binocular alignment of the eyes, but the receptive field was tiny, strongly end-inhibited, and completely directional. We had encountered nothing remotely like it in the newborn, whose circuits seemed to lack all adult mechanisms for facilitating or inhibiting a response.

We also defined the critical period for ocular dominance plasticity by monocular deprivation and explored various methods for reversing the shift in dominance. Fergus Campbell at that time was promoting a therapy to reverse amblyopia in children, which involved exposing the amblyopic eye to rotating gratings. Ramachandran persuaded Prof to try it on monocularly deprived lambs and Fergus came to see one of the experiments. Prof enthusiastically explained the experimental setup as Henry and I were mapping a receptive field. We always measured blood pressure with an arterial catheter, which occasionally blocked. Seeing the telltale loss of a pulse amplitude on the blood pressure meter, Prof picked up a large syringe, thinking it was filled with saline, and injected the contents into the artery. The syringe was filled with air. The blood pressure dropped to zero and the cell stopped responding. Henry and I looked balefully at an embarrassed Prof. Then before our eyes, the blood pressure slowly started increasing until it was back to normal, and the cell responded again. Prof smiled triumphantly at Fergus as if he had intended this demonstration of the robustness of the experimental sheep all along.

My first opportunity to attend an international meeting came at the end of my first year as a postdoc. The meeting, "The Developmental Neurobiology of Vision," was organized by Ralph Freeman and Wolf Singer (see Volume 9) and took place in Crete in 1978. It was a unique opportunity for me as a neophyte to meet the gods of vision. The retinotectal system was well-represented with luminaries like Steve Easter, Pamela Johns, Barbara Finlay, and Scott Fraser, but for me, it was a golden opportunity to put names to faces and talk to many visual system experts, including Horace Barlow, David Hubel, Pasko Rakic (see Volume 12), and Colin Blakemore. In retrospect, the most significant person for my future was Murray Sherman (see Volume 10), who had begun using HRP to label intracellularly physiologically-identified neurons in the thalamus. Alan Brown in Edinburgh was using the same technique to great effect in mapping sensory afferents and motoneurons in the cat's spinal cord, work that had greatly impressed Prof and me.

Retiring Research

Two years into my postdoc, Prof retired. We had discussed our options, and because Prof was keen to continue research, we decided to link up structure and function in the visual cortex using the intracellular-HRP technique. His aphorism, "physiology is anatomy plus thought," was to take a new turn. In the tradition of Oxford, the retiring head moved out of his department. Prof's colleague at Magdalen College, Larry Weiskrantz, offered him space in his Department of Experimental Psychology. After the cavernous space of the Waynflete Professor's office, we now shared a tiny office with no view, but it was on the same corridor as Larry, Alan Cowey (see Volume 5), Dick Passingham, and Edmund Rolls. A framed photograph of Dorothy Hodgkin, the crystallographer, reminded us she had worked on the same corridor. I had studied Jerome Bruner's and Michael Argyle's work in Cape Town, and here they were in the flesh. Under the same roof was the Zoology Department, where Richard Dawkins unselfishly showed me his simulations of artificial life on an early desktop computer. Experimental Psychology had no common room, so the department members gathered in a large communal hallway at elevenses to buy tea and donuts at a serving hatch. Larry was always present for informal discussions—it felt like a very democratic and open system—and the most convenient way to get business done with Larry.

The Medical Research Council (MRC) gave us a one-year grant to see if we could get the new technique up and running. We were now on probation, and I urgently needed to learn how to do intracellular recording *in vivo*. Alan Brown's technique was specialized for the spinal cord, so not readily adapted to neocortex. While we were mulling this over, a bolt from the blue arrived in the form of a *Nature* paper from Charles Gilbert and Torsten Wiesel entitled, "Morphology and Intracortical Projections of Functionally Characterised Neurons in the Cat Visual Cortex." It was not much different from the title of the grant application we had just submitted to the MRC.

Prof immediately wrote to Torsten, whom he knew, to ask if his postdoc could visit his lab to learn the technique. A polite letter of refusal came back, citing time limitations and raising the issue of competition. This left Murray Sherman, then in the middle of a move from the University of Virginia to The State University of New York at Stony Brook. I wrote to him and he generously said, "yes."

This was my first visit to the United States, and I flew to San Francisco to visit Ken Brown (Torsten Wiesel's erstwhile colleague) and Dale Flaming, to see the pullers and bevellers they had developed for their intracellular retinal work. I also visited Harvard Neurobiology, where there was much going on of interest to me besides Charles and Torsten's work, which remained behind closed doors. While there I gave one of their "brown bag" lunchtime talks on our sheep work. After my talk, a small man came up to me and asked many questions—indeed, apart from Prof and David Attenborough, I never met someone so interested in the sheep's visual system. Only later I discovered I had been talking to Steve Kuffler. David Ferster and Simon LeVay had been labeling thalamic afferents extracellularly with HRP so I had a chance to see their spectacular histology. Jonathon Horton was using HRP to look at fiber-ordering in the visual pathway, which was still a keen interest of mine. Then, wandering down the corridor was David Hubel holding up to the light a cytochrome oxidase-stained tangential section of macaque V1 and showing me the leopard spots that were visible to the naked eye. The discovery of the cytochrome blob system by Margaret Wong-Riley became a major research avenue for David, and led to a series of papers with Marge Livingstone (see Volume 9) on the physiology and anatomy of the cytochrome system, and a series of psychophysical experiments in which they tried to tie their discoveries of multiple parallel pathways to behavior. My own thoughts about their ambitious multilevel investigation were expressed in a *Trends in Neuroscience* article: "From Enzymes to Perception: A Bridge too Far?" The main subjects responded with an enthusiastic letter; Semir Zeki was less happy with it, as he felt they had stolen his thunder and needed no more column inches from me. Much later Geoffrey North asked me to write David Hubel's obituary for *Current Biology*, but despite being allowed extra pages, I still felt I had only given the sparest details of his extraordinarily rich contribution to science.

Juniors and Seniors

Oxford colleges have a system of competitive Junior Research Fellowships (JRFs). I applied for the Weir JRF at University College. I submitted my DPhil thesis and made it onto the short list. At the interview, I was ushered into a wood-paneled room lined with Fellows, with the Master, Lord Goodman, presiding from one corner. My examiner was Julian Jack, the renowned biophysicist and coauthor with Denis Noble and Dick Tsien (see Volume 11) of the classic, "Electric Current Flow in Excitable Cells." I imagined we would reprise my DPhil *viva* encounter with Mike Keating, but no, Julian decided to launch into a full-frontal attack on the ideas contained in the chapter on morphogenetics that I had coauthored with Tim. Deciding I had nothing to lose, I parried and thrusted back as best I could. I guess our performance was entertaining enough for the Fellows to elect me. At my first lunch in the Senior Common Room, a small elderly man limped up to ask if I would take on the job as the College's Junior Dean. My inquirer, I later discovered, was the Senior Fellow, David Cox, one of the great mountaineers of the interwar years and founder-member of the Oxford Night Climbers, who scaled college and town buildings under cover of darkness. His climbing career had sadly been cut short by polio. I said, "yes," having no idea of what a Junior Dean did. He introduced me to the Dean, David Bell, a volcanologist, who explained that I was now responsible for the discipline and welfare of the students. Since University College was known as "the Pub on the High Street," this was not welcome news. Fortunately for me, however, the combination of the sensitive hand of David Bell and the fact that the College had just admitted women undergraduates for the first time since its founding in 1249, which had a remarkably pacifying effect, made my apprenticeship as Junior Dean relatively incident-free.

The Senior Common Room seemed to be filled with philosophers. Peter Strawson, whose papers I had studied in my Logic and Metaphysics course, was an Emeritus Fellow, Gareth Evans would not let any loose thinking go unpunished, John Finnis was a Reader in legal philosophy, Ronald Dworkin held the chair of jurisprudence and was a relentless debater. In my first week, I found myself defending animal experiments to another eminent legal philosopher, Herbert Hart, who challenged me with the view of the utilitarian, Jeremy Bentham: "The question is not, can they reason? nor, can they talk? but, can they suffer?" I was getting a fast-track education in ethics. Through Herbert Hart, I met other giants like Sir Isiah Berlin and John Rawls, as well as Herbert's graduate student, Nicola Lacey, who later wrote a sensitive biography of Herbert. Dan Cunningham was the other medical Fellow along with Julian Jack. He was a respiratory physiologist who had the distinction of having had Roger Bannister and Edmund Hilary on his treadmill.

