PhySci/MiMG/CaSB M178

Homework 5

Due: 11/01/22 at 12:00PM PDT
Problems

In class, we talked about bacterial chemotaxis. Chemotactic signaling utilizes a special "Two Component" kinase system involving a phosphotransferase, the "Histidine Kinase" (HK), and its substrate, the "Response Regulator" (RR). One fascinating aspect of these systems is that the HK can serve to both phosphorylate and dephosphorylate the RR substrate. In this homework, we will model this system using the following reactions:

1. HK is phosphorylated to form HKp with rate k_a (first order reaction)
2. HKp is dephosphorylated to form HK with rate k_u (first order reaction)
3. HKp binds with RR to form HKpRR with rate k_p (second order reaction)
4. The complex HKpRR can dissociate into HKp and RR with rate k_m (first order reaction)
5. HKpRR converts into HK plus RRp with rate k_cat (first order reaction) [Note: this is the actual phosphotransferase step!]
6. HK also binds with RRp to form HKRRp with rate k_p (second order reaction)
7. The complex HKRRp can dissociate into HK and RRp with rate k_m (first order reaction)
8. HKRRp converts into HK and RR with rate k_cat (first order reaction) [Note: this is the dephosphorylation step!]

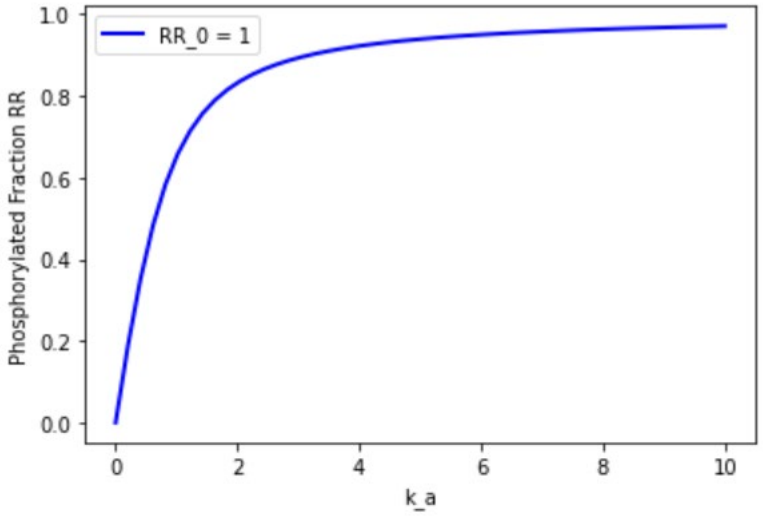
In Two Component systems, the incoming signal modulates the value of k_a (i.e. activating signals increase the value of k_a).

1. (20 points) First, write down the change equations for the model described:

HK_prime = -k_a*HK + k_u*HKp + k_cat *HKpRR -k_p*HK*RRp + k_m*HKRRp + k_cat*HKRRp
HKp_prime = -k_u*HKp + k_a*HK - k_p*HKp*RR + k_m*HKpRR
RR_prime = -k_p*RR*HKp + k_m*HKpRR + k_cat*HKRRp
RRp_prime = k_cat*HKpRR -k_p*HK*RRp +k_m*HKRRp
HKpRR_prime = -k_m*HKpRR + k_p*HKp*RR - k_cat*HKpRR
HKRRp_prime = k_p*HK*RRp -k_m*HKRRp - k_cat*HKRRp

In the section of code called "two component model" implement the change equations to stimulate the model.

In the next section of code, "STEADY-STATE responses of two component model PART 1", the initial values and parameters we will use for simulation are first set. Note we initialize the phosphorylated and complex species to zero. Here, we will vary the value of the parameter k_a (reflecting the activating signal) and plot the resulting steady state concentration of RRp divided by the initial concentration of RR. Note that the current initial concentration of RR is set to 1 and the value of k_a will be varied from 0 to 10. Run this section of code and paste the resulting graph below:

