York University BPHS 3090 (Winter 2014)

Project Overview

0.1 Project Overview → Hodgkin–Huxley Model

The overall purpose of the project is to gain some (deep) insight into the Hodgkin–Huxley (≡HH) model, develop a testable hypothesis that you rigorously explore using the course software (SoftCell), and gain practice composing/delivering an oral presentation.

More likely than not, you'll quickly come to realize how *complex* the behavior of the HH system is. As Huxley stated in 1964:

'Very often my expectations turned out to be wrong, and an important lesson I learned from these manual computations was the complete inadequacy of one's intuition in trying to deal with a system of this degree of complexity.'

Projects can involve almost any of the properties of the Hodgkin-Huxley model. However, to avoid projects whose aims are vague (e.g., 'I would like to understand how the Hodgkin-Huxley model works') the proposed project should be in the form of a specific and testable hypothesis. Projects that involve months of computation should obviously be avoided. The amount of computation time should be explicitly taken into account in planning a project. For example, any project that involves measuring the threshold of occurrence of an action potential for many different parameter values is bound to be very time consuming, because determining the threshold for a single set of parameters itself involves many computations. The task is to choose a physiological property of the excitation of the action potential that is of interest, and then to define a specific, feasible project.

Topics can involve comparing predictions of the Hodgkin-Huxley model with measurements on cells. For example, the text contains data on the effects of many external parameters (e.g., ionic concentrations, cell type) on action potentials. A project might involve reading the original papers that describe such measurements (some were made before the Hodgkin-Huxley model was formulated), and testing the hypothesis that these measurements are (or are not) consistent with the Hodgkin-Huxley model. Similarly, a project might involve examining the effect of some phar?macological substance on measurements of the action potential and testing the hypothesis that the substance produces its effect by changing one or another parameter of the model. These projects will require some reading of original literature which is often difficult and usually time consuming. However, such a project can lead to a very rewarding educational experience. Alternatively, the project might involve a purely theoretical topic in which some property of the model is explained in terms of its underlying structure. This type of project does not necessarily involve reading the original literature.

The Hodgkin-Huxley model is sufficiently complex that investigation of any of the hypotheses will most likely lead to unexpected results. You should pursue these unexpected results and try to un?derstand their bases. For example, you may find that in pursuing some hypothesis you choose to change some parameter of the model that you expect to result in some change in action potential waveform. The resulting computation might reveal, much to your surprise and chagrin, that no action potential has occurred. Determine why no action potential occurred. The explanation will usually be instructive. Your aim should

be not simply to reject or accept the hypothesis but to delve into the topic in sufficient depth so as to a deepen your understanding of the model. One outcome of the project might be to restate your original hypothesis in a new and more sophisticated form.

Beginning with the proposal and extending through the project, you should keep clearly in mind that you are not investigating nerve membrane in these exercises. You are investigating the Hodgkin-Huxley model for nerve membrane. Your explanations of all phenomena must be in terms of the primitive concepts of this model the ionic conductances, ionic concentrations, ionic currents, the capacitance, and the variables m, n, and h. Explanations in terms of molecular channel mechanisms or electrodiffusion of ions in the membrane are irrelevant in so far as they are not contained in the Hodgkin-Huxley model!

Project Components

- Gain a deep understanding of the mechanics of the HH model and its complexity
- Learn to effectively simulate the HH model (via SoftCell) to explore the HH model
- Develop a focused and testable hypothesis, as well as a plan of attack to address your hypothesis [1]
- Rigorously pursue your hypothesis
- Present your finding to the class and effectively answer questions

Students are **encouraged (but not required) to work together in pairs**. Note that if a pair of students collaborate on a project they should submit a single proposal and will also present together jointly.

Timeline

- 3/14/14 – Proposals due by 3:59 PM (soft copy okay; lateness penalty applies)
- 3/28/14 – In-class presentations (including a two hard copies of your slides)

Grading – Your proposal will account for 30% of your project grade and 70% will be based upon your presentation (more details provided below and in Fig.2).

0.2 SoftCell

There are two HH simulation modes. The first models a space- clamped axon. That model generates membrane action potentials. The second models an axon without space-clamp (although the second model can simulate a space clamp since the longitudinal resistances can be set to zero). The second model can produce propagated action potentials. The second model can be used to explore a wider range of phenomena than the first. The first model is faster and simpler than the second. Thus both models are useful, and your project can use either or both of the models.

