PhySci/MiMG/CaSB M178

Homework 9

Due: 12/07/23 at 12:00PM PDT

Notes: This homework involves performing simulations of the caspase cascade we discussed earlier in the quarter and exploring parameter sensitivity. In the same folder on BruinLearn where you obtained this document, you will also find a file called "HW9_template.ipynb" that contains a template Jupyter notebook that you can use as a starting point to complete the questions below. Please modify this notebook and use it as the starting point for answering the following problems.

To submit your homework, please answer the questions below. Note that you will have to paste in several graphs that you generate using the Jupyter notebook. After completing the questions, **save this document as a PDF and upload it to Gradescope**. You **must also upload the Jupyter notebook to BruinLearn**; to do so, navigate to the "Homework" section on the left-hand side of the course BruinLearn website. There you will see an assignment entitled "Homework 9 Jupyter submission." You can upload your Jupyter file (which should be a .ipynb file). Make sure you upload your Jupyter notebook by the due date/time (12/7/23 at 12:00PM PDT).

Problems

For this homework, we will borrow the apoptosis model from Homework 4 that included a receptor activating pro-caspase 8, reversible FLIP binding at the receptor, and positive feedback by caspase 3.

As a quick refresher: in this model we will have the following species: proC8, C8, proC3, C3, R (receptor), F (FLIP), and RF (receptor-FLIP complex).
   a) proC8 and proC3 are synthesized at rate QC8 and QC3 respectively (zeroth order reaction).
   b) proC8, C8, proC3, and C3 are all degraded at rate delta (first order reaction).
   c) proC8 binds R at rate k_ba and generates C8 (second order reaction; no intermediate complex formed).
   d) proC3 binds C8 at rate k_a and generates C3 (second order reaction; no intermediate complex formed).
   e) C3 binds proC8 at rate k_a and generates C8 (second order reaction; no intermediate complex formed).
   f) F binds R at rate kp to generate RF (second order reaction). Note that, in this case, F and R *are* forming an explicit complex (RF).

g) RF dissociates into F and R at rate km (first order reaction).

1) (2 points) This model has been implemented in the code section titled "simple caspase model with feedback and FLIP". <u>Run this section of code to load up the model.</u>

In the following code section, we define the default mean model parameter values, which we also include here for your reference. <u>Run this section of code to load up the model parameters.</u>

Initial Conditions	Default Value
proC8_0	1 µM
C8_0	0 µM
proC3_0	1 µM
C3_0	0 µM
R_0	1 µM
F_0	1 µM
RF_0	0 µM

| Parameter Values	Default Value
k_a	$0.001 \ \mu M^{-1} sec^{-1}$
k_ba	$0.001 \ \mu M^{-1} sec^{-1}$
kp	$0.01 \ \mu M^{-1} sec^{-1}$
km	$0.01 \ sec^{-1}$
delta	$2 \times 10^{-4} \ sec^{-1}$

As in the previous homework, the synthesis rates (QC8 and QC3) are determined by the initial value of pro-caspases and the degradation rate delta.

<u>Run the section of code titled "Simulation with default mean parameters".</u> This section runs a simulation of the apoptosis model using the default mean parameters and generates the trajectory of the active fraction of C3 over time.

We will assume that a cell with these default mean values as its parameter values dies. Hence, we will use the active fraction of C3 at steady state (the end of this simulation) to set a cell fate threshold, ss_C3. If the active fraction of C3 at steady state for any subsequent simulation is greater than or equal to ss_C3 times a scaling factor (set to 0.75 by default), the cell dies.
<u>Paste the resulting graph and write down the threshold value that will determine cell fate in subsequent simulations.</u>

