Emergence of Two Power-Laws in Evolution of Biochemical Network; Embedding Abundance Distribution into Topology

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Abstract. The evolutionary origin of universal statistics in biochemical reaction networks is studied, to explain the power-law distribution of reaction links and the power-law distributions of chemical abundances. Using cell models with catalytic reaction networks, we confirmed that the power-law distribution in abundances of chemicals emerges by the selection of cells with higher growth speeds, as suggested in our previous study. Through the further evolution, this inhomogeneity in chemical abundances is shown to be embedded in the distribution of links, leading to the power-law distribution. These findings provide novel insights into the nature of network evolution in living cells.

1 Introduction

Recent advances in molecular biology have provided detailed knowledge about individual cellular components and their functions. Despite its enormous success, it is increasingly clear that the nature of intra-cellular dynamics maintaining the living state is difficult to be understood only by building up such detailed knowledge of molecules, since a complex network of reactions among these molecules, such as proteins, DNA, RNA and small molecules, are essential for it. Here, one possible strategy to extract the nature of intra-cellular dynamics is to search for universal laws with regard to the networks of intra-cellular reactions common to all living systems, and then to unravel the dynamics of evolution leading to such universal features.

Indeed, recent large-scale studies revealed two universal features in cellular dynamics. First, the power-law distribution of links in reaction networks was discovered in metabolic and other biochemical reaction networks, as is termed as a scale-free network, where the connectivity distribution $P(k)$ obeys the law

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$k^{-\gamma}$ with $\gamma \approx (2 \sim 3)$[2, 3, 4, 5, 6]. Second, the abundances of chemicals in intra-cellular reaction were found to also exhibit the power-law distributions, as confirmed at the levels of gene expression [1, 7, 8] and metabolic flux [9]. Here, the chemical abundances plotted in the order of their magnitude are inversely proportional to their rank.

However, despite the potential importance of these universal statistical laws, it is still unclear how they developed through evolution, how they are mutually related, and what their biological meaning is. As the efficiency of biochemical reaction process to achieve cellular growth can depend on the statistical distribution of chemical abundances and the network structure, it is then natural to pursue the possibility that both the two statistical laws appear as a result of evolution of cellular reaction dynamics. In the present paper, we demonstrate that this possibility is indeed true, through extensive simulations of evolution of cells with catalytic reaction networks to achieve higher cellular growth, and by proposing a theory for the evolutionary link from the abundance distribution to the network structure.

Employing a simple cell model with catalytic reaction dynamics consisting of a huge number of chemicals, we first found that a power-law distribution in abundances of chemical species emerges by selecting cells with higher growth speeds. Then, this inhomogeneity in the chemical abundances is embedded into the distribution of links in the reaction networks by further evolutionary process. This embedding of abundances into the network is shown to be due to the fact that the probability with which a new reaction path is connected to the chemicals is not uniform *after selection*, but it is higher for a path to be linked to a chemical that has a larger abundance. This abundance-connectivity correlation leads to a power-law distribution in reaction networks, as is consistent with the previous reports in the metabolic networks. On one hand, these findings provide a novel insight into the evolution of intra-cellular reaction dynamics and networks. On the other hand, generality of a proposed theoretical mechanism for the evolutionary embedding of abundance distribution into network connectivity distribution suggests its possible relevance to understand the structure of biological networks in general.

2 Model

Consider a cell consisting of a variety of chemicals. The internal state of the cell can be represented by a set of concentrations $(x_1, x_2, \cdots, x_K)$, where x_i is the intra-cellular concentration of the chemical species i with i ranging from $i = 1$ to K. Depending on whether there is an enzymatic reaction from i to j catalysed by some other chemical ℓ, the reaction path is connected as $(i + \ell \to j + \ell)$. The rate of increase of x_j (and decrease of x_i) through this reaction is given by $x_i x_\ell$, where for simplicity all of the reaction coefficients were chosen to be equivalent $(= 1)$ [10].

