Wrapping up E. coli Chemotaxis (L7 & L8)

Main points of last 2 lectures:

reduction

L7: *Biological background*

what is the function of the individual molecules ?

L8: *modeling of all possible chemotactic reactions*

why doesn't this model reproduce experimentally observed perfect adaptation ?

L8-9*: strip down full model to essentials based on assumptions that are experimentally justified (or sometimes not)*

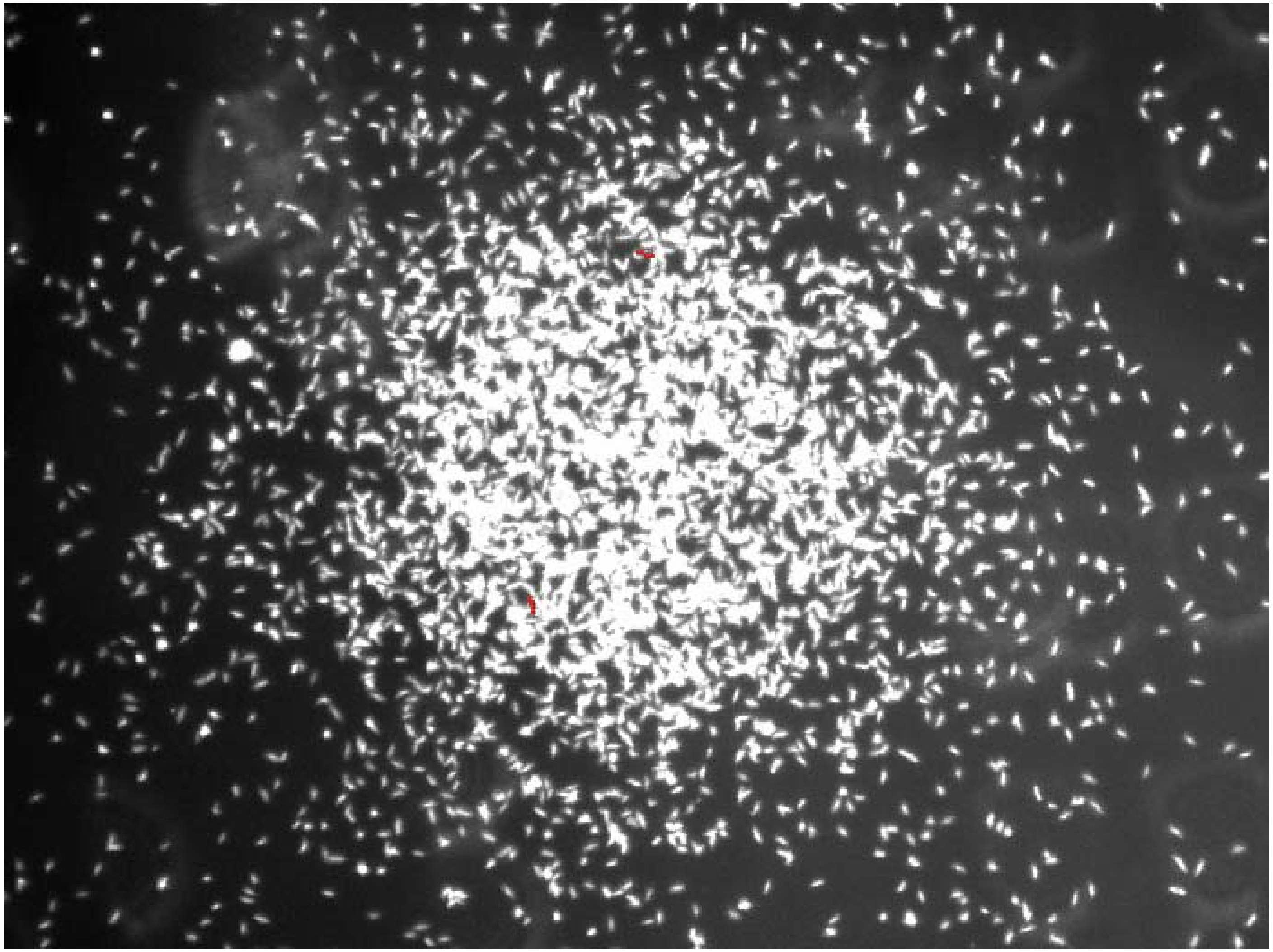


Figure 1A in Mittal, N., E. O. Budrene, M. P. Brenner, and A. Van Oudenaarden. "Motility of Escherichia coli cells in clusters formed by chemotactic aggregation." *Proc Natl Acad Sci U S A*. 100, no. 23 (Nov 11, 2003): 13259-63.

Images removed due to copyright considerations.

Absence of chemical attractant

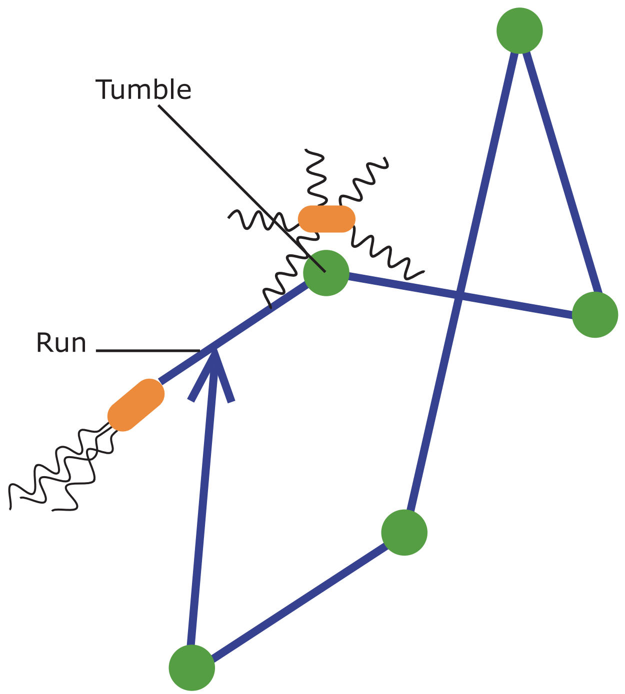
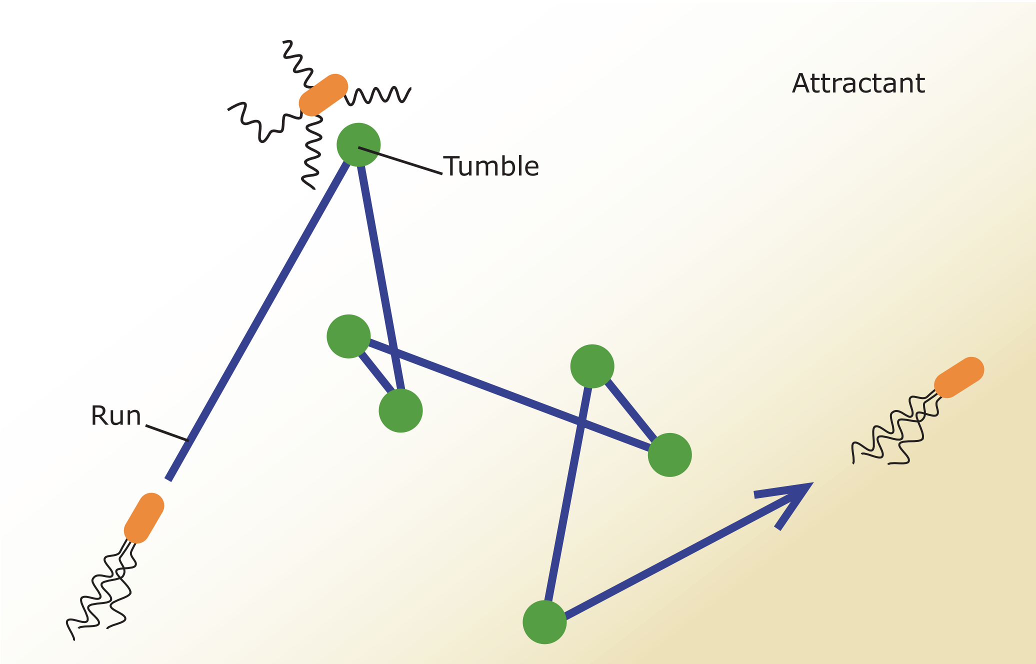


Image by MIT OCW.

Presence of chemical attractant



Chemical Gradient Sensed in a Temporal Manner

Image by MIT OCW.

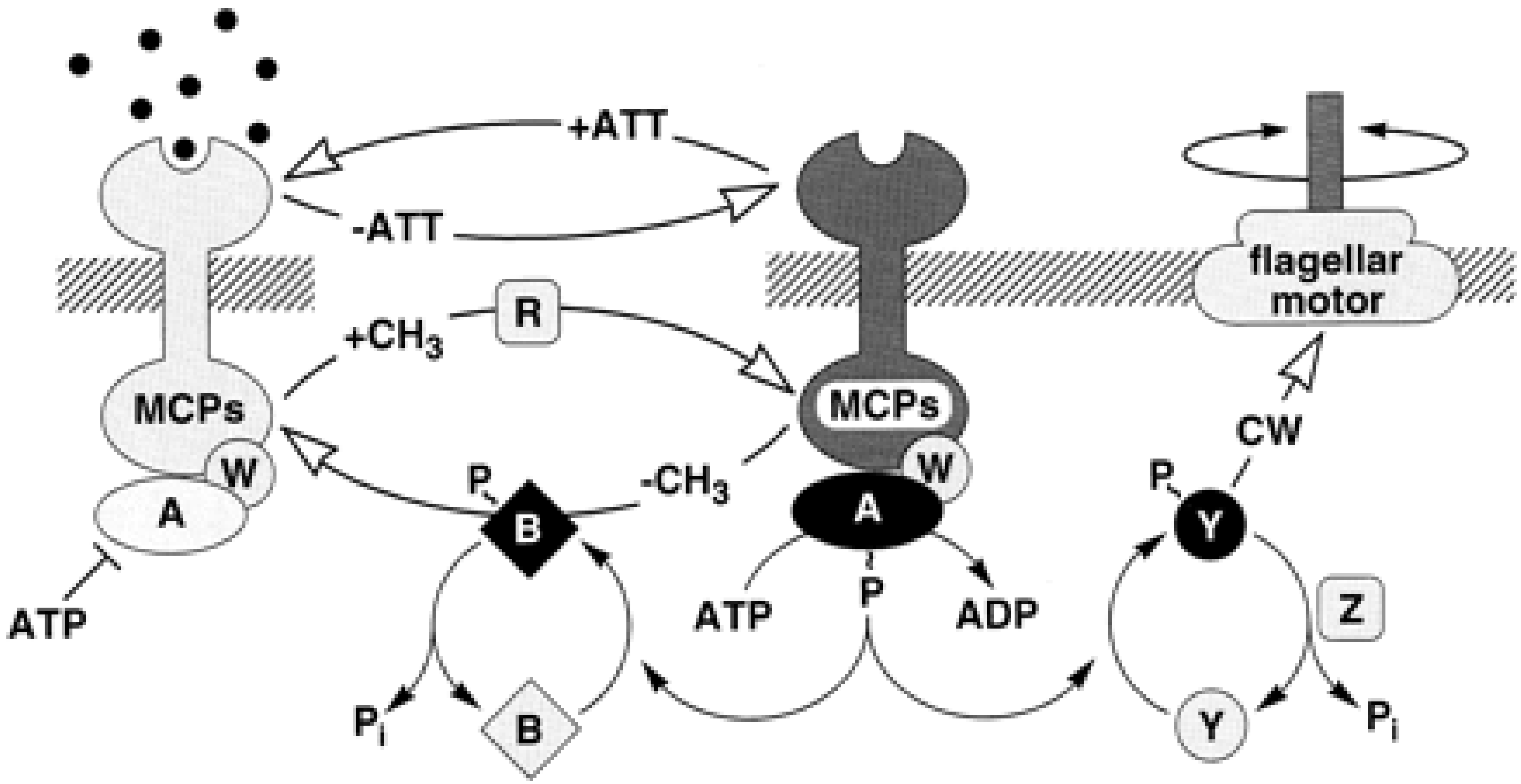


Figure 1 of Spiro, P. A., J. S. Parkinson, and H. G. Othmer. "A model of excitation and adaptation in bacterial chemotaxis." *Proc Natl Acad Sci U S A* 94, no. 14 (Jul 8, 1997): 7263-8.

