Control System-Based Reverse Engineering of Circadian Oscillators

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Motivation: Uniting approaches from engineering with problems from biology

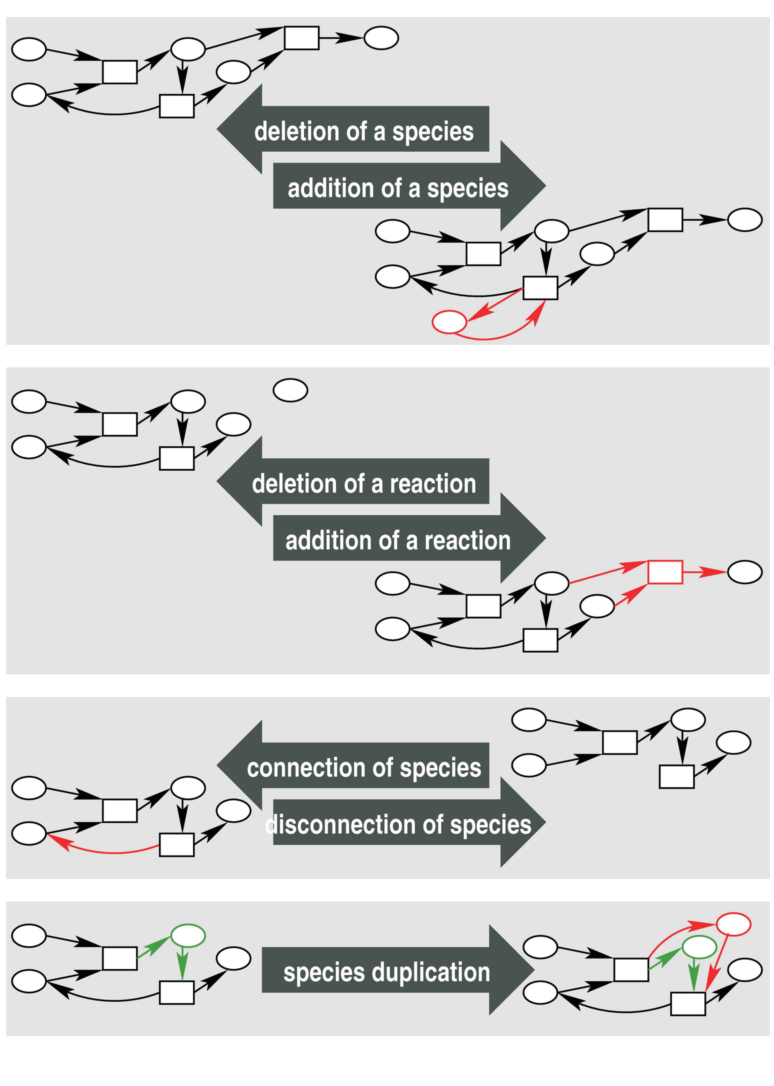
Control systems are a concept from engineering to achieve a desired dynamical behaviour like adjusting temperature. Later, they came into the scope of life sciences as part of a cybernetic approach to understand biological systems. The control system-based description of the circadian clock found in *New Zealand Weta* can be seen as pioneering example [1, 2]. Control systems benefit from a strict modularisation that allows a clear decomposition of a complex system into functional units interconnected by signalling channels. Signal processing is commonly represented by block diagrams that map input or memorised signals into output signals. Its correspondence to modular functional units and dedicated reaction network motifs was shown in [3].

Within an ongoing study, we combine the specification of block diagrams with the ability to an **artificial evolution** of reaction network candidates exhibiting a desired input/output interdependency. Here, dynamical behaviour analysis enables selection of the fittest candidates. In this way, each component of a control system (e.g. controller, actuator, plant, sensor) can be independently reconstructed by providing numerous, topologically different network candidates. Finally, the arrangement of these candidates leads to valid models of the entire system. By means of this modular network evolution, the search space is significantly reduced while keeping a high probability of heuristical success. With the SBMLevolver [5], a suitable software tool is available. We obtained building blocks with non-linear transmission behaviour to be composed towards distinct circadian control systems at various levels of description.

The SBMLevolver at a glance

Evolutionary algorithms have a long-established history as heuristic optimisation techniques [6]. While these attempts were successful for small networks, they also highlighted the complexity of evolving larger networks [7, 8].

