Cancer Module Problem Set #2

Question 1. A major goal in cancer therapy is to combine different agents with non-overlapping mechanisms of action and toxicity. The advent of new strategies for cancer therapy has introduced the potential for combining different agents that have markedly different pharmacokinetics and pharmacodynamics (i.e. cytotoxic chemotherapy and immunotherapy). Develop criteria for selecting appropriate agents from two or more groups for clinical testing in the cancer patient. Your combination should be novel and should not be based on a previous report in the literature. Explain why you chose the particular agents and how you would design a clinical trial to test your combination.

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Question 2

Modeling the cell cycle **Homework problem**

Consider the model of the cell cycle developed by Tyson that we discussed in class. In the previous homework assignment, all of you were able to successfully reproduce the plots in Tyson's Figure 3A, showing oscillations of MPF with the control set of model parameters. Most of you were also able to vary the parameters k_4 and k_6, and interpret how these affected the oscillations and the biological implications. In this assignment you will relax some of the idealizations of this highly simplified model, and examine how these influence the model's oscillatory activity.

One of the enzymes discussed by Dr. Hirsch that is now known to be important in cell cycle regulation is wee1. Tyson discusses the potential role for wee1 in cell cycle regulation but admits that he's not sure how to fit this into his framework. We'll simulate the effects of wee1 based on what we know now about this kinase.

a. Remember from Dr. Hirsch's lectures that wee1 acts to phosphorylate cdc2. For simplicity, let's assume that wee1 can only phosphorylate cdc2 when cdc2 is bound to cyclin – it cannot phosphorylate free cdc. If you wanted to simulate the effects of different concentrations of wee1, what model rate constant would you modify?

b. Modify your working version of the Tyson model to simulate cells with different concentrations of wee1. Simulate wee1 concentrations from 0 to 7, and for each value, assume that $k_X = 0.4*[wee1]$, where k_X is the wee1-dependent rate constant. For each value of [wee1], plot normalized [MPF] versus time, as in Tyson's Fig. 3A. What happens to the MPF oscillations as [wee1] increases? How can you relate this to the known function of wee1? What does your model predict would occur with extreme wee1 overexpression (i.e. the highest concentration you simulated) ?

c. One simplification of this new model you've developed is that the rate constant k_X depends linearly on [wee1]. In fact, Dr. Hirsh's notes indicate that MPF inhibits wee1 activity. How could you modify the model to take this effect into account?

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Question 3. Based on your knowledge of chemotherapy, you have designed a new drug designed to treat a specific cancer by binding to an oncogenic receptor upregulated in that cancer. In general, the combination works very well. At first, the combined regimen is effective in approximately 90% of patients, e.g. 10% of patients have absolutely no response to treatment. Over time, it is then discovered that a percentage of initial responders have a recurrence of their cancer. Explain the two major observations: one subset of patients never respond to treatment while in a second subset, the initial response is lost. Describe the expts. you would design to test your hypothesis. Interestingly, as you review the data on the initial non-responders, i.e. the 10% group, you realize that a number of these individuals share the same last name. With further questioning it becomes obvious that many of these individuals are related and indeed come from three families. How would this affect your hypothesis and how would you now test your theory?

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Question 4.
In 1980, ovarian cancer ranked as the fourth leading cause of cancer mortality among women in the United States. An estimated 18,000 new cases and more than 11,000 attributable deaths occurred among American women that year.

Several studies had noted an increased risk of ovarian cancer among women of low parity, suggesting that pregnancy exerts a protective effect. By preventing pregnancy, oral contraceptives (OCs) might be expected to increase the risk of ovarian cancer. On the other hand, by simulating pregnancy through suppression of pituitary gonadotropin release and inhibition of ovulation, OCs might be expected to protect against the subsequent development of ovarian cancer. Because by 1980 OCs had been used by more than 40 million women in the United States, the public health impact of an association in either direction could be substantial.

To study the relationship between oral contraceptive use and ovarian cancer (as well as breast and endometrial cancer), CDC initiated a case-control study – the Cancer and Steroid Hormone (CASH) Study in 1980. Case-patients were enrolled through eight regional cancer registries participating in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.

The primary purpose of the CASH study was to measure and test the association between OC use and three types of reproductive cancer) breast cancer, endometrial cancer, and ovarian cancer. Enrollment of subjects into the study began in December 1980. During the first 10 months of the study, 179 women with ovarian cancer were enrolled, as well as larger numbers of women with endometrial or breast cancer. During the same period, 1,872 controls were enrolled to equal the number of subjects with breast cancer. The same control group was used for the ovarian cancer analysis; however, the investigators excluded 226 women with no ovaries at the time of interview and four controls whose OC use was unknown, leaving 1,642 women to serve as controls. The distribution of exposure to OCs among cases and controls is shown in Table 1.

Table 1. Ever-use of oral contraceptives among ovarian cancer cases and controls, Cancer and Steroid Hormone Study, 1980-1981

		CASE-CONTROL STATUS		
		Case	Control	Total
USE OF OCs	Ever	a = 93	b = 959	H_1 = 1052
	Never	c = 86	d = 683	H_0 = 769
	Total	V_1 = 179	V_0 = 1642	T = 1821

Formulas:

Odds Ratio (OR) = 

Standard Error of the Ln(OR) = $\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$

95% Confidence Limit for the Odds Ratio = $\exp\left(\ln\left(\frac{a*d}{b*c}\right) \pm 1.96 * \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\right)$

a) Using the formulas above, calculate the OR and 95% CI.

b) How might you describe and interpret these results?