The Oxford Colleges rank their Fellows in order of seniority, with the longest serving fellows at the top and the recently appointed fellows at the bottom. This ranking determined which Fellow presided at dinner and said the grace. One vacation I found myself to be the sole Fellow at dinner, where unbeknownst to me, Stephen Hawking, an alumnus, had also signed in. Saying the Latin grace with Hawking listening was memorable. He was then still speaking with his own voice and fortunately on that occasion he was dining with colleagues who helped translate. Our later conversations were easier, if slower, when he used his famous speech synthesizer.

Experiments in Psychology

Murray Sherman's new lab in Stony Brook was being set up by Mike Friedlander, with help from Rick Lin, Jim Wilson, and Larry Stanford. Mike took me through the methods they were using for their lateral geniculate nucleus (LGN)—both the intracellular methods and the methods for classifying thalamic receptive fields. I began a long collaboration with Mike on development and plasticity of thalamic afferents when he moved to his first faculty job at the University of Alabama at Birmingham. Murray, too, was not only a generous host, but influential in my own thinking, particularly about parallel processing pathways in the visual system. His serial electron microscope (EM) reconstructions of the retinal afferents and their targets in the LGN were groundbreaking and also an encouragement for us to attempt a similar approach for cortical circuits.

Prof and I set up our lab in a tiny room next to the goods lift in the animal house on level F. This seemed a particularly inhospitable location for intracellular recording, so we improvised an isolated table by floating a solid steel lathe bed on pneumatic truck shock absorbers, which we inflated with a bicycle pump. It served for decades. I pulled pipettes on the classroom pipette puller back in Physiology and beveled them using the poor-man's beveler involving a thick slurry of alumina powder, a method developed by Tony Spindler for recording heart muscle in Denis Noble's lab. Marianne Dawkins in the next-door Department of Zoology, used pigeons for behavioral studies, so Prof decided we should start by intracellular recordings of the tiny cells in the pigeon's superior colliculus. So it was that our first HRP-labeled neuron was a pigeon's tectal neuron. We soon graduated to our familiar adult sheep, which were brought in from the university's farm

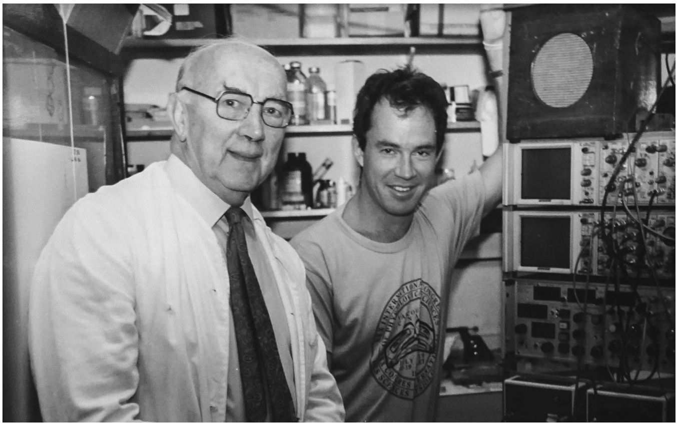


Figure 2. David Whitteridge ("Prof") and his postdoc in the Department of Experimental Psychology, Oxford. Photo credit: Rodney Douglas.

and temporarily housed on the roof. Stabilizing the brain was a formidable issue, but it was in the sheep's V1 that we obtained our first well-labeled pyramidal neurons.

We had passed the MRC's audition and wrote a three-year grant to explore the circuits of V1, but in the cat, not the sheep. Sherrington, Eccles, Kuffler, Phillips, Hubel, and Wiesel and many others had ensured that the cat had made the most significant contribution to neurophysiology of any species. Using another species for our study, like the sheep or mouse, inevitably meant the overhead of much derivative research. By selecting cat V1, the dangers of generalizing from highly specialized cortical areas, like rodent barrel cortex or primate area 17, could be avoided. Additionally, I wanted to add Jean Bullier and Geoff Henry's method of using electrical stimulation to identify the X- and Y-type inputs to visual cortex and the ordinal position of the cells in the cortex. Although Prof sniffed that electrical stimulation was something he'd left behind in the 1930s, he was persuaded, neither of us dreaming how significant the technique was to be.

We began with two experiments per week, with me doing all the preparation and post-processing in-between. Fortunately, we now had funding for a technician and we advertised the position. On our short-list was a Yorkshireman who had studied social anthropology at Oxford Polytechnic and, as employment for social anthropologists was proving elusive, he had taken a job as a forester in the local Wytham Wood. After our interviews, Prof expressed his strong preference for the forester, saying, "Well if he can cut trees into sections, he can surely cut brains into sections." With this inescapable logic John Anderson joined us in the small office and took over the post-processing in the histology section of the Department of Human Anatomy. What we had not uncovered in our interview was that in addition to fishing, which requires infinite patience, John also painted landscapes—he was an artist; much later on, he took to sculpturing in clay, and we worked together in the same pottery studio. I had been doing all the reconstructions of the neurons, and showed John what the main structure of neurons were and how to use the microscope and drawing tube. When he found a missed collateral from the axon of one of the cells I had drawn, I knew Prof had made the right choice. John's painstakingly meticulous work was an essential contribution to our research over the next four decades. His first efforts were displayed to the public in our comprehensive account of the structure and function of spiny neurons in the cat, published in the *Journal of Physiology*. His pen-and-ink drawings have appeared in touring science museum exhibits. His cumulative contribution to our understanding of the long-distance cortical circuits in primate cortex is unmatched and he more than deserved the belated reward of MSc and PhD degrees from the University of Zurich.

John's many hours at the microscope was taking its toll, however, and he began complaining of various discomforts and chronic pains, so some physiotherapy was clearly indicated. I knew of the F. M. Alexander

Technique, a method admired by Sherrington, which teaches awareness of one's body in order to move more efficiently and to improve poor posture, so acquiring a better "use of self," the term Alexander coined. I suggested to John he try a few lessons. He did, and it worked. In fact, it worked so well that both of us subsequently trained as teachers—John with Don Weed and me with David Gorman, both mavericks in the field. David Gorman handwrote and illustrated a brilliantly informative functional anatomy book, *The Body Moveable*, which became a ready reference. I later had the opportunity to work with two teachers who were trained by F. M. Alexander himself, Marjorie Barlow and Elizabeth Walker, and I invited Michael Frederick, the founder of the Alexander Technique International Congresses, to be our teacher-in-residence for a fortnight in exchange for organizing a series of plenary neuroscience talks for one of the Congresses.

Prof and I had soon discovered that there were no "low-hanging fruit" to be had in the form of simple structure-function correlations, despite hints in that direction from the Harvard investigators. Nonetheless, a far deeper analysis of the cortical circuits was now possible, not least because the HRP-filling revealed the neurons in an isolated splendor of detail that was breathtaking even to those familiar with Golgi-stained material. We now sought a collaborator to identify the targets of our labeled neurons, using electron microscopy (EM). Tom Powell demurred, believing the effort involved in looking at the axons using EM was too great. We then met Peter Somogyi, a protégé of Hungarian anatomist János Szentágothai, coauthor of *The Cerebellum as a Neuronal Machine* together with Jack Eccles and Masao Ito (see Volume 2). Peter was working on the basal ganglia with David Smith and Paul Bolam, but was eager to collaborate on cortex, particularly if the cells were smooth (inhibitory), so we began with cortical basket cells. I journeyed up to Alan Brown's lab in Edinburgh to reconstruct our best example using their new computer-aided microscope, a device known as the Joyce-Loeb Magiscan. State-of-art it may have been, but it was exceedingly laborious and it could not stitch the transverse sections together or easily correct for the 80 percent shrinkage in the z-dimension of the air-dried sections. It did give us, however, the first 3D picture of the large basket cell's dendrites and axonal arbor. The EM revealed that its major targets were dendrites and spines, not cell bodies as Ramón y Cajal had supposed with his *nids pericellulaire,* which Prof translated as "pericellular nests." It was a convincing demonstration that a combination of light-microscope and EM offered potentially huge gains and it became our standard procedure in the long march to understand the structural basis of cortical function.

