# Early Systems Biology and Prebiotic Networks

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**Abstract.** Systems Biology constitutes tools and approaches aimed at deciphering complex biological entities. It is assumed that such complexity arose gradually, beginning from a few relatively simple molecules at life's inception, and culminating with the emergence of composite multicellular organisms billions of years later. The main point of the present paper is that very early in the evolution of life, molecular ensembles with high complexity may have arisen, which are best described and analyzed by the tools of Systems Biology. We show that modeled prebiotic mutually catalytic pathways have network attributes similar to those of present-day living cells. This includes network motifs and robustness attributes. We point out that early networks are weighted (graded), but that using a cutoff formalism one may probe their degree distribution and show that it approximate that of a random network. A question is then posed regarding the potential evolutionary mechanisms that may have led to the emergence of scale-free networks in modern cells.

## 1 Prebiotic Molecular Networks

Most researchers admit that somewhere along the line towards the appearance of self-reproducing protocells, a web of interacting molecules must have been at work. Yet, investigators are divided on a crucial question related to the first reproducing entities. One set of scenarios claims that life began with a single molecular replicator, e.g. an RNA-like biopolymer [1-3]. It is further assumed that complex molecular networks came much later, and were genetically instructed by the replicating polymers. The second set of scenarios asserts that early replicating entities must have constituted complex molecular networks right from the outset. The latter view claims that the emergence of single molecules, whose inner works allowed them to instruct the synthesis of their own copies, are extremely unlikely under prebiotic conditions. It is claimed that the spontaneous accretion of specific mixtures or assemblies of simple organic molecules, capable of self-reproduction, is more probable. Furthermore, it is suggested that the capacity of such molecular assemblies to undergo a replication or reproduction-like process is a direct consequence of certain network properties parallel to those that allow present-day cells to divide and beget progeny. If the "network-first" scenario is right, then a better understanding of network properties within contemporary living cells should be a crucial tool for understanding prebiotic evolution.

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The early Systems Biology view has a promise for merging the two seemingly conflicting scenarios for prebiotic evolution. This has been recently presented by Luisi [4] as follows: "Another new wind in our field comes, in my opinion, from the development of system biology – biology seen in terms of system theory, namely the whole biological system studied in its entire complexity: proteomics, genomics, networks and non linear systems, and so on. This has brought about a revival of theoretical and experimental studies on chemical complexity, like self-organization, emergent properties, autocatalysis – concepts that were already with us, that however have acquired nowadays a new importance."

## 2 Binary and Weighted Networks

Until 1960, regular networks, such as lattices, were the typical structured mathematical entities studied in the realm of graph theory. One such regular network, a hyper-cube, underlies the dynamics described by the classical quasi-species model for early evolution [5]. Later, Paul Erdös importantly introduced random networks, and studied their mathematical properties. In this type of networks the nodes are connected in a haphazard fashion to every other, each edge having a probability p to appear. Such network inspired Kauffmann's mutual catalysis model for the origin of life (Fig. 1B) [6].

Despite their seeming generality, it was more recently shown that random networks do not correspond properly to those that often appear in biological systems. In particular, random networks have a binomial or Poisson distribution of node degrees, typified by a most probable value, while many biological networks are scale-free, and their degree distribution follows a power law (Fig.1 and 4) [7-13]. The scale-free nature of present-day protein networks (to address one example) stems from the fact that a few proteins, belonging to certain families, are capable of interacting with a large number of partners [14].

Considerable Systems Biology research has been performed in recent years on the properties of biological networks [12, 15-18]. Much of this effort pertains to unweighted - binary networks, in which a specific node is either connected or not connected to another. Classical network attributes such as degree distribution, mean path length and clustering coefficient, are based on counting these binary connections. However, in many instances, not only restricted to biology, every two nodes in a network are connected in a graded or weighted fashion. This happens when a continuous measure such as affinity or catalytic rate governs the interactions among nodes, as is the case in the Graded Autocatalysis Replication Domain (GARD) model for early evolution, described below. It is possible to explore ways in which to convert weighted networks into binary ones, so as to afford analyses with existing network tools.

