BioSystems, 11 (1979) 85—91

DISSIPATION-ERROR TRADEOFF IN PROOFREADING

CHARLES H. BENNETT

IBM Watson Research Center, Yorktown Heights, NY 10598, U.S.A.

Chemical proofreading systems, of the kind believed responsible for the extremely high fidelity of DNA replication, achieve minimum error probability (equal to the product of the error probabilities of the writing and proofreading stages) only in the limit of infinite energy dissipation. However, a considerable degree of proofreading can be obtained in less strongly driven systems, dissipation only 0.1—1 kT/step.

1. Introduction

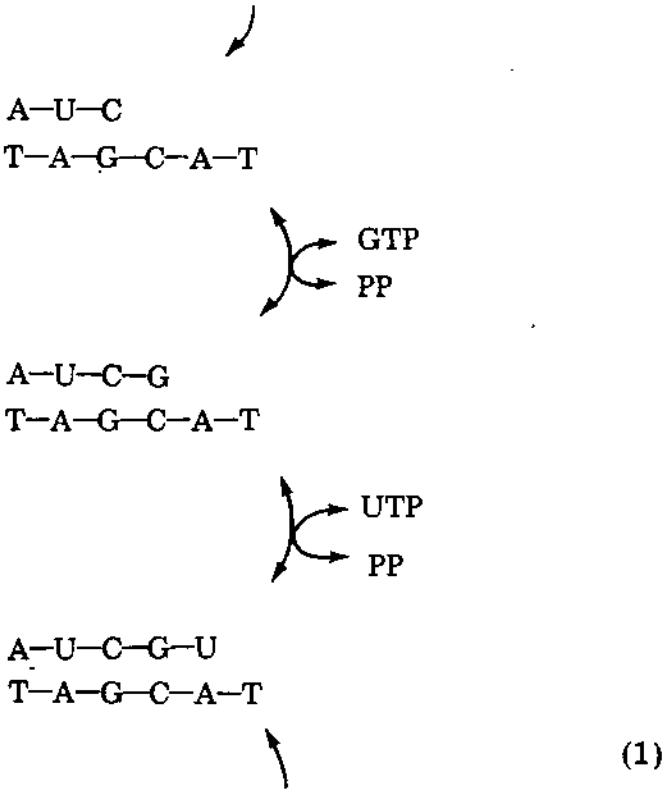
The processing of digital information in an electronic computer or in the genetic apparatus, like any other activity proceeding at finite speed with a definite direction in time, requires the dissipation of energy. However, it was not immediately clear to early workers in this field how much energy must be dissipated or entropy produced, per bit of information processed. Von Neumann (1966) suggested that at least kT ln 2 of energy (about $3 \cdot 10^{-21}$ J at room temperature, or 0.4 kcal/mol) must be dissipated per elementary binary operation. Brillouin (1962) came to a similar conclusion by analysis of a Gedankenexperiment involving detection of holes in a punched tape by photons, and argued further that energy dissipation must increase with the reliability of measurement, being approximately kT ln $(1/\eta)$ for a measurement with error probability η. These arguments have an intuitive plausibility, especially in view of the quantitative relation between entropy and information exemplified by Maxwell's demon (Szilard, 1929); however, it is now known that there is no universal, hardware-independent limit on the entropy cost of copying or processing a bit of information. One can even design a general-purpose digital computer that is reversible in the sense of a Carnot engine, but which can do an arbitrarily large amount of mathematical work per unit of entropy produced (Bennett, 1973; Fredkin, E., unpublished; Landauer, 1976). Like a reversible heat engine, such a computer may remove entropy from or release entropy to its surroundings, but these exchanges can be made arbitrarily close to reversible, so that the entropy increase in the universe as a whole, during a job of copying or computation, approaches zero.

