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C. R. Biologies 326 (2003) 459–466
COMPTES RENDUS BIOLOGIES

Biological modelling / Biomodélisation

Modelling autocatalytic networks with artificial microbiology

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Received 27 May 2002; accepted 4 March 2003

Presented by Michel Thellier

Abstract

Cells can usefully be equated to autocatalytic networks that increase in mass and then divide. To begin to model relationships between autocatalytic networks and cell division, we have written a program of artificial chemistry that simulates a cell fed by monomers. These monomers are symbols that can be assembled into linear (non-branched) polymers to give different lengths. A reaction is catalysed by a particular polymer or 'enzyme' that may itself be a reactant of that reaction (autocatalysis). These reactions are only studied within the confines of the 'cell' or 'reaction chamber'. There is a flux of material through the cell and eventually the mass of polymers reaches a threshold at which we analyse the cell. Our results indicate a similarity between the connectivity of the reaction network and that of real metabolic networks. Developing the model will entail attributing increased probabilities of reactions to polymers that are colocalised to evaluate the consequences of the dynamics of large assemblies of diverse molecules (hyperstructures) and of cell division. ***To cite this article: M. Demarty et al., C. R. Biologies 326 (2003).***

Résumé

Modélisation de réseaux autocatalytiques à l'aide de la microbiologie artificielle. Les cellules qui croissent et se divisent peuvent être schématiquement représentées par un ensemble de réseaux autocatalytiques. Pour modéliser les relations entre les réseaux autocatalytiques et la division cellulaire, nous avons écrit un programme, basé sur les principes de la chimie artificielle, qui simule une « cellule » nourrie par des nutriments (monomères). Dans notre modèle, les monomères sont représentés par des symboles, ceux-ci pouvant être assemblés pour former des polymères linéaires de différentes longueurs. Les réactions d'addition ou d'hydrolyse sont catalysées par des polymères particuliers (enzymes) qui peuvent être eux-mêmes produits ou substrats des réactions (autocatalyse). Les réactions ont été étudiées à l'intérieur d'une « chambre réactionnelle » qui schématise une « cellule ». Pendant la croissance, il existe un flux de matière à travers la surface de la « cellule » et la masse des polymères atteint éventuellement un seuil, à partir duquel la cellule se divise. Nos résultats suggèrent une similarité entre la connectivité des réseaux réactionnels obtenus et celle des réseaux métaboliques réels. Les développements futurs du modèle permettront de favoriser les réactions catalysées par des polymères co-localisés, afin d'évaluer l'influence d'hyperstructures (assemblage dynamique de macromolécules créé pour réaliser une fonction) sur la croissance et la division. ***Pour citer cet article : M. Demarty et al., C. R. Biologies 326 (2003).***

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1631-0691/03/$ – see front matter
doi:10.1016/S1631-0691(03)00097-0

Keywords: artificial chemistry; autocatalytic networks; hyperstructures

Mots-clés : chimie artificielle ; réseaux autocatalytiques ; hyperstructures ; modélisation

