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Coupled Oscillations and Circadian Rhythms in Molecular Replication Networks

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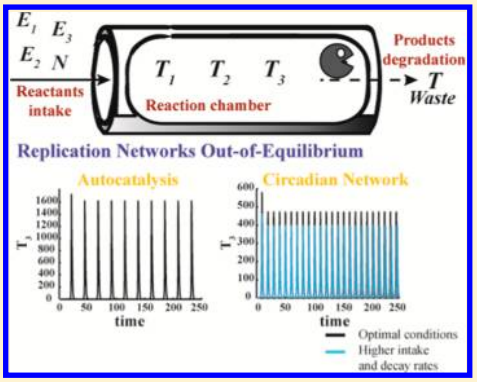
Supporting Information

ABSTRACT: Living organisms often display rhythmic and oscillatory behavior. We investigate here a challenge in contemporary Systems Chemistry, that is, to construct "bottom-up" molecular networks that display such complex behavior. We first describe oscillations during self-replication by applying kinetic parameters relevant to peptide replication in an open environment. Small networks of coupled oscillators are then constructed in silico, producing various functions such as logic gates, integrators, counters, triggers, and detectors. These networks are finally utilized to simulate the connectivity and network topology of the Kai proteins circadian clocks from the *S. elongatus* cyanobacteria, thus producing rhythms whose constant frequency is independent of the input intake rate and robust toward concentration fluctuations. We suggest that this study helps further reveal the underlying principles of biological clocks and may provide clues into their emergence in early molecular evolution.



Living organisms and individual cells function far from equilibrium, at times exhibiting steady-state behavior and always interacting with their environment by importing nutrients and energy and exporting waste products and heat. Like other open systems, living organisms are replete with rhythmic and oscillatory behavior at all levels, to the extent that oscillations have been termed as a defining attribute of life.[1] Additionally, living organisms contain internal circadian clocks that produce rhythms of a 24 h cycle. In contrast to biology, very few chemical reactions yield oscillations. The most famous one is the Belousov–Zhabotinsky (BZ) reaction that uses a specific set of inorganics, producing a nonlinear chemical oscillator as it starts far from equilibrium and remains so for a significant length of time.[2,3] By means of biomacromolecules, in vitro nucleic acid oscillators have been realized using molecular networking and transcription regulation strategies.[4−7] Recently, it was established that the biochemical network that contains proteins KaiA, KaiB, and KaiC and controls the circadian clocks in *S. elongatus* can be reconstituted in vitro.[8] This system has been extensively studied and is now well understood.[9−12]

In the context of Systems Chemistry, catalytic replication networks have served to study emergent phenomena in complex mixtures.[13−15] Such networks have been studied theoretically and computationally,[16−21] and realized experimentally.[15,22−27] Our studies with peptides have shown how small networks may be designed to perform Boolean logic operations[20−22,28,29] and mimic computational modules and network motifs.[20,21] All of this network functionality has been studied under isolated, controlled conditions that often yield tractable mathematical or computational analysis, but do not oscillate. We now show, for the first time, that studying catalytic networks in open systems allows us to probe the effects of oscillations on network behavior. We first analyze the oscillatory product formation during first order and second order self-replication using kinetic parameters relevant to experimental peptide replication. We then construct ternary networks in silico and simulate in *Matlab* the network progress when the oscillations of one or two nodes are coupled as inputs that control formation of another node. The coupled oscillators produce complex network functions, such as logic gates, integrators, counters, triggers, and detectors. Finally, we illustrate how the ternary networks can self-organize into a topology mimicking the Kai proteins circadian clocks, producing rhythms whose constant frequency is independent of the input intake rate and robust toward fluctuations in initial concentrations. Remarkably, when comparing alternate network topologies, we find that the connectivity imitating the Kai system produces a circadian clock that is robust under a wider set of conditions.

