Journal of Theoretical Biology 446 (2018) 128–136

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/jtbi

Evolutionary advantage of directional symmetry breaking in self-replicating polymers

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ARTICLE INFO

Article history:
Received 22 August 2017
Revised 2 January 2018
Accepted 11 March 2018
Available online 12 March 2018

Keywords:
DNA strand directionality
3'-5' unidirectional replication
Asymmetric cooperativity
Primordial heteropolymers

ABSTRACT

Due to the asymmetric nature of the nucleotides, the extant informational biomolecule, DNA, is constrained to replicate unidirectionally on a template. As a product of molecular evolution that sought to maximize replicative potential, DNA's unidirectional replication poses a mystery since symmetric bidirectional self-replicators obviously would replicate faster than unidirectional self-replicators and hence would have been evolutionarily more successful. Here we carefully examine the physico-chemical requirements for evolutionarily successful primordial self-replicators and theoretically show that at low monomer concentrations that possibly prevailed in the primordial oceans, asymmetric unidirectional self-replicators would have an evolutionary advantage over bidirectional self-replicators. The competing requirements of low and high kinetic barriers for formation and long lifetime of inter-strand bonds respectively are simultaneously satisfied through asymmetric kinetic influence of inter-strand bonds, resulting in evolutionarily successful unidirectional self-replicators. Within our model, circular strands, the configuration prefered by primitive life forms, have higher replicative potential compared to linear strands.

1. Introduction

The mechanism of replication of DNA, the universal genetic material of living systems, is far from simple. The two anti-parallel strands of a duplex DNA function as templates for the construction of daughter strands, resulting in two duplex DNA strands. But since the construction of daughter strand happens unidirectionally, from 3′-end of the template strand towards the 5′-end, and since the template strands are anti-parallel, one of the daughter strands, the leading strand, is constructed continuously, whereas the other lagging strand is constructed in fragments which are subsequently rejoined. Being a product of molecular evolution (Engelhart and Hud, 2010; Hud et al., 2013; Joyce et al., 1987; Leslie E, 2004), it would be natural to expect evolution to choose monomers supporting bidirectional replication and parallel duplex strand orientation for faster replication and to avoid the inherently complicated lagging strand replication mechanism. This leads us to question the evolutionary reasons for the choice of a) unidirectional construction of daughter strand and b) anti-parallel DNA strand orientation.

In this article, we examine the first of the above two questions and provide a theoretical justification for the evolutionary choice of unidirectional replica strand construction over bidirectional construction. We begin by considering primordial, non-enzymatically self-replicating polymers, that evolutionarily preceded RNA and DNA. We set the stage for evolutionary competition by imagining multiple species of autocatalytic polymers, constructed out of chemically-distinct monomers, competing for common precursors, energetic sources for activation, catalytic surfaces and niches, in the primordial oceans. Our central premise is that the simplest of the evolutionary strategies, higher rates of replication (Nowak and Ohtsuki, 2008), determined the outcome of this evolutionary competition. We identify some fundamental, common-sense functional requirements that these primordial autocatalytic polymers must satisfy in order to replicate faster than other competing species and hence be evolutionarily successful.

Evidently, the evolutionary search for the perfect non-enzymatically self-replicating molecular species in a given environment is constrained by the diversity of molecules available to be used as monomers in that environment, in the primordial oceans. But, this constraint is intractable, in the absence of well-established knowledge of the chemistry of primordial oceans. We circumvent this biochemical constraint by ignoring its existence, and thus *theoretically assume that evolution was allowed to experiment with an infinite variety of molecular species in its search for the perfectly-adapted monomer*. This assumption translates into freedom for variables and parameters describing the monomers to

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https://doi.org/10.1016/j.jtbi.2018.03.012
0022-5193/

take on any value, in our mathematical model below. The above premise statement has its roots in the supervenience of evolution over chemistry. Although RNA is widely thought to have evolutionarily preceded DNA and is thus better situated for evolution-based explanations, we are constrained to concentrate on DNA, due to the comparative lack of experimental information on the thermodynamics and kinetics of non-enzymatic RNA double-strand formation/unzipping (Szostak, 2012).

2. The model

In our simple phenomenological model of a primordial self-replicating system (Methods), we consider an autocatalytic polymer that is capable of replicating without the help of enzymes. A single strand of the polymer catalyzes the formation of another strand on top of itself, by functioning as the template. Free-floating monomers attach to the bound monomers on the template strand at lower temperatures, and facilitate covalent bonding between monomers (Anderson and Stein, 1987) and hence polymerization, leading to the formation of the replica strand. The replica strand dissociates from the template strand at higher temperatures, creating two single strands, as happens in a Polymerase Chain Reaction.

A self-replicating molecular species must satisfy certain requirements in order to be evolutionarily successful and to function as an information-carrier. In the following, we list those physically meaningful requirements to be satisfied by the molecular species, and in doing so, arrive at two conflicting requirements. Breaking of a symmetry, upon maximization of replicative potential, leads to resolution of the conflict and to simultaneous satisfaction of the two requirements. These requirements are not new, and have been included and explored individually in other models and systems elsewhere (Anderson and Stein, 1987; Breivik, 2001; Herrmann and Tsallis, 1988; Ivanov et al., 2005).

