Error Catastrophe Is Avoided by Proofreading Innate to Template-Directed Polymerization

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An important issue for the origins of life is ensuring the accurate maintenance of information in replicating polymers due to inevitable errors. Here, we investigated how this maintenance depends on reaction kinetics by incorporating elementary steps of polymerization into the population dynamics of polymers. We found that template-directed polymerization entails an inherent error-correction mechanism akin to kinetic proofreading, making long polymers more tolerant to an error catastrophe. Because this mechanism does not require enzymes, it is likely to operate under wide prebiotic conditions.

Template-directed polymerization is a fundamental chemical reaction for the sustained evolution of prebiotic systems. However, as in any chemical reaction, polymerization is subject to thermodynamically inevitable errors. Eigen[1] investigated the impact of such errors on the population dynamics of replicating polymers. Using the so-called quasi-species (QS) model, Eigen[1] showed that if the rate of error exceeds a certain threshold (error threshold), polymers are unable to hold information in their sequence because of the combinatorial explosion of incorrect (i.e., mutant) sequences, which compete with a correct (i.e., master) sequence, a phenomenon coined “error catastrophe”[2–8].

Error catastrophe poses a serious issue for the origins of life, because prebiotic systems most likely lack sophisticated error-correction mechanisms. By contrast, cells possess energy-driven mechanisms, such as kinetic proofreading (KPR)[6,10], that increase the accuracy of templated replication beyond expectations from free energy differences between correct and incorrect monomer pairs[1,3,17,18]. However, such mechanisms require multiple evolved enzymes, making them likely to be unavailable in prebiotic systems. Therefore, it remains unknown whether there exists a proofreading mechanism capable of operating under prebiotic conditions.

In this letter, we propose a prebiotic proofreading mechanism based on the positive feedback between the kinetics of polymerization and the population dynamics of replicating templates. We consider a kinetic model of polymerization, in which monomers are sequentially added to a primer in a template-directed manner. Using this model, we examined whether the effect of polymerization kinetics improves the tolerance of replicating templates to replication errors. We determined the condition for replicating templates to avoid an error catastrophe, and found that the accuracy of sequence information in replicating templates increases with the length of templates, in stark contrast with the prediction of Eigen’s QS model.

We consider a polymer (denoted by \(X_{l,s}\)) comprising a primer (denoted by ‘p’) linked to a sequence of \(l\) binary monomers (denoted by \(s \in \{0,1\}\) ) (e.g., ‘p00’, ‘p1010101’)[10]. The polymer is extended by the addition of another polymer (denoted by \(m \in \{0,1\}\) ) using another monomer pair (denoted by \(X_{l,s}\)) as a template (Fig. 1(a)): \(X_{l,s} + X_{l,s} \xrightarrow{r(l,s,m,S)} X_{l+1,s,m} + X_{l,s} \).

For the sake of comparison with the QS model, we assume that only polymers of length \(L\) can serve as templates (hereafter called templates), and that polymers cannot be longer than \(L\). The rate of monomer addition, \(r(l,s,m,S)\), comprises three factors (Fig. 1(b)):

\[
r(l,s,m,S) = \beta(l,s,S)\nu(l+1,m,S)f(S).
\]

The first factor, \(\beta(l,s,S)\), depends on the binding energy between \(X_{l,s}\) and \(X_{l,s}\). We assume that only polymers of length \(L\) can serve as templates. Thus, \(r(s,m,S)\) is proportional to the fraction of \(X_{l,s}\) bound to \(X_{l,s}\) where \(\beta(l,s,S) = \exp(\hat{\alpha}(l,s,S)\Delta)\) and where \(\hat{\alpha}(l,s,S)(\leq l)\) is the number of correct’ pairs of monomers between \(X_{l,s}\) and \(X_{l,s}\) (Fig. 1(b)). A pair is defined as correct if the monomers are of the same type[20], and \(\Delta(\geq 0)\) is a free-energy difference between a correct and incorrect monomer pair[21].

