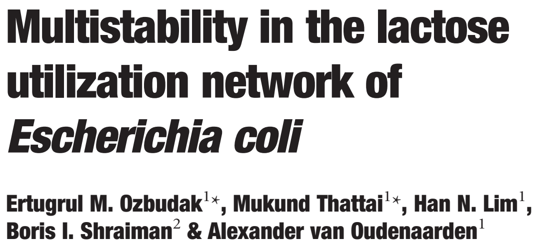
Bistability in genetic networks generates hysteresis and bimodal behaviour

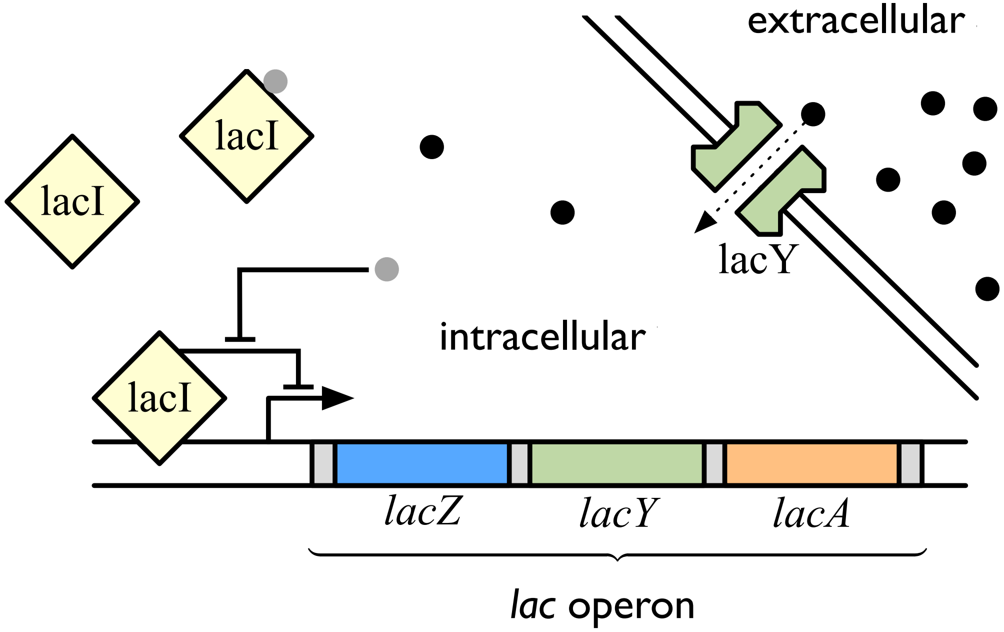
Bistable behaviour in a genetic network relies on positive feedback and exhibits hysteresis



Multistability in the lactose utilization network of *Escherichia coli*

**Ertugrul M. Ozbudak[1]*, Mukund Thattai[1]*, Han N. Lim[1],
Boris I. Shraiman[2] & Alexander van Oudenaarden[1]**

Positive feedback is through the permease LacY, which acts to increase its own expression.



Expression from the network exhibits hysteresis

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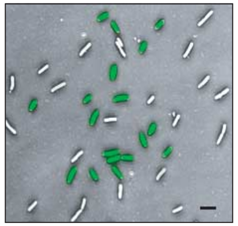
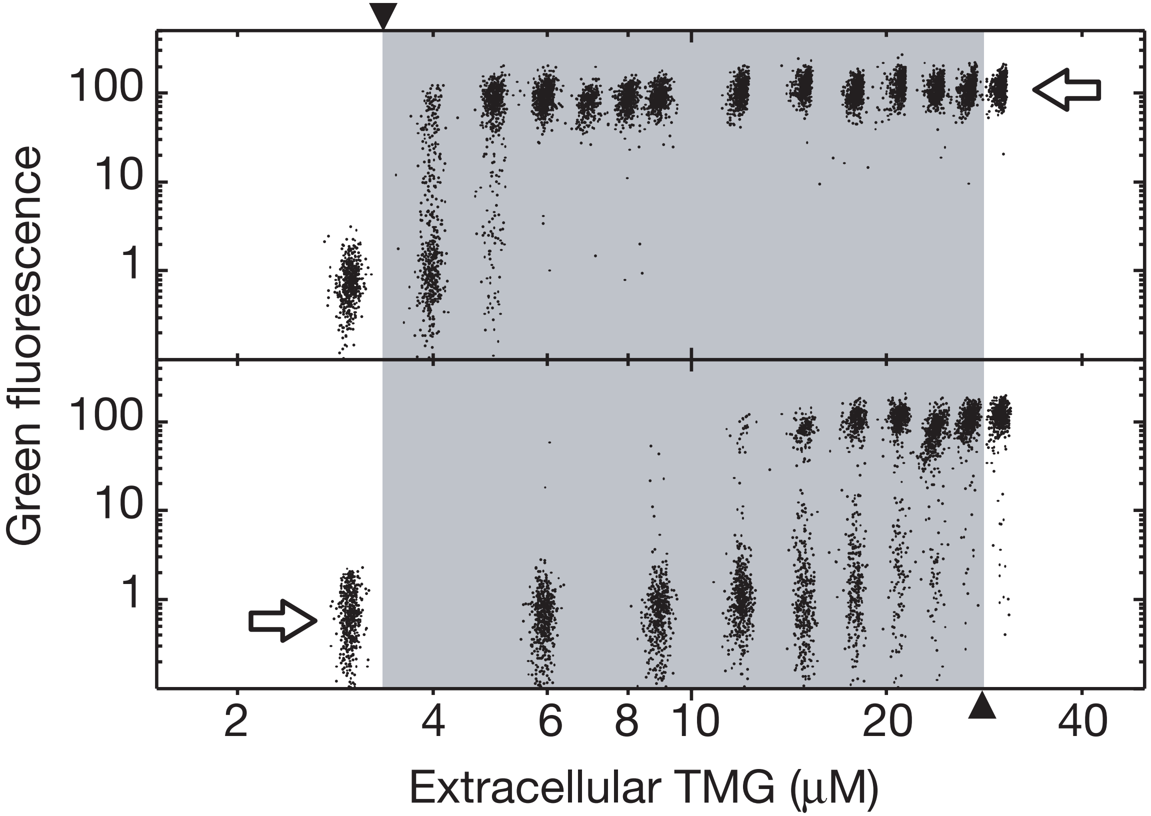
GFP synthesized from a copy of a promoter in the network is used to measure output.



Hysteresis: two different concentrations of inducer (TMG) cause switching of expression



Bimodal: the distribution of fluorescence has two peaks

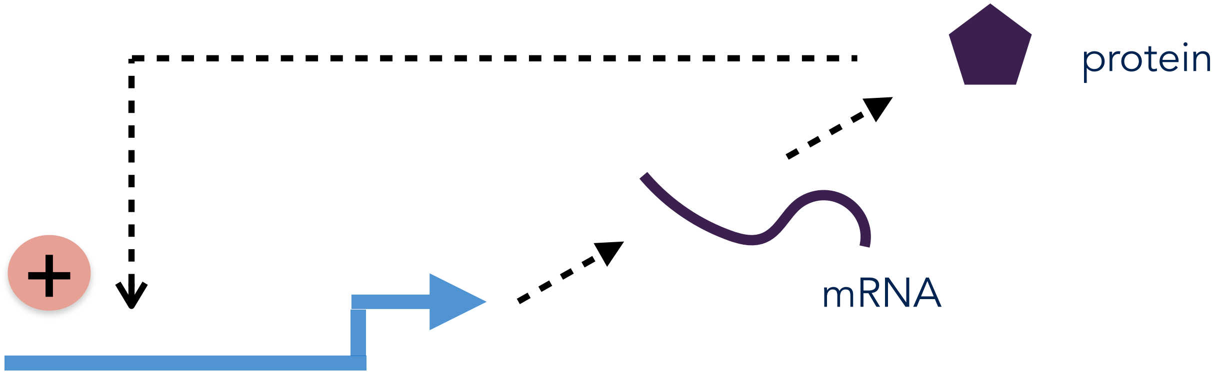
Bistability may be generated by a transcription factor directly activating its own transcription

positive feedback

mRNA $$\frac{dM}{dt} = u_b + \frac{uP^n}{K^n + P^n} - d_M M$$

protein $$\frac{dP}{dt} = M - d_P P$$

High levels of protein activate transcription creating still higher levels of protein.

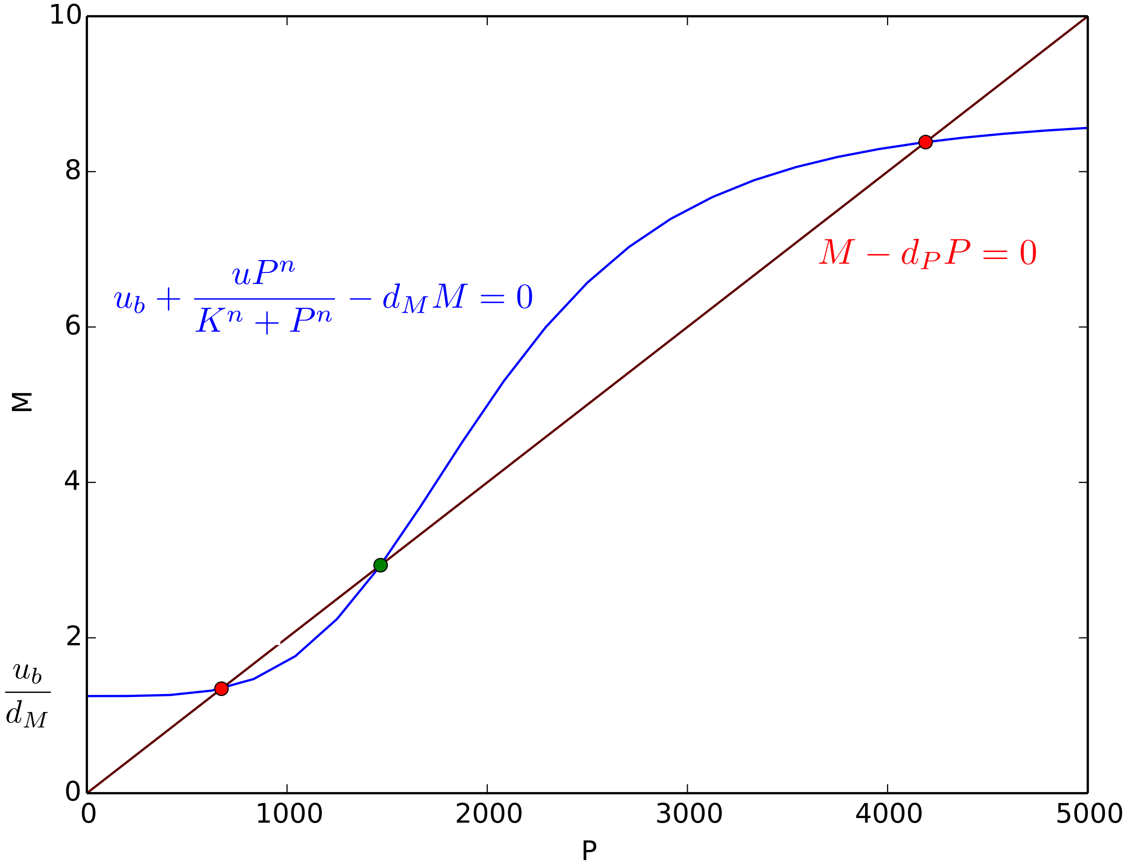


The steady-states are where the nullclines intersect

The nullclines are the lines along which the time derivatives are zero.

