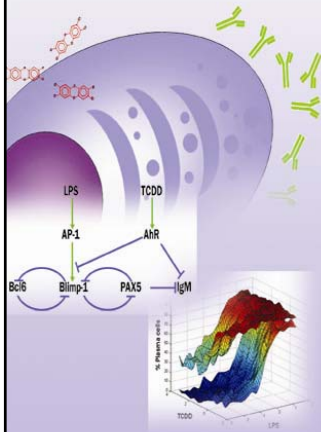


Wednesday Morning Exercise 1 – 3: Creating Feed Forward Loops and Sequential Gene Activation

September 24, 2008

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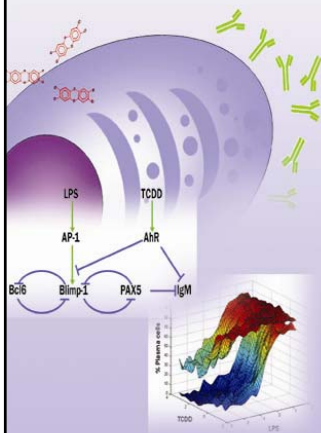


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Alon Motifs – Nature Reviews

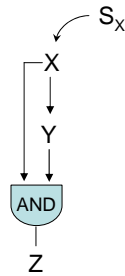
Exercise Goals

- Run and Exercise a Coherent Feed Forward Loop to see function
- Code equations for and exercise an incoherent Feed Forward Loop
- Build a motif for sequential activation of groups of gene products from a single promoter
- Where did that chemical come from?
- Consider how you would build a “developmental motif”; predict what it would do; and, how would we introduce perturbations



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Coherent FFL Type I



- *Impose an X-input to the system*

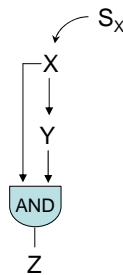
- $$\frac{dY}{dt} = B_Y + \beta_Y \cdot \frac{X^n}{K_{XY}^n + X^n} - \alpha_Y \cdot Y$$

- $$\frac{dZ}{dt} = B_Z + \beta_Z \cdot \frac{X^n}{K_{XZ}^n + X^n} \cdot \frac{Y^n}{K_{YZ}^n + Y^n} - \alpha_Z \cdot Z$$

- *Open Exercises/Wednesday/C1FFL.mmd*

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C1FFL.mmd



; Equations

X = squarepulse(t_start, t_dur) ; pulse of magnitude 1

d/dt(Y) = B_y + beta_y*(X^n/(K_xy^n+X^n)) - alpha_y*Y

d/dt(Z) = B_z+ beta_z*(X^n/(K_xz^n+X^n))*(Y^n/(K_yz^n+Y^n)) - alpha_z*Z

;Initial conditions

init Y = 0

init Z = 0

;Parameters

t_start = 1

t_dur = 3

n=2 ; Hill-coefficient for gene activation

beta_y = 1 ; X-activated transcription rate constant for Y

beta_z = 1 ; X- and Y-activated transcription rate constant for Z

alpha_y = 1 ; degradation rate constant for y

alpha_z = 1 ; degradation rate constant for z

B_y = 0 ; basal transcription rate for Y

B_z = 0 ; basal transcription rate for Z

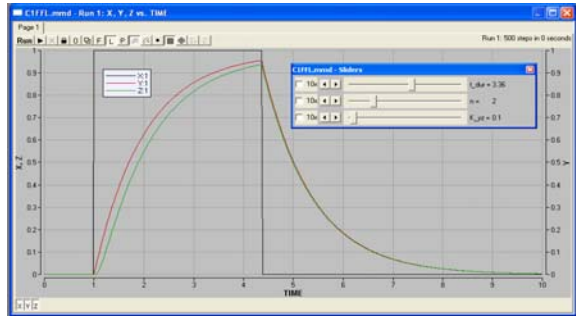
K_xy = 0.1 ; effective affinity constant for X activating Y