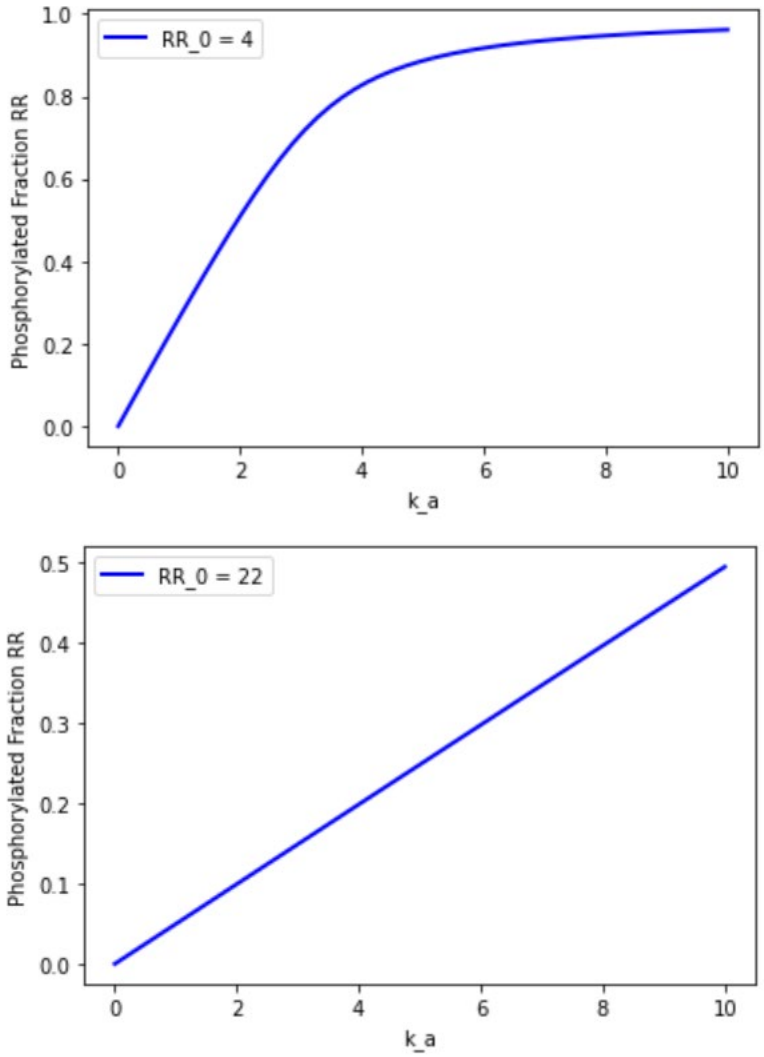


This model is somewhat similar to the PTM cycle models explored in HW1. Relate the species and reactions from our two-component model to the PTM model without synthesis and degradation. Which species/reactions from the PTM model do not have analogous species/reactions in the HK model?

Here we reach the conclusion that the RR is the substrate and HK is the kinase (phosphatase and kinase). The species that do not have analogous species or reactions in the HK model is the single-purpose phosphatase, because HK is both the phosphatase and kinase.

In HW 1, we explored how saturation affects the steady state amount of modified substrate as a function of initial kinase concentration by changing the amount of

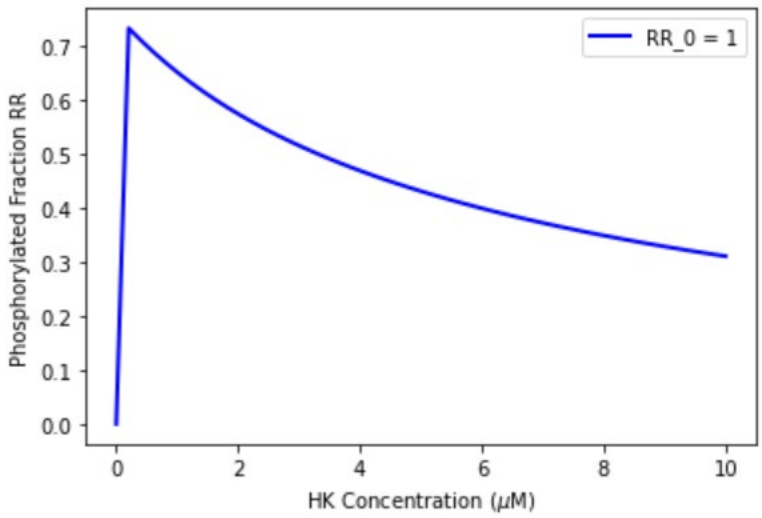
initial substrate. Rerun the section of code **at least twice** with increased values for RR_0 and paste the resulting graphs below:



How does saturation of the histidine kinase affect the value of k_a needed to achieve the maximum steady state phosphorylated fraction of response regulator?

