BENG 122A Final Project:

Cancer Tumor Response to Controlled Treatment in Mouse Model

Chad Phillips
Dmitriy Major
Romina Shirazi
Antonio Loaiza

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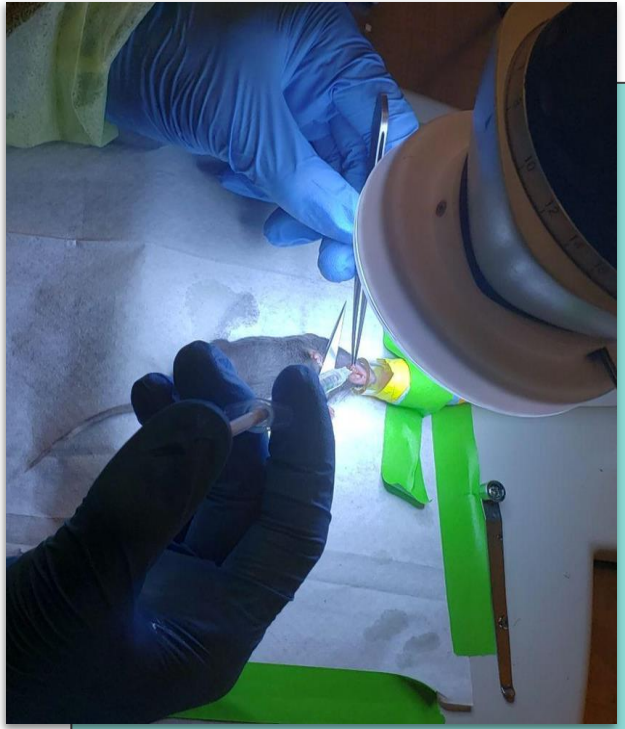


(Above) Image from aPd-1 Mouse model experiment dissection.

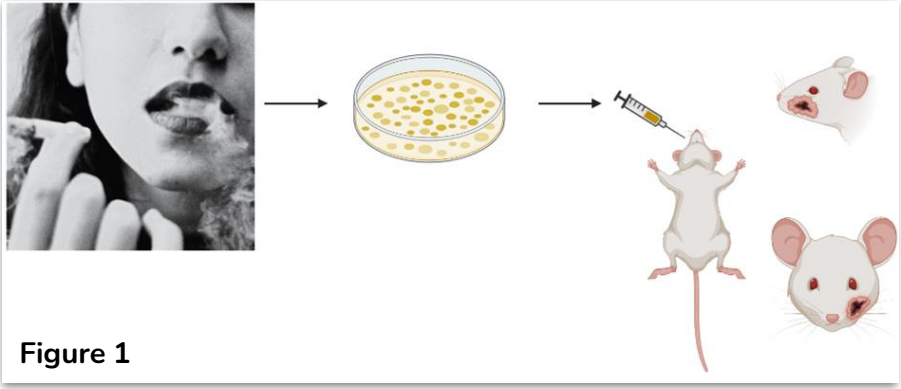


Figure 1

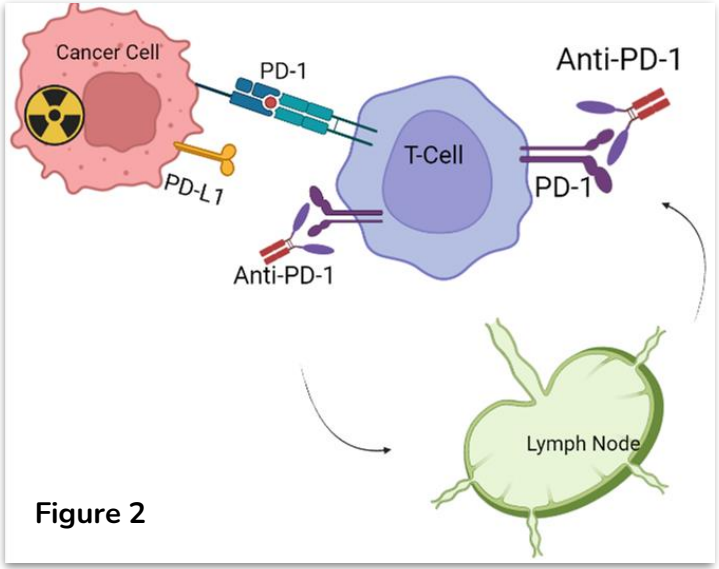
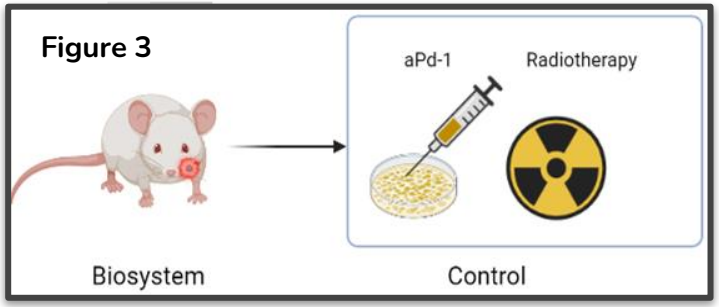