key player: Tar-CheA-CheW complex

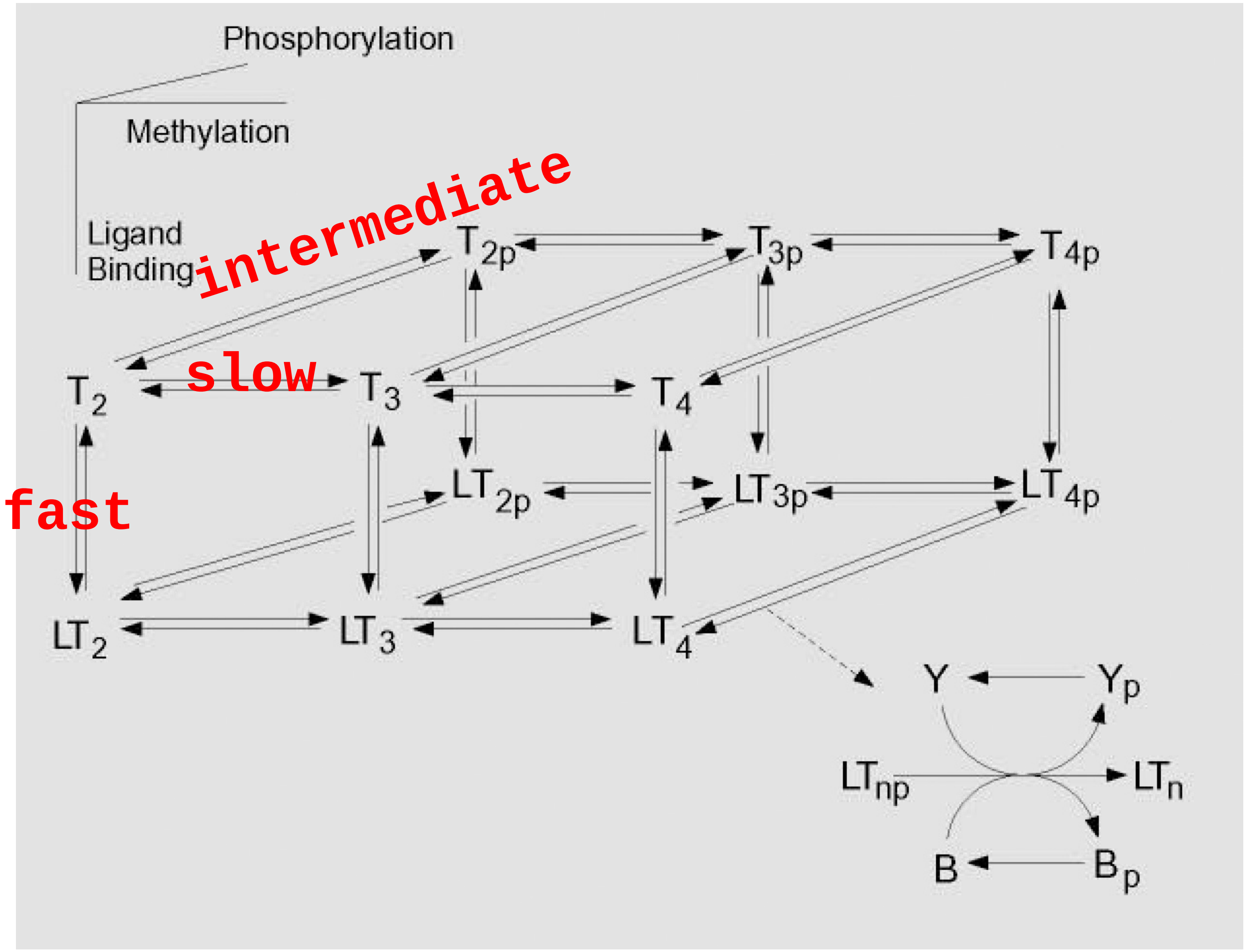
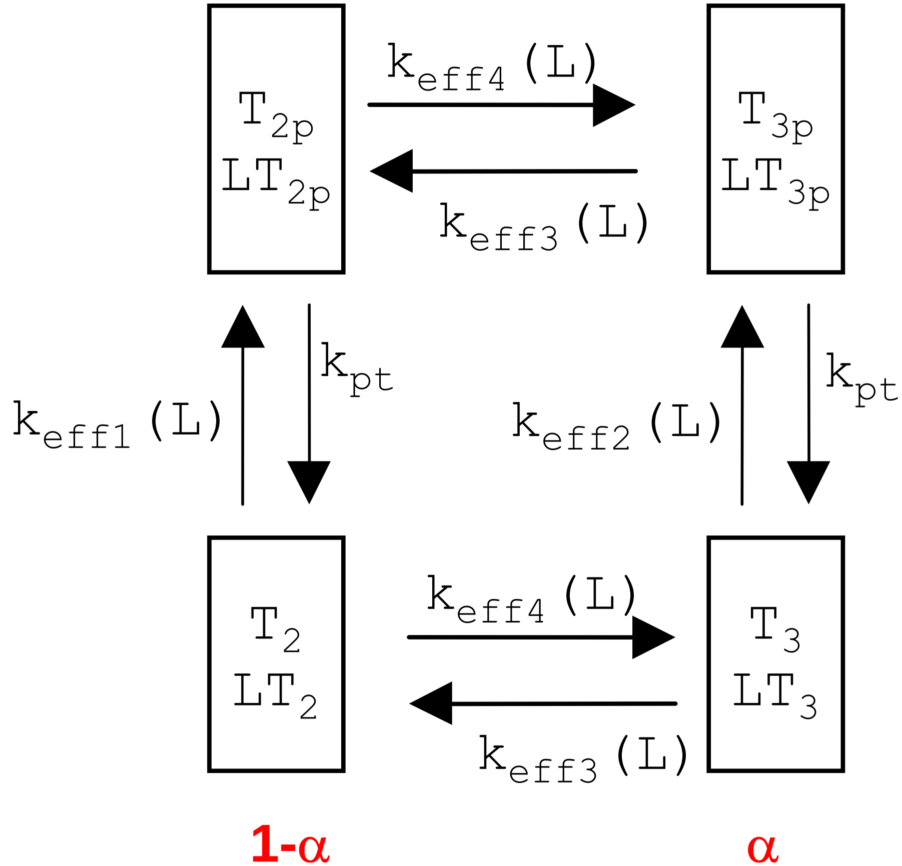


Figure 2 of Spiro, P. A., J. S. Parkinson, and H. G. Othmer.
"A model of excitation and adaptation in bacterial chemotaxis."
Proc Natl Acad Sci U S A 94, no. 14 (Jul 8, 1997): 7263-8.

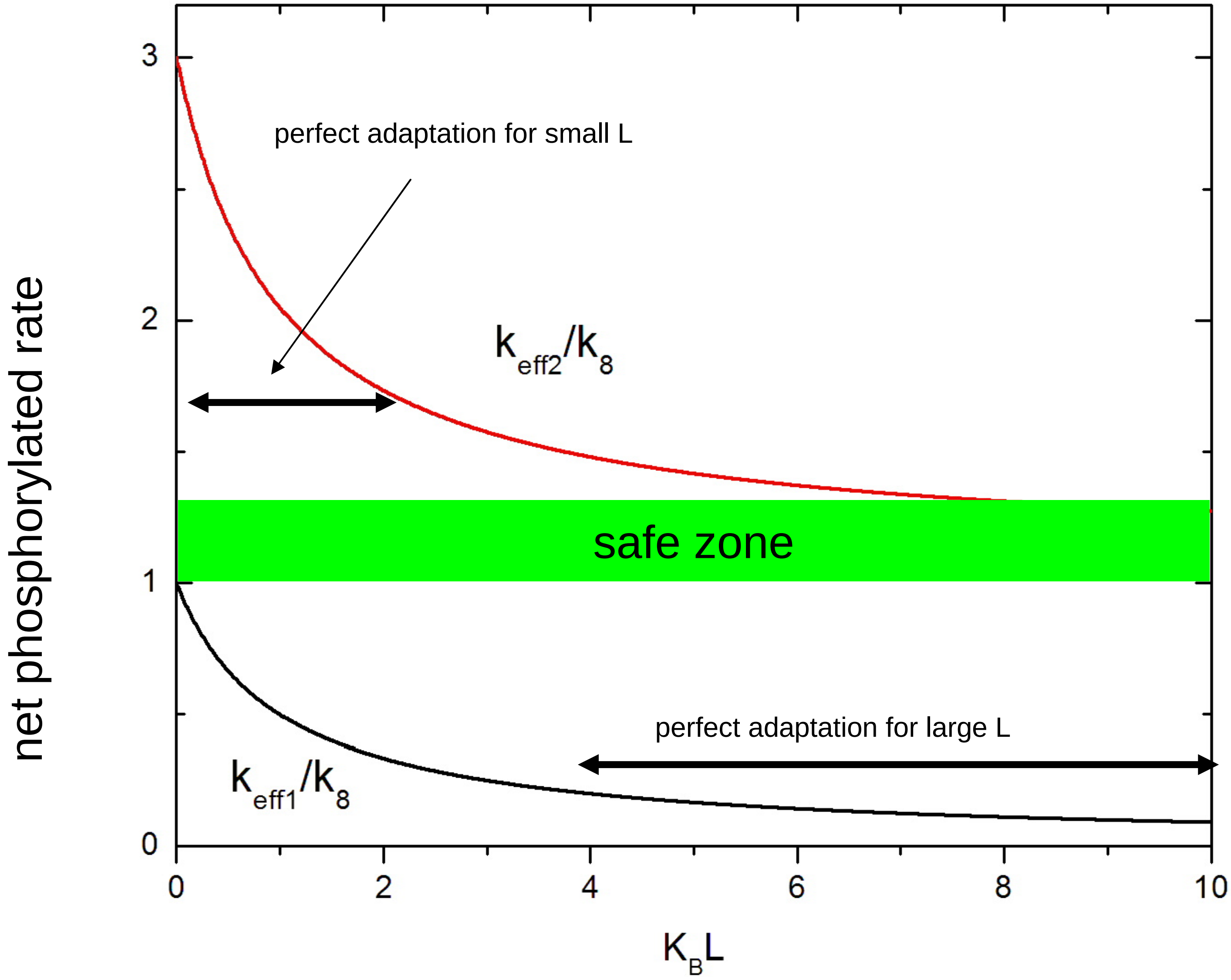
First reduction



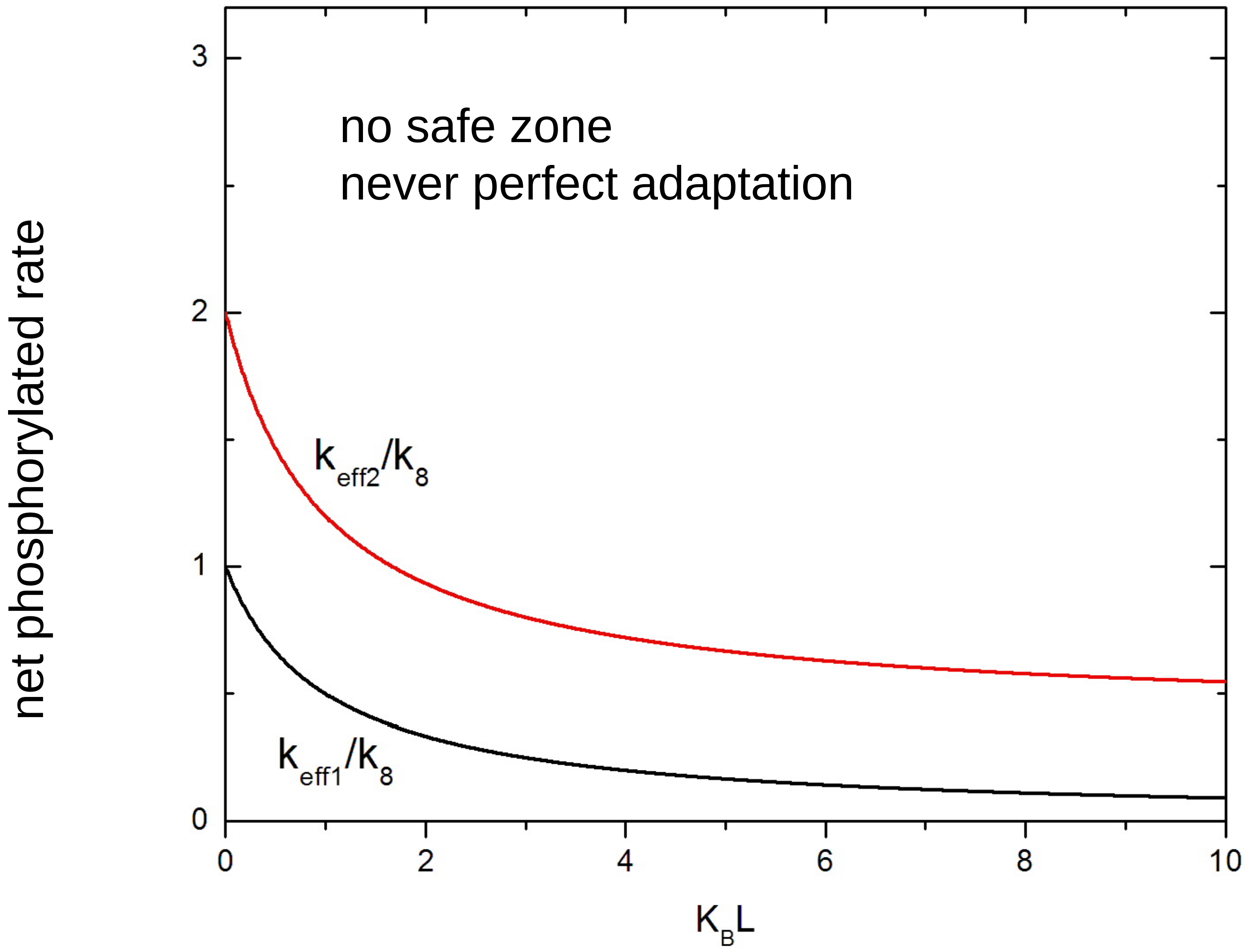
in steady state:

$$\alpha \equiv \frac{[3]}{[2]+[3]}$$

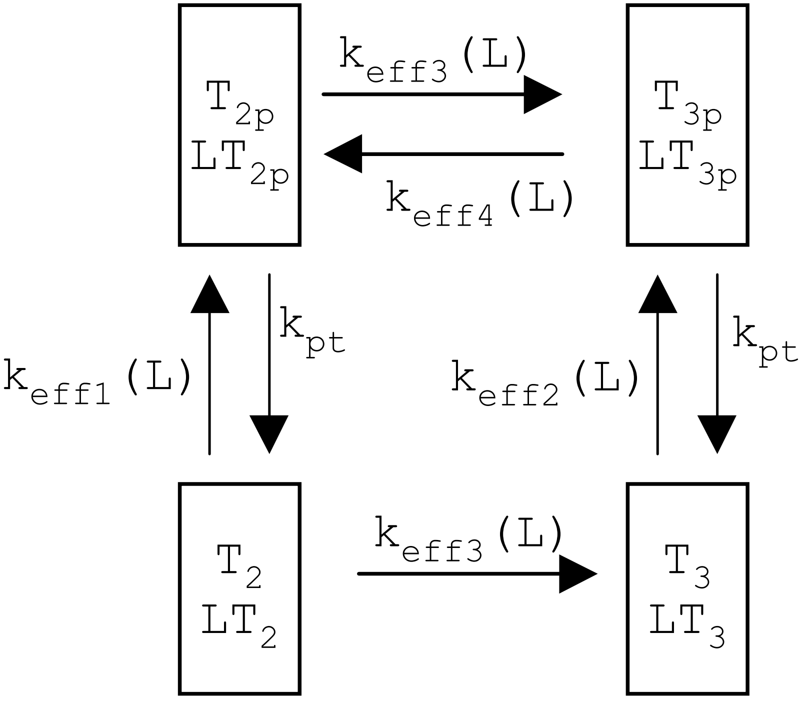
$$k_{phos} = (1-\alpha)\, k_{eff1}(L) + \alpha k_{eff2}(L)$$



fine-tune: net phoshorylation rate and k_{eff1} and k_{eff2} so that α falls in safe zone


no safe zone
never perfect adaptation
k_{eff2}/k_8
k_{eff1}/k_8
net phosphorylated rate
K_BL
0
1
2
3
0
2
4
6
8
10

