PhySci/MiMG/CaSB M178

Homework 9

Due: 12/06/22 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". Run this section of code to load up the model.

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

Initial Conditions	Default Value
proC8_0	1 uM
C8_0	0 uM
proC3_0	1 uM
C3_0	0 uM
R_0	1 uM

F_0	1 uM
RF_0	0 uM

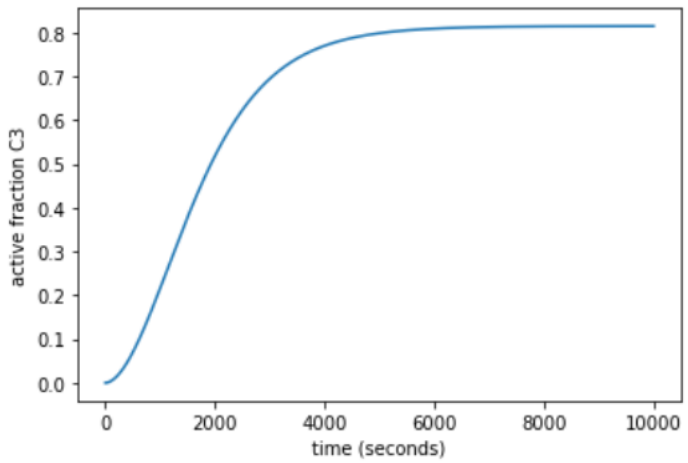
Parameter Values	Default Value
k_a	0.001 $uM^{-1}sec^{-1}$
k_ba	0.001 $uM^{-1}sec^{-1}$
kp	0.01 $uM^{-1}sec^{-1}$
km	0.01 sec^{-1}
delta	2e-4 sec^{-1}

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.

Run the section of code titled "Simulation with default mean parameters". 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.
Paste the resulting graph and write down the threshold value that will determine cell fate in subsequent simulations.

```
threshold = 0.610718
```



The threshold is 0.610718, which will determine if the cell dies since it is the steady state value of an active fraction C3.

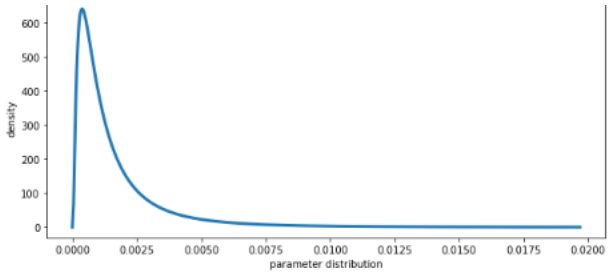
2) (15 points) We will once again explore steady state responses of the model but will now do so by sampling parameters from their underlying distribution. We will assume all model parameters have a log-normal distribution. For each parameter, we will use the default mean value as the mean of the log-normal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

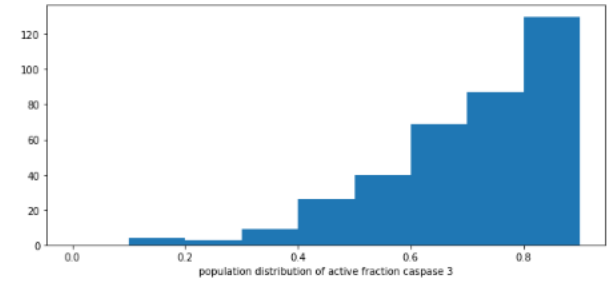
In the section titled "STEADY-STATE responses - vary single parameter", we will sample each parameter one by one while holding the remaining parameter values to their default mean values. For each parameter, we will sample its distribution 500 times to generate a "population of cells". We will examine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

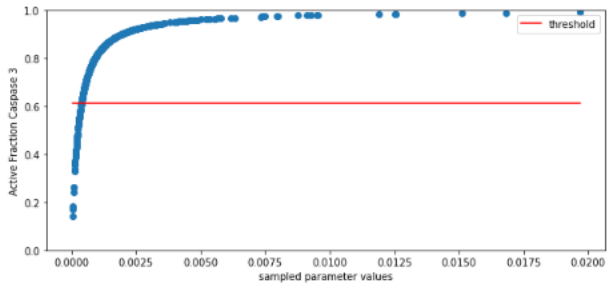
For each of the model parameters listed below, modify the variable mean_param_val to match the given mean default parameter value of the model parameter. Inside of the for loop add the name of model parameter being sampled to the beginning of the line " = param". **Run the section of code and paste the 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