## 3 Specificity Attributes Within Networks

In present-day cellular networks, connectivity is rather sparse. Thus, a protein interaction network may have many thousands of nodes, but each node is connected to only a few or at most few dozen others (Fig. 1C, D). This state of affairs could be due to the long evolutionary process, in which proteins have emerged as highly specific and selective recognition devices. However, it would be surmised that in the early stages of

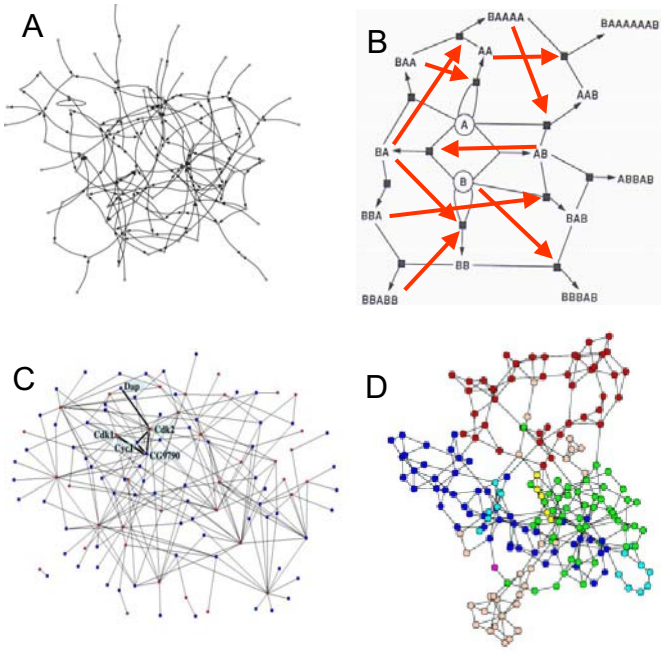


**Fig. 1.** Prebiotic and contemporary biological networks

A. The canonic composome (cf. figure 3) of a Graded Autocatalytic Replication Domain (GARD) system (cf. figure 2) with a molecular repertoire, $N_G$=1000. The total molecular count in the system, N, is taken to be 800. Only molecular species with concentration $\frac{n_i}{N} > \frac{1}{800}$ are shown. An edge is shown if the catalysis exerted on joining of molecular species $A_i$ by molecular species $A_j$ ($\beta_{ij}$) enhances the reaction by at least 100 folds.
B. Schematic illustration of an autocatalytic set as proposed by Kauffman (modified from [6]). Strings composed of A's and B's represent molecular species (oligomers) with different length and sequence. Black lines joined by a black square represent a ligation (concatenation) reaction. Wide arrows indicate catalysis on such ligation reaction by a member of the set. According to the model, if one assumes a fixed probability, *p*, for each molecular species to catalyze each reaction and if the number of molecular species is sufficiently large, then an autocatalytic set will emerge. In such set, the formation of every molecular species, except for the basic building blocks (A and B) will be catalyzed by at least one member of the set. Kaufmann pre-biotic network is binary by definition, as no gradation of catalytic potencies is assumed. Its degree distribution is clearly binomial, as every edge has the same probability p to appear.
C. Protein interaction map (PIM) generated by using ~100 known or suspected cell cycle regulators, including Cdk1 and Cdk2, in high throughput screens to detect possible interactions with ~13,000 Drosophila proteins [36]. The typical hubs that typify contemporary biological network may be seen.
D. Metabolic network of *E. coli,* where each node corresponds to a metabolite, and edges represent biochemical reactions. Figure is from [37].

molecular evolution, recognition was much more promiscuous. In particular, in prebiotic scenarios as proposed [6, 19-23] biopolymers such as folded proteins and RNAs may have not yet emerged, and smaller, simpler organic molecules may have played pivotal roles in information storage and catalysis. Under such circumstances, molecular species may have had a much larger number of interacting partners, and the corresponding network would have very high average network degree values. Thus, early networks (Fig. 1A,B), whose properties we have attempted to capture in the GARD model, are markedly different from their more modern counterparts. In such early systems, it is likely that practically all interacting pairs would have affinities in the range of what would presently be considered non-specific binding. What nowadays constitute the background noise may have been the only existing interactions at the inception of life.