The essential role of dissipation appears to be not for information processing itself, but rather for the prevention and correction of random errors, which occur at a rate η_0 depending on the hardware, e.g., the intrinsic error rate $\gtrsim 10^{-5}$ (Topal and Fresco, 1976) corresponding to a plausible free energy difference $\lesssim$ 10 kT between enzymatic reaction paths involving correctly and incorrectly matched Watson-Crick base pairs. Indeed, the machinery of DNA replication and protein synthesis offers the chief example of the efficient use of dissipation, in the form of nucleoside triphosphate-dependent proofreading enzyme systems (Hopfield, 1974; Ninio, 1975) to correct errors. Macroscopic information processing devices, such as neurons and transistors, also dissipate energy, but in such large amounts (typically 10^{10} kT/

operation, as opposed to 10^2 kT in the genetic apparatus) that its thermodynamic role is rather obscure.

Error-correction is an example of a *logically irreversible* operation on data, i.e., an operation whose inverse is not unique. Landauer (1961) showed that such operations are necessarily dissipative in the sense envisioned by von Neumann. The lack of any fundamental limit on the dissipation required to simply copy or transcribe information is a consequence of the fact that copying per se is not logically irreversible.

To see that information can in principle be copied with arbitrarily little dissipation, consider the reaction catalyzed by a reversible, non-proofreading copying enzyme such as RNA polymerase:



(1)

Ignoring errors for the moment, it can be seen that the sequence of reactions can be driven forward with arbitrarily small dissipation per step by adjusting the chemical potentials of each of the triphosphates, ATP, UTP, GTP and CTP to be marginally greater than that of the common reaction product pyrophosphate (PP). When the chemical potential difference is ϵ, the system will perform a biased random walk along the one-dimensional chain of reactions, with forward steps outnumbering backward steps in the ratio $e^{\epsilon/kT}$. (Making the driving force negative would cause the enzyme to reversibly "unread" the partly completed strand, comparing each base with the template before removing it. This "unreading" is the logical inverse of transcription).

Of course, one cannot approach the zero-speed, zero-dissipation limit without incurring excessive errors, because errors occur in some fixed proportion η_0 to the gross, rather than the net, number of forward steps. A copying speed less than η_0 times the gross step rate would therefore result in near-total infidelity of copying. The intrinsic error rate η_0 thus determines the speed, and hence the dissipation, required for reliable copying by a given apparatus. However, this does not represent a universal limit, because η_0 can in principle be made arbitrarily small by increasing the size and complexity of the recognition sites (to increase the energy difference ΔE between correct and error reaction paths), lowering the temperature (to increase the Boltzmann ratio $e^{\Delta E/kT}$, of correct to error transitions, without increasing ΔE), and making the apparatus larger or more massive (to reduce tunneling).

The accumulation of evidence (e.g., England, 1971; Nossal and Hershfield, 1971; Muzyczka et al., 1972; Lo and Bessman, 1976) in favor of enzymatic proofreading in DNA replication prompts the following general question: how may a pair of reactions with individual error rates η_0 be combined to effect copying with a lower error rate η, with the least cost in dissipation per digit copied?

2. Dissipation-error tradeoff in a model copying system

In the interest of clarity we analyze rather simple reaction schemes, which embody the

principle of proofreading without otherwise attempting to mimic the details of DNA replication (cf., Alberts and Sternglanz, 1977). In particular, the method system uses a 2-letter rather than a 4-letter alphabet, and presumes one-step rather than Michaelis kinetics for each reaction path.

2.1 Dissipation-error tradeoff without proofreading

First we consider a reaction scheme analogous to eqn. 1, not making use of proofreading. The entire set of possible correct and error chains is connected by correct and error reactions to form a large binary tree, a typical part of which is shown in Fig. 1. The symbol & represents a partly synthesized chain, possibly already including some errors, while &w and &r represent its 2 possible extensions (wrong base added, right base added, respectively). These in turn have extensions &ww, &wr, &rw, and &rr. For simplicity it is assumed that all chains, whether or not they contain errors, have the same free energy. This represents a conservative assumption in that the free energy differences that do exist favor chains with fewer errors. The steady state of the tree of reactions of Fig. 1, all sharing the same 4 rate constants, is characterized by stationary concentrations of the reactants [&], an error probability η and a net forward velocity v, which are related to the rate constants as follows:

$$[\&w]/[\&] = \eta \tag{2a}$$

$$[\&r]/[\&] = 1 - \eta \tag{2b}$$

$$k_1 - \eta k_2 = \eta v \tag{3a}$$

$$k_3 - (1-\eta)k_4 = (1-\eta)v \tag{3b}$$

If copying proceeds by a single reversible reaction with free energy discrimination δ, and if as assumed there is no free energy difference between &w and &r, the following additional relations hold among the 4 rate constants:

$$\ln(k_3/k_1) = \ln(k_4/k_2) = \delta \equiv \ln(1-\eta_0)/\eta_0 \tag{4}$$

$$\ln(k_1/k_2) = \ln(k_3/k_4) = \epsilon, \tag{5}$$

where ϵ is the driving force favoring chain extension, supplied by coupling to external reactants such as XTP/PP. Henceforth, the energies δ and ϵ will be taken in dimensionless units kT = 1. These relations are summarized in a diagram (Fig. 2) of the activation barriers opposing error (left) and correct (right) transitions. The abscissa in such figures is arbitrary, while vertical peak-to-valley distances denote simply the negative logarithms of rate constants.

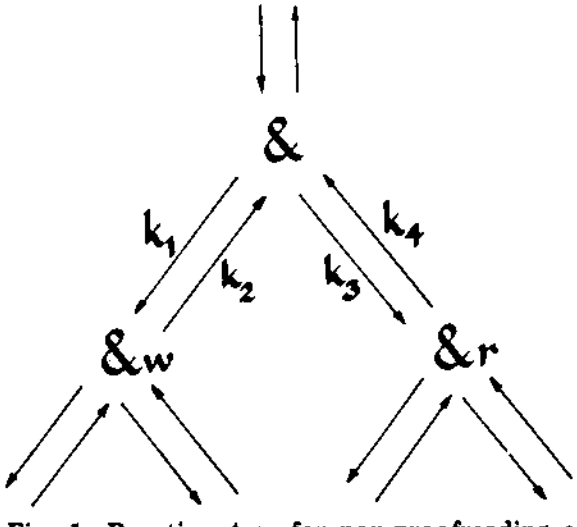


Fig. 1. Reaction tree for non-proofreading copying system.

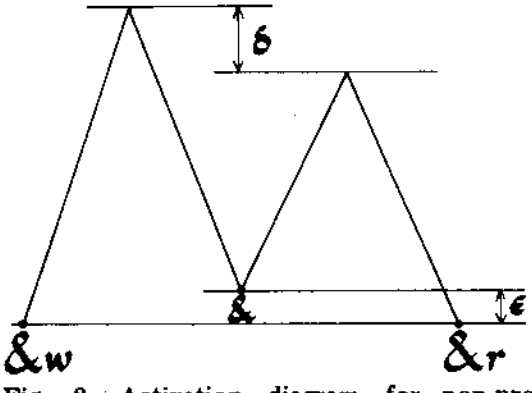


Fig. 2. Activation diagram for non-proofreading copying system.

The dissipation rate may be obtained as a sum of products of forces by fluxes for the 2 reaction paths in Fig. 2:

$$v\sigma \equiv (k_1 - \eta k_2)\ln(k_1/\eta k_2) + (k_3 - (1-\eta)k_4) \times \ln(k_3/(1-\eta)k_4) \quad (6)$$

$$= v\epsilon + v[\eta \ln(1/\eta) + (1-\eta)\ln 1/(1-\eta)]. \quad (7)$$

The second term in eqn. 7 may be recognized as the rate at which entropy, in the form of errors, is incorporated in the chain being synthesized. It is only the total entropy production $v\sigma$ that must be positive; when the error rate η is high, the external entropy production, $v\epsilon$, may be negative, meaning that the incorporation of errors is driving chain growth forward even though the external driving force is weakly backward.

