Theorem on the hard synthesis and easy destruction of complex molecules

Ikumi Kobayashi and Shin-ichi Sasa

Department of Physics, Kyoto University, Kyoto 606-8502, Japan
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We present a simple model describing the assembly and disassembly of a one-dimensional complex molecular chain consisting of two types of molecular subunits A and B, where the molecules are identified as complex when the number of A-B connections \( d \) is proportional to chain length \( n \). We show that it takes a longer time than an exponential of \( n \) to synthesize a certain amount of complex molecules for any external operation, while linear time is sufficient to decompose a certain amount of complex molecules. Our findings may facilitate research on more general asymmetry of operational hardness.

In this Letter, putting the computational complexity theory aside, we consider experimentally accessible systems where the hardness is represented by the optimal operational time. The primary purpose is to present a simple model that shows the distinct asymmetry between the hardness of the assembly and the disassembly process of complex molecules. Using the insight obtained from this simple model, we further aim to identify a universal property that can be applied to more complex natural phenomena.

Specifically, we introduce an idealized description of the synthesis and decomposition of a one-dimensional molecular chain comprising two types of molecular subunits. We then prove that the difficulty of synthesizing molecules in this system is characterized by the number of connections \( d \) between different types of molecular subunits. When \( d \) is proportional to chain length \( n \), the molecules are identified as “complex”. Then, it takes a longer time than an exponential of the molecular chain length to synthesize a certain amount of complex molecules for any external operation, while linear time is sufficient to decompose a certain amount of complex molecules. The asymmetry of the operation time results from a reaction network structure with an exponential number of branches but only one exit. This mechanism may be general, beyond the specific model considered here, and is expected to pave the way for research that will clarify fundamental questions about the irreversibility of biological death by combining insights from the theory of computation and physics.

**Synthesis process.** We consider the synthesis of a one-dimensional molecular chain by the sequential binding of molecules A and B to reaction nucleus X as displayed in Fig. 1. An external operator aims to synthesize the desired molecular chain as efficiently as possible by controlling the concentrations of A and B over time.

We assume the only possible reaction is the binding of molecule \( Z \in \{A, B\} \) to a molecular chain \( M \) to form \( MZ \),

\[
M + Z \xrightarrow{k_2} MZ, \tag{1}
\]

where the rate constant \( k_2 \) depends only on \( Z \). For simplicity, we ignore the reverse reaction in which
Here, we consider processes and from MZ total amount of molecule by an external operator. Let types of molecular subunits. For example, concentrations of molecules to the reaction tank. Third, we assume that the concentration of each chemical species and the temperature in the reaction chamber are spatially homogeneous, and the numbers of each molecule are large enough that the behavior of the system is well described by the following deterministic rate equations:

$$\frac{d}{dt}c_{M}(t) = -k_{a}c_{A}(t)c_{M}(t) - k_{b}c_{B}(t)c_{M}(t) + k_{Z}c_{Z}(t)c_{M}(t), \quad (2)$$

$$\frac{d}{dt}c_{X}(t) = -k_{a}c_{A}(t)c_{X}(t) - k_{b}c_{B}(t)c_{X}(t) + J_{X}, \quad (3)$$

where $c_{M}(t)$ is the concentration of molecule $M$ at time $t$. The first and second terms on the right-hand side of Eq. 2 correspond to the reactions $MZ + A \rightarrow MZA$ and $MZ + B \rightarrow MZB$, respectively; the third term represents the contribution from the reaction $M + Z \rightarrow MZ$.

The concentration dynamics in the reaction chamber can be divided into three types. First, the concentrations of molecules other than X, A, B evolve in time according to Eq. 2. Second, the dynamics of $c_{X}(t)$ is described by Eq. 3, where the last term represents the constant supply of reaction nucleus $X$ from the particle reservoir to the reaction tank. Third, we assume that the concentrations of molecules A and B are controllable in time by an external operator.

At time $t = 0$, the reaction chamber is empty. The total amount of molecule MZ synthesized by reaction 1 from $t = 0$ to $t = T$ is

$$\sum_{MZ}[0, T] \equiv \int_{0}^{T} dt k_{Z}c_{Z}(t)c_{M}(t). \quad (4)$$

Let $d$ be the number of connections between different types of molecular subunits. For example, $d = 2$ for $XABBA$ and $d = 5$ for $XAABABBAB$.

