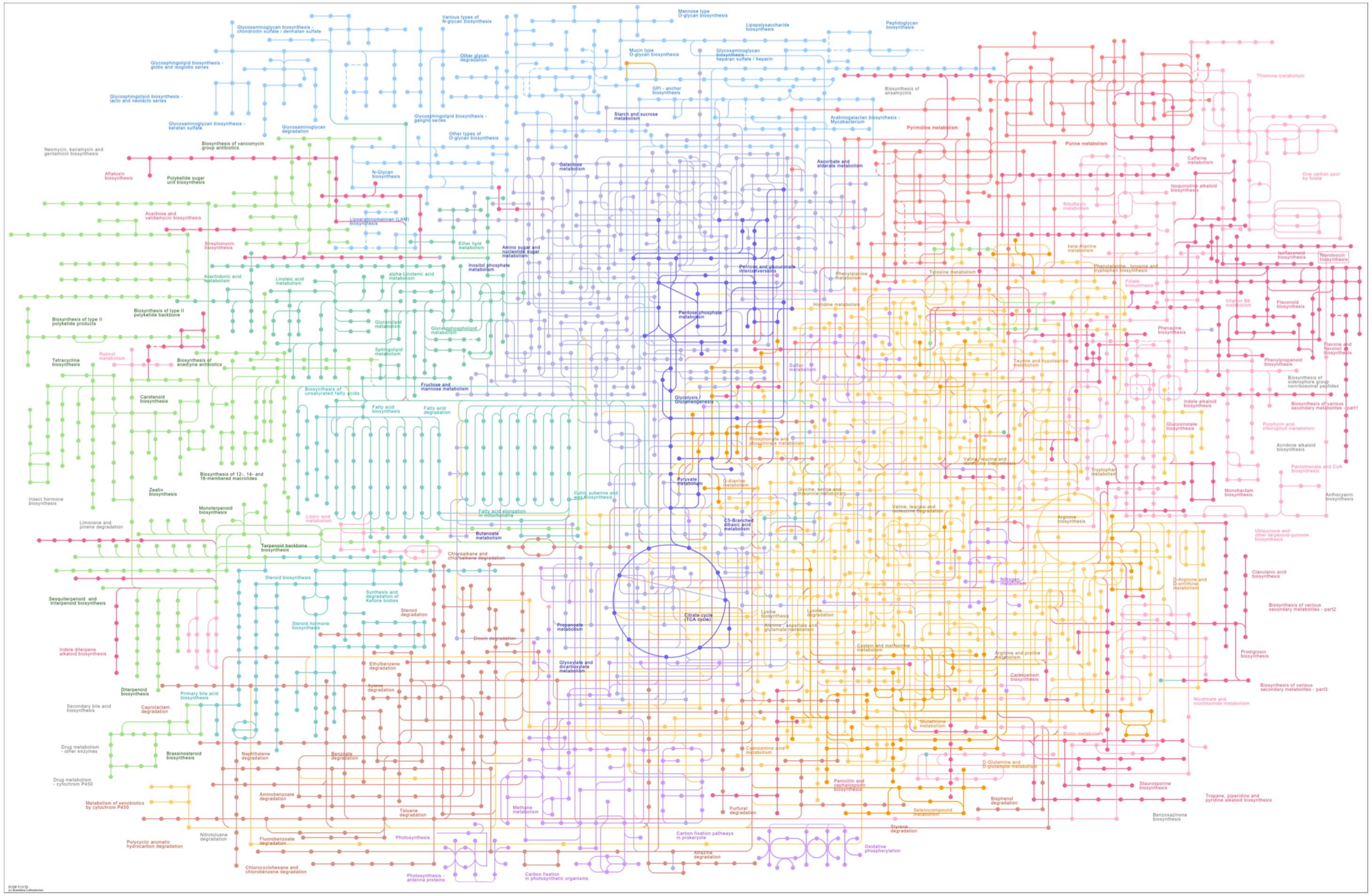
The Emergence of Complexity Using Chemical Self-replicators

Literature Seminar #2
M1 Yuki Yamanashi
20/05/28(Thu)

Overview: networks of organic chemical reactions in biological systems



https://www.genome.jp/kegg/pathway/map/map01100.html

- Complex behaviors in biological systems are created by chemical reaction networks.
- Chemists have tried to develop artificial chemical network systems which produce complex behaviors, in order to understand life.
- Chemical self-replicators are key components of such a system.

Kosikova, T.; Philp, D. *Chem. Soc. Rev.* **2017**, *46* (23), 7274–7305.

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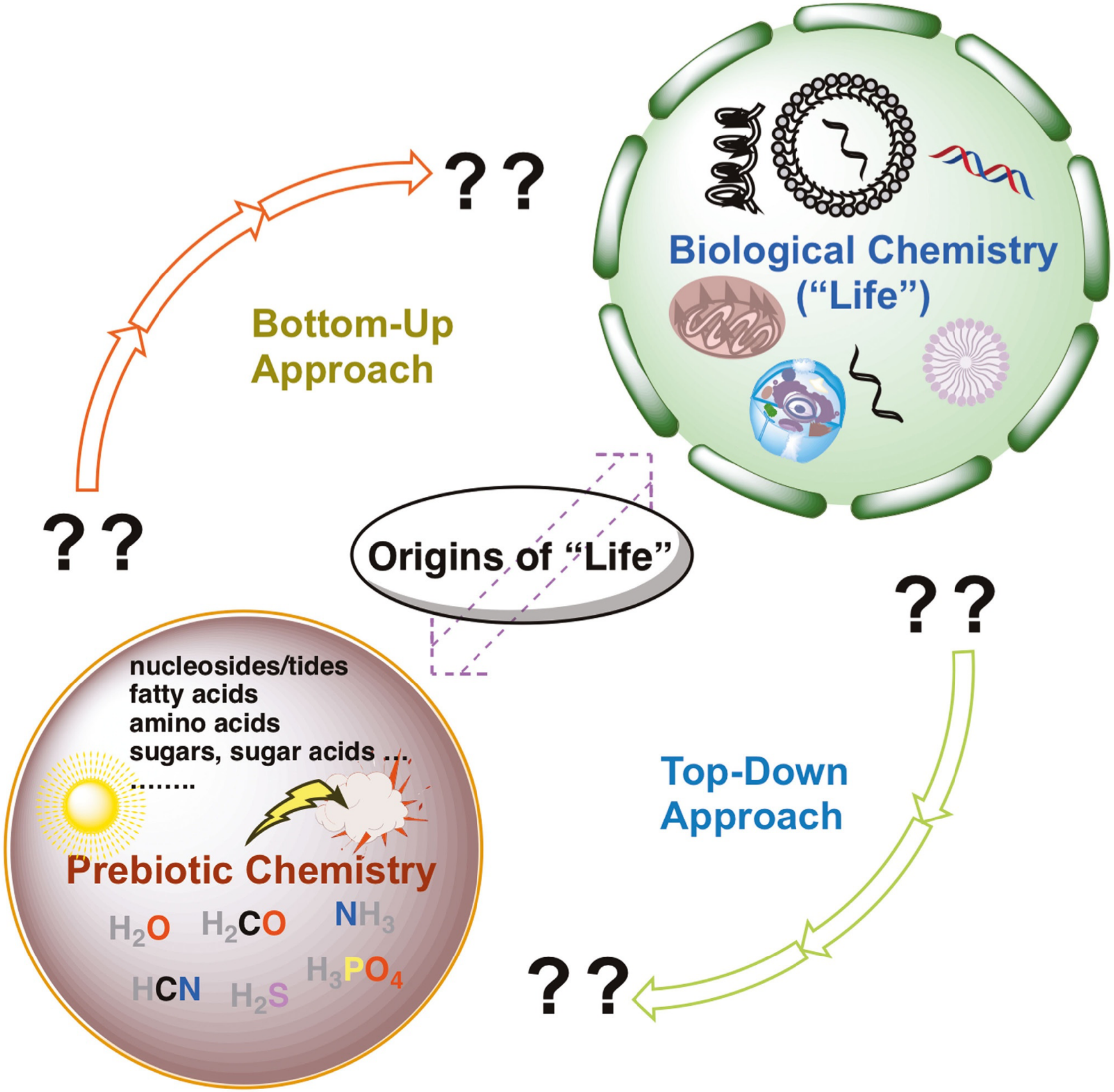
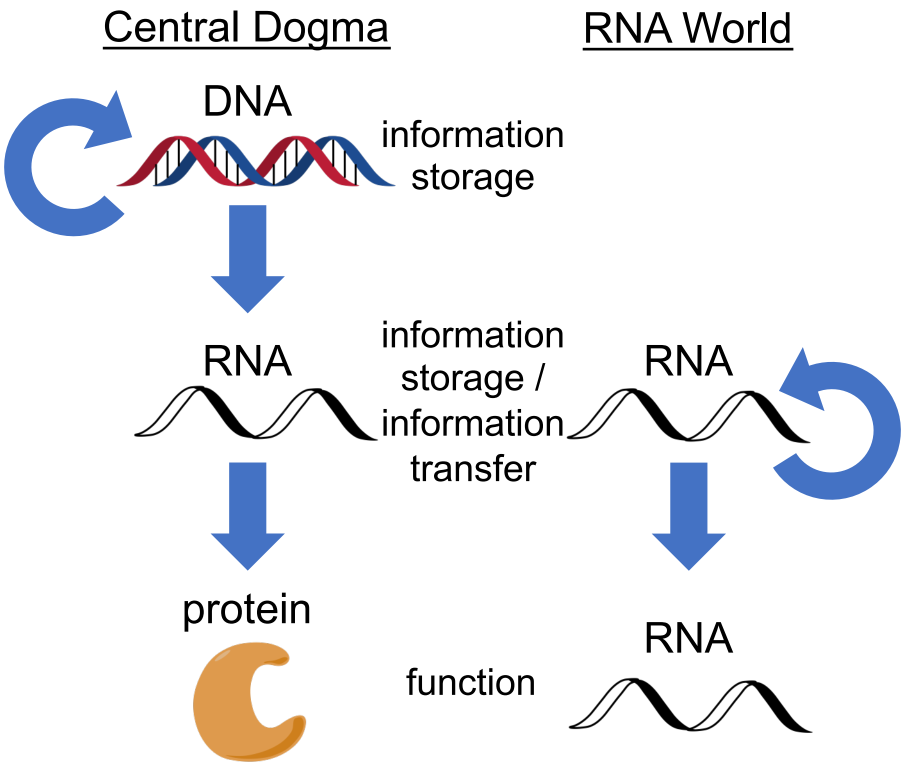
The origins of life: two approaches



- There are numerous models and theories trying to explain the origins of life, generally grouped into two approaches; bottom-up and top-down.

Krishnamurthy, R. *Chem. Eur. J.* **2018**, *24* (63), 16708–16715.

The origins of life: top-down approaches



Central Dogma

RNA World

DNA

information storage

RNA

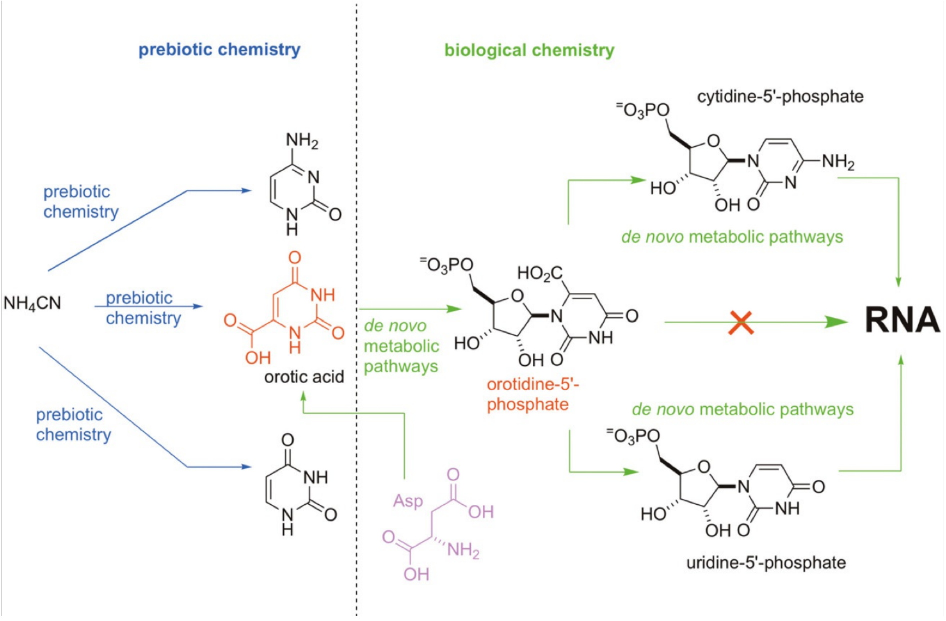
information storage / information transfer

RNA

protein

function

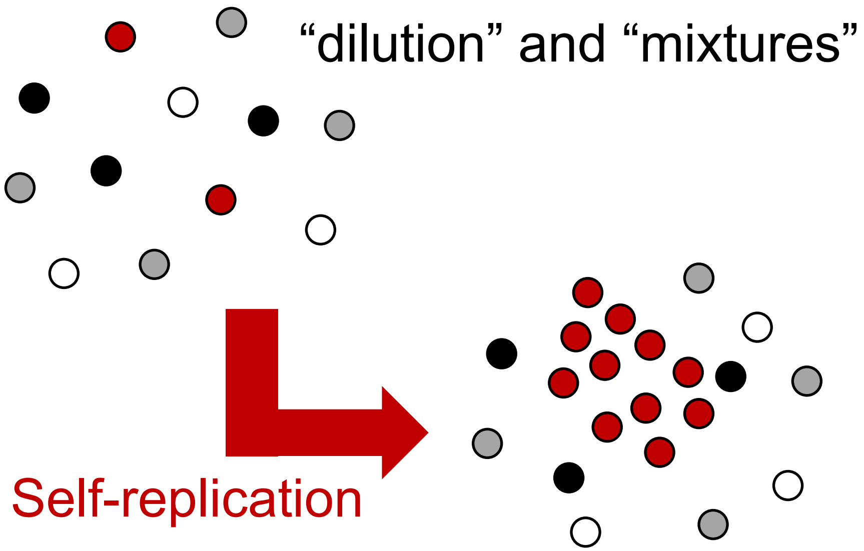
RNA



- In top-down approaches, the way how present-day biomolecules have arisen on early earth is searched.
- For example, “the RNA World” hypothesis is one of the most plausible hypothesis in top-down approaches.
- However, it tends to be difficult in top-down approaches to find solutions in connecting prebiotic chemistry to biological chemistry.

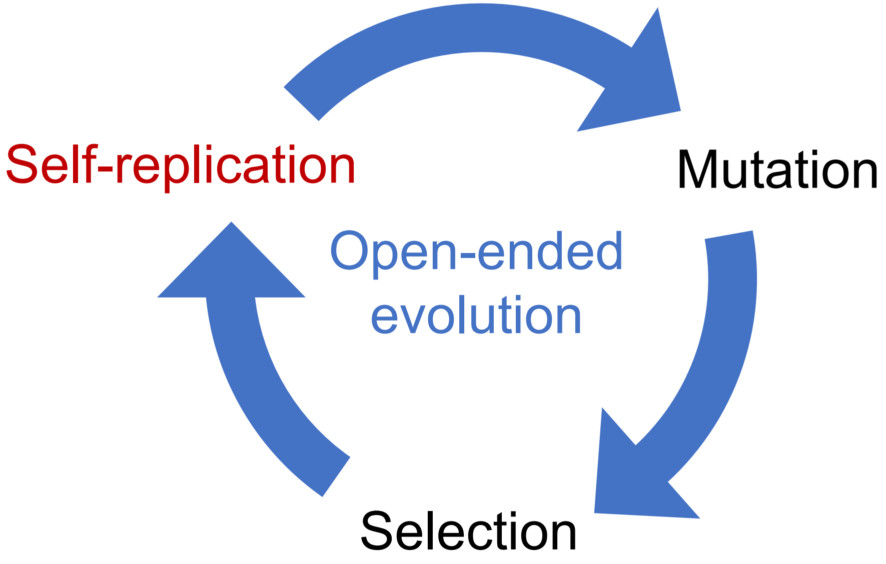
Krishnamurthy, R. *Chem. Eur. J.* **2018**, *24* (63), 16708–16715.
Sutherland, J. D. *Angew. Chemie Int. Ed.* **2016**, *55* (1), 104–121.
Cech, T. R. *Cell* **2009**, *136* (4), 599–602.

The origins of life: bottom-up approaches



“dilution” and “mixtures”

Self-replication



Self-replication

Mutation

Open-ended evolution

Selection

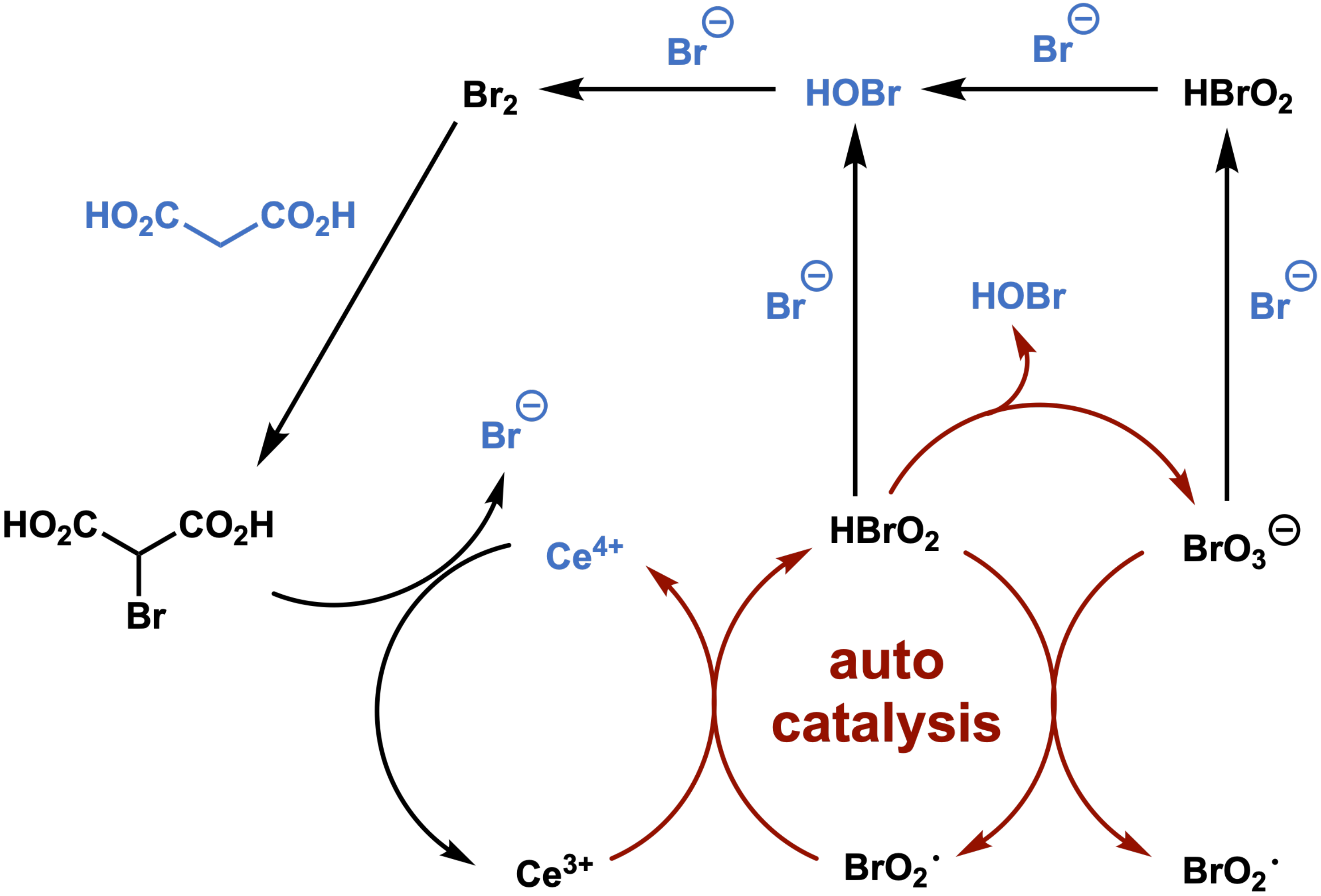
- In bottom-up approaches, systems that can emerge complexity are developed, and analyzing such systems will provides the requirements of the emergence of life.
- Development of synthetic replicators is one of them and important in some reasons.
  - Self-replication may be a solution of two core problems in the origin of life; “dilution” and “mixtures”.
  - Synthetic replicators are core elements of more complex systems (e.g. open-ended evolution, oscillation→next page)

Krishnamurthy, R. *Chem. Eur. J.* **2018**, *24* (63), 16708–16715.

Duim, H.; Otto, S. *Beilstein J. Org. Chem.* **2017**, *13*, 1189–1203.

Semenov, S. N.; Belding, L. *J. Am. Chem. Soc.* **2018**, *140* (32), 10221–10232.

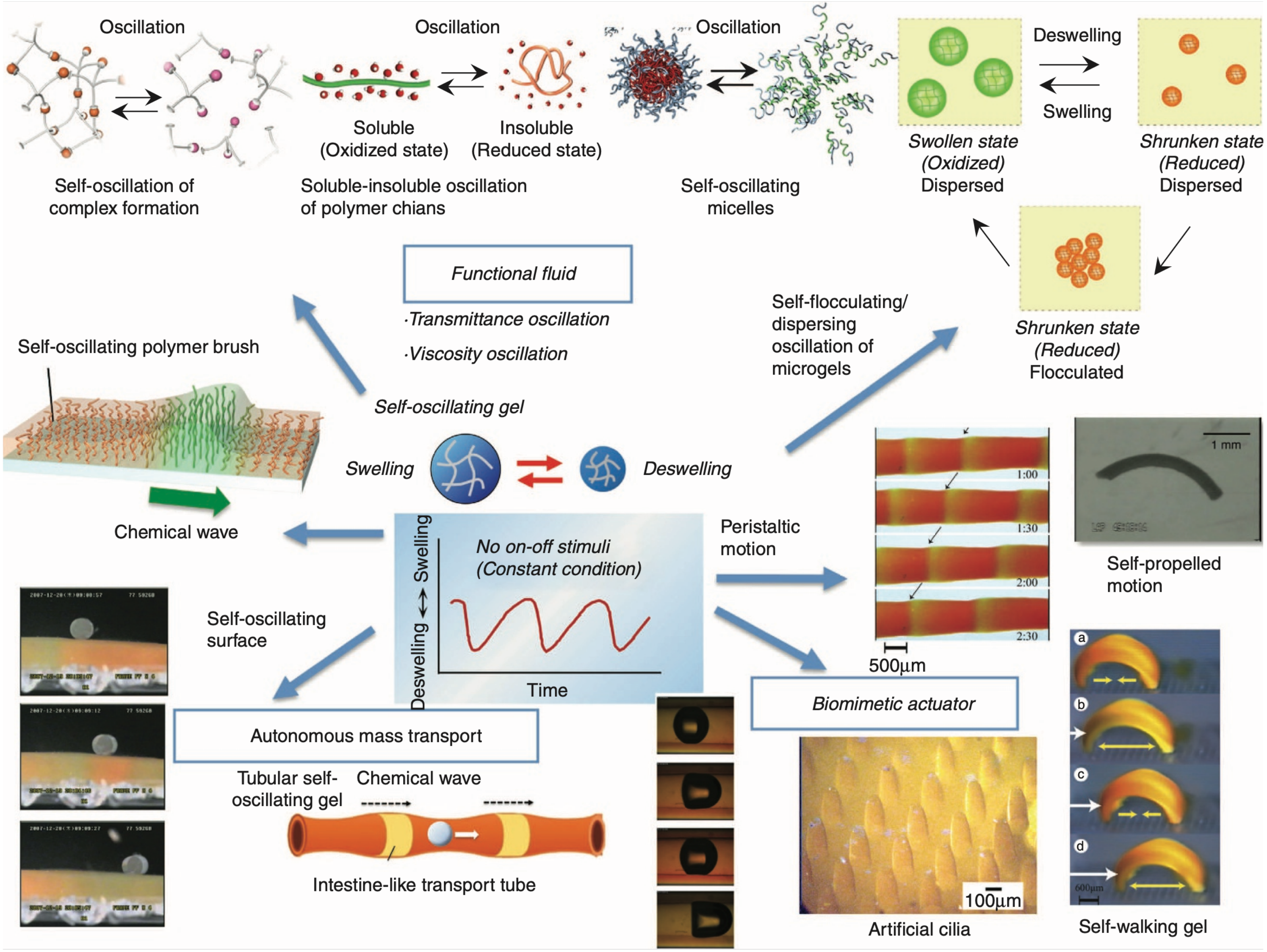
The origins of life: oscillation and synthetic replicators



- Self-replicating reaction network is a core element of chemical oscillator like Belousov-Zhabotinskii-type reaction; one of the most famous oscillator.

Field, R. J.; Koros, E *et al. J. Am. Chem. Soc.* **1972**, *94* (25), 8649–8664.
Field, R. J. *J. Chem. Phys.* **1975**, *63* (6), 2289–2296.

Applications of synthetic replicators

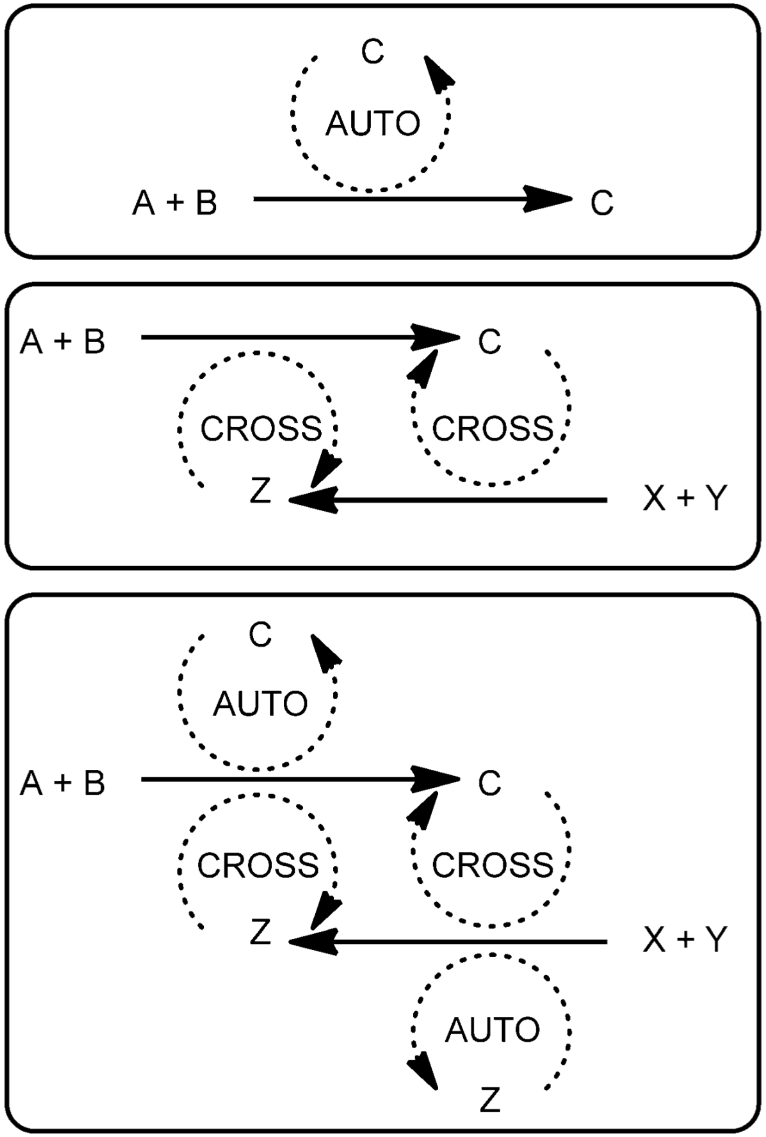


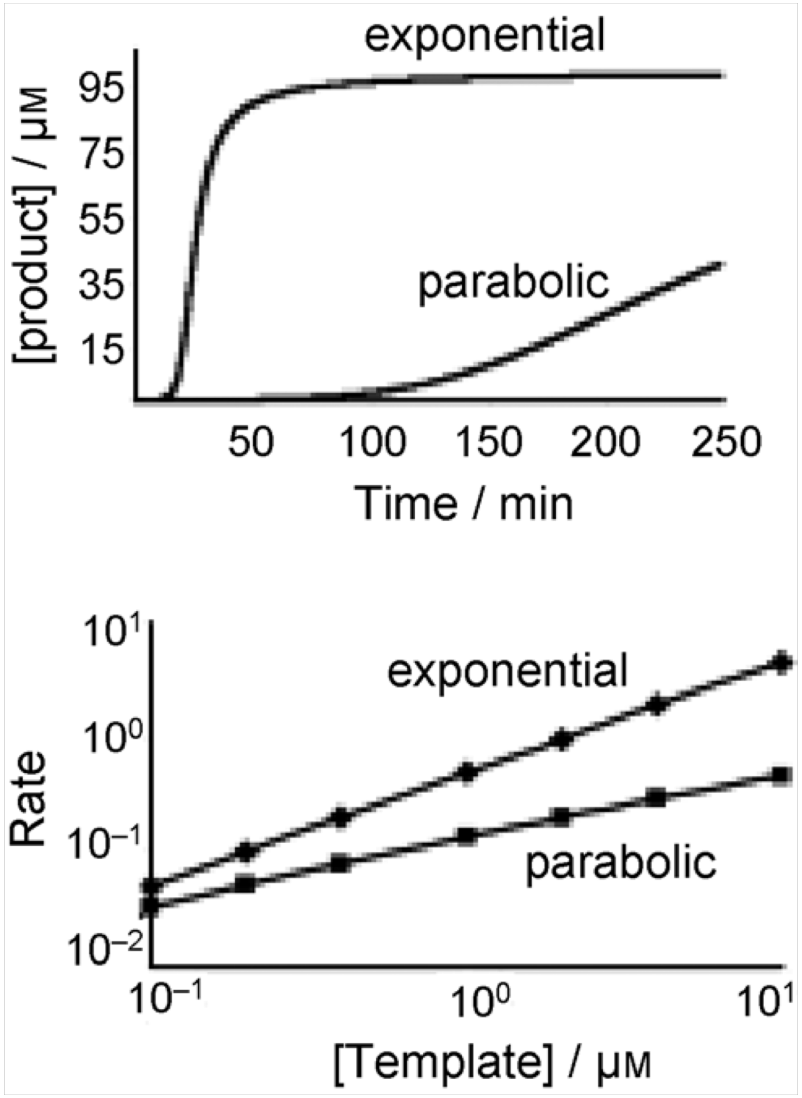
- Chemical system with complex behaviors (e.g. BZ reaction) can be applied to the development of functional material.

Yoshida, R.; Ueki, T. *NPG Asia Mater.* **2014**, *6* (6), e107–e107.

Contents

The mechanism of chemical self-replicators





Bissette, A. J.; Fletcher, S. P. *Angew. Chem. Int. Ed.* **2013**, *52* (49), 12800–12826.

Development of chemical self-replicators

component

- enzyme
- peptide
- micelle
- vesicle
- inorganic molecule
- today's topics: organic small molecule
- oligonucleotide

environment

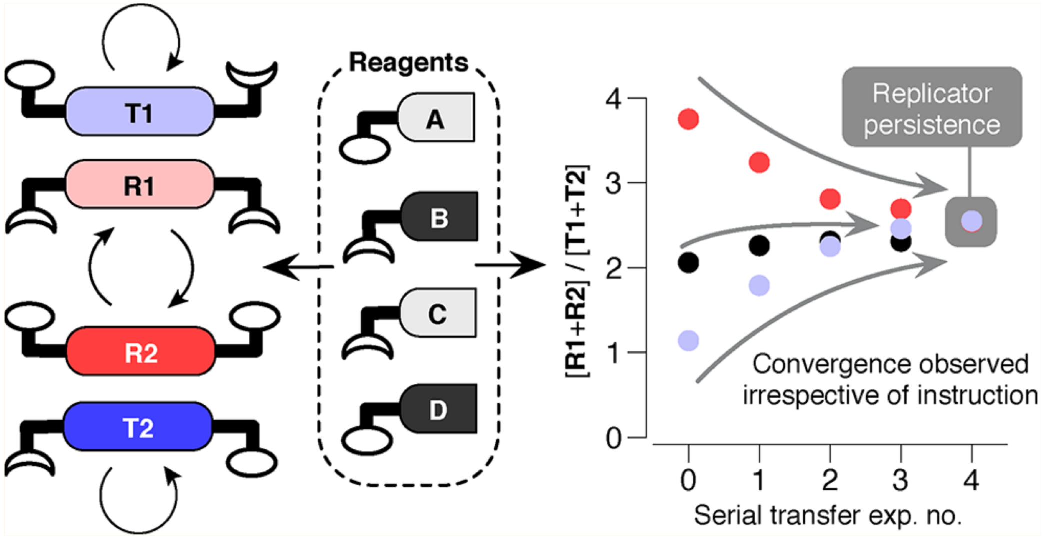
- stable
- dynamic

complex behavior

- feedback loop
- oscillation
- pattern formation
- system-level response

The emergence of complexity using chemical self-replicators

Multicyclic network



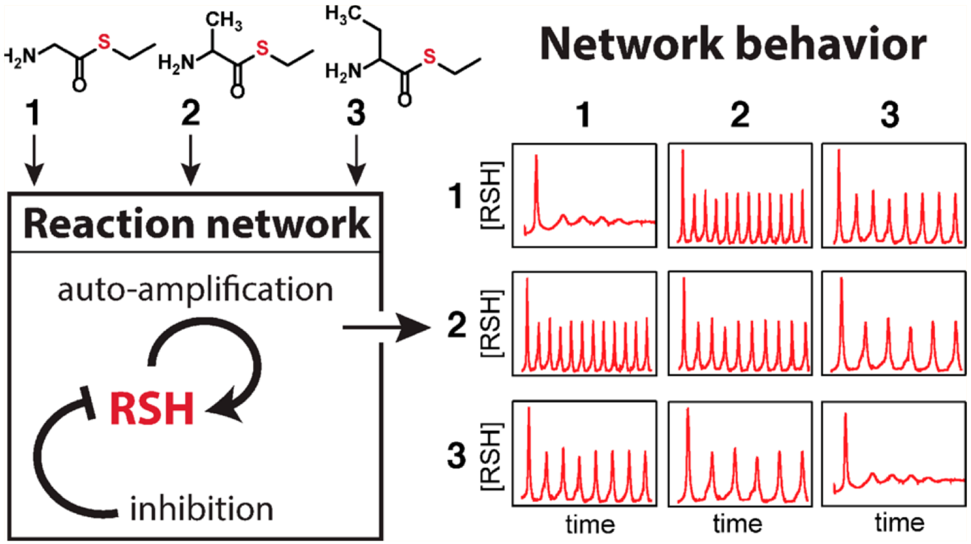
organic small molecule

stable

system-level response

Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

Oscillation network



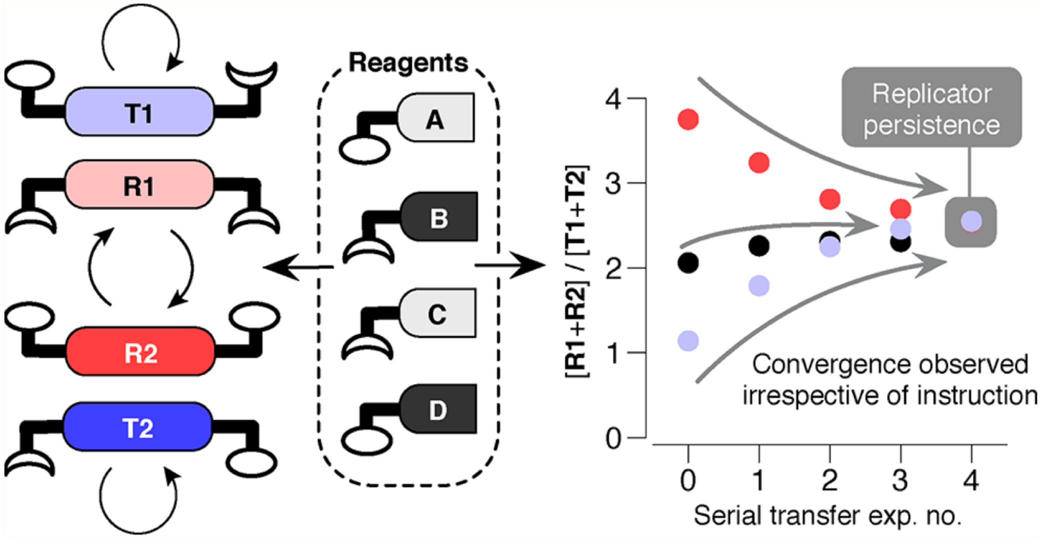
organic small molecule

dynamic

oscillation

Cafferty, B. J.; Wong, A. S. Y. *et al.* *J. Am. Chem. Soc.* **2019**, *141* (20), 8289–8295.

Multicyclic network



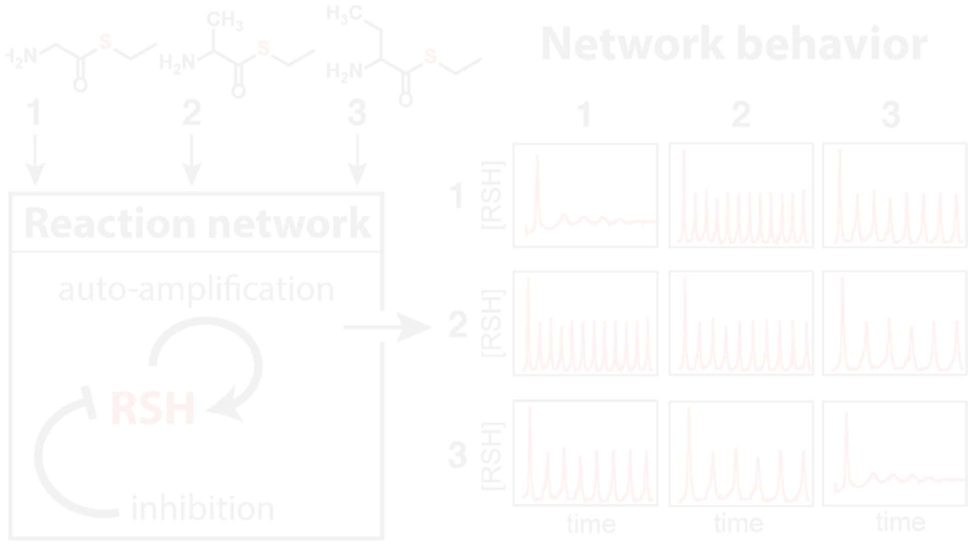
organic small molecule

stable

system-level response

Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

Oscillation network



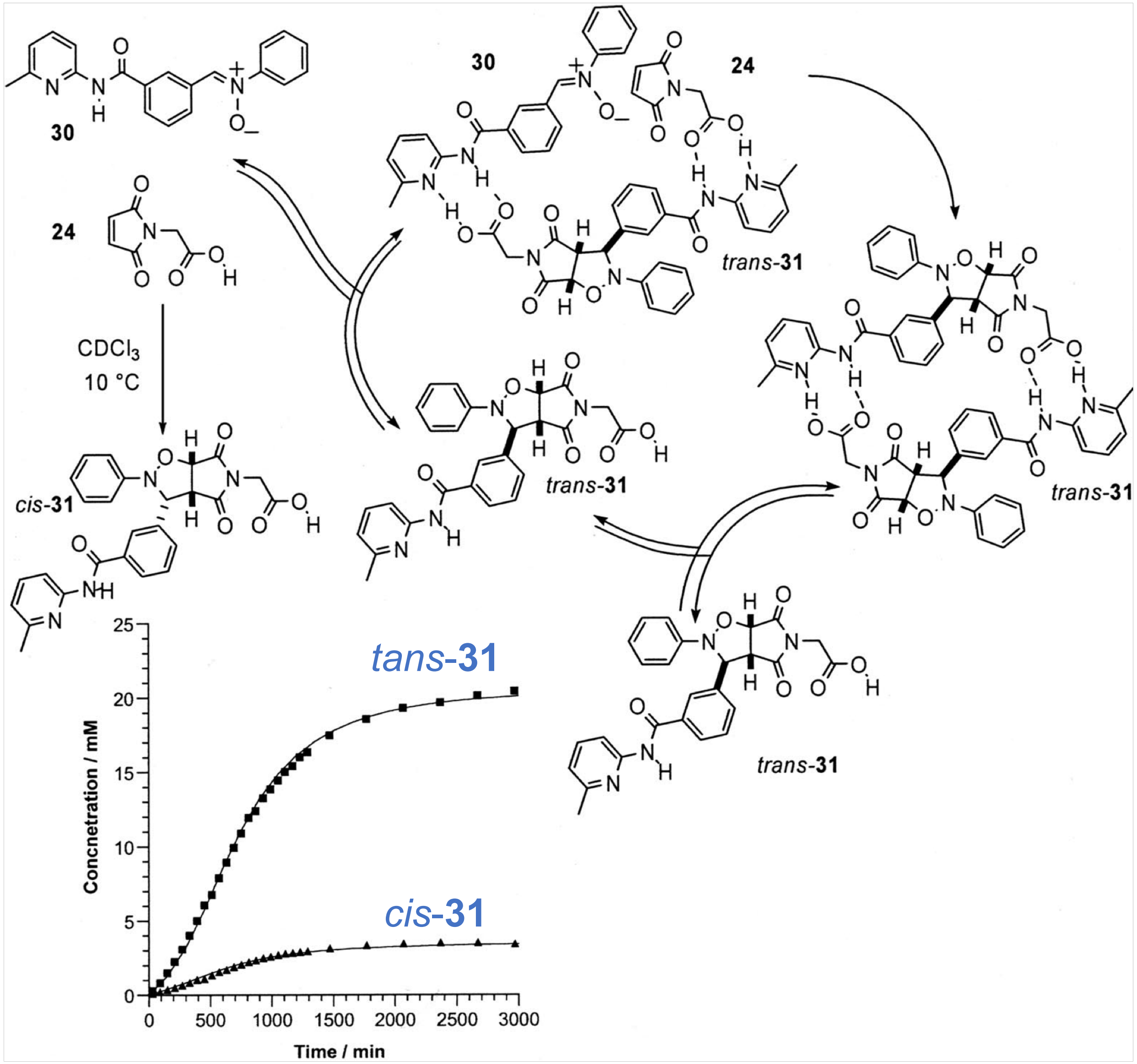
organic small molecule

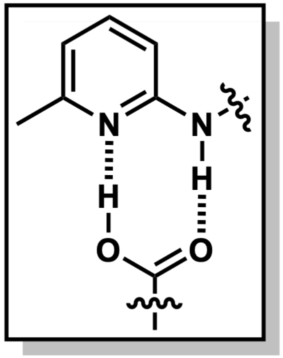
dynamic

oscillation

Cafferty, B. J.; Wong, A. S. Y. *et al.* *J. Am. Chem. Soc.* **2019**, *141* (20), 8289–8295.

Research background (1)

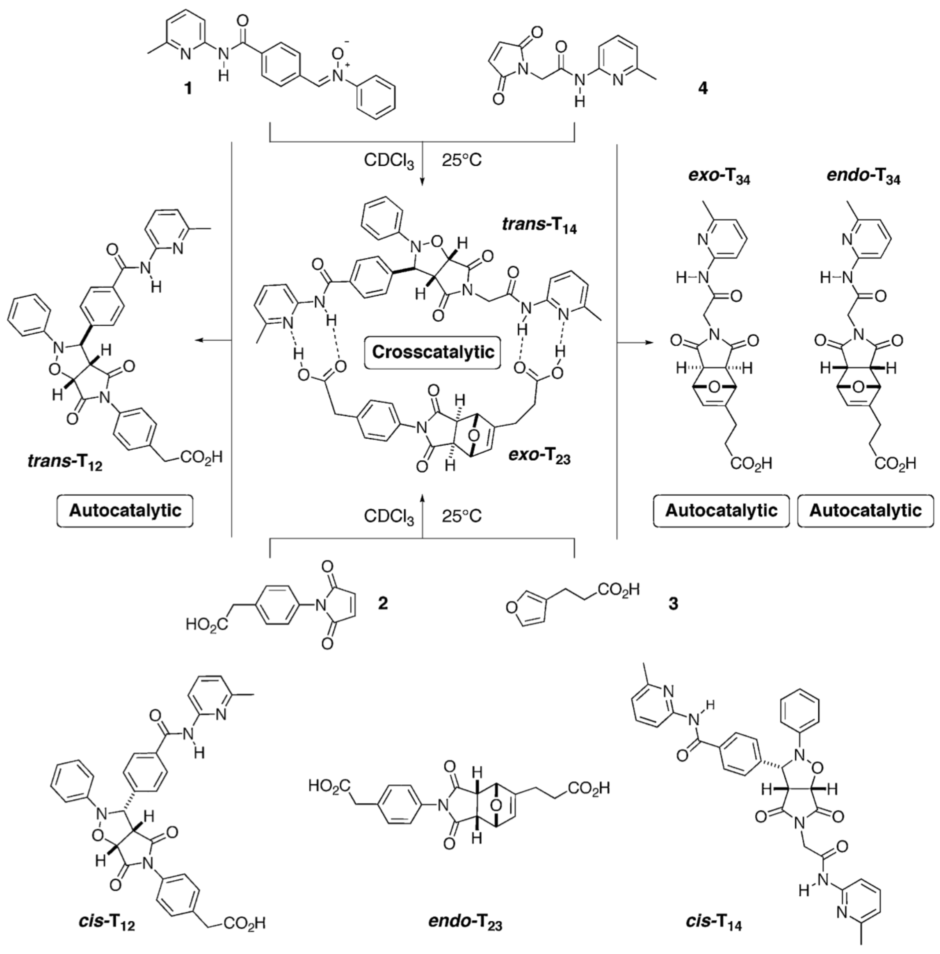


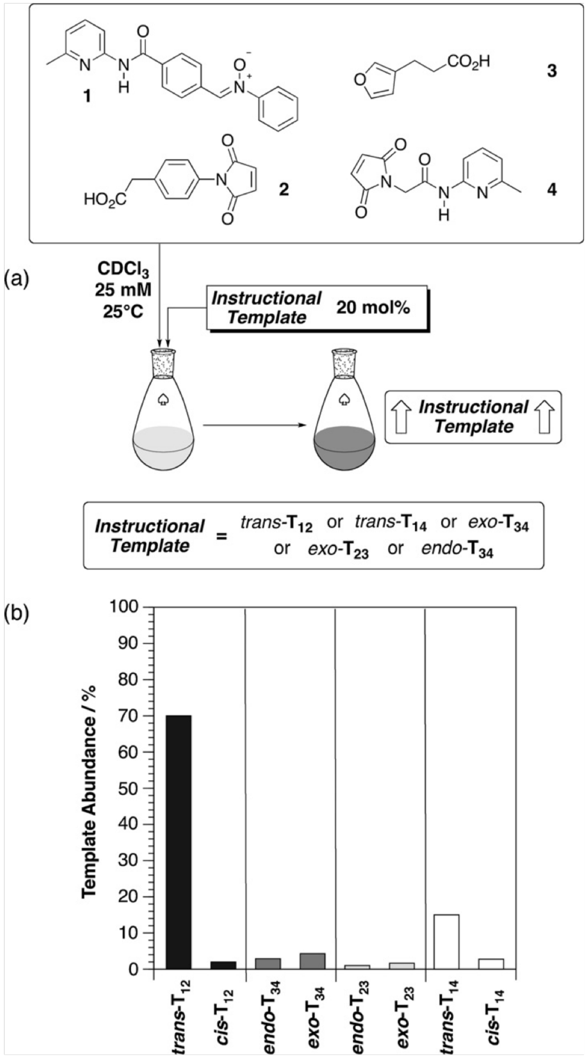


- Chemical reaction networks with self-replication activity had been developed.

Vidonne, A.; Philp, D. *European J. Org. Chem.* **2009**, No. 5, 593–610.

Research background (2)

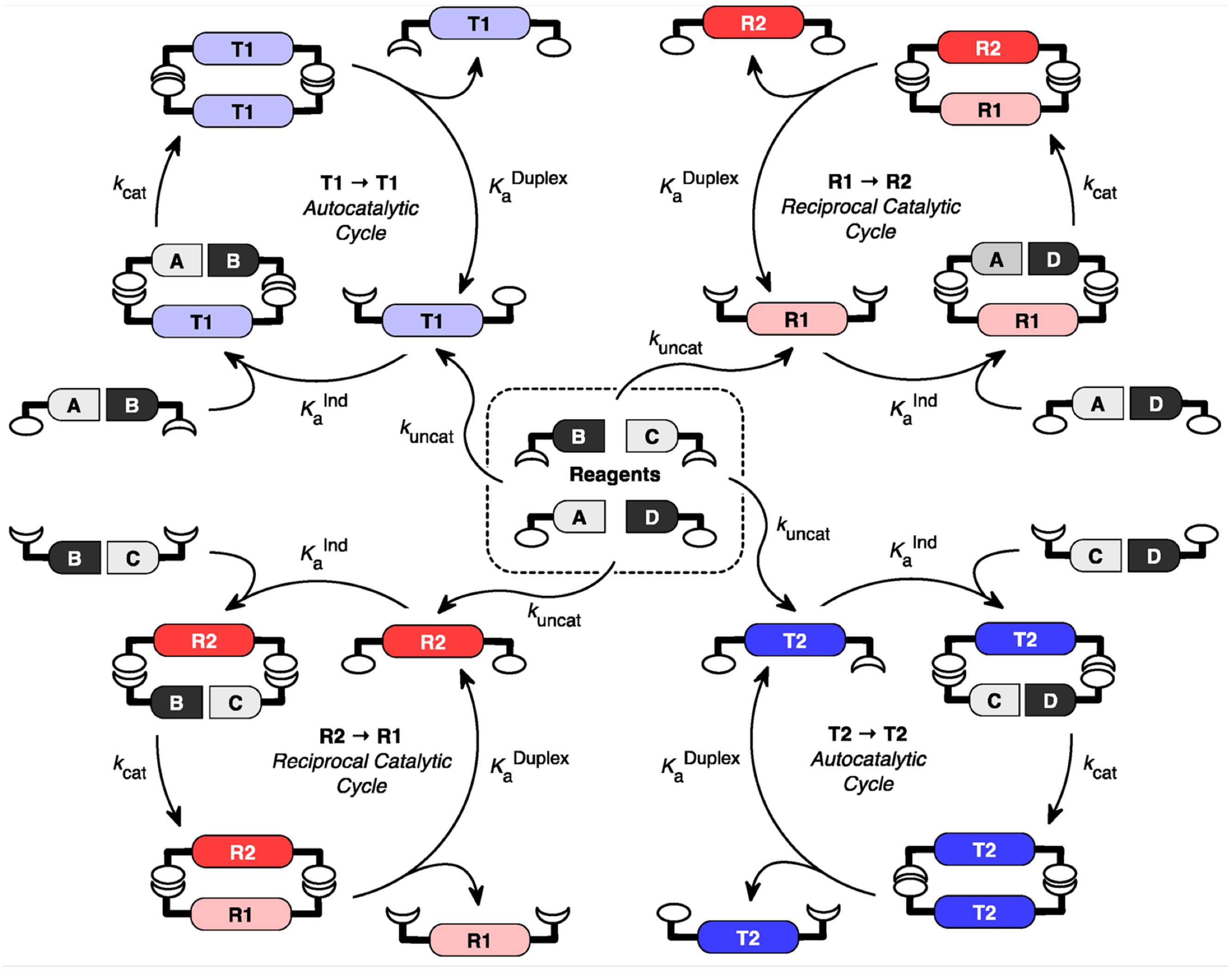




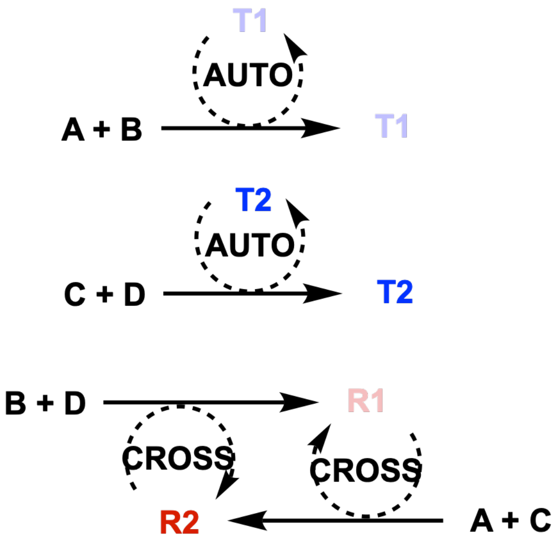
- However, multicyclic networks which can respond to the environmental change (addition of template) was still difficult, because of the different efficiency of each replicator.

Kassianidis, E.; Pearson, R. J. *et al. Faraday Discuss.* **2010**, *145*, 235–254.

Designed multicyclic network



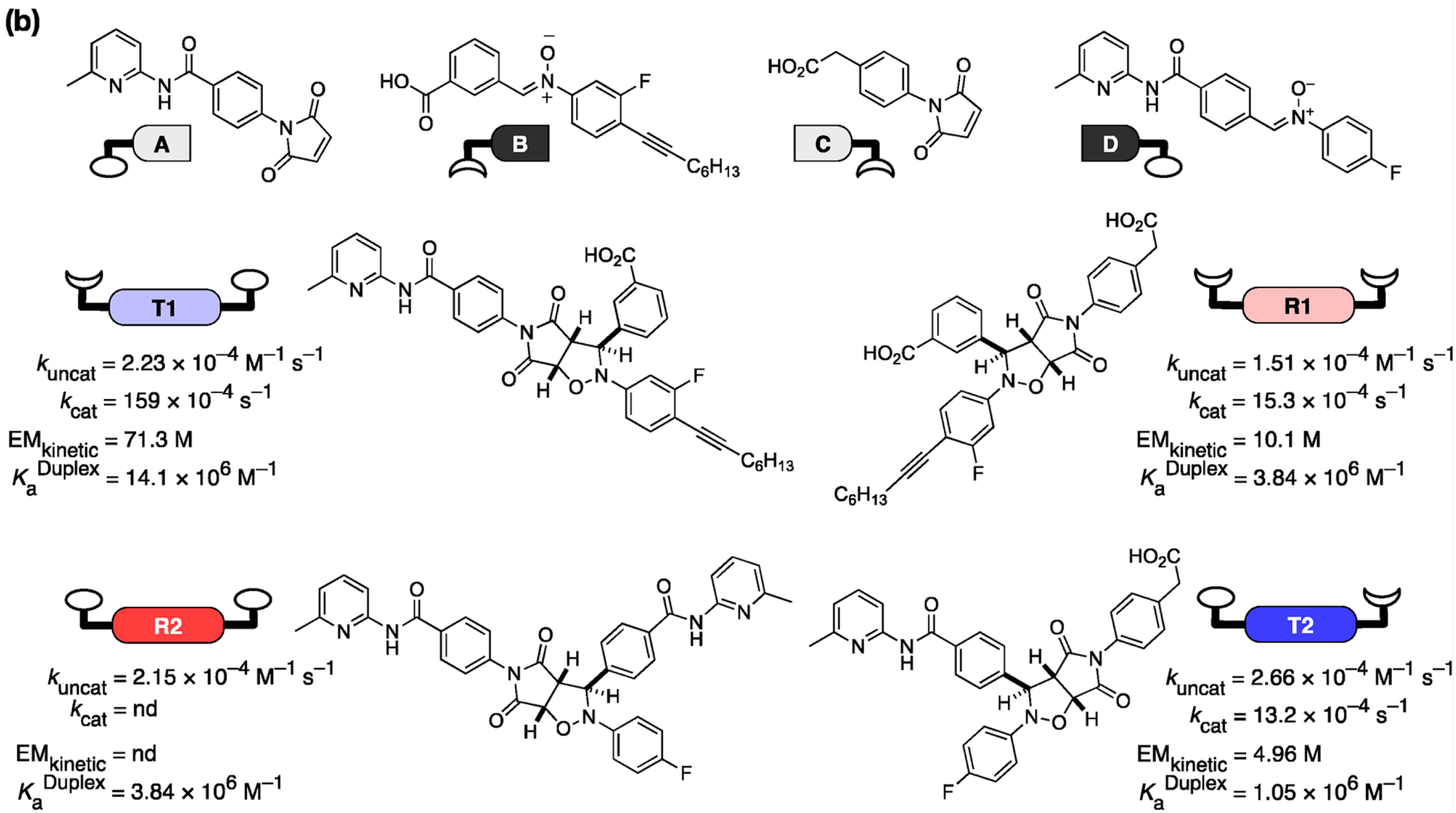
Simplified network



- Reagents **A** to **D** create a network of interdependent replicators.

Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

Components of network



T1

$k_{\text{uncat}} = 2.23 \times 10^{-4}\ \mathrm{M^{-1}\ s^{-1}}$

$k_{\text{cat}} = 159 \times 10^{-4}\ \mathrm{s^{-1}}$

$\mathrm{EM}_{\text{kinetic}} = 71.3\ \mathrm{M}$

$K_a^{\text{Duplex}} = 14.1 \times 10^{6}\ \mathrm{M^{-1}}$

R1

$k_{\text{uncat}} = 1.51 \times 10^{-4}\ \mathrm{M^{-1}\ s^{-1}}$

$k_{\text{cat}} = 15.3 \times 10^{-4}\ \mathrm{s^{-1}}$

$\mathrm{EM}_{\text{kinetic}} = 10.1\ \mathrm{M}$

$K_a^{\text{Duplex}} = 3.84 \times 10^{6}\ \mathrm{M^{-1}}$

R2

$k_{\text{uncat}} = 2.15 \times 10^{-4}\ \mathrm{M^{-1}\ s^{-1}}$

$k_{\text{cat}} = \text{nd}$

$\mathrm{EM}_{\text{kinetic}} = \text{nd}$

$K_a^{\text{Duplex}} = 3.84 \times 10^{6}\ \mathrm{M^{-1}}$

T2

$k_{\text{uncat}} = 2.66 \times 10^{-4}\ \mathrm{M^{-1}\ s^{-1}}$

$k_{\text{cat}} = 13.2 \times 10^{-4}\ \mathrm{s^{-1}}$

$\mathrm{EM}_{\text{kinetic}} = 4.96\ \mathrm{M}$

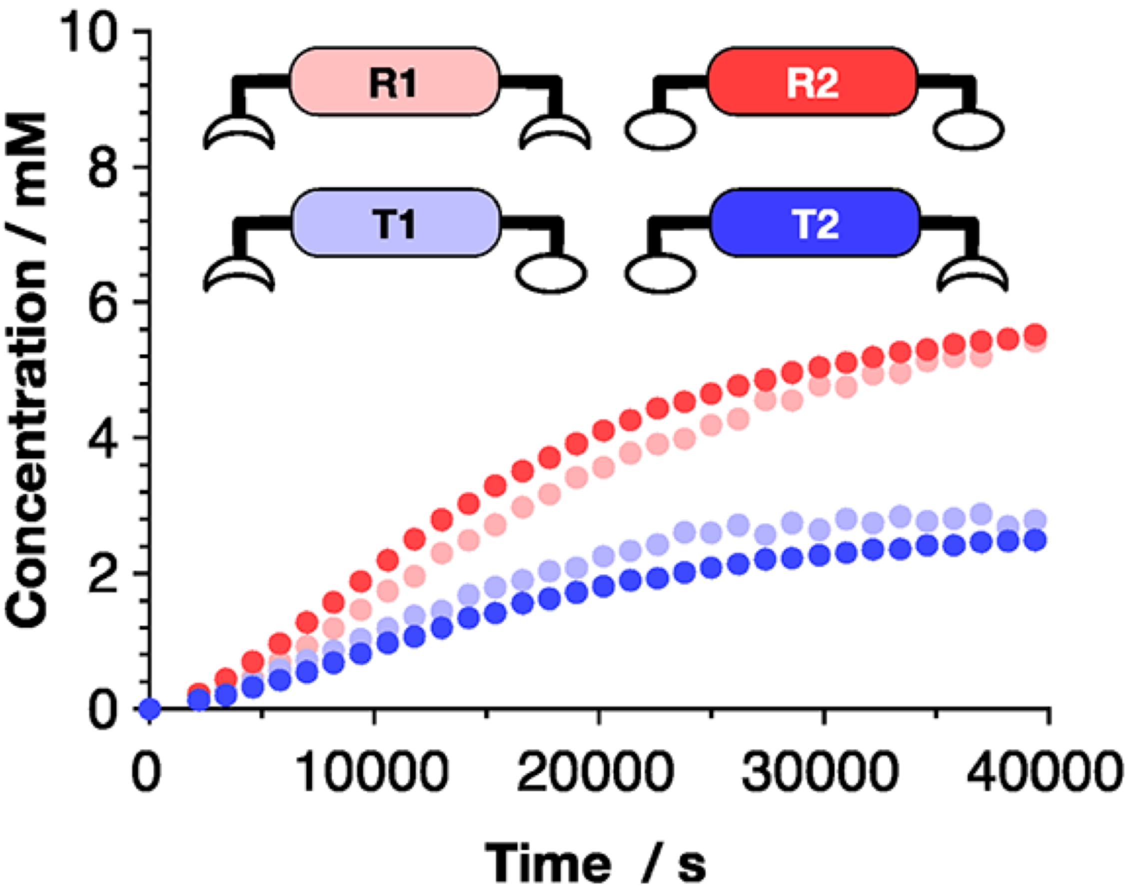
$K_a^{\text{Duplex}} = 1.05 \times 10^{6}\ \mathrm{M^{-1}}$

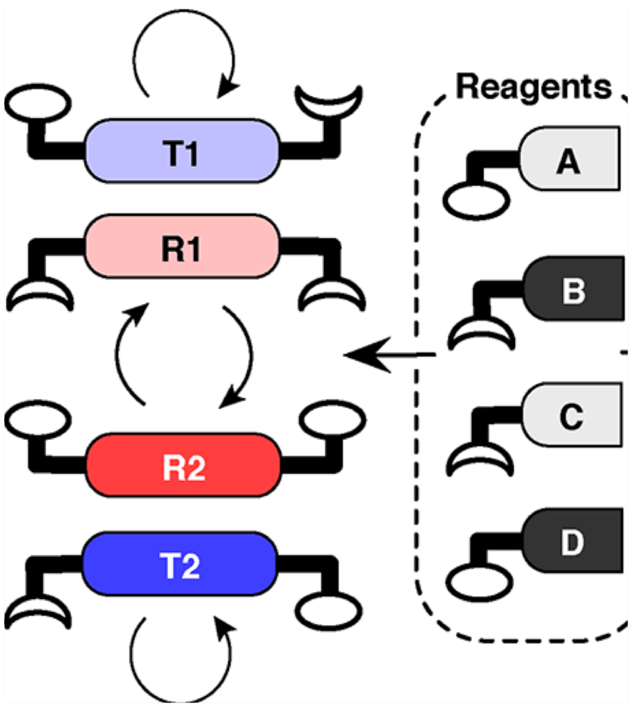
- Pairwise 1,3-dipolar cycloaddition reactions afforded two self-replicators and two reciprocal replicators.
- ^{19}F NMR spectroscopy was used to monitor the concentration of products.

Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

Self-replicating behavior of network

[A]~**[D]** = 10 mM
no T (no template)
once



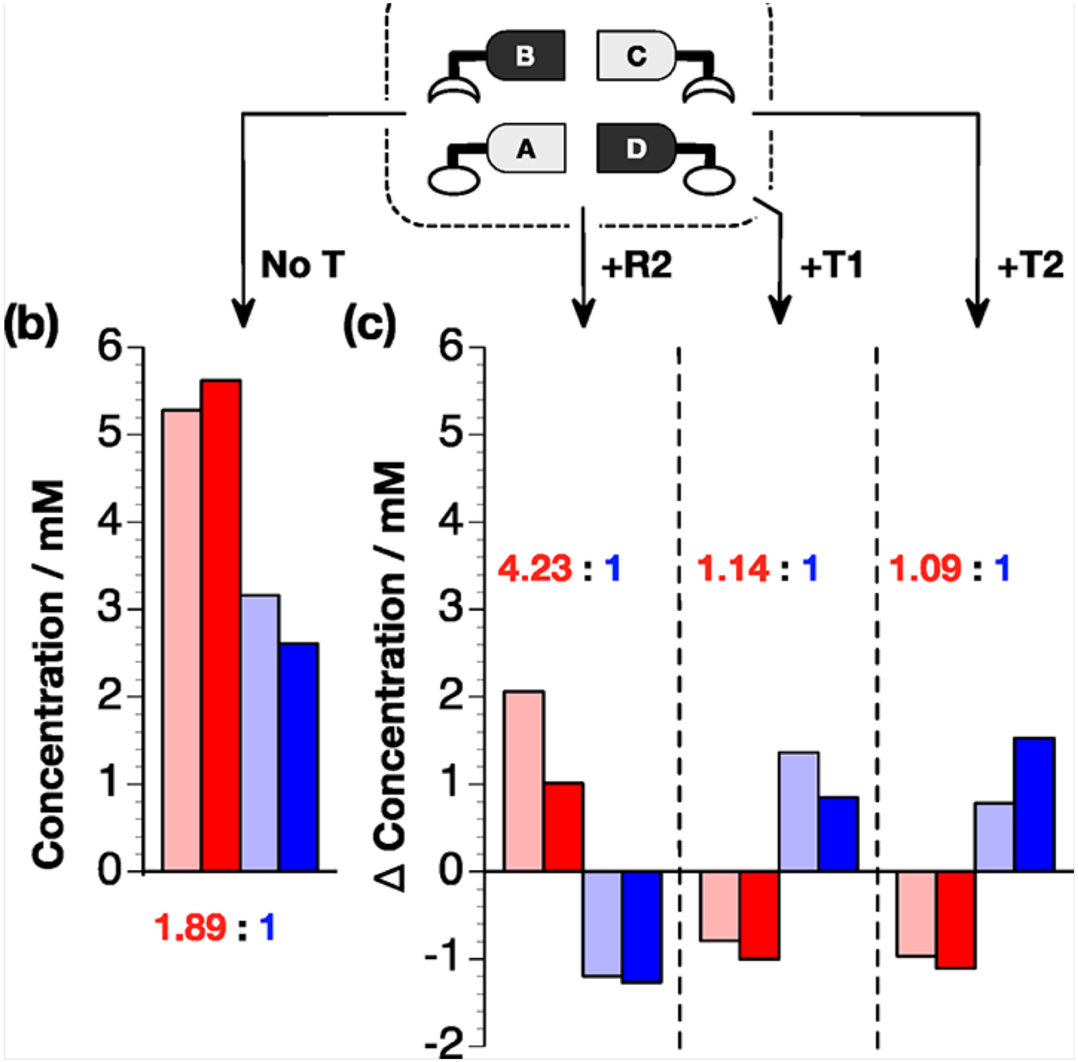


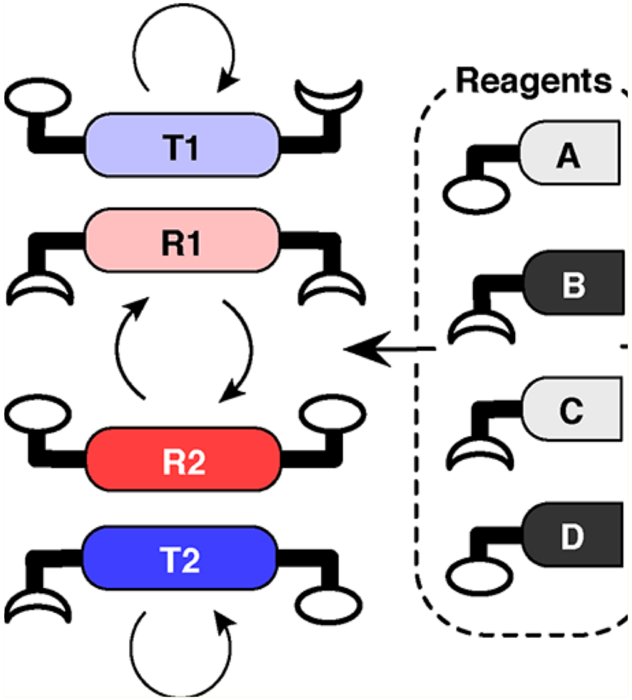
Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

The effect of template molecule to network

experiment

[A]~[D] = 10 mM
no T, R2, T1, T2
once

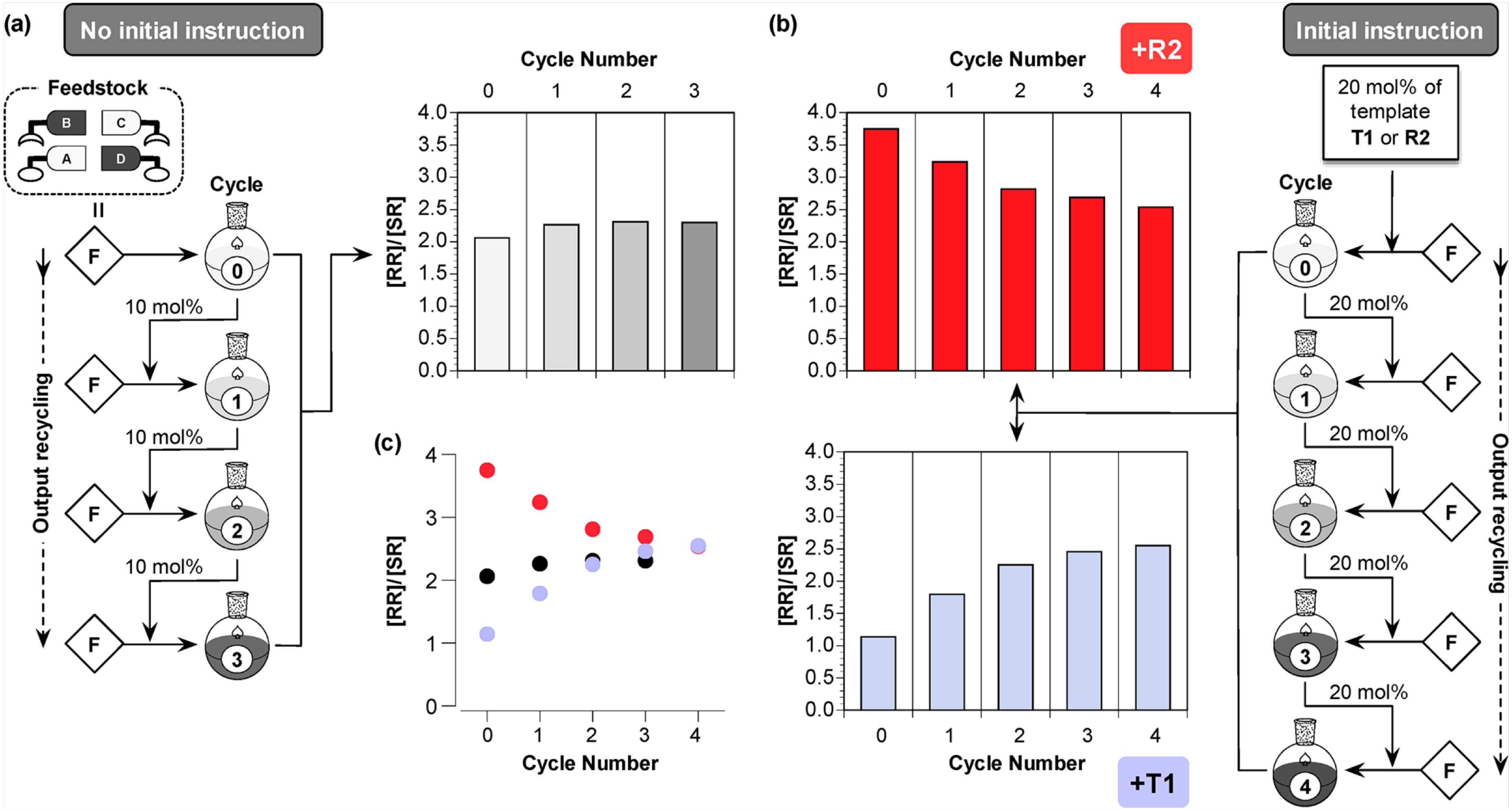




Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

The multicyclic network responded to the environmental change.

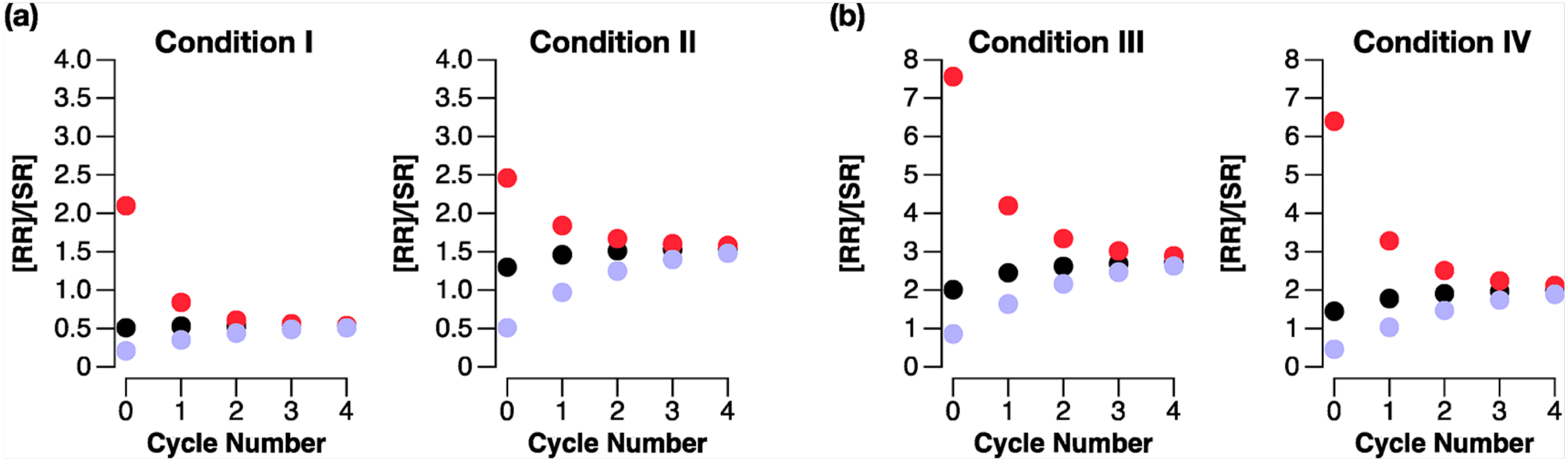
[A]~[D] = 10 mM
no T, R2, T1
5 times



- The composition of network was maintained through sets of serial transfer.

Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

The multicyclic network responded to the environmental change.



[A] = 1 mM
[B]~**[D]** = 10 mM
no T, **R2**, **T1**
5 times

[A]~**[B]** = 5 mM
[C]~**[D]** = 10 mM
no T, **R2**, **T1**
5 times

[A]~**[D]** = 10 mM
no T, **R2**, **T1**
5 times

$2 \times k_{cat}$
(**R2**, **T2**)

[A]~**[D]** = 10 mM
no T, **R2**, **T1**
5 times

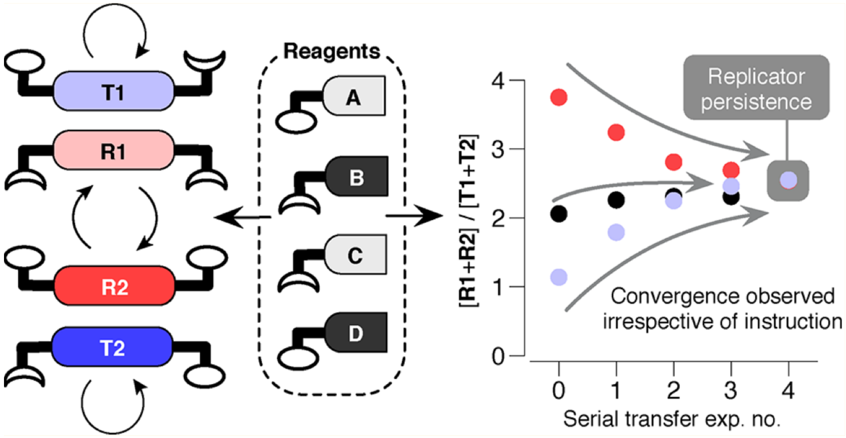
$20 \times K_a^{Duplex}$
([**R1**·**R2**], [**T1**·**T1**], [**T2**, **T2**])

- The persistence was observed when the starting condition and the kinetic or thermodynamic properties of the replicators were changed.

→The persistence observed experimentally is a direct result of the network connectivity.

Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

Multicyclic network

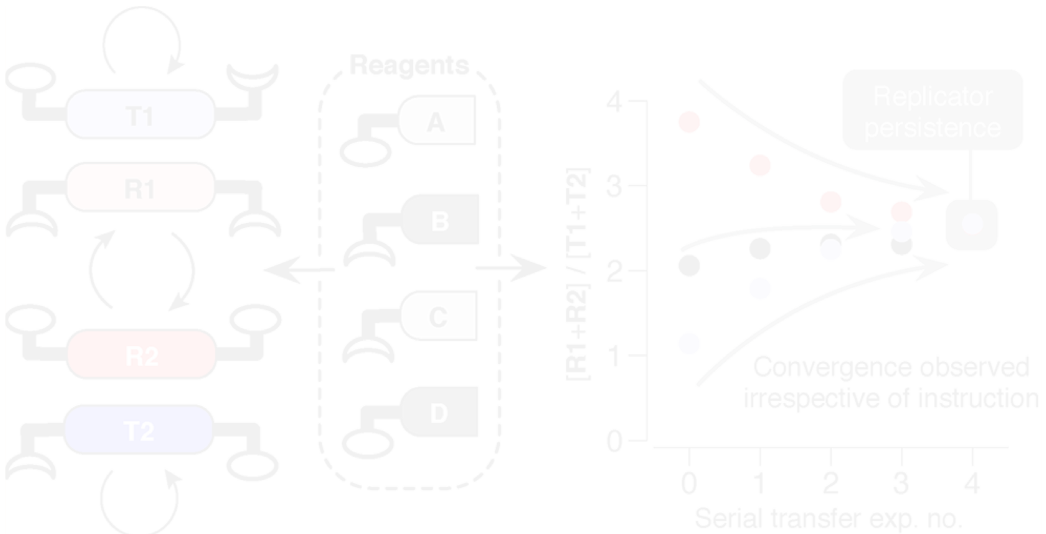


A network of multicyclic replicators can ensure the compositional stability and diversity.

Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

The emergence of complexity using chemical self-replicators

Multicyclic network



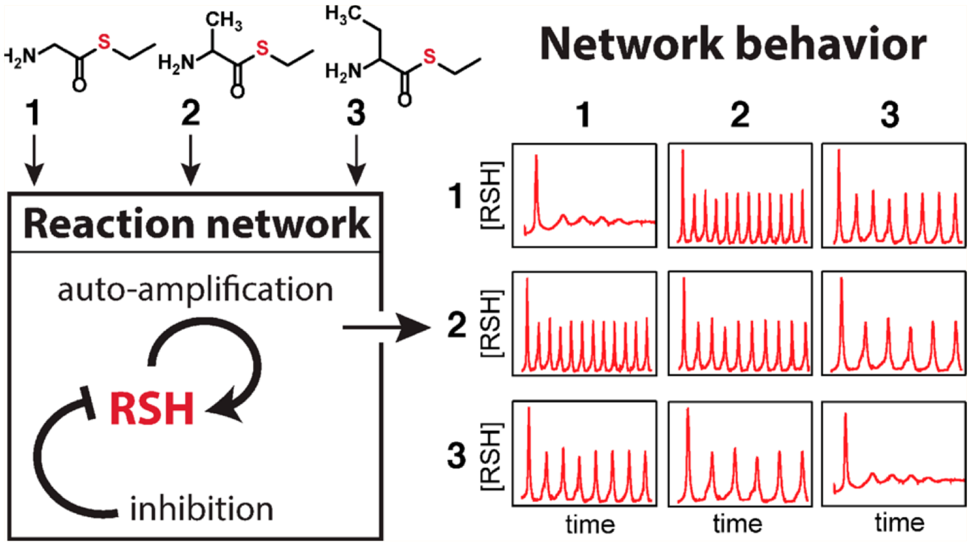
Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

organic small molecule

stable

system-level response

Oscillation network



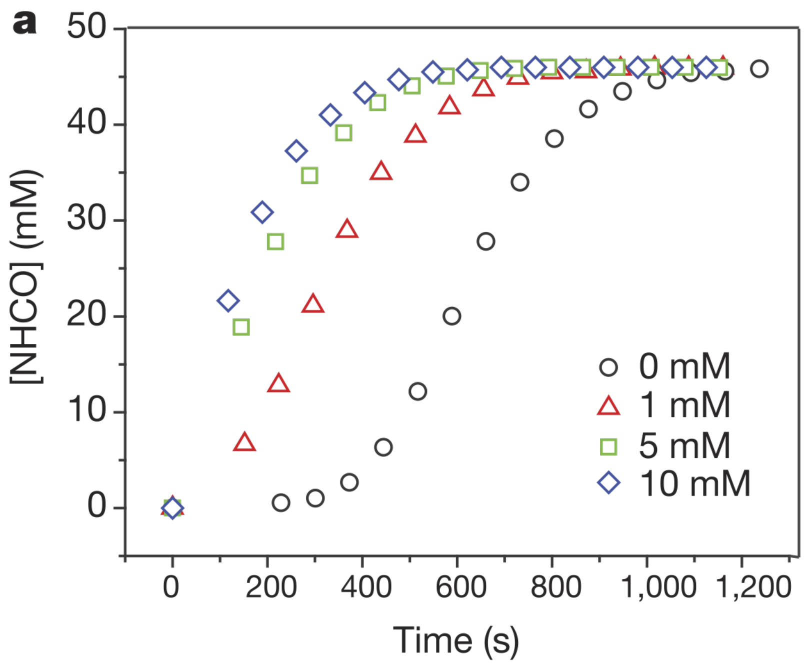
organic small molecule

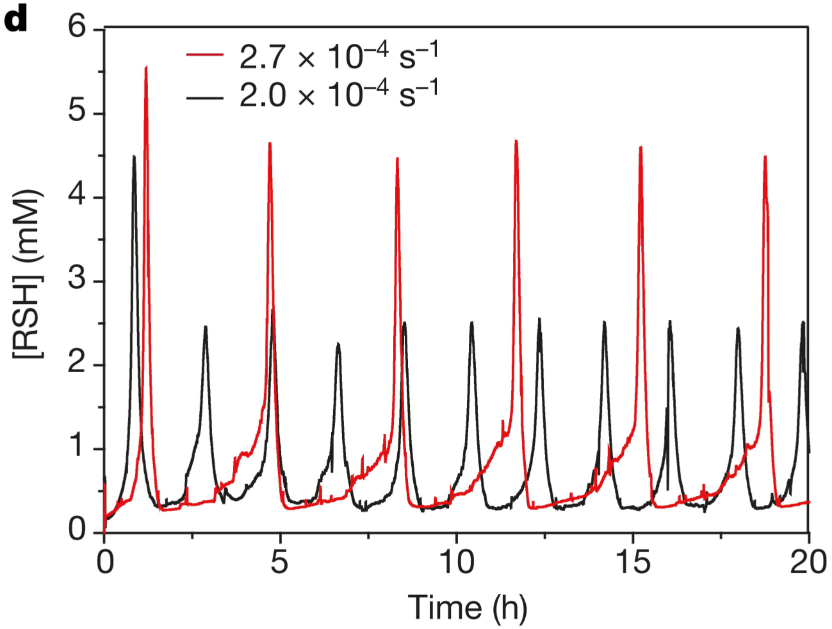
dynamic

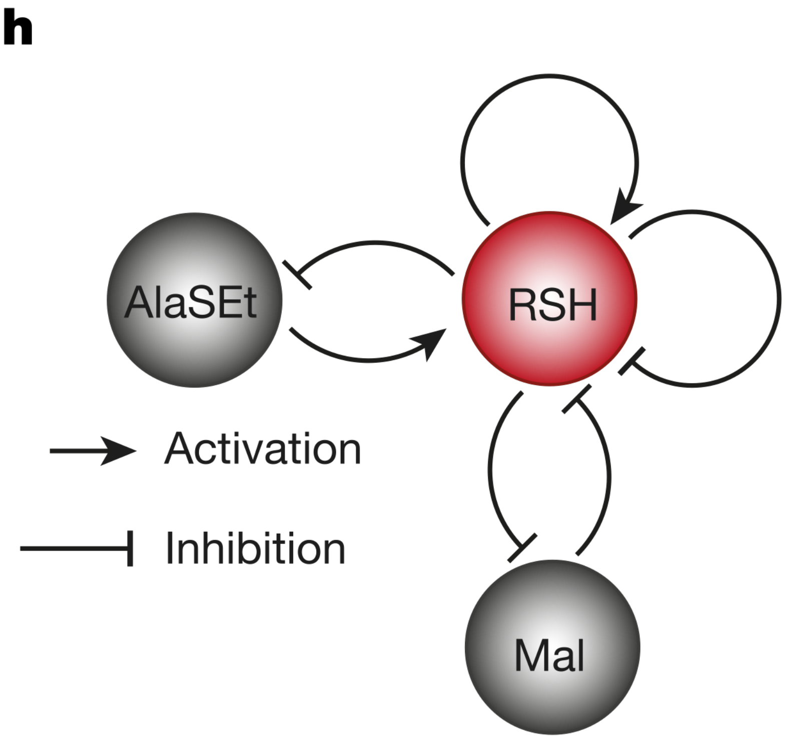
oscillation

Cafferty, B. J.; Wong, A. S. Y. *et al.* *J. Am. Chem. Soc.* **2019**, *141* (20), 8289–8295.

Research background

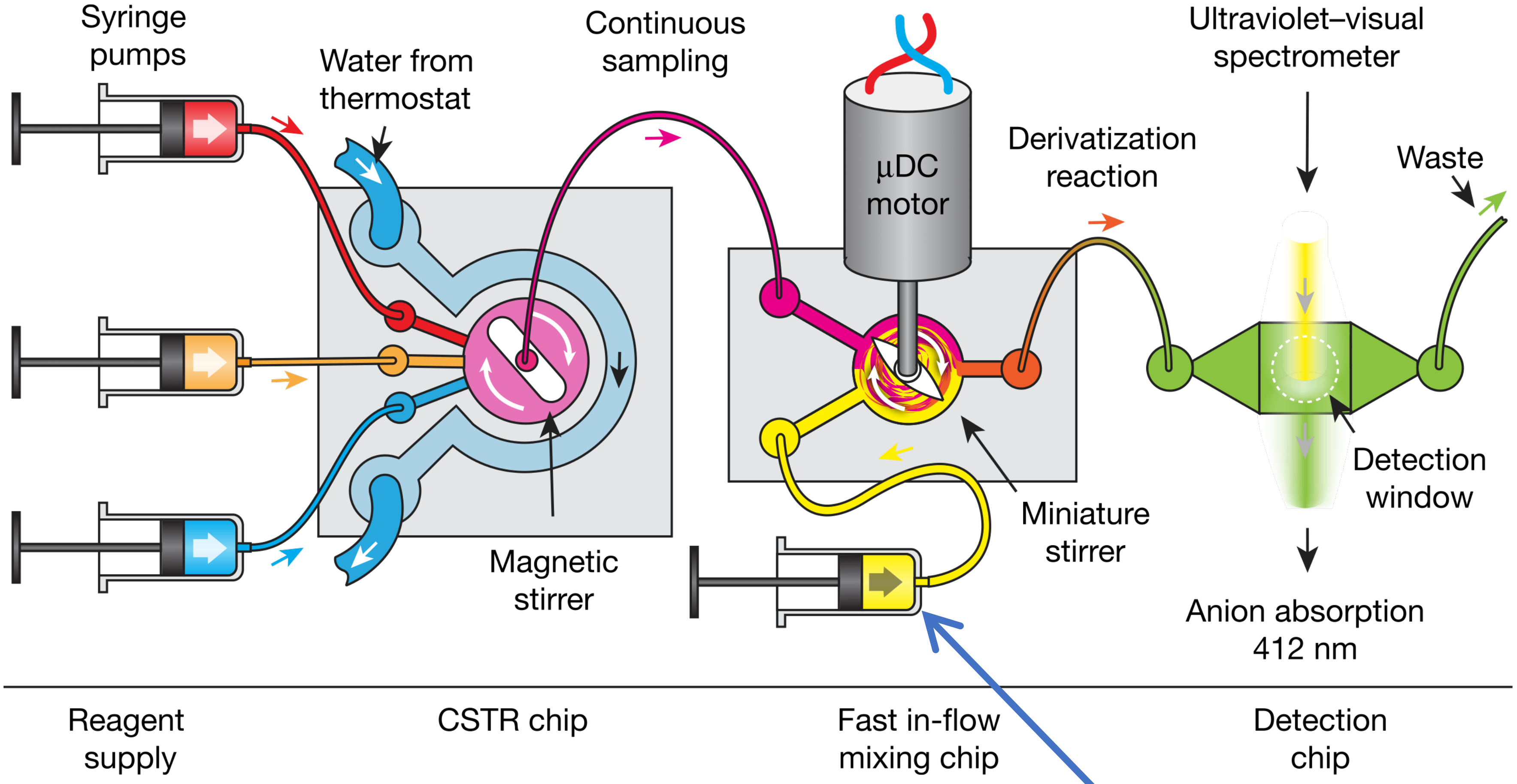






Semenov, S. N.; Kraft, L. J. *Nature* **2016**, *537* (7622), 656–660.

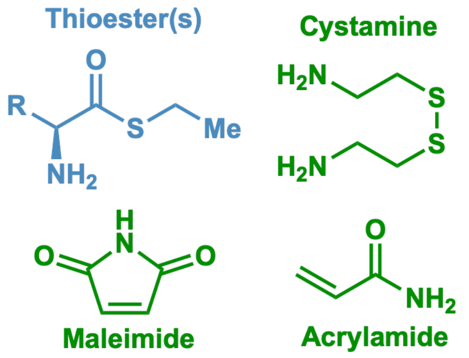
CSTR (continuously stirred tank reactor)

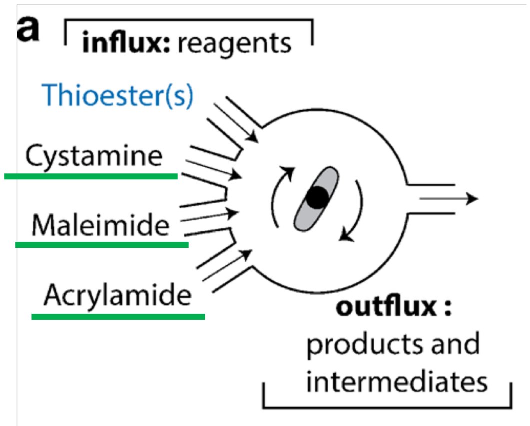


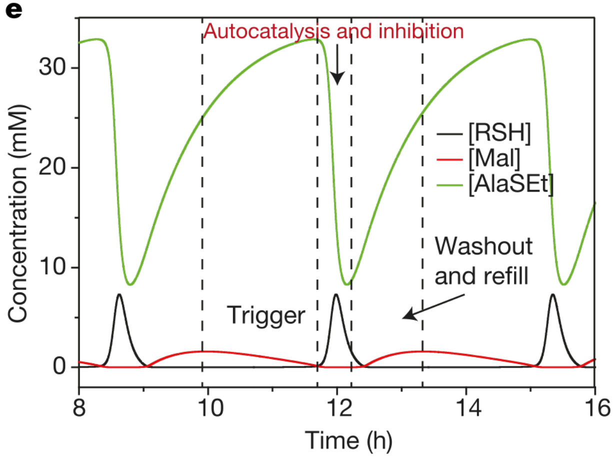
Ellman’s reagent
(to measure R-SH)

Semenov, S. N.; Kraft, L. J. *Nature* **2016**, *537* (7622), 656–660.

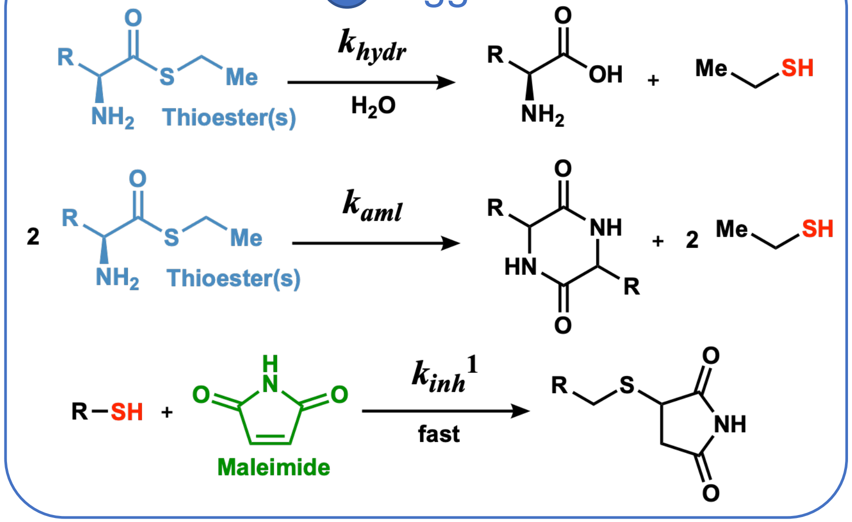
The mechanism of the oscillation network

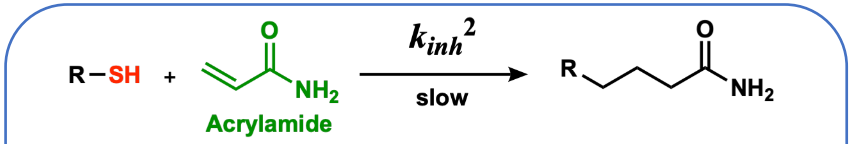






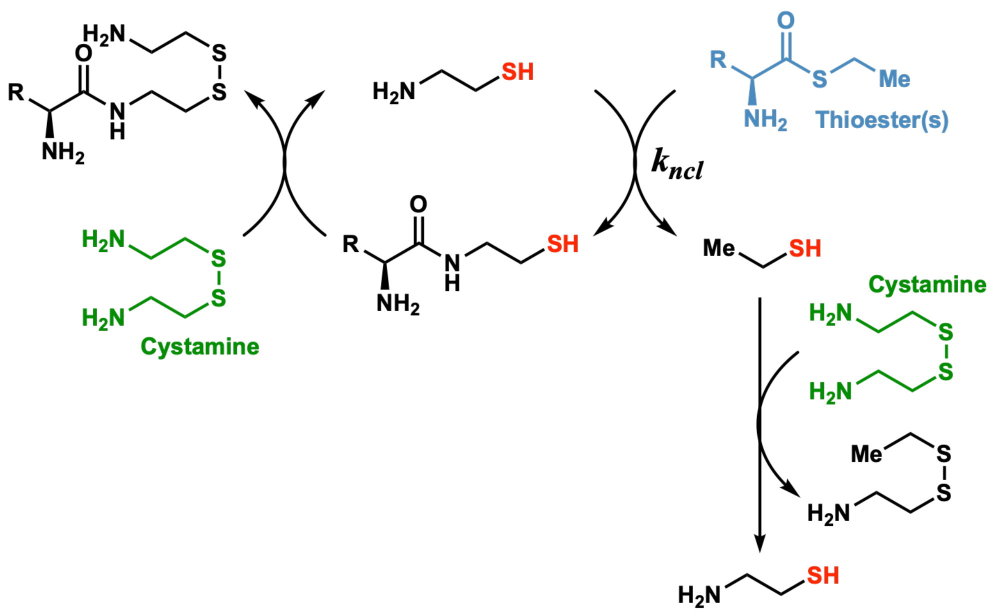
i Trigger





iii Exhaustion

ii Amplification

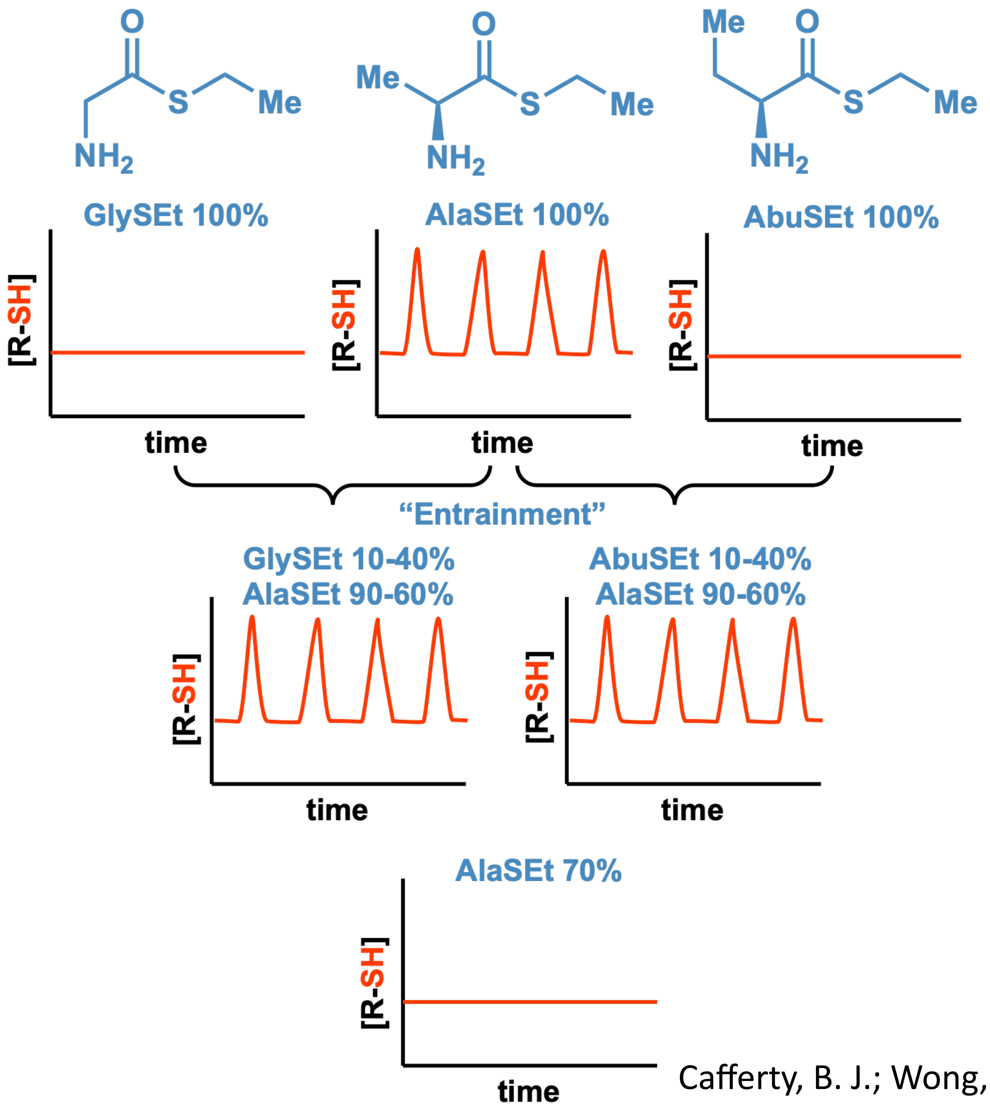


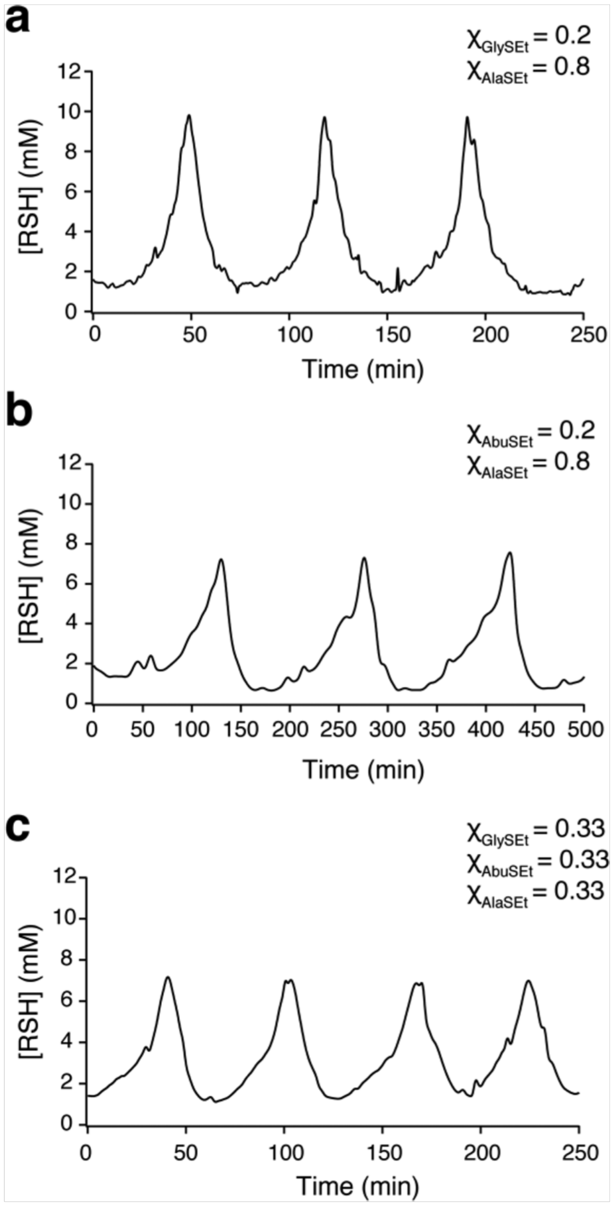
Semenov, S. N.; Kraft, L. J. *et al. Nature* **2016**, *537* (7622), 656–660.

Cafferty, B. J.; Wong, A. S. Y. *et al. J. Am. Chem. Soc.* **2019**, *141* (20), 8289–8295.

Entrainment of the non-oscillatory components by the oscillatory one

thioester	k_{hyd} (s^{-1}, $\times 10^{-5}$)	k_{aml} (M^{-1} s^{-1}, $\times 10^{-2}$)	k_{ncl} (M^{-1} s^{-1})
GlySEt	9.0	1.7	1.50
AlaSEt	1.1	n.d.^{a}	0.47
AbuSEt	0.37	n.d.	0.23



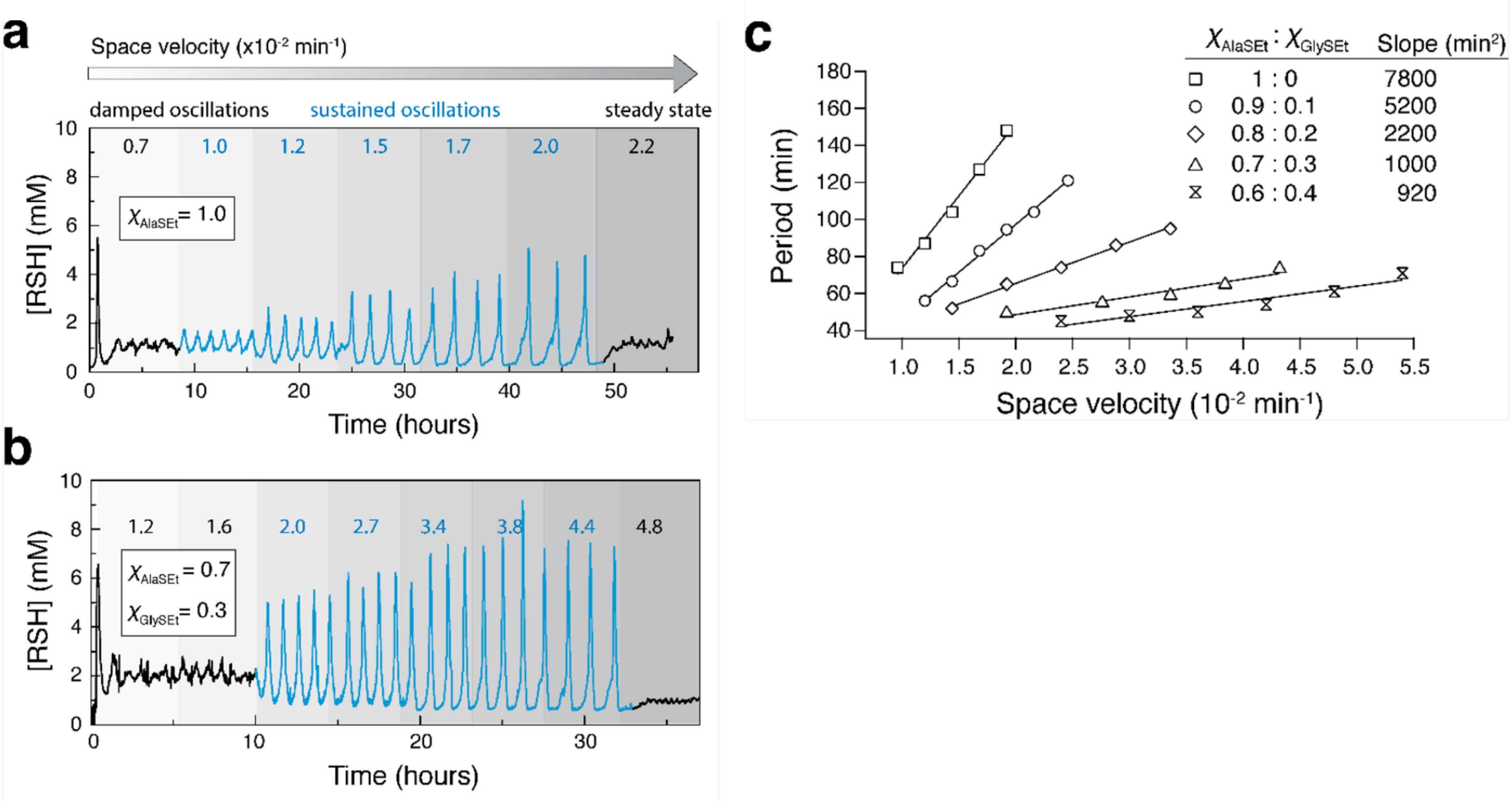


Cafferty, B. J.; Wong, A. S. Y. *et al. J. Am. Chem .Soc.* **2019**, *141* (20), 8289–8295.

Increased robustness of heterogenous networks

experiment

space velocity [min^{-1}]
= flow rate / reactor volume

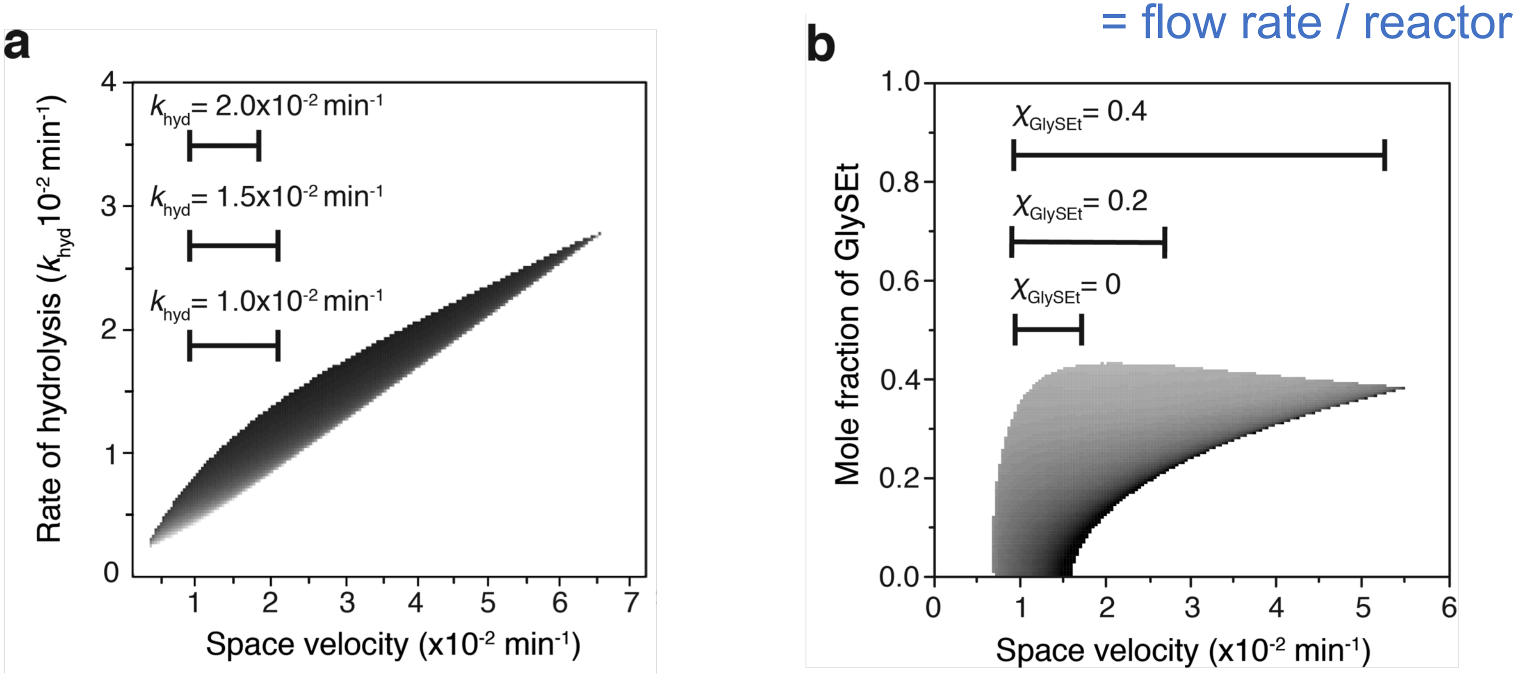


- The network with AlaSEt and GlySEt has increased robustness of ①the range of space velocity and ②the oscillation period than the network with only AlaSEt.

Cafferty, B. J.; Wong, A. S. Y. *et al. J. Am. Chem .Soc.* **2019**, *141* (20), 8289–8295.

Increased robustness of heterogenous networks (mechanism)

space velocity [min^{-1}]
= flow rate / reactor volume

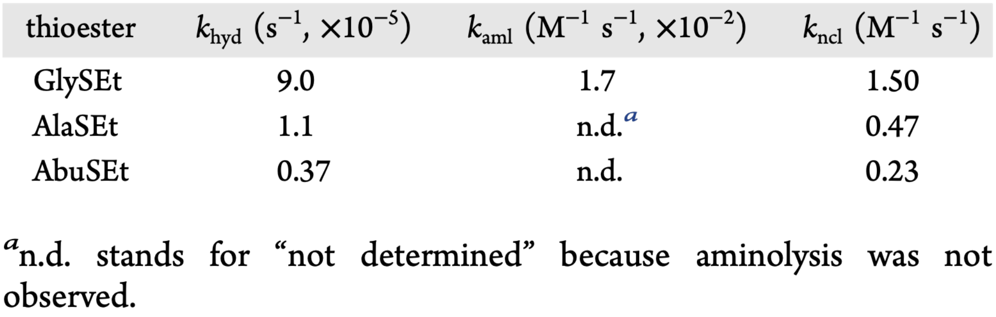


- To maintain oscillation in higher space velocity, higher hydrolysis rate is needed.
- The robustness of ①the range of space velocity was explained by two factors; (i) [thioester] increases more rapidly at larger space velocities, (ii) GlySEt is more sensitive to [thioester] because of $k_{aml}[\mathrm{GlySEt}]^2$.
- The robustness of ②the oscillation period was because more rapid ethanethiol formation decreases the oscillation period.

→The heterogenous networks can dynamically compensate for their environmental changes.

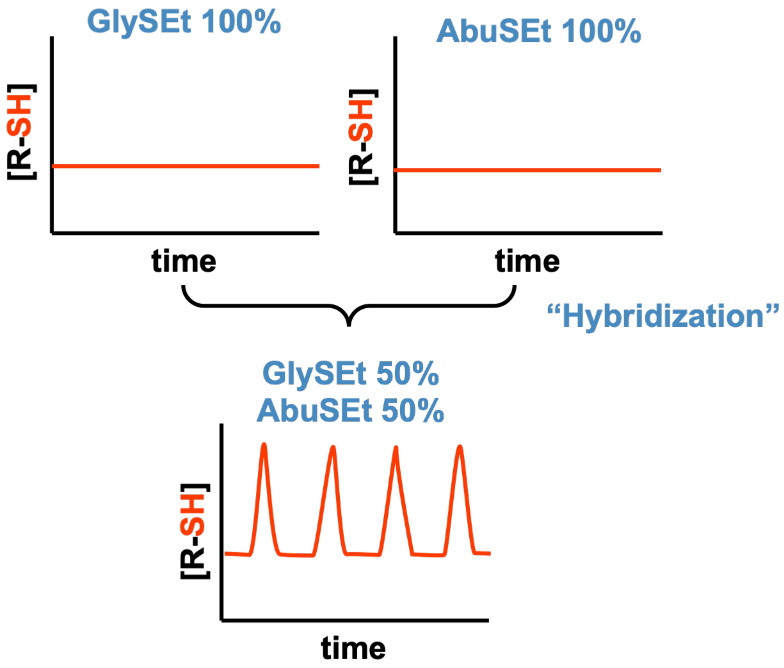
Cafferty, B. J.; Wong, A. S. Y. *et al. J. Am. Chem .Soc.* **2019**, *141* (20), 8289–8295.

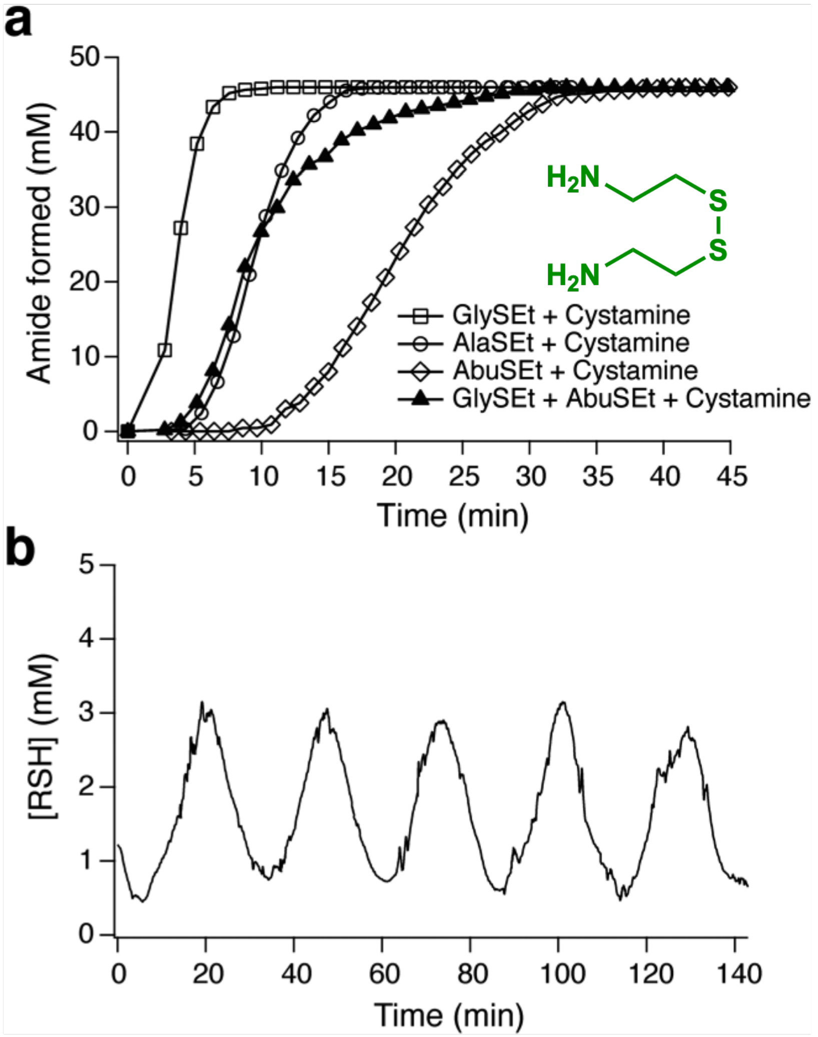
Oscillation in a mixture of non-oscillatory components (hybridization)



thioester	k_{hyd} (s^{-1}, ×10^{-5})	k_{aml} (M^{-1} s^{-1}, ×10^{-2})	k_{ncl} (M^{-1} s^{-1})
GlySEt	9.0	1.7	1.50
AlaSEt	1.1	n.d.[a]	0.47
AbuSEt	0.37	n.d.	0.23

[a] n.d. stands for “not determined” because aminolysis was not observed.





- The network with GlySEt and AbuSEt oscillated, even though neither GlySEt nor AbuSEt oscillated as a single component.

→Multiple reactions can act in a complementary way to yield complex behaviors.

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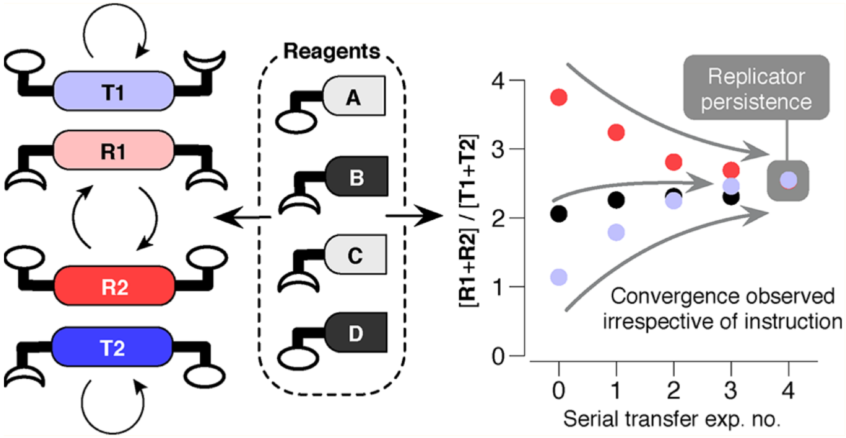
short summary

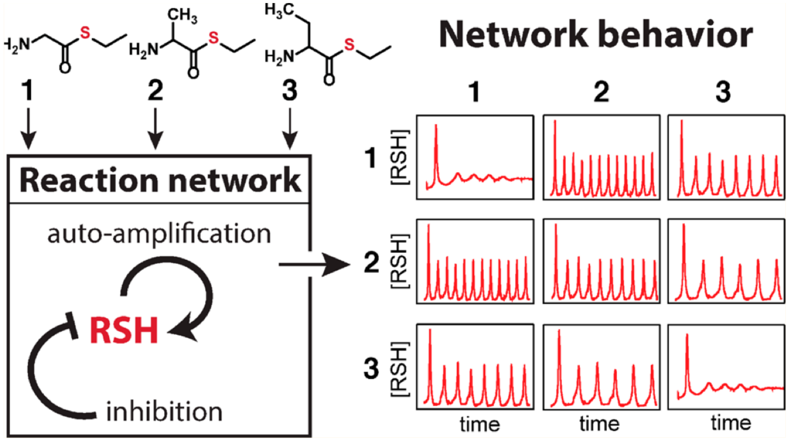
Multicyclic network



A network of multicyclic replicators can ensure the persistence of chemical constitutions.

Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

Oscillation network

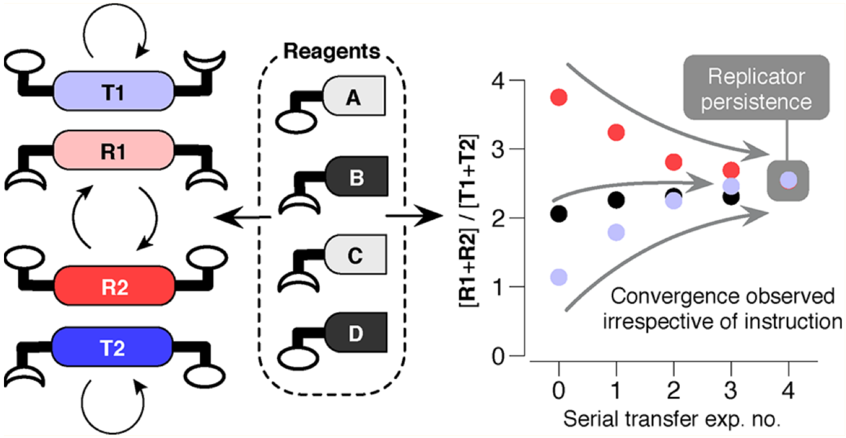


A heterogenous network of replicators can promote complex behaviors.

Cafferty, B. J.; Wong, A. S. Y. *et al.* *J. Am. Chem. Soc.* **2019**, *141* (20), 8289–8295.

short summary

Multicyclic network



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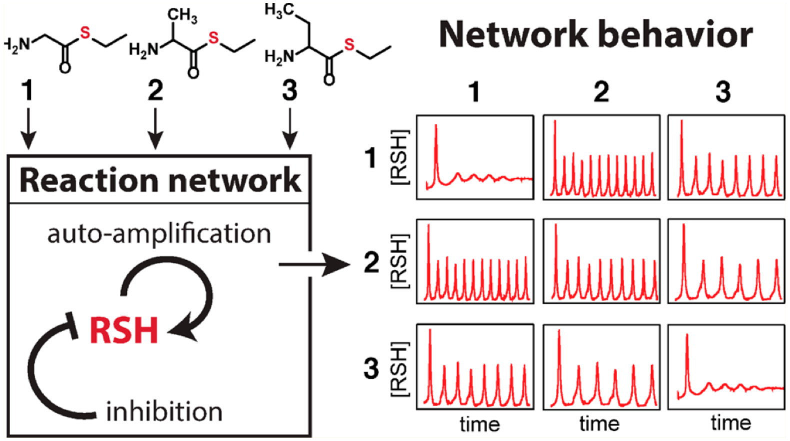
Oscillation network



A heterogenous network of replicators can promote complex behaviors.

Cafferty, B. J.; Wong, A. S. Y. *et al.* *J. Am. Chem. Soc.* **2019**, *141* (20), 8289–8295.

By building synthetic replicators using small organic molecules, we can identify principles of the emergence of complexity, which is relevant to the origin of life.

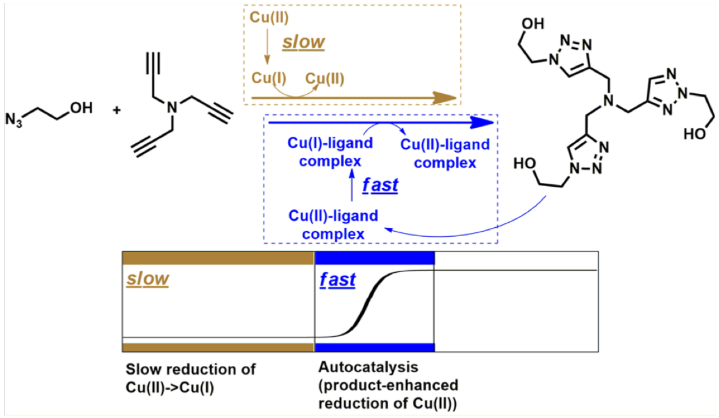
Contents

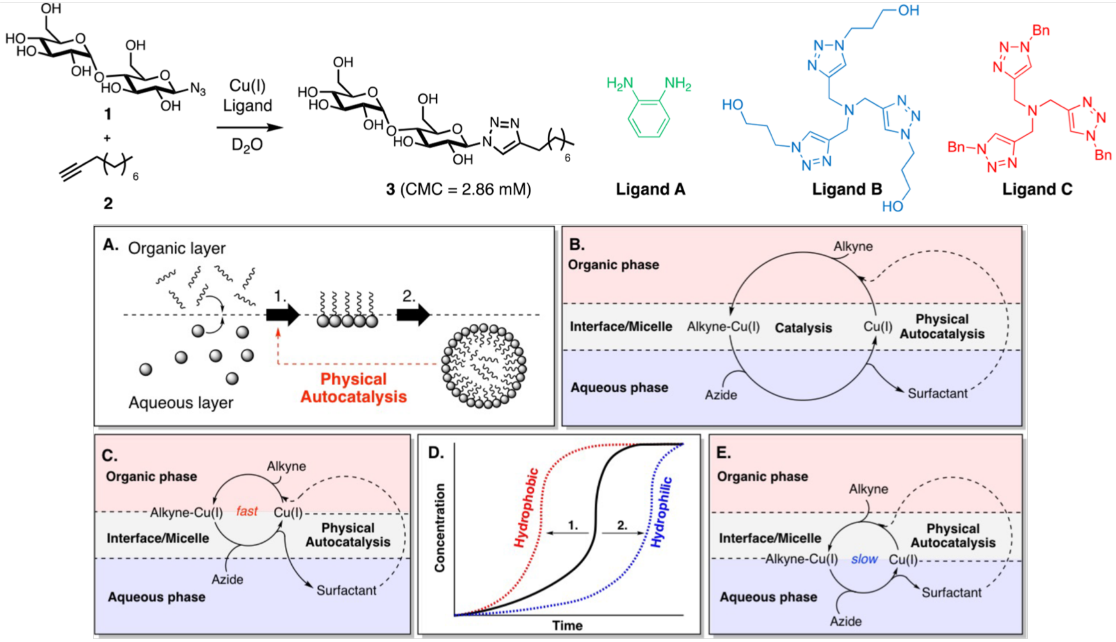
1. Introduction
    - Networks of organic chemical reactions in biological systems
    - The origin of life
        - two approaches
        - top-down approaches
        - bottom-up approaches
            - open-ended evolution and synthetic replicators
            - oscillation and synthetic replicators
    - Applications of synthetic replicators

2. The emergence of complexity using chemical self-replicators
    - The mechanism of chemical self-replicators
    - Development of chemical self-replicators
    - Multicyclic network
    - Oscillation network
    - Short summary

3. Future directions and challenges
4. Summary

Future directions and challenges





- Bridging the gap between synthetic replicators and living systems
  - Shifting away from homogenous and stable condition to heterogenous and non-equilibrium conditions
  - Integrating replication with metabolism and compartmentalization

→development of artificial replicators that can undergo open-ended evolution

- Further applications
  - Development of replicators with a broad range of substrates
  - Development of functional material

Kosikova, T.; Philp, D. *Chem. Soc. Rev.* **2017**, *46* (23), 7274–7305.
Semenov, S. N.; Belding, L. *et al. J. Am. Chem. Soc.* **2018**, *140* (32), 10221–10232.
Post, E. A. J.; Fletcher, S. P. *J. Org. Chem.* **2019**, *84* (5), 2741–2755.

Summary

- Development of chemical self-replicators is important to understand the origin of life and develop more complex systems.

- In addition to their scientific significance, chemical self-replicators may have potential to other applications.

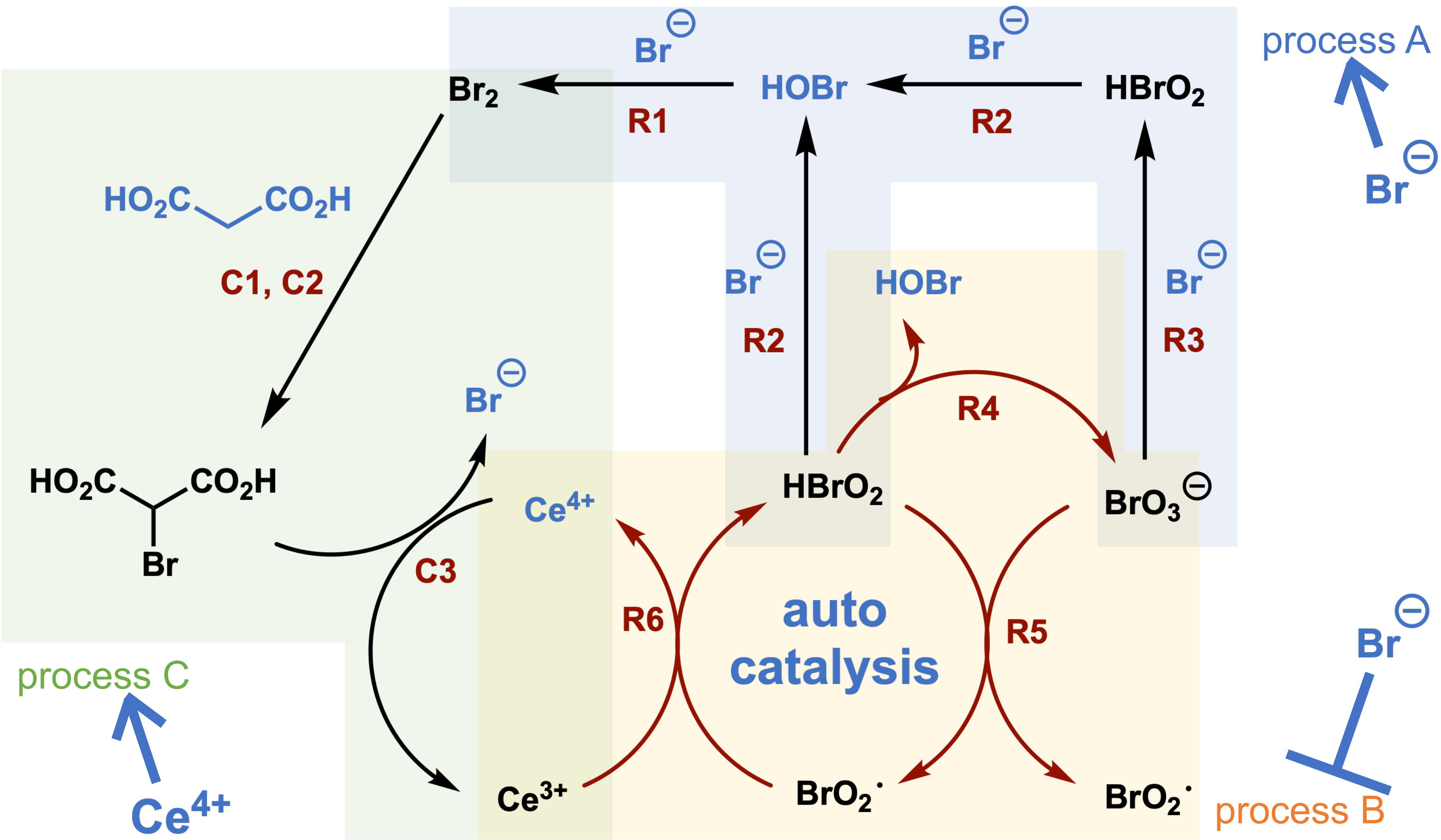
- By building synthetic replicators using small organic molecules, we have identified some principles of the emergence of complexity, which is relevant to the origin of life.

- To develop open-ended evolution system, using non-equilibrium conditions and integrating replication with metabolism and compartmentalization are needed.

- For further applications, development of replicators with a broad range may be important.

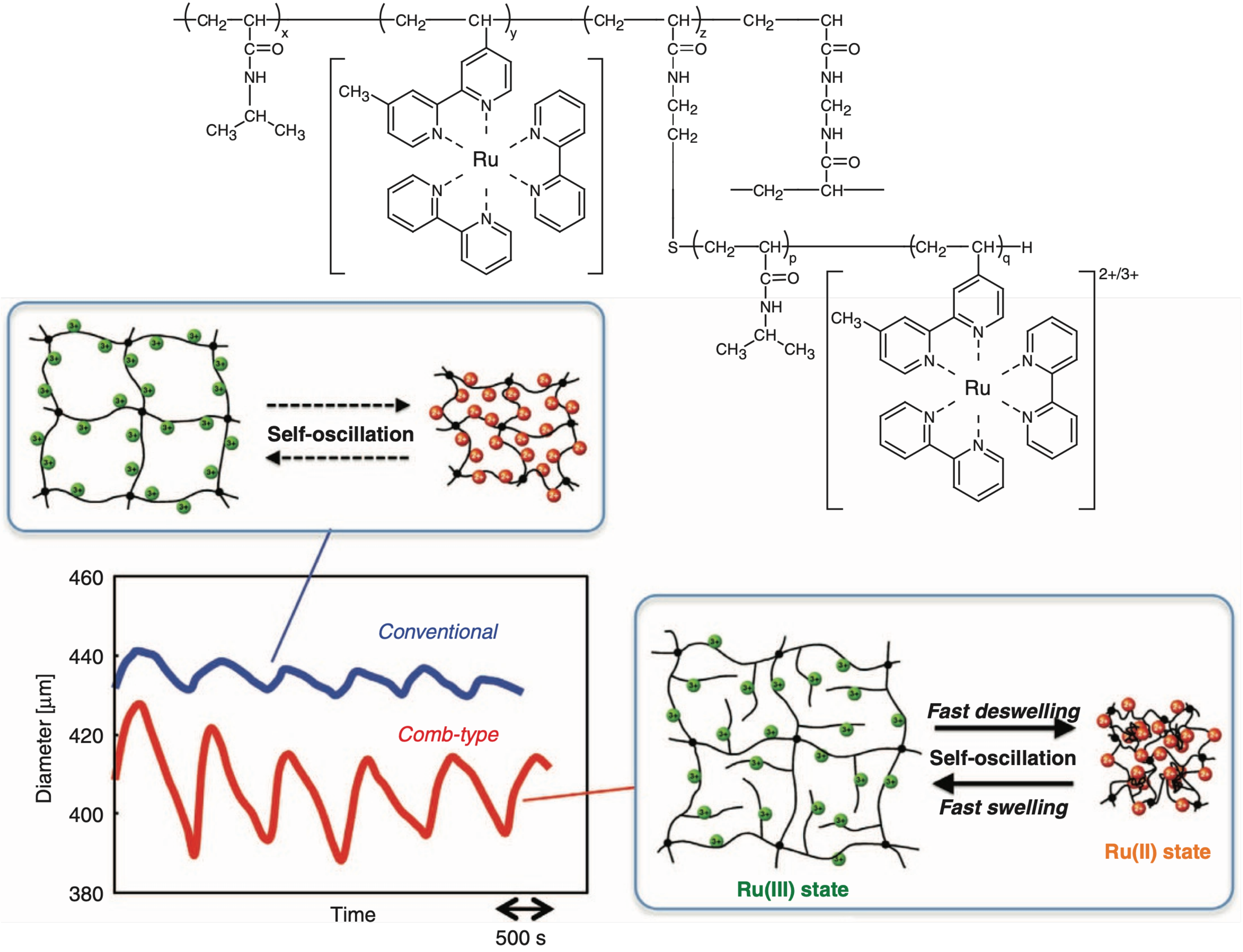
Appendix

Belousov-Zhabotinsky reaction: FKN mechanism



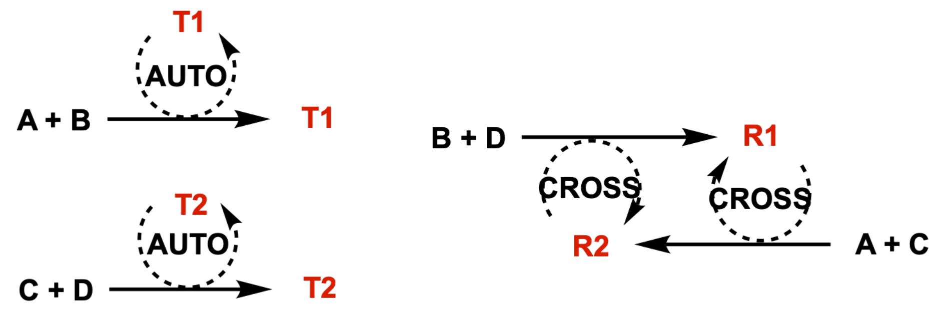
Field, R. J.; Koros, E *et al. J. Am. Chem. Soc.* **1972**, *94* (25), 8649–8664.
Field, R. J. *J. Chem. Phys.* **1975**, *63* (6), 2289–2296.

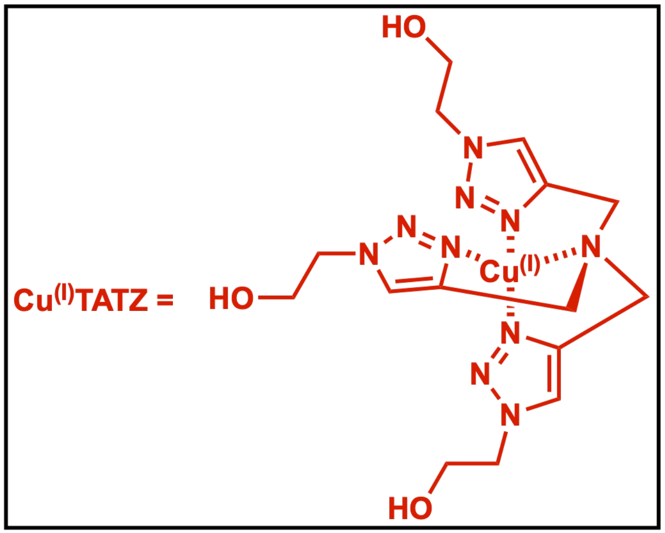
Belousov-Zhabotinsky reaction and functional material



Yoshida, R.; Ueki, T. *NPG Asia Mater.* **2014**, *6* (6), e107–e107.

Simple representation of systems mentioned in this seminar





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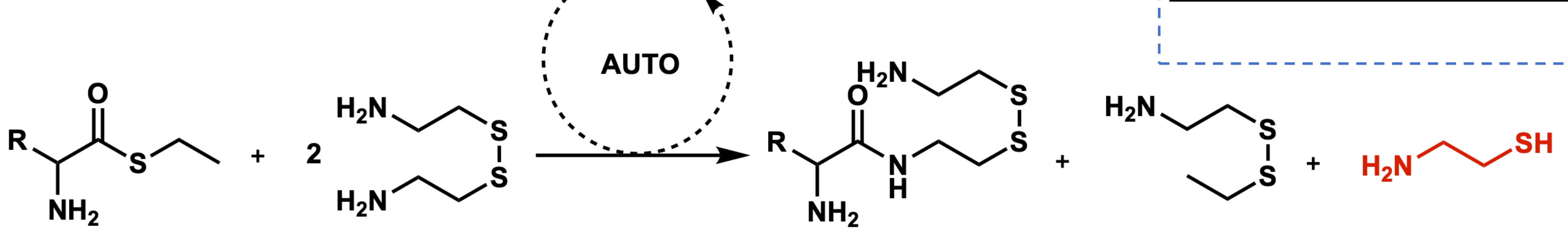

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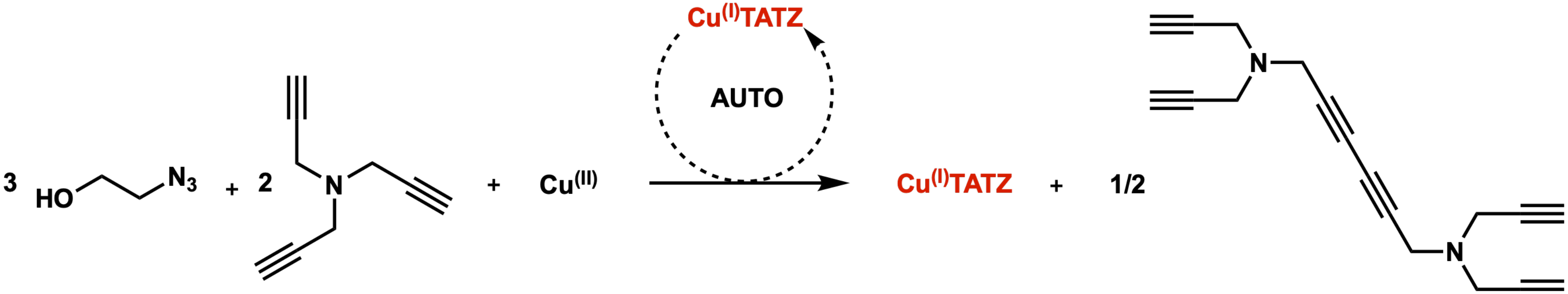


Semenov, S. N.; Belding, L. *et al.* *J. Am. Chem. Soc.* **2018**, *140* (32), 10221–10232.