K_xz = 0.1 ; effective affinity constant for X activating Z

K_yz = 0.5 ; effective affinity constant for Y activating Z

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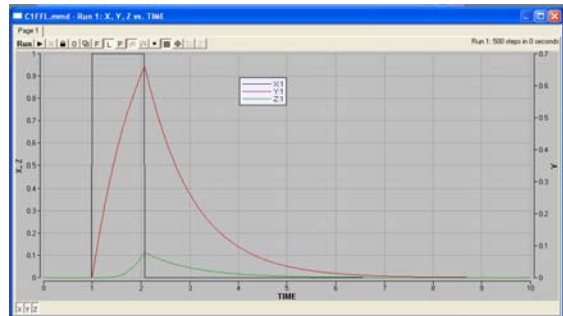
C1FFL.mmd



- Run C1FFL; units are arbitrary as in other models, reflecting time, mass, and binding affinities
- Use sliders with t_{dur} , n , K_{yz} ; evaluate expression of Z
- What behaviors can you coax from the circuit?
- What challenges do these filtered responses pose for assessing risks of exposures to chemicals?

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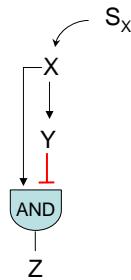
C1FFL.mmd



- Did you find a parameter range that filtered out pulse for Z ?
- Use a constant t_{dur} and model a transient peak of Z
- Use sliders with t_{dur} , n , K_{yz} ; evaluate expression of Z
- What parameters control the filtering in the circuit motif?

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Incoherent FFL Type I



• Notice differences in model schematic

• Impose an X-input to the system

•
$$\frac{dY}{dt} = B_Y + \beta_Y \cdot \frac{X^n}{K_{XY}^n + X^n} - \alpha_Y \cdot Y$$

•
$$\frac{dZ}{dt} = B_Z + \beta_Z \cdot \frac{X^n}{K_{XZ}^n + X^n} - \alpha_Z \cdot Z$$

• Open Exercises/Wednesday/I1FFL.mmd

I1FFL.mmd

;Equations

X = squarepulse(t_start, t_dur) ; pulse of magnitude 1

d/dt(Y) = B_y + beta_y*(X^n/(K_xy^n+X^n)) - alpha_y*Y

d/dt(Z) = B_z + beta_z*(X^n/(K_xz^n+X^n)) - alpha_z*Z

;Initial conditions

init Y = 0

init Z = 0

;Parameters

t_start = 1

t_dur = 3

n=2 ; Hill-coefficient for gene activation/inhibition

beta_y = 1 ; X-activated transcription rate constant for Y

beta_z = 1 ; X- and Y-regulated transcription rate constant for Z

alpha_y = 1 ; degradation rate constant for y

alpha_z = 1 ; degradation rate constant for z

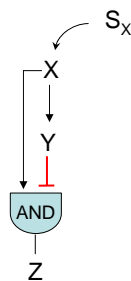
B_y = 0 ; basal transcription rate for Y

B_z = 0 ; basal transcription rate for Z

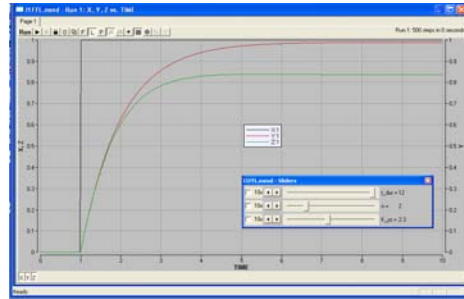
K_xy = 0.1 ; effective affinity constant for X activating Y

K_xz = 0.1 ; effective affinity constant for X activating Z

K_yz = 0.5 ; effective affinity constant for Y inhibiting Z



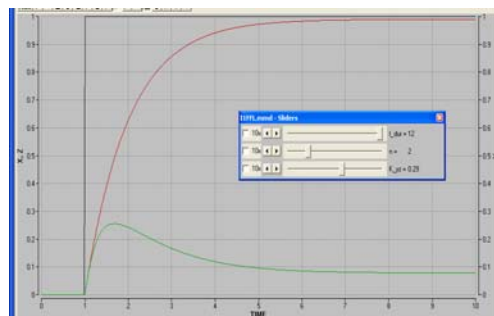
I1FFL.mmd



- Open I1FFL; units are arbitrary as in other models, reflecting time, mass, and affinities
- Add code to create the incoherent relationship; run
- Use sliders with t_{dur} , n , K_{yz} ; evaluate expression of Z
- What behaviors can you coax from the circuit in relation to Z ? Why would you design a circuit of this type?

