

Bi/CNS/NB 150 Midterm Examination

Due: Tuesday, Nov. 3, at 4:30 pm

You may not read past this cover page before beginning this timed exam.

- The exam covers lectures and readings through Monday, Oct. 26.
- The exam accounts for 30% of your final grade.
- Each of the four questions you will choose accounts for 7.5% of your final grade.
- Choose only FOUR of the five questions in the exam and indicate them clearly.
- The number of pages is provided for each question. “End of question X” at the bottom of a page indicates the final page for that question.
- The exam has a total of 13 pages. Count the pages before you begin.
- 3.5 hours are permitted for completion of the exam. Use the first 30 minutes to calmly read the exam and choose which four questions you will answer. Use the remaining 3 hours to answer these questions.
- If you pass 3.5 hours, you may draw a thick line across the page, complete the exam below that line, and indicate how much time you used beyond 3.5 hours. Credit may be given for answers completed past 3.5 hours. Doing this will aid the staff in assessing the appropriateness of the time limit.
- You may refer to lecture slides, your notes, this year’s question sets, and the Kandel textbook (including the digital version) to complete the exam.
- You may not use the Internet while taking the exam, but you may use a computer.
- You may not collaborate or discuss questions or answers with anybody before the exam’s due date.
- If you think you need to make further assumptions to answer a question, you can provide those assumptions and the reasons for them with the answer. However, no further information should be necessary to answer any questions correctly.
- Include your name and the page number on every page.
- Use a separate sheet of paper for each question.
- Use complete, grammatically correct sentences.
- Type all answers if possible.
- Submit with this cover page.
- Drop off in the Bi 150 box outside Baxter 331 or e-mail to the head TA (jcolas).
- Note that late submissions receive a 10% deduction for every day past the due date.

Name:

Time and date submitted:

Total pages (including cover page):

Time spent completing exam:

Comments:

Total grade:

Question 1. Action Potentials. 7.5 points 2 pages

A. With respect to the Nernst potential of an ion species,

A1 (0.25 pts) Which driving forces (chemical free energies) are balanced at this equilibrium?

A2 (0.25 pts) Which conditions determine these driving forces?

B. With respect to the resting potential of the electrical circuit model of a neural membrane,

B1 (0.25 pts) Which electrical quantity (or parameter, or property) is conserved to achieve this steady state?

B2 (0.25 pts) Which other electrical properties (or parameters, or quantities) determine this conservation?

C. Many studies of the electrical properties of neurons involve injecting a controlled amount of current into a cell. In a living brain, without electrodes,

C1 (0.25 pts) What naturally causes depolarizations in neurons?

C2 (0.25 pts) Where in a cell can this depolarization initiate?

D. Concerning the integration of electrical signals within neurons,

D1 (0.25 pts) Where do action potentials usually initiate? Which underlying parameters cause this to become the initiation zone?

D2 (0.25 pts) Is passive spread the only mechanism that spreads depolarization from C2's answer to D1's answer? If not, explain.

E. Describe the phases of an action potential, using a bulleted list, a timeline, and/or graphs. Make sure to explain:

E1 (0.5 pts) The time course of the opening and closing of sodium channels

E2 (0.5 pts) The time course of the opening and closing of potassium channels.

E3 (0.5 pts) The all-or-none waveform.

E4 (0.5 pts) The absolute refractory period.

E5 (0.5 pts) The relative refractory period.

F. A neuron has an action potential threshold at -50 mV, achieved by a current pulse of 3 nA. If the neuron doubles in surface area while maintaining its ion channel density,

F1 (0.5 pts) What parameter(s) would change in the equivalent circuit? Would it/they increase or decrease?

F2 (0.5 pts) What (qualitative) effect would this have on the cell's threshold for firing action potentials, and why?

F3 (0.5 pts) What (qualitative) effect would this have on the cell's firing rate in response to a 6 nA, prolonged, constant-amplitude current injection, and why?

