Robert U. Muller—In Memory

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Bob Muller, friend, colleague, and place-cell pioneer, died following a heart attack on Sept 16, 2013. He was 71 years old. Figure 1 shows Bob at the early stages of place cell recording.

BACKGROUND

“Extremely direct” is the essence of Bob Muller’s signature style. His journey toward his intensive focused study of place cells was anything but direct, veering from experimental psychology through membrane biophysics and ending in the temporal lobe. Bob was a New Yorker. Born in Queens in 1942, he went through New York City public schools, Stuyvesant High School (where he was classmate of Lynn Nadel) and City College (where he was a classmate of John O’Keefe’s wife, Eileen). Inspired by Sam Feldman at City College, he journeyed to Canada, to McMaster University to study physiological psychology with Case Vanderwolf. Vanderwolf’s seminal studies of the behavioral correlates of the theta rhythm were Bob’s first taste of the hippocampus. Incapable of being outside New York for more than 2 years, Bob retreated and began Ph.D. studies at Albert Einstein College of Medicine, where he again worked with Sam Feldman. Bob and Sam were lifelong fast friends, but in the lab they were a volatile mixture. In addition, while at Einstein, Bob’s mathematical, reductionist side took hold, and he became fascinated with membrane biophysics. In the early 1970s, he switched labs and began working with Allen Finkelstein, with whom Bob invented his middle initial “U,” making his professional name read “Are You Muller?” Bob did his Ph.D. thesis work on ion channels in artificial membranes. Never forgetting his interest in psychology, Bob focused on membrane mechanisms of memory and began a decades-long collaboration with Olaf Andersen investigating these issues.

As I think back on Bob’s and my conversations in the late ’70s, Bob’s hippocampal work grew out of his bilayer work. He was working on models of memory (based on monazomycin) and that led him to Jim Ranck and the place cells, which he felt that had the promise to offer something truly important—and that was amenable to the rigorous analysis with which he pursued the monazomycin studies.

—Olaf Andersen.

After his graduate and brief post-doctoral work at Einstein, Bob followed Vahe Amassian to Downstate Medical Center where he was appointed Assistant Professor in 1975. At Downstate he became a fabulous lecturer. (Medical students, in fear of pubic humiliation, learned the mantra “outward current depolarizes!”) While setting up a lab to study the biophysics of artificial membranes, he occasionally snuck down the hall to Jim Ranck’s lab and indulged discussions of behavioral neuroscience. Bob had heard about O’Keefe and his place cells, but it was not until 1982, when he saw one, recorded live, that he was smitten. In 1984, he became an (almost) full-time hippocampal scientist. Bob remained at Downstate for the duration his career, which included a multiyear additional appointment with the Centre for Synaptic Plasticity at the University of Bristol during the early 2000s.

BOB’S STYLE

When Bob started a sentence, “I was impressed by your last paper in ...” in his deep, rough voice I always knew that I was in deep trouble.

—Gyorgi Buzsaki

Yes, Bob was very direct, but uniquely so. In the view of many, common adjectives are inadequate to summarize his style. All agree he was a major presence. When he was in a room, you knew he was there. When he spoke, you listened. He could be tender or rough. He could be crude or thoughtful. Three...
things were certain of Bob: he was fearless, honest, and brilliant. In the realm of hippocampal science, he had certain views that were hard to change. He was certain that place cells were the fundamental units of the hippocampus and the fundamental underpinnings of navigation. Bob was fierce and brilliant in debate. Both of us (JK and AF) remember countless, hours-long arguments, with Bob inflexible. Invariably, the next day, the heat was gone, and Bob might say something like “you made some good points.”

Characteristic of his softer side were protracted discussions about how a process, such as theta-phase precession, might be implemented in the hippocampus and contribute to behavior. Finally, Bob was a gentle but incisive critic. Upon reading a draft manuscript, or after hearing a presentation rehearsal, he would start with a comment similar to Gyuri’s, above, and proceed to get to the kernel of what was weak or incorrect.

**EXPERIMENTAL STYLE**

Bob’s training in biophysics characterized his approach to behavioral neuroscience. He was a reductionist. He was also a perfectionist. Bob’s career in place-cell investigations can be characterized by simplifying the behavior to the maximum possible, without losing basic properties, followed by slow steps of elaboration. This is, perhaps, most clearly seen in the 1987 Journal of Neuroscience papers on place cells. Paper 1 set the stage: the “gray cylinder” was the simplest environment conceivable that permitted free locomotion. The behavior, food pellet chasing, was the simplest task the team could conceive that encouraged homogeneity across space and locomotion. Behavior was in a “steady-state” in that each rat had weeks of experience in the cylinder before recording. The rat-tracking system, largely designed by Bob, took about 2 years of construction and modification before reaching his critical standards.

Once steady-state conditions had been documented carefully in paper 1, simple manipulations were studied and summarized in paper 2. Among the now-familiar environmental manipulations were rotating the single cue card; changing the size of the enclosure, changing the shape of the enclosure and inserting a barrier at various locations on the otherwise homogeneous floor. Finally, the writing was arduous. Not only were the experiments atypical (at the time), but Bob was exceedingly careful, precise and, at times, obstinate.

