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Systems Biology, Homework # 5
Metabolic Networks

1. (a) Flux control coefficient (FCC) determination.

I determined the FCCs for all the reactions to be the following:

$$FCC_{MATIII} = 0.3400$$

$$FCC_{MAT1} = 0.2547$$

$$FCC_{MET} = 0.4078$$

$$FCC_{GNMT} = 0.0020$$

$$FCC_{D} = 0.0280$$

I have abbreviated the code provided by Dr. Leiderman and only included the sections I needed to change. The code is as follows:

```
for i=1:2
    if i==1
        %alpha_d = 1333*1.01;
        %v_GNMT_max = 10600*1.01;
        %v_MET_max = 4544*1.01;
        %v_MATI_max = 561*1.01;
        %v_MATIII_max = 22870*1.01;

    else
        %alpha_d = 1333;
        %v_GNMT_max = 10600;
        %v_MET_max = 4544;
        %v_MATI_max = 561;
        %v_MATIII_max = 22870;

    end
    %simulation
    [t,S]=ode45(ODEFUN, [0,Tend], S0);

    AdoHcy=S(:,2);

    % Pathway flux
    PF(i) = alpha_d*AdoHcy(end)*K_AHC/Adenosine;

end

%FCC = alpha_d/PF(2)*(PF(1)-PF(2))/(0.01*alpha_d)
%FCC = v_GNMT_max/PF(2)*(PF(1)-PF(2))/(0.01*v_GNMT_max)
%FCC = v_MET_max/PF(2)*(PF(1)-PF(2))/(0.01*v_MET_max)
%FCC = v_MATI_max/PF(2)*(PF(1)-PF(2))/(0.01*v_MATI_max)
%FCC = v_MATIII_max/PF(2)*(PF(1)-PF(2))/(0.01*v_MATIII_max)
```

I uncommented whichever code was required to calculate the given FCC. Together, these FCCs represent the control each reaction exerts on overal reaction flux. GNMT, for example, has very little effect on overal flux, as shown in part (b) of this problem. Frustratingly, these do not sum to one. I've checked through my math a handful of times, and I believe the reason either lies in an error I didn't catch, or in the fact that a simple mass action rate is used to describe V_D, where the other V_max values are determined by Michaelis-Menten kinetics.

(b) Reaction fluxes in different states.

Using the code provided by Dr. Leiderman, I calculated the rates of each of the five reactions in the model. I simply commented which steady state to use, so I will not include the code (as it is identical to that provided by Dr. Leiderman). The calculated rates for the steady states are shown below:

	Monostable	Bistable
MATI	153.9266	132.2998
MATIII	204.7526	242.8523
GNMT	1.6989	3.8086
MET	356.9820	371.3498

It is clear from these values that MATI decreases with increasing methionine levels, while MATIII increases by about 18%. MET increases by 7% while GNMT increases by a whopping 120%.

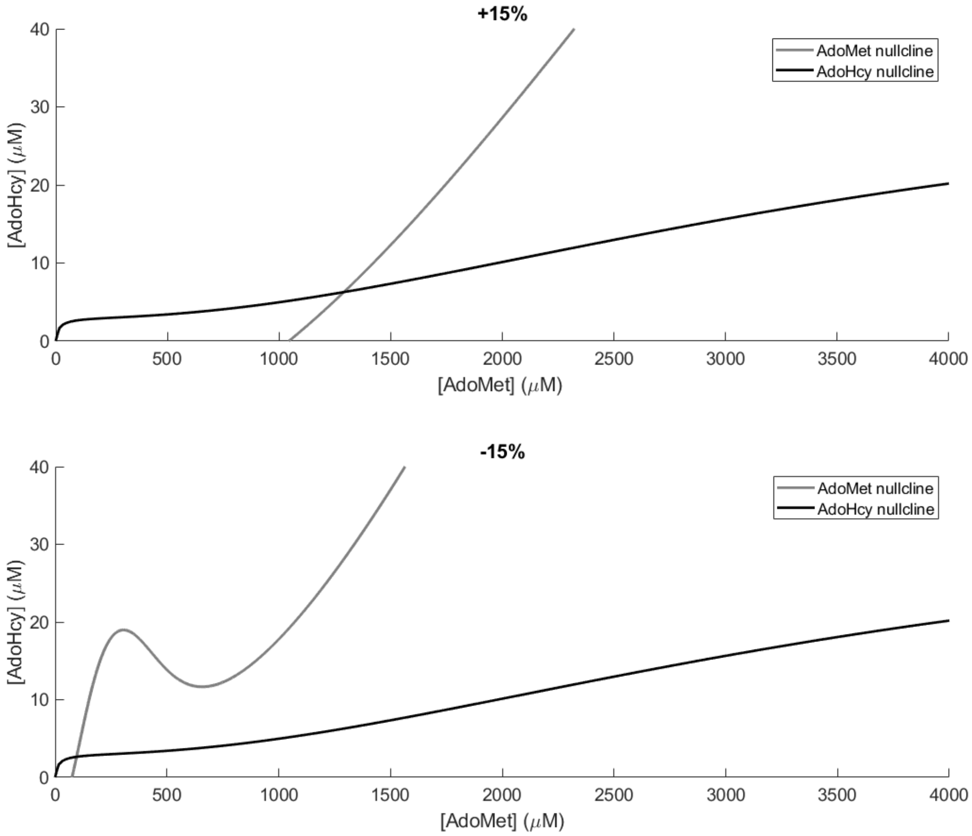
(c) Loss of bistability.