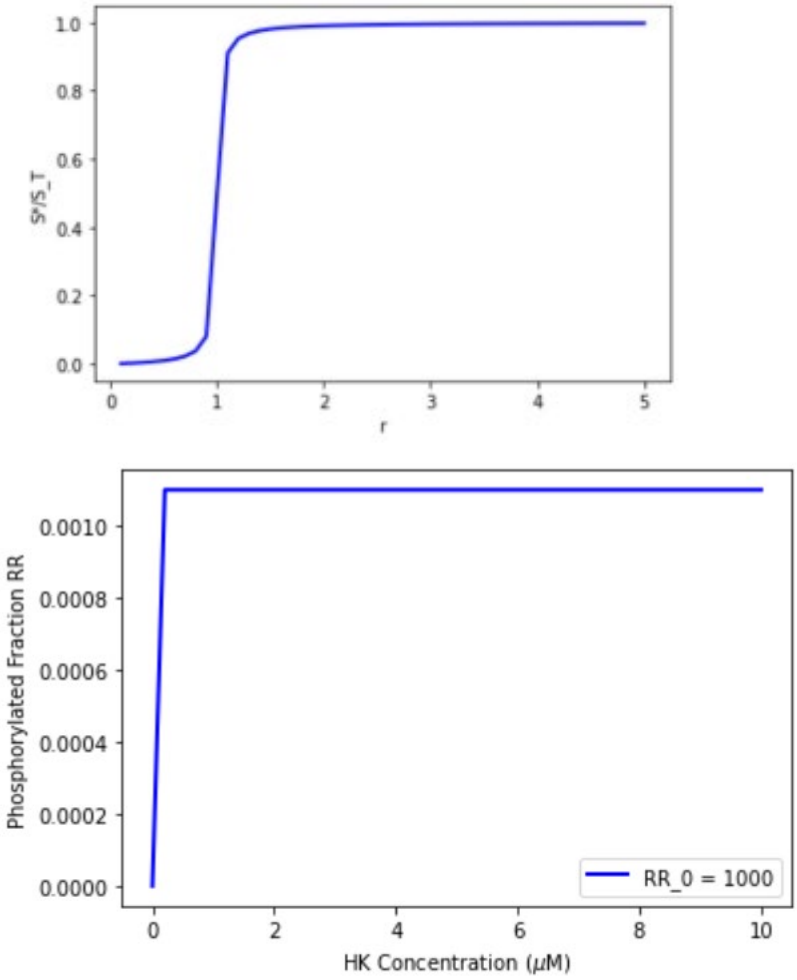
As there are more initial Response Regulator, we see a reduced value of k_a needed to achieve the maximum steady state phosphorylated fraction of Response Regulator. Histidine kinase's function is to phosphorylate and dephosphorylate the RR substrate. As Histidine kinase becomes saturated, there aren't any more Histidine kinases to phosphorylate RR, so there aren't any more incoming signals to prompt activation. Hence, inactivation decreases the value of k_a. More saturation, higher k_a.

2) (10 points) In HW 1, we also explored the steady state amount of modified substrate as a function of initial kinase concentration. We will now similarly explore the steady state concentration of phosphorylated RR as function of initial HK concentration in the section titled "STEADY-STATE responses of two component model PART2". In this section we will vary the initial concentration of HK from 0 to 10 and plot the resulting steady state concentration of RRp divided by the initial concentration of RR. Run this section of code and paste the resulting graph below:



How does this compare to the plot of steady state modified substrate versus kinase concentration for the PTM cycle? Can you explain why the differences emerge if any?

In this plot, after the maximum steady state phosphorylated fraction of response regulator is reached, no further increase in Histidine kinase will continue phosphorylation or activation. In the plot of steady state modified substrate versus kinase concentration for the PTM cycle, which is this one below, we notice a sudden increase in proportion of S*/S_T when S(0) = 1000. When I did the same to the Histidine Kinase – RR model, making RR_0(0) = 1000, we see that both go to completion. This difference is because HK can also dephosphorylate, which is different from the PTM cycle. This is a two component system.



3) (25 points) Next, we will implement a model for the Two Component signaling system that is part of the chemotactic signaling network in bacteria. In this model, the HK species is called CheA and the RR species is called CheY. There is also a separate phosphatase enzyme called CheZ. It dephosphorylates CheY instead of CheA acting as the phosphatase. We will model this system with the following reactions:

1. CheA is phosphorylated to form CheAp with rate k_a (first order reaction)
2. CheAp is dephosphorylated to form CheA with rate k_u (first order reaction)
3. CheAp binds with CheY to form CheApCheY with rate k_p (second order reaction)
4. The complex CheApCheY can dissociate into CheAp and CheY with rate k_m (first order reaction)
5. CheApCheY converts into CheA and CheYp with rate k_cat (first order reaction)

6. CheZ binds with CheYp to form CheZCheYp with rate k_p (second order reaction)
7. The complex CheZCheYp can dissociate into CheZ and CheYp with rate k_m (first order reaction)
8. CheZCheYp converts into CheZ and CheY with rate k_cat (first order reaction)