threshold = 0.610718
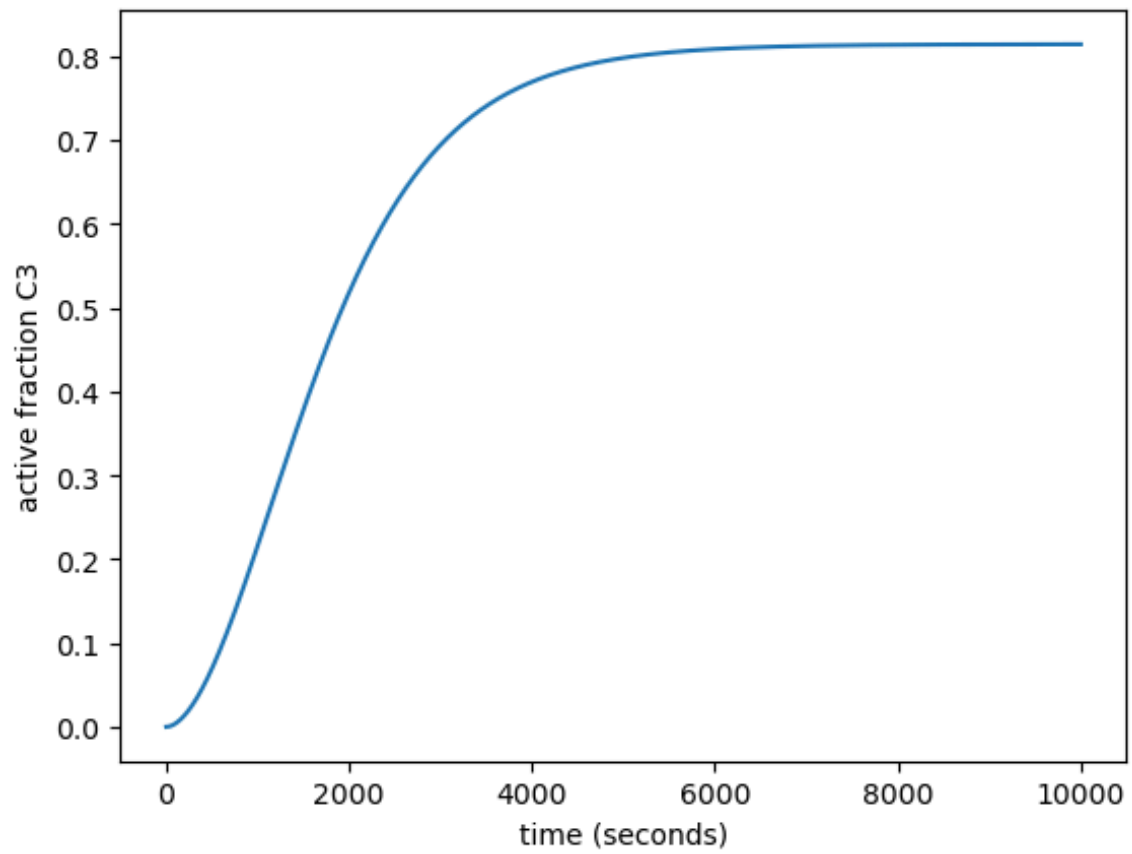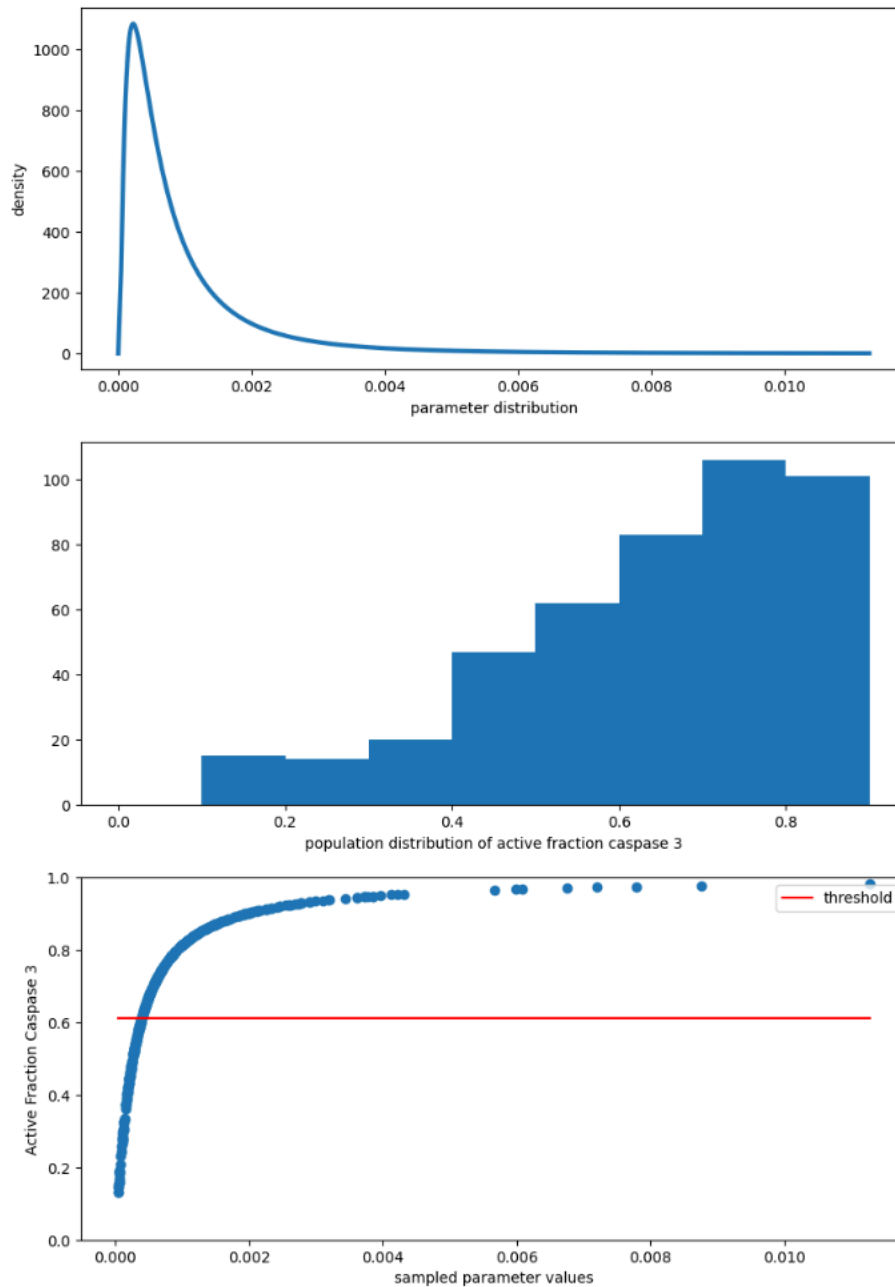

