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A Case for the Extreme Antiquity of Recombination

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Abstract. Recombination is usually assumed to be a mode of reproduction that evolved long after asexual reproduction in response to specific genetic and environmental circumstances. Here the argument is made that recombination was an evolutionary development as ancient as the origins of life. To support this proposition four lines of evidence are given, in particular, the need for primordial genomes to acquire substantial length and to escape from Muller's Ratchet.

Key words: Recombination — Origins of life — Origins of sex — Muller's Ratchet

Introduction

Recombination is the exchange of genetic information between two sources. In contemporary living systems, the sources can be entire chromosomes, as in segregation recombination, or they can be portions of chromatids, as in crossing-over recombination. Recombination can be driven either by the precise alignment of homologous regions of nucleotide sequence or by misalignments that lead to unequal crossover. In any case the basic phenomenon is that two sources of genetic information unite, swap portions of their primary nucleotide sequence, and separate to generate recombinant progeny. In contrast, non-recombinatory mechanisms of reproduction include all forms of template-directed polymerization that achieve duplication by the addition of one nucleotide (or some other monomer) at a time (Fig. 1).

The evolutionary origin of recombination, often described as the origin of sex, is a topic of much recent discussion and debate. Numerous theories have been put forward to explain its existence. Such inquiries are justified because of the presumed selective disadvantage of sex compared to strictly asexual reproduction. There are several facets to this problem, but a key issue is that in a population that propagates by simple direct genome duplication and subsequent cell fission, a mutant genotype that promotes a union with another genotype and subsequent division of the resulting genetic material should suffer a significant fitness disadvantage compared to its asexual competitors. An immediate twofold fitness reduction is materialized by the failure of the recombination-promoting allele to double in number each generation, for example (Maynard Smith 1978). Advantages to sex must overcome this drawback, and suggestions have included its promotion of diversity (Fisher 1930), its overall enhancement of the power of natural selection (Rice and Chippendale 2001), its purging of deleterious alleles (Muller 1964; Maynard Smith 1978), its metabolic potential (Redfield 1993a, b), and DNA repair (Michod et al. 1988). One common premise of all of these theories is that asexual reproduction is the primitive condition and that recombination is a derived characteristic driven by natural selection that resulted in a variety of biological mechanisms in a large number of phylogenetic lineages. In the discussion that follows, I challenge this basic premise and propose the hypothesis that recombination is in fact the ancestral reproductive

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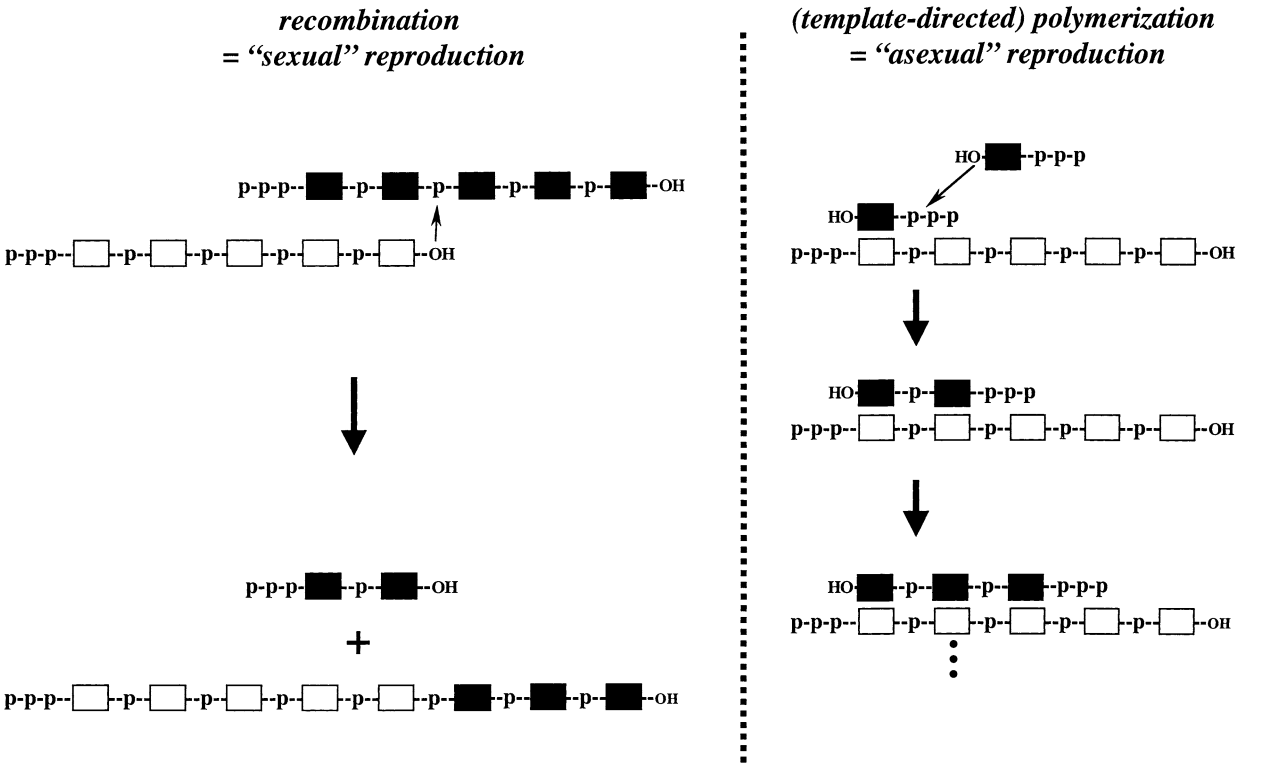