Figure 2

Background

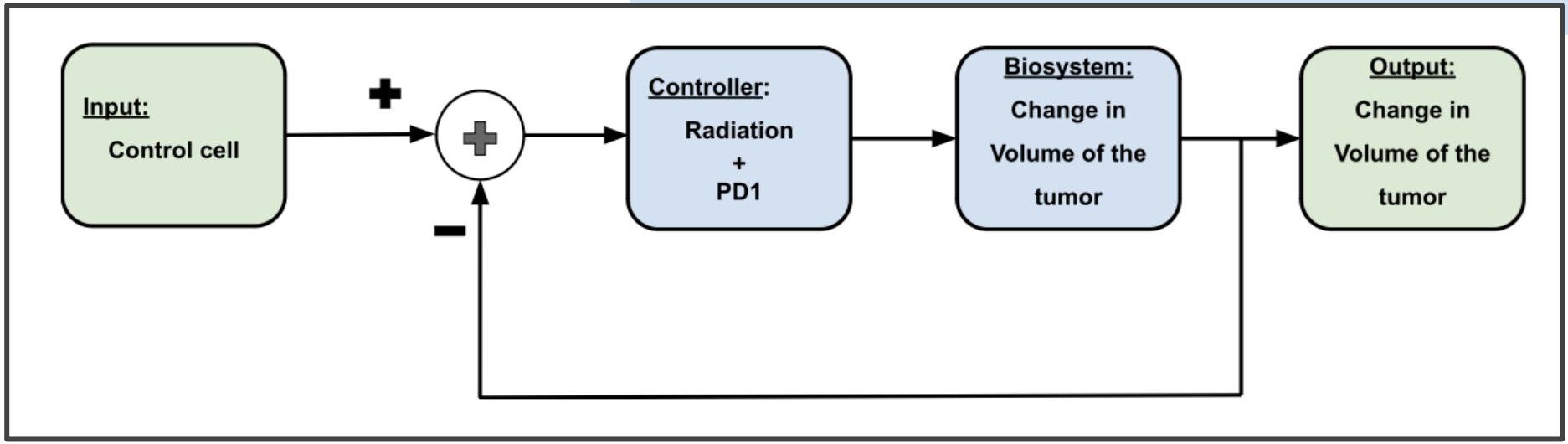
- Head and Neck Squamous Cell Carcinoma cell line is modeled as 4MOSC1, which is administered to mouse samples (**Figure 1**). These tumors develop until treatment is administered.
- The cancer mimics non hazardous cells by Pd-1 receptors to evade immune response and proliferate. (**Figure 2**)
- aPd-1 is a common immunotherapy technique that blocks T-Cell receptors, allowing them to continue to destroy cancer cells.
    - Additionally, radiation is also commonly used to reduce cancer evasion and increase immune response.
- Radiation therapy combined with aPd-1 immunotherapy should provide tumor volume reduction over time, which we plan to model.

Objectives



A. To examine the change of tumor kinetics of administered treatments of αPd-1 and Radiation therapy based on theoretical models and experimental observations (**Figure 3, left**).

B. To model the Volume profiles of tumor cells based on theoretical calculations and observation with and without control as shown in the simple block diagram (**Figure 4, below**).



