PK/PD Modeling

For this lab we will be completing two problems going over the basics of pharmacokinetic (PK) modeling. Your TA will walk you through the first problem as a demonstration, and the second problem will be done on your own with assistance from the TA. For your submission, include any requested figures, answers to all included questions, and your MATLAB code.

Problem 1 (Demo): Modeling s.c. bolus therapeutic delivery with a two-compartment model.

For this problem we will use a two-compartment model to fit blood measurements after subcutaneous delivery of a therapeutic. The table below contains measurements of the drug in the blood at several timepoints after a 0.1 mg bolus subcutaneous injection.

Time (hours)	Blood Concentration (ug/mL)
0	0
0.5	0.0161
1	0.0190
2	0.0193
4	0.0186
6	0.0179
8	0.0172
12	0.0160
16	0.0148
24	0.0127
48	0.0080
72	0.0050

a) Write a MATLAB function that can be passed into a MATLAB ODE solver that calculates the rates of change for a two-compartment model of s.c. bolus therapeutic injection. The function should output a vector with the rates of change of each species in the model (in this case, s.c. concentration and blood concentration) given time t, a vector of current concentrations c, and a vector of model parameters p = $[k_{12}, k_{CL}, V_1, V_2]$. Here we will assume that the concentration gradient between the subcutaneous space and the blood is very high such that $C_1 - C_2 \approx C_1$, thus the equations are given by:

$$\frac{dC_1}{dt} = -k_{12}C_1$$
$$\frac{dC_2}{dt} = \frac{k_{12}V_1}{V_2}C_1 - k_{CL}C_2$$

Use your function to calculate $\frac{dC_1}{dt}$ and $\frac{dC_2}{dt}$ given the parameter values $k_{12} = 2.5, k_{CL} = \frac{\ln(2)}{24}, V_1 = 1\ mL$, and $V_2 = 5000\ mL$, time = 0, and $[C_1, C_2] = [\frac{D}{V_1}, 0]$ where D = 100 ug (0.1 mg).

b) Write a MATLAB function that simulates the two-compartment model using MATLABs ode15s ODE solver given a vector of timepoints tspan, a vector of model parameters p = $[k_{12}, k_{CL}, V_1, V_2]$, and a dose amount D. Use your function to simulate your model over a period of 72 hours given the same parameters and dose amount in part a). Plot your predictions of blood concentration v. time.

c) Write a MATLAB function that outputs the sum of squared errors between model predictions and experimental measurements given a vector of timepoints t_{exp}, a vector of experimental measurements c_{exp} a vector of transport parameters p_kinetic = $[k_{12}, k_{CL}]$, and a vector of system conditions p_system = $[V_1, V_2, D]$ where D is the dose amount. Calculate the error between your model predictions and experimental data given the parameter values from part a).

d) Use MATLAB's fminsearch function to obtain estimates for the therapeutic's transport parameters (k_{12} and k_{CL}) by minimizing sum of squared errors. Use compartment volumes of $V_1 = 1\ mL$ and $V_2 = 5000\ mL$, and use initial estimates of $k_{12} = 2.5$ and $k_{CL} = \ln(2)/24$. What are your estimates for each parameter? Based on the estimated clearance rate, what is the half-life of the therapeutic? Recall from the demo problem in lecture $t_{1/2} = \frac{\ln(2)}{k_{CL}}$ Plot your model predictions of blood therapeutic concentration v. the experimental measurements.

Problem 2: Modeling IL-2 intraperitoneal cell therapy with a two-compartment model.

For this problem we will be replicating some of the results from the PK model of IL-2 intraperitoneal cell therapy presented by Nash et al. (https://www.science.org/doi/10.1126/sciadv.abm1032). This IL-2 based technology is designed to maintain high levels of IL-2 exposure to achieve sufficient tumor suppression while limiting systemic exposure to IL-2. Briefly, engineered ARPE-19 cells are encapsulated in an alginate-based polymer and implanted intraperitoneally in patients/animal models with intraperitoneal tumors. These capsules constantly produce IL-2 within the intraperitoneal space over time, with production decreasing due to the foreign body response. We aimed to use PK modeling to demonstrate safety and efficacy in translation to human treatment based on results in animal models. Here, we will replicate some of these results.

The table below contains IL-2 measurements in the intraperitoneal cavity and the blood in mice treated with 200 IL-2 producing cell capsules with an *in vitro* determined production rate of 7930.8 pg/capsule/day. This data was measured using an ELISA assay with a minimum detection limit of 30 pg/mL. This will be important later when calculating error between model predictions and experimental measurements.

