Autophosphorylation Switch: Modulation by Phosphatase Activity

The kinase activates itself and is antagonized by a phophatase. x is the fraction of kinase in the active (phosphorylated) state.

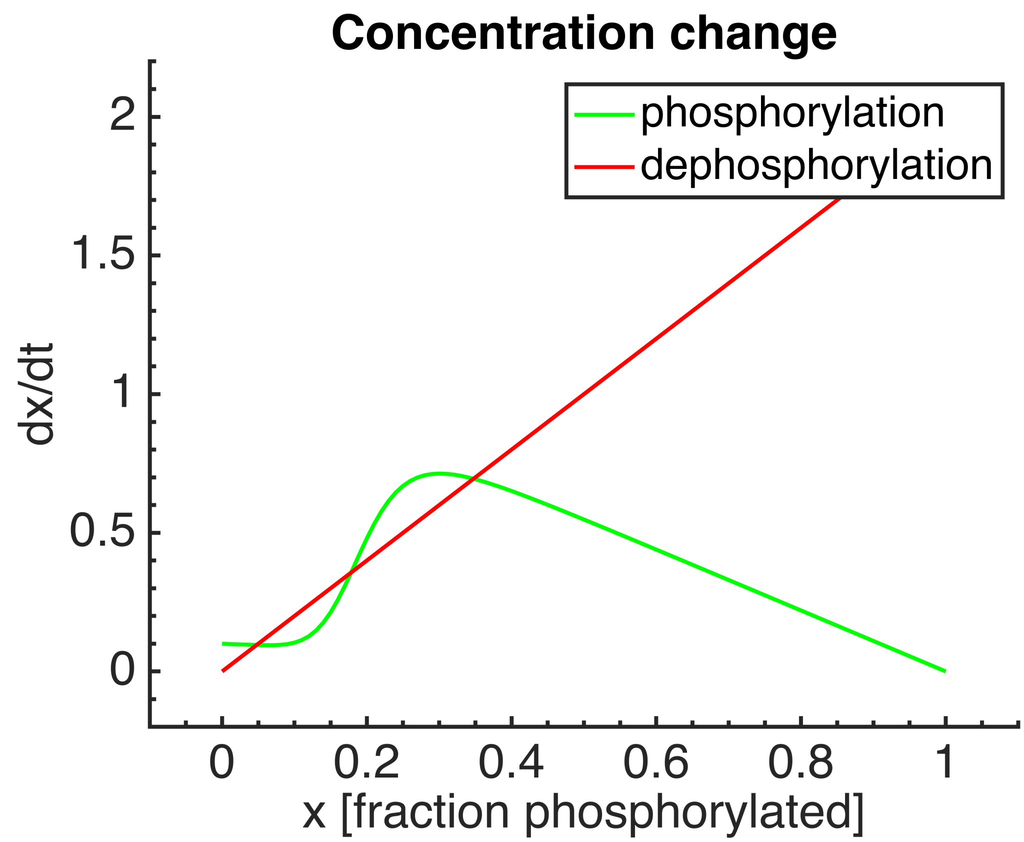
$$\frac{dx}{dt} = \dot{x} = f(x) = K(1-x)(\frac{x^n}{x^n + x_M^n} + 0.1) - Px$$

Script to make the increasing and decreasing rates

```
K = 1;    %maximum kinase activity
n = 6;    %cooperativity
xM = 0.2; %concentration for half-maximum oligomerization
P = 2;    %phosphatase activity
```

