

Dynamical Analysis of Biological Feedback & Feedforward Systems

Thesis Book of the PhD Dissertation

By

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1. Introduction

Cells integrate several processes to perform certain activities. These systems modify or change their responses to coordinate with external signals through a series of molecular processes such as chemical reactions. Cell signaling is a basic process used by all biological systems to connect with their environment [1]. Because of well-coordinated signaling networks, multicellular organisms function successfully. Biomolecules such as genes, mRNAs, transcription factors, and proteins interact with each other through signaling pathways, resulting in functional and structural differences in proteins and their complexes [2].

Small regulatory network motifs are the building blocks of larger, more complicated signaling pathways. Feedforward loops (FFLs) [3] and feedback loops [4] are two major types of regulatory motifs that are grouped by the types of regulation between interacting molecules (Figure 1).

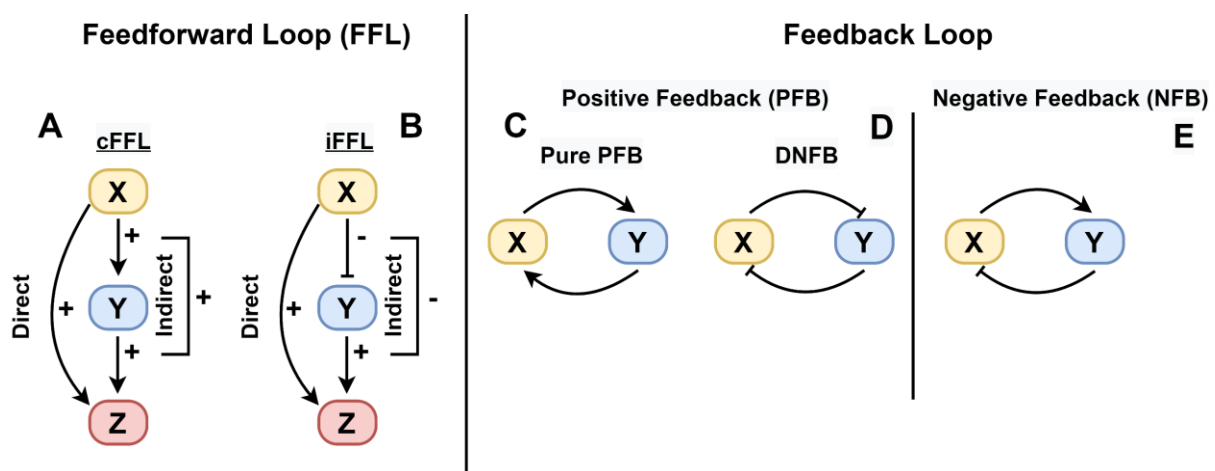


Figure 1: Influence diagram of feedforward and feedback loops.

The coherent feedforward loop (cFFL) and incoherent feedforward loop (iFFL) are presented in subplots (A and B), where cFFL has the same net effect on the direct and indirect arms (i.e. both arms are positive), whereas iFFL has the opposite net effect on the direct and indirect arms (i.e. one arm is positive while other is negative). The panels (C, D) show two forms of Positive Feedback (PFB) Loops: pure PFB (C) with all positive interactions and a double negative feedback (DNFB) loop (D) with two mutual inhibitory interactions resulting in an overall positive effect. The schematic diagram of a Negative Feedback (NFB) Loop is shown in panel (E), with two species linked by activatory and inhibitory interactions. The pointed arrows indicates activation, whereas the blunt-headed arrows implies inhibition.

It is important to remember that a feedback loop works in both directions, while a feedforward loop only works in one direction. How motifs behave dynamically can be changed by how they

are linked together in a larger network [5]. It further shows that studying isolated network motifs is not enough to explain how a biological system works as a whole in terms of its dynamic properties.

In a biological system, the FFL is a pattern of three genes. It is made up of two input transcription factors, one of which controls the other. Together, these two transcription factors control a target gene. The response time of the targeted gene can be accelerated or slowed down by these FFLs. Also they can act as a noise filter. When FFLs are connected with other FFLs (coupled FFLs) [6], their noise-reduction capabilities are altered, making them a better noise reducer.

