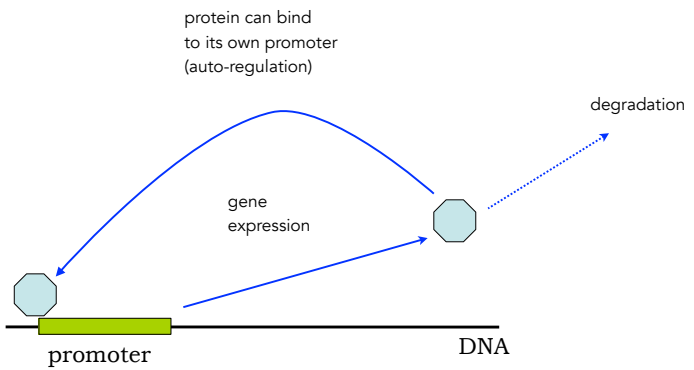
## There are two requirements for a system to oscillate

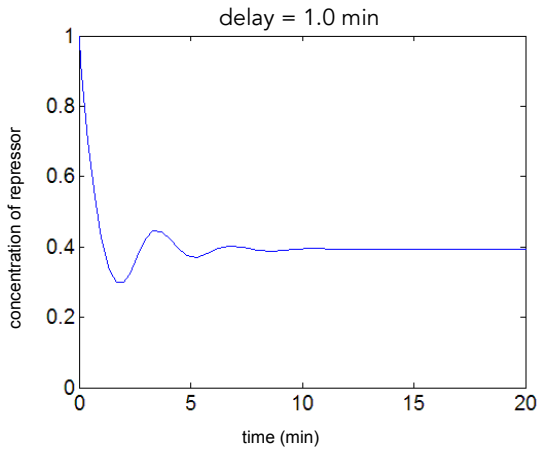
(i) negative feedback: feedback that acts to minimize deviations of the system away from steady-state

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

Example: transcriptional auto-regulation implements negative feedback

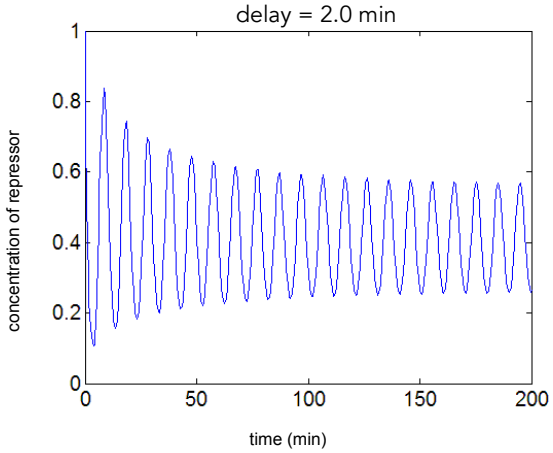


Increasing the delay induces oscillations:



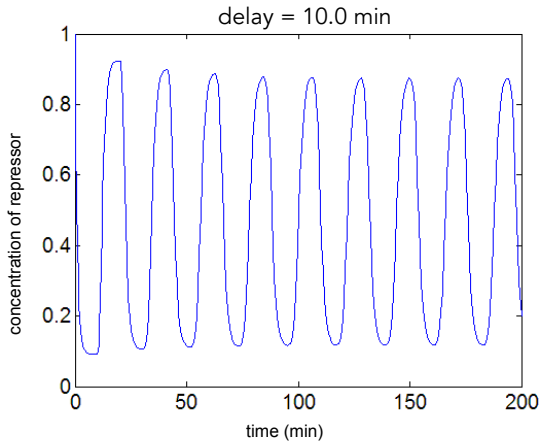

system tends
to steady state

Increasing the delay induces oscillations:




system oscillates
when the delay is
sufficiently long

Increasing the delay induces oscillations:




Natural genetic oscillators

## Properties of circadian rhythms

(i) They have a period of approximately 24 hours

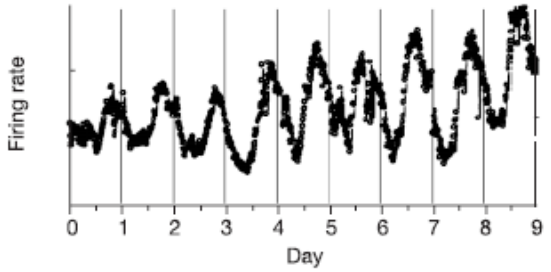
(ii) They exist in the absence of cues to the earth's 24 hour cycle (they are free-running)

(iii) They can be synchronized by environmental signals, usually light

(iv) They are temperature compensated (persist over a range of temperatures).