Threshold Value = 0.610718

2) (15 points) We will once again explore steady state responses of the model but will now do so by sampling parameters from their underlying distribution. We will assume all model parameters have a log-normal distribution. For each parameter, we will use the default mean value as the mean of the log-normal distribution, and we will assume the standard deviation (sigma) of the associated normal distribution is equal to 1 for all model parameters.

In the section titled "STEADY-STATE responses - vary single parameter", we will sample each parameter one by one while holding the remaining parameter values to their default mean values. For each parameter, we will sample its distribution 500 times to generate a "population of cells". We will examine the steady state active fraction of C3 in the resulting population and determine the fraction of cells that have died.

For each of the model parameters listed below, modify the variable mean_param_val to match the given mean default parameter value of the model parameter. Inside of the for loop add the name of model parameter being sampled to the beginning of the line "   = param". **Run the section of code and paste the resulting graph.** The top plot shows the distribution of the parameter being sampled. The middle plot shows the population distribution of steady state active fraction C3 values resulting from parameter sampling. The bottom plot shows the steady state value of active fraction C3 for each parameter value sampled. Describe the distribution of steady state active fraction C3 values and the relationship between the sampled parameter values and active fraction of C3. Additionally, the code calculates the fraction of cells that died based of the threshold determined earlier. **Record this value**; does variation in this parameter affect cell viability?

Make sure to reset all model parameters to their default mean parameter values before running each sampling by rerunning the section "Default mean model values".

k_a

threshold = 0.610718
Fraction of cells in population that dies = 0.672000

The parameter distribution of k_a is skewed right, with a sharp peak near zero, indicating that the majority of sampled values are small, but there is a long tail of infrequent larger values. The histogram of population distribution of active fraction caspase has a left-skewed distribution. Most cells have high levels of active C3, with a decreasing number of cells having low levels of active C3. This indicates that cells tend to have a high active fraction of C3 in this population. The active fraction caspase 3 tends to be proportional to the sampled parameter value of k_a. As the parameter value increases, the active fraction of C3 increases rapidly, then levels off. Lower parameter values tend to correspond with lower fraction of

active C3, which suggests lower cell death rates. Approximately 67.2% of the cells in the population dies indicating that variation in the sampled parameter affects cell viability. As the k_a parameter increases, the active fraction of C3 increases, and the proportion of cells dying increases.

