Synchronisation of clocks: Comparing mechanisms in biological and technical distributed systems

Mathias Schumann, Thomas Hinze, Stefan Schuster

Department of Bioinformatics at School of Biology and Pharmacy, Friedrich-Schiller University Jena

{mathias.schumann,thomas.hinze,stefan.schu}@uni-jena.de

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Abstract

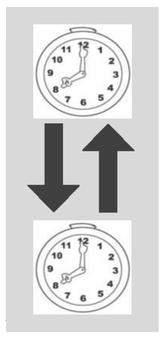
Exploration of chronobiological systems emerges as a growing research field within bioinformatics focusing on various applications in medicine, agriculture, and material sciences. From a systems biological perspective, the question arises whether biological control systems for regulation of oscillative signals and their technical counterparts utilise similar mechanisms. If so, modelling approaches and parameterisation adopted from building blocks can help to identify general components for clock synchronisation. Phase-locked loops could be an interesting candidate in this context. Both, biology and engineering, can benefit from a unified view. In a first experimental study, we analyse a model of coupled repressilators. We demonstrate its ability to synchronise clock signals in a monofrequential manner. Several oscillators initially deviate in phase difference and frequency with respect to explicit reaction and diffusion rates. Accordingly, the duration of the synchronisation process depends on dedicated reaction and diffusion parameters whose settings still lack to be sufficiently captured analytically.

Different Perspectivs of Synchronisation

In both spheres, biological and technical systems, oscillatory signals play a major role in order to trigger and control time-dependent processes. Elementary oscillators are the simplest devices for generation of continuously running clock signals. The situation becomes more complicated if several of those elementary oscillators start to interact. Resulting biological systems are commonly driven to achieve a synchronous behaviour towards an evolutionary advantage. Correspondingly, clock synchronisation in technical systems is frequently inspired by the need to follow a global time. Interestingly, the formalisation of clock synchronisation processes is quite distant from each other. While in distributed computer systems, stepwise algorithmic approaches (like Berkeley or Christian's method, [4]) dominate, biological systems adjust their clock signals more gradually. Its formalisation is either based on reaction-diffusion kinetics or employs more abstract analysis techniques like the Kuramoto method [2]. Topologically, clock synchronisation can be accomplished by two different strategies called *external* (unidirectional coupling from leading central clock) and *internal*.

Internal Synchronisation

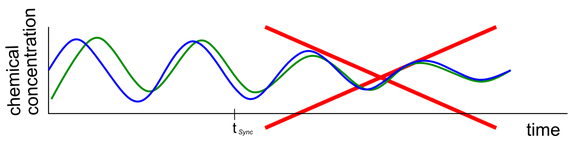
Internal strategies aim at a mutual clock exchange between the network members. The coupling topology is mostly **bidirectional**, and each involved elementary clock is going to adjust its signal based on a weighted sum of the signals released by its adjacent oscillators.



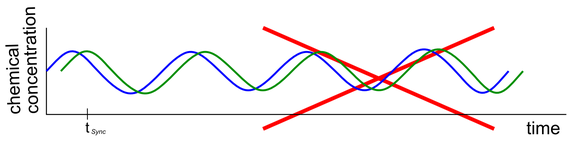
Conditions for Synchronised Clocks

Different temporally oscillating signals are *synchronous* to each other if and only if they meet three conditions:

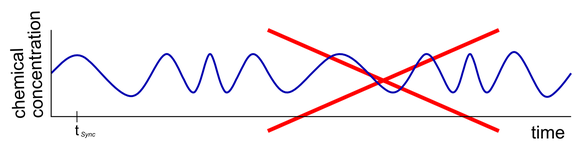
1. The oscillatory signal must run *undamped*.



2. *Asymptotical or total harmonisation* of the oscillatory signals meaning that after a finite amount of time called t_{sync} (time to synchronisation), both temporal signal courses converge within an arbitrarily small ε-neighbourhood.