0.3 Proposal

Proposals should consist of three pieces:

Hypothesis – A reasonable hypothesis is the backbone to your proposal and thus is an essential ingredient in success with the project. Formulating the hypothesis should be given considerable thought. You

[1] Keep the Huxley quote above in mind!!

need to be specific about what you are going to test. A hypothesis such as "Changes in the ion concentration will affect the action potential" is too vague. Consider that the number of combinations for concentration changes to test in order to address your hypothesis would be far too large and take up considerably more time than you have. Instead, refine the hypothesis into a single answerable question such as:

"Increasing the extracellular potassium concentration will decrease the minimum current needed to induce an action potential using the Hodgkin-Huxley model".

Specifying with detail which parameter(s) will be changed and the predicted outcome will produce a decent hypothesis. Ideally you should have a sense ahead of time whether this hypothesis will be viable by loosely testing it before hand[2].

Background – Also included in your proposal should be the background which explains your reasoning behind the hypothesis. Blindly conducting simulations without a good reason can create an excessive amount of work for you as you try to explain the results without understanding the underlying mechanisms. This is also troublesome for your eventual audience as they try tounderstand what the reasoning behind the simulations.
Consider the statement: "Changing the extracellular potassium will cause a decrease in current stimulus because the Hodgkin-Huxley model is dependent on it". This fails to explain any possible mechanism as to why potassium concentration would affect it this way. Consider instead: "By increasing the extracellular potassium concentration, the potential across the membrane will depolarize according the Goldman equation $V_m = \frac{RT}{zF} ln\left(\frac{P_K C_K^o + P_{Na} C_{Na}^o + P_{Cl} C_{Cl}^i}{P_K C_K^o + P_{Na} C_{Na}^o + P_{Cl} C_{Cl}^o}\right)$, which will thereby reduce the stimulus size needed to induce an action potential." Though this is an improvement over the last explanation, it certainly still lacks information to explain why the membrane potential affects the stimulus size. An improved background is provided later in the example.

Procedure – The procedure is designed to explain how you might go about testing the hypothesis in a rigorous way. Keeping with the theme of the proposal, the procedure should be very specific about how the data will be obtained. For this, a quantitative description is desirable: what will be the measurement intervals; what will the other, non-changing, salient parameters be set to; how will you quantify your results, etc. Instead of explaining that you will be measuring the "minimum stimuli needed to induce an action potential at various potassium concentrations" , explain as would be done in a scientific paper, i.e. "The extracellular potassium will be increased in intervals of 5 mM starting from 0 mM". **Enough information should be given that someone else could test the hypothesis independently of you.**

[2]Keep the Huxley quote above in mind!!

0.4 Proposal Example I

[*Courtesy of Kevin Cross*]

Hypothesis: By increasing the extracellular potassium concentration, there will be a increase in the threshold required to induce an action potential using the Hodgkin-Huxley model.

Background: By increasing the extracellular potassium concentration, the potential across the resting membrane will depolarize according the Goldman equation $V_m = \frac{RT}{zF} ln\left(\frac{P_K C_K^o + P_{Na} C_{Na}^o + P_{Cl} C_{Cl}^i}{P_K C_K^o + P_{Na} C_{Na}^o + P_{Cl} C_{Cl}^i}\right)$. The rate constant α increases as the difference between the membrane potential and resting potential increases and β decreases exponentially with the difference (α is the rate constant for the open channel while β is the constant for when it is closed). By increasing the resting potential, the difference between the potentials will be smaller, causing β to increase thereby reducing the number of channels open and by extension reducing the conductance (as conductance is positively correlated with the number of channels open). Therefore, to induce an action potential in a poorly conducting membrane will require a larger stimulus than in a highly conductive membrane

Procedure: The program's default parameters for the conductance and concentrations (other than the external potassium concentration) will be maintained throughout the procedure (constant values listed at end). The initial concentration for extracellular potassium will be initially set to 0 and steps of 5 mM will be used. The current stimulus will begin with a duration of 0.5 ms, zero slope and an amplitude of 10 $\mu A/cm^2$, and the amplitude will be decreased or increased accordingly by steps of 2 $\mu A/cm^2$. We will define an action potential to be a membrane voltage $V_m > 0$. To ensure the rate constant are the cause, plots of α, β, m and h will collected to see if there are variances between trials.
Constants: $G_{Na} = 120$ mS/cm^2, $G_K = 36$ mS/cm^2, $C_{Na}^o = 491$ mM, $, C_{Na}^i = 50$ mM, $C_K^i = 400$ mM, $, C_{Ca}^o = 44$ mM, $, C_{Ca}^i = 0.0001$ mM

0.5 Proposal Example II

Hypothesis: The conduction velocity of a propagated action potential produced by the HH model will increase as temperature increases.