The second factor in Eq. 1, \(\nu(l+1,m,S)\), depends on the binding energy between incoming monomer \(m\) and the \(l+1\)-th monomer of the template sequence \(S\). If this monomer pair is correct, \(\nu(l,m,S)\) is set to \(e^\Delta\); otherwise, it is set to unity[22]. We assume that both the monomer species ‘0’ and ‘1’, exist at a constant concentration. Accordingly, \(\mu = 1/(1+e^\Delta)\) gives the ‘error rate’ of each monomer addition in template replication.

The third factor in Eq. 1, \(f(S)\), represents the efficiency of sequence \(S\) as a template, which can be interpreted as
fitness of \( S \). For comparison with Eigen \[1\], we assume a single-peak fitness landscape: \( f(S) = f_0 \) if \( S = \{0\}^L \) (denoted by \( S_0 \) and called the master sequence); otherwise, \( f(S) = f_1 < f_0 \) (we set \( f_0 = 1 \) and \( f_1 = 0.1 \) unless otherwise noted).

We assume a chemostat condition, where a free primer (denoted by \( X_{0,p} \)) was supplied at rate \( \phi \), and all of the molecular species were diluted at the same rate \( \phi \):

\[
\emptyset \overset{\phi}{\rightarrow} X_{0,p}, \quad X_{l,s} \overset{\phi}{\rightarrow} \emptyset.
\]

Thus, the total concentration of all primers is unity at the steady state, \( \sum x_{l,s} = 1 \). We use the boundary condition in which the concentration of \( X_{0,p} \) (denoted by \( x_{0,p} \)) is fixed, and the dilution rate \( \phi \) is determined by \( x_{0,p} \).

In summary, the rate equation for the concentration of \( X_{l,s} \) (denoted by \( x_{l,s} \)) is

\[
\dot{x}_{l,s} = x_{l-1,s'} \sum_{S \in \{0,1\}^L} r(l-1, s', m, S) x_{L,S} - x_{l,s} \sum_{S \in \{0,1\}^L} (r(l, m, S) + r(l, m, S')) x_{L,S} - \phi x_{l,s},
\]

where \( s' \) denotes the sequence obtained by removing the \( l \)-th monomer from \( s \), and the dilution rate \( \phi \) is determined as \( \phi = \frac{x_{0,p}}{1 + e^\Delta} \sum_{S \in \{0,1\}^L} f(S) x_{L,S} \). If \( l = L \) (the maximum length), there is no second term in Eq. 2.

In the present model, the accuracy of replicated information (denoted by \( A \)) is defined as the average similarity of all templates to the master sequence \( S_0 \).

\[
A = \sum_{S \in \{0,1\}^L} \left( 1 - 2 \frac{h_{0,S}}{L} \right) \frac{x_{L,S}}{x_L},
\]

where \( x_L = \sum_{S \in \{0,1\}^L} x_{L,S} \), and \( h_{0,S} \) is the Hamming distance between \( S_0 \) and \( S \). For example, \( A = 1 \) if all the templates are the master sequence, and \( A = 0 \) if the templates are completely random sequences.

First, we demonstrate that if the dilution rate (or, equivalently, the supply of a primer) \( \phi \) is sufficiently lower than the polymerization rate (i.e., \( \phi \approx 0 \), and \( x_{0,p} \approx 1 \)), the model is reduced to the QS model. Therefore, the rate equation for \( x_{L,S} \) is reduced to

\[
\dot{x}_{L,S} = \sum_{S' \in \{0,1\}^L} \omega_{S,S'} x_{L,S'} - \phi x_{L,S},
\]

where \( \omega_{S,S'} = (1 + e^\Delta) x_{0,p} f(S') \mu^{h_{S,S'}} (1 - \mu)^{L-h_{S,S'}} \) and \( \mu \) is the error rate (i.e., \( \mu = \frac{\nu}{1+\nu} \)). This is because for low \( \phi \), a primer is extended to the maximum length \( L \) immediately after binding to a template, and the fast polymerization process does not affect the slow population dynamics of the templates.

