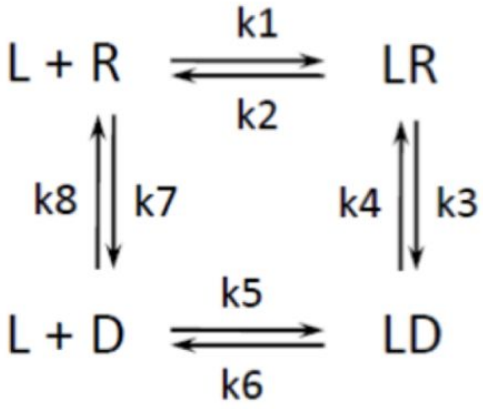
Kevin Shu
Homework 1 Report Summary
BME210, Prof. Kay

Part 1: Report Summary

An important biological concept to understand is the idea of receptor desensitization. As a brief background, in the body, ligands or agonists bind to receptors throughout the nervous system to generate biological responses whether it be through the release of neurotransmitters or hormones. Receptor desensitization is an effect of a receptor's constant exposure to a certain compound that renders it essentially inactive. In this case, we'll be looking at acetylcholine and nicotine to model the effect of chronic smoking on α2β4 nicotinic acetylcholine receptors, a common receptor-ligand interaction in the central and peripheral nervous systems. Modeling the prevalence of desensitized receptors can be done by using first order differential equations derived from the mass action principle. We can derive these said equations using this diagram modeling how the ligand and receptor undergo conformational changes as the molecules go through this cycle.



Below are the 5 equations derived using the principle of mass-action, assuming the equations are all first order, mapping the rate of change of each molecule in this cycle. The d/dt is used to show that these calculations represent the rate of change of each molecule at a certain time. The x(t) notation is to demonstrate that each molecule's concentration in each equation is depending on the time, so L(t) is the concentration of ligand, R is the concentration of receptor, LR is the concentration of bound ligand and receptor, LD is the concentration of bound ligand and desensitized receptor, and D is the concentration of desensitized receptor. The units for these calculations will be microMolar (μM) and the rates of change will be in microMolars per minute (μM/min). The rate constants (all the k's) will be in units of per minute (min^{-1}).

$$\frac{dL(t)}{dt} = k2 * LR(t) + k6 * LD(t) - k5 * L(t) * D(t) - k1 * L(t) * R(t)$$
$$\frac{dR(t)}{dt} = k8 * D(t) + k2 * LR(t) - k7 * R(t) - k1 * L(t) * R(t)$$
$$\frac{dLR(t)}{dt} = k1 * L(t) * R(t) + k4 * LD(t) - k2 * LR(t) - k3 * LR(t)$$
$$\frac{dLD(t)}{dt} = k3 * LR(t) + k5 * L(t) * D(t) - k4 * LD(t) - k6 * LD(t)$$
$$\frac{dD(t)}{dt} = k6 * LD(t) + k7 * R(t) - k5 * L(t) * D(t) - k8 * D(t)$$

In order to accurately approximate the concentrations of the molecules over time using the rates of change, we'll have to use an approximation technique called the RK2 method. Essentially, this method approximates the next value over a designated time step, h, and stores it as a value we'll call RK1. Using that new RK1 value, the RK2 method calculates the slope at the point halfway in between the initial value and the RK1 value. This slope is then multiplied by the time step, h, and added to the initial value, creating a more accurate approximation of the curve.

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Near the end of the report, you will find my simulation of the concentration of desensitized receptors, receptors, and their bound states after they have been chronically exposed to nicotine due to smoking. What was found was the gradual increase in bound ligand and desensitized receptor complex concentration, thus showing that chronic smoking will decrease receptor activity in the nervous system over time.

In this report, I will be graphing the concentrations over time of all the molecules, L, R, D, LR, and LD using the RK2 method. This report will include 1) the MATLAB graphing code, including all of of the MATLAB functions for the rates of change of the molecules, 2) the output and solution of the aforementioned MATLAB code, 3) a second MATLAB code using the MATLAB ode45 function to graph the differential equations, and 4) a simulation of receptor desensitization after chronic nicotine exposure using MATLAB.