Feedback loops, on the other hand, change the dynamics of individual units in order to preserve the system's behavior. Depending on whether the feedback loop is positive or negative, it can be a switch or an oscillator respectively [7]. Oscillators are important for many biological processes, such as the cell cycle and the circadian clock [8]. The internal clock of the body is referred to as the "circadian clock". It operates on a 24-hour cycle that is synchronized with the day/night cycle. It runs in the background to carry out essential actions and functions. One of the important and well-known example of circadian rhythms is the sleep-wake cycle. Temperature compensation [9] is another well-known basic aspects of a circadian oscillator. Temperature compensation makes it possible for the species to keep a rhythm that is similar to the day/night cycle even when the temperature changes a lot. How the circadian clock keeps temperature-compensated and robust situations are still unknown.

Mathematical modeling can be used to create a precise description of dynamical systems, allowing the investigation of the dynamical characteristics of networks. A computer simulation followed by a mathematical model could be one way to describe a biological network. Statistical analysis can help with both quantitative and qualitative understanding of such investigations.

Stochasticity, often known as chemical noise [10], is a property of chemical processes that may interfere with and impact the outcome. The goal of this thesis is to understand the dynamic properties of different regulatory networks as well as their behavioral changes in a noisy environment. In the dissertation, I have thoroughly tested the resilience of these networks using a theoretical approach.

2. Methods

The computational analysis of complicated networks delivers rapid, dependable, and cost-effective solutions. The usage of ordinary differential equation (ODE) models for research on biological systems has increased significantly in the recent decades. Object-oriented modeling, such as class diagrams or entity diagrams, static perspective, and stability analysis can all be done with commercial software [11]. For network analysis in my dissertation, I utilized Kaemika and MATLAB. Both deterministic and random simulations work well in these two applications.

Kaemika is a functional programming language that interprets chemical reaction simulations graphically [12]. It is a Microsoft program created by Luca Cardelli. Kaemika is constructed using the C# programming language. For the stochastic dynamical study of coupled and isolated FFLs, it is possible to carry out the linear noise approximation (LNA) [13] in a single click using the Kaemika tools. The LNA simulation offers several statistical measurements [14], such as standard deviations, coefficients of variation, variances, fano factors, and more.

MATLAB, on the other hand, includes advanced programming capabilities. In addition to programming and numerical operations, it provides great graphic visualization [15]. I wrote and simulated algorithms in MATLAB (ver. R2021b) for the robustness and temperature compensation study of feedback loops in various circadian oscillatory networks. During this analysis, I have described the reaction rates in terms of the Arrhenius equation [16], such that they change with temperature [17].

To account for the impact of extrinsic noise [10] on the positive and negative feedback regulatory arms of the circadian clock, I altered the parameter value about the nominal value to induce randomness. As a result, I chose some random numbers from a lognormal distribution (<https://www.mathworks.com/help/stats/lognrnd.html>). In addition, for robustness, I estimated total parameter variation [18] by using the arithmetic mean calculation. I expanded noise estimation by computing the Bayesian Information Criterion (BIC). It is generally used to assess models and decide which one best fits an observation while taking the number of fitted parameters in each model into consideration. To investigate the temperature adjustment capacity of these biological oscillators, I estimated the temperature coefficients (Q_{10}) related to their period of oscillation [19]. In order to take into account the impacts of intrinsic noise [10], I have incorporated the Gillespie algorithm [20] in the MATLAB.

3. New Scientific Results

Thesis 1a. I have discovered that coupled feedforward loops (FFLs) outperformed isolated feedforward loops in terms of robustness and signal transduction.

Related publications: [J1], [C1], [C2], [C3]

I performed linear noise approximation (LNA) simulations with two different kinds of FFLs: coupled (Figure 2A, right hand side top and bottom panel) and isolated (Figure 2A, left hand side panel) subjected to one-step posttranslational modification [21]. The coupled FFLs can be of two types: multi input coupled feedforward loop (abbreviated as ‘minp’ FFL, shown in the right hand side top panel of Figure 2A) and multi intermediate coupled feedforward loop (abbreviated as ‘mint’ FFL, shown in the right hand side bottom panel of Figure 2A).

In Figure 2B and 2C, both the noisy input and the output change over time respectively. The red rectangle shows the input value for which I have recorded the percentile coefficient of variation (% CV) of the output (marked with rectangular red box). I have also estimated the slope value I got from a plot of inputs and outputs (Figure 2D). The % CV measures noise, and the slope values of the networks from the relationships between inputs and outputs measure how well they can transfer signals.

It's interesting that the percentage CV and slope values usually go in the opposite direction. A greater % CV indicates inadequate noise reduction, but a higher slope value indicates improved signal transduction capabilities. I showed that coupled FFLs reduce noise more effectively than independent FFLs (Figure 2E). In Figure 2E, I demonstrate coupled FFLs has better signal transduction capacity than isolated FFLs.

