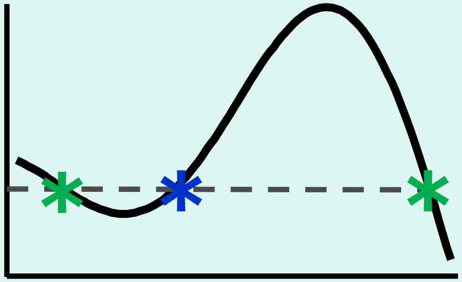
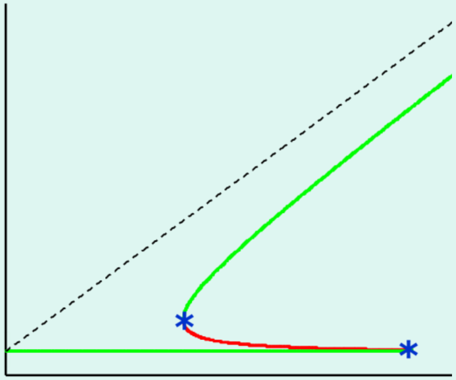
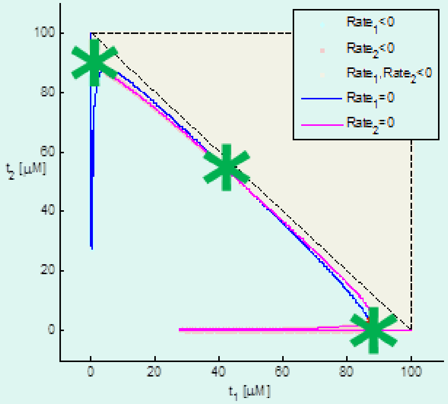
Multistationarity in Catalytic Reaction Networks







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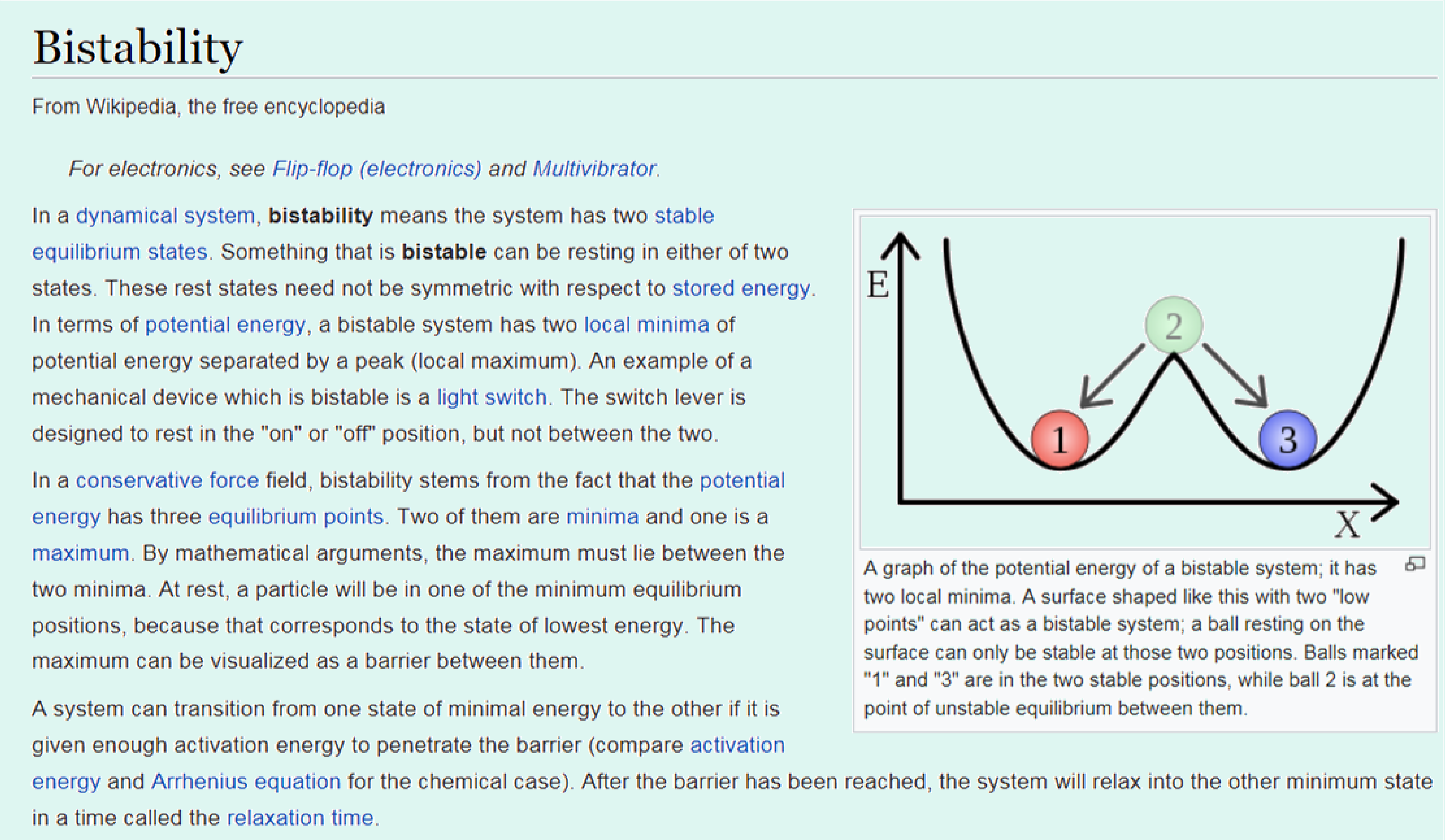


Bistability

From Wikipedia, the free encyclopedia

For electronics, see Flip-flop (electronics) and Multivibrator.

In a dynamical system, **bistability** means the system has two stable equilibrium states. Something that is **bistable** can be resting in either of two states. These rest states need not be symmetric with respect to stored energy. In terms of potential energy, a bistable system has two local minima of potential energy separated by a peak (local maximum). An example of a mechanical device which is bistable is a light switch. The switch lever is designed to rest in the "on" or "off" position, but not between the two.

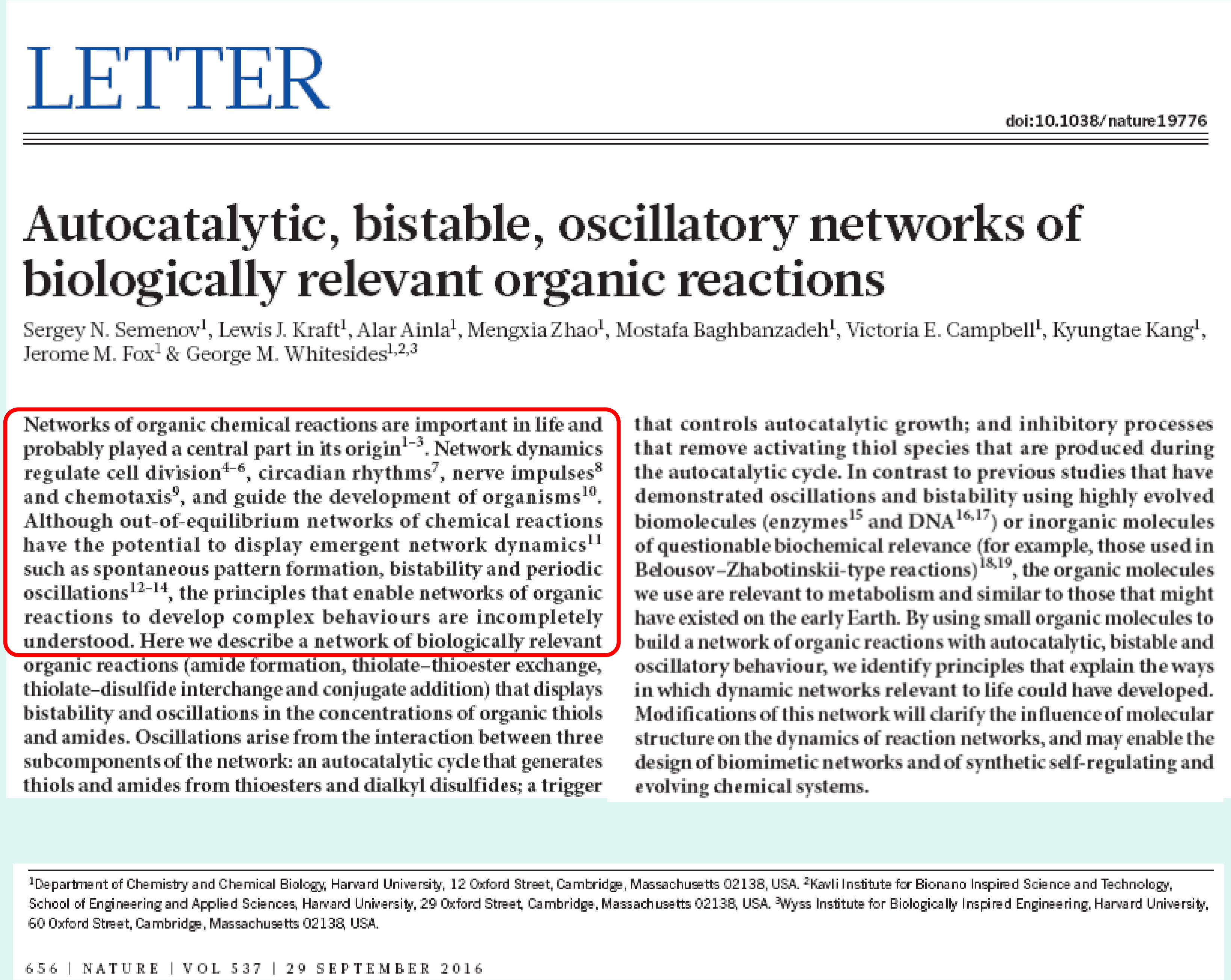
In a conservative force field, bistability stems from the fact that the potential energy has three equilibrium points. Two of them are minima and one is a maximum. By mathematical arguments, the maximum must lie between the two minima. At rest, a particle will be in one of the minimum equilibrium positions, because that corresponds to the state of lowest energy. The maximum can be visualized as a barrier between them.

A system can transition from one state of minimal energy to the other if it is given enough activation energy to penetrate the barrier (compare activation energy and Arrhenius equation for the chemical case). After the barrier has been reached, the system will relax into the other minimum state in a time called the relaxation time.

A graph of the potential energy of a bistable system; it has two local minima. A surface shaped like this with two "low points" can act as a bistable system; a ball resting on the surface can only be stable at those two positions. Balls marked "1" and "3" are in the two stable positions, while ball 2 is at the point of unstable equilibrium between them.

bifurcation point A point in parameter space where one can expect to see a change in the qualitative behaviour of a system—e.g., loss of stability of a solution or the emergence of a new solution with different properties.

THE FREE DICTIONARY BY FARLEX



LETTER

doi:10.1038/nature19776

Autocatalytic, bistable, oscillatory networks of biologically relevant organic reactions

Sergey N. Semenov[1], Lewis J. Kraft[1], Alar Ainla[1], Mengxia Zhao[1], Mostafa Baghbanzadeh[1], Victoria E. Campbell[1], Kyungtae Kang[1], Jerome M. Fox[1] & George M. Whitesides[1,2,3]

Networks of organic chemical reactions are important in life and probably played a central part in its origin[1–3]. Network dynamics regulate cell division[4–6], circadian rhythms[7], nerve impulses[8] and chemotaxis[9], and guide the development of organisms[10]. Although out-of-equilibrium networks of chemical reactions have the potential to display emergent network dynamics[11] such as spontaneous pattern formation, bistability and periodic oscillations[12–14], the principles that enable networks of organic reactions to develop complex behaviours are incompletely understood. Here we describe a network of biologically relevant organic reactions (amide formation, thiolate–thioester exchange, thiolate–disulfide interchange and conjugate addition) that displays bistability and oscillations in the concentrations of organic thiols and amides. Oscillations arise from the interaction between three subcomponents of the network: an autocatalytic cycle that generates thiols and amides from thioesters and dialkyl disulfides; a trigger that controls autocatalytic growth; and inhibitory processes that remove activating thiol species that are produced during the autocatalytic cycle. In contrast to previous studies that have demonstrated oscillations and bistability using highly evolved biomolecules (enzymes[15] and DNA[16,17]) or inorganic molecules of questionable biochemical relevance (for example, those used in Belousov–Zhabotinskii-type reactions)[18,19], the organic molecules we use are relevant to metabolism and similar to those that might have existed on the early Earth. By using small organic molecules to build a network of organic reactions with autocatalytic, bistable and oscillatory behaviour, we identify principles that explain the ways in which dynamic networks relevant to life could have developed. Modifications of this network will clarify the influence of molecular structure on the dynamics of reaction networks, and may enable the design of biomimetic networks and of synthetic self-regulating and evolving chemical systems.

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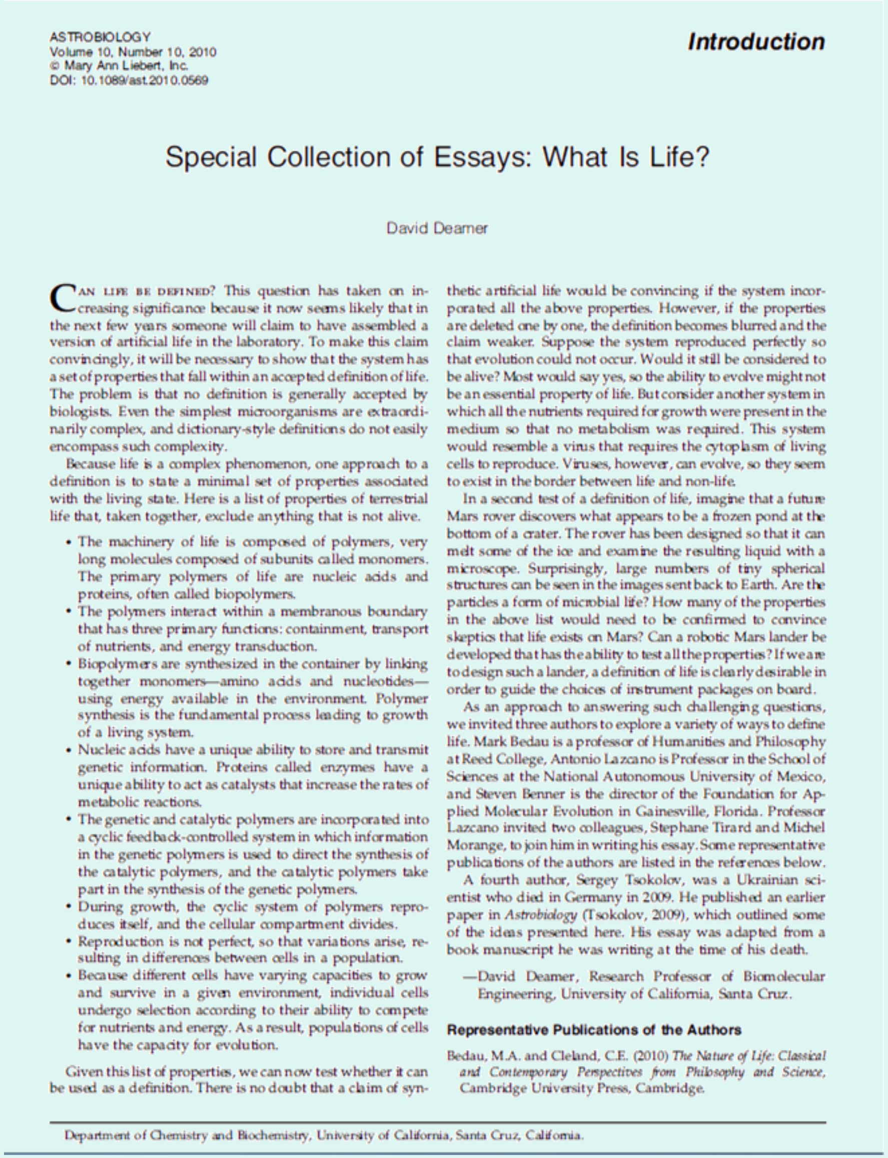

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Introduction

Special Collection of Essays: What Is Life?

David Deamer

CAN LIFE BE DEFINED? This question has taken on increasing significance because it now seems likely that in the next few years someone will claim to have assembled a version of artificial life in the laboratory. To make this claim convincingly, it will be necessary to show that the system has a set of properties that fall within an accepted definition of life. The problem is that no definition is generally accepted by biologists. Even the simplest microorganisms are extraordinarily complex, and dictionary-style definitions do not easily encompass such complexity.

Because life is a complex phenomenon, one approach to a definition is to state a minimal set of properties associated with the living state. Here is a list of properties of terrestrial life that, taken together, exclude anything that is not alive.

- The machinery of life is composed of polymers, very long molecules composed of subunits called monomers. The primary polymers of life are nucleic acids and proteins, often called biopolymers.
- The polymers interact within a membranous boundary that has three primary functions: containment, transport of nutrients, and energy transduction.
- Biopolymers are synthesized in the container by linking together monomers—amino acids and nucleotides—using energy available in the environment. Polymer synthesis is the fundamental process leading to growth of a living system.
- Nucleic acids have a unique ability to store and transmit genetic information. Proteins called enzymes have a unique ability to act as catalysts that increase the rates of metabolic reactions.
- The genetic and catalytic polymers are incorporated into a cyclic feedback-controlled system in which information in the genetic polymers is used to direct the synthesis of the catalytic polymers, and the catalytic polymers take part in the synthesis of the genetic polymers.
- During growth, the cyclic system of polymers reproduces itself, and the cellular compartment divides.
- Reproduction is not perfect, so that variations arise, resulting in differences between cells in a population.
- Because different cells have varying capacities to grow and survive in a given environment, individual cells undergo selection according to their ability to compete for nutrients and energy. As a result, populations of cells have the capacity for evolution.

Given this list of properties, we can now test whether it can be used as a definition. There is no doubt that a claim of synthetic artificial life would be convincing if the system incorporated all the above properties. However, if the properties are deleted one by one, the definition becomes blurred and the claim weaker. Suppose the system reproduced perfectly so that evolution could not occur. Would it still be considered to be alive? Most would say yes, so the ability to evolve might not be an essential property of life. But consider another system in which all the nutrients required for growth were present in the medium so that no metabolism was required. This system would resemble a virus that requires the cytoplasm of living cells to reproduce. Viruses, however, can evolve, so they seem to exist in the border between life and non-life.

In a second test of a definition of life, imagine that a future Mars rover discovers what appears to be a frozen pond at the bottom of a crater. The rover has been designed so that it can melt some of the ice and examine the resulting liquid with a microscope. Surprisingly, large numbers of tiny spherical structures can be seen in the images sent back to Earth. Are the particles a form of microbial life? How many of the properties in the above list would need to be confirmed to convince skeptics that life exists on Mars? Can a robotic Mars lander be developed that has the ability to test all the properties? If we are to design such a lander, a definition of life is clearly desirable in order to guide the choices of instrument packages on board.

As an approach to answering such challenging questions, we invited three authors to explore a variety of ways to define life. Mark Bedau is a professor of Humanities and Philosophy at Reed College, Antonio Lazcano is Professor in the School of Sciences at the National Autonomous University of Mexico, and Steven Benner is the director of the Foundation for Applied Molecular Evolution in Gainesville, Florida. Professor Lazcano invited two colleagues, Stephane Tirard and Michel Morange, to join him in writing his essay. Some representative publications of the authors are listed in the references below.

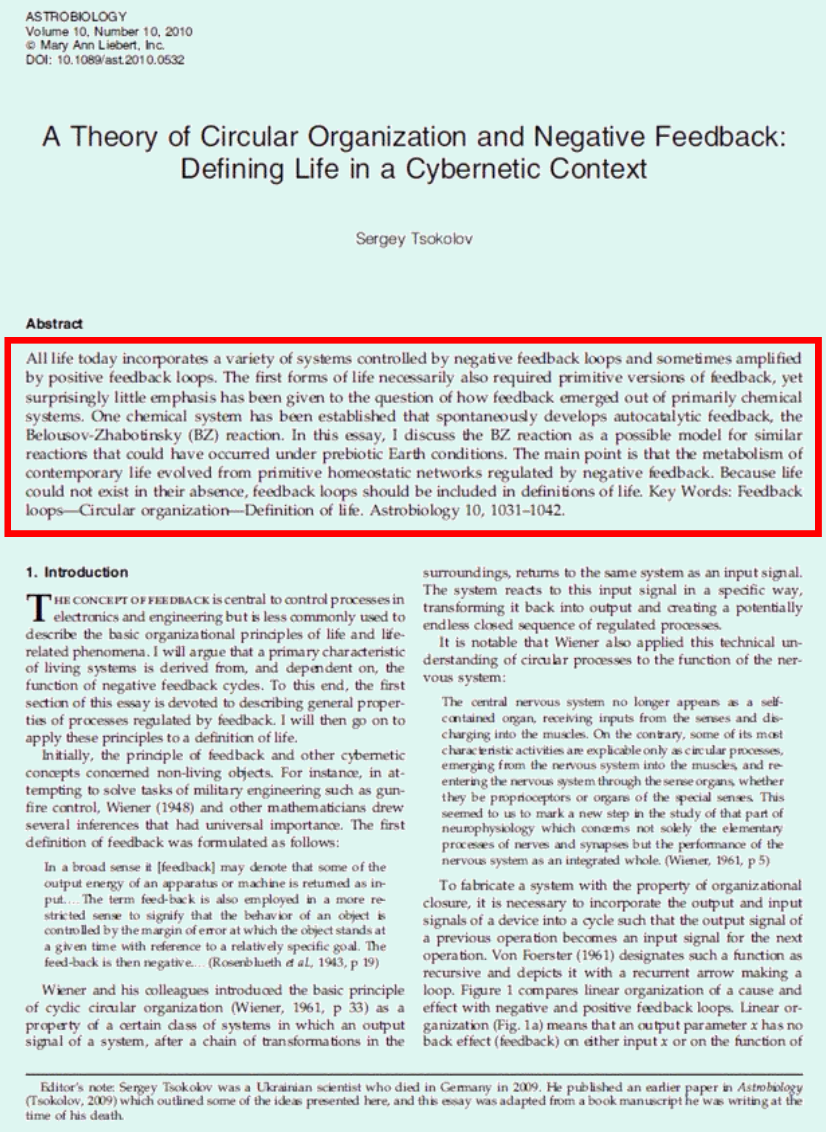
A fourth author, Sergey Tsokolov, was a Ukrainian scientist who died in Germany in 2009. He published an earlier paper in *Astrobiology* (Tsokolov, 2009), which outlined some of the ideas presented here. His essay was adapted from a book manuscript he was writing at the time of his death.