Fig. 1. A contrast of the molecular equivalents of sexual (**left**) and asexual (**right**) reproduction at the level of short single-stranded oligomers such as nucleic acids. In "sexual" reproduction, longer and shorter products than the parental molecules can result from an asymmetric exchange, as shown. In "asexual" reproduction, the polymerization process requires multiple rounds of monomer addition to accomplish a significant increase in polymer length.

condition from which asexual reproduction evolved. At the very least, it was a primitive condition whose origin was contemporaneous with asexuality. Working backward in time, I present four lines of evidence to support this proposition. Taken together, these arguments correlate the origin of recombination with the origins of life itself.

Recombination Is Found in All Phylogenetic Groups, Including Viruses

Recombination is no longer considered a feature unique to complex organisms and it has been noted that the chemical processes underlying recombination—the breakage and religation of nucleic acid strands—most likely predate sexual, meiotic, life (Maynard Smith 1978; Maynard Smith and Szathmáry 1995). Nevertheless, recombination is often still perceived as an adaptation to special environmental conditions that arose in specific lineages. However, the pervasiveness of recombination across diverse phylogenetic groups undermines this notion. Recombination at the molecular level is now recognized as a common characteristic of both eubacteria (Levin 1988) and Archaea (Luo and Wasserfallen 2001). These events are catalyzed in *E. coli* by RecA and in other prokaryotes by homologue and paralogue of RecA, proteins which are critical for many DNA metabolic processes including intergenomic recombination. Moreover, recombination is rampant among viruses, in which both DNA–DNA (Marintcheva and Weller 2001) and RNA–RNA (Biebricher and Luce 1992; Lai 1992; Negroni and Buc 2001) exchange can be observed, resulting from a minimum of two mechanisms: homologous strand breakage-and-religation recombination or illegitimate template-jumping recombination. These events are catalyzed by viral polymerases such as Qβ replicase or reverse transcriptase. Prokaryotes also experience recombination in at least two ways, direct genetic exchange through bacterial conjugation and uptake of exogenous DNA from the environment through transformation. Yet at the basal biochemical level, these exchanges of genetic information from two prokaryotic sources are accomplished via the same chemical intermediates as observed in viral or eukaryotic systems, suggesting that the *mechanisms* of recombination are universal, not just the presence of recombination (Marintcheva and Weller 2001).

