Cancer Module Problem Set #1

Question 1. Suppose that a mutation responsible for a rare inherited human disease syndrome that causes predisposition to cancer is mapped to the gene that encodes Cdc25A. The product of the mutated gene, $Cdc25A^{alt}$, contains a single change in its amino acid sequence.

a) In vitro assays show that the phosphatase activities of Cdc25A and $Cdc25A^{alt}$ are the same. Therefore, more experiments are necessary to understand the molecular basis of the disease phenotype. The genes encoding wild type and mutated forms of Cdc25A are cloned into an expression vector and transfected into normal cells. Predict the effects of expressing these genes in cycling cells and in cells treated with DNA damaging agents.

b) Propose a likely way in which the mutation that causes the disease affects the coding sequence of the Cdc25A protein. Explain why this change would result in predisposition to cancer.

c) Predict whether this mutation would be dominant or recessive at the cellular level and explain the rationale for your choice. Propose an explanation for the observation that not all cells in affected individuals become tumorigenic.

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Question 2. (complete the assignment given in class)

"Skeleton code" for Tyson's model of the cell cycle has been posted on the course web site and emailed to you. As discussed in class, to utilize matlab's ODE solvers, this is implemented as a master script ("tyson_ode.m") and a function that is called by the ODE solver ("dydt_tyson.m"). When this is working, you will type "tyson_ode" at the matlab prompt and reproduce Fig. 3A in Tyson's paper. The first steps are to 1) place both files in the same directory (or the Desktop is okay), 2) change to that directory while in matlab, and 3) open both files using matlab's editor.

Assignments

1. Modify the file "dydt_tyson.m" so that the model runs. This will require adding lines of matlab code where indicated. Remember that the purpose of dydt_tyson is to compute the model's six derivatives, and then return a vector containing the derivatives to whatever program called it.
2. Once "dydt_tyson.m" has been successfully modified, the model will run. In other words, you type "tyson_ode" at the matlab prompt, and it will not crash. At this point, all the output will be stored in the variables "time" and "statevars." So how to you look at your results? You will need to modify "tyson_ode.m" to set Y equal to the first column of "statevars", YP equal to the second column, etc.
3. Once you do this, if you run the model you will see a plot that shows the time courses of all six model variables. Hopefully some of them will oscillate, as in a real dividing cell. To determine whether your implementation is correct, you will want to compare your output to Figure 3A in Tyson's paper. Note that he does not plot individual variables here (e.g. C2, YP) but instead plots ratios. Based on what you know about the different species, determine what ratios to compute, and plot these.
4. Tyson shows in his Figure 2 that the model behavior changes qualitatively – i.e. it either oscillates or stops oscillating – when the model parameters k_4 and k_6 change. Experiment with different values of these two parameters. How different from the control values do they have to be to make the model stop oscillating? Tyson claims that Regions A and C in Figure 2 correspond to different biological states. In terms of the model, making k_6 very small will move the model to Region A and making k_6 very large will move the model to Region C. Either one will cause oscillations to cease. From the model output, how can you tell that these are different biological states?

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Question 3. A new oncogene involved in brain cancer is discovered, and mutations in the human gene are found in primary tumors. After BLAST searching, you realize this gene is highly conserved in flies. Briefly outline (1 paragraph) a strategy to use flies to study this oncogene. Make sure to cite specific examples of approaches mentioned in lecture or the supplemental readings.