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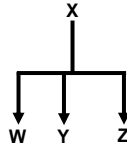
I1FFL.mmd



- Did you find a parameter range with a transient pulse?
- Use a constant t_{dur} and model a transient peak of Z
- Use sliders with t_{dur} , n , K_{yz} ; evaluate expression of Z
- What parameters affect the steepness of the peak?

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A new model – what's this one doing?



;Equations

X = squarepulse(t_start, t_dur) * Conc ; pulse of magnitude (Concentration)

d/dt(W) = B_w + beta_w*(X^nw/(K_xw^nw+X^nw)) - alpha_w*W

d/dt(Y) = B_y + beta_y*(X^ny/(K_xy^ny+X^ny)) - alpha_y*Y

d/dt(Z) = B_z + beta_z*(X^nz/(K_xz^nz+X^nz)) - alpha_z*Z

;Initial conditions

init W = 0

init Y = 0

init Z = 0

;Parameters

t_start = 1

t_dur = 3

Conc = 1.0

nw=2

ny=2

nz=2

beta_w = 1

beta_y = 1

beta_z = 1

alpha_w = 1

alpha_y = 1

alpha_z = 1

B_w = 0

B_y = 0

B_z = 0

K_xw = 0.1

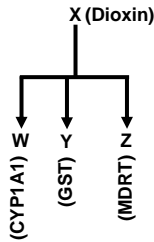
K_xy = 0.1

K_xz = 0.5

;the activating concentration of the stimulus
 ; Hill-coefficient for gene activation for W
 ; Hill-coefficient for gene activation for Y
 ; Hill-coefficient for gene activation for Z
 ; X-activated transcription rate constant for W
 ; X-activated transcription rate constant for Y
 ; X-activated transcription rate constant for Z
 ; degradation rate constant for W
 ; degradation rate constant for Y
 ; degradation rate constant for Z
 ; basal transcription rate for W
 ; basal transcription rate for Y
 ; basal transcription rate for Z
 ; effective affinity constant for X activating W
 ; effective affinity constant for X activating Y
 ; effective affinity constant for X activating Z

Open Exercises/Wednesday/Sequential.mmd

Make it more structured.



