Group: Amber DesRosiers, Eric Broussard, Kary Ritter

Paper 1

Fitzhugh-Nagumo Equations With Generalized Diffusive Coupling

MATH 452 Assignment 4

1. Describe the motivating question/novelty of the paper;

   This aim of this paper is to present graphically how dynamics within a neural network evolve. These dynamics of a neural network are investigated using the Fitzhugh-Nagumo model. Neurons described by this model are coupled by a diffusive term which aids in the description of a the dynamics of the action potential within a neural network.

   Using the Laplacian matrix, the instantaneous propagation of signals between neurons are modeled which aids in defining the connection structure among the excitable elements. By exploiting different connection rules among neurons, visualizations of the solutions can be obtained. These can show not only near neighbor interactions but the presence of inhibitory synapses.

2. Describe the discrete mathematical model/framework used, and interpretation of any model terms, along with parameters and units;

   The basis of the model uses a form of the FitzHugh-Nagumo equation shown below.

   $$\dot{v} = -v(a - v)(1 - v) - r$$
   $$\dot{r} = bv - gr$$

   Where a, b, g are positive real numbers and parameters of the model. v represents the excitation variable or fast variable and r represents the recovery variable or slow variable.

   The FitzHugh-Nagumo model with generalized diffusive coupling is expressed as:

   $$\dot{v_i} = -v(a - v_i)(1 - v_i) - r_i + d\sum a_{ij}(v_j - v_i)$$
   $$\dot{r_i} = bv_i - gr_i$$

   Where parameters a, b, g, d are all positive real numbers. For each neuron $i = 1, ..., N$ within the network. The presence of the diffusive coupling is represented by $\sum a_{ij}(v_j - v_i)$. The v, r represent the excitability behavior of neurons and the refractoriness. The excitability behavior is a characteristic where a small perturbation of a neuron can provoke a large excursion of its potential. The refractoriness is characterized by a period where the elements cannot be excited following the stimulus.

   This model represents excitable-oscillatory systems as the nullclines are cubic in shape. The aim of this model is to describe the dynamics of the action potential and recovery variable within a neural network.

3. List key assumptions;

   Assumptions:

- Each neuron is linked with a finite number of others.
- These connections are invariant under discrete neuron labels translations.
- Neuron labels are disposed over the nodes of a one dimensional chain with periodicity.

Biophysical assumptions:

- Neurons are identical entities, showing the same dynamics when stimulated in the same way.
- Infinite velocity in the exchange of communications among neurons.

4. BRIEFLY describe the authors approach (methods, analysis, etc), and their results/conclusions;

   The author describes an excitable neural network by using the FitzHugh-Nagumo model and introducing concepts proper to graph theory. With this a neural network is described by labeling neurons in a set of vertices with the links among them constituting a set of edges. Using the Laplacian matrix the author describes the connection structure among these neurons.

   In cases of one and two coupled neurons the stability of solutions equilibrium point is performed. To do this the author introduces three propositions to ensure the stability of the equilibrium point. The propositions consider the case of a single uncoupled neuron and the case of two coupled neurons that are identical. The analysis is restricted to the systems which exhibit excitability with only one equilibrium point at the origin. With this the eigenvalues are calculated for each case and the origin is shown to be stable.

   To show the results graphically two cases are explored. The case of all excitatory synapses between linked neurons and the case of both excitatiory and inhibitory synapses between linked neurons. The graphs show the modeled neurons as excitable units and then, after the excitation, they undergo a long refractory period.

   In conclusion the model describes the dynamics of the action potential and the recovery variable within a neural network. Features of the neighbor interactions and presence of inhibitory synapses of neural populations are shown. Several frames of the dynamics have been shown graphically to provide a visual explanation giving a better understanding of the solution provided by the model.

5. List at least one criticism of the work presented in the manuscript;

   The visualizations of the solutions obtained by exploiting different connection rules among neurons in a stability study are stated as the core of this paper. Yet the only main rules considered were the case of all excitatory synapses between linked neurons and the case of both excitatiory and inhibitory synapes between linked neurons.

   The conclusion states that the models describes several fundamental features of interactions in neural populations yet the features illustrated are just the neurons being excited then returning to the resting state.

6. Name at least one extension, improvement, related question, or assumption that could be relaxed that could/should be done as future work.