Pub Proceedings

Leon Isaacson had been in touch, because one of his medical colleagues at UCT wanted to use his sabbatical to study the brain rather than the kidney, and was I interested? I said, "yes," and on a visit to Cape Town, Leon invited me to the "Foresters Arms" to meet Rodney Douglas—one of my rare forays into a pub! My first encounter with Rodney sparked, and indeed, I cannot recall us ever having a dull conversation. He immediately invited me to go sailing on the South Atlantic Ocean in the yacht that he and his father had built in their back garden. In the UCT lab, we initiated a project with Lauriston Kellaway to map the visual cortex of the indigenous rock hyrax (*Procavia capensis*, locally known as a "Dassie"), whose closest relative is the elephant. We made some successful experiments, but quickly ran out of adult animals when the local villagers in the area where the "Dassies" were caught, discovered that we had (inadvertently) provided them with a cache of fresh "bush meat."

Although by reputation a brilliant diagnostician, computers were Rodney's forte: in a shed on the Medical School campus he had set up the revolutionary Data General Eclipse minicomputer, which sported a generous 64 kilobytes of RAM. On arriving for his sabbatical in Oxford, he immediately embarked on a program of computerizing our physiological stimulus and data acquisition and building a microscope system for 3D reconstructions. Brian Baker, the electronics guru in Experimental Psychology, designed and built all the interfaces. My erstwhile tutorial "student," Mike Fischer, had founded Research Machines to build some of the earliest desktop computers for schools in the United Kingdom. He was hugely supportive and provided us not only with his RML 380Z, but also a series of programmers.

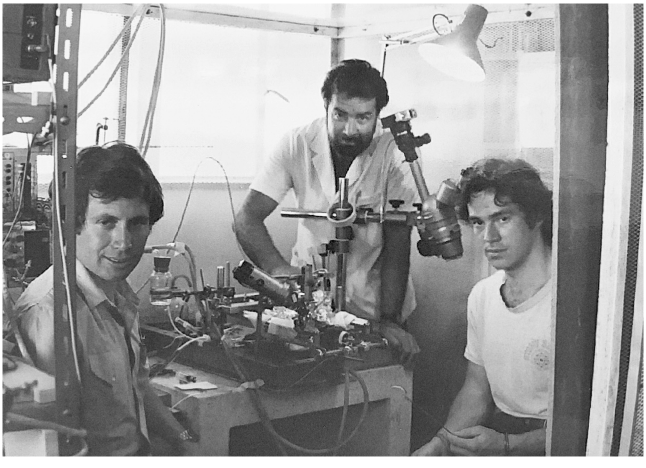


Figure 3. Mapping the visual cortex of *Procavia capensis* in the Department of Physiology at UCT with Rodney Douglas (left) and Lauriston Kellaway (middle). Photo credit: L. Kellaway.

The success of the collaboration with Peter Somogyi and his students, Tamás Freund (see Volume 11) and Zoltán Kisvárday, had not gone unnoticed and MRC decided to form a Unit to study the circuits of the neocortex and basal ganglia, headed by David Smith who was head of the Department of Pharmacology, which became our temporary home while a new MRC annex was built. We moved out of our happy home in Experimental Psychology to a tiny lab/office in Pharmacology. There was no room for John and his microscope and drawing board, so he had to camp in the passageway. Yet we started to expand. Charmaine Nelson came as an EM technician, Neil Berman arrived from Cape Town as a PhD student, Paul Gabbott came from the Open University as a postdoc, and we had sabbatical visitors like Christovam Diniz from Belem, Brazil; Colette Dehay, from Henry Kennedy's INSERM lab; and Clay Reid from Bob Shapley's lab at New York University. Larger than life in every way, Danie Botha arrived from Cape Town and the elegant 300 lines of Pascal he wrote for the 3D reconstruction system we called TRAKA served us well for decades. Rodney wrote a companion program, TRAKEM, to reconstruct serial EM sections, and this was expanded greatly by Albert Cardona and it had a second life as a key tool for connectomics.

John was tasked with making highly accurate TRAKA reconstructions of the dendritic trees of different types of cells. These seven cells, labeled

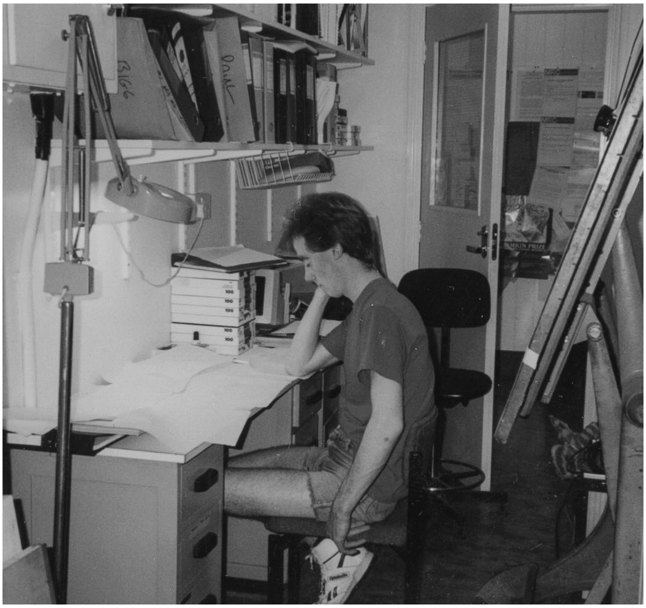


Figure 4. John C. Anderson in his passageway drafting room, Department of Pharmacology, Oxford. Photo credit: Kevan A. C. Martin.

J (for John) 1 to 7, became key datasets for biophysical modeling. Ironically, the first papers that used them were not ours, but from the labs of Terry Sejnowski and Christof Koch, so we were never cited. A layer 5 pyramidal cell, "J5," had a particularly stellar career, which was reviewed in a paper by Bartlett Mel entitled "J5 at Sweet 16." J-cells still keep popping up in various publications, with variable attributions.

Julian Jack was the principal player in another piece of theater that took place at one of the Oxford meetings of the Physiological Society. To a packed lecture hall, Rodney presented modeling work using J5 to estimate the amplitude of a unitary excitatory postsynaptic potential (epsp). The session was chaired by Peter Matthews, doyen of muscle spindles and son of Sir Bryan. There were a few straightforward questions after Rodney's 10-minute presentation and then Julian asked where we had got the conductance values from, as he doubted them. "From your book," replied Rodney, which evoked a ripple of amusement from the audience. Their reaction was unfortunate because Julian, embarrassed, now had to save face and tore in. Peter Matthews tried to moderate, but the 5 minutes allotted for questions quickly stretched to 15 as the Irresistible Force encountered the Immoveable Object. Since publication was dependent on the audience approving it, it was evident at one point that if Peter Matthews took it to a vote, we would lose. Prof, silent in the back row, left it to me to suggest modifications to the text. Julian eventually realized he might have over-reached, and backed off. We offered our compromise text and our *Proceedings* was voted through. That evening at the Society dinner, the Secretary reported on the day's meeting, noting that over years he had witnessed a regrettable and progressive decline in the quality of the debates in the sessions, but today he was glad to report that the old ways were not entirely lost. Reading our published *Proceedings* again today, our estimate turned out to be well in the range of those seen experimentally.

I reviewed our progress for an issue of the *Quarterly Journal of Experimental Physiology*. It was clear that our understanding of the machinery underlying cortical computation was still primitive and that analyses of receptive field properties and back-of-envelope models had long ago reached their limits. At the other end of the spectrum, most computational models were far removed from providing any explanation of the neural machinery we were seeing. David Marr's three levels of analysis—theory, algorithm, implementation—is still widely used as a throat-clearer in talks as it seems to many the logical route to discovery, but as Marr himself explained, an algorithm could be implemented in many different ways, so they offer no ready insights into how brain circuits are built or perform their operations. Whenever Tony Movshon was in my audience, he would tease me with his aphorism: "anatomy tells you what might be, physiology tells you what is," but the history of neuroscience begs to differ. Structure endures, physiological knowledge is highly technique- and concept-dependent (e.g., Eccles vs. Dale, or Hodgkin vs. Wald). Ramón y Cajal is still frequently cited, whereas his contemporary Sherrington is virtually forgotten. We were pursuing the "principles and technology of neural engineering," as Horace Barlow put it, and the yawning gap between the macrolevel theories and microlevel experimental data now begged for a bridging mesopic level of analysis to link a circuit level description to both the fine structure and the overall operation of the cortical circuit—and ultimately behavior.

