Phase-locked Loops for Chemical Control of Oscillation Frequency

A prototype of biological clocks and their entrainment by light?

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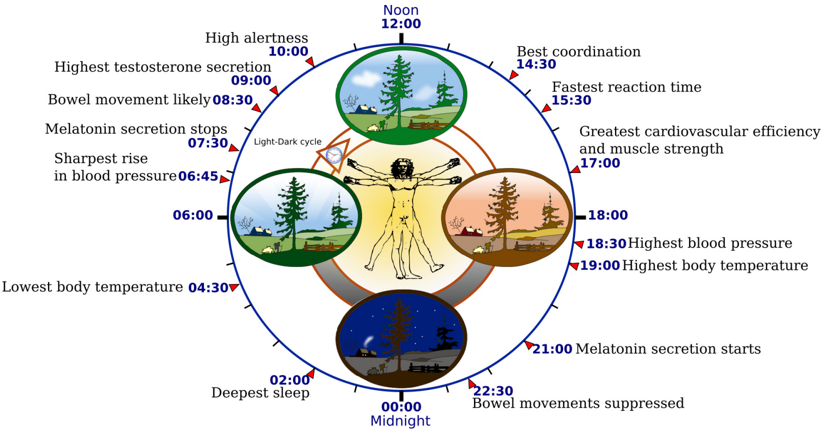
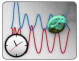
Human Daily Rhythm: Trigger and Control System



www.wikipedia.org



Chronobiology

χρονοζ
time

βιοζ
life

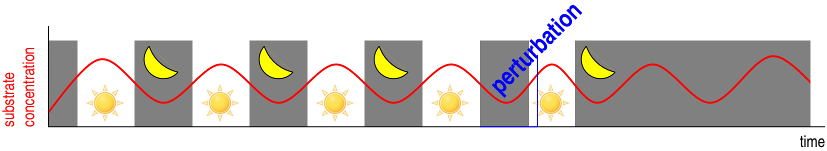
λογοζ
science

ρυθμοζ
rhythm

science of biological rhythms and clock systems

Circadian Clock

- Sustained biochemical oscillation (endogenous rhythm)
- Free-running period close to but typically not exactly 24 hours persisting under constant environmental conditions (e.g. permanent darkness DD or permanent light LL)
- *Entrainment* – adaptation to external stimuli (e.g. light-dark cycles induced by sunlight)
- Temperature compensation within a physiological range
- Reaction systems with at least one feedback loop



⟹ **Biological counterpart of frequency control system**

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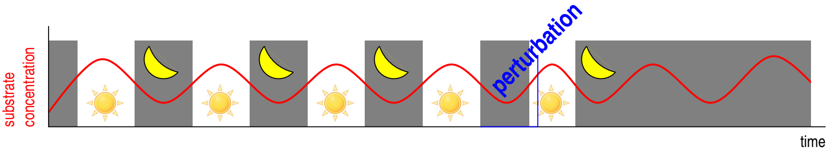

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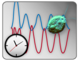

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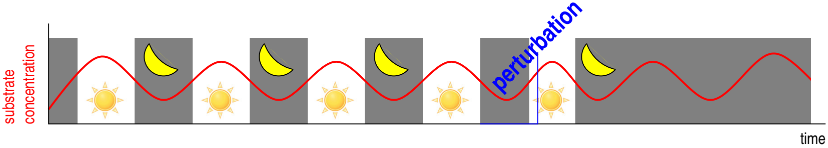

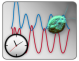

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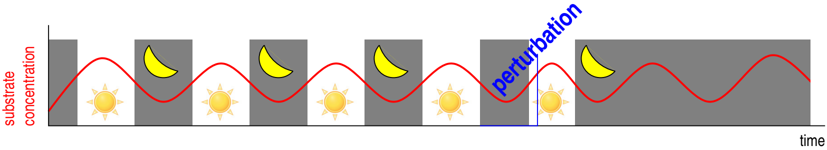

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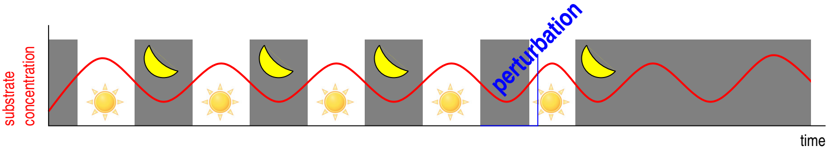

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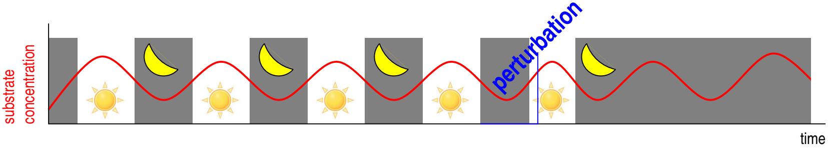