1. Introduction

Biological cells are autocatalytic networks [1] and several of their salient characteristics follow from this. For example, they take up nutrients and perform chemical reactions so as to gain mass, and then divide to form daughter cells. The evolution of autocatalytic networks within a self-contained system of artificial chemistry has been observed [2] and, in this context, the importance of simulating division has been shown [3]. We have proposed that the regulation of the bacterial cell cycle depends on cells sensing the state of their metabolic networks [4–6]. Such networks have characteristic patterns of connectivity [7–9]. It is therefore of interest to study how these patterns may vary during the cell cycle to confer for example rapid growth (to profit from the availability of nutrients) or robustness (to allow survival during starvation). Our initial objective, reported here, is to begin to model the formation and evolution of autocatalytic networks and their relationship with cell division. We have therefore written a program that can be approximated to a simulation of a cell that is fed by monomers that are the 'energy' source for the system. In this simulation, the monomers are labelled from 1 to n. Different numbers of these monomers can be assembled into linear (non-branched) polymers to give different lengths. A polymer may be cleaved or added to another polymer or monomer in a reaction in which the order and total number of monomers are conserved. A reaction is catalysed by a particular polymer or 'enzyme' that may itself be a reactant of that reaction (autocatalysis). More than one variety of enzymes may separately catalyse the same reaction; a single variety of enzyme may catalyse more than one reaction; some polymers do not catalyse reactions. These reactions are only studied within the confines of the cell. The initial cell is created by the self-association of a random number of each monomer and a random number of a random selection of polymers formed outside the cell. The cell is then supplied with monomeric nutrients at regular or intermittent intervals. The cell is also supplied with polymers but at a rate much lower than the rate of supply of nutrients. There is a flux of material through the cell, since monomers and polymers may be lost from the cell (note that this facility is not used in the version described below). The dynamics of the system is described by representations of its state at discrete time steps. At each time step, a nutrient may or may not be incorporated into the cell depending on the availability of the nutrients outside the cell. At each time step, the cell is modified by calculating, on the basis of concentrations, whether each variety of enzyme catalyses its cognate reactions; this is done so as to give some physicochemical reality. Each variety of enzymes is examined. This results in changes in the numbers and types of monomers and polymers present in the cell. The time step is repeated until the mass of polymers in the cell reaches a threshold (corresponding to the size at which cell division would occur) and the cell is then analysed in terms of the number and nature of its polymers, reactions and their connectivity.

2. The model

(**1**) We consider a set of monomeric molecules (monomers) of different nature labelled from 1 to n.

(**2**) These monomers are 'nutrients' that are present outside a 'reaction chamber' or 'cell'.

(**3**) Different numbers PD (for Polymerisation Degree) of these monomers can be assembled in linear (non-branched) polymeric molecules (polymers) to give different lengths. The symbol $P_j(\{k\})$ represents a polymer containing $\mathrm{PD} = j$ monomeric units and $\{k\}$ is an ordered set of j symbols, each symbol being an element of the set of n monomeric units defined above. For example, if the polymer $P_j(\{k\})$ is the string 23112, then $j = 5$ and $\{k\} = \{2, 3, 1, 1, 2\}$. Polymers containing $\mathrm{PD} = j$ monomeric units therefore exist in a maximum of n^j different permutations.

(**4**) A polymer containing $\mathrm{PD} = p$ monomeric units may be cleaved or added to other polymers ($\mathrm{PD} = q$) or monomers ($\mathrm{PD} = 1$) such that the order and

total number of monomeric units is conserved in the reaction. Reactions between molecules are of the form, $P_p(\{k\}) \oplus P_q(\{l\}) \leftrightarrow P_{p+q}(\{k\}\{l\})$ where $\{k\}$ and $\{l\}$ are ordered sets of the monomeric units and $(\{k\}\{l\})$ is the result of the addition of these sets in the order k to l. It is therefore the equivalent of reactions of addition (left to right) or cleavage (right to left). This reaction is reversible but is not commutative, i.e., $P_p(\{k\}) \oplus P_q(\{l\})$ is not the same as $P_q(\{l\}) \oplus P_p(\{k\})$ and $P_q(\{l\}) \oplus P_p(\{k\}) \leftrightarrow P_{p+q}(\{k\}\{l\})$ is not a valid reaction.

(**5**) Reactions are catalysed by a particular polymer $P_p(\{k\})$ that may itself be a reactant (autocatalysis) and that we term 'enzyme' for convenience. More than one variety of enzymes, e.g., $P_p(\{k\})$ and $P_q(\{l\})$, may separately catalyse the same reaction. A single variety of enzyme may catalyse more than one reaction. No monomer may catalyse a reaction. Some polymers do not catalyse reactions.

(**6**) Reactions of the above type are only studied in the confined volume of a cell or reaction chamber that, in its initial form, we regard as created by the self-association of a random number of each monomer and a random number of a random selection of polymers made outside the cell (by 'abiotic' mechanisms that may be different from those in (5) and that we do not study).

(**7**) Nutrients are then supplied to the cell at regular or intermittent intervals. The cell may also be supplied with polymers, but at a much lower rate than that of the supply of nutrients.

