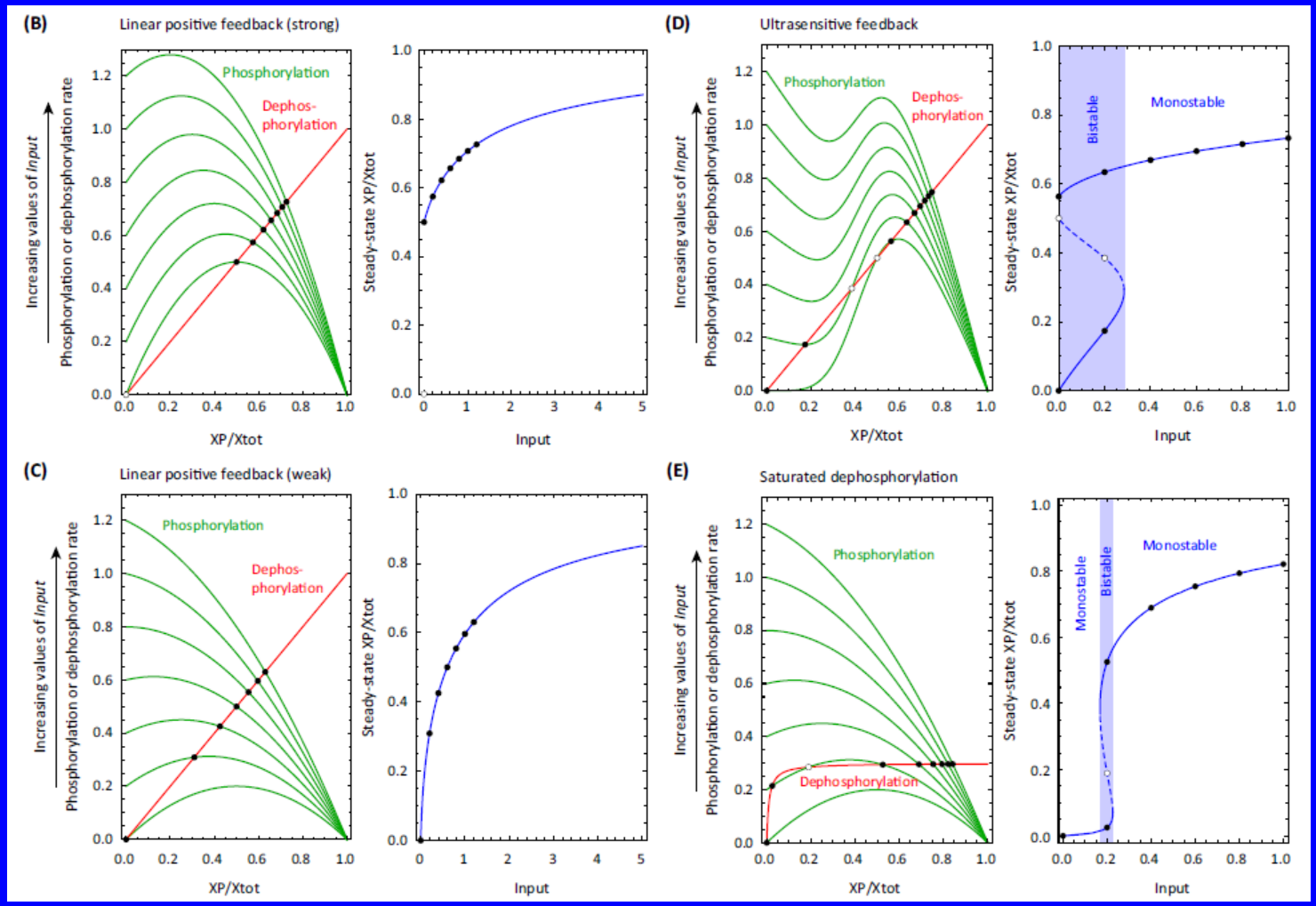
Review

Four classes of distinct mechanisms can generate ultrasensitive responses: zero-order ultrasensitivity, multistep ultrasensitivity, inhibitor ultrasensitivity, positive feedback loops.

Ultrasensitive responses can be critical for the generation of bistability and oscillations.

Assignment

Reproducing Figs3B-E in the literature : Ferrell Jr, J. E. and S. H. Ha (2014). Trends in Biochemical Sciences **39**(12): 612-618.

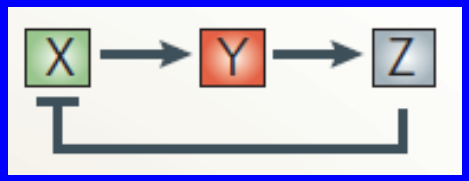


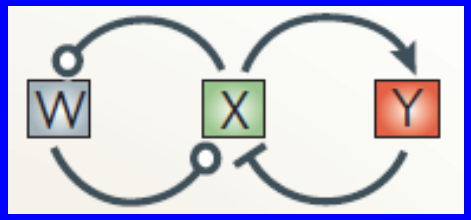
Chap 3 Dynamic modes in cell signaling

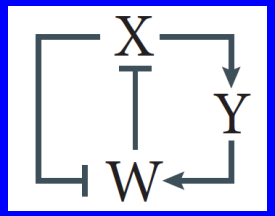
3.1 Negative feedback and oscillations

Table 1 | **Survey of biochemical oscillators**

Function	Components	Period	Class*	References
Metabolism	Glucose, ATP, phospho-fructokinase	2 min	3	52–54
Signalling	Cyclic AMP, receptor, adenylate cyclase	5 min	3	55,64
Signalling	Ca^{2+}, $Ins(1,4,5)P_3$	> 1 s	3	65
Signalling	NF-κB, IκB, IKK	~2 h	1	41,43
Signalling	p53, MDM2	5 h	1	39,40
			3	58,59
Signalling	Msn2, adenylate cyclase, cAMP, PKA	~10 min	1	66,67
Somitogenesis	Her1, Her7, Notch	30–90 min	1	40,68
Yeast endoreplication cycles	Cig2, Cdc10, Rum1	1–2 h	2	49
Frog egg cycles	CycB, Wee1, Cdc25, Cdc20	30 min	2	47, 48
Circadian rhythm	PER, TIM, CLOCK, CYC	24 h	1	26
			2	30





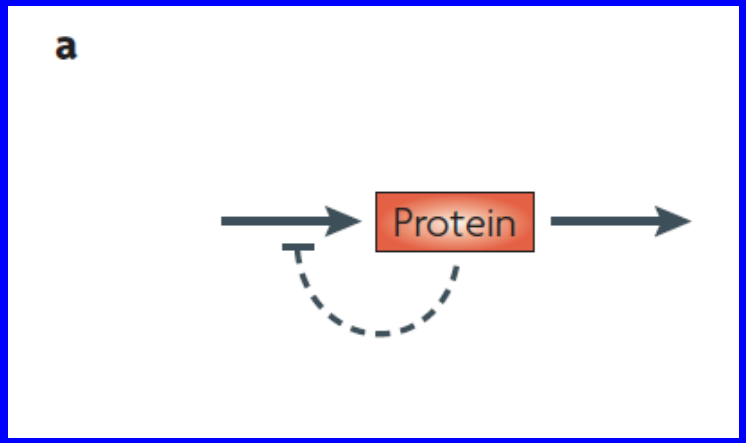


Novak B, Tyson JJ. 2008. Design principles of biochemical oscillators. *Nat Rev Mol Cell Biol* 9:981-91

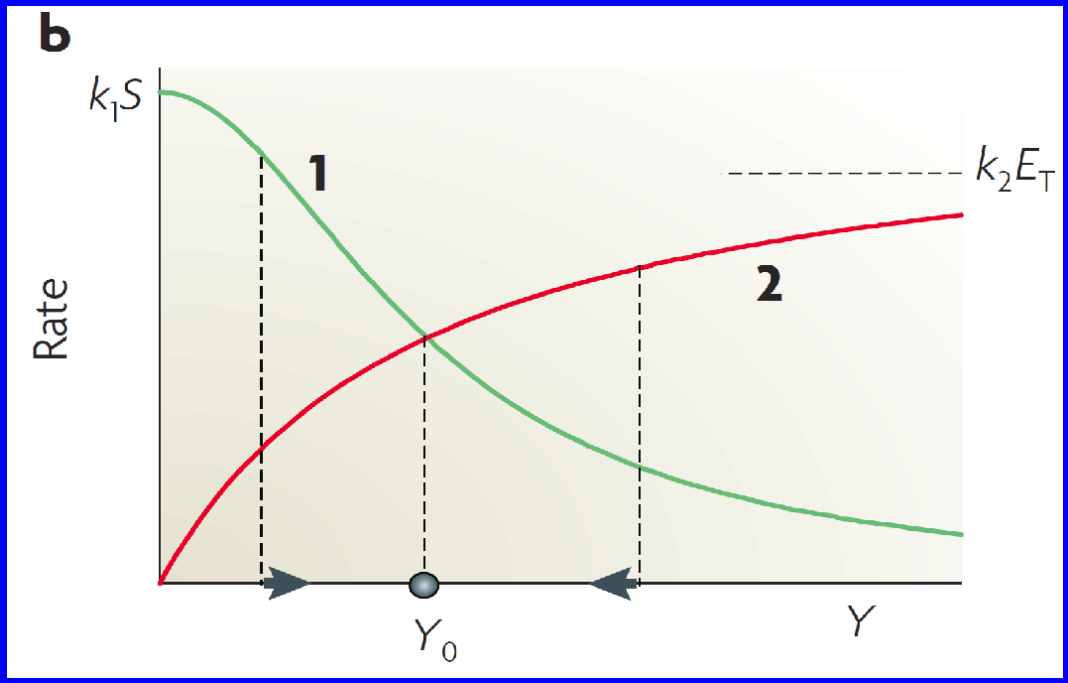
Negative feedback is required but not enough for oscillations !

One-component negative feedback : protein synthesis is repressed by the protein itself.

$$\frac{dY}{dt} = k_1 S \frac{K_d^p}{K_d^p + Y^p} - k_2 E_T \frac{Y}{K_m + Y}$$



Novak, B. and J. J. Tyson (2008). Nat Rev Mol Cell Biol **9**(12): 981-991.



The protein concentration be drawn towards its steady-state value without any oscillations，nor with any overshoots or undershoots. This is great if we are modelling ‘homeostasis’, but not if we want to model ‘oscillations’.