## 4 GARD Dynamics and Composomes

We have, in the last decade, explored a defined formalism for describing and simulating the behavior of early systems with mutual catalytic interactions among simple molecules under prebiotic conditions [24-27]. Accordingly, a formula was proposed that defined the probability for a particular value of catalytic potency for a randomly selected molecular pair. This formalism, which is based on a Receptor Affinity Distribution model [28-30], resulted in the definition of a matrix, $\beta$, specifying a non-zero interaction for every pair of molecules. A reasonable way to regard such matrix is that it represents a fully connected weighted network of interactions (Fig. 3A).

The Graded autocatalysis Replication Domain (GARD) model depicts the kinetic behavior of such networks. Along the time scale, a dynamic process unfolds, whereby inside a molecular assembly of a finite size, certain molecular species prevail and others are selected against. This results in the emergence of different "composome", quasi-stationary states of the system, with different biased compositions. Fig. 3A shows a network that characterizes a complete $\beta$ matrix. Despite the small number of components ($N_G$=300), this network is rather densely connected, because it arises from a system in which nominally every component is connected to every other (visualized with an edge cutoff of $\beta$=100).

The GARD model provides a detailed dynamic description of time-dependent changes in the concentrations of different molecular species within an assembly. In terms of concrete chemistry, it is assumed that the molecules within a GARD assembly are amphiphiles (lipid-like), held together within a micelle-like structure by hydrophobic forces. A GARD assembly, similar to a lipid bilayer, is a fluid structure, which can exchange molecules with the environment. Furthermore, rapid diffusion of molecules within it facilitates their mutual rate-enhancing interactions. Computer simulations of GARD equations allow one to view a time series of concentrations or compositions – a GARD trace. At each time point, the count of different molecular species is recorded, resulting in a trace of samples (see Figs. 2, 6B).

GARD usually considers a collection of $N_G$ different molecules, i.e. a molecular repertoire of size $N_G$. In GARD, every component of an assembly may catalyze the entry/exit or formation/breakdown of every other component. Thus, at every time point, GARD by definition constitutes a mutually catalytic network. The effectiveness of such network, that is the capacity to sustain homeostasis (Fig. 2), varies, and depends on the exact composition, and on the web of interactions that prevails among the components. Composomes are specific compositions that last over many growth-

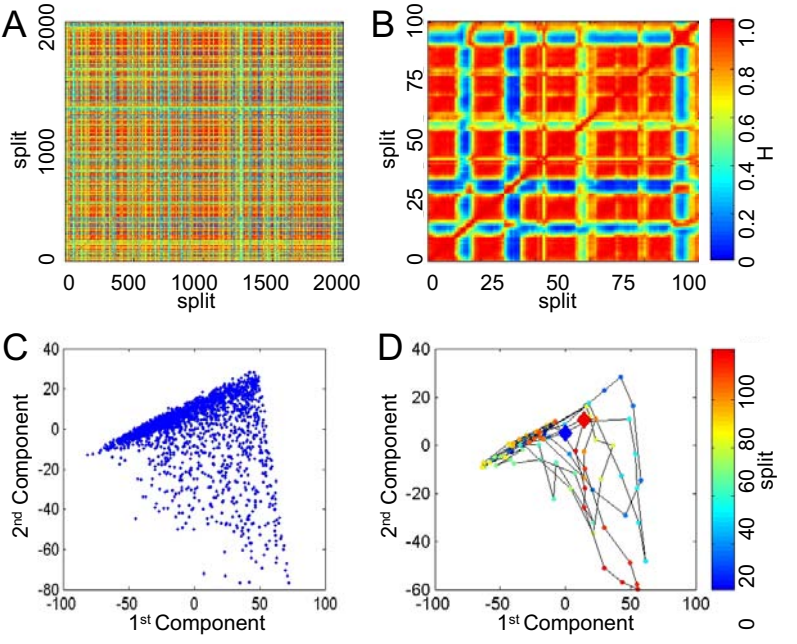


**Fig. 2.** The dynamics of a GARD assembly [25]. The composition of a molecular assembly is represented in the GARD model by a vector, **n,** with components, $n_i$, for every one of the $N_G$ different molecular species in the system. Each $n_i$ indicates the molecular counts of molecular species $A_i$ in the assembly. A crucial assumption in the model is that every reaction would be catalyzed, to some extent, by each of the molecules in the assembly. GARD presumes that molecular assemblies undergo occasional fissions that yield smaller assemblies. This is modeled by having $N_0$ molecules randomly removed from the assembly once its size ($N=\sum n_i$) exceeds a threshold of $2N_0$. A GARD trace is a series of compositional vectors as a function times

