EN.580.441/EN.580.641 Cellular Engineering HW #4
Assigned: Oct 11, 2018 **Due: Nov 1, 2018**

This HW has TWO PARTS that are weighted equally

PART ONE:

Matlab Component Instructions:

In this homework you will reproduce a model of an emergency response to a bioterrorism attack. This model is related to viral infection, immunoengineering, and public health. The article is: "Emergency response to a smallpox attack: The case for mass vaccination" by Edward H. Kaplan, David L. Craft, and Lawrence M. Wein in PNAS 99(16): 10935–10940, 2002. Some of the code to implement is provided, but you need to add missing pieces to get things to run as well as vary certain parameters. It is especially important to learn about parameter sensitivity in this model by choosing parameters to vary and then rerunning the model to observe how changes to that single parameter affect the overall model. Instead of a single perturbation, sensitivity analysis will be performed in this model. [Note for graduate students: Sensitivity analysis like this is a good component to think about for your R21 models.]

Submit via Blackboard:

1. A 1-1.5 page write up (single spaced, 12 pt font, not counting figures) that includes and discusses the following:
   a. Introduction – In the big picture, what is being simulated and why is it important?
   b. Model – What do the specific equations represent and how are they implemented as a computational model? What are the assumptions?
   c. Discussion Re: Reproduction of Figure 1 – Include (A) and (B)
      Explain what your figures show
   d. Discussion Re: Reproduction of Figure 2A
      Explain what your figure shows
   e. Sensitivity Analysis – Choose another parameter from Figure 2 or one of your own choosing. What did you change and why?
   f. Death rate comparison: How is the number of deaths different over time when following the Mass Vaccination Strategy, the Trace Vaccination Strategy, and the CDC Vaccination Strategy? Also make a Figure to describe your answer. ("CDC guidelines [modeled] by switching from TV to MV 28 days after the start of TV (e.g., on day 33 in the base case)").
   g. Results – What does your sensitivity analysis show?
   h. Conclusions – How good is the model? What are its limitations?

2. Plots/graphs (On extra pages after the write-up)
   a. Fig 1A
   b. Fig 1B
   c. Fig 2A
   d. Figure for (f) above
   e. Between 1-3 additional graphs depending on your sensitivity analysis.
   f. A figure caption under each graph that fully describes the figure.

3. Commented MATLAB code so that the TAs may execute it and read it.

PART TWO:

Complete ONE of the following options below, also to be submitted via blackboard
(Hint: look over the other options as a "study guide")

For all three options:
Your write up must be no longer than 2 pages (any material over this limit will not be graded) with 11 or 12 pt single spaced font. Suggestion: aim for ~ 1 to 1.5 pages of text, with the remainder of content consisting of references (note that a minimum of 5 references are required) and/or figures.

Option #1. iPSC (induced Pluripotent Stem Cell) Epigenetics

1. Introduction / Background.

Waddington's "Epigenetic Landscape" (as briefly introduced in KJY Lecture #2) presumes that differentiation is irreversible (i.e., in this analogy, cells "roll downhill" as they become increasingly differentiated during development without any obvious way to counter gravity and return to a less differentiated, "uphill" state). This premise is now known to be incorrect as exemplified by the "natural" example of cancer where fully differentiated somatic cells can "de-differentiate" and assume characteristics of early embryonic cells such as unlimited growth and the ability to re-differentiate into different types of cells. If you're interested in cancer, please refer to Option #2 of this assignment. An "artificial" example of de-differentiation of terminally differentiated somatic cells is provided by iPSC technology, which was first demonstrated in 2006 when Takahashi and Yamanaka induced pluripotency in mouse fibroblasts (MEF) by introducing plasmids containing the DNA coding sequences for four embryonic transcription factors (Oct4, Sox2, Klf4, c-Myc). These DNA sequences, of course, were already present in the host organism's cells, which leads to the question of what good it did in re-introducing them. The answer (of course) is "epigenetics" – the host organism's copies of these genes had been "imprinted" during development and were no longer being expressed as proteins whereas the newly-introduced copies of these genes were under control of promoter sequences that ensured expression. In the decade since iPSC technology was first reported, its epigenetic component has become well appreciated and is summarized in a recent review paper (available as the **iPSC epigenetics paper** pdf on Blackboard [in the KJY Lecture #4 folder] or directly downloadable from: http://www.scielo.br/pdf/ramb/v63n2/0104-4230-ramb-63-02-0180.pdf).

2. "Study Guide"

As a study guide (e.g., to prepare for future quiz or exam questions), it is recommended that all students briefly peruse this review paper and know 2 or 3 "bullet point" pieces of information related to each of the three sub-headings under the "Epigenetic Changes in iPSC Reprogramming" section, which are (i) DNA methylation, (ii) changes to histones, and (iii) microRNAs.

