

**Truly individualized systems medicine:
a hands-on tutorial
where participants will resolve paradoxes
by using virtual twin/digital-me**

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CaSyM Workshop on

Modeling Tools for Pharmacokinetics and Systems Medicine,
18 May 2014, Stuttgart

By way of introduction

The implications of networks for
disease:

Towards personalized medicine



LAKE COMO SCHOOL OF ADVANCED STUDIES

Systems Biology and Systems Medicine: Precision Biotechnology and Therapies

Lake Como, Italy, 21-27 September 2014

Despite omics' BIG DATA, molecular biology is not yet able to understand complex biological functions, cell factories, and multifactorial diseases (cancer, neurodegeneration). The School will explicate Systems Biology's experimental and computational approaches that together will enable the participant to begin to tackle the complex networks of life, hands-on. Computable representations of systems biology integration are about to unleash revolutions in fundamental biology, predictable biotechnology and individualized medicine.

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Matteo Barberis (Univ. of Amsterdam) Damjana Rozman (Univ. of Ljubljana)
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Sponsors



Course: Systems Biology and Systems Medicine

Similar tutorial rich format

But

Much more

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By way of introduction

The implications of networks for disease
Teaching the implications of networking for an
example that is relevant for oncology:
The MAP kinase (EGFR) signal transduction pathway

Life sciences did not yet pay off for medicine because their paradigm entailed:

Nutrient 1 → Gene 1 → function 1
Nutrient 2 → Gene 2 → function 2
Nutrient 3 → Gene 3 → function 3
Nutrient 4 → Gene 4 → function 4

If this this were true:

- Organism with 100 functions should have 100 genes
- Every disease caused by a single gene/nutrition defect
- Gene/nutrition defect causing a disease should always be the same

Systems Biology has shown that reality is

Nutrient 1 → Gene 1 → Gene 2 → Gene 3 → function 1

Nutrient 2 → Gene 1 → Gene 4 → Gene 5 → function 2

Nutrient 3 → Gene 3 ↑

Nutrient 1 → Gene 6 → function 3

Hence:

organism with 100 functions should **NOT** have 100 genes

Every disease need **NOT** already be caused by a single gene/nutrition defect

The gene/nutrition defect causing a disease need **NOT** be always the same

Could there still be a 1-1 relationship between gene and function because each pathway has a single rate-limiting step??

Food 1 → Gene 1 → Gene 2 → Gene 3 → function 1

Food 2 → Gene 4 → Gene 5 → Gene 6 → function 2

Food 3 → Gene 7 → Gene 8 → Gene 9 → function 3

How do we figure out whether an enzyme is fully rate-limiting for a pathway flux?

Food 1 → Gene 1 → Gene 2 → Gene 3 → function 1

Remove the enzyme and measure whether the flux changes

Food 1 → → Gene 2 → Gene 3 → funXction 1

Yes, no flux possible.

How do we figure out whether an enzyme is fully rate-limiting for a pathway flux?

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Yes, no flux possible.

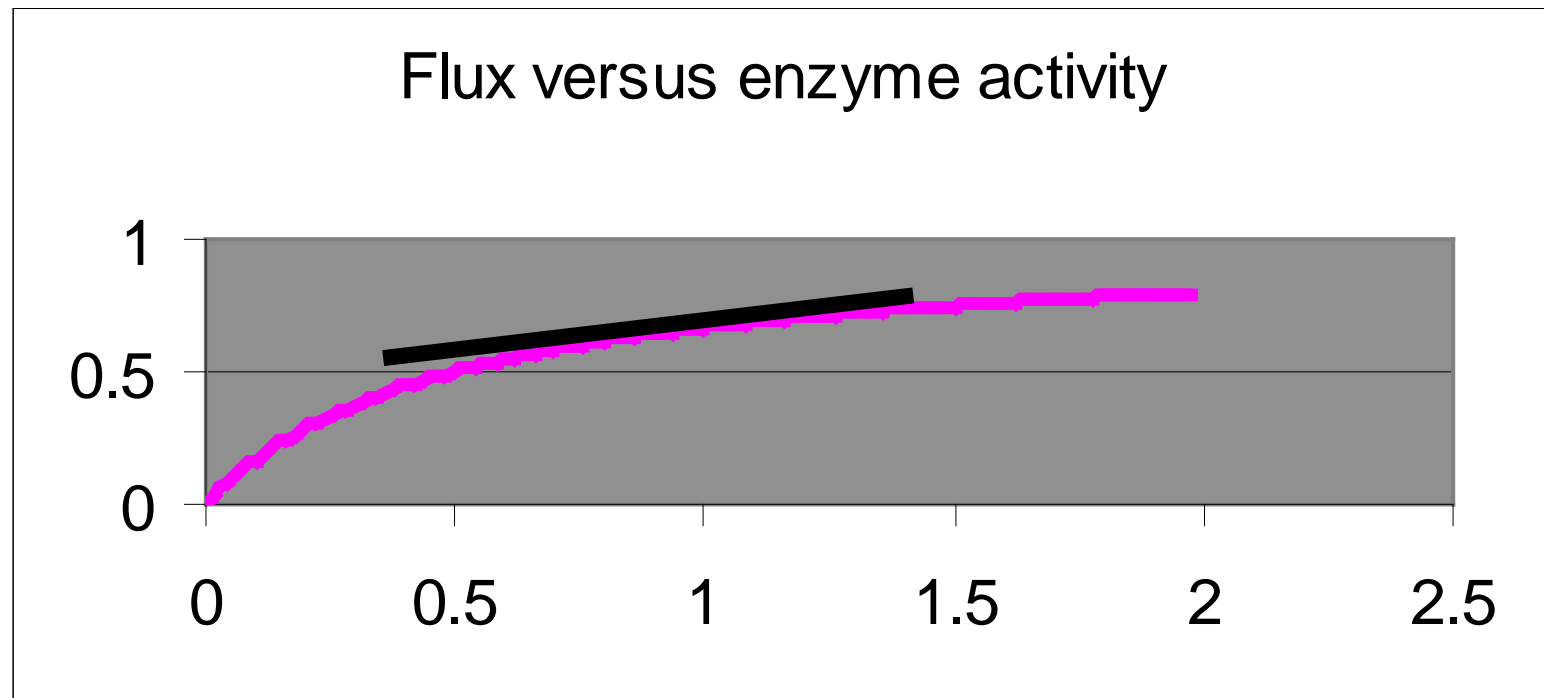
However, this is true for all genes:

Food 1 → Gene 1 → → Gene 3 → funXction 1

Food 1 → Gene 1 → Gene 2 → → funXction 1

By this criterion, all enzymes are the rate-limiting step:
therefore knock out is NOT a good strategy for this;
But a slight-knock-down strategy is a good strategy

How does function depend on gene dosage?