A. GARD "carpet" showing an autocorrelation matrix of a trace containing 2,000 splits. The similarity between two compositions, $\mathbf{n_1}$ and $\mathbf{n_2}$, is measured by the scalar product:

$$H(\mathbf{n_1},\mathbf{n_2}) = \frac{\mathbf{n_1}\cdot\mathbf{n_2}}{|\mathbf{n_1}|\cdot|\mathbf{n_2}|}$$

with a color scale (right of B) that has red for H = 1.0 (high similarity) and blue for H = 0 (indicates no similarity).

B. A partial 'carpet' for the arbitrarily sampled splits 1,700-1,800 in the trace shown in A. Red squares indicate composomes [25]. Off-diagonal red squares indicate that composition of composomes tends to be repeated.

C. The projection of all 2000 NG-dimensional compositions in the trace (shown in A) displayed in a two dimensional plane defined by the first and second components in a Principle Components Analysis (PCA). The samples form a triangle in the plane, which is not occupied uniformly. The heavily occupied edge corresponds to samples in the prominent composome and the opposing vertex to a lesser frequent composome.

D. The projection of the samples illustrated in B to the plane defined in C. Each composition is colored according to its time of appearance (color bar on right). The blue diamond corresponds to the first sample in the sub-trace and the red diamond to the last. Consecutive samples in time are connected by a line. The analysis show examples of paths taken from the dominating composome to the other one and back, e.g. samples 88-95 (red).

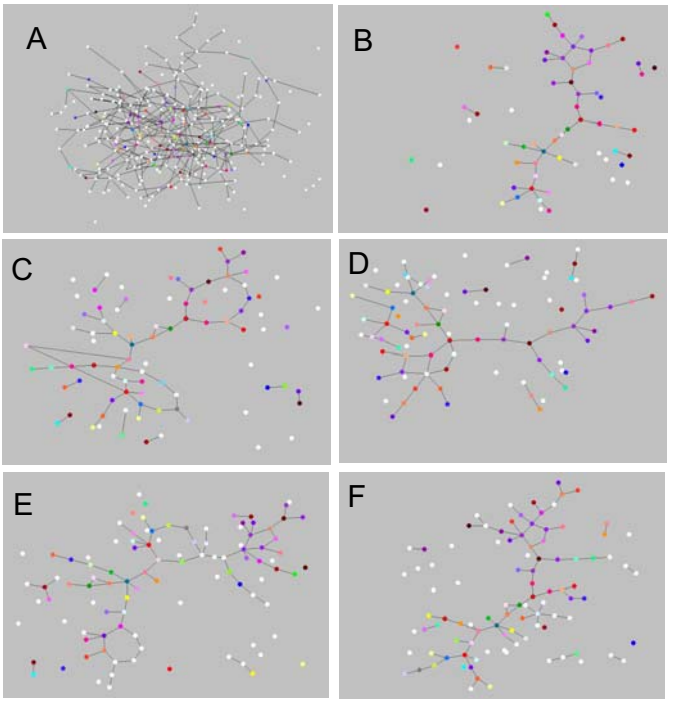


**Fig. 3.** Networks in the Graded Autocatalytic Replication Domain (GARD) model. An example of networks as found in a GARD system with $N_G$=300, where each node corresponds to a different molecular species (monomer) and edges are catalytic potencies. A cutoff was used whereby edges are shown only for β values that exceed a threshold of 100. White nodes indicate molecular species which appear only once in the composomes shown in B-F, whereas colored nodes are shared by at least two of these composomes. Colors are assigned arbitrarily but each color uniquely represents a particular molecular species, so as to allow visual inspection of similarities among composomes

A. The thresholded network corresponding to the entire rate enhancement β matrix.
B. The canonic composome. This is the composition which a GARD system assumes in the case of large assemblies ($N_0 >> N_G$). The canonic composome is approximated by the main eigenvector of the β matrix, i.e. the eigenvector with the highest eigenvalue, whose elements are all real [38]. The only molecular species shown are those whose concentration would reflect at least one molecule for an assembly size of 120.