—David Deamer, Research Professor of Biomolecular Engineering, University of California, Santa Cruz.

Representative Publications of the Authors

Bedau, M.A. and Cleland, C.E. (2010) *The Nature of Life: Classical and Contemporary Perspectives from Philosophy and Science*, Cambridge University Press, Cambridge.

Department of Chemistry and Biochemistry, University of California, Santa Cruz, California.



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A Theory of Circular Organization and Negative Feedback: Defining Life in a Cybernetic Context

Sergey Tsokolov

Abstract

All life today incorporates a variety of systems controlled by negative feedback loops and sometimes amplified by positive feedback loops. The first forms of life necessarily also required primitive versions of feedback, yet surprisingly little emphasis has been given to the question of how feedback emerged out of primarily chemical systems. One chemical system has been established that spontaneously develops autocatalytic feedback, the Belousov-Zhabotinsky (BZ) reaction. In this essay, I discuss the BZ reaction as a possible model for similar reactions that could have occurred under prebiotic Earth conditions. The main point is that the metabolism of contemporary life evolved from primitive homeostatic networks regulated by negative feedback. Because life could not exist in their absence, feedback loops should be included in definitions of life. Key Words: Feedback loops—Circular organization—Definition of life. Astrobiology 10, 1031–1042.

1. Introduction

THE CONCEPT OF FEEDBACK is central to control processes in electronics and engineering but is less commonly used to describe the basic organizational principles of life and life-related phenomena. I will argue that a primary characteristic of living systems is derived from, and dependent on, the function of negative feedback cycles. To this end, the first section of this essay is devoted to describing general properties of processes regulated by feedback. I will then go on to apply these principles to a definition of life.

Initially, the principle of feedback and other cybernetic concepts concerned non-living objects. For instance, in attempting to solve tasks of military engineering such as gunfire control, Wiener (1948) and other mathematicians drew several inferences that had universal importance. The first definition of feedback was formulated as follows:

> In a broad sense it [feedback] may denote that some of the output energy of an apparatus or machine is returned as input.… The term feed-back is also employed in a more restricted sense to signify that the behavior of an object is controlled by the margin of error at which the object stands at a given time with reference to a relatively specific goal. The feed-back is then negative.… (Rosenblueth *et al.*, 1943, p 19)

Wiener and his colleagues introduced the basic principle of cyclic circular organization (Wiener, 1961, p 33) as a property of a certain class of systems in which an output signal of a system, after a chain of transformations in the surroundings, returns to the same system as an input signal. The system reacts to this input signal in a specific way, transforming it back into output and creating a potentially endless closed sequence of regulated processes.

It is notable that Wiener also applied this technical understanding of circular processes to the function of the nervous system:

> The central nervous system no longer appears as a self-contained organ, receiving inputs from the senses and discharging into the muscles. On the contrary, some of its most characteristic activities are explicable only as circular processes, emerging from the nervous system into the muscles, and re-entering the nervous system through the sense organs, whether they be proprioceptors or organs of the special senses. This seemed to us to mark a new step in the study of that part of neurophysiology which concerns not solely the elementary processes of nerves and synapses but the performance of the nervous system as an integrated whole. (Wiener, 1961, p 5)

To fabricate a system with the property of organizational closure, it is necessary to incorporate the output and input signals of a device into a cycle such that the output signal of a previous operation becomes an input signal for the next operation. Von Foerster (1961) designates such a function as recursive and depicts it with a recurrent arrow making a loop. Figure 1 compares linear organization of a cause and effect with negative and positive feedback loops. Linear organization (Fig. 1a) means that an output parameter x has no back effect (feedback) on either input x or on the function of

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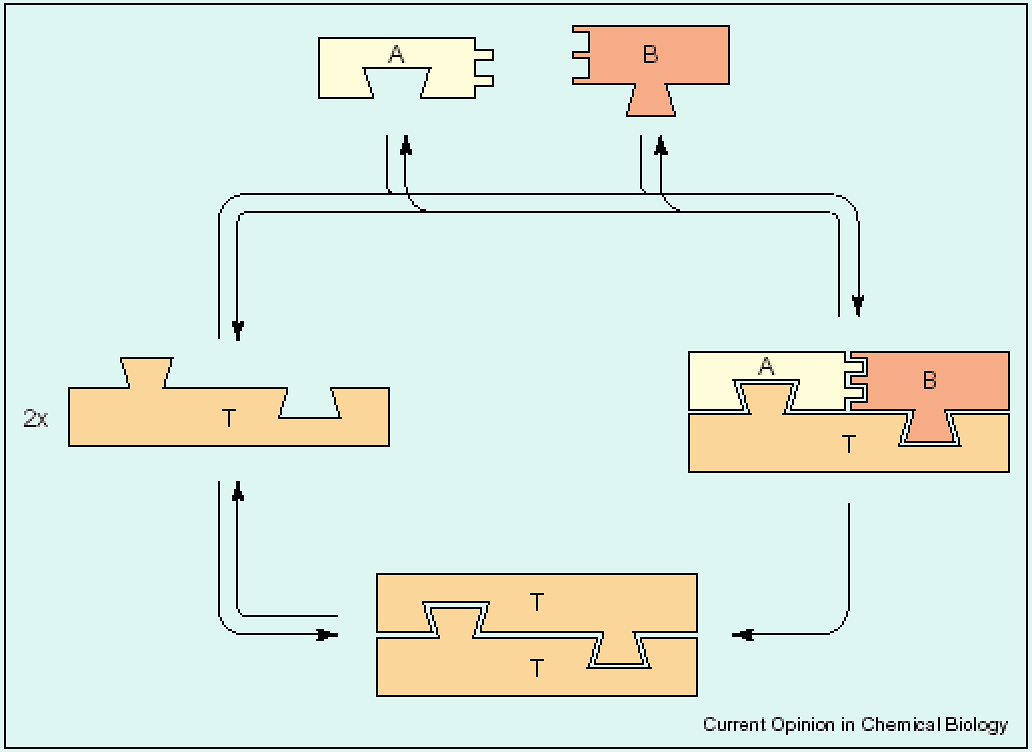
Editor's note: Sergey Tsokolov was a Ukrainian scientist who died in Germany in 2009. He published an earlier paper in *Astrobiology* (Tsokolov, 2009) which outlined some of the ideas presented here, and this essay was adapted from a book manuscript he was writing at the time of his death.

Minimal Self Replication

Figure 1



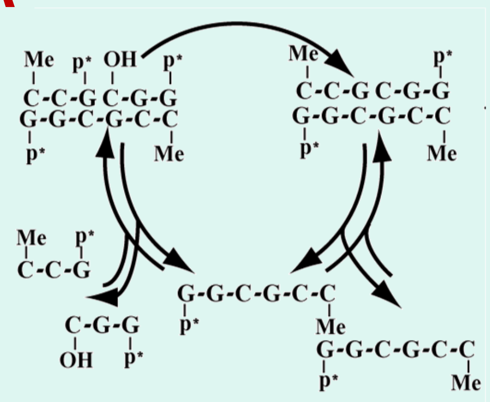
Current Opinion in Chemical Biology

Minimal self-replicating system. The template (**T**) binds two substrates (**A** and **B**), which become joined to form another copy of **T**. Following dissociation of the template–product complex, each copy of **T** can enter another replication cycle.

N. Paul, G. F. Joyce, Current Opinion in Chemical Biology 8, 634 (2004)

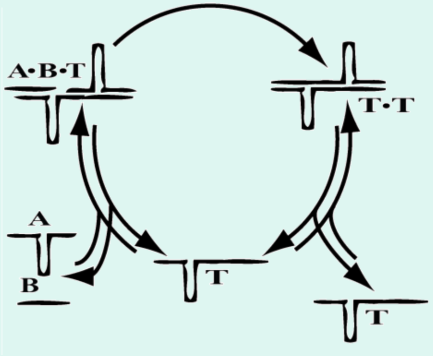
Minimal Self Replication

DNA



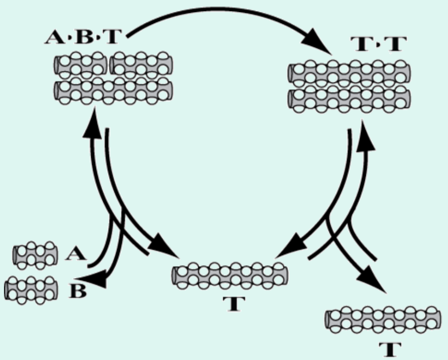
von Kiedrowski

RNA



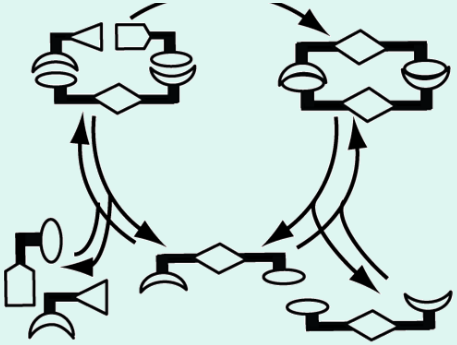
Paul & Joyce

Peptides



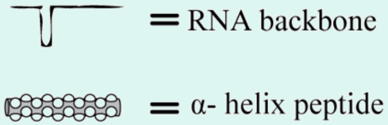
Ghadiri et al
Chmielewski et al
Ashkenasy et al

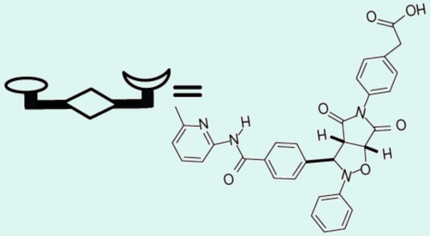
Organic Molecules



Rebek et al

Philp et al

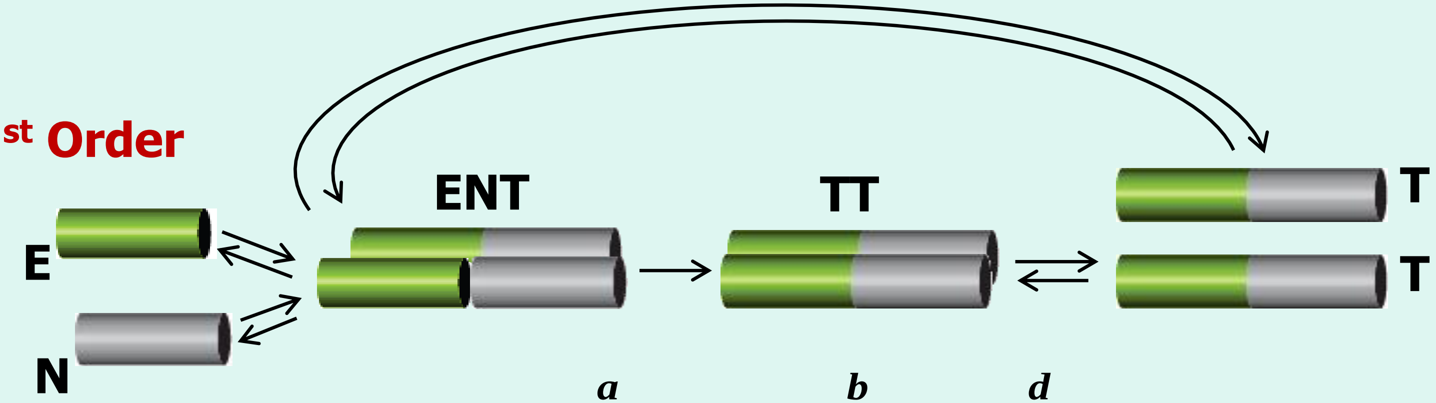




Dadon, Wagner & Ashkenasy, *Agnew Chem* (2008)

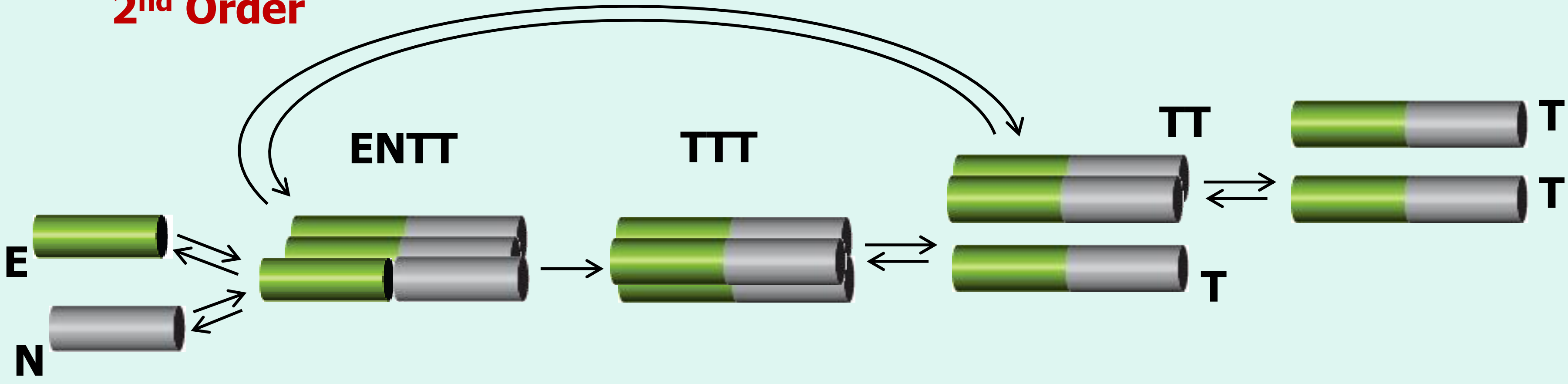
Minimal Self Replication

1st Order



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

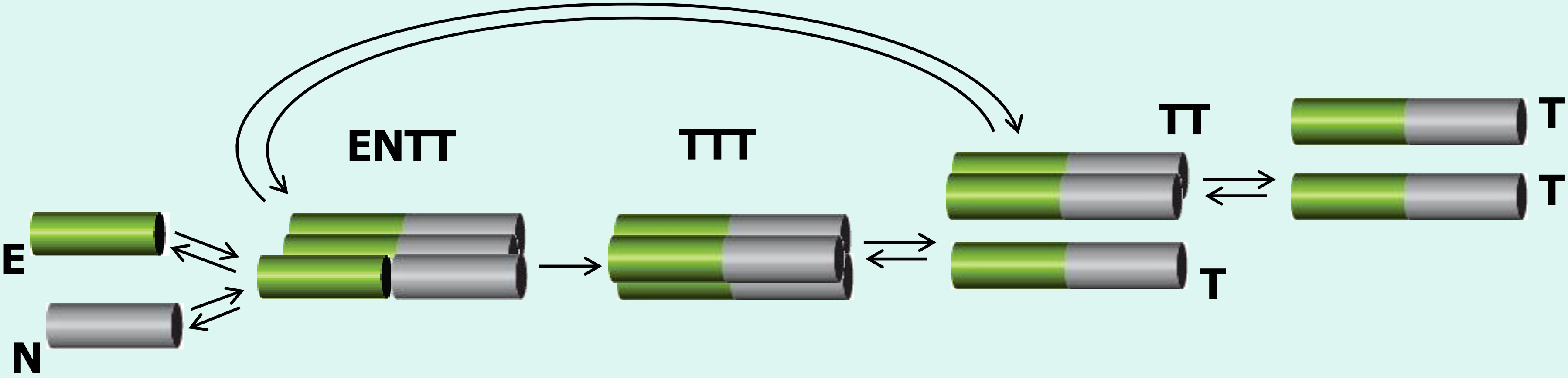
2nd Order



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

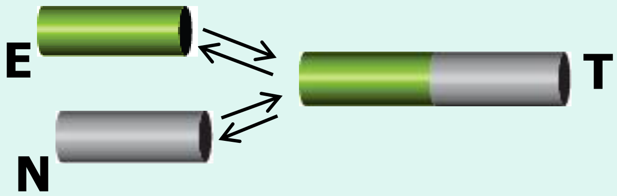
Wagner & Ashkenasy, *J Chem Phys* (2009)

Reversible Catalysis



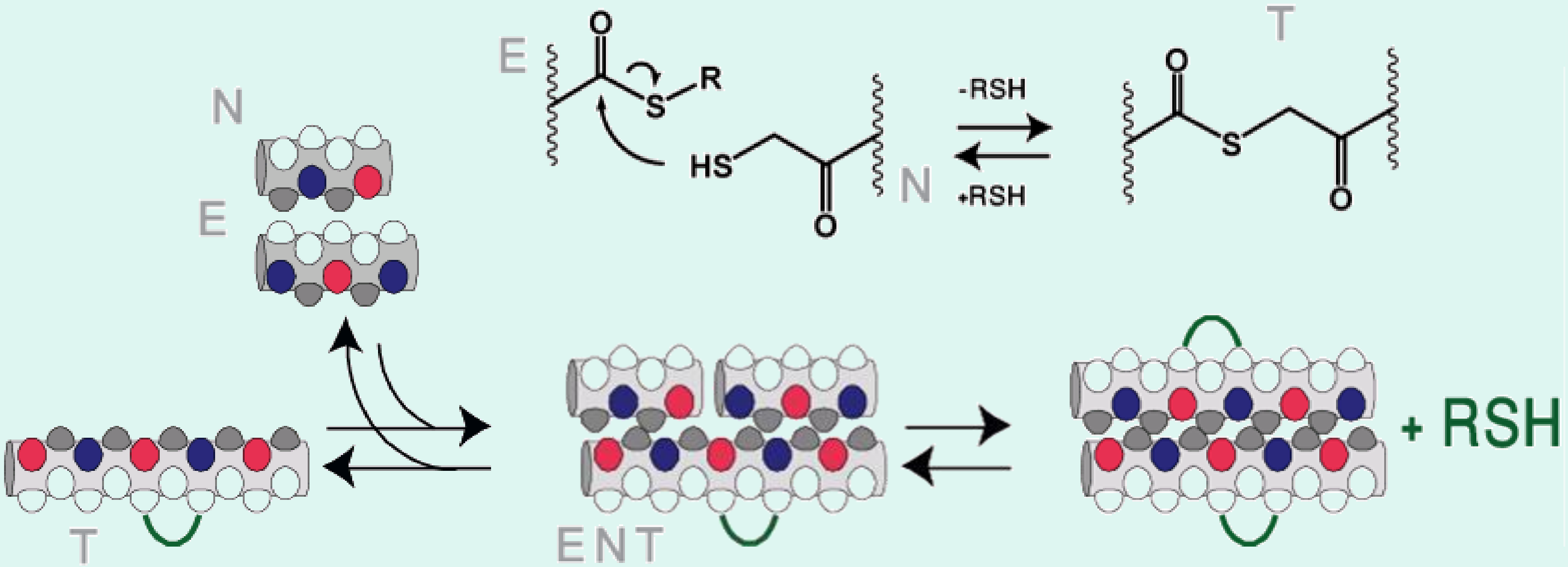
Catalysis:

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



Reversible Background: $E + N \underset{<g>}{\overset{g}{\rightleftarrows}} T + S$

Reversible Catalysis



Coiled-Coil Peptides: Amide Bond → Thioester Bond

Mathematical Analysis of the Reversible Catalytic System

$$\bar{E} + N + \bar{T}\bar{T} \underset{\langle a\rangle}{\overset{a}{\rightleftarrows}} \bar{E}N\bar{T}\bar{T} \xrightarrow{b} \bar{T}\bar{T}\bar{T} + S \underset{\langle f\rangle}{\overset{f}{\rightleftarrows}} \bar{T} + \bar{T}\bar{T} + S \underset{\langle d\rangle}{\overset{d}{\rightleftarrows}} \bar{T} + \bar{T} + \bar{T} + S \qquad \bar{E} + N \underset{\langle g\rangle}{\overset{g}{\rightleftarrows}} \bar{T} + S$$

If we assume that the reversible non-ligation reactions reach equilibrium faster than the ligation reactions (see, e.g., von Kiedrowski, Wills, Stadler, Severin, and also simulation results), then the intermediates *TT, TTT,* and *ENTT* will rapidly reach their relative equilibrium values (which actually vary with the progress of the ligation):

ENTT at equilibrium $\Rightarrow a[E][N][TT] = \left(\langle a\rangle + b\right)[ENTT] \Rightarrow \boxed{[ENTT] = \frac{a}{\langle a\rangle + b}[E][N][TT]}$

TTT at equilibrium$\Rightarrow b[ENTT] + \langle f\rangle[T][TT] = f[TTT] \Rightarrow \boxed{[TTT] = \frac{b[ENTT] + \langle f\rangle[T][TT]}{f}}$

TT at equilibrium $\Rightarrow \langle a\rangle[ENTT] + f[TTT] + \langle d\rangle[T]^2 = a[E][N][TT] + \langle f\rangle[T][TT] + d[TT]$

Replacing *f* [*TTT*] yields: $\left(\langle a\rangle + b\right)[ENTT] + \langle d\rangle[T]^2 = a[E][N][TT] + d[TT]$

Now replacing (<*a*>+*b*) [*ENTT*] : $\langle d\rangle[T]^2 = d[TT] \Rightarrow \boxed{[TT] = [T]^2/\tilde{d}} \qquad \tilde{d} = d/\langle d\rangle$

The rate of production of total template *t* per time τ is due only to the ligation:

$$\frac{d[t]}{d\tau} = g[E][N] - \langle g\rangle[T][S] + b[ENTT] \approx g[E][N] - \langle g\rangle[T][S] + c[E][N][T]^2 \quad , \quad c = \frac{ab/\tilde{d}}{\langle a\rangle + b}$$