Canonical Concerns

To probe the whole cortical circuit, Rodney, Prof and I took an alternative "engineering" approach and recorded the intracellular impulse response of identified cells to a brief electrical pulse delivered by stimulating electrodes placed in the optic tracts. To the intracellular electrode we glued an extracellular "piggy-back" multibarreled pipette so that we could deliver agonists and antagonist of the type a and b receptors for the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). By labeling the cells, we had exact information as to their morphology and laminar position. We found distinct differences in the time course of the inhibitory responses of superficial and deep layer pyramidal cells. Rodney developed a rate model to predict how the GABAa and GABAb receptors shaped the excitatory pulse response. This combination of experiment and simulation revealed three main features: the thalamic input was small, it was amplified by recurrent excitation, and the positive feedback of recurrent excitation was balanced by recurrent inhibition. It was clear from their elaborate local axons that pyramidal cells must connect mainly to other pyramidal cells, so the recurrent excitation was expected. But having grown up with Hubel and Wiesel's textbook models of "simple" and "complex" cells, we had not appreciated that the thalamic input was functionally so weak, and by identifying a role for recurrent excitation in amplifying the thalamic input we introduced a completely novel mechanism. That excitation and inhibition would wax and wane together seemed paradoxical, but in the presence of strong recurrent excitation, inhibition acted as a governor.

With Rodney's stimulus presentation and data-collection system now in full swing, we were doing two long experiments each week. For light relief, Rodney and I took it in turns to cook elaborate dinners for a dozen people every Saturday. Danie Botha was a fixture and took us on a tour through the winelands of Bordeaux with his highly researched purchases. On a visit to Oxford, David Hubel was a guest at one of these dinners and forever after reminded me of "the fish"—a whole salmon baked in puff pastry that we served up on that occasion. These delights and distractions were all to end with the return of Rodney to Cape Town to take up a senior lectureship in the Department of Physiology at UCT.

I went to Cape Town to write up our findings on the cat's cortex for Terry Sejnowski's new journal *Neural Computation*. Our paper was modestly titled, "A Canonical Circuit for Neocortex," taking a cue from Tom Powell's concept of the uniformity of neocortex. It was a significant synthesis, for our canonical circuit not only gave an immediate logic for components that Prof and I had identified, but it was also a short step to "canonical computations," which we proposed were composed of computational "primitives," like linear gain, nonlinear gain control, soft winner-take-all, and signal-restoration, all functions later realized in various models and in neuromorphic circuits. Although our term "canonical circuit" rapidly become common currency, it took longer to show that it could seamlessly link synapses to behavior. The cat's cortex was the ideal bridge between mouse and primates, and the canonical circuit even played a key role in Karl Friston's theory of dynamic causal modeling for human functional imaging.

Silicon Alley

After two years at UCT, Rodney decided to return to the MRC Unit as a non-tenured scientist. We had moved into an annex of the new Department of Pharmacology and had more space. John Anderson, at least, was no longer camping in a corridor. We had begun a collaboration with Christof Koch, who was then at the California Institute of Technology (Caltech). Rodney went to Pasadena for some months to work with Christof's students and while there he met Carver Mead, who had created critical tools for designing very large scale integrated (VLSI) circuits. Carver had also taught a course with Richard Feynman and John Hopfield on neural computation and had the insight that by using transistors in subthreshold mode, he could mimic the physics of nerve membranes and began designing analogue rather than digital VLSI circuits. With one of the few women at Caltech, the biology graduate Misha Mahowald, he created the first silicon retina in analogue VLSI (aVLSI), which was featured in a cover article in *Scientific American*. Rodney decided to see if an action potential could be realized in an aVLSI circuit and set to work with Misha, with Carver looking over their shoulders. They succeeded in designing and fabricating the Hodgkin-Huxley action potential in aVLSI, and their advance was rewarded with a *Nature* letter: "A Silicon Neuron," with a cover illustration of the layout.

Soon after their publication, I was invited to give a talk at King's College, Cambridge as part of a conference on "The Neuron as a Computational Unit" organized by Richard Durbin, Chris Miall, and Graeme Mitchison. Rodney and Misha came along, so at the end of my talk, I mentioned their silicon neuron. At the tea interval, Andrew Huxley (see Volume 4) came up to me and asked about the silicon neuron.

I beckoned Misha over and introduced her, "Misha, this is Andrew Huxley, he is interested to know more about your silicon neuron."

As happens, she missed the name and launched straight in with: "Do you know anything about the action potential?"

Without missing a beat, Huxley twinkled, "A little."

By coincidence, I was then sharing a house in Oxford with Alan Hodgkin's daughter, Deborah, so I heard many stories of the legendary pair, who set a mark for computational neuroscience that has never been surpassed, although, as Alan Hodgkin reminisces in *Chance and Design*, he saw their model as ultimately a failure, because the mechanisms of the voltage gates within the channels remained beyond their grasp.

Prof, Misha, Rodney, and I went to London to present our work at one of the Royal Society's evening soirées. Prof had been elected a fellow in 1953, and I was soon to be the Royal Society's Henry Head Research Fellow. The soirées were invitation only for the great and the good, and the science on display was a cross-section of cutting-edge research assembled for their Summer Science Exhibition. In true British tradition, we were in formal evening garb. Prof seemed to know everyone and introduced us to eminences like Paul Fatt and Miriam Rothschild. For Misha it was a voyage into antiquity, but she gamely demonstrated her silicon chips to the assembled elite.

Misha had now arrived in Oxford as a postdoc. She was passionately convinced that her form of neuromorphic engineering could lead to the solution of biological problems and that in turn biology could point her to engineering solutions. Her mission was to use the machine as a means to understand the brain. For her science, was a dynamic network, not a process

Figure 5 (left to right): Prof Whitteridge, Kevan A. C. Martin, Misha Mahowald, and Rodney Douglas at the Royal Society Soiree. Photo credit: Janet Whitteridge.

of constructing an edifice. Her influence is strongly evident in a paper we wrote for *Science* magazine on recurrent circuits, in which we used the electronic circuit metaphor to explain aspects of recurrent excitation and inhibition. We summarized some of the wider ideas we had been discussing in a short article, "Neuroinformatics as Explanatory Neuroscience." Often in the evenings, Misha would appear at my desk with a question, "what do you think about . . . ?" This typically would be the start of hours-long discussions that explored in depth some aspect of biological computation she had been pondering. I came very much to value her probing questions, her ability to synthesize, and her deep and original ways of thinking. It was an acute shock and long-lasting loss when some years later Rodney phoned on a late December evening to break the devastating news that Misha had taken her own life.

Synaptic Mapping

Our main experimental work was to test predictions of the canonical circuit. We began by mapping the synapses formed by the different inputs to the thalamorecipient layer 4, where the "simple cells" of Hubel and Wiesel lived. Such quantitative mappings were to become a theme of our research, but on our first pass, we found that thalamic synapses in cat and monkey V1 formed less than 10 percent of the excitatory synapses in their target layer 4, as the canonical model predicted. We also found a strong recurrent connection between layer 4 cells, but the surprise was the input from layer 6 pyramidal cells, which formed nearly half of the complement of excitatory synapses in layer 4. Highly unusually for pyramidal cells, they formed most of their synapses with dendritic shafts, not spines. This quantitative synaptic map raised the intriguing question of whether the different anatomical inputs had different physiological properties. I took advantage of the College lunchtimes to discuss with Julian Jack how best to tackle this question experimentally.

Julian and his team had used the method of "minimal-stimulation" to study synaptic plasticity in slices of hippocampus, and I thought we might adopt the method to screen for the presence of the different classes of synaptic inputs to layer 4 of cat V1. I carried out the experiments in Julian's lab with his PhD student Kristina Tarczy-Hornoch, postdoc Neil Bannister, and Julian's research assistant, Ken Stratford. For reasons never fully explained, Kristina felt the need to slice the cat's cortex while barefooted, but it worked: from the first experiment, when we evoked very different types of epsps in layer 4. Strikingly, one type we encountered was large in amplitude, had virtually no variance, and showed strong paired-pulse depression. We followed up the minimal-stimulation survey with paired intracellular recordings and convinced ourselves, and our referees, that the large amplitude potential was the thalamic afferent input—and characterized the excitatory inputs from layer 4 spiny stellate cells and layer 6 pyramidal cells.