I modified the original model code to create a more visually readable graph, and also increased the simulation axes to allow the new model behavior to be visualized. The modified portion of the code is as follows.

```
%Figure 5.11A

%define nullclines:
v_MATIII_max = 26300.5;
myfun1 = @(m,h) (v_MATI_max * (1./(1+ (K_MATI_m./Met)*(1+m./K_MATI_i))) + ...
     v_MATIII_max * (1/(1+ ((20000/(1+ ...
     5.7*(m./(m+600)).^2))*K_MATIII_m2)./(Met^2+Met*K_MATIII_m2)))) - ...
     (v_GNMT_max * (1./(1+(K_GNMT_m./m).^2.3)) * (1./(1+h./K_GNMT_i))+v_MET_max ...
     * (1/(1+ (10 * (1 + h./4))./m + 1/A_over_K_MET_m2 + ...
     (1/A_over_K_MET_m2)*((10 * (1 + h./4))./m))))
myfun2 = @(m,h) ((v_GNMT_max * (1./(1+(K_GNMT_m./m).^2.3)) * ...
     (1./(1+h./K_GNMT_i))+v_MET_max * (1/(1+ (10 * (1 + h/4))./m + ...
     1./A_over_K_MET_m2 + (1/A_over_K_MET_m2)*((10 * (1 + h./4))./m)))) - ...
     alpha_d * (h*K_AHC/Adenosine))./(1+K_AHC/Adenosine)

figure(2)
hold on

[m,h] = meshgrid(0:1:4000);    %# Create a mesh of m and h points
f = (v_MATI_max.*(1./(1+ (K_MATI_m./Met).*(1+m./K_MATI_i))) + ...
     v_MATIII_max.*(1./(1+ ((20000./(1+ ...
     5.7*(m./(m+600)).^2))*K_MATIII_m2)./(Met^2+Met*K_MATIII_m2)))) - ...
     (v_GNMT_max.*(1./(1+(K_GNMT_m./m).^2.3)).*(1./(1+h./K_GNMT_i))+v_MET_max.*(1./(1+ ...
     (10.*(1 + h./4))./m + 1./A_over_K_MET_m2 + (1./A_over_K_MET_m2).*((10.*(1 ...
     + h./4))./m))));                %# Evaluate f at those points
contour(m,h,f,[0 0],'b');      %# Generate the contour plot
setcurve('color',[0.5 0.5 0.5],'Linewidth', 2)
```

```
axis([0 4000 0 40])

%adohcy nullcline
a2=ezplot(@(m,h) myfun2(m,h), [0 4000 0 40])
setcurve('color','black','Linewidth', 2)

set(gca, 'fontsize', 14)
axis([0 4000 0 40])
legend('AdoMet nullcline', 'AdoHcy nullcline')
xlabel('[AdoMet] (\muM) ')
ylabel('[AdoHcy] (\muM)')
title('+15%')


%set simulation length
Tend=15;

%Figure 5.11A

v_MATIII_max = 19439.5;

%define nullclines:
myfun11 = @(m,h) (v_MATI_max.*(1./(1+(K_MATI_m/Met).*(1+m./K_MATI_i))) + ...
    v_MATIII_max * (1./(1+ ((20000/(1+ ...
    5.7*(m./(m+600)).^2))*K_MATIII_m2)./(Met^2+Met*K_MATIII_m2)))) - ...
    (v_GNMT_max * (1./(1+(K_GNMT_m./m).^2.3)) * (1./(1+h./K_GNMT_i))+v_MET_max ...
    * (1./(1+ (10 * (1 + h./4))./m + 1./A_over_K_MET_m2 + ...
    (1./A_over_K_MET_m2)*((10 * (1 + h./4))./m))))
myfun22 = @(m,h) ...
    ((v_GNMT_max.*(1./(1+(K_GNMT_m./m).^2.3)).*(1./(1+h./K_GNMT_i))+v_MET_max ...
    * (1./(1+ (10 * (1 + h./4))./m + 1/A_over_K_MET_m2 + ...
    (1/A_over_K_MET_m2)*((10 * (1 + h./4))./m)))) - alpha_d .* ...
    (h*K_AHC./Adenosine))./(1+K_AHC/Adenosine)

figure(3)
hold on

[m,h] = meshgrid(0:1:4000);    %# Create a mesh of m and h points
f = (v_MATI_max.*(1./(1+ (K_MATI_m./Met).*(1+m./K_MATI_i))) + ...
    v_MATIII_max.*(1./(1+ ((20000./(1+ ...
    5.7*(m./(m+600)).^2))*K_MATIII_m2)./(Met^2+Met*K_MATIII_m2)))) - ...
    (v_GNMT_max.*(1./(1+(K_GNMT_m./m).^2.3)).*(1./(1+h./K_GNMT_i))+v_MET_max.*(1./(1+ ...
    (10.*(1 + h./4))./m + 1./A_over_K_MET_m2 + (1./A_over_K_MET_m2).*((10.*(1 ...
    + h./4))./m))));              %# Evaluate f at those points
contour(m,h,f,[0 0],'b');      %# Generate the contour plot
setcurve('color',[0.5 0.5 0.5],'Linewidth', 2)
axis([0 4000 0 40])

%adohcy nullcline
a2=ezplot(@(m,h) myfun22(m,h), [0 4000 0 40])
setcurve('color','black','Linewidth', 2)

set(gca, 'fontsize', 14)
axis([0 4000 0 40])
legend('AdoMet nullcline', 'AdoHcy nullcline')
xlabel('[AdoMet] (\muM)')
ylabel('[AdoHcy] (\muM)')
title('-15%')
```

Using this code, I generated the following two figures, which demonstrate the loss of bistability with plus/minus 15% V_{max}^{MATIII}.



It is clear from these figures that bistability is lost (over a reasonable range of AdoMet concentrations) because there are no longer multiple intercepts between the nullclines.