Write the change equations for this new model below:

```
### implement the change equations
  CheA_prime = -k_a*CheA + k_u*CheAp + k_cat*CheApCheY
  CheAp_prime = k_a*CheA -k_u*CheAp + k_m*CheApCheY - k_p*CheAp*CheY
  CheY_prime = -k_p*CheAp*CheY + k_m*CheApCheY + k_cat*CheZCheYp
  CheYp_prime = k_cat*CheApCheY - k_p*CheZ*CheYp + k_m*CheZCheYp
  CheZ_prime = -k_p*CheZ*CheYp + k_m*CheZCheYp + k_cat*CheZCheYp
  CheApCheY_prime = k_p*CheAp*CheY - k_m*CheApCheY - k_cat*CheApCheY
  CheZCheYp_prime = k_p*CheZ*CheYp -k_m*CheZCheYp -k_cat*CheZCheYp
  ###
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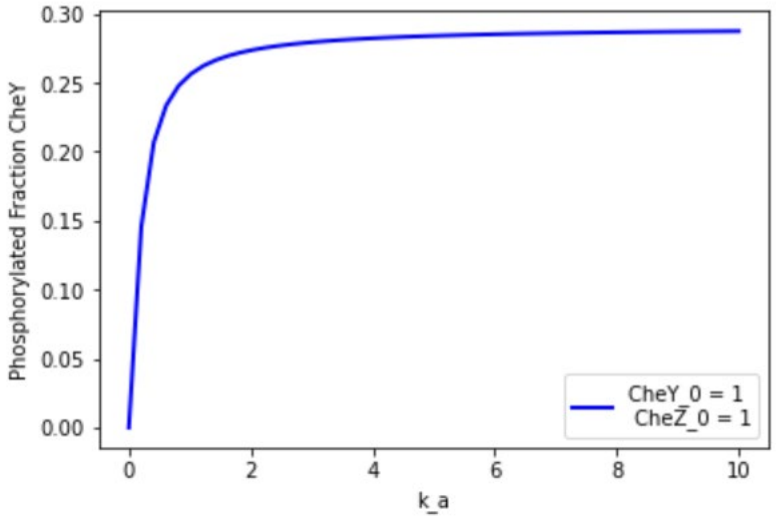
Now add these change equations to the section of code called "chemotaxis model".

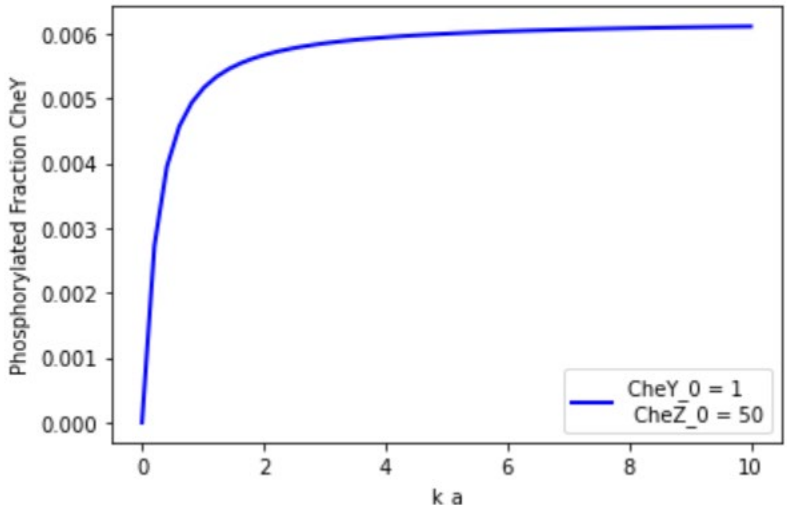
We will once again explore steady state responses of the model in the section "STEADY-STATE responses of chemotaxis model". Note we initialize the phosphorylated and complex species to zero. We will again vary the value of the parameter k_a (reflecting the activating signal) and plot the resulting steady state concentration of CheYp divided by the initial concentration of CheY. Note that the current initial concentration of CheY is set to 1 and the value of k_a will be varied from 0 to 10. Run this section of code and paste the resulting graph below:

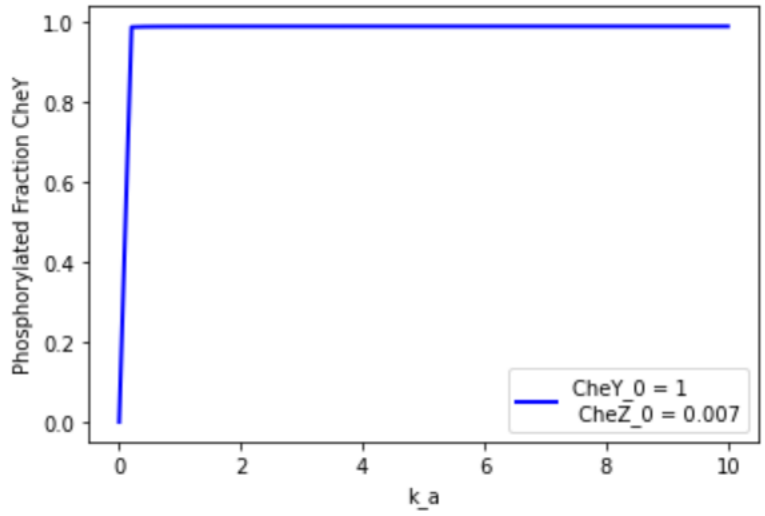


How does this result compare to your initial graph from problem 1?

This result is a graph that shows plateau-ing trends. This is reflective of the dephosphorylating agent CheZ at work, not allowing the phosphorylated fraction of CheY go to 1 but instead saturating at 0.3 in this case of k_a ranging from 0 to 10. We can also recall that CheZ is very fast from lecture, so this is the expected result graph for this Hk-RR reaction. This result is very different from problem 1 because the rate of increase is smaller toward larger k_a value for this graph, whereas for problem 1 the rate of increase is much larger to achieve the maximum steady state phosphorylated fraction of RR.