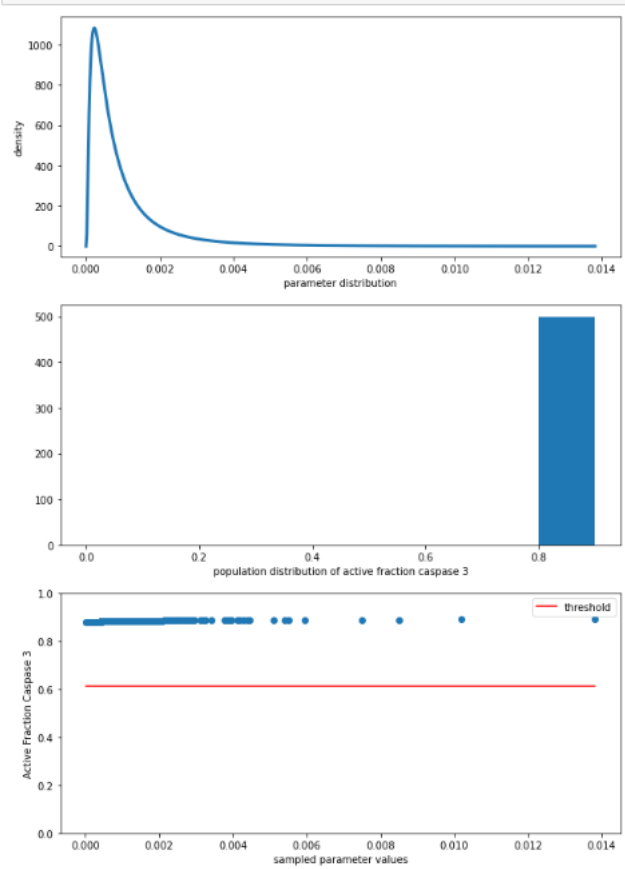





```
threshold = 0.610718
Fraction of cells in population that dies = 0.820000
```

The relationship between the sampled parameter values and the proportion oof active fraction caspase 3 is that it increases logarithmically, approaching 1. This corresponds to a population distribution (pdf) of active fraction caspase 3 predominantly above 0.5. The relationship between the sample parameter values and active fraction of C3 is that there is a rapid increase of active caspase 3 ad the sampled parameter values increase. In the first graph, we notice a peak between 0.0000 and 0.0025 as the most dense for parameter distribution. The fraction of cells that died was 0.820000, and I ran multiple trials, another trial I got the fraction of cells that died was 0.682. This shows that variation in this parameter does affect cell variability since over half of the cells died.

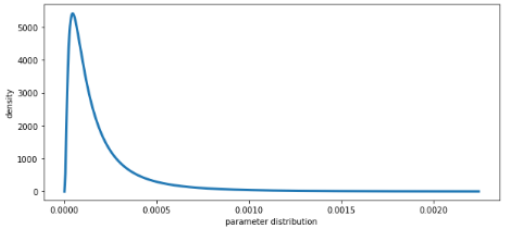
k_ba

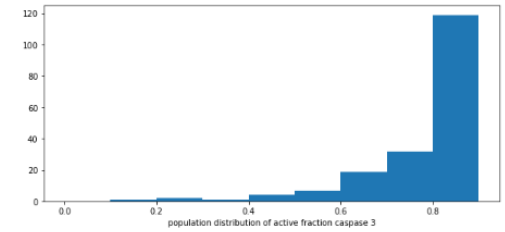


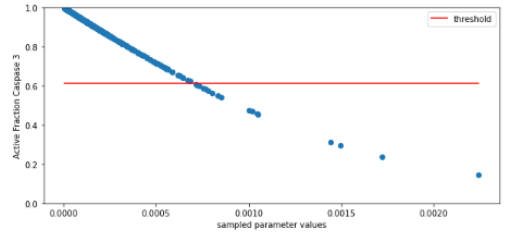

```
threshold = 0.610718
Fraction of cells in population that dies = 1.000000
```