Basic Assumptions and Important Constants

Variable	Value	Units
α	1	mL^{-1}
τ	1	s^{-1} (time constant)
k	18	$mg*ml*s^{-1}$
V_0	1	mL
C_0	0	$mg*mL^{-1}$
I(t)	N/A	$mg*s^{-1}$
C(t)	N/A	$mg*mL^{-1}$
V(t)	N/A	mL

- Mouse sample immune systems are uniform in response
- All treatment controls are administered in a uniformed method and rate
  - Experiment conducted at standard temperature and pressure
  - No external stimuli or reaction other than the drug treatment
  - Constant drug source (syringe) and constant drug sink (tumor cell)
- Model response is limited to selected variables
- Mouse model mass, volume, and viscosity modelled after water (simplification)
- No measurement error for theoretical model

Table 1 (left): Important constants used in volume and concentration profile models, linearization, and frequency response calculations.

System of Equations

$$\frac{dC}{dt} = \dot{C} = \alpha I(t) - \frac{1}{\tau} C(t)$$

Eqn. 1: Concentration profile for cancer drug treatment aPD-1 with concentration C(t) and drug injection over time I(t).

$$\frac{dV}{dt} = \dot{V} = \frac{1}{\tau} V(t) + kC(t)V(t)$$

Eqn. 2: Volume profile over time based on conservation of mass, including the influx of volume from the concentration of drug treatment being added.

Due to the nature of the interaction between the drug treatment and the volume profile, it is necessary to linearize the system to allow us to solve for V.

Linearized System

$$[J] = \begin{bmatrix} \frac{\delta}{\delta C}(\dot{C}) & \frac{\delta}{\delta V}(\dot{C}) \\ \frac{\delta}{\delta C}(\dot{V}) & \frac{\delta}{\delta V}(\dot{V}) \end{bmatrix} = \begin{bmatrix} -\frac{1}{\tau} & 0 \\ kV_0 & \frac{1}{\tau} + kC_0 \end{bmatrix}$$

$$\begin{bmatrix} \frac{d\tilde{C}}{dt}_{lin} \\ \frac{d\tilde{V}}{dt}_{lin} \end{bmatrix} = [J] \begin{bmatrix} \tilde{C} \\ \tilde{V} \end{bmatrix} = \begin{bmatrix} -\frac{1}{\tau} & 0 \\ kV_0 & \frac{1}{\tau} + kC_0 \end{bmatrix} \begin{bmatrix} \tilde{C} \\ \tilde{V} \end{bmatrix}$$

$$\frac{d\tilde{C}}{dt}_{lin} = \alpha I(t) - \frac{1}{\tau}\tilde{C}(t)$$

Eqn. 3: Linearized equation for the concentration profile of the aPD-1 treatment added to the mouse. This system was already linear previously so nothing much changed

$$\frac{d\tilde{V}}{dt}_{lin} = kV_0\tilde{C}(t) + (\frac{1}{\tau} + kC_0)\tilde{V}$$

Eqn. 4: Linearized equation for the Volume profile of the tumor size for the mouse model. Since the original profile had a nonlinear element, the new iteration takes into consideration the operating point.

Transfer Function (Stability and Control)

$$H(s) = \frac{V(s)}{I(s)} = \frac{kV_0\alpha}{(s+\frac{1}{\tau})(s-\frac{1}{\tau}+k*C_0)} = \frac{kV_0\alpha}{(s^2-\frac{1}{\tau^2})}$$