G. Return to the “before” conditions of part F. If the density of potassium channels in the neuron's membrane doubles,

G1 (0.5 pts) What parameter(s) would change in the equivalent circuit? Would it/they increase or decrease?

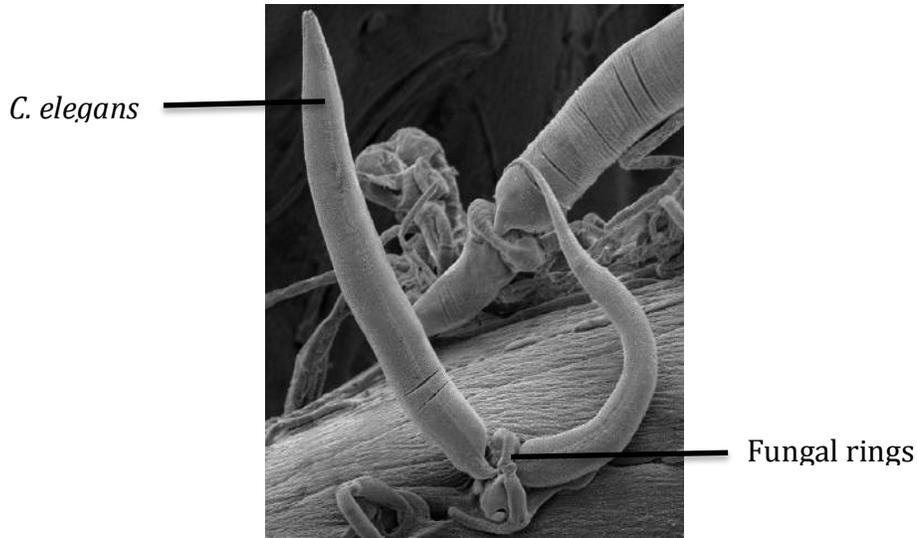
G2 (0.5 pts) What (qualitative) effect would this have on the cell's threshold for firing action potentials, and why?

G3 (0.5 pts) What (qualitative) effect would this have on the cell's firing rate in response to a 6 nA, prolonged, constant-amplitude current injection, and why?

End of Question 1

Question 2. Ligand-gated Ion Channels: Escaping Worms (7.5 pts total, 3 pages)

The world can be a very dangerous place for the tiny nematode, *Caenorhabditis elegans*. During foraging attempts, these worms run the risk of encountering predators such as nematode-eating fungi. These ferocious fungi catch worms by setting noose-like traps that begin to constrict upon contact. Death is not certain, however, as *C. elegans* may escape from these traps by simultaneously executing backwards locomotion and suppressing their head oscillations as they slip out of the fungus's noose.



C. elegans trapped in constricting fungal rings.

The ion channel, IC-55, is expressed in the AVB neuron, which provides inhibitory inputs to neurons that promote backward locomotion in the worm. IC-55 is also expressed in the worm's neck muscles.

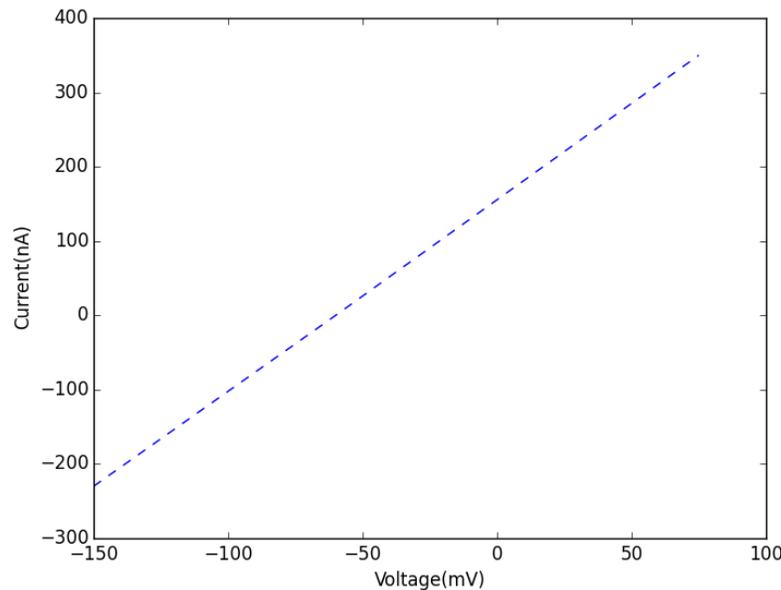
- a) As a researcher who is fascinated by the worm's escape response, you characterize the IC-55 channel. As your first step, you employ a conventional, well-understood technique: you express IC-55 channels in *Xenopus* oocytes (frog eggs) by mRNA injection. You then measure voltage-clamp current (I_m) vs time for IC-55 at a holding potential of -70 mV when various neurotransmitters are applied to the oocyte. The black bars in the plot indicate the duration of neurotransmitter application to IC-55. (OA=octopamine, 5HT=serotonin, DA=dopamine, TA=tyramine)