Next, some nutrients were supplied from the environment by transportation through the cell membrane with the aid of some other chemicals, i.e.,

"transporters". Here, we assumed that the transport activity of a chemical is proportional to its concentration, and the rate of increase of x_i by the transportation is given by $Dx_{m(i)}(X_i - x_i)$, where $m(i)$-th chemical acts as the transporter for the nutrient i and $x_{m(i)}$ is concentration of m_i-th chemical. The parameter D is a transport constant, and the constant X_i is the concentration of the i-th chemical in the environment. In addition, we took into account the changes in cell volume, which varies as a result of transportation of chemicals into the cell from the environment. For simplicity, we assumed that the volume is proportional to the sum of chemicals in the cell, which can increase by the intake of nutrients. The concentrations of chemicals are diluted due to increases in volume of the cell, Based on the above assumption, this dilution effect is equivalent to imposing the which imposes the restriction $\sum_i x_i = 1$. When the volume of a cell is doubled due to nutrient intake, the cell is assumed to divide into two identical daughter cells.

To summarize these processes, the dynamics of chemical concentrations in each cell are represented as

$$dx_i/dt = R_i - x_i \sum_j R_j \tag{1}$$

with

$$R_i = \sum_{j,\ell} Con(j,i,\ell)\ x_j\ x_\ell - \sum_{j',\ell'} Con(i,j',\ell')\ x_i\ x_{\ \ell'} \\ (+Dx_{m(i)}(X_i - x_i)), \tag{2}$$

where $Con(i,j,\ell)$ is 1 if there is a reaction $i+\ell \to j+\ell$, and 0 otherwise, while the last term in R_i is added only for the nutrients, and represents its transportation into a cell from the environment. The last term in dx_i/dt with the sum of R_j gives the constraint of $\sum_i x_i = 1$, due to the growth of the volume.

Of course, how these reactions progress depends on the intra-cellular reaction network. Here, we study the evolution of the network in a GA-like rule, by generating slightly modified networks and selecting those that grow faster. First, n mother cells are generated, where the connection paths of catalytic network were chosen randomly such that the number of incoming, outgoing, and catalyzing paths of each chemical is set to the initial path number k_{init}. From each of n mother cells, m mutant cells were generated by random addition of one reaction path to the reaction network of the parent cell. Then, reaction dynamics were simulated for each of the $n \times m$ cells to determine the growth speed of each cell, i.e., the inverse of the time required for division. Within the cell population, n cells with faster growth speeds were selected as the mother cells of the next generation, from which m mutant cells were again generated in the same manner.

3 Result: Power Laws in Abundances and Network Structure Achieved Through Evolution

A number of network evolution simulations were performed using several different initial networks, different parameters and various settings. We found that all

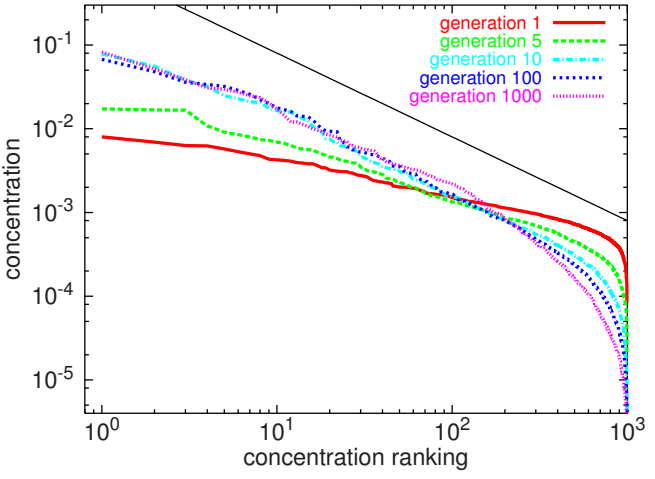

Fig. 1. Rank-ordered concentration distributions of chemical species. Distributions with several different generations are superimposed using different colors. The solid line indicates the power-law $x \propto n^{-1}$ for the reference. This power-law of chemical abundance is established around the 10th generation, and is sustained for further evolutions in the network. In the simulation, the growth speeds of 10×2000 networks were measured, and the top 10 networks with regards to the growth speed were chosen for the next generation. The parameters were set as $K = 1000$, $D = 4.0$, and $k_{init} = 4$. Chemicals x_m for $m < 5$ are considered as nutrient chemicals, and the concentration of them in the environment are set as $X_m = 0.2$. For each nutrient chemical, one transporter chemical is randomly chosen from all other chemicals.

of the simulations indicated common statistical properties with regard to both reaction dynamics and topology of networks. Here, we present an example of simulation results to show the common properties of our simulations.

