Problem Set 1

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Clint Valentine
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Biomolecular Control and Dynamics
Prof. Anand Asthagiri

Contents

Phase Portrait of the EGF Receptor-Ligand Interaction

The formation of the complex can be modeled using the equation:

$$u(\tau) = \frac{L_o}{K_d}(1 - \eta u)(1 - u)$$

The dissociation of the the complex can be modeled using the equation:

$$u(\tau) = u$$

The following code generates a phase portrait for the receptor-ligand interaction interaction of EGF binding to EGF receptor. Fixed points that are stable are labeled with a solid circle. Fixed points that are unstable are labeled with a hollow circle.

Conditions:

$$\frac{L_o}{K_d} = 1$$

$$\eta = 2$$

```
warning('off', 'all') % Avoid warnings of imaginary numbers

sat = 1;   % Lo/Kd
eta = 2.0; % (n*Rt)/(Lo*Avagadro)

syms u;
roots = solve(sat * (1 - (eta * u)) * (1 - u) == u, 'u');

tau = 0:.001:2;
y1 = tau;
y2 = sat .* (1 - (eta .* tau)) .* (1 - tau);

figure;
plot(tau, y1, tau, y2, roots(1), roots(1), 'ro',...
```

Of course, from the perspective of a Matlab code, it is ok to call this variable anything you'd like, but from the math/ dynamics perspective, keep in mind that this is not \tau but

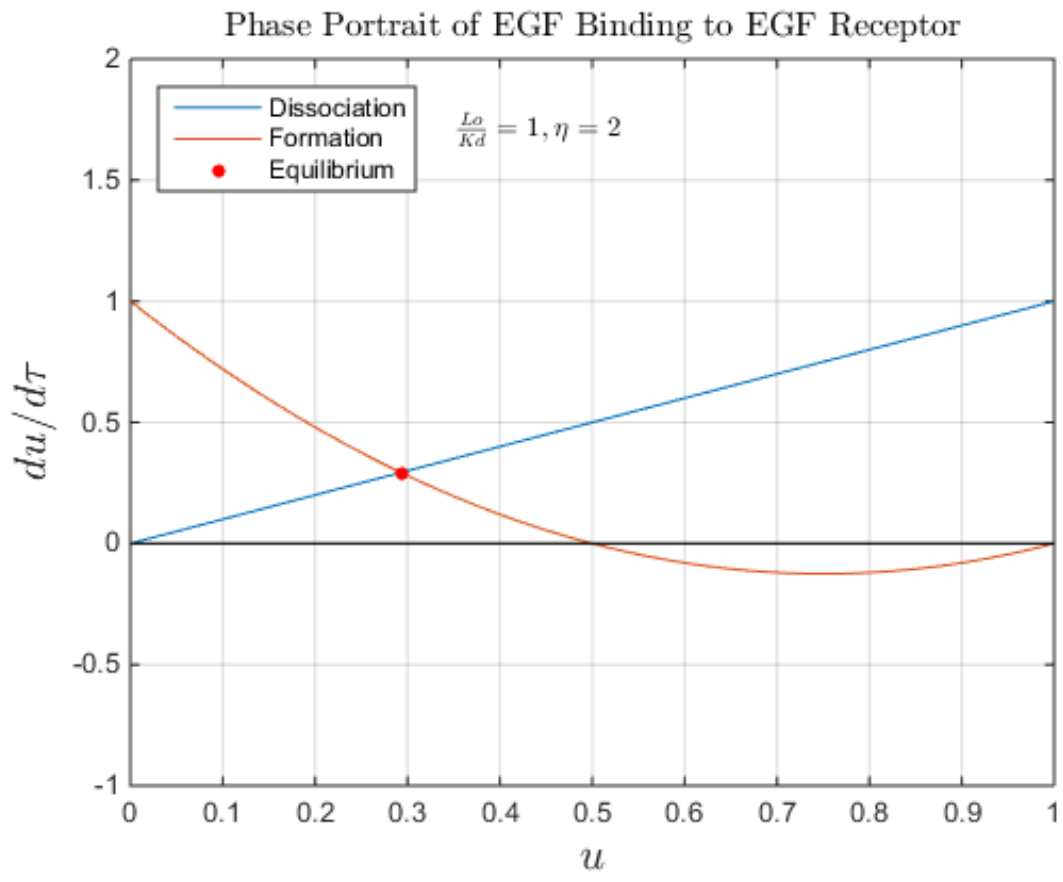
```
     'MarkerFaceColor', 'r', 'MarkerSize', 4);

axis([0, 1, -1, 2]);
axis('on');
grid('on');

h = xlabel('$u$', 'FontSize', 16);
set(h, 'Interpreter', 'latex');
h = ylabel('$du/d\tau$', 'FontSize', 16);
set(h, 'Interpreter', 'latex');
legend('Dissociation', 'Formation', 'Equilibrium',...
       'location', 'northwest');
h = title('Phase Portrait of EGF Binding to EGF Receptor', 'FontSize', 12);
set(h, 'Interpreter', 'latex');

strconst = '$\frac{Lo}{Kd} = 1, \eta = 2$';
h = text(0.35, 1.7, strconst, 'HorizontalAlignment', 'left');
set(h, 'Interpreter', 'latex');

xL = xlim;
line(xL, [0 0], 'color', 'k');  %x-axis
```



nice plot.