Background: According to the software manual (Equations 5.14 to 5.20), the rate constants for the Hodgkin Huxley model increase exponentially with temperature. Hence, we expect that the time course for m, n, and h will be faster at higher temperatures. Since these factors determine the sodium and potassium conductances that generate the action potentials, increasing temperature should increase the speed of action potentials.

Procedure: We will perform simulations at different temperatures starting at 0 degrees (freezing point of water) and incrementing by 10 degrees up to 50 degrees (half way to the boiling point). For each simulation, we will determine how long it takes the peak of the action potential to travel 1 cm. The time for the peak to reach a point 1 cm from the stimulus electrode will be determined by plotting membrane potential versus time at the 1 cm place. The time to reach a point 2 cm from the stimulus electrode will be determined from a similar plot at the 2 cm place. The velocity will be computed by dividing 1 cm by the difference in times. In addition to showing a plot of velocity versus temperature, we will also show plots of m, n, and h to show that our reasoning is correct.

0.6 Other Hypothesis Examples

1. The conduction velocity of a propagated action potential produced by the HH model will increase as temperature increases.

2. Lowering G_k causes forward-propagating self-sustaining 'train' of APs. This effect is due to an increase in resting membrane potential and thereby a decrease in threshold for firing. The combination of these two is eventually significant enough for an overshoot in membrane potential returning to its resting value from the undershoot (after the peak of the AP) to fire off an additional AP.

3. The effect of temperature on the conduction velocity of the squid giant axon can be fit by the Hodgkin-Huxley model. Articles in the literature should be consulted for this project:

   - Chapman, R. A. (1967). Dependence on temperature of the conduction velocity of the action potential of the squid giant axon. J. Physiol. 213:1143-1144.
   - Easton, D. M. and Swenberg, C. E. (1975). Temperature and impulse velocity in giant axon of squid loligo pealei. Am. J. Physiol. 229:1249-1253.

4. When two action potentials are elicited, one just after another, the velocity of the second is slower than the velocity of the first action potential. This phenomenon is predicted by the Hodgkin-Huxley model. Articles in the literature should be consulted for this project:

   - George, S. A., Mastronarde, D. N., and Dubin, M. W. (1984). Prior activity influences the velocity of impulses in frog and cat optic nerve fibers. Brain Res. 304:121-126.

5. The threshold current for eliciting an action potential with an intracellular electrode is higher for a space-clamped than for an unclamped model of an axon.

6. Increasing the membrane capacitance will decrease the conduction velocity.

7. Increasing the membrane conductance (by scaling all the ionic conductances) will increase the conduction velocity.

8. Increasing the external concentration of sodium will increase the conduction velocity.

9. Increasing the external concentration of potassium will increase the conduc? tion velocity.

10. Increasing the external concentration of calcium will increase the conduction velocity.

11. Increasing the temperature will increase the conduction velocity.

12. The difference in waveform of the action potential of a frog node of Ranvier and of a squid giant axon (Figure 1.9 in volume 2 of the text) can be reproduced by the Hodgkin-Huxley model of a squid giant axon by a change in temperature.

13. The membrane capacitance determines the time course of the rising phase of the action potential. Increasing the membrane capacitance decreases the rate of increase of the rising phase of the action potential.

14. The falling phase of the action potential (repolarization) can occur in the absence of a change in potassium conductance.

15. Increasing the temperature sufficiently blocks the occurrence of the action potential because the membrane time constant limits the rate at which the membrane vari? ables can change and prevents the difference in time course of the sodium and potassium activation which is responsible for initiation of the action potential.

16. The initiation of the action potential is independent of the potassium conduc? tance.

17. The prolonged plateau of the cardiac muscle action potential can be accounted for by the Hodgkin-Huxley model with a potassium conductance that has a slow activation.

18. The effect of tetraethylammonium chloride (TEA) on the action potential of the squid giant axon can be modeled with the Hodgkin Huxley model by decreasing K_n and increasing K_h. Articles in the literature should be consulted for this project:

    - Armstrong, C. M. (1966). Time course of TEA+-induced anamalous rectification in squid giant axons. J. Gen. Physiol. 50:491-503.
    - Armstrong, C. M. and Binstock, L. (1965). Anomalous rectification in the squid giant axon injected with tetraethylammonium chloride. J. Gen. Physiol. 48:859-872.
    - Tasaki, I. and Hagiwara, S. (1957). Demonstration of two stable potential states in the squid giant axon under tetraethylammonium chloride. J. Gen. Physiol. 40:859-885.