Like previously the parameter distribution and density graph is peaking around 0.0000 to 0.002. The distribution of steady state active fraction C3 values is not really a distribution, instead, it is concentrated around >0.8 to 1. The relationship between the sampled parameter values and the active fraction of caspase 3 ends around 0.8. We also notice the fraction of cells in the population that dies is 1 and that is because they are all above the threshold. Therefore, variation in this parameter does not affect cell variability since no matter how we manipulate this parameter they will all die.

delta








```
threshold = 0.610718
Fraction of cells in population that dies = 0.966000
```

The distribution of steady state active fraction C3 values is a distribution dependent on the higher values of C3 from 0.6 to 1. The relationship between the sampled parameter vale and active fraction of C3 is the low values of the parameter are over the threshold or correlate to a higher fraction of active C3. The fraction of cells that died is 0.966 and so we can deduct that variation in this parameter does affect cell variability because different parameter values were under or over the threshold.

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.

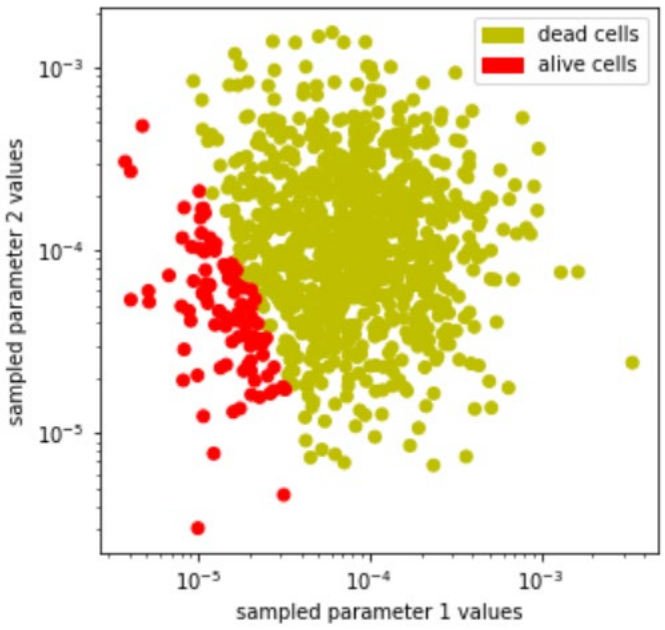
For each of the model parameter pairs listed below (param1, param2), modify the variable mean_param1_val and mean_param2_val to match the mean default parameter values. Inside of the for loop, rewrite the lines " = param1_values[i]" and " = param2_values[i]", adding the name of model parameters being 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

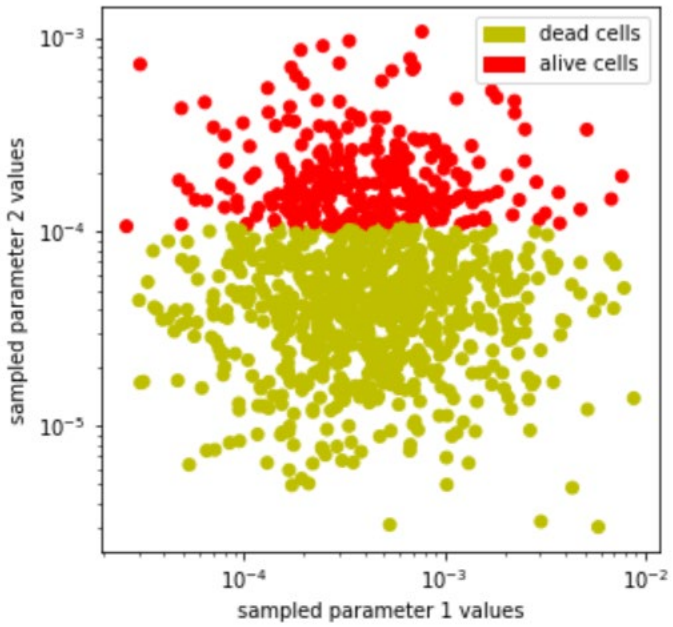
```
threshold = 0.610718
Fraction of cells in population that died = 0.897000
```