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The phase portrait shown above shows one fixed point for the system in the physical domain. This point is stable because when u is of a lesser value than the fixed point, formation of the complex is at a higher rate than dissociation of the complex which drives u higher. The opposite is also true. When the value of u is greater than the stable point, the rate of dissociation of the

complex is greater than the rate of formation of the complex which drives u lower.

The stable equilibrium point can be found at:

```
fprintf('u = %g      ', eval(subs(roots(1))));
fprintf('du/dtau = %g\n', eval(subs(roots(1))));
```

```
u = 0.292893    du/dtau = 0.292893
```

yes. this is the fixed pt... but, note... $du/d\tau = 0$ when $u = 0.29$

Plotting u as a Function of τ and Detecting the Time at 90% EGF Steady-State

This method was my first attempt which failed.

```
% ode1=@(u, t)sat*(1-eta(1)*u)*(1-u)-u;
% ode2=@(u, t)sat*(1-eta(2)*u)*(1-u)-u;
% ode3=@(u, t)sat*(1-eta(3)*u)*(1-u)-u;

% [u1, t1]=ode45(ode1, 0:0.01:10, 0.1);
% [u2, t2]=ode45(ode2, 0:0.01:10, 0.1);
% [u3, t3]=ode45(ode3, 0:0.01:10, 0.1);
```

This was my second attempt and I found a useful solution. The solution to this differential equation can not simply be solved in terms of elementary functions. First, $u(\tau)$ is described symbolically and a solution is found for all values of η. The limit as $\tau \to \infty$ is then found and the differential equation solutions are then solved for 90% the asymptote value.

Conditions:

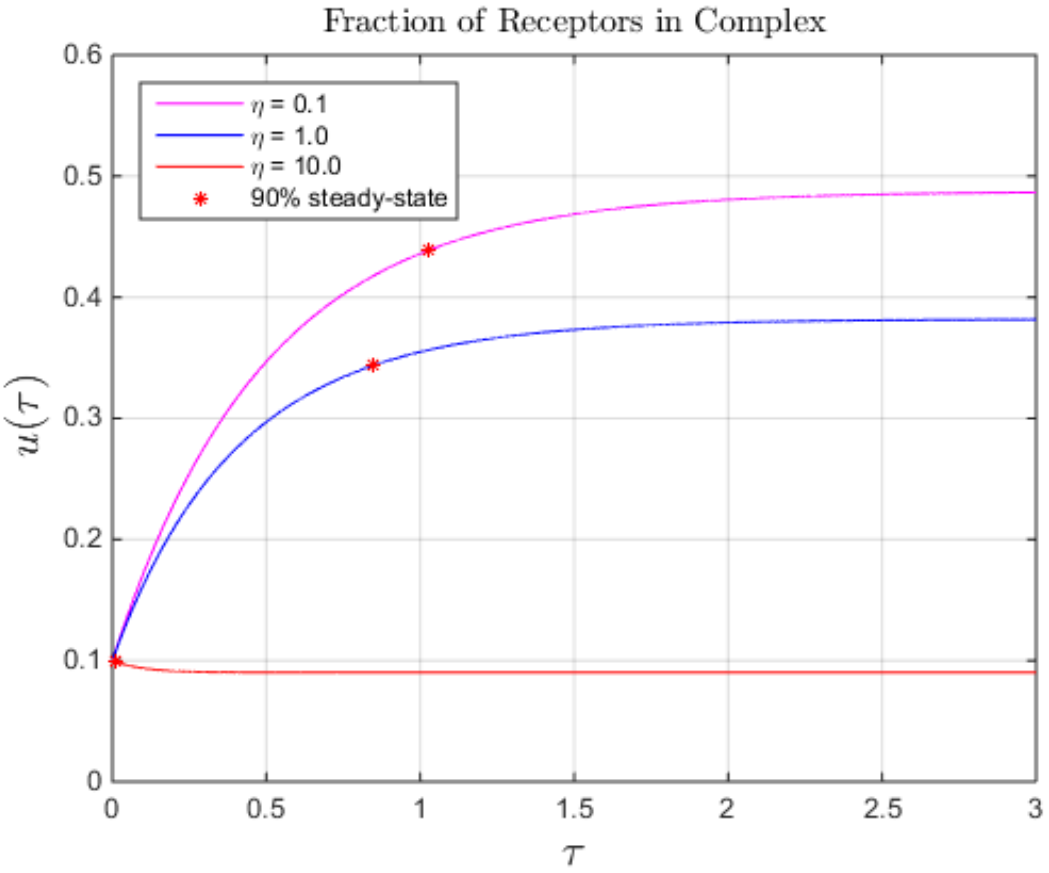
$$\frac{Lo}{Kd} = 1$$

$$u(0) = 0.1$$

$$\eta = [0.1, 1.0, 10.0]$$

```
Kr = 0.12; % units: 1/min
eta = [0.1, 1.0, 10.0];

syms u(t);
a = dsolve(diff(u,t) == sat*(1-eta(1)*u)*(1-u)-u, u(0) == 0.1);
b = dsolve(diff(u,t) == sat*(1-eta(2)*u)*(1-u)-u, u(0) == 0.1);
c = dsolve(diff(u,t) == sat*(1-eta(3)*u)*(1-u)-u, u(0) == 0.1);

alim90 = 0.9 * limit(a, inf); % Find asymptote and find 90% or 110%
blim90 = 0.9 * limit(b, inf);
clim90 = 1.1 * limit(c, inf);

lim_timea = solve(a == alim90); % Solve tau for 90% asymptote
```

```
lim_timeb = solve(b == blim90);
lim_timec = solve(c == clim90);

tau = linspace(0, 3, 10000); % Build tau axis

a1 = matlabFunction(a);
y1 = a1(tau);
b1 = matlabFunction(b);
y2 = b1(tau);
c1 = matlabFunction(c);
y3 = c1(tau);

figure;
plot(tau, y1, 'm', tau, y2, 'b', tau, y3, 'r');
hold on;

plot(lim_timea, alim90, 'r*', 'MarkerSize', 5);
plot(lim_timeb, blim90, 'r*', 'MarkerSize', 5);
plot(lim_timec, clim90, 'r*', 'MarkerSize', 5);

axis([0, 3, 0, 0.6]);
axis('on');
grid('on');

h = xlabel('$\tau$', 'FontSize', 16);
set(h, 'Interpreter', 'latex');
h = ylabel('$u(\tau)$', 'FontSize', 16);
set(h, 'Interpreter', 'latex');
legend('\eta = 0.1', '\eta = 1.0', '\eta = 10.0', '90% steady-state', 'location', 'northwest')
;
h = title('Fraction of Receptors in Complex', 'FontSize', 12);
set(h, 'Interpreter', 'latex');
```



The following code prints the dimensionalized time at which the system has reached 90% steady-state under the three values of η.

```
fprintf('eta = 0.1,  time = %g minutes\n', eval(lim_timea / Kr));
fprintf('eta = 1.0,  time = %g minutes\n', eval(lim_timeb / Kr));
fprintf('eta = 10.0, time = %g minutes\n', eval(lim_timec / Kr));
```

```
eta = 0.1,  time = 8.55714 minutes
eta = 1.0,  time = 7.07052 minutes
eta = 10.0, time = 0.0778756 minutes
```

Kinetic Models for the Bivalent Receptor Model PDGF

Constants to be considered:

L_o = ligand concentration $(\frac{mol}{vol.})$

L = free ligand

R_t = total receptors in cell

R_1 = free first valency of receptors

R_2 = free second valency of receptors

C = total complexes in cell with both valencies filled

The elementary reactions for the system of a monovalent ligand binding to a bivalent receptor are as follows. The assumptions of this system is that both valencies on the receptor have an equal opportunity of binding a ligand

$$R_1 + R_2 + 2L \rightleftharpoons C$$

this requires 4 molecular species to come together at one moment ... unlikely.

The formation rate of C can be modeled using the diff.equation:

$$\frac{dC}{dt} = k_f R_1 R_2 [L] - k_r C$$

Since R_1 and R_2 are equally likely to bind a ligand we can assume:

$$R_1 + R_2 = 2R$$

Our new rate law becomes:

$$\frac{dC}{dt} = k_f R^2 [L] - k_r C$$

These mass balances can then be used to put the rate law in terms of the state variable:

$$R = \frac{R_t - C}{2}$$

$$[L] = L_o - C\frac{n}{N_A}$$

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Our new rate law becomes:

$$\frac{dC}{dt} = k_f (R_t - C)^2 (L_o - C\frac{n}{N_A}) - k_r C$$

Non-dimensionalization is achieved with the following equivalencies:

$$u = \frac{C}{R_t}$$

$$\tau = K_r t$$

The final bivalent receptor kinetic model for this system is:

$$\frac{du}{d\tau} = \frac{L_o}{K_d}\frac{(1-u)^2}{4}(1-u) - u$$

Elementary Reactions for a Dimer Ligand and Bivalent Receptor

In these three elementary reactions a dimer is formed and then binds both binding sites in the receptor siultaneously.

$$L + L \rightleftharpoons Dimer_{AB}$$

$$Dimer_{AB} + R_{A'B'} \rightleftharpoons C$$

In the following example the A site of the dimer then binds the A' site on the receptor. The B site of the dimer then binds the B' site of the receptor forming the complex.

$$L + L \rightleftharpoons Dimer_{AB}$$

$$Dimer_A + R_{A'} \rightleftharpoons Dimer_B + R_{B'} \rightleftharpoons C$$

This example is the same as the one above only the B domain of the ligand binds the binding site B' first and then the A domain binds the A' site.

$$L + L \rightleftharpoons Dimer_{AB}$$

$$Dimer_B + R_{B'} \rightleftharpoons Dimer_A + R_{A'} \rightleftharpoons C$$

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