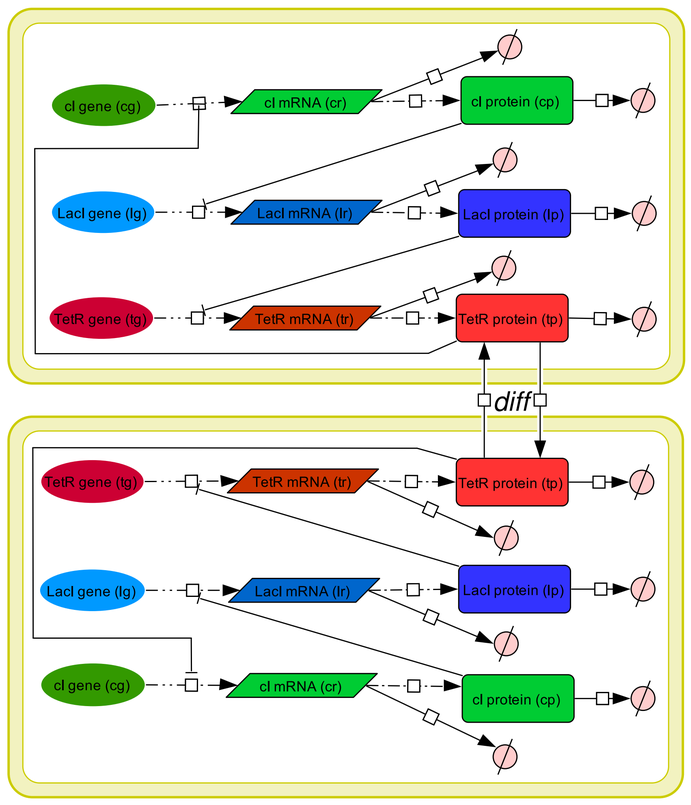
3. The resulting oscillatory signal after t_{sync} has to be *monofrequential* to ensure chronoscopy.



Case Study: Internal Synchronisation

We identified a network of bidirectionally coupled repressilators to be an appropriate candidate to explore internal synchronisation within a biological system. A repressilator is a gene regulatory network consisting of three focal proteins (LacI, TetR, cI) that mutually inhibit their expression from genes (*lacI, tetR, cI*) [1]. We employ a system composed of two coupled repressilators located in two adjacent cells. Let TetR be a protein able to migrate between the cells, it acts as coupling element. Its diffusion rate specifies the bidirectional coupling strength. For species names in the ODEs, we abbreviate (LacI, TetR, cI) $= (lp, tp, cp)$ for the proteins and (*lacI, tetR, cI*) $= (lr, tr, cr)$ for the mRNA.

Network Topology



Differential Equations

$$\frac{\mathrm{d}\,lp}{\mathrm{d}\,t} = k_{lr} \cdot lr - k_{lp} \cdot lp$$

$$\frac{\mathrm{d}\,tp}{\mathrm{d}\,t} = k_{tr} \cdot tr - k_{tp} \cdot tp - \mathit{diff} \cdot tp + \mathit{diff} \cdot tp_{external}$$

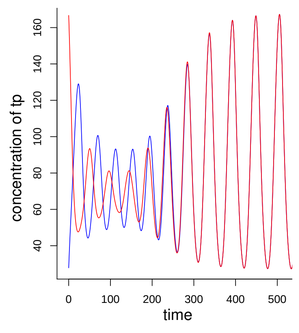
$$\frac{\mathrm{d}\,cp}{\mathrm{d}\,t} = k_{cr} \cdot cr - k_{cp} \cdot cp$$

$$\frac{\mathrm{d}\,lr}{\mathrm{d}\,t} = \alpha_0 + \frac{\alpha \cdot k_m^n}{k_m^n + cp} - k_{lr} \cdot lr - k_{lr2} \cdot lr$$

$$\frac{\mathrm{d}\,tr}{\mathrm{d}\,t} = \alpha_0 + \frac{\alpha \cdot k_m^n}{k_m^n + lp} - k_{tr} \cdot tr - k_{tr2} \cdot tr$$

$$\frac{\mathrm{d}\,cr}{\mathrm{d}\,t} = \alpha_0 + \frac{\alpha \cdot k_m^n}{k_m^n + tp} - k_{cr} \cdot cr - k_{cr2} \cdot cr$$