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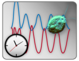
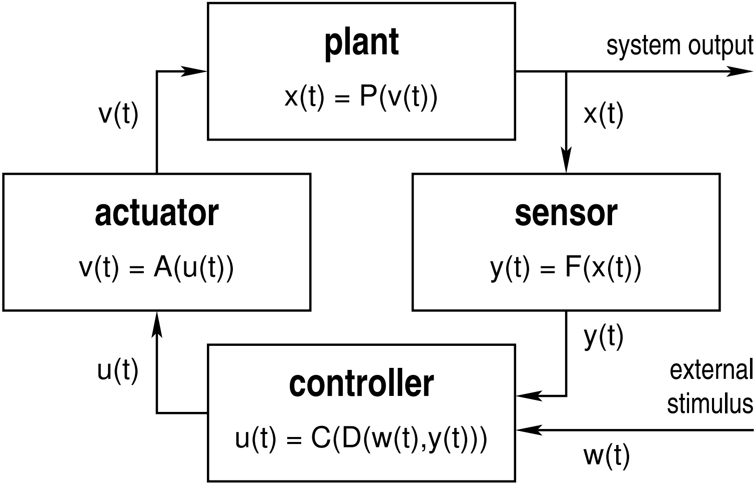
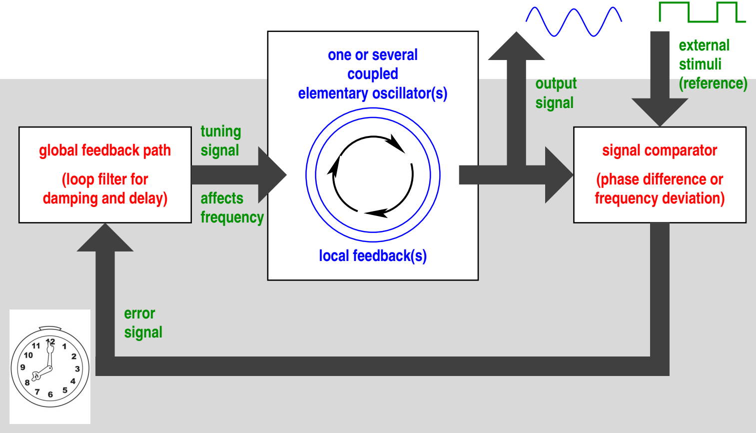


General Scheme of a Simple Control Loop



Frequency Control using Phase-locked Loop



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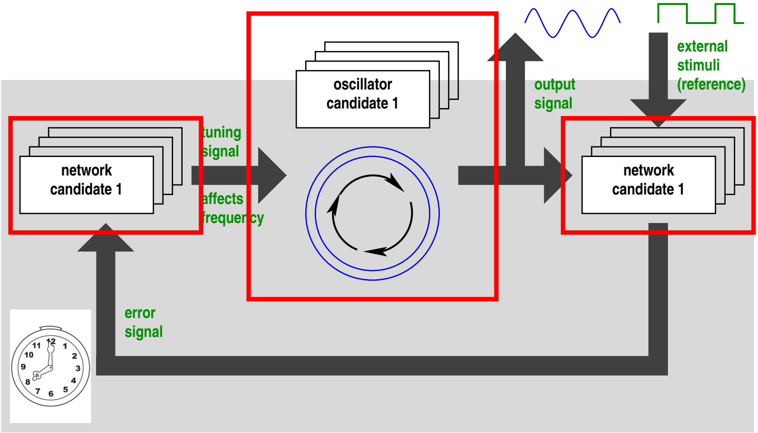
Combine Reaction Network Modules



T. Hinze, C. Bodenstein, I. Heiland, S. Schuster. Capturing Biological Frequency Control of Circadian Clocks by Reaction System Modularization. ISSN 0926-4981, ERCIM News 85:27-29, 2011

Mass-action Reaction Kinetics at a Glance

Modeling Temporal Behaviour of Chemical Reaction Networks

Assumption: number of effective reactant collisions Z proportional to reactant concentrations (Guldberg 1867)

$A + B \xrightarrow{\hat{k}} C$ .... $Z_C \sim [A]$ and $Z_C \sim [B]$, so

$$Z_C \sim [A] \cdot [B]$$

Production rate generating C:

$$v_{prod}([C]) = \hat{k} \cdot [A] \cdot [B]$$

Consumption rate of C: ...... $v_{cons}([C]) = 0$

$$\frac{d\,[C]}{d\,t} = v_{prod}([C]) - v_{cons}([C])$$

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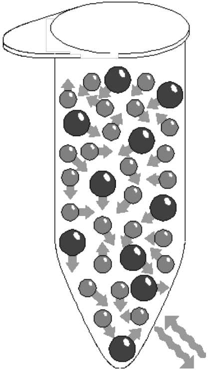
Initial conditions: $[C](0), [A](0), [B](0)$ to be set



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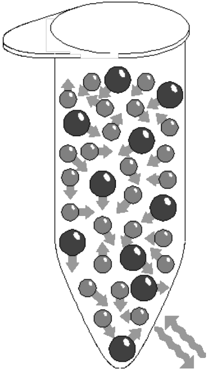