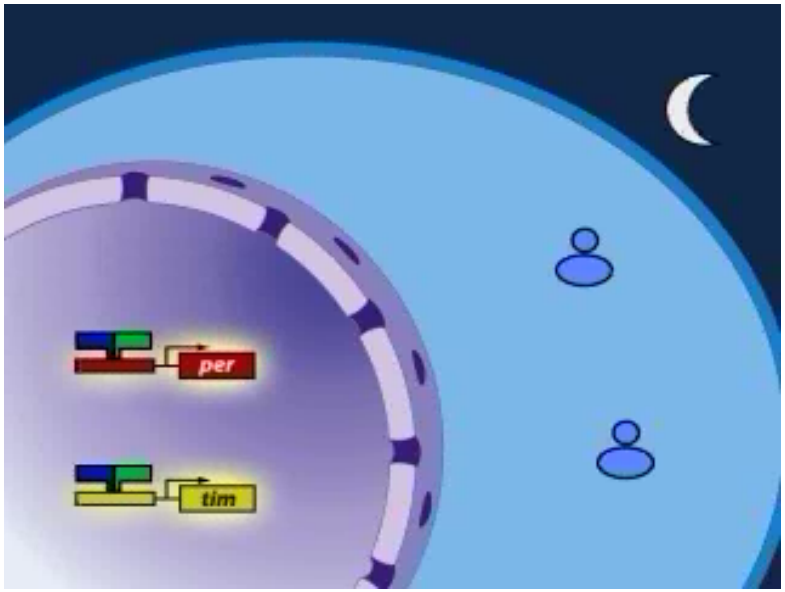
## Circadian rhythms occur in single cells

The suprachiasmatic nucleus is composed of numerous clock cells, but a single neuron from the nucleus in culture expresses circadian rhythms.




Reppert, Weaver 2002

Negative transcriptional feedback through a heterodimer controls circadian rhythms in *Drosophila*