The rank-ordered concentration distributions of chemical species in several generations are plotted in Fig.1, in which the ordinate indicates the concentration of chemical species x_i and the abscissa shows the rank determined by x_i. The slope of the rank-ordered concentration distribution increased with generation, and within a few generations converged to a power-law distribution with an exponent -1, which was maintained over further generations. Or equivalently, the distribution $p(x)$ of the species with abundance x is proportional to x^{-2} [13].

Indeed, the emergence of such power-law by selecting cells with higher growth speeds is a natural consequence of our previous study [1]. In our previous study, we found that there is a critical amount of nutrient uptakes beyond which the cell cannot grow continuously. When the nutrient uptake is larger than the critical amount, the flow of nutrients from the environment is so fast that the internal reactions transforming them into chemicals sustaining 'metabolism' and transporters cannot keep up. At this critical amount of nutrient uptake, the growth speed of a cell becomes maximal, and the power-law distribution of chemical abundance appears in the intra-cellular dynamics. This power-law distribution

at the critical state is maintained by a hierarchical organization of catalytic reactions, and based on this catalytic hierarchy, the observed exponent -1 can be explained using a mean field approximation. Experimentally, the power-law distributions of chemical abundances were confirmed in large-scale gene expression data of various organisms and tissues, including yeast, nematodes, human normal and cancer tissues, and embryonic stem cells, which suggests that the intra-cellular reaction dynamics in real cell systems universally lie close to the critical state (see [1] for the details).

In the evolutionary dynamics of the present simulations, to increase the growth speed of cells, change in the network which enhances the uptake of nutrients from the environment is favored. This nutrient uptake is facilitated by increasing the concentrations of transporters, while if the uptake of nutrient is too large, the cell can no longer grow continuously due to the excess of the critical amount of them, as mentioned above. Now, with the evolutionary process as

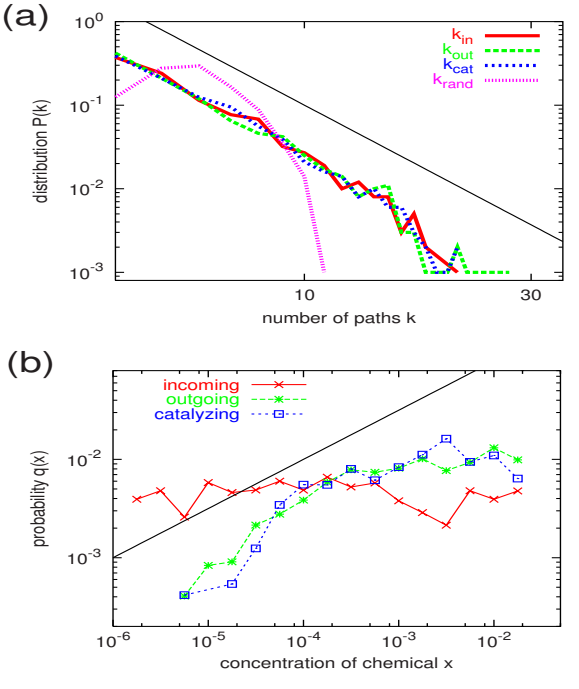

Fig. 2. Evolution of the network topology. **(a)**, Connectivity distribution $P(k)$ of chemical species obtained from the network of the 1000th generation. The solid line indicates the power-law $P(k) \propto k^{-3}$. For comparison, the distribution of k_{rand}, obtained by a randomly generated reaction network with the same number of paths with the network of 1000th generation, is shown. **(b)**, Probability $q(x)$ that a path to a chemical with abundance x is selected in evolution. The probabilities for incoming ($q_{in}(x)$), outgoing ($q_{out}(x)$), and catalyzing paths ($q_{cat}(x)$) are plotted. The data were obtained by 1.5×10^5 trials of randomly adding a reaction path to the network of the 200th generation, and the paths giving the top 0.05% growth speeds were selected.

shown in Fig.1, the nutrient uptakes increase to accelerate the growth speed of cells, until further mutations of the network may result to exceed the above critical value of the nutrient uptake. Here, successive increase in the growth speed by the 'mutation' to the reaction network is possible only when the enhancement of nutrient uptakes by it is in step with the increase in the other catalytic activities. As a natural consequence, selected are such networks that the nutrient uptake is kept near this critical point, where successive catalytic reaction process maximizes the use of nutrients, and form a power-law distribution of abundances.