(**8**) The dynamics of the system is described by representations of its state at discrete time steps. At each time step, a nutrient may or may not be incorporated into the cell, depending on the availability of the nutrients outside the cell. In principle, there could be an efflux of material through the cell, since the possibility also exists of losing monomers and polymers from the cell (for example, the probability of a monomer or polymer being lost could be inversely proportional to the number of reactions in which it is involved). This possibility is not implemented in the version described here.

(**9**) At each time step, two lists that describe the system are updated. The first list, the MoleculeList, contains a reference to each molecule present in the cell. Each molecule has a description comprising its label (name), the number of copies, whether it is a monomer or a polymer and in the latter case, whether it is an enzyme. The second list, the EnzymeList, contains a reference to each enzyme present in the cell. Each enzyme has a description comprising its label, the number of copies, its activity status (the possibility of using the parameter 'active or inactive' is built into the model but has not been used to generate the data shown here) and the reaction(s) it catalyses. A reaction is defined by three molecules, corresponding to two substrates, $P_p(\{k\})$ and $P_q(\{l\})$, and one product, $P_{p+q}(\{k\}\{l\})$, and by the k_f and k_r for this reaction where k_f and k_r are the equivalent of the rate constants for the forward and reverse reactions, respectively. An enzyme can catalyse more than one reaction. Initially, the number of varieties of enzyme is chosen at random. Then the cell is fed in accord with (7).

(**10**) At each time step, the system is updated by calculating whether each variety of enzyme catalyses its cognate reactions. Each variety of enzymes is examined. The forward reaction can take place if the enzyme $P_\mathrm{r}(\{m\})$ is present and active and if $k_\mathrm{f} \times N(\{k\}) \times N(\{l\}) > k_\mathrm{r} \times N(\{k\}\{l\}) \times N_\mathrm{t}$, where N_t is the total number of molecules in the cell and k_f and k_r are the rate constants for the particular reaction as catalysed by the enzyme. If the inequality is reversed, the reverse reaction occurs. Nothing happens at equilibrium.

(**11**) Iteration during the time step. A variety of enzyme is chosen from the EnzymeList either according to its concentration (as presented here) or at random (in this case, the choice is weighted by the number of copies, N_m, of the enzyme of a given variety, $P_\mathrm{r}(\{m\})$, such that the probability of choosing this variety is proportional to $N_\mathrm{m}/N_\mathrm{Et}$, where N_Et is the total number of enzymes).

The total increase and decrease in the number of copies of each molecule involved in a single catalysed reaction during the time step is obtained from:

$$\Delta N\big(\{k\}\{l\}\big) = -\Delta N\big(\{k\}\big) = -\Delta N\big(\{l\}\big) \tag{1}$$

(note that in the version presented here the concentration of the enzyme determines how many times the same reaction occurs within the time step). The set of molecules in the cell is therefore altered after every reaction. After one variety of enzymes has been treated as above, another variety is chosen and its cognate reaction performed in the same way. Each variety of en-

Table 1
Summary of the cell. **o**, present at start; **ez**, enzyme activity; C_0 number of copies at start; **Id**, identity of molecule; C_f number of copies at end; N_t total connectivity; N_s connectivity as substrate; N_p connectivity as product; **Reactions**, number of reactions involving molecules (arrows indicate direction of reactions); C_n overall number of reactions