Question a(i): plot phosphorylation (green) and dephosphorylation (red) rates

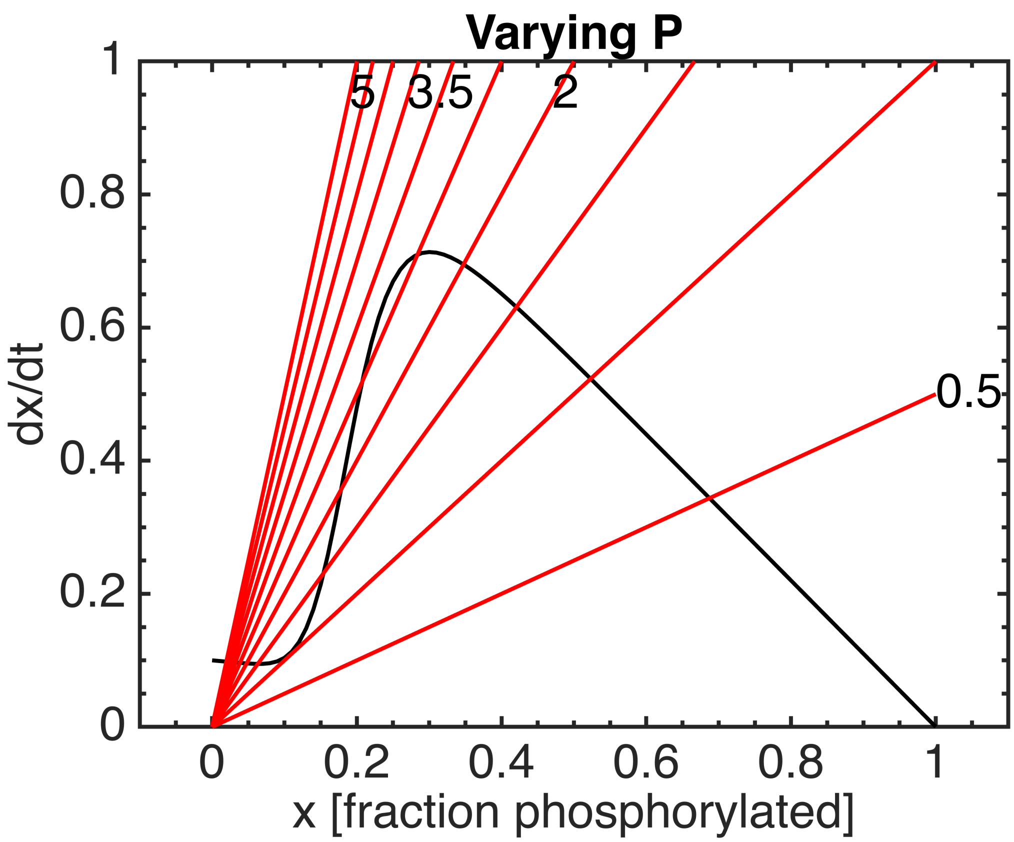
```
xa = 0:.01:1;  %array of x values
figure; hold on;
% plot the increasing rate in green
dx_increase = K.*(1 - xa).*(((xa.^n)./(xa.^n + xM^n))+0.1);
plot(xa, dx_increase, 'g-');
% plot the decreasing rate in red;
dx_decrease = P*xa;
plot(xa, dx_decrease, 'r-');
% set plot parameters.
title('Concentration change');
xlabel('x [fraction phosphorylated]');
ylabel('dx/dt');
legend('phosphorylation','dephosphorylation');
PrettyFig;
```



Question a(ii): plot of a bunch of decay rates

```
Parray = 0.5:0.5:5;
figure; hold on; clf; zoom on;

%plot the phosphorylation (increasing) curve in black)
dx_increase = K.*(1 - xa).*(((xa.^n)./(xa.^n + xM^n))+0.1);
plot(xa, dx_increase, 'k-');
hold on;

%Plot the dephosphorylation curves for each element of the Parray
for k=1:length(Parray)
    P = Parray(k);
    dx_decrease = P * xa;
    plot(xa, dx_decrease, 'r-');

    % if(P==5)
    % plot(xa, abs(dx_decrease-dx_increase), 'g-');
    % end

    % find x index at y=1.
    [discard, xBoundIdx] = min(abs(dx_decrease-0.95));
    xBound = xa(xBoundIdx);

    % display P values.
```

```
    if((k-1)/3 == round((k-1)/3))
        text(xBound, min([0.95, dx_decrease(end)]), num2str(P))
    end
end

set(gca,'ylim',[0 1]);
xlabel('x [fraction phosphorylated]');
ylabel('dx/dt');
title('Varying P');
PrettyFig;
```



Question a(iii) What are the two approximate values of P where the number of fixed points changes

At lower values of P, there is only *one fixed point*. At about **P = 1**, there are *two fixed points*, when the dephophorylation rate curve "kisses" the phosphorylation curve at a lower x value. Beyond this value of P, there are *three fixed points*.