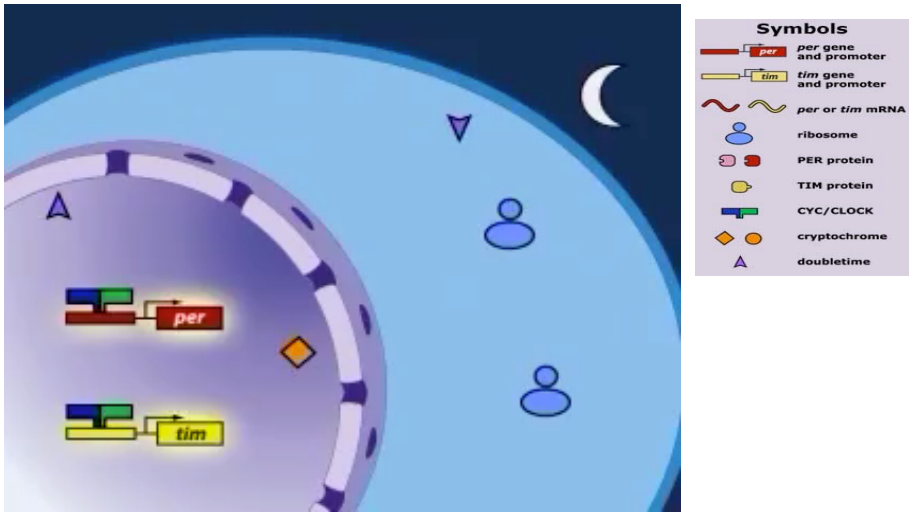



from Howard Hughes Medical Institute

## Oscillations in PER/TIM levels are fundamental to the clock

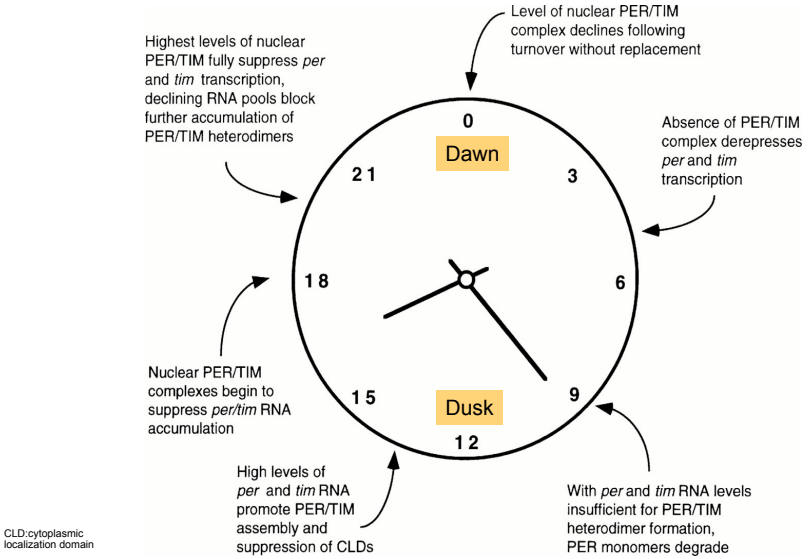
1. Initially (around midday), there are low concentrations of Period and Timeless proteins. Clock and cycle transcription factors activate both *per* and *tim* genes.
2. Doubletime (kinase) phosphorylates PER in cytosol causing its degradation. DBT cannot phosphorylate PER if it binds to TIM.
3. With high TIM concentration in cytosol, PER is rescued from DBT, and DBT/PER/TIM complexes enter nucleus.
4. PER represses *per* and *tim* transcription.
5. TIM degrades slowly over 8-10 hours. If activated by light, cryptochrome rapidly accelerates TIM degradation. DBT can then re-phosphorylate PER.
6. DBT slowly phosphorylates PER within the DBT/PER complex causing PER to be degraded.

The behaviour is more complex because the clock can be reset by sunlight.



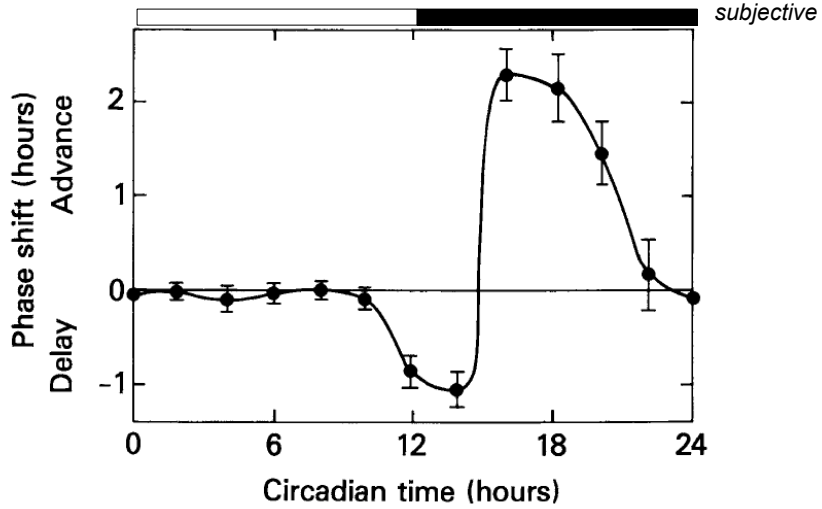

from Howard Hughes Medical Institute

Nuclear PER/TIM levels decline after dawn and increase after dusk.




CLD:cytoplasmic localization domain

A phase response curve shows how the phase of the rhythm is reset by light.




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.