a1 (0.5 pts) From the plot, what is the molecule X that activates the IC-55 channel?

a2 (0.5 pts). Is the receptor that X binds to likely to be an ionotropic receptor (IC-55 itself) or a metabotropic receptor (that eventually activates IC-55)? Give your reasoning in one sentence.

b) (0.5 pts). To investigate the ion selectivity of the IC-55 response (either direct ionotropic or indirect metabotropic), you hold the *Xenopus* oocyte membrane potential at various levels in a NaCl-rich external solution. You obtain the following current–voltage relationship:



Based on the plot, which two ions are likely to permeate IC-55?

c) C1 (1 pt). Now that you know the ligand that activates IC-55 and the ions that IC-55 is likely to be permeable to, how would you expect the AVB neuron to respond when the neuron presynaptic to it releases molecule X? (Assume that AVB has intracellular and extracellular ionic concentrations similar to those of the oocyte experiment.)

C2 (0.5 pt) How would you expect the neck muscles to respond?

C3 (1 pt) What subsequent changes in the worm's movement do you expect to observe? Give your reasoning (2 sentences).

d) From your extensive reading of the worm escape literature you discover that a molecule called DeadWorm (DW) is an IC-55 antagonist. Draw and label the expected traces of I_m vs. Time for the application of molecule X to IC-55:

a) (0.5 pts) in the absence of DW

b) (0.5 pts) in the presence of DW

c) (0.5 pts) after DW is completely washed off.

Refer back to the plot given in part a) of this question as needed.

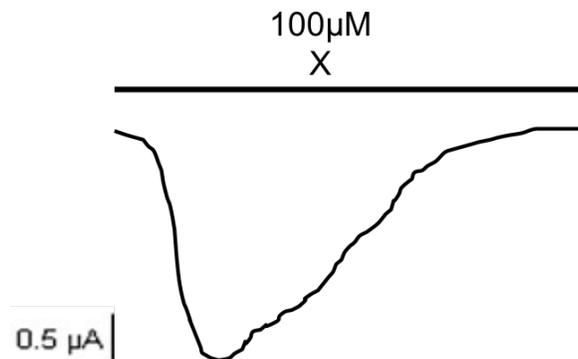


e) (2 pts) Based on the data you have obtained thus far about IC-55 channels, you devise a plan to increase the worms' chances of survival in the presence of the fungi. You add a 100 μM solution of molecule X to some plates containing the fungi and worms in the hope that the worms take up the exogenous X. Interestingly, you discover that the survival rates on the plates with X added are lower compared to the plates without X added.

To get to the bottom of this unexpected result, you conduct a modified version of the experiment you performed in part a). The modifications you make are:

- A 100 μM solution of molecule X is applied
- The solution of X is applied for a **10 s** duration

You obtain the following I_m vs. Time plot:



From the data collected during your experiment, suggest a possible explanation for this observation. 3 sentences.