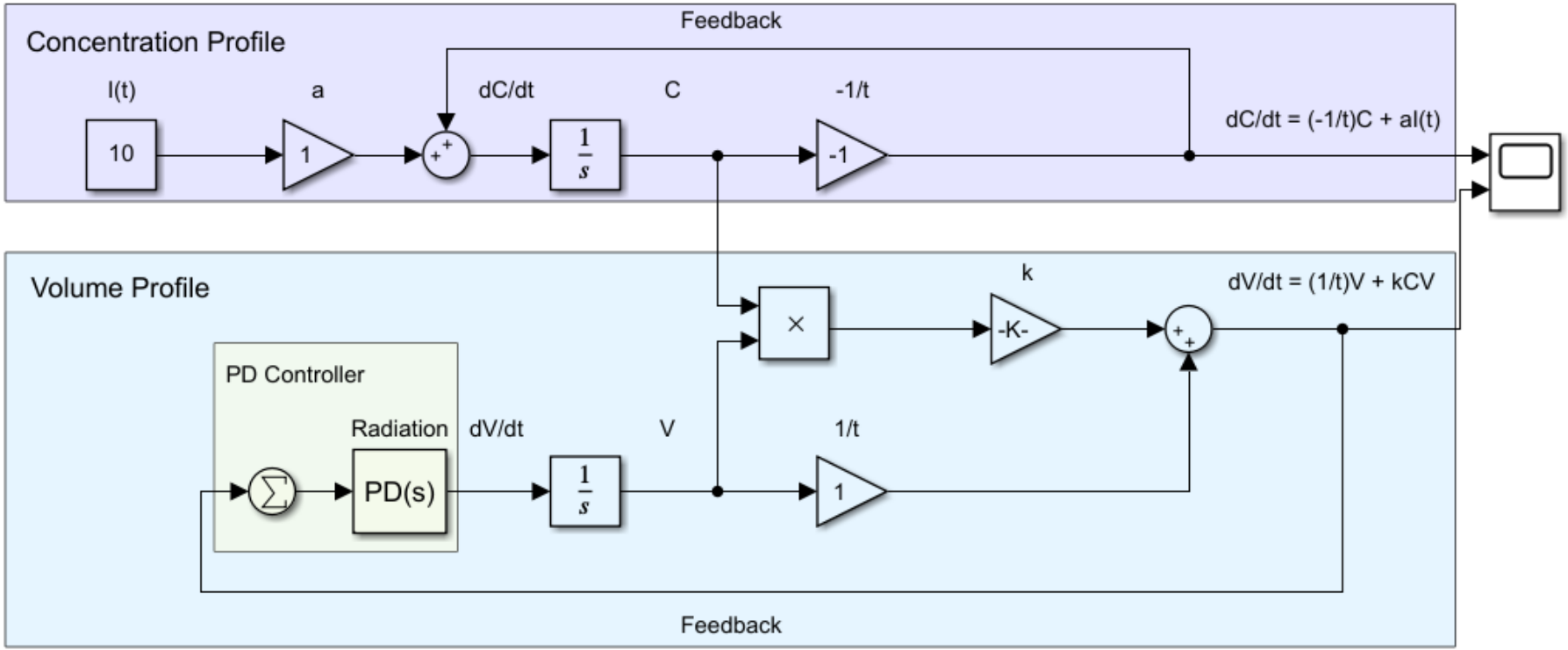
Eqn. 5: The first transfer function is a non-controlled model of the volume (V) ratio with the inflow rate of drug treatment (I). The model is unstable due to the positive pole at 1/τ.

$$G(s) = PD * H(s) = \left(s+\frac{1}{\tau}\right)\frac{kV_0\alpha}{\left(s+\frac{1}{\tau}\right)\left(s-\frac{1}{\tau}\right)} = \frac{kV_0\alpha}{\left(s+\frac{1}{\tau}\right)}$$

Eqn. 6: The second transfer function now utilizes PD control (representative of the radiation treatment used in addition to the drug) as a control to increase the stability of the response at high frequencies. Now there is just one stable pole at -1/τ since the P-D system adds a zero to stabilize the positive pole.

Simulink Diagram

Model 1: Simulink Block Diagram of aPD-1 Concentration/Volume Profiles



Bode Plots (Experimental)

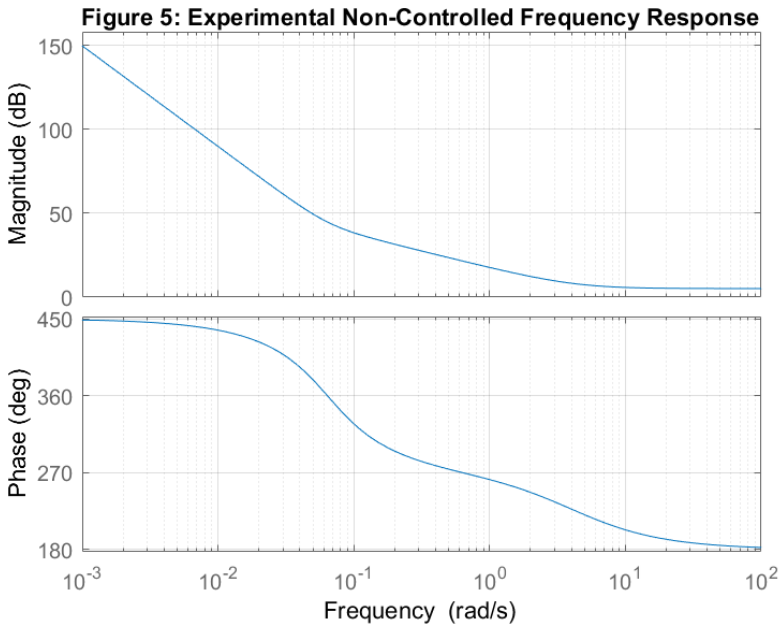


Figure 5: Shows the experimental bode plot of the measured control group without PD-Control. Notice that it is unstable at low frequencies, and critically stable at higher frequency.