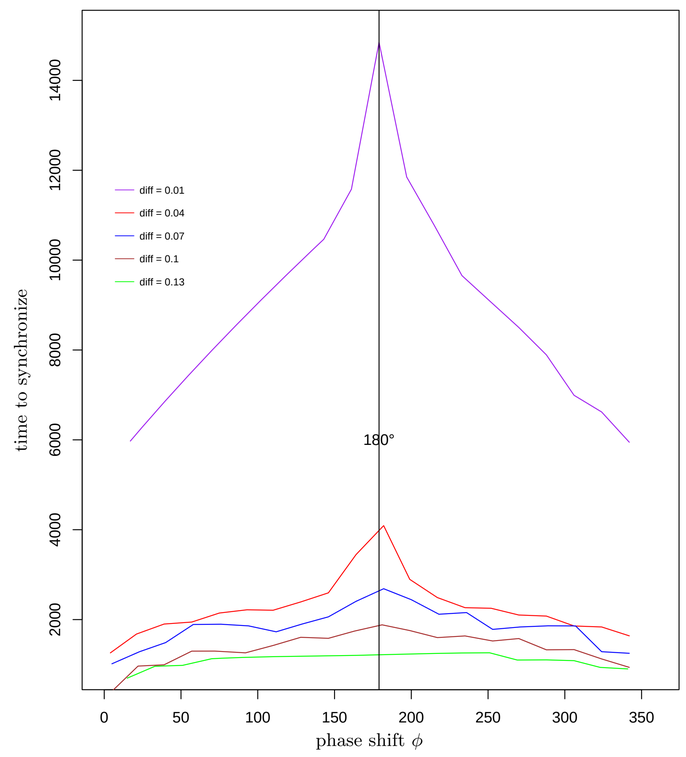
Typical synchronisation run with initial phase shift $\phi = 182°$ and coupling strength *diff* $= 0.04$. Further parameter settings: $lr(0) = 0.819, tr(0) = 2.388, cr(0) = 0.068, lp(0) = 36.263, tp(0) = 166.685, cp(0) = 64.26, \alpha_0 = 0.03, \alpha = 29.97, k_m = 40, n = 3, k_{\{lp2,tp2,cp2\}} = 0.069, k_{\{lr,tr,cr\}} = 6.93, k_{\{lr2,tr2,cr2\}} = 0.347$



Results

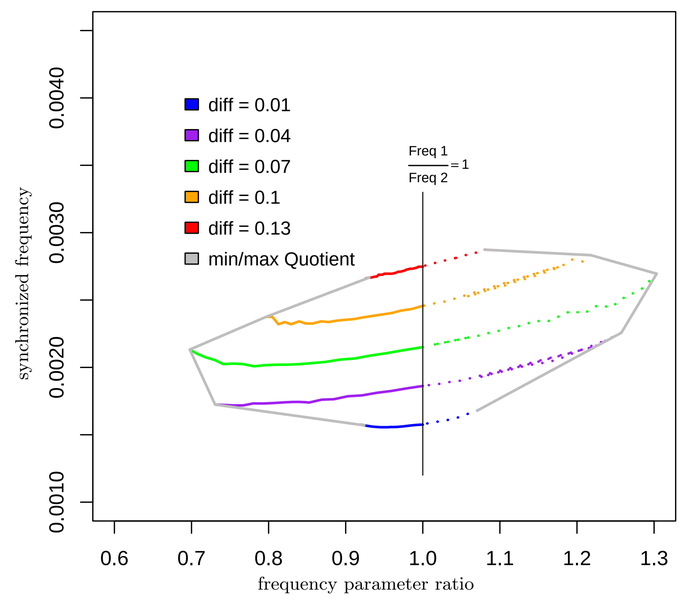
Phase Synchronisation

For the synchronisation study, we set up both repressilator's initial concentrations at the limit cycle in order to avoid effects occurring within the stabilisation phase. Afterwards, a two-dimensional parameter scan was conducted varying the initial phase shift of both repressilators between $0°$ and $360°$ and simultaneously varying the coupling strength *diff* $= 0.01$ to 0.13 (weak to medium coupling). The time to synchronisation was obtained assuming a signal convergence of one minute per day, see Figure below.



Frequency Synchronisation

The figure below shows the ability of the repressilator coupling to synchronise different initial frequencies in the elementary repressilators. To this end, individual protein degradation rates k_{lp}, k_{tp}, k_{cp} had been modified in conjunction with setting up all initial concentrations at the limit cycle. From this, we conducted a parameter scan taking into account the ratios of initial frequencies. We obtain a synchronisation range (window) delimited by polyfrequential oscillations with respect to the ratios and loss of undamped oscillation with respect to the coupling strength.



Conclusion and Acknowledgements

The system of coupled repressilators can be seen as a part of a biological control system based on the concept of phase-locked loops [3]. Further research has been directed to finalise the entire frequency-control system by integration of additional components for signal comparison and damping, demonstrated by low-pass filters biologically implemented as specific signal transduction cascades.

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