C-F. Networks that correspond to four dynamic composomes, computed by numeric simulation of the GARD stochastic differential equation. These are as observed in a trace of 2,000 splits using the same size limit. The similarity of the composomes to each other (measured by H, cf. figure 2):

| | B | C | D | E | F |
|---|---|---|---|---|---|
| Canonic (B) | 1.0 | | | | |
| Composome1 (C) | 0.6 | 1.0 | | | |
| Composome2 (D) | 0.7 | 0.6 | 1.0 | | |
| Composome3 (E) | 0.8 | 0.7 | 0.4 | 1.0 | |
| Composome4 (F) | 0.9 | 0.6 | 0.6 | 0.7 | 1.0 |

Some networks modules (subset of connected nodes) are clearly shared by several composomes, e.g. the pentameric cycle in B, E and F.

split cycles due to efficient mutual catalysis that underlies homeostatic growth. These resemble fixed points of a dynamic system (Fig. 2).

A specific GARD system, defined by a particular β matrix, may have numerous composomes, and each of these defines a weighted network of catalytic interactions (Fig. 3). It is, however, legitimate to investigate such network and their properties through conversion to a binary network, based on a judiciously selected cutoff. This analysis may be equally applied to individual composomes (Fig. 3C-F), or to the calculated canonic composome (Fig. 3B). The different composomes may bear different degree of mutual similarities, as manifested in sharing of molecular species and in the values of mutual similarity measure H (Fig. 3, legend).

In the basic GARD formalism, the only chemical reactions being modeled are catalyzed exchange reactions – joining and leaving of molecules. The resulting dynamics involves compositional transitions that may be considered by some as resulting from mutations. When viewed within a limited time frame, the dynamics of this simple GARD model manifests graded transitions between different molecular networks, resembling an evolutionary process.

## 5 How Did Scale-Free Networks Arise

An important attribute of GARD is its parsimony, as it involves very few pre-assumptions, and stems directly from chemical kinetics of small molecules. As mentioned above, the resulting networks are graded or weighted, and therefore cannot be readily analyzed by the standard tools of degree distribution analysis.

Yet, with a threshold-based procedure it is possible to see that the degree distribution of a GARD network roughly obeys a binomial distribution (Fig. 4). This is to be expected, as these networks are derived from a randomly disposed matrix of interactions. Importantly, GARD dynamics, leading to composomes select molecular species such that the β values deviate from the original lognormal distribution (Fig. 5), showing an increased preponderance of high β values.

The scale free - power law behavior of biological networks is usually rationalized as being related to the formation of a few hubs with a large number of connections [31]. A parallel potential explanation could be in terms of selective preservation of very richly connected nodes. That the early GARD networks are not scale free is in agreement with the notion that such property is a result of a long evolutionary process. A crucial question is at what stage in evolution these properties arose, and how they are related to what distinguishes very early biological systems from later ones.

As described above, in the basic "joining GARD" model, the concentrations of different molecular species may undergo profound changes, but the basic properties of the molecules may not change. A more open-ended configuration is afforded by later GARD versions that include chemical reactions, in which oligomers are formed by covalent concatenation of monomers. In this extended GARD model the number of molecular species is an exponent of $N_G$ (the size of the monomer repertoire). Preliminary analyses [32] show a more life-like behavior, and it appears that this polymer GARD formalism may also harbor a potential for a graded transition from random networks to scale-free ones. An intuitive rationalization is that a few of the vast number of oligomers that form in such a scenario might interact with or catalyze reactions of a large number of other compounds, hence become network hubs. This is by virtue