Next, we investigated the topological properties of the reaction networks. The connectivity distributions $P(k)$ of chemical species obtained from the network of the 1000th generation are plotted in Fig.2a, where k_{in}, k_{out} and k_{cat} indicate the numbers of incoming, outgoing and catalyzing paths of chemicals, respectively. These distributions were fitted by power-laws with an exponent close to -3. Thus, a scale-free network was approached through evolution, while this power-law behavior was maintained for further evolutionary processes.

As shown in Fig.3, in this simple model, the evolved reaction network formed a cascade structure in which each chemical species was mainly synthesized from more abundant species. That is, almost no chemical species disrupted the flow

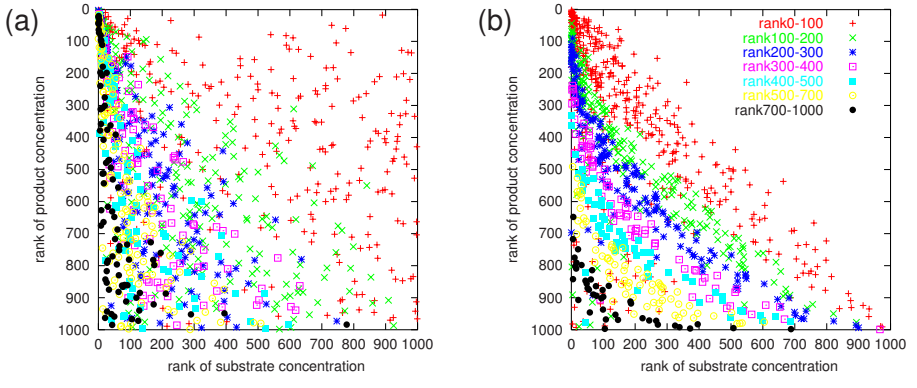

Fig. 3. Changes in the network structure. The abscissa shows the rank determined by the abundance of substrate i, and the ordinate shows the rank for the product j: the top left is the most abundant and the bottom right is the least abundant. A point is plotted when there is a reaction path $i \to j$, while the abundance of catalyst for the reactions is given by different colors determined by rank. As each product is dominantly synthesized from one of the possible paths, we plotted only the path with the highest flow, since the use of reaction paths from a chemical is quite uneven, and such a path with the highest flow can characterize the flow through the chemicals. **(a)**, The network at the 10th generation, where the network structure is rather random, even though the power-law in abundance has already been established. **(b)**, The network at the 1000th generation. Only a small number of paths are located in the upper-right triangular portion of the figure, indicating that almost all chemical species were synthesized from more abundant species.

of chemical reaction from the nutrients, as the network approached that with optimal cell growth. It should also be noted that the reaction dynamics for each chemical were also inhomogeneous in that synthesis of each chemical species had a dominant reaction path. Such uneven use of local reaction paths was also reported previously in real metabolic networks [9].

4 Mechanism: Embedding the Power Law in Abundances into Network Structure

The reason why the scale-free-type connectivity distribution emerges in this evolution is explained by selection of preferential attachment of paths to the chemicals with larger abundances. Note that the power-law distribution of chemical abundance has already been established through evolution. Here, we found that when a new reaction path is attached to an abundant chemical species, it gives a larger influence on the whole cellular state, as is expected from reaction kinetics. As a natural consequence, change in the growth speed after the mutation of the network is also larger when a path is attached to an abundant chemical species, as shown in Fig.4. Thus, when a certain number of cells with higher growth speeds are selected from the mutant pool, the probability that those selected cells have new links to such abundant chemicals is statistically higher than those expected from random change without selection. Therefore, there is a positive correlation between the abundance of chemical species and the probability that new links are added to such species in evolutionary dynamics, that is, the preferential attachment to such abundant chemicals appears. To represent this probability, we use variable $q(x)$ which indicates the probability that a new reaction path is attached to a chemical with abundance x after selection. For example, assume that change of the growth speed by the addition of a path outgoing from a chemical increases linearly with its abundance x. This assumption is rather natural since the degree of influence on the cellular state is generally proportional to the flux of the reaction path added to the network, i.e., the product of substrate and catalyst abundances. In this simple case, $q_{out}(x)$, which represents the probability of attachment for outgoing path will increase linearly with x, even though the network change is random. Here, the connectivity distribution $P(k_{out})$ is obtained by the transformation of variable as follows. Suppose that the probability of selection of a path attached to a chemical with abundance x is given by $q(x)$, then the path number $k \propto q(x)$. By the transformation $k = q(x)$, the distribution

$$P(k) = \frac{dx}{dk} p(x) = \frac{p(q^{-1}(k))}{q'(q^{-1}(k))} \tag{3}$$

is obtained. By applying the abundance power-law $p(x) \propto x^{-2}$, we obtain $P(k) = k^{-(\alpha+1)/\alpha}$ when $q(x) = x^{\alpha}$. Consequently, a scale-free network with exponent -2 should be evolved if $q_{out}(x) \propto x$.