Now let's rerun this section of code with some initial conditions altered. First, let's focus on the phosphatase, CheZ. Choose **two different values** for CheZ_0, and paste the resulting graphs below. [Note: try one value that is smaller than the default value you had, and one that is larger].

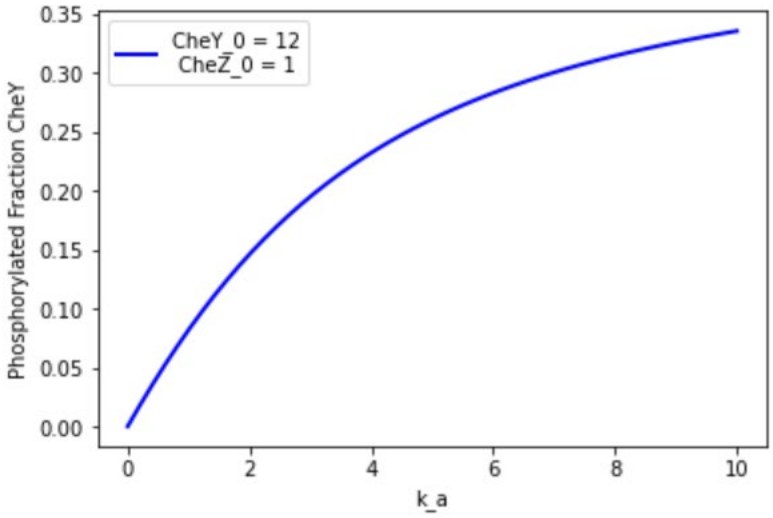


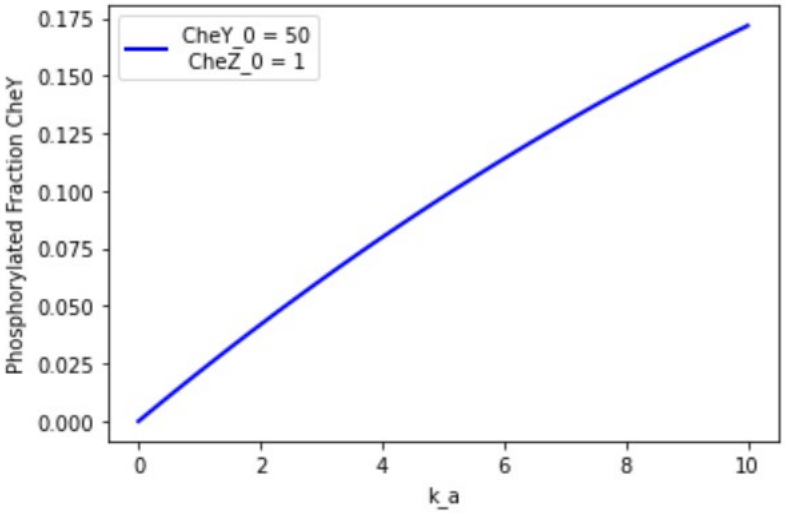


How does modifying the initial amount of CheZ affect the steady-state response of CheY?

CheZ is a phosphatase for CheY, and is activated by CheA. If we modify the amount of CheZ present in the system, then if there are a lot of CheZ, there is going to be little activated CheY (0.0006, first case) because of the abundance of phosphatase (inactivation). On the other hand, if there are little CheZ, the activation of CheY is going to go to near completion (~1, second case).

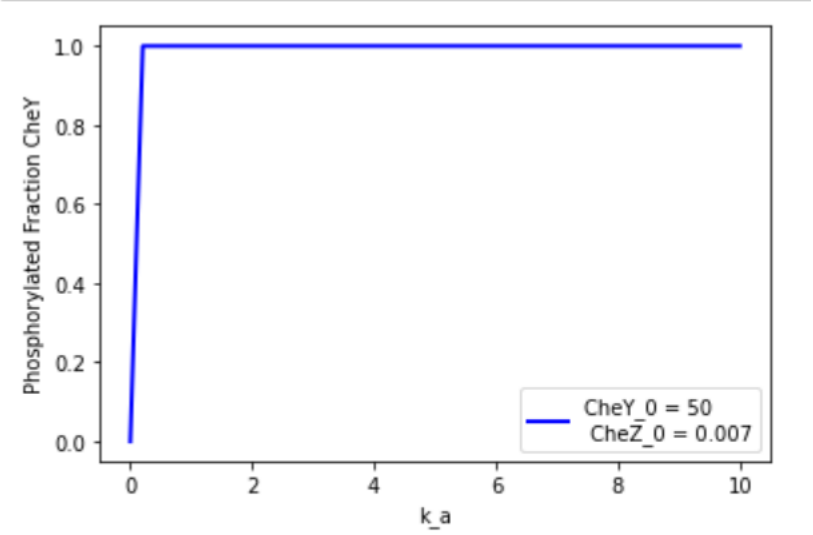
Reset the initial conditions for CheZ to its default value. Now we will look at how changing the total amount of CheY affects the system. As above, **choose two new values** CheY_0 and paste the resulting graphs below: [Note: we suggest increasing CheY levels, as this will *increase* saturation!]





Modifying the amount of CheY, especially increasing it to many magnitudes higher, will linearize the Phosphorylated fraction of CheY vs. k_a because there is not a restriction to CheY's activation.

Now, as a final exploration, keep CheY_0 at one of the larger values you chose, and try changing CheZ_0 to the **smaller** value that you tried above (in other words, *increase* CheY_0 from the default value, and *decrease* CheZ_0). Paste the resulting graph below:



Overall, how do these results compare now to the results from problem 1? Does increasing CheY always have the same effect? How does changing the phosphatase levels affect the behavior. Overall, how does the behavior of this system compare to the original PTM cycle model results from HW1?

If we have no phosphatase behaving enzyme like CheZ, there will be an immediate increase in the proportion of CheY phosphorylated. Increasing CheY to a point will have no effect on the linearity of the graph, because CheY can only increase at a limited rate, and the slope of the graph is not going to change to a greater value. The original PTM cycle is very similar to this graph in both: there is going to be saturation at some point AND the eventual proportion of phosphorylation goes to 1.

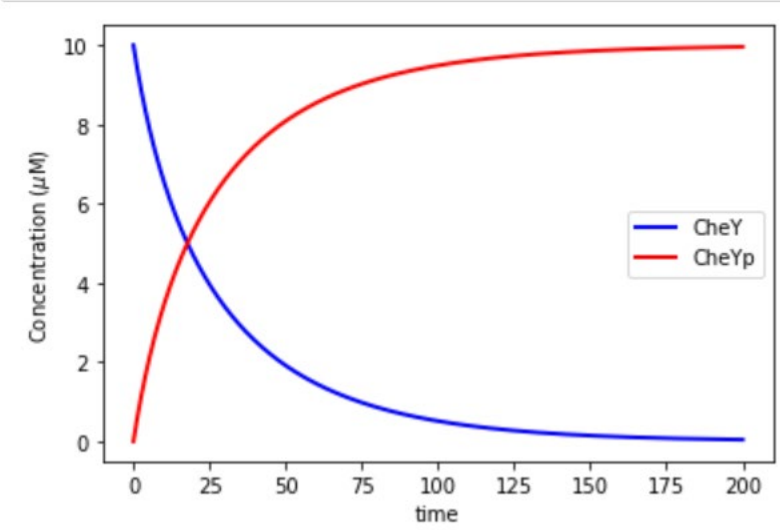
We should note that the original PTM cycle has a switch-like behavior, which is what we see here. The shape of the curve has become more rigid, meaning that its rate of change is much greater than the original PTM cycle graph.

4) (20 points) Next, we will implement a simple model for perfect adaptation. The model consists of the following two change equations:

$$CheY' = -V^A_{max} + V^Z_{max}\frac{CheYp}{K_z + CheYp}$$
$$CheYp' = V^A_{max} - V^Z_{max}\frac{CheYp}{K_z + CheYp}$$

In this model, we assume that CheA is phosphorylated and operating at its maximum velocity, V_{max}^{A}, to phosphorylate CheY. CheZ, which dephosphorylates CheYp is not; its rate is dependent on the amount of $CheYp$ present. The maximum velocity of CheA, V_{max}^{A}, is less than the maximum velocity of CheZ, V_{max}^{Z}, for this model.

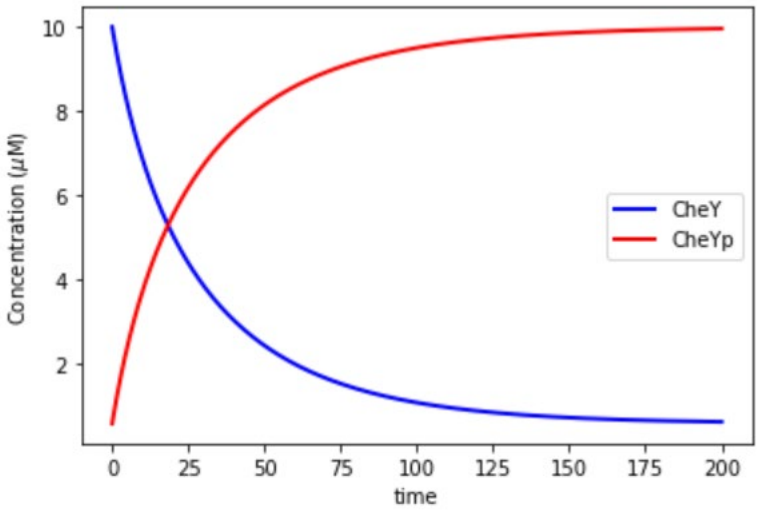
