Chemical Analog Computers for Clock Frequency Control Based on P Modules

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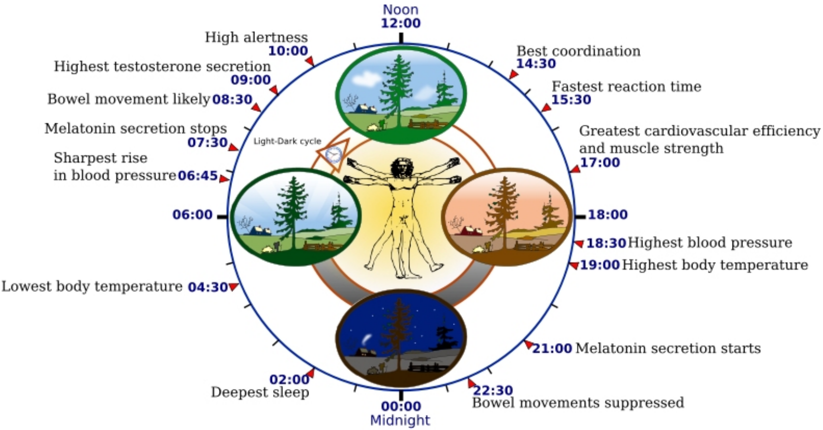
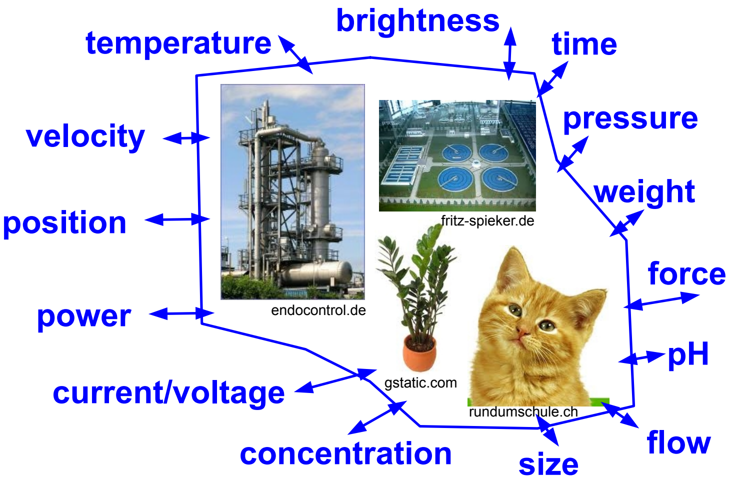
Human Daily Rhythm: Trigger and Control System



www.wikipedia.org

Continuous or Fine-grained Real-valued Signals



temperature
brightness
time
velocity
pressure
weight
position
force
power
pH
current/voltage
flow
concentration
size

endocontrol.de

fritz-spieker.de

gstatic.com

rundumschule.ch

⟹ measurable system's input and output on the fly

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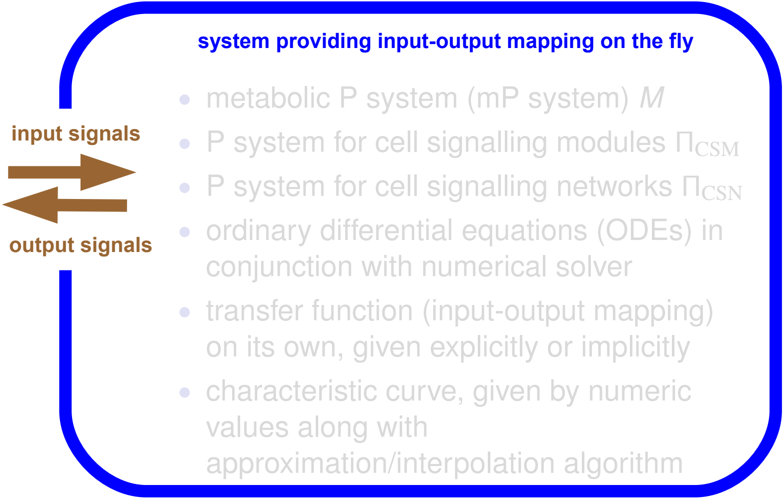
Module as a Processing Unit for Computational Tasks



system providing input-output mapping on the fly

input signals

output signals

- metabolic P system (mP system) M
- P system for cell signalling modules Π_{CSM}
- P system for cell signalling networks Π_{CSN}
- ordinary differential equations (ODEs) in conjunction with numerical solver
- transfer function (input-output mapping) on its own, given explicitly or implicitly
- characteristic curve, given by numeric values along with approximation/interpolation algorithm