;Equations

X = squarepulse(t_start, t_dur)*Conc ; pulse of toxicant (e.g., dioxin) in body

d/dt(CYP1A1) = B_w + beta_w*(X^nw/(K_xw^nw+X^nw)) - alpha_w*CYP1A1

d/dt(GST) = B_y + beta_y*(X^ny/(K_xy^ny+X^ny)) - alpha_y*GST

d/dt(MDRT) = B_z + beta_z*(X^nz/(K_xz^nz+X^nz)) - alpha_z*MDRT

;Initial conditions

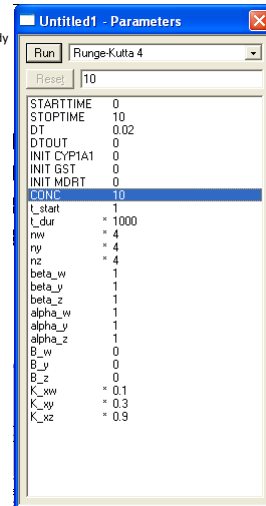
init CYP1A1 = 0

init GST = 0

init MDRT = 0

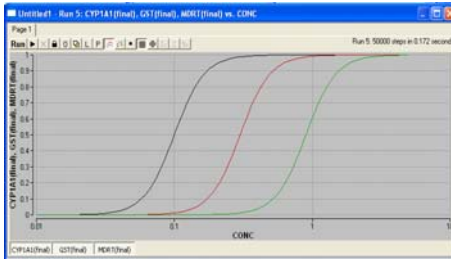
;Parameters

t_start = 1 ; time of introduction of dioxin (X) in the target tissue
 t_dur = 3 ; duration of dioxin (X) in the target tissue
 Conc=10 ; concentration of dioxin in the target tissue
 nw=2 ; Hill-coefficient for activation of CYP1A1 gene
 ny=2 ; Hill-coefficient for activation of GST gene
 nz=2 ; Hill-coefficient for activation of MDRT gene
 beta_w = 1 ; X-activated transcription rate constant for CYP1A1
 beta_y = 1 ; X-activated transcription rate constant for GST
 beta_z = 1 ; X-activated transcription rate constant for MDRT
 alpha_w = 1 ; degradation rate constant for CYP1A1
 alpha_y = 1 ; degradation rate constant for GST
 alpha_z = 1 ; degradation rate constant for MDRT
 B_w = 0 ; basal transcription rate for CYP1A1
 B_y = 0 ; basal transcription rate for GST
 B_z = 0 ; basal transcription rate for MDRT
 K_xw = 2.5 ; effective affinity constant for X activating CYP1A1
 K_xy = 10 ; effective affinity constant for X activating GST
 K_xz = 50 ; effective affinity constant for X activating MDRT



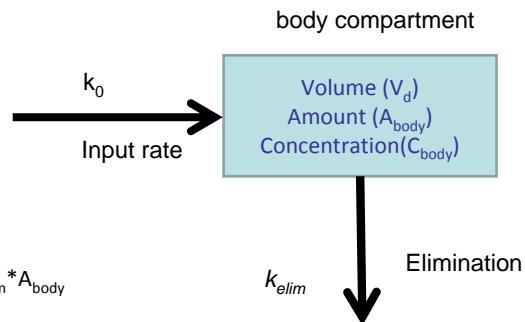
Sequential.mmd

Make it more structured.



- What do you need to do to get a plot of the activation of the three gene products with these shapes?
- Try different parameters and see how the curve shape changes.
- In a test tube in vitro we could impose a concentration on a group of hepatocytes and then change media, how would we change the model for dosing, distribution and elimination of dioxin?

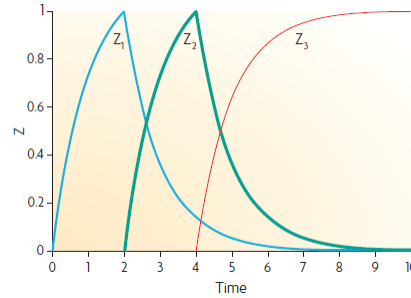
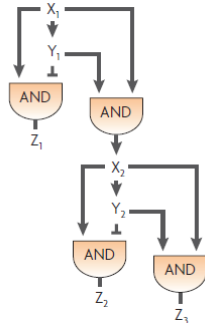
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- $d/dt(A_{\text{body}}) = k_0 - k_{\text{elim}} * A_{\text{body}}$
- $C_{\text{body}} = A_{\text{body}}/V_d$
- $\text{Init } A_{\text{body}} = 0.0$
- How would you add to sequential model?
- Where have you seen this "motif"?

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“Developmental Cascade”

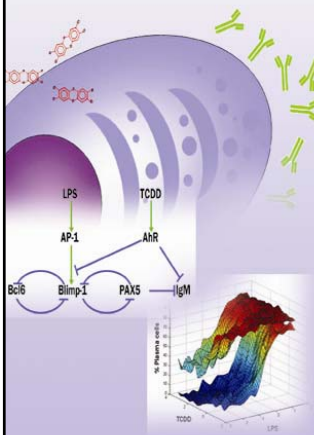


- What equations do we need?
- $X_1, Y_1, Z_1, X_2, Y_2, Z_2,$ and Z_3
- How would you describe chemical perturbations in the network?

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Some comments



- Even complex networks will be constructed from repeating motifs
- While simplified in their equations, these ‘empirical’ descriptions of switches and ultrasensitivity can help us understand motif dynamics
- Dose response analysis requires us to think about the circuit structure and the perturbation to be introduced
- Try adding chemical kinetics in the sequential motif yourself

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