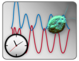

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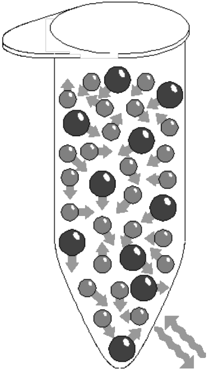

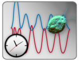

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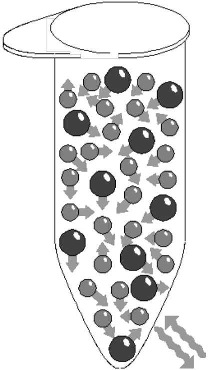

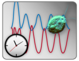

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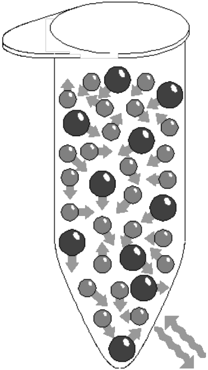

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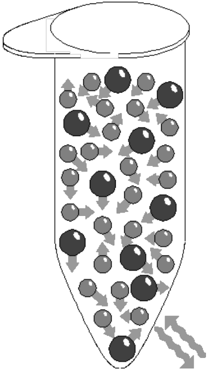


Mass-action Kinetics: General ODE Model

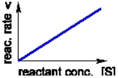
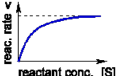
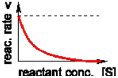
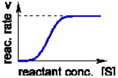
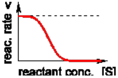
Chemical reaction system

$$
\begin{aligned}
a_{1,1}S_1 + a_{2,1}S_2 + \ldots + a_{n,1}S_n &\xrightarrow{\hat{k}_1} b_{1,1}S_1 + b_{2,1}S_2 + \ldots + b_{n,1}S_n \\
a_{1,2}S_1 + a_{2,2}S_2 + \ldots + a_{n,2}S_n &\xrightarrow{\hat{k}_2} b_{1,2}S_1 + b_{2,2}S_2 + \ldots + b_{n,2}S_n \\
&\vdots \\
a_{1,h}S_1 + a_{2,h}S_2 + \ldots + a_{n,h}S_n &\xrightarrow{\hat{k}_h} b_{1,h}S_1 + b_{2,h}S_2 + \ldots + b_{n,h}S_n,
\end{aligned}
$$

results in ordinary differential equations (ODEs)

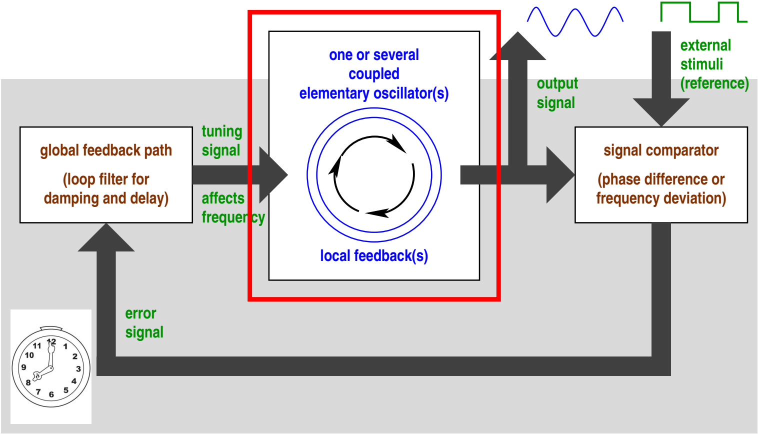
$$
\frac{d\,[S_i]}{d\,t} = \sum_{\nu=1}^{h} \left(\hat{k}_\nu \cdot (b_{i,\nu} - a_{i,\nu}) \cdot \prod_{l=1}^{n} [S_l]^{a_{l,\nu}} \right) \quad \text{with} \quad i = 1, \ldots, n.
$$

Mass-action vs. Saturation Kinetics

Kinetics	Activation (rate law)		Repression (rate law)	
Mass-action (no saturation)		$v = k \cdot [S]$		–
Michaelis-Menten (saturation)		$v = K \cdot \frac{[S]}{T+[S]}$		$v = K \cdot \left(1 - \frac{[S]}{T+[S]}\right)$
Higher-Order Hill (saturation)		$v = K \cdot \frac{[S]^n}{T+[S]^n}$		$v = K \cdot \left(1 - \frac{[S]^n}{T+[S]^n}\right)$

- Michaelis Menten: Typical enzyme kinetics
- Higher-order Hill ($n \geq 2$): Typically for gene expression using sigmoidal transfer function