19. Theshapeoftheactionpotentialinthepresenceoftetraethylammoniumchlo? ride (TEA) can be accounted for by the Hodgkin-Huxley model with a reduced maximum value of the potassium conductance. Articles in the literature should be consulted for this project:

    - Armstrong, C. M. (1966). Time course of TEA+-induced anamalous rectification in squid giant axons. J. Gen. Physiol. 50:491-503.
    - Armstrong, C. M. and Binstock, L. (1965). Anomalous rectification in the squid giant axon injected with tetraethylammonium chloride. J. Gen. Physiol. 48:859-872.
    - Tasaki, I. and Hagiwara, S. (1957). Demonstration of two stable potential states in the squid giant axon under tetraethylammonium chloride. J. Gen. Physiol. 40:859-885.

20. Increasing the external calcium concentration will block the occurrence of the action potential because this will reduce the difference in the time constant of sodium and potassium activation which is responsible for the initiation of the action potential.

21. Increasing the external concentration of potassium will decrease the refractory period; decreasing this concentration will lengthen the refractory period.

22. Increasing the external concentration of sodium will decrease the refractory period; decreasing this concentration will lengthen the refractory period.

23. Absolute and relative refractory periods are decreased by increasing the rate constants for sodium inactivation and for potassium activation.

24. Repolarization cannot occur if the potassium activation rate constant is zero.

25. The threshold of the action potential to a brief pulse of current decreases as the external potassium current is increased.

26. The Hodgkin-Huxley model with default parameters does not exhibit accommodation. Hy? pothesis Accommodation occurs if the leakage conductance is increased.

27. The Hodgkin-Huxley model with default parameters does not exhibit accommodation. Hy? pothesis Accommodation occurs if the potassium conductance is increased.

28. Increasing the leakage equilibrium potential will block the action potential.

29. The effect of the changes in concentration of sodium ions on the action po? tential of the giant axon of the squid can be accounted for by the Hodgkin-Huxley model. Articles in the literature should be consulted for this project:

    - Hodgkin A. L. and Katz, B. (1949). The effect of sodium ions on the electrical activity of the giant axon of the squid. J. Physiol. 108:37-77.
    - Baker, P. F., Hodgkin, A. L., and Shaw, T. I. (1961). Replacement of the protoplasm of a giant nerve fibre with artificial solutions. Nature 190:885-887.

30. In response to rectangular pulses of current, the rheobase of the strength- duration relation increases as temperature increases.

31. An increase in temperature results in a decrease in the duration of the refrac? tory period.

32. The threshold membrane potential at which the Hodgkin-Huxley model pro? duces an action potential in response to a brief pulse of current is equal to the membrane potential for which the linearized Hodgkin-Huxley equations have unstable eigenvalues.

33. Application of a long-duration constant current to the Hodgkin-Huxley model produces a train of action potentials. Hypothesis: The frequency of the action potentials increases with increasing current amplitude.

34. Application of a long-duration constant current to the Hodgkin-Huxley model produces a train of action potentials. Hypothesis: The frequency of action potential increases as the parameter K_n is increased.

35. Application of a long-duration constant current to the Hodgkin-Huxley model produces a train of action potentials. Hypothesis: The frequency of action potential increases as the temperature is increased.

36. An increase in the external concentration of potassium increases the threshold potential at which an action potential is elicited.

37. Increasing K_h will result in an increase in the steepness of the repolarization phase of the action potential.

$\rightarrow$ Any of these (or other) hypotheses can be the starting point for a project. Most of the hypotheses given above are simplistic, and a careful investigation will reveal their shortcomings.

0.7 Presentation

Logistics – The presentations will take place in class. You will be allowed 12 minutes total: 10 minutes for your talk and 2 minutes for questions. You will be timed, so it is crucial that you do not exceed your allotted time (otherwise you may be penalized). If working together in pairs, you will both be expected to contribute significantly to the content and presentation. Ideally, get your presentation to Prof. Bergevin before class so he can load them onto a flashdrive and bring them to the classroom.