Mechanism to generate oscillation

Negative feedback with time delay

Explicit time delay

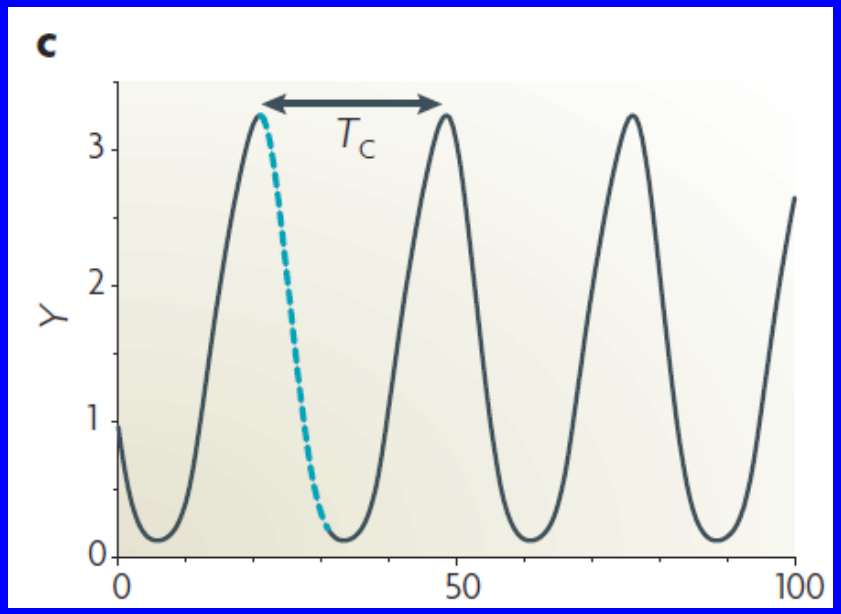
Suppose that the rate of protein synthesis at present (at time t) depends on the concentration of protein at some time in the past (at time $t-\tau$), where τ is the time delay that is required for transcription and translation.

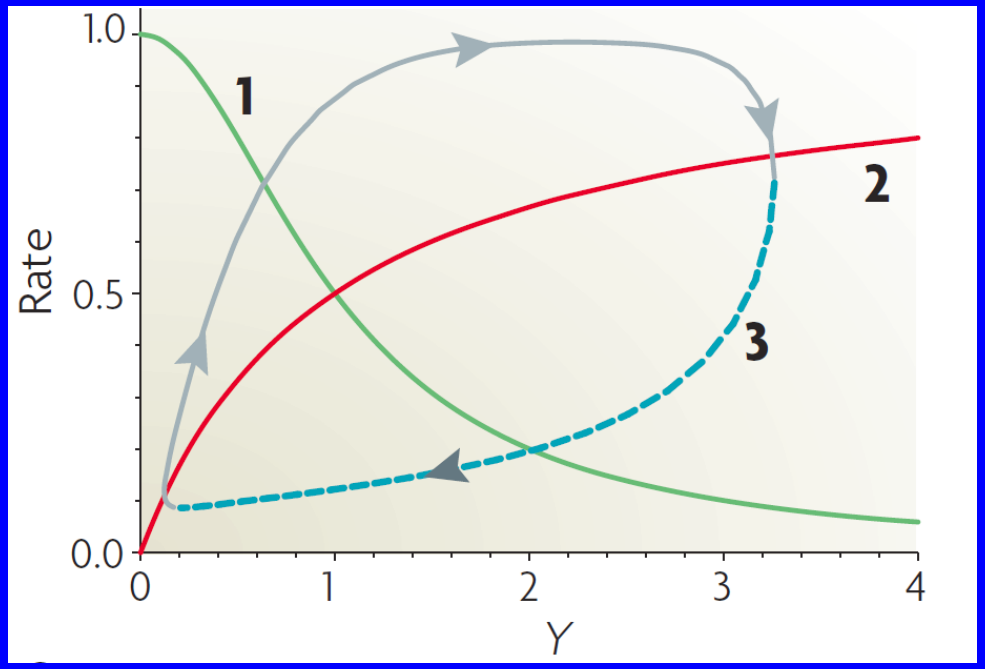
$$\frac{\mathrm{d}Y(t)}{\mathrm{d}t} = k_1 S \frac{K_\mathrm{d}^p}{K_\mathrm{d}^p + Y(t-\tau)^p} - k_2 E_\mathrm{T} \frac{Y(t)}{K_\mathrm{m} + Y(t)}$$

Simulation tools for DDE

- Xpp/Winpp
  http://www.math.pitt.edu/~bard/bardware/
- Matlab DDE23
- DDE Biftool
  http://sourceforge.net/projects/ddebiftool/

```
# protein inhibits its own synthesis with explicit time delay
# protein is degraded by a protease according to Michaelis-
#Menten kinetics

dy/dt = k1*S*Kd^p/(Kd^p + delay(y,tau)^p) - k2*ET*y/(Km + y)
aux dly = delay(y,tau)

aux Fy=k1*S*Kd^p/(Kd^p + delay(y,tau)^p)

p k1=1, S=1, Kd=1, p=2, tau=10
p k2=1, ET=1, Km=1

@ XP=t, YP=y, TOTAL=100, METH=stiff, XLO=0, XHI=100,
YLO=0, YHI=3.5,
delay=20
done
```





τ = 10 min. The period of oscillation, T_c, is 27.2 min.

The time delay causes the negative feedback control repeatedly to overshoot and undershoot the steady state.

Three requirements for oscillation

First, the time delay, τ, must be sufficiently long.

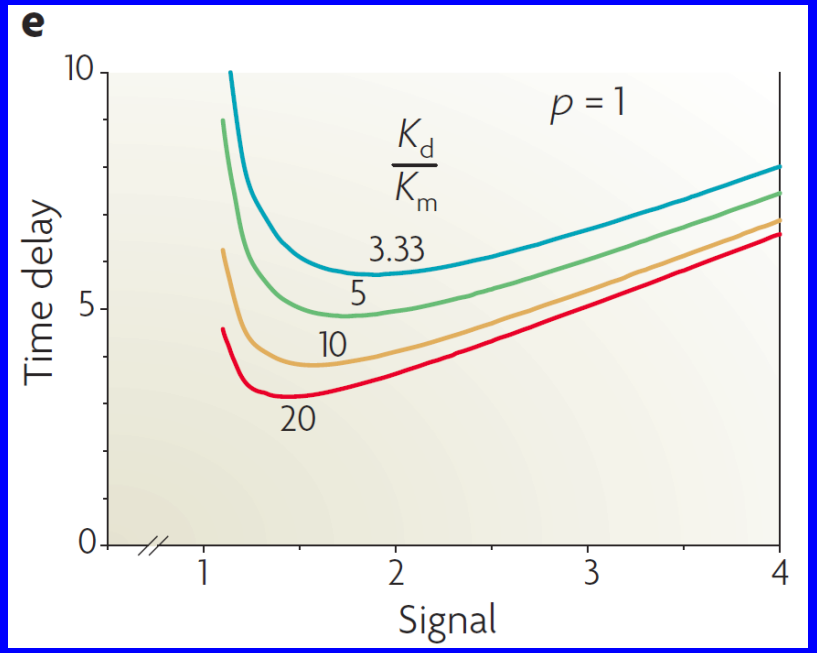
Second, the reaction rate laws must be sufficiently 'nonlinear'.

Third, the rates of opposing processes must be appropriately balanced.

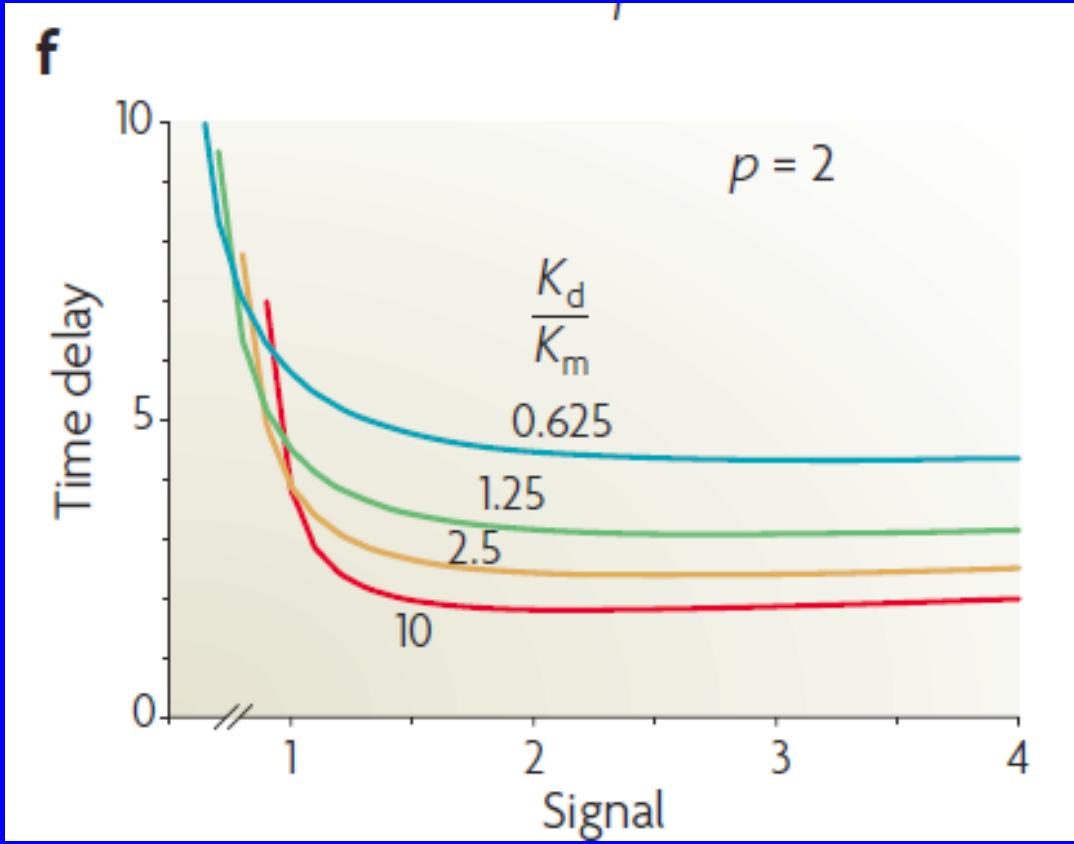
$$\frac{dY(t)}{dt} = k_1 S \frac{K_d^p}{K_d^p + Y(t-\tau)^p} - k_2 E_T \frac{Y(t)}{K_m + Y(t)}$$

$$\frac{k_1 S}{k_2 E_T} = \frac{K_d / k_2 E_T}{K_d / k_1 S} = \frac{T_{degr}}{T_{syn}}$$

$$= \frac{\text{time scale for protein degradation}}{\text{time scale for protein synthesis}}$$



$$\frac{k_2 E_T \tau}{K_d} = \frac{\tau}{K_d / k_2 E_T} = \frac{\tau}{T_{degr}} = \frac{\text{time delay}}{\text{time scale for protein degradation}}$$



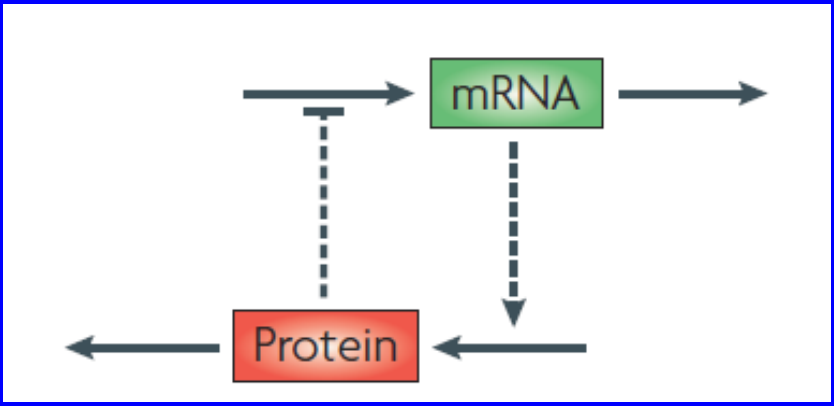
Oscillations become easier — that is, τ_{min} gets smaller — as either p or K_d/K_m increases

The two ratios must (roughly speaking) satisfy the inequalities: $\tau/T_{degr} > 2$ and $T_{degr}/T_{syn} > 1$

Estimating the time delay for transcription and translation to be ~20 min, we predict that for the negative-feedback loop to oscillate, the timescale for protein degradation must be < 10 min and the timescale for protein synthesis must be even shorter. If these conditions are satisfied, then the period of oscillation is (again, roughly speaking) between twice and four times the time delay; that is, ~40–80 min.