Second reduction



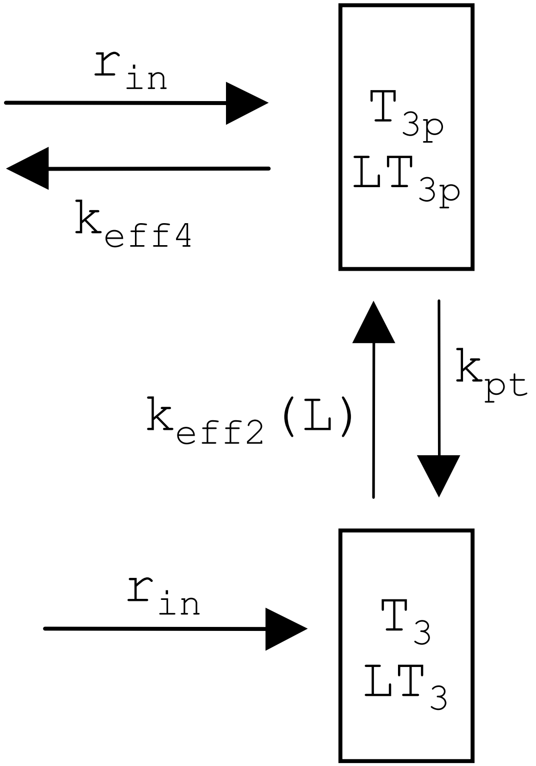
additional assumption:

- CheB only demetylates phosphorylated receptors

experimental backup:

- not possible to directly measure if CheB demethylates only active receptors
- rate of methylation drops immediately after addition of ligand indicates that CheB works on active receptors

Third reduction



additional assumption:

- [CheR]<< [receptors], methylation operates at saturation (r_{in} is independent of receptor concentrations)

experimental backup:

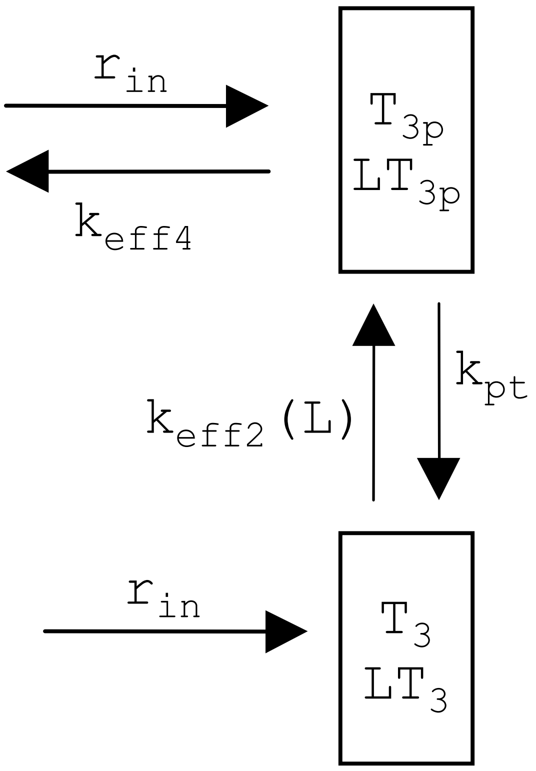
- Michaelis constant of CheR binding << [receptors] so $R_{tot} \sim R_{bnd}$

ok

Fourth reduction

additional assumption:

- demethylation is identical for bound and unbound receptors, so k_{eff4} is independent of L.



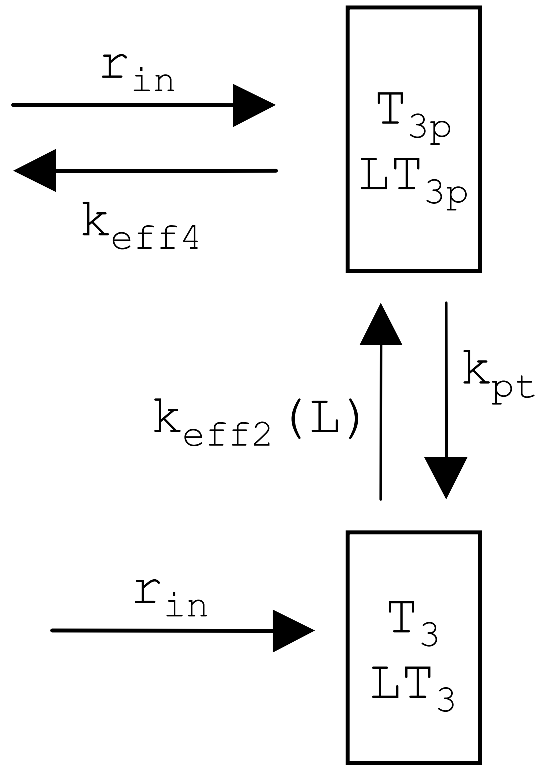
experimental backup:

- kinetics of demethylation almost independent of level of methylation and ligand binding.

ok

This final module obeys perfect adaptation for any value of L.

$$[3_p] = \frac{2r_{in}}{k_{eff4}}$$



Coming lectures: Biological oscillators

Biological relevance: Cell division cycle
Circadian Rhythms
etc.

What do you need to make an oscillator ?

How is an oscillator different from the systems we already discussed (switches, chemotactic network) ?

$\Rightarrow$ Graphical way to represent differential equations.

Refresh: Autocatalysis (Problem set #1).

$$A + X \underset{}{\overset{k_{-1}, k_{+1}}{\longleftrightarrow}} 2X$$

$$\dot{x} = k_1 a x - k_{-1} x^2$$

x=[X]
a=[A] = constant
(e.g. enormous surplus)

This equation is of the type: $\dot{x} = f(x)$

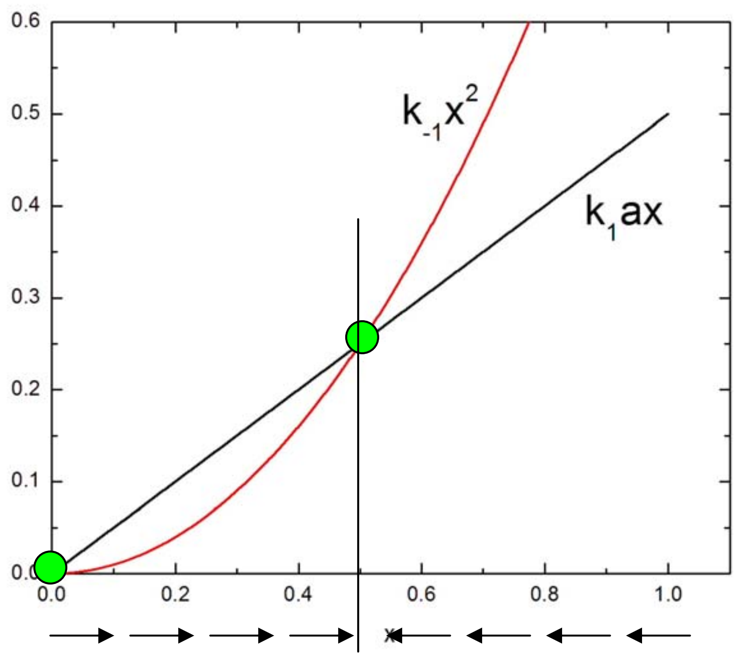
first order differential equation

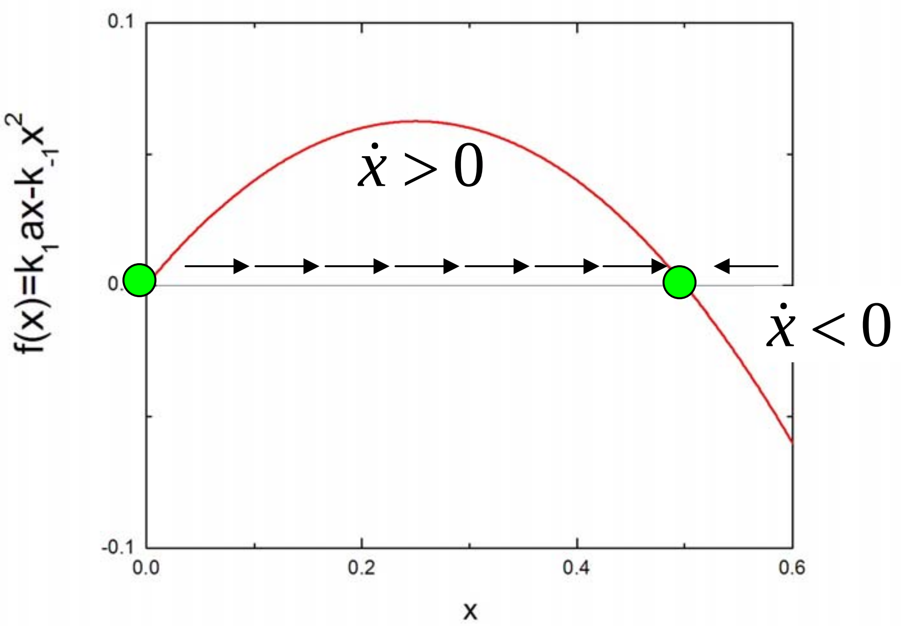
Analysis recipe:	1. determine fixed points 2. stability analysis

Fixed points: f(x*) = 0:

$$x_1^* = 0$$

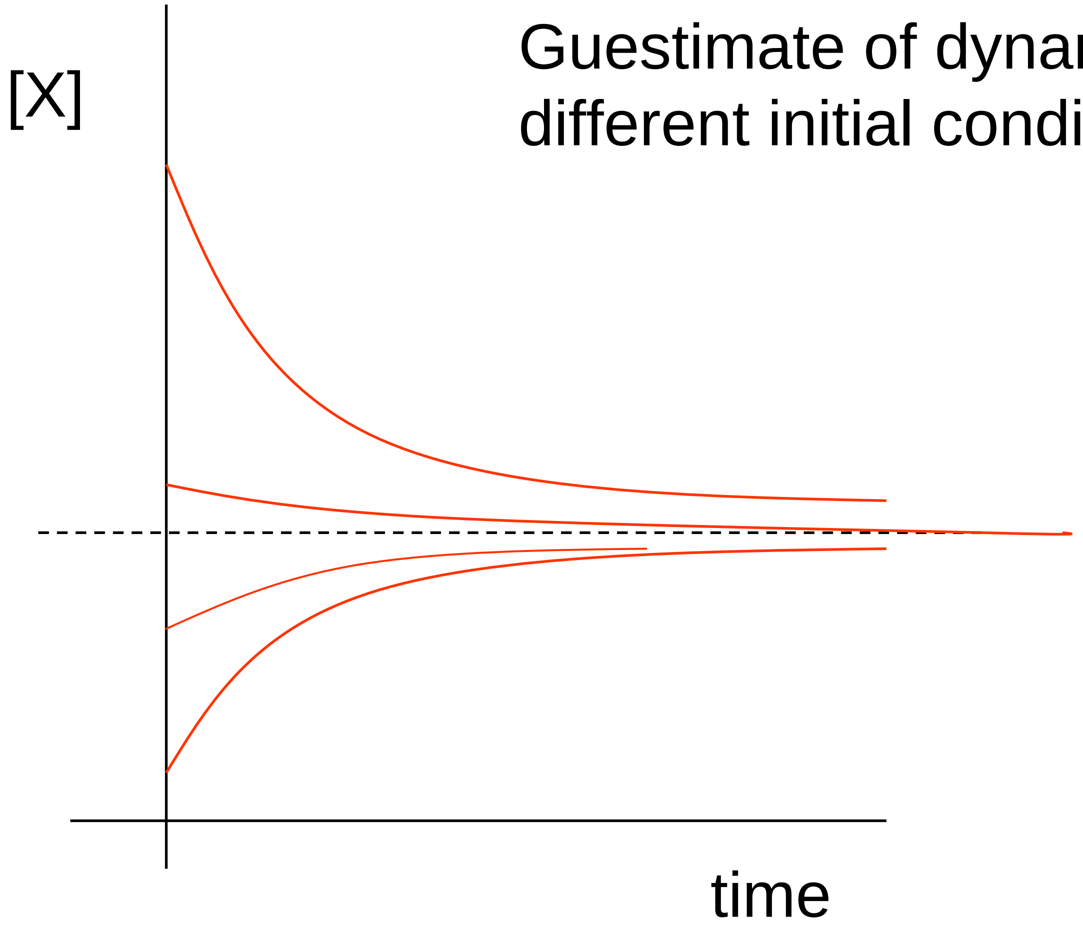
$$x_2^* = \frac{k_1 a}{k_{-1}}$$





2 fixed points: one stable and one unstable

Guestimate of dynamics for different initial conditions



more quantitative stability analysis:

small perturbation from fixed point:

$$\eta(t) = x(t) - x^*$$

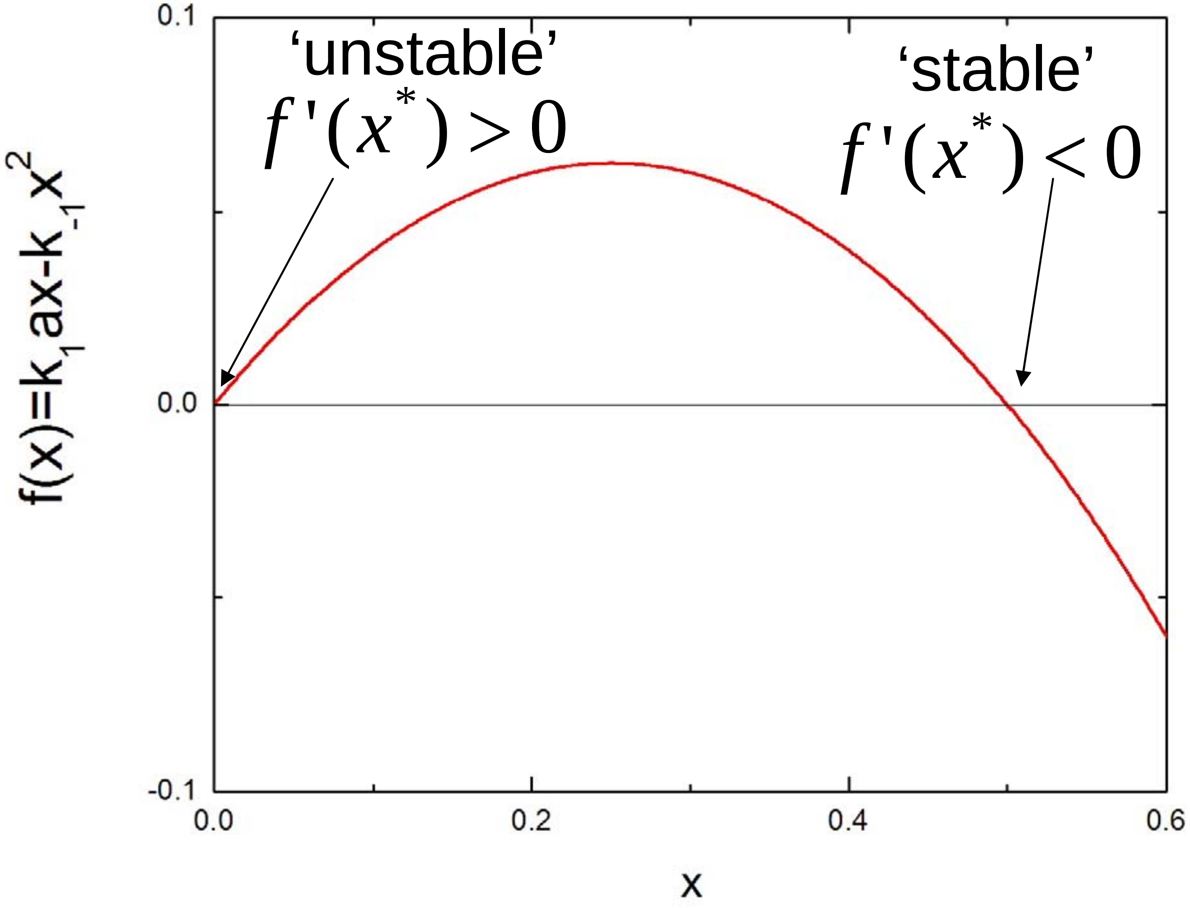
$$f(x^* + \eta) = f(x^*) + \eta f'(x^*) + O(\eta^2) \approx \eta f'(x^*)$$

$$\dot{\eta} \approx \eta f'(x^*)$$

$$\eta(t) \sim \exp(f'(x^*)t)$$

$f'(x^*) > 0$ unstable fixed point

$f'(x^*) < 0$ stable fixed point


'unstable'
$f'(x^*) > 0$
'stable'
$f'(x^*) < 0$
0.1
0.0
-0.1
0.0
0.2
0.4
0.6
x
f(x)=k$_1$ax-k$_{-1}$x^2

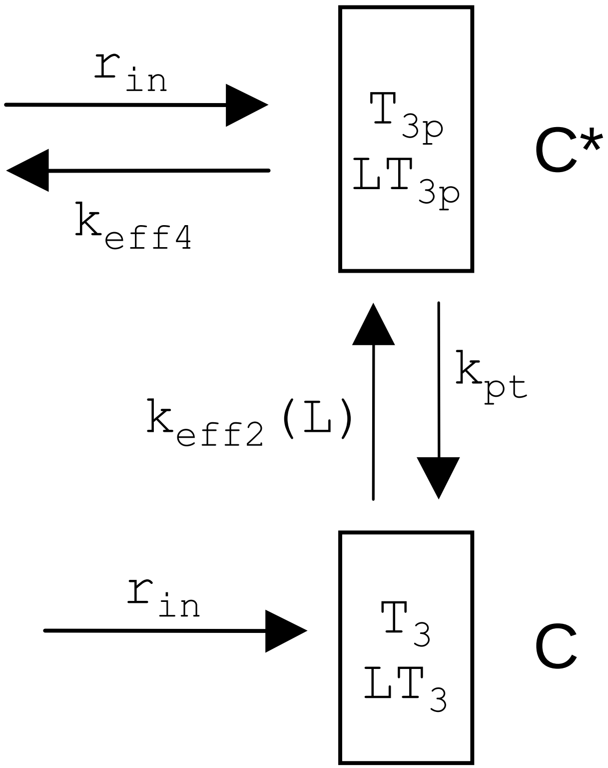
Other example:

$$\dot{C}^* = (-k_{pt} - k_{eff\,4})C^* + k_{eff\,2}C + r_{in}$$

$$\dot{C} = k_{pt}C^* - k_{eff\,2}C + r_{in}$$

$$\dot{x} = ax + by + r_{in}$$
$$\dot{y} = cx + dy + r_{in}$$

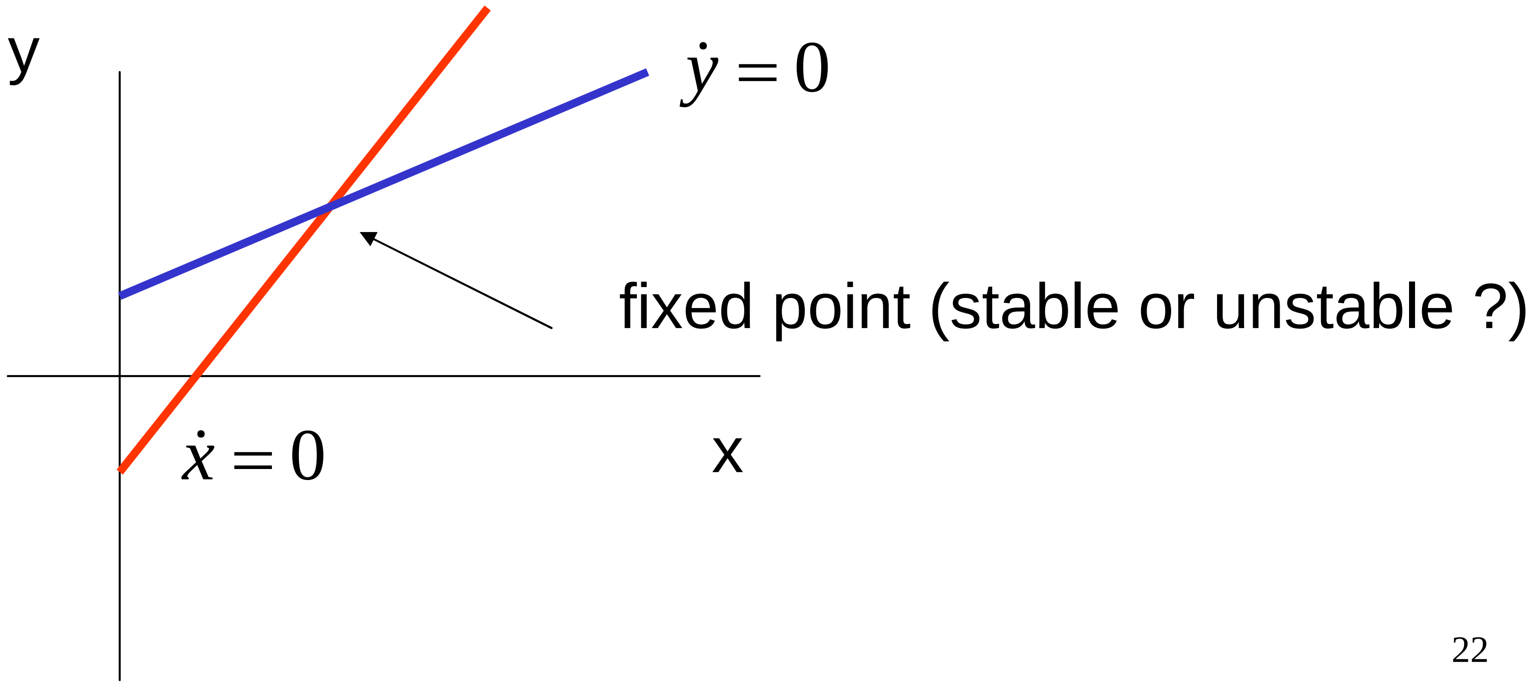
$$x \equiv C^*$$
$$y \equiv C$$
$$a \equiv (-k_{pt} - k_{eff\,4})$$
$$b \equiv k_{eff\,2}$$
$$c \equiv k_{pt}$$
$$d \equiv -b$$

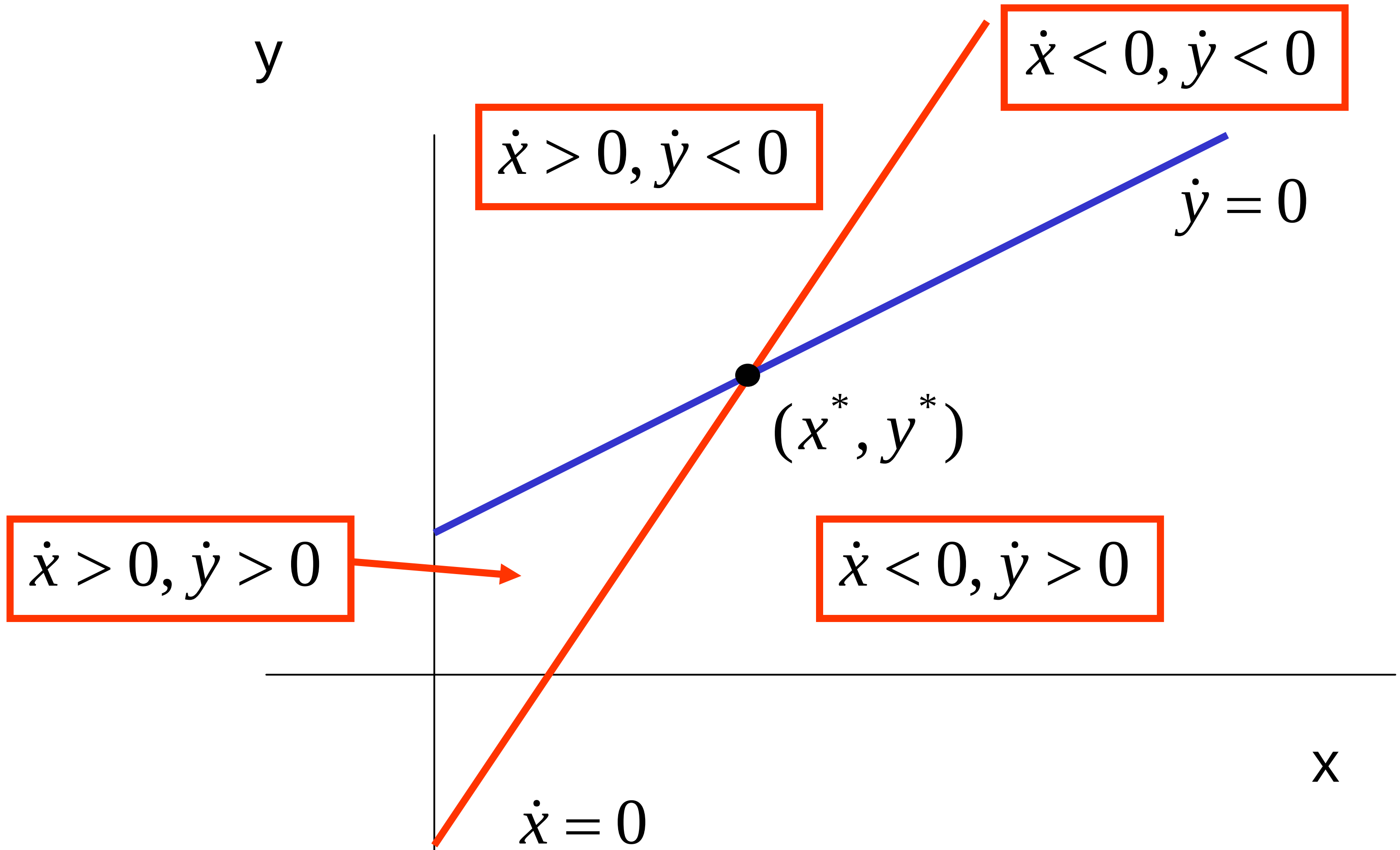


Nullclines:

$$\dot{x} = 0 \quad\longrightarrow\quad y = \frac{-r_{in}}{b} - \frac{a}{b}x = \frac{-r_{in}}{k_{eff\,2}} + \frac{k_{pt} + k_{eff\,4}}{k_{eff\,2}}x$$