Ligation will reach final equilibrium when $\frac{d[t]}{d\tau} = 0 \quad \Rightarrow \boxed{gE_1N_1 - \langle g\rangle T_1S_1 + cE_1N_1T_1^2 = 0}$

Equilibrium solution for one template with autocatalysis

The **total** concentrations: $[e]=[E]+[ENTT] \quad [n]=[N]+[ENTT] \quad [t]=[T]+2[TT]+2[ENTT]+3[TTT]$

Assume low intermediate concentrations of *ENTT* and *TTT* as a first approximation:

$$[E]\approx[e] \qquad [N]\approx[n] \qquad [T]\approx[t]-2[TT]=[t]-2[T]^2/\tilde{d} \quad \Rightarrow \quad [T]=\frac{-1\pm\sqrt{1+8[t]/\tilde{d}}}{4/\tilde{d}}=\frac{1}{4}\left(\sqrt{\tilde{d}^2+8\tilde{d}[t]}-\tilde{d}\right)$$

Iterative solution: $[TT]=[T]^2\big/\tilde{d} \qquad [ENTT]=\dfrac{a}{\langle a\rangle+b}[E][N][TT] \qquad [TTT]=\dfrac{b[ENTT]+\langle f\rangle[T][TT]}{f}$

$$[E]\approx[e]-[ENTT] \quad [N]\approx[n]-[ENTT] \quad [T]=\frac{1}{4}\left(\sqrt{\tilde{d}^2+8\tilde{d}\left([t]-2[ENTT]-3[TTT]\right)}-\tilde{d}\right)$$

The approach to equilibrium can be described by:

$$[e]\approx[E]\Rightarrow\Delta E=\Delta e \qquad [n]\approx[N]\Rightarrow\Delta N=\Delta n \qquad [T]\approx\frac{1}{4}\left(\sqrt{\tilde{d}^2+8\tilde{d}[t]}-\tilde{d}\right)\Rightarrow\Delta T=\frac{\Delta t}{\sqrt{1+8[t]/\tilde{d}}}=\theta\,\Delta t$$

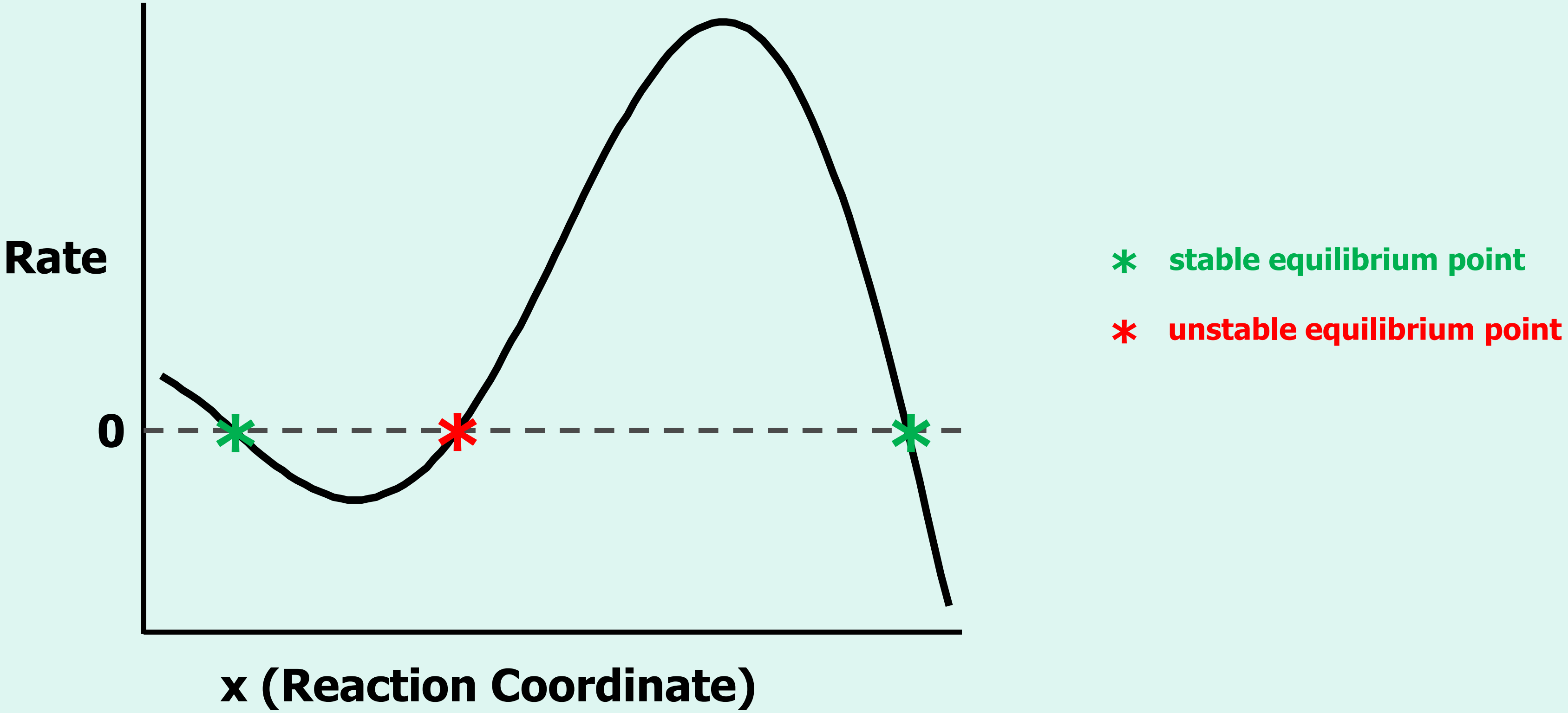
One Reaction Coordinate: $x=\Delta t=\Delta S=-\Delta e=-\Delta n \qquad \dfrac{d[t]}{d\tau}=J\,x \qquad J=\dfrac{\partial}{\partial[t]}\left(\dfrac{d[t]}{d\tau}\right)$

$$-J=g\left(E_1+N_1\right)+c\left(E_1+N_1\right)T_1^2+\langle g\rangle T_1+\theta\left(\langle g\rangle S_1-2cE_1N_1T_1\right) \qquad \theta=\frac{1}{\sqrt{1+8t_1/\tilde{d}}}$$

$$\frac{d[\Delta t]}{d\tau}=J\,d[t]\Rightarrow\frac{d[\Delta t]}{\Delta t}=J\,d\tau\Rightarrow\Delta t=(\Delta t)_0\,e^{J\tau}$$

In order for the equilibrium point to be stable,
the Jacobian must be negative.

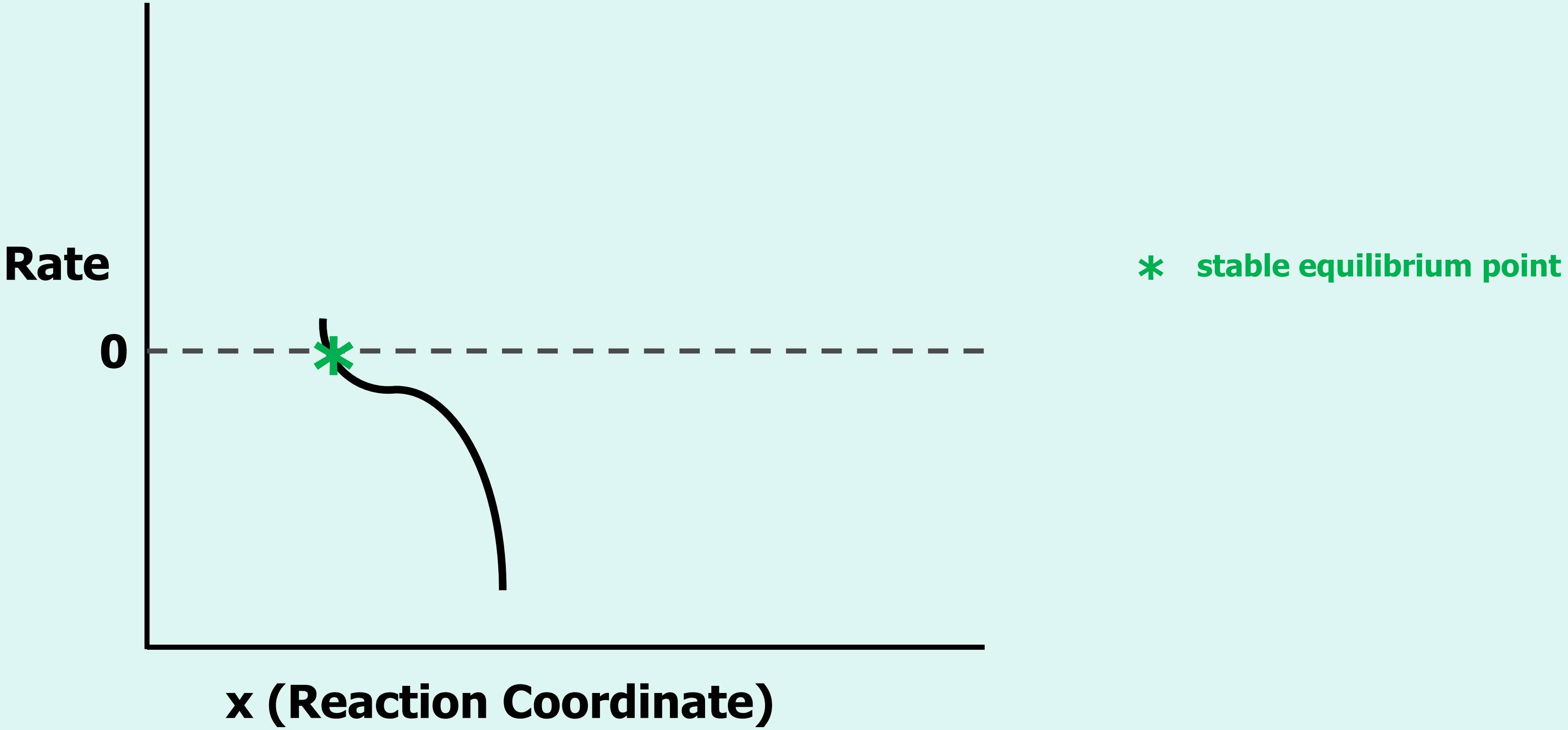
Bistability



Total Material: T + E = T + N = 100 μM

Wagner, Mukherjee, Maity, Peacock-Lopez & Ashkenasy, *Chem Phys Chem* (2017)

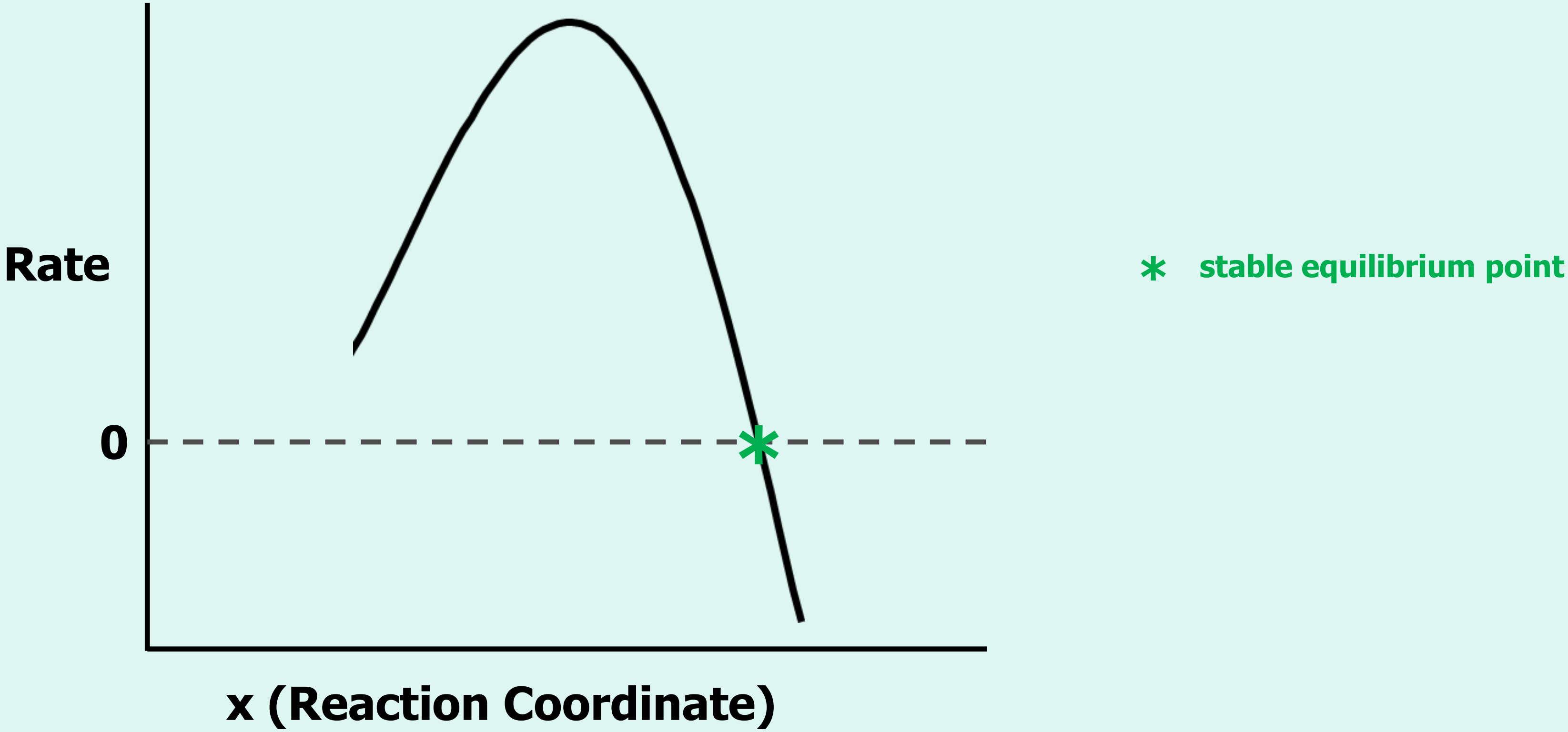
No Bistability



Total Material: T + E = T + N = 50 μM

Wagner, Mukherjee, Maity, Peacock-Lopez & Ashkenasy, *Chem Phys Chem* (2017)

No Bistability

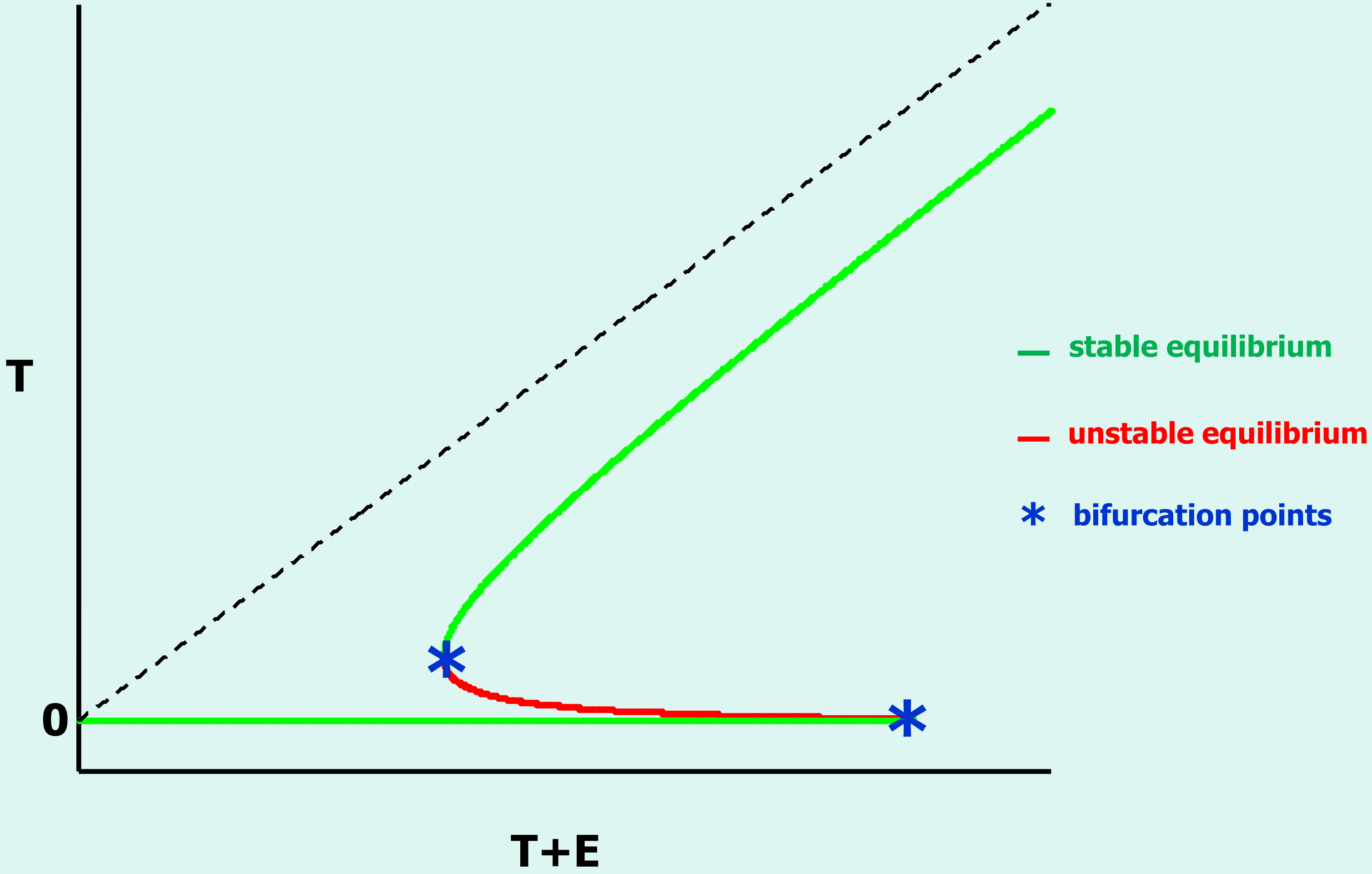


Total Material: T + E = T + N = 200 μM

Wagner, Mukherjee, Maity, Peacock-Lopez & Ashkenasy, *Chem Phys Chem* (2017)

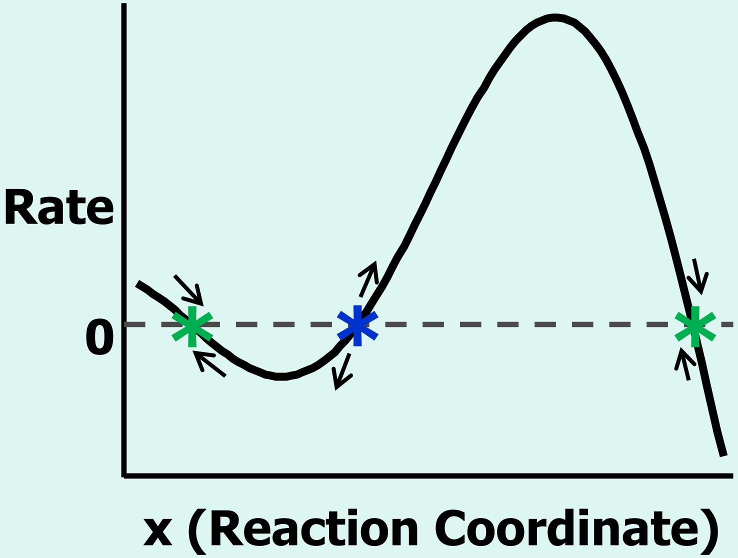
Bifurcation Diagram

Equilibrium Solutions vs. Total Material



Mukherjee, Cohen-Luria, Wagner & Ashkenasy, *Agnew Chem* (2015)

Stability of Equilibrium Solution



Jacobian: $J = \dfrac{d\,Rate}{d\,x}$

$$\frac{d[\Delta t]}{d\tau} = J\,d[t] \Rightarrow \frac{d[\Delta t]}{\Delta t} = J\,d\tau \Rightarrow \Delta t = (\Delta t)_0\,e^{J\tau}$$

$J < 0 \Rightarrow$ **stable equilibrium point**

$J > 0 \Rightarrow$ **unstable equilibrium point**

$$[t] = t_0 + x\,,\ [S] = S_0 + x \approx S_0\,,\ [e] = e_0 - x\,,\ [n] = n_0 - x\,;$$

$$Rate = \dot{t} = \frac{d[t]}{d\tau} = g[E][N] - \langle g\rangle [T][S] = g(E_0 - x)^2 - \langle g\rangle S_0 (T_0 + x) = gx^2 - 2gE_0x - \langle g\rangle S_0 x$$

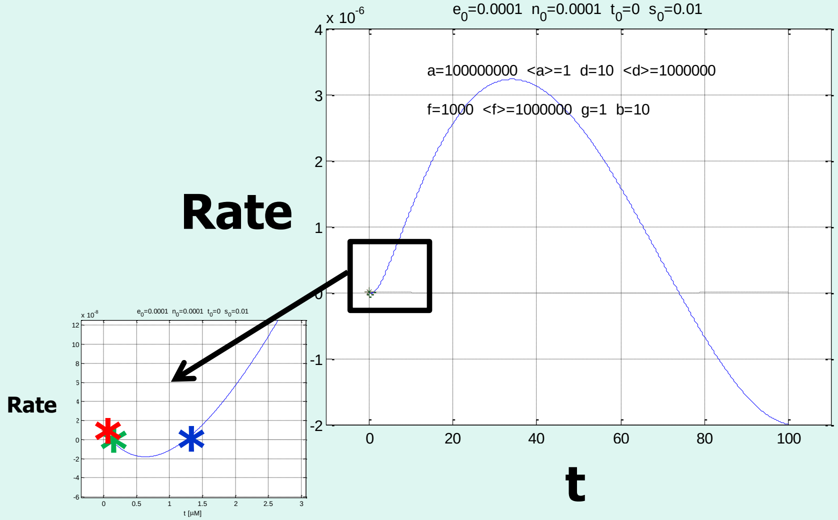
$$J = \frac{d\dot{t}}{dx} = 2gx - 2gE_0 - \langle g\rangle S_0$$

At equilibrium $x = 0 \Rightarrow J = -2gE_0 - \langle g\rangle S_0 < 0 \Rightarrow$ **Stable equilibrium**