We have built the SBMLevolver [5], an open source software tool implementing our approach of artificial network evolution. Seven specific operators affecting the network topology as well as stoichiometry enables an effective structural evolution along with consecutive mutational modification of kinetic parameters. Currently, we exclusively employ mass-action kinetics.

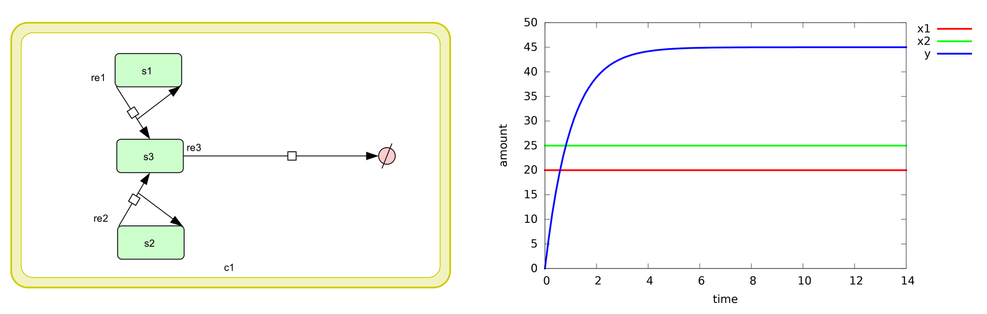


In order to successfully manage the technical process of artificial network evolution, we propose a separation of structural network evolution from kinetic parameter fitting which yields a pronounced increase in the algorithm's fitness performance [5]. Our studies show that this separation helps to prevent premature convergence when evolving networks executing arithmetic calculations. The SBMLevolver is available at: http://users.minet.uni-jena.de/∼biosys/esignet

Examples of previously derived networks

Using the SBMLevolver, reaction networks for elementary mathematical functions like addition, non-negative subtraction, multiplication and division could be obtained. Here, initial concentrations of dedicated species x_i act as input while the concentration of the output species y provides the result within its steady state. More complicated mathematical expressions can be composed by elementary functions (e.g. by means of Taylor series) or algorithmic formulation [9]. We propose network candidates whose dynamical behaviour is governed by mass-action kinetics:

Addition

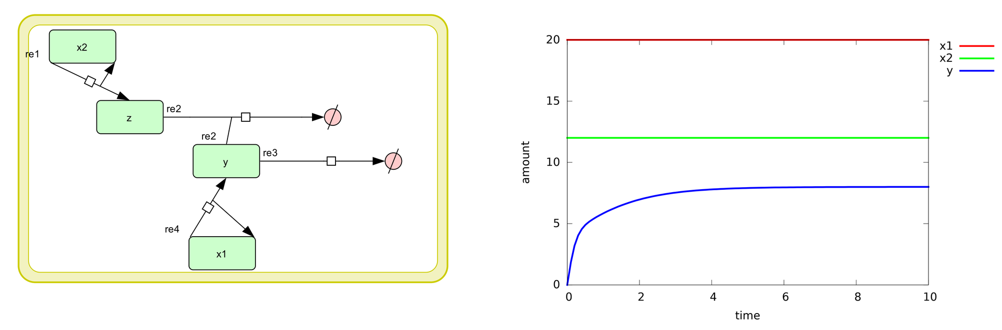


$$\frac{dx_1}{dt} = 0 \qquad \frac{dx_2}{dt} = 0 \qquad \frac{dy}{dt} = k_1x_1 + k_2x_2 - k_3y$$

Let $k_1 = k_2 = k_3 > 0$. Steady state:

$$y(t) = \lim_{t\to\infty} \left(1 - e^{-k_1t}\right) \cdot (x_1(t) + x_2(t)) = x_1(t) + x_2(t)$$