Consideration to keep in mind –

- Your time is valuable, so use it wisely!
- Before getting your presentation together, you have one key task: **Complete your project!** First, organize your data. Then locate trends in your data and isolate specific results. Finally, distill information to key points.
- Preparing an effective presentation is much more difficult and time-consuming than you would think. Not only do you need to probe deeply into the model to gain a deep understanding as to what is going on, you also need to determine (*and practice*!) how to best convey your findings to others in a digestible way.
- Primary goal is to explain a technical finding.
- If there is no content, there is no presentation.
- Presentation style/delivery enhances and clarifies your content. Slides provide visual reinforcement of the spoken message, as the focus should be on you the speaker (not a screen!)[3]. Bad slides can distract the audience by being irrelevant, confusing, or inconsistent[4].
- Length: 7-8 slides for 12 minute presentation. Budget under time!
- Introduction: Explains the goals and purpose of the project. Ideally, these goals and purpose relate to the Discussion points.
- Methods: Distill Methods to key procedures. Numbered list is fine. Ideally, do not show equations (unless they are extremely simple and friendly).
- Results: For your results, develop 2-3 relevant figures. Include key words in figures to remind yourself (and audience) of each bullet point. Figure should allow listener to fill in gaps due to lapses in attention. An example of an effective result slide is shown in Fig.1.
- Discussion: should be limited to most important details (related to Results). Succinct is ideal.
- Drafting Your Presentation (sequential tips for success): Complete your project & organize ideas. Plan the presentation. Sketch candidate slides. Combine slides to create story-board. Develop 2-3 bullet points for each slide. Draft the presentation ('slide sorter view' in Powerpoint is very useful here!). Edit & revise. Prepare for Q&A. Practice.

[3] One need not use Powerpoint or any other type of ''slide' (e.g., Keynote, overhead transperancies, etc.) in order to give a 'good' talk. In fact, some of the best talks have speakers not using any sort of electronic visual aid (e.g., a 'chalk talk'). However for technical talks such as this, visual reinforcement of the points helps significantly to convey your message. Thus, it is good to get in the practice of effective slide preparation/delivery.

[4] A very useful reference you may want to examine at some point is *The Visual Display of Quantitative Information* by Edward Tufte. Well worth the effort of tracking down, at least to get exposed to the idea that there is actually some deep thought already in place as to how to best visually convey complex sets of data.

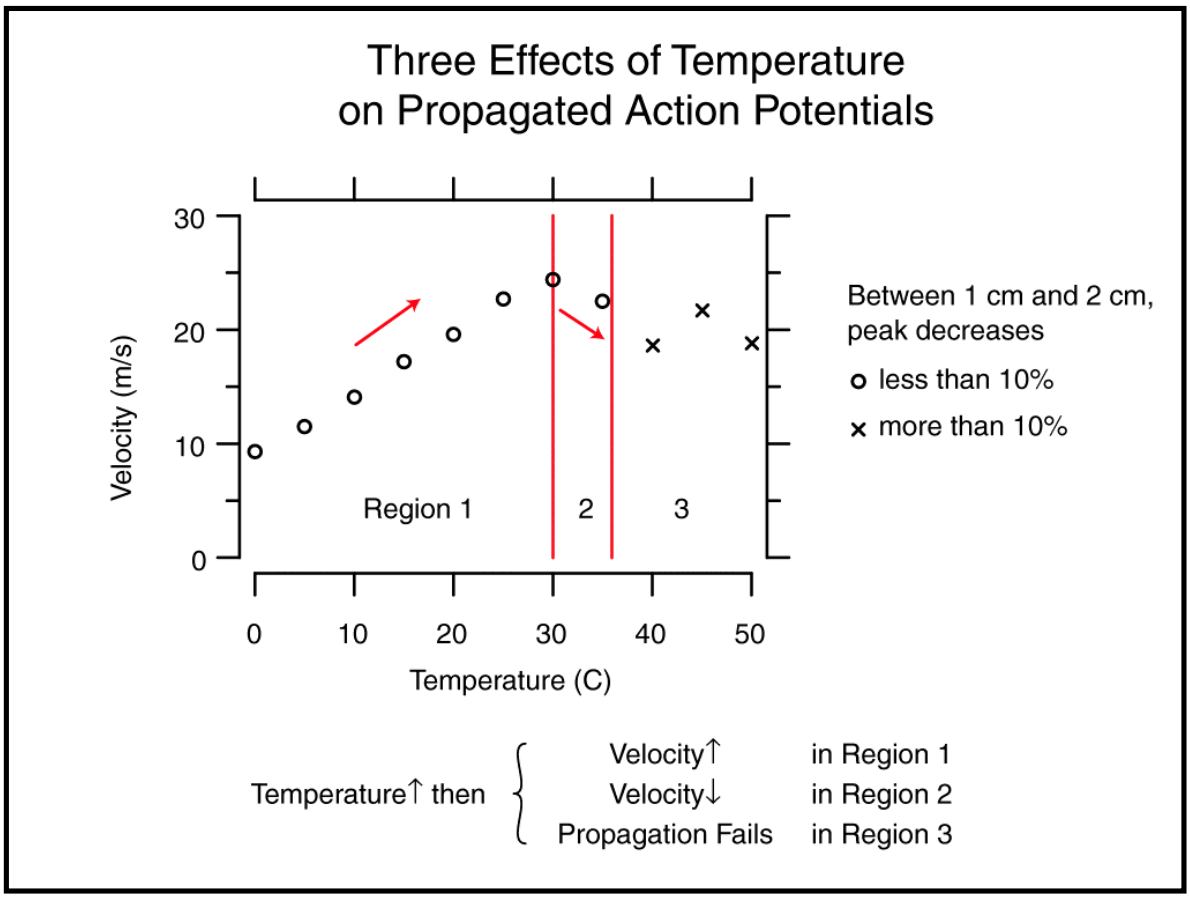
Three Effects of Temperature
on Propagated Action Potentials
Velocity (m/s)
30
20
10
0
Region 1
2
3
0
10
20
30
40
50
Temperature (C)
Between 1 cm and 2 cm,
peak decreases
less than 10%
more than 10%
Temperature↑ then
Velocity↑
Velocity↓
Propagation Fails
in Region 1
in Region 2
in Region 3