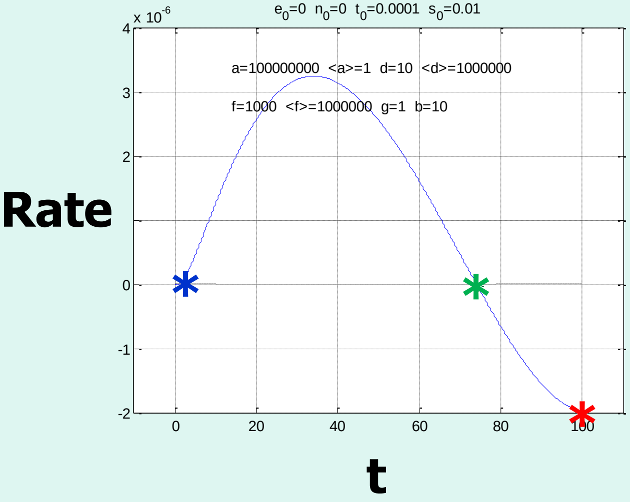
$t + e = t + n = 100\ \mu M << S$

* initial point   * final point   * critical point

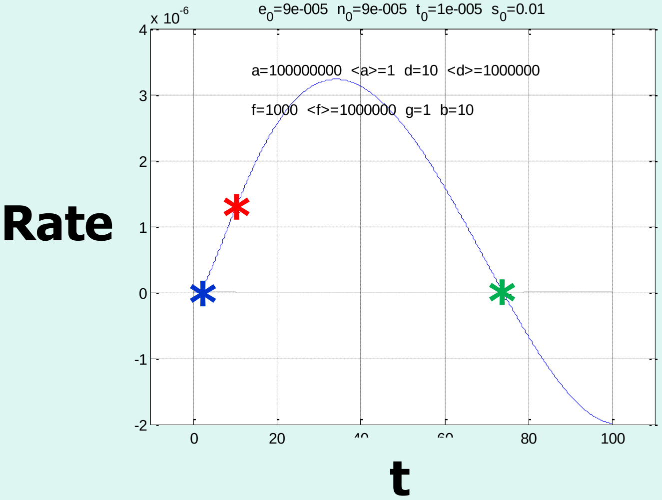
$t_{init} = 0$ $e_{init} = n_{init} = 100\ \mu M$



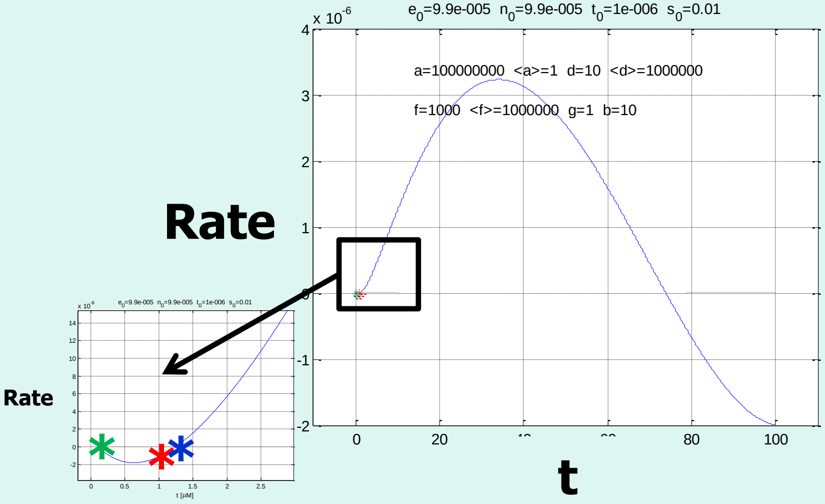
$t_{init} = 100\ \mu M$ $e_{init} = n_{init} = 0$



$t_{init} = 10\ \mu M$ $e_{init} = n_{init} = 90\ \mu M$



$t_{init} = 1\ \mu M$ $e_{init} = n_{init} = 99\ \mu M$



One template with autocatalysis

$$\frac{d[t]}{d\tau} = g[E][N] - \langle g\rangle[T][S] + b[ENTT] \approx g[E][N] - \langle g\rangle[T][S] + c[E][N][T]^2 \quad , \quad c = \frac{ab/\tilde{d}}{\langle a\rangle + b}, \quad \tilde{d} = d/\langle d\rangle$$

High solution: $t \gg \tilde{d}$

$$gEN - \langle g\rangle ST + cENT^2 \approx -\langle g\rangle ST + cENT^2 = 0 \qquad T = \frac{\sqrt{\tilde{d}^2 + 8\tilde{d}t} - \tilde{d}}{4} \approx \frac{\sqrt{8\tilde{d}t}}{4} \qquad E = N = A - t$$

$$\langle g\rangle ST = cENT^2 \Rightarrow (A-t)^2 \frac{\sqrt{8\tilde{d}t}}{4} = \frac{<g>S}{c} \Rightarrow (A-t)^2\sqrt{t} = \frac{4<g>S}{\sqrt{8\tilde{d}}\,c} \equiv K \Rightarrow \boxed{(A-t)^4 t = K^2}$$

Only one high solution $\Rightarrow K^2$ meets $(A-t)^4 t$ at its maximum

Maximum of $(A-t)^4 t \Rightarrow \frac{\partial (A-t)^4 t}{\partial t} = (A-t)^4 - 4t(A-t)^3 = 0 \Rightarrow (A-t) = 4t \Rightarrow t = A/5$

$$(A - A/5)^4 (A/5) \ge K^2 \Rightarrow (256/3125)(A)^5 \ge K^2 \Rightarrow \boxed{A \ge 1.65K^{2/5}}$$

Low solution: $t \ll \tilde{d}$

$$\sqrt{\tilde{d}^2 + 8\tilde{d}t} = \sqrt{\tilde{d}^2\left(1+\frac{8t}{\tilde{d}}\right)} = \tilde{d}\left(1+8\frac{t}{\tilde{d}}\right)^{1/2} \approx \tilde{d}\left(1+\frac{4t}{\tilde{d}}\right) = \tilde{d} + 4t \Rightarrow T \approx t$$

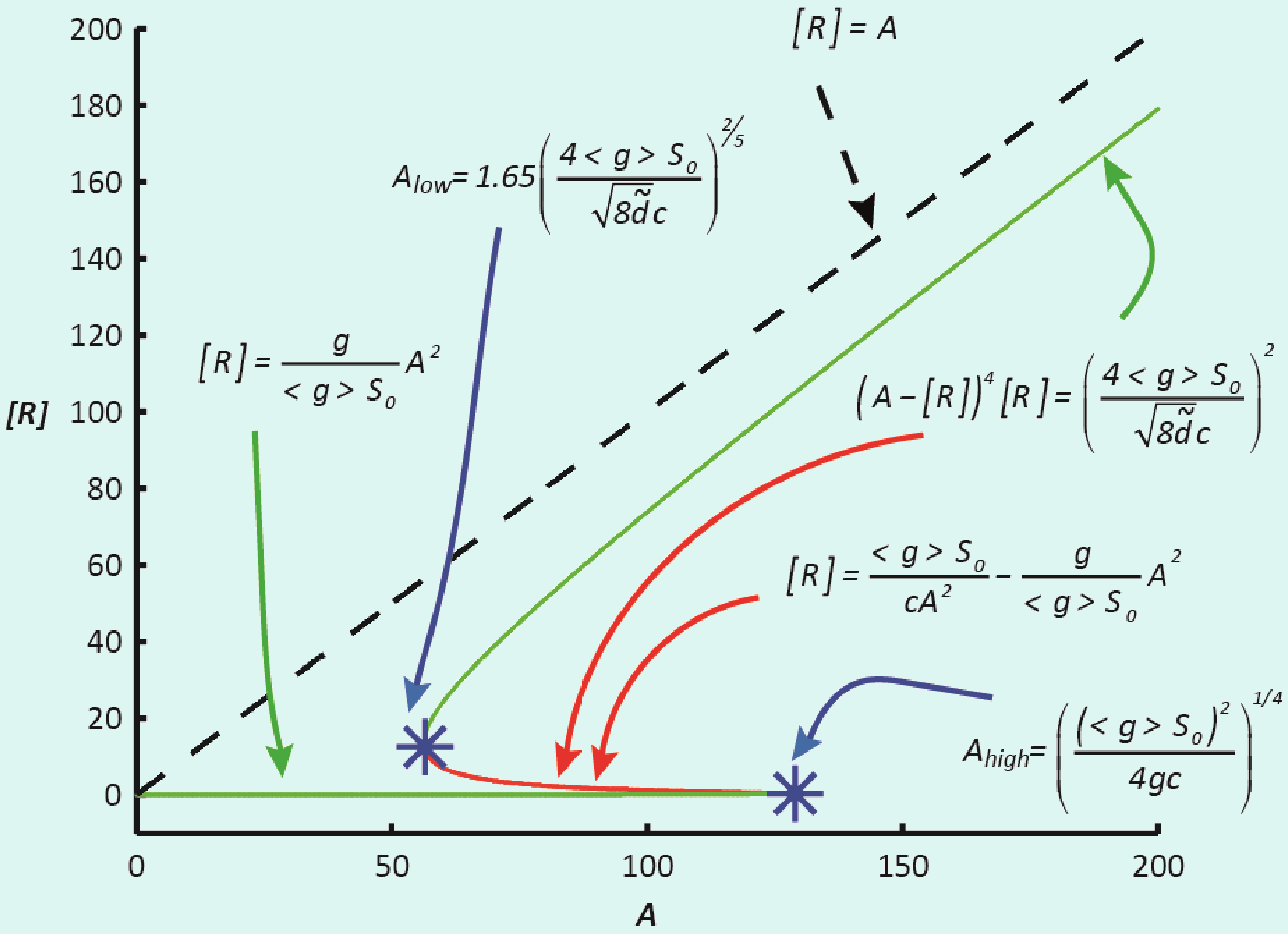
$$gEN - \langle g\rangle St + cENt^2 = 0 \Rightarrow g(A-t)^2 - <g>St + c(A-t)^2t^2 = 0 \qquad t \ll A \Rightarrow (A-t) \approx A \Rightarrow gA^2 - <g>St + cA^2t^2 = 0$$

$$\Rightarrow t = \frac{<g>S \pm \sqrt{(<g>S)^2 - 4gcA^4}}{2cA^2} = \frac{<g>S}{2cA^2}\left(1 \pm \sqrt{1 - \frac{4gcA^4}{(<g>S)^2}}\right) \approx \frac{<g>S}{2cA^2}\left(1 \pm \left(1 - \frac{2gcA^4}{(<g>S)^2}\right)\right) = \boxed{\begin{cases} \dfrac{<g>S}{cA^2} - \dfrac{g}{<g>S}A^2 \\ \dfrac{g}{<g>S}A^2 \end{cases}}$$

Real solution $\Rightarrow (<g>S)^2 - 4gcA^4 \ge 0 \Rightarrow A^4 \le \frac{(<g>S)^2}{4gc} \Rightarrow \boxed{A \le \left(\frac{(<g>S)^2}{4gc}\right)^{1/4}}$

Bifurcation Diagram

Equilibrium Solutions vs. Total Material



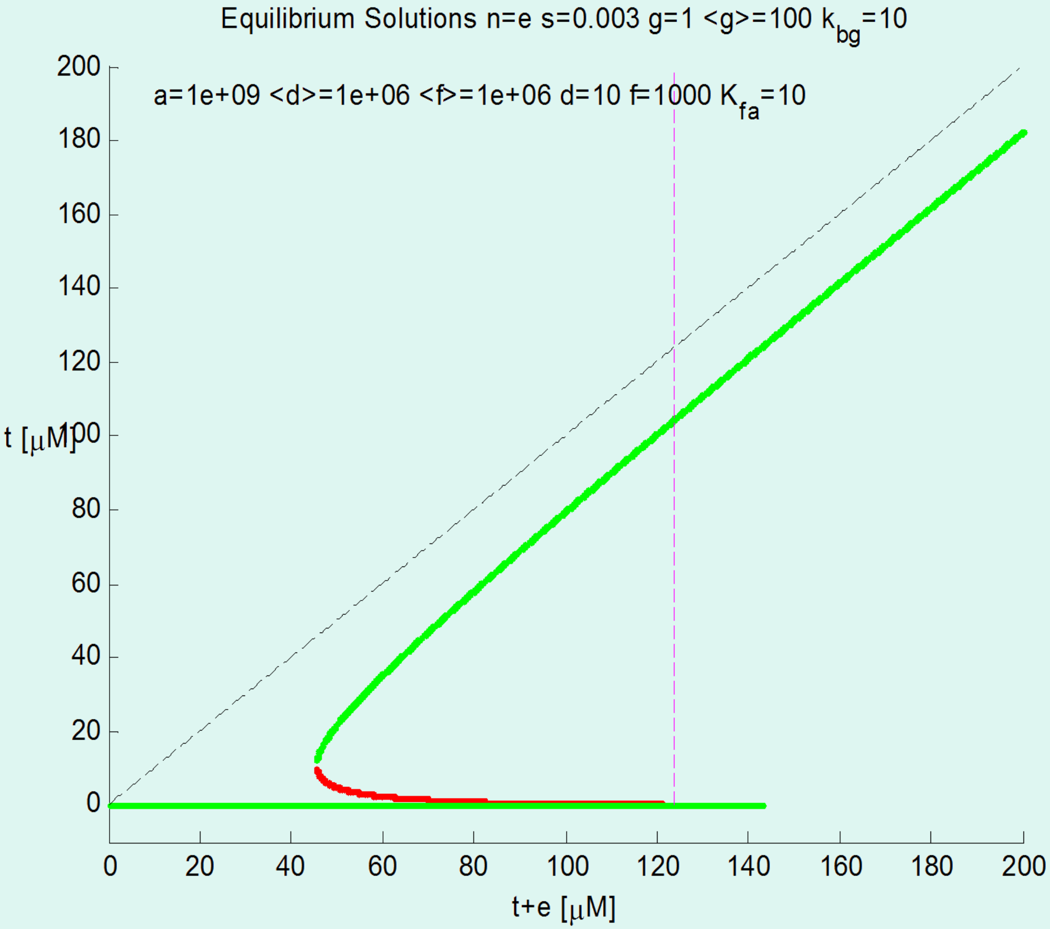
Wagner, Mukherjee, Maity, Peacock-Lopez & Ashkenasy, *Chem Phys Chem* (2017)

“Optimal”

$a = 1.e9$ $<d> = <f> = 1.e6$ $<a> = 10$ $d = 10$ $f = 1000$

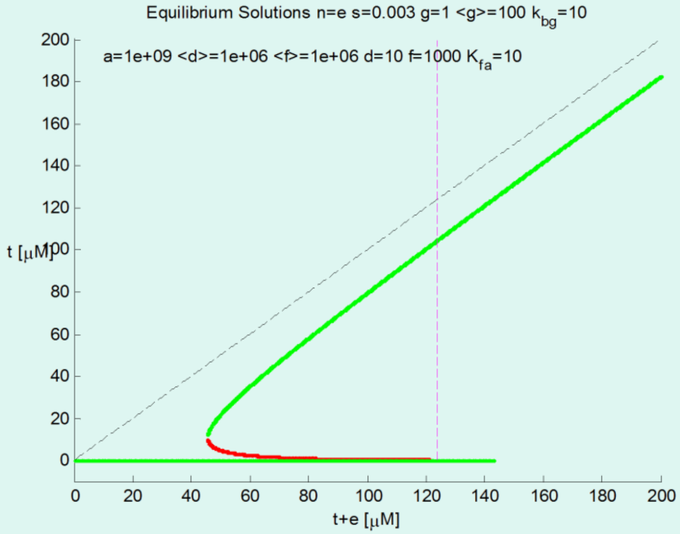
$g = 1$ $b = 10$ $<g> = 100$ $S = 3000\ \mu M$

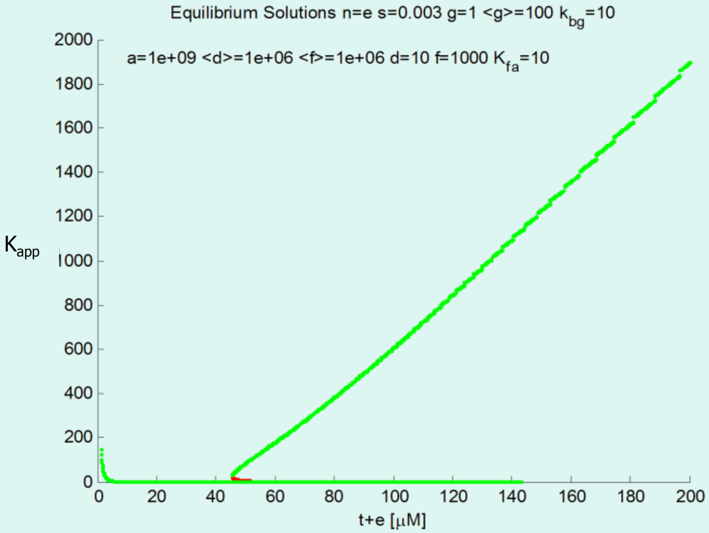
$A_{low} = 39$ $A_{high} = 146$



“Optimal”

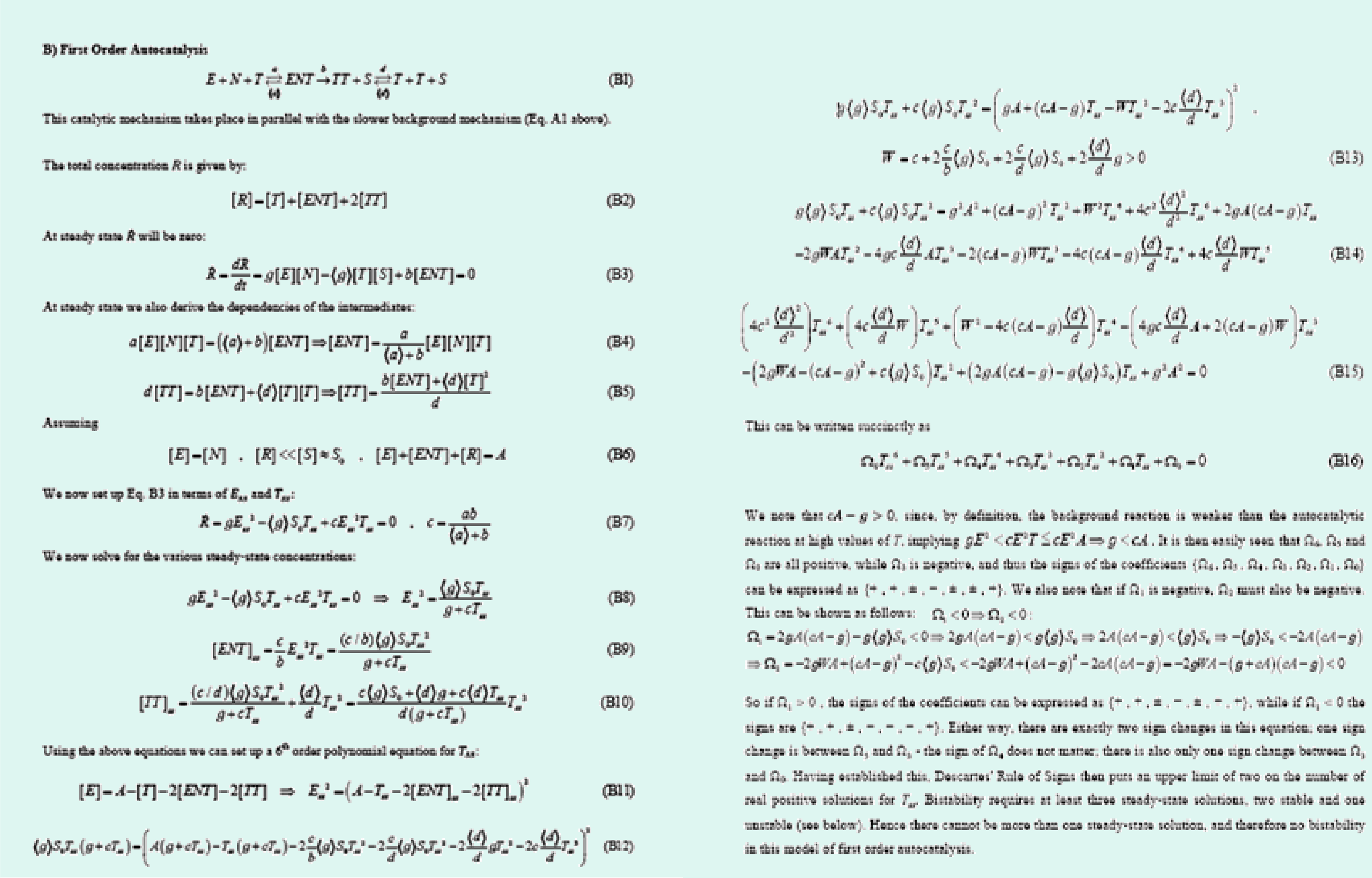
a = 1.e9 <d> = <f> = 1.e6 <a> = 10 d = 10 f = 1000
g = 1 b = 10 <g> = 100 S = 3000 μM
A_{low} = 39 A_{high} = 146





$$K_{app} = \frac{[T][S]}{[E][N]} = \frac{[R][S]}{[E][N]}$$

First Order Catalytic Systems Cannot Mathematically Display Bistability



B) First Order Autocatalysis:

$$E+N+T \underset{(a)}{\overset{a}{\rightleftharpoons}} ENT \xrightarrow{b} TT+S \underset{(d)}{\overset{d}{\rightleftharpoons}} T+T+S \qquad \text{(B1)}$$

This catalytic mechanism takes place in parallel with the slower background mechanism (Eq. A1 above).