End of Question 2

Question 3: Synaptic Transmission (7.5 points total, 3 pages)

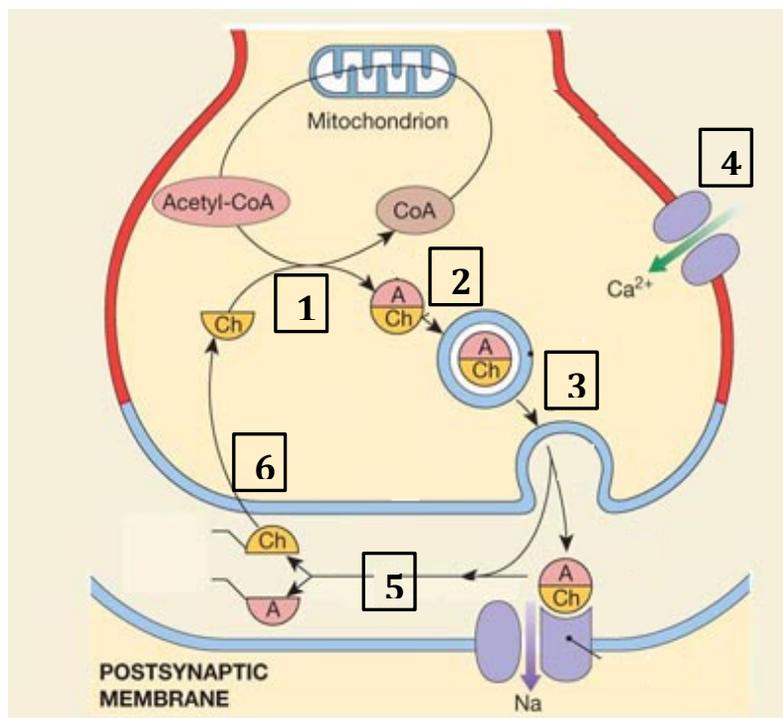
Part A: Snakes (4.8 points)

It is the year 2025. You are on a flight to a conference to present your research as a leading neuroscientist in your field, when suddenly you find that your plane has been filled with many very aggressive, exceedingly venomous snakes. (For a documentary of a highly similar situation, see *Snakes on a Plane* [2006] <http://www.imdb.com/title/tt0417148>).

Six passengers have been bitten, each by one snake. Here are the “presentations”: three are limp and unresponsive, the others have severe muscle spasms. The crew requires your assistance to determine which toxin is poisoning each. Fortunately, there is an ophidiologist (snake scientist) on board who is familiar with the snakes and their venoms, but cannot distinguish which snake bit which passenger. It is critical to make this distinction because administering the wrong antivenom (antivenin) will very likely be lethal to the victims. The ophidiologist gives you the following information:

Snake	Toxin	Toxin description	Affects step #:
<i>Viperidae voldemortensis</i>	A	Acetylcholine synthase inhibitor	
<i>Elapidae basiliskae</i>	B	SNARE protein cleaving enzyme	
<i>Viperidae samjacksonis</i>	C	Voltage-gated Ca^{2+} channel blocker	
<i>Elapidae ekans</i>	D	Plasma membrane choline reuptake inhibitor	
<i>Pythoninae arbok</i>	E	Acetylcholinesterase inhibitor	
<i>Colubridae snakus</i>	F	Potent voltage-gated Ca^{2+} channel agonist	

A1 (1.2 points). In the table above, **fill in** which step of acetylcholine (ACh) synaptic transmission each toxin is most likely to affect (numbers can be used once, more than once, or not at all). A/Ch is ACh, A is acetate, and C is choline.



You happen to have with you two tools (*you invented both in 2020, as a graduate student, with support from the BRAIN initiative*):

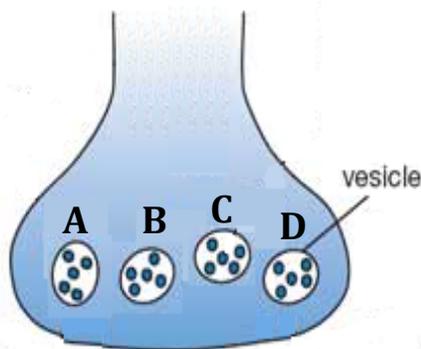
- 1) Transdermal microelectrode: Capable of measuring presynaptic conductances (G_{Na} , G_K , G_{Ca} , G_{Cl})
- 2) Acetylcholine test kit: Can read presence of acetylcholine at the neuromuscular junction (nerve-muscle synapse) and determine whether it is absent, exclusively in the presynaptic terminal, exclusively in the synaptic cleft, or in both the presynaptic terminal and synaptic cleft.