Time delay by a series of intermediates

There is a sufficiently long time delay between the action of the protein Y on the gene and the appearance of new protein molecules in the cytoplasm.



$$\frac{dX}{dt} = k_1 S \frac{K_d^p}{K_d^p + Y^p} - k_{dx} X$$

$$\frac{dY}{dt} = k_{sy} X - k_2 E_T \frac{Y}{K_m + Y}$$

Nullclines

- X-nullcline

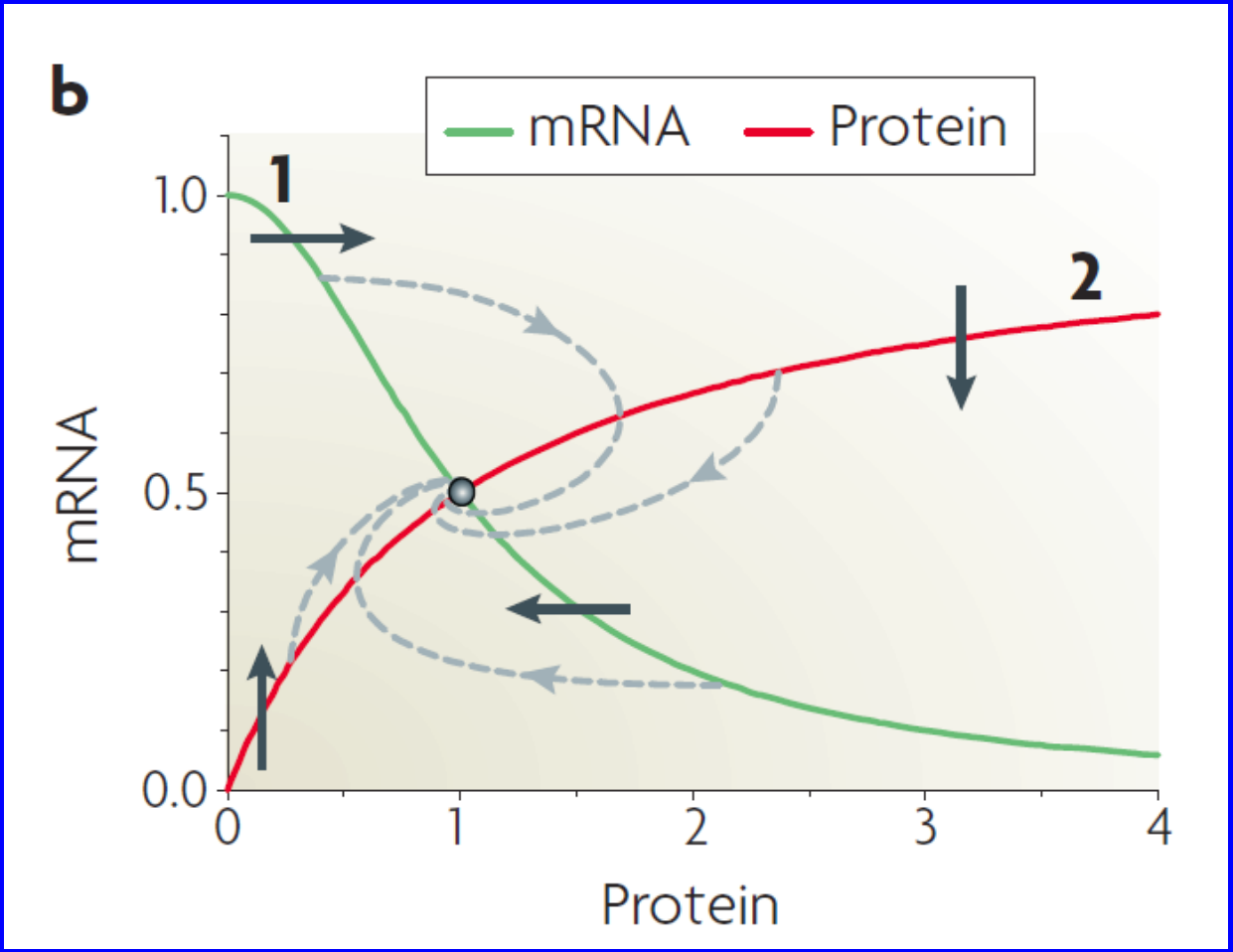
$$\frac{dX}{dt} = 0$$

$$X = \frac{k_1 S}{k_{dx}} \frac{K_d^p}{K_d^p + Y^p}$$

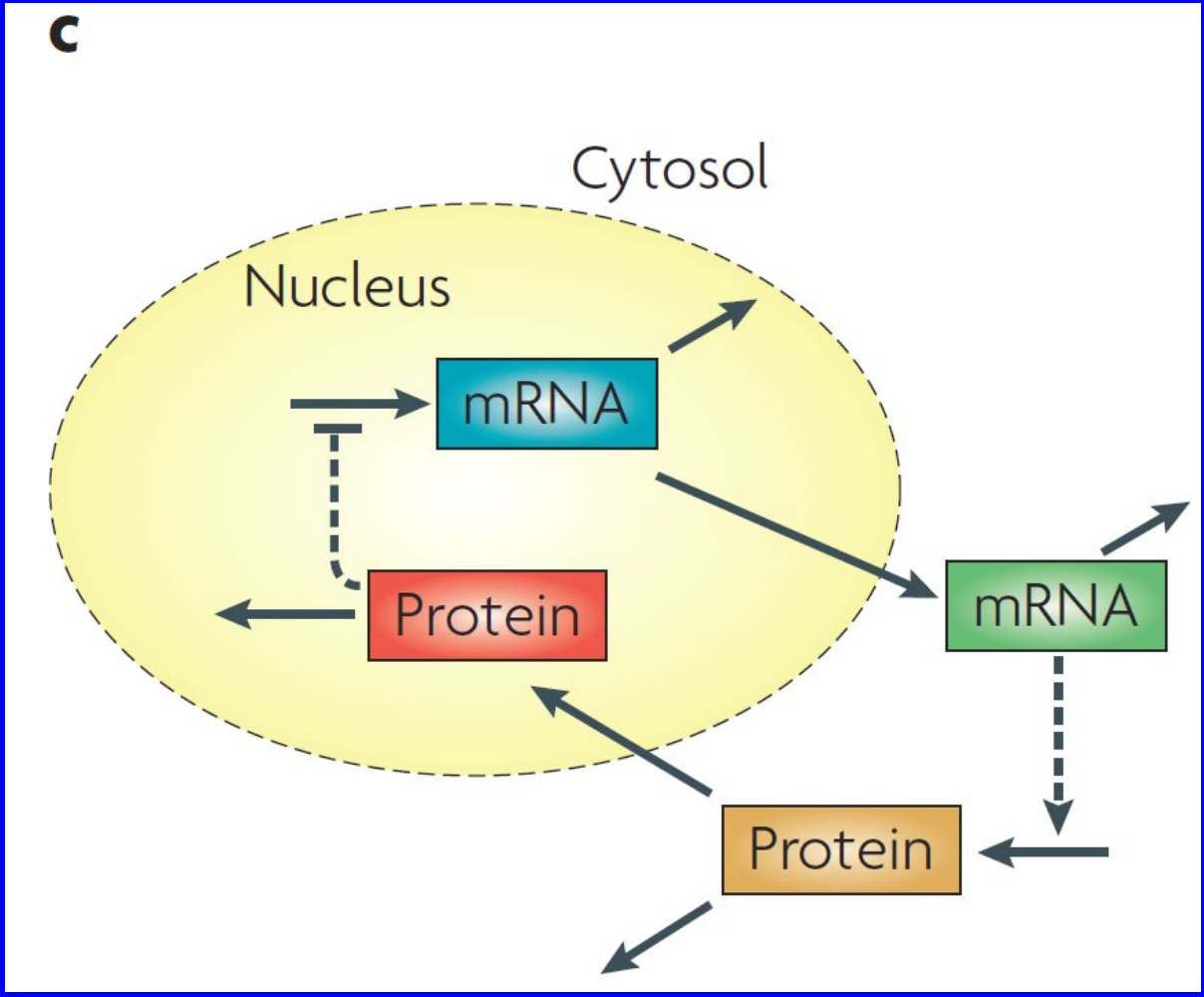
- Y-nullcline

$$\frac{dY}{dt} = 0$$