The relationship between the sampled parameter pairs and cell fate is that the values of parameter 2 lead to cells being alive, but only lower values of parameter 1 leads to cells being alive. In order to have more proportions of alive cells, the value of parameter has to be low enough. The fraction of cells in population that died is 0.897, which is similar to k_a values, and this indicates a difference in cell variability.

k_ba & delta

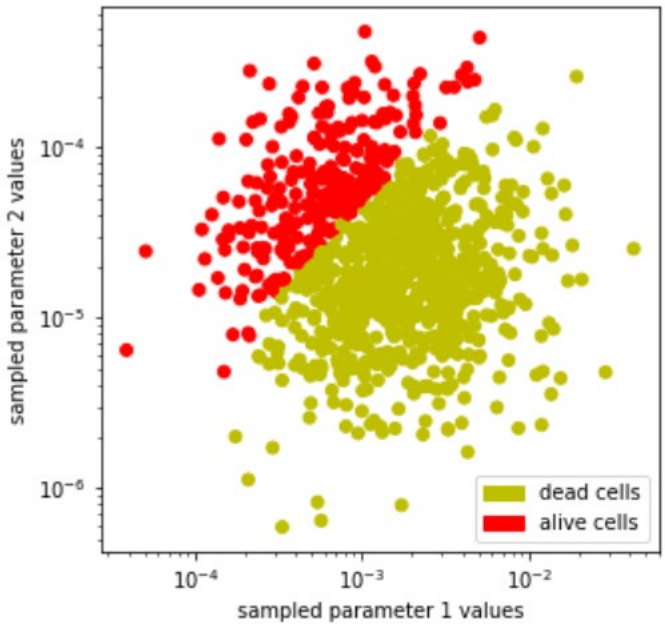
```
threshold = 0.610718
Fraction of cells in population that died = 0.727000
```



The relationship between the sampled parameter pairs and cell fate is that the value of parameter two is being more of the driver, since all values of parameter one leads to cells alive and dead. Parameter two is the delta value which is close to 0.966 as indicated in this graph too.

k_a & delta

```
threshold = 0.610718
Fraction of cells in population that died = 0.752000
```



The relationship between the sampled parameter pairs and cell fate is that this specific relationship seems to have both parameters affect the cell viability. There is a slant (50-50) divide between dead and alive cells. The value is 0.752 which is between the value of k_a and delta, in this context it makes sense since both are affecting cell viability.

