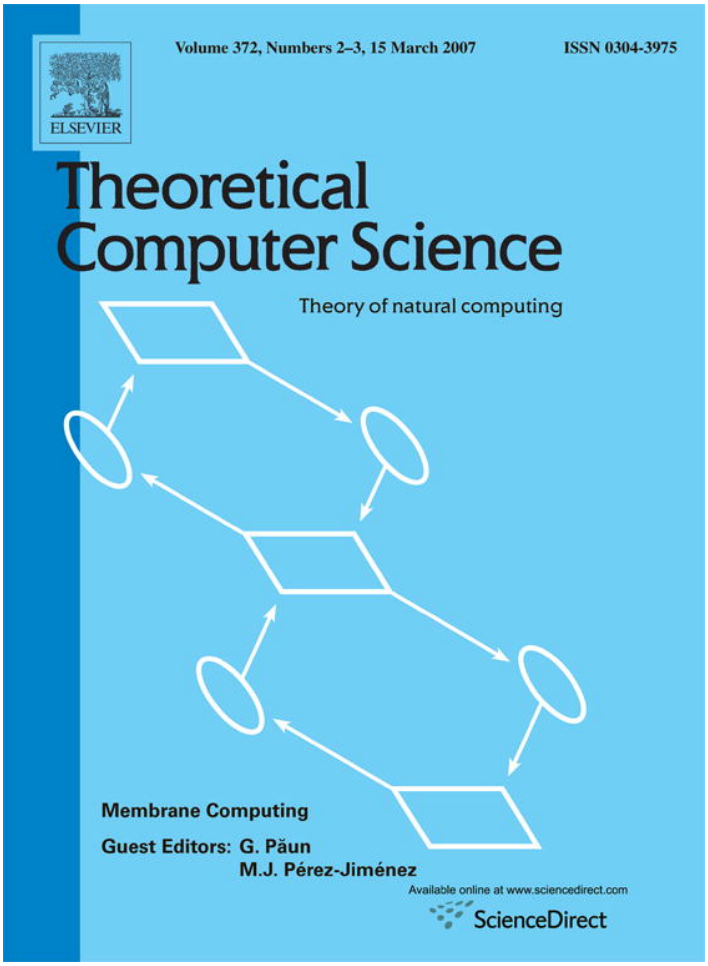

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Discrete solutions to differential equations by metabolic P systems

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Abstract

The relationships existing between metabolic P systems and ODE systems are investigated. Formal results show that every MP system determines a structure, called an MP graph, which results in an ODE system whose solution equals, in the limit, the evolution of any *non-cooperative* MP system that can be derived from the initial one by means of a systematic procedure. Examples based on the model of a mitotic oscillator in early amphibian embryos, the Lotka–Volterra predator–prey population dynamics, and the Lorenz strange attractor are provided, showing the applicability of the proposed computational approach.

Keywords: Metabolic networks; Ordinary differential equations; P systems; MP systems; MP graphs

1. Introduction

P systems were introduced as a new computation model inspired by biology [27,28]. The two main aspects of a P system are *multisets* and *membranes*. The notion of multiset is related to the way sets are *implemented* in terms of physical entities which can occur in a certain number of instances, that is, different *concrete* individuals, (*objects, occurrences, copies*) located in space and time, which can be seen as expressing the same *abstract* individual identity, or for short the same *type*. The theory of P systems has grown very fast by studying different kinds of evolution rules (reactions) and different kinds of evolution strategies [28,36]. Important results have been established on the computational completeness of this model and on its relationships with other computational models. In P systems, the passage from one state to another one is produced by the application of rules which act, independently and in a *maximal parallel way* in each membrane, by transforming the state of the systems, that is the multisets of objects inside each membrane.

The P system paradigm has been used to mathematically model several biomolecular phenomena acting at the cellular level, such as trans-membrane transport [24,26] and communication [2], consumption of energy [12,29] and even more specific biological processes [11,3,25,34]. Non-biological applications have been proposed as well [7].