Not surprisingly, then, the protein enzymes that accomplish recombination are primitive and often exhibit sequence conservation. Recent comparative studies are coming to the conclusion that recombina-

tion and replication are interdependent processes that utilize many of the same enzymes (Cox 2001). DNA replication under normal growth conditions is in fact dependent on homologous recombination, and such DNA reproduction is now even termed recombination-dependent replication (Asai et al. 1994; Kowalczykowski 2000). The protein sequence of RecA is highly conserved across eubacteria, and amino acid residues in its active sites show high values (41–56%) of sequence similarity even with recombination proteins from T-even phages and *Saccharomyces* (cf. Kowalczykowski et al. 1994). Beyond sequence similarities, the structural features of RecA while DNA bound are remarkably preserved among RecA homologue from the three domains of life and from viruses (Ogawa et al. 1993).

In the RecA and related systems, the enzymes that actually carry out DNA strand breakage and ligation, such as RuvC (breakage), ligase (ligation), and topoisomerases (both breakage and ligation), share distinct amino acid sequence similarities in key substrate-binding motifs such as the 100-amino acid Toprim domain (Aravind et al. 1998). Cavalier-Smith (2002) argues that these similarities point to vestiges of recombination that predate the last common ancestor and that DNA ligase, in particular, could have been, along with DNA polymerase, one of the earliest DNA-handling enzymes. However, he discounts the role of primordial and RNA-based recombination (Cavalier-Smith 2001, 2002), postulating instead that recombination followed the advent of asexual reproduction but developed rapidly as the role of ligase expanded to encompass a variety of DNA handling functions. In any event, there is a growing body of evidence to suggest that the proteins involved in recombination possess deep molecular phylogenies. This concept is implicit in Woese's (1998) view of the universal ancestor, in which lateral gene transfer (essentially intergenomic recombination) prevailed in early protoorganismal populations until individual genomes could crystallize by limiting exchange with others.

Maintenance of Primitive Genomes Would Not Have Been Possible with Strictly Asexual Reproduction

The above argument does not bear directly on the issue of the *extreme* (i.e., concomitant with the origins of life) antiquity of recombination. The remaining three arguments do, supposing that the essence of the recombination machinery that is today borne by protein enzymes had their origins in catalytic RNA-like molecules under an RNA World scenario (Gilbert 1986). In considering the advent of cellular life, several key issues must be taken into account. The first is that the Earth's earliest organisms, of whatever constitution, must have had a mechanism to counteract informational decay through persistent mutation. The first argument for the extreme antiquity of recombination is that strictly asexual reproduction cannot maintain the integrity of a genome in a clonal lineage (cf. Bernstein et al. 1985). Assuming that genotypes with high fitness with respect to self- or hypercyclic replication could arise by polymerization, they can easily and spontaneously degrade through mutational events. In modern cellular organisms, the accumulation of a genetic load through the successive inheritance and generation of slightly deleterious mutations is correlated with the extinction of strictly asexual lineages (Muller 1964; Lynch and Gabriel 1990). This is the consequence of the so-called Muller's Ratchet, a statistical phenomenon that ensures that the mutational load in a population must inexorably increase. This happens in part because the vast majority of mutations reduce fitness, not enhance it, and in part because back mutations that restore the wild-type state are infrequent during asexual reproduction. In smaller populations this problem is intensified by the synergistic effect of an increased probability of the loss of the most fit genotypes through random genetic drift and the increased contribution each mutation has on the population's genetic load (Lynch et al. 1993). It has even been suggested that some RNA editing functions are adaptations for asexual genomes, such as metazoan mitochondria, to salvage otherwise lethally mutated RNA primary transcripts (Börner et al. 1997).

Recombination has repeatedly been proposed as an escape from Muller's Ratchet, in that the wild-type state can be regenerated in a single reproduction event from low- or even medium-error mutants. This logic has been invoked to explain the origin of sex in multicellular organisms, the alternation of sexual and asexual phases of reproduction in several taxa, and the young age of most obligately asexual taxa. The rationale for the latter is that asexual lineages are constantly being derived from sexual ones by the acquisition of a short-term fitness advantage but ultimately going extinct through Muller's Ratchet.