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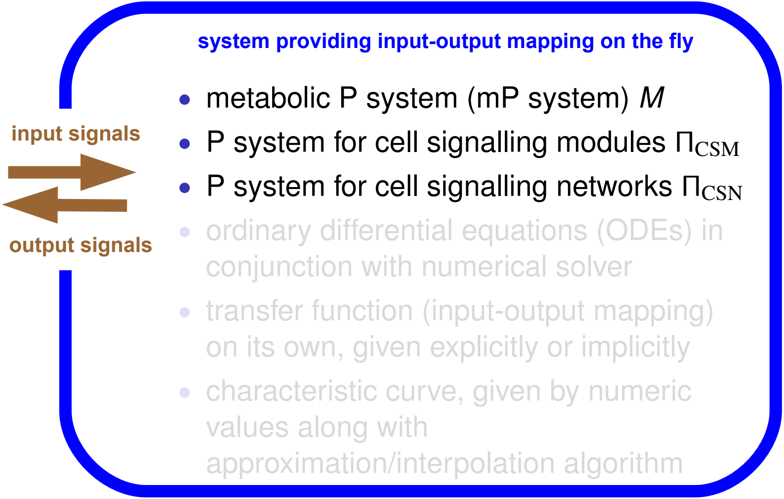

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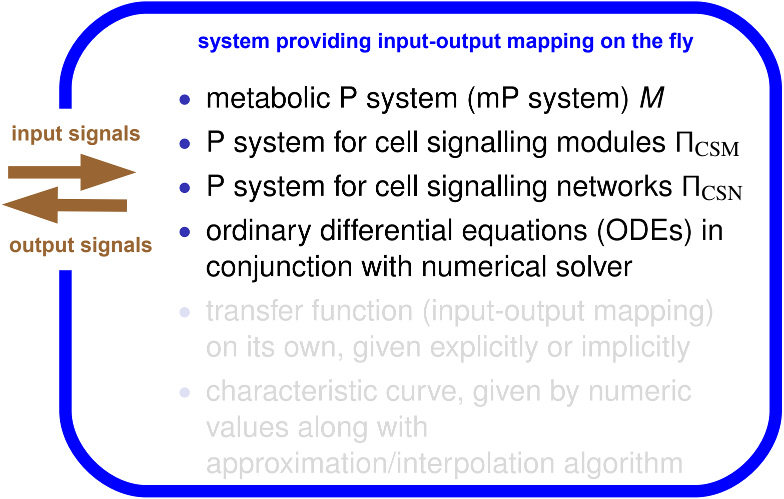

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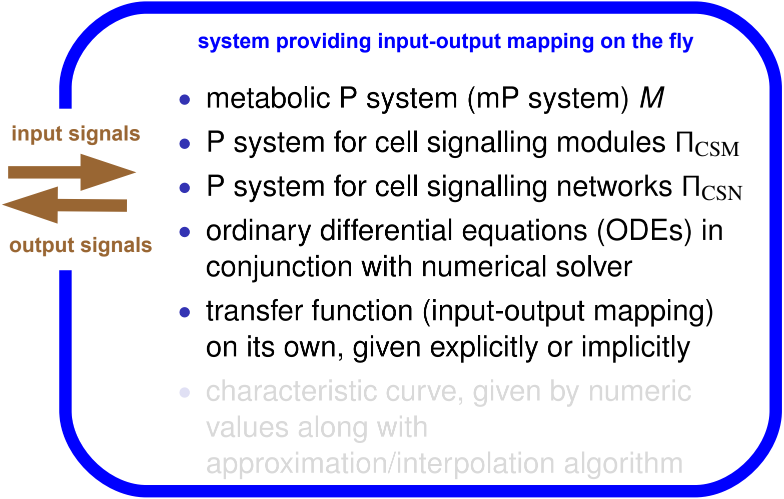