k_ba
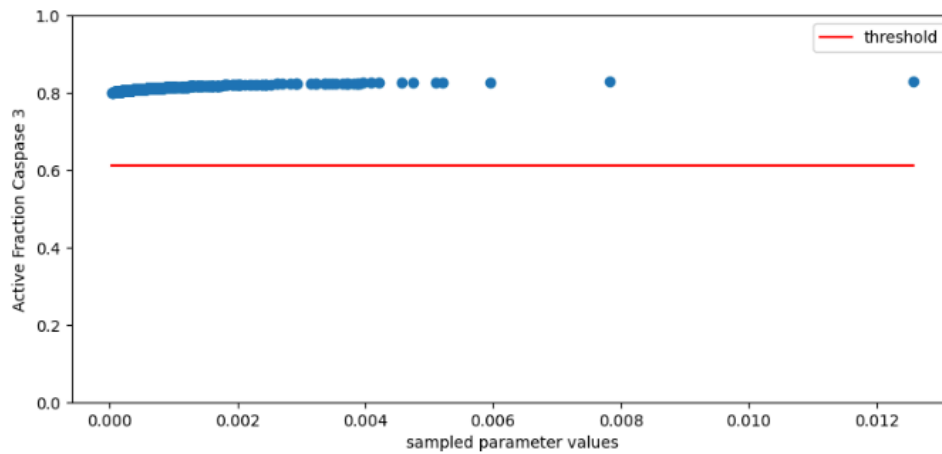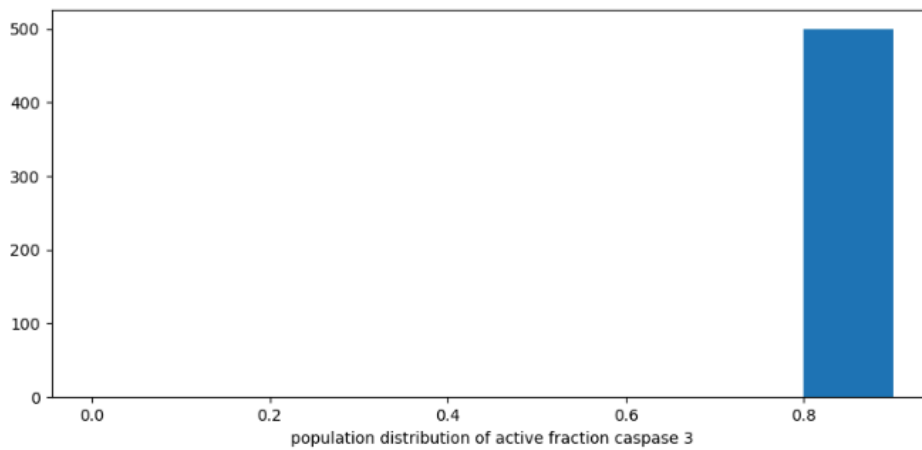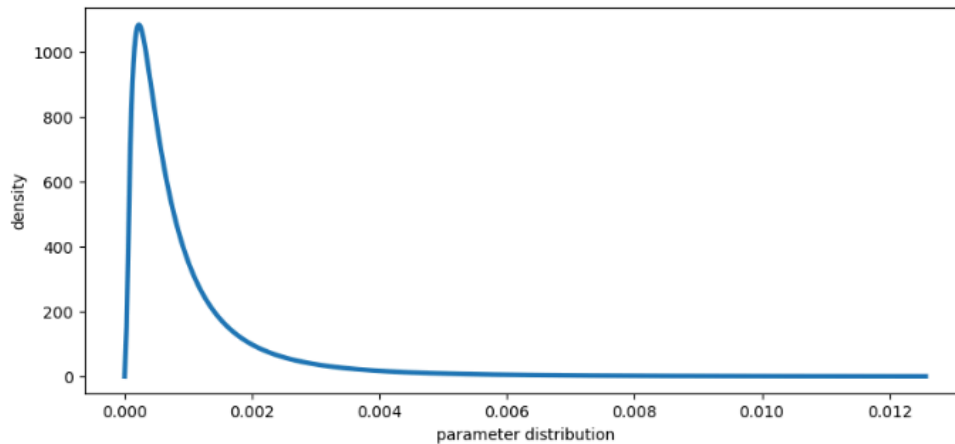
threshold = 0.610718
Fraction of cells in population that dies = 1.000000

The distribution of the k_b parameter is right-skewed with majority of the values concentrated near zero and very few extending to higher values. The distribution of steady state active fraction C3 is extremely concentrated to the right, indicating that essentially all cells have a high active fraction of C3. In the bottom plot, the k_b parameter is already above the threshold of 0.610718 when k_b is 0 and remains above the threshold the entire time. As the parameter value of k_b

increases, there is little change in the active fraction of caspase 3 because it remains above 0.8 nearly the entire time. The calculated fraction of cells that died is 100%. This suggests that variation in the k_b parameter does not significantly affect cell viability because most cells remain above the threshold for C3 activity that would result in cell death. Parameter changes have minimal impact on increasing or decreasing cell death.