$$\frac{dM}{dt} = u_b + \frac{uP^n}{K^n+P^n} - d_M M$$

$$\frac{dP}{dt} = M - d_P P$$



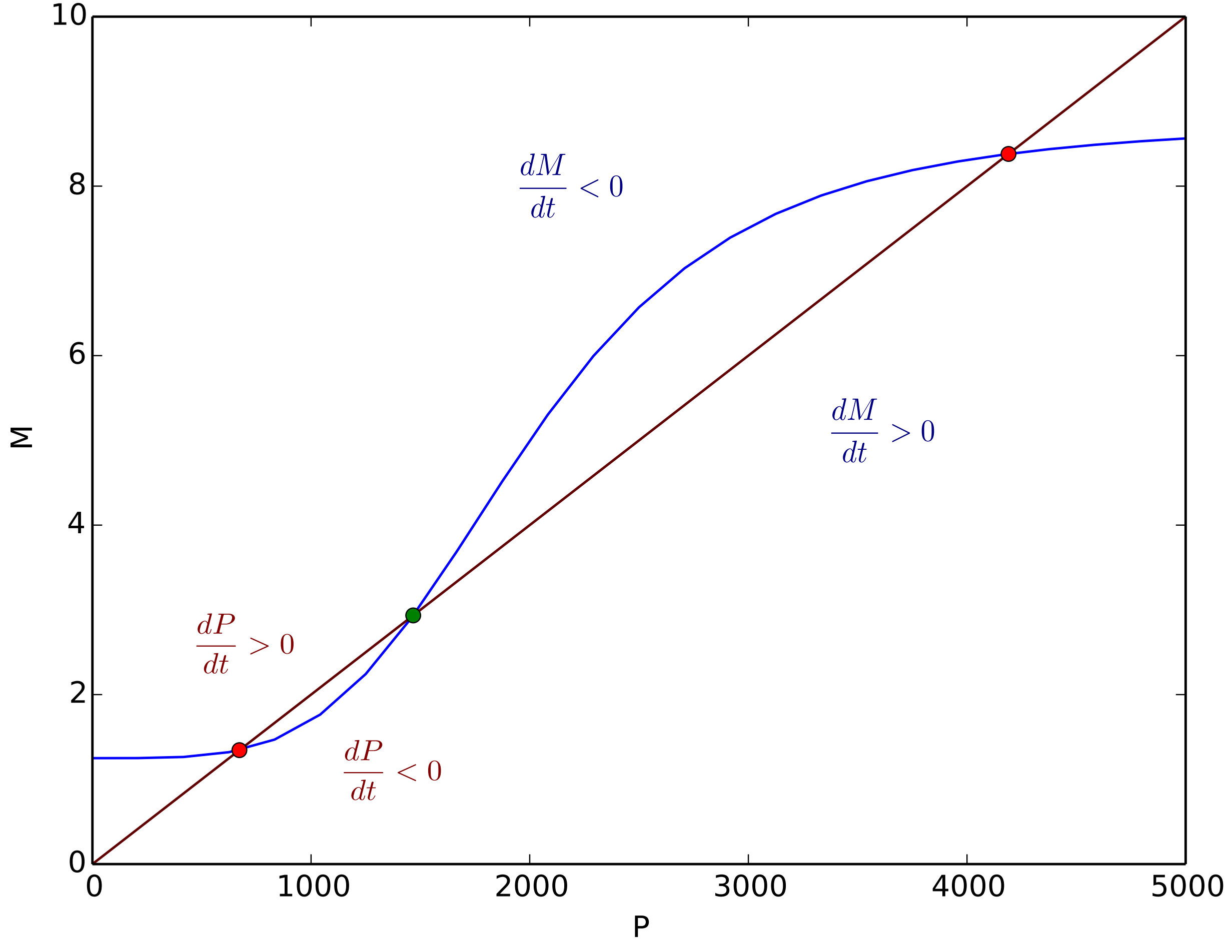
At the intersections of the nullclines, both *M* and *P* are at steady state because both *dM/dt* and *dP/dt* are zero.

On the blue nullcline, *dM/dt* is zero; on the red nullcline, *dP/dt* is zero.

We find the stability of the steady states by determining the local dynamics

$$\frac{dM}{dt} = u_b + \frac{uP^n}{K^n + P^n} - d_M M$$

$$\frac{dP}{dt} = M - d_P P$$



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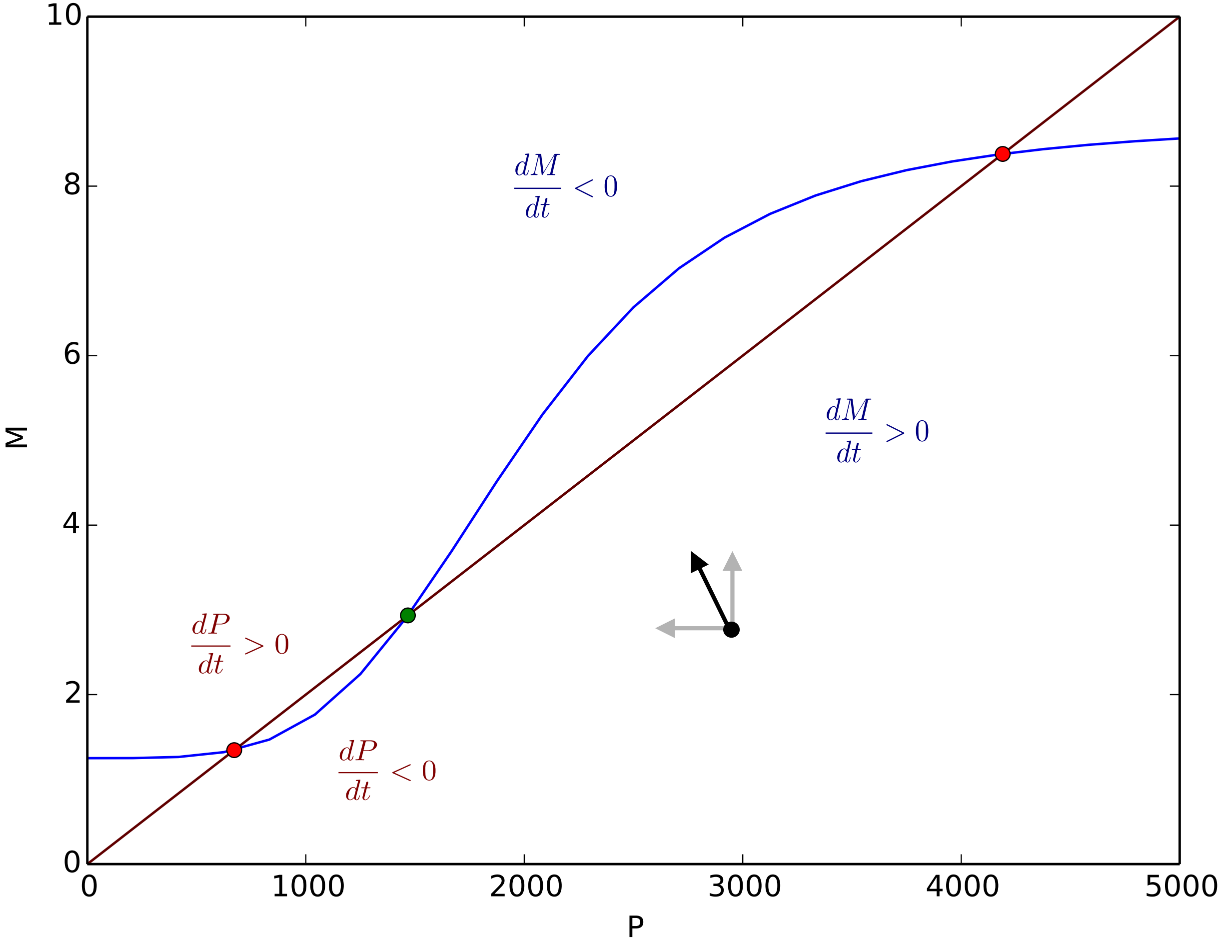

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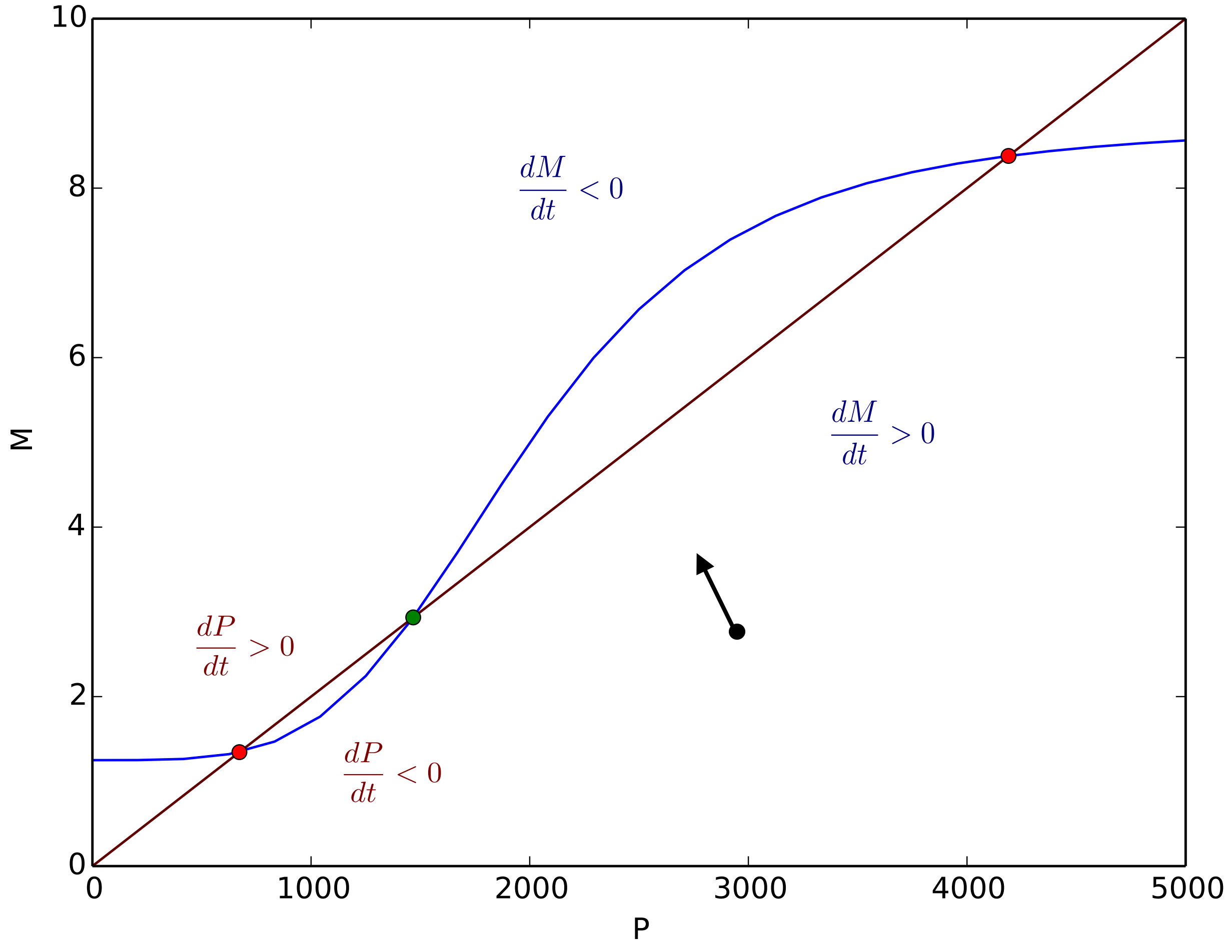

