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From: Terry Sejnowski <terry@salk.edu> Subject: Qualifying Examination

Computational Neurobiology Training Program Qualifying Examination

August 3, 2003

There are 4 areas of examination:

1. Mathematics/Physics/Engineering 2. Molecular/Cellular/Development 3. Systems/Behavior/Cognition 4. Modeling/Computation/Theory

Each student should pick one question from each area. No question should be answered by more than one student so some coordination is required.

Each question should be answered with a 1-2 page essay and no more than 5 citations to the literature.

A good answer will contain a concise summary of a large body of work and specifics. You should be able to draw out important organizing principles from specific data.

The essays should be turned in to John Staight at the INC office by Monday Sept 1 at noon.

There will be a 30 min oral exam on each question, which will start with a brief 5-10 min summary of the essay followed by questions from the faculty. In addition to probing specific issue raised by the question chosen by the student, more general issues will also be explored.

Wed Sept 3 - 8:00 AM - 12:30 PM: Mathematics/Physics/Engineering
Robert Hecht-Neilsen and Henry Abarbanel Th Sept 4 - 8:00 AM - 12:30 PM:

Molecular/Cellular/Development
Marla Feller and Massimo Scanziani (tentative)

Fri Sept 5 - 8:00 AM - 12:30 PM: Systems/Behavior/Cognition
William Kristan and Mark Whitehead

Sat Sept 6 - 8:00 AM - 12:30 PM: Modeling/Computation/Theory
Terrence Sejnowski and David Kleinfeld

Students are encouraged to read through the relevant chapters on each topic in basic introductory texts since we will expect and will probe the command of each students of fundamental knowledge as well as recent research.

QUESTIONS

Mathematics/Physics/Engineering

1. A new electrode array design features a regular square array of 10,000 identical full-cortical-depth multi-contact electrodes, with 50 micrometer spacing, all mounted perpendicularly on a common structural backplane. When slowly plunged perpendicularly into cortex these electrodes cause little tissue damage (like knitting needles plunging into a ball of yarn). Following recovery from surgical implantation of

the array, it can remain in place and be monitored indefinitely via a cap with a radio link. Because of its detailed design, the array essentially only receives signals from pyramidal neurons that vertically span a more than half of the full cortical depth (and these received signals are essentially the same 2 ms long pulse waveform, independent the depth of the transmitting neuron's soma). Thus, we can treat cortex as two-dimensional. Assume that all of the neurons in the population of neurons that can be sensed produce an identical brief output signal every time they launch an action potential. Further assume that the transmission medium is isotropic and homogeneous. However, because of the shielding action of the conductive medium, the signals being monitored attenuate in amplitude as the inverse fourth power of distance. Nonetheless, each neuron action potential within the volume of cortex being monitored is seen in at least eight electrodes (each at the appropriate level of attenuation). Assume that the probability of two action potential waveform signals exactly superposing at one electrode is low. Propose a method for using this array to build an exhaustive database of the firing histories of all of the million or so neurons within the population which can be monitored by the array. [Hint: start by considering the received signals at nearby electrodes from a single arbitrarily positioned neuron. Knowing these received signals, then consider how you might identify all future action potential outputs from that single neuron.]

2. A 50 nm diameter neurotransmitter vesicle within a synapse does a "kiss and run" delivery of a tenth of its cargo of 2,000 molecules during a 10 microsecond merger with the cell membrane adjacent to the synaptic cleft (which can be assumed to have a constant concentration of the molecule equal to 1% that of the pre-merger vesicle). Ignoring edge effects, and assuming that the opening and closing of the circular vesicle pore was sinusoidal, calculate the diffusion coefficient for this molecule assuming that Fick's law holds. Assume all the solvents have the properties of water. In your answer, use an annotated diagram to illustrate your detailed reconstruction and analysis of this "kiss and run" neurotransmitter release event. Note all assumptions (both given above and introduced by you) in your diagram of the event.

3. A magical new nanoparticle is linked to a ligand that selectively binds to the axon hillock of pyramidal neurons. Whenever an action potential is launched by such a cell this nanoparticle momentarily changes its fluorescence properties - emitting green photons if the particle is bathed in infrared light of roughly twice this wavelength. Many skull 'windows' have been created that allow light detecting devices to view a large volume of brain tissue from different directions (and to provide the required infrared illumination). These devices each consist of a two-dimensional array of millions of photodetectors, each equipped with its own perpendicular collimator - allowing each pixel detector to only see flashes from a narrow cone of tissue. Propose a method for using the outputs of these detectors to accurately record the three-dimensional brain position and time of each green flash. What might be some of the problems with such a system?

4. A 30 micron diameter spherical neuron at equilibrium maintains a uniform membrane potential of -70 mV. Calculate the effective areal resistivity of the membrane (Ohms per square meter), given that only sodium and potassium channels are involved. Obtain, cite, and use published estimates for the areal density and number of ions per second pumped for each of these channel types for some specified type of cell. Comment on the physical meaning of the concept of areal resistivity in this case.