Specification of the intrinsic and desired error probabilities η_0 and η is sufficient to determine $v\sigma$, v, and all the rate constants to within a common multiplicative factor; therefore, the dissipation *per step*, σ, is uniquely determined by η_0 and η, according to the following relation, derivable from eqns. 3a through 7:

$$\sigma = \ln[\eta(1-\eta)(1-2\eta_0)/(\eta(1-\eta_0) - \eta_0 \times (1-\eta))] + \eta \ln(1/\eta) + (1-\eta)\ln 1/(1-\eta). \quad (8)$$

The final 2 terms, as remarked earlier, represent entropy generated in the form of incorporated errors. The solid curve in Fig. 3 shows the error dissipation tradeoff given by equation 8 for a non-proofreading system with intrinsic error probability $\eta_0 = 10^{-5}$. As expected the minimum error probability attainable in the limit of infinite dissipation is 10^{-5}. The tradeoff curve is not monotonic, and displays a minimum around $\eta = 10^{-3}$. To the left of this minimum, the dissipation

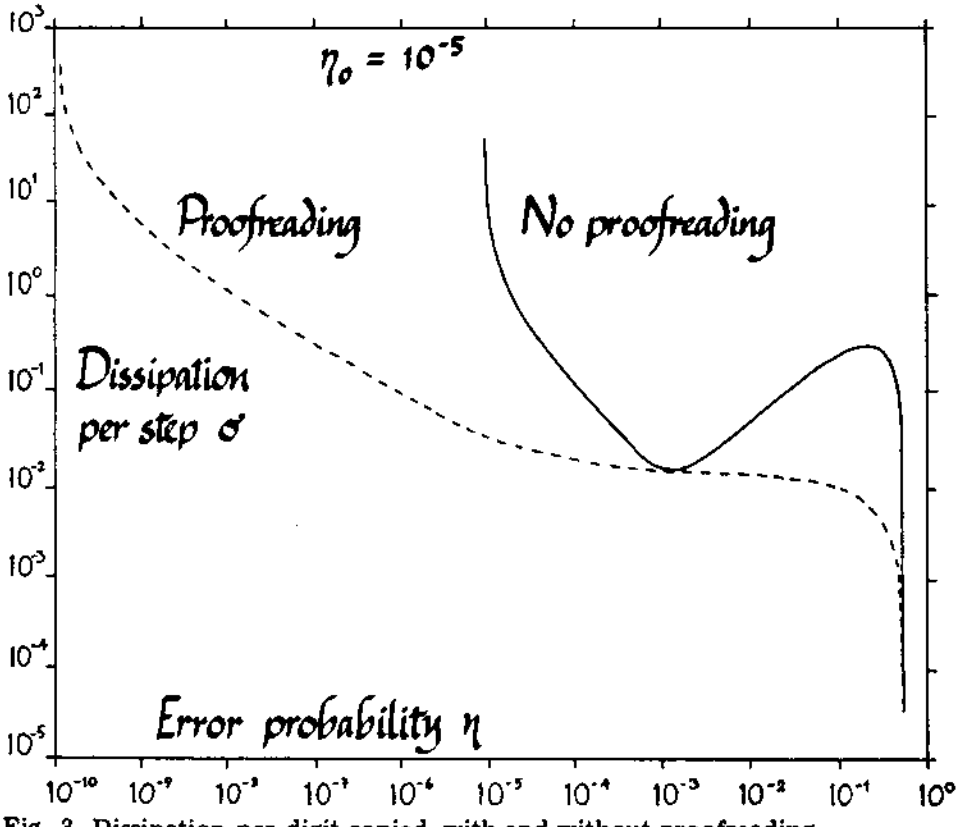


Fig. 3. Dissipation per digit copied, with and without proofreading.

occurs chiefly in the external driving reactions; whereas to the right of it, the external driving force is weak or negative, and the dissipation is chiefly due to incorporated errors. Of course, the error probability in the limit of zero dissipation is 50 per cent, corresponding to the random polymer that would be produced if the system were allowed to relax to complete thermal equilibrium. This limit occurs when the external driving force is made sufficiently negative, $\epsilon = -\ln 2 = -0.693$, to exactly balance the internal forward driving force of error incorporation.

