A well-know mathematical model of circadian rhythms that also serves as an example paper for the research project

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

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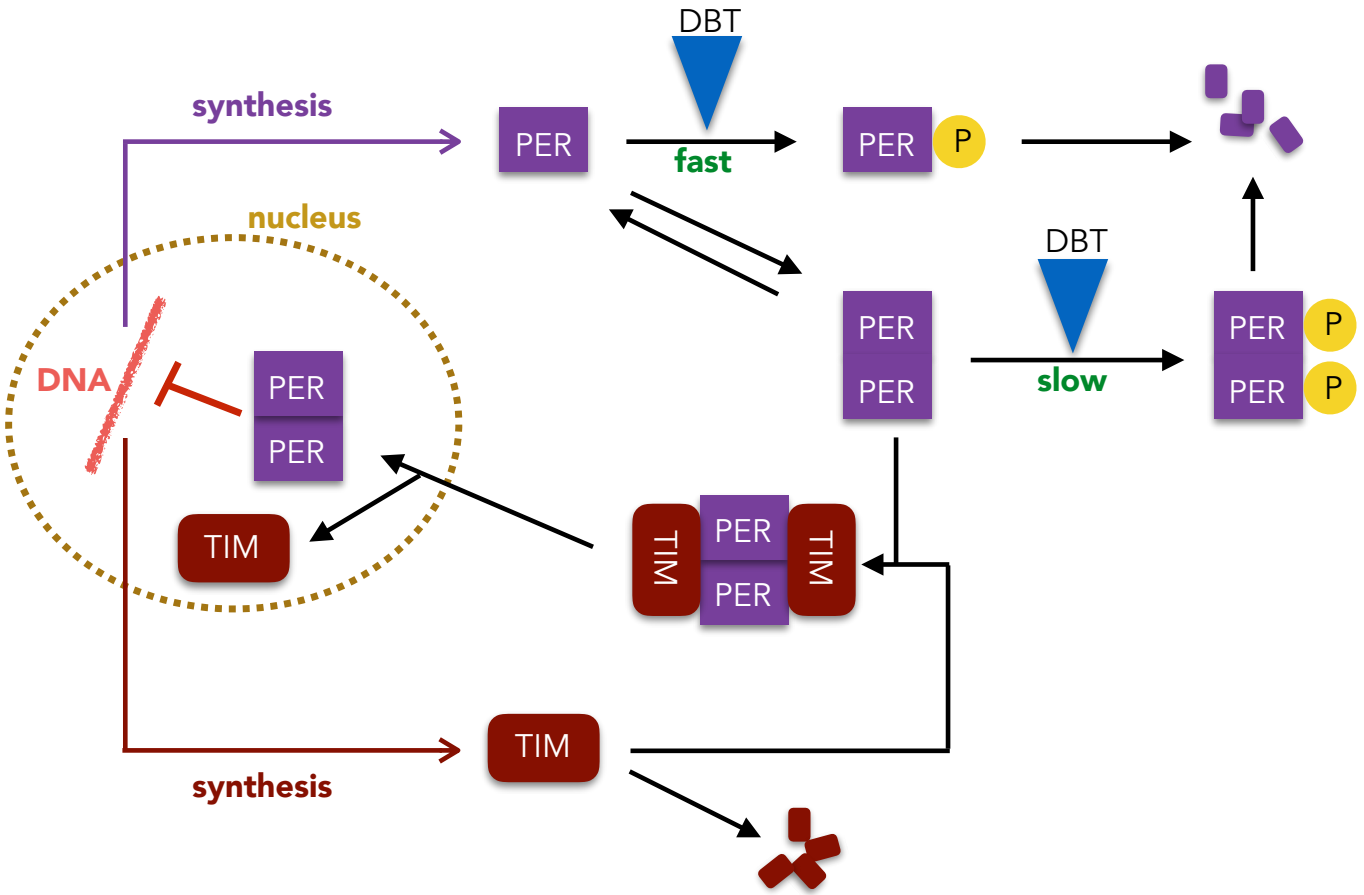
ABSTRACT Many organisms display rhythms of physiology and behavior that are entrained to the 24-h cycle of light and darkness prevailing on Earth. Under constant conditions of illumination and temperature, these internal biological rhythms persist with a period close to 1 day ("circadian"), but it is 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



They do not model TIM but focus on PER.