Figure 1:

- Tips for slides: Fonts matter (Title 44 pt; Subtitles 28 pt; Other text 20 pt; sans serif). Understandable at a glance. Use animation sparingly (if at all). Color-wise, use a light background with dark text dim and keep colors consistent. Add slides to fill in gaps, remove slides to eliminate redundancy.
- Format-wise, Powerpoint and/or PDF work best. Preferably both: PDF works as a good backup in case there are issues with a .ppt file (e.g., incompatible versions, fonts all messed up, etc...).
- PowerPoint Tips: Easy to create irrelevant slides with little content. Easy to waste 'real estate' with nifty borders. Avoid.
- Your title slide is important! Typically, it is the one slide that is up on the screen the longest (and before you even start!), so it can really help set a tone. Make sure that your title is informative, specific, and understandable at a glance. It should contain your name(s) and the date.
- Edit the Slides: Edit slides for coherence. Check for irrelevant bullets, plots. Check for balance and coherency in storyboard. Spell-check and proofread.
- Presentation Tips: Arrive early. Check equipment. Check voice projection. Have a printed copy of your presentation in hand as a backup. If you use the pointer, do not block the screen. If you get lost, stop and regroup. Your audience wants you to succeed.
- **Practice!!**: Make sure that you meet the time limit. Practice speaking slowly. Breathe. Know your quirks. Work around your nervous habits. Use visuals as cues, not note cards.
- Prepare for Q&A: Anticipate questions not covered in the presentation. Typically, questions ask you to extend (or refute) an idea. Brainstorm, considering audience & scope. OK to acknowledge gaps in knowledge. OK to prepare extra slides.

Grading – Rubric for grading is provided in Fig.2

HH Grade Sheet

Proposal (30%).

Presentation Structure (15%).
A: all information is well organized in proper sections with smooth transitions between sections. Visual elements were effective.
B: overall organization is understandable but could be improved in one section of the presentation or in minor instances throughout the presentation.
C: repeated organizational problems that interfere with presentation coherence. Poor presentation of visual information.

Delivery of Presentation (10%).
A: delivery was clear with appropriate use of non-verbal gestures. Verbal articulation and timing were appropriate.
B: several awkward moments or slips in verbal clarity.
C: repeated awkwardness in presentation, and/or repeated problems with verbal clarity. Presentation too long.

Clarity and Conciseness of Technical Information (10%)
A: technical flow is clear: introduction motivates a topic, results focus on that topic, conclusions follow from results, relevant methods are described.
B: no more than 1 major lapse in tech. clarity.
C: more than one major lapse in technical clarity.

Conceptual Correctness (15%).
A: interpretations of results are tech. correct.
B: interpretations are not well supported.
C: major errors.

Insightfulness (20%).
A: Recognized an interesting issue and developed at least one way to understand it.
B: Thorough description of WHAT happened without a clear understanding of WHY it happened.
C: Confusion about what happened.

Figure 2: