**<u>Educational Experience</u>. Describe any personal, professional, or educational experiences or situations that have contributed to your desire to pursue advanced study in science, mathematics, or engineering. (1 page)**

My serious interest in scientific inquiry began the first year of college. I was taking an experimental biology course, offered for the first time and funded by an NSF grant. The professor, Dr. Steve Kron, took an uncommon approach to teaching biology: he wanted first year undergraduates to read primary literature, and analyze it at the level of first year graduate students. . He believed that undergraduates shouldn't begin their studies by memorizing scientific conclusions in "fact-based" courses, only to have the rug pulled out from under them four years later, when they would be confronted by the challenges of sifting through evidence, reinterpreting data, and, ultimately, accepting or rejecting the published conclusion based on their own reasoning. Dr. Kron believed that science should be learned as detective work, that primary literature should be read and weighed from the beginning. His course taught a sense of craftsmanship in experimental design and laid a foundation of academic skepticism.

In addition to biology, as an undergraduate I was also engaged in serious mathematics. In high school and before, I'd participated at regional and national competitions, and mathematics was most like a hobby. In college, I found myself unable to go without taking the advanced track of math courses. One important course, Honors Analysis, was like Dr. Kron's course in that it intended to bring undergraduates very near to the level of graduate study. Honors Analysis covered a wide range of theoretical topics, each rigorously developed through lectures and assigned problems: group theory, metric spaces, formal vector spaces, the Lebesgue integral, measure theory, character theory, and others. As the course progressed, the pace increased and the material became more difficult. By the end of the year, I felt prepared to sit down with any mathematics text and work at the level of the text. Honors Analysis, like Dr. Kron's course, taught primarily a fluency—the desire, confidence, and ability to work in the primary literature of the field.

From those two experiences, one in biology and one in math, I felt I'd begun to see the real substance of the fields. I was fascinated by the workings of biological systems, and nervous systems in particular, but I also saw the beauty of mathematics.

I first began to see a connection between my interests in studying statistics. With the mathematical constructs of Honors Analysis still circling in my mind, I'd imagined that statistics would fit beside them as another fundamentally tautological aid to human reasoning, albeit one more directly aimed at the empirical world. Nevertheless, my professor, Stephen Stigler, was an acclaimed historian as well as statistician, and he made a point of connecting our mathematical formulae to the context and tensions of their development. Studying the history of statistical debates, I realized how broad and narrow were the forefronts of research: broad in that some fundamental questions still do not have universally agreed upon answers, and narrow in the specific circumstances to which each statistical tool must be tailored. My vision of a static mathematical framework was erased, and I concluded that a scientist must also be a statistician. The core of empirical science is probability theory, and this has nontrivial consequences for conducting experiments. Each system needs to be understood in terms of its unique probability model. Widely applicable methods such as the student's t-test can strengthen experimental evidence, but stuffing a complex dataset into one dimension might mangle the interesting parts.

I was ultimately spurred on to neuroscience by a new course, "Computational Neuroscience", designed for the University of Chicago's new Ph.D. program of the same name. Surveying the past 50 years of research, my professor, Dr. Philip Ulinski, pointed to great successes in the marriage of experiment and theory, an approach long appreciated by physicists but relatively new to neuroscientists. It seemed that findings in neuroscience were proving less and less amenable to purely qualitative measures. At the same time, few researchers in computational or quantitative fields had the training and interest to seriously understand and pursue the biological problems.

I realized I would not need to decide between biology and math, and I joined a new interdisciplinary program in Computational Neurobiology at the University of California-San Diego. Here I've found the resources and the intellectual climate required to make sense of experimental findings in a framework of theoretical and computational models.

At UCSD, my understanding of neuroscience has been further shaped by taking on the approach of biophysics. Essentially, this approach is to treat a neurobiological system as one would treat a purely physical system. For example, in neurons the question arises what it means for there to be a resting voltage across the membrane. Most neuroscience texts teach that the voltage is like an RC circuit equivalent: a battery and resistor in series. But the system can be reduced further. The biophysicist begins by considering a simple diffusion process across a membrane with two additional factors: an electric field biasing particle movement, and selective permittivity in the membrane. Under these condition, the modified diffusion equation predicts that voltage will tend to lie in a narrow range with small noise fluctuations, on the order of microvolts. This understanding is fundamentally different from the common neuroscientific conception, in which voltage is an irreducible property of the cell. While that traditional conception is extremely useful and will suffice in the vast majority of situations, I feel that the ideas of biophysics can reveal new dimensions of the biological systems we study. UCSD has a strong biophysics community, and I hope to draw upon this resource in my research.

