Recursiveness, Switching, and Fluctuations in a Replicating Catalytic Network

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(Dated:)

A protocell model consisting of mutually catalyzing molecules is studied in order to investigate how chemical compositions are transferred recursively through cell divisions under replication errors. Depending on the path rate, the numbers of molecules and species, three phases are found: fast switching state without recursive production, recursive production, and itinerary between the above two states. The number distributions of the molecules in the recursive states are shown to be log-normal except for those species that form a core hypercycle, and are explained with the help of a heuristic argument.

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In a cell, a huge number of chemicals is synthesized by mutual catalyzation leading to replication of molecules that allow a cell to grow until it is large enough to divide into two. How the underlying reaction networks give rise to the recursive production of cells is an important question, not only when considering the origin of life but also when trying to understand the general features of a modern cell’s biochemical reaction dynamics.

As a simple prototype of a reproducing cell, let us consider a set of chemicals with some catalytic activities. How can such a system consisting of chemicals connected by a catalytic reaction network sustain recursive production? Are there any generic properties in the dynamics and fluctuations of such reproducing systems?

These questions were originally addressed in connection with the origin of life. Eigen and Schuster proposed the hypercycle as a mechanism to overcome an inevitable loss in the catalytic activities through mutations, while Dyson argued that it is possible for a collection of chemicals to be sustained by mutual catalytic activity. Although the hypercycle itself may be susceptible to destruction by parasitic molecules, i.e., molecules which are catalyzed by the hypercycle species but themselves do not catalyze other molecules, it was later shown that compartmentalization by a cell structure or localized patterns in reaction-diffusion systems may suppress the invasion of parasitic molecules.

Here, we study a simple model of mutually catalyzing molecules and classify the biochemical states according to their ability for recursive reproduction. Besides fixed recursive states, we find fast switching states and several quasi-recursive states that allow for both recursive reproduction and evolution. Last, we study the characteristics of the number distributions of the molecular species in these replicating cells.

We envision a (proto)cell containing $k$ molecular species with some of the species possibly having a zero population. A chemical species can catalyze the synthesis of some other chemical species as

$$[i] + [j] \rightarrow [i] + 2[j]. \quad (1)$$

with $i, j = 1, \ldots, k$ according to a randomly chosen reaction network (with a connection rate of the catalytic path given by $\rho$) which is kept fixed throughout each simulation. Furthermore, each molecular species $i$ has a randomly chosen catalytic ability $c_i \in [0, 1]$. (I.e., the above reaction $\mathbf{1}$ occurs with the rate $c_i$). Assuming an environment with an ample supply of chemicals available to the cell, the molecules then replicate leading to an increase in their numbers within a cell. It is the dynamics of these molecule numbers $N_i$ of the species $i$ under replication that are our main concern here.

During the replication process, structural changes, e.g. the alternation of a sequence in a polymer, may occur that alter the catalytic activities of the molecules. The rate of such structural changes is given by the replication ‘error rate’ $\mu$. As a simplest case, we assume that this ‘error’ leads to all other molecule species with equal probability, (i.e., with the rate $\mu/(k-1)$). In reality of course, even after a structural change, the replicated molecule will keep some similarity with the original molecule, and this equal rate of transition to other molecule species is a drastic simplification. We therefore carried out also some simulations where the errors in replication only lead to a limited range of molecule species and found that the simplification does not affect the basic conclusions presented here.

The model is simulated as follows: At each step, a pair of molecules, say, $i$ and $j$, is chosen randomly. If there is a reaction path between species $i$ and $j$, and $i$ ($j$) catalyzes $j$ ($i$), one molecule of the species $j$ ($i$) is added with probability $c_i$ ($c_j$), respectively. The molecule is then changed to another randomly chosen species with the probability of the replication error rate $\mu$. When the total number of molecules exceeds a given threshold (denoted as $N$), the cell divides into two such that each daughter cell inherits half ($N/2$) of the molecules of the mother cell, chosen randomly. In order to take the importance of the discreteness in the moluclue numbers into account, we adopted a stochastic rather than the usual differential equations approach.