Non-negative Subtraction



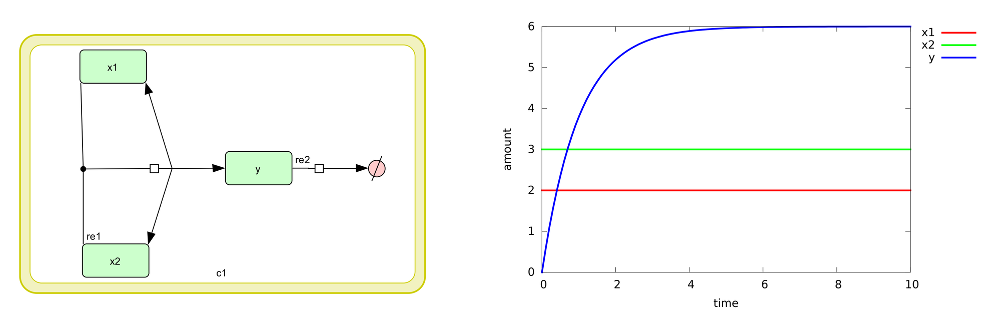
$$\frac{dx_1}{dt} = 0 \qquad \frac{dx_2}{dt} = 0$$

$$\frac{dy}{dt} = -k_2yz - k_1y + k_1x_1 \qquad \frac{dz}{dt} = k_1x_2 - k_2yz$$

Let $k_1 > 0$ and $k_2 > 0$. Steady state:

$$y(t) = \begin{cases} x_1 - x_2 \text{ iff } x_1 > x_2 \\ 0 \text{ otherwise} \end{cases}$$

Multiplication

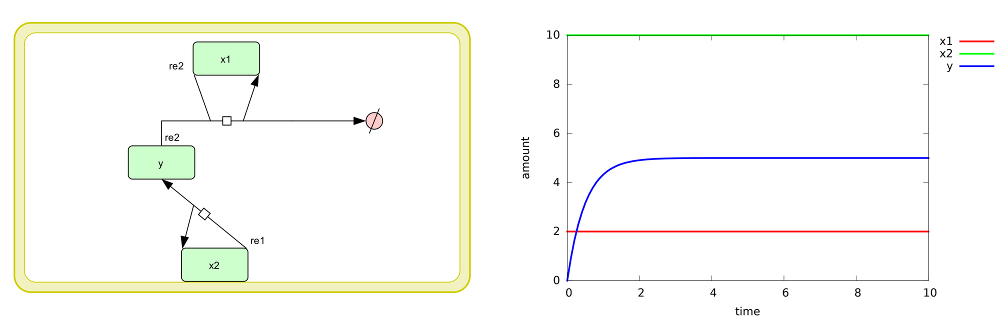


$$\frac{dx_1}{dt} = 0 \qquad \frac{dx_2}{dt} = 0 \qquad \frac{dy}{dt} = k_1x_1x_2 - k_2y$$

Let $k_1 = k_2 > 0$. Steady state:

$$y(t) = \lim_{t\to\infty} \left(1 - e^{-k_1t}\right) \cdot x_1(t)x_2(t) = x_1(t)x_2(t)$$

Division



$$\frac{dx_1}{dt} = 0 \qquad \frac{dx_2}{dt} = 0 \qquad \frac{dy}{dt} = k_2x_2 - k_1x_1y$$

Let $k_1 = k_2 > 0$. Steady state:

$$y(t) = \begin{cases} \lim_{t\to\infty} \left(1 - e^{-k_1t}\right) \cdot \frac{x_2(t)}{x_1(t)} \text{ iff } x_1 > 0 \\ \lim_{t\to\infty} \int k_2x_2dt \text{ otherwise} \end{cases}$$

$$= \begin{cases} \frac{x_2}{x_1} & \text{iff } x_1 > 0 \\ \to \infty & \text{iff } x_1 = 0 \text{ and } x_2 > 0 \\ 0 & \text{iff } x_1 = 0 \text{ and } x_2 = 0 \end{cases}$$