MP systems introduced in [21] reconsider P systems by including a deterministic procedure for computing their evolution. This procedure, called the MP algorithm, for short MPA,[1] generalizes an algorithm introduced in [23],

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[1] In [22] this algorithm is called PMA (P metabolic algorithm), but for a more uniform notation here we swap the first two initials.

0304-3975/$ - see front matter
doi:10.1016/j.tcs.2006.11.030

and aims at capturing the salient chemical mechanisms that are responsible for the dynamics of a wide class of biomolecular processes [1]. MP systems are similar to AMR (abstract multiset rewriting systems) [32,33]. However, they adopt a population rewriting perspective and a mass partition strategy which have very important consequences in the modeling of metabolic processes.

For the sake of their comprehension MP systems can be well represented by using MP graphs [22]. MP graphs, in fact, yield an immediate depiction of the structural aspects of a biodynamic model which is similar to that offered by other graphical representation such as signal transduction networks, metabolic pathways and so on [20,35,31]. However, MP graphs are directly related to the computational structure of the MP algorithm.

We have shown that MP systems effectively model the dynamics of several biochemical processes: the Belousov–Zhabotinsky reaction (Brusselator) [4,6], the Lotka–Volterra dynamics [5,4,6], a susceptible–infected–recovered epidemic [4], the leukocyte selective recruitment in the immune response [11], the protein kinase C activation [6], circadian rhythms [9], and mitotic cycles [22]. Despite this, still there is a gap of knowledge concerning the relationships existing between the representation made with an MP system and the more traditional differential equation-based modeling of a given biochemical phenomenon.

We briefly recall that a general autonomous system of ordinary differential equations (ODEs) in the functions $x_1(t)$, $\ldots, x_N(t)$ is given in the following form [19]:

$$\begin{aligned} x_1' &= g_1(x_1, \ldots, x_N) \\ &\ldots \\ x_N' &= g_N(x_1, \ldots, x_N), \end{aligned} \tag{1}$$

in which $x_1', \ldots, x_N'$ are time derivatives of $x_1, \ldots, x_N$ and $g_1, \ldots, g_N$ are time-independent functions. Since the models proposed in biochemistry and biology are normally described by nonlinear systems, the respective ODEs in most cases can be solved only numerically [18]. Several biologically oriented mathematical frameworks have been developed upon the theory of autonomous systems, such as Stoichiometric Network Analysis [30], that investigates the stability properties of complex chemical reactions, as well as Metabolic Control Analysis and Biochemical Systems Theory, that aim at calculating a system's sensitivity against variations of its parameters [8,17].

In this paper, after a synthetic presentation of MP systems, MP graphs, and the MP algorithm, we analyze the relationships existing between MP and ODE systems. Originally started in a study of predator–prey models [10], the analysis is here proposed in a more systematic formal arrangement. Application examples are provided, showing the performance of MP systems in computing the evolution of the Lotka–Volterra dynamics and the Lorenz model, as well as their versatility in expressing the model of a mitotic oscillator in early amphibian embryos.

2. Metabolic P systems and graphs

MP systems are deterministic P systems where (i) the state of the system, at each time instant, is given by the amount of matter that is assigned to any (chemical) substance present in the system (with respect to some mass unit chosen for that substance), and (ii) the transition to the next state (after some specified interval of time) is calculated according to some *mass partition strategy*, that is, the available matter of each substance is partitioned among all reactions which need to consume it for producing their products. The policy of matter partition is regulated at each instant by some real values, call them *reactivities*, which represent the strength of any reaction.

We summarize the principles of mass partition strategy with four statements:

(1) Rules compete for object populations.
(2) Objects are allocated to rules according to a *mass partition principle*.
(3) Partition factors are determined by *reaction maps*.
(4) A "metabolic rule" r consumes/produces integer multiples of a *reaction unit* u_r which generalizes the notion of molar unit (Avogadro's principle).