Hence, in this low-dilution-rate limit, our model gives the same error catastrophe and threshold as given by the QS model: the accuracy of the replicated information \( A \), defined as Eq. 3, decreases monotonically with increases in \( \mu \), and the decrease is accelerated as the sequence length of templates \( L \) increases. Based on the correspondence of Eqs. 4 and the QS model, the error rate \( \mu \) has to be smaller than the error threshold in order to maintain \( A \approx 1 \):

\[
\mu \lesssim \log(W)/L,
\]

where \( W \equiv \frac{L^L}{2^L} \) is the advantage of the master sequence. This agrees exactly with the error threshold derived by Eigen \[1\].

We then consider the situation in which the dilution rate \( \phi \) is comparable to the polymerization rate. In this situation, the model is not reduced to the QS model, and the polymerization kinetics significantly affect the accuracy of replicated information \( A \). We computed the \( A \) in the steady state in Eq. 2 varying the fixed concentra-
an infinite dilution rate \( \phi \) (Fig. 2(a)). If \( x_{0,p} \) (i.e., \( \phi \)) is low, the accuracy \( A \) approaches that of the QS model, as expected (Fig. 2(b)). As \( x_{0,p} \) increases, \( A \) monotonically increases for any error rate \( \mu \). In other words, slow polymerization relative to dilution improves the accuracy \( A \).

The increased accuracy is due to the polymerization process, which works as a multistep error correction for each monomer site in the template sequence. Here, we derive the maximally achievable accuracy in the limit of an infinite dilution rate \( \phi \) (i.e., \( x_{0,p} \sim 1 \)), as follows.

First, we consider how the concentrations of polymers depend on the monomer at a specific site. Let the concentration of the polymers of length \( l \) whose \( i \)-th monomer is \( m \in \{0, 1\} \) be expressed as \( \xi_{i,m}^{(l)} x_i \), where \( \xi_{i,0}^{(l)} + \xi_{i,1}^{(l)} = 1 \), \( x_i = \sum_{s \in \{0, 1\}} x_{i,s} \), and \( i \leq l \leq L \). Using Eq. 3 we can show that as \( \phi \to \infty \),

\[
\frac{\xi_{i,0}^{(l)}}{\xi_{i,1}^{(l)}} = \frac{F_0^{(i)} \xi_{i-1,0}^{(l)}}{F_1^{(i)} \xi_{i-1,1}^{(l)}}.
\]

(6)

where \( F_m^{(i)} \) is the relative rate at which the polymers of length \( l - 1 \) are extended to the polymers of length \( l \) whose \( i \)-th monomer is \( m \) (see Fig. S1 in the Supplemental Material [24]). The values of \( F_m^{(i)} \) are estimated as

\[
F_0^{(i)} = e^{\Delta} \xi_{L,m}^{(i)} f_0 + e^{\Delta} (\xi_0^{(i)} - \xi_0) f_1 + \xi_1^{(i)} f_1,
\]

\[
F_1^{(i)} = \xi_0 f_0 + (\xi_0^{(i)} - \xi_0) f_1 + e^{\Delta} \xi_1^{(i)} f_1,
\]

(7)

where \( \xi_m^{(i)} = \xi_{L,m}^{(i)} \) and \( \xi_0 \) is the fraction of the master sequence, i.e., \( \xi_0 = \prod_{i=0}^{L} \xi_0^{(i)} \) (see the derivation in the Supplemental Material [24]). To derive Eq. 8 we assumed that monomer additions at different positions in a sequence are independent of each other [25]. In both lines of Eq. 7 the first term represents the rate of monomer addition using the master sequence as a template, and the second and third terms represent rates using other templates with the \( i \)-th monomer ‘0’ and ‘1’, respectively.

Next, polymer sequences of length \( i - 1 \) must undergo \( L + 1 - i \) steps of monomer-addition reactions in order to complete the synthesis of a template with length \( L \). Using Eq. 6 recursively, the fractions \( \xi_0^{(i)} \) and \( \xi_1^{(i)} \) are derived by self-consistently solving

\[
\frac{\xi_1^{(i)}}{\xi_0^{(i)}} = \frac{F_0^{(i)}}{F_1^{(i)}} \xi_{L-1,0}^{(i)} \xi_{L-1,1}^{(i)}.
\]

(8)

As shown in Fig. 2(b), we calculated the accuracy \( A \) using this estimate for \( \xi_0^{(i)} \) as \( A = \frac{1}{L} \sum_{i} \xi_0^{(i)} - 1 \), which agrees well with the simulation result for \( x_{0,p} = 0.9 \).

The effective error rate \( \xi_1^{(i)} \) given by the solution of Eq. 8 is less than the original error rate \( \mu \), which suggests a proofreading effect working. By assuming the dominance of the master sequence \( (\xi_0^{(i)} \sim 0, \xi_1^{(i)} \sim 0) \), \( \xi_1^{(i)} \) is approximated as

\[
\xi_1^{(i)} \sim \frac{1}{1 + e^{L+1-i} \Delta} \sim e^{-(L+1-i) \Delta},
\]

(9)

because \( F_0^{(i)}/F_1^{(i)} \) is approximated by \( e^{\Delta} \). Eq. 9 agrees with the minimum error rate that can be achieved in the KPR model with \( L + 1 - i \) steps, when the binding energy between enzyme and correct/incorrect substrate differs by \( \Delta \) [6, 12]. Furthermore, even if the fraction of the master sequence \( \xi_0 \) is close to zero (i.e., \( \Delta \) is small), the small difference between \( F_0^{(i)} \) and \( F_1^{(i)} \) is amplified with the powers of \( L + 1 - i \), possibly resulting in a significant difference between \( \xi_0^{(i)} \) and \( \xi_1^{(i)} \), and high \( A \) accordingly.

Given the effective error rate in Eq. 8 at each monomer site, we calculate the error threshold for the correct information to be dominant. In Fig. 3(a), we plotted the dependence of the accuracy of the information \( A \) on the
error rate $\mu$ with various template lengths $L$. Interestingly, the error threshold for $\mu$, at which the information is lost ($A \sim 0$), increases with the length of the template $L$ (Fig. 3(b)). This is in sharp contrast with the QS model, where the fraction $A$ declines sharply with $L$, and the error threshold for $\mu$ approaches zero with an increase in $L$, as expressed by Eq. \(5\).

This increase in accuracy with length $L$ is achieved, because increasing $L$ increases the number of reaction steps a monomer site in the sequence undergoes before completion of template synthesis. The effective error rate at each monomer site in the template is exponentially reduced with the number of steps, as in multistep KPR. Although the variety of incorrect sequences increases exponentially with $L$, as in the QS model, this is overcome by the proofreading effect (see the Supplemental Material). Finally, we discuss the trade-off relationship between the accuracy and yield of the templates. This trade-off is inevitable, because the accuracy of the KPR is generally achieved at the expense of synthesis efficiency \([1,12]\). In our model, we computed the yield as the actual concentration of the master sequence $x_{L,0}$. In Fig. 4 the yield is plotted against the accuracy of information $A$ by varying the dilution rate $\phi$. With an increase in $\phi$, the accuracy increases, but the yield decreases.

In summary, in our template-polymerization system, the proofreading effect reduces the effective error rate as long as the dilution is not too slow. The effective error rate decreases with the template length (in sharp contrast with the QS model), which is obtained in the slow dilution limit, where the error increases with the length. This proofreading effect entails a trade-off between the accuracy of replicated information and the production yield, as in the KPR scheme.