Plant: Controllable Core Oscillator



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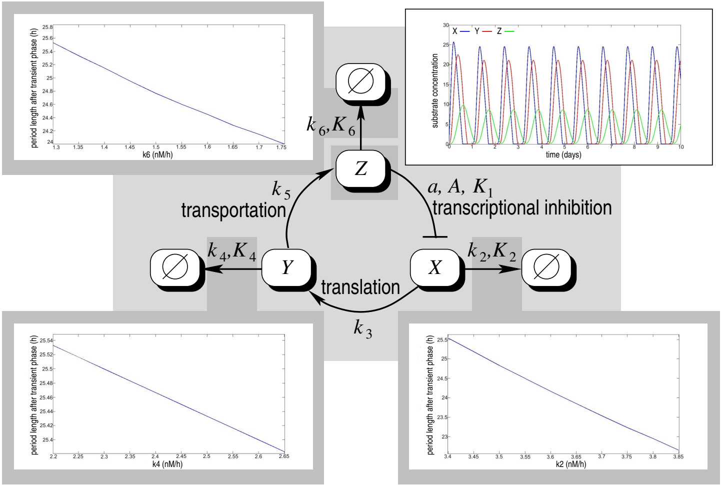
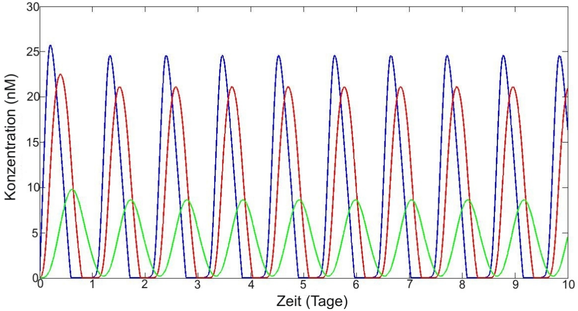
Controllable Goodwin-type Core Oscillator



T. Hinze, C. Bodenstein, B. Schau, I. Heiland, S. Schuster. Chemical Analog Computers for Clock Frequency Control Based on P Modules. Proceedings of the Twelfth International Conference on Membrane Computing, to appear within series Lecture Notes in Computer Science, Springer Verlag, 2011

Core Oscillator: Dynamical Behaviour



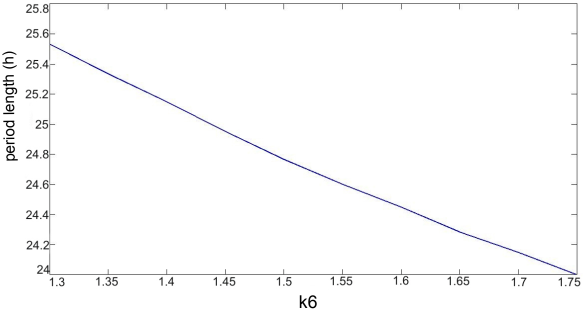
$$[\dot{X}] = \frac{a}{A + K_1[Z]^2} - \frac{k_2[X]}{K_2 + [X]}$$

$$[\dot{Y}] = k_3[X] - k_5[Y] - \frac{k_4[Y]}{K_4 + [Y]}$$

$$[\dot{Z}] = k_5[Y] - \frac{k_6[Z]}{K_6 + [Z]}$$

B. Schau. Reverse-Engineering circadianer Oszillationssysteme als Frequenzregelkreise mit Nachlaufsynchronisation. Diploma thesis, 2011

Affecting Frequency by Degradation Rate of Z



- Velocity parameter k_6 of Z degradation notably influences oscillation frequency
- Period control coefficients assigned to each reaction quantify influence on frequency

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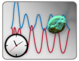
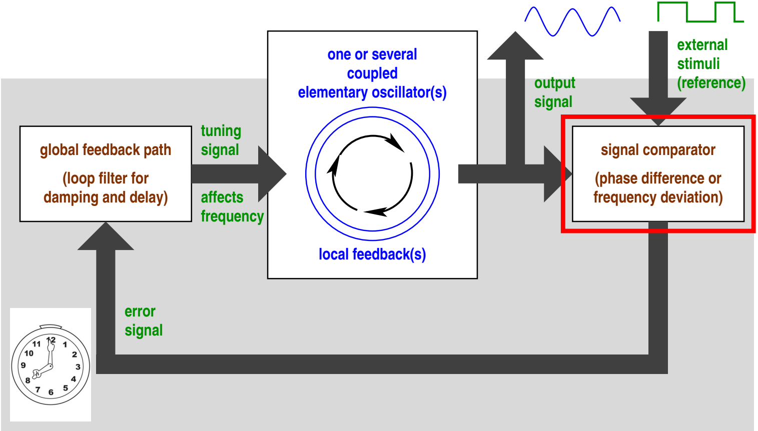


Controller: Signal Comparator



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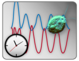
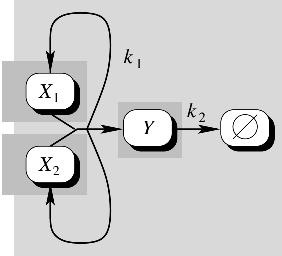
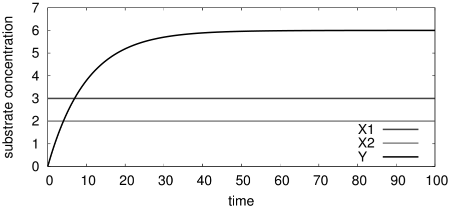


