Simulation of the KaiABC Circadian Oscillation by Matlab

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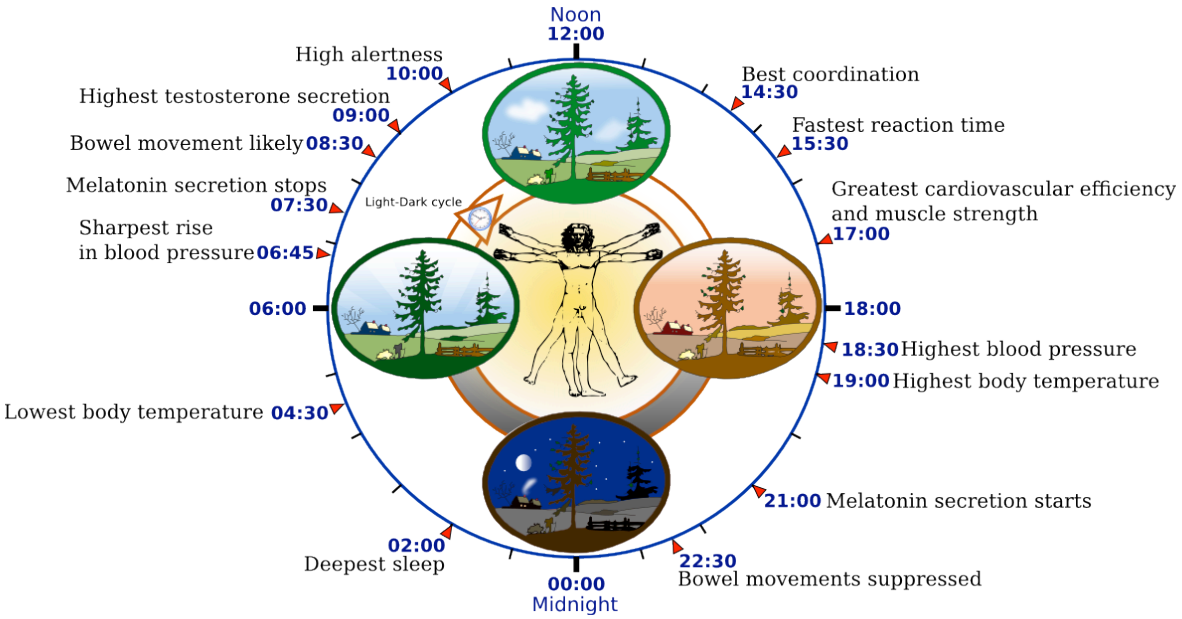
Circadian Rhythm



- A roughly-24-hour cycle in the biochemical, physiological or behavior processes of living entities, including plants, animals, fungi and **cyanobacteria**
- **Endogenously generated**
- Can be entrained by **external cues** (called Zeitgebers), such as daylight
- Allow organisms to anticipate and prepare for precise and regular environmental changes

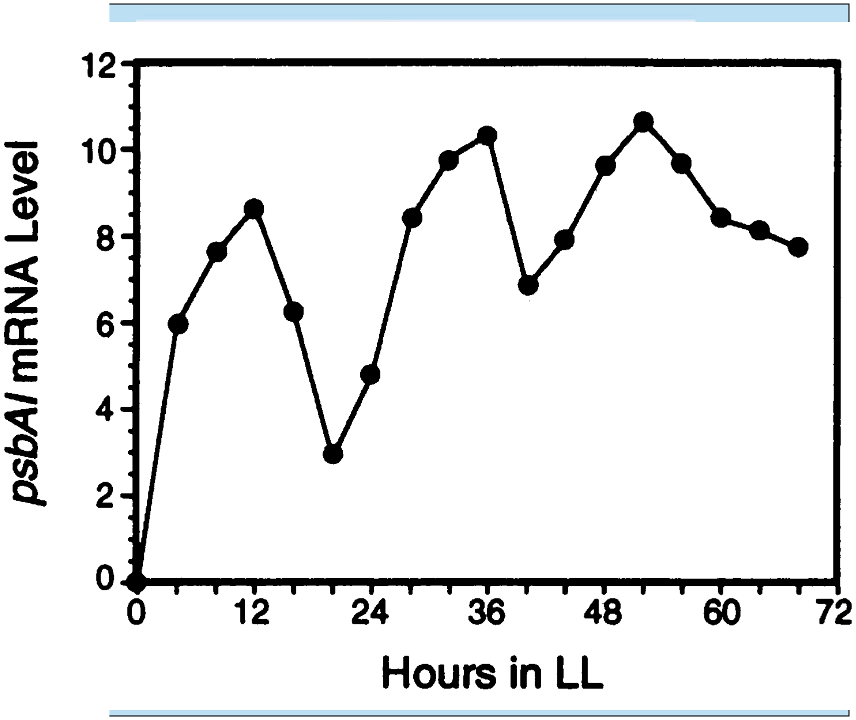
Three General Criteria

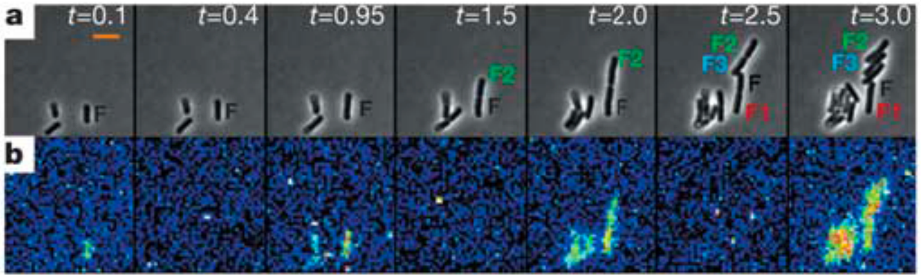
1. The rhythms persist in the absence of cues.
2. They persist equally precisely over a range of temperatures (i.e. temperature-compensation).
3. The rhythms can be adjusted to match the local time.

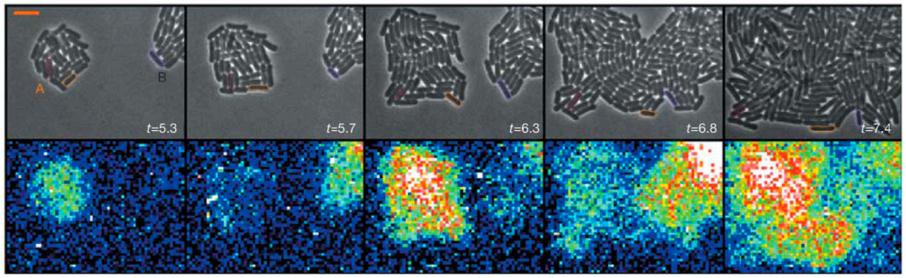
- Are **prokaryotes** capable of circadian rhythmicity?
- “Why have a timer for a cycle that is longer than your life time?”