delta
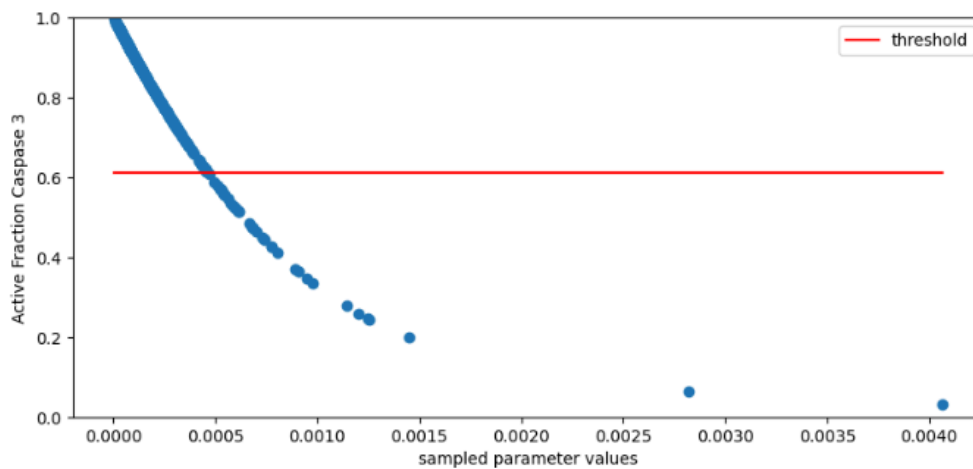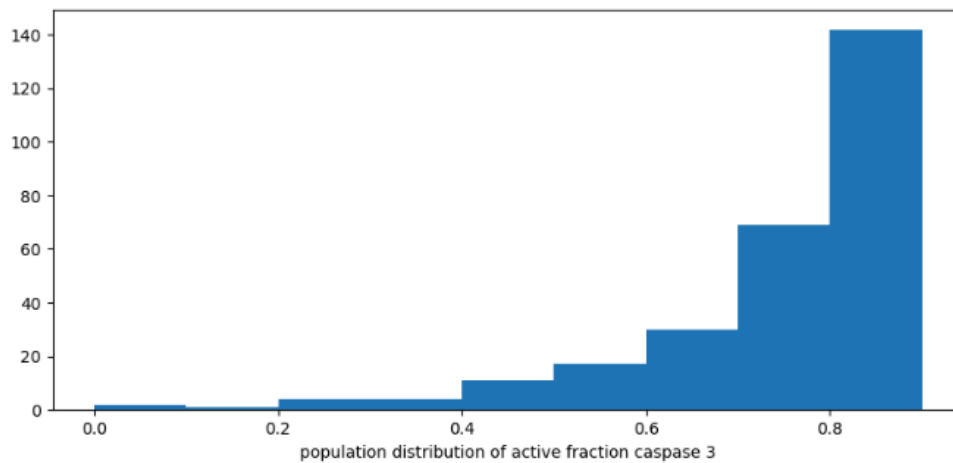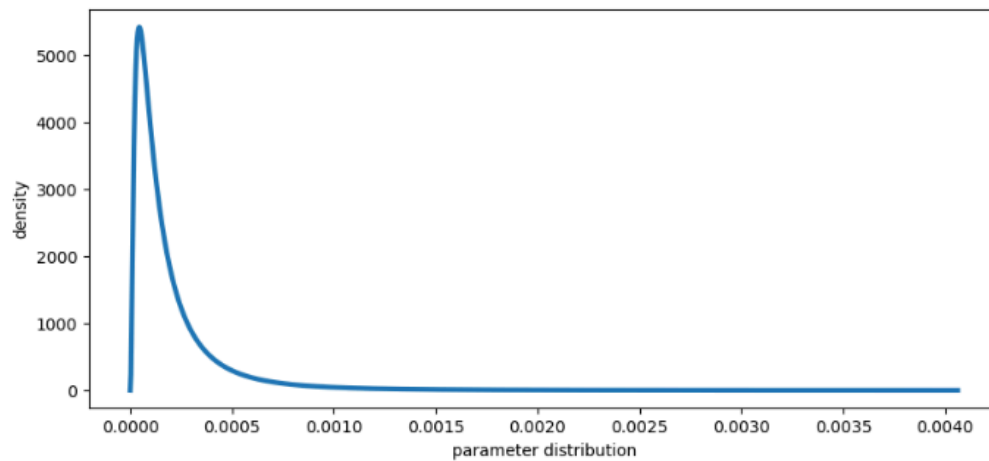
threshold = 0.610718
Fraction of cells in population that dies = 0.920000

The parameter distribution of delta is skewed right with a long tail, indicating that most sampled values are low, and only a few have larger values. The population distribution of active fraction caspase 3 is left-skewed suggesting that a larger number of cells have high active fraction of caspase 3 and fewer cells have lower active fraction of caspase 3. The bottom plot shows an inverse relationship

between the sampled parameter values and the active fraction of C3. As the parameter values increases, the active fraction of C3 decreases. The simulation calculated that the fraction of cells that died based on the threshold of 0.610718 is approximately 92%. So, an increase in the delta parameter correlates with decreased cell death. Variation in the parameter delta does affect cell viability.

3) (15 points) We will now simultaneously sample two model parameter distributions independently and explore the steady state active fraction of C3 in the resulting population of cells.

In the section titled "STEADY-STATE responses - vary two parameters", we will sample two parameters independently while holding the remaining parameter values to their default mean values. For each parameter, we will sample its distribution 1000 times to generate 1000 sampled parameter pairs representing now a "population of cells". We will examine the steady state active fraction of C3 in the resulting population and determine the fraction of cells that have died.

For each of the model parameter pairs listed below (param1, param2), modify the variable mean_param1_val and mean_param2_val to match the mean default parameter values. Inside of the for loop, rewrite the lines " = param1_values[i]" and " = param2_values[i]", adding the name of model parameters being sampled to the beginning of the line. **Run the section of code and paste the resulting graph.** The scatter plot shows the distribution of sampled parameter pairs, and each point is colored by the fate of cell. Describe the relationship between the sampled parameter pairs and cell fate. Additionally, the code calculates the fraction of cells that died based of the steady state active fraction C3 threshold determined earlier. **Record this value**. How do they compare to values from problem 1?