Signal Comparator: Multiplication Unit





$$
\begin{aligned}
[\dot{X_1}] &= 0\\
[\dot{X_2}] &= 0\\
[\dot{Y}] &= k_1[X_1][X_2] - k_2[Y]
\end{aligned}
$$

ODE solution for asymptotic steady state in case of $k_1 = k_2$:

$$[Y](\infty) = \lim_{t\to\infty} \left(1 - \mathrm{e}^{-k_1 t}\right) \cdot ([X_1](t) \cdot [X_2](t)) = [X_1](0) \cdot [X_2](0)$$

Input-output mapping: $[Y] = [X_1] \cdot [X_2]$

T. Hinze, C. Bodenstein, B. Schau, I. Heiland, S. Schuster. Chemical Analog Computers for Clock Frequency Control Based on P Modules. Proceedings of the Twelfth International Conference on Membrane Computing, to appear within series Lecture Notes in Computer Science, Springer Verlag, 2011

Comparing Phases: Mathematical Background

Output of core oscillator $\omega = 2\pi/\tau$:

$$y(t) = y(t+\tau) = A_0 + \sum_{n=1}^{\infty} A_n \cos(n\omega t + \varphi_n)$$

Input of external reference signal $\omega' = 2\pi/\tau'$:

$$z(t) = z(t+\tau') = A'_0 + \sum_{n=1}^{\infty} A'_n \sin(n\omega' t + \varphi'_n)$$

For simplicity we assume that all higher harmonics are removed by a filter.

Comparing Phases by Multiplication

Multiplication module:

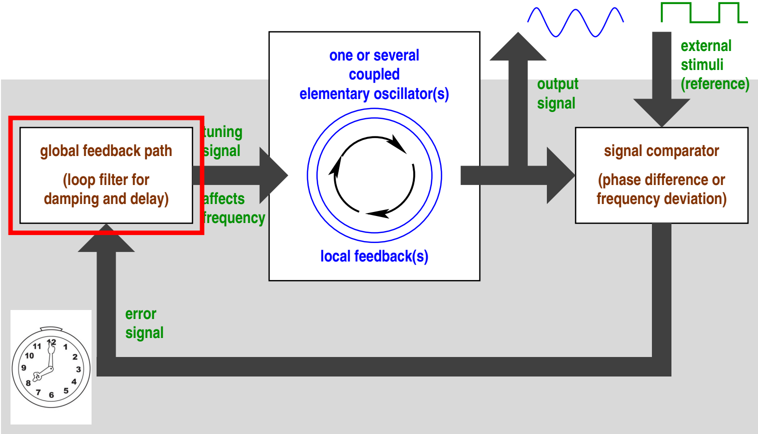
$$\dot{x} = k(z(t)y(t) - x) \qquad \lim_{k\to\infty} x(t) = z(t)y(t)$$

Output of multiplication:

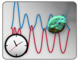
$$z(t)y(t) = A'_0 A_0 + A'_0 A_1 \cos(\omega t + \varphi_1) + A_0 A'_1 \sin(\omega' t + \varphi'_1) + \frac{A'_1 A_1}{2}\left(\sin((\omega' - \omega)t + \varphi'_1 - \varphi_1) + \sin((\omega' + \omega)t + \varphi'_1 + \varphi_1)\right)$$

Low frequency term ($\omega' \approx \omega$) carries the phase-difference information: $\phi' - \phi$.

Actuator: Global Feedback with Low-pass Filter



Adapted from T. Hinze, M. Schumann, C. Bodenstein, I. Heiland, S. Schuster. Biochemical Frequency Control by Synchronisation of Coupled Repressilators: An In-silico Study of Modules for Circadian Clock Systems. Computational Intelligence and Neuroscience 2011:262189, 2011



Low-pass Filter as Global Feedback

- Desensibilise global feedback by
  signal smoothing, damping, and delay
- Eliminate high-frequency oscillations by a low-pass filter

Simple linear reaction cascade forms a low-pass filter.

Samoilov et al. J Phys Chem 106, 2002

B. Schau. Reverse-Engineering circadianer Oszillationssysteme als Frequenzregelkreise mit Nachlaufsynchronisation. Diploma thesis, 2011

Adjust kinetic parameters to obtain desired filtering.

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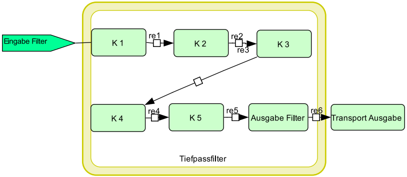

