Chemical Oscillation Frequency Control using Phase-locked Loops

A prototype of biological clocks and their entrainment by light?

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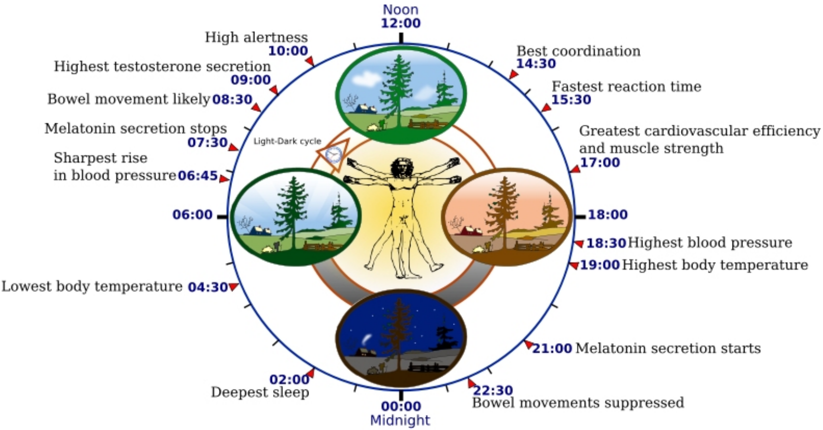
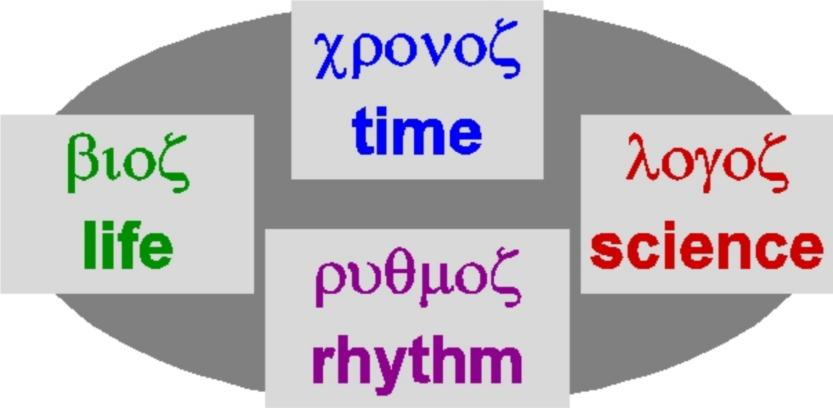
Human Daily Rhythm: Trigger and Control System



www.wikipedia.org

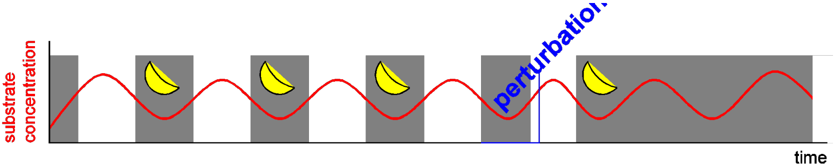
Chronobiology



science of biological rhythms and clock systems

Circadian Clock

- Undamped biochemical oscillation
- 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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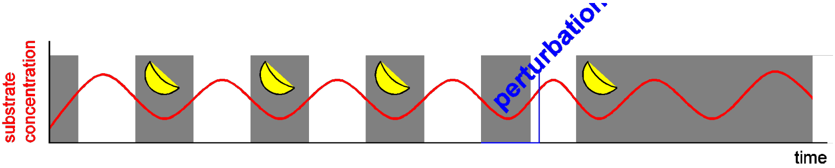

$\Longrightarrow$ Biological counterpart of frequency control system

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Mass-action Kinetics: Background

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:

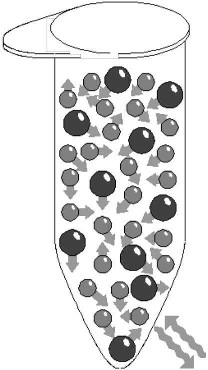
$$v_{prod}([C]) = \hat{k} \cdot [A] \cdot [B]$$