**<u>Broader Impacts</u>. Describe experiences in the following, or describe how you would address the following in your professional career: integrating research and education, advancing diversity in science, enhancing scientific and technical understanding, or otherwise benefiting society. (1 page)**

Teaching makes universities unique among research institutions. In every research institution, scientists must "teach" their

findings to colleagues who work on closely related problems—but the professor has two additional audiences: students, who have no specialized knowledge of any field, and colleagues who have a great deal of specialized knowledge but in other fields. This environment transforms the character of academic research by making it a holistic enterprise, framed in the context of other disciplines and informed by them.

In practice, however, students and colleagues are often only *potential* audiences, to be ignored or minimized as the professor pleases. Many scientists seem to believe that developing one's abilities as an educator automatically hinders work in the lab. Strictly speaking, that's true. Lecturing on the canon to undergraduates won't generate publishable data.

This attitude partly stems from the way in which most undergraduate courses are organized. Courses in biology tend to emphasize the structure of information rather than how the information was gained. An effective researcher needs to know the current state of knowledge, so courses are right to seek that emphasis. But researchers also need criteria for deciding which questions to answer and which experiments to perform, criteria which can not be gleaned from a set of facts. Therefore it is vital to teach research methods by reading primary literature and engaging it critically.

For the professor, reiterating established data can be a chore because it is far removed the activity of research. Teaching research skills, however, will always be relevant to the professor's practice. The state of knowledge changes over time, but careful application of the scientific method will not go out of date. Undergraduate courses are usually directed towards the former and away from the latter, and in my opinion this has led many scientists to take a negative view of teaching.

As described in my essay on educational experiences, some courses are springing up which do focus on the intellectual issues driving research rather than the specific content. (I took such a course, and it pulled me away from mathematics to empirical science.) As a professor, I hope to teach my courses in a similar manner as far as possible. Undergraduates are prepared to understand what it means to perform research, and they need only the encouragement and guidance from their professors to do so.

As an undergraduate and in graduate school, I've taken advantage of many opportunities to teach. My first formal experience was for a biology course I'd taken the previous year, Dr. Steve Kron's course, in which students read a journal article each week. As a TA for one week, I was responsible for finding a published paper for the class to work with, giving a review lecture to introduce the topic and specific problems in the field, preparing the paper's author to give presentation on his research, designing a laboratory exercise, and giving students feedback on their written work. This was my first formal experience in teaching, and it impressed upon me how a teacher or mentor provides the greatest benefit: not only by conveying knowledge, but engaging the student in inquiry.

I've also taught some mathematics. As an undergraduate I participated in the University of Chicago's Young Scholars Program, a tutoring initiative designed to teach advanced (and unusual) math topics to gifted middle school and high school students. Our role as tutors was not so much to teach as it was to facilitate discovery. In helping small groups of students work through math problems, I made sure each student spent much more time at the blackboard than I did.

In graduate school , I've taken many opportunities to teach, and also generated some for myself. Each entering class of students in Computational Neurobiology, along with students from the graduate program in Neuroscience, begin their time at UCSD with the two week Boot Camp. Students spend 12 hours a day, 6 days a week, learning about and performing experiments in various fields. Half of the laboratory activities are organized by older graduate students, and this past fall I had my first chance to work at Boot Camp. I worked closely with students daily, helping them to set up their electrophysiology rigs and identifying recorded neurons, as well as explaining principles of circuits and basic neurobiology.

Teaching needs to be learned through experience, so I've tried to find opportunities where I can give lectures. During my first year of graduate school, the topic of information theory came up frequently but it wasn't covered in our regular courses. In order to learn more, another student and I organized an informal series of lectures to be given by students. Over the past summer, I also organized a similar series on control theory. For both series, I talked with professors to establish a syllabus and convinced a few professors to give lectures. I also presented three lectures myself, which was a valuable experience.

