BioSystems 152 (2017) 1–10

Contents lists available at ScienceDirect

BioSystems

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

Review article

Chasing the tail: The emergence of autocatalytic networks

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ARTICLE INFO

Article history:
Received 4 November 2016
Received in revised form
13 December 2016
Accepted 15 December 2016
Available online 25 December 2016

Keywords:
Autocatalytic sets
Origin of life
Binary polymer model
RNA world

ABSTRACT

A ubiquitous feature of all living systems is their ability to sustain a biochemistry in which all reactions are coordinated by catalysts, and all reactants (along with the catalysts) are either produced by the system itself or are available from the environment. This led to the hypothesis that 'autocatalytic networks' play a key role in both the origin and the organization of life, which was first proposed in the early 1970s, and has been enriched in recent years by a combination of experimental studies and the application of mathematical and computational techniques. The latter have allowed a formalization and detailed analysis of such networks, by means of RAF theory. In this review, we describe the development of these ideas, from pioneering early work of Stuart Kauffman through to more recent theoretical and experimental studies. We conclude with some suggestions for future work.

Contents

1. The origin of life

In the early 17th century, the Flemish chemist Jan Baptist van Helmont wrote the following (Pasteur, 1864):

> "If you press a piece of underwear soiled with sweat together with some wheat in an open mouth jar, after about 21 days the odor changes and the ferment coming out of the underwear and penetrating through the husks of the wheat, changes the wheat into mice."

This reflected the commonly held belief at that time, even among scientists, of *spontaneous generation*. Life arises spontaneously and continuously: mice from wheat, maggots from meat, frogs from mud, etc. Hence, the origin of life was not considered a scientific question.

It was not until more than two centuries later, in 1862, that Louis Pasteur won a price from the French Academy of Sciences for definitively putting to rest the idea of spontaneous generation. He performed a simple but clever experiment, showing that nothing happened to a sterilized broth contained in a flask in which dust particles could not reach the broth, but that micro-organisms quickly appeared in the broth after the curved neck of the flask was broken (Pasteur, 1864). Pasteur thus concluded that all life comes from other life.

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http://dx.doi.org/10.1016/j.biosystems.2016.12.002
0303-2647/

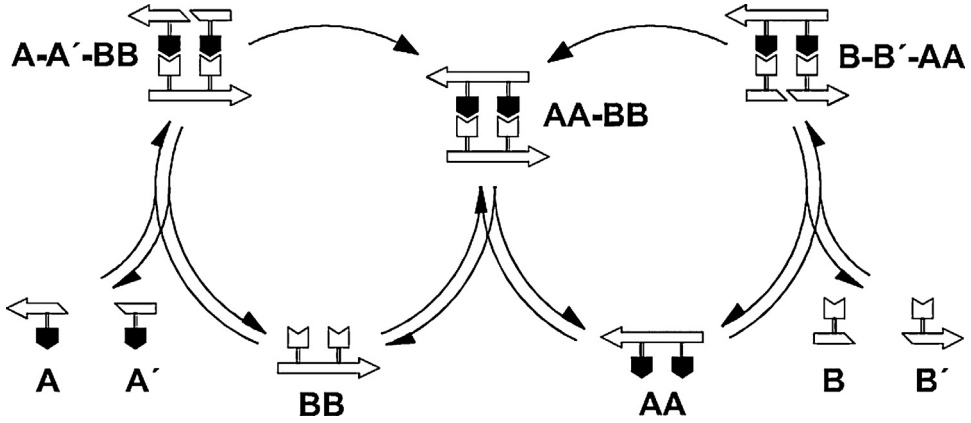

Fig. 1. A chemical network representation of the nucleotide-based oligomer autocatalytic set of Sievers and von Kiedrowski (1994). Reproduced from Patzke et al. (2007).

At around the same time, in 1859, Darwin published his now famous book *On the Origin of Species* (Darwin, 1859). One of the main ideas underlying his theory of evolution by natural selection is that of *common descent*: any (arbitrary) group of currently living species will, if you go far enough back in time, have a common ancestor. As a consequence, *all* life on earth must have come from one (or just a few) common ancestor(s).

So, if all life comes from life, going all the way back to a "last universal common ancestor" (LUCA), then where did this common ancestor, one of the very first living organisms, come from? The origin of life had become a genuine scientific problem.