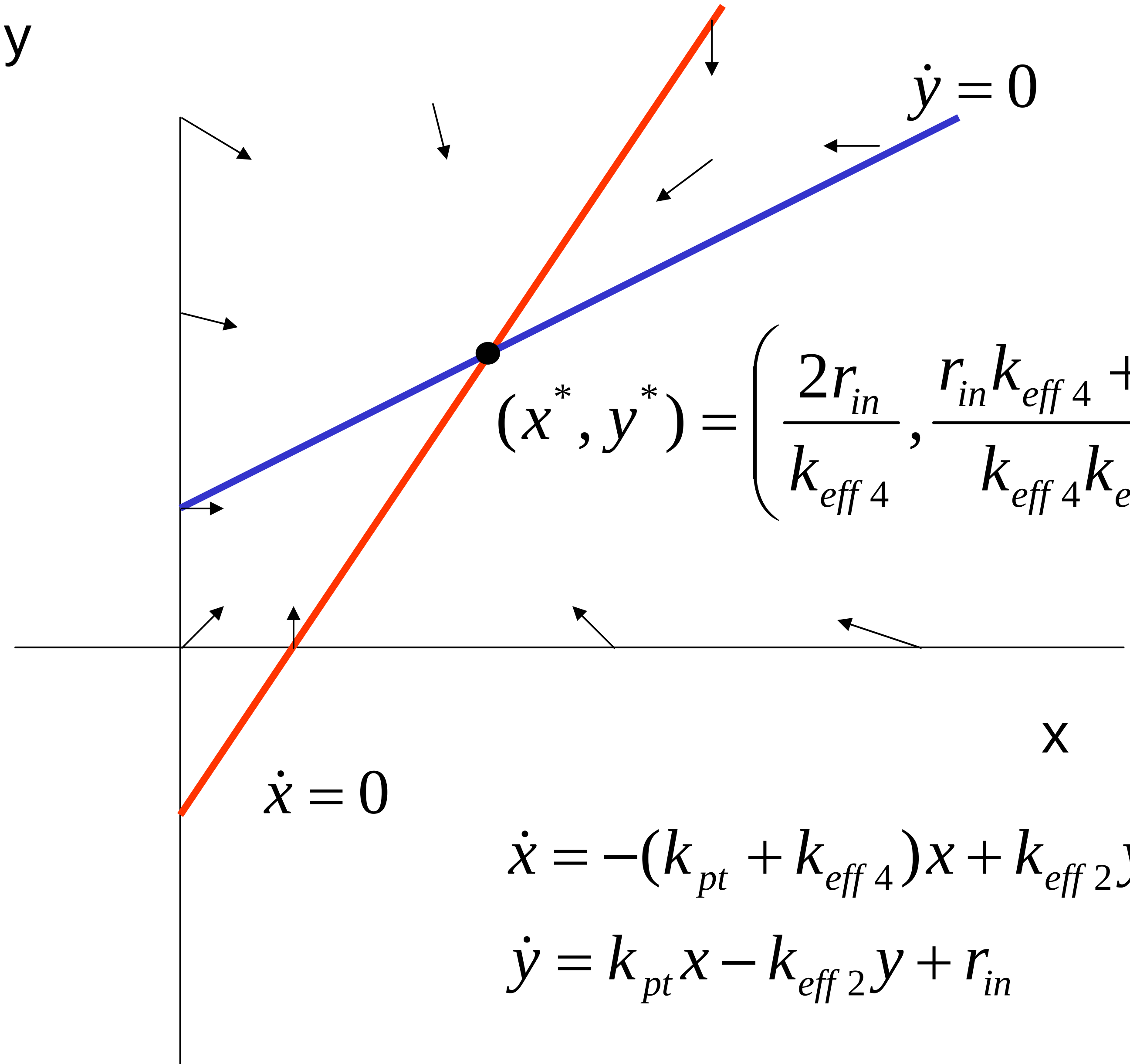
$$\dot{y} = 0 \quad\longrightarrow\quad y = \frac{-r_{in}}{d} - \frac{c}{d}x = \frac{r_{in}}{k_{eff\,2}} + \frac{k_{pt}}{k_{eff\,2}}x$$





$$\dot{x} = -(k_{pt} + k_{eff\,4})x + k_{eff\,2}y + r_{in}$$

$$\dot{y} = k_{pt}x - k_{eff\,2}y + r_{in}$$

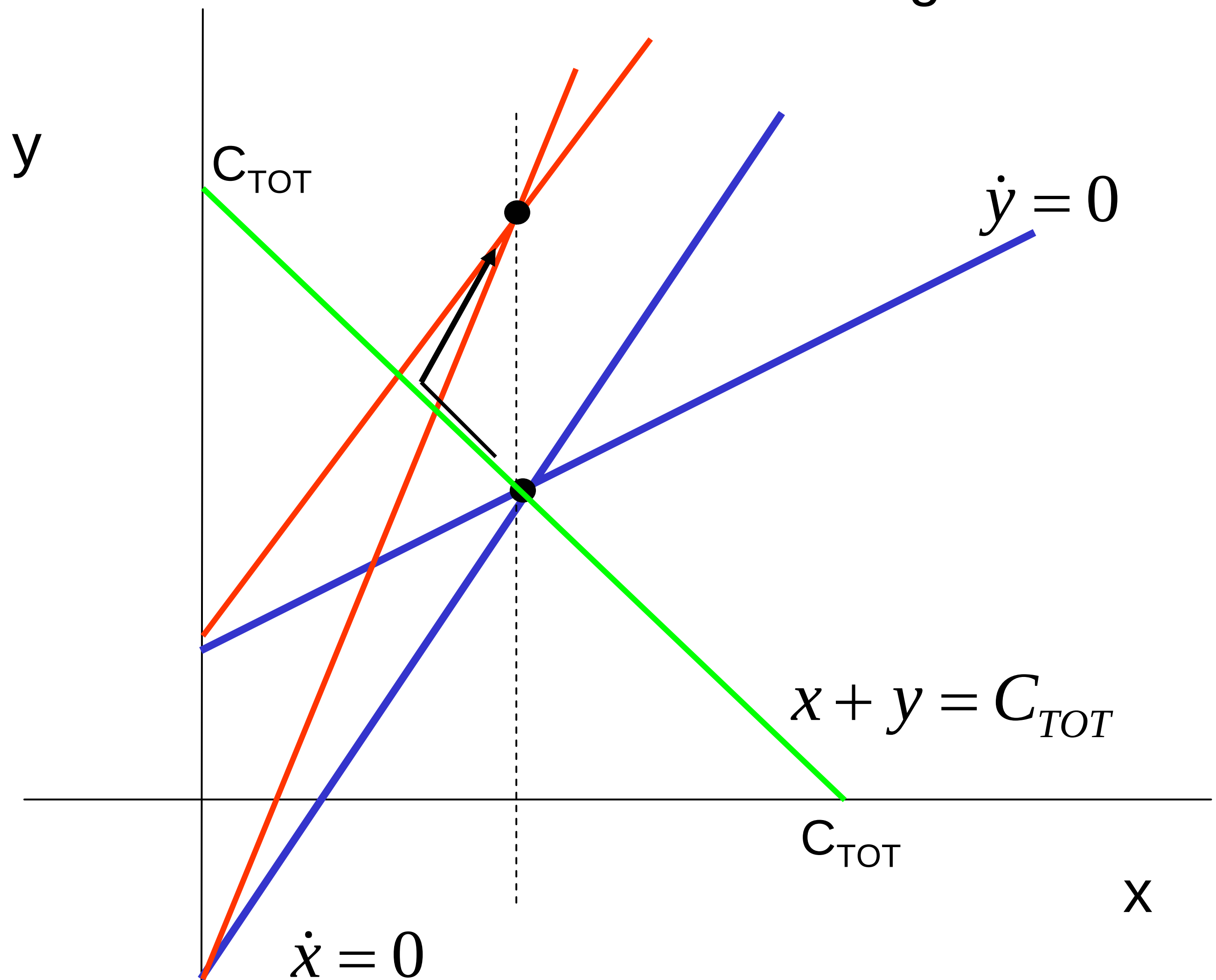


$$(x^*, y^*) = \left(\frac{2r_{in}}{k_{eff\,4}}, \frac{r_{in}k_{eff\,4} + 2r_{in}k_{pt}}{k_{eff\,4}k_{eff\,2}(L)} \right)$$

$$\dot{x} = -(k_{pt} + k_{eff\,4})x + k_{eff\,2}y + r_{in}$$

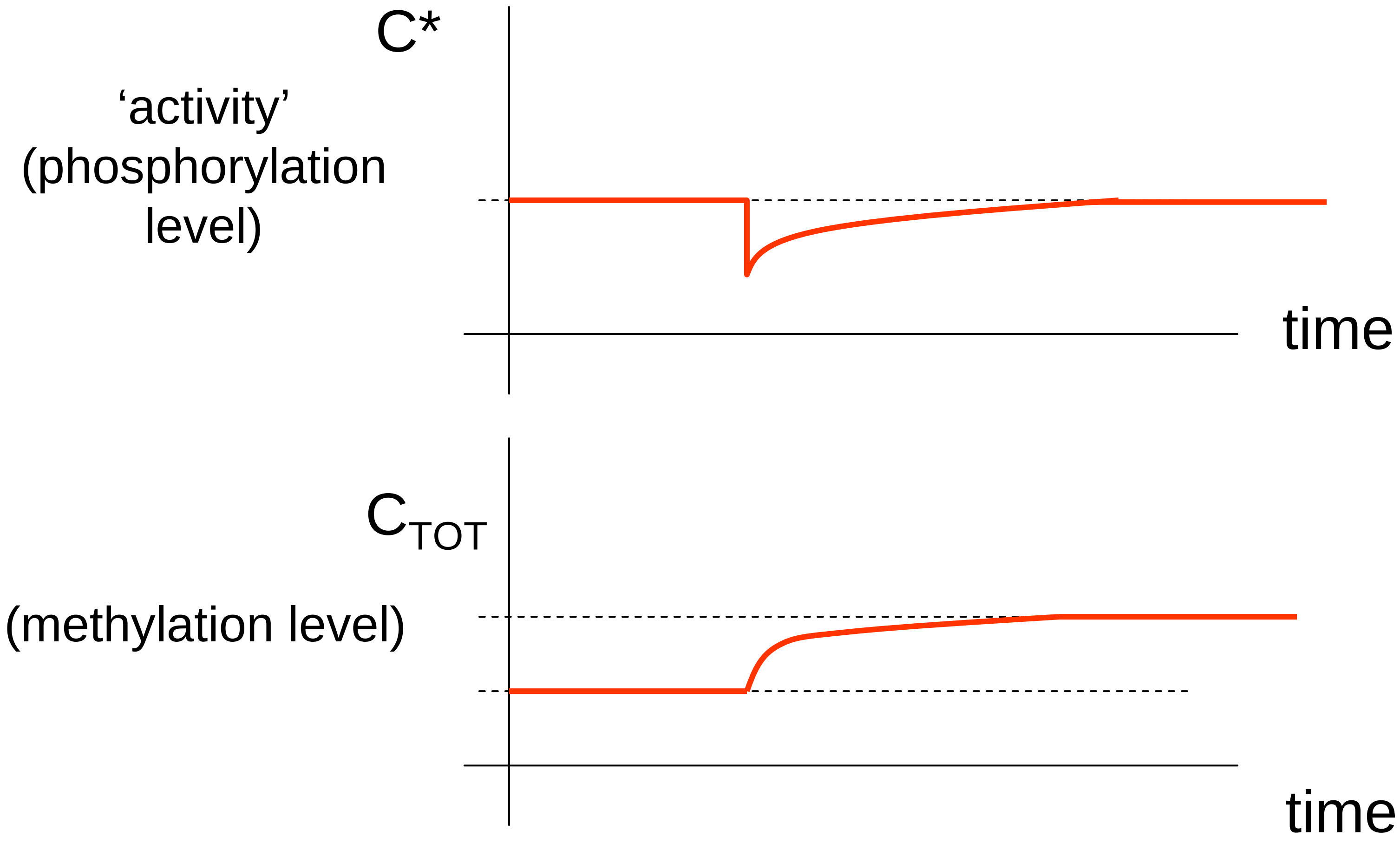
$$\dot{y} = k_{pt}x - k_{eff\,2}y + r_{in}$$

increased ligand concentration



$$(x^*, y^*) = \left(\frac{2r_{in}}{k_{eff\,4}}, \frac{r_{in}k_{eff\,4} + 2r_{in}k_{pt}}{k_{eff\,4}k_{eff\,2}(L)} \right)$$

Guestimated response



Oscillators ?