Make sure to reset all model parameters to their default mean parameter values before running each sampling by rerunning the section "Default mean model values".

k_a & k_ba

```
threshold = 0.610718
Fraction of cells in population that died = 0.671000
```
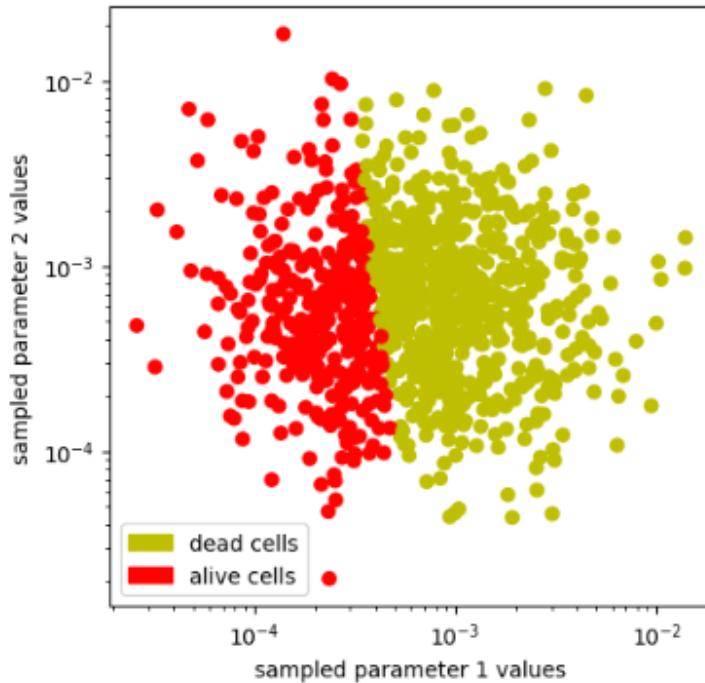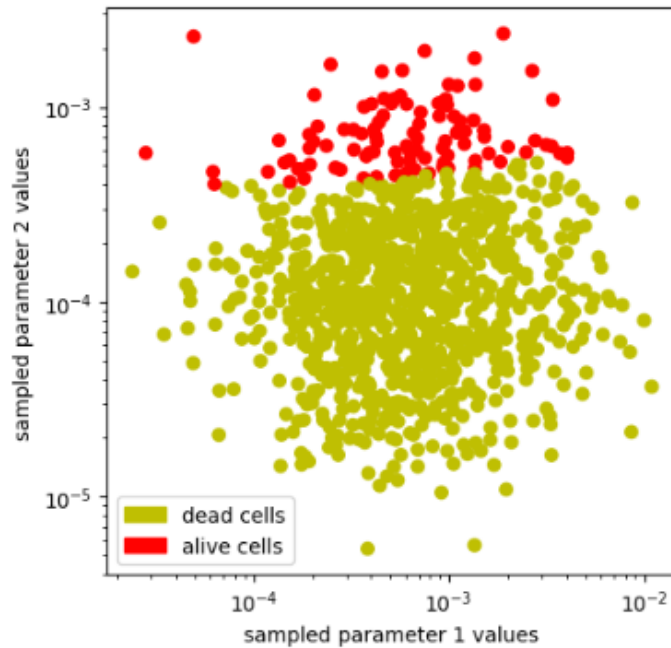

The scatterplot shows that as the sampled parameter of k_a reaches above a certain value, the cell will die regardless of the parameter value of k_ba. When the sampled parameter of k_a is above 10^{-3}, the cells will be dead. There is a clear vertical separation boundary where alive cells are concentrated on the left and dead cells are concentrated on the right. Cells with lower values of k_a tend to be alive, while cells with higher values of k_ba tend to be dead. There doesn't appear to be any relationship between k_ba and cell death when k_a is also present because when k_ba is low, cells are both dead and alive and when k_ba is high, cells are both dead and alive. The fraction of cells dead is 0.671, which is extremely similar to the fraction of cells dead when modifying only k_a.

k_ba & delta

```
threshold = 0.610718
Fraction of cells in population that died = 0.900000
```
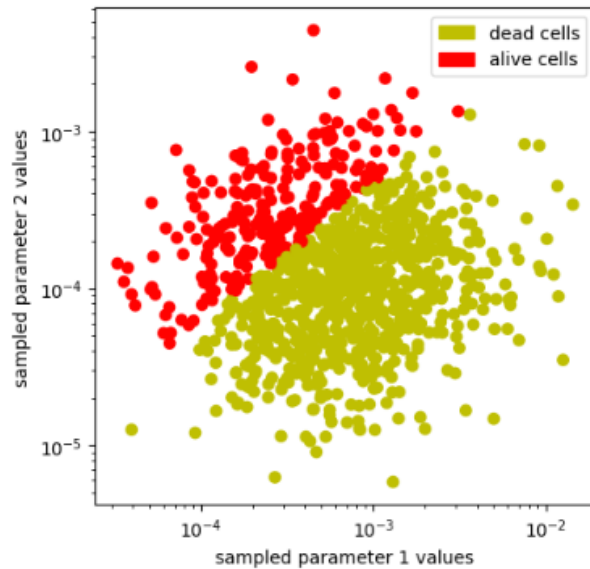