In the future, I will be a teaching assistant for courses in biology and math. I plan to take advantage of UCSD's program for TAs known as Preparing Professional Faculty (PPF) in which graduate students work with a faculty mentor. TAs receive feedback on their leading of discussion sections, including the possibility of a section being videotaped and reviewed with a member of the PPF staff. I think it is important to develop classroom skills in tandem with work in the laboratory.

Above I've emphasized that academia is unique in the degree to which researchers are responsible for communicating their work. Such communication means more than teaching; it is important for scientists to at least contemplate the relationship between their research and the rest of the world, in particular how it relates to the work of other academics. If the latest scientific findings can only be understood by those focusing on the same narrow problem, what is the intellectual status of the findings? Research may be useful and clever, but often no one outside the small audience can understand or appreciate it. On the other hand, professors are not academic entertainers. Especially in science, our work has tangible consequences, such as new technologies and medicines. Nevertheless, focusing solely on material benefits is, I think, not the purpose of universities, or at least not the only one.

For me, the most important aims of a university are threefold: to facilitate teaching and learning in each of the specialized disciplines, to achieve a kind of intellectual unity among the community of specialists, and to spread the specialists' shared understanding to the world. Technical progress at the edge of science is an important commitment, but the professor has other obligations, too.

In my view, academic researchers must approach all of their responsibilities with enthusiasm, not only research. Undergraduate classrooms need professors who are among the most skilled in their fields. At the same time, professors can bring new life to their work by teaching it in a greater context. Successful research and effective, meaningful teaching can coexist, and in academia I think they should.

**Proposed Plan of Research Form (2 pages)**

**In a clear, concise, and original statement, describe research topics you may pursue while on fellowship tenure, and include how you became interested in these topics. Your statement should reflect your own thinking and work, demonstrate your understanding of research principles necessary to pursue these interests, and explain the relationship to your previous research, if any. Present your plan with a clear hypothesis or questions to be asked by the research. If you have not yet formulated a plan of research, your statement should include a description of one question that interests you and an analysis of how you think the question may best be answered. A listing of courses alone is not sufficient. Research topics discussed in your proposed plan may be used in determining eligibility.**

We fundamentally understand the visual system as a series of receptive fields (RFs), in which each neuron uses the simpler RFs of its inputs to generate a more complex output. My aim is to understand how a RF is built from the supporting anatomy. In cortex, the detailed connectivity which gives rise to the physiologically observed RFs is extremely difficult to study. An elegant alternative is to approach this problem in the first stage of visual processing: the retina. It is a compact, neatly organized network, with well-defined inputs and outputs, in which evolution has conserved the essential structure across unusually many species. The basic anatomy has been known since the time of Ramon & Cajal, and physiological recordings were first made in the 1930s. Such extensive knowledge allows us to begin to answer the fundamental question: exactly how does the retina's form support its function?

These questions have been given answers which seem generally true. For a common retinal ganglion cell (RGC), such as the primate parasol cell, the basic physiology is simple: spike rate is roughly proportional to a linear filter of photon input, where the filter is a 2-dimensional gaussian surface (e.g. Meister, et al 1999). Anatomically, the dendritic branches of a parasol cell roughly form a disc whose size is similar to the linear filter (e.g. Brown, et al 2000). The obvious hypothesis is that the dendritic tree gives the linear filter its shape, and inputs are summed linearly at the soma.

In such vague terms, the hypothesis is likely to be true. However, we know anatomical and physiological detail at a much finer resolution than gaussian surfaces or rough discs. The filter can be treated as linear for some stimuli (e.g. Chichilnisky et al 2002), but its shape is not gaussian. Recordings from isolated retinas and optic nerve recordings of intact animals show that the filter has fine structure, sometimes resembling a letter C more than a smooth lump (Brown, et al 2000). In addition, certain patterns of light show that the filter is not always linear, but behaves more like an aggregate of linear filters which combine nonlinearly (Victor et al 1979). In RGC anatomy, the disc approximation of dendritic trees also breaks down. The tree is only a finite number of branches, with different densities at different points in space.

