Excess mutual catalysis is required for effective evolvability

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Simulations suggest that networks of chemical reactions in which components catalyze the formation of one another are better able to respond to selective pressure than those in which components mostly catalyze their own formation.

Life's origin is shrouded with mystery. Yet, a rather general consensus invokes organic complementarity and catalysis in the path from simple prebiotic compounds to organized molecular sets, capable of metabolism and reproduction (Lifson 1997; Szathmáry and Smith 1997). A central question is whether the first seeds of life involved complex biopolymers, such as RNA, endowed with self-replication, or in a chemical embodiment – self-catalysis (Orgel 1992). The alternative is a metabolism-first scenario, invoking a molecular network in which cross (mutual) catalysis is more prevalent. A major challenge for the latter scheme is to find evolution-like behavior without the presence of self-replicating polymers. In other words, one may ask whether a molecular network can show life-like behavior without a central role for autocatalysts.

The 'Lipid World' concept combines the potential chemical activities of lipids and other amphiphiles, with their capacity to undergo spontaneous self-organization into supra-molecular structures such as micelles and bilayers (Segre, Ben-Eli et al. 2001). This concept suggests that non-covalent assemblies of simple molecules can hold information in the form of *composition* and can undergo evolution. Compositional information is different than sequential information as it does not consider the internal order of molecules, only their relative ratios. The difference is apparent when considering the analogy of a shopping list vs. a book: when shopping, the key property is the content of the shopping cart irrespective of the purchase order, whereas the letters and words in a book have to be read in the right order in order to (hopefully) understand its meaning.

A common lipid-world simulator is the graded autocatalysis replication domain (GARD) model (Segre, Ben-Eli et al. 2000; Segre and Lancet 2000). The model describes the homeostatic growth of assemblies based on a graded network of rate enhancement parameters, □. A rate enhancement parameter describes how a lipid type biases the rate of joining of other lipid types (mutual catalysis, or cross catalysis) or same type (self-catalysis, or autocatalysis) into an assembly.

An important corollary of GARD is a central role for compositionally stored information which may be transferred from one generation to the next; much like sequence information is passed along when templating biopolymers are at work. A *composome* is

defined as an assembly with a unique set of lipids, which exhibits a high replication fidelity (Segre, Ben-Eli et al. 2000) and is assumed to have distinct physical properties stemming from this combination of lipids, such as stability and permeability. *Compotypes* are clustered sets of composomes, which may be regarded as analogous to species or quasi-species. This is due to the fact that a compotype is a distinct entity, different from other compotypes, but still harboring considerable internal variability of constituents. Therefore, compotypes are considered as natural targets of selection and the focus of lipid world studies.

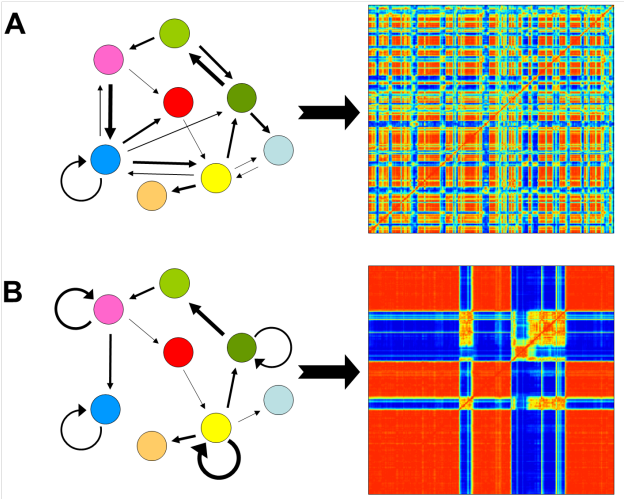

Figure 1: Excess mutual catalysis is required for effective evolvability. The right hand side presents segments of similarity carpets, showing the degree of compositional similarity between any pair of assemblies during a simulation. Composomes appear as dense red blocks near the main diagonal. (A) A mutualistic catalytic network leads to the formation of more composomes. (B) A selfish network leads to the formation of few composomes.

We have used the GARD model to quantitatively study the relative evolutionary importance self-catalysis as compared to mutual catalysis (often referred to as auto- and cross- catalysis) (Markovitch and Lancet 2012). By examining a continuous gradient of decreasing self-catalysis and increasing mutual catalysis, we found that networks with high mutual catalysis tend to have higher diversity (**Error! Reference source not found.**), as well as better response to selection in populations of compositional assemblies. Thus, autocatalysts might be less essential than often considered, and mutually catalytic networks emerge as more acceptable precursors to life. To enhance the statistical significance of our results, we carried out 10,000 simulations, each with parameters.
Significantly, we found that excess mutual catalysis is necessary, though not sufficient to allow for a high number of composome types and for a significant response to selection.
Our selection results are illuminating also when compared to those of a recent report (Vasas, Szathmáry et al. 2010), which claimed that metabolism-first models, as

exemplified by the GARD model, cannot show maintenance by selection, and therefore lack the ability to evolve. We argue that such assertions may be flawed in several ways. First, the earlier study based its conclusions, to a large degree, on a highly simplified GARD version, with extremely small assembly and molecular repertoire sizes. Second, selection was examined with respect to randomly chosen compositions, rather than to dynamically meaningful composomes. Third, the statistics were derived from only one simulation with one set of □ matrix parameters. Our analyses address such points of weakness, and they reveal different conclusions (Markovitch and Lancet 2012).

Our novel finding is that high levels of mutual catalysis with relatively small contribution of autocatalysis are favorable for several evolution-related faculties of the model. It may be interpreted as showing that a system merely composed of a collection of autocatalysts is disadvantaged as early life precursor. This is relevant to the origin of life models, as often they either focus on autocatalysts or completely rule them out, but rarely consider the two catalytic modes acting together.

Finally, it is also interesting to note that the notion that excess mutual interactions is beneficial is hidden around us, as it can enhance ribozyme replication (Lincoln and Joyce 2009), allow for adaptation of replicating peptides (Dadon, Wagner et al. 2008) and cause ribozyme fragments to outcompete others (Vaidya and Lehman 2011). This might suggest that mutual catalysis as a scheme to push evolution forward could be a general design in Nature.

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