A2 Explain (6 x 0.6 = 3.6 pts) your criteria for how you would determine which passenger was bitten by which snake. Be sure to include the results you expect from each victim, comment on whether they would be one of the limp or spastic passengers, and the logic behind how this allows you to pinpoint the identity of the toxin (and snake). Please fill in the last three columns of this table.

Toxin	Toxin description	Patient test results		
		G_{ion}	ACh localization	Presentation
A	Acetylcholine synthase inhibitor			
B	SNARE cleaving enzyme			
C	Voltage-gated Ca channel blocker			
D	Plasma membrane choline reuptake inhibitor			
E	Acetylcholinesterase inhibitor			
F	High affinity voltage-gated Ca channel agonist			

Part B: Quantal analysis (2.7 points)

We have touched on the topic quantal synaptic transmission- the idea that neurons release neurotransmitters in quantized packets at terminals. This was the work of Bernard Katz and colleagues, one of many papers that contributed to Katz winning the 1970 Nobel Prize. We will perform a similar theoretical analysis. Consider a synaptic terminal containing a pool of just 4 vesicles (labeled A-D):



If we know that with a pool size $n = 4$, and a low probability of fusion $f = 0.1$ following an action potential, that the average activity of the synapse will be to release $nf = 0.4$ packets of neurotransmitter. But let's see how this figure is obtained quantally.

B1 0.9 pts)

Calculate the probability $P(x)$ where x is the number of vesicles fused. Show work and feel free to attach pages, though it shouldn't be necessary.

Two hints:

- 1) You will need to know that the probability of a vesicle *not fusing* is $1-f$
- 2) Vesicles A and B fusing are distinct events from C and D fusing. Indeed, there are six ways to have 2 vesicles fuse.

$P(0)$:

$P(1)$:

$P(2)$:

$P(3)$:

$P(4)$:

B2 (0.9 pts)

Show mathematically that this set of descriptions completely accounts for the averaged behavior:

B3 (0.9 pts)

Increasing the duration of the action potential greatly increases the probability of vesicular fusion. If f becomes 0.7, **what number of quanta is most frequently released?**

End of question 3

Question 4 (7.5 points, 2 pages): Neuroanatomy

This year marks the inaugural Bi 150 field trip through spacetime! Caltech engineers have kindly lent us a time machine and C-3PO. You are visiting several major contributors to the history of neuroscience. Each of them is eager to find out what you have learned so far in the course. Please answer the questions below given your current knowledge about the brain to update these folks from the past!

4.A (5 x 0.3 = 1.5 points): Humors

Galen of Pergamon (b. 129) is curious about the validity of his now-discredited proposal that nerves convey fluid secreted by the brain and spinal cord to the periphery.

- 4.A.a. What fluid is the central nervous system in fact suspended in?
- 4.A.b. What are each of the membranes enveloping the brain and spinal cord called?
- 4.A.c. Where is this fluid located relative to the aforementioned layers?
- 4.A.d. Name the general regions inside and outside of the nervous system where this fluid is located. (You may wish to also draw a diagram and clearly label it.)
- 4.A.e. Which ion has the highest concentration in this fluid?

4.B (5 x 0.3 = 1.5 points): Functional localization

Franz Joseph Gall (b. 1758), the founder of phrenology, and Jean Pierre Flourens (b. 1794), one of phrenology's most outspoken opponents, are debating the extent to which specific functions of the brain can be localized to distinct regions.