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

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

$$\frac{d\,[C]}{d\,t} = \hat{k} \cdot [A] \cdot [B]$$

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



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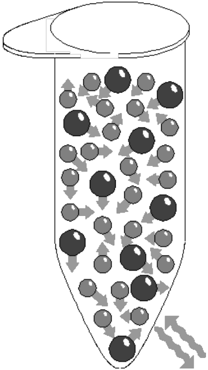

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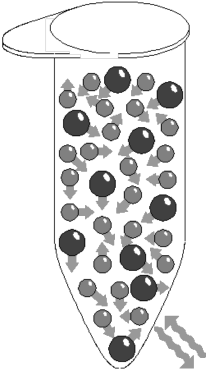

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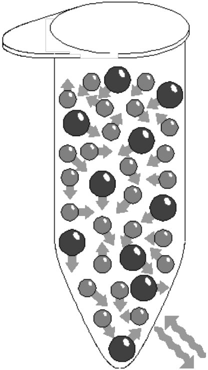

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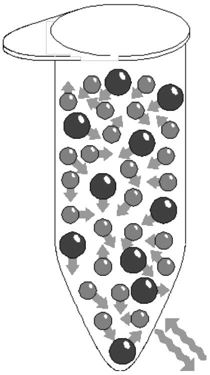

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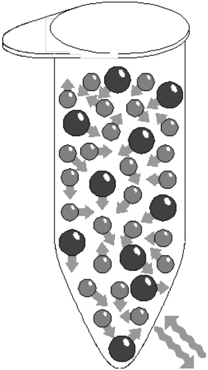

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Mass-action Kinetics: General ODE Model

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

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

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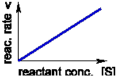
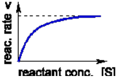
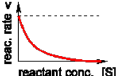
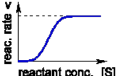
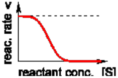
Mass-action vs. Saturation Kinetics

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

1. Reaction Kinetics at a Glance
2. **Processing Units: Components of Chemical Control Loops**
   - Addition
   - Multiplication
   - Low-pass Filter
   - Controllable Goodwin-type Core Oscillator
3. Phase-locked Loop (PLL): Continuous Frequency Control
4. Simulation Studies for Circadian Clock Systems
5. Theoretical Background of PLLs
6. Prospectives

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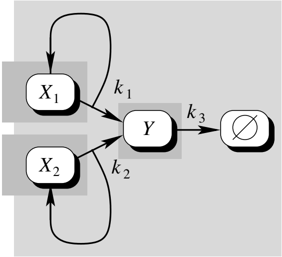
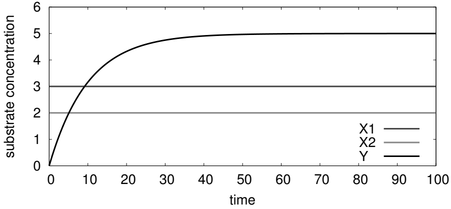
Addition





$$
\begin{aligned}
[\dot{X_1}] &= 0 \\
[\dot{X_2}] &= 0 \\
[\dot{Y}] &= k_1[X_1] + k_2[X_2] - k_3[Y]
\end{aligned}
$$

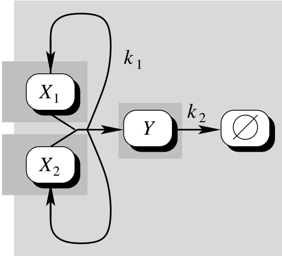
ODE solution for asymptotic steady state in case of $k_1 = k_2 = k_3$:

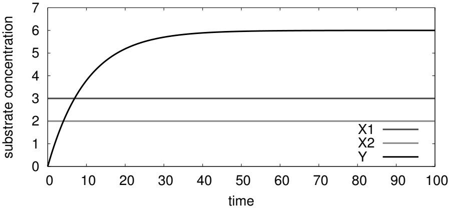
$$[Y](\infty) = \lim_{t\to\infty} \left(1 - \mathrm{e}^{-k_1 t}\right) \cdot ([X_1](t) + [X_2](t)) = [X_1](0) + [X_2](0)$$