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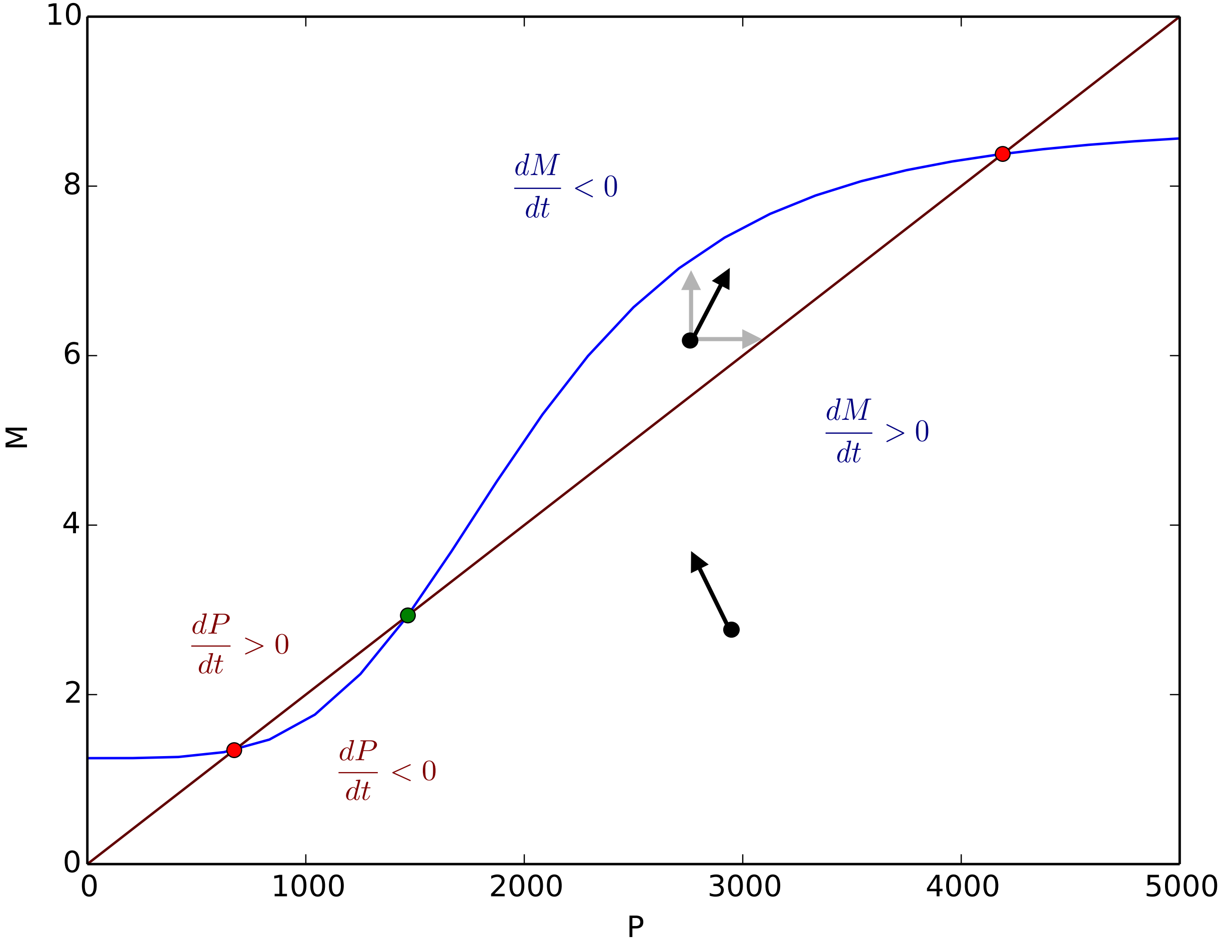

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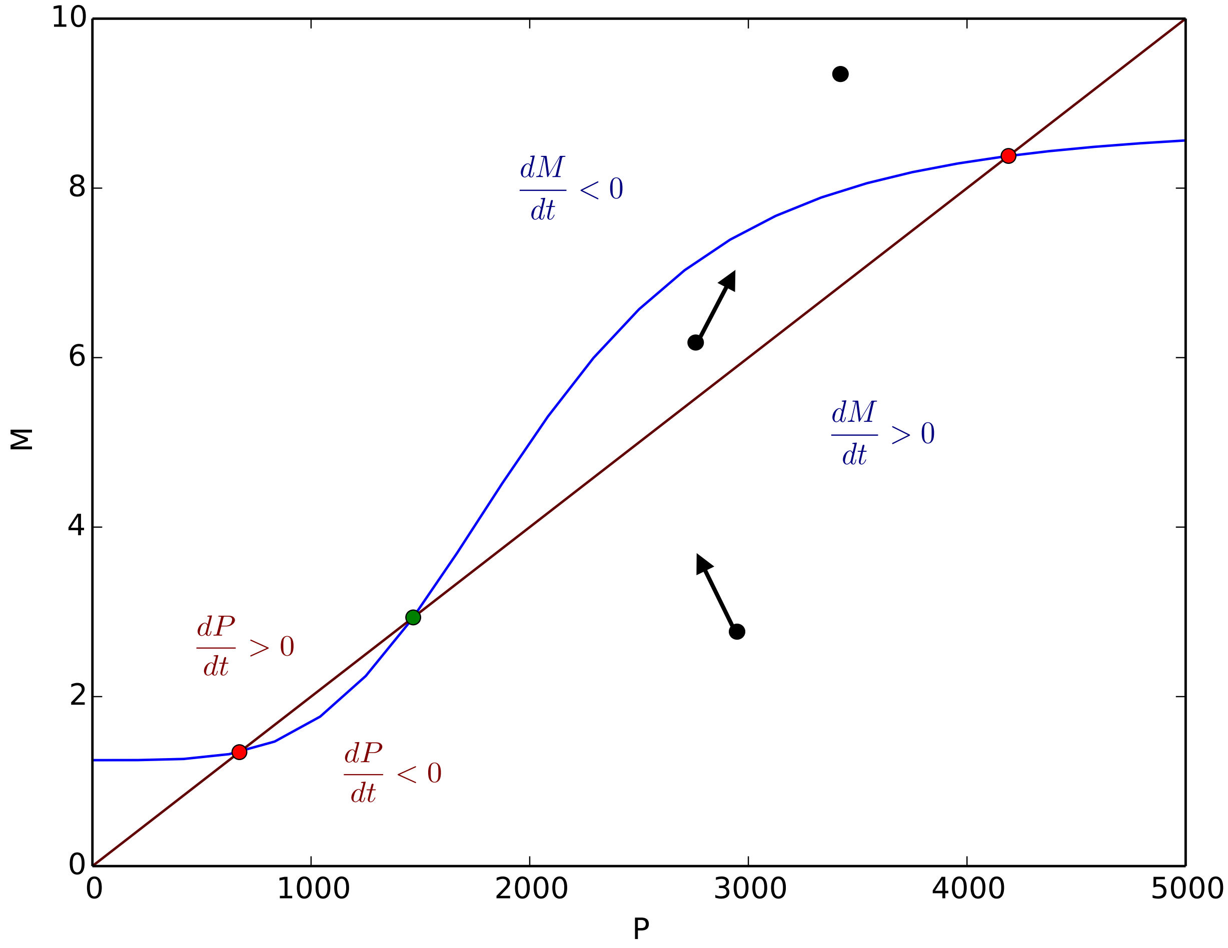

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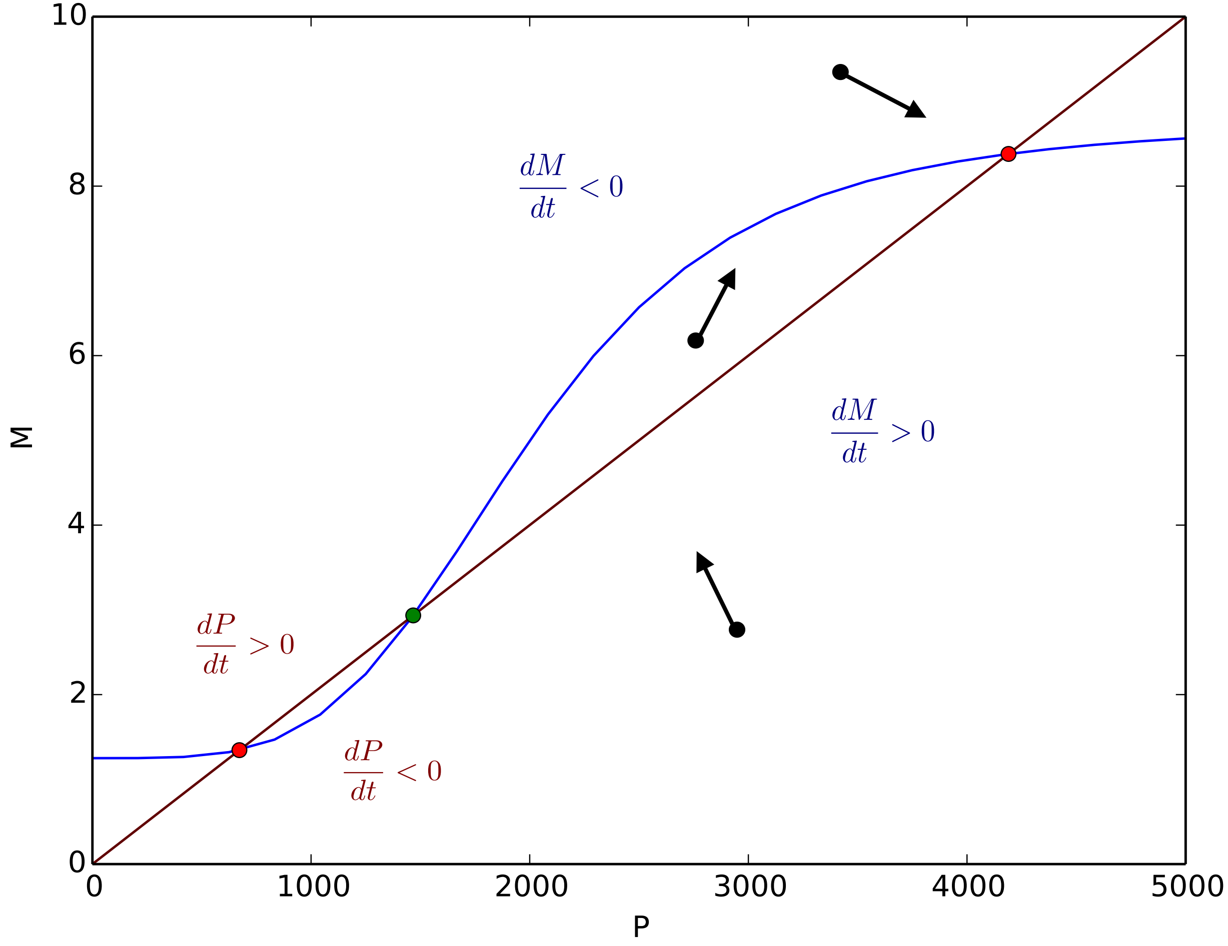
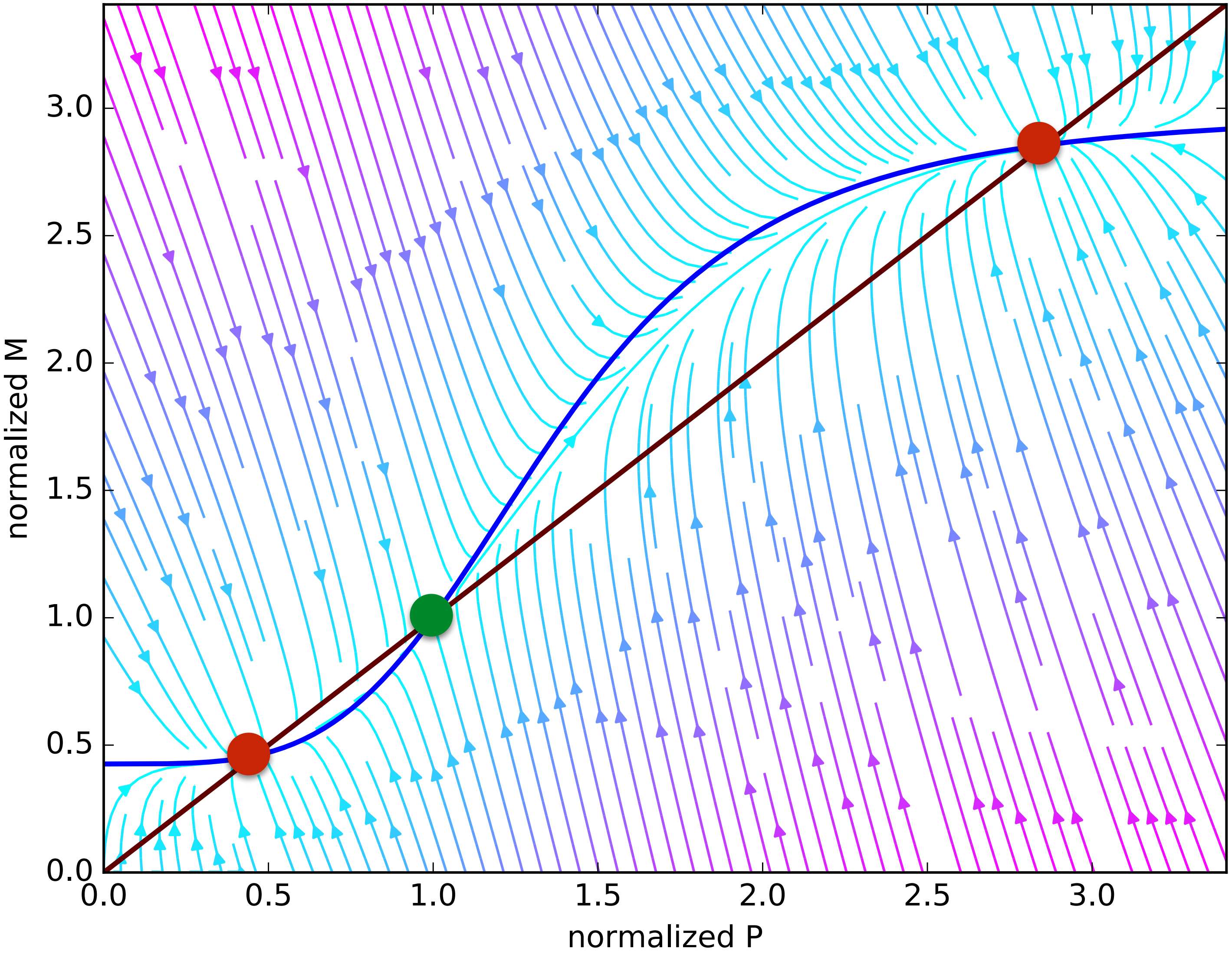
We find the stability of the steady states by determining the local dynamics



On the blue nullcline,
dM/dt is zero;
On the red nullcline,
dP/dt is zero.