Control systems

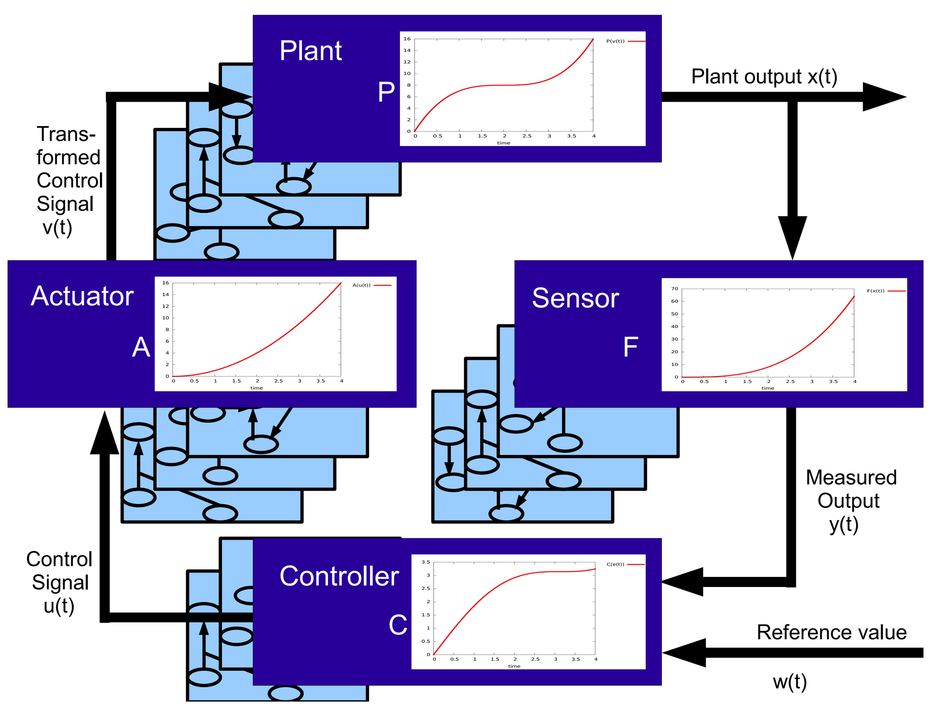
Control systems are of a modular nature [10]. Most of them consist of at least four modules forming a feedback loop:

Plant/System: The system is constituted by one or more physical quantities whose temporal behaviour is controlled. Its temporal input is given by an input signal $v(t)$ which passes through the system leading to its output $x(t) = P(v(t))$. The transfer function P might include signal weakening, delay, or perturbation.

Sensor: transforms $x(t)$ into the measured output $y(t) = F(x(t))$ where F acts as transfer function.

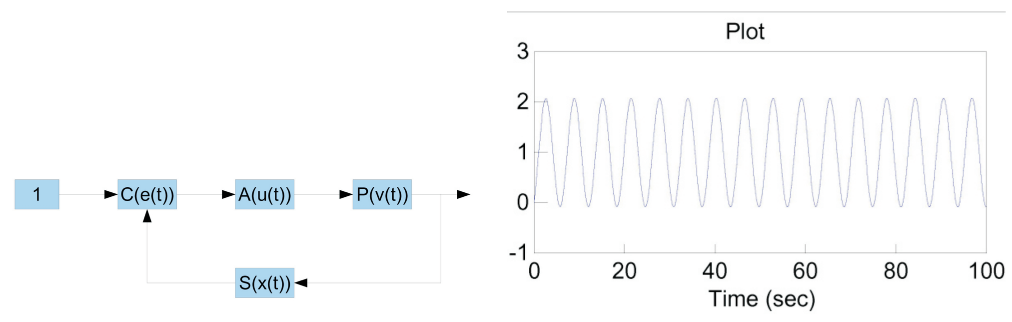
Controller: compares $y(t)$ to the externally defined reference signal $w(t)$ and calculates the error signal $e(t) = w(t) - y(t)$. Subsequentially, it provides the control signal $u(t) = C(e(t))$. The underlying transfer function C might include integration or differentiation with respect to t.

Actuator: affects the plant by transforming $u(t)$ into signal $v(t) = A(u(t))$



Each module is separately characterised by its transfer function. This gives the opportunity to identify reaction network candidates having the same effect on input signals represented by species concentrations. Using elementary functions as defined above in concert with networks for differentiation and integration [4], a variety of transfer functions P, F, C, A can be obtained by artificial evolution.

A simple example emphasising this idea is given below. Here, we demonstrate a basic oscillator formulated within the control system's scheme which is reduced to two parameters (a, b). We employ the transfer functions $x(t) = \int v(t)dt$, $y(t) = x(t)$, $u(t) = a - y(t - b)$, $v(t) = u(t)$, depicted for $(a, b) = (1, \frac{\pi}{2})$. Simulation case studies of control systems have been carried out using VisSim.



Future prospects: Applying control systems to achieve results about the circadian clock of *Chlamydomonas reinhardtii*

We intend to use the SBMLevolver on a **phase locked loop** that is often used in control system theory to achieve a signal whose deviance from the reference signal – which can, using biological terms, for example be interpreted as changes in the intensity of light – is as small as possible. We expect that entrainment to light and maybe even temperature can be shown in this way.

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