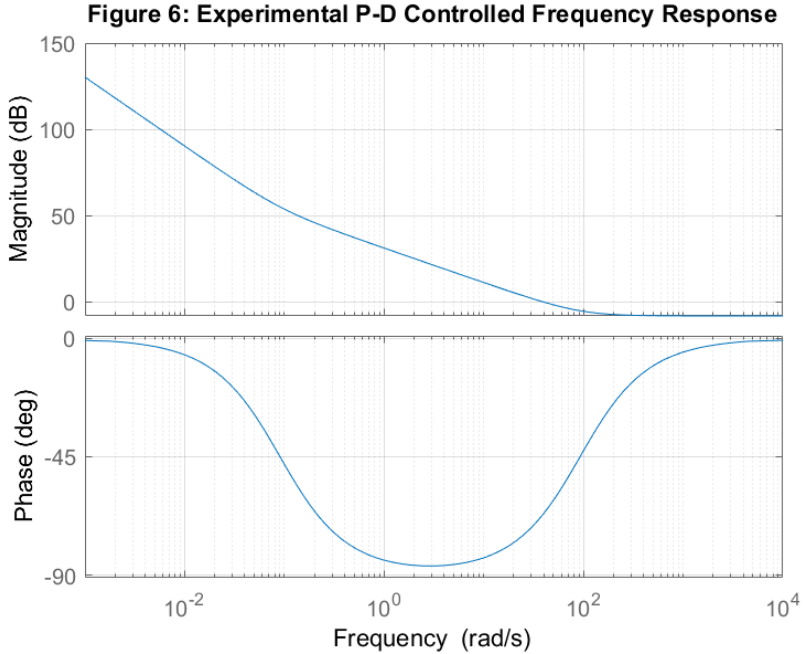


Figure 6: Shows to bode plot of the measured radiation and aPd-1 control. Notice that the administered control provides stability to the system, including a stable phase margin.

Step Function (Experimental)

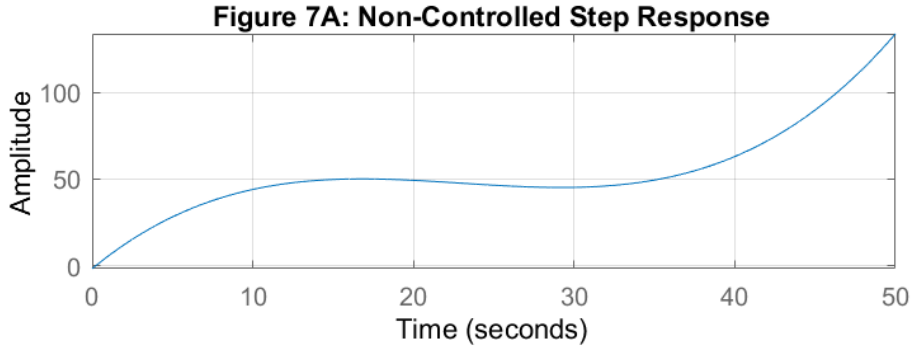


Figure 7A: Depicts the step function response of the non-controlled response. Shows response diverging as time increases.

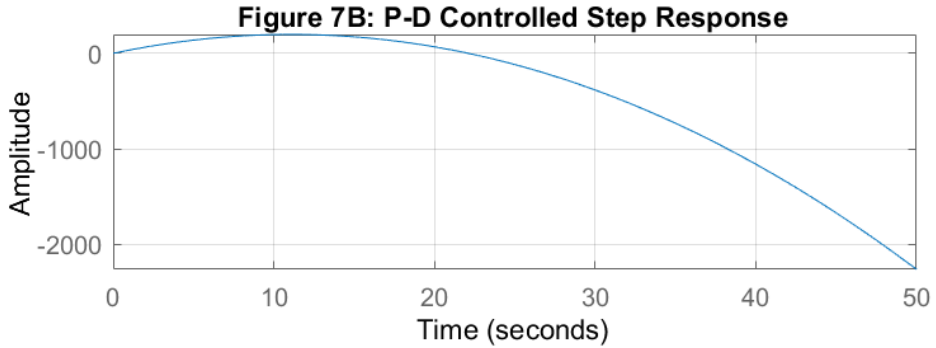


Figure 7B: Depicts the step function response of the PD-controlled response. Shows amplitude response converging as time increases.