We made the following three major assumptions to make our model comparable with the QS model. Notably, these are also required for proofreading to work in our model.

First, we assumed that templates immediately separate from the substrate polymers after the monomer-addition reactions, as is also assumed in the QS model \([26]\). Experimentally, this condition can be realized by adopting fast hybridization kinetics \([27–30]\).

Second, only the longest polymers were assumed to work as templates. If shorter polymers of length $L'$ could work as well as the long ones, then the shorter templates would replicate faster and out-compete the longer ones. In this case, the length $L$ of a template in our model can be replaced by a smaller $L'$ \([31]\). Because the proofreading in our model works better for a larger $L$, our results suggest that if there is any mechanism for selecting longer polymers (e.g., \([32–33]\)), it would resolve the error-catastrophe problem because of the proofreading effect.

Third, we considered the simplest ‘fitness landscape’ $f(S)$, in which only the master sequence has a high fitness. It is possible to consider the arbitrary fitness landscape in our model (e.g., a multimodal or more rugged landscape) \([4,6]\). We expect that the proofreading effect is relevant for the error catastrophe, even for such fitness landscapes; although this issue requires additional investigation \([31]\).

In principle, our scheme works, even in synthetic replicating systems without complex reaction pathways, such as a non-enzymatic primer-extension system \([32,33]\) or a template-directed ligation system \([30]\) (see review articles, e.g., \([37,38]\)). In closing, we briefly compare other schemes with ours. The standard KPR presently used in biological systems requires the specific design of the reactions at each monomer addition during the replication process: a reaction pathway involving several intermediate states associated with polymerases \([4]\) or a reverse reaction catalyzed specifically by exonucleases \([11]\). Recently, proofreading based on a detailed polymerization mechanism coupled with cyclic temperature changes was proposed \([39]\). By contrast, our scheme is based on general thermodynamics and the multistep nature of template replication. The error-correction effect works at each polymerization step, and the positive feedback from the template population reinforces it, thus enabling long templates to avoid error catastrophe. Therefore, it will guide the design of accurate template-replication systems and provide a plausible scenario for the inheritance of sequence information in the prebiotic world.

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19. A primer is interpreted as a specific short polymer sequence. Primers are generally required to initiate the polymerization reaction in experimental template-directed replication, given that a monomer alone cannot bind to a template polymer.
20. Complementarity and directionality of templates are ignored for simplicity.
21. The Boltzmann constant multiplied by the temperature, $k_BT$, is taken to be unity.
22. Here, we assume that the joining of a monomer to a polymer is an irreversible reaction. This situation is realized if we use an energetically activated monomer, so that covalent bond formation is energetically favorable.
23. By substituting the condition at the steady state $\sum_{i=0}^{L} \sum_{j=1}^{l,s} \bar{x}_{i,j} = 0$ for Eq.2 $\phi$ is determined as $x_{0,p}(1+e^2)\sum_{j=1}^{l,s} f(S)\bar{x}_{1,j} - (1 - x_{0,p})\phi = 0$. Note that we assume the boundary condition that $x_{0,p}$ is a constant.
24. See Supplemental Material at ?? for the detailed derivations of equations.
25. This situation is satisfied, at least under the fitness landscape assumed in this letter.
26. Without this assumption, the template-replication system also suffers from the ‘product-inhibition’ problem [11, 12]; we discuss polymerization- and template-replication dynamics with product inhibition in another paper.
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34. For example, in multimodal landscapes, the system could show multi-stability because of frequency-dependent selection among templates [18, 19, 20].
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Reduction of the model into the QS model in a case with slow dilution \((x_{0,p} \sim 0)\)