It may be useful to clarify these principles by means of an example. Let $T = \{A, B, C, ...\}$ be an alphabet of biological species (or types). We define $q : T \to \mathbb{R}$ as the state of the system, that is the concentration of each type at a certain observation instant. Assuming that at a given instant four rules, say r_2, r_3, r_5 and r_7, need molecules of a certain type A for performing some biochemical reactions (see Fig. 1), then a partition strategy for the species

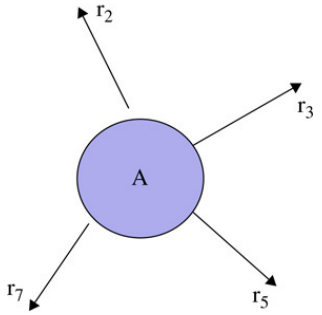

Fig. 1. Competition for object A.

A is needed. Our approach considers a real number as the *strength* of a rule. This real number is the value that the *reaction map* associated with the rule assumes in the considered instant. For example, again see Fig. 1, if a, b, c are the concentrations of the species A, B, C, respectively, then the reactivities associated with the rules r_2, r_3, r_5 and r_7 which ask for the A molecules could be:

$$f_2 = 200a, \quad f_3 = 0.5a^{1.25}b^{-1}, \quad f_5 = a^{1.25}(b+c)^{-1} \quad \text{and} \quad f_7 = 10.$$

We define, for any state q,

$$K_{A,q} = \sum_{i=2,3,5,7} f_i(q)$$

as the *total pressure* on A. Then, for each of the rules r_j we consider the *partial pressure* (or *weight*) of r_j on type A as

$$w_{A,q}(r_j) = \frac{f_j(q)}{K_{A,q}}.$$

In order to avoid inessential complications we assume that for any type A and for any state q we have $K_{A,q} \neq 0$. Coming back to the example discussed before, it is easy to see that

$$w_{A,q}(r_2) = \frac{200a}{200a + 0.5a^{1.25}b^{-1} + a^{1.25}(b+c)^{-1} + 10}$$

and

$$w_{A,q}(r_3) = \frac{0.5a^{1.25}b^{-1}}{200a + 0.5a^{1.25}b^{-1} + a^{1.25}(b+c)^{-1} + 10}.$$

The other weights can be calculated analogously. Weights determine the partition factors of the species A in the state q.

Let us assume that at a given instant, according to the reaction competition, n objects of type A and m objects of type B are allocated to a rule $r : AAB \to AC$. The corresponding reaction unit turns out to be

$$u_r = \min\{n/2, m\}.$$

If a *mole* is intended to be a (conventional) population unit, this means that $2u_r$ moles of type A and one mole u_r of type B are consumed, while a mole u_r of type A and a mole u_r of type C are produced. Overall, this states that a mole u_r of type A and a mole u_r of type B are replaced by a mole u_r of type C.

It is important to point out that rule r is completely different from a rule r' having the form $AB \to C$. This is due to the fact that the two rules imply different competition factors and, consequently, different mass partitions. In fact, in the latter case the reaction unit would have been $u_{r'} = \min\{n, m\}$.

An important class of rules are the *transparent* rules, having the form $X \to X$ (X being whatever symbol of the considered alphabet). If, in a given state, the reaction map of this rule has a value k, then a percentage of the mass of X, depending on the values of the reaction maps of all rules competing for X, is allocated to this transparent rule. Hence, this mass remains inert. As we will see, the role of transparent rules is of fundamental importance in tuning the dynamics of metabolic processes.

The intuition of P systems with a mass partition-driven evolution is formalized by the notion of an MP system, that we are going to define here in general terms. A *discrete multiset* over an alphabet T is a function from T to the set $\mathbb{N}$ of natural numbers. A *continuous multiset* over an alphabet T is a function from T to the set $\mathbb{R}$ of real numbers. As is customary in P systems, we will adopt the string notation for discrete multisets. This implies that when a string denotes a multiset, then the order of its symbols is not essential (see [28] for more details on P system notations) and, for any string α, we will safely write $X \in \alpha$ for saying that X is a symbol occurring in α.

The notion of an MP system we consider here should be better identified by that of a *zero level* MP system, because only one membrane is considered. We will always assume implicitly this feature along the paper.