By systematically determining the local dynamics, we find two stable steady states and one unstable one

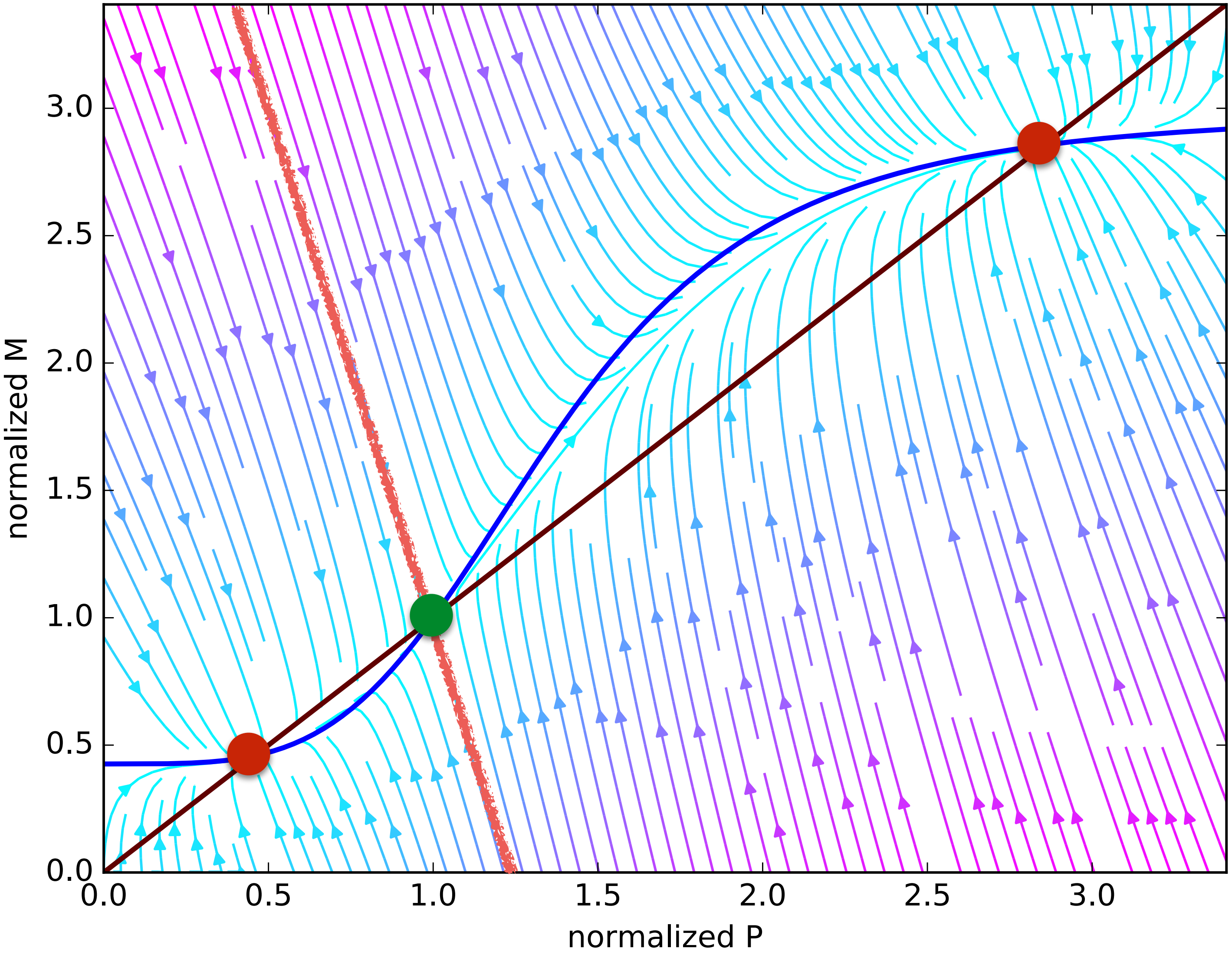


node

saddle point

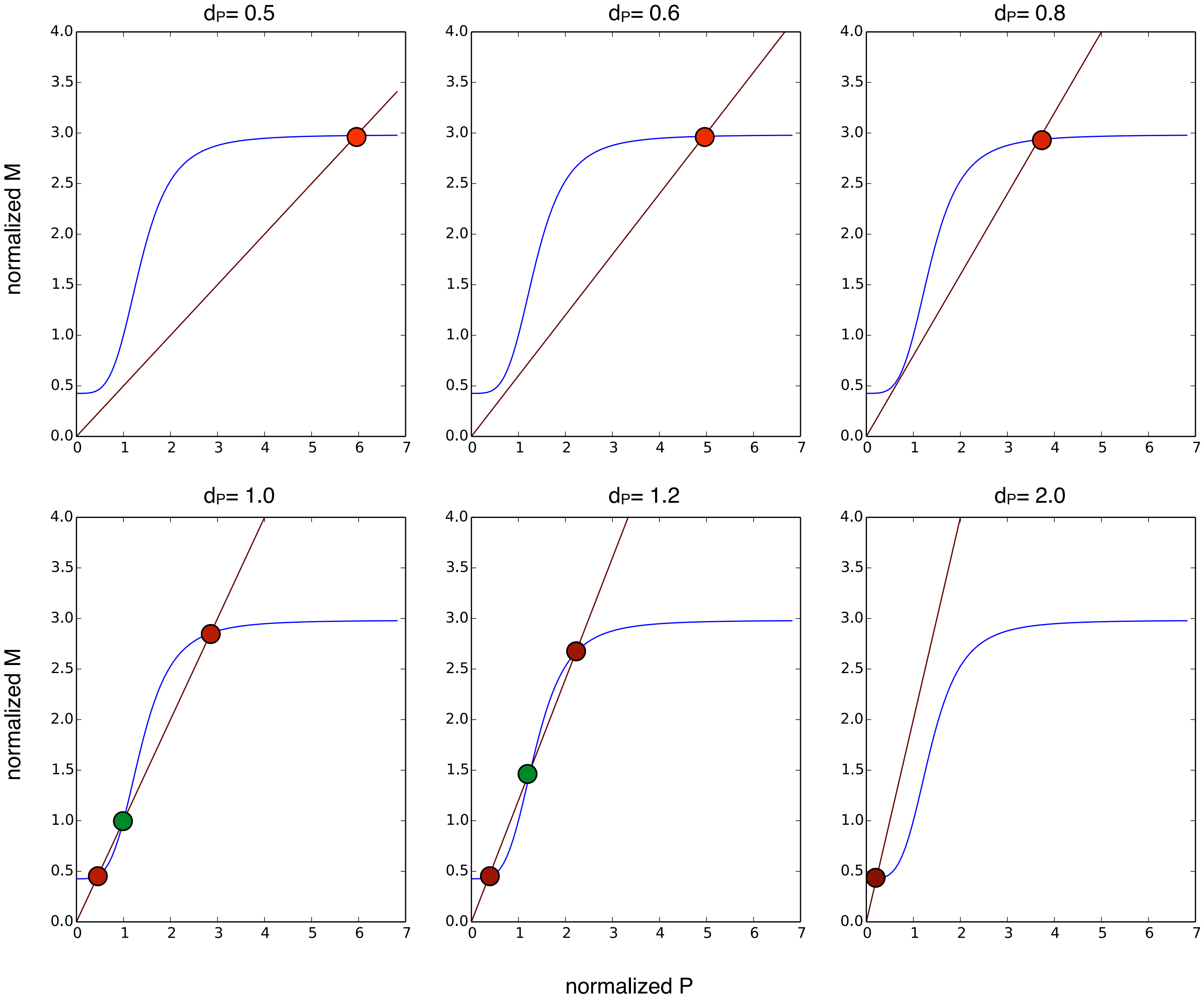
node

The separatrix, or stable manifold, is the boundary between the two basins of attraction

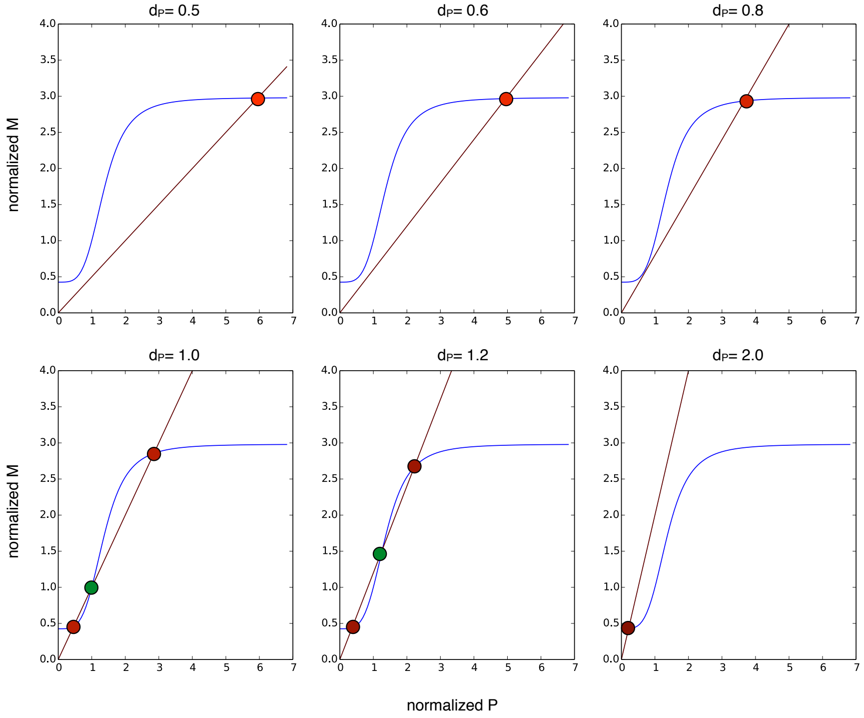


The system can undergo a bifurcation from one to three steady states and vice versa