3. Option #1 Assignment

Choose one of the "bullet points" from just above; more specifically, select a single aspect of one of the epigenetic factors that contribute to iPSC technology (or the basic biology of the cells involved). Specifically, focus on a single sentence (or two) where an idea or a result is given, for example this sentence: "For the expression of genes essential for reprogramming,such as Oct3/4 and Nanog, demethylation of cytosines is necessary in the respective promoter regions[32]" (there are many other possibilities in the "Epigenetic changes in iPSC reprogramming" section of this paper). For whatever result/statement that you select complete the following:

(a) Provide a 2 to 4 sentence description of the topic, essentially expanding the description given in the review paper (this section should include 3 to 5 additional references).
(b) Select a single research paper (in the example given above, that would be reference 32) and describe the "research approach" in about ¼ to 1/3rd of a page.
(c) Then, describe the "results" in about ¼ to 1/3rd of a page. This section should include one or two figures (which can be cut and pasted from the paper [or someplace like Google Images] as long as they are properly cited or they can be made by yourself if you wish, by adapting or presenting the data from the study in your own way). A typical research paper has several (e.g., 4 to 12) figures, so the key point here is for you to decide what the more important and significant data is in the original research paper that you wish to highlight here).
(d) Finally, a summary/conclusions/future directions section should be provided that will again be ¼ to 1/3rd of a page in length. This section could include an evaluation of the quality of the original research paper, what next steps should be taken (or, if the paper completely solved the problem under investigation, that'd be worth noting and explaining), or the practical implications of the results (e.g., how can the findings be applied by a "cell engineering" for achieving a biomedical endpoint).

Option #2. Cancer Epigenetics

1. Introduction / Background.

Waddington's "Epigenetic Landscape" (as briefly introduced in KJY Lecture #2) has also been invoked to explain cancer development, for example in the **Cancer epigenetics paper** pdf on Blackboard [in the KJY Lecture #4 folder] or directly downloadable from: http://science.sciencemag.org/content/357/6348/eaal2380/tab-pdf). Today, "epigenetics" has been firmly embedded as a necessary concept to understand (and ultimately treat) cancer; the review paper mentioned here largely focuses on DNA methylation but all modes of epigenetic mechanisms are in play in cancer.

2. "Study Guide"

As a study guide (e.g., to prepare for future quiz or exam questions), it is recommended that all students briefly peruse the "Cancer epigenetics" review paper mentioned above and know 2 or 3 "bullet point" pieces of information related to these ideas presented in this paper (i) how does DNA methylation relate to chromatin homeostasis / restriction (relatedly, what *is* chromatin homeostasis and/or restriction) in cancer and (ii) how do epigenetic factors contribute to one or two of the classic "hallmarks of cancer" (e.g., see Figure 4 of the review paper).

3. Option #2 Assignment

Similar to Option #1, choose one of the "bullet points" from just above to focus on; more specifically for this option, select a single aspect of one of the methylation-related epigenetic factors that contribute to cancer (or the basic biology of the cells involved) by focusing on a single sentence (or two) where an idea or a result is given. For whatever idea/result/statement that you select complete the following:

(a) Provide a 2 to 4 sentence description of the topic, essentially expanding the description given in the review paper (this section should include 3 to 5 additional references).
(b) Select a single research paper referenced in this review paper and describe the "research approach" in about ¼ to 1/3rd of a page.

(c) Then, describe the "results" in about ¼ to 1/3rd of a page. This section should include one or two figures (which can be cut and pasted from the paper [or someplace like Google Images] as long as they are properly cited or they can be made by yourself if you wish, by adapting or presenting the data from the study in your own way). A typical research paper has several (e.g., 4 to 12) figures, so the key point here is for you to decide what the more important and significant data is in the original research paper that you wish to highlight here).

(d) Finally, a summary/conclusions/future directions section should be provided that will again be ¼ to 1/3rd of a page in length. This section could include an evaluation of the quality of the original research paper, what next steps should be taken (or, if the paper completely solved the problem under investigation, that'd be worth noting and explaining), or the practical implications of the results (e.g., how can the findings be applied by a "cell engineering" for achieving a biomedical endpoint).

Option #3. sLe^x (sialyl Lewis X) Glycoengineering

1. Introduction / Background.

Sialyl Lewis X is (most likely) KJY's favorite glycan structure (if not all time favorite molecule); it turns out that other people like it too! For example Robert Sackstein's group (from Harvard, but we won't hold that against them) has exploited "glycoengineering" methods involving this molecule to endow MSCs with homing abilities (covered in this assignment); their group has conducted similar studies with HSCs (not covered). The key paper to focus on for this assignment is provided as a pdf on Blackboard (in the KJY Lecture #4 folder) under the name "HCELL MSC homing paper." For anyone interested, more perspective on Dr. Sackstein's interest in this topic is available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4847618/ .

2. "Study Guide"

As a study guide (e.g., to prepare for future quiz or exam questions), the suggestion is to know (in "bullet point" format) things such as (i) what is "HCELL"? (ii) are does "MSC" refer to? And (iii) why is MSC homing relevant? (e.g., in a biomedical context).

3. Option #3 Assignment

Based on the paper provided on Blackboard (but not limited to it, a total of [at least] 5 references are required for this assignment), provide

(a) An introductory section (of ¼ to 1/3rd page in length) discussing the "homing" of MSCs (e.g., if these cells are to be used therapeutically, how does the researcher or clinician ensure that they "home" to the appropriate site in the body [as a corollary, the discussion could focus on whether or whether not this is a "real" problem]). Hint, this would be a good section of the report to meet the "5 reference" requirement.

(b) A description of the research approach in the highlighted paper (the HCELL MSC homing paper pdf on Blackboard); this should be ¼ to 1/3 of a page in length).

(c) A description of key results (following guidelines provided above for Assignment #3 Option 1 or 2); this should be ¼ to 1/3rd of a page in length).

(d) The highlighted paper was published 4 years ago (meaning that the actual work was done 5 or more years ago); is there any follow-up work (from the Sackstein lab or elsewhere) that is continuing to advance MSC homing (or other types of cells?). Discuss this in ¼ to 1/3rd of a page.