They use Michaelis-Menten to model DBT phosphorylating PER monomers and dimers

$$\mathrm{D} + \mathrm{P}_1 \underset{b_1}{\overset{f_1}{\rightleftharpoons}} \mathrm{C}_1 \xrightarrow{k_1} \mathrm{P}_1^* + \mathrm{D}$$

$$\mathrm{D} + \mathrm{P}_2 \underset{b_2}{\overset{f_2}{\rightleftharpoons}} \mathrm{C}_2 \xrightarrow{k_2} \mathrm{P}_2^* + \mathrm{D}$$

Quasi-steady state implies

$$\frac{dC_1}{dt} = f_1 D P_1 - (b_1 + k_1) C_1 \simeq 0$$
$$\frac{dC_2}{dt} = f_2 D P_2 - (b_2 + k_2) C_2 \simeq 0$$

$$\Rightarrow \quad C_1 \simeq \frac{f_1 D P_1}{b_1 + k_1} \quad ; \quad C_2 \simeq \frac{f_2 D P_2}{b_2 + k_2}$$

Conservation of the enzyme DBT implies

$$D + C_1 + C_2 = D_T \qquad \text{and} \qquad D = \frac{D_T}{1 + \frac{f_1 P_1}{b_1 + k_1} + \frac{f_2 P_2}{b_2 + k_2}}$$

and so the rate of formation of phosphorylated monomer is

$k_1 C_1$

$$k_1 \times \frac{f_1 P_1}{b_1 + k_1} \times \frac{D_T}{1 + \frac{f_1 P_1}{b_1 + k_1} + \frac{f_2 P_2}{b_2 + k_2}}$$

Monomers prevent dimers from being phosphorylated, and dimers prevent monomers from being phosphorylated

$$\frac{dP_1^*}{dt} = \frac{k_1 D_T P_1}{\frac{b_1+k_1}{f_1} + P_1 + \frac{f_2(b_1+k_1)}{f_1(b_2+k_2)} P_2}$$

$$\frac{dP_2^*}{dt} = \frac{k_2 D_T P_2}{\frac{b_2+k_2}{f_2} + P_2 + \frac{f_1(b_2+k_2)}{f_2(b_1+k_1)} P_1}$$

extended Michaelis-Menten equations

$$\begin{aligned} \frac{dP_1^*}{dt} &= \frac{V_1 P_1}{K + P_1 + P_2} \\ \frac{dP_2^*}{dt} &= \frac{V_2 P_2}{K + P_1 + P_2} \end{aligned}$$

symmetric case

Each substrate inhibits the other by sequestering the enzyme DBT.

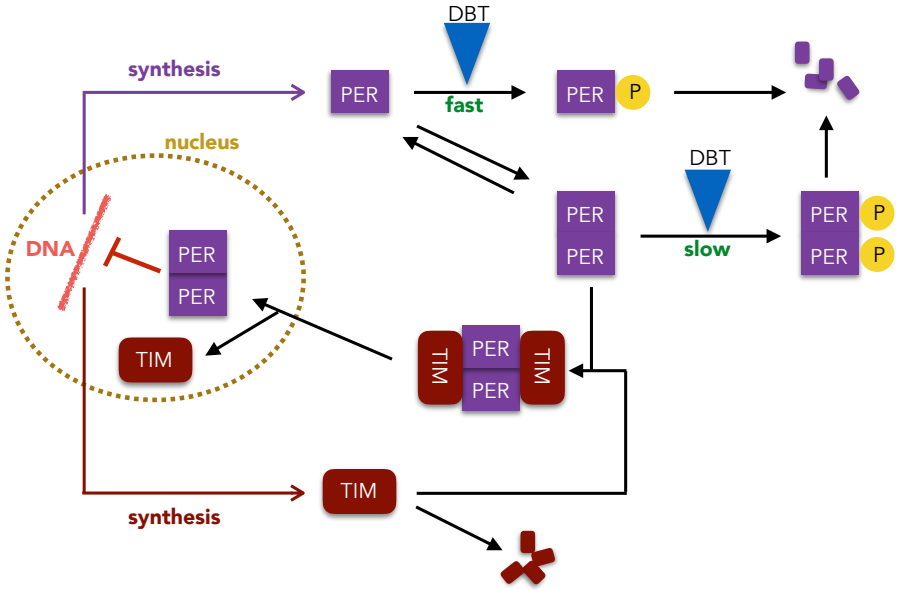
The *per* gene is repressed by PER dimers