The protein degradation rate d_P is the bifurcation parameter



There are two saddle-node bifurcations



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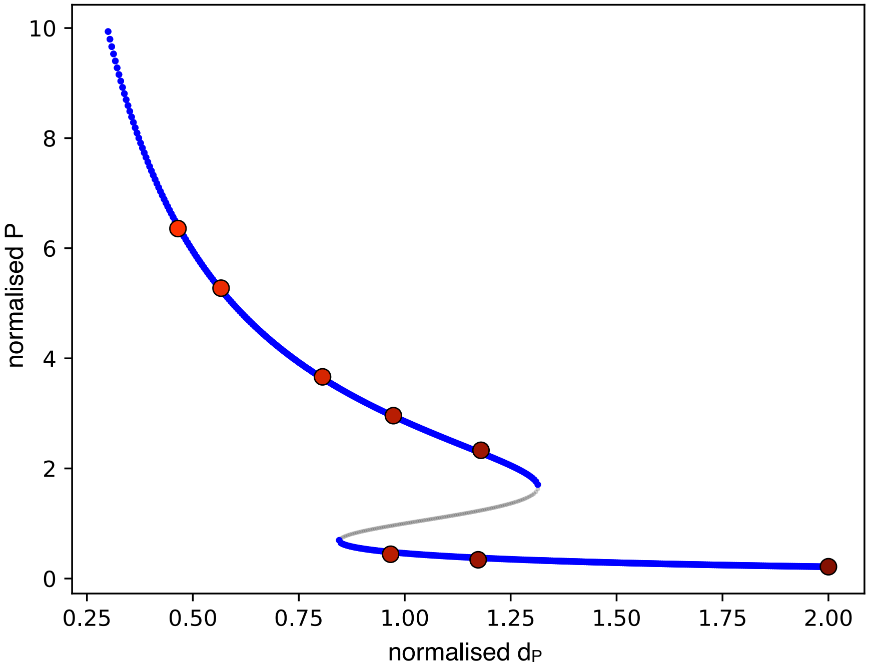
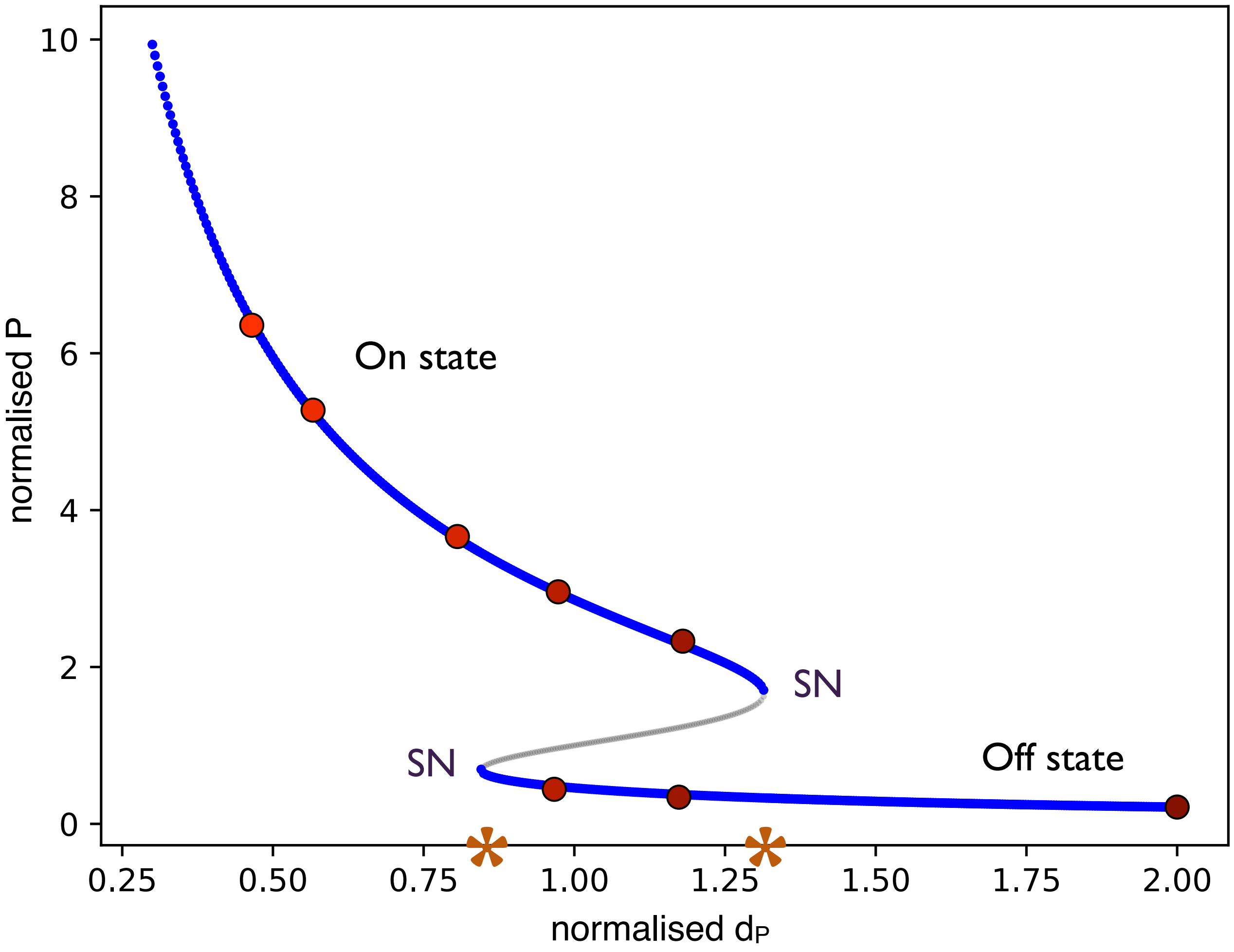


There is hysteresis



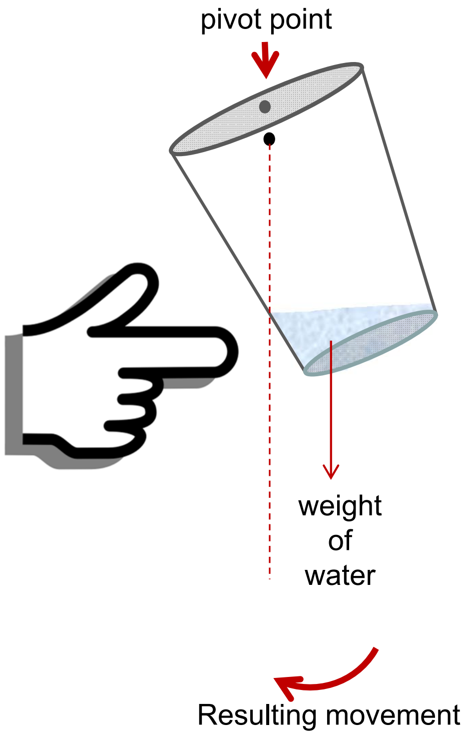
The value of d_P at which the system flips between states (*) depends on whether d_P is increasing or decreasing.

SN: saddle-node bifurcation

Negative feedback and biological oscillators

Negative feedback can generate oscillations

Negative feedback is process where an effect diminishes itself.

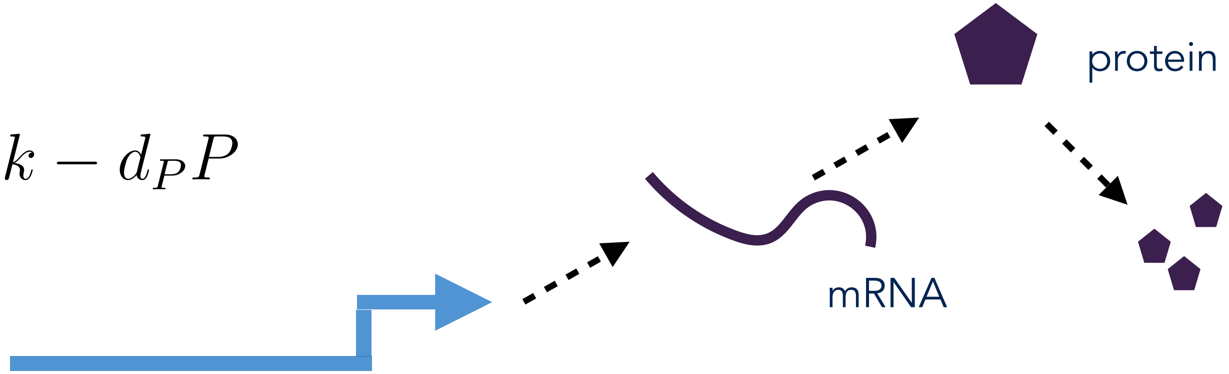


If an increase in the output causes the system to act to decrease that output, then the system has negative feedback.

A preliminary remark: Degradation is stabilising

Consider constitutive expression

$$\frac{dP}{dt} = k - d_P P$$



At steady state

$$k = d_P P^*$$

synthesis rate is constant, but
degradation rate is not

For a fluctuation **above** steady state

$$d_P P > d_P P^* = k$$

degradation **increases**

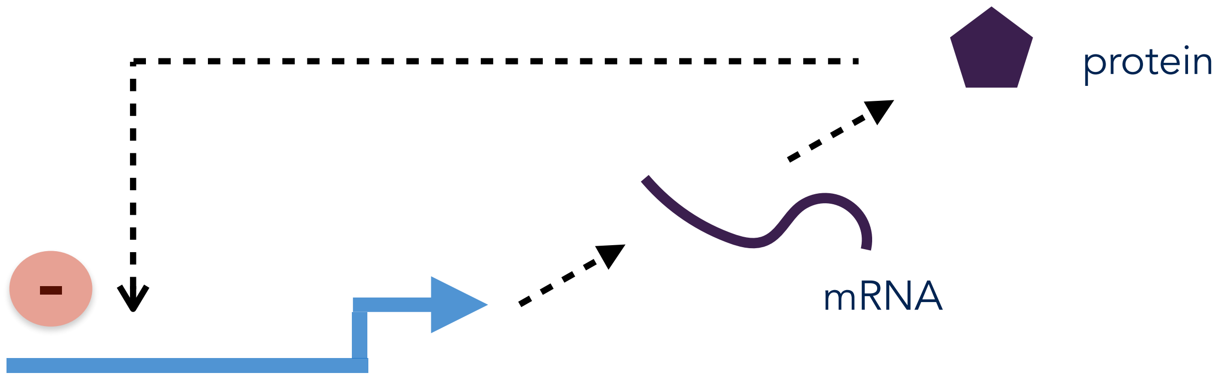
For a fluctuation **below** steady state

$$d_P P < d_P P^* = k$$

degradation **decreases**

Negative feedback is stabilising

Consider negative autoregulation



The rate equation is

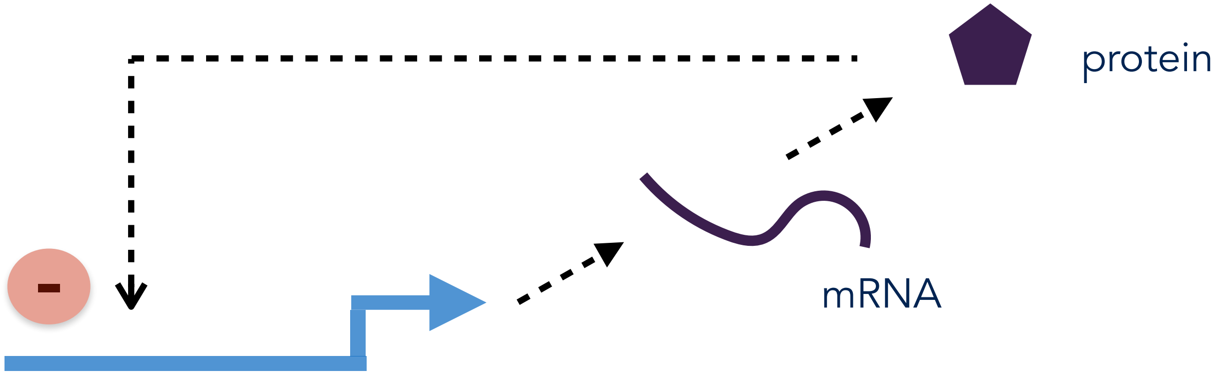
$$\frac{dP}{dt} = \frac{k}{1 + (P/K)^n} - d_P P$$

and at steady state

$$\frac{k}{1 + (P^*/K)^n} = d_P P^*$$

Like degradation, negative feedback adjusts to perturbations

$$\frac{k}{1+(P^*/K)^n} = d_P P^*$$



Negative feedback on protein synthesis works together with degradation

For fluctuations **above** steady state, synthesis **decreases**

$P > P^*$

$$\frac{k}{1+(P/K)^n} < \frac{k}{1+(P^*/K)^n}$$

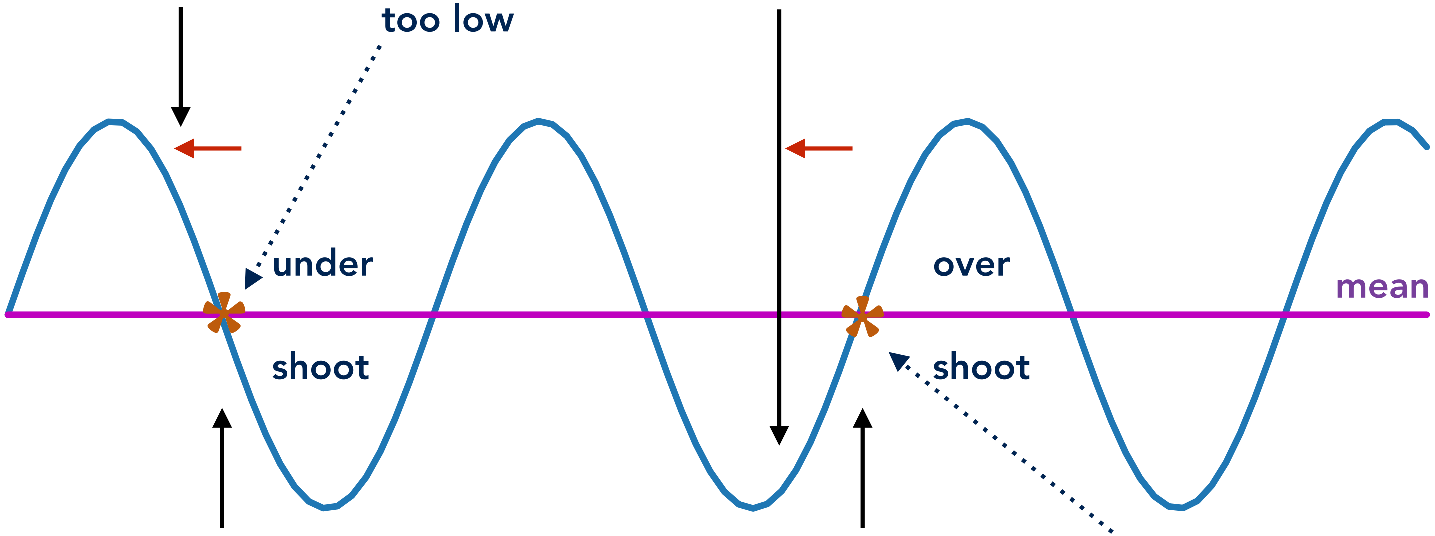
For fluctuations **below** steady state, synthesis **increases**