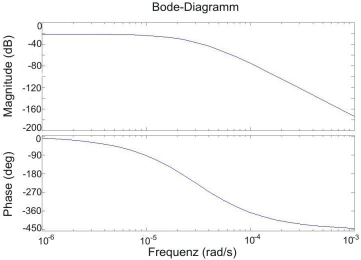

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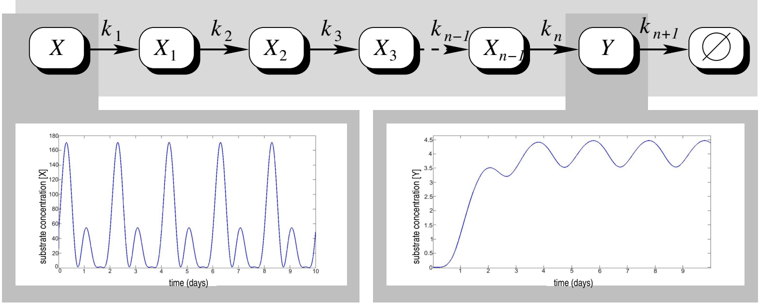
Low-pass Filter



$$
\begin{aligned}
[\dot{X}_1] &= k_1[X] - k_2[X_1] \\
[\dot{X}_2] &= k_2[X_1] - k_3[X_2] \\
&\vdots \\
[\dot{X}_{n-1}] &= k_{n-1}[X_{n-2}] - k_n[X_{n-1}] \\
[\dot{Y}] &= k_n[X_{n-1}] - k_{n+1}[Y]
\end{aligned}
$$

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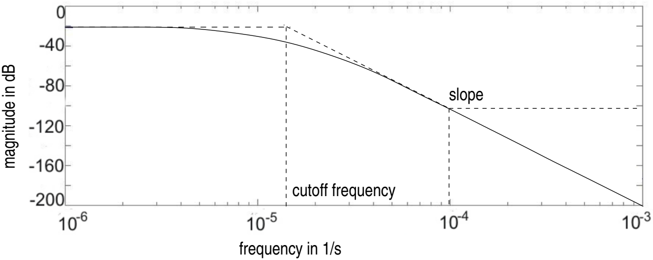
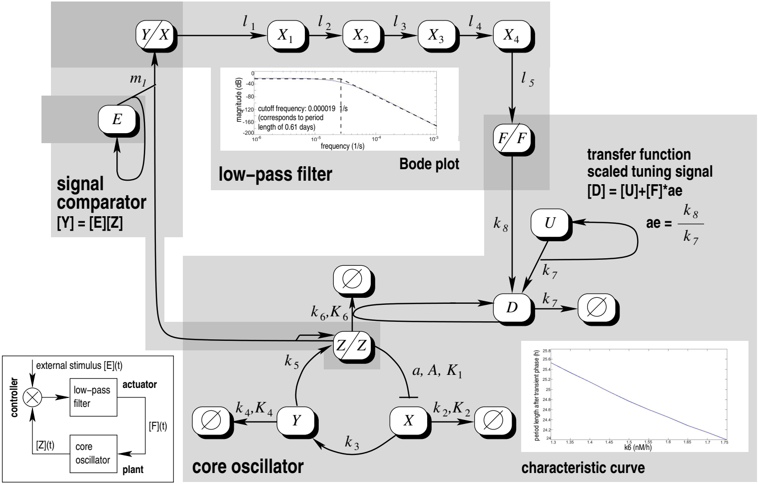
Low-pass Filter: Bode Plot as Characteristic Curve



$$\text{Magnitude dB} = 10 \cdot \lg \left(\frac{\text{amplitude of output signal}}{\text{amplitude of input signal}} \right)$$

- Signals affected by smoothing delay throughout cascade
- Oscillation waveform harmonisation into sinusoidal shape
- Global filter parameters:
  passband damping, cutoff frequency, slope

Model of a Chemical Frequency Control Based on PLL



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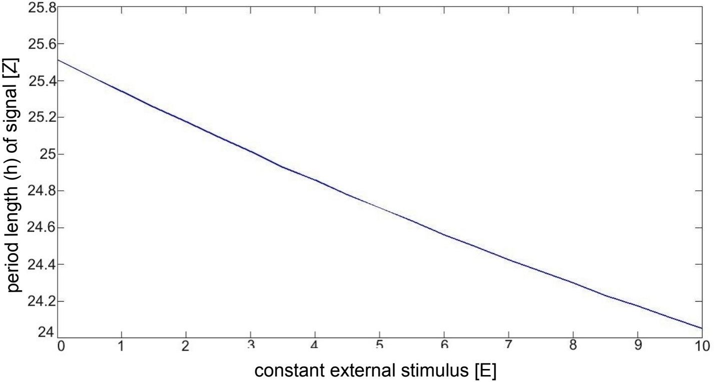
Period Lengths subject to Constant External Stimulus



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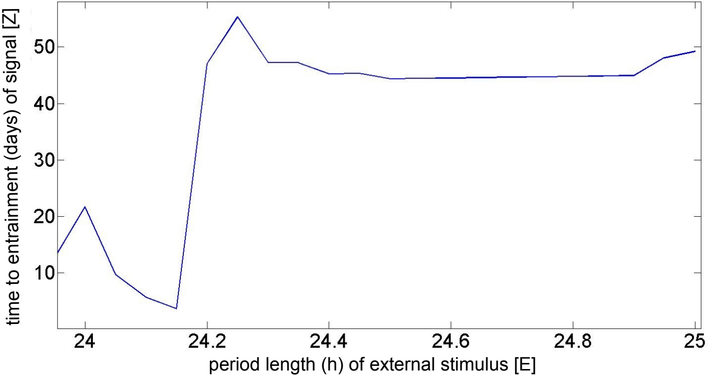
Time to Entrainment to Different Period Lengths