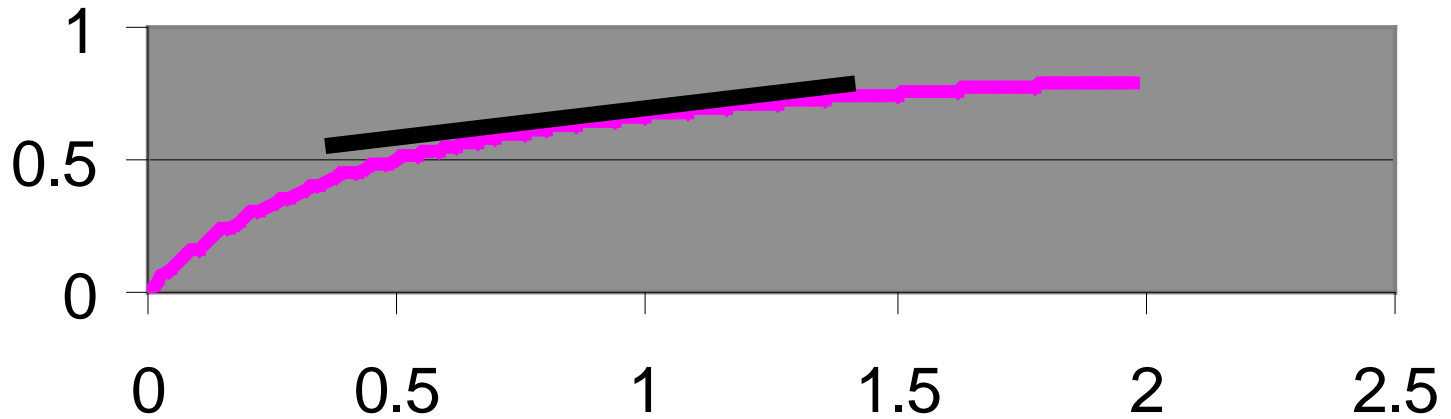


The Flux Control Coefficient C

$$\frac{\%dJ}{1\%de_i}$$

%change in flux
upon a 1 %
change in
enzyme activity

Flux J versus enzyme activity e_i

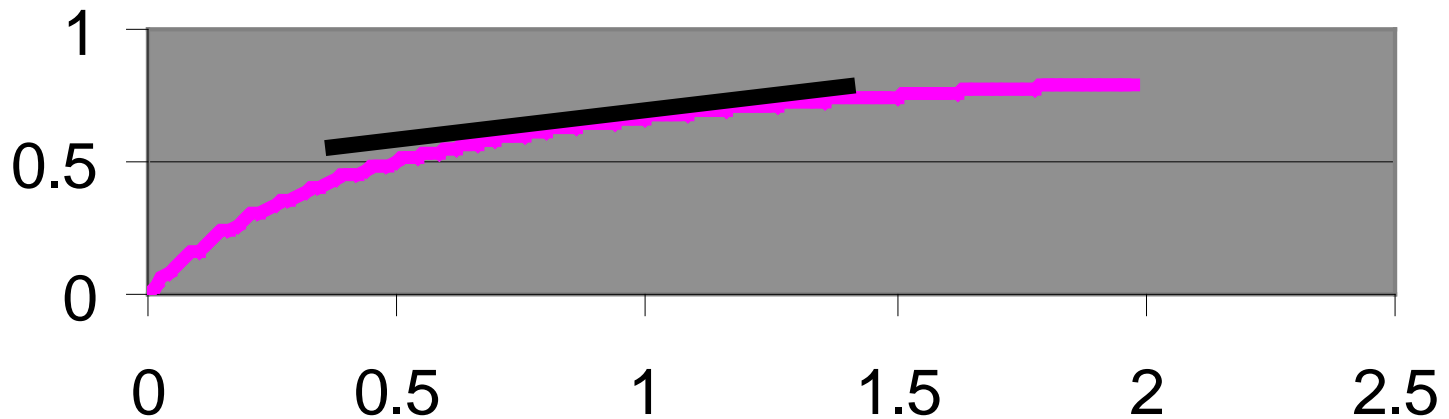


The Control Coefficient C

$$\frac{\frac{dJ}{J}}{\frac{de_i}{e_i}} = \frac{\%dJ}{1\%de_i}$$

%change in flux
upon a 1 %
change in
enzyme activity

Flux J versus enzyme activity e_i

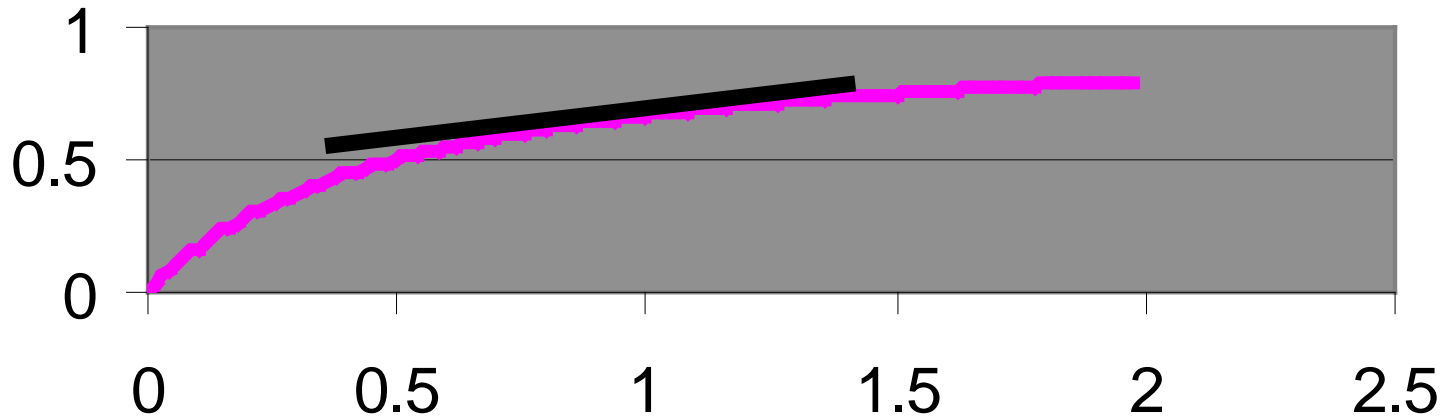


The Control Coefficient C

$$\left(\frac{d \ln |J|}{d \ln e_i} \right)_{steady\ state} = \frac{dJ/J}{de_i/e_i} = \frac{\%dJ}{1\%de_i}$$

%change in flux
upon a 1 %
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Flux J versus enzyme activity e_i

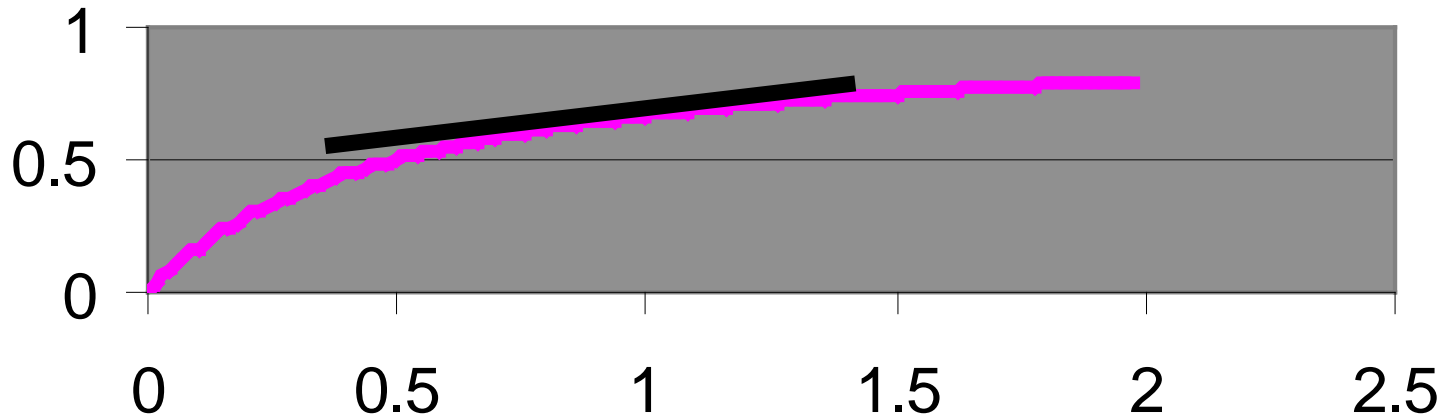


The Control Coefficient C

$$C_i^J = \left(\frac{d \ln |J|}{d \ln e_i} \right)_{steady\ state} = \frac{dJ/J}{de_i/e_i} = \frac{\%dJ}{1\%de_i}$$

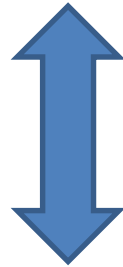
%change in flux
upon a 1 %
change in
enzyme activity

Flux J versus enzyme activity e_i



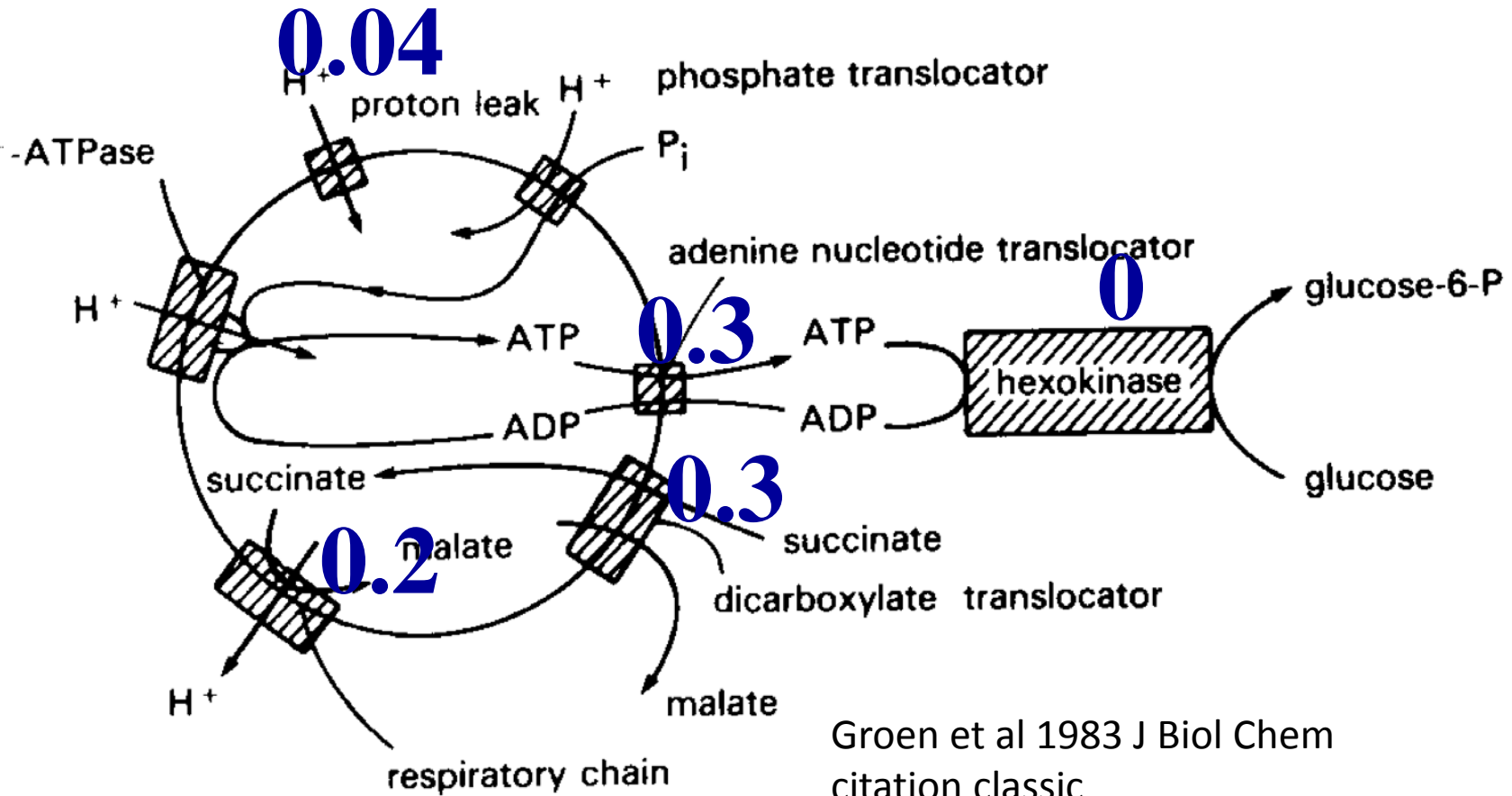
Now we have a way to test whether pathways have a single rate limiting step

- If so, then one C equals 1 and all others zero.