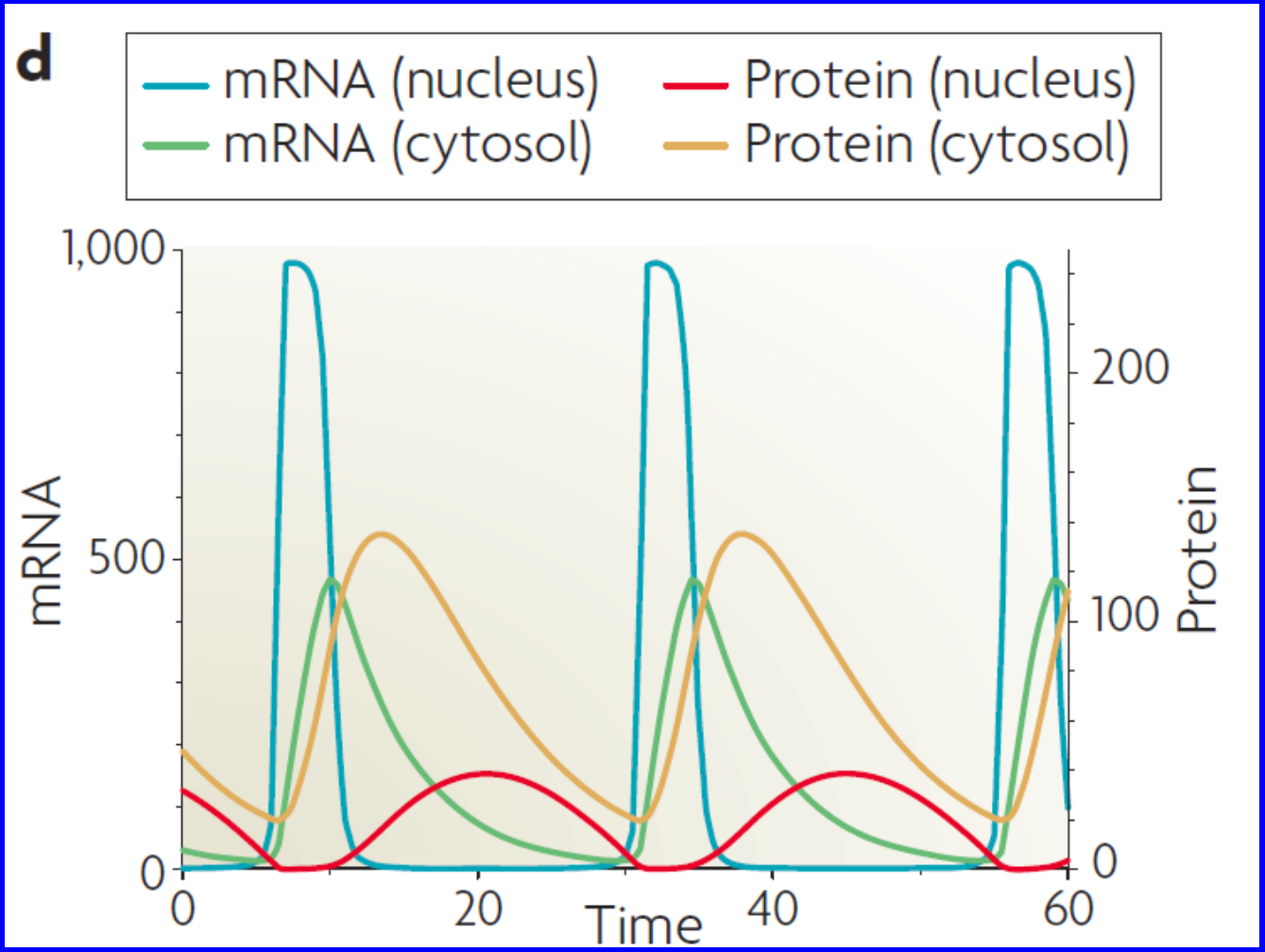
$$X = \frac{k_2 E_T}{k_{sy}} \frac{Y}{K_m + Y}$$



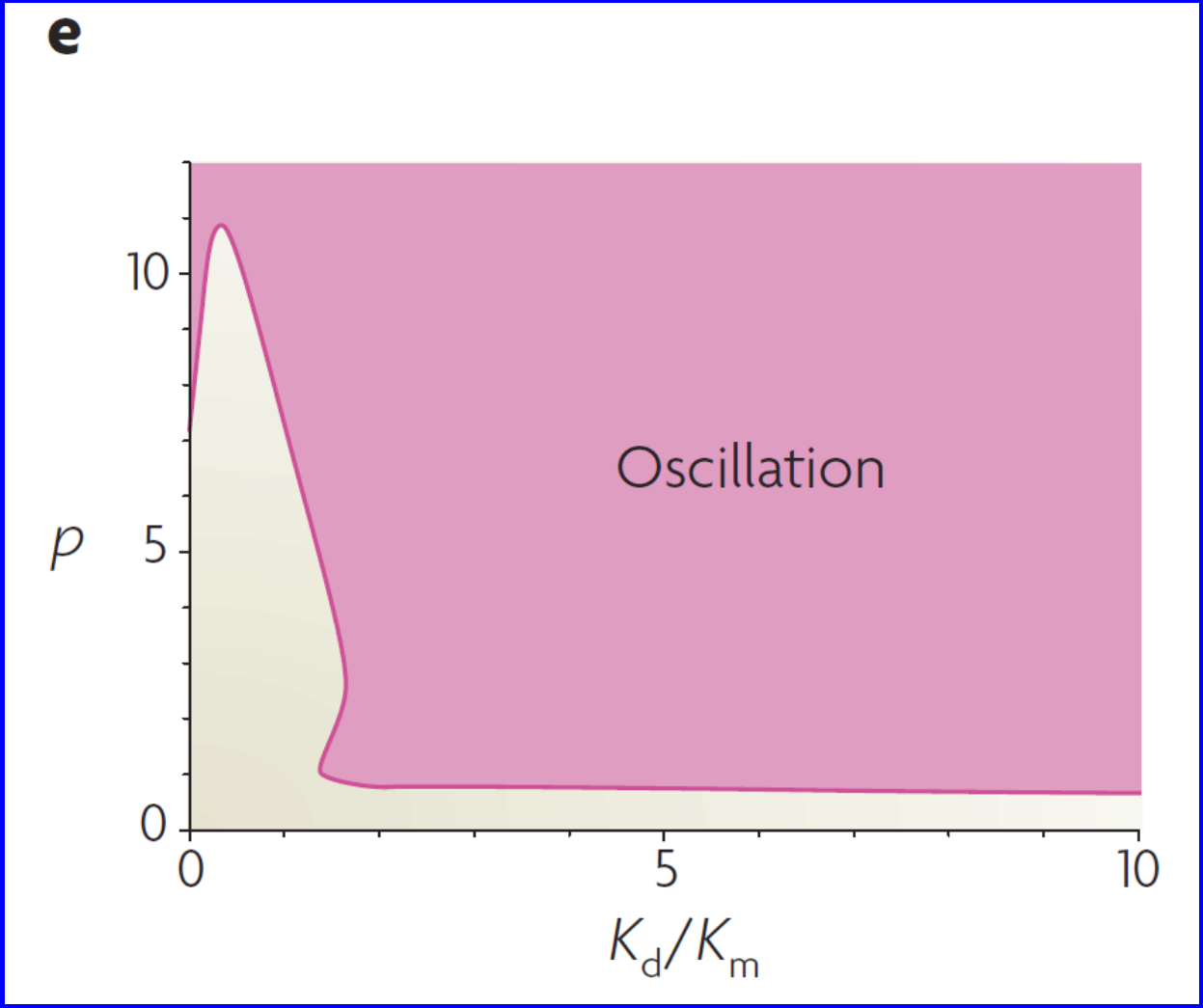
Every trajectory spirals into the stable steady state located at the grey circle.



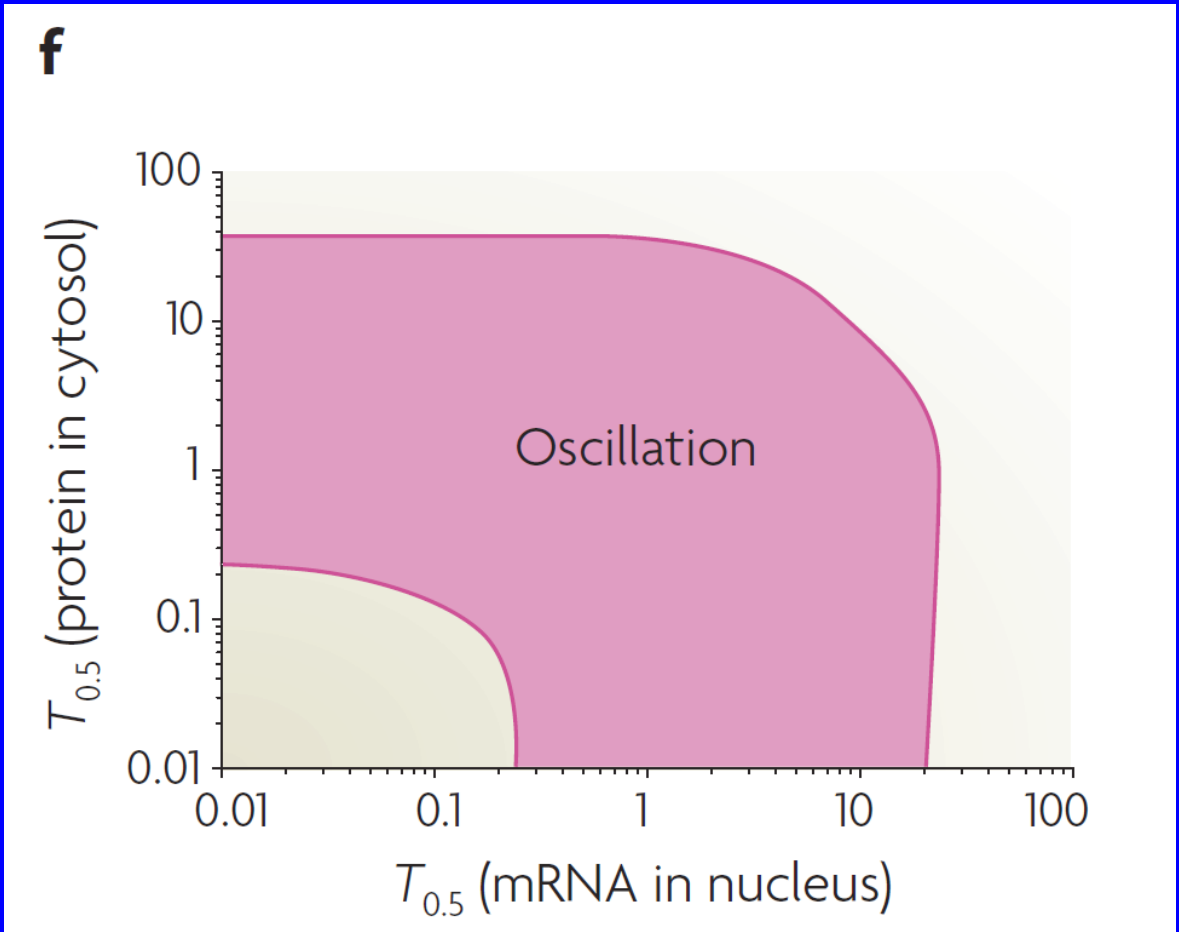
The negative-feedback loop taking into account transport of macromolecules between the nucleus and the cytoplasm.



Sustained oscillations for the four-component loop



Nonlinearity constraint. For the negative-feedback loop to oscillate, p and K_d/K_m must be sufficiently large.