Our study starts with the analysis of oscillations in the course of nonenzymatic self-replication (eq 1−3), arguably a fundamental process in the molecular origin of life.[30,31] Two models are used to describe realistic mechanisms of peptide replication, in which the ligation of electrophilic and nucleophilic fragments (*E* and *N*; eq 1) is speeded up via either first order (eq 2) or second order (eq 3) autocatalysis

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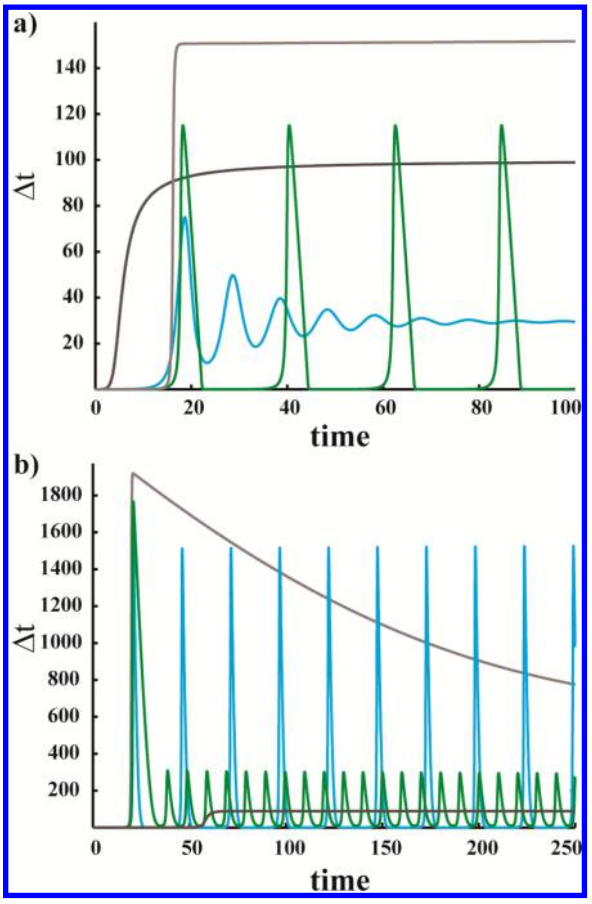


Figure 1. Product formation as a function of time for (a) first order autocatalysis and (b) second order autocatalysis. The graphs display product formation under the following conditions (see parameters in Supporting Information): dark gray, closed system, without any intake or sink; blue, green, and light gray, open systems with intakes for E and N, and linear, enzymatic, and constant sinks for T, respectively. The green and light gray first order curves (in panel a) have been normalized by a factor of 10 to allow for easy comparison.

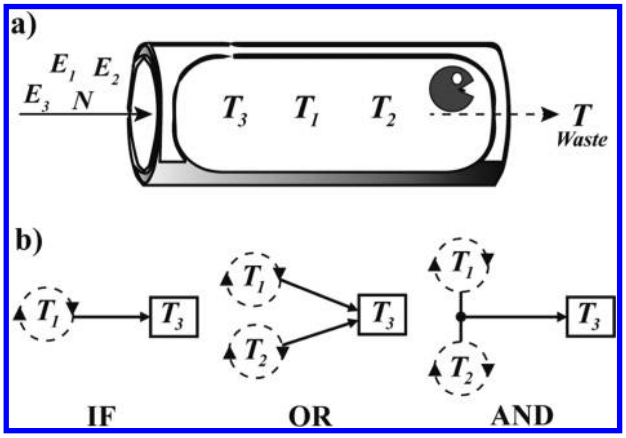
$$E + N \xrightarrow{g} T \tag{1}$$

$$E + N + T \underset{\langle a \rangle}{\overset{a}{\rightleftarrows}} ENT \xrightarrow{b} TT \underset{\langle d \rangle}{\overset{d}{\rightleftarrows}} T + T \tag{2}$$

$$E + N + TT \underset{\langle a \rangle}{\overset{a}{\rightleftarrows}} ENTT \xrightarrow{b} TTT \underset{\langle f \rangle}{\overset{f}{\rightleftarrows}} TT + T \underset{\langle d \rangle}{\overset{d}{\rightleftarrows}} T + T + T \tag{3}$$

It has been shown using various models, such as Lotka, Lotka−Volterra, Higgins, Brusselator, FKN, Oregonator, Autocatalator, and Templator,[2,3,32−35] that open catalytic systems can oscillate. Consequently, Peacock-Lopez has found that minimal self-replication, in open systems under the appropriate conditions, leads to oscillatory behavior.[19,36] The two above models have accordingly been expanded to describe open system kinetics with continuous E and N intake, and a chemical decay "sink" of the product T, obeying the enzymatic Michaelis−Mentin kinetics (eq 4). Note that when $K_m \gg [T]$, this decay process effectively becomes linear, and when $K_m \ll [T]$ the rate becomes constant