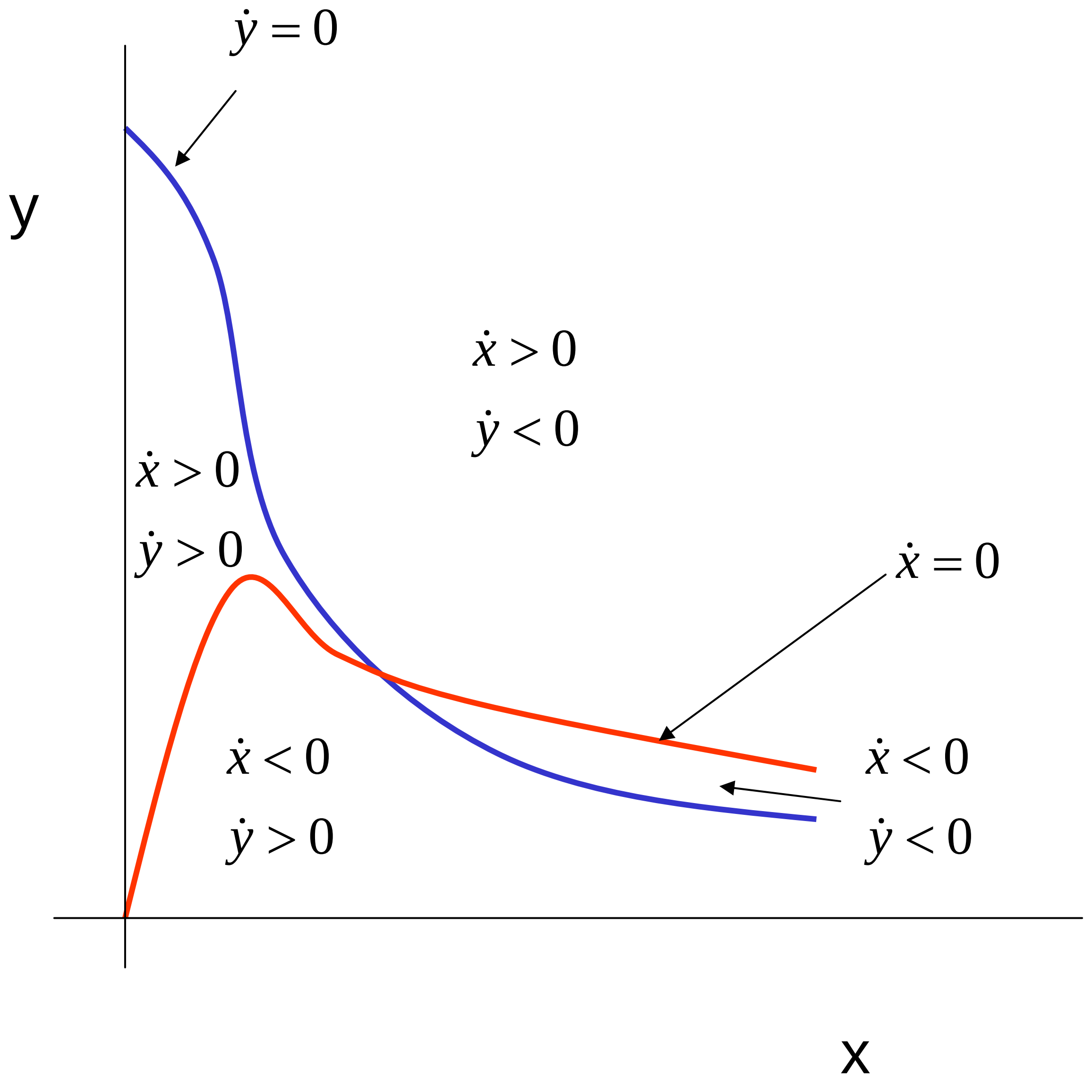
$$\dot{x} = -x + ay + x^2 y$$
$$\dot{y} = b - ay - x^2 y$$

model for glycolysis

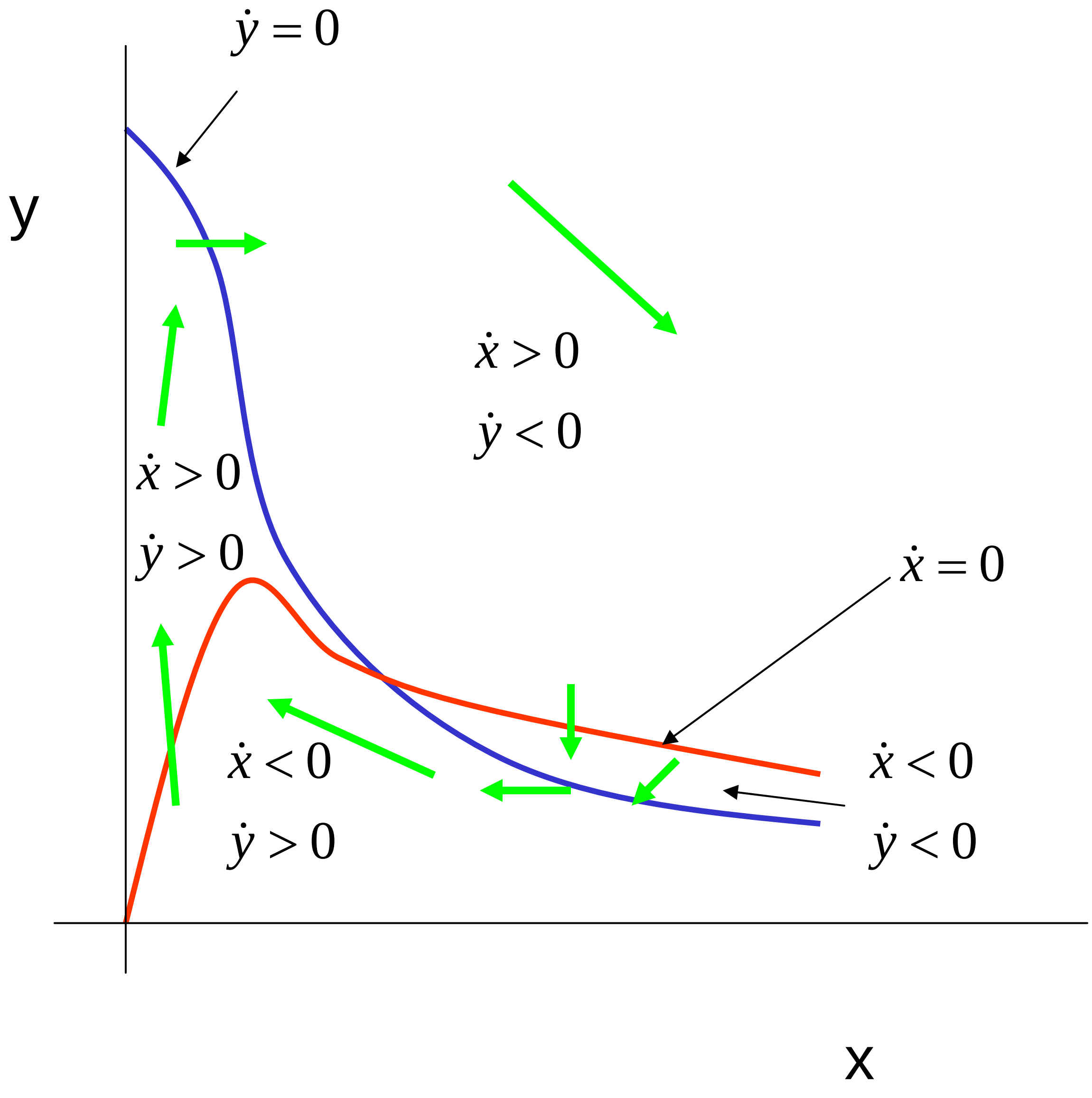
nullclines:

$$y = \frac{x}{a + x^2}$$

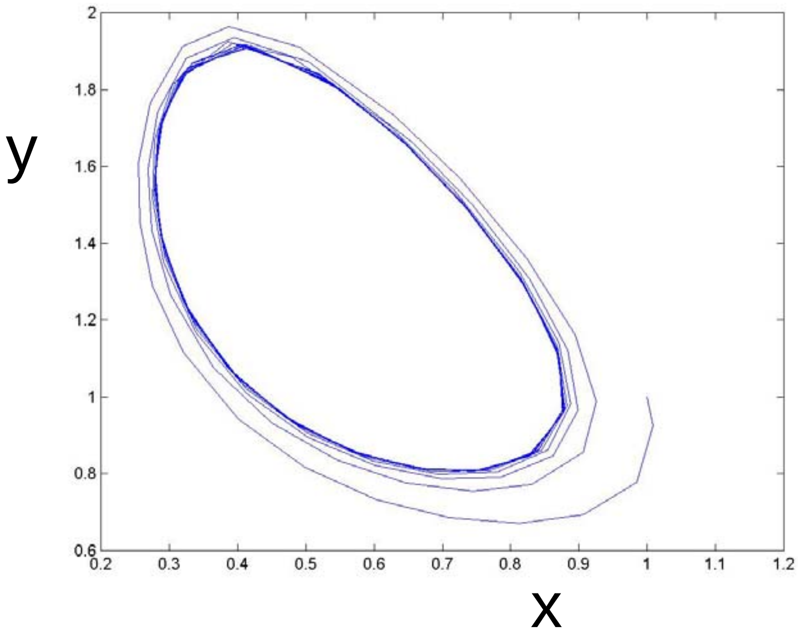
$$y = \frac{b}{a + x^2}$$

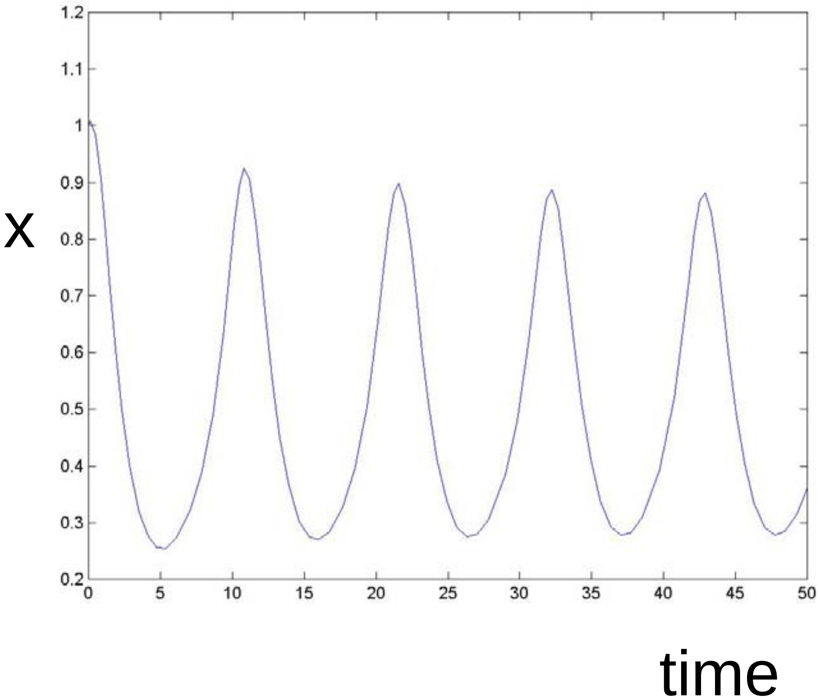


$\dot{y} = 0$
y
$\dot{x} > 0$
$\dot{y} < 0$
$\dot{x} > 0$
$\dot{y} > 0$
$\dot{x} = 0$
$\dot{x} < 0$
$\dot{y} > 0$
$\dot{x} < 0$
$\dot{y} < 0$
x


$\dot{y} = 0$
y
$\dot{x} > 0$
$\dot{y} < 0$
$\dot{x} > 0$
$\dot{y} > 0$
$\dot{x} = 0$
$\dot{x} < 0$
$\dot{y} > 0$
$\dot{x} < 0$
$\dot{y} < 0$
x