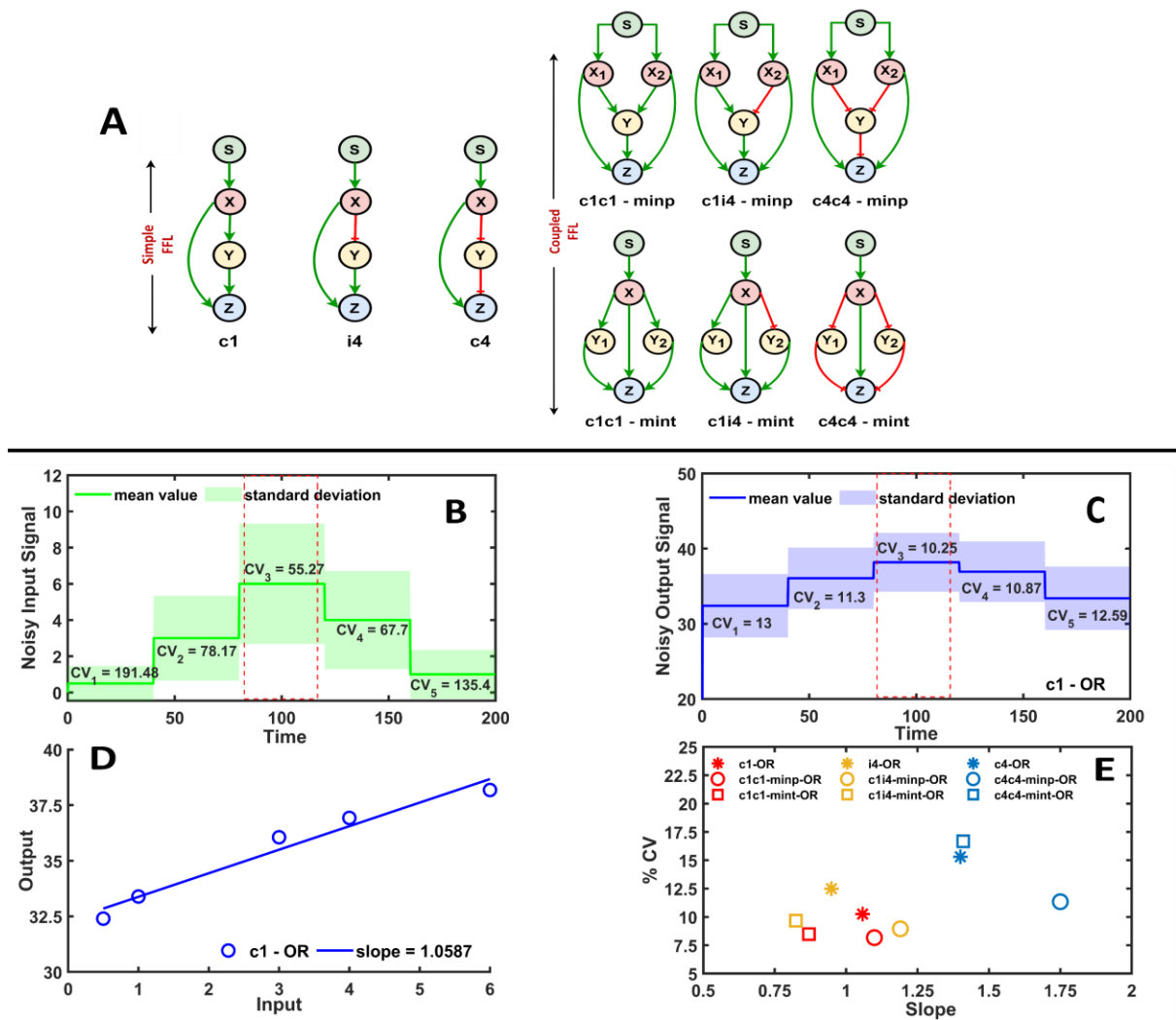


Figure 2: Noise attenuation and signal transduction abilities of coupled and isolated FFLs.