5. A neuropharmacological experiment with nematodes causes the population of animals receiving the compound to wiggle somewhat more vigorously than the control population. There are 35 subjects and 42 controls and both populations can be considered to be statistically homogeneous. The wiggles are measured using two variables. The first

variable appears, in both the subject and control populations, to obey a Gaussian distribution with respective sample means of 565 and 412 and variances of 245 and 198. The second variable appears to be Poisson in both cases, with means 9.2 and 7.3, respectively. Present a carefully reasoned quantitative analysis (including some sort of overall confidence level determination) of whether the subjects really are wiggling more vigorously than the controls (in both variables, larger values mean more wiggle).

6. We are going to study the dynamics of two pools of mathematical neurons, called A and B, which are constituted as follows. Each pool contains 50,000 neurons. During a development process (not considered here) each pool has become equipped with a fixed set of 35,481 tokens. For simplicity, assume each such token consists of a subset of 400 neurons from its pool. Because their development process involves random axonal growth processes, each token can be considered to have been created by selecting 400 neurons uniformly and independently at random to make up that token (for analysis purposes it is OK to assume that this selection process is with replacement). The individual token formation processes can be assumed to be independent from one token to another. Index each set of tokens from 1 to 35,481. Then assume that each neuron of token k of pool A is connected by an axon collateral to each neuron of token k of pool B, and vice versa; for all k from 1 to 35,481. These are the only axonal connections between the neurons of the pools (connections between the neurons within a pool are ignored here). Given this structure, assume that the neurons of token m of pool A are active (sending out 'strong' signals to the neurons of pool B to which they connect) and that the other neurons of pool A are inactive (not sending signals to the neurons of pool B). Now activate the 400 neurons of pool B which individually receive the largest numbers of active inputs from pool A (all other pool B neurons are inactive). Then go back to pool A and activate the 400 neurons which individually then receive the largest numbers of active inputs from pool B (with all other pool A neurons inactive). Roughly quantify the overlap that will exist between this new collection of active neurons of pool A and the neurons of token m. Bound the probability of 'small' overlaps (use your own definition of 'small'). Explain what is going on. Discuss what would happen if the initial state were not token m but a perturbation of token m.

7. Two neurons are found to be interacting in a complicated local neuronal circuit. Analysis of the details of this circuit (synaptic dynamics, channel dynamics, receptor dynamics, etc.) has suggested that the firing rates x(t) and y(t) (in a particular zero-centered unit of frequency measure) of these neurons satisfy the following equations: dx/dt =3D -y + x(1 - x^2 - y^2) and dy/dt =3D x + y(1 - x^2 - y^2). Present the 4-dimensional phase portrait of the solutions of this set of equations and comment on its geometrical structure (use any projections you deem useful). Note any limit cycles, strange attractors, or bifurcation situations of the solutions. Comment on the total possible ensemble of solutions and rule out those that would not be physiologically meaningful.

8. You have a large set of recordings from 1000 simultaneously recorded ganglion cells from the retina in response to a moving visual stimulus. How would you analyze this large data set to determine the amount of information it contains about the velocity of the moving stimulus?

9. A future MRI machine with improved magnets, RF system, and sensing coils can map the volume molarity of a particular molecular species in 3-D. At the time this map is made (a specific developmental epoch), this molecule is being used to guide the growth of a fascicle of axons, emerging from its particular brain nucleus of origin, towards its desired destination nucleus. In unspecified units, the volume molarity map is given by M(r,theta,phi) = 1 + r^2 + cos(theta) + sin(phi), where r, theta, and phi are spherical

coordinates and where r is non-negative and the azimuthal and elevation angles theta and phi, respectively, are limited to the range 0 to pi/2. Assuming that the nucleus issuing the fascicle is at the origin and assuming that the fascicle (the distal end of which can be viewed as a single point at each time) always grows in the direction of the highest concentration gradient at each point, plot the 3-D path that the fascicle will take out to the point where one of the angle limits is exceeded. Illustrate this path using multiple projections with judiciously chosen constant-coordinate lines shown. Use color for increased clarity. If the speed of growth is proportional to the square of the concentration gradient, graphically show the fascicle velocity and acceleration vectors at several points along its growth path. Calculate how long (in t units) it will take for the fascicle to traverse the depicted path.

10. The average adult human cerebral cortex is postulated to consist of 120,000 largely disjoint, roughly convex, functional 'hypercolumns' or regions which traverse all six layers. Each such region is organized at various points during development to implement a finite lexicon of, typically, thousands of descriptive tokens, at most one of which can be used at a time to describe one attribute of an object or action of the mental world. These lexicons are largely frozen for life at the end of childhood and the tokens become the fixed descriptive terms that are required for the accumulation and use of knowledge over decades. Assume that each token is a group of 400 pyramidal neurons (which become active at the same time to express that particular symbolic token) and that each token is chosen uniformly and independently at random from a collection of 50,000 neurons (the numbers are so large that you can assume replacement if you want to). Each token is selected independently from the others. How many tokens (N) would have to be selected before the most overlapping pair of tokens (out of the total of N(N-1)/2 pairs) would be expected to overlap by more than 10%? By 20%?