PER mRNA

$$\frac{dM}{dt} = \frac{u}{1 + \left(\frac{P_2}{P_c}\right)^2} - d_M M$$

Autorepression is modelled through a Hill function with *n= 2*

There are three rate equations



dimerisation

$$\mathrm{P}_1 + \mathrm{P}_1 \underset{b}{\overset{f}{\rightleftharpoons}} P_2$$

translation from DBT dimerisation

$$\frac{dP_1}{dt} = vM - \frac{V_1 P_1}{K + P_1 + P_2} - d_P P_1 - 2fP_1^2 + 2bP_2$$

$$\frac{dP_2}{dt} = -\frac{V_2 P_2}{K + P_1 + P_2} - d_P P_2 + fP_1^2 - bP_2$$

$$\frac{dM}{dt} = \frac{u}{1 + \frac{P_2^2}{P_c^2}} - d_M M$$

To simplify, they assume that PER monomer and dimers are in equilibrium

$$\mathrm{P}_1 + \mathrm{P}_1 \underset{b}{\overset{f}{\rightleftharpoons}} P_2 \qquad\qquad P_2 = \frac{f}{b} P_1^2$$

Let the total number of monomers be P_T

$$P_T = P_1 + 2P_2$$

P_T changes with time

Combining these equations gives

$$P_1^2 + \frac{b}{2f} P_1 - \frac{b}{2f} P_T = 0$$

and so both can be expressed in terms of P_T

$$P_1 = qP_T \quad ; \quad P_2 = \tfrac{1}{2}(1-q)P_T$$

with $q = \dfrac{2}{1 + \sqrt{1 + 8\frac{f}{b} P_T}}$

By assuming dimerisation is at equilibrium, only two rate equations are necessary

$$\frac{dP_T}{dt} = vM - \frac{V_1 q + V_2(1-q)}{K + \frac{1}{2}(1+q)P_T} P_T - d_P P_T$$