Scheme 1. Schematic Description of the Ternary Network Reaction in an Open System, Emphasizing the Intake of Starting Materials E_i and N, Product Formation in the Reaction Chamber, and Enzymatic Decomposition of the Products[a] and Network Configurations for the Logic Gates Driven by Oscillatory Inputs[b]



[a]Panel a. [b]Panel b. These gates can also produce counters, integrators, triggers, and detectors under the appropriate conditions (Figure 2 and Supporting Information Table s2).

$$\frac{dT}{d\tau} = \frac{k_t T}{K_m + T} \tag{4}$$

The two models were implemented by running numerical simulations in *Matlab* using initial concentrations corresponding to peptide replication experiments and relevant rate constants (see Supporting Information).[20,21] Figure 1 displays the production of T in all of its forms (t; Supporting Information eq s1 and s2) for first and second order autocatalysis and allows a comparison of their kinetics under four typical scenarios. Thus, the control reactions in closed systems display standard autocatalytic behavior with a lag phase followed by a fast rise until the resources are exhausted. As expected, the reactions in an open system with constant sinks show no oscillations. Interestingly, reactions in an open system with a linear sink display damped oscillations in first order catalysis and sustained oscillations in second order, whereas reactions with an enzymatic sink display sustained oscillations in both cases. This oscillatory behavior observed is consistent with previous theoretical predictions.[34,36] It emphasizes again that although first order catalysis accounts for the simplest self-replication model, higher order catalysis often plays a crucial role in nature by enabling more complex functionality. Additional discussion regarding the mechanistic aspects affecting the oscillatory autocatalytic behavior may be found in the Supporting Information (Section 3.1). The simulations of replication in open systems have also allowed us to monitor the effects of changing the (i) decay rate k_t, (ii) dimer TT dissociation constant, and (iii) initial template concentrations, as further shown and discussed in the Supporting Information (Figure s1−s5).

The replication system is further used to design and construct networks of coupled oscillators, unprecedentedly allowing us to investigate the functionality of synthetic networks as a whole in response to oscillatory, as opposed to linear, inputs. The second order reaction was applied to wire a three-element network (Scheme 1), in which we followed product formation of a specific node, T_3, in response

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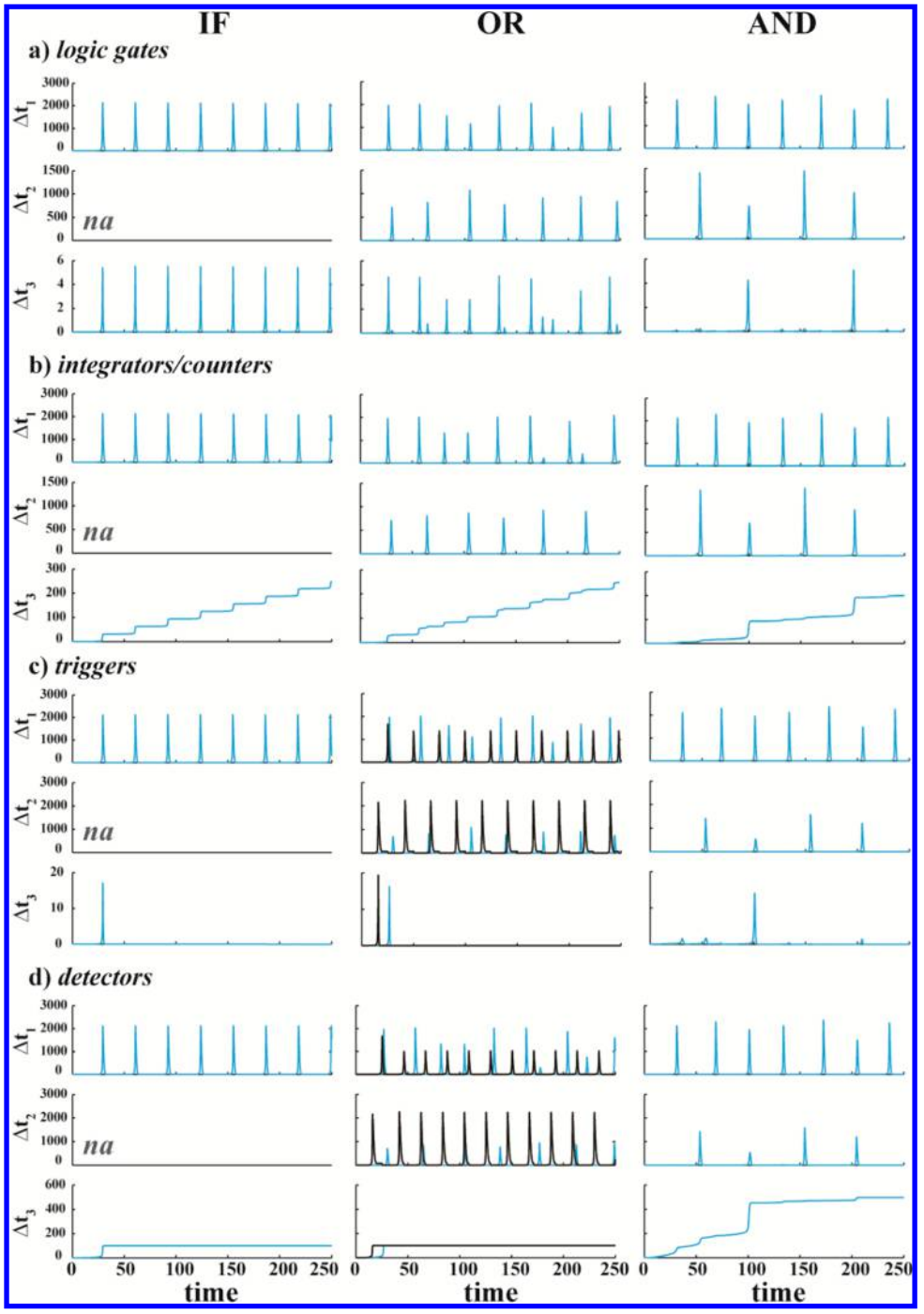