Bacterial Circadian Rhythms

- Cyanobacteria display daily rhythms of nitrogen fixation in both LD cycle and in constant light (1985-1986)
- Satisfy the three criteria
- Keep track of two timing processes
- Adaptive significance



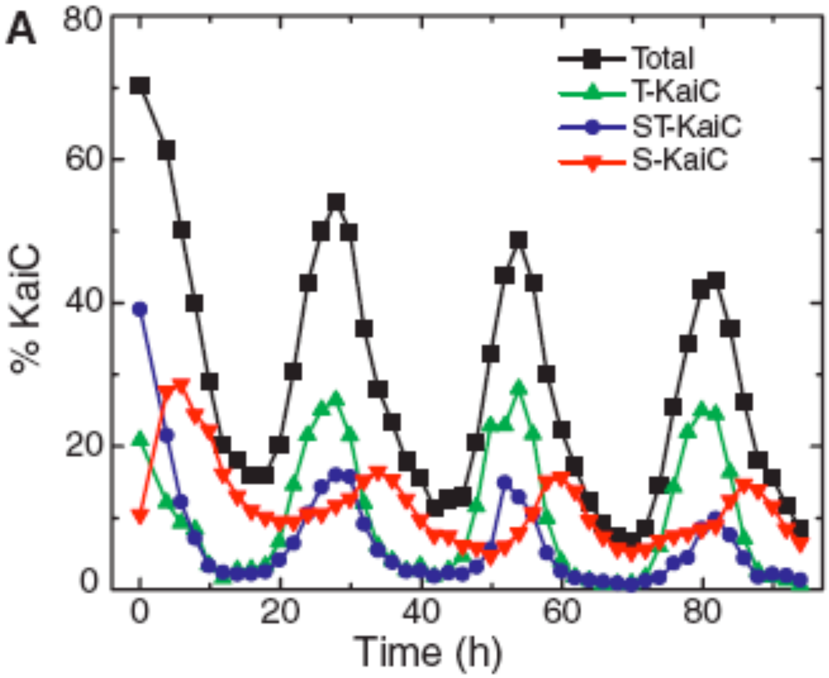




Kondo, T., et. al. PNAS 1993; Wihalcescu, I., et. al. Nature 2004; Johnson, C. H. Nature 2004.

Molecular Mechanism of the Cyanobacterial Clockwork - KaiABC

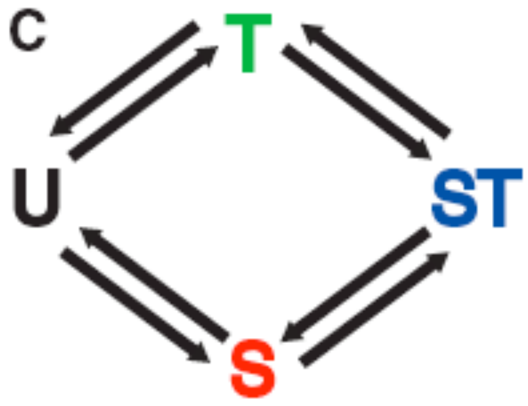
- **Traditional view:** transcriptional feedback oscillators
- **Reconstitution in vitro** using only KaiA, KaiB, and KaiC
- **KaiC**: a hexameric enzyme that can autophosphorylate (**KaiA-dependent**) and autodephosphorylate at both **S431** and **T432**
- **KaiA**: its dimer enhances the autophophorylation of KaiC
- **KaiB**: antagonizes the activity of KaiA

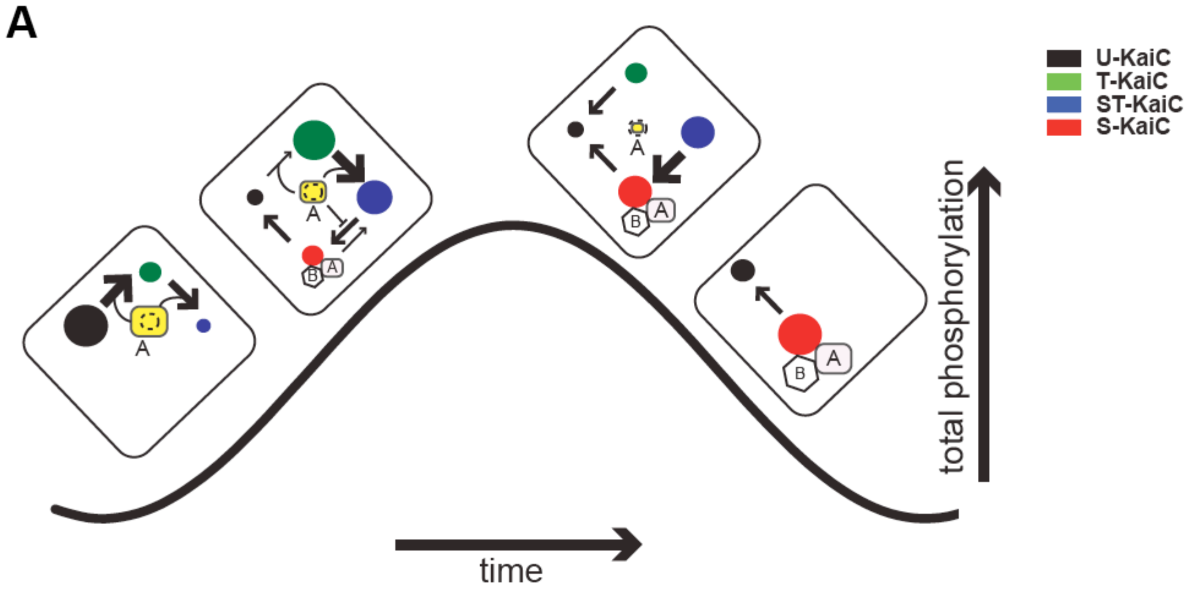


New model: The phosphoform distribution (or a combination tightly linked to the phosphorylation state) determines the phase of the oscillator.

Rust, M.J., et. al. Science 2007.

Four-state model with first-order kinetics of interconversion of KaiC phosphoforms

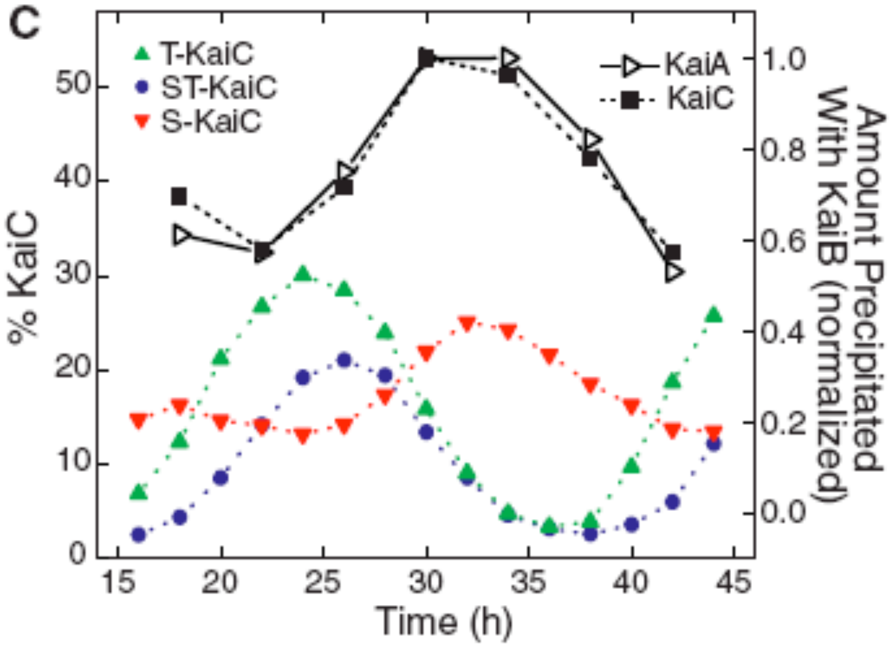


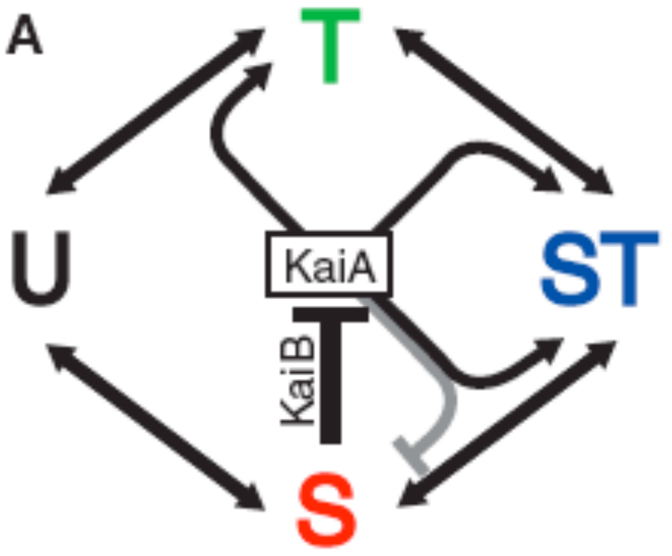


New model: The phosphoform distribution (or a combination tightly linked to the phosphorylation state) determines the phase of the oscillator.