Though such high resolution knowledge of physiology and anatomy is available, no one knows how these features correlate because it is difficult to record them simultaneously. One study (Brown, et al 2000) attempted to relate dendritic trees to RFs (i.e. the shape and time dependence of the "linear filters" above), but this study suffered from three problems: relatively noisy and low resolution RF recordings, a small number of cells, and ambiguous summary statistics.

I aim to answer that study's essential question, how RF physiology relates to the supporting anatomy, at the finest resolution which technology allows. The physiology of the RFs I will measure includes many parameters: the linear filter's intricate shape, its time course, the nonlinearity of spike rate, and the correlation of spikes with other ganglion cells. The "anatomy" also comprises many potential influences: the dendritic tree, the bipolar and amacrine cells which contact it, and the number and location of photoreceptors. It must be the case that nuances of RFs are constructed from variations in network connectivity, cell morphology, and synapse pharmacology. To learn exactly how the nuances and variations interact would help us establish principles of circuit dynamics. In this way, a careful, narrow study of the retina would lead to broader understanding of how neurons can work together in any circuit.

In essence, my experimental strategy is to use a multielectrode array to record physiological responses of many RGCs in rodent or primate retinas, and use imaging techniques to visualize the morphology of the recorded cells.

The first technique in this approach, using the multi-electrode array, is already well established. My lab uses custom manufactured arrays which contain 61 current-measuring extracellular electrodes spaced 30 or 60 microns apart in a hexagonal layout. These arrays have been used to simultaneously record the RFs of dozens of RGCs (Chichilnisky et al 2002). The advantage of simultaneous recording is that it eliminates the confounding factor of time difference when comparing cells. Serial recordings can be misleading because any tissue undergoes subtle changes during the recording session. By making simultaneous recordings, the data reflect intrinsic variability between cells. The multi-electrode array also makes it easier to collect data from many cells.

The second technique, visualizing the morphology of recorded cells, is a technology I plan to develop. To identify the locations of recorded cells, I will fill many RGCs with calcium-sensitive dye and take the spike-triggered average of the optical data. When an RGC spikes, its internal calcium concentration increases for a brief period, and the dye in that cell effectively changes color. The cell can be located by comparing the optical frames recorded when the cell spiked to the frames when it didn't spike. Other cells will also be changing color, but at different times. By collecting many images, the variable light emission from other cells are averaged away. Loading dye into RGCs is difficult without intracellular electrodes, but it has been possible to fill many neurons in cortical slice by incubation in the right mix of chemicals (Tashiro et al 2001). I am currently adapting this method to work in the retina.

The spike-triggered average will probably identify the cell's soma but not the detail of finer structures. After the somas of recorded cells have been located, I will completely fill a sparse set of RGCs with a uniformly fluorescent dye. If any of those filled

cells has a soma which lines up with a recorded cell's soma, the entire morphology can be seen in detail using high resolution microscopy. To see the morphology of additional recorded cells, I will bleach the dye away, and fill another sparse set of RGCs. This procedure will reveal the morphology of many recorded cells. Filling a sparse set of cells can be accomplished in several ways. My lab has used a gene gun to label cells with a lipophilic dye which reveals all the fine features of dendritic morphology. If the gene gun is not sufficient for my purpose, I will also try electrophoresis or retrolabeling via the optic nerve or lateral geniculate nucleus to completely fill a sparse set of RGCs.

I aim to understand how a RGC's RF arises in terms of the supporting anatomy. The first natural hypothesis is that RFs are largely specified by the ganglion cell's dendritic tree. Under this hypothesis, areas with greater dendritic coverage are more heavily weighted. The data to test this hypothesis can be gathered using the techniques described above, but the analysis is nontrivial. I plan to develop a statistical test to decide whether the heterogeneities of dendritic trees are significantly correlated with the heterogeneities of RFs. Using the multi-electrode array and imaging techniques that can visualize many cells, it should be possible to acquire enough data to test the hypothesis at a statistically significant level.

If the dendritic tree density fails to explain the RF, another possibility is that RF shape is partly determined by the location of the bipolar cells which connect photoreceptors to RGCs. In the mouse genome, a promoter (L7) has been discovered which, in the retina, is only expressed in rod bipolar cells. A strain of mice expressing GFP at the L7 promoter has been developed by the Du Lac lab at the Salk Institute, and I have access to those mice. With GFP illuminating all bipolar cells, I will be able to compare bipolar cell locations to the RF. A statistical test similar to the one described above could be developed to determine how well bipolar cell location predicts RF shape.