Numerically, we found that the probabilities $q_{out}(x)$ and $q_{cat}(x)$ were fitted by $q(x) \propto x^{\alpha}$ with $\alpha \approx 1/2$, as shown in Fig.2b. Then, using the above transformation the connectivity distribution was obtained as $P(k) = k^{-3}$. Here,

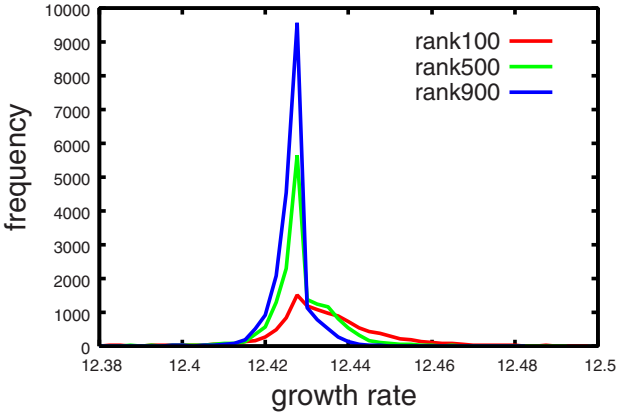

Fig. 4. Changes in growth speed with addition of a reaction path. Reaction paths were added to the network of the 200th generation from the 100th, 500th and 900th most abundant chemical species to investigate the changes in growth speed, while product and catalyst of the path were chosen randomly. Here, the concentrations of 100th, 500th and 900th most abundant chemicals were 1.80×10^{-3}, 2.03×10^{-4} and 2.98×10^{-5}, respectively. The histograms show growth speeds obtained by 20000 trials. In some trials, the growth speeds decreased markedly with the addition of a path, as the amount of nutrient uptake exceeded the limit of cellular dynamics. For the paths from the 100th, 500th and 900th most abundant chemical species, 39%, 23% and 4% of such trials showed growth speeds of less than the given threshold (we choose 12.38), respectively. Such data are not plotted in the figure. As shown in the figure, adding a reaction path from a more abundant chemical was more effective in changing the growth speed of the cell.

it is interesting to note that the connectivity distribution observed from real metabolic and other biochemical networks follows the power-law $P(k) \propto k^{-\gamma}$ with γ between 2 and 3, as often seen in experimental data [2, 3].

The probability $q(x)$ is determined through the evolutionary process. To clarify the reason for $q(x) \sim x^{\alpha}$ with $\alpha < 1$ in outgoing and catalyzing paths, we investigated the relationship between substrate abundance x and catalyst abundance y of a path to be selected. For this, we simulated changes in growth speeds by random addition of a reaction path to the network of 200th generation. For 1.5×10^5 trials, paths giving 0.05% of the highest growth speeds were regarded as being selected, and are plotted in Fig.5 as blue points on the x-y plane, while others are plotted as red points. As shown in the figure, a path with small flux is not selected since adding such path cannot change the cellular state enough, while a path with large flux is not selected also, since such large change destroys hierarchical structure of catalytic reactions, which results the decrease of nutrient intakes or exceeding the critical point so that the "cell" can no longer grow. Then, the fluxes of the selected paths satisfy $\Delta < xy < \Delta + \delta$, with Δ and δ being constants. We also found that the density of paths to be selected is almost constant in the above region. Consequently, for each chemical x, the probability