Natural period of core oscillator: 24.2h

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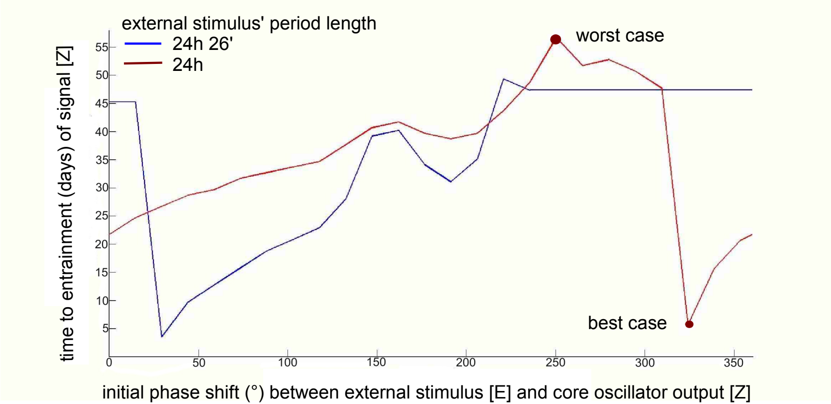
Time to Entrainment to Different Initial Phase Shifts



Entrainment reached within convergence interval 1min

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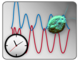
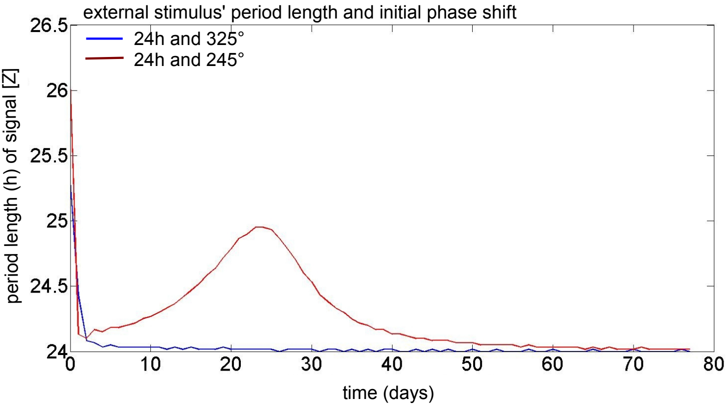


Best Case and Worst Case Entrainment



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Perturbed Core Oscillator

Unperturbed core oscillator at constant external signal A'_0:

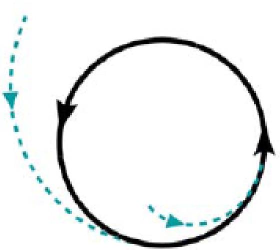
$$\frac{\mathrm{d}\mathbf{X}}{\mathrm{d}t} = \mathbf{F}(\mathbf{X})$$

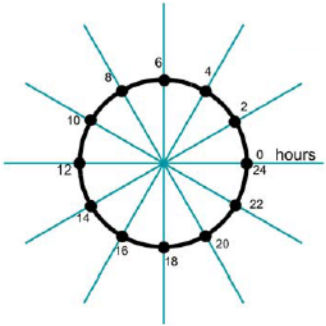
with limit cycle solution $\mathbf{X}^0(t) = \mathbf{X}^0(t+\tau)$.
Perturbed core oscillator:

$$\frac{\mathrm{d}\mathbf{X}}{\mathrm{d}t} = \mathbf{F}(\mathbf{X}) + \varepsilon \sin(\ldots)\, k_1 \frac{\partial \mathbf{F}}{\partial k_1}(\mathbf{X}).$$

Since ε is small the amplitude of the limit cycle is not affected and we can reduce the model to the phase dynamics!

Amplitude and Phase

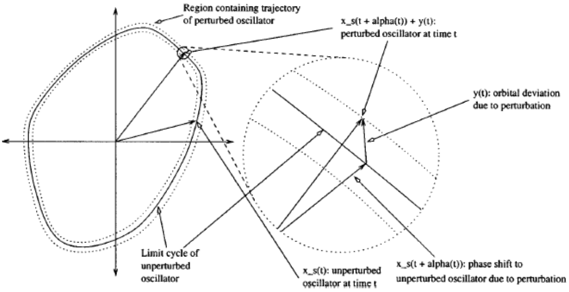




Granada & Herzel. PLoS ONE 4(9): e7057, 2009

We can assign each point on the limit cycle $\mathbf{X}^0$ a specific phase value ϕ.