The cell state at the $n$-th division is character-
ized by the molecule numbers of the chemical species \( \{N_1^n, N_2^n, \ldots, N_k^n\} \) (with \( \sum_j N_j^n = N \)), while there are four basic parameters; \( N, k, \mu, \) and \( \rho \). By investigating the dynamics of one thousand randomly chosen networks, and changing the four parameters, we have found that the behaviors of the system can be classified into just the following three types:

(A) Fast switching states without recursiveness

(B) Fixed recursive states

(C) Itinerancy over several quasi-recursive states

In phase (A), even though each generation has some dominating species as with regards to the molecule numbers, the dominating species change every few generations and information regarding the previously dominating species is totally lost often to the point that its population drops to zero. Indeed, by autocatalytic reactions, the population of one dominant species can be amplified, but soon it is replaced by another chemical that is catalyzed by it (see Fig.1a).

In phase (B), a recursive state is established where the chemical composition is stable enough to withstand the division process. Once reached, this state lasts very long (e.g., for as long the simulation lasts, say \( 10^9 \) generations) (see Fig.1b).

The recursive state (‘attractor’) here is not necessarily a fixed point (with fluctuations) since the molecule numbers may oscillate in time. Nevertheless, the overall chemical compositions remain within certain ranges: for example, the major species (i.e. those that are synthesized by themselves, not by an error in the replication process) are not altered over the generations. Generally, all the observed recursive states consist of 5-12 species, except for those species which exist only as a result of replication errors. (see also [10] for recursive transmission of state in a network model with some structure).

For example, in the recursive state depicted in Fig.1b, there are 11 species whose populations remain in existence throughout the simulation. As is shown in Fig.2, the replication of the molecules is sustained by the ‘core hypercycle’ \( 109 \to 11 \to 13 \to 109 \) where the catalytic activities of these core species satisfy \( c_{13} > c_{109} > c_{11} \), and accordingly we have for the respective populations \( N_{11} > N_{109} > N_{13} \). This relationship is natural, since molecules with higher catalytic activities result in the synthesis of more molecules other than themselves thus suppressing their own population fraction [8].

Here, through mutual catalysis, molecules with higher catalytic activities are catalyzed by molecules with lower activities but larger populations. To destroy such a network of mutual support, large fluctuations in molecule numbers are required, which are rare for large \( N \). Hence parasitic molecule species cannot easily invade the core.

In phase (C), the system alternates between quasi-recursive states similar to phase (B) that last for many generations and fast switching states similar to phase (A). The quasi-recursive state itself can be subjected to switches between core hypercycles as can be seen in Fig.1c where a switch occurs from an initial core hypercycle (109,11,13), to the next core hypercycle (11,13,195,155) around the 8500th generation. Subsequently, around the 12000th generation, the core network is taken over by parasites to enter the phase (A) like fast switching state which in turn gives way for a new quasi-recursive state around the 14000th generation.

When \( N \) is not so large, the molecule number of the
species with the highest catalytic activity in the core hypercycle can become small due to fluctuations, and subsequently succumb to parasitic molecules. Then, the core hypercycle loses its main catalyst resulting in its collapse giving way to a fast switching state that in turn will allow the formation of a new core hypercycle (which can but does not have to be identical to the previous one).

Which one of the phases (A), (B), (C) appears, of course, depends on the parameters and the specific structure of the network. There is however, a clear dependence of the fraction of the networks leading to each of these phases on the parameter values. The fraction of (B) increases and the fraction of (A) decreases for increasing $N$, or for decreasing $k$, $\rho$ or $\mu$. For a more systematic investigation, it is useful to classify the phases by the similarity of the chemical compositions between two cell division events\cite{10}. This can be done by defining a $k$-dimensional vector $V_n=(p_n(1),...,p_n(k))$ with $p_n(i)=N_n(i)/N$ and measuring the similarity between $\ell$ successive generations with the help of the inner product $H_\ell=V_n\cdot V_n+t\sum_i\langle |V_n| |V_{n+i}| \rangle$. In Fig.3, the average similarity $H_{20}$ and the average division time are plotted for 50 randomly chosen reaction networks as a function of the path probability $\rho$. For $\rho>0.2$, phase (A) is observed for nearly all the networks (e.g. 48/50), while for lower path rates, the fraction of (C) (with a few (B)) increases. (Roughly speaking the networks with $H_{20}>.9$ belong to C, and those with $H_{20}<.4$ to A).