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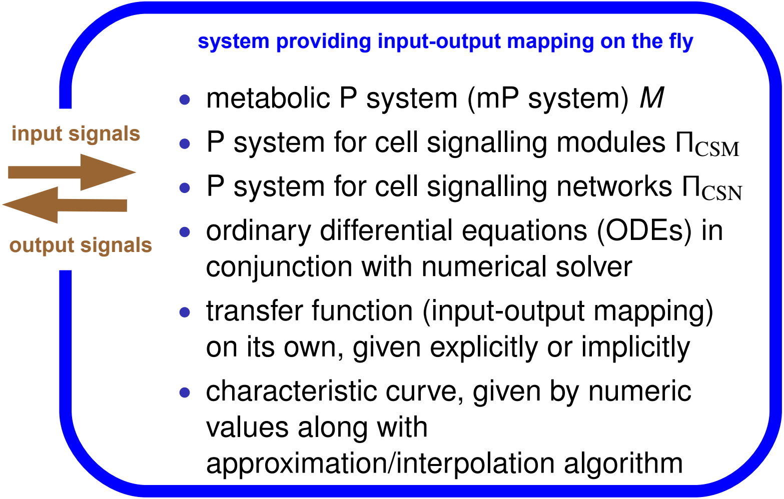

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P Module

- is able to fulfill an elementary computational task on the fly
- building block of an analog computer or in a control loop
- represents a container encapsulating a formal description of its dynamical behaviour
- specifies the interface of a general real-valued system or its approximation
- aims to bridge building blocks in systems theory and membrane systems

More formally, a P module is a triple $(\downarrow, \uparrow, \Box)$ where

$\downarrow = (I_1, \ldots, I_i)$ .... indicates a list of input signal identifiers
$\uparrow = (O_1, \ldots, O_o)$ ...... indicates a list of output signal identifiers
$\Box$ .... underlying system specification with or without inherent auxiliary signals

Each signal is a real-valued function over time.

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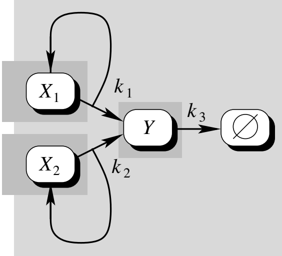
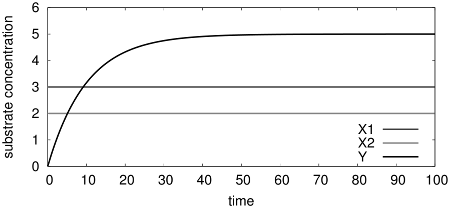
2. **Processing Units: Components of Chemical Control Loops**
   - Arithmetic Functions (add, sub, mul, div, sqrt)
   - Low-pass Filter
   - Controllable Goodwin-type Core Oscillator
3. Phase-locked Loop (PLL): Continuous Frequency Control
4. Simulation Studies for Circadian Clock Systems
5. Prospectives

Addition



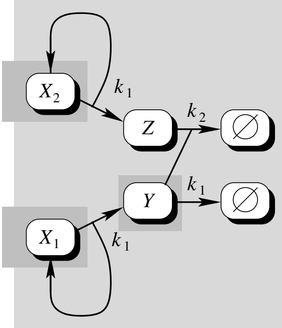


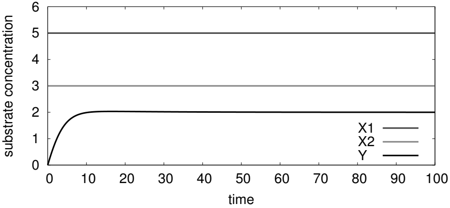
$$
\begin{aligned}
[\dot{X}_1] &= 0 \\
[\dot{X}_2] &= 0 \\
[\dot{Y}] &= k_1[X_1] + k_2[X_2] - k_3[Y]
\end{aligned}
$$

ODE solution for asymptotic steady state in case of $k_1 = k_2 = k_3$:
$[Y](\infty) = \lim_{t \to \infty} \left(1 - \mathrm{e}^{-k_1 t}\right) \cdot ([X_1](t) + [X_2](t)) = [X_1](0) + [X_2](0)$

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

Non-negative Subtraction





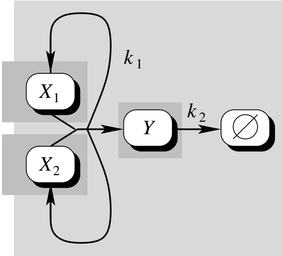
$$
\begin{aligned}
[\dot{X}_1] = [\dot{X}_2] &= 0 \\
[\dot{Y}] &= -k_2[Y][Z] - k_1[Y] + k_1[X_1] \\
[\dot{Z}] &= k_1[X_2] - k_2[Y][Z]
\end{aligned}
$$

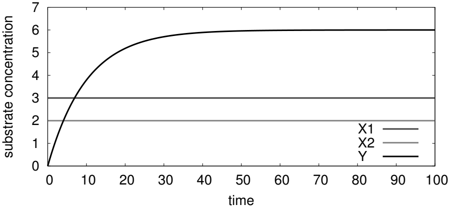
ODE solution for asymptotic steady state in case of $k_1 = k_2 > 0$:

$$[Y](\infty) = \begin{cases} [X_1](0) - [X_2](0) \text{ iff } [X_1](0) > [X_2](0) \\ 0 \text{ otherwise} \end{cases}$$