Time (days)	**Mean Blood IL-2 (pg/mL)**	**Blood IL-2 Error (pg/mL)**	**Mean IP IL-2 (pg/mL)**	**IP IL-2 Error (pg/mL)**
0	0	0.01	0	0.01
1	1135.15	350.05	448568.7	87937.6
4	288.04	95.27	156181.1	77579.66
7	1.46	0.82	7948.23	2885.65
14	0	0.01	661.44	355.29
21	0	0.01	0	0.01
30	0	0.01	0	0.01

a) Write a MATLAB function that can be passed into an ODE solver that calculates the rates of change for the two-compartment model used to simulate this system:

$$\frac{dC_1}{dt} = \frac{k_{prod}}{V_1} \mathrm{N}_0 \exp\{-\lambda t\} - k_{trans} C_1$$

$$\frac{dC_2}{dt} = k_{trans} \frac{V_1}{V_2} C_1 - \frac{k_{clear}}{V_2} C_2$$

Note that this model is very similar to the two compartment model we used in the first problem with a few small changes. First, we add the term $\frac{k_{prod}}{V_1} N_0 \exp\{\lambda t\}$ to account from cytokine production from cell factories. This term assumes that productive capsules have a cytokine production rate of $k_{prod}\left(\frac{pg}{capsule*day}\right)$, and that due to the body's foreign body response the number of producing capsules decreases exponentially with time according to $N(t) = \mathrm{N_0}\exp\{\lambda t\}$. We finally divide this term by the IP compartment volume to convert to concentrations. The other minor difference between this model and that from Problem 1 is the notation used for systemic clearance. Often times, clearance is given as a volumetric clearance rate $k_{clear}[=]\frac{volume}{time}$, and is therefore normalized by compartment volume. In our previous model we combine terms into single clearance rate equal to $\frac{k_{clear}}{V_2}$. For consistency with model in the paper we will use the volumetric clearance rate notation for this problem.

Your function should output a vector of rates of change $dcdt = \left[\frac{dC_1}{dt}, \frac{dC_2}{dt}\right]$ given time t, a vector of concentrations $C = [C_1, C_2]$, and a vector of parameter values $p = [k_{prod}, N_0, \lambda, k_{trans}, k_{clear}, V_1, V_2]$. Using the parameter values $k_{prod} = 7930.8\frac{pg}{capsule*day}$, $N_0 = 200\ capusles, \lambda = 1, k_{trans} = 1.5, k_{clear} = 500, V_1 = 1\ mL$, and $V_2 = 1.2\ mL$, determine $\frac{dC_1}{dt}$ and $\frac{dC_2}{dt}$ at time = 0 based on concentrations $C_1 = 0$ and $C_2 = 1$.

b) Write a MATLAB function that uses your function from part a) to simulate the two-compartment model. Your function should output a vector of intraperitoneal IL-2 concentrations $C1 = [C_{1,t0} \dots C_{1,tf}]$ and a vector of blood IL-2 concentrations $C2 = [C_{2,t0} \dots C_{2,tf}]$ given the following inputs: a vector of timepoints $tspan = \left[t_0 \dots t_f\right]$ and a vector of parameter values $p = \left[k_{prod}, N_0, \lambda, k_{trans}, k_{clear}, V_1, V_2\right]$. For initial conditions for the simulation use $C_0 = [0,0]$. Simulate your model over a period of 25 days with the same parameter values used in part a). Plot your results on the same set of axes with the y axis on a log scale.

c) Write a MATLAB function that calculates a modified version of standard squared error between our model predictions and experimental data. The inputs to this function should be a vector of predicted IP IL-2 concentrations $C1$, a vector of predicted blood IL-2 concentrations $C2$, a vector of measured IP IL-2 concentrations $C1\_exp$, and a vector of measured blood IL-2 concentrations $C2\_exp$. This function should output the sum of calculated error that is determined at each point as defined by the function below:

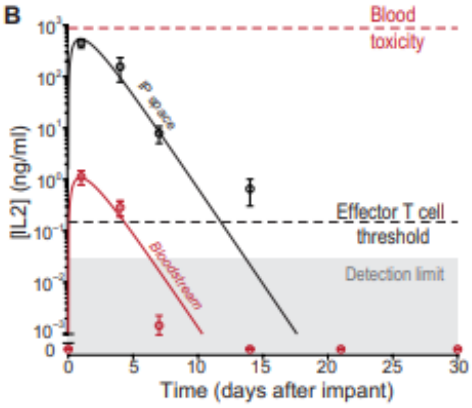
$$error = \sum \begin{cases} \frac{(C - C_{exp})^2}{1 + C_{exp}^2}, & C_{exp} \geq D \\ \frac{(C - D)^2}{1 + D^2}, & C \geq D \ and \ C_{exp} < D \\ 0, & C < D \ and \ C_{exp} < D \end{cases}$$