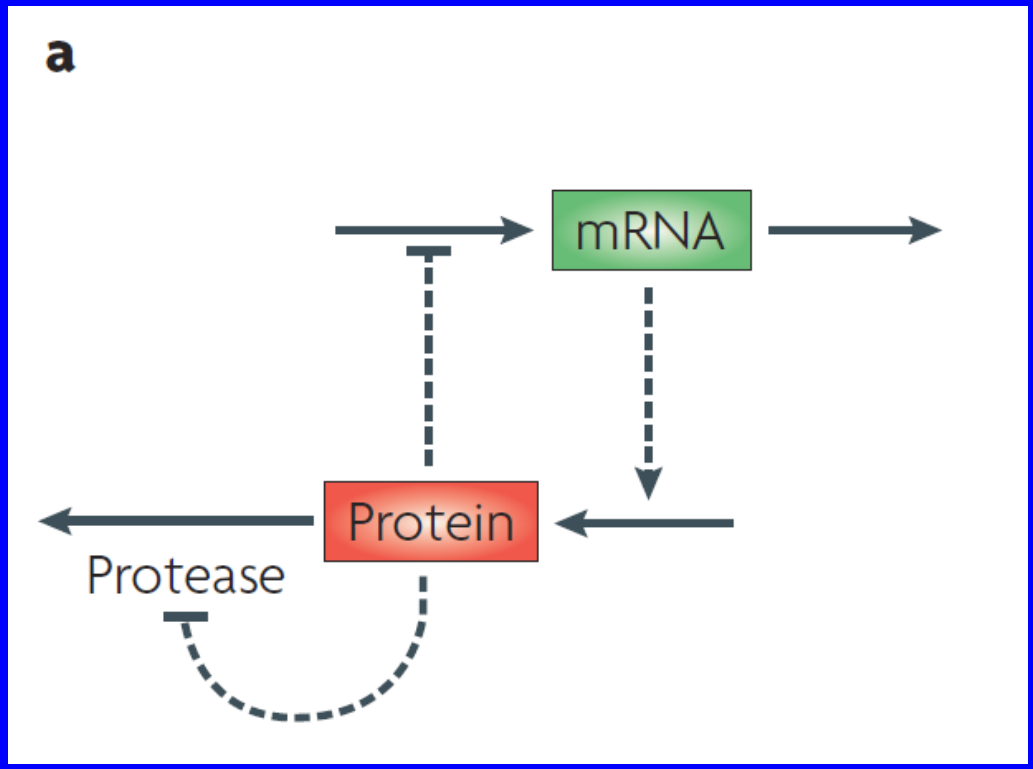
Timescale balancing constraint.

Oscillations are impossible in a two-component negative-feedback loop, but are possible in a three-component negative-feedback loop.

Time delay by positive feedback

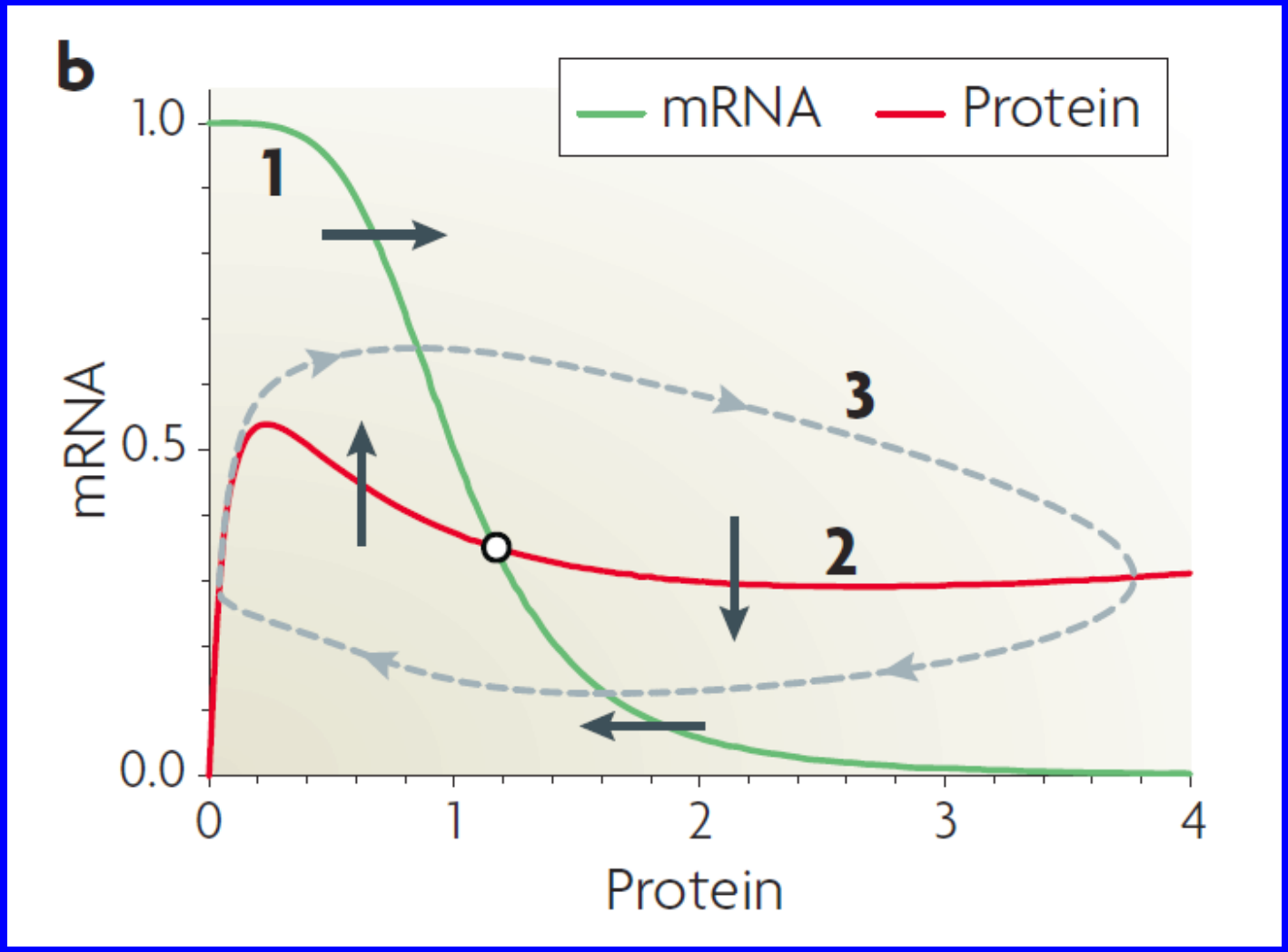
Time delay is a sort of memory: protein synthesis rate at the present time depends on protein concentration over some time in the past.

Memory is a property of biochemical systems with bistability: under identical chemical conditions, the system can be in either of two alternative stable steady states. Which state a system occupies depends on its recent history (a phenomenon called hysteresis). Hysteresis can prevent a system with negative feedback from finding its homeostatic steady state.