There is no reason to preclude Muller's Ratchet from operating on Earth's earliest organisms or from influencing the advent of life itself. The primordial replicating genetic systems would possess the very features that would make them the most susceptible to Muller's Ratchet. Their fitnesses were not likely to be anywhere near optimized but instead scattered throughout rugged fitness landscapes, their population sizes were likely to be locally small, and the mutation rates of their replication enzymes (ribozymes?) were likely to be quite high, especially during the initial coalescence of life from abiotic materials. Computer simulations of error propagation in asexually reproducing replicator populations reveal that the error

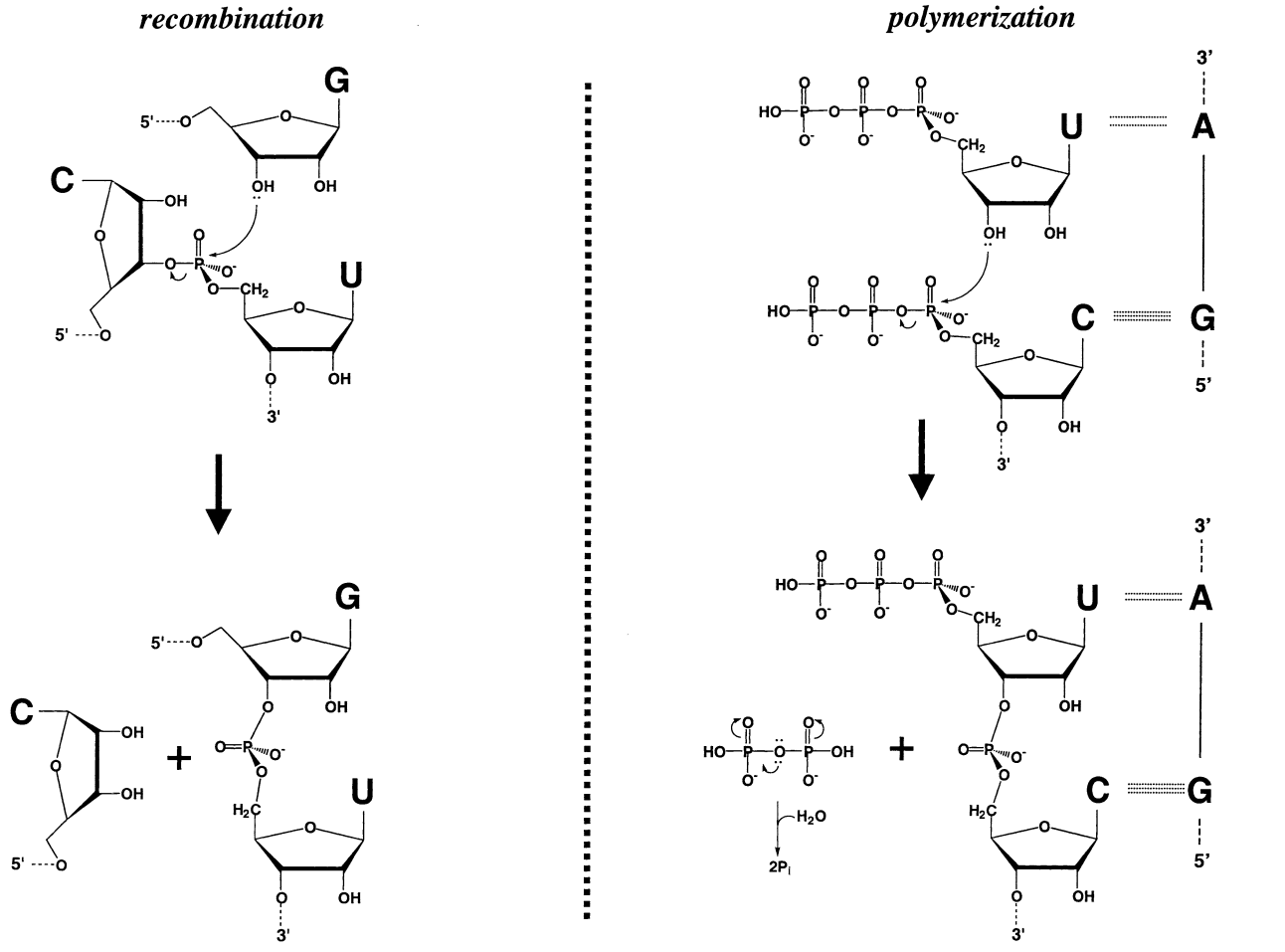

Fig. 2. A contrast of the molecular equivalents of sexual (**left**) and asexual (**right**) reactions in RNA showing the conservation of phosphoester bonds in the former and the need for high-energy bond hydrolysis in the latter (adapted from Breaker and Joyce 1994).

threshold is inversely related to the square root of the population's size (Nowak and Schuster 1989). Thus smaller populations, such as those of emerging self-replicating systems, would in fact require a *higher* replicator accuracy in the absence of recombination because of the greater probability that high-fitness genotypes will be lost from the population by random drift. However, the earliest template-directed replicators were undoubtedly very error-prone, a characteristic that could have persisted as late as the universal ancestor of all extant lineages (Woese 1998). Recently, Zintzaras et al. (2002) demonstrated through Monte Carlo simulations that small populations of autonomously replicating protocells could withstand a relatively high input of deleterious alleles and that hypercyclic modes of replication do not fare as well. Unfortunately these simulations focused on mutation rates at ≤2.5% and have not yet explored rates above 5%, while many have optimistically proposed that the earliest polymerization events had error rates in the 5–10% range (Orgel 1992; Ekland and Bartel 1996; Joyce and Orgel 1999). Future such simulations that can accommodate high error rates, synergistic "mutational meltdowns" (Lynch et al. 1993), and recombination will be of great utility. In this case, recombination is taken to involve primarily homologous and precise alignment of the parental templates. In the two sections that follow, attention will shift to recombination events that lead to unequal crossover.

Recombination Can Accomplish the Buildup of Genetic Potential Without Much Need for High-Energy Intermediates

Another key issue in life's origin is energetics. The genesis of template-directed polymerization is challenging to model or mimic because contemporary mechanisms rely on the use of high-energy building blocks, such as nucleotide triphosphates (cf. Orgel 1998). Recombination, however, can swap blocks of nucleotides with a conservation of phosphoester bonds. For example, contemporary RNA-mediated phosphoester transfer reactions (Fig. 2)—such as Group I intron catalyzed self-splicing, U6 RNA-catalyzed mRNA splicing within the spliceosome complex, and guide RNA-directed mRNA editing—all rely on the nucleophilic attack of the 2′- or

3′-OH group from the ribose of a ribonucleotide onto a phosphodiester linkage that bridges two adjacent nucleotides in a substrate chain. Neither the attacking nor the target nucleotides need be di- or triphosphorylated (i.e., activated with a high-energy bond). The leaving group is always a mono- or polynucleotide with a free 3′-OH. The conservation of phosphoester bonds means that no input of energy is required for the overall reaction; the driving force for these transfers is often simply a local molar excess of the nucleophile (Cech 1990).

In contrast, the "asexual" polymerization reactions, such as those that are today catalyzed by DNA and RNA polymerases, rely on the nucleophilic attack of the 3′-OH from a growing polynucleotide onto a phosphoanhydride linkage of an incoming triphosphorylated (activated) nucleotide. Consequently, the leaving group in this case is inorganic pyrophosphate (PP_i) and the overall reaction can be driven by the subsequent hydrolysis of the highenergy bond in PP_i (Fig. 2). Protein-mediated nucleotidyl transfer reactions, such as homologous recombination, are usually multistep events in which the strand breakage, strand swapping, and strand ligation functions are divided among several protein enzymes. While the first and last of these (endonucleases and ligases) often proceed with the hydrolysis of high-energy cofactors, it is notable that in many cases the central strand-swapping event has been shown not to require high-energy nucleotides. This is the case for RecA protein in *E. coli* and for type II topoisomerases (Kowalczykowski and Krupp 1995).