Definition 1 (*MP System*). An MP system is a construct

$$M = (T, Q, R, F, q_0)$$

in which

- T is a finite set of symbols;
- Q is the set of possible states. Every state q is a continuous multiset over T, that is, a function $q : T \to \mathbb{R}$, where for every $X \in T$, $q(X)$ represents the *mass* of X, i.e. the amount of substance of type X present in M in the state q with respect to a specified measure unit for X (grams, moles, concentrations, percentages, ...);
- R is a finite set of rules, i.e., pairs of discrete multisets over T (represented by strings);
- F is the set of *reaction maps*, such that $F = \{f_r | r \in R\}$, where $f_r : Q \to \mathbb{R}$. Although a map f_r associates with any state $q \in Q$ the *reactivity* $f_r(q)$, that is, the reaction strength which r has in that state q, very often this value depends only on the mass associated with some of the symbols of T. For this reason it is convenient to introduce a real variable $x = q(X)$ to any symbol $X \in T$, in such a way that a reaction map f_r is naturally represented to depend on variables $x, y, \ldots$;
- q_0, the initial state of M, is an element of Q.

The temporal evolution of an MP system M is calculated by means of a *metabolic difference operator* Δ_q, which provides for any state $q \in Q$ a function

$$\Delta_q : T \to \mathbb{R}$$

such that, for every $X \in T$, the state following q in the temporal evolution of M is given by $q(X) + \Delta_q(X)$, where a time measure unit is also assumed which defines the temporal interval between two successive states of M.

In order to define our MPA algorithm, which formalizes the intuition given at the beginning of Section 2, we introduce the following notation, that will be adopted in the rest of the paper and will be always related to a metabolic system $M = (T, Q, R, F, q_0)$ [22]:

Notation 2 (*MP Notation*).

- *Each $r \in R$ is denoted by $\alpha_r \to \beta_r$; α_r identifies the multiset of the substrates of the reaction r, and β_r identifies the multiset of the products of the reaction r;*
- *$h_r(X)$ is the number of occurrences of X in α_r;*
- *$g_r(X)$ is the number of occurrences of X in β_r;*
- $R_\alpha(X) = \{r \in R \mid X \in \alpha_r\}$;
- $R_\beta(X) = \{r \in R \mid X \in \beta_r\}$;
- $R(X) = R_\alpha(X) \cup R_\beta(X)$;
- $R_\lambda(X) = \{r \in R(X) \mid \alpha_r = \lambda\}$;
- $R_+(X) = R(X) - R_\lambda(X)$;
- $\Pi(\alpha_r) = \prod_{X \in \alpha_r} q(X)^{h_r(X)}$.

Definition 3 (*MPA*). For every $X \in T$ the value of the metabolic difference operator Δ_q of an MP system, in a state $q \in Q$ and on a symbol $X \in T$, is given by:

$$\Delta_q(X) = \sum_{r \in R_+(X)} (g_r(X) - h_r(X)) \cdot u_r(q) + \sum_{r \in R_\lambda(X)} f_r(q) \cdot g_r(X)$$

where

$$u_r(q) = \min\left\{ w_{Y,q}(r)\frac{q(Y)}{h_r(Y)} \mid Y \in \alpha_r \right\}$$

and, for every $Y \in T$

$$K_{Y,q} = \sum_{r \in R_\alpha(Y)} f_r(q) \quad \text{and} \quad w_{Y,q}(r) = \frac{f_r(q)}{K_{Y,q}},$$

where it is assumed that $K_{Y,q} \neq 0$.

Various graphic formalizations of coupled chemical reactions and biochemical processes exist in the literature [30,35,31]. The MP graphs introduced in [23,21,22] are directly related to MP systems, and combine a precise quantitative reading of a metabolic process with the possibility to express typical notions of biological networks. As we will show, the three components (T, R, F) of an MP system uniquely define an MP graph.

We give, here, a compact definition of MP graph, and refer the reader to the cited references for a more comprehensive treatment.