$$\frac{dM}{dt} = \frac{u}{1 + \frac{(1-q)^2 P_T^2}{4P_c^2}} - d_M M$$

Using

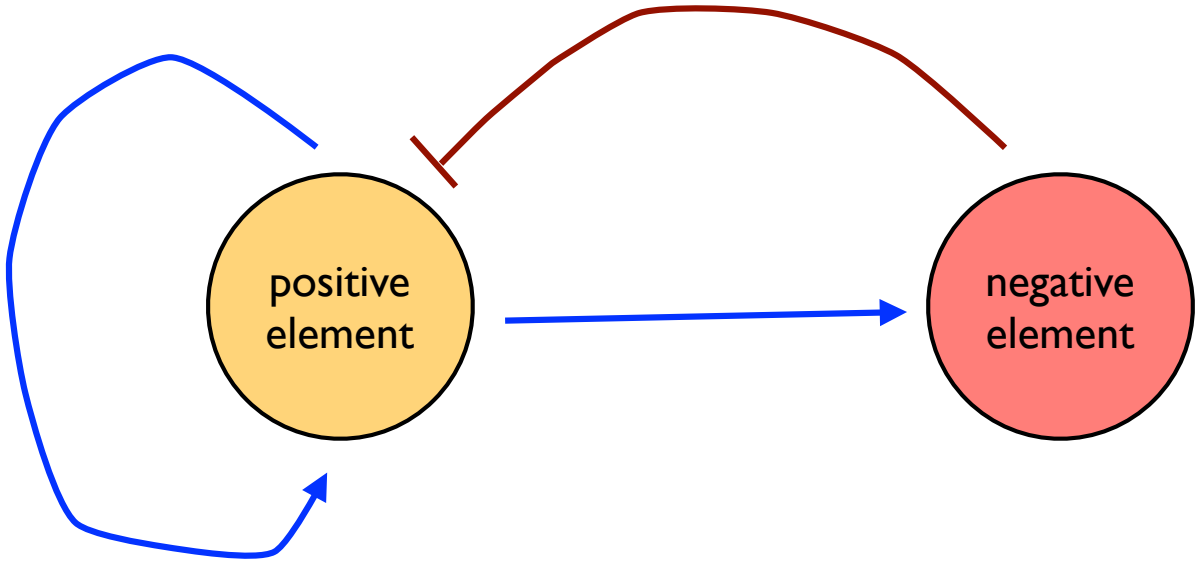
$$P_T = P_1 + 2P_2$$

and so

$$\frac{dP_T}{dt} = \frac{dP_1}{dt} + 2\frac{dP_2}{dt}$$

Relaxation oscillators are selected for their robustness

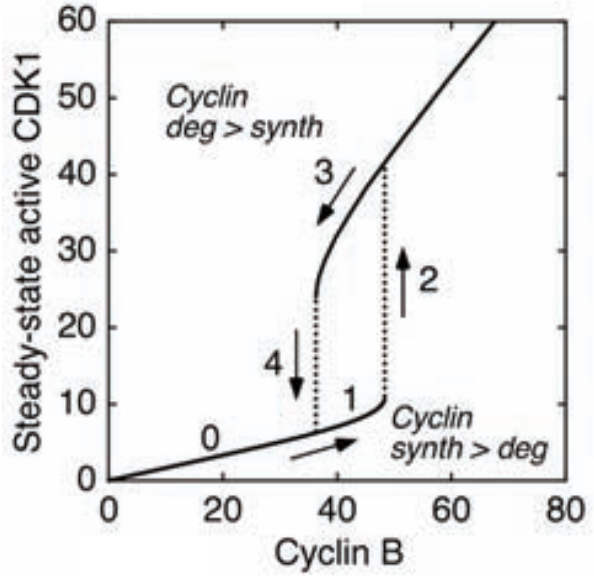
Circadian networks have a core structure of negative *and* positive feedbacks



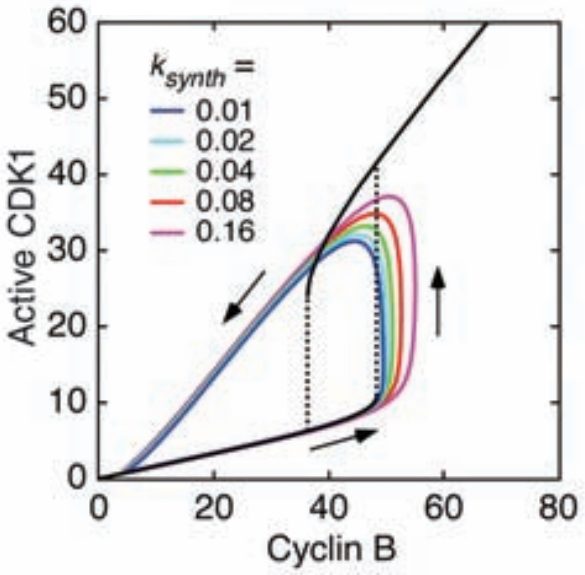
Why?