In general, we have found a positive correlation between the growth speed of a cell, the similarity $H$, and the diversity of the molecules. (In Fig.3, networks with larger $H$ have smaller division times). The recursive states, established by a variety of species, maintain higher growth speeds than networks with larger $H$. On the other hand, species that are peripheral to but catalyze the core hypercycle have log-normal distributions $P(N_i)\approx\exp(-\frac{(\log N_i-\log \bar{N}_i)^2}{2\sigma^2})$, as shown in Fig.4. We have also plotted the variance $(\bar{N}_i-N_i)^2$ ($\bar{N}_i$ is the average of the distribution $P(N_i)$) and the deviation between the peak of $P(N_i)$ and $\bar{N}_i$, divided by the average $N_i$. As can be seen, the variance and the fluctuations in the core network are small, especially for the minority species (i.e., 13). For molecule species that do not belong to the core hypercycle, the variance scaled by the average increases as the average decreases. Furthermore, there is a distinct deviation between the peak and the average (except for the core species), since the distribution has a tail for larger sizes. On the other hand, if we use the variable $\log N_i$ when plotting the distribution, it is closer to a Gaussian, and the difference between the peak and the average is suppressed.

The origin of the log-normal distributions here can be understood by the following rough argument: for a replicating system, the growth of the molecule number $N_m$ of the species $m$ is given by $dN_m/dt=\pi N_m$ where $\pi$ is the average effect of all the molecules that catalyze $m$. We can then obtain the estimate $d\log N_m/dt=\pi+\eta(t)$ by replacing $\pi$ with its temporal average $\bar{\pi}$ plus fluctuations $\eta(t)$ around it. If $\eta(t)$ is approximated by a Gaussian noise, the log-normal distribution for $P(N_m)$ is suggested (this argument is valid if $\bar{\pi}>0$). For the fast switching state the growth of each molecule species is close to zero on the average and in this case, by considering the Langevin equation with boundary conditions, the power law follows as discussed in\cite{11,12}.

If several molecules mutually catalyze each other, due
and evolution compatible mutually catalyzing systems for making recursive growth, we pointed out the relevance of minority molecules in order to ensure evolvability. Previously, growth, variability of cells in their chemical compositions and divisions are classified into three phases. Recursive states (B) and switching over quasi-recursive states intermittently [13].

Power-law distributions for parasitic molecules that appear intermittently, e.g. the size of bacteria [14], and some cells in blood [15] (as well as human body weight) obey log-normal distributions.

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To sum up, features of a protocell with catalytic reactions and divisions are classified into three phases. Recursive states (B) and switching over quasi-recursive states (C) should be noted, that maintain catalytic activities for cell reproduction. Besides the establishment of recursive growth, variability of cells in their chemical compositions is necessary, in order to ensure evolvability. Previously, we pointed out the relevance of minority molecules in mutually catalyzing systems for making recursive growth and evolution compatible [?] . Indeed, phase (C) satisfies both the features, since novel quasi-recursive states with different chemical compositions are visited successively, triggered by extinctions of minority molecules in the core hypercycle networks.

We showed suppression of the fluctuation of molecules at a core hypercycle network and ubiquity of log-normal distribution of those at a peripheral network, which can be testified for the present cell, using recent advances in quantitative measurements of the fluctuations. Indeed, it is interesting to note that the distributions of the abundances of fluorescent proteins, measured by flow-cytometry are often closer to log-normal than Gaussian [14]. Furthermore, e.g. the size of bacteria [14] and some cells in blood [17] (as well as human body weight) obey log-normal distributions.

To the central limit theorem, one would expect their distributions to be close to Gaussian, and this is indeed the case for the three core species.

By studying a variety of networks, the observed distributions of the molecule numbers can be generally summarized as: (1) Distribution close to Gaussian form, with relatively small variances in the core (hypercycle) of the network. (2) Distribution close to log-normal, with larger fluctuations for a peripheral parts of the network. (3) Power-law distributions for parasitic molecules that appear intermittently.

To sum up, features of a protocell with catalytic reactions and divisions are classified into three phases. Recursive states (B) and switching over quasi-recursive states (C) should be noted, that maintain catalytic activities for cell reproduction. Besides the establishment of recursive growth, variability of cells in their chemical compositions is necessary, in order to ensure evolvability. Previously, we pointed out the relevance of minority molecules in mutually catalyzing systems for making recursive growth and evolution compatible [? ]. Indeed, phase (C) satisfies both the features, since novel quasi-recursive states with different chemical compositions are visited successively, triggered by extinctions of minority molecules in the core hypercycle networks.

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