I will further test any correlations I discover between anatomy and RF by recording the physiology of a modified retina. A technique has recently been developed by the Callaway lab at the Salk Institute to selectively "shut off" neurons, and my lab has access to this technology. The technology involves a gene which expresses an exogenous potassium channel, a channel whose agonist is found only in plants. I would use a strain of mice which expresses this gene at the L7 promoter. Under normal condition, the exogenous channels would be closed and physiology would be unaffected. When the agonist is added, the exogenous potassium channels open and the bipolar cells would not be able to transmit their signal. I will use this technique to compare locations of rod bipolar cells to the RF which results when all bipolar cells are deactivated. Such physiological modifications will further corroborate hypotheses suggested by correlations between RFs and anatomy.

Given our knowledge of the details of physiology, it is natural to ask *why* RGCs respond as they do. Questions of neural coding go beyond the scope of my current research agenda, but I hope to address them indirectly. Learning more about anatomy's influence on activity can lead to novel experiments to test RGC physiology. For example, some RGC's RF nonlinearity can be explained by a model of independent subunits in the RF (Victor et al 1979). Based on purely physiological evidence, some RGCs appear to represent the input from many linear filters combined in a nonlinear fashion. If we can localize the anatomical correlates of these physiological subunits, then hypotheses about interaction between subunits will follow. Through physiological tests of those hypotheses, the RFs would be better characterized, and this could lead to new ideas about what the cell's signal means.

If we understand how anatomy contributes to the unique RF of each RGC, we could learn how the retina coordinates the available tools to fine tune physiology. Evolution is a conservative process, and strategies for fine tuning in the retina almost certainly occur throughout the nervous system.

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**Previous Research Experience Form (2 pages)**

**Describe any scientific research activities in which you have participated, such as experience in undergraduate research programs, or research experience gained through summer or part-time employment or in work-study programs, or other research activities, either academic or job-related. Explain the purpose of the research and your specific role in the research, including the extent to which you worked independently and/or as part of a team, and what you learned from your research. In your statement, distinguish between undergraduate and graduate research experience. If you have no direct research experience, describe any activities that you believe have prepared you to undertake research. At the end of your statement, list any publications and/or presentations made at national and/or regional professional meetings.**

For short term learning of a simple task, we know that a finger's representation grows when the finger learns a complex task. In the case of musicians, there are two additional factors. The first is that the musician's training is long term rather than short term. There might be an additional consolidation of the learning in cortex that affects the representation's size. The second factor is that the same representations are probably used for widely different tasks. For the musician, executing a precisely timed trill and dialing a telephone number use the same muscles and mechanoreceptors, and, presumably, the two tasks correlate with activity in the same regions of M1 and S1.

As an undergraduate I devoted my time during the academic year primarily to coursework. During the summers (2000, 2001, and 2002), I worked on a research project in the University of Chicago's Brain Research Imaging Center, a new suite of functional magnetic resonance imaging scanners (fMRI), where my research advisor was the BRIC's director, Dr. Steven Small. I was interested in sensorimotor systems, which matched the Center's focus on recovery from stroke.

The cortical correlates of movement have been known for many years: when a part of the body moves or is stimulated, a set of corresponding regions of cortex become active (e.g. Penfield et al 1950). The cortical patches are known as representations, and they are found in several cortical areas. I was interested in the regions with the most robust response, primary motor cortex (M1) and primary somatosensory cortex (S1). In these regions, the topology of representations resemble the topology of the body (e.g. neighboring fingers have neighboring representations).

Representations can change over time as a function of usage patterns (e.g. Recanzone et al 1992). For example, it was found in monkeys that if two neighboring fingers are bound together, their S1 representations fuse. If a finger is amputated, the nearby fingers encroach on its former territory. If a finger is used extensively for a task, its representation enlarges and encroaches upon neighboring representations. These changes were observed in the relatively short term, periods of a few months, and the tasks were relatively simple. To get a broader understanding of cortex's capabilities, I wanted to know how the sensory and motor systems change under conditions on the opposite end of the spectrum: for a very complex task, learned over the course of decades.