From Barkai & Leibler 2000 and Dunlap 1999

Relaxation oscillators operate around the hysteresis loop of an underlying, former bistability



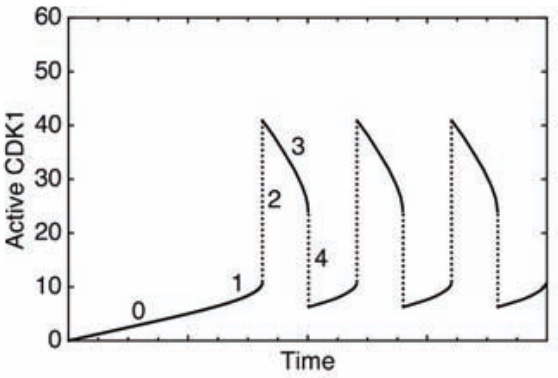
Steady-state response with only positive feedback has hysteresis.



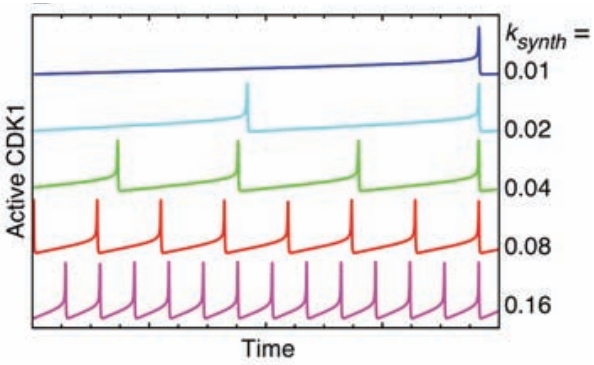
Relaxation oscillations occur with additional negative feedback.