The Worst of Times

Our knowledge of the canonical circuit and its operations now made it possible to embark on a program to build a "silicon cortex." Mike Fischer generously supported this, with his programmer Adrian Whatley coming on board to develop the software interfaces. It was a hugely ambitious undertaking, but driven with great energy. Then one day the sky fell in. Rodney arrived with a letter from the MRC Unit directors, informing him that his five-year contract would not be renewed. Unfortunately, the directors, David Smith and his deputy, Peter Somogyi, had neglected to mention their decision to me beforehand. The timing was particularly unfortunate, for Rodney's daughter was being treated for a serious illness at a specialist pediatric cancer unit in Oxford, and without a work permit, he would have to leave the country, with dire consequences for his daughter's life. No amount of rational argument would persuade the directors to extend his contract, for even a year. Relations became so sour that I also was shown the door, which is how I found myself without a lab, sharing a small office in Experimental Psychology, but this time not with Prof, but with J. Z. Young (see Volume 1), the eminent anatomist who discovered the squid's giant axon.

The White Knight who rode to our rescue was the Gatsby Charitable Foundation in the form of Roger Freedman. He had been a regular visitor to our lab because the settlor, David Sainsbury, was keen to invest in computational neuroscience. Roger rapidly negotiated a salary and space for Misha and Rodney at Imperial College, London. Then, out of the blue, an emissary arrived from the Swiss Federal Institute of Technology (*Eidgenössische Technische Hochschule*, ETH) in Zurich, who had decided to team up with the cantonal University of Zurich (UZH) to create a joint *Institut für Neuroinformatik*. The emissary, Klaus Hepp, was a theoretical particle physicist turned theoretical systems neuroscientist. The Brain Research Institute in Zürich was then headed by Michel Cuenod, who had been urged by Eberhard Fetz to establish computational neuroscience in Switzerland. Klaus and Michel were intrigued by our combination of experiment, theory, computation, and engineering and we were invited to Zurich for interviews, discovering on arrival that a source in Oxford had been briefing against us. The Zurich interest galvanized the Gatsby, and they offered us generous funding to create a computational neuroscience unit, an initiative that eventually became the Gatsby Computational Neuroscience Unit under Geoff Hinton, who steered it strongly in the direction of machine-learning rather than neuroscience. It was clear our days in Oxford were over: Prof had mapped his last receptive field and was no longer with us, and at our erstwhile directors' instigation, the MRC was suing me for the heirloom equipment that Prof and I had brought into the Unit; fortunately sanity eventually prevailed at the MRC Head Office, and they dropped the case. It was the right time to make a clean break and move to Zurich.

The Institute of Neuroinformatics

Rodney and I arrived in Zurich in late 1995 to find ourselves proud double professors and directors of a to-be double institute, our positions and institute equally funded by the ETH and the UZH. But we had no instruction manual, no "guide for dummies," and all official business was in German, which neither of us yet read or spoke. Our ignorance and naïvety now seems risible, for what followed was years of trial-and-error learning, with rather too much error for comfort. There were no models for double institutes or double professors like us—we were *Versuchskaninchen*—guinea pigs. The UZH and ETH differed in every way, including academic and administrative structures, salary scales, pension schemes, subjects, semester dates, and lecture timetables. Nothing was in synch. ETH professors were appointed by the President himself (always a him) and were lords of their fiefdoms. But what institute professors chose to locate themselves in or what other professors they associated with was largely irrelevant to the President. Years later, this came back to bite us when we read in the Friday evening edition of the local free newspaper that the President had decided, unilaterally, that the Institute of Neuroinformatics (INI) was to be transferred from our happy home in the Department of Physics (the Department of Einstein and Pauli), to a newly created health sciences department, and that double professorships, equally funded by the ETH and UZH, were now history. The level playing field we had worked so hard to create between ETH and UZH within INI had tilted, and we no longer had any control over the appointment of new ETH professors in INI. It was a top-down decision quite at odds with the admirable system of direct democracy and consensus government that the Swiss justifiably regard with pride.

The tradition of German science was that the *Professor* was the top of a hierarchy of *Oberassistents*, *Assistents*, and *technische Mitarbeiter* (technicians), all devoted to the professor's research. We intended to use our *Oberassistent* positions to create independent groups, and finance from our own budget their lab set-up, a PhD student, and some running costs, with the agreement that they would seek external grant funding to continue. For professors to give away their resources was seen as wildly eccentric, but it worked very well and year-on-year about half of the Institute's funding was from external sources—highly atypical for Swiss Institutes, which run mainly on internal funding.

We packed into a temporary space in the center of Zurich while a building was being planned and built for the INI and the Brain Research Institute on a former farm on the outskirts of Zurich. The institute they had designed for us was in the form of the standard German-style “container,” a long rectangular plan with two long corridors flanking a windowless central spine containing communal services, with laboratory-cum-offices lining the outside walls. From visits to similar buildings in Germany, I knew that one could gaze down the long empty corridors all day and never see another soul, as everyone worked behind closed doors. It wouldn’t do. We had to prise biologists, engineers, psychologists, computer scientists, physicists, applied mathematicians, and other disciplines out of their silos and get them to learn each other’s argot and ways of thinking, which meant taking down every wall possible to provide large spaces where we could mix all these cultures, maximizing osmosis. White boards were to line the corridor walls, encouraging spontaneous discussions. To emphasize in the architecture our flat organizational structure there were to be no private offices, not even for the directors. And then there was the matter of a kitchen . . .

Thankfully, the architects responded creatively and deconstructed our space. Rodney and I positioned our desks as far as possible from the administrative offices, sharing one end of the “Big Room,” with its long refectory table, sofas inviting conversation, piano, journals, jungle of plants, tie-dyed wall hangings, circus equipment, and adjacent (small) kitchen. One unintended consequence of taking away the walls of the silos was the emergence of a grassroots’ network of expertise. The students rapidly discovered who among them was the go-to person for a particular corner of knowledge, and so they created organically a self-perpetuating network of competences. The endless flow of visitors, from schools to lay public, gave them many opportunities to rehearse simple and short explanations of their research.

The animal house was in the building and included large outside enclosures filled with an endlessly changing landscape of ladders, ropes, boxes, and trees, to which the cats and monkeys had free access. Visitors were always astonished to discover our “zoo.” The animal caregivers were exceptionally devoted and could call any cat to them by name. I made it a rule that all the PhD students working with these animals should spend time with them, for this produced calmness on both sides. One student, Franziska Sägesser, was our champion cat whisperer and held long conversations with the cats in Swiss German, which they certainly understood better than I. Experiments with large animals present large challenges, and it typically took two or three of us several hours of concentrated and well-rehearsed preparation before we could begin recording, even longer if optical imaging was involved. After training the students to do the experiments, I always assisted them (but never quite finessed the tuneless whistle that Prof emitted when things were not going smoothly) and in the old tradition, I always helped with the endgame.

Soon after we had moved into our new *Bau 55* we became embroiled in a public controversy. In Switzerland, some fraction of the cost of public building was devoted to *Kunst am Bau* (“art within architecture”). The building occupants had no say over the choice of artists, so one day we found Thomas Hirschhorn—renowned for his *Wegwerf Kunst* (“disposable art”)—building a large carboard “Kiosk” in our entrance hall. Eight were planned, each wallpapered inside and out with photocopies of a particular artist or writer’s work, starting with one dedicated to Robert Walser. Inside were books by, and videos about, the artist. After six months the Kiosk was torn down and a new one was erected, all at a cost of SFr 400000. We protested at the waste, but found ourselves vilified in the press as the “philistine professors.” We quickly cottoned-on that we were now part of the exhibit and shut-up. For the *vernissage* of the final Kiosk, we all arrived dressed up in carboard costumes, to Hirschhorn’s amused surprise. It was a wonderful piece of Dada, quite fitting for a Zurich art event.