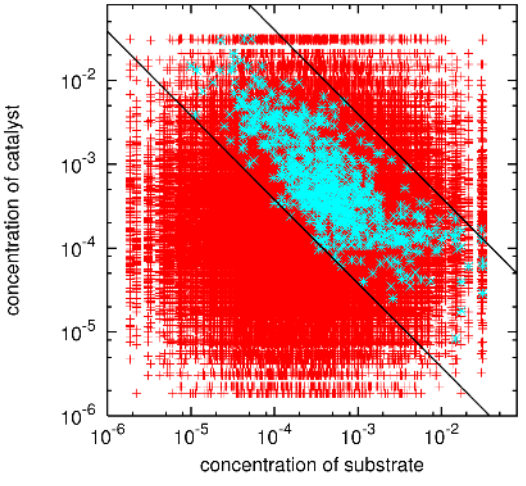

Fig. 5. Relationship between substrate abundance x and catalyst abundance y for the selected paths. A randomly chosen reaction path was added to the network of the 200th generation, and the growth speed of a cell after adding the path was simulated. For 1.5×10^5 trials, paths giving 0.05% of the highest growth speedss were regarded as being selected, and are plotted as blue points on the x-y plane, while others are plotted as red points. As shown, the selected paths satisfy $\Delta < xy < \Delta + \delta$, with $\Delta = 3.8 \times 10^{-8}$ and $\delta = 4.0 \times 10^{-6}$, respectively.

that such a path exists is given by the probability that there is such a partner chemical with abundance y, which satisfies $\Delta/x < y < (\Delta + \delta)/x$.

That is,

$$q(x) = \int_{\Delta/x}^{(\Delta+\delta)/x} p(z)dz \approx p(\Delta/x)(\delta/x) \tag{4}$$

By using the equation (1), we obtain

$$P(k) = \frac{-p(\Delta/y)}{(p(y) + ydp(y)/dy))y^2}, \tag{5}$$

with $yp(y) = k$. Indeed, if $p(x) = x^{-2}$, the above expressions lead to $q(x) \propto x$, as well as $P(k) = k^{-2}$. This expression holds when the evolved network is just at the critical point. The evolved network is near this critical point but there is a slight deviation, as can be seen in the deviation from the power-law in Fig.1, for small abundance of chemicals. Note that the asymptotic behavior for large k is given for small y. Then, the asymptotic behavior for large k is given by $P(k) \approx 1/((p(y) + ydp(y)/dy))$ depends on $p(y)$ for small y. If the asymptotic behavior of $p(y)$ for small y is given by $y^{-\beta}$ with $\beta < 2$, then $P(k) \approx k^{\beta/(1-\beta)}$. As $\beta < 2$, the exponent of the power is smaller than -2. For example, for $\beta = 3/2$ (which corresponds to the relationship between x and rank n as $x \sim n^{-2}$ for large n, as seen in Fig.1), $P(k) \approx k^{-3}$ is obtained. In general, even if the behavior of

$p(y)$ for small y is not fitted by a power-law, its increase with $y \to 0$ is slower than y^{-2}. Then the decrease of $P(k)$ with k is faster than k^{-2}, as often seen in experimental data [2, 3].

On the other hand, the probabilities $q_{in}(x)$ to have incoming path after selection show no dependence on the chemical abundance x, and therefore the above explanation is not directly applicable for the incoming paths. As for incoming paths, we have found 'hot' chemical species which facilitate the synthesis of the transporters for the nutrient uptakes, while others promote the formation of cascade structure of reaction dynamics as shown in Fig.3. These hot species have higher probability to acquire incoming path after selection. Such inhomogeneity of the probability among chemicals results in the inhomogeneity of the number of incoming paths as shown in Fig.2a. Still, further studies are necessary if such inhomogeneity results in the same power law as $q_{out}(x)$ and $q_{cat}(x)$.

5 Universality

Through several simulations, we have found that the emergence of two statistical features here is quite general and we expect that does not rely on the details of our model. To be specific, we have first checked the results by changing the initial conditions of the simulation, i.e., the initial concentrations of chemicals and the reaction network in the first cell, and confirmed that the results are independent of the initial conditions. Next, we have studied a model by changing parameters. Still, by restricting parameter values at which a cell reproduces efficiently, Zipf's law for abundances is generally observed. Furthermore, we have found the Zipf's law for the following class of models, for a cell that reproduces efficiently:

1. universality against network structure: we have studied the models with homogeneous as well as highly inhomogeneous path distribution. The distribution includes Gaussian and the power laws (i.e., the scale-free network).
2. universality against parameter distribution: instead of homogeneous parameter values for for reaction and diffusion coefficients, studied is the case with distributed parameters depending on each chemical species. The distribution includes Gaussian and log-normal.
3. universality against reaction kinetics: studied is the case with higher order catalytic reaction (for example to include the reaction kinetics $x_j x_\ell^2$ instead of $x_j x_\ell$ in eq.(2) for all chemicals)
4. universality against the form of transport of nutrient chemicals: studied is the cases with active transport mediated by some chemical, as well as passive diffusion term for the transport of nutrient.
5. universality against the condition for the cell division: Instead of setting a threshold for cell division by the sum of all chemicals, the condition is set for the amount of a specific chemical accumulated.