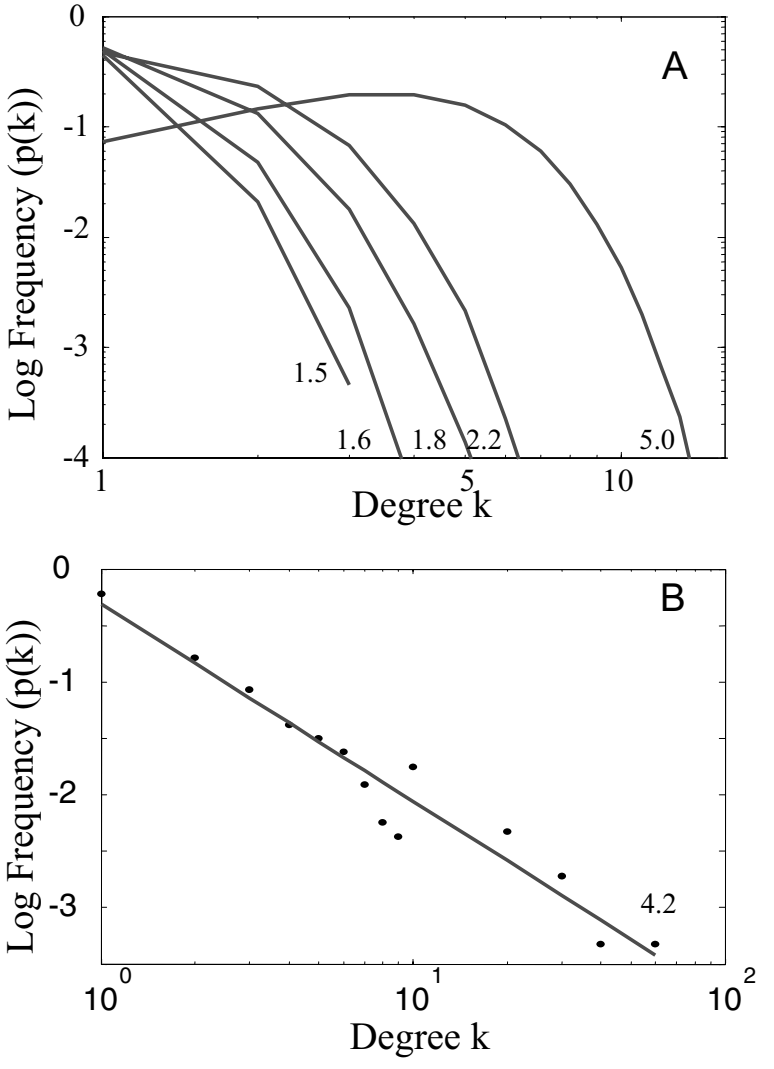


**Fig. 4.** Comparison of distribution p(k) of degree values k for composomes vs. protein networks, drawn as a double-logarithmic plot. For each curve, the average degree is shown next to its bottom

A. The degree distribution for GARD networks of canonic composomes with different cutoff values on concentration of selected molecular species. The distribution resemble a Binomial distribution with N equals $N_E$ and p equals the probability for a catalysis $\beta_{ij}$ to exceed the cutoff on $\beta$ values. The range of degree values is much narrower than for a highly evolved network as shown in B. The distribution was computed for 1,000 canonic composomes with $N_G$ =1,000. Similar distribution was also found for composomes observed in 150 GARD simulations with the same $N_G$ and 1,000 GARD simulations with $N_G$ = 300.

B. Degree distribution for yeast proteins interaction map [8], with 2114 proteins and with a total number of interactions of 4480 (average degree of 4.23). A linear power law relationship is seen, with the best fit equation of $p(k) = 0.494 * k^{-1.75}$.