Input-output mapping: $[Y] = [X_1] -_{(\geq 0)} [X_2]$

Multiplication





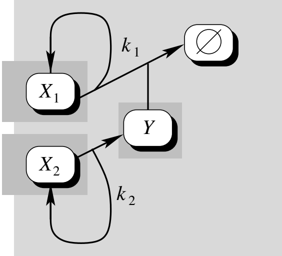
$$\begin{aligned}[\dot{X_1}] &= 0\\ [\dot{X_2}] &= 0\\ [\dot{Y}] &= k_1[X_1][X_2] - k_2[Y]\end{aligned}$$

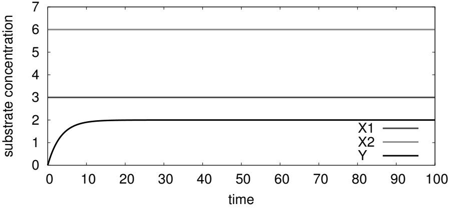
ODE solution for asymptotic steady state in case of $k_1 = k_2 > 0$:

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

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

Division





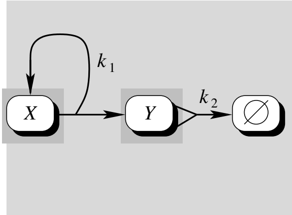
$$
\begin{aligned}
[\dot{X_1}] &= 0 \\
[\dot{X_2}] &= 0 \\
[\dot{Y}] &= k_2[X_2] - k_1[X_1][Y]
\end{aligned}
$$

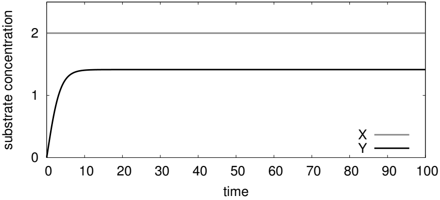
ODE solution for asymptotic steady state in case of $k_1 = k_2 > 0$:

$$
[Y](\infty) = \begin{cases} \lim\limits_{t\to\infty} \left(\left(1 - \mathrm{e}^{-k_1 t}\right) \cdot \frac{[X_2](t)}{[X_1](t)} \right) & \text{iff } [X_1](t) > 0 \\ \lim\limits_{t\to\infty} \left(\int k_2[X_2](t)\ dt \right) & \text{otherwise} \end{cases}
$$

Input-output mapping: $[Y] = [X_2]/[X_1]$ iff $[X_1] > 0$

Square Root





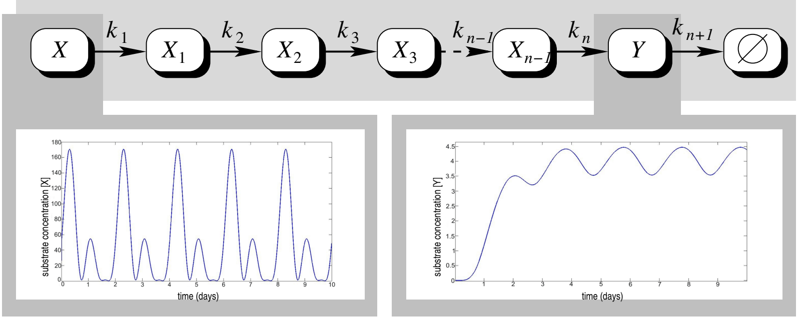
$$\begin{aligned} [\dot{X}] &= 0 \\ [\dot{Y}] &= k_1[X] - 2k_2[Y]^2 \end{aligned}$$

ODE solution for asymptotic steady state in case of $k_1 = 2k_2 > 0$:

$$[Y](\infty) = \lim_{t \to \infty} \left(\sqrt{[X](t)} \cdot \tanh(k_1 t \sqrt{[X](t)}) \right)$$

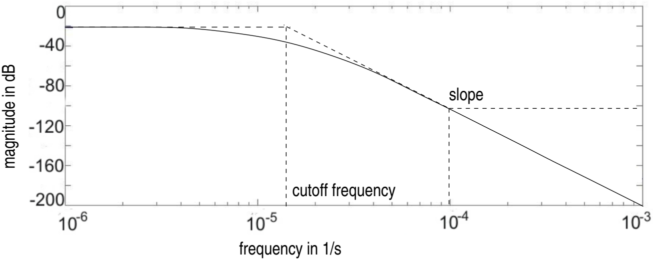
Input-output mapping: $[Y] = \sqrt{[X](0)}$