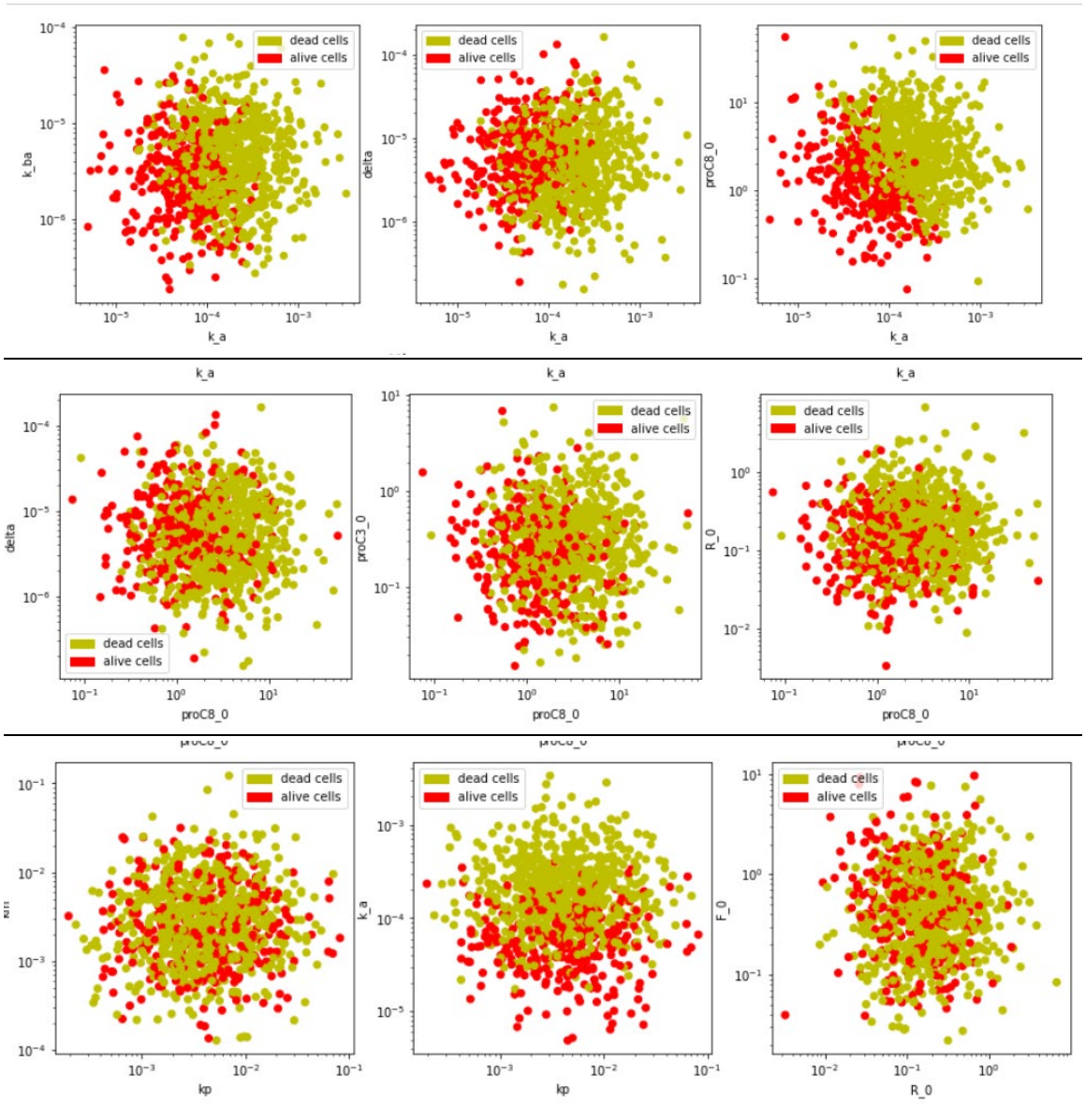
4) (28 points) We will finally simultaneously sample all model parameter distributions independently and explore the steady state active fraction of C3 in the resulting population of cells. Assuming our parameter distribution choices are appropriate, this process is representative of sampling cells from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



1.k_a vs. k_ba
There is a relationship between the two parameters where the alive cells are indicatd by lower values of k_a and the spread for alive cells is for all values of k_ba.

2. delta vs. k_a
There is a clear relationship between the two parameters, the alive cells are correlated with low to mid values of k_a and mid to high values of delta. Both parameters play a role an effect in cell viability.

3. k_a vs. proC8_0
There is a defined relationship between the two parameters because cell death and the alive cells are located in very separated parts of the graph. There are cells alive at all values of k_a until 10^2.5 and there are cells still alive until 10^0.5

4. proC8_0 vs. delta
There is not a definite relationship between the two parameters, but there are more dead cells congregated at higher values of proC8_0.

5. proC8_0 vs. proC3_0
There is not a definite relationship between the two parameters, but there are more dead cells congregated at higher values of proC8_0.

6. proC8_0 vs. R_0
There is a relationship between the two parameters, notably that we can see a higher concentration of cells that are alive with higher values of proC8_0.

7. kp vs. km
There seems to be no defined relationship between the two parameters

8. kp vs. k_a
There is a difference between this graph and the previously described graphs. With higher values of k_a, there are more dead cells. There is a clear separation of these two parameters.

9. R_0 vs. F_0
There seems to be no defined relationship between the two parameters. Both seem to be a scatterplot.