The first main result of this Letter is that the synthesis of a constant amount of the molecular chain takes exponentially long time with respect to the molecular length $n$ unless $d = O(\log n)$, no matter how the concentrations of material molecules are manipulated. Specifically, we can prove that the time $T$ required to synthesize a certain amount $\sum_{M}[0, T]$ of molecular chain $M$ satisfies

$$T > \frac{\sum_{M}[0, T]}{J_{X}} \times 2^{d/3} \quad (5)$$

for any synthesis protocol $[c_{A}(t), c_{B}(t)]_{0 \leq t \leq T}$.

**Destruction process.** Here, we consider processes that fragment the molecular chain into monomers X, A, and B by sequential detachment of $Z \in \{A, B\}$ as displayed in Fig. 1. The possible reactions are desorption of material molecule $Z$ from molecular chain $MZ$,

$$MZ \xrightarrow{k_{Z}} M + Z. \quad (6)$$

Similar to synthesis process, we assume that the rate constant $k_{Z}$ depends only on $Z$ and that the reverse reaction...
(recombination) does not occur. The rate equations are then
\[
\frac{d}{dt}c_{MZ}(t) = -k_Z'c_{MZ}(t) + k_A'c_{MA}(t) + k_B'c_{MB}(t),
\]
(7)
\[
\frac{d}{dt}c_X(t) = -\tau^{-1}_Xc_X(t) + k_A'c_{XA}(t) + k_B'c_{XB}(t),
\]
(8)
where \(\tau^{-1}_X\) is the recovery rate constant of \(X\) from the reaction vessel to the particle bath (see Fig. 2(b) for an illustration). The concentration of the molecular chain to be decomposed \(c_M\) is assumed to be constant.

At \(t = 0\), the reaction chamber is empty. The total amount of molecular chains completely disassembled from \(t = 0\) to \(t = T\) is equal to the total amount of reactant nuclei \(X\) recovered in the particle reservoir:
\[
\Sigma_x'[0,T] \equiv \int_0^T dt\,\tau^{-1}_Xc_X(t).
\]
(9)

We can then show that a linear time with respect to the molecular length \(n\) is sufficient to decompose a constant amount \(\Sigma_x[0,T]\) of the molecular chain. That is,
\[
T < \frac{2\tau\Sigma_x[0,T]}{c_M},
\]
(10)
where \(\tau\) is the average molecular detachment time.

Outline of the derivation.— First, we outline the outline of the proof that the synthesis reaction takes an exponentially long time with respect to the length of the molecular chain. We focus on the processes where different types of molecules are connected. Given a specific synthesis protocol \([c_A(t),c_B(t)]_{0\le t\le T}\), we can express \(c_{MAB}(t)\) as a function of \(c_M(t)\) for any \(Z \in \{A,B\}\) and show that \(\Sigma_{MAB}[0,T] < \Sigma_{MZ}[0,T] \times 1/2\) for any \(Z,Z' \in \{A,B\}\). Because this relation applies to each connection [23] between \(A\) and \(B\) in the molecular chain, the upper limit to the amount synthesized becomes exponentially smaller for larger values of \(d\) and the corresponding time required to synthesize a fixed amount of the molecular chain becomes exponentially longer [20].

Next, we outline the proof that the decomposition time is shorter than a linear function of the molecular chain length. Although it is possible to directly solve Eqs. (7) and (8), we instead consider the probability that the molecular chain \(M\) is completely degraded within time \(t\). Using Markov’s inequality, we find that \(c_X(t)\) has a lower bound, which leads to Eq. (10) [20].

Mechanism behind the hard synthesis and easy destruction.— The asymmetry exhibited by our model can be understood from its reaction network structure, which is a Cayley graph of depth \(n\) (See Fig. 3). Because of byproduct formation, the proportion of molecules that can reach the desired vertex (\(XABA\) in this case) becomes exponentially smaller than initial amount. As a result, the synthesis rate is markedly reduced. In contrast, during chain decomposition, no byproducts are produced and the reaction proceeds along a single path. Thus, decomposition only requires a time that is linear with respect to the chain length.

Although we have focused on a specific example, the scheme shown in Fig. 3 — an exponentially branched maze with only one exit — may capture a universal aspect that can be applied to more complex and general asymmetries of operational difficulty.