Low-pass Filter



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

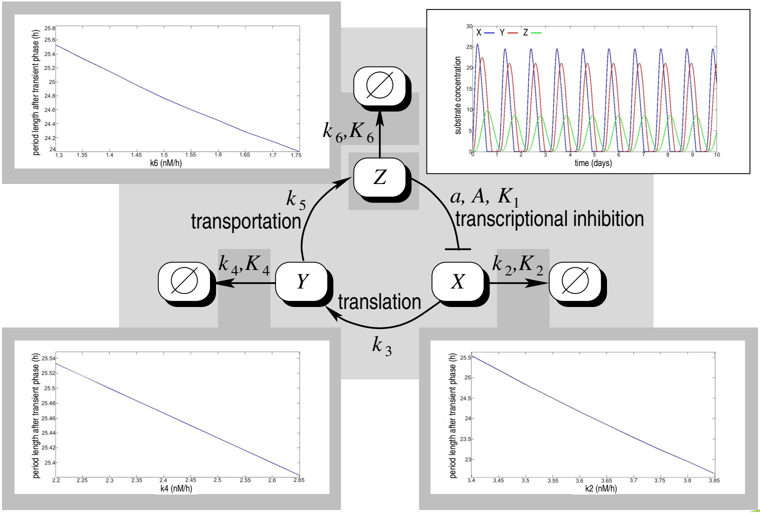
Low-pass Filter: Bode Plot as Characteristic Curve



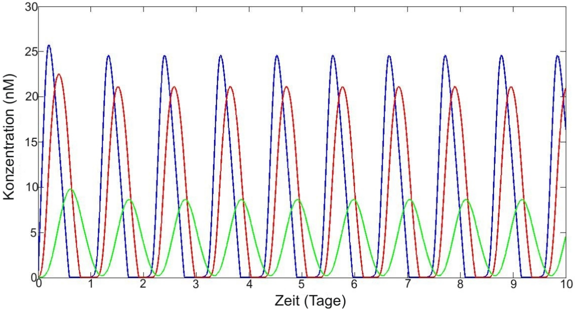
Magnitude $\mathrm{dB} = 10 \cdot \lg \left(\frac{\text{amplitude of output signal}}{\text{amplitude of input signal}} \right)$

- 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



Core Oscillator: Dynamical Behaviour



$$
\begin{aligned}
[\dot{X}] &= \frac{a}{A + K_1[Z]^2} - \frac{k_2[X]}{K_2 + [X]} \\
[\dot{Y}] &= k_3[X] - k_5[Y] - \frac{k_4[Y]}{K_4 + [Y]} \\
[\dot{Z}] &= k_5[Y] - \frac{k_6[Z]}{K_6 + [Z]}
\end{aligned}
$$

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

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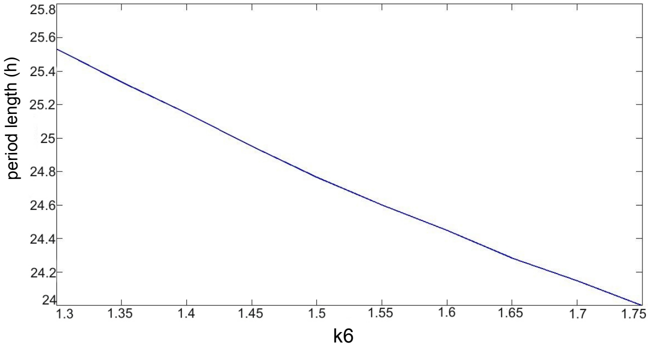
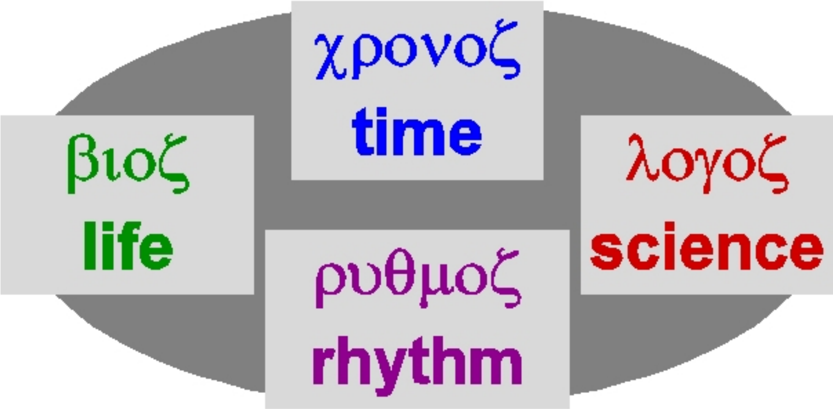
Core Oscillator: Dynamical Behaviour