- If not, then various C 's may have values in between 1 and 0

Experimental: mitochondrial respiration



Biology is too subtle to have one single rate-limiting step for each pathway/function;
Therefore: **NOT 1 gene – 1 function**; but each function is determined by a network



OK, if it *is* networks

then deal with it as networks

We will now deal with the MAPkinase cascade

Target for many precision anti-cancer drugs
Because the dynamics of ERK-P is involved
in differentiation versus proliferation

Precision models have been
made for this pathway

De Graaf et al (Astra Zeneca)

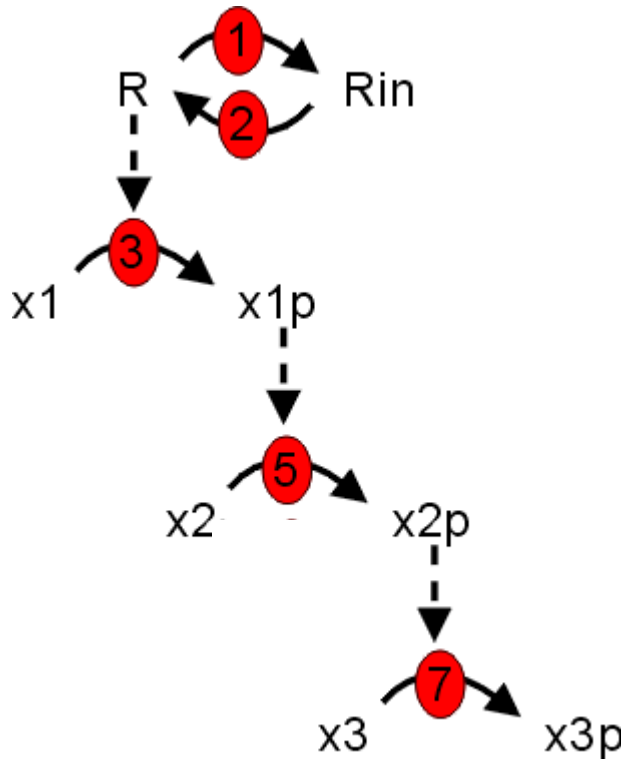
Kholodenko et al (Dublin)

Lauffenburger et al (Boston)

Hornberg et al (Amsterdam)



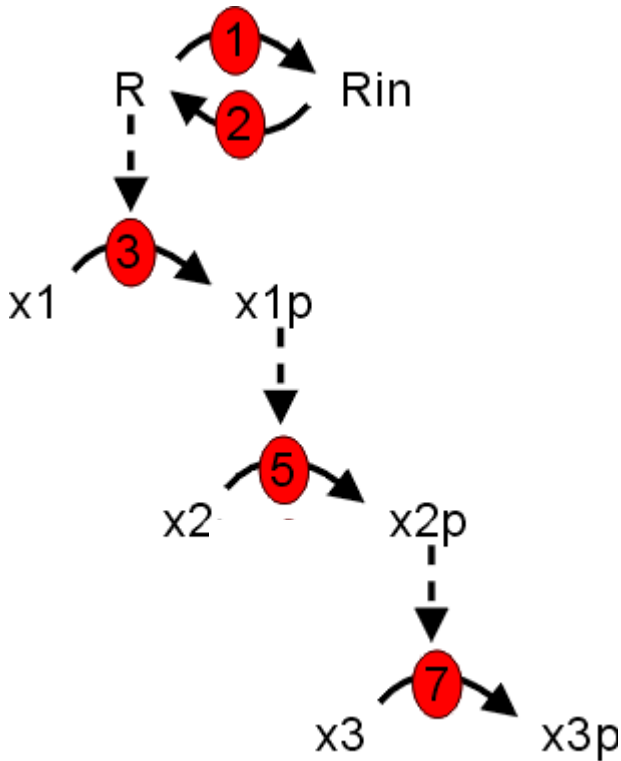
Strategy



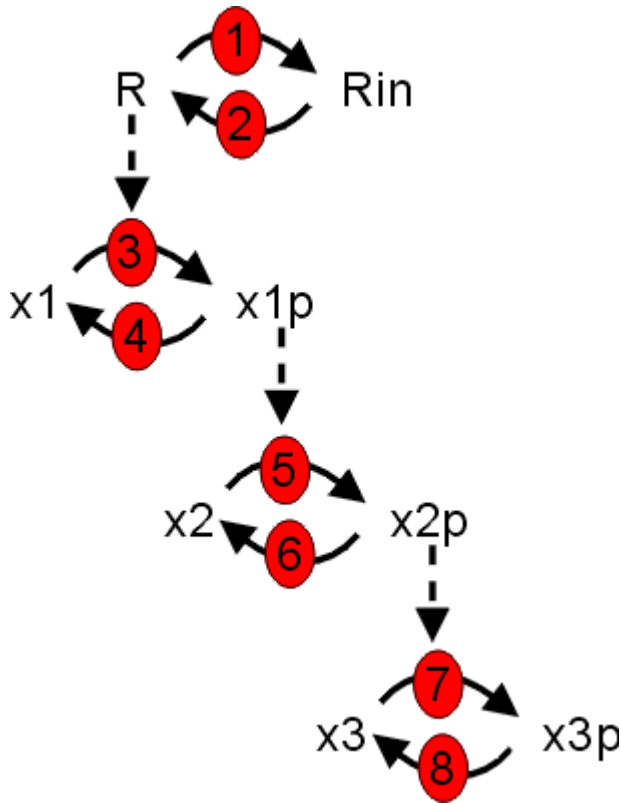
- Map the pathway
- Write rate equation for each step
- Let the computer play the pathway game

Strategy

- R= EGFR
- x1 is RAF
- x2 is MEK
- x3 is ERK



The simplest version for now:



- $v[1] = Vm1 * R[t] / (Km1 + R[t])$
- $v[2] = Vm2 * Rin[t] / (Km2 + Rin[t])$
- $v[3] = k3 * R[t] * x1[t] / (Km3 + x1[t])$
- $v[4] = Vm4 * x1p[t] / (Km4 + x1p[t])$
- $v[5] = k5 * x1p[t] * x2[t] / (Km5 + x2[t])$
- $v[6] = Vm6 * x2p[t] / (Km6 + x2p[t])$
- $v[7] = k7 * x2p[t] * x3[t] / (Km7 + x3[t])$
- $v[8] = Vm8 * x3p[t] / Km8 / (1 + x3p[t] / Km8 + Inh / Ki8)$

Good news for you

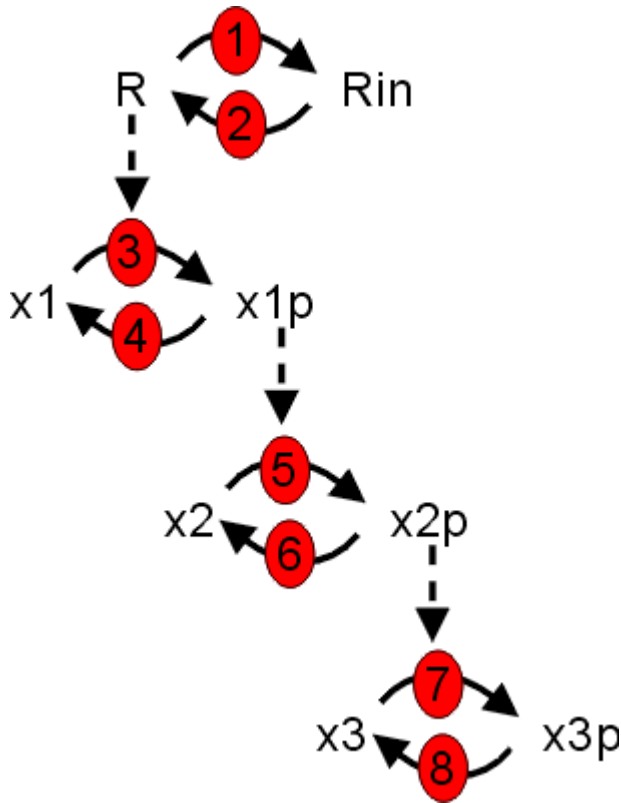
You do not need to model

Just work with a model we made

Use it as a replica of reality

To discover network behavior

The simplest version for now:



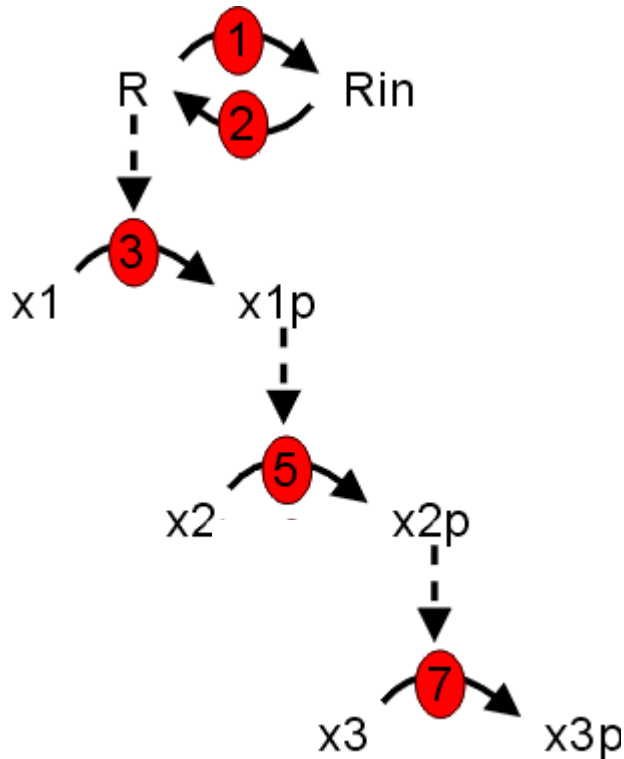
- $v[1] = Vm1 * R[t] / (Km1 + R[t])$
- $v[2] = Vm2 * Rin[t] / (Km2 + Rin[t])$
- $v[3] = k3 * R[t] * x1[t] / (Km3 + x1[t])$
- $v[4] = Vm4 * x1p[t] / (Km4 + x1p[t])$
- $v[5] = k5 * x1p[t] * x2[t] / (Km5 + x2[t])$
- $v[6] = Vm6 * x2p[t] / (Km6 + x2p[t])$
- $v[7] = k7 * x2p[t] * x3[t] / (Km7 + x3[t])$
- $v[8] = Vm8 * x3p[t] / Km8 / (1 + x3p[t] / Km8 + Inh / Ki8)$

**The idea is that you forget about the math,
just use the model as if it is an experiment**

Our aim is to show how these models can be used to

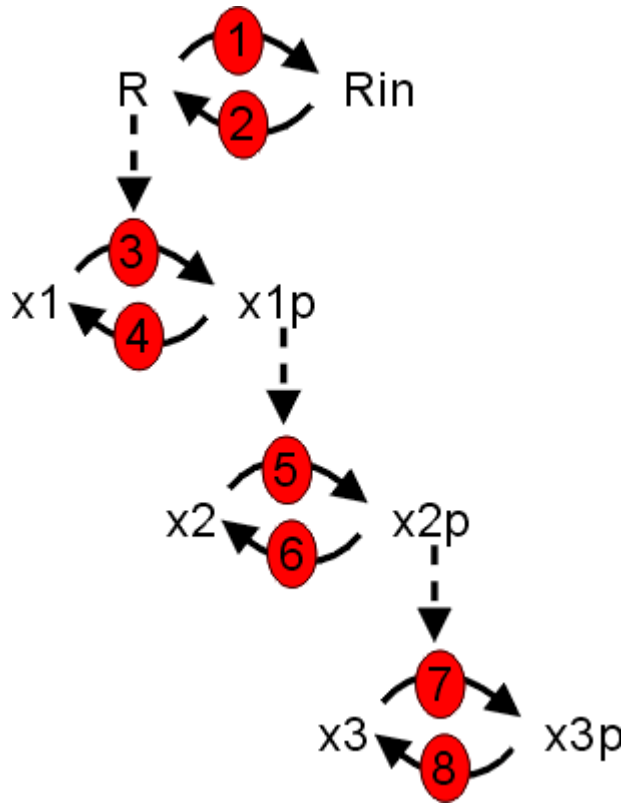
resolve paradoxes by looking at reality through virtual reality (i.e. precise models of reality)

Paradox 1



- In most textbooks these routes are shown like this.
- Does this make sense?

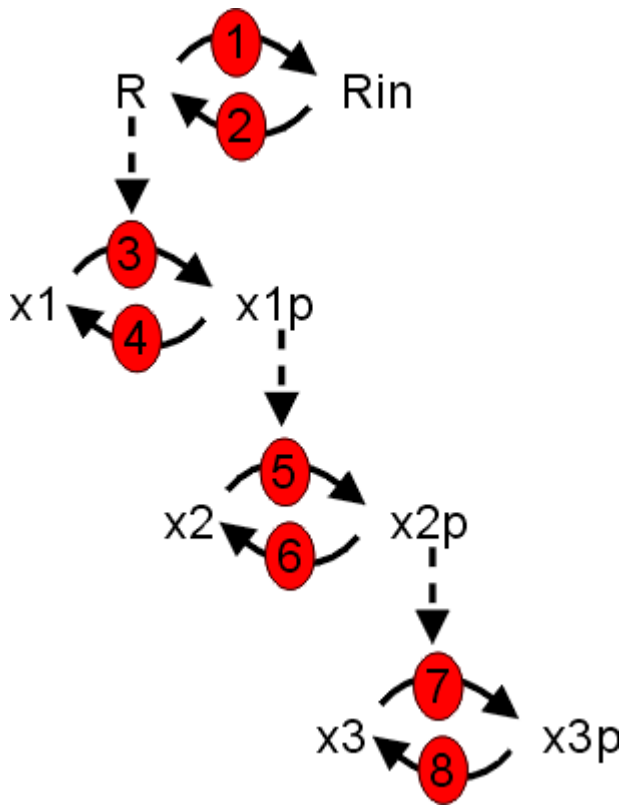
Paradox 2:



- Is only the first kinase the limiting step? Because once this has been set in motion the rest is inescapable.
- Yet, all three kinases have been reported as oncogenes.
- Paradox?

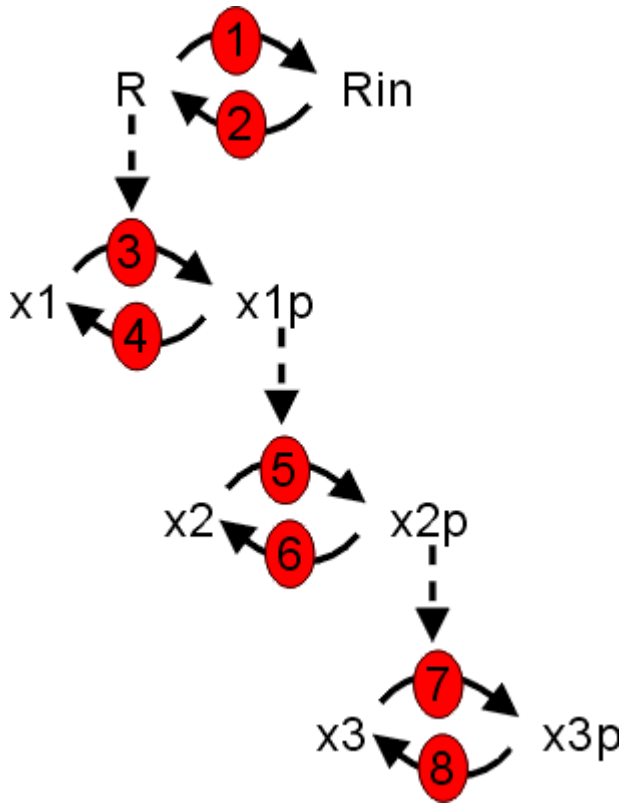
Paradox 3:

- Are the phosphatases at all important? Surely not, as they only work negatively. (??)



Paradox 4:

- Could the phosphatases be more important than the kinases? Surely not, at most equally important (??)



Well, please sort this out
yourselves...

By using:

- **the modelling handout ‘Interrogating a simple MAP kinase network in a silicon cell model’ (below)**
- **Your PC**
- **The model through the network (www or local)**

1. Getting the silicon cell environment

up and running

- Go to web browser:
- Google for JWS online or move directly to <http://jij.bio.vu.nl/index.html> , or, if a local web has been set up, type <http://jij.local> or to <http://192.168.0.1> in your browser window .
- Click model database.
- At keyword search replace 'Model name' with 'Author' and replace 'Enter the keyword' with 'Westerhoff'. Then click 'submit'
- At the homo sapiens line, on the far right, click: **run v1.0.**
- Accept risks, click *do not show*, and **run** if asked in subsequent windows about accepting all risks.
- Next a window should appear (see right) with: On the left a subwindow with parameter values; in the middle a subwindow headed by the button 'evaluate model', and on the right a subwindow with a diagram of the pathway (see the screenshot) [If the middle panel does not show correctly, adjust the browser's zoom (click page then click zoom)].