Figure 2. Coupled oscillations in ternary replication networks. Each of the four panels compares product vs time in three cases corresponding to the IF, OR, and AND Boolean functions (Scheme 1b). Oscillations in production of T_1 and T_2 are coupled to production of T_3, resulting in oscillating *Logic gates* (a), *Integrators/Counters* (b), *Triggers* (c), and *Detectors* (d). The network was simulated using standard parameters (Supporting Information) and the specific conditions for each function (Supporting Information Table s2). The additional *black* plots (c-OR and d-OR), corresponding to higher E_2 intake rates, are shown to emphasize the T_3 response to the first appearing signal from either T_1 or T_2. Expanded discussion of these network functions is given in Supporting Information (Section 3.2).

to oscillations in one or two inputs, T_1 and T_2 (Figure 2). The replication model has been expanded to describe a network reaction of three distinct electrophiles E_i and a common nucleophile N, producing three products/templates T_i (eqs 5, 6; i, j, k = 1,2,3). The $i = j = k$ cases (eq 6) correspond to autocatalysis, whereas the $i \neq j, k$ cases describe cross-catalytic pathways. Significantly, in order to study these networks of coupled oscillators, we have implemented them in open systems (Scheme 1a), where each of the reactants has a continuous inflow and the products may decay (eq 4)

$$E_i + N + T_jT_k \underset{\langle a\rangle_{ijk}}{\overset{a_{ijk}}{\rightleftharpoons}} E_iNT_jT_k \xrightarrow{b_i} T_iT_jT_k \underset{\langle f\rangle_{ijk}}{\overset{f_{ijk}}{\rightleftharpoons}} T_i + T_jT_k$$
$$\underset{\langle d\rangle_{jk}}{\overset{d_{jk}}{\rightleftharpoons}} T_i + T_j + T_k \qquad (5)$$