Bode Plots (Theoretical)

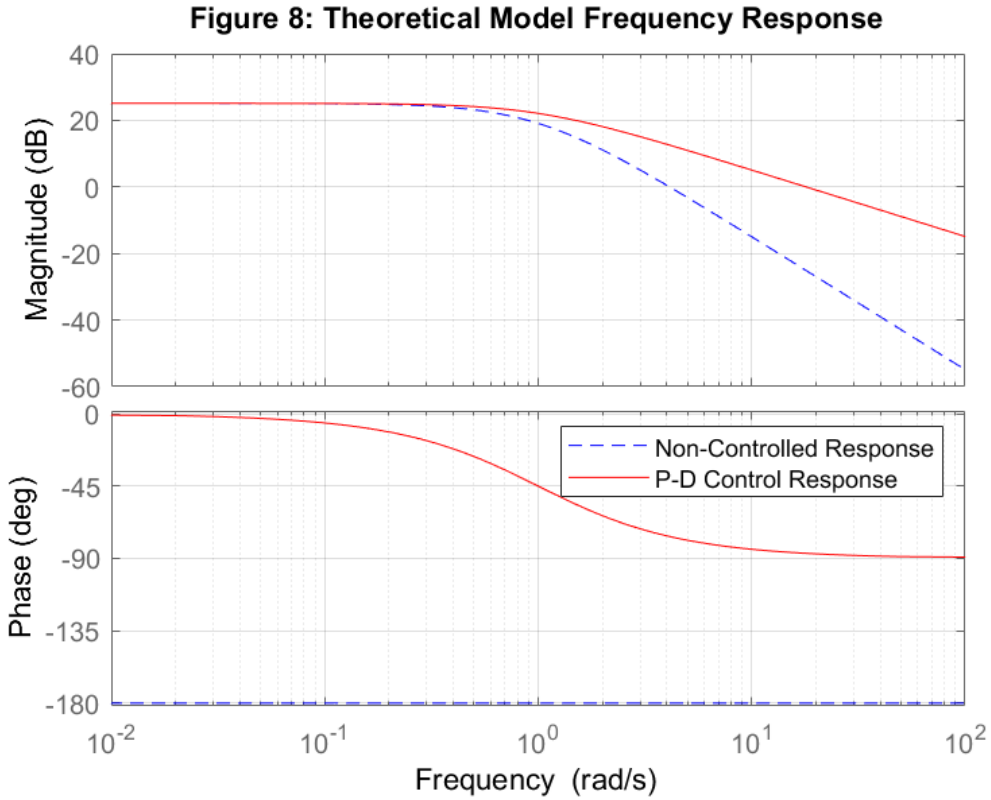
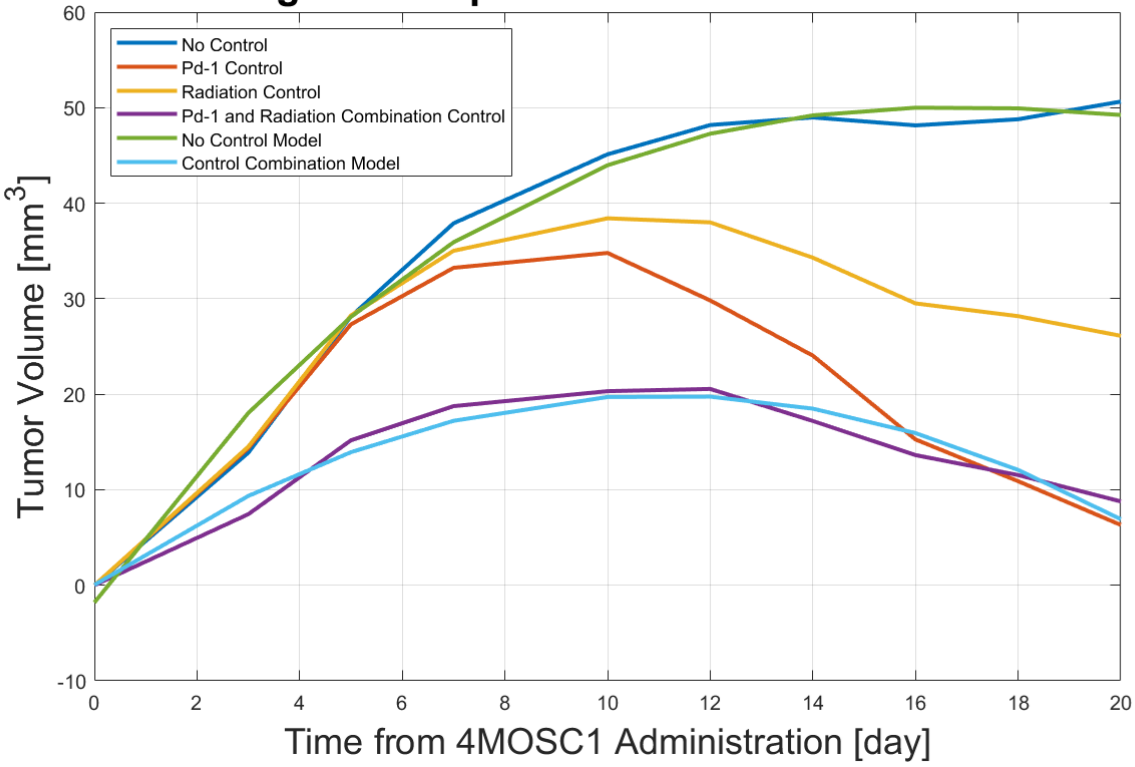