A future work should address the issue of delay in synapses. Considering a non-negligible time delay in coupling would make the model more biophysically relevant. This would eventually allow a new technique to study signal dynamics within large populations of neurons.

The model should eventually take into account signals reaching even non-neighboring neurons without passing through the adjacent ones. This would show direct links between vertices in accordance with the connection structure which exists in a specific neural network.

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Assignment 4

Paper 2

Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection

1. Describe the motivating question / novelty of the paper.

   In this paper the authors are treating HIV-1 infected patients with ABT-538 and looking at the HIV-1 plasma levels as well as the CD4 lymphocyte counts. There is relatively little information available on the kinetics of the virus and CD4 lymphocyte turnover in vivo (within the living).

2. Describe the discrete mathematical model/ framework used, and interpretation of any model terms, along with parameters and units.

   The only model really talked about in the paper is the following:

   Before drug administration, the change in viral load with time can be expressed by the differential equation:

   $$\frac{dV}{dt} = P - cV$$

   P: viral production rate
   c: the viral clearance rate constant
   V: the number of plasma virions

   During the pretreatment steady state, $\frac{dV}{dt} = 0$ and hence $P = cV$.

   Based on the data, the authors were not able to determine whether the rise was linear or strictly exponential.

   It also says in the paper that the authors also tested more intricate models, in which the viral decay is governed by two or three exponential rates, namely the viral clearance rate, the decay rate of virus producing cells, and the decay rate of latently infected cells.

   The paper also talks about irrespective of the model, on a log plot, $S = \frac{-d(lnV)}{dt} = c - \frac{P}{V}$. If drug inhibition is complete and virus producing cells are rapidly lost ($P = 0$), then $S = c$.

3. List key assumptions.

The authors made the following assumptions:

(a) ABT-538 administration does not affect viral clearance.

(b) There exists a steady state and hence the calculated clearance rate is equal to the minimum virion production rate before drug therapy.

4. BRIEFLY describe the author's approach (methods, analysis, etc), and their results/ conclusions.

   The authors administered 600 - 1200 mg of ABT-538 orally daily to twenty HIV-1 infected patients. Post treatment CD4 lymphocyte counts were monitored sequentially, as were copy numbers of particle associated HIV-1 RNA in plasma, using an ultrasensitive assay based on a modification of the branched DNA signal application technique.

   Following treatment every patient had a rapid and dramatic decline in plasma viraemia over the first two weeks. The initial decline was always exponential which was demonstrated by a straight-line fit to the data on a log plot.

   In Table 1, the viral decay slopes varied from -0.21 to -0.54 per day, with a mean of -0.34 ± 0.06 per day; correspondingly, $t_{1/2}$ varied from 1.3 to 3.3 days with a mean of 2.1 ± 0.4 days.

   The authors' observations strongly suggest that the viral clearance rate constant is not dependent on the stage of HIV-1 infection. Instead they indicate that viral load is largely a function of viral production, because clearance rate constants vary by about 2.5 fold whereas the initial loads vary by almost 40 fold.

5. List at least one criticism of the work presented in the manuscript.

   One criticism is that it was hard to understand the paper unless you had knowledge of the biology behind HIV-1. I had to do research to fully understand the paper. Also, it would have been nice if more attention was paid to the mathematical model. I almost missed it and did not even see the model at first, since it was in the notes for Figure 1..

6. Name at least one extension, improvement, related question or assumption that could be relaxed that could/should be done as future work.

   The patients had a wide variety of baseline values. It would be interesting to do the study on a group with very similar baseline values to see if the results are consistent from one patient to another or if they vary greatly.

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The biotechnology of hydrogen production by Nostoc agelliforme grown under chemostat condition

Paper 3

1. Describe the motivating question/novelty of the paper;

   The authors of the paper explored cyanobacteria's ability to produce hydrogen. Using biochemical processes to generate hydrogen from water was/is a well explored topic, but the authors look into nitrogen-fixing cyanobacteria's ability to produce hydrogen under certain conditions. Nitrogen-fixing cyanobacteria possess the enzyme nitrogenase and is the primary enzyme involved in hydrogen production within the cell. The particular interest on nitrogen-fixing bacteria is that activity of nitrogenase varies signficantly with input.