In primitive living systems driven by catalytic RNAs, recombination could have allowed an accumulation of potential genetic information with less of a need to have a large pool of activated monomers available. In the extreme, a pool of 2-mers is theoretically sufficient to drive the synthesis of higher-length polymers via successive rounds of asymmetric recombination (disproportionation) in which one of the progeny is longer than the parents (Fig. 1, left). The production of 2-mers would be the only stage where high-energy bond usage may be indispensable. An oligomer N monomer units long would require $N - 1$ high-energy bonds, regardless of how it was constructed, and thus the net *amount* of energy needed would be the same for polymerization- and recombination-based pathways. However, because only a single condensation step would be required for 2-mer pool synthesis, low yields for this step would be tolerable, and relatively poor leaving groups on the monomers could suffice. Consequently, the *efficiency* (and speed; see the next section) of disproportionation reactions in building up longer oligomers in a prebiotic pool should be greatly enhanced over that of strict polymerization.

With pools of short polymers, disproportionation exchanges would increase the length complexity of the population, much like the proliferation of length mutants among the microsatellite alleles in modern animal populations (Fig. 1, left). This mechanism of recombination is indeed catalyzed by naturally occurring ribozymes today in reactions where the triphosphate moiety of an NTP is not needed; for example, any derivative of guanosine will drive the Group I ribozyme reaction. In fact, shortly after the discovery of the *Tetrahymena* ribozyme, Zaug and Cech (1986) demonstrated its ability to catalyze *in vitro* the production of a continuum of RNA oligomers from 3 to 30 nucleotides in length, starting solely with a pool of 5-mers. As described by Cech (1985), "If the earliest genes were made of RNA, then RNA splicing can be considered to be the first form of genetic recombination." It is of some curiosity that the χ recombination signal for RecA is 5′-GCTGGTGG-3′, while the internal guide sequence (IGS) of the *Tetrahymena* ribozyme is 5′-GGAGGG-3′, two sequences that bear some superficial similarity. In fact, many other Group I ribozymes possess IGS sequences that contain motifs such as GUGG and GCN (Michel and Westhof 1990).

Looking back at the RNA World (Gilbert 1986), considerable efforts over the last decade, some with significant successes, have been put forth in coercing ribozymes to catalyze template-directed polymerization. In contrast, the feasibility of a recombination-based RNA-like World has received relatively little attention (but see Biebricher and Luce 1992). One disadvantage that the "Recombinatory RNA World" would face compared to the "Asexual RNA World" is a need to separate reactants and products (Joyce and Orgel 1999), lest the latter drive the reverse reaction and shut down any net accumulation in length. Such separation could readily be achieved in a spatially structured environment, such as at a solid/liquid interphase or in a mildly turbulent liquid. Alternatively, the products could be participating in a catalytic network (Kaufman 2000) such that they are rapidly shuttled into other recombination reactions once made. In any case, through successive recombination events, the genetic potential of a pool of oligomers could be rapidly established. Natural selection for polymerase activity (an "autoreplicase") could then operate on this pool to instill the information needed to sustain life.

Construction of Primitive Genomes of Significant Length May Not Have Been Possible Without Recombination

The final realm in the origins of life where recombination could play a significant role is the buildup of genetic information. A long-standing goal of artificial

monomer condensation experiments in the laboratory has been to create polymers of sufficient length for biological function. The target length ranges from about 30 monomers (the size of the smallest naturally occurring ribozymes) to about 70 monomers (the minimum size of a tRNA) or more. A common problem is the multiplicative influence that single chain addition failures have on the total yield. If each monomer addition could even be achieved with a yield (and/or accuracy with respect to monomer identity) of 90%, the total yield for a 30-mer is only 4%. Primitive replication systems likely had much less chemical yield per addition and a much lower accuracy, thereby greatly heightening this problem. With respect to accuracy, it has long been recognized that mutation rates greater than roughly the inverse of the target polymer length will not allow long-term retention of biological information in the polymer (cf. Eigen 1971). This error threshold—the maximum allowable mutation rate of the replicator that will permit maintenance of a population's genetic integrity—predicts that highly inaccurate replicases cannot serve to polymerize long polymers, a potential Catch-22 because greater accuracy often derives from the addition of structural motifs to polymerases. The use of dimers, trimers, etc., as substrates for linear polymerization may not circumvent either the yield or the accuracy problems because of the geometric increase in the number of possible substrates that must be available or differentiated (Joyce and Orgel 1999).