At a little higher than **P = 2.5**, the system goes back to *two fixed points,* where the curves "kiss" at a higher x value. Beyond this value of P, there is again only *one fixed point.*

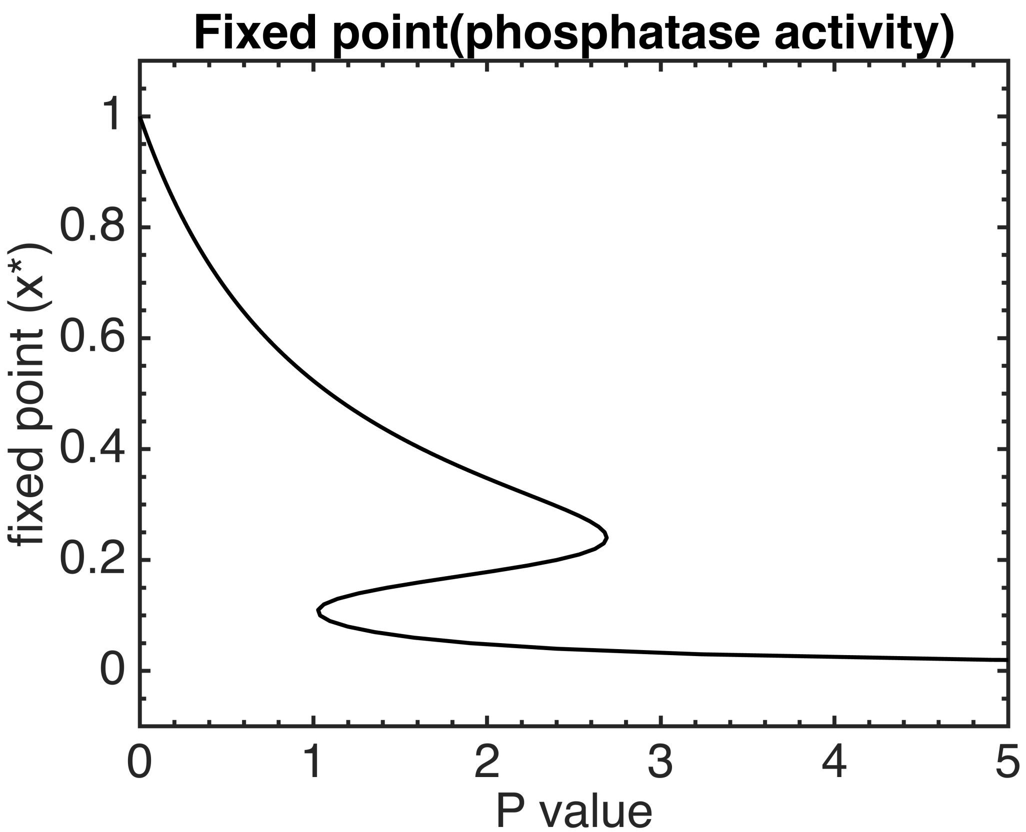
Hence, the number of fixed points changes at **P = 1** and a little over **P = 2.5**, from one to three and three to one fixed points, respectively. (Based on the plot in question (b)(ii), the second value of P is close to **2.69**).

Question b(i): You need to rearrange the equation so P(x*) = and put it into the code below

Numerical solution included in PDF writeup document.

Question b(ii): solution for fixed points x* vs. P

```
xa = 0:.01:1;
% this line of code answers b(i)
Psolve = K.*((1 - xa)./xa).*(((xa.^n)./(xa.^n + xM^n))+0.1);
figure; zoom on;
%plotPsolve on the x-axis, x* on the y-axis
plot(Psolve, xa, "k-");
xlabel('P value');
ylabel('fixed point (x*)');
title('Fixed point(phosphatase activity)');
set(gca,'xlim',[0 5]);
PrettyFig;
```



c(i): What are the approximate values of the critical points for P? Answer here ...

The critical values of P at which the system undergoes fast transitions are at:

(1) About **P = 2.69**, when the system switches from the higher values of fixed points to the lower ones as P increases.

(2) About **P = 1**, when the system switches from the lower values of fixed points to the higher ones as P decreases.

c(ii): Add arrows

Arrows added.

c(iii): Describe in words how this plot shows hysteresis. Answer here ...