o	ez	Id	C_0	C_f	Food	N_t	N_s	N_p	Reactions	→	←	C_n
°		1	53	107	54	1	1	0	0	0	0	0
°		2	54	0	54	6	6	0	1946	919	1027	−108
°		3	97	58	64	3	3	0	1307	602	705	−103
			204	**165**	**172**	**10**	**10**	**0**	**3253**	**1521**	**1732**	**−211**
°	*	11	14	6		5		5	1960	976	984	−8
°	*	12	2			4		4	2		2	−2
°	*	13	6			3		3	286	140	146	−6
°	*	21	13			7		7	1481	734	747	−13
°	*	22	3	3		1		1				
°	*	23	3	100		2		2	1021	559	462	97
°	*	31	6	3		2		2	1639	818	821	−3
°	*	32	15	1		3		3	14		14	−14
°	*	33	6			3		3	786	390	396	−6
	*	233		5		2	1	1	215	110	105	5
	*	312		3		2	1	1	443	223	220	3
	*	313				6	5	1	566	283	283	
	*	1121				7	5	2	1198	599	599	
	*	1131				1		1	1196	598	598	
	*	1212				2	1	1				
		3131				1		1				
	*	3232		6		3	2	1	10	8	2	6
	*	3321				4	2	2	618	309	309	
	*	21121				4	3	1	248	124	124	
		22233				1		1				
	*	23321				3	2	1	48	24	24	
	*	31321				6	5	1	162	81	81	
	*	323232				1		1				
	*	1123321		1		1		1	1	1		1
	*	1221121				1		1				
	*	2112112		2		3	2	1	24	13	11	2
	*	3131121				3	2	1	152	76	76	
	*	3133232		1		1		1	3	2	1	1
		112131321				1		1				
		132112112				3	2	1				
	*	211211121				2	1	1	26	13	13	
	*	212112112				2	1	1	22	11	11	
	*	313211121		5		2	1	1	37	21	16	5
	*	332131321				1		1				
	*	11132112112				1		1				
	*	21132112112				1		1				
	*	211211121313				1		1				
	*	212112112312				2	1	1				
	*	313213131121				1		1				
	*	1212313211121				3	2	1				
	*	131212313211121				2	1	1				
	*	23321212112112312				1		1				
	*	12123132111213131121				1		1				
		31321131212313211121				1		1				
		Total	**68**	**136**		**107**	**68**	**39**	**12158**	**6113**	**6045**	**68**

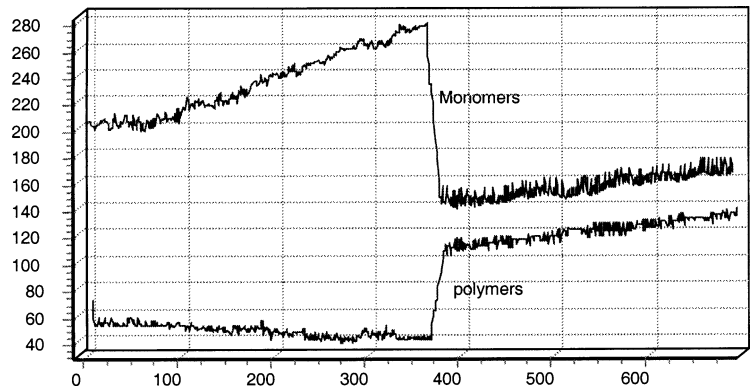

Fig. 1. Numbers of copies of monomers and polymers vs timestep.

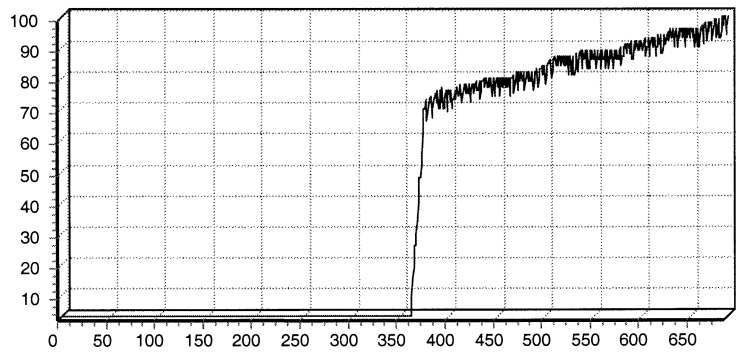

Fig. 2. Numbers of copies of polymer 23 vs timestep.

Table 2
A reaction network: k_f and k_r are the forward and reverse rate constants (other symbols as in Table 1)

	Id	Step	Reaction	k_f	k_r
a	11	360	$2+3 \leftrightarrow 23$	20	222
b	23	0	$33+21 \leftrightarrow 3321$	74	426
c	3321	60	$2+33 \leftrightarrow 233$	43	823
d	233	80	$11+31 \leftrightarrow 1131$	1	102
e	1131	100	$313+21 \leftrightarrow 31321$	15	168

zymes is chosen from the Enzymelist until all varieties have had the possibility of catalysing their reaction.