The successes that have been achieved in the laboratory for nonenzymatic—either template-directed (e.g., Wu and Orgel 1992) or non-template-directed (e.g., Ferris et al. 1996)—or ribozyme-directed (e.g., Johnston et al. 2001) polymer synthesis have been impressive, demonstrating the production of polymers 50 nucleotides or more in length. Yet these reactions all employ high concentrations of energy-rich monomers and necessarily result in an overabundance of shorter products in comparison to longer products. Both of these characteristics would be unfavorable to the buildup of biologically meaningful information under primordial conditions.

In contrast, recombinatory mechanisms, especially when working in conjunction with inefficient polymerization processes, could quickly piece together longer fragments from shorter ones even in the absence of a biological catalyst. In fact, unequal crossovers (Fig. 1, left) could be exploited in the production of longer oligomers: The long product would be raw material for natural selection, while the short product would be either lost (invisible to the selection process; Scott 1986, p. 164) or rapidly recycled into subsequent crossovers because it need not be reactivated with a high-energy bond. From entropic considerations, it can be seen that prebiotic pools containing longer oligomers can be amassed more rapidly with recombination than without. Consider the construction of 30-mers via successive disproportion reactions. A 33-mer could be synthesized in a minimum of five sequentially dependent steps: (*i*) 2-mer + 2-mer → 3-mer + 1-mer; (*ii*) 3-mer + 3-mer → 5-mer + 1-mer (*iii*) 5-mer + 5-mer → 9-mer + 1-mer; (*iv*) 9-mer + 9-mer → 17-mer + 1-mer; and (*v*) 17-mer + 17-mer → 33-mer + 1-mer. Of course, each of these reactions as described generates the most extreme disproportionation possible, and each reaction requires that at least two events of the previous reaction occurred previously. Yet compared to the 32 sequentially dependent steps needed to polymerize a product of the same length (assuming that primordial polymerases had low, if any, processivity), the speed advantage of recombination in building up pool length becomes obvious—an advantage that actually increases as the target polymer length increases.

This argument is analogous to the superiority of subassembly use in systems theory or to the benefits of parallel processing in computer science. As first noted by Jacobson (1955), a complex system at any stage of synthesis will be constructed in an expected period of time that increases exponentially with the information content (= negentropy) of that stage. Simon (1996) extended this concept to estimate that assemblies of 1000 parts each (i.e., 1000-mers) would take only 1/4000 as long to assemble on average if 10-mers were first assembled and then pieced together as would a linear sequence of 1000 assemblies of monomers. This is a direct consequence of the time lost upon abortive assemblies, assumed in this example to occur with a 1% probability each time a chemical bond is formed. The time lost is always much greater in the case of linear polymerization. Recombination thus offers prebiotic pools a utility to make long polymers. Interestingly, such utility need not have originally been subject to natural selection; a multiuser recombinase activity in the local environment could be used to generate all (replicator) genotypes, which could later evolve to encode their own recombinase functions.

Summary

Under prebiotic conditions, the creation and maintenance of replication information may have been prohibitively unfavorable for life-like strategies that relied strictly on polymerizing chemistries. I suggest that instead such information could have been pieced together via a combination of polymerization and fragment-swapping mechanisms, the latter serving also to preserve any fitness gains that had been achieved. A streamlined model would proceed as

follows. Activated monomers would spontaneously condense, perhaps with the aid of an inorganic surface catalyst, with a low efficiency to generate a pool of oligomers in the 2- to 5-mer range. These would aggregate through complementarity events, more often than not forming staggered duplexes. Noncatalyzed disproportionation reactions could engender longer oligomers through swapping reactions functioning at near-neutral free energy change. Extended oligomers with slight recombinase activity would be favored, as they would tend to direct the disproportion of like sequences via complementarity. Natural selection would then be provided with a pool of polymers of sufficient sequence to promote polymerization reactions and others that involve greater free energy changes. In this hypothesis, which awaits testing through further simulation *in silico* and *in vitro*, recombination is a primitive and conserved feature of life that coevolved with polymerization.

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