Self-replication involves both bond formation between free-floating monomers and monomers on the template strand, and bond-breaking between monomers on the two strands, requiring these inter-strand bonds to be relatively weak compared to other bonds in the polymer. On the other hand, information storage requires stronger intra-strand bonds that withstand strong environmental variations, as pointed out by Schrödinger (1992). Hence, the self-replicating polymer needs to be composed of two complementary components, mutable inter-strand "hydrogen bonds" and relatively immutable intra-strand "covalent bonds"(Anderson and Stein, 1987; Breivik, 2001; Herrmann and Tsallis, 1988; Ivanov et al., 2005).

The intrinsic covalent bonding rates among free-floating monomers should be lower than the covalent bonding rates between the monomers hydrogen-bonded to the template strand, so that monomers become available for self-replication and not for *de novo* strand formation. This requirement makes self-replication viable and information transfer across generations possible. Evolution could have solved this by identifying monomers whose kinetic barrier for covalent bonding between themselves is lowered when they are attached to the template strand (Anderson and Stein, 1987; Herrmann and Tsallis, 1988; Minetti et al., 2003). We term this barrier reduction "*covalent bond catalysis*".

If a hydrogen bond catalyzed the formation (and hence dissociation as well) of another hydrogen bond in its neighborhood (Fernando et al., 2007), the strand would be replicatively more successful, since covalent bond formation requires two contiguous monomers hydrogen-bonded to the template. Also, higher rate of monomer attachment to the template would allow for more monomers to be drawn in for polymerization, away from other competing processes such as dimerization through hydrogen bonding. Thus, reduction of kinetic barrier for hydrogen bond formation would be advantageous for the self-replicating system. The foregoing justifies the need for "*hydrogen bond cooperativity*", catalysis of hydrogen bond formation/dissociation by their neighboring hydrogen bonds (Dauxois et al., 1993; Manghi and Destainville, 2016; Poland and Scheraga, 1966; Steiner, 2002). Aforementioned cooperativity, the increasing ease of hydrogen bonding between unbonded monomers (zippering) when two single strands are already hydrogen-bonded at one of the ends, is a very well-established phenomenon in DNA, and has been well-studied both experimentally and theoretically (Manghi and Destainville, 2016). The experimental signature of cooperativity in DNA melting is the sharpness of the melting transition, where the DNA goes from a double strand to two single strands within a narrow range of temperature (Lazurkin et al., 1970). Cooperativity in DNA has also been abundantly documented in DNA zipping and unzipping experiments (Danilowicz et al., 2003; Huguet et al., 2009; Rief et al., 1999; Woodside et al., 2006). The presence of cooperativity in RNA double-strand is an open question due to the lack of such unzipping experiments on double-stranded RNA, to our knowledge.

Obviously, the probability for the covalent bond formation between two contiguous monomers on the replica strand will increase with the lifetime of the hydrogen bonds of the monomers with the template strand. Thus, higher the kinetic barrier for hydrogen bond dissociation, higher the probability for the successful formation of the covalent bond and hence the replica strand. Thus, we notice that, *while covalent bond catalysis requires higher kinetic barrier for hydrogen bond dissociation, hydrogen bond cooperativity requires lower kinetic barrier for hydrogen bond formation*. Since self-replication requires the replicating polymer to be at or near the melting point of the hydrogen bonds, the kinetic barriers for formation and dissociation are nearly equal, and we arrive at the competing requirement of both higher and lower kinetic barrier height, or equivalently, to fine-tuning of the hydrogen bond lifetime. We could solve this conundrum by introducing an environment with oscillating ambient temperature, where, the hydrogen bond lifetime is longer at lower temperatures and thus enables covalent bond formation, whereas, higher temperatures facilitate strand separation. Nevertheless, strands that *intrinsically* satisfy these two competing requirements would still be evolutionarily more successful, by being able to colonize regions with temperature oscillations of much smaller amplitude.

The solution that simultaneously and intrinsically satisfies these two competing requirements is to break the symmetry (Anderson, 1972) of the catalytic influence of a hydrogen-bonded monomer-pair on its two neighboring hydrogen bonds on either side. The hydrogen-bonded monomer-pair can reduce the kinetic barrier for hydrogen bond formation/dissociation to its right, while increasing the barrier for hydrogen bond formation/dissociation to its left, (or vice versa) which we call "asymmetric hydrogen bond cooperativity". An illustration of replica strand construction in the presence of symmetric and asymmetric cooperativities is shown in Fig. 1. This solution is similar in spirit to Kittel's single-ended zipper model for DNA (Kittel, 1969). Asymmetric cooperativity has also been proposed earlier to explain other biophysical processes (Lakhanpal and Chou, 2007). Such an arrangement would prolong the lifetimes of the already-formed hydrogen bonds to the pair's left, and thus would increase the probability for covalent bonding among those bonded monomers. It will also enable rapid extension of the replica strand to the right, drawing monomers away from competing processes, by allowing monomers to hydrogen bond with the template easily through the reduction of the kinetic barrier. Thus, the broken symmetry of unequal and non-reciprocal catalytic influence leads to simultaneous satisfaction of the above-mentioned two competing requirements. Surprisingly, the replicative advantage of strands with asymmetric cooperativity over symmetric strands turns out to be crucial for understanding various intrinsic physico-chemical properties of the extant heteropolymer,