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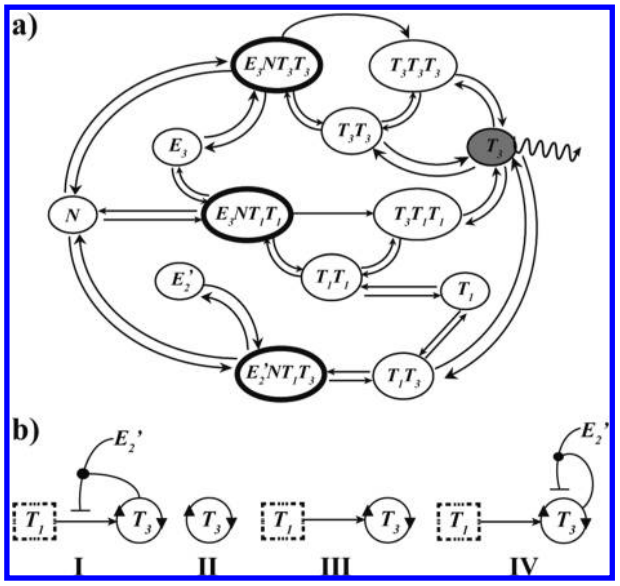
Scheme 2. Proposed Diagram of the Circadian Network[a] and Alternate Circadian Network Configurations[b]



[a]Panel a. The network oscillatory production of T_3 is governed by the three following pathways: T_3 autocatalysis, T_3 cross catalytic production by T_1, and a negative feedback loop due to formation of the $E_2'NT_1T_3$ inhibitory complex. The key intermediates formed along these pathways are highlighted by bold circles. [b] Panel b. Arrows represent catalytic pathways and the horizontal stops inhibition. (I) the proposed circadian network from panel a, (II) autocatalytic T_3, (III) T_3 formation via autocatalysis and cross catalysis by T_1, and (IV) an alternate ternary network, similar to (I) but with direct inhibition of T_3 autocatalysis.

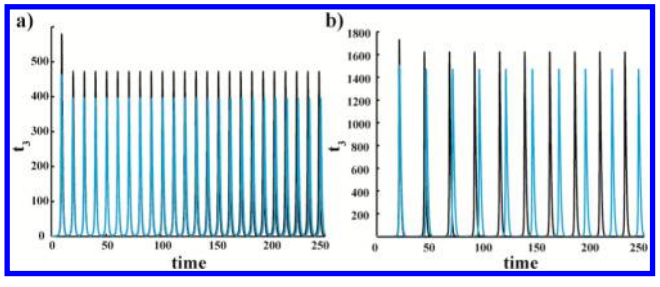


Figure 3. T_3 oscillations over time in the proposed circadian network (a; Scheme 2a) and for the simple autocatalyst (b, Scheme 2b case II). Each case compares two sets of E_3 intake and T_3 decay rates that differ by 20%. The progress of all reactions was simulated using the apparent optimal circadian network conditions (Supporting Information).

$$E_i + N \xrightarrow{g_i} T_i \qquad (6)$$

Scheme 1b shows the network configurations, corresponding to three basic Boolean logic motifs, which were applied to wire the oscillating inputs T_1 and T_2 to the output T_3. The one-input IF (YES) gate is made of an oscillatory autocatalytic path which, in turn, activates a cross-catalytic pathway to form T_3. The OR gate, besides two oscillating autocatalytic paths for the templates T_1 and T_2, consists of two cross catalytic paths, from T_1 to T_3 and from T_2 to T_3. The AND gate also consists of two autocatalytic paths for T_1 and T_2, but with only one cross catalytic path, from the T_1T_2 heterodimer to T_3, allowing for enhanced production of T_3 only when both T_1 and T_2 are present. We have implemented these simple *logic gates* by constructing and simulating the relevant networks (Figure 2a), namely activating or disabling specific network connections (eq 5 and 6),[20] using the default network parameters, together with an intake for E_3 and linear decay for T_3 (Supporting Information Table s2). Two distinct intake and decay values were used for T_1 and T_2, allowing each of these inputs to oscillate at a different frequency. For the IF gate, T_3 output oscillates in a manner similar to the T_1 input. For the OR gate, product formation of either T_1 or T_2 induces the production of T_3. However, there is a finite recovery time in these rapid oscillations, because once a T_3 signal appears and decays, its ability to immediately be produced again is impaired. For the AND gate, significant T_3 signals are produced with a frequency that combines the formation of T_1 and T_2. When the network is simulated with the exact same parameters but without a T_3 decay, its output T_3 functions as an *integrator*, which integrates the input signals, or a *counter*, which counts the number of input signals (Figure 2b). This is due to the absence of any mechanism that decreases the concentration of T_3, thus enabling T_3 to remember and record its previous history. By repeating these simulations with an initial E_3 supply but no intake, together with a T_3 decay, we construct networks that function as *triggers* (Figure 2c). Here, T_3 is formed as a one-time nonrepeating output signal upon arrival of the first appropriate input due to the absence of a continual intake, preventing additional T_3 from forming once E_3 is depleted. Finally, using the same parameters without a T_3 decay, we have constructed the network *detector* response (Figure 2d) that produces one-time indicators that an input signal has arrived, leaving the output concentration in an indefinite state of high concentration.