Definition 4 (*MP Graph*). An MP graph is made of

- source nodes denoted as white-filled triangles, representing input *gates*, with an incident non-oriented arc;
- element nodes denoted as unfilled circles and labeled by element names, representing substrates or products of reactions;
- reaction nodes denoted as black-filled circles and labeled by reaction names;
- regulation nodes denoted as black-filled squares and labeled by reaction maps;
- sink nodes denoted as unfilled triangles, representing output gates, with an incident oriented arc;
- branches connecting source, element, reaction, regulation, and sink nodes, according to the schematics given in Fig. 2 where we distinguish connections in solid and dashed lines with or without orientation. For a rule r (black circle), type (a) translates $\alpha_r = \lambda$; type (b) translates $\alpha_r \to \beta_r$ (on the left nodes in α_r, on the right nodes in β_r); type (c) translates a reaction map regulating r (on the right) and depending on the nodes on the left; type (d) translates $\beta_r = \lambda$.

The MP graph of Fig. 3 [22] describes a model proposed by Goldbeter [14] for a minimal structure of the mitotic oscillator in early amphibian embryos. The two main entities of this model are cyclin (C) and cdc2 kinase. The signaling protein cyclin is produced at a constant rate and it triggers the activation (by means of a dephosphorylation) of cdc2 kinase that switches from the inactive form labeled M^+ to the active one, M. This modification is reversible and the other way round is performed by the action of another kinase (not considered in this model) that brings back M in its inactive form M^+. Moreover, active cdc2 kinase (M) elicits the activation of a protease X^+, that when in the active (phosphorylated) form X is able to degrade the cyclin. This activation, as the previous one, is reversible as stated by the arrow connecting X to X^+ ($k_1, k_2, \ldots, k_{13}$ are constants). In the structure of the MP graph two components are clearly distinguishable: (i) a *reaction part* which is the first level metabolic layout, constituted by the elements and the reactions among them, and (ii) a *regulation part* which is a second level metabolic layout, constituted by the reaction maps which regulate the first level layout. The first level is usually dictated by well known biomolecular features, while the right definition of the second level is the real modeling problem, and must be based on the correct tuning of the mutual influences among elements and reactions.

2.1. MP systems and MP graphs

An MP graph can be seen as a graphical representation of the symbols, the rules, and the reaction maps of an MP system. In other words, in an MP system we can distinguish a *form* and a *realization*. The former component is given by the triple (T, R, F), the latter component lies in the remaining part (Q, q_0). The triple (T, R, F) is exactly what is graphically expressed by an MP graph.

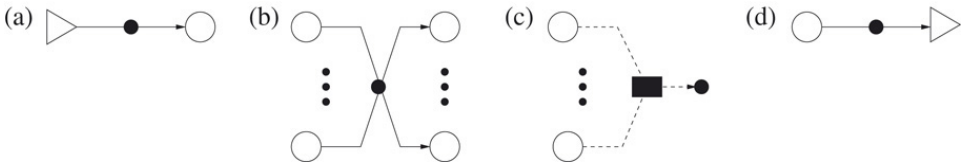

Fig. 2. MP graph basic blocks.