Transfer function: $[Y] = [X_1] + [X_2]$

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, accepted

Multiplication





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

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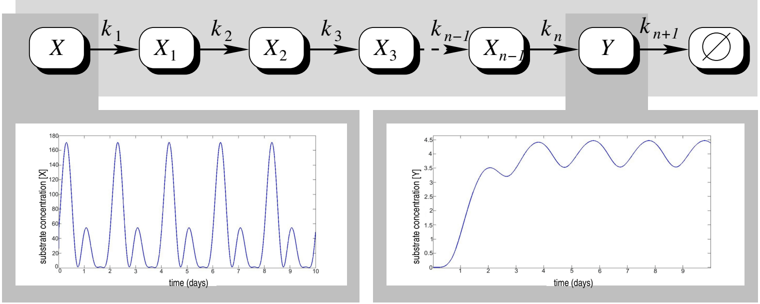
Low-pass Filter



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

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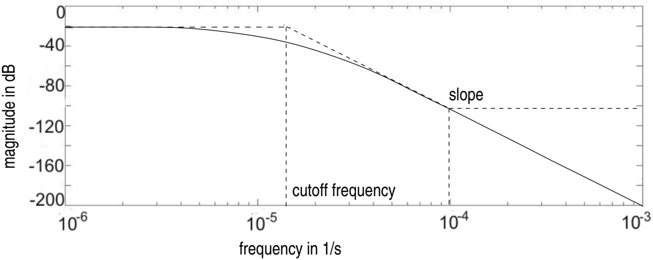
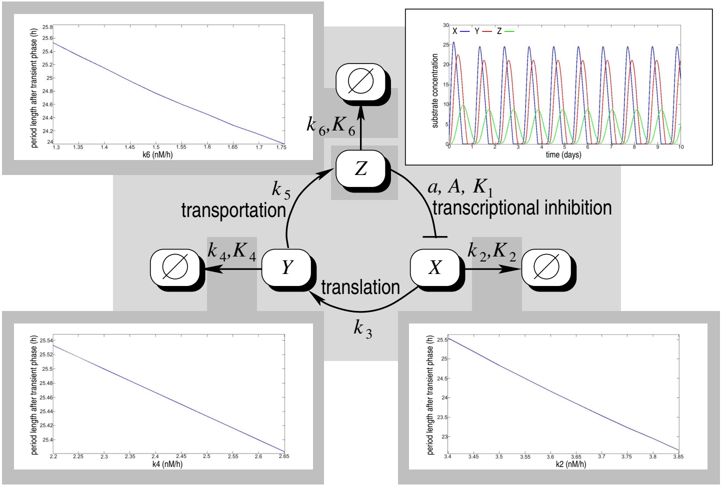
Low-pass Filter: Bode Plot as Characteristic Curve



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

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

Controllable Goodwin-type Core Oscillator



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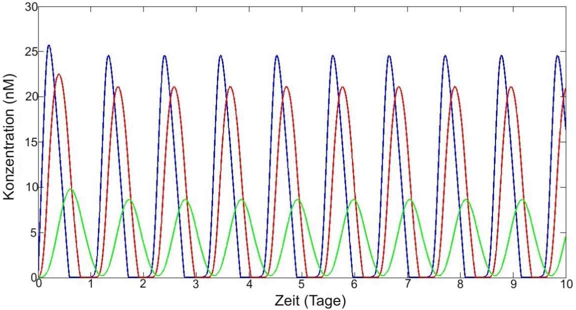
Core Oscillator: Dynamical Behaviour



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

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

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

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

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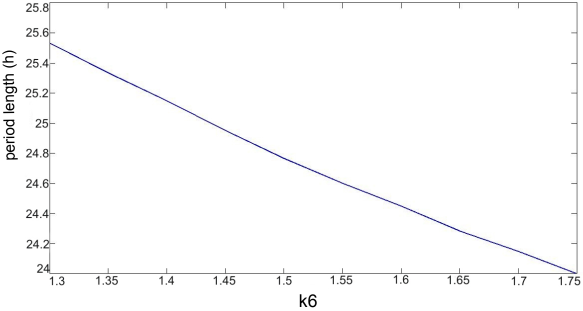

- Velocity parameter k_6 of Z degradation notably influences oscillation frequency
- Period control coefficients assigned to each reaction quantify influence on frequency