A model of the cell cycle

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

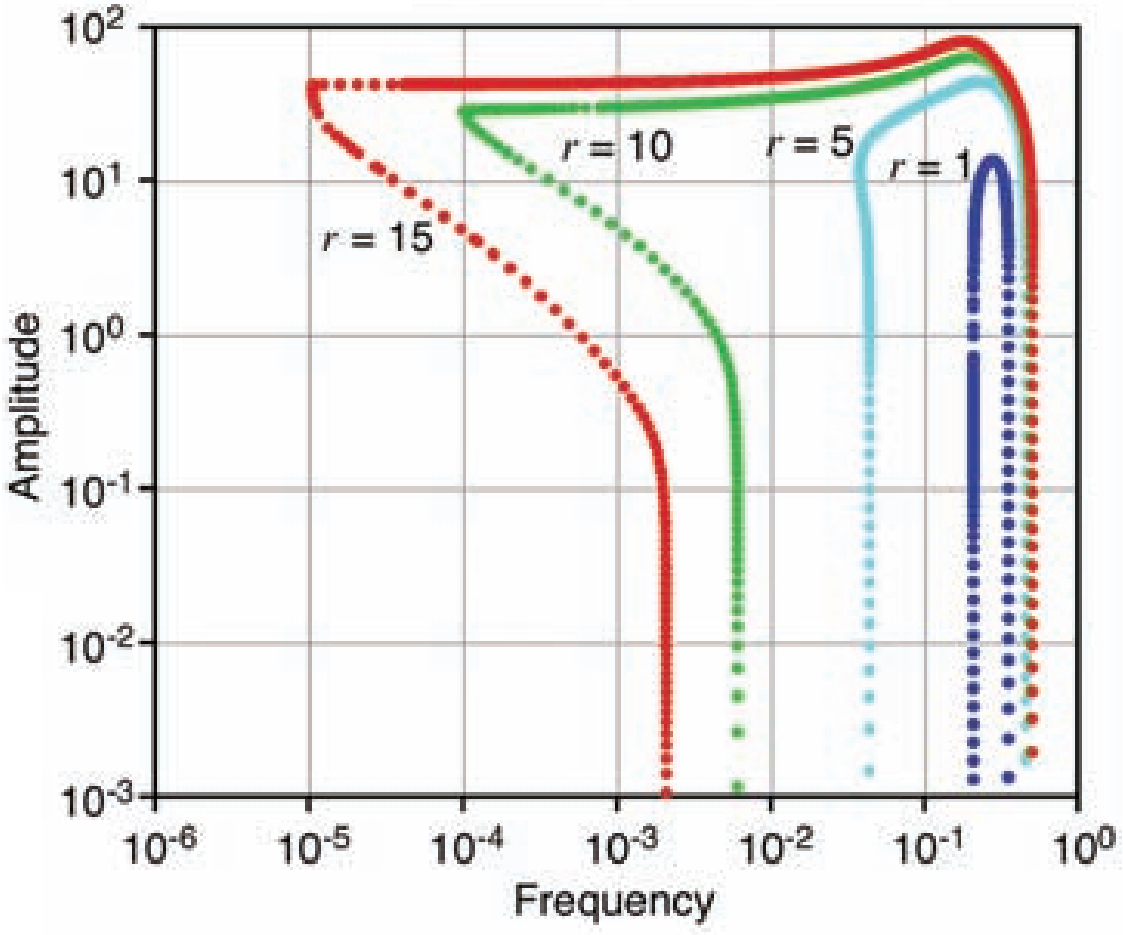


Relaxation oscillations



From Tsai *et al*, 2008

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

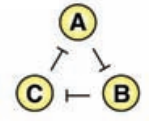


r controls the strength of positive feedback

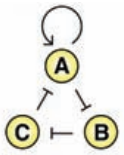
frequency is systematically changed by changing the synthesis rate

From Tsai *et al.*, 2008

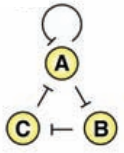
Relaxation oscillators are able to oscillate for wider ranges of parameters than negative feedback oscillators