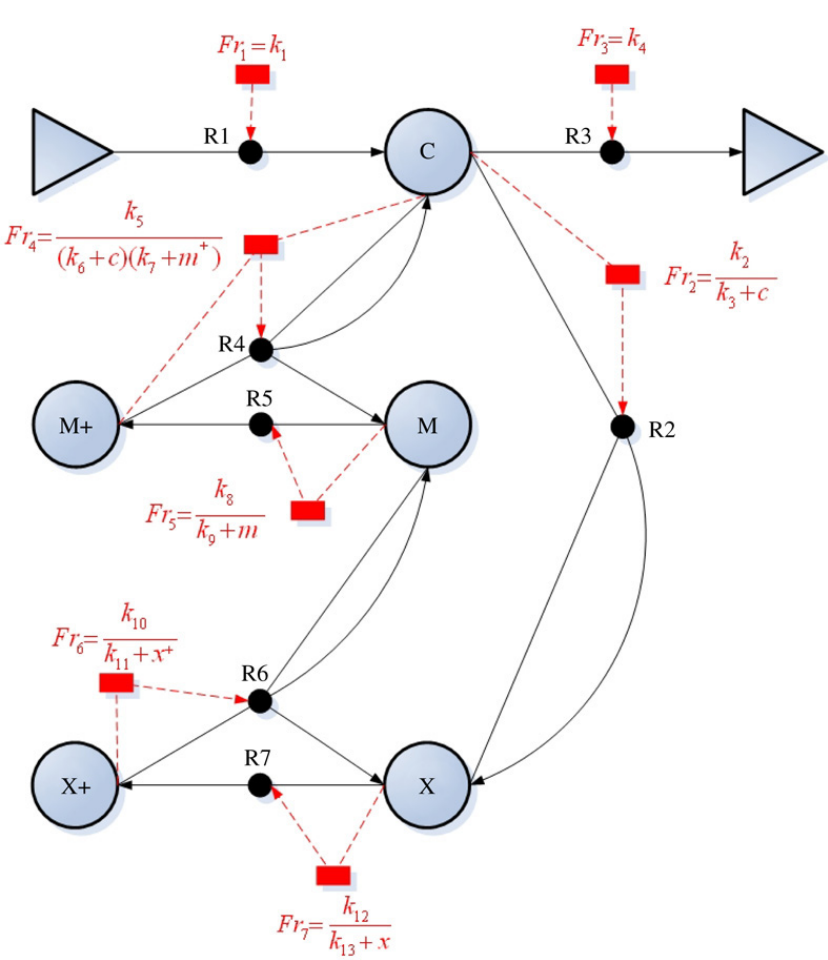

Fig. 3. Goldbeter's mitotic oscillator represented with an MP graph.

For example, from the MP graph of Fig. 3 we easily derive the following symbols, rules and reaction maps (lower case letters c, x, x^+, m, m^+ are the real variables $q(C), q(X), q(X^+), q(M), q(M^+)$ expressing the amount of the corresponding substances in the state q):

$$
\begin{aligned}
R_1 &: \lambda \rightarrow C, & F_{r_1}(q) &= k_1 \\
R_2 &: XC \rightarrow X, & F_{r_2}(q) &= \tfrac{k_2}{k_3+c} \\
R_3 &: C \rightarrow \lambda, & F_{r_3}(q) &= k_4 \\
R_4 &: M^+C \rightarrow MC, & F_{r_4}(q) &= \tfrac{k_5}{(k_6+c)(k_7+m^+)} \\
R_5 &: M \rightarrow M^+, & F_{r_5}(q) &= \tfrac{k_8}{k_9+m} \\
R_6 &: X^+M \rightarrow XM, & F_{r_6}(q) &= \tfrac{k_{10}}{k_{11}+x^+} \\
R_7 &: X \rightarrow X^+, & F_{r_7}(q) &= \tfrac{k_{12}}{k_{13}+x}.
\end{aligned}
\tag{2}
$$

2.2. From MP graphs to ODE systems

MP graphs translate naturally into ODE systems according to the mass action principle: the amount of a product generated by a reaction is proportional to the product of substrate quantities (considered with their multiplicity). This idea is formalized by the following definition where the MP notation 2 is assumed.

Definition 5 (*MP-ODE Transformation*). Let $G = (T, R, F)$ be an MP graph. For every $X \in T$, let $x = q(X)$. The following is the ODE-transform of G:

$$x' = \sum_{r \in R_\beta(X)} g_r(X) f_r(q) \Pi(\alpha_r) - \sum_{r \in R_\alpha(X)} h_r(X) f_r(q) \Pi(\alpha_r). \tag{3}$$

Note that $h_r(X)$ and $g_r(X)$ are equal to zero when X does not appear in the left and right part of r, respectively. Hence, (3) can be rewritten in the following more compact form:

$$x' = \sum_{r \in R(X)} \{g_r(X) - h_r(X)\} f_r(q) \Pi(\alpha_r). \tag{4}$$

Furthermore note that a symbol X appearing both at the left and the right part of the rule r, with $h_r(X) = g_r(X)$, translates into a null component of the summation in (4).