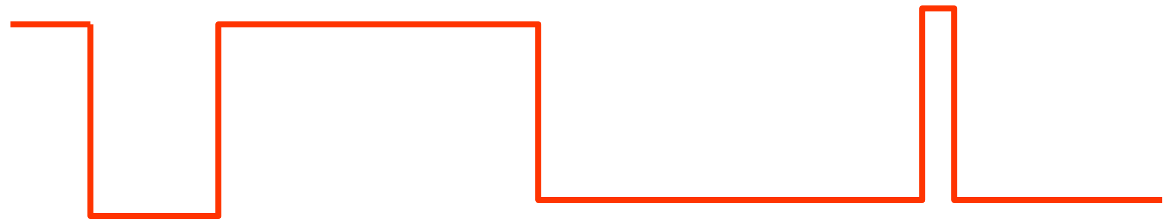
limitcycle


y
x
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
1.2

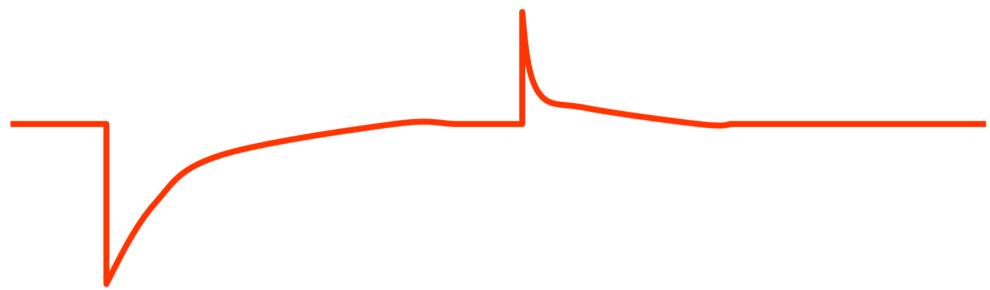

x
time
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0
5
10
15
20
25
30
35
40
45
50

Dynamical response of switches, chemotactic network and oscillators

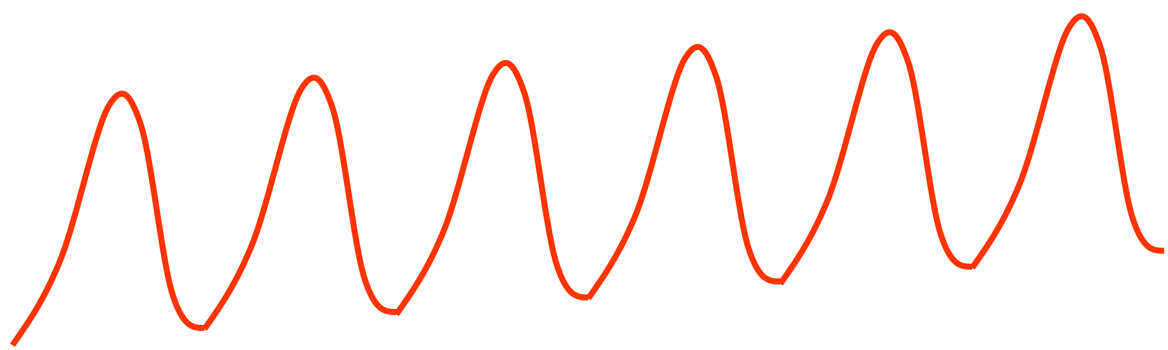
‘switch’



adaptation
(differentiator,
at least for small
frequencies)



oscillator

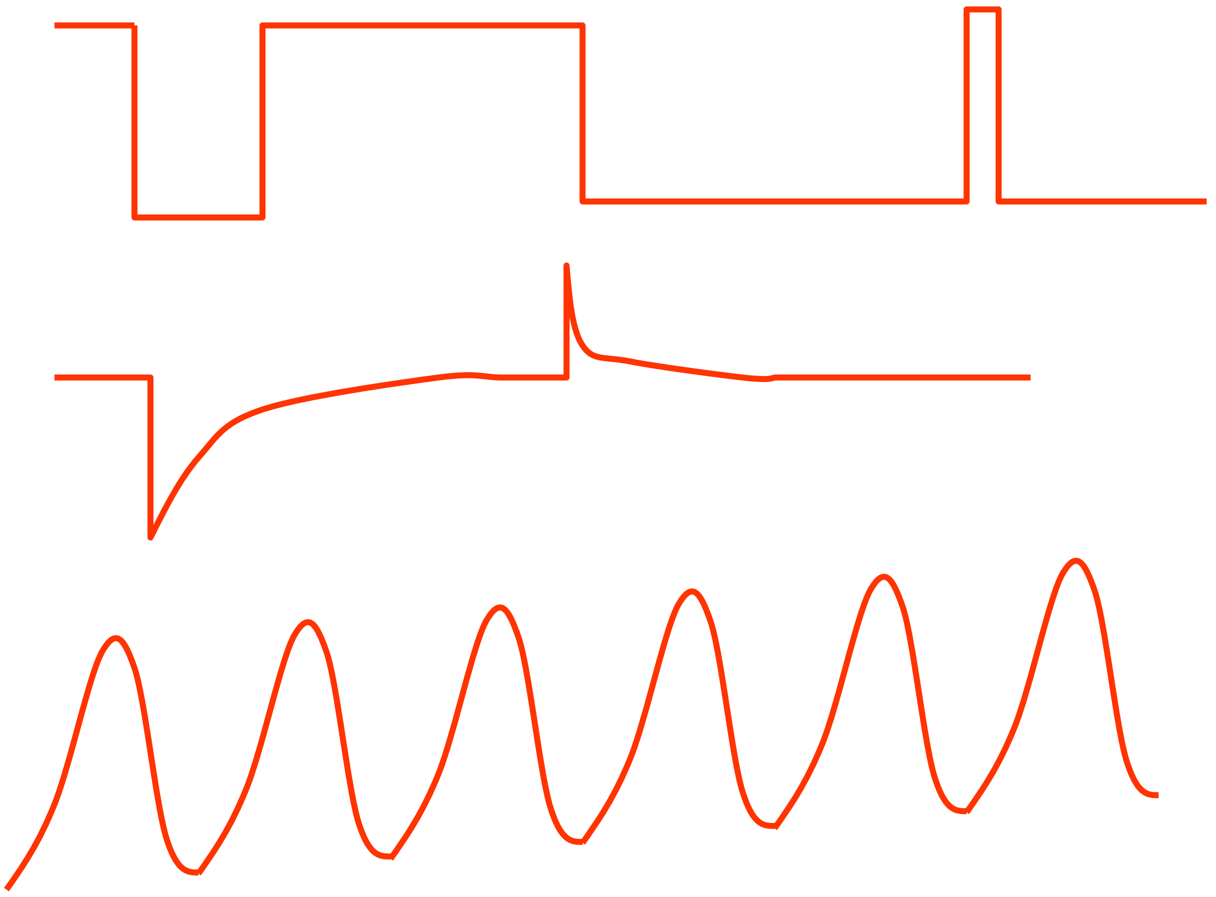


Dynamical response of switches, chemotactic network and oscillators

two stable
fixed points

one stable
fixed point

unstable
fixed point



nullclines:

$$u = \frac{\alpha_1}{1 + v^{\beta}}$$

$$v = \frac{\alpha_2}{1 + u^{\gamma}}$$

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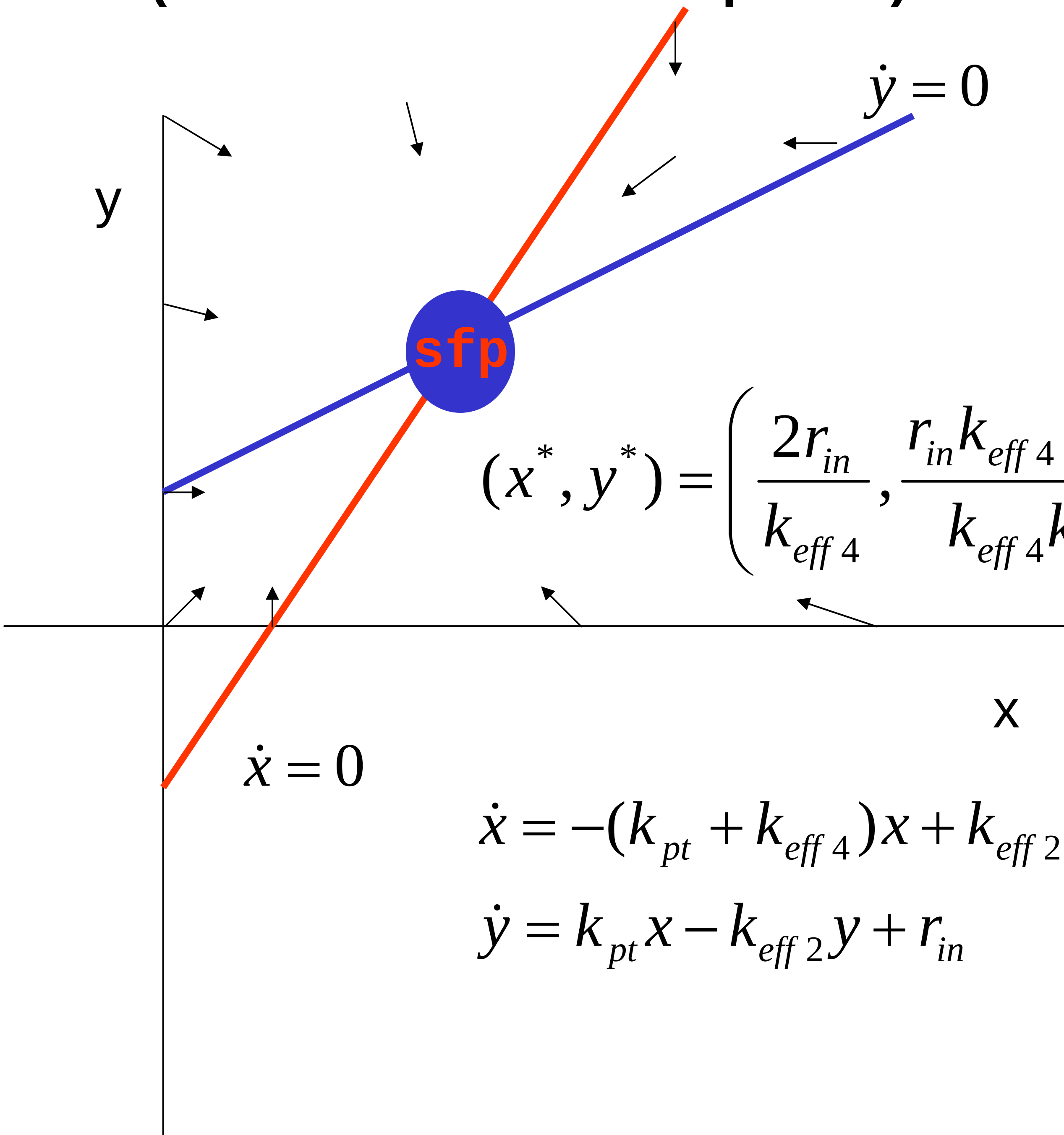
$$\frac{du}{dt} = \frac{\alpha_1}{1 + v^{\beta}} - u$$

$$\frac{dv}{dt} = \frac{\alpha_2}{1 + u^{\gamma}} - v$$

Adaptation (one stable fixed point)

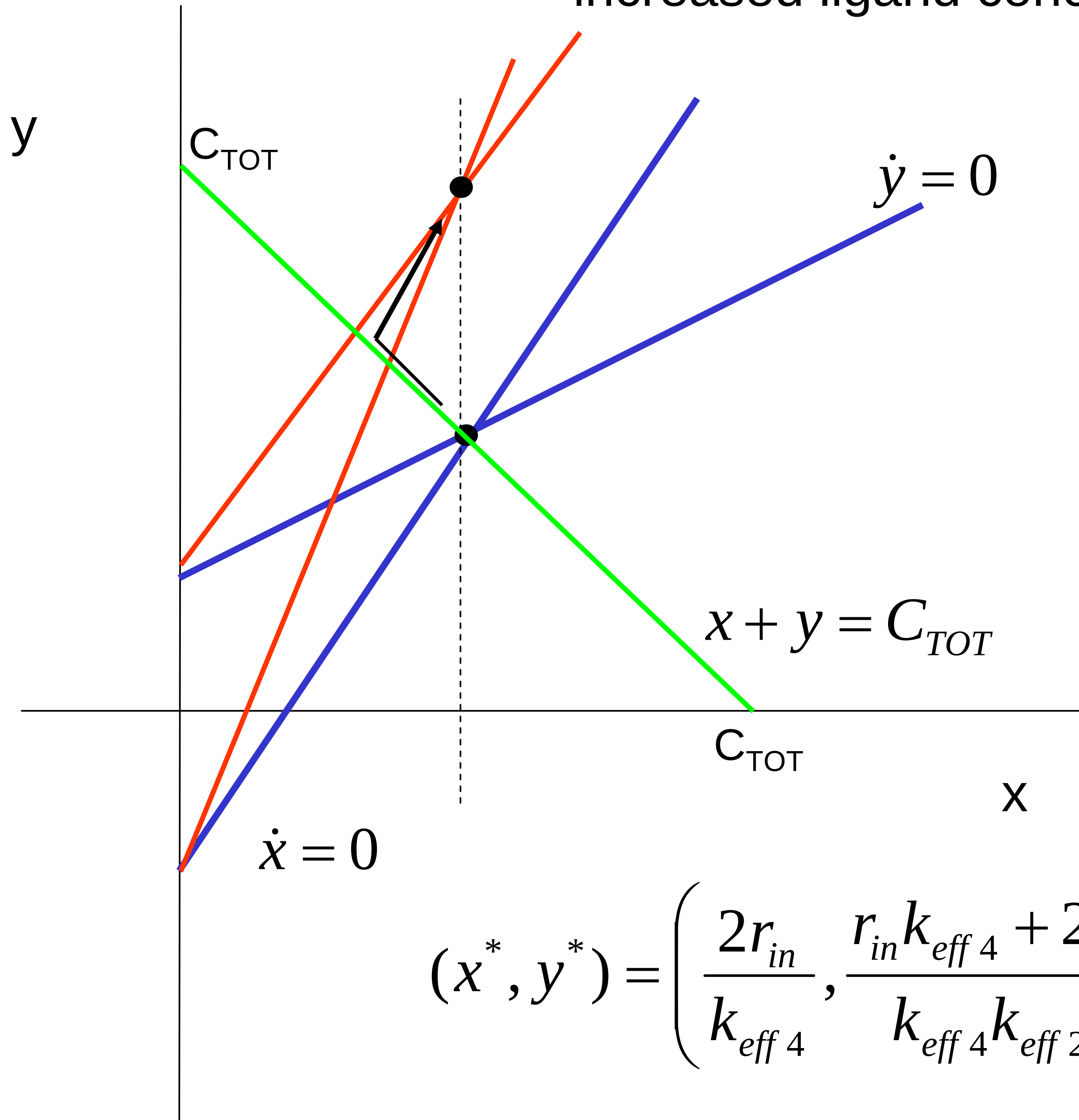


$$(x^*, y^*) = \left(\frac{2r_{in}}{k_{eff\,4}}, \frac{r_{in}k_{eff\,4} + 2r_{in}k_{pt}}{k_{eff\,4}k_{eff\,2}(L)} \right)$$