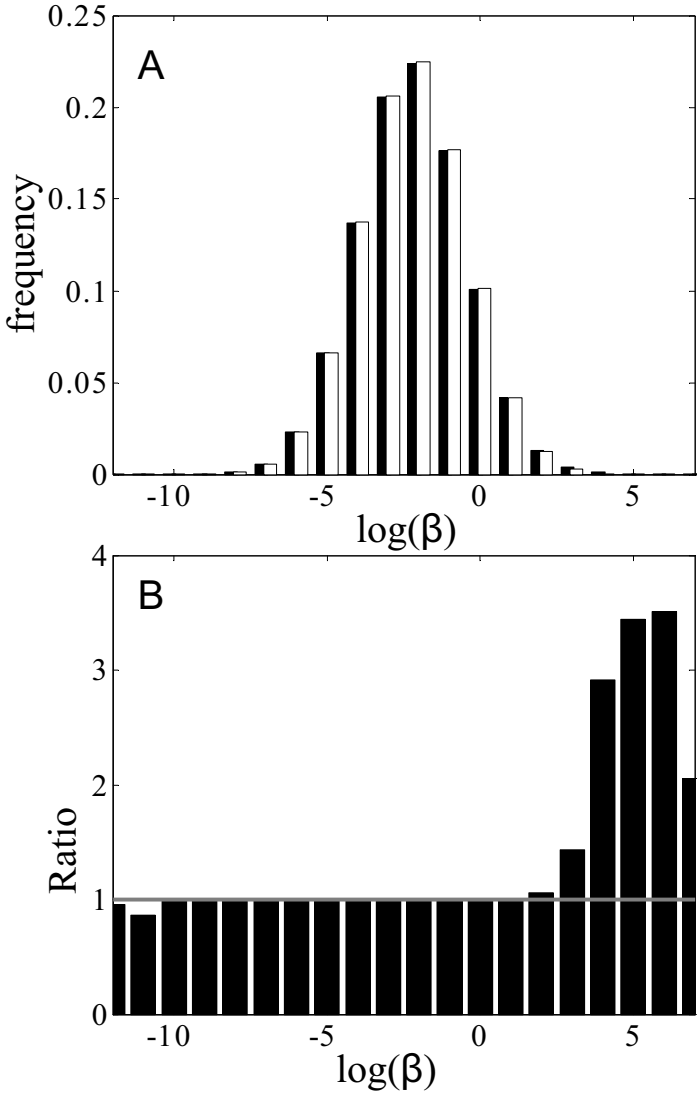


**Fig. 5.** Comparing the distributions of rate enhancement values (β) for composomes and their original β matrices

A. The distribution of rate enhancement values in the entire β matrix (light) and in the canonic composome (dark). The analysis was performed for 1,000 different β matrices with $N_G$ = 1,000, whose values were randomly selected using a lognormal distribution with $\mu = -4$ and $\sigma = 4$ in accordance to previous work [25].

B. The ratio the two distributions of Fig. 5A (canonic composome as the numerator). These two distributions are seen to differ significantly only for values of β larger than 10. In this range there is enrichment in the composome, suggestive of selection that favors species with higher values of rate enhancement. A similar phenomenon was observed also for 1000 dynamic composomes obtained from traces similar to those from which the networks in Fig. 3C-F were derived.

of "molecular adaptors" – sub-strings of the oligomers that may be shared by a large molecular repertoire, possibly in similarity to the small-world phenomenon describe for the repetitive Diels-Alder reactions networks [33].

## 6 Network Motifs

Molecular networks underlie many different functions in contemporary cells. Analysis of network motifs in biological networks shows that some embody distinct network motifs indicative of information processing [34]. We set out to explore the existence of such motifs in the GARD networks delineated above. In a preliminary analysis for network motifs in the canonic composomes of 1,000 different GARD system with $N_G$=1,000, we have observed that the feed-forward loop motif and feed backward loop motif tend to be overrepresented (Z score > 2) for about 5% of the composomal networks. To verify that these values are statistically significant, 10 control sets consisting of 1,000 random networks with the same size distribution of the original set, were subjected to the same analysis. Table 1 summarizes the results, showing that the enrichment of the feed-forward loop motif is not higher than expected by chance. On the other hand, feed-backward loop enrichment is statistically significant. This motif, which is a cycle of size 3, supports in a straightforward manner a process of homeostatic growth. It is thus suggested that in some GARD systems this motif may serve the role in the dynamics of the composomal network. Further investigation, including consideration of motifs of larger sizes, is currently underway both for monomer GARD and Polymer GARD.

**Table 1.** GARD network motifs

| Motif | GARD | Control |
|---|---|---|
| None | 952 | 976±4 |
| Feed forward loop (A→B, B→C, A→C) | 20 | 18.5±4.0 |
| Feed backward loop (A→B, B→C, C→A) | **27** | 4.5±1.9 |
| Both | 1 | 0.4±0.5 |

## 7 Sensitivity to Mutations in GARD Networks

Cells maintain a homeostatic composition despite variations to their external milieu. They are also often robust towards internal variations such as genomic mutations that may be as severe as gene deletions [35] In fact, in yeast, only about 20% of the genes were shown to be essential producing a non-viable phenotype upon deletion and about 40% of the genes hardly show any growth defect upon deletion. It was further shown [8] that genes encoding proteins which are highly connected in the interaction network produced more deleterious phenotypes. We asked whether GARD composomes and the networks that they represent have somewhat similar invariance properties.