(**12**) At the start of each time step, the cell is tested to see whether it has grown to a threshold at which cell division could occur. This test is based on the total number of polymers in the cell but alternatives include the number of monomers in the form of polymers as well as the number of copies of a specific polymer. In the present model, all reactions cease at this critical cell size and the program ends.

3. Results

Here, we present a typical run of the program using only three types of monomer. The number of copies of these monomers present in the cell is given in C_0, for concentration at origin (column 4, Table 1). The open circle symbol in column 1 (Table 1) indicates which of the polymers in ID, for *identity* (column 3), were present in the cell at the start of the experiment. C_0 also gives the number of copies of polymers at the start – note that this cell did *not* initially contain polymers of types ID 233 to ID 31321131212313211121. C_f, for final concentration (column 5), gives the number of copies of the polymer at the end of the experiment – note that if a polymer has neither an entry in C_0 nor C_f, it is because it was formed during the experiment but disappeared before the end. N_s for node class of substrate (column 8) indicates the number of different reactions in which a molecule was involved as a substrate – in other words, it is the node class of the

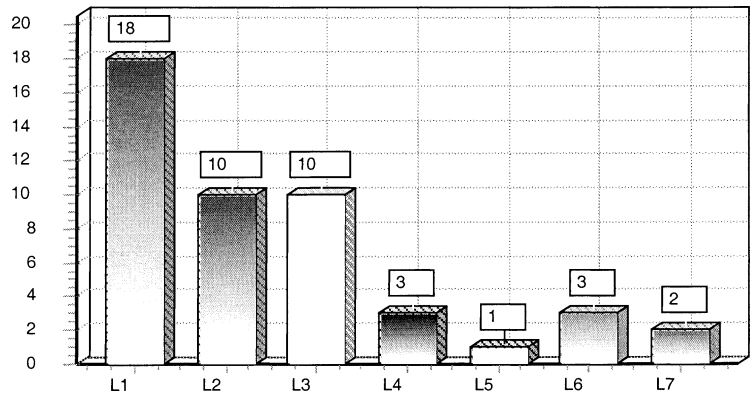

Fig. 3. Distribution of node classes. Number in Node Class vs Node Class.

molecule with respect to the reactions in which it has been consumed; N_p for node class of products (column 8) indicates the number of different reactions in which a molecule was involved as a product; N_t for total number (column 7) is the sum of N_s and N_p. We can therefore consider each molecule as a node belonging to a network of either substrates or products or both; a molecule that can be made into 3 different molecules (i.e. is a substrate) and that is made from two others (i.e. is a product) has a node class of $N_s = 3$, $N_p = 2$ and $N_t = 5$. In this analysis, the cell can be regarded as a network of molecules that are connected by catalysed reactions. Reactions (column 9) is the number of times the reaction occurred in the course of the experiment. The right arrow (column 10) is the number of times the molecule was consumed, the left arrow (column 11) is the number of times the molecule was produced and C_n is the difference between consumption and production.

The asterisks in ez (column 2, Table 1) indicate which of the polymers were enzymes. Polymers either started as enzymes or acquired activity later. This latter is simply a device to model the entry of a new enzyme by ascribing at random an activity to a polymer present in the original cell (column 1, Table 1); an alternative possibility not explored here is that acquisition of activity is due to a cofactor entering the cell.

The kinetics of the numbers of monomers and polymers (Fig. 1) show that an event occurred at time step 360 when enzyme 11 'entered' the cell. The reaction catalysed by 11 is $2 + 3 \leftrightarrow 23$ and this led to a rapid increase in the numbers of 23 (Fig. 2). There were no enzymes catalysing the reaction $1 + 1 \leftrightarrow 11$, so catalytic closure did not occur [1]. Nevertheless, the system grew using its initial complement of polymer 11 until time step 688 when it had doubled the number of its polymers (from 68 to 136). 23 was also an enzyme and catalysed the reaction leading to another enzyme $33 + 21 \leftrightarrow 3321$; 3321 catalysed $2 + 33 \leftrightarrow 233$; 233 catalysed $11 + 31 \leftrightarrow 1131$, a reaction that consumes or generates 11 (Table 2). Hence there is a cycle. (Note that the reactions of all enzymes are easily displayed, although we do not show them here; many other reactions are indicated in Table 1.) It might be expected that enzymes that catalyse the addition of monomers to other molecules would be the most abundant. This is not the case in this example, where 11, present in six copies at the end, is not as abundant as 23, present in a hundred copies at the end. Note that another enzyme in the cycle, 3321, also catalysed addition of the monomer, 2 (Table 2), and that this enzyme was present neither at the start nor the end of the experiment. Such fluctuations in potentially key enzymes were common in the program.

