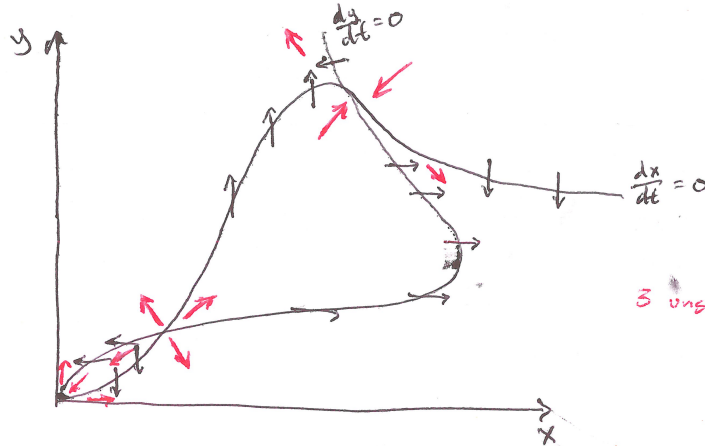


PoSB 2013 Pset 3 Solutions

Stability

$$\frac{d[x]}{dt} = \frac{k_1 [x]^n}{k_2 + [x]^n} - k_3 [x] [y]$$

$$\frac{d[y]}{dt} = \frac{k_4 [y]^m}{k_5 + [y]^m} - k_3 [x] [y]$$

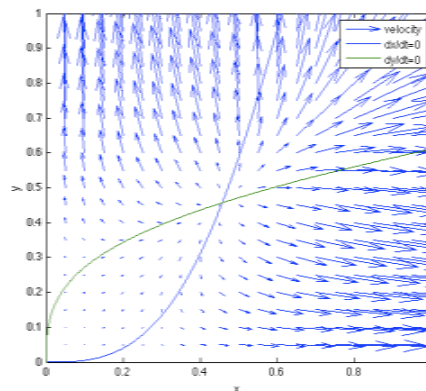
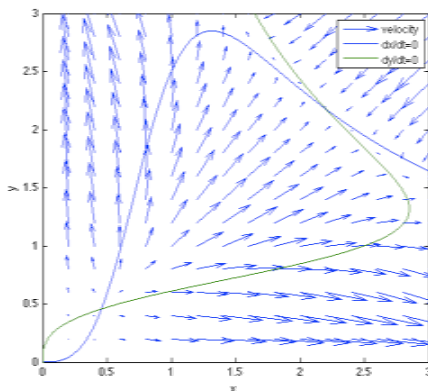


3 unstable steady-states

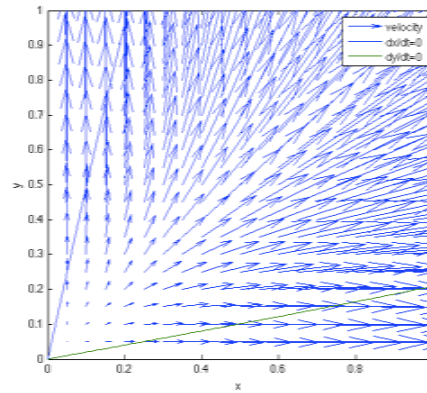
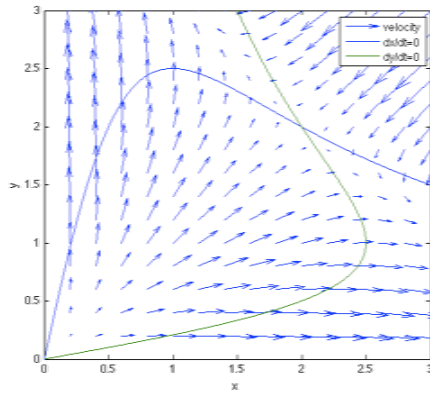
$$\frac{d[x]}{dt} = 0 : [y] = \frac{k_1 [x]^{n-1}}{k_3 (k_2 + [x]^n)}$$

$$\frac{d[y]}{dt} = 0 : [x] = \frac{k_4 [y]^{m-1}}{k_3 (k_5 + [y]^m)}$$

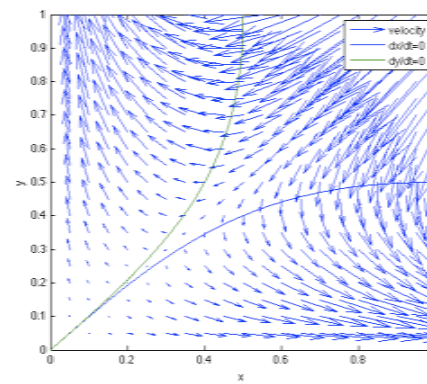
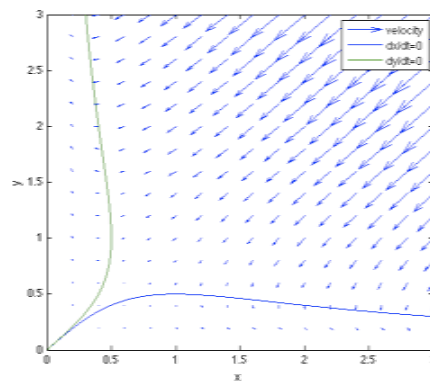
Parameter Set 1