The total concentration R is given by:

$$[R]=[T]+[ENT]+2[TT] \qquad \text{(B2)}$$

At steady state $\dot{R}$ will be zero:

$$\dot{R}=\frac{dR}{dt}=g[E][N]-(g)[T][S]+b[ENT]=0 \qquad \text{(B3)}$$

At steady state we also derive the dependencies of the intermediates:

$$a[E][N][T]=\left((a)+b\right)[ENT] \Rightarrow [ENT]=\frac{a}{(a)+b}[E][N][T] \qquad \text{(B4)}$$

$$d[TT]=b[ENT]+(d)[T][T] \Rightarrow [TT]=\frac{b[ENT]+(d)[T]^2}{d} \qquad \text{(B5)}$$

Assuming

$$[E]=[N] \quad , \quad [R]<<[S]\approx S_0 \quad , \quad [E]+[ENT]+[R]=A \qquad \text{(B6)}$$

We now set up Eq. B3 in terms of E_{ss} and T_{ss}:

$$\dot{R}=gE_{ss}{}^2-(g)S_0T_{ss}+cE_{ss}{}^2T_{ss}=0 \quad , \quad c=\frac{ab}{(a)+b} \qquad \text{(B7)}$$

We now solve for the various steady-state concentrations:

$$gE_{ss}{}^2-(g)S_0T_{ss}+cE_{ss}{}^2T_{ss}=0 \quad \Rightarrow \quad E_{ss}{}^2=\frac{(g)S_0T_{ss}}{g+cT_{ss}} \qquad \text{(B8)}$$

$$[ENT]_{ss}=\frac{c}{b}E_{ss}{}^2T_{ss}=\frac{(c/b)(g)S_0T_{ss}{}^2}{g+cT_{ss}} \qquad \text{(B9)}$$

$$[TT]_{ss}=\frac{(c/d)(g)S_0T_{ss}{}^2}{g+cT_{ss}}+\frac{(d)}{d}T_{ss}{}^2=\frac{c(g)S_0+(d)g+c(d)T_{ss}}{d(g+cT_{ss})}T_{ss}{}^2 \qquad \text{(B10)}$$

Using the above equations we can set up a 6th order polynomial equation for T_{SS}:

$$[E]=A-[T]-2[ENT]-2[TT] \quad \Rightarrow \quad E_{ss}{}^2=\left(A-T_{ss}-2[ENT]_{ss}-2[TT]_{ss}\right)^2 \qquad \text{(B11)}$$

$$(g)S_0T_{ss}(g+cT_{ss})=\left(A(g+cT_{ss})-T_{ss}(g+cT_{ss})-2\frac{c}{b}(g)S_0T_{ss}{}^2-2\frac{c}{d}(g)S_0T_{ss}{}^2-2\frac{(d)}{d}gT_{ss}{}^2-2c\frac{(d)}{d}T_{ss}{}^3\right)^2 \qquad \text{(B12)}$$

$$g(g)S_0T_{ss}+c(g)S_0T_{ss}{}^2=\left(gA+(cA-g)T_{ss}-WT_{ss}{}^2-2c\frac{(d)}{d}T_{ss}{}^3\right)^2 \quad ,$$

$$W=c+2\frac{c}{b}(g)S_0+2\frac{c}{d}(g)S_0+2\frac{(d)}{d}g>0 \qquad \text{(B13)}$$

$$g(g)S_0T_{ss}+c(g)S_0T_{ss}{}^2=g^2A^2+(cA-g)^2T_{ss}{}^2+W^2T_{ss}{}^4+4c^2\frac{(d)^2}{d^2}T_{ss}{}^6+2gA(cA-g)T_{ss}$$
$$-2gWAT_{ss}{}^2-4gc\frac{(d)}{d}AT_{ss}{}^3-2(cA-g)WT_{ss}{}^3-4c(cA-g)\frac{(d)}{d}T_{ss}{}^4+4c\frac{(d)}{d}WT_{ss}{}^5 \qquad \text{(B14)}$$

$$\left(4c^2\frac{(d)^2}{d^2}\right)T_{ss}{}^6+\left(4c\frac{(d)}{d}W\right)T_{ss}{}^5+\left(W^2-4c(cA-g)\frac{(d)}{d}\right)T_{ss}{}^4-\left(4gc\frac{(d)}{d}A+2(cA-g)W\right)T_{ss}{}^3$$
$$-\left(2gWA-(cA-g)^2+c(g)S_0\right)T_{ss}{}^2+\left(2gA(cA-g)-g(g)S_0\right)T_{ss}+g^2A^2=0 \qquad \text{(B15)}$$

This can be written succinctly as

$$\Omega_6T_{ss}{}^6+\Omega_5T_{ss}{}^5+\Omega_4T_{ss}{}^4+\Omega_3T_{ss}{}^3+\Omega_2T_{ss}{}^2+\Omega_1T_{ss}+\Omega_0=0 \qquad \text{(B16)}$$

We note that $cA-g>0$, since, by definition, the background reaction is weaker than the autocatalytic reaction at high values of T, implying $gE^2<cE^2T\leq cE^2A \Rightarrow g<cA$. It is then easily seen that Ω_6, Ω_5 and Ω_0 are all positive, while Ω_3 is negative, and thus the signs of the coefficients $\{\Omega_6, \Omega_5, \Omega_4, \Omega_3, \Omega_2, \Omega_1, \Omega_0\}$ can be expressed as $\{+,+,\pm,-,\pm,\pm,+\}$. We also note that if Ω_1 is negative, Ω_2 must also be negative. This can be shown as follows: $\Omega_1<0 \Rightarrow \Omega_2<0$:

$$\Omega_1=2gA(cA-g)-g(g)S_0<0 \Rightarrow 2gA(cA-g)<g(g)S_0 \Rightarrow 2A(cA-g)<(g)S_0 \Rightarrow -(g)S_0<-2A(cA-g)$$
$$\Rightarrow \Omega_2=-2gWA+(cA-g)^2-c(g)S_0<-2gWA+(cA-g)^2-2cA(cA-g)=-2gWA-(g+cA)(cA-g)<0$$

So if $\Omega_1>0$, the signs of the coefficients can be expressed as $\{+,+,\pm,-,\pm,-,+\}$, while if $\Omega_1<0$ the signs are $\{+,+,\pm,-,-,-,+\}$. Either way, there are exactly two sign changes in this equation; one sign change is between Ω_5 and Ω_3 - the sign of Ω_4 does not matter; there is also only one sign change between Ω_1 and Ω_0. Having established this, Descartes' Rule of Signs then puts an upper limit of two on the number of real positive solutions for T_{ss}. Bistability requires at least three steady-state solutions, two stable and one unstable (see below). Hence there cannot be more than one steady-state solution, and therefore no bistability in this model of first order autocatalysis.

Wagner, Mukherjee, Maity, Peacock-Lopez & Ashkenasy, *Chem Phys Chem* (2017)

nominal experimental conditions

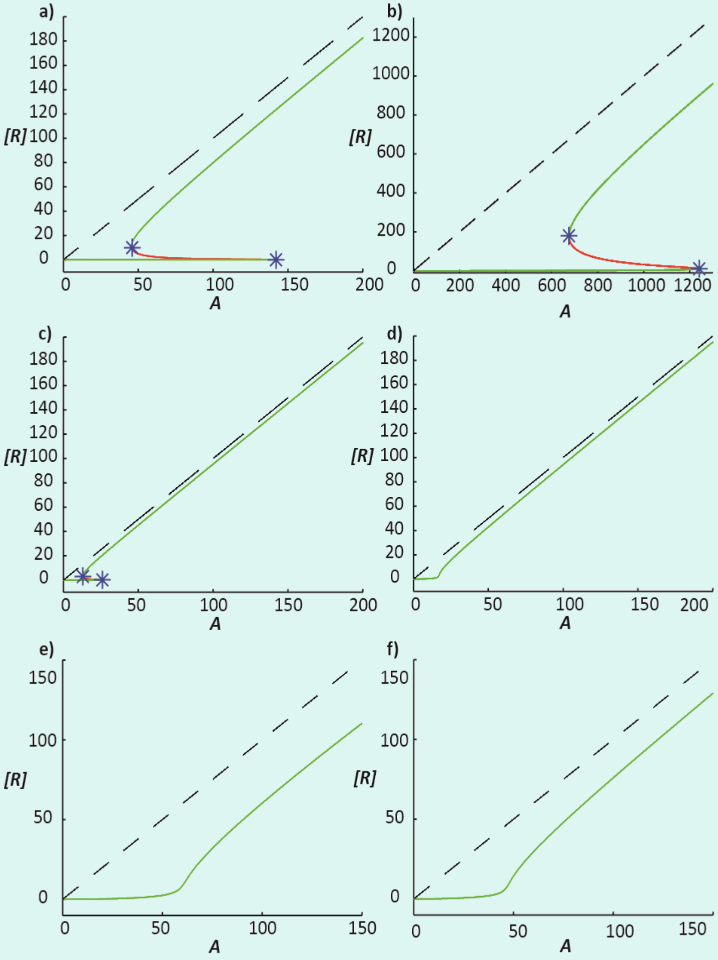
destabilizing unfolding conditions

very low S concentration

very strong background reaction

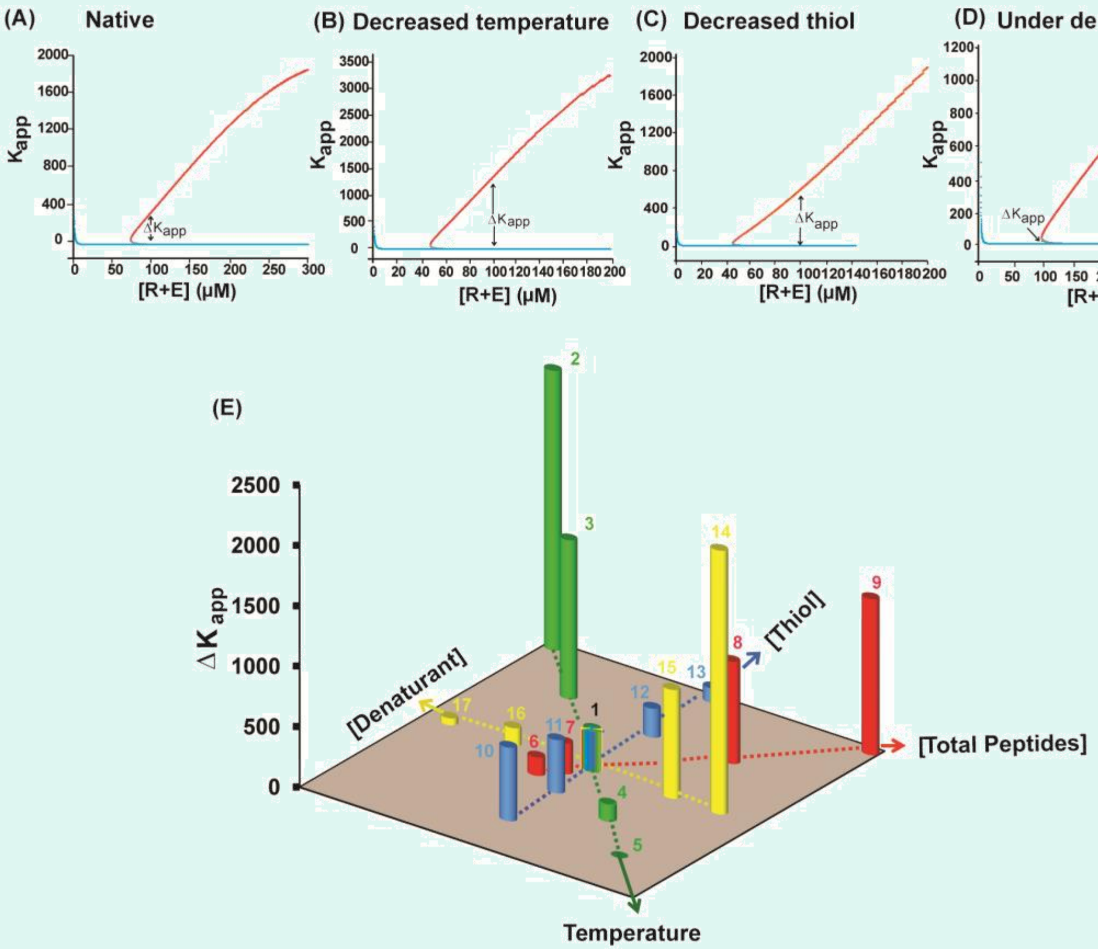
very weak catalytic ligation

very strong ligation



Numerically computed concentrations (and bifurcation diagrams) for various $A = B$ scenarios, displaying steady-state solutions (stable in green, unstable in red) as a function of A (μM). The dotted line corresponds to $[R] = A$, and the bifurcation points are shown with blue stars. a) using nominal experimental conditions, $a = 10^9$, $\langle d\rangle = \langle f\rangle = 10^6$, $\langle a\rangle = 10$, $d = 10$, $f = 1000$, $g = 1$, $b = 10$, $\langle g\rangle = 100$, $S_0 = 3000$ μM. b) like **a** but under destabilizing unfolding conditions, applying $\langle a\rangle = 1000$, $d = 1000$, $f = 10^5$; c) like **a** but with very low S concentration, $S_0 = 100$ μM; d) like **a** but with a very strong background reaction and a weaker reverse reaction, $g = 100$, $\langle g\rangle = 10$; e) like **a** but with very weak catalytic ligation, $g = 6$, $b = 0.06$, $\langle g\rangle = 1$, $S_0 = 10^4$ μM; f) using the standard parameters, but with very strong ligation, $g = 100$, $b = 1000$.

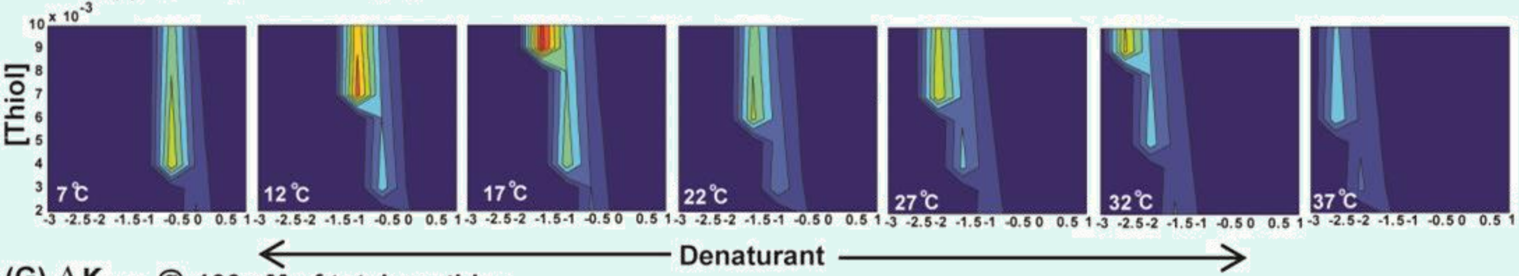
Wagner, Mukherjee, Maity, Peacock-Lopez & Ashkenasy, *Chem Phys Chem* (2017)



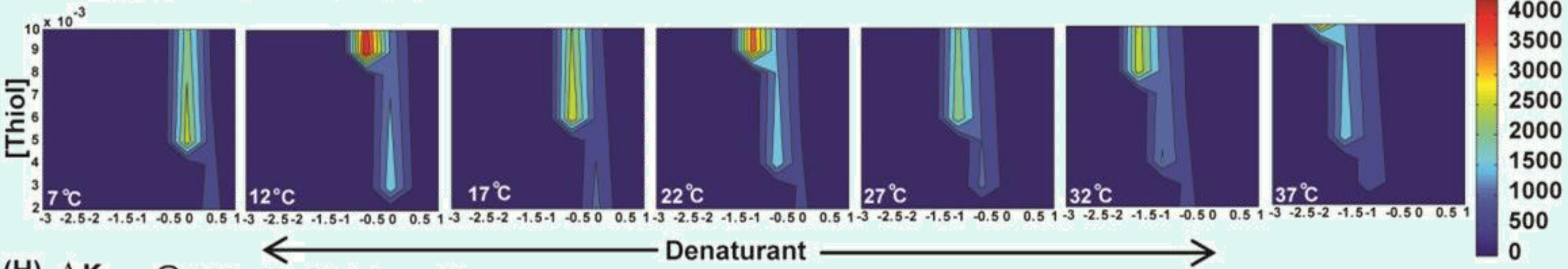
Normalized SS solutions for Kapp as a function of total peptide [R + E] concentration, computed numerically by zeroing the rate of product formation. In all cases, [E] = [N]. The ΔKapp value for each case is evaluated at 100 μM of total peptide concentration. The computed bistable picture at **(A)** native conditions and rate constants, corresponding to nominal experimental conditions: a = 10^9, <d> = <f>= 10^6, <a> = 10, d = 10, f = 1000, g = 1, b = 10, <g> = 100; **(B)** With decreased temperature at 12°C, corresponding to nominal experimental conditions: a = $0.97*10^9$, <d> = <f>= $0.97*10^6$, <a> = 5, d = 5, f = 500, g = 0.5, b = 5, <g> = 50; **(C)** With decreased thiol concentration of 3000 μM, corresponding to nominal experimental conditions: a = 10^9, <d> = <f>= 10^6, <a> = 10, d = 10, f = 1000, g = 1, b = 10, <g> = 100. **(D)** Under the denaturant conditions, corresponding to nominal experimental conditions: a = 10^9, <d> = <f>= 10^6, <a> = 19, d = 19, f = 1900, g = 1, b = 10, <g> = 100. **(E)** The (ΔK_{app}) as the function of various perturbations. ΔK_{app} values obtained from computation, highlighted as the function of temperature (*t*), concentration of total peptide (*m*), concentration of thiol (*s*) and factor of guanidine hydrochloride (*g*) along the green line, red line, blue line and yellow line.

Maity et al, *in preparation* (2018)

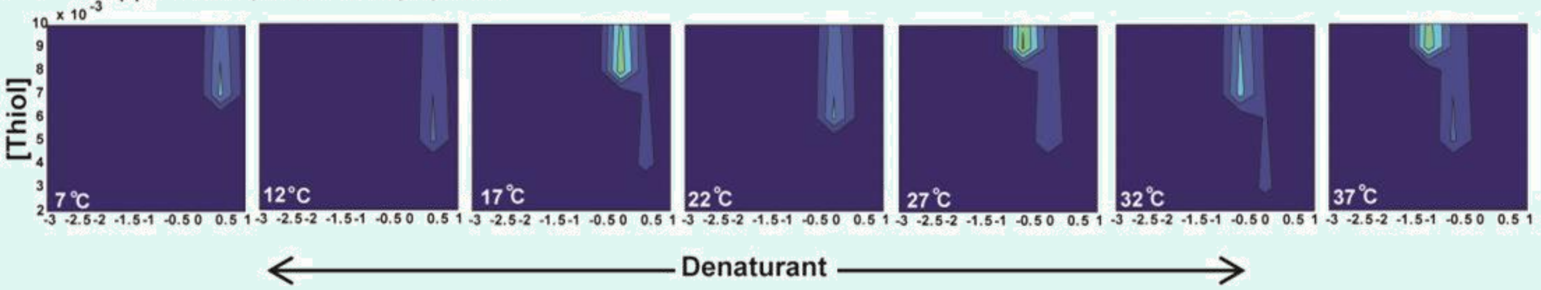
(F) ΔK_{app} @ 50 μM of total peptides



(G) ΔK_{app} @ 100 μM of total peptides



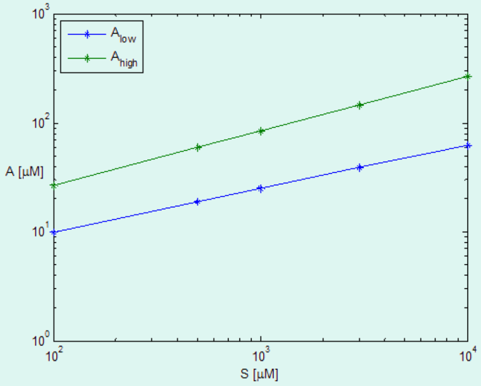
(H) ΔK_{app} @ 200 μM of total peptides

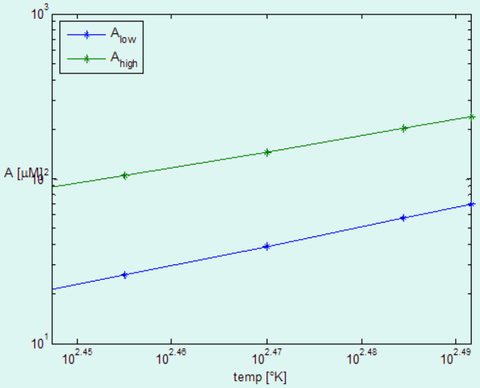


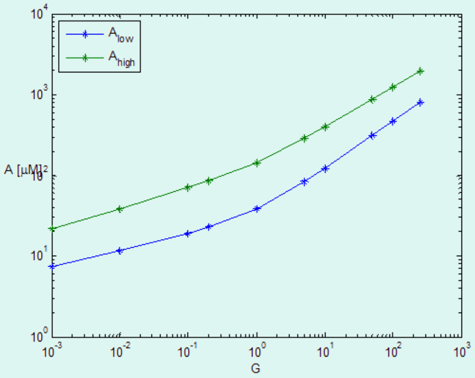
(F), (G) and **(H)** are the phase diagrams to locate the bistable zone with the degree of SS separation along all over the parameter spaces.