$P < P^*$

$$\frac{k}{1+(P/K)^n} > \frac{k}{1+(P^*/K)^n}$$

Delayed negative feedback can cause oscillations

The delay in changing synthesis causes a mismatch between the synthesis rate and the degradation rate.



The duration of the delay is in red.

synthesis
determined by
protein here

synthesis
too low

synthesis
determined by
protein here

under
shoot

over
shoot

mean

degradation
determined by
protein here

degradation
determined by
protein here

synthesis
too high

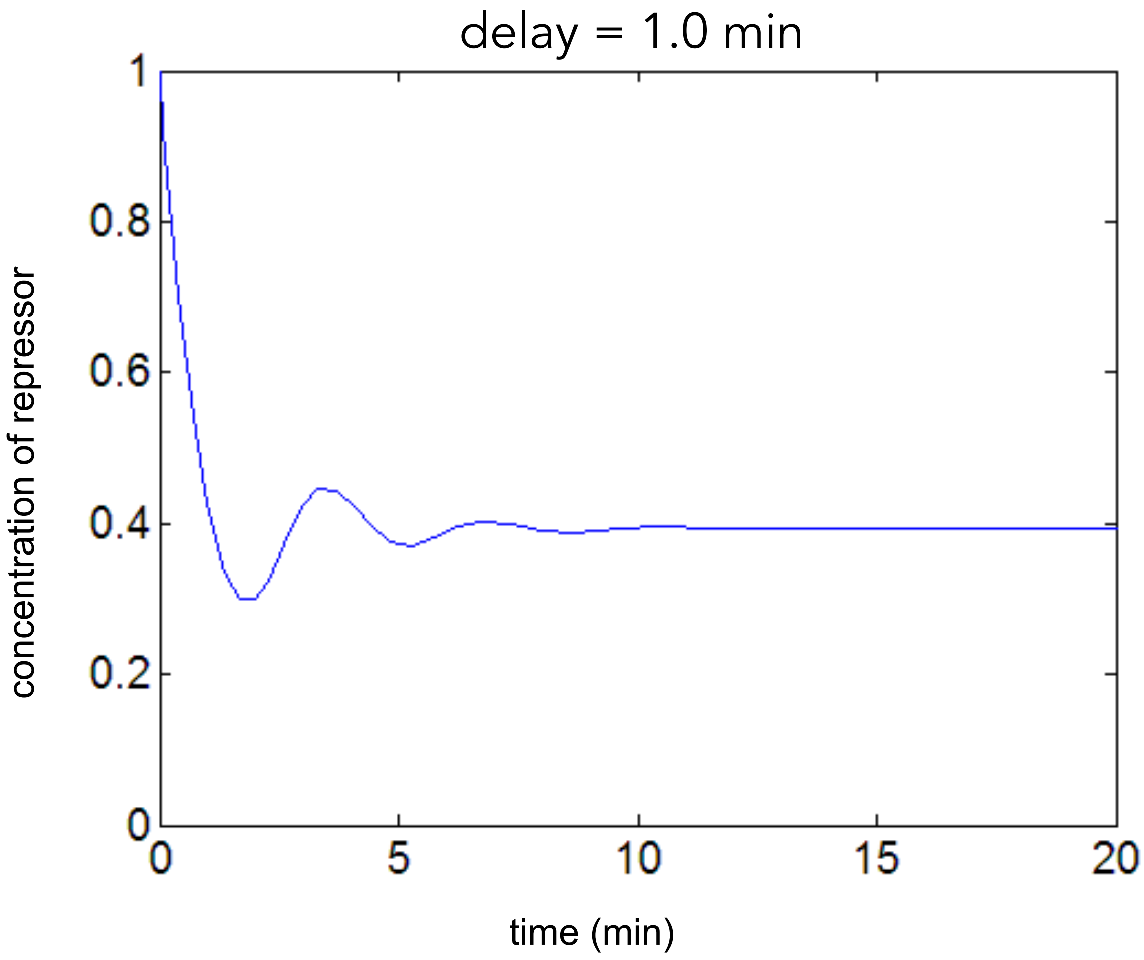
Oscillations are continual overshoots and undershoots because of the mismatch.

There are two requirements for a system to oscillate

(i) negative feedback: feedback that acts to reduce deviations of the system away from steady state

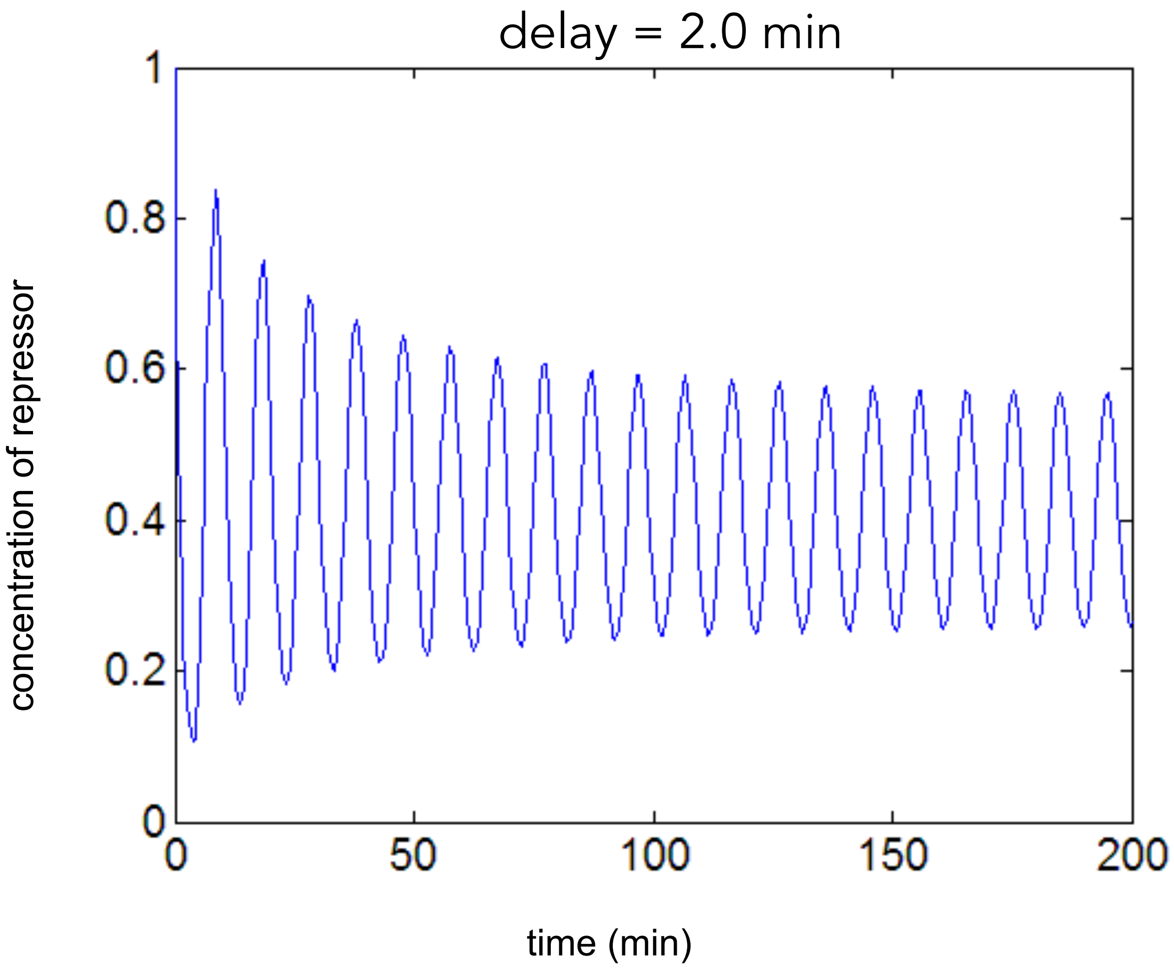
(ii) a delay: a sufficiently long time delay before the feedback acts.

For example: increasing the delay induces oscillations



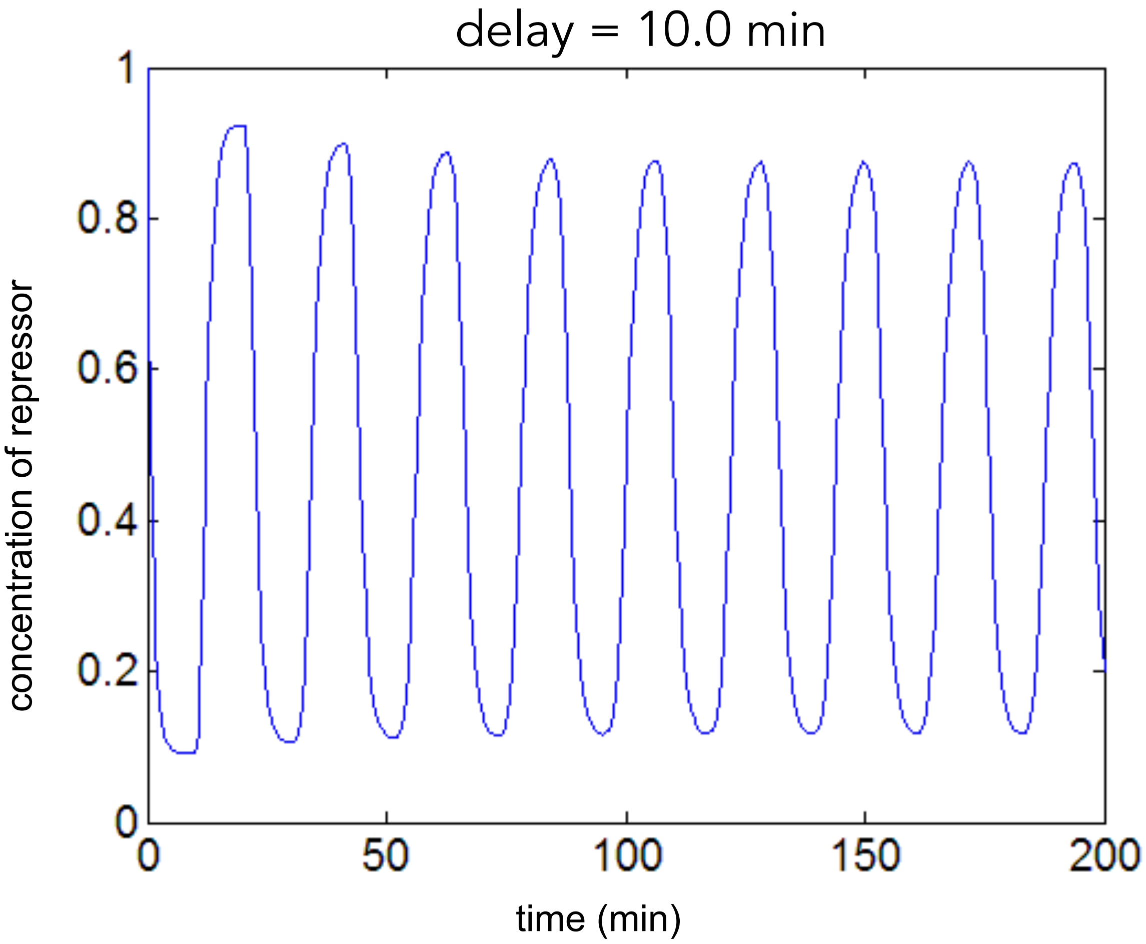
system tends
to steady state

For example: increasing the delay induces oscillations, through a Hopf bifurcation



system oscillates
when the delay is
sufficiently long

For example: increasing the delay in this example increases the amplitude of the oscillations