We performed an analysis analogous to gene deletion within the GARD model. Repeated GARD simulations were carried out using the same molecular repertoire (β matrix) but in each round a different compound was completely depleted from the

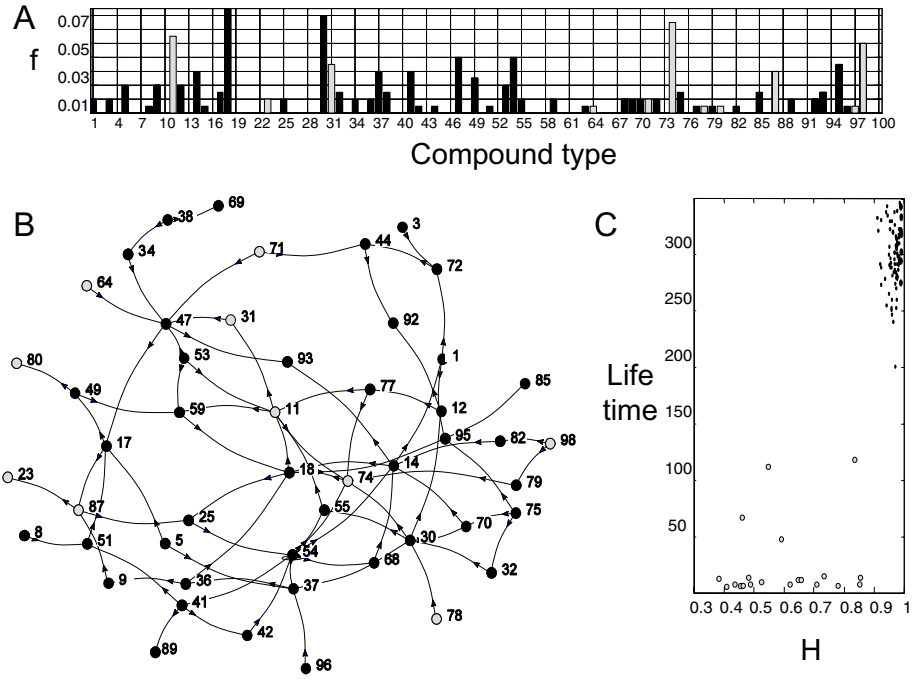


**Fig. 6.** Robustness of GARD networks to compositional mutations. A GARD simulation with $N_G$=100 was performed and the composome with the longest life-time selected. This simulation was subsequently repeated 100 times, each time with a different monomer depleted from the composomes external environment, hence also from its internal composition. For every resulting GARD trace the longest-living composome was tested for its cumulative lifetime and for its similarity (using a scalar product H) to the original composome

A. Compositional diagram for undepleted original composome, with compounds that are essential for homeostatic growth (H<0.7) labeled light grey. It is seen that essentiality is not necessarily correlated with monomer concentration.
B. The thresholded composome catalytic interaction network, with nodes colored light grey as in A. Essential monomers are not necessarily those that are highly connected hubs, and includes a significant number of terminal nodes with only one edge.
C. Correlation between the life-time of monomer-depleted composomes and their similarity (H) to the composome with no depletion. A majority of the depletion events appear to have a weak "phenotype (high lifetime and high H), while some are more severely affected. There is a broad correlation between the two quantitative measures for composome effectiveness.

composomes external environment, and thus from the network itself. We found that most compounds have only a small effect on both growth rate and molecular composition of the composome (Fig. 6C). A minority compounds (10-20%) are essential, and

have a marked effect on the functional properties of the composomal network, as their removal significantly changes the assembly composition and/or reduces its growth rate. Fig. 6A, B respectively show the composition and the interaction network of a typical composome, highlighting the compounds essential for network stability. Surprisingly, essential compounds were not necessarily those with the highest concentration or highest connectivity within the network, suggesting non-trivial network properties.

## 8 Conclusion

The GARD model provides elaborate computing tools that help address prebiotic entities via the tools of present day Systems Biology. Since some characteristics of early GARD assemblies are shared with modern biological networks, the analyses described here may also lead to a better understanding of networks in present day life. In parallel, System Biology tools could assist in constructing better models for probing the important question of life's emergence.

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