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

1. Motivation and Concept of P Modules
2. Processing Units:
   Components of Chemical Control Loops
3. **Phase-locked Loop (PLL):**
   Continuous Frequency Control
   - Chronobiology
   - Circadian Clocks and Entrainment
   - General Scheme of a Control Loop
   - Scheme of a Phase-locked Loop
   - Model of a Chemical Frequency Control Based on PLL
4. Simulation Studies for
   Circadian Clock Systems
5. Prospectives

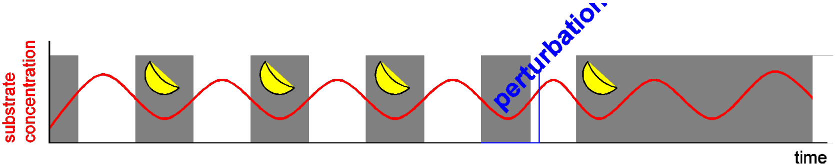
Chronobiology



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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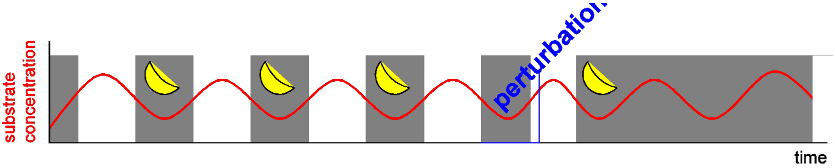
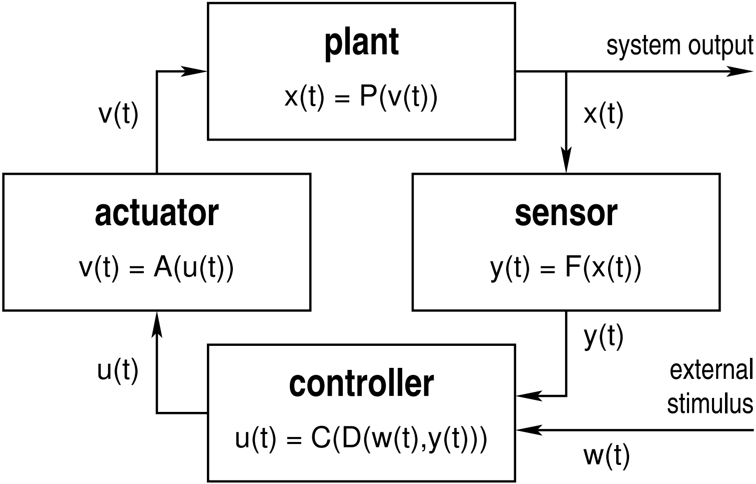
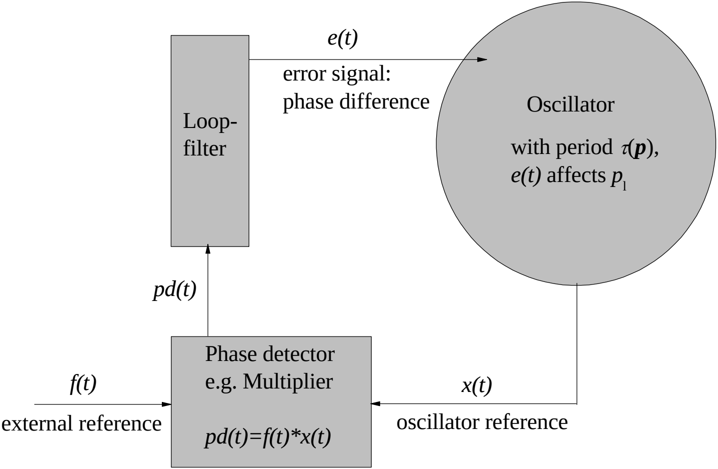