Persons

We kept busy recruiting. One key position was the system manager. Dave Lawrence, Terry Sejnowski’s former System Manager had been a key component of the NSF Telluride Neuromorphic Engineering Workshop, which had been initiated by the group around Carver Mead, including Rodney. Rodney invited Dave to come to Zurich, and he was eventually persuaded, “I’ll just come for 6 months to set up the network.” He is still there now, as the INI manager. We were hugely impressed with the quality of the administrative staff in Switzerland for everyone we interviewed had formal training and seemed to speak at least four languages fluently. Kathrin Hofacker was one early arrival who became the senior administrator, ably supported by staff that included a former dancer from Balanchine’s New York City Ballet, Simone Schumacher. This dependable core of competence created the critical interfaces we needed with our two central administrations. Marie-Claude Hepp-Reymond, a motor cortex physiologist, retired from the Brian Research Institute and, along with Dan Kiper, became an indefatigable promoter of our outreach activities.

Another innovation was a weekly plenary meeting, for the whole institute—mandatory attendance for everyone year-round—one of our few *diktats*. The first part was the “business meeting,” where anything could be raised and discussed, followed by one or two presentations by graduate students on their work in progress, chaired by the students themselves. Various embellishments were added, like “Swiss German for beginners,” “word of the week,” or “puzzle of the week,” which built the *esprit de corps*.

Swiss women had (finally) won the vote, but school hours were still designed for stay-at-home mothers and childcare was complicated and expensive, so when a pregnant postdoc arrived in our first year to work with Peter König, we immediately made the policy decision that mothers could be with their children in the INI and bring them to any meeting. We converted one room into a crèche, but infants could be found cradled under their mother's desks. Surprisingly, the students were unphased by this unusual situation and became adept supplementary caregivers. The benefits were that the parents were less stressed, their work was less interrupted, and the children enjoyed being in the INI. Indeed, we could quickly identify which children had been raised in the INI—they were the quieter, socialized ones who just got on with entertaining themselves. Visiting children, by contrast, were noisy and excitable, scribbling all over the boards lining the corridor walls and being generally disruptive.

After a year in Zurich, we were ready for a formal opening of the INI and invited the great and the good and asked Terry Sejnowski to give the inaugural lecture. I worked hard with my German tutor, Verena Müller, to give the vote of thanks in German. We had arrived.

ADA, the Intelligent Space

Through Rodney and Misha's connections with Carver Mead's alumni, we rapidly built up a formidable critical mass in neuromorphic engineering. Tobi Delbrück, Shih-Chii Liu, Giacomo Indiveri, and Jörg Kramer (a Swiss) arrived and rapidly attracted students to their innovative theoretical and practical courses. It then made sense to create a Europe-based neuromorphic engineering workshop, like Telluride, which brought together the same constellation of skills we had in the INI. Thus, the Capo Caccia Workshop was conceived. Located on the remote coast of Sardinia and lasting a fortnight, it quickly became the international annual meeting place for a cross-section of brain-interested scientists, engineers, entrepreneurs, and students. Another unintended consequence of removing the silo walls in INI and giving our students international exposure at gatherings like Telluride and Capo Caccia was that employees saw our engineering graduates as having an added-value over their peers because they knew something about brains, and similarly, our biology graduates were viewed as having the added-value of exposure to the neuromorphic engineering and neural computation that their peers lacked. About half our PhD graduates are recruited by industry, some founding start-ups with projects originating in INI.

We pulled some of these strands together in an INI-wide project to make an "intelligent space," which would sense, learn, and act in response to its occupants. The catalyst for this was an invitation to propose an exhibit for the Swiss Expo. We submitted a proposal for "ADA, the Intelligent Space," which was named after Ada Lovelace, who wrote the first computer program for Charles Babbage's analytical engine. ADA was intended to evoke wider discussions about two premises: first, that brains continuously construct their own interpretation of the world, and second, that intelligent technologies of the future will share this property with the brain. This was a mammoth undertaking with a very hard deadline, so it was driven with great urgency by Rodney, Tobi Delbrück, and Paul Verschure, a computational psychologist who had joined us from Gerry Edelman's Institute, along with multiple students and associated scenographers, lighting designers, musicians, and even H. R. Giger of *Alien* fame, who contributed artworks, most notably his "Biomechanoid" metal cubes, one of which ended up as a frieze in the INI's entrance hall. After multiple iterations and stress testing, ADA appeared on a platform in Lake Neuchâtel, where she operated with virtually no downtime for six months and was experienced by half a million visitors. It was the only exhibit from a German Swiss university and was a convincing demonstration of the power of harnessing multiple disciplines in a common cause. Its influence is still felt: a decade later, Michael Arbib used ADA as the case study to discuss the implications of neuromorphic engineering for the future of architecture. The dislocation caused by half our students and senior staff working in Neuchâtel for extended times made an added challenge for me to keep the home fires burning in our fledgling institute.

Canonical Advances

Rodney and I wanted to elaborate our canonical circuit. A mathematician, Tom Binzegger, one of our first PhD students, had worked with John Anderson to create a database of cat V1 neurons reconstructed in 3D using TRAKA. We then applied "Peters Rule," a term coined by Valentino Braitenberg after Alan Peters proposed that cells connect in proportion to the boutons and dendrites that the different cell types contribute to a given volume of neuropil. We also took into account known cases of specificity, like the chandelier cell connection to the pyramidal cell's axon. From this, we synthesized a quantitative map of the circuit of V1 of the cat, which was soon used by other groups to make supercomputer simulations and by us to explore the dynamical aspects of the pulse response. Getting Tom to finish the project, however, did require the patience of a saint, because just as we were nearing a version of a typescript I thought we could submit, Tom would pop up with another idea of how he could extend, cross-check, fine-tune, or rearrange the results, which usually meant another extensive redraft. But far better to work with someone who keeps worrying the data than with one who jumps ahead to a conclusion too easily won.

The quantitative "Binzegger circuit" provided the ideal opportunity for a proof-of-principle exercise to explore the universality of the canonical circuit by (virtually) translocating a piece of cat primary visual cortex into the prefrontal cortex of the primate to test if it could do something useful. Klaus Hepp proposed we use saccadic generation by the frontal eye field area (FEF) as the behavioral read-out, and he enthusiastically piled high the desk of our student Jakob Heinzle with reprints of every electrophysiological study of FEF in behaving monkeys he could find. Our spiking neuron model behaved excellently and predicted some novel properties discovered later in experimental studies in behaving monkeys. Buoyed by this success, we then applied the model to explain saccadic eye movements during reading, for which there was a large experimental literature. My one-and-only paper in *Psychological Reviews* was the delightful outcome.

Widening Horizons

Smaller internal meetings that required the directors' presence began to proliferate, so for efficiencies sake, we scheduled them all on the same day. Wednesdays began with my breakfast meeting around the refectory table to which everyone was invited, and ended at 5 p.m. with the whole INI gathering. Breakfast was the occasion for wide-ranging discussions about questions of science and of being a scientist. Students who saw me active in the lab, were surprised to learn that most of my contemporaries had become managers, fundraisers, and conference-circuiteers around the age of 35 and were seldom active again in the lab—quite the opposite of Prof's generation, who died with their boots on. But out-of-lab activities were necessary skills, as were refereeing papers, writing grants, choosing and mentoring students, preparing for committee meetings, and public engagement. How to learn these skills was an important topic that we discussed and practiced. The Nobel Prize awards were a perennial breakfast topic, to which I usually offered the opinion that prizes in science were like awarding a gold medal for a winning relay team only to the member who actually crossed the finish line, and then heaping yet more honors on that individual for "winning" the same race.

All the students found giving talks particularly stressful, even when faced with a friendly critical audience. To give an overly polished, overly sunny, TED-style talk seemed their ambition, but such presentations clearly lacked an authentic voice, so as an antidote I decided that we would practice some of the exercises I had learned in many of the theater and music workshops I had participated in over the years while researching for a book on, "the performer's brain." The exercises helped the students to remain grounded and authentic, themselves, even when faced with the powerful and distracting stimulus of an audience. One such exercise was playing "pass-the-story," in which one person in the group would begin an improvised story and then point to the person they wanted to continue it. The difficulty of not knowing whether you were next, and then having to extemporize on the spot, was not too different from having to think on your feet when faced with random questions from an audience, but the exercise often proved paralyzing. To help them further, I organized workshops for the INI members with outside teachers. One memorable weekend was with the late Kristin Linklater, author of *Freeing the Natural Voice*, who at end of her workshop, gave us the gift of a 15-minute voice warm-up that she had distilled for attendees of the World Economic Forum at Davos. I still use it.

