Name: ______________________________

Thesis Advisor: ______________________________

BIOENGINEERING Ph.D QUALIFIYING EXAM

June 2, 2008

Answer questions in all THREE required subjects- Bioinstrumentation, Biomodeling, and Biomaterials. Select ONE of the questions from 4 concentration areas such as Bioimaging, Biomechanics, Cell & Tissue Engineering, and Neuroengineering. You must specify which one of the concentration area questions you wish to answer by checking an appropriate box below. Please show all work. No additional sheets will be allowed.

Required Questions

Bioinstrumentaiton	(25 points)
Biomaterials	(25 points)
Biomodeling	(25 points)

Concentration (25 points)

( ) Bioimaging
( ) Biomechanics
( ) Cell & Tissue Engineering
( ) Neuroengineering

Bioinstrumentation (Required)

In his novel "Blindness", the Portuguese Nobel prize winning author Jose Saramargo describes a city in the future in which a virus epidemic causes instant blindness. The novel addresses the response of the citizens and government to this biological catastrophe. Place yourself, a biomedical engineer, in this novel situation. Think about how the practice of medicine and the operation of biomedical instruments would need to change if everyone (patients, nurses, doctors and engineers) were blind. The good news is that you have been found to be immune to the sickness, so you can redesign and remodel the biomedical instruments needed by physicians to diagnose disease. In this problem you will focus on an instrument for assessing cardiac function.

I. (10 points)

Draw a block diagram of a modified ECG monitor and arrhythmia detector that would adapt the measurement of heart rate and interbeat intervals (S-T interval, for example) for operation by blind nurse, for use on a blind patient, and to be interpreted by a blind physician. How will you make the heart's electrical signals visible? What will you detect? Could you also amplify heart sounds? What would they tell you? Are they sufficient? What transducers will you use? How will you display the results (sounds, smells, taste, tactile sensations)?

II. (10 points)

Describe how you would model the dynamics of the new "blind" ECG monitor. What instrument factors would be affected? Would the electrodes change, the amplifiers, the controls? How would you display changes in amplitude, frequency, time delay? What features of the heart disease (e.g. arrhythmia, AV heart block, tachycardia) could be detected? What conditions could not be observed?

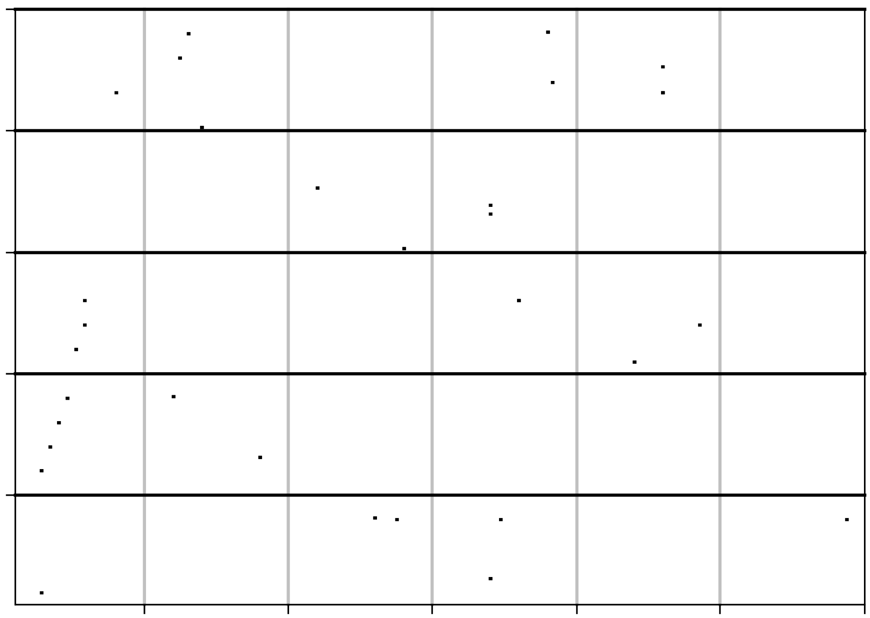
III. (5 points)

Assume now, that the disease of “blindness” miraculously goes away. Select one or more features of your new “blind” ECG monitor for incorporation into existing ECG machines. Such modifications could be used by visually impaired doctors and nurses to better understand their patients’ condition. Explain how your modified instrument will improve or extend health care of the cardiac patient.