⟹ Biological counterpart of frequency control system

General Scheme of a Simple Control Loop



Scheme of a Phase-locked Loop



Loop-filter

e(t)

error signal:
phase difference

Oscillator

with period $\tau(\boldsymbol{p})$,
e(t) affects p_1

pd(t)

f(t)

external reference

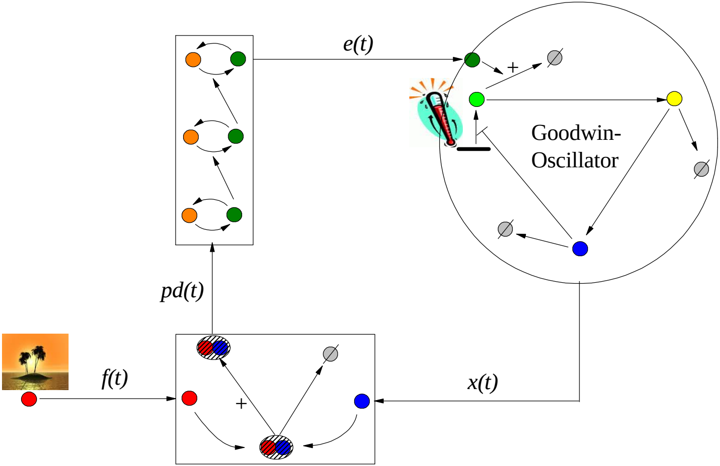
Phase detector
e.g. Multiplier

$pd(t)=f(t)*x(t)$

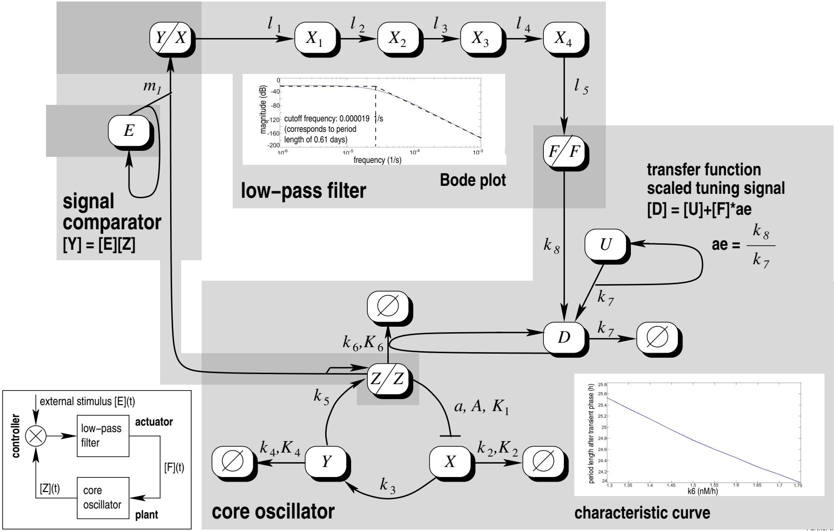
x(t)

oscillator reference

Scheme of a Phase-locked Loop



Model of a Chemical Frequency Control Based on PLL



signal comparator
[Y] = [E][Z]

low–pass filter

Bode plot

transfer function
scaled tuning signal
[D] = [U]+[F]*ae

ae $= \dfrac{k_8}{k_7}$

core oscillator

characteristic curve

1. Motivation and Concept of P Modules
2. Processing Units:
   Components of Chemical Control Loops
3. Phase-locked Loop (PLL):
   Continuous Frequency Control
4. **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
5. Prospectives

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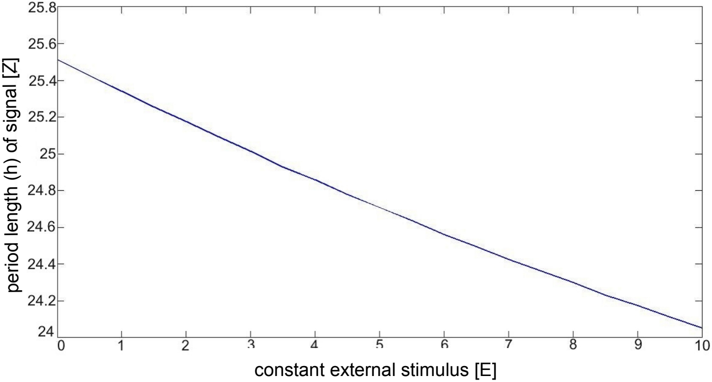
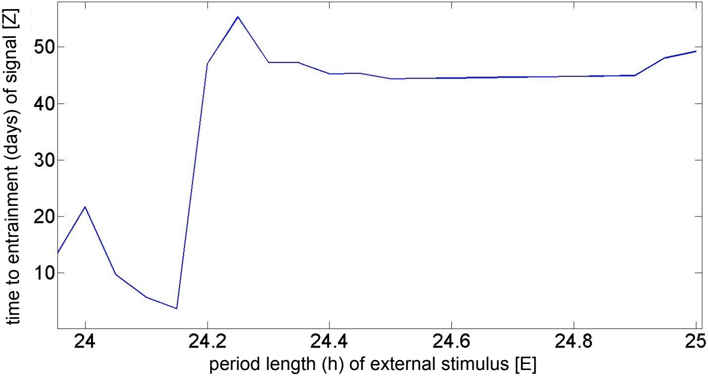
Period Lengths subject to Constant External Stimulus