Rust, M.J., et. al. Science 2007.

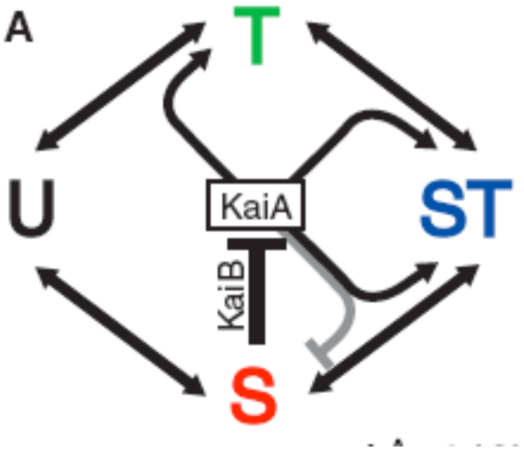
1. KaiA activity alters the first-order rate constants for interconversion of KaiC phosphoforms
2. KaiB suppresses KaiA activity in an S-KaiC-dependent manner





Rust, M.J., et. al. Science 2007.

Description of the Model



Assumptions:

1. The concentrations of the three phosphorylated species are the only slow dynamical variables;

$$\frac{dT}{dt} = k_{UT}(S)\,U + k_{DT}(S)\,D - k_{TU}(S)\,T - k_{TD}(S)\,T \qquad (1)$$

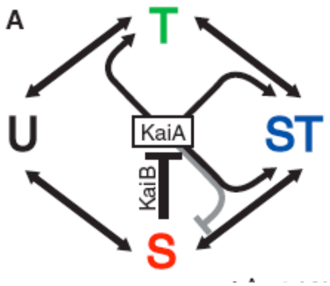
$$\frac{dD}{dt} = k_{TD}(S)\,T + k_{SD}(S)\,S - k_{DT}(S)\,D - k_{DS}(S)\,D \qquad (2)$$

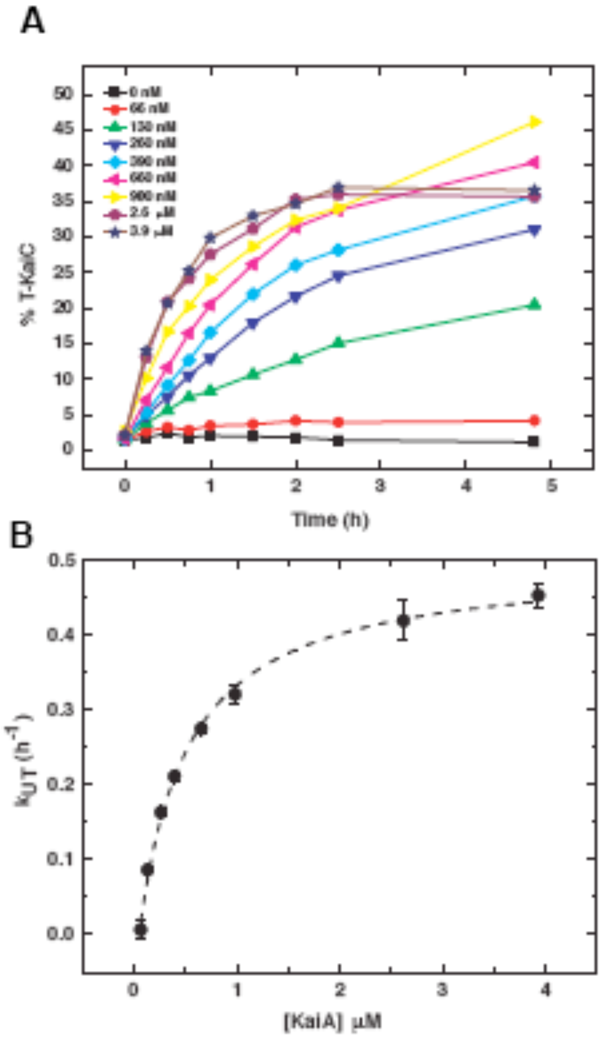
$$\frac{dS}{dt} = k_{US}(S)\,U + k_{DS}(S)\,D - k_{SU}(S)\,S - k_{SD}(S)\,S \qquad (3)$$

Rust, M.J., et. al. Science 2007.

$$k_{XY}(S) = k^0_{XY} + \frac{k^A_{XY} A(S)}{K_{1/2} + A(S)}$$

$$A = \max\{0, [\mathrm{KaiA}] - 2mS\}$$





Assumptions:

1. The concentrations of the three phosphorylated species are the only slow dynamical variables;
2. The interconversions are first-order reactions with rates that dependent hyporbolically on the concentration of active KaiA;

Rust, M.J., et. al. Science 2007.

Summary of the model

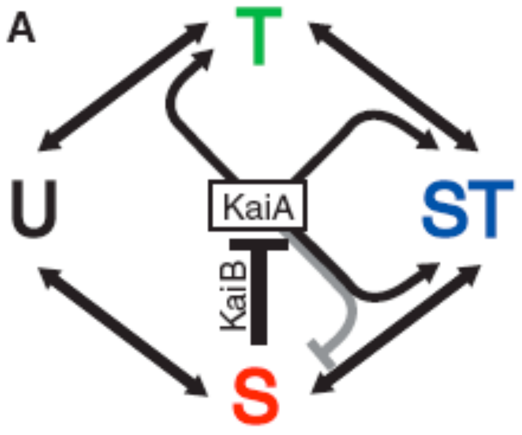
$$\frac{dT}{dt} = k_{UT}(S)\,U + k_{DT}(S)\,D - k_{TU}(S)\,T - k_{TD}(S)\,T \tag{1}$$

$$\frac{dD}{dt} = k_{TD}(S)\,T + k_{SD}(S)\,S - k_{DT}(S)\,D - k_{DS}(S)\,D \tag{2}$$

$$\frac{dS}{dt} = k_{US}(S)\,U + k_{DS}(S)\,D - k_{SU}(S)\,S - k_{SD}(S)\,S \tag{3}$$

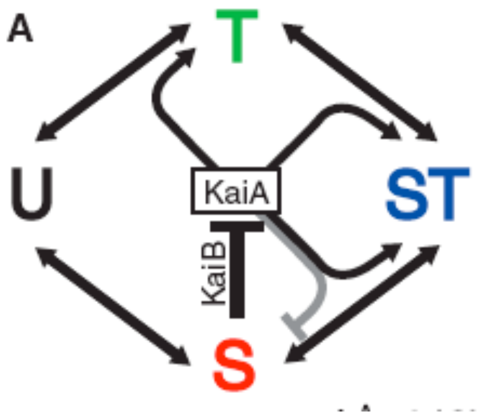
$$A = \max\{0, [\mathrm{KaiA}] - 2mS\} \tag{4}$$

$$k_{XY}(S) = k^0_{XY} + \frac{k^A_{XY}A(S)}{K_{1/2} + A(S)} \tag{5}$$



$$k_{XY}(S) = k^0_{XY} + \frac{k^A_{XY} A(S)}{K_{1/2} + A(S)}$$

$$A = \max\{0, [\mathrm{KaiA}] - 2mS\}$$



Assumptions:

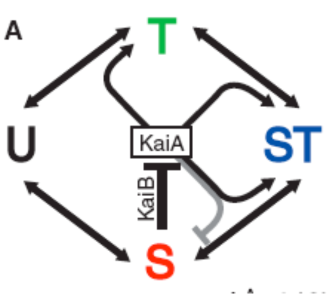
1. The concentrations of the three phosphorylated species are the only slow dynamical variables;
2. The interconversions are first-order reactions with rates that dependent hyporbolically on the concentration of active KaiA;
3. Each S-KaiC monomer (together with KaiB) inactivates one KaiA dimer (m=1).