We assume that polymerization is completed on a much faster time scale than that for the dilution (and the supply of primers) (i.e., \(\phi \sim 0\), which is realized when \(x_{0,p} \ll 1\)). Because the last term is negligible in Eq. 2, using the steady-state condition \(\dot{x}_{l,s} = 0\) allows adiabatic elimination of variables \(x_{l,s}\) where \(l \leq L - 1\) as

\[
x_{l,s} = x_{l-1,s'} \frac{\sum_{S \in \{0,1\}^L} f(S) \beta(l - 1, s', S) \nu(l, m, S) x_{L,S}}{(1 + e^\Delta) \sum_{S \in \{0,1\}^L} f(S) \beta(l, s, S) x_{l,S}}.
\]

(S1)

Because \(s'm\) and \(s\) are identical sequences in Eq. 2, it follows that \(\beta(l - 1, s', S) \nu(l, m, S) = \beta(l, s, S)\). Therefore,

\[
x_{l,s} = x_{l-1,s'}/(1 + e^\Delta).
\]

(S2)

Using this equation, we can transform the rate equation for template polymers (i.e., polymers of length \(L\)) as follows:

\[
\dot{x}_{L,s} = x_{L-1,s'} \sum_{S \in \{0,1\}^L} f(S) \beta(L - 1, s', S) \nu(L, m, S) x_{L,S} - \phi x_{L,s}.
\]

(S3)

Because \(\beta(L - 1, s', S) \nu(L, m, S) = \beta(L, s, S)\), it follows that

\[
\dot{x}_{L,s} = \frac{x_{0,p}}{(1 + e^\Delta)^{L-1}} \sum_{S \in \{0,1\}^L} f(S) e^{\Delta} x_{L,s} - \phi x_{L,s}
\]

(S4)

\[
= x_{0,p}(1 + e^\Delta) \sum_{S \in \{0,1\}^L} f(S) e^{\Delta} x_{L,s} - \phi x_{L,s},
\]

where \(h_{i,j}\) is the Hamming distance between sequences \(i\) and \(j\). Using \(\mu = \frac{1}{1+\Delta}\), Eq. 4 in the main text is obtained.

Derivation of the upper limit of the accuracy of information in a case with fast dilution \((x_{0,p} \sim 1)\)

First, we assume that the frequencies of ‘0’ and ‘1’ at different locations along the polymers are independent of each other. Let \(\xi_{i,0}^{(i)}\) and \(\xi_{i,1}^{(i)}\) denote the relative frequencies of polymers of sequence length \(l\) whose \(i\)-th bit is ‘0’ and ‘1’, respectively, where \(\xi_{i,0}^{(i)} + \xi_{i,1}^{(i)} = 1\). The concentration of polymers of sequence length \(l\) and sequence \(s\) is then expressed as follows:

\[
x_{l,s} = x_l \prod_{i=1}^l \xi_{i,m_i}^{(i)}.
\]

(S5)

where \(m_i\) is the \(i\)-th bit of sequence \(s\), and \(x_l\) is the sum of the concentrations of the polymers of sequence length \(l\) \((x_l = \sum_s x_{l,s})\).

From the steady state of Eq. 2, \(x_{l,s}\) is calculated as follows:

\[
x_{l,s} = x_{l-1,s'} \sum_{S \in \{0,1\}^L} r(l - 1, s', m, S) x_{L,S}/\phi,
\]

(S6)

where we assumed that the first and last terms are dominant in Eq. 2, because we assumed \(x_{0,p} \sim 1\) to allow a large \(\phi\). \(s'\) represents a sequence in which the end monomer of sequence \(s\) is deleted. Here, substituting Eq. 5 and summing all the concentrations of the sequences whose \(i\)-th bit is ‘0’ gives

\[
\phi \sum_{s' \in s_0^{(i)}} x_{l,s} = \sum_{s \in s_0^{(i)}} x_{l-1} \prod_{j=1}^{l-1} \xi_{l-1,m_{j},j}^{(j)} \sum_{S \in \{0,1\}^L} r(l - 1, s', m_{l}, S) x_{L} \prod_{k=1}^L \xi_{L,M_k}^{(k)},
\]