We have implemented this mode in the section called perfect adaptation
We will explore this model in the section "Responses of perfect adaptation model". This section first implements the initial conditions and parameters for this model. By default, Chey_0 is set to 10 and CheYp_0 is set to 0. Va (the maximum velocity of CheA) is set to 0.5, Vz (the maximum velocity of CheZ) is set to 1, and Kz is set to 10. Run this section of code to simulate the perfect adaptation model for this set of initial condition and paste the resulting graph here:



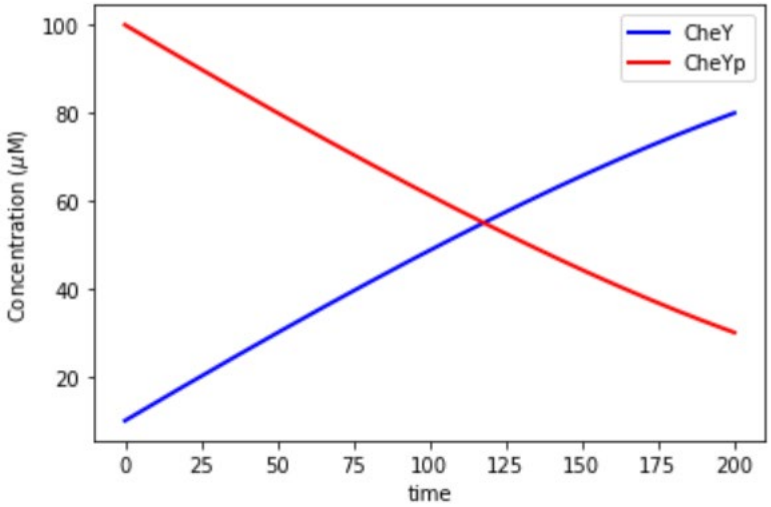
What is the steady state value of CheYp?

The steady state concentration of CheYp is 10 micromolar, and is reached when time is around 170 seconds.

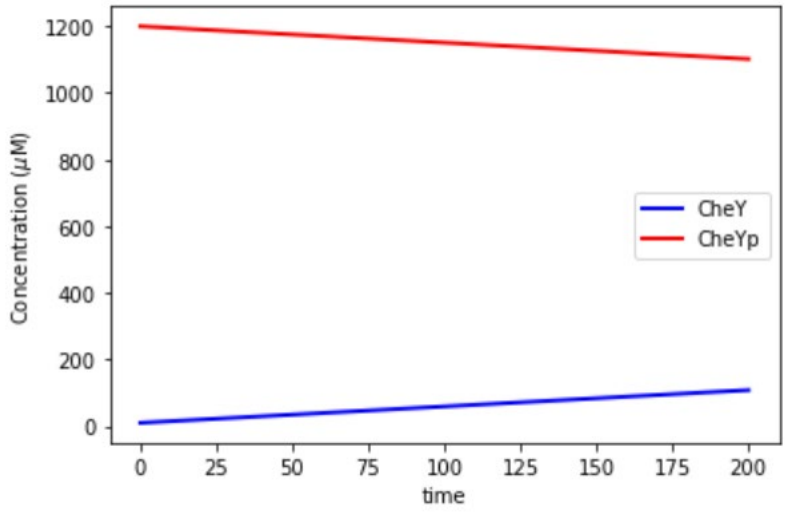
Rerun the code twice. In the first case, set an initial value of CheYp **below** the steady state value you found. In the second case, set an initial value of CheYp **above** this steady-state value. Paste the resulting graphs below:



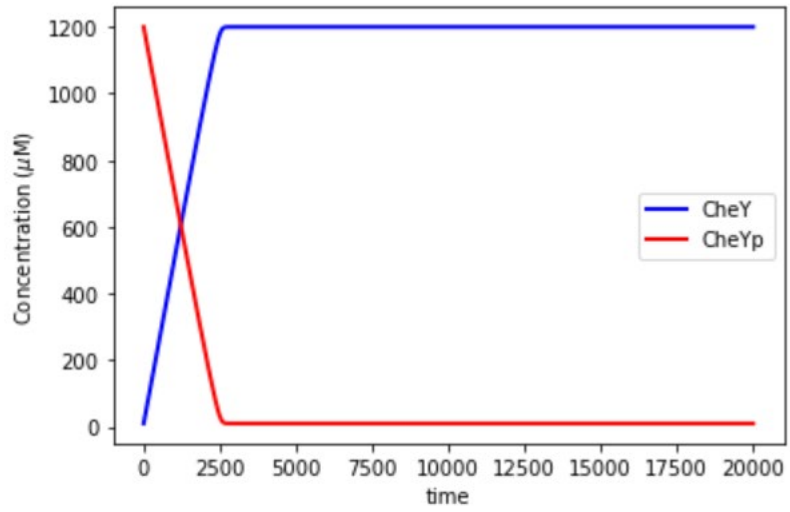
In this graph, I put CheYp_0 value to be 0.6.



In this graph, I put CheYp_0 value to be 100. I couldn't arrive at a conclusion for the steady state because when I increased the time to 2000 seconds, the linear trend continued.



In this graph, I set the initial condition to be 1200. This time, the slopes' magnitude seem to be smaller, but I can conclude that eventually, when we let time go on running, it will be depleted.



What are the steady state values of CheYp now?

The steady state values of CheYp should still be 10. I was just testing some very big numbers to see different results.

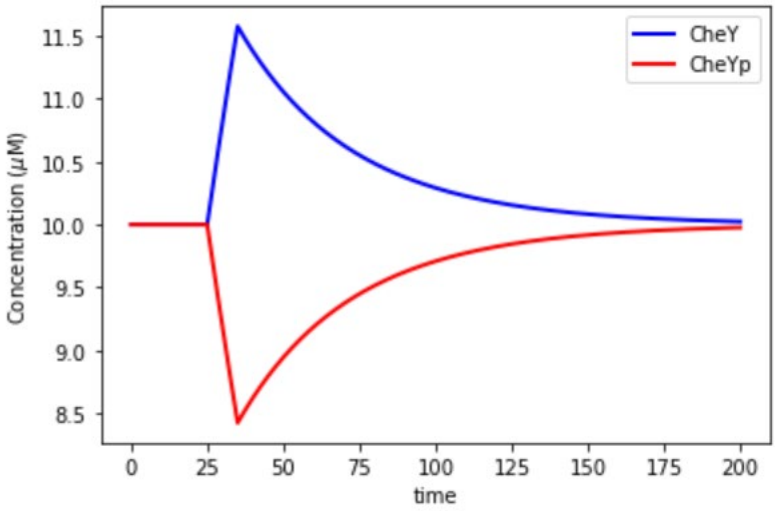
Explain how this model demonstrates perfect adaptation. Why is this important for chemotaxis?