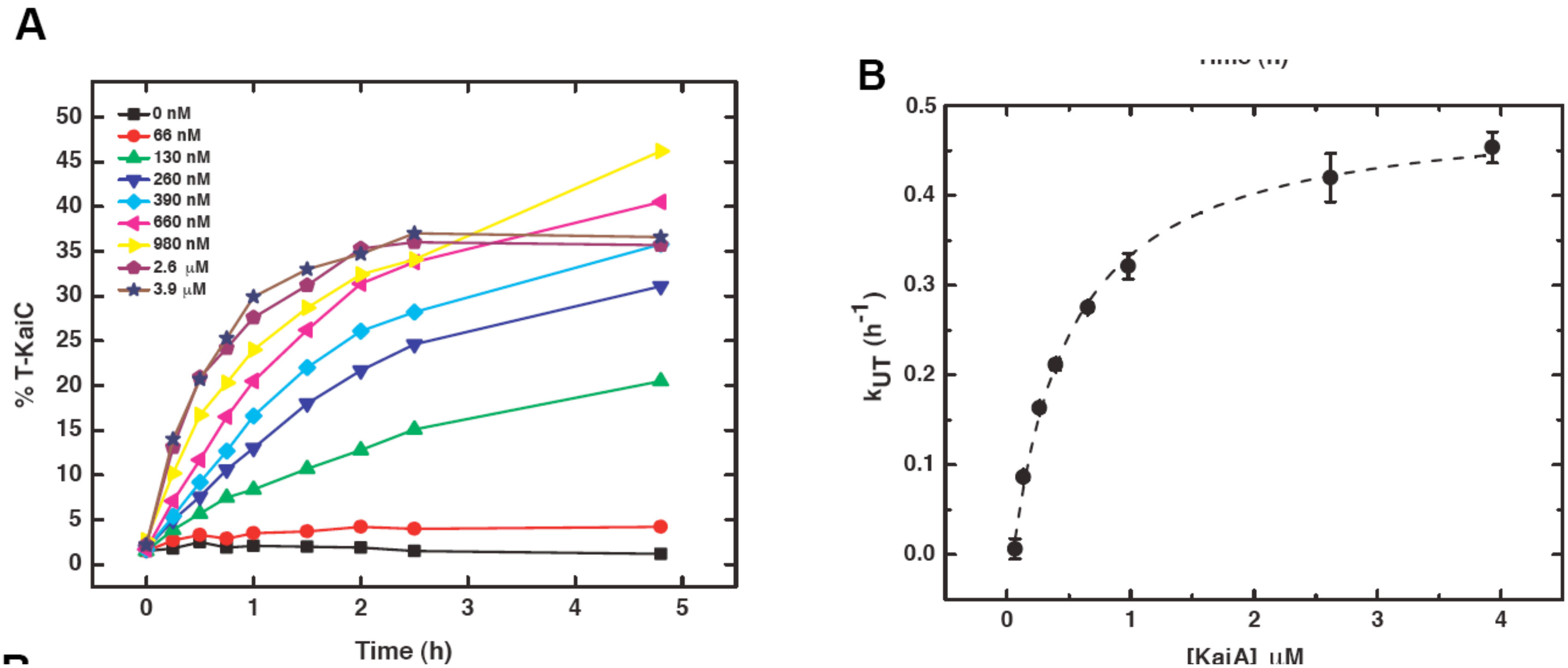
Rust, M.J., et. al. Science 2007.

Determine $K_{1/2}$: $K_{1/2} = 0.43 \pm 0.05 \mu M$

$$k_{XY}(S) = k^0_{XY} + \frac{k^A_{XY} A(S)}{K_{1/2} + A(S)}$$

$$A = \max\{0, [\text{KaiA}] - 2mS\}$$

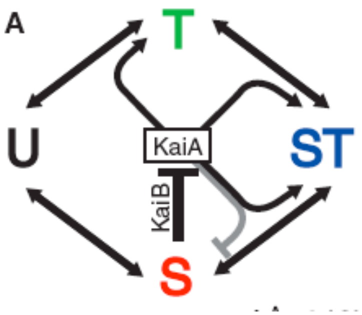


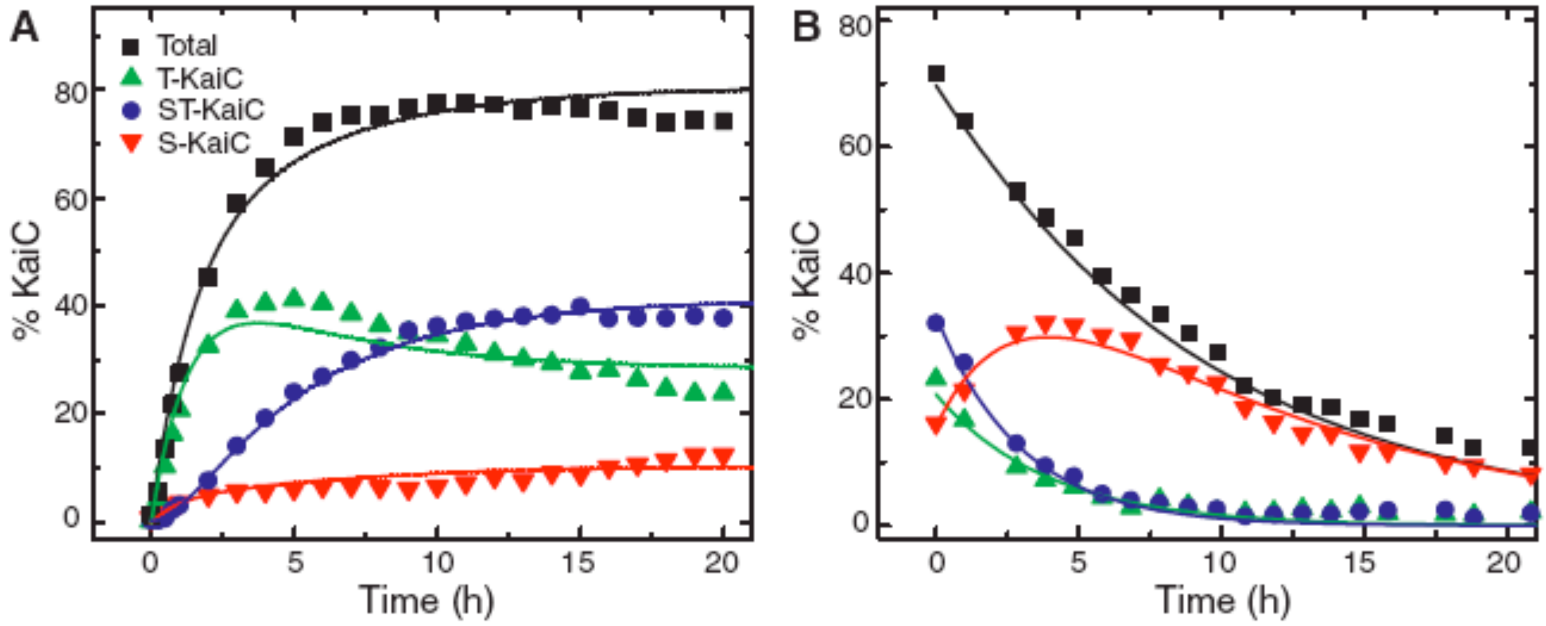


Rust, M.J., et. al. Science 2007.

Determine k^0 and k^A:

$$k_{XY}(S) = k_{XY}^{0} + \frac{k_{XY}^{A} A(S)}{K_{1/2} + A(S)}$$




+ 1.3 µM of KaiA

Remove KaiA

Rust, M.J., et. al. Science 2007.