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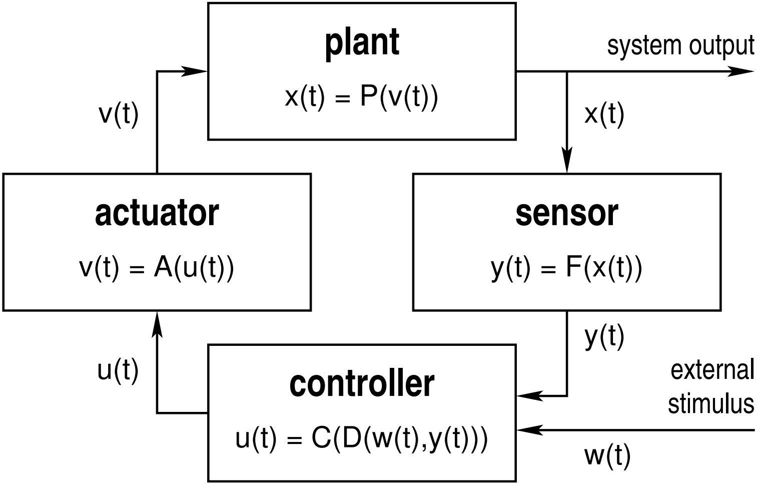
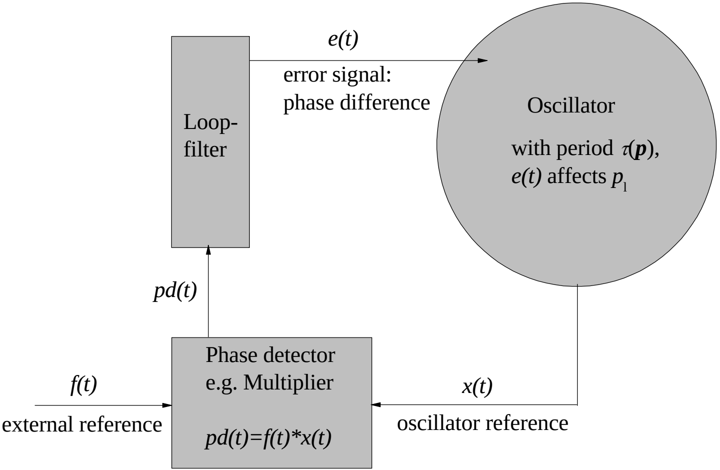
General Scheme of a Simple Control Loop



Scheme of a Phase-locked Loop



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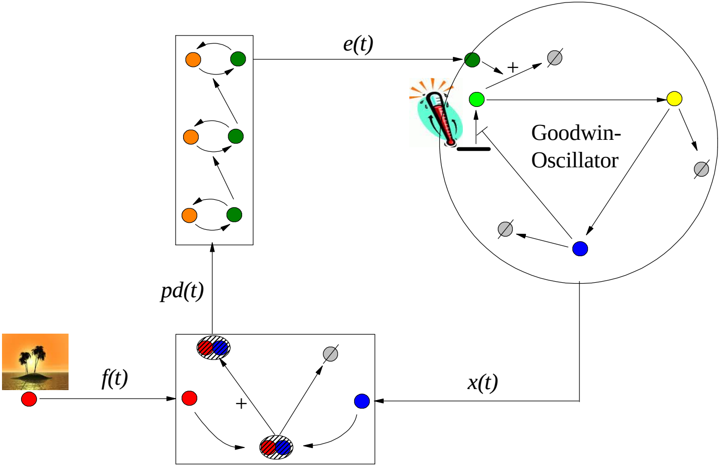
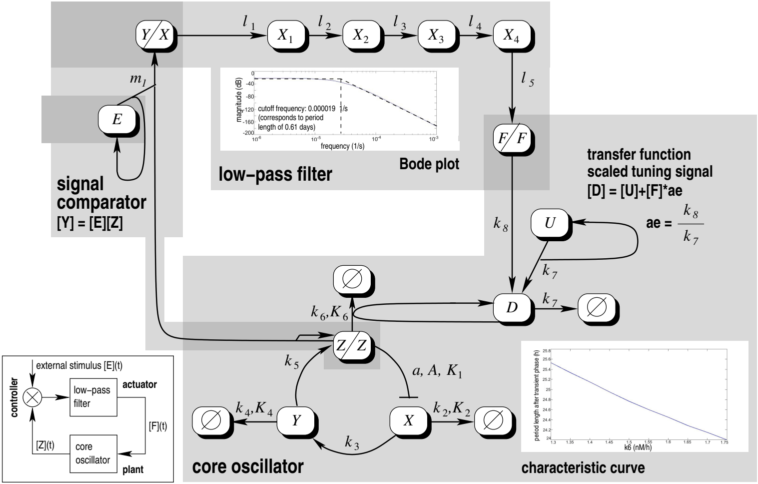