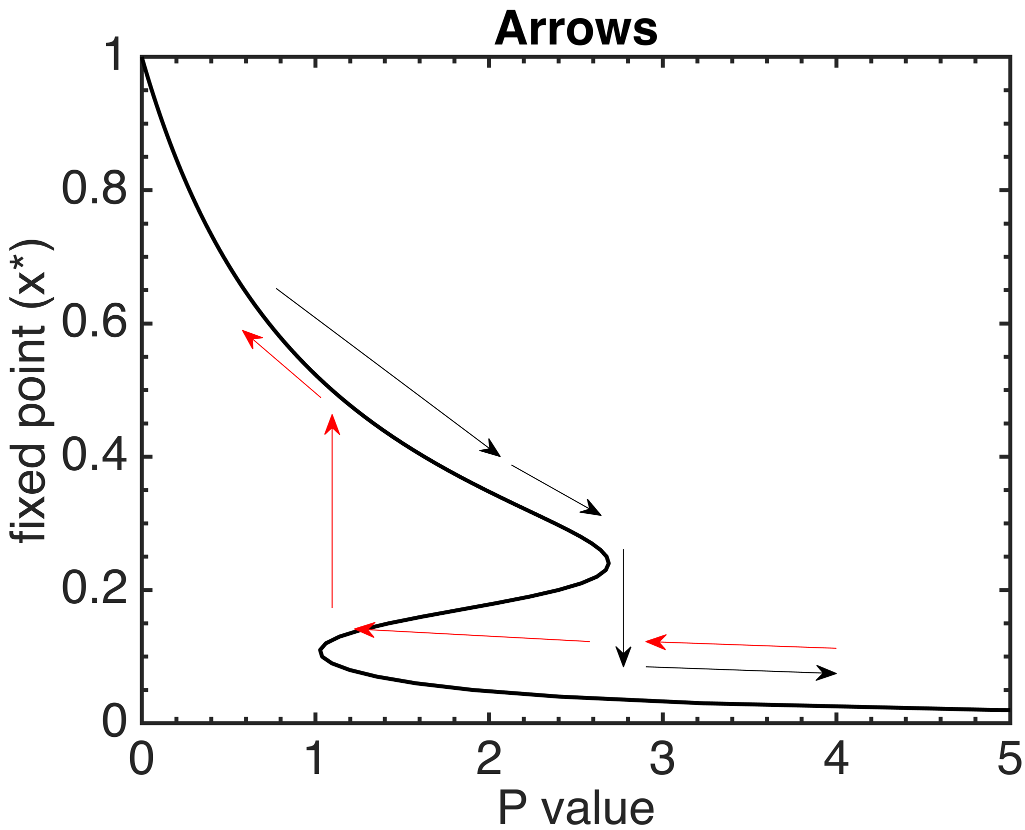
The *black* and *red* arrows show the approximate trajectories of the fixed point, x*(T), as P *increases* and *decreases*, respectively.

As P increases from 0.5 to 5 slowly over time, allowing the system to reach equilibrium every step of the way, x*(T) moves along the upper curve of stable fixed points. Once P crosses its critical value of **P = 2.69** and moveed toward 5, x*(T) jumps to the lower curve of stable fixed points. However, when P decreases again from P, x*(T) continues to stay on the lower curve of fixed points, even after P cross the critical value of 2.69.

As P continues to decrease toward 0.5, x*(T) jumps to the upper curve of fixed points again when the P value reaches the lower critical value of **P = 1**. It stays on this curve as P decreases. If P starts to increase again, x*(T) stays on the upper curve until **P = 2.69**.

Hence, the system switches from the "high" to "low" state when P is increasing in the "high" state and reaches **P = 2.69** (the black arrow trajectory). It switches back from "low" to "high" state when P is decreasing in the "low" state and reaches **P = 1** (the red arrow trajectory).