Circadian rhythms as genetic oscillators

Rhythms are circadian if they have four characteristics

They have a period of approximately 24 hours;

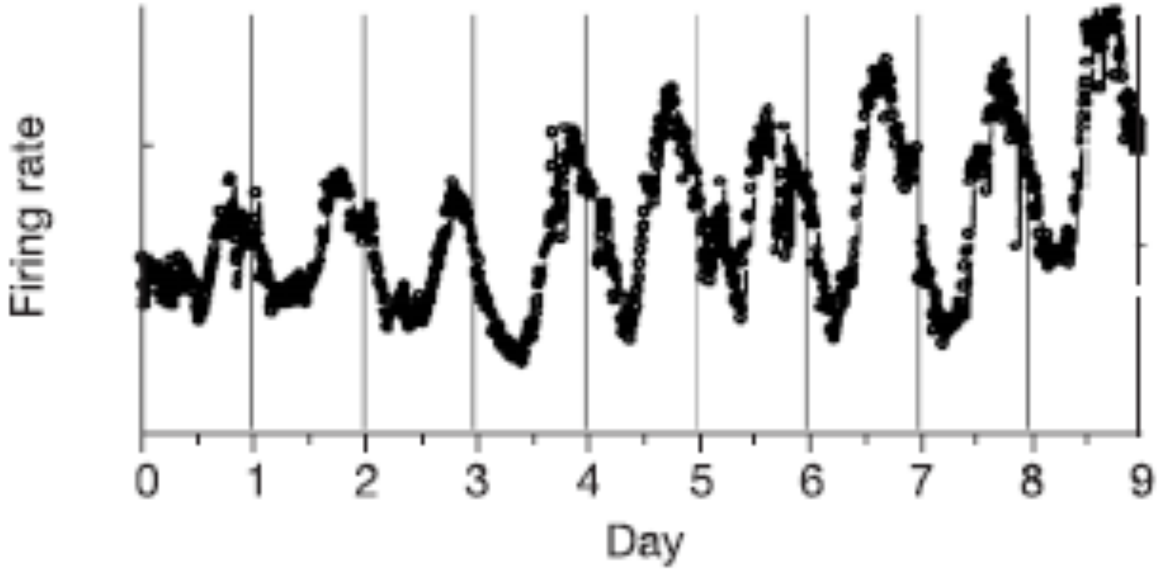
are free running and exist in the absence of cues to the earth’s 24-hour rotation;

are synchronised by environmental signals, usually light;

are able to run over a range of temperatures.

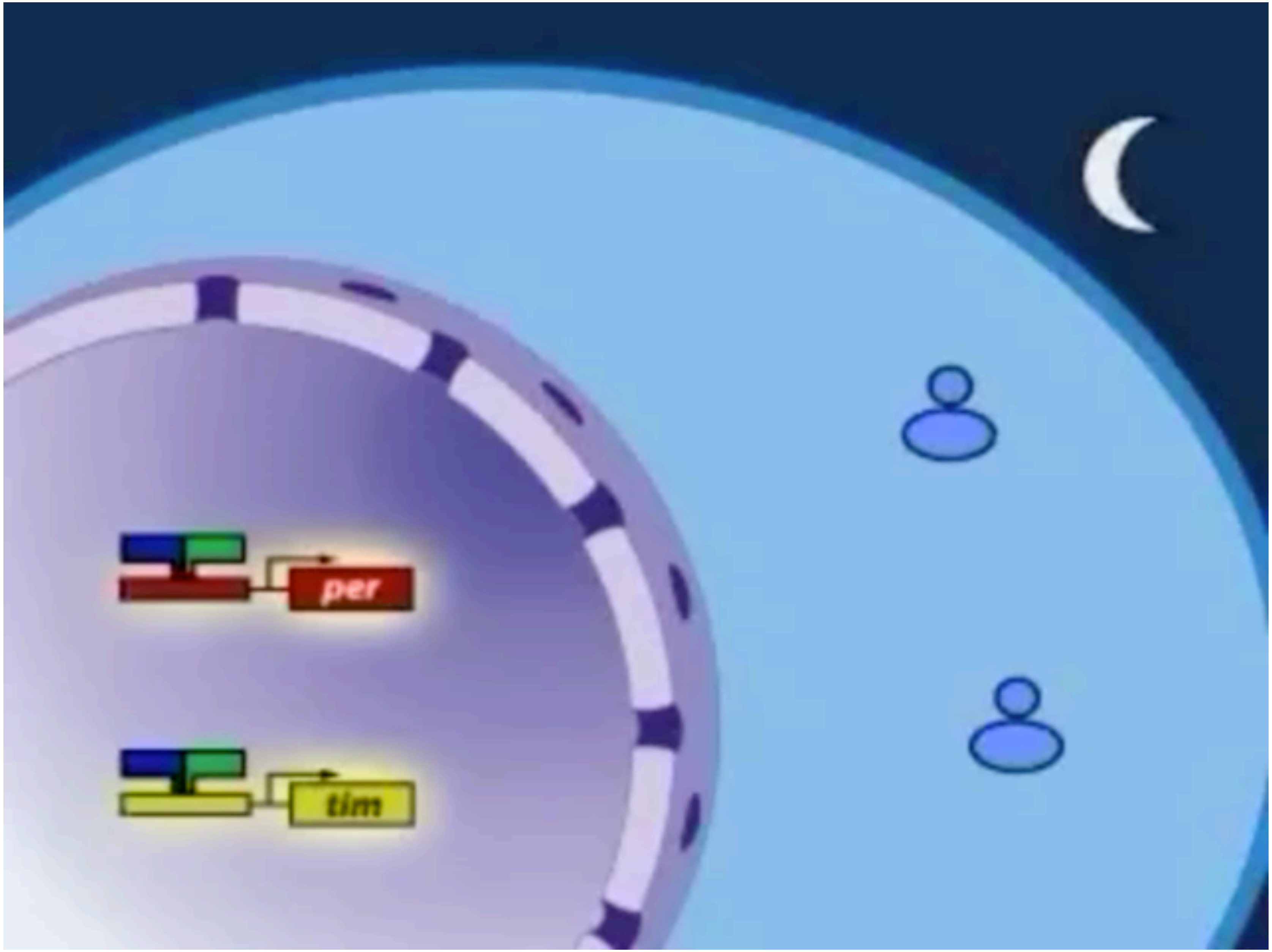
Circadian rhythms occur in single cells

The suprachiasmatic nucleus comprises numerous clock cells, but a single neuron from the nucleus has circadian rhythms in culture.



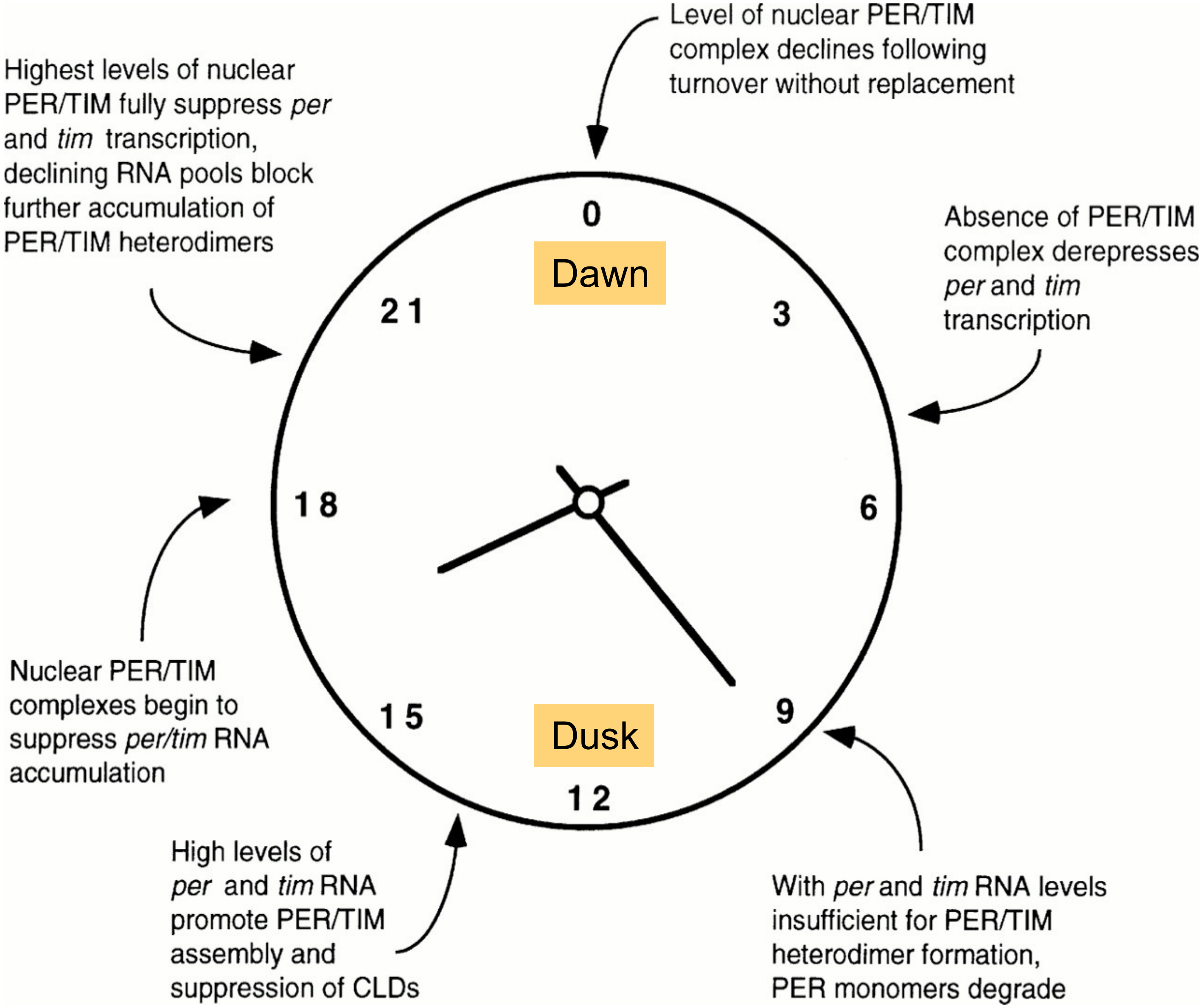
Reppert, Weaver 2002

Negative transcriptional feedback controls circadian rhythms in *Drosophila*



from Howard Hughes Medical Institute

Changes in the levels of PER/TIM are fundamental



Level of nuclear PER/TIM complex declines following turnover without replacement

Absence of PER/TIM complex derepresses *per* and *tim* transcription

With *per* and *tim* RNA levels insufficient for PER/TIM heterodimer formation, PER monomers degrade