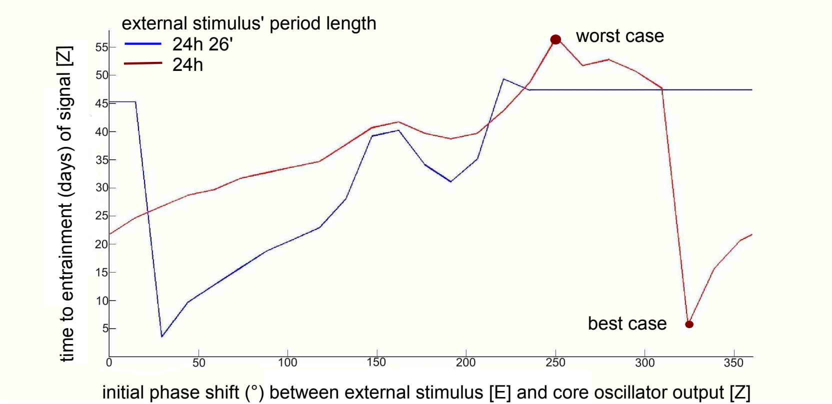
Increase of external stimulus' species concentration [*E*] decreases period (accelerates oscillation)

Time to Entrainment to Different Period Lengths



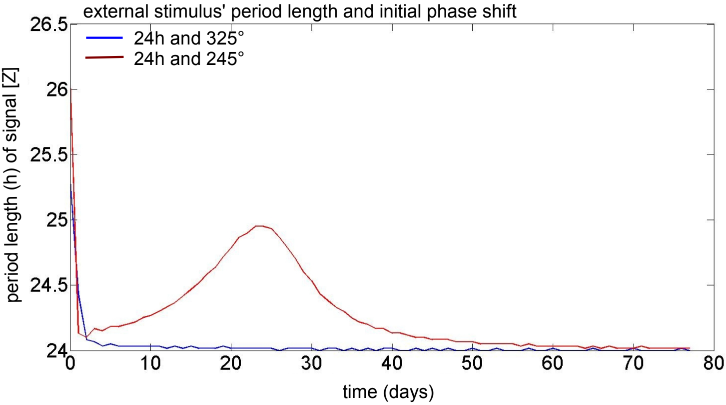
Natural period of core oscillator: 24.2h
Fast adaptation to slightly shorter periods
Slow (gradual) adaptation to longer periods

Time to Entrainment to Different Initial Phase Shifts



Entrainment reached within convergence interval 1min

Best Case and Worst Case Entrainment



Entrainment reached within convergence interval 1min

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3. Phase-locked Loop (PLL):
   Continuous Frequency Control
4. Simulation Studies for
   Circadian Clock Systems
5. **Prospectives**
   - Conclusions and Open Questions
   - Acknowledgements

Conclusions

- Chemical frequency control can utilise PLL
- Prototypic modelling example for entrainment of circadian clockworks
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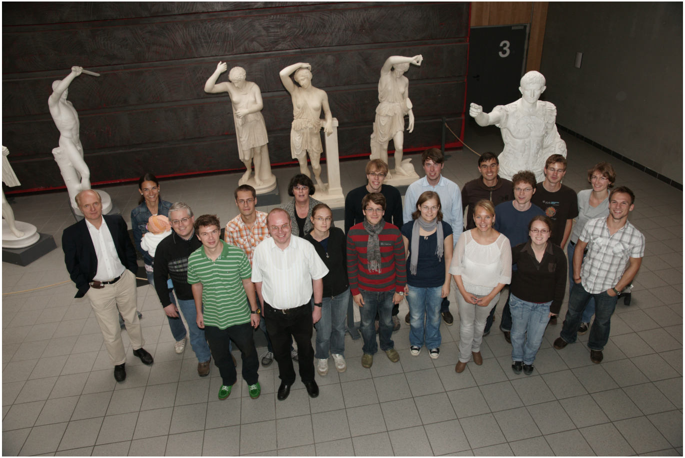

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Research Initiative in Systems Biology

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