Cellular/Molecular/Development

1. Describe a homeostasis model for synaptic plasticity. Include a detailed example.

2. Describe a Hebbian model for synaptic plasticity. Include a detailed example

3. Pick a synapse that undergoes long-term potentiation and present the evidence that the expression of LTP is pre or postsynaptic.

4. What factors dictate dendritic development? Include 2-3 specific examples.

5. Describe how voltage-gated channels on the dendrites of a cortical pyramidal cell, shape post-synaptic potentials

6. How many different types of cell are there in the retina? In the cortex? Your answer will depend on your definition of cell type, so give a precise operational definition of how you would decide on whether two cells were different.

7. How is the topographic map formed between the ganglion cells in the retina and the map in the superior colliculus during development?

8. New olfactory receptor cells are born in the adult mouse every day. How do the axons of these cells find their way to the correct target in the olfactory bulb?

9. Pick a synapse and describe in detail how calcium levels, kinetics and localization affect/determine short term plasticity

10. How many genes are uniquely expressed in the brain? Give three examples: give the locations of the cells that express them and their function in those cells.

Systems/Behavior/Cognition

1. How are the diverse chemicals that stimulate the taste and smell senses coded my the peripheral and central nervous system?

2. Describe the organization of sensory and motor elements of the autonomic nervous system. Include the roles of the hypothalamus and nucleus of the solitary tract.

3. To be a meaningful concept, "population coding" must mean some thing more than that "a lot of neurons are active". Give a concise definition of population coding and describe at least one case in which a population code has been shown to be important.

4. "Neural coding" is a hot topic, but identifying a true neural code is very difficult. Discuss what kinds of experiments are required for a candidate neural code to become a certifiable, true code. Give two examples of real neural codes.

5. Electrical connections, once thought to be rare in vertebrate nervous systems, are being found in a variety of locations in the mammalian brain. Pick one instance of electrical coupling among neurons, discuss how the electrical coupling affects the function of the neuronal system, and discuss how such a function depends upon the connection being electrical rather than chemical.

6. Discuss the difference between feed-forward inhibition and feed-back inhibition. Give an example of each, and discuss how each kind of inhibition is important for the function of that system.

7. Discuss the role of the primary motor cortex in motor control in light of recent work from the Graziano lab which suggests that M1 might function to command complex behavioral acts rather than specific, localized movements. In particular, propose experiments (ideally involving modeling) that could potentially distinguish among the various functions ascribed to M1.

8. What is the function of the anterior cingulate cortex? Bring to bear evidence from lesions studies, event-related potential measurements, single unit recordings, and anatomical connectivity.

9. Multitaper spectral methods are being used to analyze field potentials recorded by extracellular electrodes in the cortex. Explain how you would use this method to analyze the coherence between the spikes from single neurons recorded on the same electrode. In particular, design an experiment that could be used to explore the neural correlates of visual search.

10. The stomatogastric ganglion of the lobster is a central pattern generator. Characterize its different rhythms and explain how these oscillatory states emerges as a consequence of the intrinsic properties of the neurons and their connectivity.

Models/Computation/Theory

1. Most ion channels have only one open state but many closed states. How is it possible to determine the number of closed states and their transition probabilities based on patch clamp recordings of single channels? In particular, how many closed states dose the fast Na channel have that is responsible for the action potential in the quid axon?

2. Estimate the energy consumption of synaptic transmission, of action potential firing, and lastly the power consumed by a cubic millimeter region of cortex.

3. Intracellular recordings from neurons in the cortex reveal that the membrane voltage fluctuates around the resting level with a peak-to-peak amplitude of 10 mV. What are all the sources of this noise? The noise amplitude does not change when the cell is depolarized? What impact will this noise have on the firing rate vs input curve?

4. In the hippocampus of rats, many neurons have a low spontaneous activity and are activated when the rat is located in a restricted region of the environment. What are the inputs to the hippocampus that endow these neurons with these "place fields". What happens to the place fields when the lights are turned out? What is the function of these neurons? Do humans also have such neurons?

5. Neurons in the primary visual cortex have been categorized as simple and complex on the basis of their response properties. What tests have been used? How good is the evidence that these neurons are distinct types rather than being the ends of a continuum? out and the rat?

6. An isolated passive soma acts as a low-pass filter to subthreshold inputs. Yet the addition of active channels and dendrites, which may also contain active channels, can change the subthreshold electrical characteristics of a neuron. Describe how a neuron with a subthreshold resonant response, or equivalently a bandpass response, can be formed from dendrites and from active channels.

7. Behavioral data suggests that bats can detect both the range of their prey and the speed of their prey. What operations does the bat's echolocation circuitry need to perform to carry out these operations? Can you suggest a neurons circuits for each of these operations?

8. Mammals with substantial binocular vision use vergence to adjust for visual depth. How do animals that cannot change the vergence of their eyes solve the problem of visual depth perception?

9. Explain, both qualitatively and quantitatively, the observation of bistability in the firing patterns of single motoneurons.

10. Explain, both qualitatively and quantitatively, how synaptic depression may be used to remove the constant (DC) part of a stimulus stream, so that time varying changes in an input are accentuated.