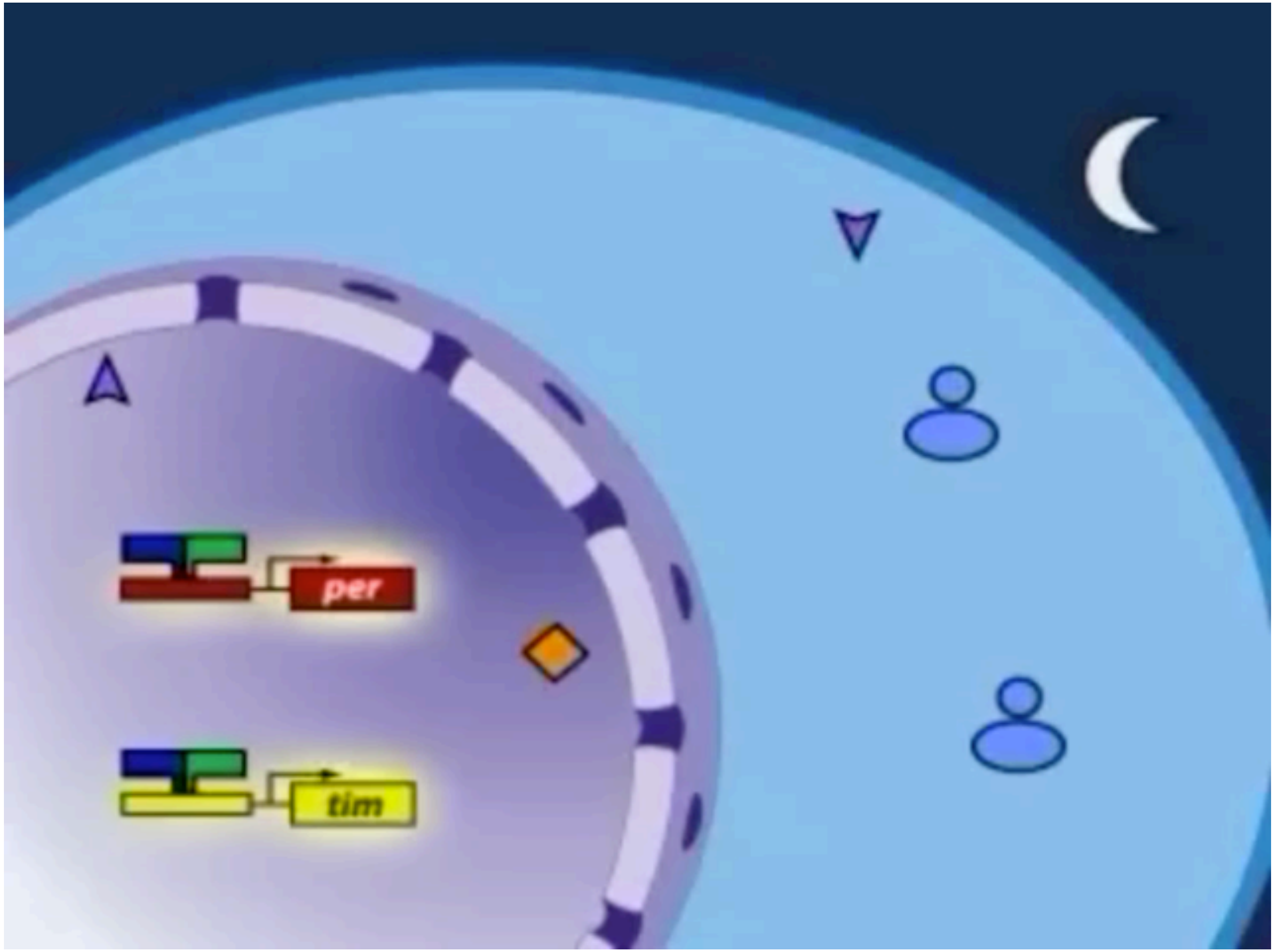
High levels of *per* and *tim* RNA promote PER/TIM assembly and suppression of CLDs

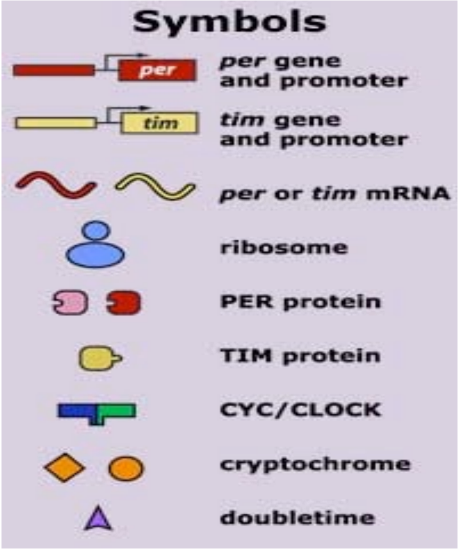
Nuclear PER/TIM complexes begin to suppress *per/tim* RNA accumulation

Highest levels of nuclear PER/TIM fully suppress *per* and *tim* transcription, declining RNA pools block further accumulation of PER/TIM heterodimers

CLD:cytoplasmic localization domain

The behaviour is more complex because light resets the clock





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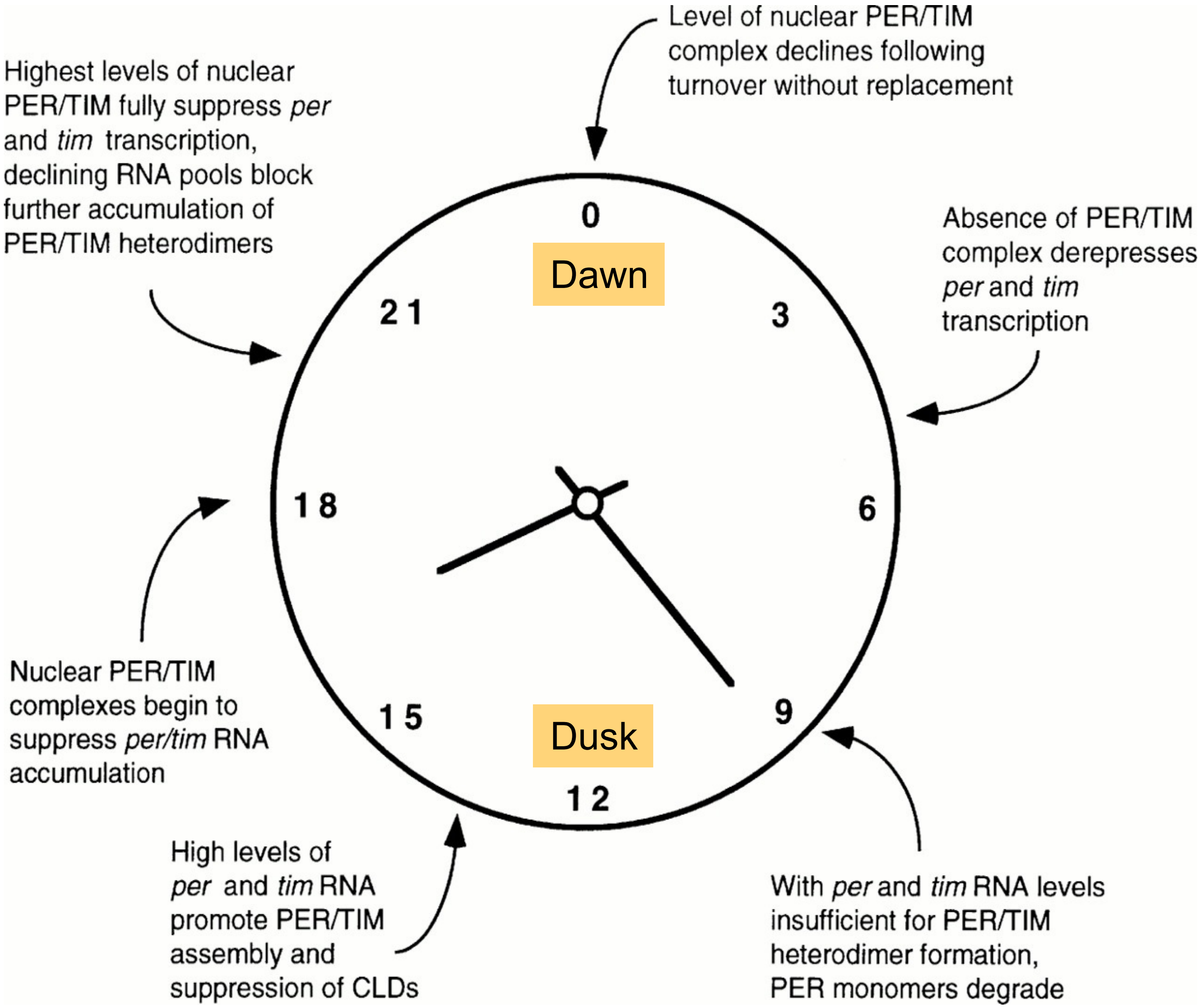

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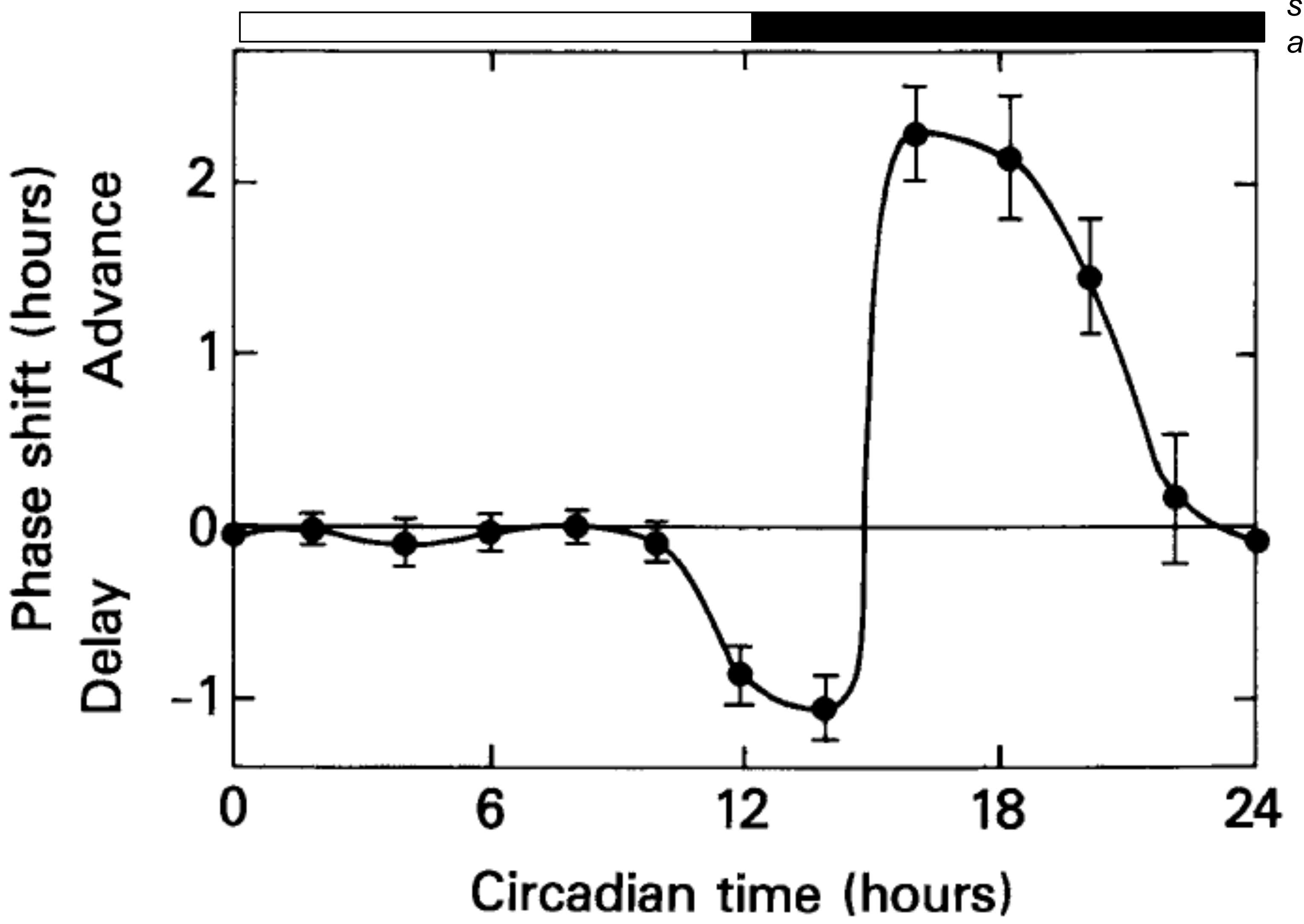
CLD:cytoplasmic localization domain

Through cryptochrome, the rhythms adjust to the seasons



subjective day and night

phase response curve

Pulse of light early in subjective night delays rhythm and extends day time.
Pulse of light late in subjective night advances rhythm and reduces night time.