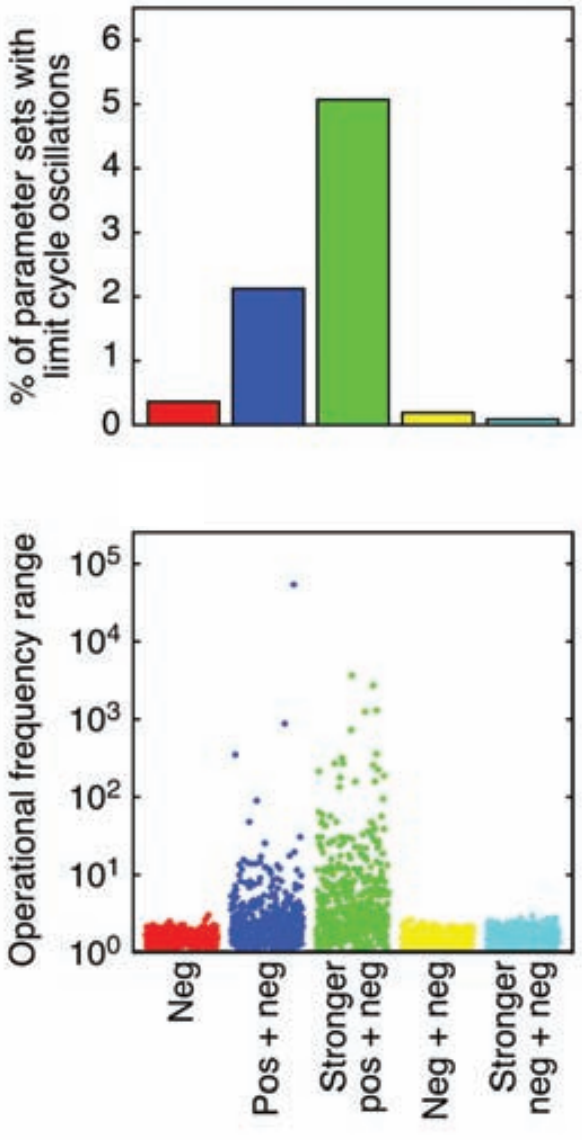
negative feedback



negative and positive feedback



negative and negative feedback

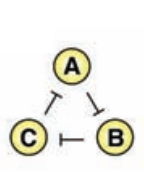


$\frac{freq_{max}}{freq_{min}}$

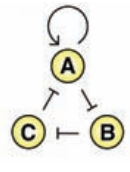
as they vary one synthesis rate

From Tsai *et al*, 2008

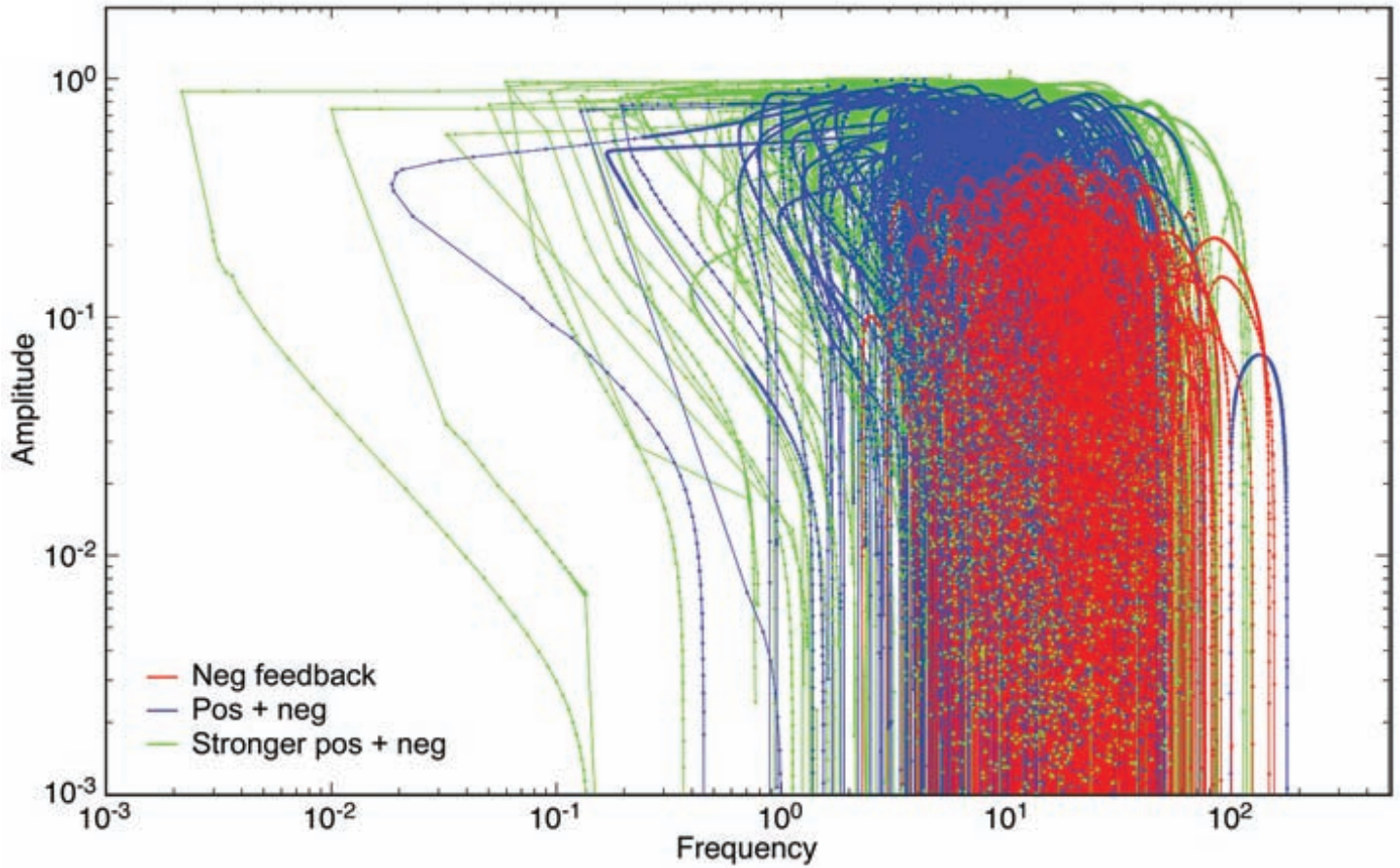
Relaxation oscillators can maintain the amplitude of oscillations more than negative feedback oscillators



negative feedback



negative and positive feedback



From Tsai *et al*, 2008