The following is the original ODE system given by Goldbeter [14] for modeling the mitotic process depicted in Fig. 3:

$$\begin{aligned} c' &= v_i - v_d x \frac{c}{K_d + c} - K_d c \\ m' &= V_1 \frac{(1-m)}{K_1 + (1-m)} - V_2 \frac{m}{K_2 + m} \\ x' &= V_3 \frac{(1-x)}{K_3 + (1-x)} - V_4 \frac{x}{K_4 + x}. \end{aligned} \tag{5}$$

All the details about the elements involved in this set of differential equations can be found in Goldbeter's paper [14], but we recall their meaning here for ease of reading. Symbol c denotes concentration of cyclin, m and x the fraction of active kinase and protease, while $(1 - m)$ and $(1 - x)$ represent respectively the fraction of inactive cdc2 kinase and of inactive cyclin protease (M^+, X^+). Parameters v_i and v_d are the constant rate of cyclin synthesis and the maximum rate of its degradation, K_d and K_c are the Michaelis constants for cyclin degradation and for the activation of the phosphatase acting on M, while k_d is the first-order rate constant of degradation of cyclin. Moreover, V_i and K_i, $1 \leq i \leq 4$, represent the normalized parameters characterizing the kinetics of the four enzymes involved in the reactions dealing with cdc2 kinase and cyclin phosphatase. More precisely, for each of the four enzymes (not explicitly represented as entities of the model) V_i and K_i are the effective maximum rate and Michaelis constant divided by the total amount of relevant protein target. In particular it is $V_1 = \frac{c}{K_c + c} V_{M1}$, where V_{M1} denotes the maximum rate of the enzyme associated with the dephosphorylation of M^+.

From the biochemical knowledge of this phenomenon, i.e. the process modeled by (5), we are able to draw the reaction part of the MP graph given in Fig. 3 which is completely equivalent to the following rules:

$$\begin{aligned} R_1 &: \lambda \rightarrow C \\ R_2 &: XC \rightarrow X \\ R_3 &: C \rightarrow \lambda \\ R_4 &: M^+C \rightarrow MC \\ R_5 &: M \rightarrow M^+ \\ R_6 &: X^+M \rightarrow XM \\ R_7 &: X \rightarrow X^+. \end{aligned} \tag{6}$$

Now, an interesting question arises. We know the biochemical reactions of our phenomenon plus an ODE system describing it. Is it possible to recover a set of reaction maps for the rules (6) directly from the ODE system (5)? An answer is given by the following proposition. In fact, its proof shows a way to obtain the regulation part of an MP graph from an ODE system. This procedure has a general nature, and it is interesting because, as we will prove in the next section, in some cases the MP graph associated with an ODE system provides, via the metabolic algorithm, an approximation to the differential solution of the ODE system.

Proposition 6. *If the Eq.* (3) *of Definition* 5 *is applied to the MP graph in Fig.* 3*, then the ODE system* (5) *is obtained.*

Proof. Let us denote by q a generic state and by $f_1, f_2, \ldots, f_7$ the unknown reaction maps of rules (6). By using Eq. (4) of the MP-ODE transformation we obtain:

$$\begin{aligned} c' &= f_1(q) - f_2(q)xc - f_3(q)c \\ m' &= f_4(q)(1-m)c - f_5(q)m \\ x' &= f_6(q)m(1-x) - f_7(q)x. \end{aligned} \tag{7}$$

Now, for a more uniform notation we set the following equations: $k_1 = v_i, k_2 = v_d, k_3 = k_d, k_4 = K_d$, $k_5 = V_{M1}, k_6 = K_c, k_7 = K_1, k_8 = V_2, k_9 = K_2, k_{10} = V_3, k_{11} = K_3, k_{12} = V_4$ and $k_{13} = K_4$. Therefore, recalling also that $V_1 = \frac{c}{K_c+c} V_{M1}$, then Goldbeter's differential model (5) becomes:

$$\begin{aligned} c' &= k_1 - k_2 \tfrac{xc}{k_3+c} - k_4 c \\ m' &= \tfrac{k_5 c(1-m)}{(k_6+c)(k_7+1-m)} - \tfrac{k_8 m}{k_9+m} \\ x' &= \tfrac{k_{10}(1-x)}{k_1 1+(1-x)} - \tfrac{k_{12} x}{k_1 3+x}. \end{aligned} \tag{8}$$