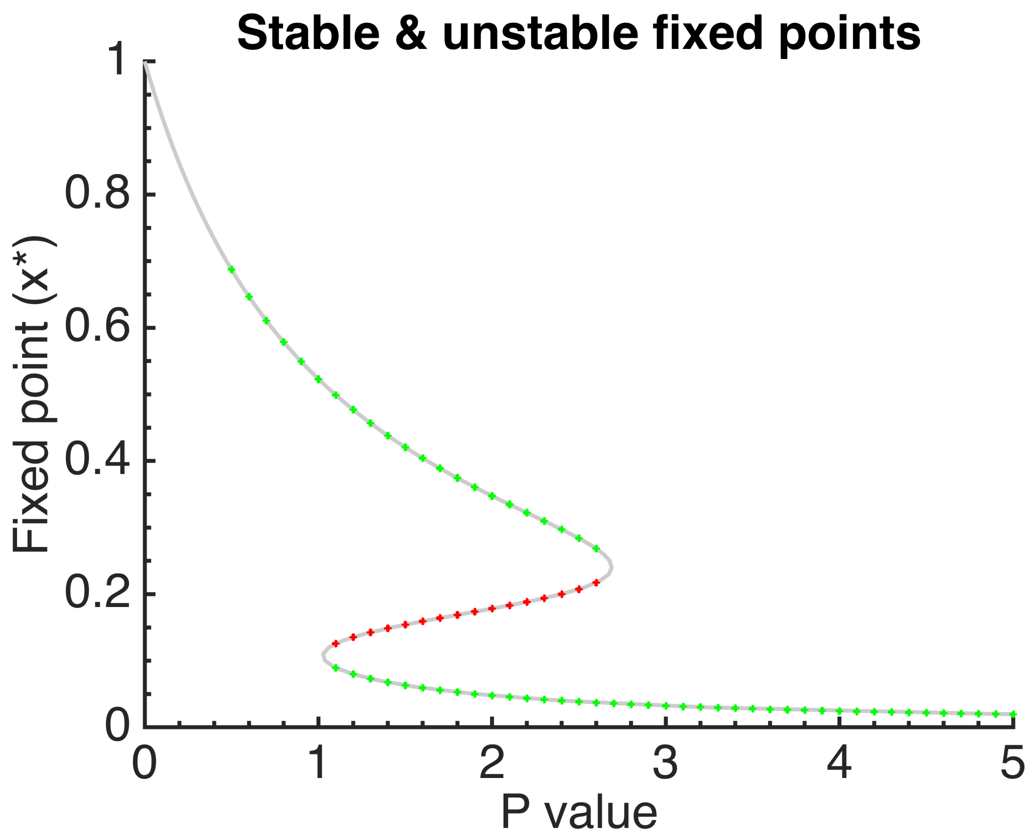
```
% adding arrows
figure; zoom on;
%plot xa vs Psolve again
plot(Psolve, xa, "k-");
xlabel('P value');
ylabel('fixed point (x*)');
set(gca,'xlim',[0 5]);
title('Arrows');
hold on;
%here is one arrow
% TRANSITION 1 (increasing).
annotation('textarrow',[.25 .45],[.65 .45]);
annotation('textarrow',[.46 .54],[.44 .38]);
annotation('textarrow',[.56 .56],[.34 .20]);
annotation('textarrow',[.58 .75],[.20 .192]);
% TRANSITION 2 (decreasing).
annotation('textarrow',[.75 .58],[.222 .23], 'Color', 'red');
annotation('textarrow',[.53 .32],[.23 .245], 'Color', 'red');
annotation('textarrow',[.30 .30],[.27 .50], 'Color', 'red');
annotation('textarrow',[.29 .22],[.52 .60], 'Color', 'red');
%add the other arrows
set(gca,'ylim',[0 1]);
PrettyFig;
```



d(i): do a ton of integrations to get the fixed points by method in (a)

```
xstart = [0:0.05:1]; %starting values of x
Pchoose = [0.5:0.1:5]; %Values of phosphatase activity

Tend = 15.0; %Final time (may not be long enough)

figure; hold on; zoom on;

%plot the fixed-point curve again in black.
% plot analytical solution for reference.
Psolve = K.*((1 - xa)./xa).*(((xa.^n)./(xa.^n + xM^n))+0.1);
plot(Psolve, xa, '-', 'Color', [0.8 0.8 0.8 0.8], 'LineWidth', 1);

%you are going to cycle through all the P values.
for ii=1:length(Pchoose)

    P = Pchoose(ii);
    for jj=1:length(xstart) % for each P value solve the ODE.

        % here is the
        % ode45 code - just an an expression for dx/dt
        [tout, xout] = ode45(@(t,x) differential_equation(t, x, K, P, xM,
n), ...
            [0.0 Tend], xstart(jj));
```

```
        % plot the last point of xout in green;
        plot(P, xout(end), 'go', 'MarkerSize', 2);

        %d(iii) delineate the unstable region on the P axis
        %d(iii) Pmin=??;Pmax=??
        Pmin = 1.00;
        Pmax = 2.80;
        %d(iii) note you have to have xstart in the unstable region as well
        %d(iii) xstartmin=??;xstartmax=??;
        xstartmin = 0.10;
        xstartmax = 0.28;

        %% The min and max values are set such that they encroach slightly
into the
        %%  stable region so that no points in the unstable region is
missed.

        %d(iii) if your are in the unstable region then run the ode
backwards
        %d(iii) if ...
        if(xstart(jj)>=xstartmin && xstart(jj)<=xstartmax)

            %d(iii) run time backwards in ode45 by putting dx/dt(-t) =
-dx/dt (i.e. solve dx/dt=-f(x)
            [tout, xout] = ode45(@(t,x) differential_equation_reverse(t, x,
K, P, xM, n), ...
                [0.0 Tend], xstart(jj));

            %d(iii) plot the the last point of xout in red
            plot(P, xout(end), 'ro', 'MarkerSize', 2);
        end
    end
end
set(gca, 'xlim',[0 5], 'ylim', [0 1]);
xlabel('P value');
ylabel('Fixed point (x*)');
title('Stable & unstable fixed points');
PrettyFig;
```