The scatterplot shows that there is a clear horizontal separation between dead and alive cells with alive cells concentrated in the upper section and dead cells concentration in the lower section. This suggests that lower parameter values of delta are associated with cell death when k_ba and delta are both varied. When the parameter value of delta exceeds ~$4.5*10^{-4}$, cells tend to be alive. The fraction of cells in the population that died is approximately 0.90, which is near the death rate of 0.92 when only modifying delta.

k_a & delta

The scatterplot shows that there is a slanted separation boundary between alive cells and dead cells. Alive cells are located in the upper left section while dead cells are located in the lower right section. There is a gradual transition from alive to dead cells as the parameter value of k_a increases and the parameter value of delta decreases indicating that cell viability is influenced by a range of values for k_a and delta. The fraction of cells that died in the population is 0.759, which is not too similar to any of the values found in problem 1. It is closest to the scenario with only k_a modified where the fraction of cells died is 0.671. The relationship here is more nuanced because cell viability decreases as k_a increases, but also when delta decreases.

4) (28 points) We will finally simultaneously sample all model parameter distributions independently and explore the steady state active fraction of C3 in the resulting population of cells. Assuming our parameter distribution choices are appropriate, this process is representative of sampling cells from a biological population, such as a population of cancerous cells.

In the section titled "STEADY-STATE responses - vary all parameters", we will sample all model parameters (nine in total). For each parameter, we will sample its distribution 1000 times to generate 1000 sampled parameter sets. We will examine the steady state active fraction of C3 in the resulting population and determine the fraction of cells that survive, i.e. cancer cells.

Make sure to reset all model parameters to their default mean parameter values before running the sampling by rerunning the section "Default mean model values".

The code calculates the fraction of cells that survive based of the steady state active fraction C3 threshold determined earlier. **Record this value.**

Next run the section of code titled "Plotting Parameter Pairs". For a predefined selection of parameter pairs, scatter plots like those from problem 3 will be generated. **Paste the resulting graph.** For each parameter pair plot, describe the relationship if any between the sampled parameter pairs and cell fate. Additionally, focusing on the sampled parameter pair values that generate alive cells, is there correlation between the parameter values in the pair.

threshold = 0.610718
Fraction of cells in population that survive = 0.421000
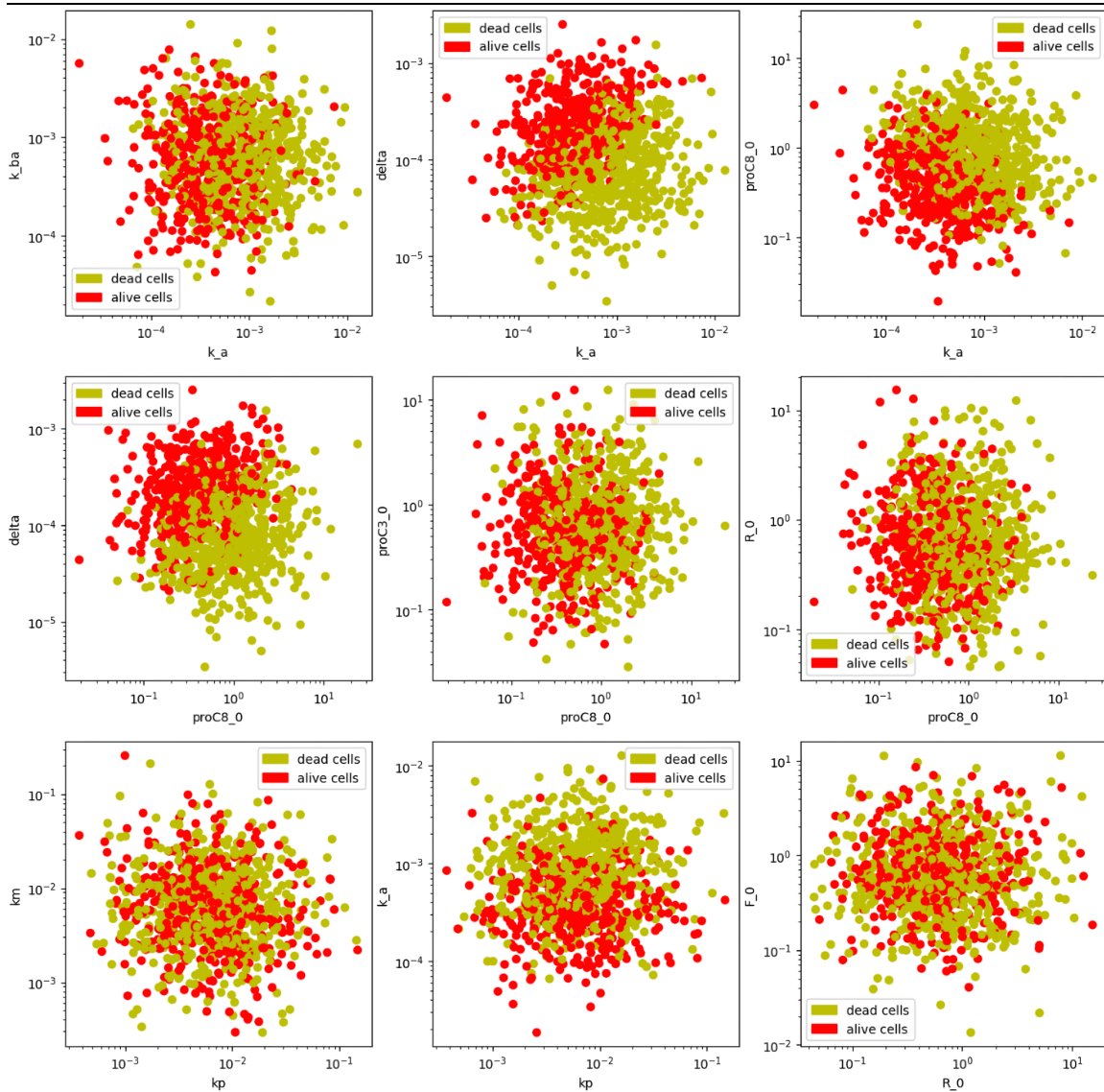
For each parameter pair plot, describe the relationship if any between the sampled parameter pairs and cell fate. Additionally, focusing on the sampled parameter pair values that generate alive cells, is there correlation between the parameter values in the pair.