Currently, the main paradigm in the origin of life field is that of an RNA world (Gilbert, 1986). Given the common (and apparently ancient) functionality of RNA in the molecular machinery underlying all life as we know it (Joyce, 2002), one of the earliest stages in (or towards) life is assumed to have existed exclusively of RNA molecules that were responsible for both the replication and expression of genetic information (through their catalytic properties). However, despite progress towards the experimental spontaneous formation of RNA (Powner et al., 2009), the RNA world hypothesis is not without problems (Szostak, 2012; Benner et al., 2012), and so far nobody has been able to show that RNA can catalyze its own template-directed replication.

What has been shown experimentally, though, is that some RNA molecules can efficiently catalyze the formation of *other* RNA molecules from shorter RNA fragments (Horning and Joyce, 2016). Moreover, there are experimentally constructed sets of RNA molecules that *mutually* catalyze each other's formation (Sievers and von Kiedrowski, 1994; Kim and Joyce, 2004; Vaidya et al., 2012). In other words, rather than having each RNA molecule replicate itself (a tall order), they all help each other's formation from their basic building blocks, in a network of molecular collaboration (Higgs and Lehman, 2015; Nghe et al., 2015).

2. Autocatalytic sets (RAFs)

Such a collaborative molecular network is an instance of an *autocatalytic set*, a concept that was originally introduced by Kauffman (1971, 1986, 1993). Initial (computational) investigations into such sets were done in the late 80s and early 90s (Farmer et al., 1986; Bagley and Farmer, 1991; Bagley et al., 1991), and the first experimental autocatalytic set was constructed in the lab in 1994, consisting of two complementary nucleotide-based oligomers (Sievers and von Kiedrowski, 1994). Later on, the concept was made mathematically more rigorous and studied in more detail, both theoretically and computationally, through the development of RAF (Reflexively Autocatalytic and F-generated) theory (Steel, 2000; Hordijk and Steel, 2004; Mossel and Steel, 2005; Hordijk, 2013).

To understand the basic idea behind the concept of an autocatalytic set, consider the cross-catalytic set of oligomers of Sievers and von Kiedrowski (1994), which is depicted in a chemical network representation in Fig. 1 (reproduced from Patzke et al., 2007). The basic building blocks are the trimers **A** and **B**, which are each other's base-pair complement when read in opposite directions, indicated by the thick white arrows in Fig. 1. The fully formed hexamers **AA** and **BB** now serve as templates to which the complementary trimers can bond through base-pairing (again, in the opposite direction, as in RNA double strand formation). For example, two **A** trimers can attach to a **BB** template, allowing them to ligate into a fully formed **AA** hexamer. After strand separation, the original **BB** template is regained, plus a new **AA** template. In a similar way, such an **AA** template can catalyze the formation of another **BB** template from two **B** trimers. In other words, the two oligomers **AA** and **BB** cross-catalyze each other's formation from their basic building blocks.

Sievers and von Kiedrowski (1994) were able to create such a system experimentally using **A** = CCG and **B** = CGG. In practice, there were some hurdles to overcome, such as efficient strand separation, but it was the first experimental proof of principle of an autocatalytic set. Later on, a similar autocatalytic set of two much longer cross-catalytic RNA ligases (>70 bp) was constructed experimentally by Kim and Joyce (2004). Moreover, these RNA ligases were subjected to an artificial form of evolution, significantly increasing their catalytic efficiency (Lincoln and Joyce, 2009).

Such a cross-catalytic RNA network can be represented more abstractly as shown in Fig. 2, where round dots represent molecule types and square boxes represent reactions. Solid black arrows indicate reactants going into and products coming out of a reaction, and dashed gray arrows indicate catalysis. The network in Fig. 2 represents an autocatalytic set consisting of two reactions where the two products mutually catalyze each other's formation from their basic building blocks (the four reactants). Note that none of the molecules in this network is a self-replicator, but the set as a whole is able to efficiently reproduce itself given a steady supply of building blocks.

Of course, this basic idea of an autocatalytic set can be generalized to any number of molecule types and reactions, and can be defined more formally. First, we define a *chemical reaction system* (CRS) as a tuple $\mathcal{Q} = (X, \mathcal{R}, C)$, where:

- X is a set of molecule types: $X = \{a, b, c, \ldots\}$,
- $\mathcal{R}$ is a set of reactions of the form $r_i = a + b + \cdots \rightarrow c + \cdots$,