Maity et al, *in preparation* (2018)

Scaling Law







$$A_{low}, A_{high} \sim G^x T^y S^z$$

$$x \approx \tfrac{1}{3}, \quad y \approx 10, \quad z \approx \tfrac{1}{2}$$

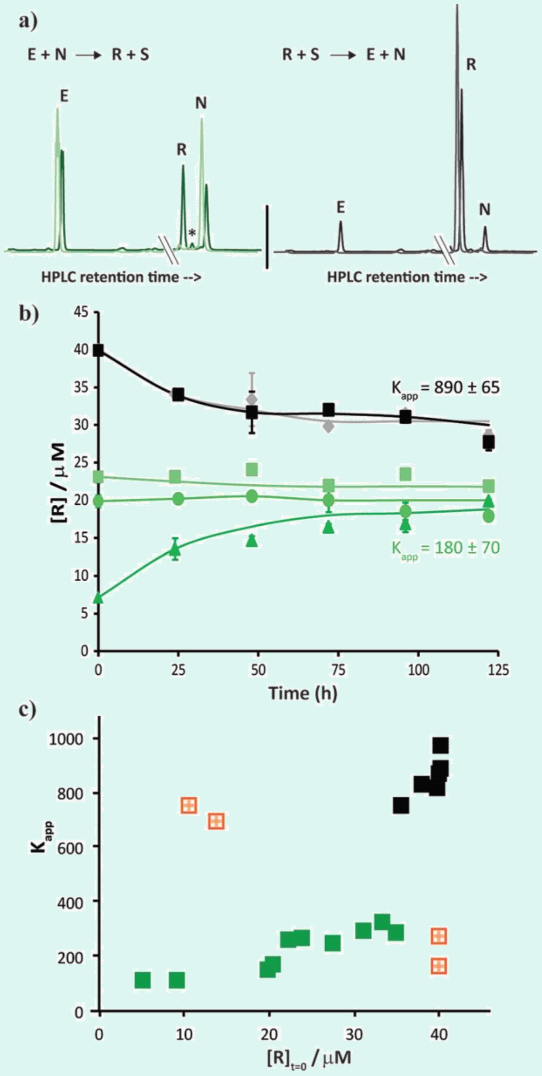
Maity et al, *in preparation* (2018)

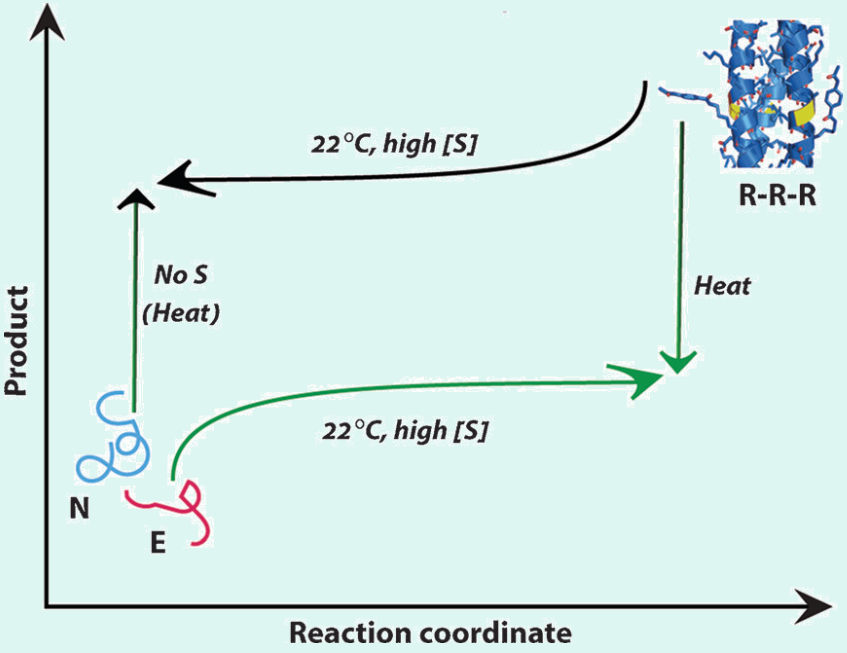
Conclusions

Bistability requires:

- ***At least second order catalysis***
- ***Feedback mechanism***
- ***Mismatch between forward and reverse processes***
- ***Balancing act among relevant parameters***

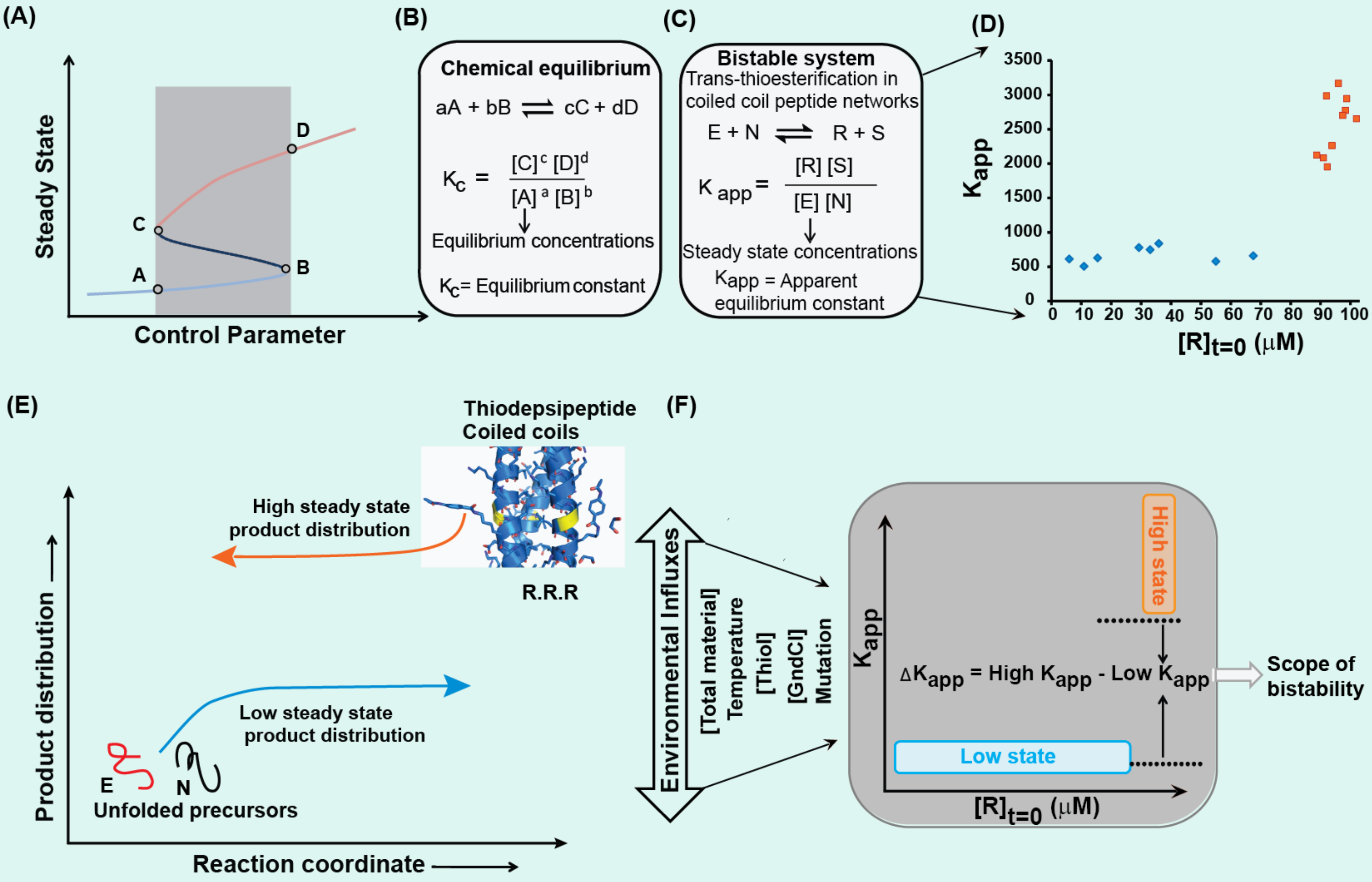
Experimental Results





Mukherjee, Cohen-Luria, Wagner & Ashkenasy, *Agnew Chem* (2015)

Experimental Results



(B)

Chemical equilibrium

$aA + bB \rightleftharpoons cC + dD$

$$K_c = \frac{[C]^c [D]^d}{[A]^a [B]^b}$$

↓

Equilibrium concentrations

K_c = Equilibrium constant

(C)

Bistable system

Trans-thioesterification in coiled coil peptide networks

$E + N \rightleftharpoons R + S$

$$K_{app} = \frac{[R]\,[S]}{[E]\,[N]}$$

↓

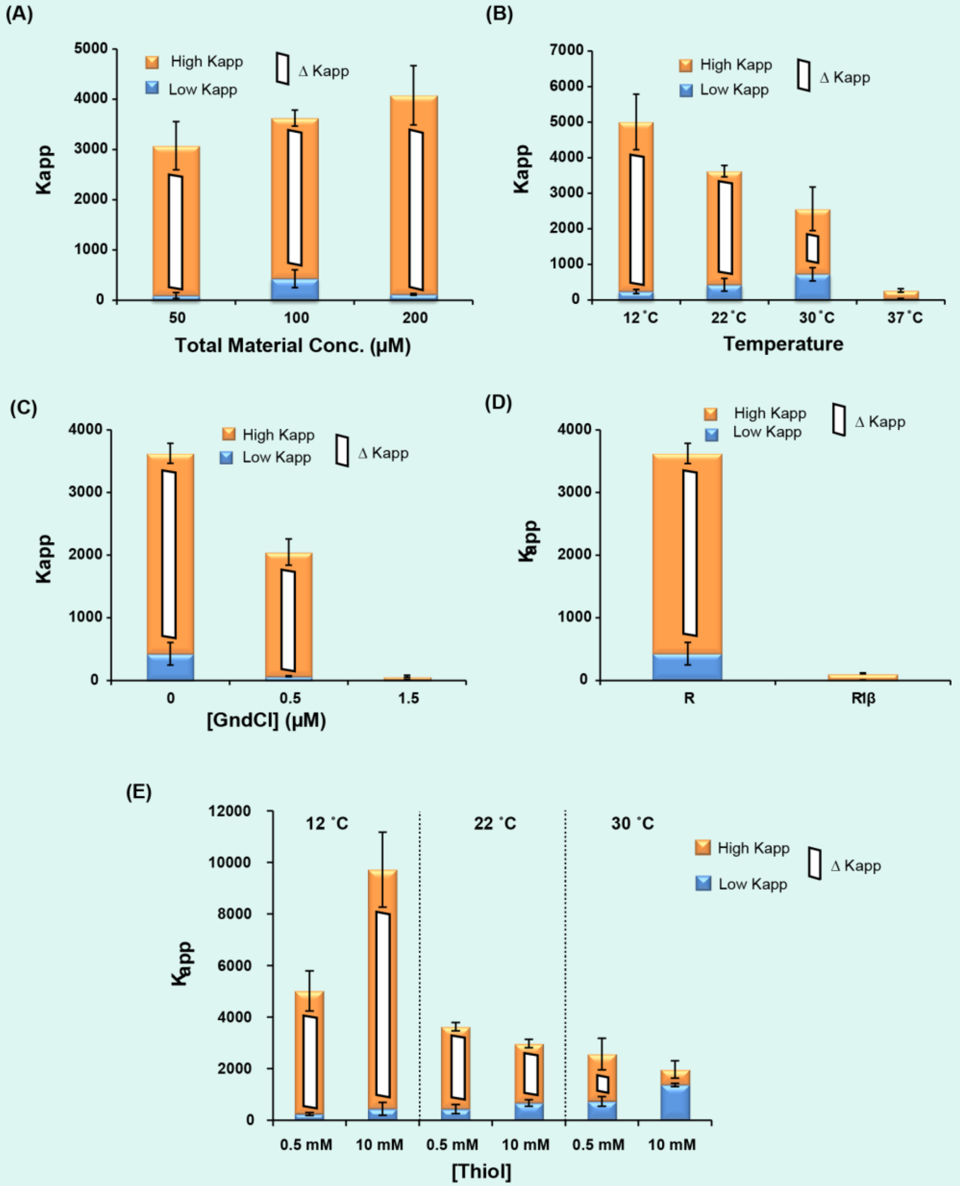
Steady state concentrations

K_{app} = Apparent equilibrium constant

ΔK_{app} = High K_{app} - Low K_{app}

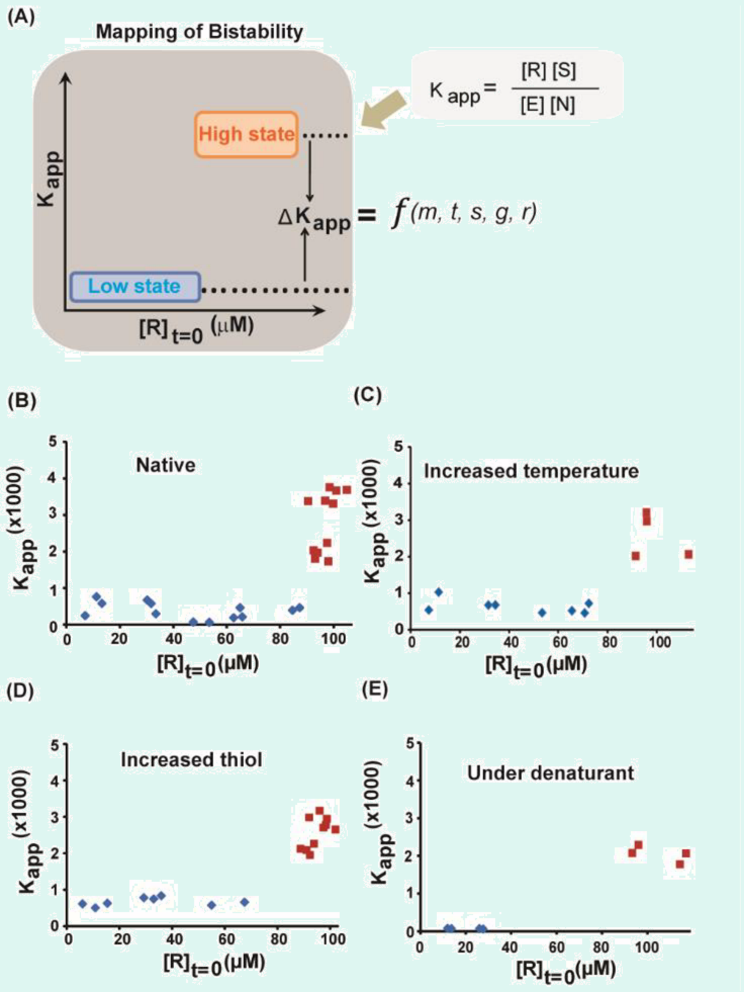
Maity et al, *in preparation* (2018)

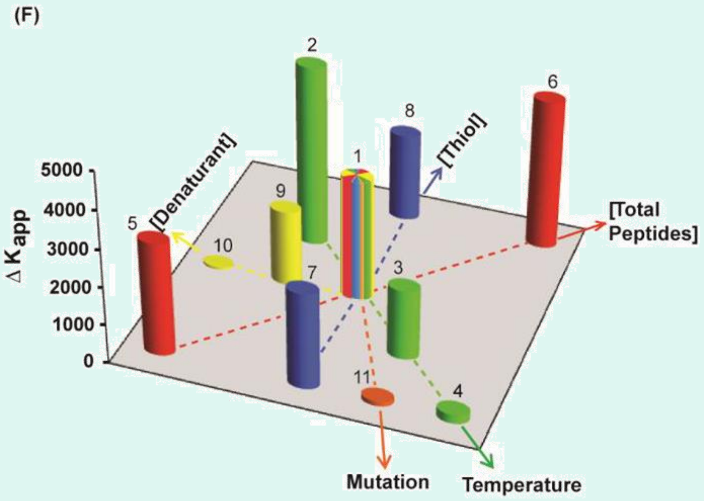
Experimental Results



Maity et al, *in preparation* (2018)

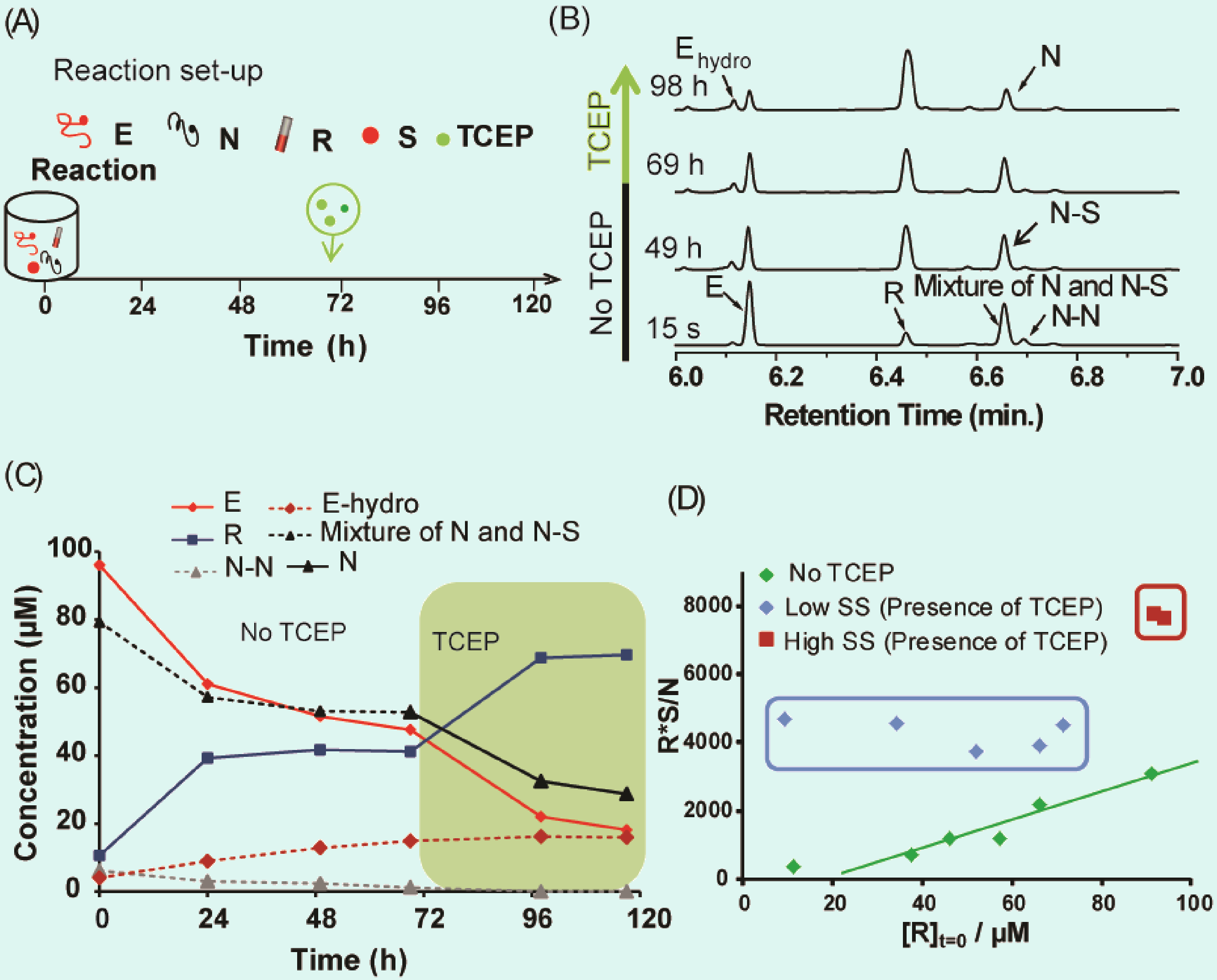
Experimental Results





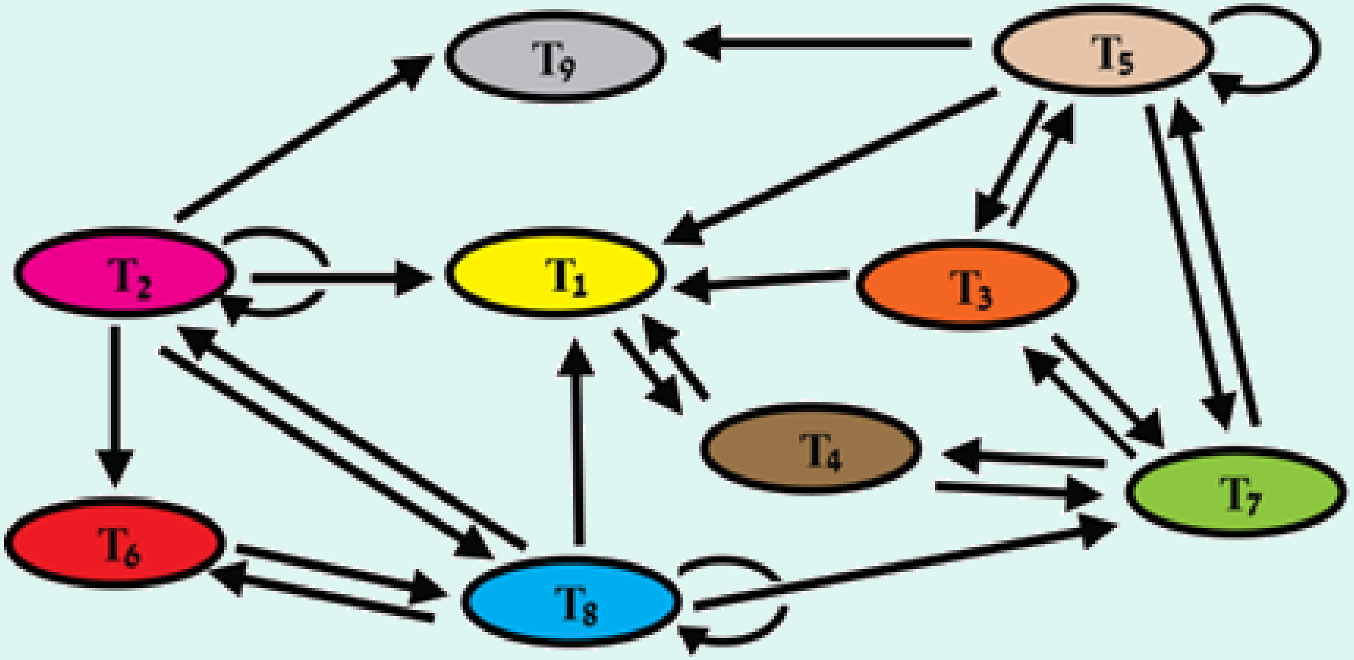
Maity et al, *in preparation* (2018)