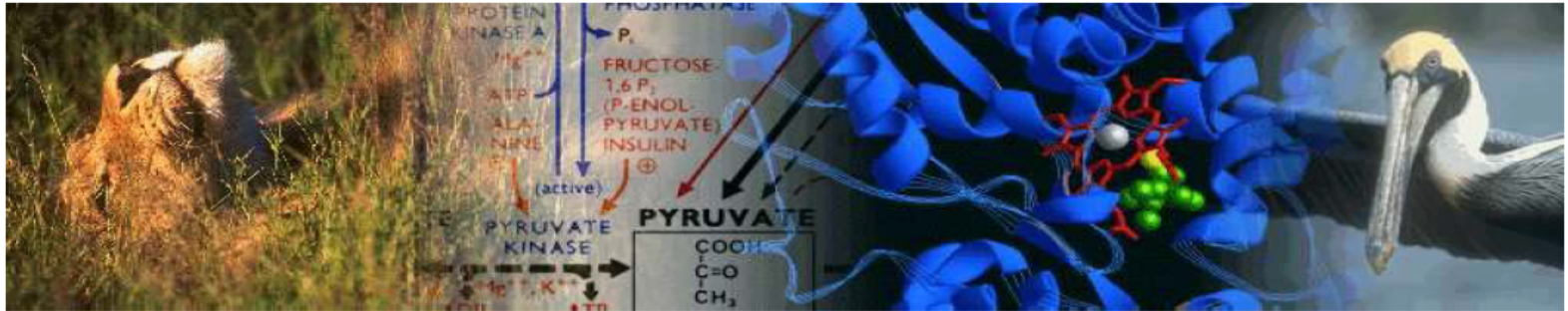
JWS Online - hornberg model

The screenshot displays the JWS Online interface for the 'hornberg model'. At the top, there is a navigation bar with links for Home, Model Database, Project Info, News, Upload, and Help. Below this is a banner image featuring a bird and a metabolic pathway diagram. The main content area is divided into three panels:

- Left Panel:** A table of parameter values for the model. The table has columns for Parameter, Value, and a checkbox for 'Estimate Model'.
- Middle Panel:** A subwindow titled 'Evaluate Model' with a 'Sim' button and a 'State' dropdown menu. It also includes a 'Start Time' and 'End Time' field.
- Right Panel:** A metabolic pathway diagram showing a sequence of reactions. The diagram includes metabolites labeled R, R_{in}, x₁, x₁p, x₂, x₂p, x₃, and x₃p. Reactions are represented by red circles with arrows indicating the direction of flow.

Below the main content area, there is a 'JWSAPPLET' label and a 'Reset' button.

JWS Online - hornberg model



Home

Model Database

Project Info

News

Upload

Help

Online servers

JWSApplet - ver 5.0.7c hornberg

Parameter	Value
P1_v1	Vm1 1
P2_v1	Km1 0.1
P3_v1	Vm2 0.01
P4_v1	Km2 0.1
P5_v1	k3 1
P6_v1	Km3 0.1
P7_v1	Vm4 0.3
P8_v1	Km4 1
P9_v1	k5 1
P10_v1	Km5 0.1
P11_v1	Vm6 0.3
P12_v1	Km6 1
P13_v1	k7 1
P14_v1	Km7 0.1
P15_v1	Vm8 0.3
P16_v1	Km8 1
P17_v1	Ki8 1
P18_v1	Inh 0
I1	R[0] 0.5
I2	x1[0] 1

POWERED BY **Wolfram** webMathematica

Evaluate Model

Sim State MCA

StartTime: 0 EndTime: 10

Rates Metabolites

Type	Output	Plot
M1	R	<input checked="" type="checkbox"/>
M2	x1	<input checked="" type="checkbox"/>
M3	x2	<input checked="" type="checkbox"/>
M4	x3	<input checked="" type="checkbox"/>
M5	Rin	<input checked="" type="checkbox"/>
M6	x1p	<input checked="" type="checkbox"/>
M7	x2p	<input checked="" type="checkbox"/>
M8	x3p	<input checked="" type="checkbox"/>
F1	v[1]	<input checked="" type="checkbox"/>
F2	v[2]	<input checked="" type="checkbox"/>
F3	v[3]	<input checked="" type="checkbox"/>
F4	v[4]	<input checked="" type="checkbox"/>
F5	v[5]	<input checked="" type="checkbox"/>
F6	v[6]	<input checked="" type="checkbox"/>

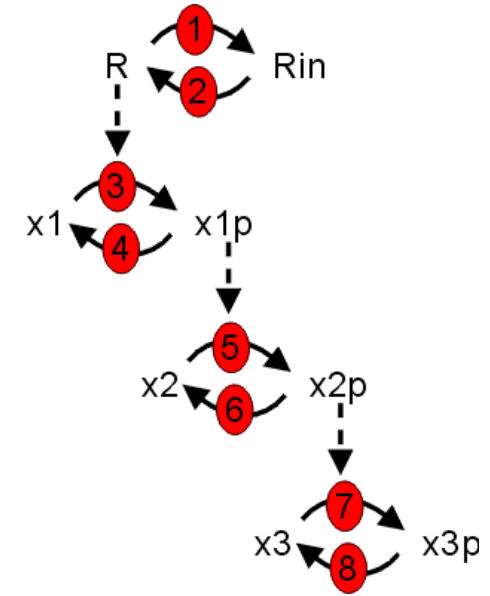
Hover over a reaction to view details.
Doubleclick on image to view in new window.

JWSAPPLET

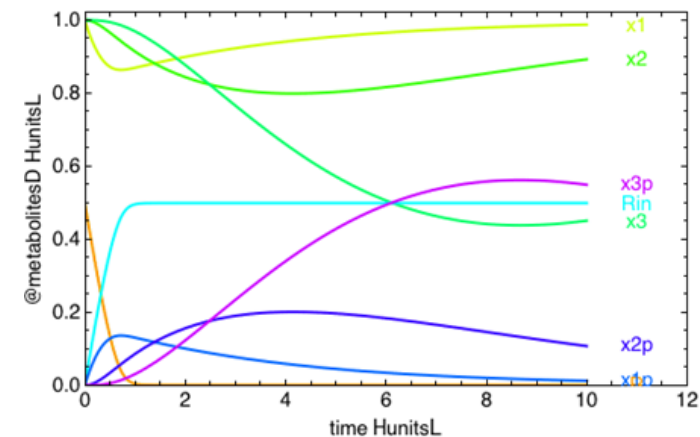
1b. If you do not see the three windows (e.g. only a pathway window on the right)

- The picture may not show, with an error message. This has to do with computers not accepting Java applications any more.
- If this happens, make sure you use the Amsterdam online server (upper right box) (or if not, see below) (browser address jjj.bio.vu.nl etc)
- Then do the following;
- *Click 'system preferences' (clockwork icon) for Apple or Control Panel for PC. Click the Java (coffee cup) icon (the word Java next to it on PC) [In case you do not have this icon, you may need to download Java: type Java download in your internet browser window and proceed from there to download]. Click Security. Click Edit Site List. Click Add. Type <http://jjj.bio.vu.nl> (to use the Amsterdam site) Click Add. Type <http://jjj.mib.ac.uk> (no blue or underlining typing necessary) to use the Manchester site), or <http://jjj.biochem.sun.ac.za> to use the Stellenbosch site. In case you use the server you set up yourself, also add its address, e.g. <http://192.168.1.60> (or ask the tutor). Click OK. (You may now repeat this for the other two sites for you to become site independent). Click Continue. Click OK. Retrace a step in the above sequence (or start all-over) and click run v1.0. Now you should see the diagrams.*

2a. The standard state of the model pathway

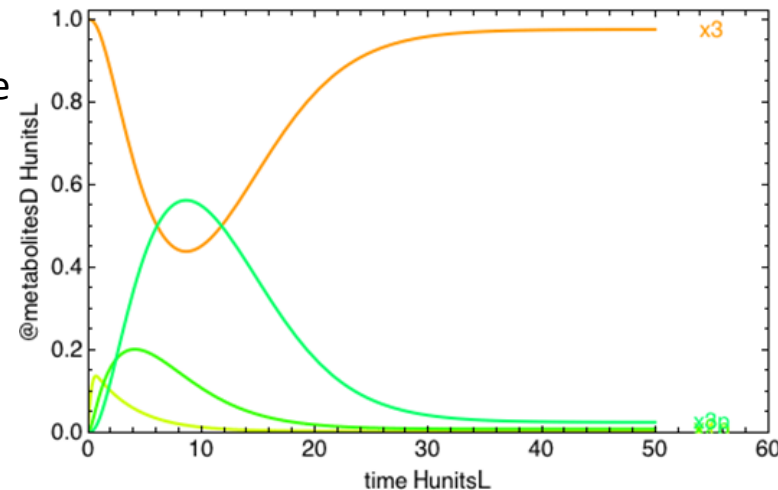
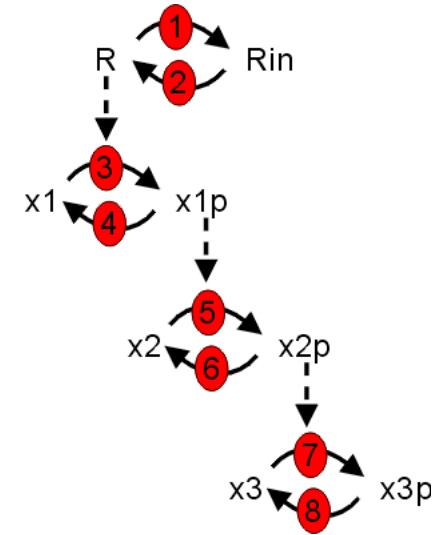


- The model will work such that at $t=0$ a certain amount of R (membrane receptor, e.g. EGFR) is formed instantaneously, after which the ligand (EGF) that activated Rin to become R, disappears rapidly; R should decay quickly to Rin.
- Please click '*evaluate model*' in the web browser and examine if this is indeed what happens. [Note that a message saying that the pop-up window has been blocked may appear; follow this up and accept all pop up windows from the jjj site]. A new window will appear in which all concentrations are shown as functions of time (see the screen shot). Note that indeed the dark yellow line for R goes quickly to zero and Rin becomes 0.5 within a minute.