Model of a Chemical Frequency Control Based on PLL



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Comparing Phases

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.

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Comparing Phases: Multiplication

Multiplication module:

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

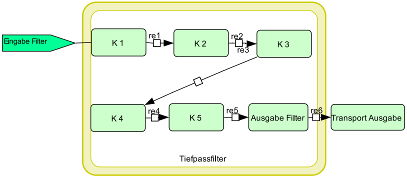
Output of multiplication:

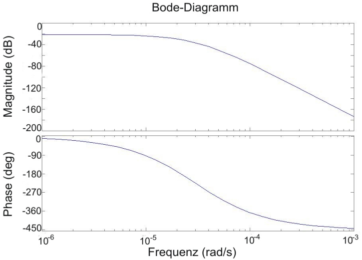
$$z(t)y(t) = A'_0A_0 + A'_0A_1\cos(\omega t + \varphi_1) + A_0A'_1\sin(\omega' t + \varphi'_1) + \frac{A'_1A_1}{2}\left(\sin((\omega' - \omega)t + \varphi'_1 - \varphi_1) + \sin((\omega' + \omega)t + \varphi'_1 + \varphi_1)\right)$$

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

Extract Phase-difference Information: Filtering

Filter out high-frequency terms from $x(t)$. Simple linear signalling cascade works as a low-pass filter[1]:





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

Adjust kinetic parameters to obtain desired filtering.

[1] Samoilov et al. *J Phys Chem* 106 (2002)

Error Signal and Feedback

Output of cascade:

$$e(t) = a_0 + a_1 \sin((\omega' - \omega)t + \varphi_1' - \varphi_1 + \varphi_{lpf})$$

Weakly (!) feed back the signal to the oscillator, e.g. by changing the kinetic rate constant of l-th reaction:

$$\begin{aligned} k_l^* &= k_l(1 + \varepsilon e(t)) = k_l + k_l \varepsilon a_0 + k_l \varepsilon a_1 \sin(\ldots) \\ &= \tilde{k}_l (1 + \tilde{\varepsilon} \sin(\ldots)) \,. \end{aligned}$$

$\tilde{k}_l$ reaction rate at constant external signal A_0'. Drop tilde for convenience.

Perturbed Core Oscillator

Unperturbed core oscillator at constant external signal A'_0:

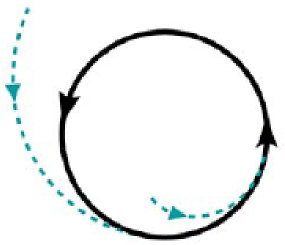
$$\frac{\mathrm{d}\mathbf{X}}{\mathrm{d}t} = \mathbf{F}(\mathbf{X})$$

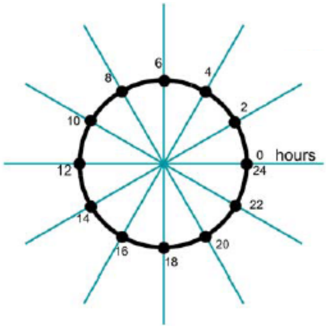
with limit cycle solution $\mathbf{X}^0(t) = \mathbf{X}^0(t+\tau)$.
Perturbed core oscillator:

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

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

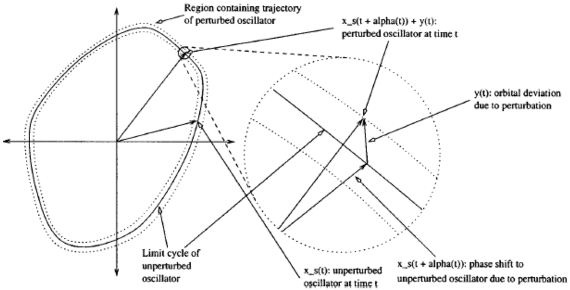




Granada & Herzel *PLoS ONE* 4(9): e7057 (2009)

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

Phase Reduction (Kuramoto 1984)



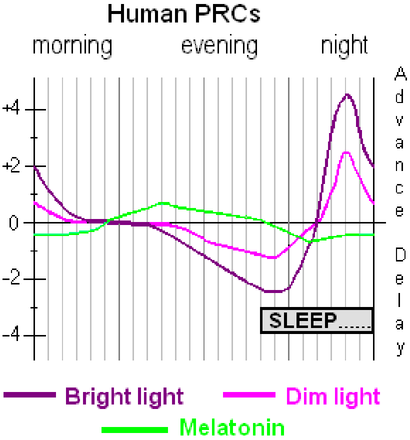
Demir et al. *IEEE Transactions on circuits and systems* 47:5 (2000) 655-674

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:

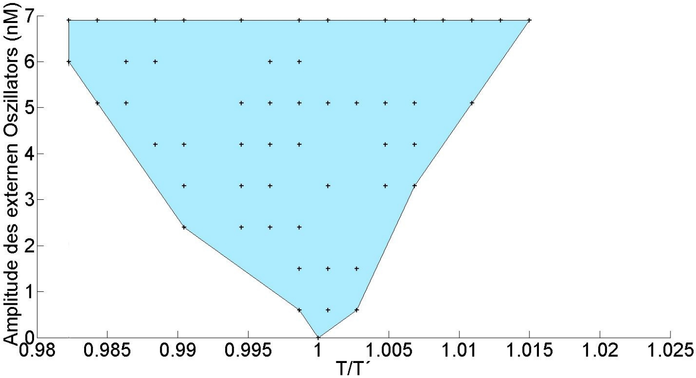
$$\phi(t) = \phi'(t) + \psi_0.$$

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



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

Phase Lag

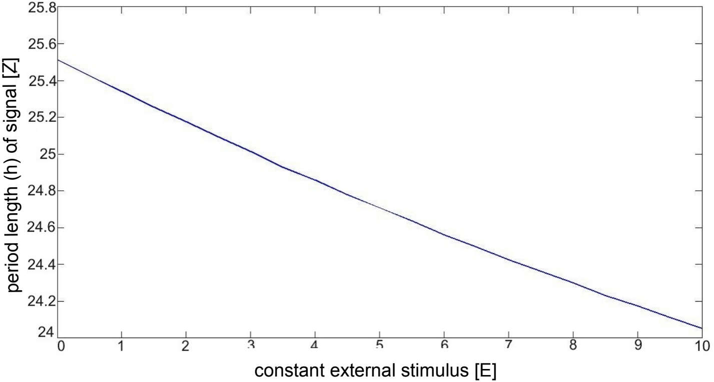
The phase lag can be easily determined from the derived equation. For example consider $\omega = \omega'$ and $C_{\mathrm{I}}^{\tau} < 0$, the stable solution then is:

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

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

1. Reaction Kinetics at a Glance
2. Processing Units:
   Components of Chemical Control Loops
3. Phase-locked Loop (PLL):
   Continuous Frequency Control
4. Theoretical Background of PLLs
5. **Simulation Studies for**
   Circadian Clock Systems
   - Period Lengths subject to Constant Ext. Stimulus
   - Time to Entrainment to Different Period Lengths
   - Time to Entrainment to Different Initial Phase Shift
   - Best Case and Worst Case Entrainment
6. Prospectives