Experimental Results

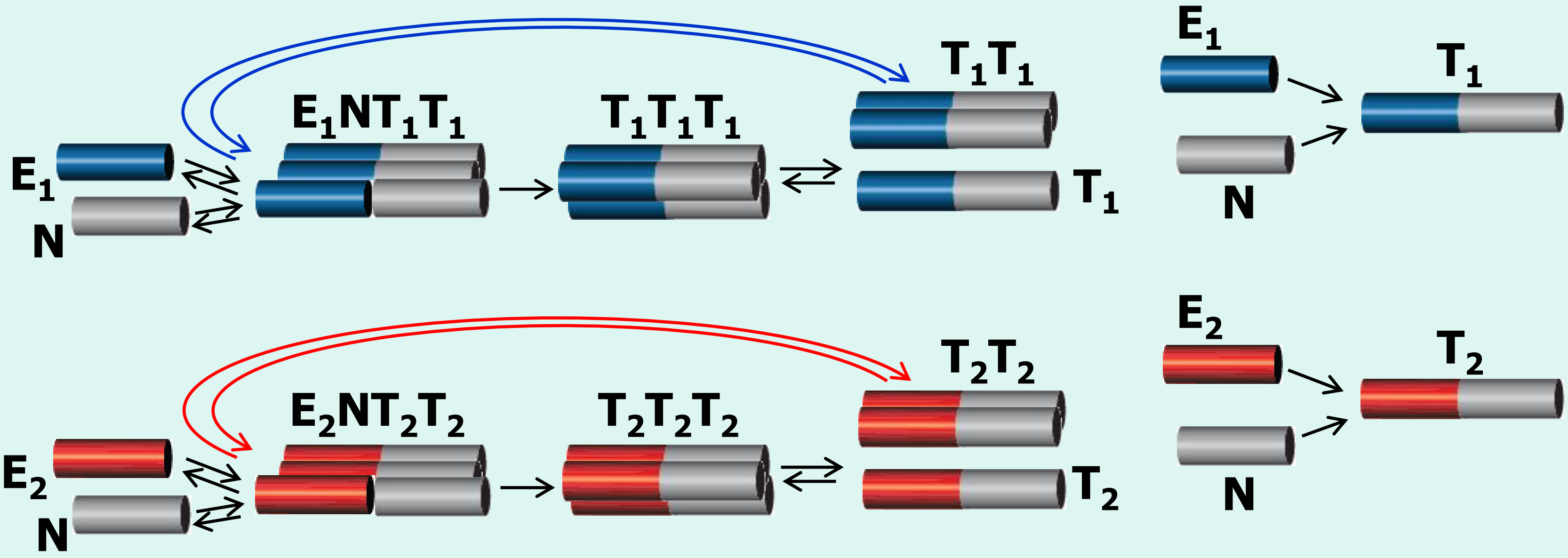


Maity et al, *in preparation* (2018)

Catalytic Reaction Networks



Two-Template Reversible Auto Catalysis



Two templates with Autocatalysis

We now assume two reversible templates T_1 and T_2, produced separately from E_1 and E_2 while sharing common N and S, with negligible cross catalysis.

$$[E_1NT_1T_1] = \frac{a}{\langle a\rangle_1 + b_1}[E_1][N][T_1T_1] \qquad [E_2NT_2T_2] = \frac{a}{\langle a\rangle_2 + b_2}[E_2][N][T_2T_2]$$

$$[T_1T_1T_1] = \frac{b_1[E_1NT_1T_1] + \langle f\rangle[T_1][T_1T_1]}{f_1} \qquad [T_2T_2T_2] = \frac{b_2[E_2NT_2T_2] + \langle f\rangle[T_2][T_2T_2]}{f_2}$$

$$[T_1T_1] = [T_1]^2/\tilde{d}_1 \qquad \tilde{d}_1 = d_1/\langle d\rangle \qquad [T_2T_2] = [T_2]^2/\tilde{d}_2 \qquad \tilde{d}_2 = d_2/\langle d\rangle$$

$$Rate_1 = \frac{d[t_1]}{d\tau} = g_1[E_1][N] - \langle g\rangle_1[T_1][S] + b_1[E_1NT_1T_1] \boxed{\approx g_1[E_1][N] - \langle g\rangle_1[T_1][S] + c_1[E_1][N][T_1]^2}$$

$$Rate_2 = \frac{d[t_2]}{d\tau} = g_2[E_2][N] - \langle g\rangle_2[T_2][S] + b_2[E_2NT_2T_2] \boxed{\approx g_2[E_2][N] - \langle g\rangle_2[T_2][S] + c_2[E_2][N][T_2]^2}$$

$$c_1 = \frac{ab_1/\tilde{d}_1}{\langle a\rangle_1 + b_1} \quad , \quad c_2 = \frac{ab_2/\tilde{d}_2}{\langle a\rangle_2 + b_2}$$

Two templates with Autocatalysis

$$[E_1] \approx [e_1] \qquad [E_2] \approx [e_2] \qquad [N] \approx [n]$$

$$[T_1] \approx [t_1] - 2[T_1T_1] = [t_1] - 2[T_1]^2 / \tilde{d}_1 \Rightarrow [T_1] = \frac{-1 \pm \sqrt{1 + 8[t_1]/\tilde{d}_1}}{4/\tilde{d}_1} = \frac{1}{4}\left(\sqrt{\tilde{d}_1^{\,2} + 8\tilde{d}_1[t_1]} - \tilde{d}_1\right)$$

$$[T_2] \approx [t_2] - 2[T_2T_2] = [t_2] - 2[T_2]^2 / \tilde{d}_2 \Rightarrow [T_2] = \frac{-1 \pm \sqrt{1 + 8[t_2]/\tilde{d}_2}}{4/\tilde{d}_2} = \frac{1}{4}\left(\sqrt{\tilde{d}_2^{\,2} + 8\tilde{d}_2[t_2]} - \tilde{d}_2\right)$$

$$[T_1T_1] = [T_1]^2 / \tilde{d}_1 \qquad [E_1NT_1T_1] = \frac{a}{\langle a \rangle_1 + b_1}[E_1][N][T_1T_1] \qquad [T_1T_1T_1] = \frac{b_1[E_1NT_1T_1] + \langle f \rangle [T_1][T_1T_1]}{f_1}$$

$$[T_2T_2] = [T_2]^2 / \tilde{d}_2 \qquad [E_2NT_2T_2] = \frac{a}{\langle a \rangle_2 + b_2}[E_2][N][T_2T_2] \qquad [T_2T_2T_2] = \frac{b_2[E_2NT_2T_2] + \langle f \rangle [T_2][T_2T_2]}{f_2}$$

$$[E_1] \approx [e_1] - [E_1NT_1T_1] \quad [N] \approx [n] - [E_1NT_1T_1] \quad [T_1] = \frac{1}{4}\left(\sqrt{\tilde{d}_1^{\,2} + 8\tilde{d}_1\left([t_1] - 2[E_1NT_1T_1] - 3[T_1T_1T_1]\right)} - \tilde{d}_1\right)$$

$$[E_2] \approx [e_2] - [E_2NT_2T_2] \quad [N] \approx [n] - [E_2NT_2T_2] \quad [T_2] = \frac{1}{4}\left(\sqrt{\tilde{d}_2^{\,2} + 8\tilde{d}_2\left([t_2] - 2[E_2NT_2T_2] - 3[T_2T_2T_2]\right)} - \tilde{d}_2\right)$$

First order Approximations:

$$g_1(E_1 + \Delta E_1)(N_{12} + \Delta N) = g_1E_1N_{12} + g_1E_1\Delta N + g_1N_{12}\Delta E_1 + g_1\Delta E_1\Delta N \approx g_1E_1N_{12} + g_1E_1\Delta N + g_1N_{12}\Delta E_1$$

$$g_2(E_2 + \Delta E_2)(N_{12} + \Delta N) = g_2E_2N_{12} + g_2E_2\Delta N + g_2N_{12}\Delta E_2 + g_2\Delta E_2\Delta N \approx g_2E_2N_{12} + g_2E_2\Delta N + g_2N_{12}\Delta E_2$$

Two templates with Autocatalysis

$$[e_1]\approx[E_1]\Rightarrow\Delta E_1=\Delta e_1 \qquad [e_2]\approx[E_2]\Rightarrow\Delta E_2=\Delta e_2 \qquad [n]\approx[N]\Rightarrow\Delta N=\Delta n$$

$$[T_1]\approx\frac{1}{4}\left(\sqrt{\tilde{d}_1^{\,2}+8\tilde{d}_1[t_1]}-\tilde{d}_1\right)\Rightarrow\Delta T_1=\frac{\Delta t_1}{\sqrt{1+8[t_1]/\tilde{d}_1}}=\theta_1\,\Delta t_1 \qquad \theta_1=\frac{1}{\sqrt{1+8t_1/\tilde{d}_1}}$$

$$[T_2]\approx\frac{1}{4}\left(\sqrt{\tilde{d}_2^{\,2}+8\tilde{d}_2[t_2]}-\tilde{d}_2\right)\Rightarrow\Delta T_2=\frac{\Delta t_2}{\sqrt{1+8[t_2]/\tilde{d}_2}}=\theta_2\,\Delta t_2 \qquad \theta_2=\frac{1}{\sqrt{1+8t_2/\tilde{d}_2}}$$

Two Reaction Coordinates: $\Delta t_1=-\Delta e_1=x_1 \quad \Delta t_2=-\Delta e_2=x_2 \quad \Delta S=-\Delta n=x_1+x_2$

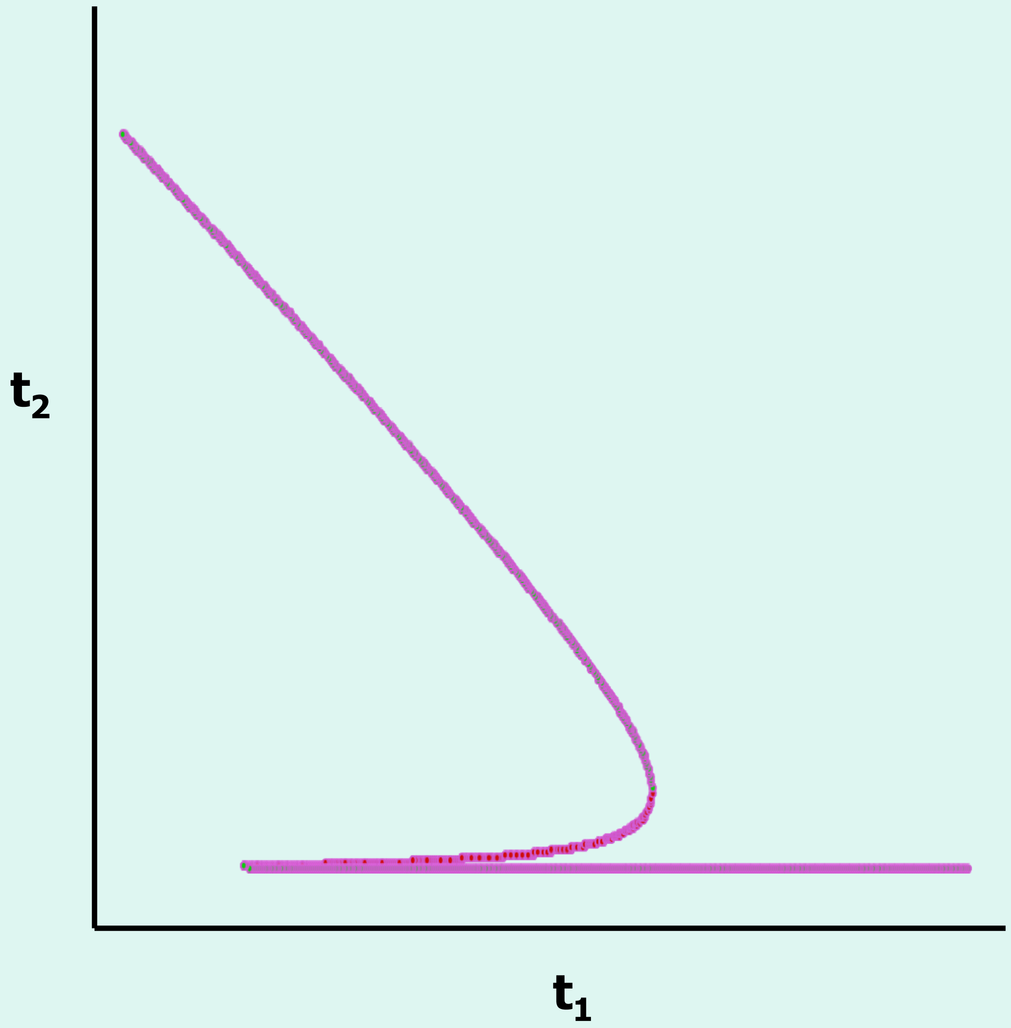
$$Rate_1=\frac{d[t_1]}{d\tau}=g_1[E_1][N]-\langle g\rangle_1[T_1][S]+c_1[E_1][N][T_1]^2$$

$$Rate_2=\frac{d[t_2]}{d\tau}=g_2[E_2][N]-\langle g\rangle_2[T_2][S]+c_2[E_2][N][T_2]^2$$