(S7)
where $\sum_{s \in S_0}^{(i)}$ denotes the summation of all of the sequences where the $i$-th monomer is ‘0’, and $m_j$ and $M_j$ denote the $j$-th bits of the sequences $s$ and $S$, respectively. Note that if $l = i$, we should read $\xi_{l-1,0}^{(i)}$ as $\xi_{l-1,0}^{(i)} = 1$. Here, we assume that $f(S) = f_0$ if $S$ is the master sequence, and $= f_1$ if that is the other sequence. This gives

$$ \phi \sum_{s \in S_0}^{(i)} x_{l,s} = x_{l-1,x_L} \sum_{s \in S_0}^{(i)} \xi_{l-1,0}^{(i)} \prod_{j=1,j \neq i}^{t-1} \xi_{l-1,m_j}^{(j)} \left( \sum_{S \in \{0,1\}^L} f_1 \nu(l, m_l, S) \beta(l-1, s', S) \prod_{k=1}^{L} \xi_{L,M_k}^{(k)} \right) + (f_0 - f_1) \nu(l, m_l, S_0) \beta(l-1, s', S_0) \prod_{k=1}^{L} \xi_{L,0}^{(k)}, $$

(S8)

By applying the definition of $\beta(l-1, s', S)$ and $\nu(l, m_l, S)$ for each pair of polymers, $x_{l,s} = x_l \prod_{i=1}^{l} \xi_{l,m_i}^{(i)}$ and a template $x_{l,S} = x_L \prod_{i=1}^{L} \xi_{l,M_i}^{(i)}$,

$$ x_{l-1,x_L} f_1 \xi_{l-1,0}^{(i)} (e^{\Delta \xi_{l-1,0}^{(i)} L_0} + e_{L,1}) \prod_{j=1,j \neq i}^{l} (e^{\Delta \xi_{l-1,0}^{(j)} L_0} + \xi_{l-1,0}^{(j)} e_{L,1} + \xi_{l-1,1}^{(j)} e_{L,0} + e^{\Delta \xi_{l-1,1}^{(j)} L_1}), $$

(S9)

$$ + x_{l-1,x_L} (f_0 - f_1) e^{\Delta \xi_{l-1,0}^{(i)} L_0} \prod_{j=1,j \neq i}^{L} (e^{\Delta \xi_{l-1,0}^{(j)} L_0} + \xi_{l-1,1}^{(j)}), $$

where we define $\xi_{l-1,0}^{(i)} = \xi_{l-1,1}^{(i)} = 1$. By using $e^{\Delta \xi_{l-1,0}^{(i)} L_0} + e_{L,1} = 1$,

$$ e^{\Delta \xi_{l-1,0}^{(i)} L_0} + e_{L,1} = \prod_{j=1,j \neq i}^{l} (e^{\Delta \xi_{l-1,0}^{(j)} L_0} + \xi_{l-1,0}^{(j)} e_{L,1} + \xi_{l-1,1}^{(j)} e_{L,0} + e^{\Delta \xi_{l-1,1}^{(j)} L_1}), $$

(S10)

In the last line, we assume that the last term is much smaller than the first term, because $(1 - e^{\Delta}) (\xi_{l-1,1}^{(i)} - \xi_{l-1,0}^{(i)}) \sim 0$ if $\Delta$ is small, and $\xi_{l-1,1}^{(i)} \sim 0$ if $\Delta$ is large; thus,

$$ e^{\Delta \xi_{l-1,0}^{(i)} L_0} + \xi_{l-1,1}^{(i)} \sim (e^{\Delta \xi_{l-1,0}^{(i)} L_0} + \xi_{l-1,0}^{(i)} e_{L,1} + \xi_{l-1,1}^{(i)} e_{L,0} + e^{\Delta \xi_{l-1,1}^{(i)} L_1}). $$

(S11)