At first sight it would seem that a reversible copying reaction of the type of eqn. 1 could be driven backward by even a marginally negative driving force, and indeed it would if the copy and template strands matched perfectly. However, any error in the copy strand acts as an obstacle to "unreading" because, by the principle of microscopic reversibility, it is just as hard (in the absence of proofreading) to unread an error as to incorporate it the first place. An initially perfect copy strand, if subjected to a driving force less negative than -0.693, will at first undergo "unreading" until an equilibrium concentration of errors is established, then the net direction of motion will shift from backward to forward, because of the errors' ability to obstruct backward motion. The expected number of digits of perfect copy removed in the initial phase of net unreading depends on ϵ and η_0, tending to infinity as η_0 approaches zero or ϵ approaches $-\ln 2$.

2.2 Error-dissipation tradeoff with proofreading

The simplest way to introduce proofreading is by another one-step reaction parallel to but independent from the reaction path depicted in Figs. 1 and 2. Biologically this would correspond to placing the proofreading exonuclease activity in a separate reaction path from the polymerase activity, rather than having the 2 activities belong to a single branching reaction path, as they do in Hopfield's model. The

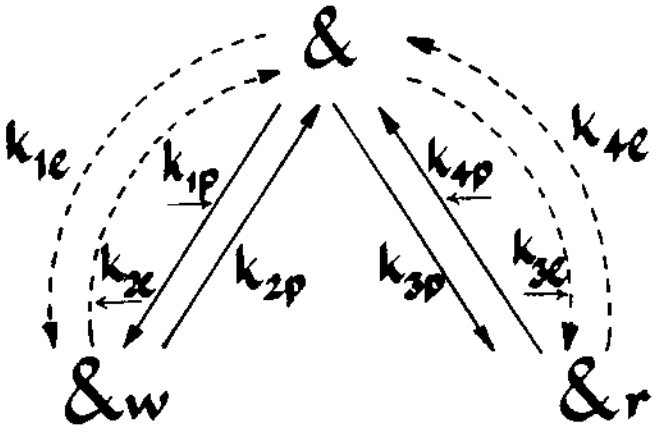


Fig. 4. Reaction tree for proofreading copying system. The dashed arrows refer to the exonuclease, the solid arrows to the polymerase.

proofreading exonuclease (Figs. 4 and 5) is presumed to have the same intrinsic discrimination δ as the polymerase, but with the lower barrier on the error side (between & and &w), instead of between & and &r, where the polymerase has its lower barrier. Because it is coupled to different external reactants, its driving force may differ in sign and magnitude from that of the polymerase. The activation diagram of Fig. 5 is of approximately the proper form to achieve a considerable degree of error correction without much dissipation. The driving force for the polymerase, ϵ_p is fairly small to keep the dissipation low when

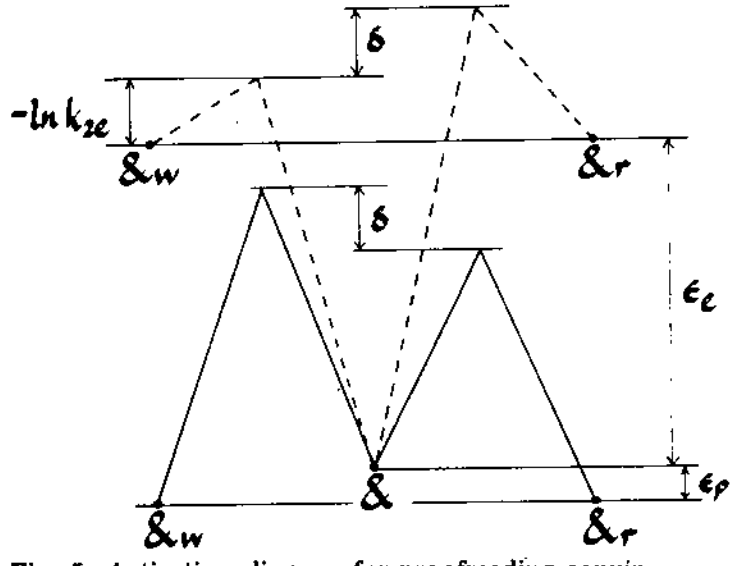


Fig. 5. Activation diagram for proofreading copying system.

no error has been made. The exonuclease, on the other hand, has a large driving force, and particularly a fast k_{2e} rate, so as to be able to rapidly undo most error transitions & → &w performed by the polymerase k_{1p}.