JK: I lived through this.

AF: Bob routinely, in the process of experimental design and writing referred to the first two papers and said “this is how you do it.”

**REMAPPING**

But most importantly, embedded in these (1987) papers was the discovery of place-cell remapping. This is a fundamental property of hippocampal neurons, which shows that hippocampal cells can participate in multiple seemingly independent representations, i.e. exactly what is needed for a system that can store large quantities of independent memories—it links place cells to memory.

—Edvard Moser (Figure 2).

Place cell “remapping” was, perhaps, Bob’s key experimental finding. We suspect (with support from personal conversations) that it is at the center of Bob’s concept of the hippocampus. Figure 2 below, constructed from the dataset of the second paper illustrates the phenomenon. Although remapping was described in the second of the 1987 papers, the term was coined in a pair of papers in 1991 (Bostock et al., 1991; Kubie and Muller, 1991).

Remapping has two critical features:

1. If a cell has firing fields in two environments, knowing the location of the firing field in the first environment will not predict the location of the firing field in the second environment.
2. If a cell has a firing field in one environment, there is no predictable indication that the cell will have a firing field in the second environment.

The phenomenon of remapping is robust and has remained a focus of analysis.

Additionally, the word “remapping” can be used in two ways. First, as Bob and John described it, as a reference to a...
scrambling of the map representation of two familiar environments. Second, “remapping” can be used as an active verb, to describe the establishment of a new (unpredictable) map in a novel environment. As will be described below, Bob and colleagues came to use remapping as a tool to explore the neural substrate of memory.

**LEARNING AND MEMORY**

Throughout much of the 1990s, Bob lectured, wrote, and argued about place cells as the essential substrate for navigation, but as the millennium approached he uncloaked his original hopes and intuitions that place cells were a major clue to the fundamental basis of learning and memory. Bob’s first steps into learning were tentative. He stuck to the navigation story in a 1996 review in Neuron. Then, emboldened through a collaboration with Eric Kandel and his post-doc Cliff Kentros, in 1998 Bob published the first in a series of papers that explored the molecular basis of place cell remapping. Over the course of the next decade, Bob adopted and refined this position: he advocated for remapping as the most practical and natural, paradigm for investigating the neuronal mechanism of episodic memory in a functional network. He explored the roles of NMDA receptors, CaMKII, and PKA in place cell remapping and firing field stability. During his association with Bristol Bob investigated the role of kainate receptors in the spatial discharge of place cells, how the discharge patterns of place cell pairs interact to cause synaptic plasticity in hippocampus slices, and identified functionally distinct hippocampal interneuron classes on the basis of their temporal discharge properties during behavior. At Downstate, most recently, he teamed up with former student Jeremy Barry, Todd Sacktor and André Fenton, to investigate the role of PKMζ (PKM<sub>f</sub>) on the stability of memory networks. PKM<sub>f</sub> had been celebrated since 2006 as the first molecule demonstrated to be essential to the maintenance of memory, but to Bob that claim would remain controversial until memory was evaluated properly, which of course meant that PKM<sub>f</sub> had to be necessary for the stability of place cell firing. In 2012 Bob’s team published a paper saying it was. Eric Kandel’s words summarize the learning and memory epoch of Bob’s career: “Bob Muller was an outstanding scientist and one of the first scientists to study hippocampal place cells in the rat. I had the privilege of collaborating with Bob when Cliff Kentros was in my lab. This proved a most rewarding experience for both Cliff and myself as we learned a great deal from Bob. He was not only rigorous and imaginative but he also had a wonderful historical perspective on the field, which helped Cliff and me greatly.” Ever understated, Eric speaks for many of us, Bob in his inimitable way helped many of us understand learning and memory, and how to investigate it, greatly.
Bob trained a good number of us. He was a committed mentor who took the responsibility of mentoring almost as if were a moral calling. When he was not preoccupied with undermining his own authority with jokes and anarchistic play, Bob perceived that it was his duty to mold and forge in each of his intellectual children the same intuitions and practice of rigor, intellectual honesty, and amazement with place cells, that Bob understood had been effectively perfected in his own person. To our knowledge all but two of his trainees remain active, productive explorers of neuroscience, although many of us have diversified or taken the place cell research program to different parts of the brain and different questions than navigation, learning and memory. We continue to investigate fundamentals of neuroscience, neural computation, representation and how these might be compromised by disease and dysfunction. Yes we each have our style, and while many of us have taken pains to develop a voice and style that is differentiated from Bob’s, there’s remains a good measure of Bob that the community will continue to see in our work for a long time to come. Indeed, we can expect the last research that Bob directly supervised to be published in the next year. The work is from Kevin Bolding a graduate student and Eunyoung Song a post-doc, both now at Duke. This research is vintage Bob, conducted true to his spirit intuitions and style so long in the making. Kevin's work investigated whether hippocampal theta oscillations are essential to location-specific place cell firing, Eunyoung investigated whether grid cells are essential to

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*Hippocampus*