<u>Biomaterials</u> (Required)

1.

a. (6 points) The yield stress of titanium is 275 MPa, the ultimate tensile strength is 345 MPa and the Young's modulus is 100GPa. Draw the corresponding stress-strain curve on the graph below and indicate where the yield, ultimate tensile strength, and Young's modulus are on the plot. Be sure to label your axis with units AND numbers accordingly.



b. (6 points) Stainless Steel has similar properties (250 MPa yield, 500 MPa UTS, and Young's Modulus of 200GPa, yet the overwhelming majority of hip implants are made with titanium. Why?

2. (3 points)
   Starting with a linear vinyl polymer such as polyethylene –$(CH_2\text{-}CH_2)_n$-, list and describe the mechanisms of 3 strengthening strategies to modify this basic linear polymer.

3. (4 points) Explain and describe the mechanisms causing ceramics to exhibit little plastic deformation.

4. (6 points) Dr. Anderson recently discovered an extract of a cephalopod facilitates wound healing when applied to large area burns. Describe a hypothesis to explain this phenomenon and plan an experiment to prove your hypothesis in vitro along with in vivo.

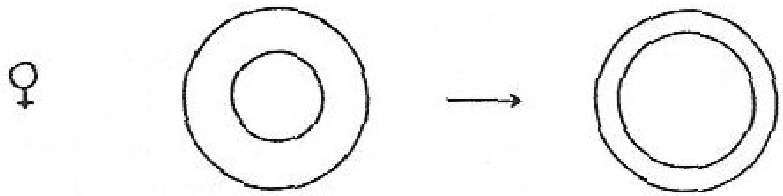
Biomodeling (Required)

A popular method for demonstrating that experimental outcome X has a different expected value than the expected value of outcome Y is to sample these outcomes and determine the distribution of the sample mean difference z = mean(X) – mean(Y). Suppose that E(X) = μ_x and E(Y) = μ_y and that n_1 and n_2 independent samples of X and Y , respectively, are observed. If the variances of X and Y are equal at σ^2 and n_1 and n_2 are very large, what is the probability distribution of z and what is E(Z) and var(Z) ?

Extra worksheet

Biomechanics (Selective Concentration)

A schematic representation of cortical bone remodeling with age in females at the femoral mid-diaphysis is shown below. Assume that (i) an axial load of 1500 N and a bending moment of 45 Nm act at the femoral mid-diaphysis in both the young and old females, and (ii) the ultimate strength of cortical bone in tension decreases from 140 MPa to 120 MPa due to age. Calculate the effect of age on the fracture risk at the femoral mid-diaphysis in females.



Age = 25 years	Age = 85 years
Outer radius = 1.25 cm	Outer radius = 1.25 cm
Inner radius = 0.625 cm	Inner radius = 0.75 cm

Extra worksheet

Bioimaging (Selective Concentration)

The success of the International Space Station and the recent Mars Landers points to the need in the future to practice medicine in space. A key component of a clinic on a space station would be the imaging center. Your job as a newly hired biomedical engineer at NASA is to design "space" compatible x-ray/ CT, Ultrasound, Nuclear Medicine and MRI systems for safe and effective operation in space. In addition to their operation in a weightless environment, you must design such systems to function using low power, be very light, and to be resistant to high energy gamma rays (from solar flares).

I. (10 points)

Choose one of the four principal types of medical imaging devices and draw a complete block diagram for its configuration in a space station laboratory. Explain how each block would be powered, packaged, tested and assembled in space. What new or different materials would have to be developed or introduced? Explain any changes to the patient scanning procedure that would be needed.

II. (10 points)

Explain how the resolution, signal to noise ratio, and contrast in your medical imaging system would be affected by the modifications that you have suggested in part I. What about the safety, sensitivity and selectivity of its diagnostic capabilities. How would you “test” the new system in space to guarantee its performance? How would you calibrate the system?

III. (5 points)

Your boss, like Professor Magin, an advocate for MRI, insists that an MR machine should be installed in the space station. How can this be done? What parts of an MR system could easily be transported and operated in space? What parts could not? How do you propose building a superconducting magnet for a 3 Tesla MRI in (or outside of!) the space station. Would you use cryogens like liquid He or N_2 to cool the magnet? Would you need them in space? Explain.

Extra worksheet

<u>Cell & Tissue Engineering</u> (Selective Concentration)

1. (5 points) One of the required components for successful tissue engineering is the cell.
   a) Using a Van diagram, list three additional components that are thought be just as important for successful tissue engineering.
   b) Provide 3 brief but specific interactions between these components.
   c) The latest effort in tissue engineering is to use stem cells. List and discuss two advantages and two disadvantages of using stem cells.