We modify our error function like this to account for the minimum detection limit of the ELISA assay used to measure IL-2. Here, C refers to the model prediction of a given time point, C_{exp} refers to the measured concentration at that given time point, and D refers to the minimum detection

limit of the assay used for experimental measurements. In our case, the minimum detection limit of the ELISA assay is 30 pg/mL, so set D = 30 in your function. Here, when our model predicts concentrations below the detection limit at timepoints where the measurement was non-detectable there is no penalty, even though the model is not predicting concentrations of zero. Similarly, if the measured value is below the detection limit and our model predicts detectable concentrations, error is calculated against the detection limit. We calculate error normally when the measured concentrations are above the detection limit. Make sure you are calculating the sum of squared error of all data points, i.e. both blood and IP measurements. Simulate your model at the experimental time points using your function from part b) and use the function you wrote for part c) to calculate the error.

d) Write a MATLAB function that combines the three functions you wrote in parts a)-c) that simulates the model and calculates the sum of squared error given a vector of timepoints $tspan$, a vector of IP measurements $C1\_exp$, a vector of blood measurements $C2\_exp$, a vector of kinetic parameters $p\_kinetic = [\lambda, k_{trans}, k_{clear}]$, and a vector of system/dosing parameters $p\_system = [k_{prod}, N_0, V_1, V_2]$. This function should simulate the model given the kinetic parameters in p_kinetic and the system/dosing parameters in p_system with the initial conditions for both C_1 and C_2 as zero. The simulation results should then be passed into your function from part c) to determine error. Use this function to calculate the error between model predictions, using the parameter values from part a) for $p\_kinetic$ and p_system.

e) Use MATLAB's fminsearch function to obtain estimates for the model's kinetic parameters λ, k_{trans}, and k_{clear} by fitting your model to the data in the table above (ensure that your timepoints and data are column vectors). For initial parameter estimates use $p_0 = [1, 2, 500]$. For your system/dosing parameters use $k_{prod} = 7930.8 \frac{pg}{capsule*day}$, $N_0 = 200\ capsules$, $V_1 = 1\ mL$, and $V_2 = 1.2\ mL$. What are your parameter estimates for each of the kinetic parameters? What does this suggest the half life of IL-2 in the blood is? Plot your model predictions and experimental data for the IP space and blood on the same set of axes with the y-axis on a log scale. Include error bars for experimental data (use MATLAB's errorbar function to plot).



f) Now that we have estimates for the model parameters from fitting our mouse data, we want to predict how IL-2 cell capsules will behave in humans. Our model parameters we determined in mice will not apply in humans, but we can apply allometric scaling techniques to convert our

determined parameters to human values. Using the equation for allometric scaling of parameters introduced in lecture:

$$P_{human} = P_{mouse} x \left(\frac{M_{human}}{M_{mouse}}\right)^{b}$$

Convert your estimates for IL-2 peritoneal transport rate (k_{trans}) and IL-2 systemic clearance (k_{clear}) to human values. For transport rate use b = -0.074, and for clearance rate use b = 0.70. Assume the average human mass is 70 kg and the average mouse mass is 25g. Using your human parameter values simulate the model for a period of 25 days. Assume a dose of $N_0 = 5000$, a production rate $k_{prod} = 7930.8 \frac{pg}{capsule * day}$, a blood volume of $V_2 = 5000\, mL$, and an intraperitoneal volume of $V_1 = 20\, mL$. Plot your simulation results for IP and blood IL-2 on the same set of axis on a semi-log (y axis on log scale) plot. If IL-2 needs to be at concentrations above ~0.1 ng/mL to cause T-cell activation but is toxic at levels of ~1000 ng/mL, what do our results suggest about the safety of our treatment? Include these thresholds on your plot to help visualize (see MATLAB's yline function).

g) An important prediction we can make for this cell therapy is the ratio between blood and IP IL-2 concentrations at long timepoints. Using the same parameters you used in part f), calculate the ratio of IP IL-2 concentration (C_1) to blood IL-2 concentration (C_2) five days after dosing. What if our estimate of transport rate was inaccurate and the value is double what we used in part f)? What about if we dose patients with 7500 capsules instead? What does this imply about the robustness of our model predictions?