The numbers of members of a particular node class (where the class is the sum of the reactions in which the molecule is either a substrate or product) reveals a distribution with a long tail (Fig. 3). The molecules with the highest connectivities were 21 and 1121 and those with the next highest were 2, 313 and 31321 (Table 1). We have not analysed connectivity in terms of catalysts in a context where an enzyme could catalyse several reactions, although this would be possible. In summary, these results show that even in this simple model, autocatalytic networks form readily. It should be noted that, reassuringly, the

system does not grow if it does not use the monomeric food set in its reaction network!

4. Discussion

Artificial chemistry offers a powerful possibility for both testing existing biological concepts and for deriving new ones [2,10]. To contribute to an ambitious, integrative modelling of biological cells, I-cell [11], we have used a variant that we term *artificial microbiology* to study how autocatalytic networks develop when they are confined to cells that are allowed to grow to a fixed size. The results from a limited range of simulations, with a restricted set of molecules, are compatible with the idea that the most abundant enzymes are those that catalyse the addition of monomers. This appears obvious – as a network evolves, the first limiting step in the growth of the cell is the flow of monomers into the cell and the second limiting step is the addition of these monomers onto polymers or onto other monomers. The enzymes that add monomers may therefore correspond to the ancestral precursors of modern polymerases and ribosomes, which also add monomers onto polymers; such enzymes can constitute a major proportion of cell mass. That said, the proportion of cell mass in the form of ribosomes varies with the nutrient supply in bacteria such as *Escherichia coli* and it should be noted that the most abundant enzyme in the example given in this paper does not catalyse monomer addition.

Abstract networks or graphs consist of nodes and the connections or links between them. A particular node belongs to a node class that corresponds to the number of connections per node. By allocating a metabolite to a node class on the basis of its connections to other metabolites, we and – independently – others found that real metabolic networks have a power law distribution of node classes characterized by a long tail [7,8,12]. Similar distributions have been found for proteins [13]. Artificial microbiology permits the origin and properties of real metabolic distributions to be investigated. In many individual runs of the system presented here, the distribution of the connectivities did indeed show a long tail. Hence, the system may be useful in answering such questions as: What network structure confers robustness to fluctuations in nutrition? Where should the highest node classes be located so as to assure a maximum use of inputs and a steady output? What allows the network to be regenerated after starvation?

In the version presented here, the program ends when the cell attains a size at which division might occur. The importance of cell division in the evolution of autocatalytic networks has recently been described [3, 5]. Our program offers the possibility of exploring how competing autocatalytic networks within the mother cell may be separated by cell division into individual ones. By selecting the faster growing daughter cell, the role of cell division in the evolution of networks can then be studied. This role may be facilitated by the co-localisation of many different macromolecules into a non-equilibrium *hyperstructure* in response to the cellular need to perform a function [14,15]. Cell division in bacteria, for example, would be performed by a hyperstructure comprising division genes, their mRNA and enzymes, together with particular lipids and ions such as calcium [5]. Future development of the model will therefore entail attributing increased probabilities of reactions to polymers that are colocalised so as to allow evaluation of the consequences of hyperstructure formation. Finally, artificial microbiology may be extended to study what happens when other types of reactions are introduced [16], when the cell shifts from a growing to a non-growing state, when inactive enzymes are preferentially inhibited, and when a coding polymer (DNA/RNA) is present.

Acknowledgements

We thank Dick D'Ari, Michel Thellier, the members of the epigenesis atelier in Genopole and an anonymous referee for helpful comments.

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