Concluding remarks.— We have described a simple model of the synthesis and decomposition of molecular chains composed of two types of molecular subunits. Equations (4) and (10) highlight the distinct asymmetry between assembly and destruction. The time required to assemble a complex molecular chain is an exponential function of the chain length regardless of how the concentrations of the reactants are manipulated, while the corresponding function for chain destruction is linear. The result in this Letter is located at the starting point for the study of a general question about the hardness of operations. We thus expect that the exact form of the bound given in this Letter would be useful for seeking a general principle.

In closing, we present five future challenges. First, this
study ignored the reverse reaction for simplicity, but we expect from the following naive discussion that explicitly considering the reverse reaction would not affect the results. In the present model, molecular chain $M\AA A$ is inevitably generated as a byproduct of $M\AB$ creation and is the cause of the slow synthesis. If we included the reverse reaction (detachment of $A$), we would reduce the amount of byproducts but also reduce the amount of the desired product, $M\AB$. Therefore, we would not accelerate the rate of molecular synthesis. The analysis of the model with a reverse reaction is left as a future task.

A second problem is related to stochastic thermodynamics, where an upper bound of the current in nonequilibrium steady-state or a lower bound of the operation time to convert a probability distribution to another one is intensively studied as thermodynamic uncertain relation \[27, 28\] and thermodynamic speed limit \[29, 30\]. Although the settings are different in these relations and the results presented in this Letter, they share the same motivation of searching for a limit that cannot be exceeded regardless of the operational protocol. Thus, it is natural for future research to explore the relationship among them by extending the present results to stochastic systems.

A third problem is related to entropy and complexity theory \[31\]. One may expect that our result is obtained from a fact that the thermodynamic entropy of a molecular chain is lower than that of disconnected monomer units. While it is impossible to make a lower entropy state from a higher one in thermally isolated systems, the system we study operates out of equilibrium. Thus, the thermodynamic entropy is not directly related to the asymmetry of operational hardness. Moreover, recalling that the time required to synthesize $X\AAAA\cdots$ is linear in the length $n$, we find that the essence of the problem is to characterize complex sequences of $A$ and $B$ by some generalized entropy-like quantity (or “complexity”). For example, one may conjecture that a smaller data compression ratio of the alignment of molecular chains corresponds to a longer time to synthesize it, where the data compression rate is closely related to the Shannon entropy \[32, 33\]. However, this conjecture is not correct, because Eq. \[16\] provides the most stringent restriction on $X\AB\AB\AB\cdots$ for fixed $n$, while the data compression ratio is large. We rather speculate that the concept of “logical depth” proposed by Bennett \[34\] provides a better representation of the complexity in the present case. It is an important future task to clarify the “complexity” in our system and how it is extended to more general systems.

A fourth problem is related to feedback control. Information thermodynamics \[35, 36\], which extends thermodynamics to include the effects of measurement and feedback control by using information-theoretic quantities, was formulated in the last decade. The system discussed in this Letter is described by deterministic rate equations and therefore does not include the concept of feedback. However, in small fluctuating systems, error correction by feedback mechanisms is expected to be important to generate complex objects \[38, 39\]. Extending our results to stochastic systems where feedback effects become significant is an important research direction to discuss structure formation at small scales.

Finally, we remark that the synthesis of one-dimensional molecular chains has been experimentally studied \[40, 41\]. Since the base of the exponential function in Eq. \[5\], $2^{1/3}$, is a model-specific parameter, its experimental determination may yield information about the underlying chemical reactions. Formulating a general relationship between chemical reaction networks and operational hardness represents the most significant future challenge.

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\[\text{(1)}\] D. Deutsch, Constructor theory, Synthese 190, 4331 (2013).
\[\text{(2)}\] C. Marletto, Constructor theory of life, J. R. Soc. Interface 12, 20141226 (2015).
\[\text{(3)}\] J. L. Bernat, The definition and criterion of death, Handbook of clinical neurology 118, 419 (2013).
\[\text{(4)}\] S. Arora and B. Barak, Computational complexity: a modern approach (Cambridge University Press, 2009).
\[\text{(5)}\] C. Moore and S. Mertens, The nature of computation (OUP Oxford, 2011).
\[\text{(6)}\] F. Barahona, On the computational complexity of Ising spin glass models, J. Phys. A 15, 3241 (1982).
\[\text{(7)}\] C. H. Bennett, The thermodynamics of computation—a review, Int. J. Theor. Phys. 21, 905 (1982).
\[\text{(8)}\] M. Mézard and G. Parisi, The Bethe lattice spin glass revisited, Eur. Phys. J. B 20, 217 (2001).
\[\text{(9)}\] R. Monasson, R. Zecchina, S. Kirkpatrick, B. Selman, and L. Troyansky, Determining computational complexity from characteristic ‘phase transitions’, Nature (London) 400, 133 (1999).
\[\text{(10)}\] R. Unger and J. Moult, Finding the lowest free energy conformation of a protein is an NP-hard problem: proof and implications, Bull. Math. Biol. 55, 1183 (1993).
\[\text{(11)}\] W. H. Zurek, Algorithmic randomness and physical entropy, Phys. Rev. A 40, 4731 (1989).
\[\text{(12)}\] Y. Fu and P. W. Anderson, Application of statistical mechanics to NP-complete problems in combinatorial optimisation, J. Phys. A 19, 1605 (1986).
\[\text{(13)}\] T. S. Cubitt, D. Perez-Garcia, and M. M. Wolf, Undecidability of the spectral gap, Nature (London) 528, 207 (2015).
\[\text{(14)}\] A. Hjelmfelt, E. D. Weinberger, and J. Ross, Chemical implementation of finite-state machines, Proc. Natl. Acad. Sci. U. S. A. 89, 383 (1992).
\[\text{(15)}\] M. O. Magnasco, Chemical kinetics is Turing universal, Phys. Rev. Lett. 78, 1190 (1997).
\[\text{(16)}\] D. S. Abrams and S. Lloyd, Nonlinear quantum mech-
ics implies polynomial-time solution for NP-complete and
#P problems, Phys. Rev. Lett. 81, 3992 (1998).
[17] A. Lucas, Ising formulations of many NP problems, Front. Phys. 2, 5 (2014).
[18] L. Kari and G. Rozenberg, The many facets of natural
computing, Commun. ACM 51, 72 (2008).
[19] D. Deutsch, Quantum theory, the Church–Turing prin-
ciple and the universal quantum computer, Proc. Phys.
Soc. London, Sect. A 400, 97 (1985).
[20] S. Wolfram, Undecidability and intractability in theore-
tical physics, Phys. Rev. Lett. 54, 735 (1985).
[21] M. Ziegler, Physically-relativized Church–Turing Hy-
potheses: Physical foundations of computing and com-
plexity theory of computational physics, Appl. Math.
Comput. 215, 1431 (2009).
[22] S. Aaronson, Guest column: NP-complete problems and
physical reality, SIGACT news 36, 30 (2005).
[23] B. J. Copeland and O. Shagrir, The Church-Turing the-
osis: logical limit or breachable barrier?, Commun. ACM
62, 66 (2018).
[24] Physically, this assumption corresponds to a situ-
ation in which the structure of the binding site at the end of
the molecular chain does not change, regardless of the type
of the previously bound molecule.
[25] Strictly speaking, this inequality cannot be applied to all
connections, which results in a factor of 1/3 in Eq. (5).
Please refer to Supplemental Material for details.
[26] See Supplemental Material for a detailed derivation.
[27] A. C. Barato and U. Seifert, Thermodynamic uncertainty
relation for biomolecular processes, Phys. Rev. Lett. 114,
158101 (2015).
[28] J. M. Horowitz and T. R. Gingrich, Thermodynamic uncertainty
relations constrain non-equilibrium fluctuations, Nat.
Phys. 16, 15 (2020).
[29] N. Shiraishi, K. Funo, and K. Saito, Speed limit for clas-
sical stochastic processes, Phys. Rev. Lett. 121, 070601
(2018).
[30] S. Ito and A. Dechant, Stochastic time evolution, infor-
mation geometry, and the Cramér-Rao bound, Phys.
Rev. X 10, 021056 (2020).
[31] C. Bennett, How to Define Complexity in Physics, and
Why, in Complexity, Entropy and the Physics of Infor-
mation, edited by W. Zurek (Addison-Wesley, Redwood
City California, 1990) pp. 137–148.
[32] C. E. Shannon, A mathematical theory of communica-
tion, Bell Syst. tech. j. (Online) 27, 370 (1948).
[33] T. M. Cover and J. A. Thomas, Elements of Information
Theory 2nd Edition (Wiley Series in Telecommunications
and Signal Processing) (Wiley-Interscience, 2006).
[34] C. Bennett, Logical depth and physical complexity, in
The universal Turing machine: a half century survey,
edited by R. Haken (Oxford University Press; Kammerer &
Unverzagt, 1988) pp. 227–258.
[35] T. Sagawa and M. Ueda, Second law of thermodynamics
with discrete quantum feedback control, Phys. Rev. Lett.
100, 080403 (2008).
[36] J. M. Parrondo, J. M. Horowitz, and T. Sagawa, Ther-
modynamics of information, Nature (London) 11, 131
(2015).
[37] S. Toyabe, T. Sagawa, M. Ueda, E. Muneyuki, and
M. Sano, Experimental demonstration of information-
to-energy conversion and validation of the generalized
Jarzynski equality, Nature (London) 6, 988 (2010).
[38] J. J. Juárez and M. A. Bevan, Feedback controlled col-
loidal self-assembly, Adv. Funct. Mater. 22, 3833 (2012).
[39] P. W. K. Rothemund, N. Papadakis, E. Winfree, and
A. Condon, Algorithmic self-assembly of DNA Sierpinski
triangles, PLOS Biol. 2, e424 (2004).
[40] M. Rubinstein, R. H. Colby, et al., Polymer physics,
Vol. 23 (Oxford university press New York, 2003).
[41] C. J. Hawker and K. L. Wooley, The convergence of
synthetic organic and polymer chemistries, Science 309,
1200 (2005).
[42] C. B. Mast, S. Schink, U. Gerland, and D. Braun, Esca-
clation of polymerization in a thermal gradient, Proc.
Natl. Acad. Sci. U. S. A. 110, 8030 (2013).
[43] S. I. Cohen, S. Linse, L. M. Luhihoi, E. Hellstrand, D. A.
White, M. Rajah, D. E. Otzen, M. Vendruscolo, C. M.
Dobson, and T. P. Knowles, Proliferation of amyloid-β42
aggregates occurs through a secondary nucleation mech-
nism, Proc. Natl. Acad. Sci. U. S. A. 110, 9758 (2013).
[44] P. A. Korevaar, S. J. George, A. J. Markvoort, M. M.
Smulders, P. A. Hilbers, A. P. Schenning, T. F. De Greef,
and E. Meijer, Pathway complexity in supramolecular
polymerization, Nature (London) 481, 492 (2012).
SUPPLEMENTAL MATERIAL: DETAILED DERIVATION

Derivation of Eq. (5)

To derive Eq. (5), we first consider the sequential addition of molecules A, B, and Z* to the chain MZ to synthesize MZABZ* (Z, Z* ∈ {A, B}). The rate equations are

\[
\begin{align*}
\frac{d}{dt}c_{MZ}(t) &= -w(t)c_{MZ}(t) + w_Z(t)c_M(t), \\
\frac{d}{dt}c_{MZA}(t) &= -w(t)c_{MZA}(t) + w_A(t)c_{MZ}(t), \\
\frac{d}{dt}c_{MZAB}(t) &= -w(t)c_{MZAB}(t) + w_B(t)c_{MZA}(t),
\end{align*}
\]  
\tag{S.1}

where \(w_Z(t) \equiv k_Zc_Z(t)\) and \(w(t) \equiv w_A(t) + w_B(t)\). Solving the differential equations (S.1) under the initial condition \(c_{MZ}(0) = c_{MZA}(0) = c_{MZAB}(0) = 0\), we obtain

\[
c_{MZAB}(t) = \int_0^t dt_3 w_B(t_3) \int_0^{t_3} dt_2 w_A(t_2) \int_0^{t_2} dt_1 w_Z(t_1)c_M(t_1) \exp\left( -\int_{t_1}^t dt \right).
\]  
\tag{S.2}

From Eq. (4), we have

\[
\Sigma_{MZABZ*}[0,T] = \int_0^T dt w_{Z*}(t)c_{MZAB}(t).
\]  
\tag{S.3}

We then substitute Eq. (S.2) into Eq. (S.3) and transform the integration variables as

\[
\begin{align*}
s_1 &= t_1, \\
s_2 &= t_2 - t_1, \\
s_3 &= t_3 - t_1, \\
s_4 &= t - t_1,
\end{align*}
\]  
\tag{S.4}

where the domain of integration is \(D_s = \{(s_1, s_2, s_3, s_4) | 0 \leq s_1 \leq T, 0 \leq s_2 \leq s_3 \leq s_4 \leq T - s_1\}\). Because the corresponding Jacobian is unity, we have

\[
\Sigma_{MZABZ*}[0,T] = \int_0^T ds_1 w_Z(s_1)c_M(s_1) \int_0^{T-s_1} ds_4 w_Z(s_1 + s_4)e^{-W(s_4;s_1)} \int_0^{s_4} ds_3 w_B(s_1 + s_3) \int_0^{s_3} ds_2 w_A(s_1 + s_2).
\]  
\tag{S.5}

where \(W(s_4;s_1) \equiv \int_0^{s_4} du w(s_1 + u)\). Using \(w_A(s_1 + s_2) \geq 0\) and \(s_3 \leq s_4\), we evaluate the underlined part of Eq. (S.5) as

\[
\int_0^{s_4} ds_3 w_B(s_1 + s_3) \int_0^{s_3} ds_2 w_A(s_1 + s_2) \leq \int_0^{s_4} ds_3 w_B(s_1 + s_3) \int_0^{s_4} ds_2 w_A(s_1 + s_2).
\]  
\tag{S.6}

Here, by applying the inequality of arithmetic and geometric means, we find that the right-hand side is less than

\[
\frac{1}{4} \left( \int_0^{s_4} ds_3 w_B(s_1 + s_3) + \int_0^{s_4} ds_2 w_A(s_1 + s_2) \right)^2,
\]  
\tag{S.7}

which is written as

\[
\frac{1}{4} W(s_4;s_1)^2.
\]  
\tag{S.8}

Substituting Eqs. (S.6), (S.7), and (S.8) into Eq. (S.5) and using \(w \geq w_{Z*}\), we obtain

\[
\Sigma_{MZABZ*}[0,T] \leq \frac{1}{4} \int_0^T ds_1 w_Z(s_1)c_M(s_1) \int_0^{T-s_1} ds_4 w(s_1 + s_4)W(s_4;s_1)^2 e^{-W(s_4;s_1)}.
\]  
\tag{S.9}
FIG. S.1. Schematic diagram of the proof of the synthesis process. When $A, B$ and $Z^*(Z^* \in \{A, B\})$ are sequentially connected to the molecular chain $MZ$, no matter how $w_A(t)$ and $w_B(t)$ are manipulated, $\sum_{MZABZ^*}[0, T]$ cannot exceed the half of $\sum_{MZ}[0, T]$. Note that at most three connections between $A$ and $B$ are consumed in order to perform this evaluation once. Indeed, the number of connections in $MB$ is three less than that in $MBABA$ (corresponding to the case where $Z = B, Z^* = A$). Therefore, if the number of connections between $A$ and $B$ in the target chain is $d$, then this inequality (or swapping version of $A$ and $B$) can be used at least $d/3$ times, and the maximum synthesis amount decreases exponentially by $2^{-d/3}$.

FIG. S.2. Example of iterative application of Eq. (S.12) or Eq. (S.13). In this example, either Eq. (S.12) or Eq. (S.13) is iteratively applied to the molecular chain $XAABABAA$. In the first step, by applying Eq. (S.13) with $MZ = XAAB$ and $Z^* = A$, we find that $\sum_{XAABABAA}[0, T] < \sum_{XAABA}[0, T] \times 1/2$. Next, by applying Eq. (S.12) with $MZ = XA$ and $Z^* = A$, we find that $\sum_{XAABA}[0, T] < \sum_{XA}[0, T] \times 1/2$. In this example, $n = 7, d = 4$, and one of Eqs. (S.12) and (S.13) is applied twice, which is larger than $d/3 = 1.333...$ times.