   Formerly, the production of hydrogen and the metabolic stabilities of hydrogen production in cyanobacteria were low and have yet to be resolved, and the use of continuous microbial cultures for hydrogen production in cyanobacteria had not been studied. The authors look to optimize hydrogen production by nitrogen-fixing, heterocystous cyanobacteria in continuous cultures

2. Describe the discrete mathematical model/framework used, and interpretation of any model terms, along with parameters and units;

   In this chemostat model, the researchers are looking to optimize the production of hydrogen from cyanobacteria by varying the nutritional concentration, atmospheric pressure, and temperature in the chemostat,

$$\dot{h} = h\left(y\frac{r(C)}{1+kN_2^{-k}}\right)$$
$$\dot{C} = D(N_2^{(0)} - N_2) - y\frac{r(C)}{M+N_2}$$

D	Dilution rate
N_2	Concentration by volume of N_2 in the Chemostat
$N_2^{(0)}$	Concentration inflow to Chemostat ("constant")
r(C)	Exponential per-capita growth-rate of bacteria w/ C being dependent on N_2 and Temperature
r(C)	A ratio representing the hydrogen production per the biomass of the bacteria (dependent on y)
h	The biomass of the bacteria
y	Constants determined by experimental verification
k,λ	Constants determined by experimental verification

3. List key assumptions;

   Assumptions:

   (a) Short-phase exponential reproduction rate.

   (b) Hydrogen production rate highest during short-phase exponential growth period

   (c) Temperature, nutrient dilution rate, and nitrogen concentration can be adjusted within chemostat such that hydrogen production during short-phase exponential growth period can be optimized.

   (d) A number of assumptions related to Biological and Chemical Science:

      i. Biological nitrogen fixation (BNF) occurs when atmospheric nitrogen is converted to ammonia by an enzyme called nitrogenase. The reaction for BNF is:

      $$N_2 + 8H^+ + 8e^- \rightarrow 2NH_3 + H_2$$

      The process is coupled to the hydrolysis of 16 equivalents of ATP and is accompanied by the co-formation of one molecule of H_2.

      ii. Heterocysts are specialized nitrogen-fixing cells formed during nitrogen starvation by some filamentous cyanobacteria. They fix nitrogen from dinitrogen (N_2) in the air using the enzyme nitrogenase, in order to provide the cells in the filament with nitrogen for biosynthesis.

      iii. Cyanobacteria are able to reduce nitrogen and carbon dioxide under aerobic conditions.

      iv. The water-oxidizing photosynthesis is accomplished by coupling the activity of photosystem II and I.

      v. In anaerobic conditions, they are also able to use only PS I cyclic photophosphorylation with electron donors other than water bacteria.

4. BRIEFLY describe the authors approach (methods, analysis, etc), and their results/ conclusions;

   The authors received the initial cyanobacteria macrofilaments in a liquid-culture suspension and the cyanobacteria were incubated in a growth medium under "natural" conditions. They began supplying the culture with a mixture of CO_2, N_2, and Ar filtered before being pumped into the system. They then filtered and dried the culture and weighed it to get a growth rate of the culture.

   Nitrogenas activity was measured by the reduction of $CH = HC \rightarrow H_2C = CH_2$ by "stealing" the hydrogens from water in anaerobic conditions. In low CO_2 environments (strictly anaerobic conditions) hydrogenase is inhibited and it prevents the re-utilizations of H_2. This hydrogen molecule is lost to the cell. They then measure concentration of H_2 using a gas chromatograph. Hydrogen production rates were expressed on the basis of chlorophyll. They found that H_2 was indeed higher during the short-phase exponential growth period. They then attempted to extend this growth phase in hopes of long term production of H_2.

   They analyzed the effect of temperature, N_2 and dilution rate. With further analysis, they found optimal values of those parameters (mostly through "best guess" methods) such that the bacteria in the chemostat were in a continuous optimal short-phase exponential growth period.

5. List at least one criticism of the work presented in the manuscript;

   There is no explicit mathematical model in the paper. It is obvious to me that this is not a paper written for or by a mathematician, thus it's rather difficult to understand the " lingo" used by the authors of this paper. Moreover, it seems that they did not even use a mathematical model, and instead did a trial and error experiment based off of "good places to start" based off of other papers

6. Name at least one extension, improvement, related question, or assumption that could be relaxed that could/should be done as future work

   A mathematical model would be nice. It would allow for analytical optimization tested against real world results. You could then know your model is/is not good based off of that result.