One breakfast exercise that turned out to be unexpectedly moving was when I asked everyone to draw on the whiteboard the story of the work they did. It was an exercise that they clearly thought about a lot, because week-on-week one of them would produce a sketch that captured in a very creative way the essence of what they did, as well as revealing to the rest of us unexpected insights as to how they saw their own work.

I also invited people I knew with interesting life stories for conversations with students in our Big Room. The musicians ranged from David James, the counter-tenor of the Hilliard Ensemble; to David Earl, a concert pianist-composer with whom I had collaborated on a song-cycle, *Island Owl*; to Suggs, the singer-songwriter for the hit Ska band Madness. Matthieu Ricard, the Buddhist monk who has spent more time meditating in a brain scanner than most, came to discuss his book *Happiness*, and Rod McKinnon entranced his young audience with tales of crystals of potassium channels. All of these visitors had unusual trajectories, and their

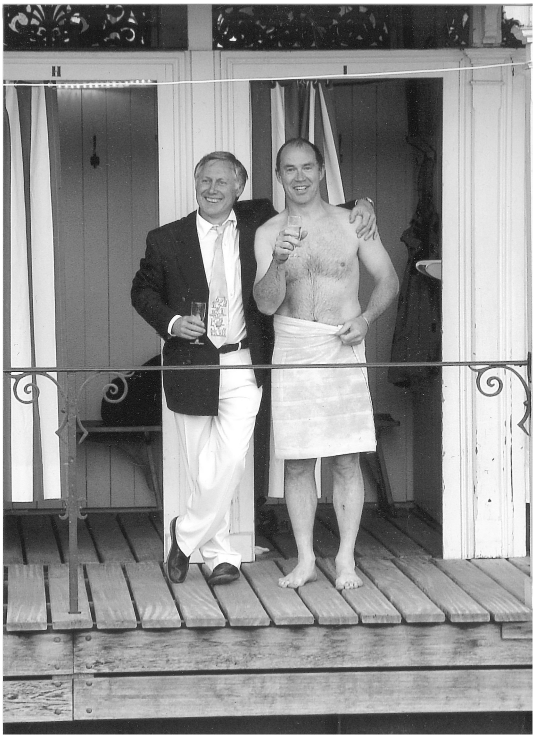


Figure 6. Rodney Douglas (in fancy dress) and Kevan A. C. Martin at INI's tenth birthday party at Zurich's *Frauenbad*. Photo credit: Simone Schumacher.

stories helped inspire and expand the horizons of the students. In house, we also grew a team of qualified teachers of language, music, meditation, tango, yoga, and the Alexander Technique. Were these activities good for anything in an academic institute? At one level, these were simply offers of positive relaxation and a change of gear for a very head-centric people. At a deeper level, these activities joined mind and body—the psychophysical unity of self as Karl Popper and F. M. Alexander termed it—and were an effective, lived experience that reminded them that our brains are not us.

As a student in Oxford, I had made a sponsored parachute jump to raise money for a clinic in Khayelitsha, one of the informal settlements that had grown up on the Cape Flats. This experience led skydiving to be added to my list of sports. I was a member of a number of teams, most notably with "4-Brain," led by a well-known Swiss skydiver, Mafalda Fent. In competition, a "four-way" skydiving team is scored by how many different formations of a predetermined sequence the four skydivers can complete in 35 seconds of free fall. Bemused passers-by in the lobby of INI would see us clad in multicolored jumpsuits, sliding around on trolleys—"dirt diving"—as we rehearsed the mechanics of the transitions between successive formations. We competed in a number of Swiss National Championships and won medals, but with the introduction of vertical wind-tunnels, the sport has become exceedingly technical, and now only professionals have any chance for medals in the open category.

One of the delights of being on the UZH campus was bumping into Rüdiger Wehner, the sometime director of the Institute of Zoology, whose research on mechanisms of navigation in the desert ant *Cataglyphis* ranks among the classics of neuroethology. Rudiger was always brief on casual chat, and long on telling me about his latest discoveries. He seemed to know everybody, and invited luminaries like E. O. Wilson to Zurich. We shared an interest in the history of neuroscience and ethology and from time to time he sent me the draft of something he had just written for comment. He did not need my help—his book *Desert Navigator*, shows what a fine writer and photographer he is.

Student Life

When I began teaching neuroinformatics to non-English speakers, I adopted a lecture-demonstration, "volunteers-please?" approach and, *contra* the fashion, used no PowerPoint, supplied no handouts, and delivered only old-fashioned "chalk-talks." I assured the students that I would ask nothing in the exam that was not in my lecture, which seemed to concentrate their minds wonderfully, and they even began practicing note-taking and neuroxing, for which atavistic strategy the ETH Students' Association awarded me their Golden Owl for excellence in teaching!

The quality of the master's students was a revelation. The first MSc projects I supervised were those of Sylvia Schröder and Antonia Drinnenberg, who set a very high bar for their successors. Sylvia went on to do her PhD with me and introduced natural stimuli to our studies of cat V1. An informal seminar I began on the foundational literature of neuroscience, became a set course for our in-house MSc degree in Neural Systems and Computation, which was initiated and directed by our new professor, Richard Hahnloser, a former PhD student of Rodney and Klaus Hepp. My first assistant, Georg Keller, devised an experiment to accompany each week's set of historic papers. One example was his working replica of the Hodgkin-Keynes mechanical model of the potassium channel, something that had inspired Rod McKinnon in his structural studies. The attendees soon understood the meaning of the word "tralaticious" when we read Roy and Sherrington's 1890 paper, which had spiked in citations after the discovery of the BOLD signal. I had written "A Brief History of the Feature Detector," which highlighted Horace Barlow's early work, and the seminar gave me an opportunity to introduce some of his fellow travelers in the legendary Ratio Club, the hub for British cyberneticists. The 1950s was an exceptionally fertile era that generated new ways of thinking about the nervous system in a quantifiable way. The interchange between engineers, physiologists, psychologists, mathematicians, and computer designers in the Ratio Club was hugely productive and something we tried to emulate on a daily basis in INI. The famous photograph of the Ratio Club, taken in May 1952 outside Peterhouse College, Cambridge, shows Horace (at the time a PhD student of E. D. Adrian) sitting on the ground in the front row holding a glass of wine. Cross-legged at the other end of the row is Alan Turing. I once asked Horace why he was the only one in the photograph holding a glass. He replied, straight-faced, "It must be because I'm a slow drinker."

Idan Segev, whom I'd not met, invited me to a conference at the Hebrew University in Jerusalem. It was the beginning of a friendship and a long collaboration. He had worked at National Institute of Mental Health with Wilfred Rall and is surely the inheritor of Rall's mantle. As an advocate for the biophysical modeling of neurons he is unsurpassed, always clear and passionate, full of insights. Mike Shadlen, a jazz guitarist of note and sometime graduate of "Uncle" Bill Newsome's Monkey Business, was at the same conference. He had hired a car and offered to take us on a day trip to the Mediterranean. I suggested we try swimming in every sea and, Red Sea excepted, we did, but it involved driving along the West Bank, from the Dead Sea up to the Sea of Galilee, something Mike had been strongly advised against. It was a fascinating, if disturbing journey, now quite impossible. On a later occasion, Idan took Tobias Bonhoeffer and me to Petra along the opposite bank of the Jordan river.

Tobias taught a summer school at the Gulbenkian Institute in Lisbon, and while there, advised a young biology student to apply to me to do a PhD.