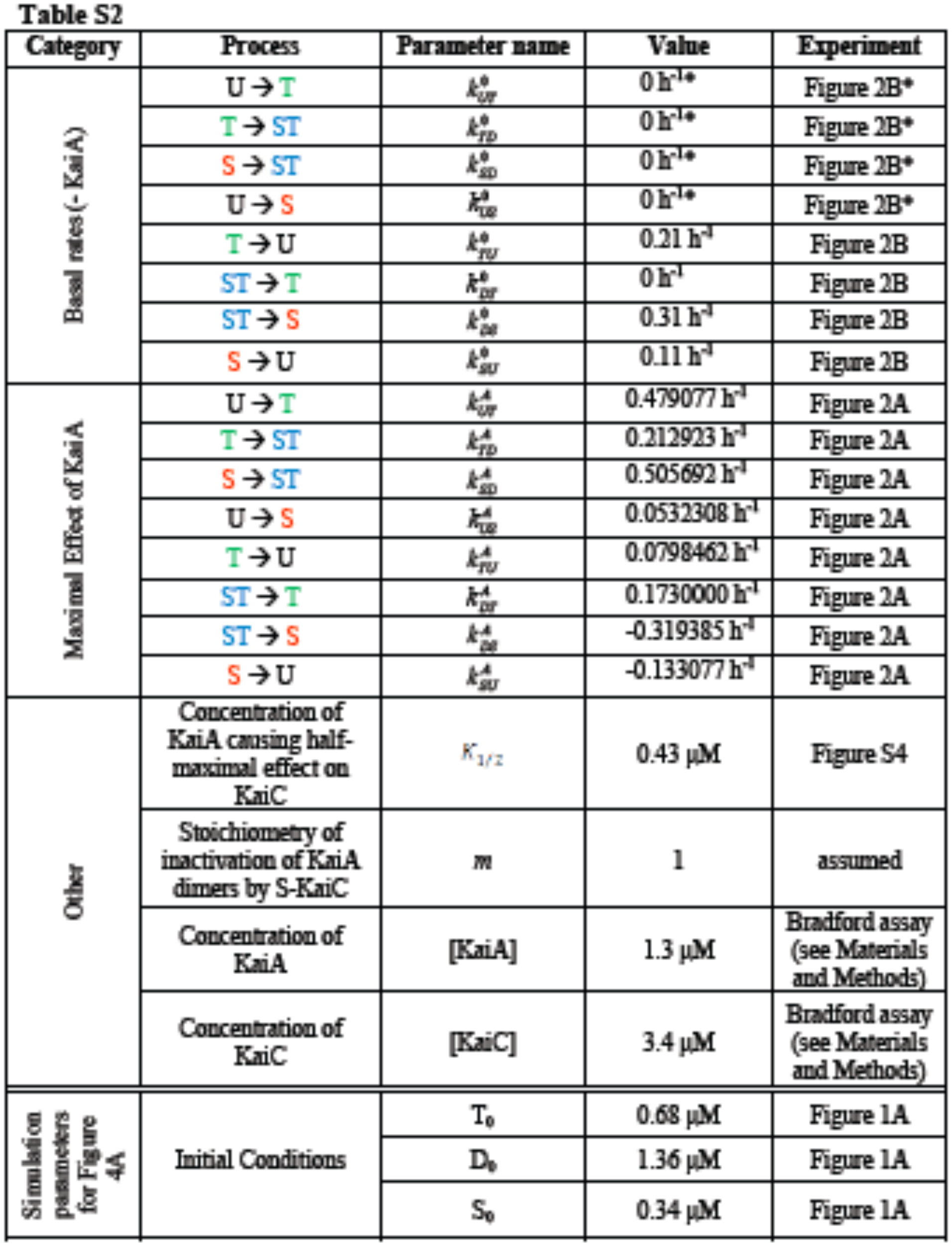
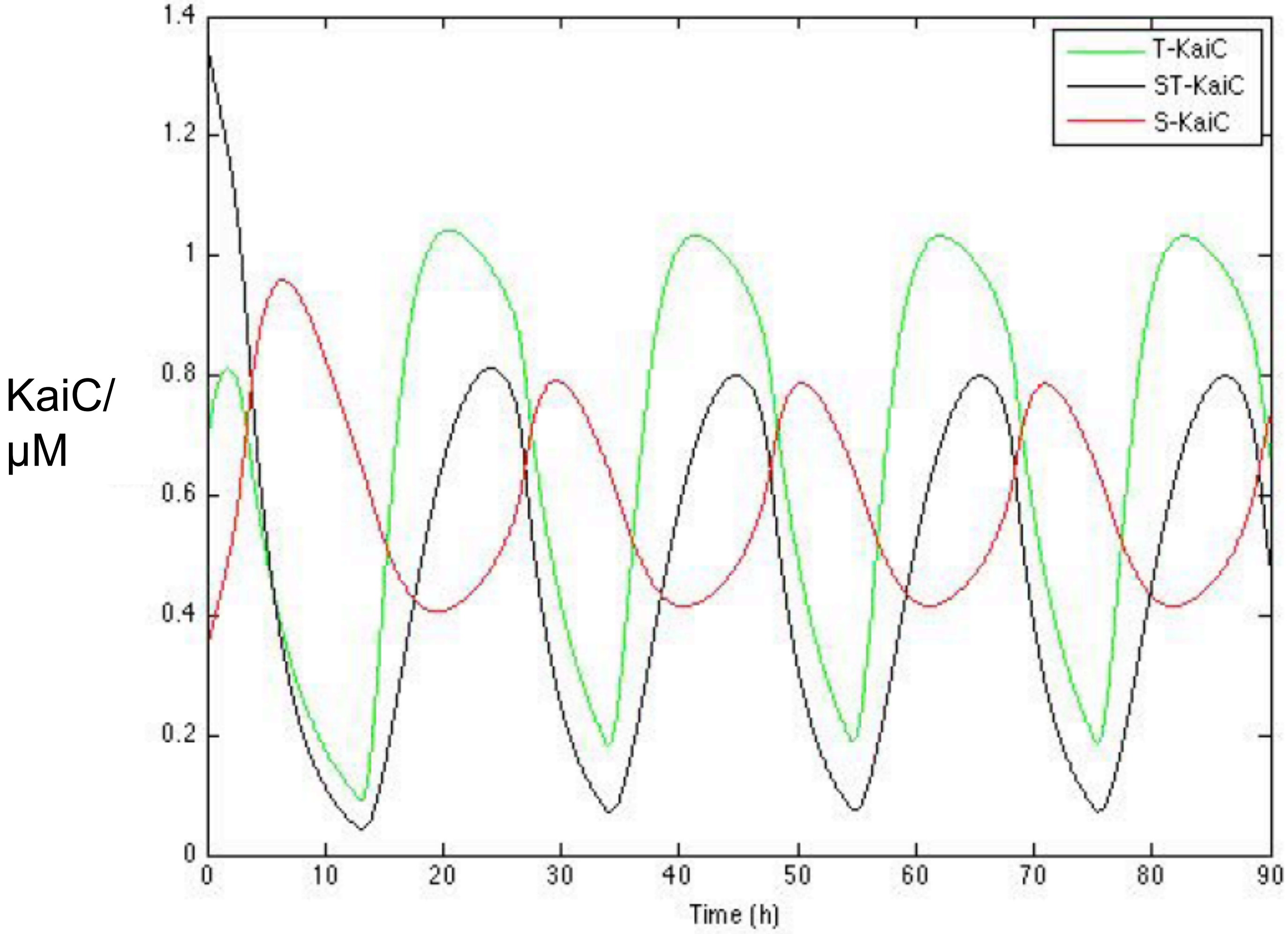