- 4.B.a. Name the four lobes of the brain.
- 4.B.b. What separates the most rostral lobe from the lobe that is adjacent and caudal to the most rostral lobe?
- 4.B.c. Which lobes are the most basic processes underlying vision, audition, somatosensation, and motor control primarily associated with?
- 4.B.d. Which lobe is disproportionately large in humans relative to other species?
- 4.B.e. What is the main feature of human cerebral cortex that complicates estimating its local surface area via measurements on the skull?

4.C (5 x 0.3 = 1.5 points): Neuropsychology

Paul Pierre Broca (b. 1824) and Carl Wernicke (b. 1848) are proud to announce that they have identified specific areas of the brain concerned with language by studying patients with focal brain lesions that result in particular functional deficits.

- 4.C.a. If one were to finely slice the entire brain along the horizontal plane, only the rostral-caudal and medial-lateral axes would be defined for each slice in that plane. Which pairs of cardinal axes are defined for each of the remaining cardinal planes?
- 4.C.b. Which cardinal plane(s) of the brain exhibit(s) approximate bilateral symmetry?
- 4.C.c. Which cerebral hemisphere is language primarily associated with for right-handed people?
- 4.C.d. Which cerebral hemisphere controls movements of the right hand for left-handed people?
- 4.C.e. What is the largest structure connecting the two cerebral hemispheres in a human brain?

4.D (5 x 0.3 = 1.5 points): The neuron doctrine

Camillo Golgi (b. 1843) and Santiago Ramón y Cajal (b. 1852), who applied Golgi's tissue-staining method, wonder about the implications of Ramón y Cajal's groundbreaking hypothesis that the nervous system is made up of discrete neural cells.

- 4.D.a. How many neurons, glial cells, and synapses are in an average adult human brain?
- 4.D.b. Are there more neurons in cerebral cortex or in cerebellar cortex?
- 4.D.c. How many cell layers does neocortex have?
- 4.D.d. Are there more synapses in an adult human brain or in a five-year-old human brain?
- 4.D.e. What is the difference between axons and dendrites? Give both a functional explanation (i.e., what they do differently) and an anatomical explanation (i.e., how they look different).

4.E (5 x 0.3 = 1.5 points): Cytoarchitecture

Korbinian Brodmann (b. 1868) is delighted to hear that his system for classifying regions of cerebral cortex based on the structure and organization of cells is still widely accepted and used in the 21st century.

- 4.E.a. What do gray matter and white matter each primarily consist of?
- 4.E.b. What do Brodmann areas 1, 2, 3, 4, and 17 have in common in terms of functional roles?
- 4.E.c. Which of the five aforementioned Brodmann areas exhibit topographic organization?
- 4.E.d. Which subcortical structure do the five aforementioned Brodmann areas all receive direct input from?
- 4.E.e. How much bigger is a human brain than a chimpanzee brain?

End of question 4

Question 5. Development. 7.5 points, 2 pages

A (9 x 0.3 = 2.7 points)

Pair these developmentally important signalling molecules

- 1 Cadherin
- 2 Dystrophin
- 3 Ephrin
- 4 Laminin
- 5 Netrin
- 6 Neuroligins
- 7 Neurotrophins
- 8 Notch
- 9 Slit

. . . with their receptors (not all signals have receptors, and vice-versa)

- A Cadherin
- B DCC
- C Delta
- D Eph kinase
- E Integrin
- F MuSK
- G Neurexins
- H Robo
- I Tyrosine receptor kinase

e.g, write “9K”

B. (12 x 0.4 = 4.8 points) Give a one-sentence example, during development, of each process:

1 Growth along pioneer axons

2 Growth along glia

3 Gradient sensing

4 Matching of intermediate targets at waystations

5 Chemoaffinity arising from complementary interactions in molecules encode by two gene families(**not** “chemo-repulsion”)

6 Transcription factors in collinear gene clusters

7 Lateral inhibition sharpening the boundaries among cell fates

8 Limiting neurotrophic factor secreted from a target organ

9 Switching of a neurotransmitter’s effect, from depolarizing to hyperpolarizing

10 Molecular motors

11 Crossing the midline

12 Pruning of excess synapses

End of question 5