So a tassel-haired, bearded and braces-clad Portuguese, Nuno Maçarico da Costa, arrived in the lab, staying long enough to get a PhD and start his own junior group before moving on to lead a connectomics project at the Allen Brain Institute. By the time he completed his 10,000-hour apprenticeship in INI, he was the master of his trade. He was extraordinarily generous with his time and knowledge and helped me train another generation of experimentalists, including Georg Keller's younger brother Andi, who introduced the strangely silent world of two-photon imaging into our cat studies (making me grateful for the inestimable boon of Lord Adrian's insight to play the voltage transients of neurons over a loudspeaker). Nuno's own PhD project was the impossible dream: to discover how synaptic inputs from the thalamus relate to the functional ocular dominance of their target cells in layer 4. There was almost no technique we did not deploy in an attempt to winkle out the answer, including optical imaging, tract tracing, immunochemistry, intracellular recording, and an inordinate amount of correlated light and EM. His project had the unintended and significant consequences of not only introducing new technologies to the lab, but also of driving the skills of key people to new levels. For his dream, though, we had to admit defeat. Nonetheless, the spin-offs were significant and his quantitative map of the thalamic input to spiny cells in cat V1 was used in a biophysical model of the simple cell with Idan Segev and Yoav Banitt, which alerted us to the importance of synchrony and stochastic resonance.

Lines of Communication

John Anderson and I had been working on the quantitative ultrastructure of the long-distance connections between visual areas in the macaque. With Kathy Rockland, we described the anterograde pattern of synapses for the V1 projection to MT, which resembled the magnocellular thalamic projection to layer 4 in V1. John and I subsequently found that, while every projection we studied had a unique laminar pattern of innervation, all contributed only a tiny fraction of the synapses in their target layer. This matched well the quantitative results obtained by Henry Kennedy using retrograde tracers to label the cells of origin. How could such tiny numbers of synapses be effective? It was not by making large synapses, for when we reconstructed in 3D the postsynaptic densities, we found that their sizes typically ranged over at least two orders of magnitude. We were particularly intrigued by the presence of so-called perforated synapses, which took on horseshoe-like shapes, which we had seen previously for the thalamocortical synapses in cat and monkey. This prompted a recurring thought: how could a single vesicle of neurotransmitter ever saturate all the postsynaptic receptors at a such synapses, as distinguished investigators like Julian Jack and Bert Sakmann assured us it did?

Primate Matters and Moonshots

For her PhD, Isabelle Spühler had mapped the pattern of dopamine boutons in macaque frontopolar cortex. She then teamed up with Andreas Hauri, a student of Rodney's, who had co-developed the Cx3D, a program for simulating millions of cells interacting with each other both biochemically and physically. They produced an insightful paper that used the structural data to model the nonsynaptic release and receptor-binding of dopamine. Their study, along with our FEF modeling papers, made me even more curious to explore the circuits of prefrontal cortex. Thus, when I applied to the Zurich Animal Commission for a renewal of my animal license, I proposed making a quantitative analysis of the local circuits in prefrontal cortex. Another group leader, Dan Kiper applied at the same time to continue his behavioral studies on visual acuity. Zurich is the only one of the 26 Swiss Catons where a minority of members could block, through a mechanism called a *Rekurs*. a license being granted. Three positions on the commission were reserved for animal welfare organizations, so this mechanism was highly likely to be used. The chair of the Zurich Animal Commission was Klaus Pieter Rippe, a philosopher who wore another hat as president of the Swiss Ethics Committee of Non-human Biotechnology, which had been commissioned by the Zurich Animal Commission to assess the ethics of using marmosets as a model for depression. They took this particular case as a remit to consider all Swiss primate experiments. Their deliberations led to both our license applications being subject to a *Rekurs*. Dan and I engaged in a wearying legal battle to have it overturned, but eventually the Swiss High Court declared that fundamental research should not be carried out on primates—only research that had a direct outcome for human health and welfare. It is not difficult to point out the flaws in their reasoning, which if universally applied, would actually have devastating consequences for human health and welfare. Ours was far from an isolated instance, as similar cases were repeated across Europe.

Our planned work was stopped in its tracks, but research involving monkeys did continue in INI with Hans-Jörg Scherberger, who was studying the cortical representation of grasp and precision grip. Later, after another lengthy legal process and a very supportive UZH vice president of research, Danny Wyler, Valerio Mante was granted a license to study decision-making and coding in monkeys. The Swiss Ethics Committee meanwhile had assigned themselves the task of advising the Swiss Federation on "the dignity of plants" (*sic*), where they came to the conclusion that decapitation of wild flowers at the roadside without rational reason is "morally impermissible." Even Jeremy Bentham would demur.

An important source of funding for the INI was the European Union's (EU's) Future and Emerging Technologies (FET) program, which funded consortia of labs across Europe. Because of its portfolio of skills, INI members had been very successful in obtaining FET grants. All this was to end, however, when the EU decided to fund just a few flagship projects. At the front of the queue was a former UCT student of Rodney's, Henry Markram, who had started the Blue Brain Project at ETH's sister institution EPFL (*École Polytechnique Fédérale Lausanne*). Neuroscience is a cottage industry, but Henry's proposal for an FET flagship project was presented as neuroscience's moonshot: to simulate the human brain within a decade, and by large-scale simulations, find cures for neurological diseases, thus eliminating any further need for animal experiments. Rodney and I were convinced the extravagant claims made for the Human Brain Project (HBP) were bogus and that it would be a tragic waste of Swiss academic funding. Because no new money was involved, a flagship project would also divert much-needed funds away from many EU neuroscience projects for at least a decade and signal the end the very successful FET program. Henry's public relations machine swung into action and he convinced the Swiss politicians, the president of EPFL, and the ETH Board to back his bid. We did point out the absurdity and hubris of HBP's claims in person and in print, but to our surprise, many eminent scientists climbed aboard and the HBP flagship was funded to the tune of 1 billion Euros over 10 years. Now after a decade, the failure of the HBP to realize its ambition to simulate a human brain, or publish any groundbreaking insights from their simulations, is plain for all to see.

Daisies and Bouquets

The clustered lateral connections made by pyramidal cell axons, which we called a "daisy," had long intrigued us. These originally were discovered by Kathy Rockland and Jennifer Lund (see Volume 3) and had been assigned many roles, including forming an inhibitory surround for the receptive field and for linking domains that had the same orientation preference—the so-called "like-to-like" connectivity. In an epic series of experiments led by Elisha Rüsch and German Köstinger that required intrinsic imaging, intracellular labeling, and correlated light and electron microscopic reconstructions, we overturned most of the previous speculations, not the least of which showed convincingly that the daisies did not create the surrounds of receptive field and did not exclusively connect like-to-like orientation domains. Our new interpretation was that daisies provided a structure for local context-dependent processing, something for which we had supporting evidence from our previous physiological experiments with Cyrille Girardin, Anita Schmidt, and Sylvia Schröder.

Rodney and I decided to mark the 20th birthday of INI by thanking all our supporters. The Hilliard Ensemble was tempted out of retirement to give us a concert in the majestic Semper Aula of the ETH main building. It was a moment to savor and enjoy; to remember the friends we'd made, and lost; to give credit to all the people who helped us build our collective enterprise; and for me to say a prayer of thanks to Leon Isaacson for introducing me to Rodney. We had been roped together on the same mountain for four decades, ascending in tandem by the best routes we could find, leading, following, endlessly debating and creating science and environments for science.

Quantum and Solace

The question of the relation of synaptic structure to epsp amplitude reared its head whenever we did correlated LM and EM, but to get a definitive answer required high-risk experiments, so I was reluctant to offer it ever as a PhD project. An MSc student, Gregor Schuhknecht, who had been studying thalamic synapses in the mouse motor cortex with Rita Bopp, an EM expert, expressed a strong desire to try. Knowing it was now or never, I sent him to Hamburg to take an advanced patch-recording course with Ora Ohana. Ora had done her PhD with Bert Sakmann before setting up her own group in INI, so she was the perfect tutor. I tapped Ken Stratford, then busy with ecology research in Namibia, to look over Gregor's shoulder at the quantal analyses, and with German Köstinger and Simone Holler taking on the structural side, we now had a once-in-a-generation A team, and they played a blinder. We established that there was a linear relationship between the amplitude of the epsp and the area of the postsynaptic density, and more significantly, we provided definitive evidence that individual synapses had multiple transmitter release sites, thus overturning decades of authoritative assertions that neocortical synapses possess only a single release site. The shades of gray EM structure could now be colored with functions beyond a simple plus or minus. The project epitomized INI's ethos of collective endeavor. Another door had opened, beckoning us to explore further the nature of cortical synapses and the circuit functions they enable.

Charles Sherrington, who made the link from synapses to behavior surer than anyone, gave us the indelible image of the "enchanted loom," by whose means we weave our dreams into realities: how favored are we who can explore its secrets?