In this figure, few examples of isolated and coupled FFL networks are presented (A). Mean of the noisy input (displayed with green color), its % CV (with shading) values at each of 5 input steps are shown. (B). Across all the input levels, the mean output levels (displayed with blue color) and the estimated noise for the output are recorded. These indicate lower % CV values than it was at the input layer (C). The slope of the input-output relation is plotted as a measure of signal transduction (D). To demonstrate how each coupled and isolated FFL system operates in noise reduction and signal transduction, the % CV of each FFL is computed at input = 6 (marked with red rectangular box on panels B and C) and displayed against the slope values (E).

Thesis 1b. I have been able to distinguish between FFLs that perform better at minimizing noise and signal transduction based on their network architecture.

Related publications: [J1], [C1], [C2], [C3]

I have shown a number of fascinating traits that come out of the analysis: The FFLs (Figure 2A) with the higher signal transduction capacity (Figure 2E) have an activatory direct connection between the input and output nodes. This suggests that node X should directly activate the node Z to provide the best signal transduction. Successful signal transduction occurs when input node X suppresses at least one copy of intermediate species Y and output gates follow OR logic. All of these claims are true for FFLs with maximal signal transduction capability, including c4-OR, c4c4-mint-OR, c1i4-mint-OR, and c4i1-minp-OR.

Effective noise reduction may be shown in FFLs with the same activatory direct link between nodes X and Z, but this is augmented by a reaction in which Z is activated by Y (Figure 2A) and follows OR logic. The best FFLs are i4-OR, c1-OR, c1i4-mint-OR, c1c1-mint-OR, and c1i4-minp-OR (Figure 2E).

Based on this study, coherent type-1 and type-4 and incoherent type-4 with OR connection can perform well as noise reducers and signal transducers (Figure 2E). The results show that c1c1-minp-FFL-OR is the best noise filter (with the lowest % CV) and c4c4-minp-OR is the best signal transducer (with highest value for slope).

Thesis 1c. I discovered that the FFLs' noise reducing capability trends remained unchanged even with the addition of stochastic input signal.

Related publications: [J1], [C1], [C2], [C3]

Noise through each level of posttranslational modification to FFLs is inherent and unaffected by noise at the input nodes. Therefore, changing the input noise level to higher or lower value maintains the conclusion's consistency (Thesis 1a., Thesis 1b.) (Figure 3).

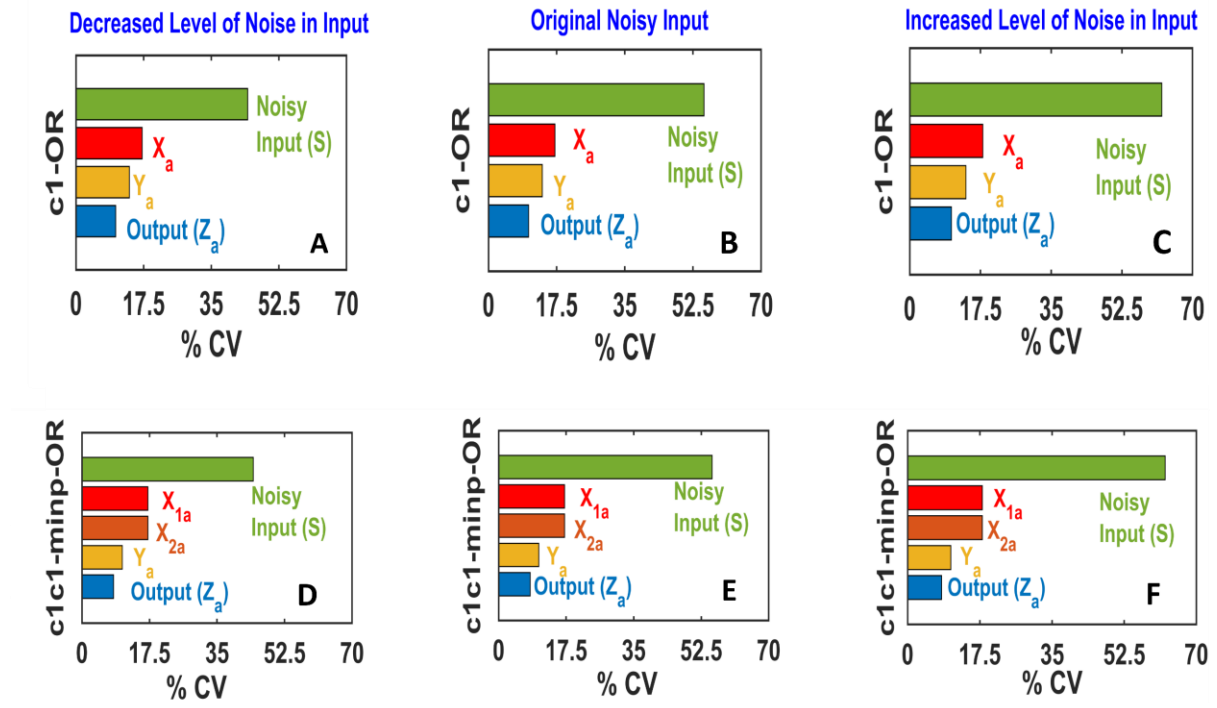


Figure 3: Estimation of the noise at every node of the networks, by altering the input noise level.