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Assignment 4

Paper 4

HIV-1 Dynamics in Vivo: Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time

1. Describe the motivating question / novelty of the paper.

   In this paper the authors are closely monitoring the viral load in five HIV-1 infected patients after the administration of a potent protease inhibitor, Ritonavir. The authors used a mathematical model to obtain estimates of the virion clearance rate, the infected cell life span and the average viral generation time in vivo (within the living).

2. Describe the discrete mathematical model/ framework used, and interpretation of any model terms, along with parameters and units.

   The model that is used to represent the dynamics of cell infection and virion production before drug treatment is:

$$\frac{dT*}{dt} = kVT - \delta T^*$$
$$\frac{dV}{dt} = N\delta T^* - cV$$

   Then the authors tweaked the model while assuming that ritonavir does not affect survival rate of virion production of infected cells and after pharmacological delay all newly produced virions are noninfectious. Infectious virions produced before the drug effect are still present until cleared so after treatment with ritonavir the authors used the model:

$$\frac{dT^*}{dt} = kV_1T - \delta T^*$$
$$\frac{dV_1}{dt} = -cV_1$$
$$\frac{dV_{NI}}{dt} = N\delta T^* - cV_{NI}$$

   The parameters for the two models above are as follows:

V: concentration of viral particles in plasma
δ: rate of loss of virus-producing cells
N: number of new virions produced per infected cell during its lifetime
c: rate constant for virion clearance
k: rate constant that HIV-1 infects target cells
T^*: productively infected cells
V_1: plasma concentration of virions in the infectious pool
V_{NI}: concentration of virions in the noninfectious pool

From the previous model, the authors used the following equation that shows how the total concentration of plasma virions, $V = V_1 + V_{NI}$, varies:

$$V(t) = V_0 e^{-ct} + \frac{cV_0}{c-\delta}\left(\frac{c}{c-\delta}[e^{-\delta t} - e^{-ct}] - \delta t e^{-ct}\right)$$

This equation differs from the one derived by Wei.

3. List key assumptions.

   The authors made the following assumptions:

   (a) HIV-1 infects target cells (T) with a constant rate k and causes them to become productively infected cells (T*).

   (b) Ritonavir does not affect the survival rate of virion production of infected cells, and that after the pharmacological delay all newly producted virions are noninfectious.

   (c) The system is at a quasi steady state before drug treatment and the uninfected cell concentration T remains at approximately its steady state value, T_0, for one week after drug administration.

4. BRIEFLY describe the author's approach (methods, analysis, etc), and their results/ conclusions.

   The authors took an empirical approach by experimenting with actual patients and analyzing the results. Initially 600 mg twice daily of Ritonavir was administered orally to five HIV-1 infected patients. After treatment, the authors measured HIV-1 RNA concentrations in frequent intervals by means of an ultrasensitive modification of branched DNA assay. The authors had fifteen data points over a seven day period which allowed careful analysis of the results by means of a mathematical model.

   The results showed that the average lifespan of a productively infected cell is 2.2 days and these cells are lost with an average of $t_{1/2}$ of approximately 1.6 days. Also, the authors calculated that on average half of the population of plasma virions turns over approximately every six hours. From the study it is clear that the raging fire of HIV-1 replication could be put out by potent antiretroviral agents in two to three weeks but other dynamics of other viral compartments must be understood.

   The authors' results provided several theoretical principles to guide the development of treatment strategies:

(a) An effective antiviral agent should detectably lower the viral load in plasma afer only a few days of treatment.

(b) On the basis of previous estimates of the viral dynamics and data on the mutation rate of HIV-1 and the genome size Coffin hasx argued that on average every mutation at every position in the genome would occur numerous times a day. Because of the reults of this study it makes this consideration even more applicable.

5. List at least one criticism of the work presented in the manuscript.

   It was a little hard to follow the paper unless you had a vast knowledge about the HIV-1 virus. I had to research what a lot of terms meant in order to understand what I was reading.

6. Name at least one extension, improvement, related question or assumption that could be relaxed that could/should be done as future work.

   The five patients that were studied had vastly different baseline values of CD4 cells and plasma virions. It could be interesting to have several groups studied where each group had similar baseline values and see if the results were consistent within each group as well as across the groups.