2. (6 points) Many tissue engineering studies have focused extensively on cell adhesion.
   a) Why is cell adhesion so critical for tissue engineering?
   b) What would be required to promote cell adhesion to natural scaffolds (e.g., collagen gel) and to synthetic scaffolds (e.g., polyethylene glycol)?
   c) Cell migration highly depends on cell adhesion. What is the general relationship between cell migration and adhesion (assume 2D adhesion)?
   d) Design an experiment to test the hypothesis that the cell migration speed is a function of integrin receptor density.

extra worksheet

3. (10 points) Suppose you discovered that there is a family of adhesion proteins expressed at the cell surface (we will call these protein stickins). Although stickins are thought to act like integrins, it remains to be elucidated whether stickins have the similar functionality.

a) Design an experiment to validate or refute the hypothesis that stickins act as mechanotransducers.
b) Stickins are found to compete with integrins for ECM proteins. Formulate a set of first order differential equations that describe the formation of two complexes; integrin-ligand complex (call it X) and stickin-ligand complex (call it Y). Do not assume steady state. Assume rates are constant but provide a short description of each rate used in the formulation.
c) The formulation above assumes that the total number of stickin receptors remains constant. This is often not physiologically correct. Let us suppose that there are at least two additional processes- endocytosis of the complex Y and the stickin receptor synthesis- that cannot simply be ignored. Reformulate the first order differential equation that describe the formation of the stickin-ligand complex (Y). Do not assume steady state.

4. (4 points)
   a) Briefly describe the difference in how cells can be added to a PEGDA or PLGA scaffold.
   b) Describe why hydrophilic biological signaling molecules (gene therapy, proteins, or small molecules) release quickly from PEGDA scaffolds.

<u>Neuro Engineering</u> (Selective Concentration)

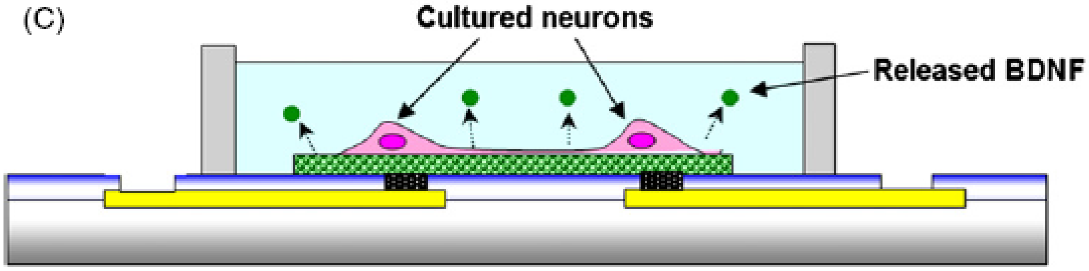


Figure from **Jun et al. *Modulation of cultured neural networks using neurotrophin release from hydrogel-coated microelectrode arrays*. Journal of Neural Engineering, May 2008.**

1. (7 points) In the system above, a thin layer of hydrogel exhibits a slow release of brain-derived neurotrophic factor (BDNF). Provide the following:

   a. An experimental question (or a hypothesis) that could be explored with this hybrid neural system.
   b. The protocol you would use to collect the data needed to answer the question (or test the hypothesis), including a clear identification of the independent and dependent variables, and the experimental control.
   c. A statement of the relevance of your question (or hypothesis) to a neural engineering application.