Demonstrated how noise propagates along the pathways for c1-OR (A,B,C) and c1c1-minp-FFL (D,E,F) models by raising (right panel) and reducing (left panel) the degree of noise in the input and comparing it to the initial noisy input (middle panel). The estimation has been done at input = 6 and single step posttranslational modification is considered.

Thesis 1d. I discovered that OR gates in FFLs are better than AND gates in terms of noise reduction.

Related publications: [J1], [C1], [C2], [C3]

FFLs with AND logical gates reduce noise less than those with OR gates (Figure 4A). The OR configuration of a model has a lower % CV than the AND configuration of a similar model.

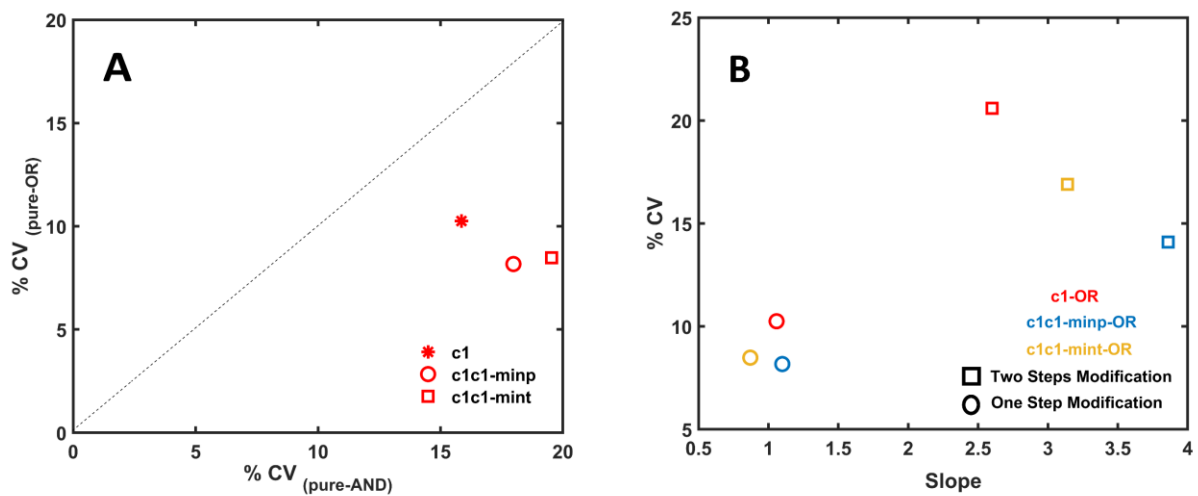


Figure 4: Comparison of noise reducing abilities of FFLs with OR and AND logic gates (A), and with one-step and two-step posttranslational modifications (B).

Panel A illustrates how the % CV of networks driven by OR gates compare to that of networks including AND gates. Networks that incorporate OR gates have a lower coefficient of variation (%CV) than those that contain AND gates (placed at the below of the diagonal). This result is valid for all types of FFLs, including isolated FFLs, minp-FFLs, and mint-FFLs with considering single step posttranslational modification. The models with both the AND and OR type of connectivity is plotted here. The slope and the % CV are displayed along with the comparable models that undergo two-step modification processes before being activated at each layer (Panel B). Two-step modification process have a greater % CV than one-step modification for isolated FFLs, coupled minp-FFL, and coupled mint-FFL. The estimation has been done at input = 6.

Thesis 1e. I evaluated one-step and two-step post translational modification in FFLs and discovered that multisite modification improves signal transduction but decrease noise reduction capability.

Related publications: [J1], [C1], [C2], [C3]

I have shown that multisite alteration improves both signal transduction and % CV based on an analysis of the input-output correlation slopes and the % CV produced by these motifs and equivalent networks with single modifications (Figure 4B). As a result, multisite alteration does not increase FFLs' noise-reduction abilities (Figure 4B), but it does improve FFL motifs' signal transducing abilities.