A musician's training is well-suited to a study of long term motor and sensory learning. Professional musicians play their instruments for many hours each day, actively attending to and modifying their performance. When I looked at the fMRI literature on motor studies of musicians, however, I found it consisted of essentially one kind of experiment (e.g. Hund-Georgiadis et al 1999 and Krings et al 2000): musicians and nonmusicians performed a difficult finger movement task while in the scanner, and the researchers looked for differences in brain activation to describe how the musician's motor system differs from a nonmusician's.

The problem with such an experiment is that the two groups are not performing the same task. Nonmusicians make significantly more mistakes and can't perform the task as quickly as musicians. Moreover, musicians have experience training themselves to learn complex movements, so they probably use a different learning algorithm than the nonmusicians. Since the two groups performed different tasks, we can not directly compare the corresponding brain activation.

This problem is not just an isolated technical flaw. It arises in the study of any "expert" system: the experts can do things which nonexperts can't, and if the nonexperts are trained on a complicated task, they are no longer nonexperts. Therefore experts have no control group for direct comparison. This logic led me to realize that a better question to ask is whether becoming an expert changes the performance of simple tasks. In the case of musicians, does learning to play an instrument alter the sensory and motor pathways that underlie everyday movements?

To estimate those alterations, I measured representations active during a simple finger tapping task: subjects in the scanner received visual cues (a number or letter on the right or left side of the screen) and responded by tapping the corresponding finger. At rest, the hands were in a relaxed, palm down position, and the fingers were slightly curved. Tapping a finger meant picking it up, moving it forwards about an inch and tapping down, then returning to rest. The task was very easy to learn, and no subject took more than a couple minutes to master it.

My hypothesis was that musicians would have M1 representations of the same size and in the same location as nonmusicians. I reasoned that although the musician's cortex learns many additional movements, it is not drawing on these capabilities when it simply taps one finger at a time. I further hypothesized that S1 representations would be larger, and possibly more spread out, consisent with changes observed following short term training.

I planned to begin the study by scanning intermediate musicians from the University of Chicago's Chamber Orchestra and comparing them to subjects who had never played an instrument or learned any fine motor skills. When I left Chicago to attend graduate school in fall of 2002, I had scanned and analyzed the performance of 3 musicians and 4 control subjects. Such a small population did not provide enough data to adequately test my hypothesis. However, my protocol and analysis are documented and I expect another student will scan the remaining necessary subjects within the next few years. If none does, I will most likely return to Chicago for a summer to finish the study.

My work in the BRIC was largely independent. Once I became familiar with the kinds of experiments made possible by fMRI, I read the literature and developed the question mostly on my own, though I discussed my ideas with Dr. Small and other lab members frequently. To develop the experimental design, I worked with Dr. Small and his postdocs. Once I learned the data analysis methods, I performed them myself and wrote my own scripts to execute them. I was also responsible for training and testing subjects.

In graduate school, I've completed four research rotations, quarter-long projects in prospective thesis labs. The most meaningful for me was the rotation with David Kleinfeld. In his lab, my goal was to make a computational model of ion channel dynamics which could be related to experimental findings in the Kleinfeld lab.

The finding was that motor neurons in young rats begin to show a physiological property known as subthreshold resonance (which I don't describe here) at just about the same time as they incorporate a new ion channel into their membranes. My goal was to discover whether the new ion channel alone could induce subthreshold resonance in a normal neuron. My method was to model a single-compartment neuron using Hodgkin-Huxley style equations, and then add in a term describing the ion channel's dynamics.

I found that the new ion channel was sufficient to induce subthreshold resonance. But this finding wasn't the end of my study. Since the phenomenon could be modeled, I could explore its mechanism in extremely fine detail. I examined the state of the cell as it began to show subthreshold resonance, going so far as to follow the ion channels' internal variables at submillisecond resolution. Through such a close study, I was able to make conclusions about the mechanism of subthreshold resonance.

Of course, my model might have reproduced the phenomenon through a different mechanism than neurons actually use. But the model suggested a plausible mechanism, and my work led to new physiological experiments that tested my predictions. In this rotation, I saw firsthand how models can be used to gain a deeper understanding of biological systems.

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