Part 2: Program using the RK2 Method (20 points)

```
clc; clear; close all;
initialTime = 0.0;
finalTime = 1/60; % 1 second
h = 0.00001;
tRange = initialTime:h:finalTime;
n = length(tRange);

%initial conditions
%index 1 is L, 2 is R, 3 is LR, 4 is LD, 5 is D
conc(1,:) = [11 11 0 0 11];%concentration of each molecule
k = [600 6000 28.8 0.288 600 60 0.06 0.06]; %rate constants in one matrix

%actually implementing the RK2 method.
for i = 1:n-1
   rk1 = h*DE1(tRange(i), conc(i, :), k)';
   rk2 = h*DE1(tRange(i)+h/2, conc(i,:)+rk1/2, k)';
   conc(i+1, :) = conc(i, :)+rk1;
end

%plotting into subplots
figure(1);
subplot(2, 2, 1);
plot(tRange, conc(:,2));
title('Receptor Concentration (μM) vs. Time (min)');
ylabel('Receptor Concentration (μM)');
xlabel('Time (min)');

subplot(2,2,2);
plot(tRange, conc(:, 3));
title('Bound Ligand and Receptor Concentration (μM)vs. Time(min)');
ylabel('Bound Ligand and Receptor Concentration (μM)');
```

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```
xlabel('Time (min)');

subplot(2,2,3);
plot(tRange, conc(:, 4));
title('Bound Ligand and Desensitized Receptor Concentration (µM)vs. Time(min)');
ylabel('Bound Ligand and Desensitized Receptor Concentration (µM)');
xlabel('Time (min)');

subplot(2,2,4);
plot(tRange, conc(:, 5));
title('Desensitized Receptor Concentration (µM)vs. Time(min)');
ylabel('Desensitized Receptor Concentration (µM)');
xlabel('Time (min)');

function dxdt = DE1(t, conc, k)
   %index 1 is L, 2 is R, 3 is LR, 4 is LD, 5 is D
   dxdt = [k(2)*conc(3)+k(6)*conc(4)-k(5)*conc(1)*conc(5)-k(1)*conc(1)*conc(2);
      k(8)*conc(5)+k(2)*conc(3)-k(7)*conc(2)-k(1)*conc(1)*conc(2);
      k(1)*conc(1)*conc(2) + k(4)*conc(4) - k(2)*conc(3) - k(3)*conc(3);
      k(3)*conc(3) + k(5)*conc(1)*conc(5) - k(4)*conc(4) - k(6)*conc(4);
      k(6)*conc(4) + k(7)*conc(2) - k(5)*conc(1)*conc(5) - k(8)*conc(5)];
end
```

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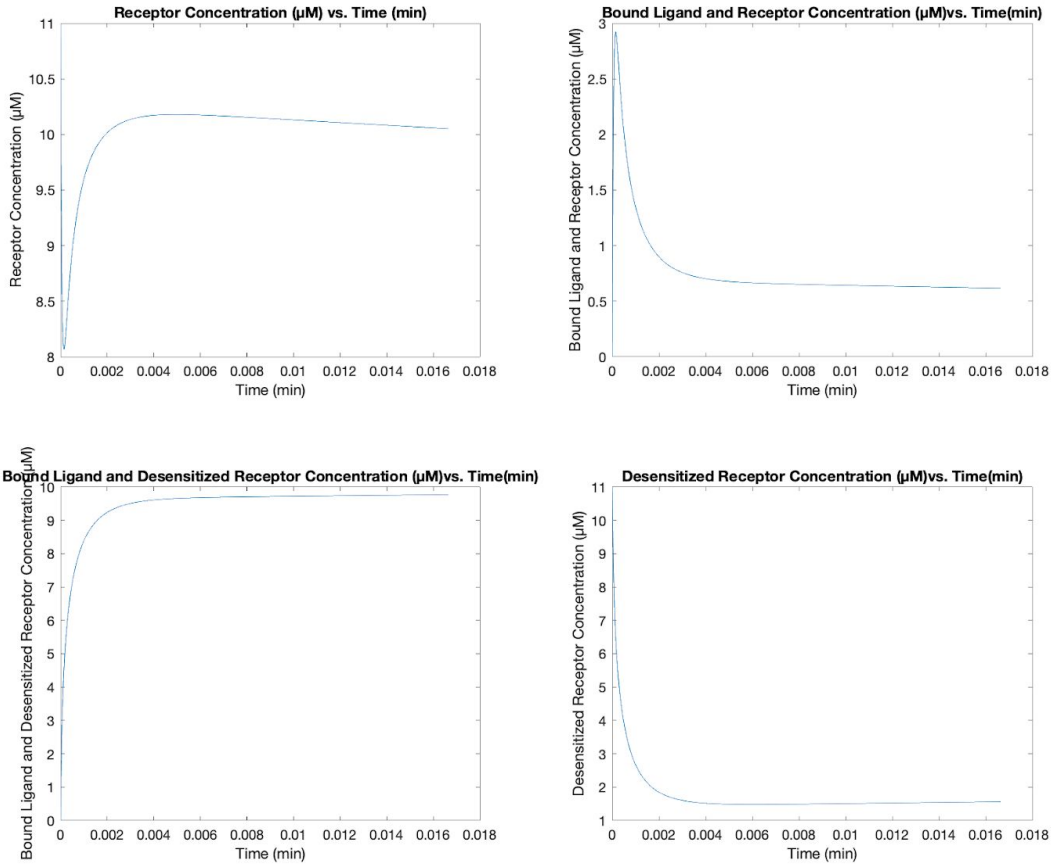
Part 3: Solution using the RK2 Method (10 points)



The chosen step size was 0.00001 minutes. First, I tried using 0.001 as a step size, but since the time range really wasn't long at all, there were very few data points, and the rates of change multiplied by the step size was simply far too large, making MATLAB unable to compute the rk1 and rk2 values very well. I then decreased it ten-fold, and the graphs above were generated. Additionally, the rk1 and rk2 values looked more reasonable, and the script didn't take long to run, so that's how I decided on a step size of 0.00001 minutes. Additionally, the calculated maximum relative error was 0.58 micromolar, and the calculated maximum absolute error was 0.62 micromolar. These errors were smaller than the others and if I were to change the step size to smaller, the script would simply run far too slowly.

Part 4: Program and Solution using ODE45:

```
clc; clear; close all;
initialTime = 0;
finalTime = 1/60;

tspan = [initialTime finalTime];

%initial conditions
```

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```
%index 1 is L, 2 is R, 3 is LR, 4 is LD, 5 is D
conc0 = [11; 11; 0; 0; 11];%concentration of each molecule
k = [600; 6000; 28.8; 0.288; 600; 60; 0.06; 0.06]; %rate constants in one matrix

tolerance = 1e-5;
options = odeset('RelTol', tolerance, 'AbsTol', tolerance);
[t, conc] = ode45(@DE1, tspan, conc0, options, k);

%all the plotting into subplots
figure(1);
subplot(2, 2, 1);
plot(t, conc(:,2));
title('Receptor Concentration (μM) vs. Time (min)');
ylabel('Receptor Concentration (μM)');
xlabel('Time (min)');

subplot(2,2,2);
plot(t, conc(:, 3));
title('Bound Ligand and Receptor Concentration (μM)vs. Time(min)');
ylabel('Bound Ligand and Receptor Concentration (μM)');
xlabel('Time (min)');

subplot(2,2,3);
plot(t, conc(:, 4));
title('Bound Ligand and Desensitized Receptor Concentration (μM)vs. Time(min)');
ylabel('Bound Ligand and Desensitized Receptor Concentration (μM)');
xlabel('Time (min)');

subplot(2,2,4);
plot(t, conc(:, 5));
title('Desensitized Receptor Concentration (μM)vs. Time(min)');
ylabel('Desensitized Receptor Concentration (μM)');
xlabel('Time (min)');
```