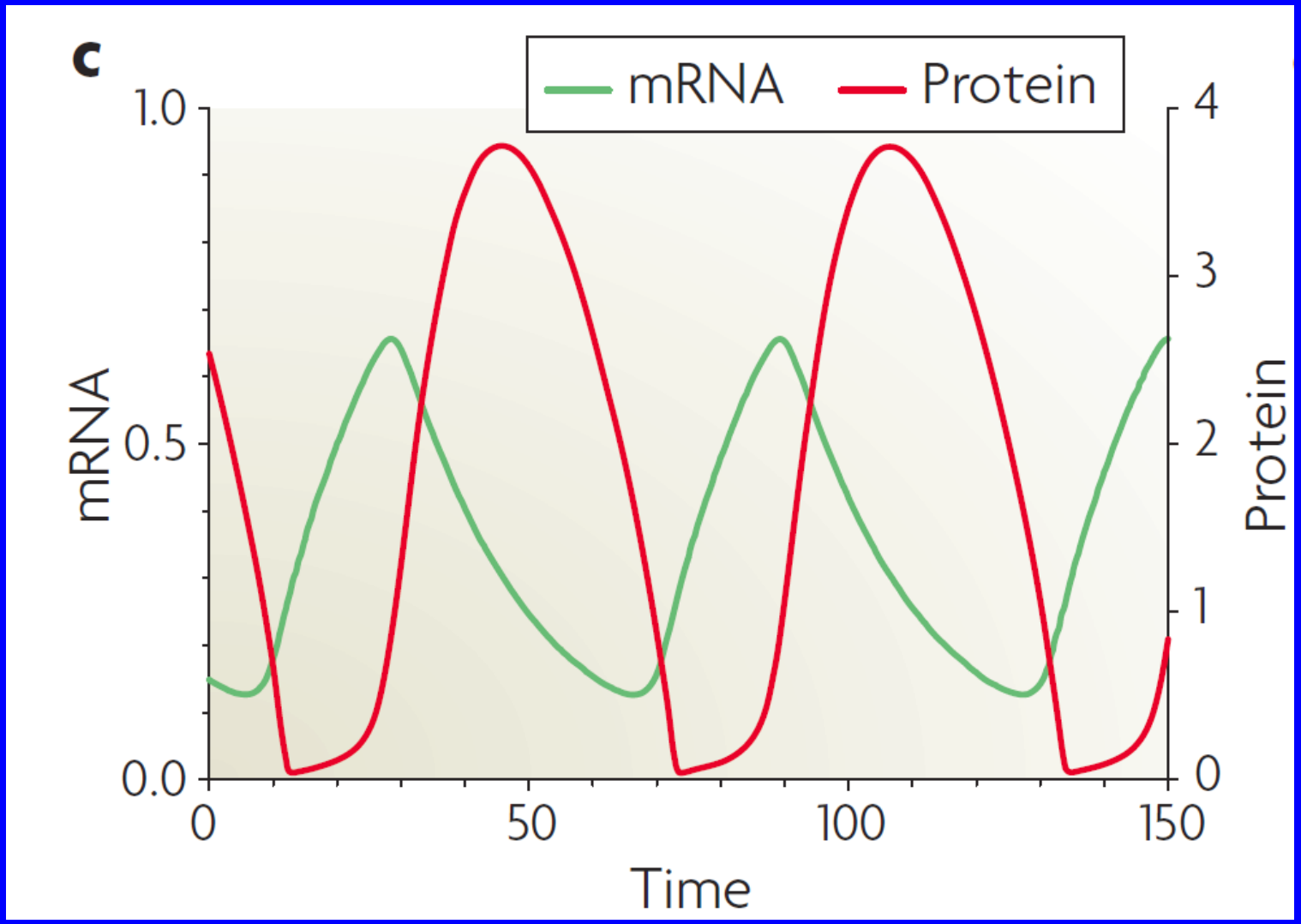


$$\frac{dX}{dt} = k_1 S \frac{K_d^p}{K_d^p + Y^p} - k_{dx} X$$

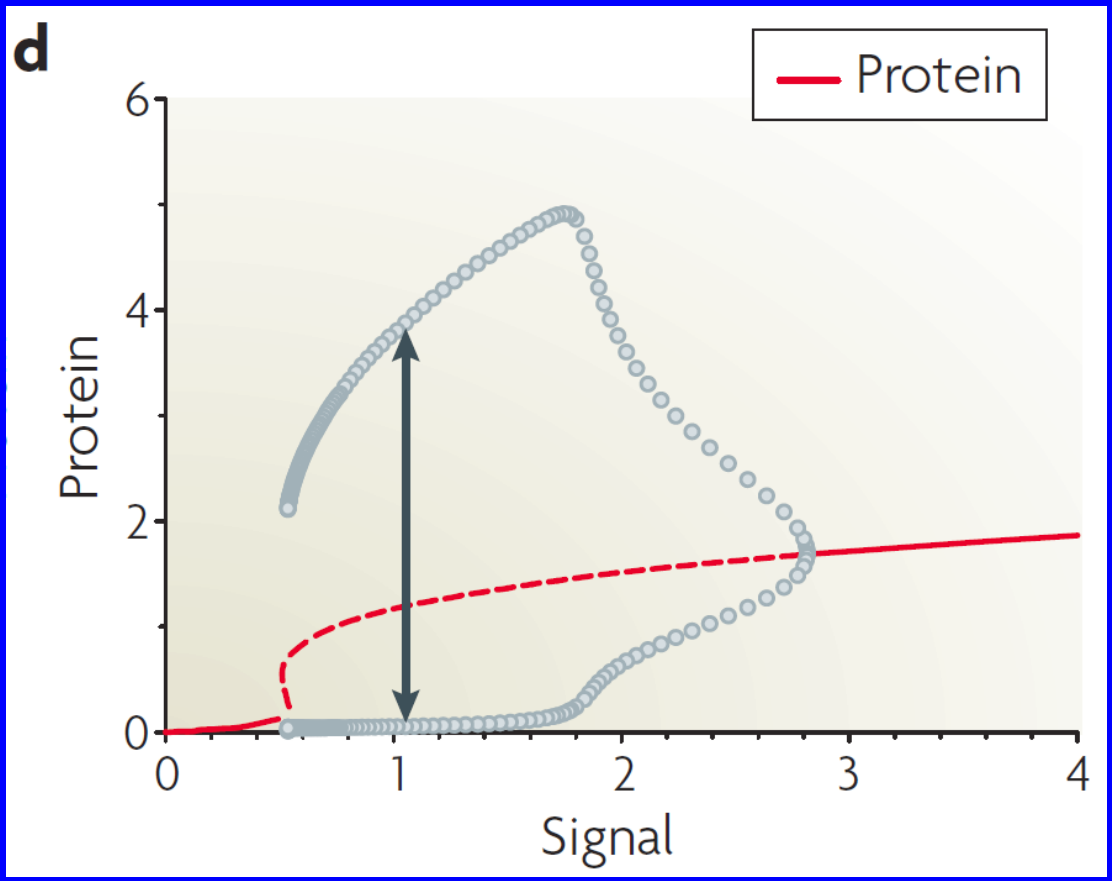
$$\frac{dY}{dt} = k_{sy} X - k_{dy} Y - k_2 E_T \frac{Y}{K_m + Y + K_I Y^2}$$



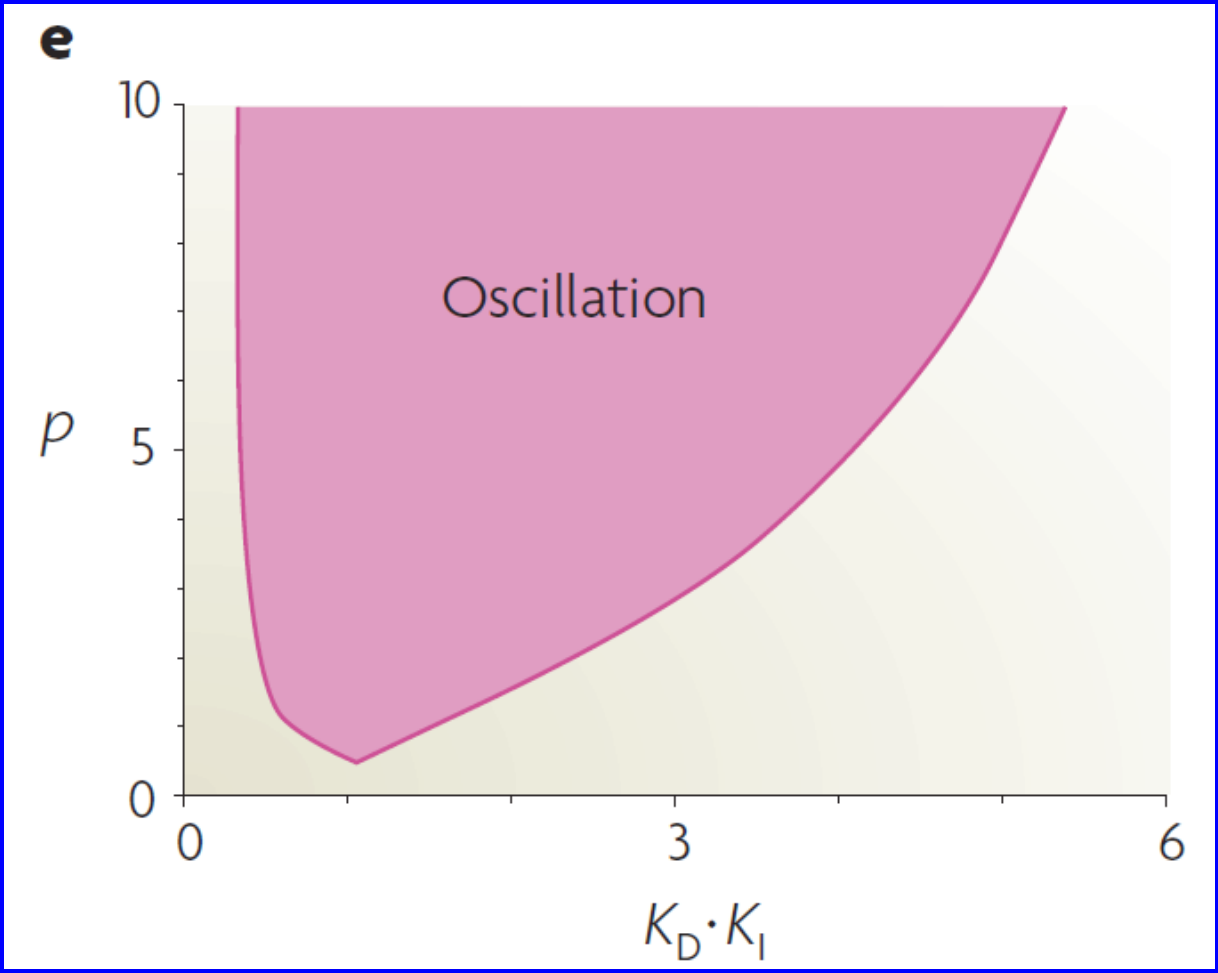
Limit cycle solution



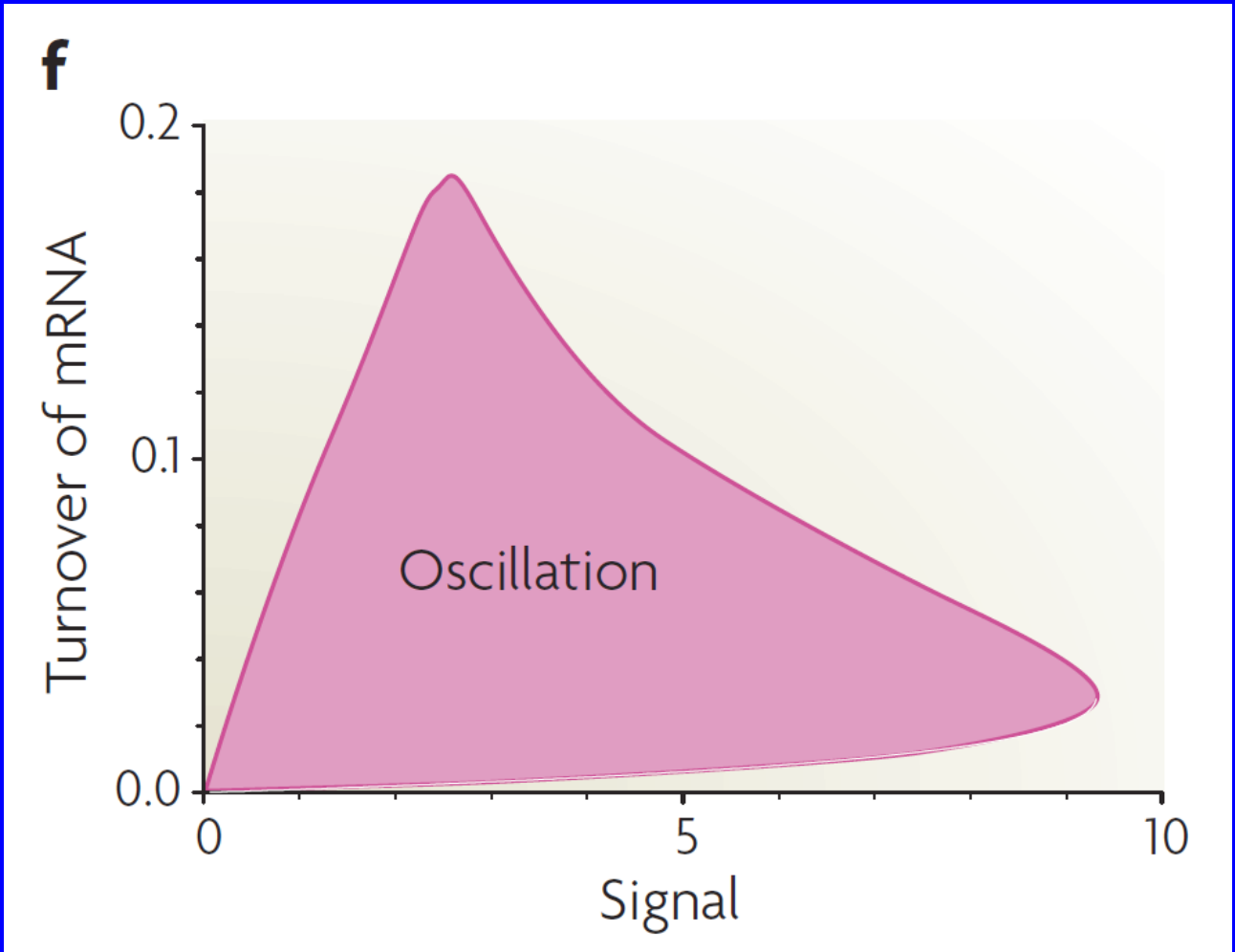
Sustained oscillations of mRNA and protein.



Signal–response curve. Solid lines represent stable steady states; dashed lines represent unstable steady states; grey circles represent maximum and minimum excursions of $Y(t)$ during a limit cycle oscillation.