Thesis 2a. I have investigated four distinct oscillatory modules and identified that the delayed negative feedback loop model is the least robust in terms of noise reduction, while a model combining positive and negative feedbacks is the most robust among the four investigated ones against noise.

Related publications: [J2], [C4], [C5]

In Figure 5, each of the four oscillating networks are shown. Figure 5 shows several oscillatory systems, including the cyanobacterial oscillatory system in KaiABC (cyano-KaiABC) [22], which implements multiple positive and negative feedback loops but operates based on a nonlinear equation (A); the Goodwin-NFB network [23], which is a delayed NFB model (B); the cPNFB models, which combine positive and negative feedback loops but follow mass action kinetics (C) [7]; and Selkov's substrate depletion oscillatory system [24] (Selkov-PFB), which has the basic positive feedback loop (D).

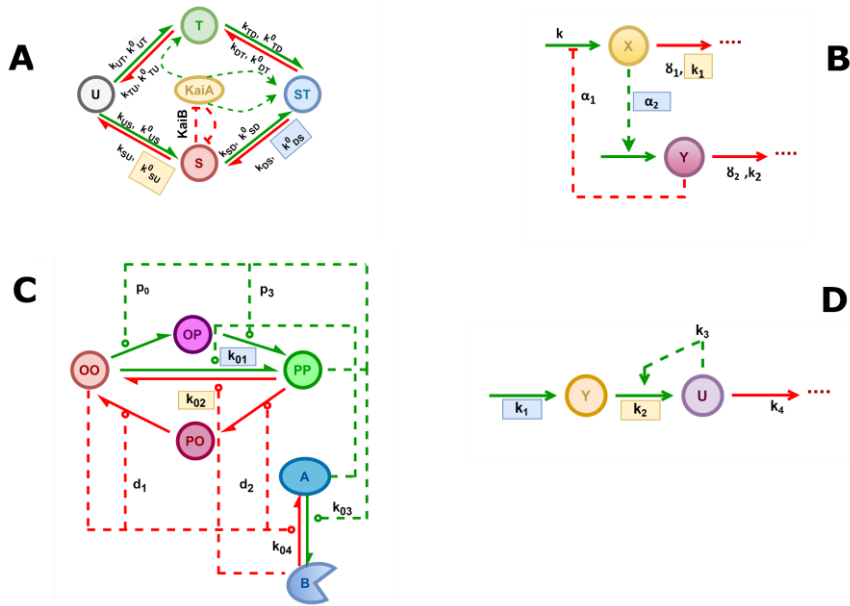


Figure 5: Oscillatory networks with positive and negative feedback.

Schematic illustration of Rust's cyanobacterial oscillatory system in KaiABC (cyano-KaiABC) [22], which works through many complex positive and negative feedback loops (A); Goodwin's negative feedback loop between two species (Two-Variable-Goodwin-NFB) [23] (B); a single molecule with both positive and negative feedback that passes through four chemically changed states while communicating with an outside molecule with two states (A and B) [7] (cPNFB) (C); and Selkov's substrate depletion oscillatory system (Selkov-PFB) [24], which has the basic positive feedback loop and is driven by substrate depletion (D). The green and red arrows show the reactions of activation (phosphorylation) and inhibition (dephosphorylation) respectively. Processes that are inhibited are shown by arrows with flat heads, while processes that are activated are shown by arrows with pointed heads. A dual arrow in both ways represent the reversible reactions. The direct responses (synthesis/degradation, phosphorylation/dephosphorylation) are shown with solid arrows, whereas the regulatory interactions (activation/inhibition) are shown with dashed arrows.

In Figures 6A, I have demonstrated that the Two-Variable-Goodwin-NFB network (delayed NFB model) is the least resistant to parameter variations (it has a high% CV value for oscillation periods), while cPNFB models (which is a combination of positive and negative feedback loops) produces the lowest noise for parameter changes.