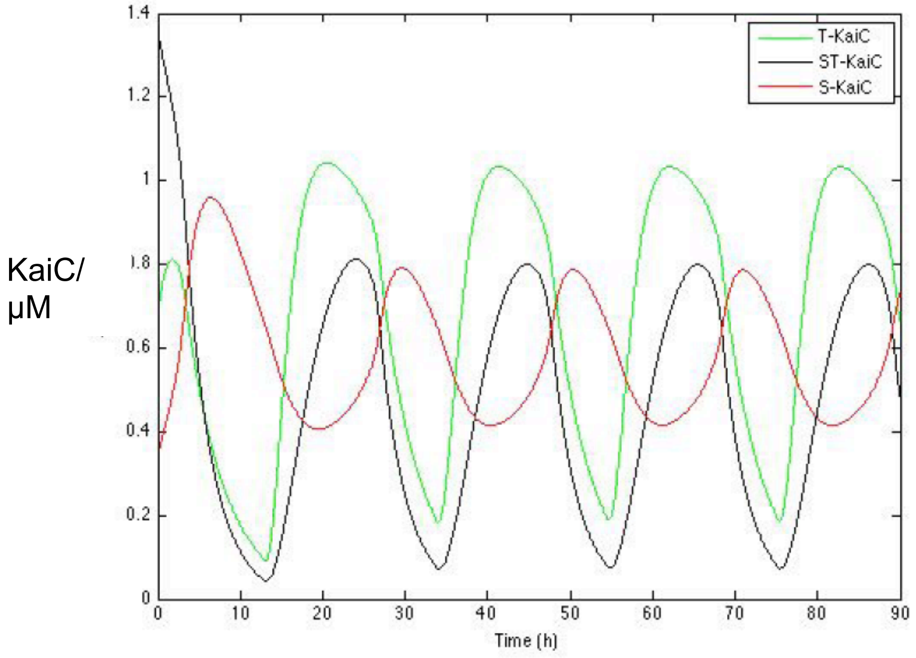
Table S2

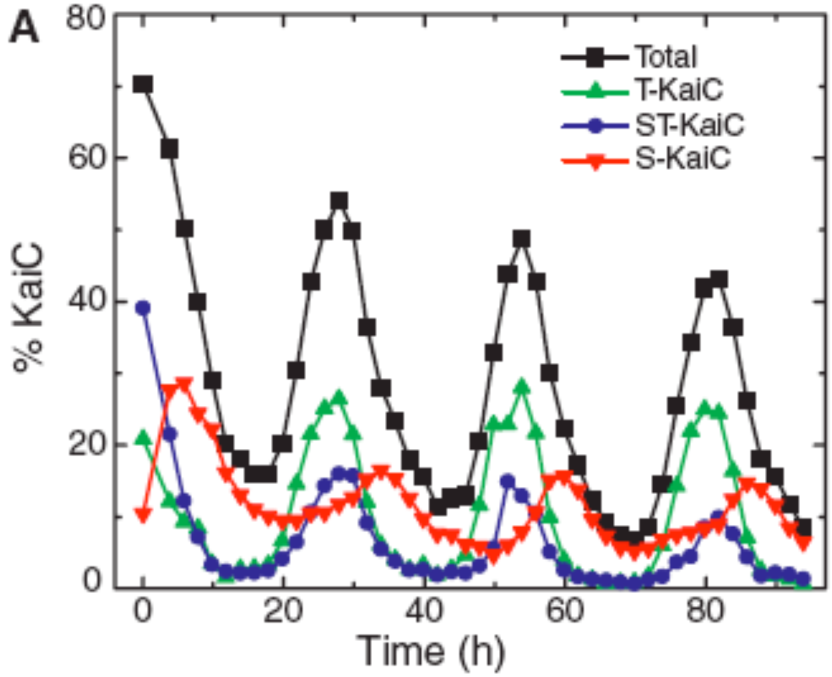
Category	Process	Parameter name	Value	Experiment
Basal rates (- KaiA)	U → T	k_{UT}^{0}	$0\ h^{-1*}$	Figure 2B*
	T → ST	k_{TD}^{0}	$0\ h^{-1*}$	Figure 2B*
	S → ST	k_{SD}^{0}	$0\ h^{-1*}$	Figure 2B*
	U → S	k_{US}^{0}	$0\ h^{-1*}$	Figure 2B*
	T → U	k_{TU}^{0}	$0.21\ h^{-1}$	Figure 2B
	ST → T	k_{DT}^{0}	$0\ h^{-1}$	Figure 2B
	ST → S	k_{DS}^{0}	$0.31\ h^{-1}$	Figure 2B
	S → U	k_{SU}^{0}	$0.11\ h^{-1}$	Figure 2B
Maximal Effect of KaiA	U → T	k_{UT}^{A}	$0.479077\ h^{-1}$	Figure 2A
	T → ST	k_{TD}^{A}	$0.212923\ h^{-1}$	Figure 2A
	S → ST	k_{SD}^{A}	$0.505692\ h^{-1}$	Figure 2A
	U → S	k_{US}^{A}	$0.0532308\ h^{-1}$	Figure 2A
	T → U	k_{TU}^{A}	$0.0798462\ h^{-1}$	Figure 2A
	ST → T	k_{DT}^{A}	$0.1730000\ h^{-1}$	Figure 2A
	ST → S	k_{DS}^{A}	$-0.319385\ h^{-1}$	Figure 2A
	S → U	k_{SU}^{A}	$-0.133077\ h^{-1}$	Figure 2A
Other	Concentration of KaiA causing half-maximal effect on KaiC	$K_{1/2}$	0.43 μM	Figure S4
	Stoichiometry of inactivation of KaiA dimers by S-KaiC	m	1	assumed
	Concentration of KaiA	[KaiA]	1.3 μM	Bradford assay (see Materials and Methods)
	Concentration of KaiC	[KaiC]	3.4 μM	Bradford assay (see Materials and Methods)
Simulation parameters for Figure 4A	Initial Conditions	T_0	0.68 μM	Figure 1A
		D_0	1.36 μM	Figure 1A
		S_0	0.34 μM	Figure 1A

Rust, M.J., et. al. Science 2007.

Simulation results of oscillation with matlab:







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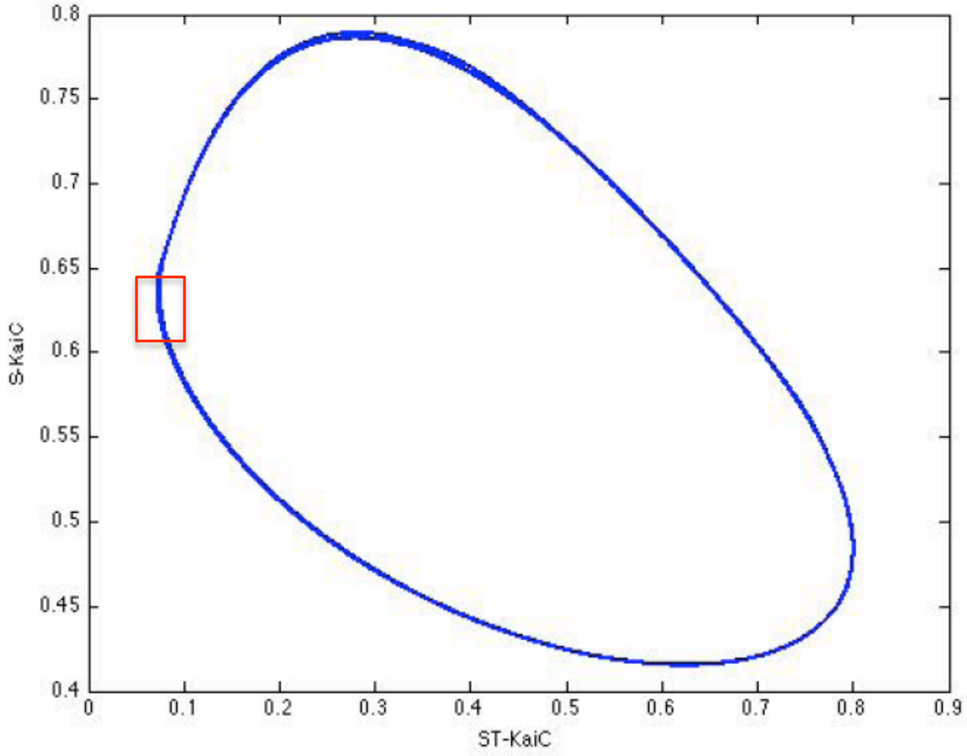
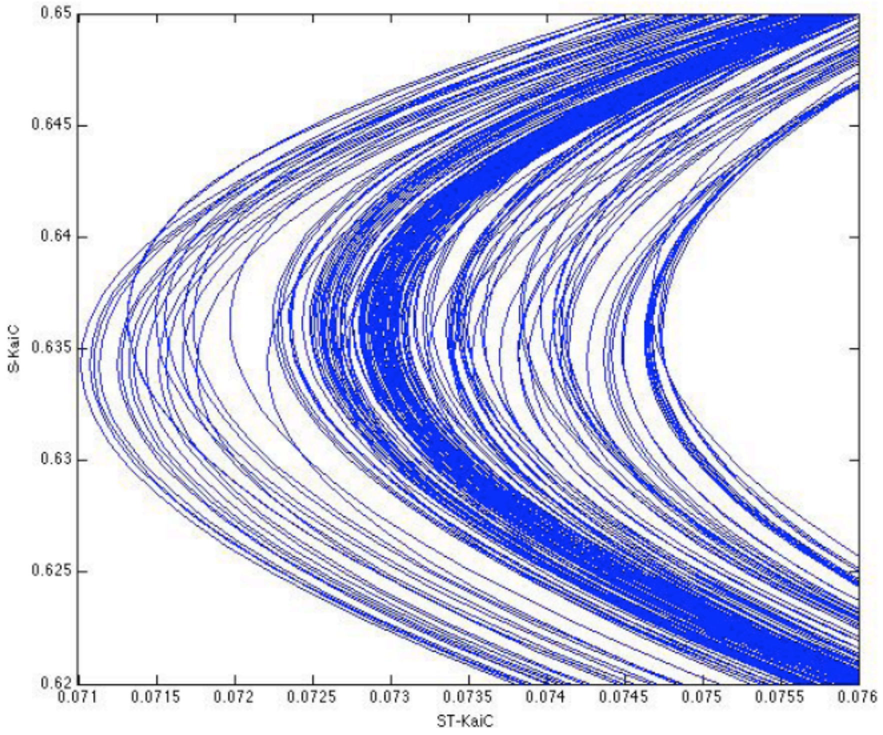
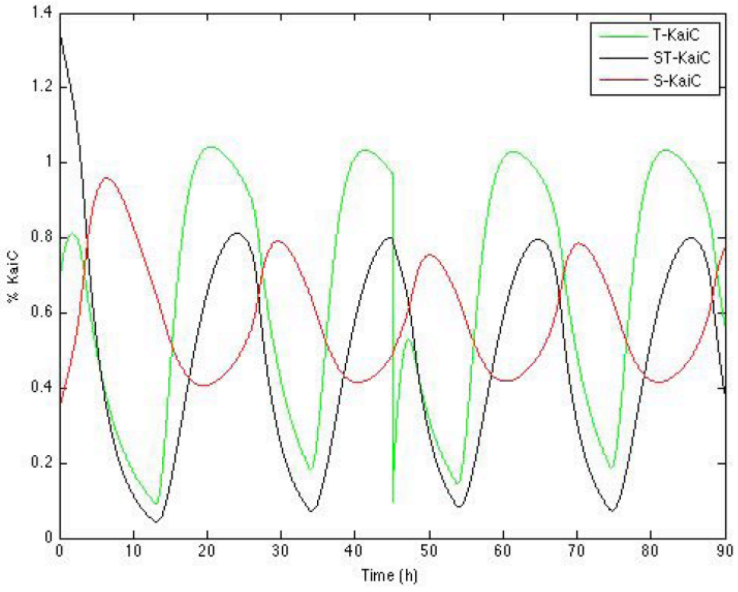
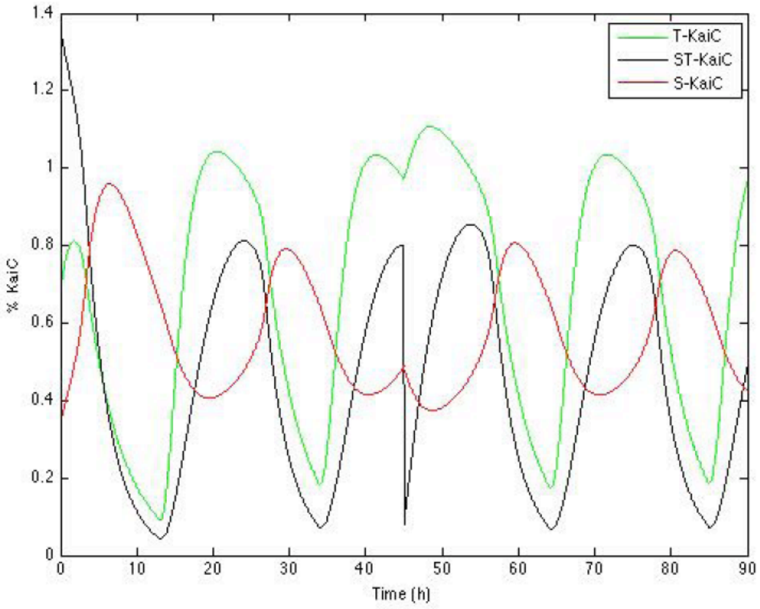
2-D phase portrait:





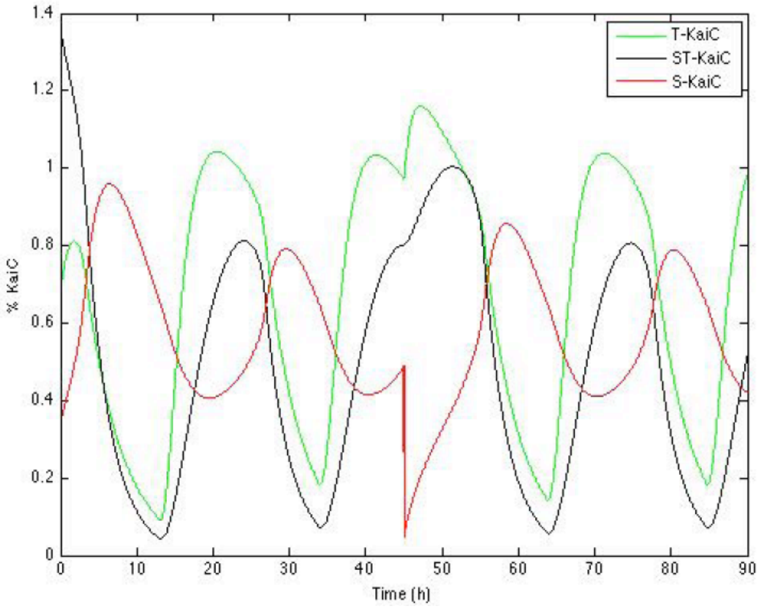
- Not exactly periodical, but “chaotic” or periodical with a very long period
- Long-term average period is 20.6865h