Parameter Set 2



Parameter Set 3

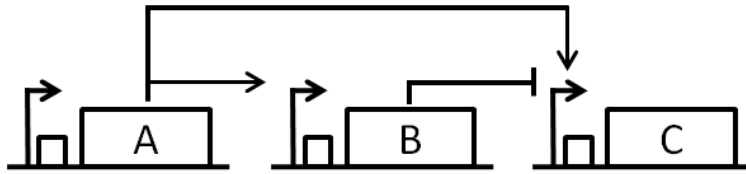


The circuit is not strictly a toggle as there are no stable steady states in any of the parameter sets. There is some semblance of toggling behavior since when you go to a high x / low y area, you tend to stay at high x /low y (though the system will continue to be pushed toward higher x /lower y).

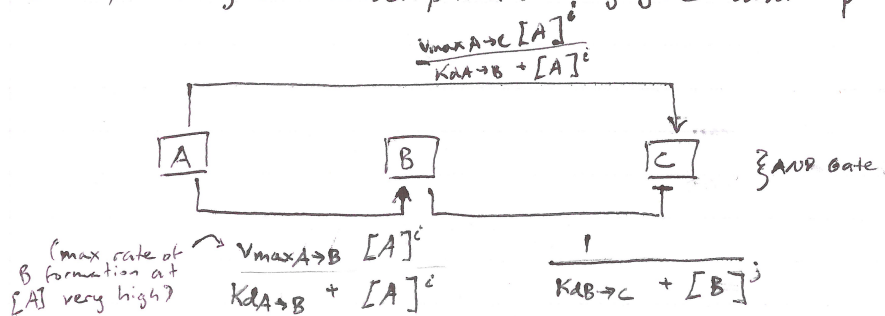
Higher k_1 and k_4 promote more steady states as that increases the amplitude of the nullclines, making them more likely to intersect. Higher n and m promote more steady states since that sharpens up the shape of the nullclines making them more likely to intersect at low x and y . None of the above steady states are stable.

Feedforward and feedback

There are multiple ways to implement this behavior, one way is the incoherent type I feedforward loop we discussed in class with AND gate behavior.



We will assume fast repressor/activator binding. Negligible effect of protein-DNA binding on protein concentration. Repressors/activators bind with some cooperativity ($A:i$, $B:j$, $C:k$). Neglect transcription. Negligible basal production.



$$\frac{d[A]}{dt} = ? \quad (\text{depends on your model})$$

Let's take A to be repressed by LacI and at time = 0 we add IPTG. This can be approximated by 0th order formation and 1st order degradation

$$\frac{d[A]}{dt} = k_{formA} - k_{degA} [A]$$

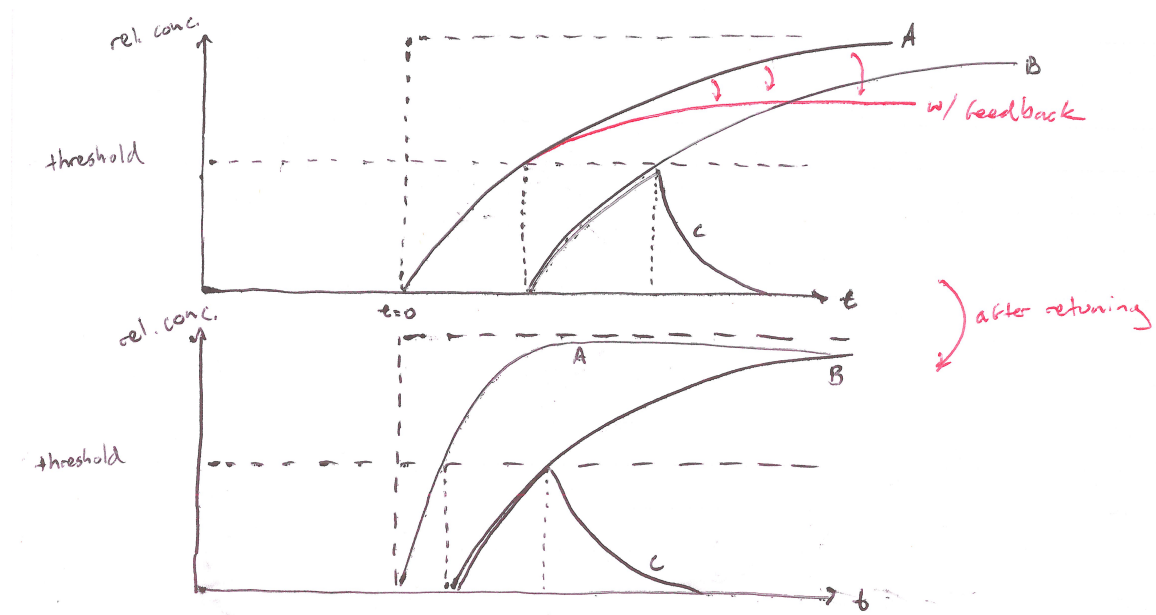
$$\frac{d[B]}{dt} = \frac{v_{maxA \rightarrow B} [A]^i}{K_{AA \rightarrow B} + [A]^i} - k_{degB} [B]$$