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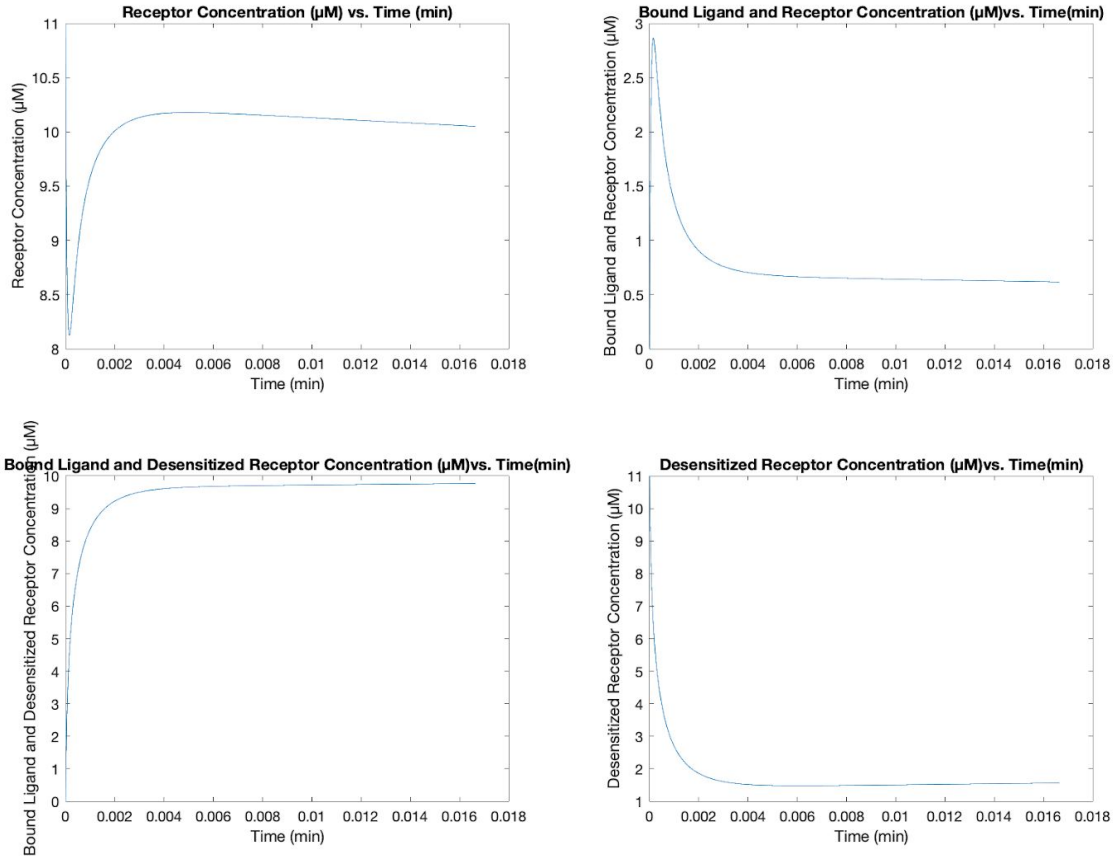

Part 5: Desensitization (40 points)

```
clc; clear; close all;
initialTime = 0.0;
finalTime = 3; % 1 second
h = 0.0001;
tRange = initialTime:h:finalTime;
n = length(tRange);
tspan = [initialTime finalTime];

%initial conditions
%index 1 is L, 2 is R, 3 is LR, 4 is LD, 5 is D
conc0 = [11; 11; 0; 0; 11];%concentration of each molecule
k = [600; 6000; 28.8; 0.288; 600; 60; 0.06; 0.06; 120]; %rate constants in one matrix

%setting tolerance and running ode45
tolerance = 1e-5;
options = odeset('RelTol', tolerance, 'AbsTol', tolerance);
%conc will be the matrix holding all 5 dependent variables
```

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```
[t, conc] = ode45(@DE2, tspan, conc0, options, k);

%all the plotting into subplots.
figure(1);
subplot(2, 2, 1);
plot(t, conc(:,2));
title('Receptor Concentration (μM) vs. Time (min)');
ylabel('Receptor Concentration (μM)');
xlabel('Time (min)');
xlim([-0.5 3.0]);

subplot(2,2,2);
plot(t, conc(:, 3));
title('Bound Ligand and Receptor Concentration (μM)vs. Time(min)');
ylabel('Bound Ligand and Receptor Concentration (μM)');
xlabel('Time (min)');
xlim([-0.5 3.0]);

subplot(2,2,3);
plot(t, conc(:, 4));
title('Bound Ligand and Desensitized Receptor Concentration (μM)vs. Time(min)');
ylabel('Bound Ligand and Desensitized Receptor Concentration (μM)');
xlabel('Time (min)');
xlim([-0.5 3.0]);

subplot(2,2,4);
plot(t, conc(:, 5));
title('Desensitized Receptor Concentration (μM)vs. Time(min)');
ylabel('Desensitized Receptor Concentration (μM)');
xlabel('Time (min)');
xlim([-0.5 3.0]);