2b. The standard state of the model pathway

- Return to the previous window with the three subwindows.
- Now, in the JWS window, change the parameter 'end time' from 10 to 50, by putting your cursor behind the zero of 10, back delete the 10 and then type 50 and then press *Enter* on your keyboard.
- Press 'evaluate model' and notice that the simulation is repeated but now for a longer time.
- Below 'evaluate model', there is a column called 'plot', with little $v(v)$'s in squares. Click on each of these v 's (only required for the metabolites M), except for the ones for $x1p$, $x2p$, $x3$ and $x3p$. Then again click 'evaluate model'.
- At the bottom of the figure that then appears (see screen shot on the right) you should see three waves. The first one is that of $x1p$, the second one is that of $x2p$ and the third one is the wave of $x3p$. They peak at 0.5, 4 and 9 time units, respectively.
- Please explain in words why the activation of $x3$ is much delayed as compared to that of the receptor and $x1$.
- Had you expected all three amplitudes for $x1p$, $x2p$ and $x3p$ to be equally high? Why are they not so?

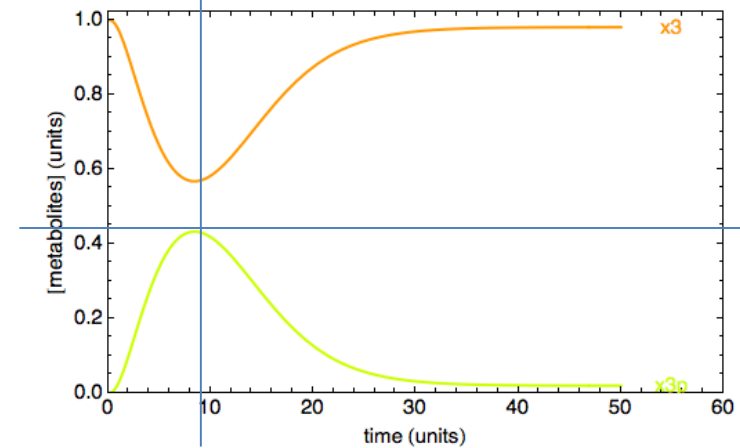
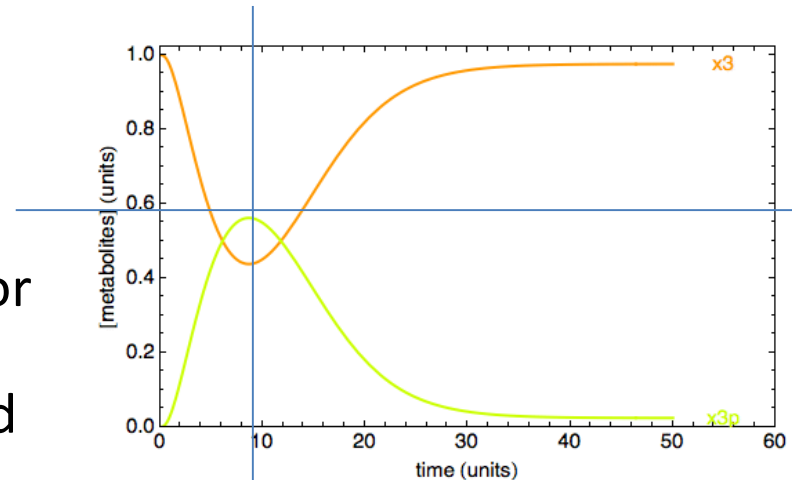


3a. The effect of kinase activities on x3p (ERK-P)

Click on each of the v 's for x1p and x2p, maintaining the ones for x3 and x3p. Then again click 'evaluate model'. You should now get a window showing only the time dependence of x3p and x3, which are mirror images. Why should they be?

Please note down the amplitude of x3p and also the time at which this amplitude is achieved. We find 0.56 and 9.0, respectively.

Now inhibit the activity of the second kinase activity (x1P carrying out reaction v_5) by reducing $k_5 (=V_{\max 5})$ from 1 to 0.8. Then click 'Evaluate model'. What has changed in the curve for x3p? Amplitude is now 0.44 at $t=8$. What had you expected for an inhibition of the second kinase activity?
Compare your expectations with the results.



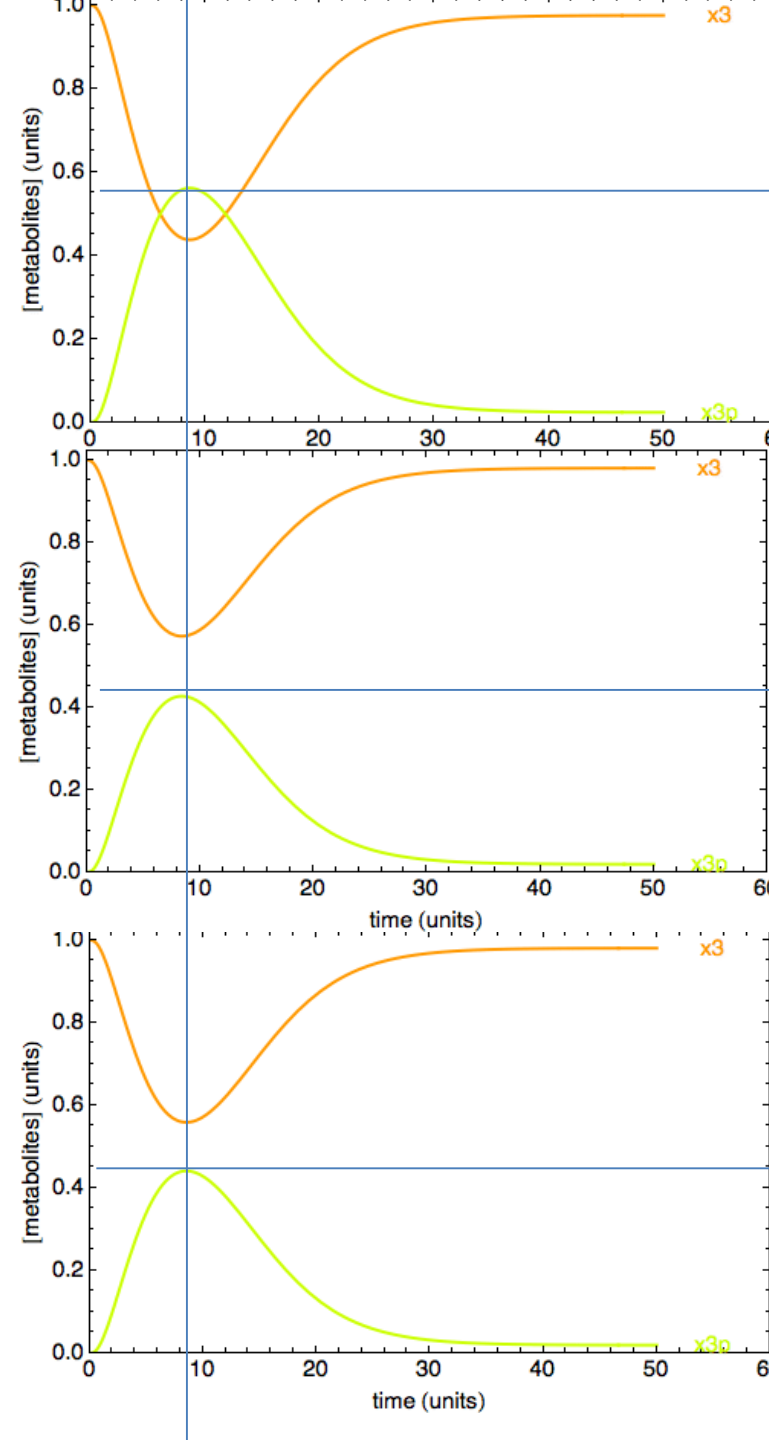
3b. The effect of kinase activities on x3p (ERK-P)

We may conclude that the second kinase has a strong control on the *amplitude* of the peak of x3p. Kinases are important for signal transduction. What was perhaps more surprising, is the lack of control of the second kinase over the time and *duration* of the x3p peak.

Please do the corresponding *in silico* experiments in order to examine how the other two kinases control the amplitude and timing of x3p. Discover that the kinases control the amplitude of the peak of x3p but neither the time at which the peak occurs nor the half-life (decay) of the peak. Also note that all three kinases appear to be in control, not just the first one; there is no single limiting, controlling step for x3p-amplitude.