Understanding the mechanisms of most biological oscillators has proven difficult. Yet, it was found that the circadian clock of *S. elongatus* is rather simple. It requires neither transcription nor translation,[8] and it is driven by a core of only three proteins: KaiA, KaiB, and KaiC.[9−12] In a somewhat simplified view of their activity, KaiA stimulates KaiC autophosphorylation, resulting in accumulation of the latter, whereas a negative feedback mechanism operates by KaiC inactivation of KaiA in a KaiB-dependent manner. Mixing these proteins in vitro with ATP resulted in oscillations with a period of 24 h in the (total) level of KaiC phosphorylation.[8] We now show that a simple configuration of our ternary network (eq 5−6), mimicking quite closely the connectivity in the Kai system (Scheme 2), effectively functions as an internal clock.

The network product T_3 oscillates with a constant frequency, independent of the input intake rate, while exhibiting robust behavior with respect to fluctuations in initial concentrations. T_3 is formed autocatalytically, via the intermediate $E_3NT_3T_3$, and through a cross-catalytic pathway by T_1 via the intermediate $E_3NT_1T_1$. The negative feedback of the latter reaction is affected by a competing pathway, where an E_2 analog (E_2') joins the T_1T_3 dimer in forming an inhibiting intermediate $E_2'NT_1T_3$ (which does not ligate to form T_2). Figure 3a compares the T_3 oscillation dynamics under an apparent optimal set of conditions for two sets of E_3 intake and T_3 decay rates that differ by 20%. Such a difference in intake and decay rates is expected to yield significantly different oscillation frequencies (vide infra), but the results show that our network leads to almost identical T_3 frequencies. We have then investigated the robustness of the

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network under additional conditions resulting from two runs with higher initial E_2' and T_1 concentrations (Supporting Information Figure s6). Under these apparent "suboptimal" conditions we observe that the frequencies and their amplitudes have somewhat changed, but most importantly, the two different sets of intake and decay rates still lead to almost identical T_3 production frequencies. In order to further test the performance of the proposed circadian network, we have investigated and compared three other network configurations (II, III, IV; graph presentation[20] in Scheme 2b). Figure 3b shows that the simple autocatalyst configuration (II) yields two sets of frequencies that differ by >5%, highlighting the role of the circadian network. The binary network (III) results under the optimal conditions were similar to those of our proposed network (Supporting Information Figure s7a), but under the suboptimal conditions this network's performance was not robust to fluctuations in initial concentrations (Supporting Information Figure s7b). Furthermore, the performance of the alternate ternary network (IV; Supporting Information Figure s7c) also falls short of the performance of our suggested network.

Based on these results, we suggest a mechanism for our circadian network. The T_3 autocatalytic oscillatory behavior is due to intake and decay of E_3 and T_3 (as in Figure 1), whereas its oscillation frequency is stabilized by cross-catalysis from T_1. For this to work properly, however, T_1 concentration must be kept low. The feedback loop, operating via E_2' association with N and the T_1T_3 dimer, facilitates siphoning off excess T_1 and allowing the network to be less sensitive to T_1 fluctuations. We suggest that a similar mechanism may operate on the Kai proteins circadian clocks.

This work has enabled us to shed light on the Systems Chemistry of open oscillating catalytic reaction networks and on the nature of these oscillations. As in previous numerical studies of chemical networks, many features of the dynamic behavior are difficult to predict without numerical simulation. In that context, it should be mentioned that, except for the BZ reaction, the first chemical networks operating out-of-equilibrium have only been presented very recently[37,38] and that no demonstration of a replication network out of equilibrium has been made available so far. This is accordingly the next research challenge for the authors and potentially for other groups as well.

■ ASSOCIATED CONTENT

Supporting Information

(i) Detailed description of simulation, parameters and initial conditions, (ii) additional figures, and (iii) expanded discussion. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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