Period Lengths subject to Constant External Stimulus



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, accepted

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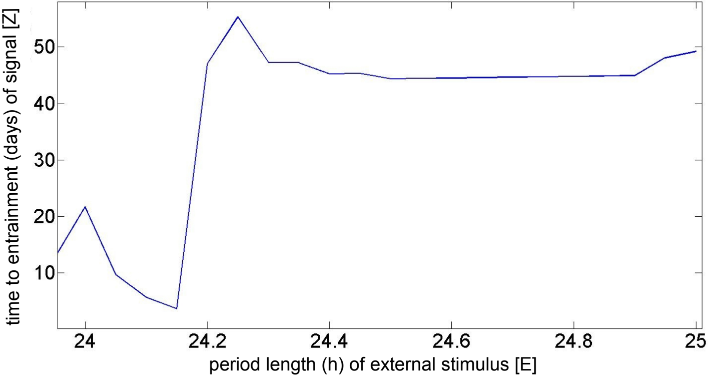
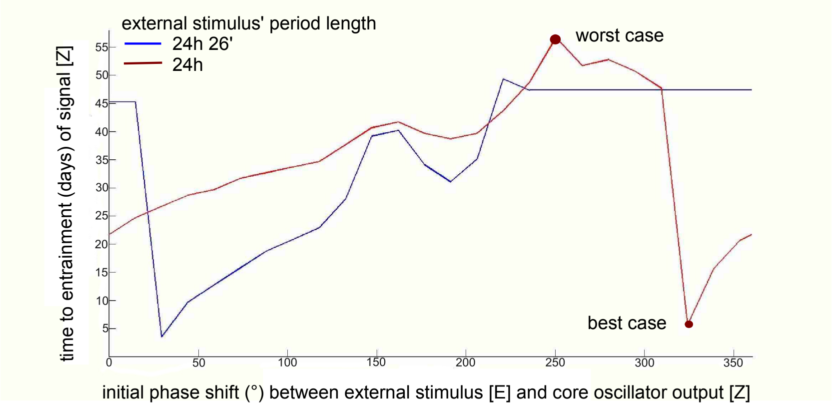
Time to Entrainment to Different Period Lengths



Natural period of core oscillator: 24.2h

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, accepted

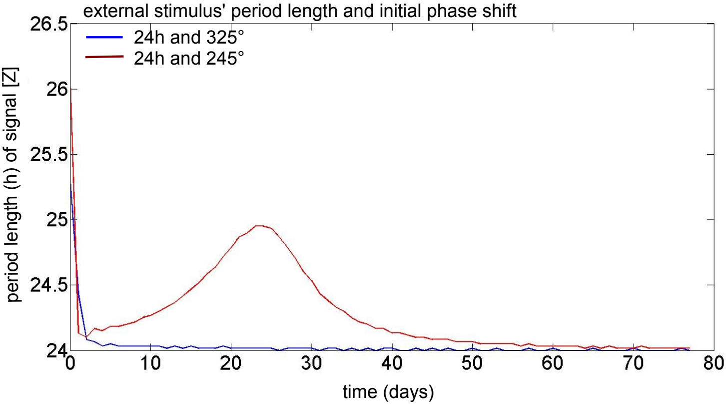
Time to Entrainment to Different Initial Phase Shifts



Entrainment reached within convergence interval 1min

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, accepted

Best Case and Worst Case Entrainment



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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)
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- Inclusion of temperature entrainment (by Arrhenius terms)
- Alternative concepts of frequency control

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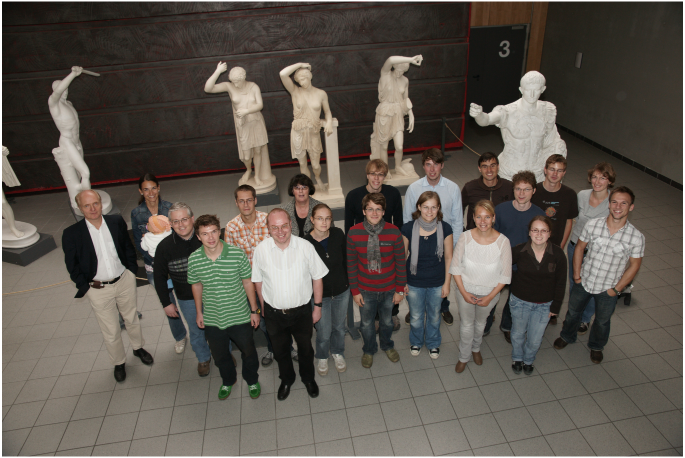

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Research Initiative in Systems Biology

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