From the definition of $W(s_4; s_1)$, $ds_4w(s_1 + s_4)$ is equal to $dW(s_4; s_1)$. We then obtain

$$\sum_{MZABZ^*}[0, T] \leq \frac{1}{4} \int_0^T ds_4 w_Z(s_1)c_M(s_1) \int_0^{W(T-s_1; s_1)} dW W^2e^{-W}. \quad (S.10)$$

Because $W^2e^{-W} \geq 0$ and $0 \leq W(T - s_1; s_1) < \infty$, the last part of Eq. (S.10) is evaluated as

$$\int_0^{W(T-s_1; s_1)} dW W^2e^{-W} < \int_0^{\infty} dW W^2e^{-W} = 2. \quad (S.11)$$

By combining Eq. (S.10) and Eq. (S.11), we obtain

$$\sum_{MZABZ^*}[0, T] < \frac{1}{2} \sum_{MZ}[0, T]. \quad (S.12)$$

Because this model is symmetric with respect to the interchange of molecules $A$ and $B$, we also obtain

$$\sum_{MZBAZ^*}[0, T] < \frac{1}{2} \sum_{MZ}[0, T]. \quad (S.13)$$

Now, suppose that the molecular chain $M$ contains $d$ times of connections between $A$ and $B$, we attempt to apply Eq. (S.12) and Eq. (S.13) iteratively. For example, in Fig. (S.2), we show how the inequalities work for a sequence. As seen in the example, Eq. (S.12) or Eq. (S.13) can be used at least $d/3$ times.

We thus obtain

$$\sum_{M}[0, T] < 2^{-d/3} \times \sum_{XZ}[0, T], \quad (S.14)$$
where $Z_1$ is the molecular subunit connected to the reaction nucleus $X$ ($Z_1 \in \{A, B\}$).

Finally, we evaluate $\sum_{XZ_1[0,T]}$. Eq. (S.15) is written as

$$\frac{d}{dt}c_X(t) = -w(t)c_X(t) + J_X.$$  (S.15)

From Eq. (S.15), we have

$$\sum_{XZ_1[0,T]} = \int_0^T dt w_{Z_1}(t)c_X(t).$$  (S.16)

By using $w_{Z_1} \leq w$, the right-hand side of Eq. (S.16) is less than

$$\int_0^T dt w(t)c_X(t).$$  (S.17)

By integrating Eq. (S.15) from $t=0$ to $t=T$, we obtain

$$\int_0^T dt w(t)c_X(t) = \int_0^T dt \left( J_X - \frac{d}{dt}c_X(t) \right)$$
$$= J_XT - c_X(T) + c_X(0).$$  (S.18)

Because $c_X(0) = 0$ and $c_X(T) \geq 0$, the last line is less than

$$J_XT.$$  (S.19)

From Eqs. (S.10), (S.17), (S.18), and (S.19), we obtain

$$\sum_{XZ_1[0,T]} \leq J_XT.$$  (S.20)

Combining Eq. (S.13) and Eq. (S.20), we obtain

$$\sum_M[0,T] < 2^{-d/3} \times J_XT,$$  (S.21)

which is equivalent to Eq. (5).

**Derivation of Eq. (10)**

Next, we derive Eq. (10). Let $p_n(t)$ be the probability distribution of the time it takes for a molecular chain $M = XZ_1Z_2\cdots Z_n$ of length $n$ to be completely degraded. Then

$$c_X(t) = \int_0^t dt' c_M p_n(t-t')$$
$$= c_M \int_0^t dt' p_n(t')$$
$$= c_M P_n(t),$$  (S.22)

where $P_n(t)$ is the cumulative distribution function of $p_n(t)$. Using Markov’s inequality, we evaluate $P_n(t)$ as

$$P_n(t) > 1 - \frac{\langle t \rangle_{p_n}}{t}$$
$$= 1 - \frac{1}{t} \sum_{i=1}^n \frac{1}{k_{Z_i}}$$
$$= 1 - \frac{\tau_n}{t},$$  (S.23)
FIG. S.3. Schematic illustration of Eq. (S.25). The area of painted in light blue $\int_0^T dt \ c_X(t)$ is larger than the area of the shaded rectangle $c_X(t')(T-t')$.

where

$$\tau \equiv \frac{1}{n} \sum_{i=1}^{n} \frac{1}{k_{Z_i}'} \quad (S.24)$$

is the average molecular detachment time.

Because $c_X(t)$ is a monotonically increasing function of $t$, we can evaluate $\int_0^T dt \ c_X(t)$ as shown in FIG. S.3 to obtain

$$\Sigma_X'[0,T] = \int_0^T dt \ \tau_X^{-1} c_X(t)$$

$$> \tau_X^{-1} c_X(t')(T-t') \quad (S.25)$$

$$> \tau_X^{-1} c_M \left(1 - \frac{\tau_n}{t'}\right)(T-t')$$

for $0 < t' < T$. Setting $t' = 2\tau_n$, we obtain Eq. (10).