The kinetics of the 2-enzyme system can be analyzed in a fairly straightforward manner, given the experience of the 1 enzyme non-proofreading system. Equations 2 and 3, defining the steady state, can be taken over without change and apply to sums of the exonuclease and polymerase rate constants, e.g. $k_1 = k_{1p} + k_{1e}$. Equation 7, defining the dissipation in terms of forces and flows, must be modified to sum over all 4 force-flow pairs instead of only 2. The chief difference from the non-proofreading case is that specification of $\eta_0 \equiv 1/(1 + e^{\delta})$ and η no longer uniquely determines the per step dissipation σ, but instead leaves the system with 2 non-trivial degrees of freedom. The dissipation-error tradeoff shown in Fig. 3 for the 2-enzyme proofreading system (dashed curve) was obtained by numerical minimization with respect to the 2 remaining degrees of freedom.

The tradeoff curve, as expected, has an asymptotic error rate $\eta = 10^{-10}$, the square of the intrinsic error rate η_0. The proofreading system is never more dissipative than the non-proofreading one, being better able to correct errors when driven forward, and better able to exploit errors to pump the driving reactions uphill when driven backward, than the non-proofreading system.

3. Discussion

It is clear from Fig. 3 that proofreading can considerably reduce errors even in the absence of driving forces stronger than about 0.1 kT/step. On the other hand, the tradeoff curve for the proofreading system displays what looks like a soft threshold at about 0.01 kT/step, with dissipation less than that apparently incompatible with much error reduction. Certainly the proofreading scheme described here, or other proofreading schemes (Hopfield, 1974; Ninio, 1975), can be cascaded to obtain, at high dissipation, an error probability approaching η_0^{k+1}, where k is the number of extra reaction paths. Again it is unclear whether there is a threshold driving force, above which the cascading strategy pays off, and below which it yields little improvement, no matter how many stages are used. Similarly, it should be determined to what extent it helps to have the error probability η_0 already fairly low (say 10^{-5} instead of 10^{-1}). These questions are reminiscent of von Neumann's (1963) finding, in his classic paper on the synthesis of reliable automata from unreliable components, that arbitrarily high reliability could be obtained if the reliability of the basic components was above a certain threshold, but not otherwise.

References

Alberts, B. and R. Sternglanz, 1977, Nature 269, 655—661.

Bennett, C.H., 1973, IBM J. Res. Dev. 17, 525—532.

Brillouin, L., 1962, Science and information theory, second edition (Academic Press, London) pp. 261—264, 194—196.

England, P.T., 1971, J. Biol. Chem. 246, 5684—5687.

Hopfield, J.J., 1974, Proc. Natl. Acad. Sci. USA 71, 4135—4139.

Landauer, R., 1961, IBM J. Res. Dev. 3, 183—191.

Landauer, R., 1976, Ber. Bunsenges. Phys. Chem. 80, 1048—1059.

Lo, K.-Y. and M.J. Bessman, 1976, J. Biol. Chem. 251, 2475—2479.

Muzyczka, N., R.L. Poland and M.J. Bessman, 1972, J. Biol. Chem. 247, 7116—7122.

Ninio, J., 1975, Biochimie 57, 587—595.

Nossal, N.G. and M.S. Hershfield, 1971, J. Biol. Chem. 246, 5414—5426.

Szilard, L., 1929, Z. Phys. 53, 840—856.

Topal, M.D. and J.R. Fresco, 1976, Nature 263, 285—289.

von Neumann, J., 1966, Fourth University of Illinois lecture, in: Theory of self-reproducing automata, A.W. Burks (ed.) (Univ. of Illinois Press, Urbana) p. 66.

von Neumann, J., 1963, "Probabilistic logics and the synthesis of reliable organisms from unreliable components", lectures at Calif. Institute of Technology, in: Collected works, Vol. 5, A.H. Taub (ed.) (MacMillan, New York) pp. 329—378.