Biophysical Journal Volume 77 November 1999 2411–2417


## A Simple Model of Circadian Rhythms Based on Dimerization and Proteolysis of PER and TIM

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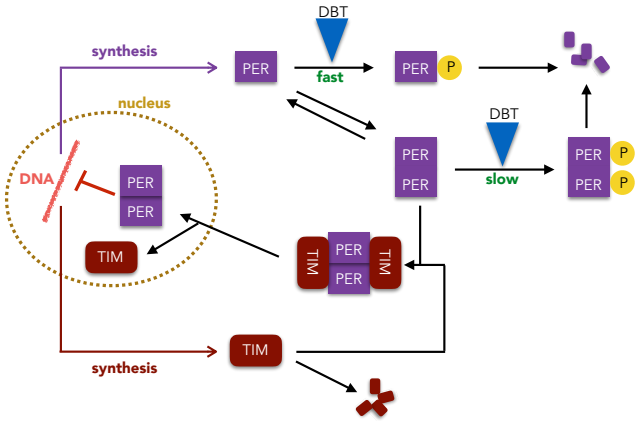
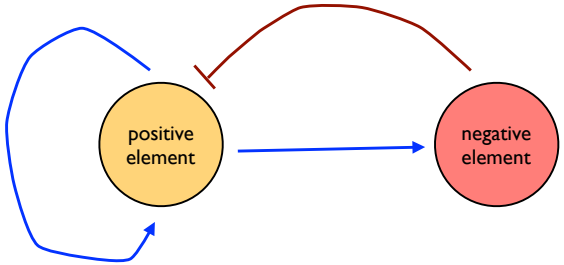
ABSTRACT Many organisms display rhythms of physiology and behavior that are entrained to the 24-h cycle of light and darkness prevailing on Earth. Under constant conditions of illumination and temperature, these internal biological rhythms persist with a period close to 1 day ("circadian"), but it is usually not exactly 24 h. Recent discoveries have uncovered stunning similarities among the molecular circuitries of circadian clocks in mice, fruit flies, and bread molds. A consensus picture is coming into focus around two proteins (called PER and TIM in fruit flies), which dimerize and then inhibit transcription of their own genes. Although this picture seems to confirm a venerable model of circadian rhythms based on time-delayed negative feedback, we suggest that just as crucial to the circadian oscillator is a positive feedback loop based on stabilization of PER upon dimerization. These ideas can be expressed in simple mathematical form (phase plane portraits), and the model accounts naturally for several hallmarks of circadian rhythms, including temperature compensation and the *per*$^{L}$ mutant phenotype. In addition, the model suggests how an endogenous circadian oscillator could have evolved from a more primitive, light-activated switch.

The Tyson *et al.* model focuses on the negative feedback of dimers of PER protein on the transcription of the *per* gene



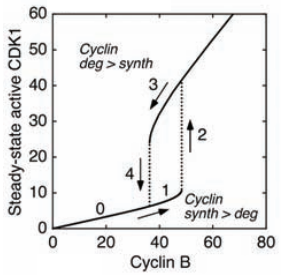

Circadian networks have a core structure of positive and negative feedbacks



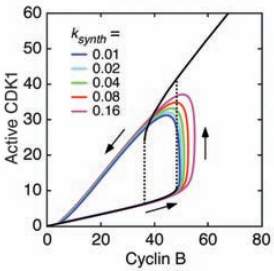

From Barkai & Leibler, 2000, and Dunlap, 1999

Relaxation oscillators operate around the hysteresis loop of the underlying bistability

A model of the cell cycle

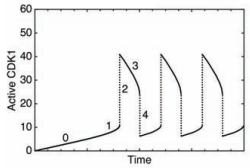



Steady-state response with no negative feedback exhibits hysteresis.

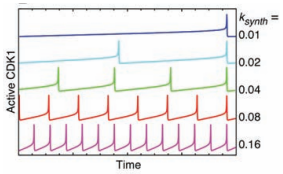



Relaxation oscillations occur with negative feedback.

Levels of CDK1 as cyclin B is slowly and periodically changed.