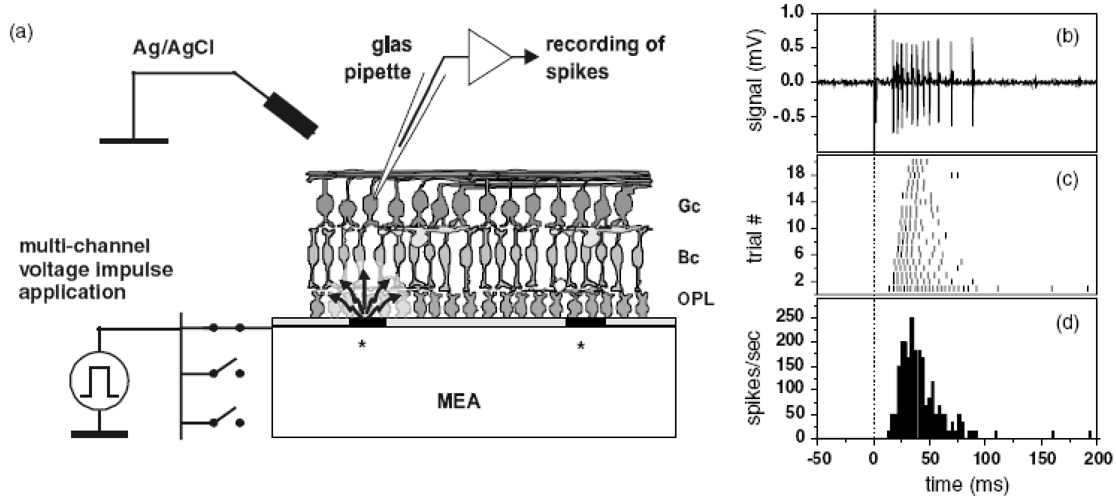
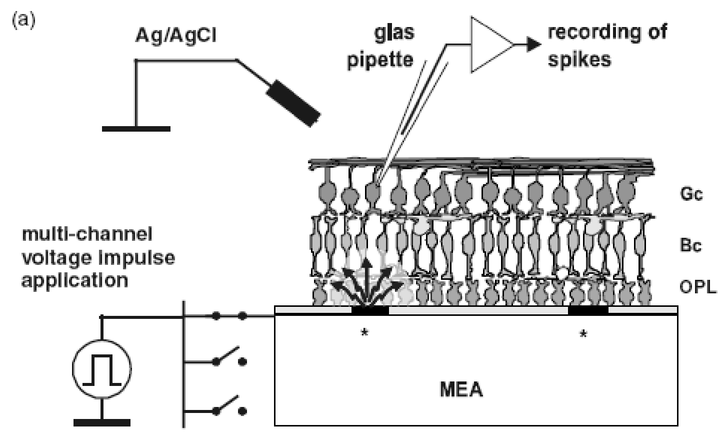
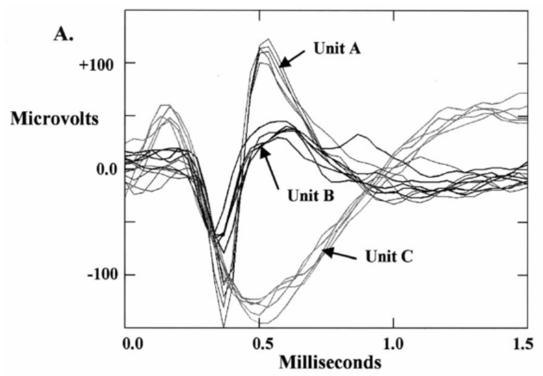


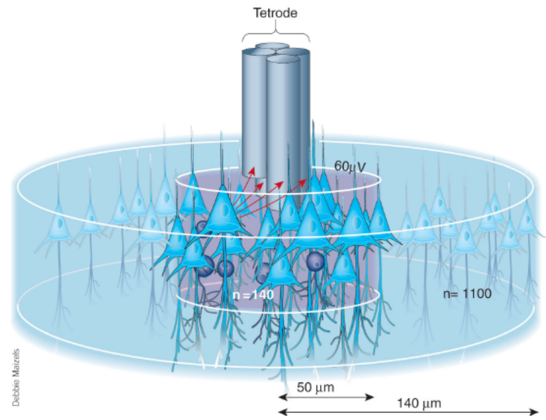
Figure from **Stett et al.** ***Retinal charge sensitivity and spatial discrimination obtainable by subretinal implants: key lessons learned from isolated chicken retina.*** **Journal of Neural Engineering, February 2007.**

2. (6 points) The diagram above depicts a system for studying the response of retinal ganglion cells (**Gc**) to electrical stimulation delivered to the outer plexiform layer (**OPL**) *in vitro*. Write a detailed legend describing panels (b), (c) and (d).



3. (6 points) Design an equivalent circuit model that would describe the current path(s) from the ***stimulus source*** to the ***recording amplifier*** in the system used by Stett et al. (2007) shown above. Include as much detail as possible, and label each of the components in your model with the physical structure that it represents. State any assumptions. You do not need to give component values.





4. (6 points) There are two basic approaches to performing spike sorting with multi-unit recordings, depending on whether a single recording electrode was used (typical data shown at left above), or multiple recording electrodes placed in a strategic arrangement (e.g. a tetrode, as shown at right above). Choose ***one*** approach, and provide an algorithm (series of instructions, e.g. step 1, step 2, step 3 . . .) that could be used to isolate the spikes from individual neurons. Be quantitative where necessary. Use of sketches to illustrate your strategy is encouraged. (Figures above are for general reference only; you do not need to refer to them in your answer.)

extra worksheet