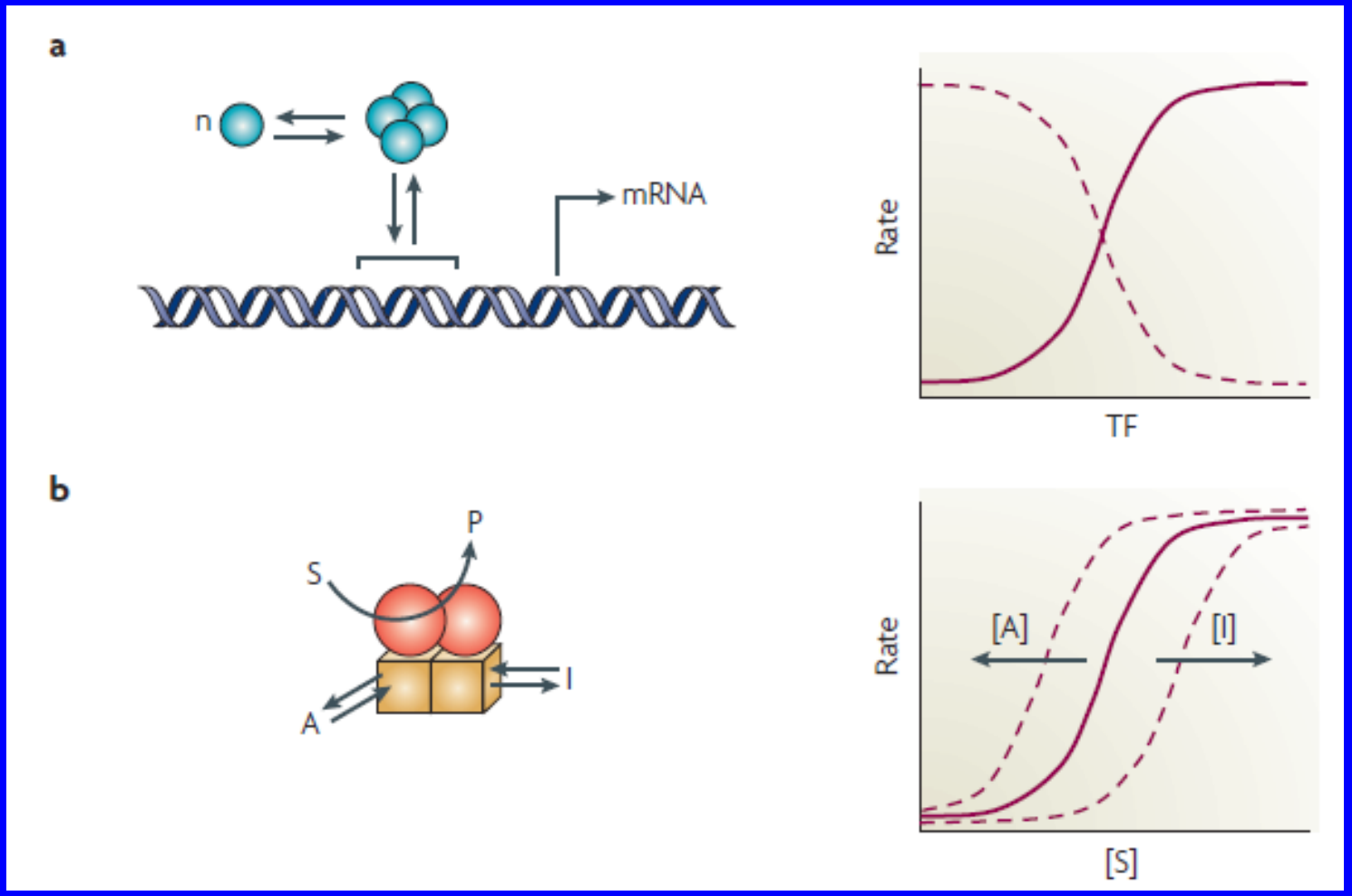


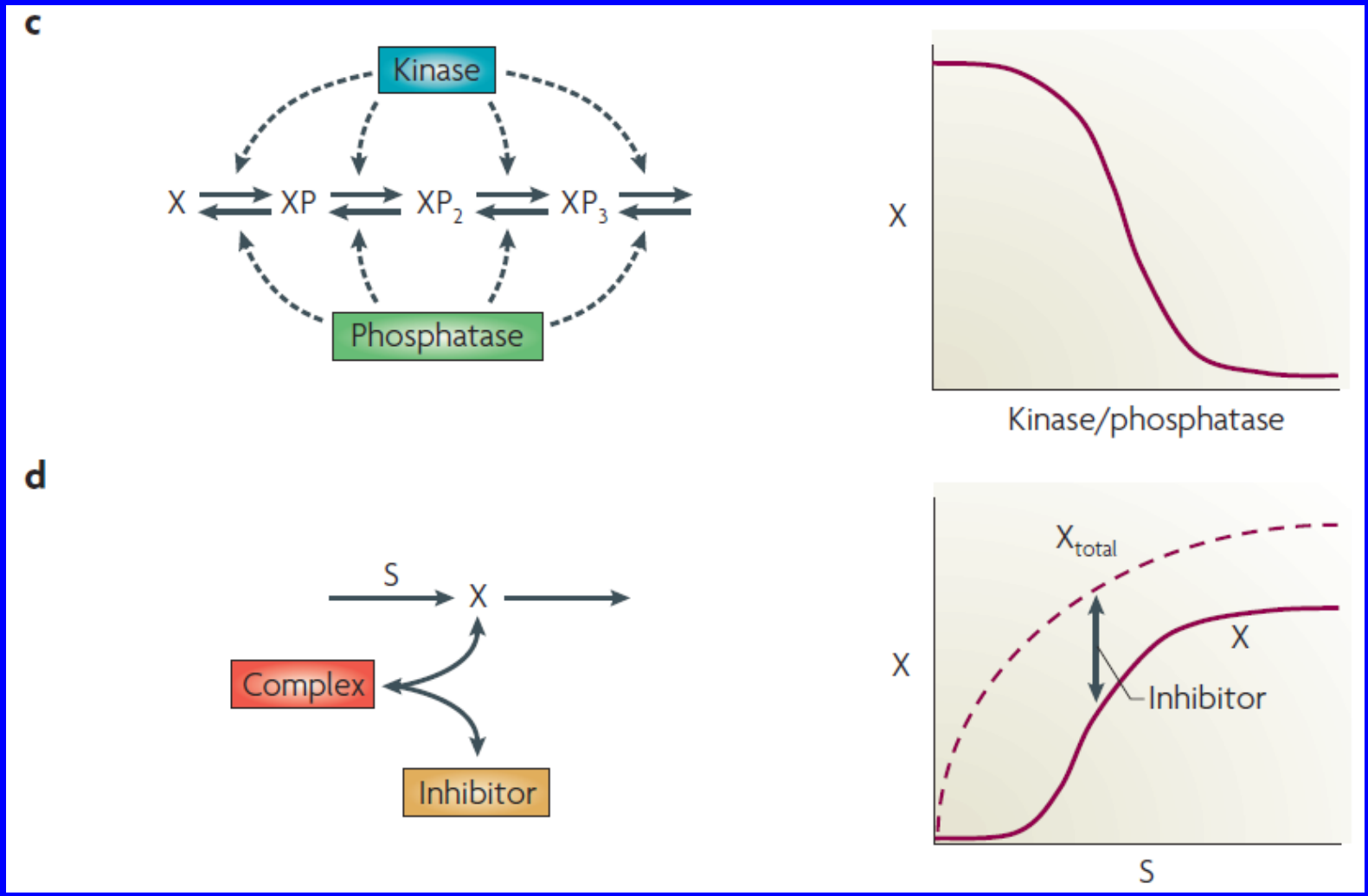
Nonlinearity constraint. For this mechanism to oscillate, the positive-feedback loop must be strong enough and the negative-feedback loop must be sufficiently nonlinear



Timescale balancing constraint. The turnover rate of mRNA cannot be too large, and S must be within specific bounds for this system to oscillate.

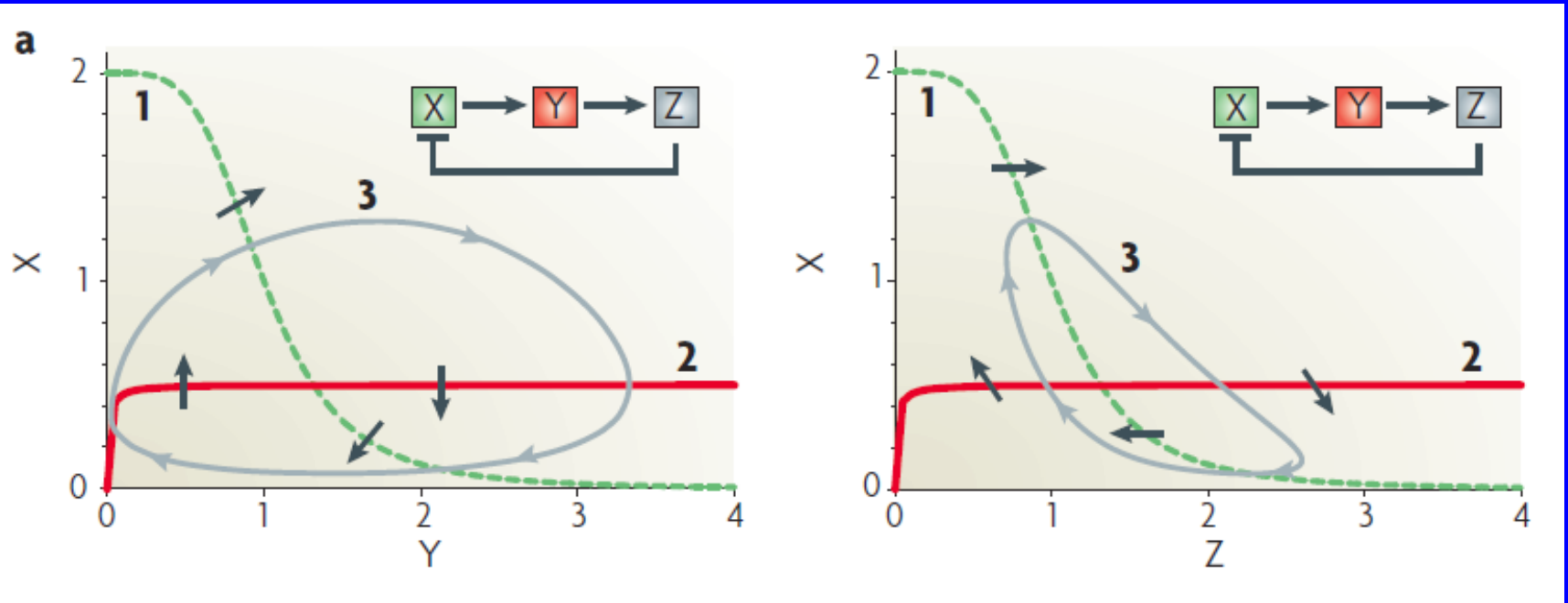
Source of ultrasensitivity




c
Kinase
X
XP
XP2
XP3
Phosphatase
X
Kinase/phosphatase
d
S
X
Complex
Inhibitor
Xtotal
X
Inhibitor
X
S