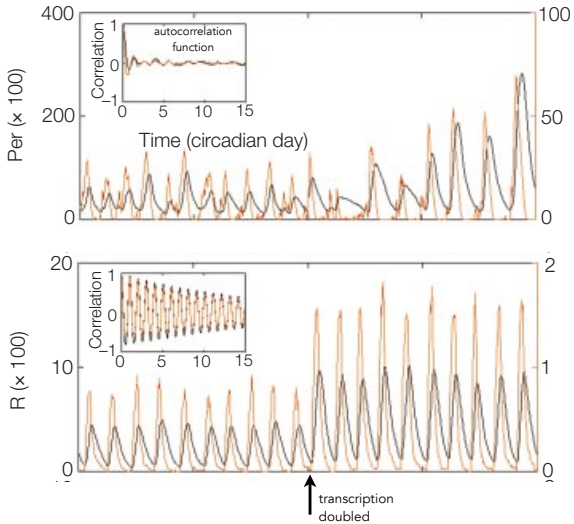



Relaxation oscillations




From Tsai *et al.*, 2008

Negative feedback oscillators are less robust than relaxation oscillators to stochastic fluctuations.

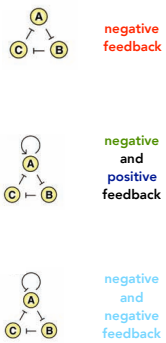



With negative feedback

With negative and positive feedback.

From Barkai & Leibler, 2000

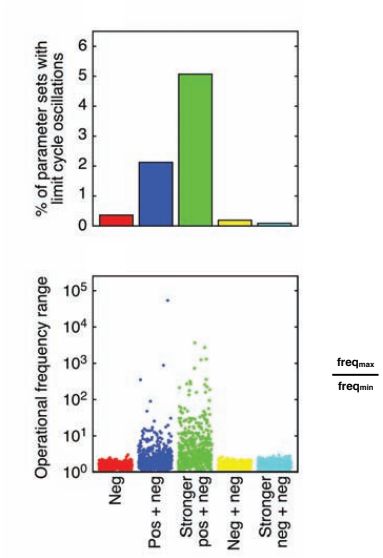
Relaxation oscillators are able to oscillate for wider ranges of parameters than negative feedback oscillators




negative feedback

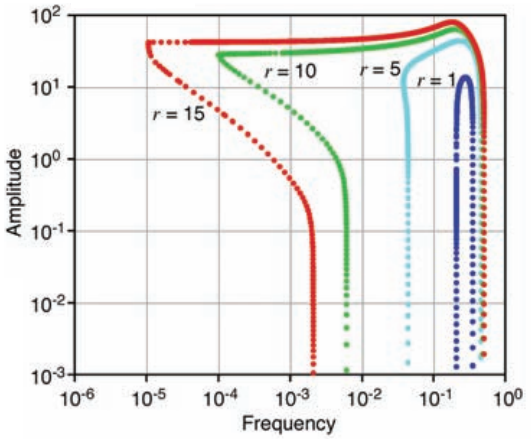
negative and positive feedback

negative and negative feedback




From Tsai *et al.*, 2008

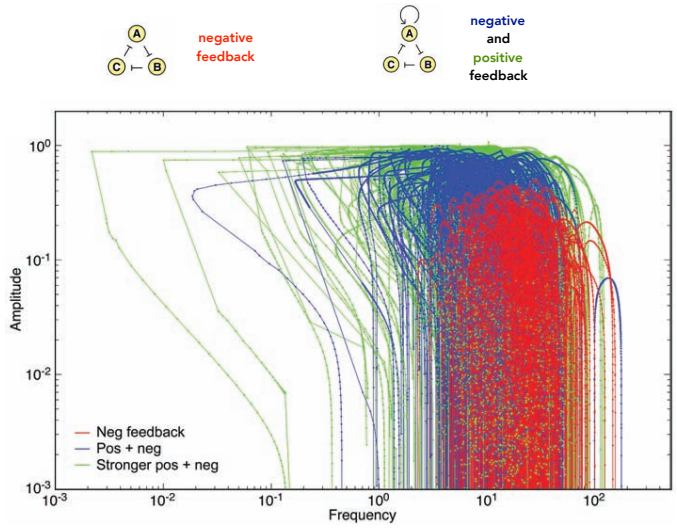
Relaxation oscillators can maintain the amplitude of oscillations as the frequency of the oscillations changes.




*r* controls the strength of positive feedback

From Tsai *et al.*, 2008

Relaxation oscillators can maintain the amplitude of oscillations more than negative feedback oscillators




From Tsai *et al.*, 2008