$$\frac{d[C]}{dt} = \frac{v_{maxA \rightarrow C} [A]^i}{K_{AA \rightarrow B} + [A]^i} \cdot \frac{1}{K_{AB \rightarrow C} + [B]^j} - k_{degC} [C]$$

(optional basal production rates can be included)

One can also take $d[A]/dt=0$ if considering the step function case.

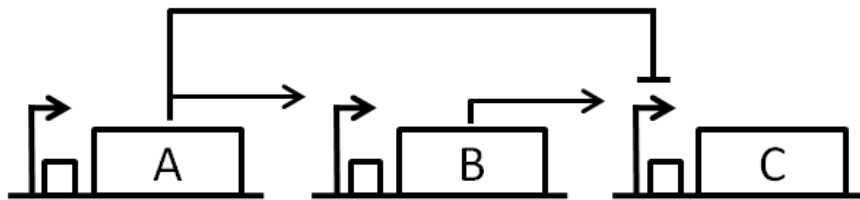
It should be possible to increase the response rate by adding negative feedback. For instance, if we use IPTG inducible A and sketch simplified time courses, we might get:



When taking the concentration of A as a step function, you would get similar speed-up using other kinds of feedback like sequestration or degradation of A.

The process is reversible for this model, since when you remove A, C will remain off. With some delay, B will be reduced so eventually the repression will be removed as well. This brings us back to the original low A/ low B/ low C state. There is nothing very peculiar about the reverse process, as the output C will most likely be at the end of the pulse when you go to do the reverse. There might be more interesting dynamics if you initiated the reverse process in the middle of a pulse.

It should be possible to make a negative pulse generator. For instance, you might have high basal production of C, A represses the basal expression to low levels, B dominates A and activates (with some time delay since A activates B) production of C back to high levels.



```

%% Stability Problem

k1=5;
k2=1;
k3=1;
k4=5;
k5=1;
n=7;
m=7;

%% large scale
res = 0.2;
max = 3;
figure(1)
subplot(1,2,1)

%find velocities
[x,y] = meshgrid(res:res:max,res:res:max);
u=k1*x.^n./(x.^n+k2)-k3*x.*y;
v=k4*y.^m./(y.^m+k5)-k3*x.*y;

%find nullclines
x1=0:0.001:max;
y2=0:0.001:max;
y1=k1/k3*x1.^(n-1)./(x1.^n+k2);
x2=k4/k3*y2.^(m-1)./(y2.^m+k5);

%plot velocities
quiver(x,y,u,v,2)

%plot nullclines
hold on
plot(x1,y1,x2,y2)
axis([0 max 0 max])
xlabel('x')
ylabel('y')
legend('velocity','dx/dt=0','dy/dt=0')
hold off

%% zoomed in
res = 0.05;
max = 1;
subplot(1,2,2)

%find velocities
[x,y] = meshgrid(res:res:max,res:res:max);
u=k1*x.^n./(x.^n+k2)-k3*x.*y;

```

```

v=k4*y.^m./(y.^m+k5)-k3*x.*y;

%find nullclines
x1=0:0.001:max;
y2=0:0.001:max;
y1=k1/k3*x1.^(n-1)./(x1.^n+k2);
x2=k4/k3*y2.^(m-1)./(y2.^m+k5);

%plot velocities
quiver(x,y,u,v,5)

%plot nullclines
hold on
plot(x1,y1,x2,y2)
axis([0 max 0 max])
xlabel('x')
ylabel('y')
legend('velocity','dx/dt=0','dy/dt=0')
hold off

```