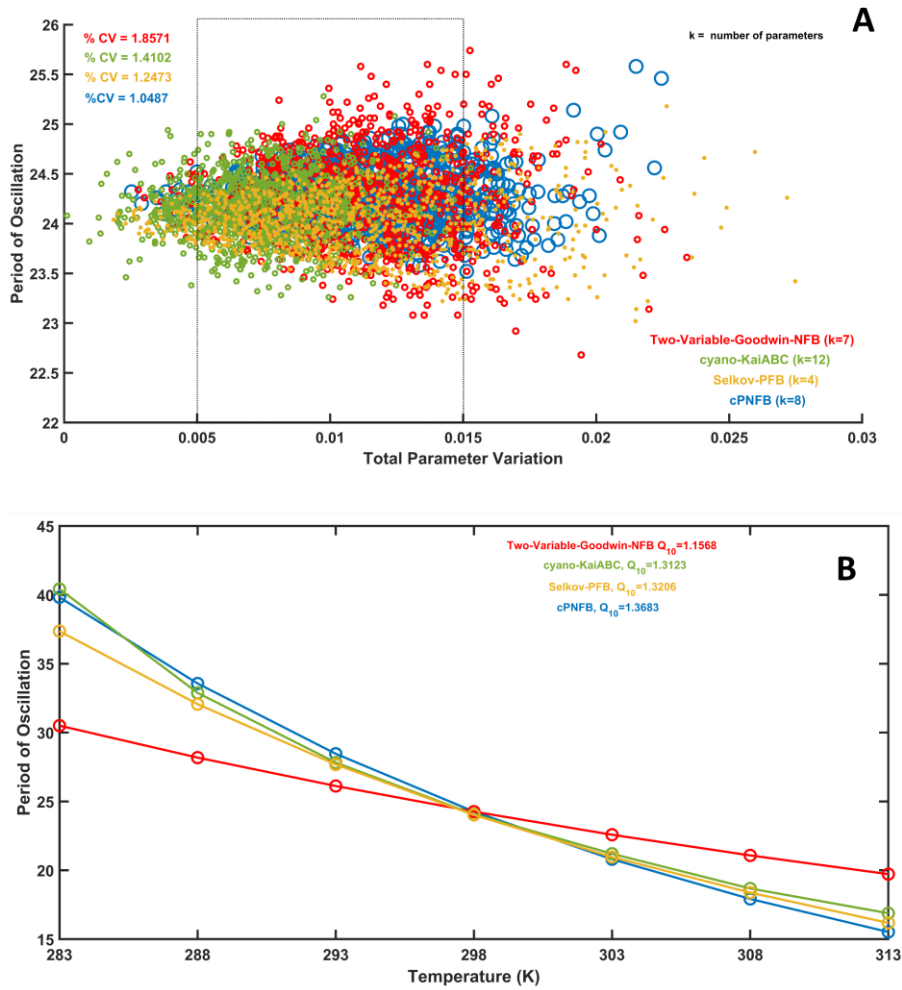


Figure 6: Analysis of robustness and temperature compensation properties of different oscillatory networks.

The subplot A shows how the duration of oscillations varies in accordance with the total parameter changes for the four separate oscillatory systems shown in Figure 5. For 1000 randomly chosen parameter combinations, at 298K, the four distinct models are plotted in different colors. The inset on the upper left records the percentage value of the co-efficient of variation (% CV) along with the matching colors for all networks for 200 sampled parameter sets for each between 0.005 and 0.015 ($0.005 < \text{Total parameter variation} < 0.015$), shown by the dashed rectangular box). In the subplot B, the Q_{10} values between the temperature 293K and 303K for every motif are also included in the table inset on the upper right.

Thesis 2b. I have discovered that the delayed negative feedback loop model is better at temperature compensation, while the model combining positive and negative feedbacks shows the least temperature compensation from the four investigated models.

Related publications: [J2], [C4], [C5]

In Figure 6B, I showed that the Two-Variable-Goodwin-NFB model (delayed NFB model) is better at temperature compensation because its Q_{10} value is lower, while the cPNFB circadian oscillatory network (which is a combination of positive and negative feedback loops) is worse at temperature compensation because its Q_{10} value is higher.

Thesis 2c. I have found that in all the investigated cases, temperature-insensitive parameters are either direct or indirect controllers of negative feedback.

Related publications: [J2], [C4], [C5]

On Figures 7 all models were tested, how their period dependence on temperature changes if a reaction rate is temperature insensitive. The Two-Variable-Goodwin-NFB model shows the best temperature compensation when the rate (α_2) is fixed, which directly controls the negative feedback loop.