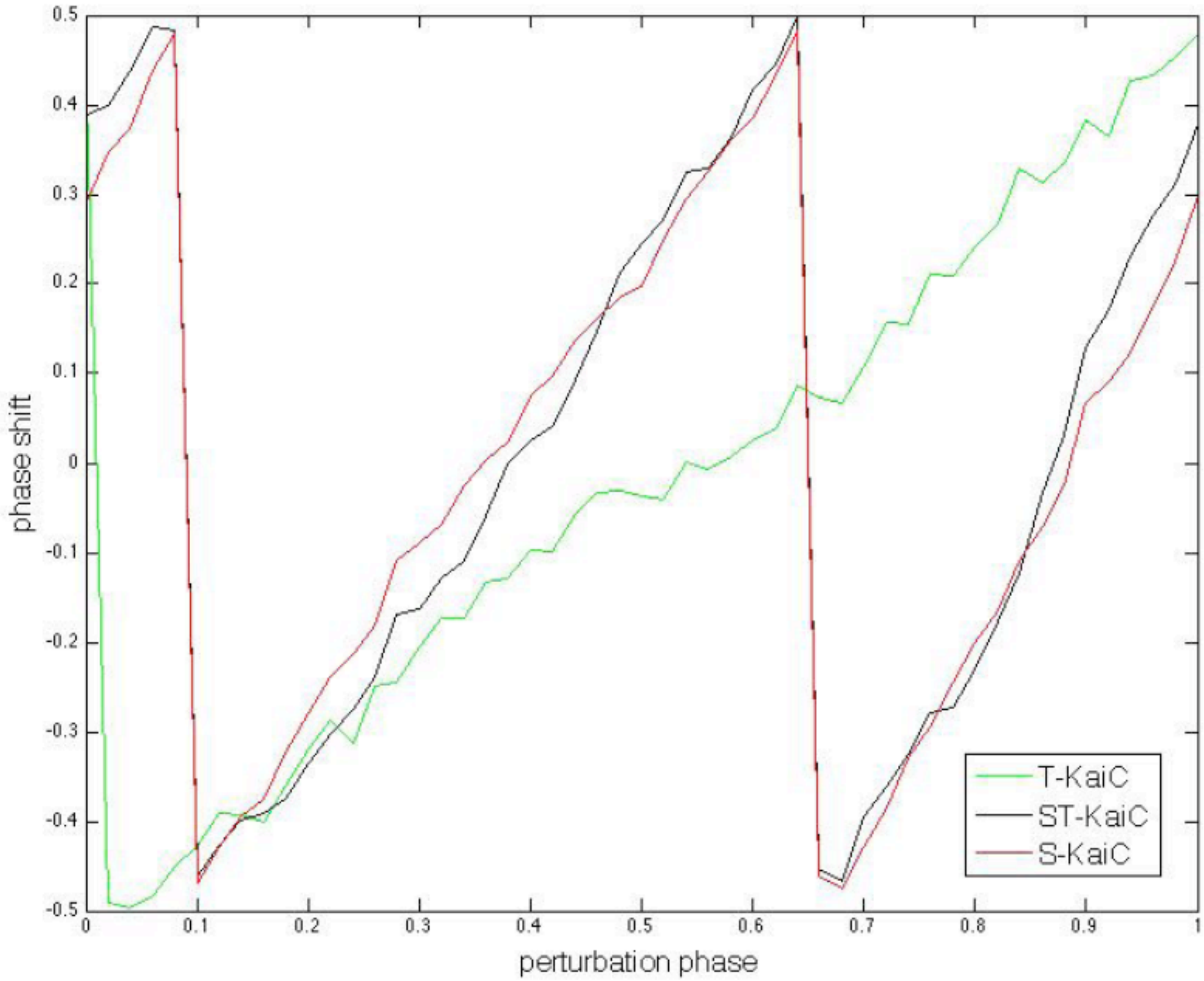


- **Perturbation simulations:** 1/10 of the value of T-KaiC, ST-KaiC, or S-KaiC at 45h
- **Phase shift:** 2π × the fraction of a period that the original unperturbed oscillatory curves would have to be shifted in time to match the perturbed oscillation once it recovers its full amplitude oscillation

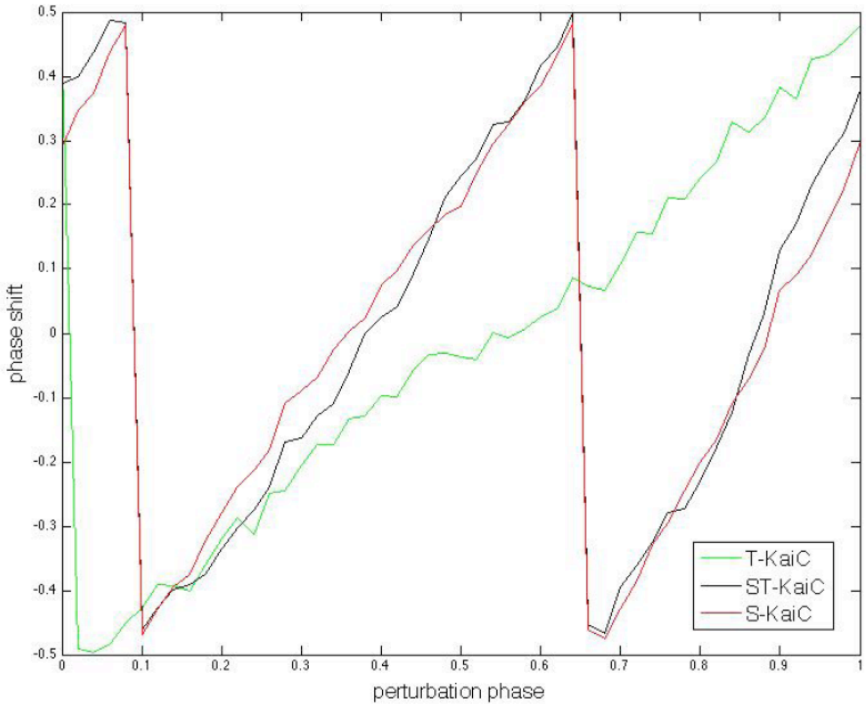
	T-KaiC	ST-KaiC	S-KaiC
phase-shift	1.00	2.20	2.26

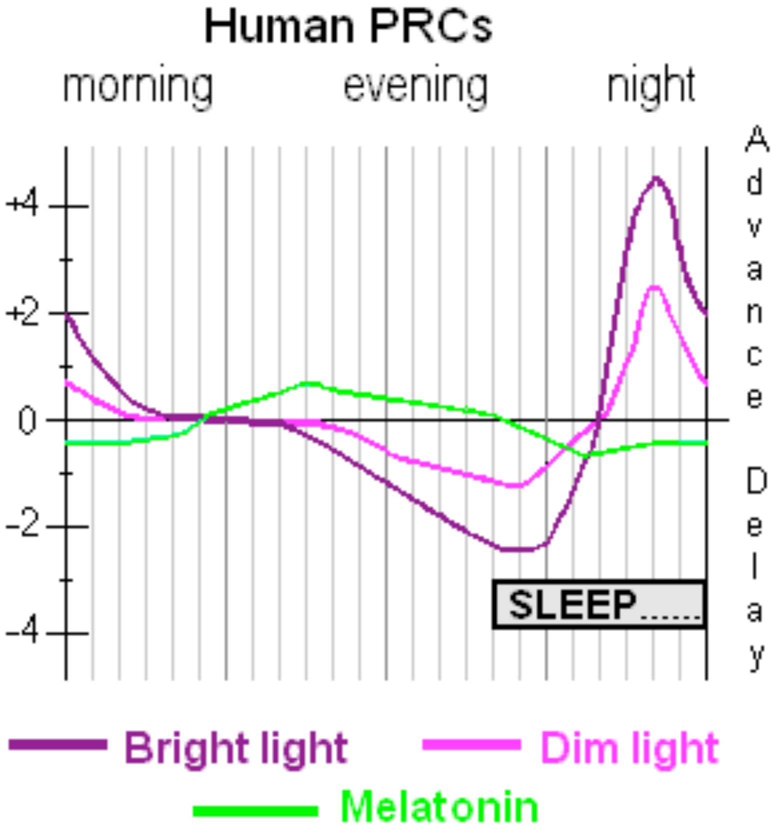


Phase response curve (normalize 2π to 1 here)



Phase response curves





Summary

- Successful simulation of the KaiABC minimal model by Matlab
- Discussion about periodicity and perturbations in the KaiABC oscillator
- Phase response curve (PRC) generation for the model and comparison to natural PRC
- Some discussion