d(ii) Why are some points not on the line? What if you change the final time

At lower values of T_end (amount of time for which the system evolves), the system spuriously shows stable (or unstable, for backwards ODE) fixed points at points on the y-axis where there aren't any. This is because the system is still evolving toward the stable (or unstable) fixed point; at the end of which, the points will have settled on the fixed point curve.

Experimenting with values of T_end, increasing it by 1 at each step, it appears that all systems, i.e. each with a different P value, reach their fixed points at about **T_end = 15**. I also set the value to a very high T_end of 1000 to cross-check and the plot does not appear any different than at 15, suggesting that the system has, in fact, reached its fixed point by T_end = 15.

Please Note: This response is included again in the attached writeup with sample plots when T_end is too low.

d(iii): find unstable fixed points by adding code in the indicated area above

Code implemented.

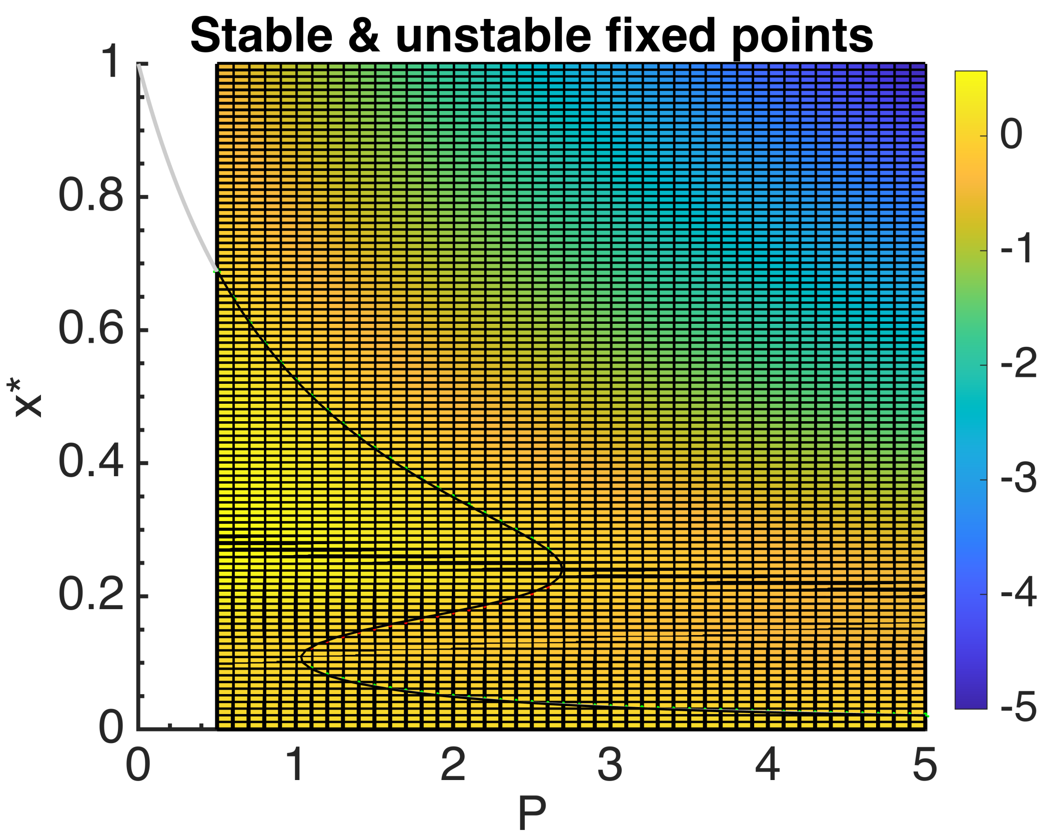
e(i) now, plot up the contour method (graduate student question)

use the surf function to plot the surface with xarray on the x-axis, Parray on the y-axis and dx/dt on the z-axis