Inhibit the first and the last kinase by 20%

Top: no inhibition,
middle first kinase, and
bottom, third kinase inhibited by 20%



3c. The effect of kinase activities on x3p (ERK-P)

- How would you define a quantitative measure for the control of kinase 2 over the amplitude of the x3p peak? Think of a 1 % decrease of k5 and then..... How has this type of coefficient been called? Please write a definition here:

3d. The effect of kinase activities on x3p (ERK-P)

- How would you define a quantitative measure for the control of kinase 2 over the amplitude of the x3p peak? Think of a 1 % decrease of k5 and then..... How has this type of coefficient been called? Please write a definition here:
- Control: The percentage increase in peak amplitude for a 1% activation of the kinase V_{\max} or k_{cat} . Or the % decrease in amplitude for a 1 % decrease in kinase V_{\max} . This has been called the control coefficient.
- $C_{\text{kinase}}^{x3p_{\max}} \stackrel{\text{def}}{=} \%$ decrease in amplitude for 1 % inhibition of kinase
- $= \frac{d(\text{amplitude})/\text{amplitude}}{dk_5/k_5} = \frac{d\ln(\text{amplitude})}{d\ln(k_5)}$ at the peak

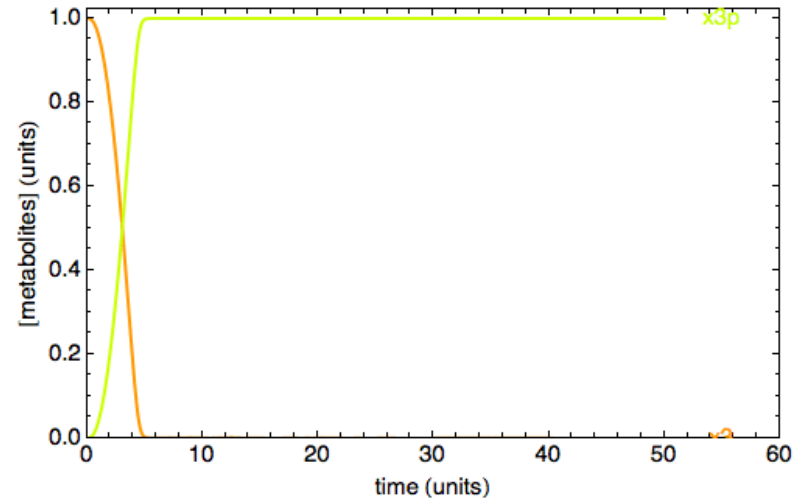
3e. The effect of kinase activities on x_{3p} (ERK-P): control coefficient

- It is hard to read values when changes are 1 % only. Estimate the value of the amplitude of x_{3p} for $k_5=1$ and for $k_5=0.8$ and estimate the magnitude of the control of k_5 on that amplitude, following the above definition.
- We find that the amplitude changes from 0.55 to 0.43, which is a drop by 22 %, hence the control coefficient is $22/20=1.1$; pretty high (110%) control by MEK on ERKPP (x_{3P}).
- Calculate also the control coefficients of the other three kinases and examine whether the sum of the control is lower or higher than 1; is there more than total control by the kinases?

4a. The effect of the phosphatase activities on x3p (ERK-P)

Please click "Reset", and then set Vm4, Vm6 and Vm8 to zero and click 'Evaluate model'. You will find that now x3p increases to 1 and remains 1 forever. Please explain this finding.

Clearly the phosphatases are important for the signal transduction. Do they also exert subtle control however? Click 'Reset', click 'Evaluate model', then increase the Vm8 from 0.3 to 0.6 and click 'Evaluate model'. Again the amplitude is affected (reduced to 0.33), but now the peak occurs earlier (we find at $t=6.3$) and also the life time of the peak is reduced, as is the area under the curve.



4b. The effect of the phosphatase activities on x3p (ERK-P)

To compare the effect of inhibiting the kinases and activating the phosphatases more closely, please click 'Reset', click 'Evaluate model'. Then alter k7 from 1 to 0.3, then click 'Evaluate model', then click reset and increase Vm8 from 0.3 to 1.3 and click 'Evaluate model' and compare the three plots.

When doing all of this one should find for:

- the physiological state: a maximum of 0.55 at time=8 and reduced to half maximal at t=15

- kinase inhibition state: a maximum of 0.15 at time=8 and reduced to half maximal at t=14

- phosphatase activation state: a maximum of 0.15 at time=5 and reduced to half maximal at t=9.

Clearly, both kinase (7) and phosphatase (8) control the amplitude, but the kinase controls neither when the maximum occurs nor the duration of the signal. The phosphatase do control the time of the amplitude and the duration.

By further *in silico* experimentation you may wish to check that the phosphatases control the peak amplitude and its timing. The kinases do not control these timings, only the amplitude.

5. Is a phosphatase just the reverse of the corresponding kinase; i.e. just the corresponding tumour suppressor gene?

We click *Reset* and then increase V_{m8} again from 0.3 to 1.5 and now *increase* the kinase k_7 from 1 to 3. Then we click '*Evaluate model*'. We find that kinase activation only partly compensates for phosphatase activation: the peak amplitude now remains at 0.55, but the peak still occurs much earlier, at $t=7$, and only lasts (half value) to $t=10$, whereas in the standard state the peak had the same amplitude but occurred at $t=8$ and reduced to half maximal at $t=15$. The point can be seen more clearly by combining the results of both simulations into a single excel file.

6a. Individualized medicine

Upon transient stimulation by EGF of the EGF receptor (R), ERK-P undergoes a transient increase. ERK-P is an active transcription factor. There are indications that the height of the ERK-P peak is proportional to the probability of differentiation, whereas the duration of ERK-P activation is proportional to the probability of cell growth and correlates positively with tumorigenesis.

Please click “Reset”. And then plot only x_{3p} , and click Evaluate Model. Use/store this as individual 1.

Then click Reset, and increase k_3 from 1 to 3, and click Evaluate Model. Use/store this as individual 2. This individual has a SNP (mutation) in RAS, doubling its activation of x_1 .

Then click reset, and decrease V_{m4} from 0.3 to 0.1 and click Evaluate Model. Use/store this as individual 3. This individual has a SNP in the phosphatase activity that counteracts RAF.

Discuss which of these three individuals will have an improved function in the sense of improved differentiation.

Discuss which of the three individuals will have an increased probability of contracting cancer.

Discuss how this explains that if more frequent activation of the MAPkinase cascade by EGF is the cause of the cancer, some individuals are much more susceptible than others, and how one may be able to predict this from their SNPs.

6b. Individualized medicine

Upon transient of the EGF receptor (R) stimulation by EGF, ERK-P undergoes a transient increase. ERK-P is an active transcription factor. There are indications that the height of the ERK-P peak is proportional to the probability of differentiation, whereas the duration of ERK-P activation is proportional to the probability of cell growth and may correlate with tumorigenesis.

Please click “Reset” and decrease V_{m8} from 0.3 to 0.1, and click Evaluate Model. Use/store this as individual 4. This individual has a SNP (mutation) in the third phosphatase.

Please discuss that individuals 3 and 4 both have an enhanced risk of contracting cancer. Also note that the corresponding molecular mutation on the phosphatases has more effect when it is on the first phosphatase than when it is on the final phosphatase.

Now add an activator of phosphatase 6 to both patients, creating individual 3+drug and individual4 plus drug from 3 and 4, respectively. Do this by tripling V_{m6} from 0.3 to 0.9.

The next slide show results that you may obtain.

Discuss whether this same inhibitor will be equally effective in both patients.

Discuss what this could mean for selecting the best drugs for patients.

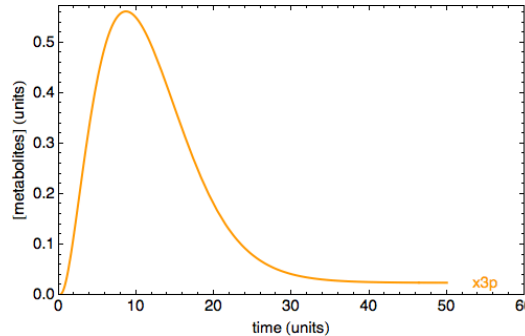
6c. Calculated effect of the same drug on two different individuals

Healthy (shown twice for comparison with the individuals 3 and 4)