$$\dot{x} = -(k_{pt} + k_{eff\,4})x + k_{eff\,2}y + r_{in}$$

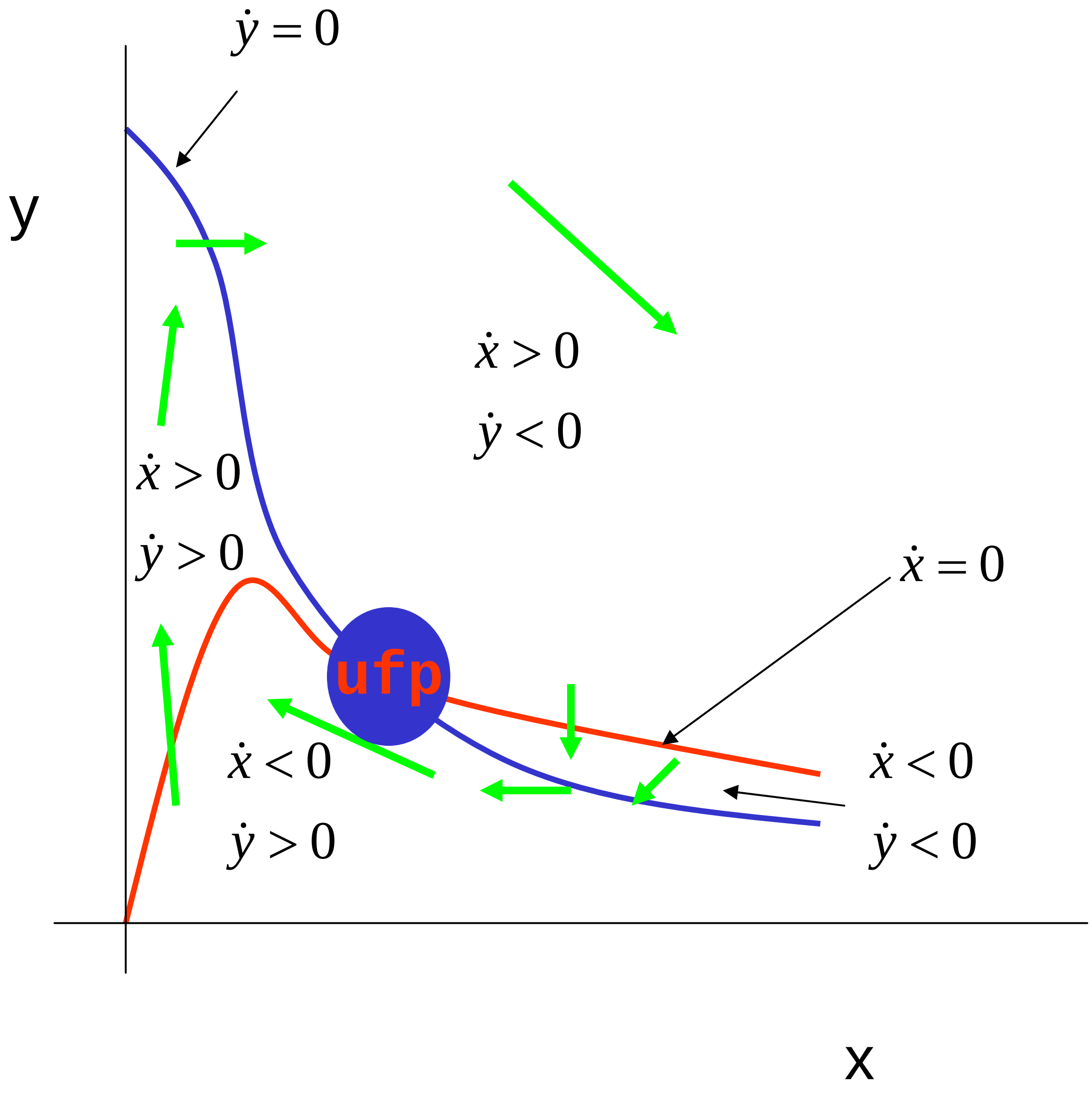
$$\dot{y} = k_{pt}x - k_{eff\,2}y + r_{in}$$

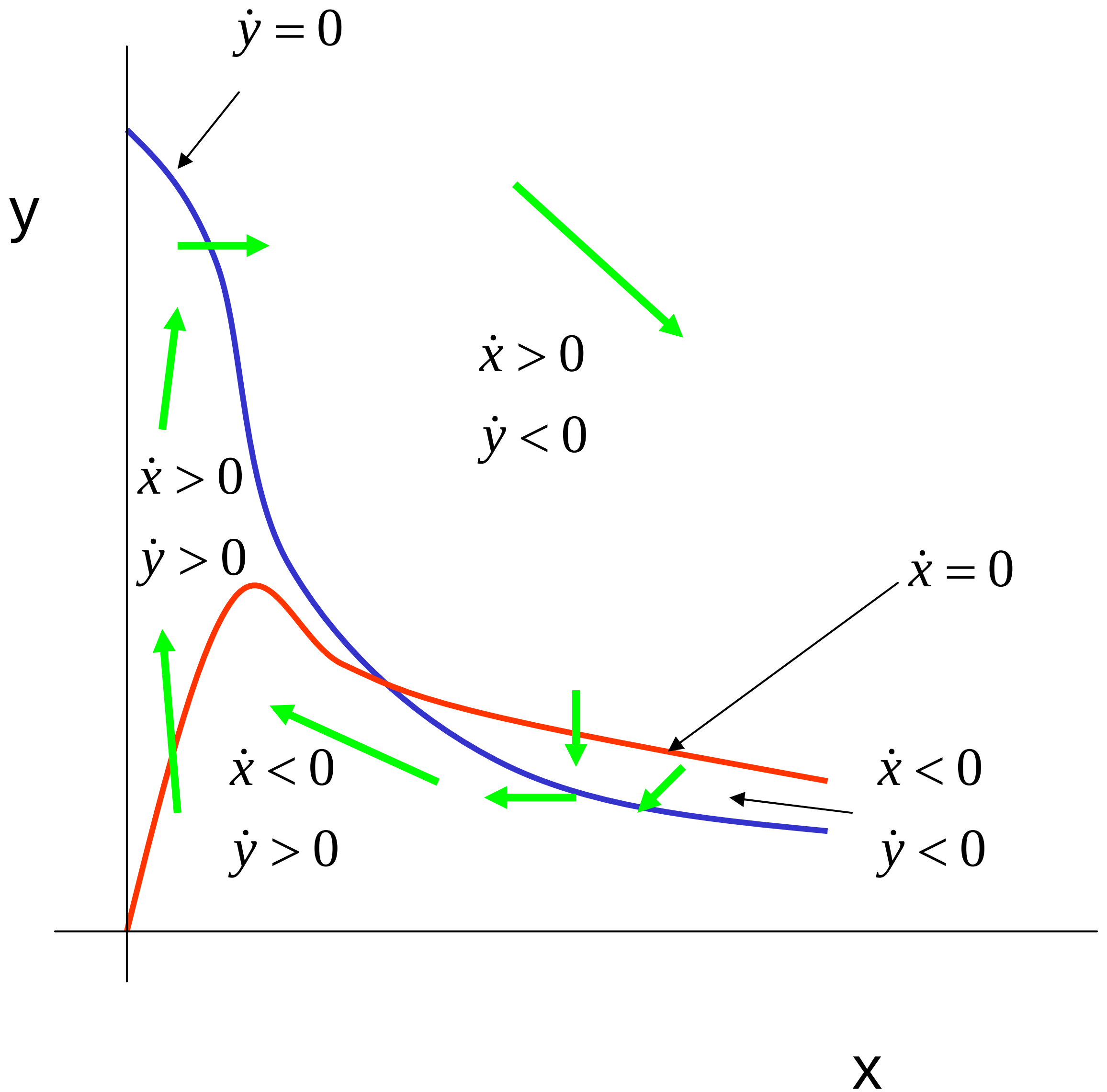
increased ligand concentration

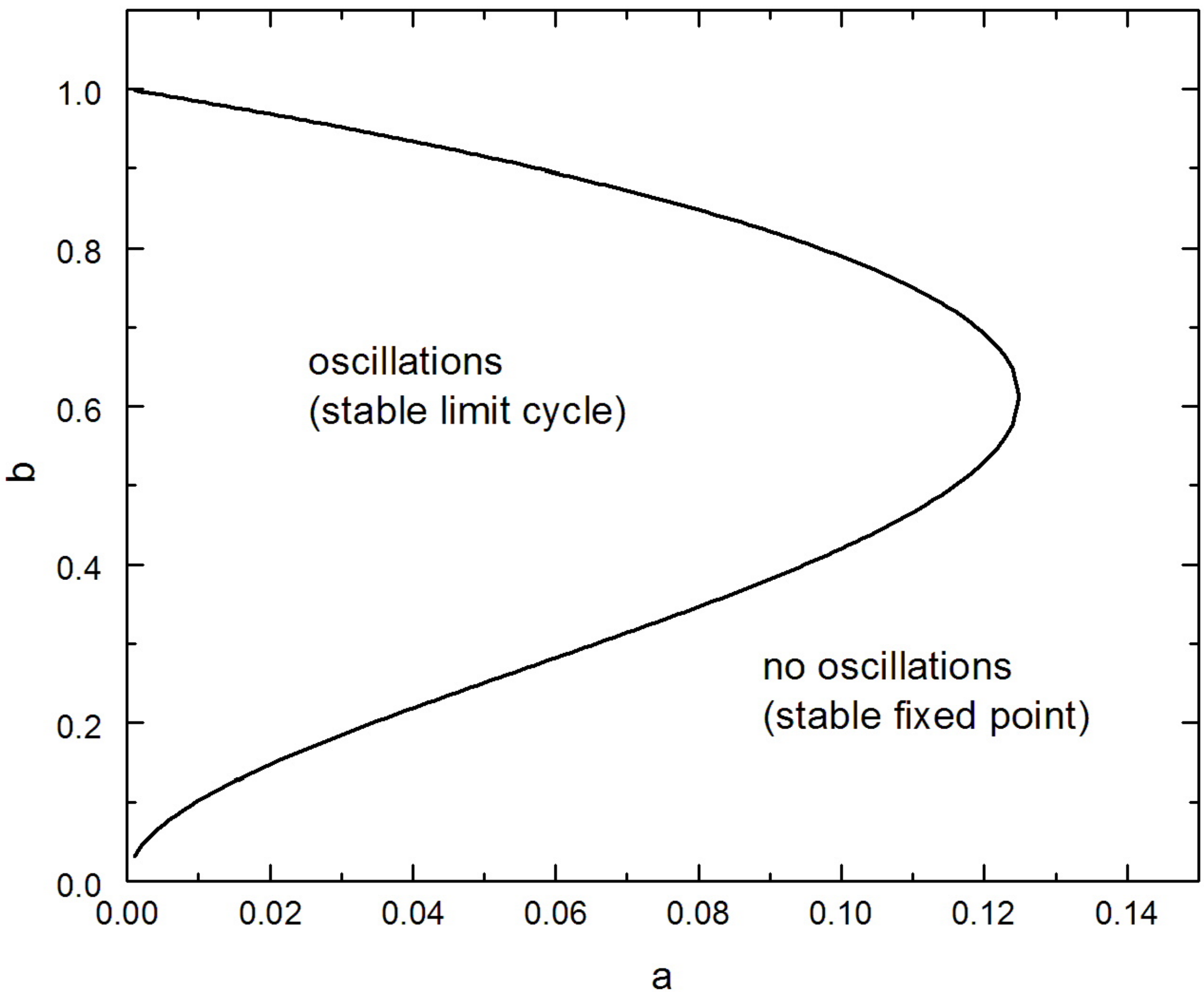


$$(x^*, y^*) = \left(\frac{2r_{in}}{k_{eff\,4}}, \frac{r_{in}k_{eff\,4} + 2r_{in}k_{pt}}{k_{eff\,4}k_{eff\,2}(L)_{35}} \right)$$

Oscillator (unstable fixed point)




$\dot{y} = 0$
y
$\dot{x} > 0$
$\dot{y} < 0$
$\dot{x} > 0$
$\dot{y} > 0$
$\dot{x} = 0$
$\dot{x} < 0$
$\dot{y} > 0$
$\dot{x} < 0$
$\dot{y} < 0$
x


oscillations
(stable limit cycle)
no oscillations
(stable fixed point)
b
a
0.0
0.2
0.4
0.6
0.8
1.0
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14

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