Phase Reduction (Kuramoto 1984)



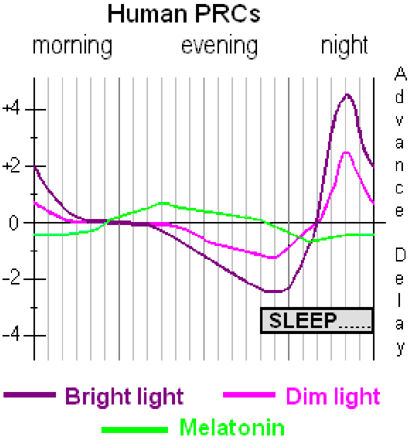
Demir et al. IEEE Transactions on circuits and systems 47(5):655-674, 2000

Oscillator phase dynamics:

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = \omega + \varepsilon \, \mathrm{PRC}_l(\phi) \sin\left(\phi' - \phi + \varphi_{lpf}\right).$$

PRC_l is the 2π-periodic phase response curve of k_l.

Phase Response Curve



http://en.wikipedia.org/wiki/Phase_response_curve

Phase Difference

Phase difference ψ between oscillator and external signal:

$$\psi = \phi - \phi'$$
$$\frac{\mathrm{d}\psi}{\mathrm{d}t} = \omega - \omega' - \varepsilon\, \mathrm{PRC}_l(\phi' + \psi) \sin\left(\psi - \varphi_{lpf}\right)$$

ψ is a slowly changing variable compared to $\phi' = \omega' t$, therefore we may average the perturbation over one external cycle and consider ψ on the slow time scale:

$$\frac{1}{\tau'} \int_0^{\tau'} \mathrm{PRC}_l(\phi'(t) + \psi)\, \mathrm{d}t = -C_{\mathrm{l}}^{\tau},$$

where $C_{\mathrm{l}}^{\tau} = k_{\mathrm{l}}/\tau \frac{\partial \tau}{\partial k_{\mathrm{l}}}$ is the period control coefficient.

Phase Difference

Phase difference equation:

$$\frac{\mathrm{d}\psi}{\mathrm{d}t} = \frac{\omega - \omega'}{\varepsilon} + C_{\mathrm{l}}^{\tau} \sin\left(\psi - \varphi_{lpf}\right)$$

Phase-locking corresponds to (stable) steady-state solutions ψ_0 of this equation:

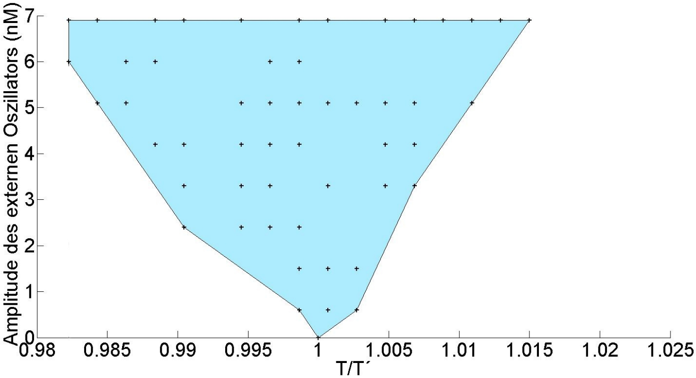
$$\phi(t) = \phi'(t) + \psi_0.$$

Phase locking exists in a region enclosed by:

$$\varepsilon^{\pm} = \mp\left(\omega - \omega'\right)\frac{1}{C_{\mathrm{l}}^{\tau}},$$

the so called *Arnold* tongue.

Arnold Tongue



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Phase Lag

The phase lag can be easily determined from the derived equation. For example consider $\omega = \omega'$ and $C_1^{\tau} < 0$, the stable solution then is:

$$\psi_0 = \varphi_{lpf}.$$

That means the phase lag is completely determined by the low-pass filter.

Conclusions

- Chemical frequency control can utilise PLL
- Prototypic modelling example for entrainment of circadian clockworks
- Chemical processing units in minimalistic manner
- Variety of chemical implementations
- Modularisation in (bio)chemical reaction systems

Some open questions

- Identification of *in-vivo* counterparts
- Replacement of individual processing units (like different core oscillators)
- Balancing advantages and limitations of the PLL approach
- Inclusion of temperature entrainment (by Arrhenius terms)
- Alternative concepts of frequency control

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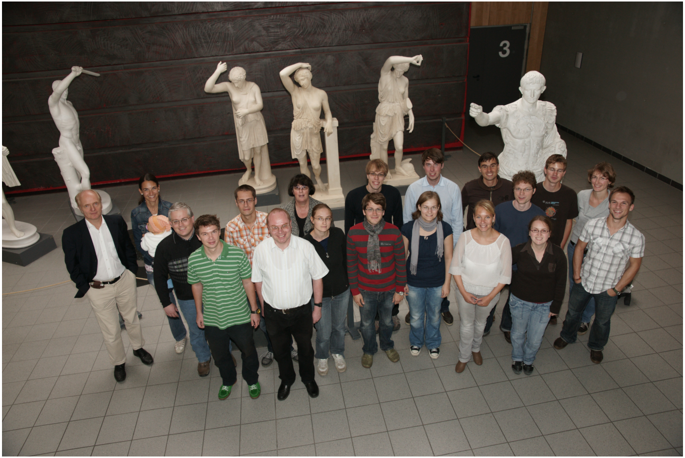

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