NMR measurement

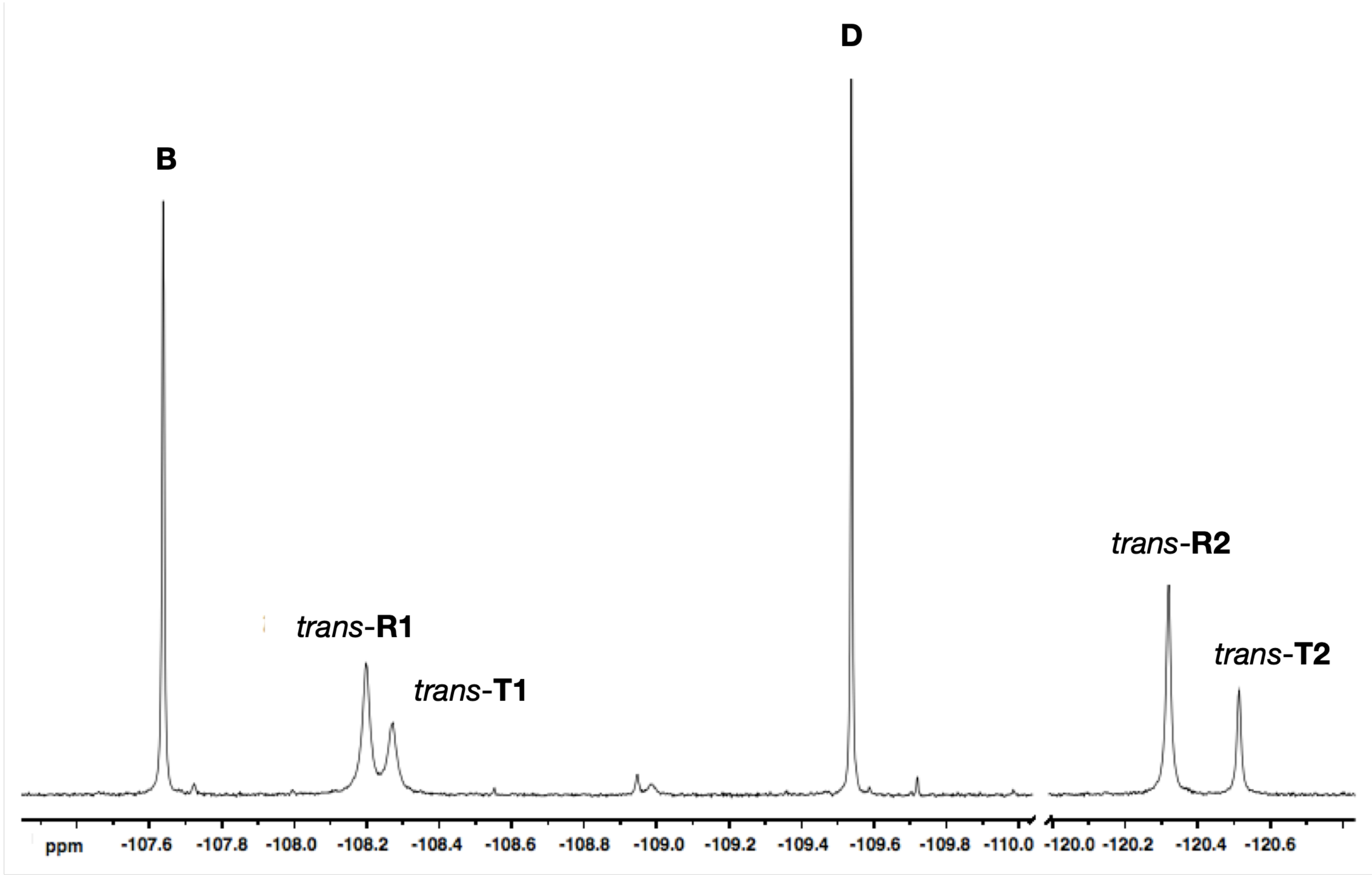
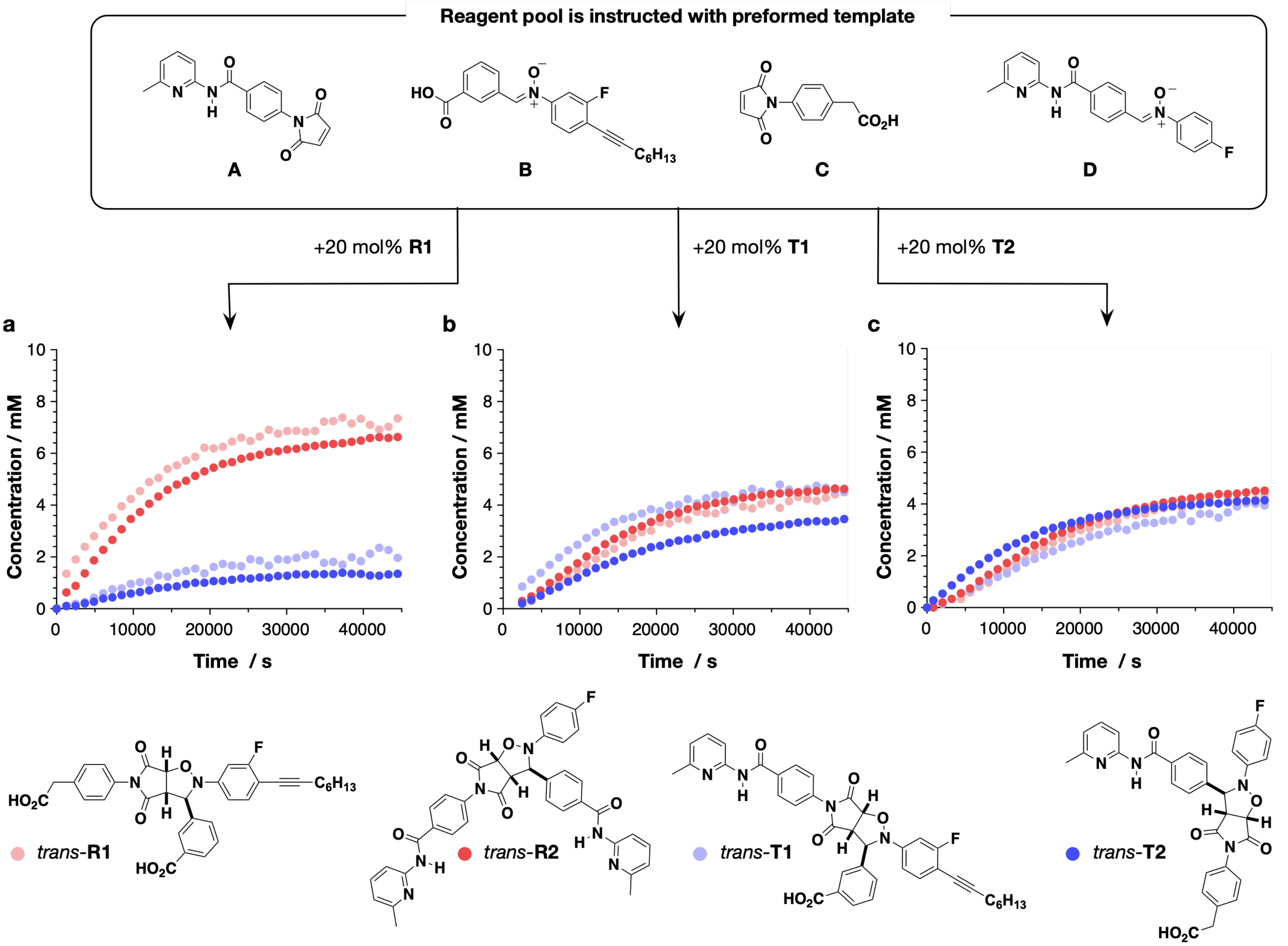


Figure S1. Partial 470.4 MHz $^{19}F\{^1H\}$ NMR spectrum recorded at 10 °C after 17800 s for the multicyclic network, in which nitrones **B** and **D** react with maleimides **A** and **C** ([**A**] = [**B**] = [**C**] = [**D**] = 10 mM) to give two self-replicators, *trans*-**T1** and *trans*-**T2**, and a pair of reciprocal replicators, *trans*-**R1** and *trans*-**R2**.

Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

The effect of template molecule to network (concentration-time)

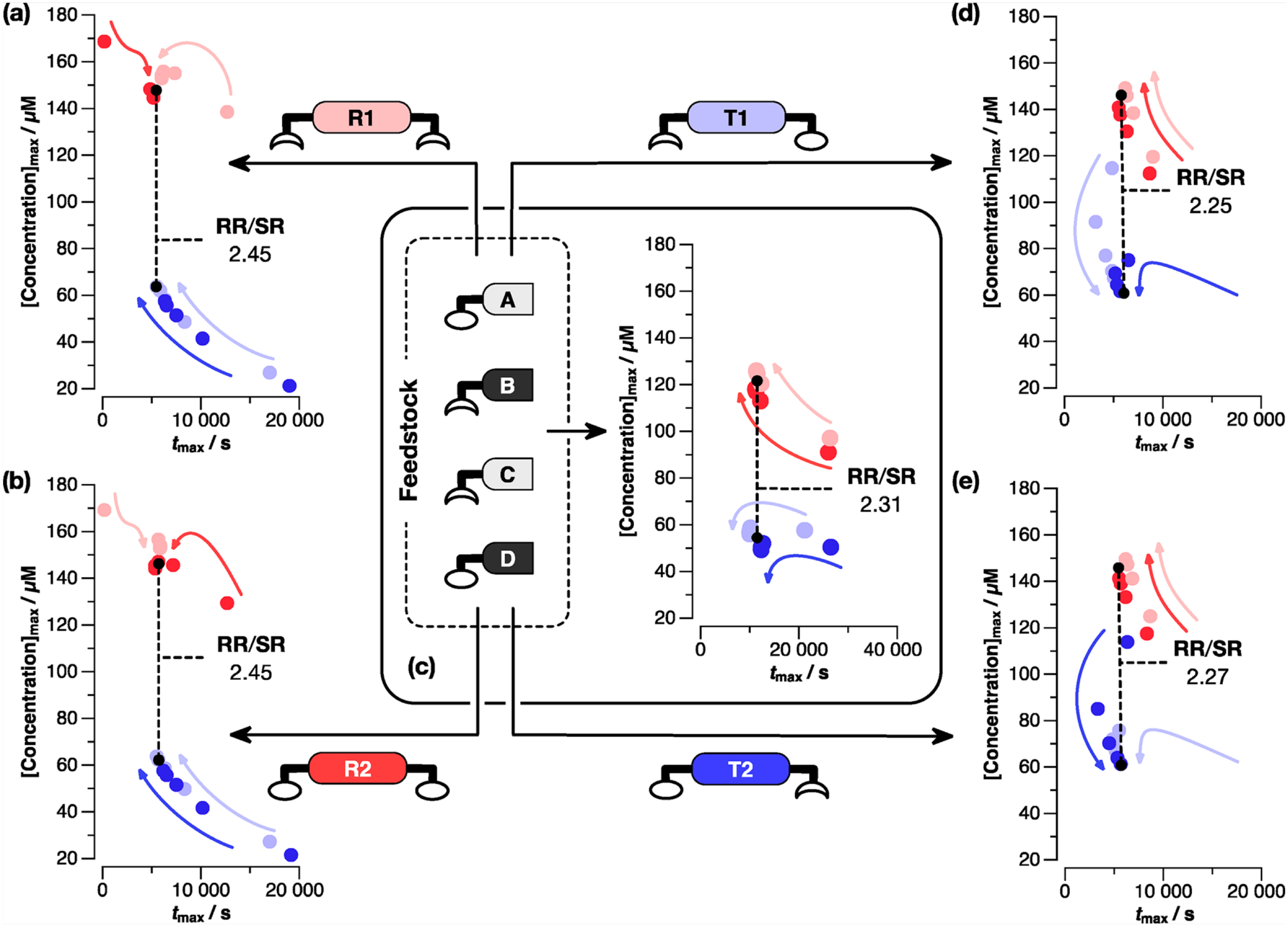
experiment



Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

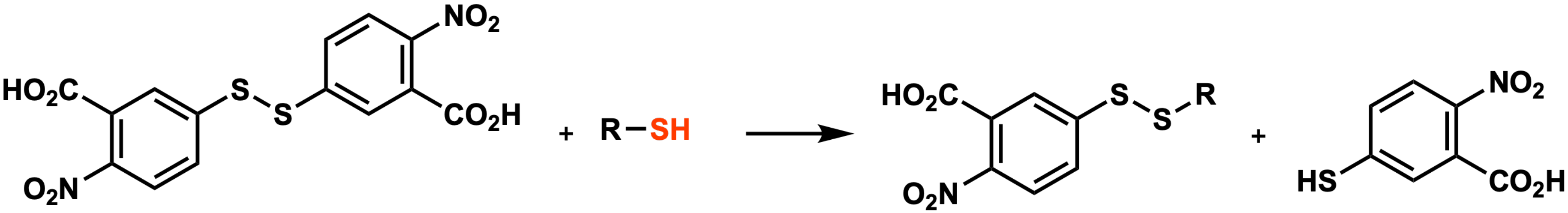
The multicyclic network responded to the environmental change.

simulation



Huck, J.; Kosikova, T.; Philp, D. *J. Am. Chem. Soc.* **2019**, *141* (35), 13905–13913.

Ellman’s reagent

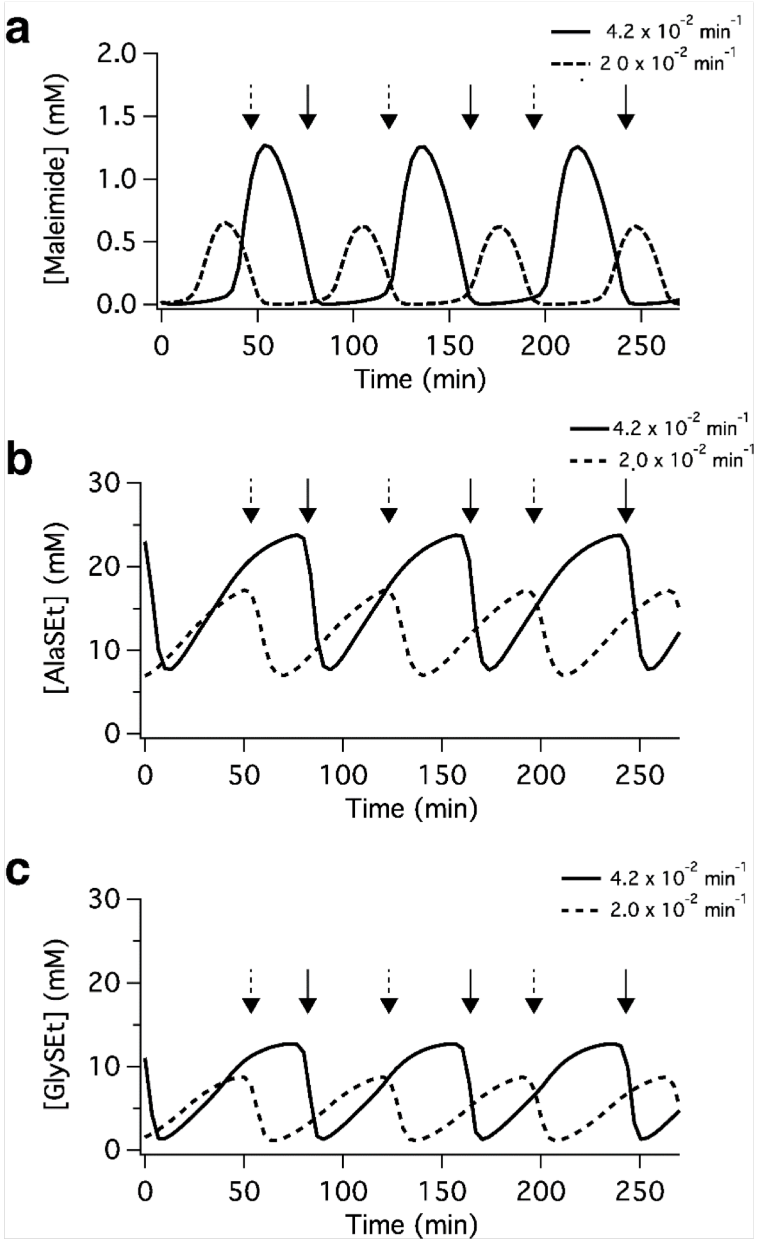


DTNB

TNB

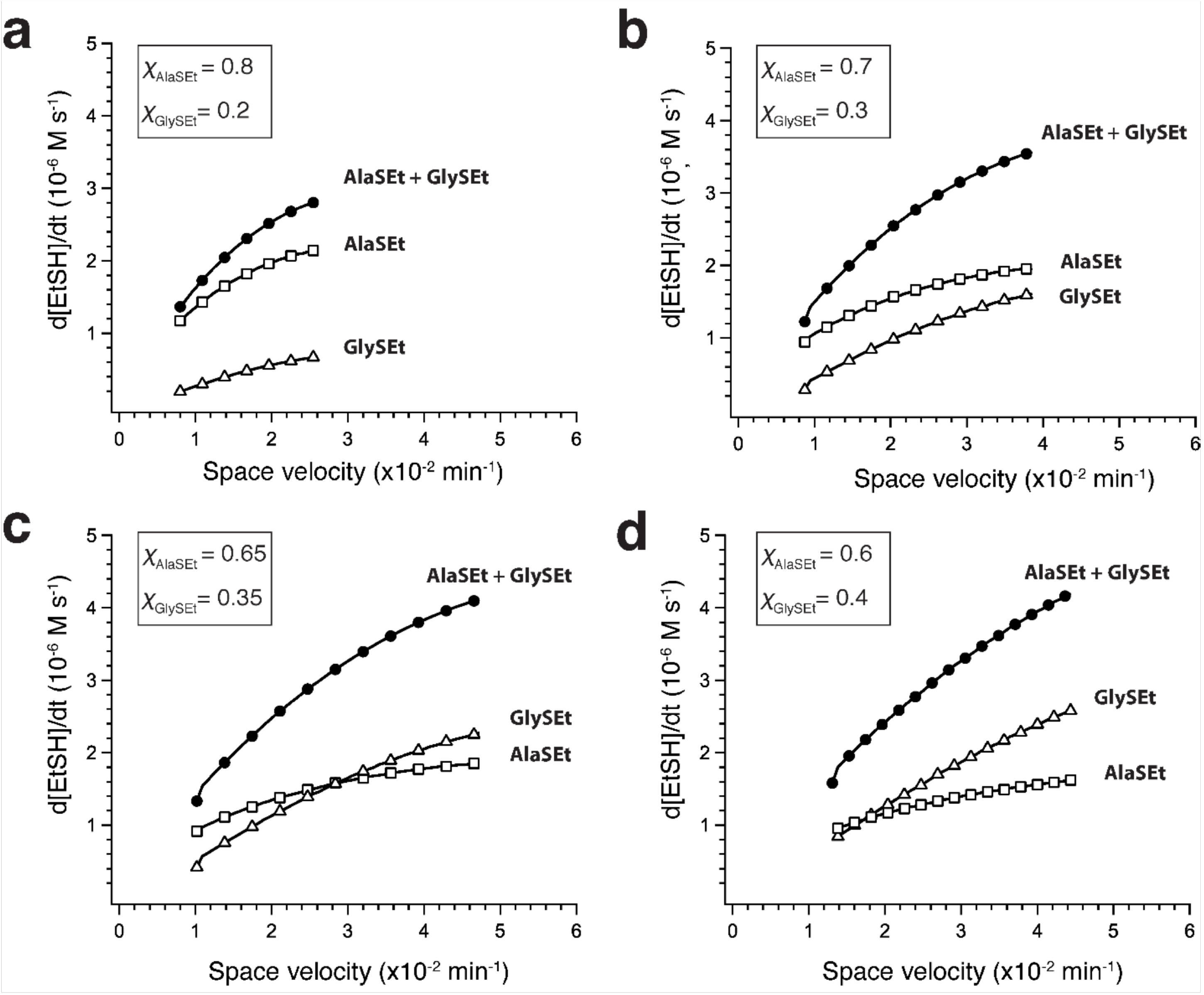
detected by
absorption at 412 nm

The origin of robustness(1)



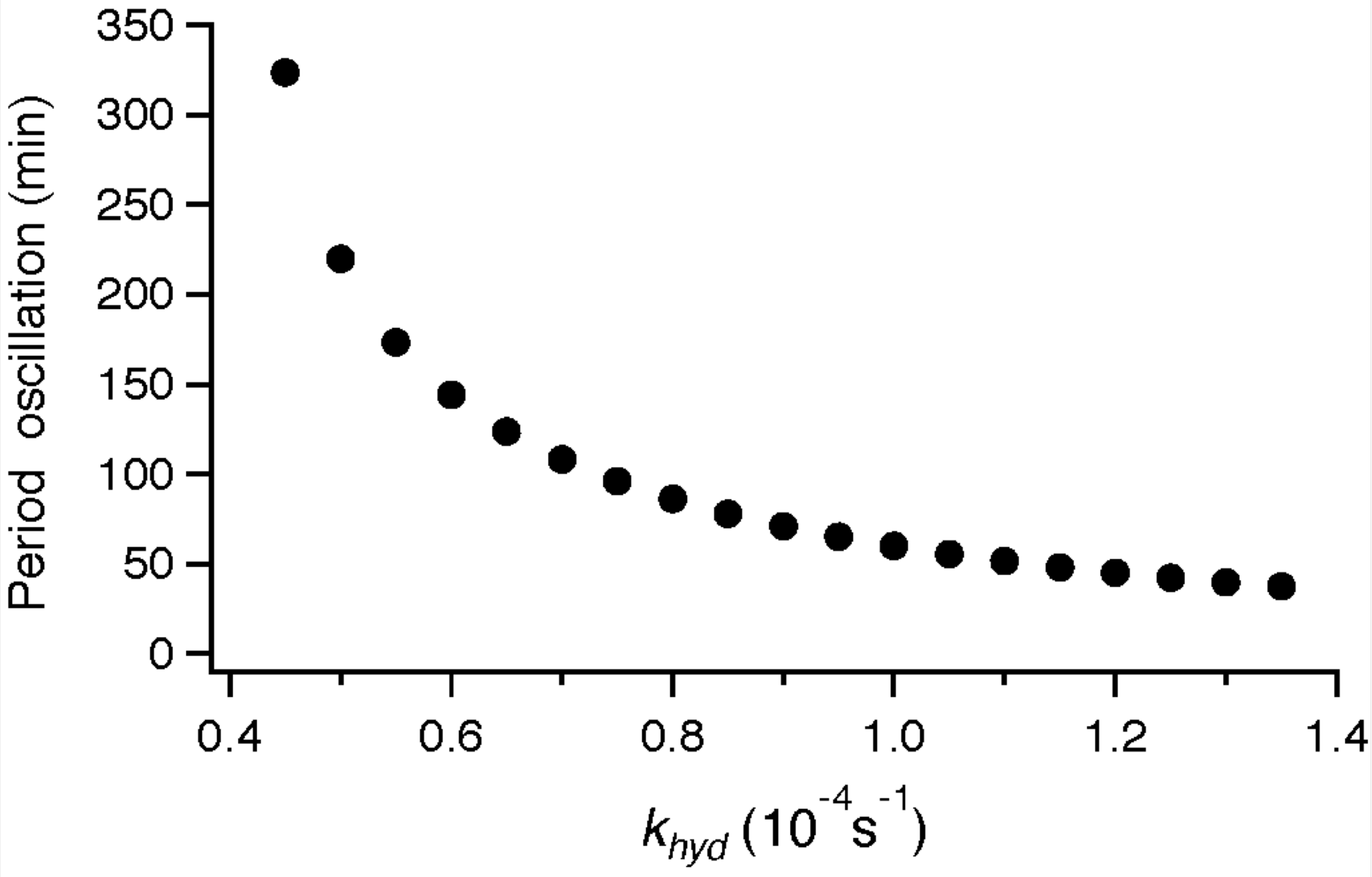
- (i) [thioester] increases more rapidly at larger space velocities

The origin of robustness (2)



- (ii) GlySEt is more sensitive to [thioester] because of $k_{aml}[\mathrm{GlySEt}]^2$.

The origin of robustness (2)



- more rapid ethanethiol formation decreases the oscillation period.