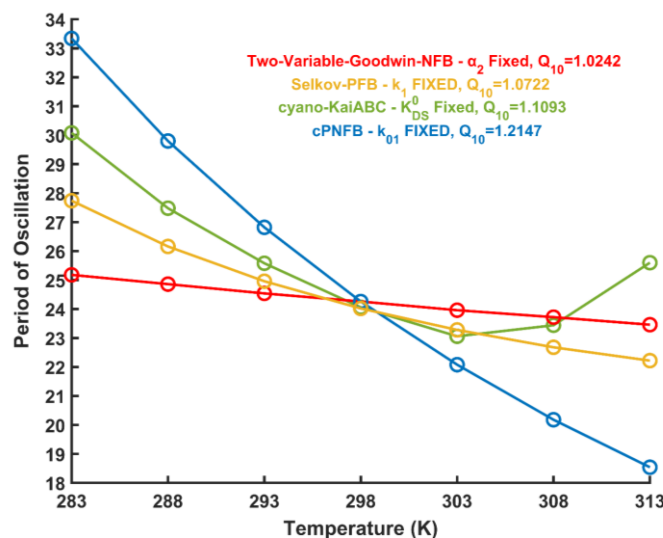


Figure 7: Temperature dependence of the periods of oscillations in four oscillatory models, where reaction rates are temperature insensitive.

The figure shows how far the periods of oscillations vary with temperature across all four analyzed oscillatory networks, where a single reaction rate is fixed (indicated on the legend and shaded with blue color boxes on Figure 5), while all other rates are responsive to temperature variations. Similar tests were performed for all

individual parameters, here the results with the best performing fixed rate are plotted. The image also depicts the Q_{10} values for each model measured in the range from 293K to 303K.

The parameter, which must be temperature insensitive for temperature compensation, is also a negative feedback loop controller for both the cyano-KaiABC (the k_{DS}^0 rate) and cPNFB (the k_{OI}) networks. Since the Selkov-PFB lacks an NFB loop, there the most essential parameter is the PFB loop's substrate synthesis (k_I rate). The parameters associated with each model are indicated in the Figure 5. The primary parameter that is temperature insensitive has been displayed with blue color and the secondary temperature insensitive parameter has been indicated with yellow color (Figure 5). Based on these, it can be concluded that rates controlling negative feedback loops need to be less temperature sensitive to have better temperature compensation of oscillation periods.

4. Publications

The dissertation is based on the following articles:

[J1] **S. Chakravarty** and A. Csikász-Nagy, “Systematic analysis of noise reduction properties of coupled and isolated feedforward loops,” *PLOS COMPUTATIONAL BIOLOGY*, vol. 17, no. 12, pp. e1009622, 2021.

[J2] **S. Chakravarty**, C. I. Hong , and A. Csikász-Nagy, “Systematic analysis of negative and positive feedback loops for robustness and temperature compensation in circadian rhythms,” *NPJ SYSTEMS BIOLOGY AND APPLICATIONS*, vol. 9, no. 1, pp. 5, 2023.

Other contributions:

[C1] **S. Chakravarty** and A. Csikász-Nagy, “Biological noise can be reduced by coupled feed forward loops,” *JEDLIK LABORATORIES REPORTS*, vol. 7, no. 4, pp. 78–80, 2019. (Poster)

[C2] **S. Chakravarty**, “Reducing the Effects of Biological Noise by Coupled Feed Forward Loops,” *PHD PROCEEDINGS ANNUAL ISSUES OF THE DOCTORAL SCHOOL FACULTY OF INFORMATION TECHNOLOGY AND BIONICS*, vol. 14, pp. 13, 2019.

[C3] **S. Chakravarty**, “Feed forward loops towards potential noise reduction,” *PHD PROCEEDINGS ANNUAL ISSUES OF THE DOCTORAL SCHOOL FACULTY OF INFORMATION TECHNOLOGY AND BIONICS*, vol. 15, pp. 13, 2020.

[C4] **S. Chakravarty**, “Studying the robustness of biological oscillators,” *PHD PROCEEDINGS ANNUAL ISSUES OF THE DOCTORAL SCHOOL FACULTY OF INFORMATION TECHNOLOGY AND BIONICS*, vol. 16, pp. 13, 2021.

[C5] **S. Chakravarty**, “Investigating the robustness of biological oscillators,” *PHD PROCEEDINGS ANNUAL ISSUES OF THE DOCTORAL SCHOOL FACULTY OF INFORMATION TECHNOLOGY AND BIONICS*, vol. 17, pp. 14, 2022.

[O1] **S. Chakravarty** and A. Csikász-Nagy, “Noise reducing capabilities of feed-forward loops,” *Information and Computation special issue (not published yet)*, HSB 2020: 7th International Workshop on Hybrid Systems Biology. (Oral Presentation)

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