function dxdt = DE2(t, conc, k)
   %k is a vector of size 9
   %index 1 is L, 2 is R, 3 is LR, 4 is LD, 5 is D
   dxdt =
[k(2)*conc(3)+k(6)*conc(4)-k(5)*conc(1)*conc(5)-k(1)*conc(1)*conc(2)+NicDelivRate(t)-k(9)*conc(1);
      k(8)*conc(5)+k(2)*conc(3)-k(7)*conc(2)-k(1)*conc(1)*conc(2);
      k(1)*conc(1)*conc(2) + k(4)*conc(4) - k(2)*conc(3) - k(3)*conc(3);
      k(3)*conc(3) + k(5)*conc(1)*conc(5) - k(4)*conc(4) - k(6)*conc(4);
      k(6)*conc(4) + k(7)*conc(2) - k(5)*conc(1)*conc(5) - k(8)*conc(5)];

end
function dxdt = NicDelivRate(t)
```

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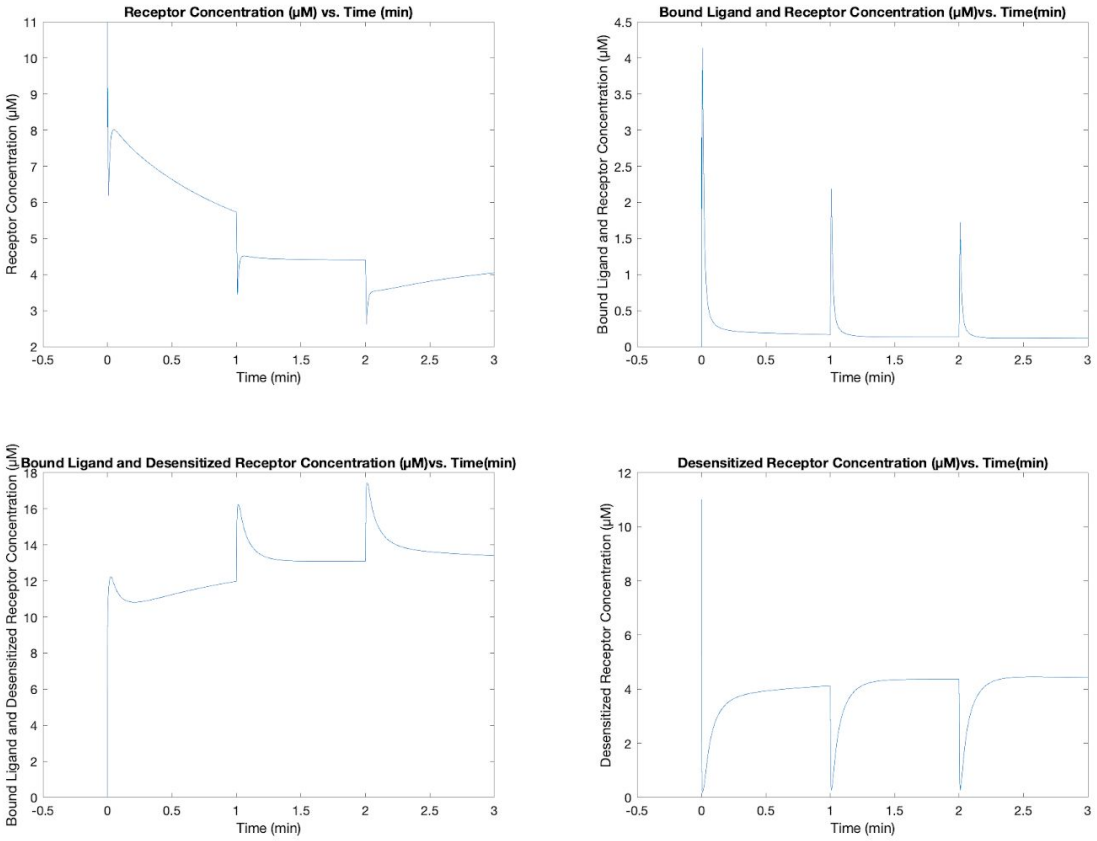
```
    %conditional statements to set nicotine delivery rate based on time.
    if t>0 && t<=0.5/60
        dxdt = 36 + 15/(0.5/60);
    elseif t>1 && t<=1+(0.5/60)
        dxdt = 36 + 15/(0.5/60);
    elseif t>2 && t<=2+(0.5/60)
        dxdt = 36 + 15/(0.5/60);
    else
        dxdt = 36;
    end
end
```



As seen in the top right subplot, the bound ligand and receptor graph sees three distinct peaks as the nicotine is put into the system. Gradually, the peaks diminish, creating a gradual increase in bound ligand to desensitized receptors as seen in the bottom left corner. This demonstrates a decrease in response to nicotine and acetylcholine through the receptor's constant exposure to nicotine through smoking.