For all the cases, the power law distribution is obtained when the cell volume increase is optimal. Hence we believe that the result is general when a reaction network system that synthesizes chemicals in a cell shows recursive growth.

Now it is expected that the Zipf's law generally emerges through evolution, for a "cell" system consisting of the following processes:

(i) intra-cellular reaction dynamics within cells
(ii) intake of nutrients (that may depend on the internal chemical concentration)
(iii) synthesis of chemicals through the above process lead to the cell growth so that the cell is divided when a certain condition is satisfied
(iv) evolutionary process together with this cell division, i.e., random mutations to reaction networks and selection of cells with higher growth speed,

since the higher growth in cell is selected through (iv) and the Zipf's law in abundances is generally reached for a cell with optimal growth. Furthermore, as the embedding mechanism is also general, the evolution to power law in network paths is also expected to be rather universal.

Indeed, we have performed simulations with several different evolutionary criteria, and the results are essentially same, as long as the degree of mutation is not large. For example, when we assume that the probability to be selected as parent cells of the next generation is proportional to cellular growth speed, the evolutionary dynamics is qualitatively same as those presented here. As another example, we have performed simulations in which a fixed (large) number of cells is put in a given environment and when a cell divides into two cells, a randomly chosen cell is removed to keep a total cell number constant, instead of introducing discrete generations as in Genetic algorithm rule adopted in the present paper. In such rules of simulation also, cells having higher growth speeds are selected, and the power-law distribution of chemical abundances emerges as a result of evolutionary dynamics[14].

6 Summary and Discussion

In the present paper, we have shown that the power law in abundances of chemicals and network paths naturally emerges through evolution, by taking a class of cell models consisting of catalytic reaction networks. It is shown that the power law in abundances is later embedded into that of network path distribution, while the relation between the two powers is analyzed.

With regard to evolution of reaction networks, preferential attachment to a more connected node has often been discussed [2, 15]. In the previous models, preference of path attachment is simply defined as a function of number of existing paths, and the origin of such preference in evolutionary dynamics remains obscure. On the other hand, our study is different from them in two important respects. First, the dynamics of chemical abundance in the networks were introduced explicitly (described as node 'strength' in [16]), while previous models generally considered only the topological structure of the network. Second, selection only by cellular growth speed results in such a preference, even though attachment itself is random. Here, we found that more abundant chemical species acquired more reaction links as attachments of new links to such chemicals have

both a greater influence on the cellular state and a higher probability of being selected. With these mechanisms, the power-law in abundance is naturally embedded in the intracellular reaction network structure through evolution, which is simply a process of selecting cells with faster growth speeds.

As discussed, the emergence of the power-law distribution of chemical abundance is expected to be a universal feature of growing cells, since this feature seems to necessarily appear in any systems having both intra-cellular reaction dynamics and intake of nutrients from an environment, when the cellular growth speed is maximized. Similarly, our simulations support that the evolutionary dynamics toward the power-law distribution of reaction path numbers emerges when cells having higher growth speeds are selected and mutations are randomly added to reaction networks. An important point here is that the emergence of universal features is independent of details of the system, as long as the conditions required for such features are satisfied. The power-laws of both abundance and connectivity, which are often observed in intracellular reactions, can be simply consequences of our mechanism by Darwinian selection.

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13. The rank distribution, i.e., the abundances x plotted by rank n can be transformed to the density distribution $p(x)$, the probability that the abundance is between x and $x + dx$. Since $dx = dx/dn \times dn$, there are $|dx/dn|^{-1}$ chemical species between x and $x + dx$. Thus, if the abundance-rank relation is given by a power-law with exponent -1, $p(x) = |dx/dn|^{-1} \propto n^2 \propto x^{-2}$.
14. As for the number distribution of reaction links, the simulation has not yet reached the stage to show the scale-free statistics in a network clearly, (since the simulation requires much longer time than the present method), but still we found that the number distribution of such network show heterogeneity in number of reaction links, with significant deviation from those of random networks.
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