Similarly, we obtain the expressions for the sequences whose $i$-th monomer is ‘1’, $\sum_{s \in S_1}^{(i)} x_{l,s}$. Thus, the relative production rate of a polymer with $i$-th monomer ‘0’ and ‘1’ is given by

$$ \phi \sum_{s \in S_0}^{(i)} x_{l,s} = \phi x_l \xi_{l,0}^{(i)} = A_1^{(i)} [e^{\Delta \xi_0 f_0 + e_{L,0}} + e^{\Delta (\xi_0 - \xi_0) f_1 + \xi_{l-1,0}^{(i)}}], $$

(S12)

$$ \phi \sum_{s \in S_1}^{(i)} x_{l,s} = \phi x_l \xi_{l,1}^{(i)} = A_1^{(i)} [\xi_0 f_0 + (e_{L,0} - \xi_0) f_1 + e^{\Delta \xi_1 f_1}] x_{l-1} \xi_{l-1,1}^{(i)}, $$

where $A_1^{(i)}$ is a constant that satisfies $A_1^{(i)} = x_L \prod_{j=1,j \neq i}^{l} (e^{\Delta \xi_{l-1,0}^{(j)} L_0} + \xi_{l-1,1}^{(j)} L_1)$. Here, we define $F_0^{(i)}$ and $F_0^{(i)}$ as

$$ F_0^{(i)} = e^{\Delta \xi_0 f_0 + e_{L,0} - \xi_0} f_1 + \xi_{l-1,1}^{(i)} f_1, $$

$$ F_1^{(i)} = \xi_0 f_0 + (e_{L,0} - \xi_0) f_1 + e^{\Delta \xi_1 f_1}, $$

(S13)

respectively, which are interpreted as the relative rates of the monomer addition to the sequence whose $i$-th monomer is ‘0’ and ‘1’, respectively (Fig.S1). Note that $F_0^{(i)}$ and $F_0^{(i)}$ do not depend on the length of the sequence. Recursive
FIG. S1. Schematic of reaction pathways from the addition of the $i$-th monomer to the completion of the template of length $L$ whose $i$-th monomer is '0' or '1'. As in Fig. 1(a), each arrow represents the monomer addition to a substrate polymer using a template.

FIG. S2. The fraction of the error at each bit in the template sequence with length $L = 4$. The solid lines represent the fraction of the template polymer, $\xi_1^{(1)}$, $\xi_1^{(2)}$, and $\xi_1^{(3)}$. The dotted lines represent the minimum error rate that can be achieved in the KPR scheme of steps 2, 3, and 4, respectively. The inset shows the same plot with log-log axes.

The error threshold for a replicating template with error correction

The threshold value for the error catastrophe is roughly estimated in the case with a fast dilution limit (i.e., $x_{0,p} \sim 1$). Based on the discussion in the main text, for multistep reactions, the effective error rate at the $i$-th bit of the template during replication is modified as $\mu^{L+1-i}_{1+\exp(-(L+1-i)\Delta)}$. In this case, the error threshold at which the growth rate of the master sequence is overwhelmed by that of the others is estimated from the condition

$$\prod_{i=1}^{L} \frac{1}{1 + e^{-\Delta} f_0} \sim f_1,$$

(S15)
FIG. S3. The dependence on the error rate $\mu$ of the fraction of the master sequence among all of the templates $\xi_0$ in a case with $x_{0,0} \sim 1$. The dashed line represents the error-rate value $\mu^*$ in the solution of Eq. S15 in a case with a large $L$ limit.

where $f_0$ and $f_1$ are the fitness of the master sequence and the others, respectively. If we assume that $L$ is infinitely large, then the threshold for $\mu$ is derived numerically as $\mu^* \sim 0.4268$ (Fig. S3). It should be noted that although the fraction of the master sequence $\xi_0$ is small if $\mu > \mu^*$, the threshold for $A$ is higher than $\mu^*$, because the difference between $\xi_0^{(i)}$ and $\xi_1^{(i)}$ is magnified exponentially.