Classification of oscillatory motifs

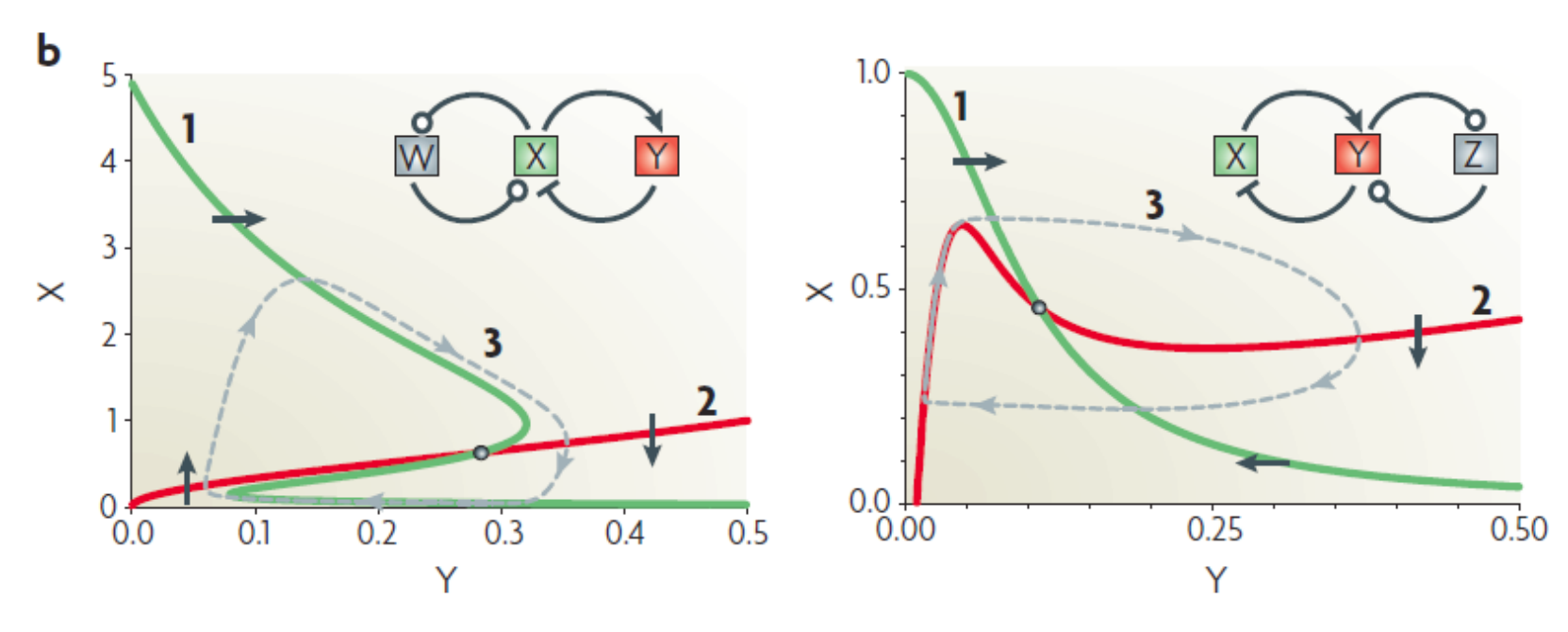
Class 1: delayed negative-feedback loops



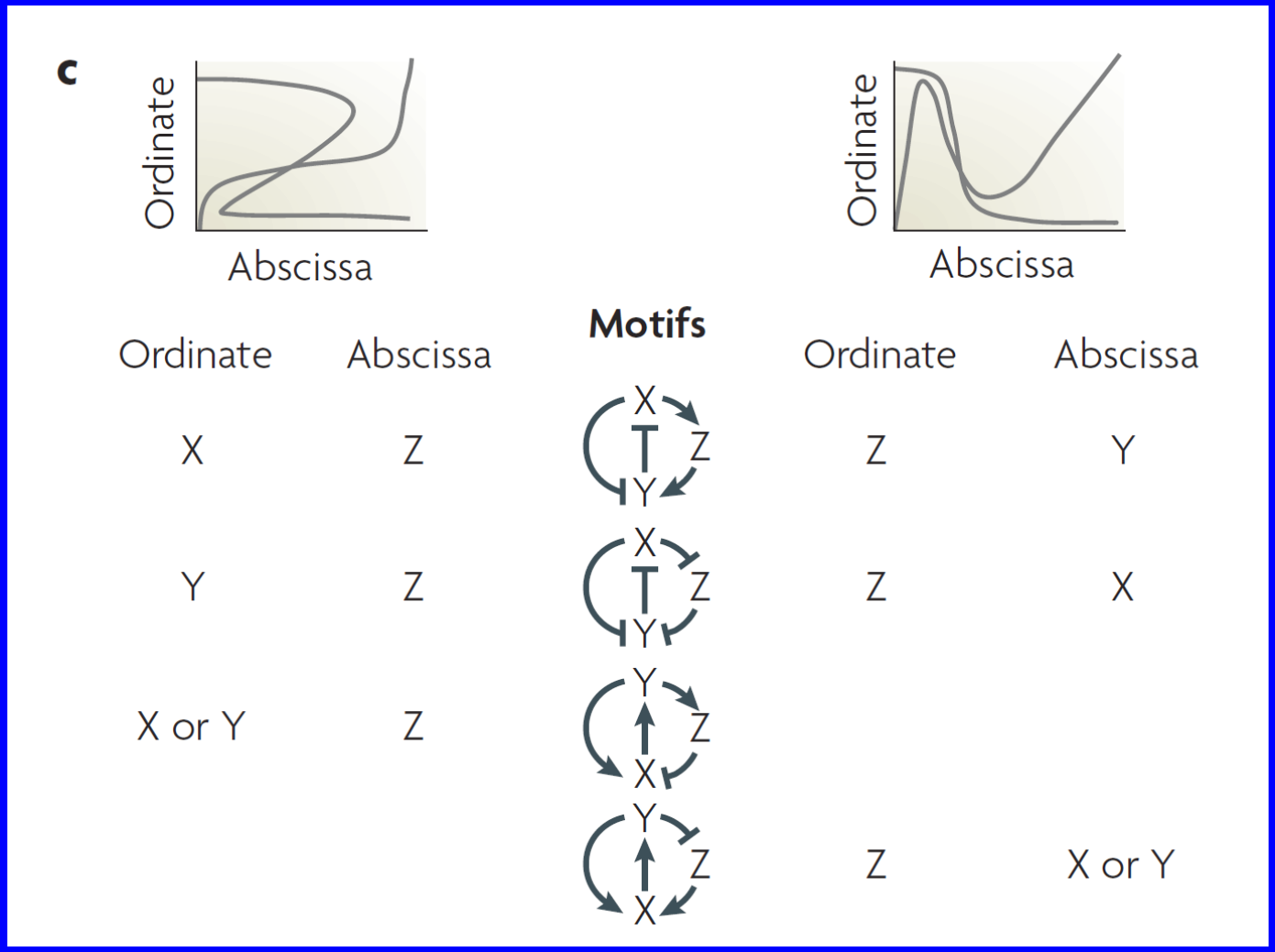
P53-Mdm2 loop

NF-κB -IκB loop

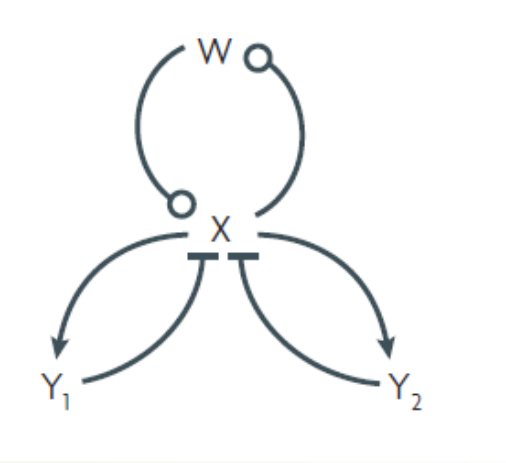
Class 2: amplified negative-feedback loops

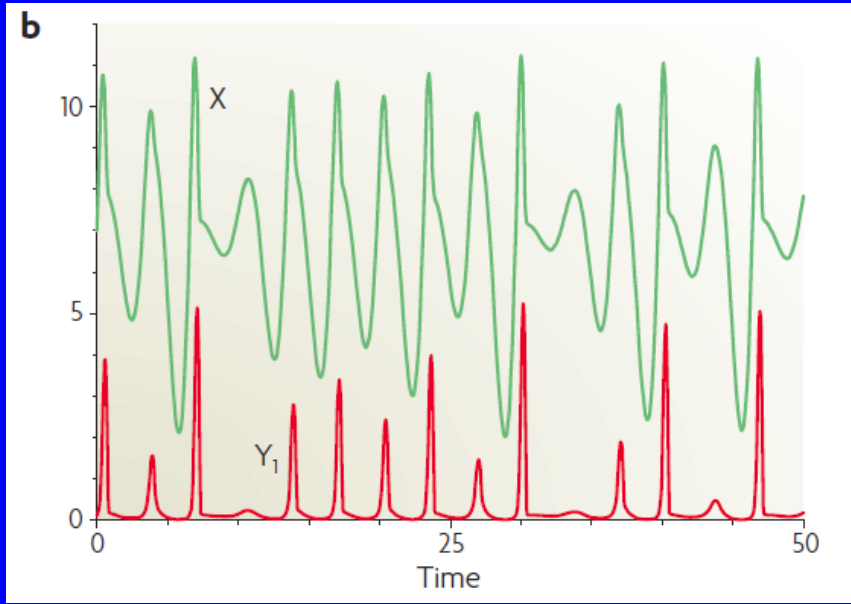


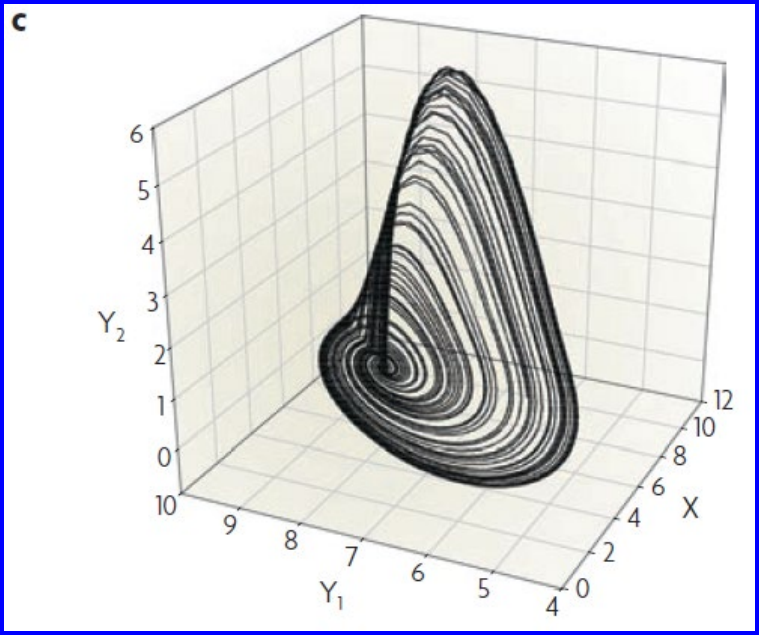
Class 3: incoherently amplified negative-feedback loops.



More complex topologies and oscillatory behaviours







Chaotic oscillators

Summary

First, negative feedback is necessary to carry a reaction network back to the 'starting point' of its oscillation.

Second, the negative feedback signal must be sufficiently delayed in time so that the chemical reactions do not settle on a stable steady state.

Third, the kinetic rate laws of the reaction mechanism must be sufficiently 'nonlinear' to destabilize the steady state.

Fourth, the reactions that produce and consume the interacting chemical species must occur on appropriate timescales that permit the network to generate oscillations.

Assignment 5

Figure 3

Novak, B. and J. J. Tyson (2008). Nat Rev Mol Cell Biol **9**(12): 981-991.