Equilibrium points : $Rate_1=Rate_2=0$

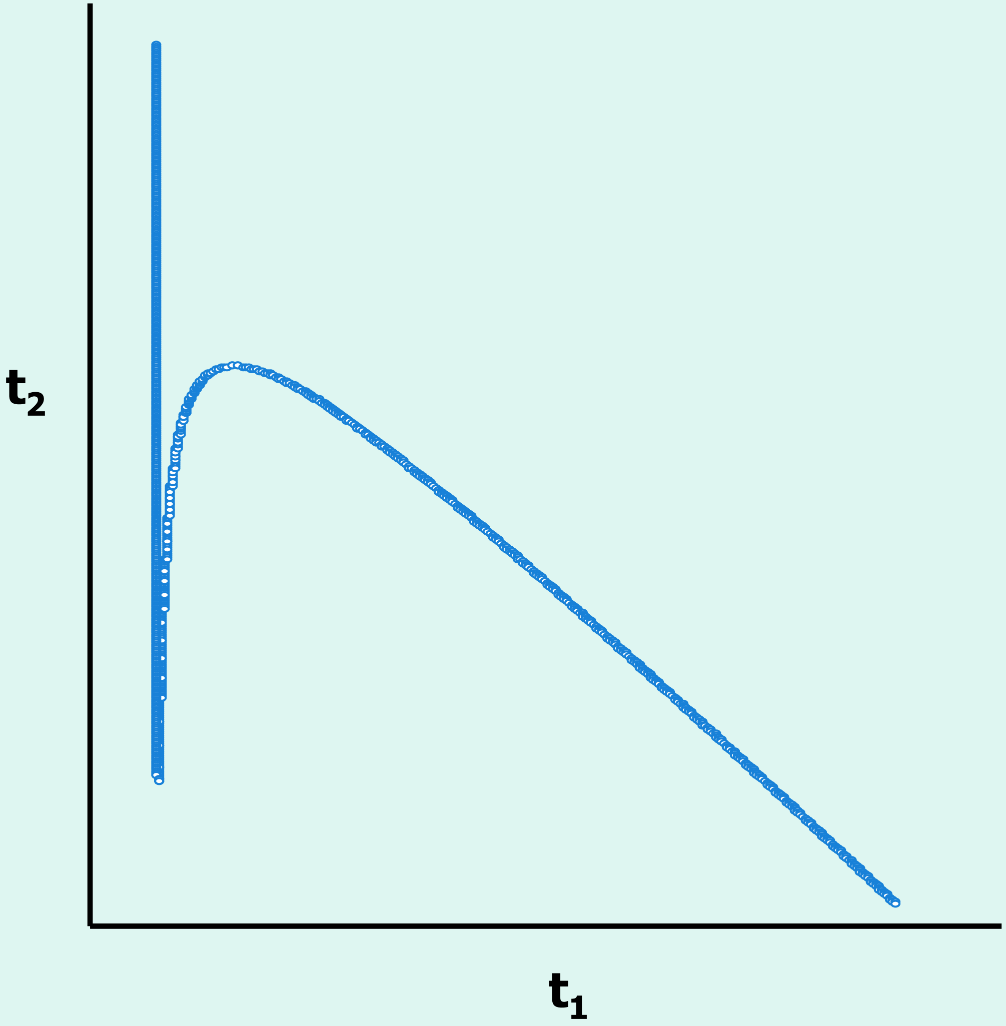
Two templates with Autocatalysis

t_2 Equilibrium vs. Total Material



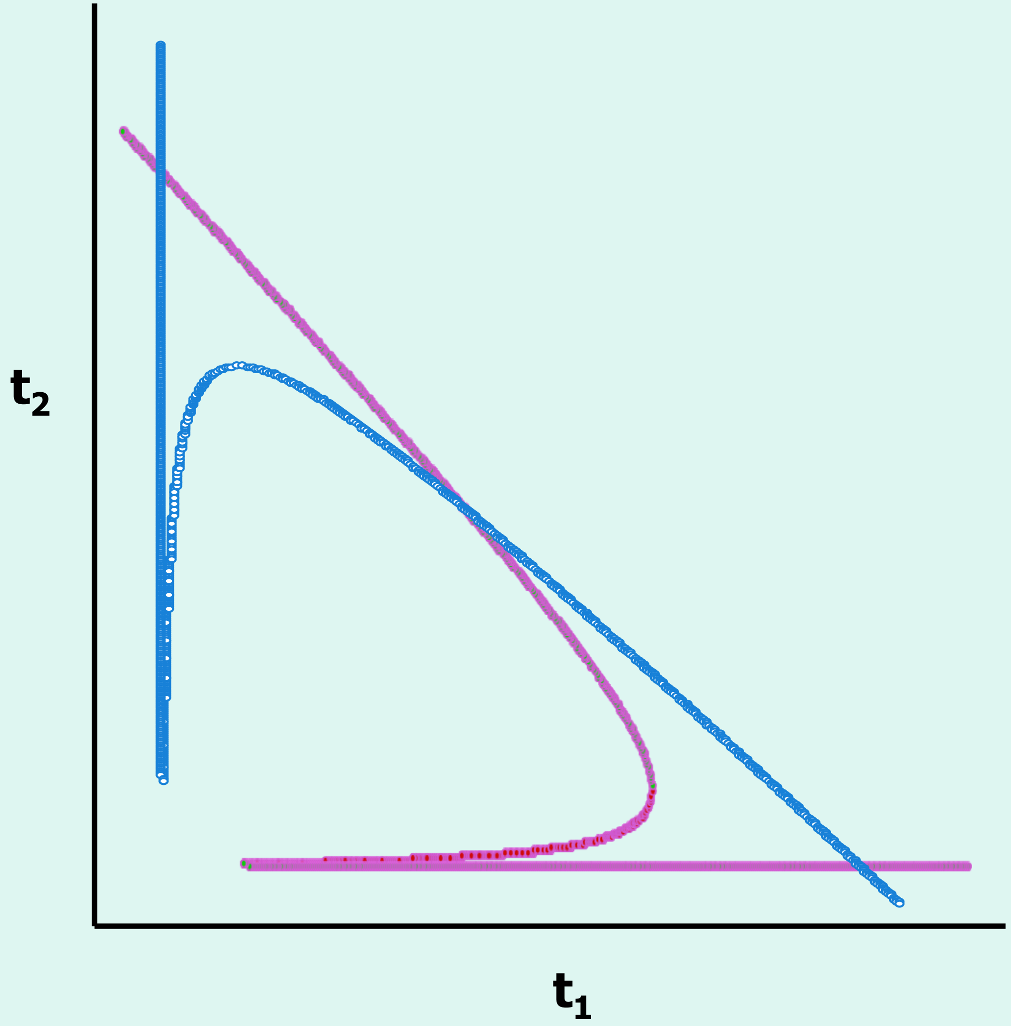
Two templates with Autocatalysis

t_1 Equilibrium vs. Total Material



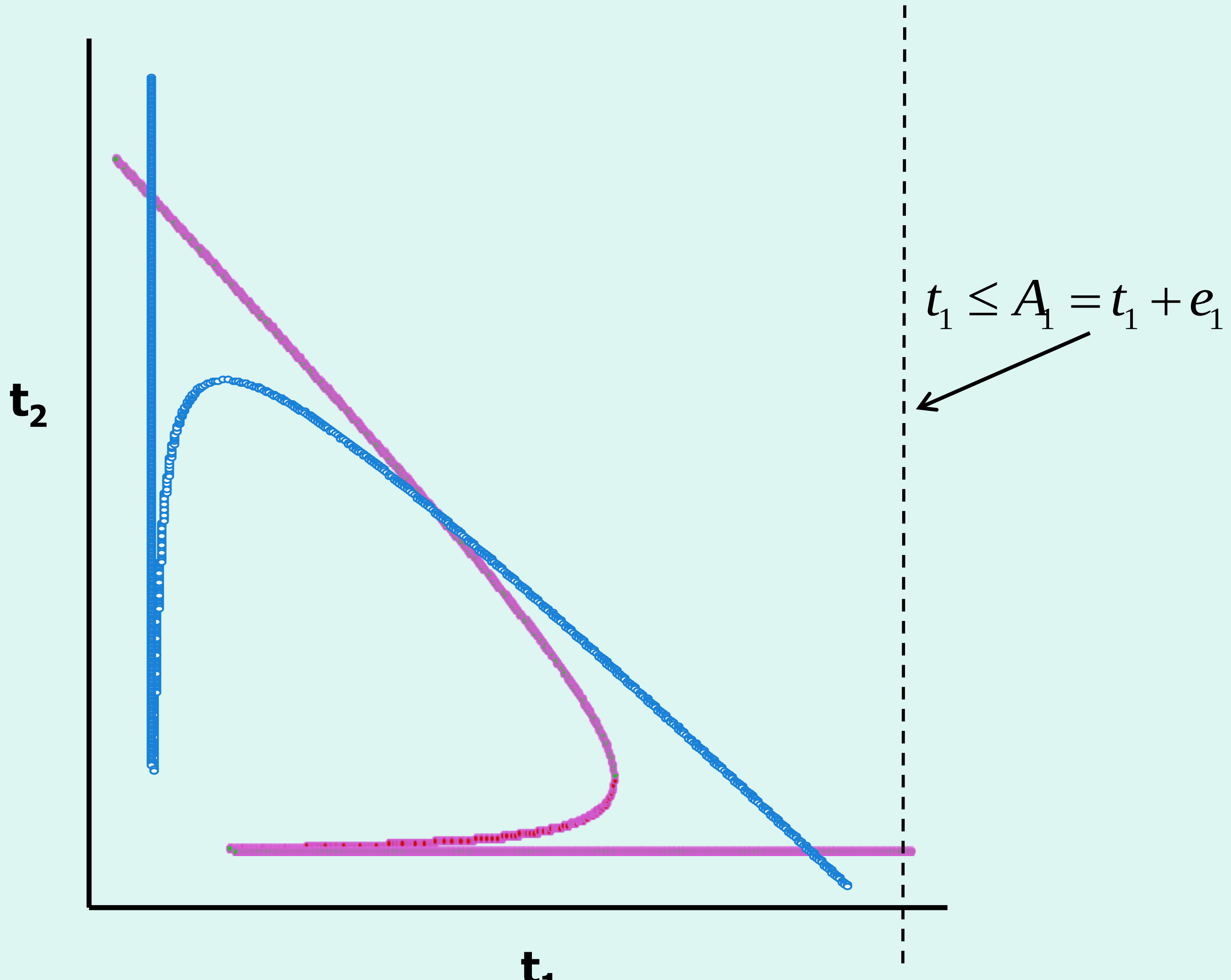
Two templates with Autocatalysis

t_1 / t_2 Null Clines



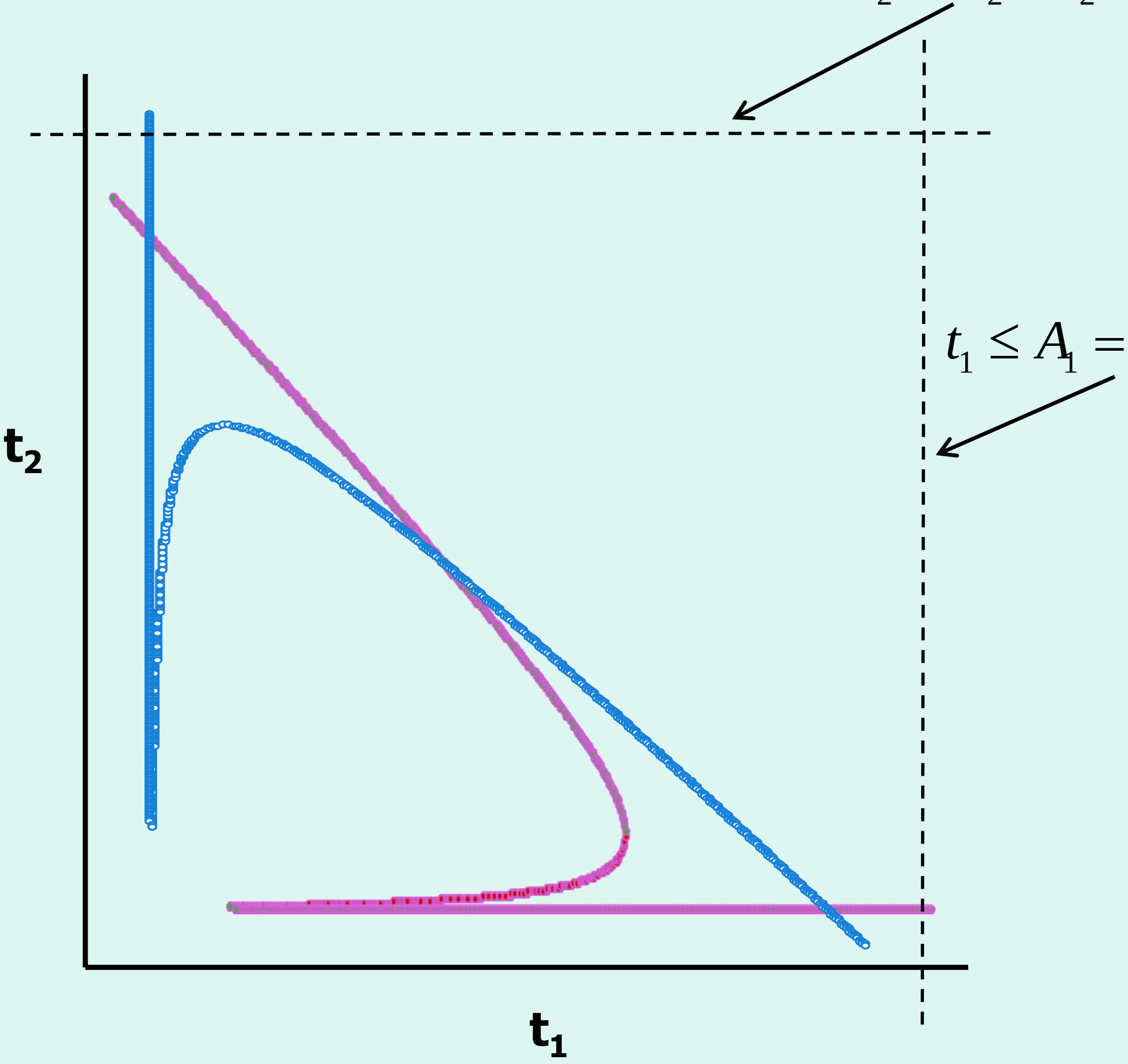
Two templates with Autocatalysis

t_1 / t_2 Null Clines



Two templates with Autocatalysis

t_1 / t_2 Null Clines

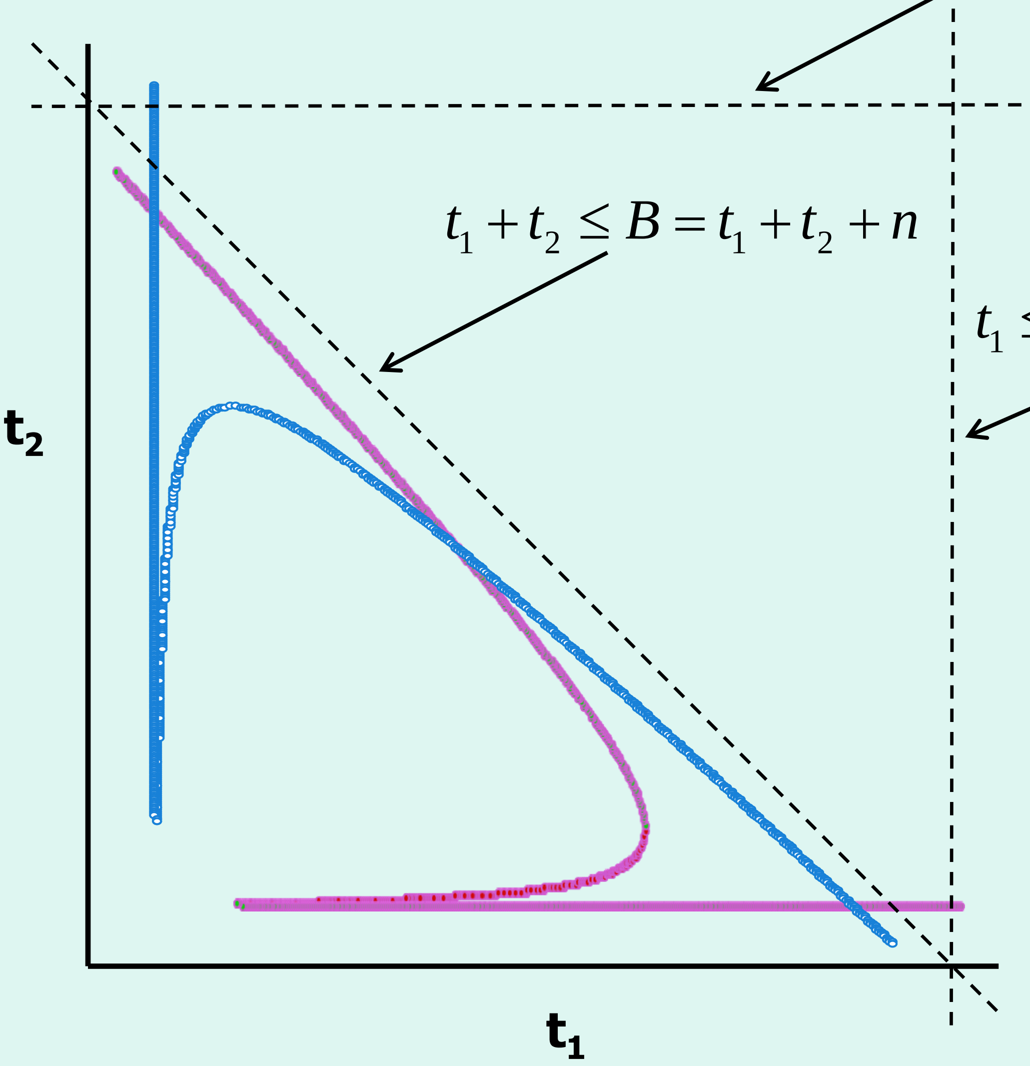


$t_2 \leq A_2 = t_2 + e_2$

$t_1 \leq A_1 = t_1 + e_1$

Two templates with Autocatalysis

t_1 / t_2 Null Clines



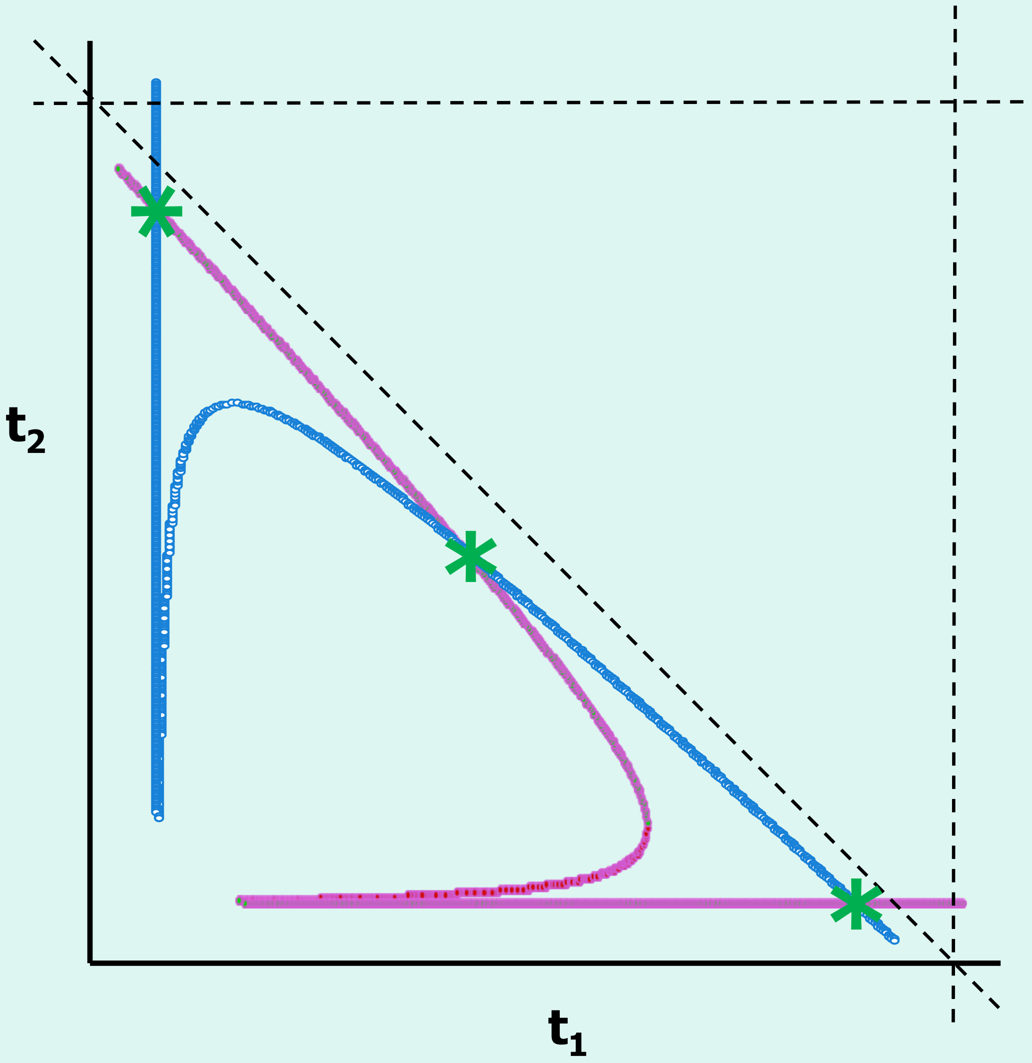
$t_2 \le A_2 = t_2 + e_2$

$t_1 + t_2 \le B = t_1 + t_2 + n$

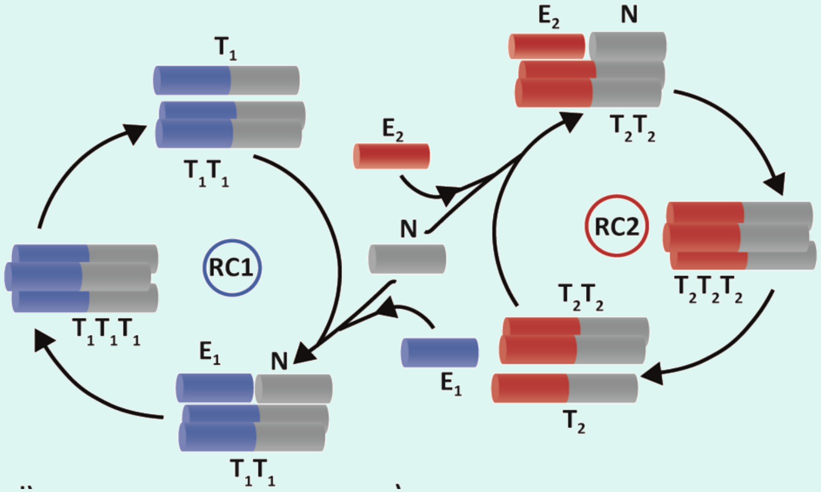
$t_1 \le A_1 = t_1 + e_1$

Two templates with Autocatalysis

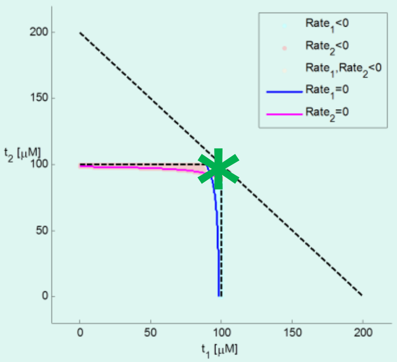
t_1 / t_2 Null Clines



Two Templates with Reversible Catalysis ⇒ Multistationarity



1



e_0= [0.0001 0.0001 0] n_0= 0.0002 t_0= [0 0 0] s_0= 0.01 h_0= 0

K_{fa} = [10 10 10] g = [1 1 0] k_{bg} = [10 10 10] <g> = [10 10 0] a = 1000000000

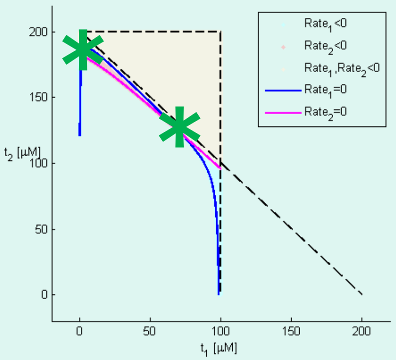
<d> = 1000000 <f> = 1000000 d = [10 10 10; 10 10 10; 10 10 10]

f = 1000* [1 1 1 1 1 1; 1 1 1 1 1 1; 1 1 1 1 1 1]

a * [1 0 0 0 0 0; 0 1 0 0 0 0; 0 0 0 0 0 0]

u = [0 0 0] v = [0 0 0] w = [0 0 0]

2



e_0= [0.0001 0.0002 0] n_0= 0.0002 t_0= [0 0 0] s_0= 0.01 h_0= 0

K_{fa} = [10 10 10] g = [1 1 0] k_{bg} = [10 10 10] <g> = [10 10 0] a = 1000000000

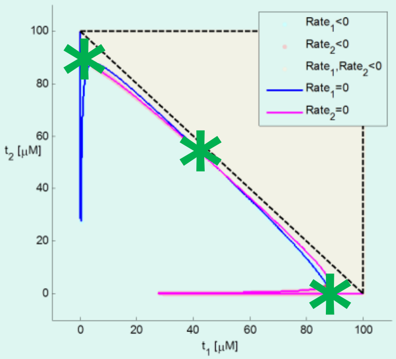
<d> = 1000000 <f> = 1000000 d = [10 10 10; 10 20 10; 10 10 10]

f = 1000* [1 1 1 1 1 1; 1 2 1 1 1 1; 1 1 1 1 1 1]

a * [1 0 0 0 0 0; 0 1 0 0 0 0; 0 0 0 0 0 0]

u = [0 0 0] v = [0 0 0] w = [0 0 0]

3



e_0= [1.3e-05 9.7e-05 0] n_0= 1e-05 t_0= [8.7e-05 3e-06 0] s_0= 0.01009 h_0= 0

K_{fa} = [10 10 10] g = [1 1 0] k_{bg} = [10 10 10] <g> = [10 10 0] a = 1000000000

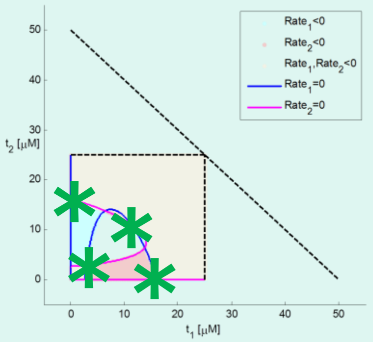
<d> = 1000000 <f> = 1000000 d = [10 10 10; 10 10 10; 10 10 10]

f = 1000* [1 1 1 1 1 1; 1 1 1 1 1 1; 1 1 1 1 1 1]

a * [1 0 0 0 0 0; 0 1 0 0 0 0; 0 0 0 0 0 0]

u = [0 0 0] v = [0 0 0] w = [0 0 0]

4



e_0= [2.5e-05 2.5e-05 0] n_0= 5e-05 t_0= [0 0 0] s_0= 0.01 h_0= 0

K_{fa} = [10 10 10] g = [1 1 0] k_{bg} = [10 10 10] <g> = [10 10 0] a = 1000000000

<d> = 1000000 <f> = 1000000 d = [10 10 10; 10 10 10; 10 10 10]

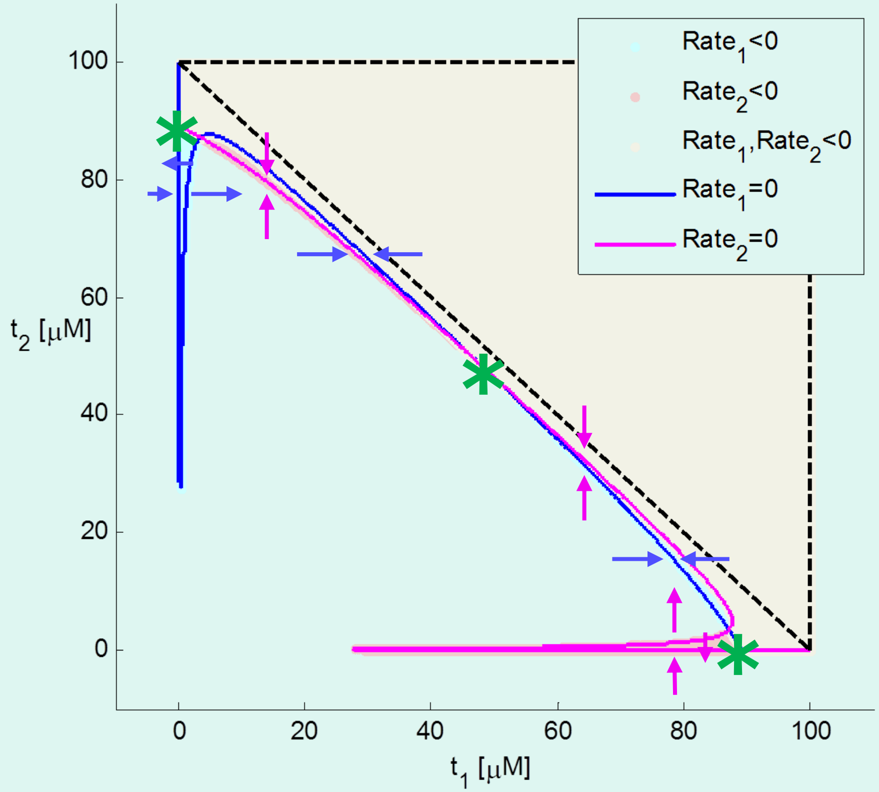
f = 1000* [1 1 1 1 1 1; 1 1 1 1 1 1; 1 1 1 1 1 1]

a * [1 0 0 0 0 0; 0 1 0 0 0 0; 0 0 0 0 0 0]

u = [0 0 0] v = [0 0 0] w = [0 0 0]

Wagner, Mukherjee, Kraun, Maity, Peacock-Lopez & Ashkenasy, *in preperation* (2018)

$e_1 + t_1 = 100$ μM , $e_2 + t_2 = 100$ μM
$n = e_1 + e_2 - 100$ μM , $s = 0.01$ M $+ t_1 + t_2$



e_0= [0.0001 0.0001 0] n_0= 0.0001 t_0= [0 0 0] s_0= 0.01 h_0= 0

K_{fa} = [10 10 10]   g = [1 1 0] k_{bg} = [10 10 10]   <g> = [10 10 0]   a = 1000000000

<d> = 1000000   <f> = 1000000   d = [10 10 10; 10 10 10; 10 10 10]

f = 1000* [1 1 1 1 1 1; 1 1 1 1 1 1; 1 1 1 1 1 1]

a * [1 0 0 0 0 0; 0 1 0 0 0 0; 0 0 0 0 0 0]

u = [0 0 0]   v = [0 0 0]   w = [0 0 0]

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Dr. Rivka Cohen-Luria

Prof. Enrique Peacock-Lopez

Thank you for your attention !

www.bgu.ac.il/~nwagner

Multistationarity in Catalytic Reaction Networks

Multistationarity, an emergent property of catalytic reaction networks, is widely found in living systems, and may be a fundamental prerequisite of life. By studying relatively simple and then progressively more complex catalytic reaction networks, we can observe the onset of bistability and multistability and probe their scope and properties, both in steady state and switching modes. Recent experiments have confirmed our theoretical and computational findings. Our findings continue our efforts towards understanding fundamental processes of evolution, complexification and emergence.