Figure 8: Theoretical Bode Plots of the frequency response of the mouse volume relation to amount of PD1 treatment drug used in the model. Like the transfer functions, the uncontrolled model (blue) has an unstable phase margin of 0 at -180° and pole at $1/\tau$, whereas the P-D response (red) has an increased and stable phase margin at approximately 90°.

Results

Figure 9: Experimental Tumor Kinetics

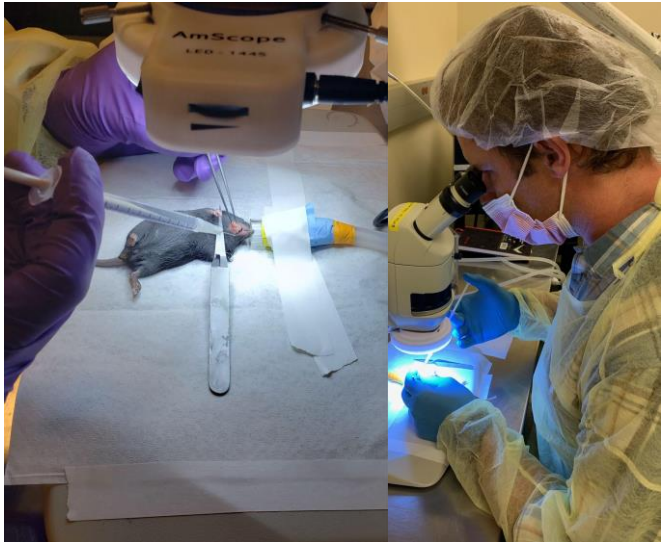


The experimental tumor kinetics were measured and graphed as shown in **Figure 9** (left).

The aPd-1 treatment provided a better decrease in tumor volume than simply radiation; however, the combination of radiation *and* aPd-1 is even more highly effective at providing stability to the system and decreasing the tumor volume quicker over time as compared to no treatment at all or each treatment on its own.

This lines up with theoretical predictions and models.

Discussion and Future Direction



The photos (above) show a lab worker (Chad) administering treatment to mouse samples.

- This model can be beneficial to predicting cancer growth under controlled conditions and using the similar variables. Observing the effects of combinations of treatments (such as the aPd-1 treatment and radiotherapy) on mouse models can allow researchers to test efficacy of treatment for eventual applications for medical treatment.

- Future projects can reinforce the control methods and procedures and smooth out some of the assumptions made. Additional models can be modified to demonstrate a more robust cause and effect relationship that will enhance Head and Neck Squamous Cell Carcinoma treatment on human patients.

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Thank You!

Thank you Dr. Cauwenberghs and our TAs Becky and Will for assisting us during this quarter with learning biosystems!

Any Questions?