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Letter to Editor

Comment on "Tibor Gánti and Robert Rosen" by Athel Cornish-Bowden

1. Introduction

In a recent article published in this journal (Cornish-Bowden, 2015), a comparison is made between Tibor Gánti's chemoton model and Robert Rosen's (*M*,*R*) systems. This comparison is very insightful indeed. As the author remarks, these models seem to be two contrasting approaches, but upon closer inspection have more in common than one would initially think.

At the end of the article, the author also briefly mentions related models, such as autopoietic systems and autocatalytic sets. In particular, autocatalytic sets are presented as follows (Cornish-Bowden, 2015):

> "Autocatalytic sets (Kauffman, 1986) are the most different, because all of the others incorporate, at least implicitly, the idea that a minimal self-organizing system must be *small*, i.e. that it must have a minimum of components. Kauffman, in contrast, made no such condition, but instead imagined self-organization as a property that might arise spontaneously in a system with enough weakly interacting components. As he assumed (reasonably) that the probability that any given component might catalyse a particular condensation reaction would be very small, this inevitably leads to the conclusion that the total number of components must be very large (at least millions) in order to have certainty that every reaction will have a catalyst."

However, work on autocatalytic networks over the past 15 years has clearly established a contrary conclusion: autocatalytic sets of small size are not only predicted, but observed in simulations and the laboratory.

2. Small autocatalytic sets

The above mentioned conclusion that "*the total number of components in an autocatalytic set must be very large* (*at least millions*)", is indeed a conclusion derived from Kauffman's original work based on a simple polymer model (Kauffman, 1986). And as Lifson later pointed out, correctly, according to Kauffman's argument it would require an exponentially increasing level of catalysis for increasing system sizes (i.e. increasing maximum polymer lengths) to get autocatalytic sets to appear spontaneously (Lifson, 1997). Here, "level of catalysis" is expressed as the average number of reactions that need to be catalyzed per molecule. Thus, this would lead to chemically unrealistically high levels of catalysis, if autocatalytic sets indeed require millions of molecules.

However, already back in 2000 one of us (MS) showed theoretically that only a quadratic (instead of exponential) growth rate in the level of catalysis, with increasing maximum polymer length, is sufficient to get autocatalytic sets with high probability in Kauffman's polymer model (Steel, 2000). Moreover, several years later it was shown, through computer simulations, that even a linear growth rate in the level of catalysis appears to be sufficient (Hordijk and Steel, 2004), which was subsequently verified theoretically (Mossel and Steel, 2005). We also showed that these autocatalytic sets often consist of a hierarchical structure of smaller and smaller autocatalytic subsets (Hordijk et al., 2012), which can be as small as a dozen reactions or even less. These results clearly refute the original conclusion and criticism that autocatalytic sets require large systems and unrealistically high levels of catalysis.

Furthermore, small autocatalytic sets with chemically realistic levels of catalysis do not only exist in computational models, but also in real chemical reaction networks. For example, 2-member autocatalytic sets of nucleotide polymers have been constructed in the lab (Sievers and von Kiedrowski, 1994; Lincoln and Joyce, 2009), a 9-member peptide autocatalytic set has been investigated experimentally (Ashkenasy et al., 2004), and a 16-member autocatalytic set of ribozymes has been achieved more recently (Vaidya et al., 2012).

3. Practical applicability

Finally, as the author remarks in his article, "no working chemoton (…) has yet been constructed", and "(*M*,*R*) systems are highly abstract." However, as the above mentioned examples show, several real autocatalytic sets have been constructed and studied experimentally. Moreover, such real chemical networks can be analyzed in detail using a formal framework for autocatalytic sets known as RAF theory (Hordijk and Steel, 2013; Sousa et al., 2015). In other words, autocatalytic sets are not just a theoretical or abstract concept, but they exist in real (and small) reaction networks, and the theory can be (and has been) applied in a practically useful way (Hordijk, 2015).

To conclude, we very much agree with the author that we need "a real effort to work towards a synthesis" of the various concepts and models of minimal life, something we have worked on ourselves as well (Hordijk and Steel, 2015). As a further contribution towards such an effort, we have presented here a brief but more recent overview of one such model, that of autocatalytic sets, thereby providing an updated perspective on the author's original article.

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