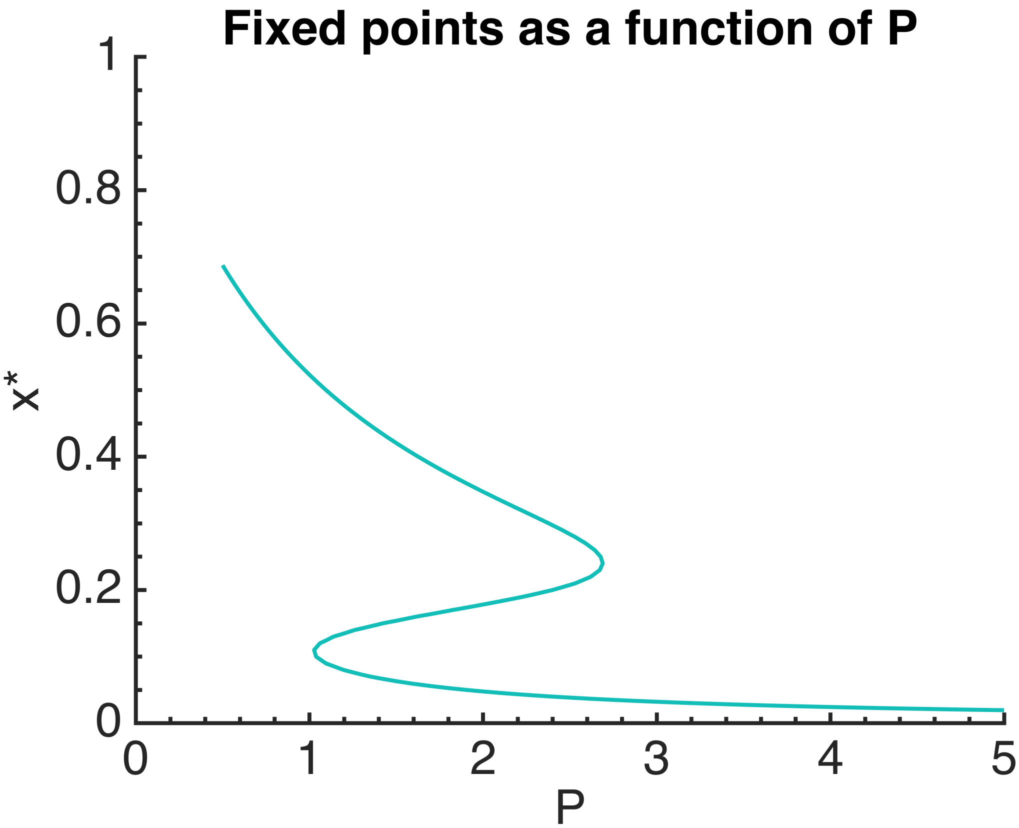
use the contour function to plot a section through

```
xa = 0:0.01:1;
Pchoose = [0.5:0.1:5];
[xarray, Parray] = meshgrid(xa, Pchoose);
```

```
%plot dx/dt on the mesh and plot the surface
dxdt = K.*(1 - xarray).*(((xarray.^n)./(xarray.^n + xM^n))+0.1) -
Parray.*xarray;
surf(Parray, xarray, dxdt); hold on;
contour(Parray, xarray, dxdt, [0 0], 'Color', 'black'); hold off;
colorbar;
set(gca, 'xlim',[0 5], 'ylim', [0 1]);
xlabel('P');
ylabel('x*');
zlabel('dx/dt');
PrettyFig;
```




```
figure; hold on;
set(gca,'xlim',[0 5],'ylim',[0 1]);
%now plot the contour
contour(Parray, xarray, dxdt, [0 0]);
xlabel('P');
ylabel('x*');
title('Fixed points as a function of P');
PrettyFig;
```



This method reproduces the fixed point curve.