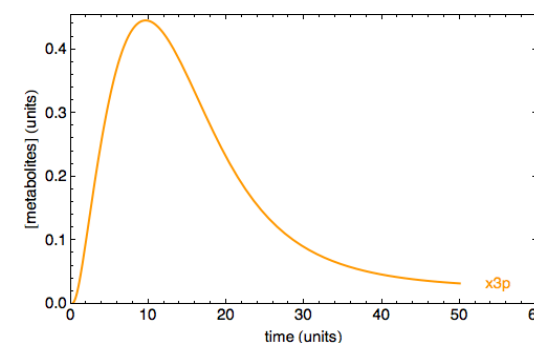
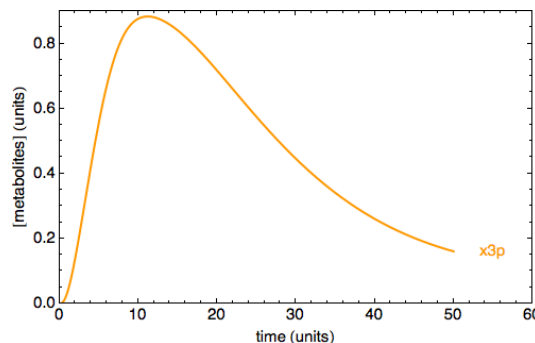
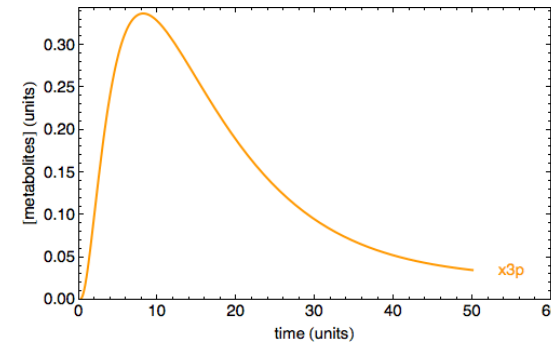
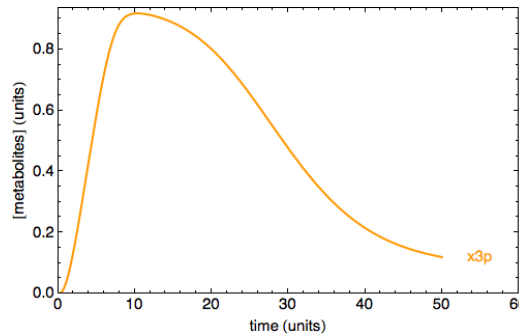
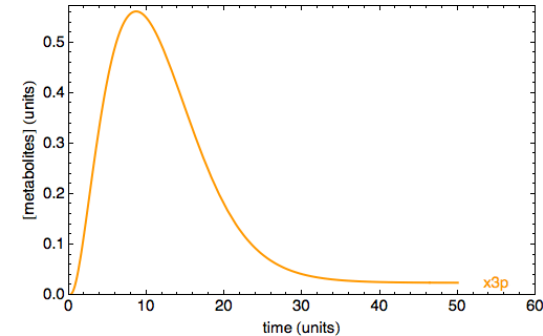
Individuals without drug
3 and 4, both with prolonged x3p but for different reasons

Drug working on middle phosphatase more effective in individual 4 than individual 3.

Healthy and individual 3
(decreased first phosphatase)



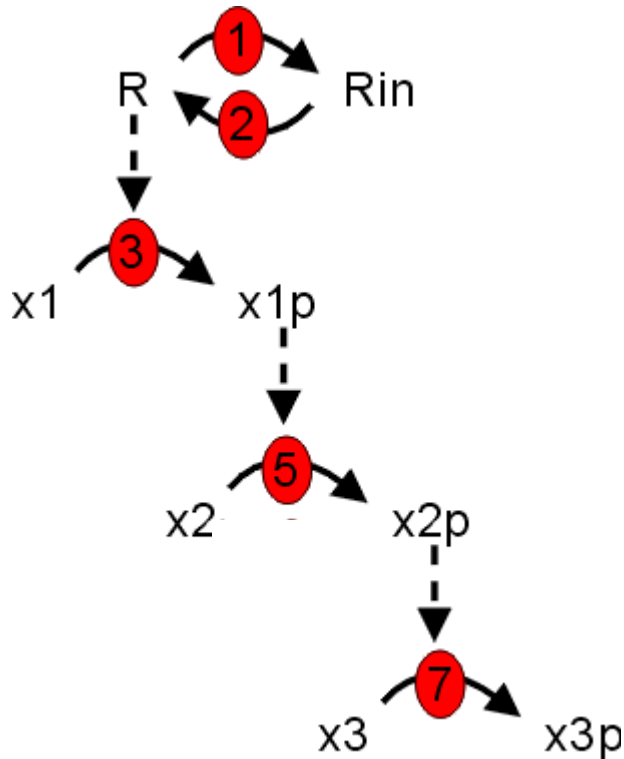
Healthy and individual 4
(decreased last phosphatase)



Results

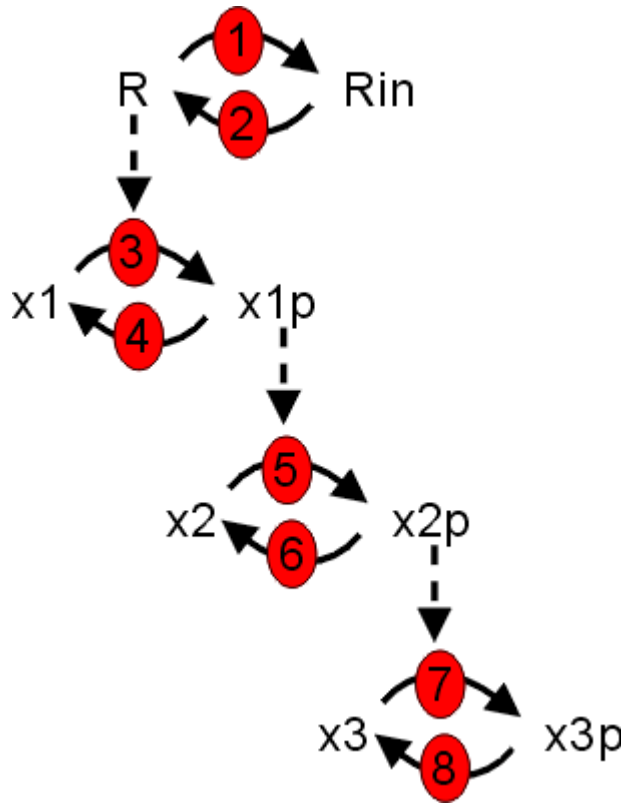
Please contribute

Paradox 1



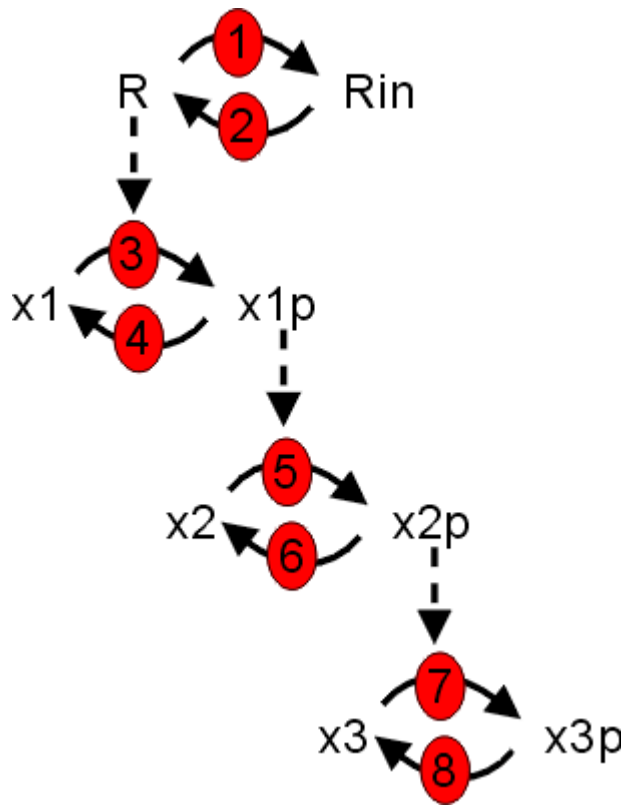
- In most textbooks these routes are shown like this.
- Does this make sense?
 - No it does not.
 - We have shown that $x3p$ would become 1 and stay 1.
 - Even minor fluctuations in R would cause all $x3$ to be continuously phosphorylated

Paradox 2:



- Is only the first kinase the limiting step? Because once this has been set in motion the rest is inescapable.
- Yet, all three kinases have been reported as oncogenes.
- Paradox?
- **All three kinases exercise strong control; position in pathway is irrelevant**

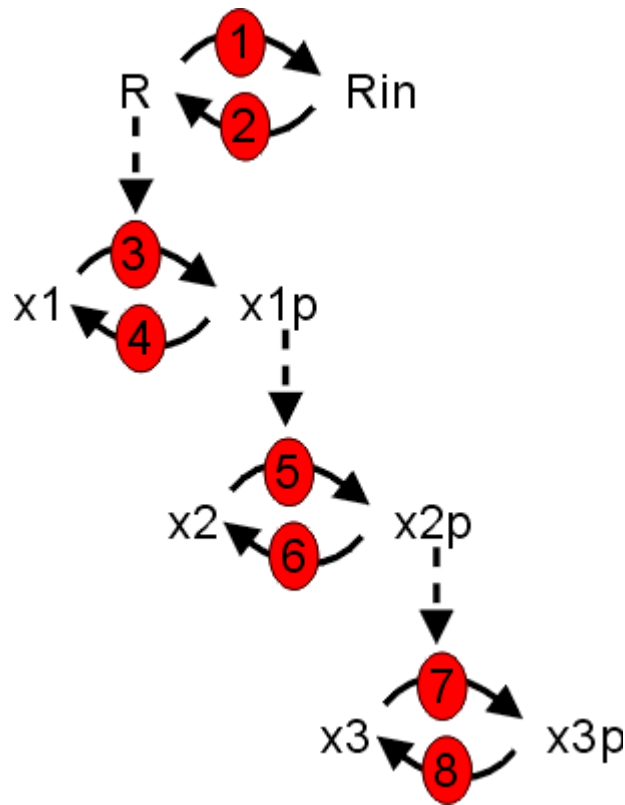
Paradox 3:



- Are the phosphatases at all important? Surely not, as they only work negatively. (??)
- **Yes, they work negatively, but this makes them important; the amplitude of x3P is set by the balance between kinase and phosphatase activities.**

Paradox 4:

- Could the phosphatases be more important than the kinases? Surely not, at most equally important (??)



- **Yes, the phosphatases are more important than the kinases for the timing and timing may matter most for differentiation versus proliferation.**



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