Perfect adaptations reactions can adapt to change. This model demonstrated perfect adaptation because no matter the initial value of CheYp, the resulting concentration

is steady and returns to the same value. This is important for chemotaxins because it allows them to be able to stop and adapt to the environment over time. From our model here, they can find good senses of food and remain in the position as a signal result.

5) (10 points) Finally we will explore the effects of adding a transient spike of CheYp on the results of the perfect adaptation model in the section "perfect adaptation model with transient spike". In this model, when the time in the simulation is greater than "t_on" but less than "t_off", an additional amount of CheYp will be added to the model, called "spike".

We will explore this model in the section "Responses of perfect adaptation model with spike". This section first implements the initial conditions and parameters for this model. By default, Chey_0 is set to 10.05 and CheYp_0 is also set now to 10. We additionally have a parameters section to implement the transient spike in CheYp. Run this section of code to simulate the perfect adaptation model with CheYp spike for this set of initial condition/parameters and paste the resulting graph here:



What happens to the value of CheYp once the spike is initiated and after it's turned off?

It returns back to the initial concentration, in the principle of perfect adaptation.

Rerun the code with an altered initial condition for CheYp and see how the trajectory changes? Paste your graph below. Do you still end up with the same steady state value? Based on your results, does this model exhibit perfect adaptation after exposure to a stimulus?

Yes! Since it does, it demonstrates perfect adaptation.