k_a and k_ba:
There doesn't appear to be any relationship between the sampled parameter pairs and cell fate. The dead and alive cells are intertwined with each other and there isn't any clear separation boundaries. However, there does tend to be more alive cells when k_a is low but there's still a few dead cells, and there's more dead cells when k_a is high but with still a few alive cells.

k_a and delta:
There does seem to be a relationship between k_a and delta. When delta is high and k_a is low, there tends to be more alive cells with very few dead cells. When delta is low and k_a is high, all the cells will be dead. At intermediate values of k_a and delta, there is a mix of dead and alive cells, indicating a gradient rather than a clear separation boundary of dead and alive cells as the k_a and delta parameter values vary. When k_a is high and delta is low, there is a high likelihood of cell death.

k_a and proC8_0:
There does seem to be a relationship between k_a and proC8_0 because when k_a is low and proC8_0 is low, there is mostly alive cells and when k_a is high and proC8_0 is high, there are mostly dead cells. There is a gradient from alive to dead cells when k_a and proC8_0 transition from low parameter values to high parameter values. When k_a is low and proC8_0 is low, the cell is more likely to die.

proc8_0 and delta:
There does seem to be a relationship between proC8_0 and delta because when proC8_0 is low and delta is low, there tends to be alive cells but when proC8_0 is high and delta is low, cells will be dead. There is a gradient of alive to dead cells, rather than a distinct separation boundary, when proC8_0 transitions from low values to high values and when delta transitions from high values to low values. When proC8_0 is low and delta is high, there is a high probability of cell death.

proC8_0 and proC3_0:
There does not seem to be a relationship between proC8_0 and proC3_0 because dead and alive cells are intertwined at nearly all values of proC8_0 and proC3_0.

proC8_0 and R_0:
There does not seem to be a relationship between proC8_0 and R_0 because there doesn't appear to be any clear boundaries between dead and alive cells sections. Dead and alive cells are intertwined at nearly all values of proC8_0 and R_0.

kp and km:
There doesn't appear to be any relationship between kp and km because there's no clear boundary or distinct region where there's majority alive cells or majority dead cells suggesting that neither high nor low values of "kp" or "km" exclusively determine cell fate. Alive and dead cells can arise from a wide range of kp and km values.

kp and k_a:
There is a relationship between kp and k_a because alive cells tend to be found at lower values of kp and dead cells tend to be found at higher values of kp. There is a gradient of alive to dead cells as kp transitions from low parameter values to high parameter values where there are dead and alive cells intertwined at intermediate kp values. Higher k_a values are likely associated with increased likelihood of cell death.

R_0 and F_0:
There is not a relationship between R_0 and F_0 because alive and dead cells are spread across the entire range of both parameters without a clear pattern separating alive and dead cells. Both alive and dead cells are present at low and high values of R_0 and F_0, indicating that a wide range of parameter combinations can result in either cell fate (dead or alive).