By comparing the two systems (7) and (8) we obtain:

$$\begin{aligned} f_1(q) &= k_1 \\ f_2(q)xc &= k_2 \tfrac{xc}{k_3+c} \\ f_3(q)c &= k_4 c \\ f_4(q)c(1-m) &= \tfrac{k_5 c(1-m)}{(k_6+c)(k_7+1-m)} \\ f_5(q)m &= \tfrac{k_8 m}{k_9+m} \\ f_6(q)(1-x) &= \tfrac{k_{10}(1-x)}{k_1 1+(1-x)} \\ f_7(q)x &= \tfrac{k_{12} x}{k_{13}+x}. \end{aligned} \tag{9}$$

The solutions of these equations are exactly the reaction maps $F_{r_1}, \ldots, F_{r_7}$ which are in the MP graph given in Eqs. (2) and Fig. 3 (state q, as the argument of reaction maps, may be omitted for the sake of simplification). □

The procedure of the proof of the previous proposition can be defined in general terms, in such a way that: given a set of reaction rules and an ODE system describing their differential dynamics, then we can derive an MP graph having exactly, as ODE-transformation, the initially given ODE system. In all the cases we modeled by means of MP systems, we considered the differential models given in the literature and applied to them this procedure for setting the value of numerical parameters occurring in the reaction maps of our MP graphs.

It is clear, from Definition 5, that by applying Eq. (4) to different MP graphs we can obtain the same ODE system, therefore we make the following definition.

Definition 7. Two MP graphs, and therefore also two MP systems which have these graphs, are ODE equivalent if according to Eq. (4) they provide the same ODE system (apart from variable renamings).

In the following section we will prove that there exists a class of MP systems whose temporal evolutions asymptotically converge, according to a suitable limit process, to the solutions of the ODE systems assigned to them by Eq. (4).

3. Non-cooperative MP systems

In this section we consider a class of MP systems for which, by using the machinery of the previous sections, we show that the metabolic and the differential perspectives meet each other, or in other words, "mass partition" and "time partition" results to be strictly related one to the other.

Definition 8 (*Non-cooperative MP System*). A non-cooperative MP system is an MP system whose rules are non-cooperative, i.e., $\alpha_r \in T$ for every r.

It is immediate to see that a non-cooperative MP system is associated with an MP graph in which no more than one branch enters any reaction node.

Definition 9 (*Uniformly Transparent MP System*). For some $\phi \in \mathbb{R}$, an MP system is ϕ-uniformly transparent if, for every $X \in T$, the transparent rule $X \to X$ has a constant reaction map having value ϕ in any possible state.

Definition 10 (*Input Closed MP System*). An MP system is input closed if no rules $r \in R$ exist in the system such that $\alpha_r = \lambda$.

Theorem 11. *The computation of a non-cooperative, input closed ϕ-uniformly transparent MP system converges, as $\phi \to \infty$, to the solution, when it is unique, of the ODE system provided by the MP-ODE transformation.*

Proof. Let us compute the weight $w_{Y,q}(r)$, $r \in R$, $Y \in T$, as prescribed by the MP algorithm (Definition 3). By uniform transparency $K_{Y,q}(r)$ necessarily contains an additional term that is equal to ϕ. Moreover, by non-cooperation, $\alpha_r \in T$, hence reaction weights depend on only one symbol. For this reason we denote $w_{Y,q}(r)$ simply as $w_q(r)$:

$$w_q(r) = \frac{f_r(q)}{\phi + \sum_{\rho \in R_\alpha(\alpha_r)} f_\rho(q)} = \frac{f_r(q)}{\phi + \psi_r(q)}, \quad r \in R \tag{10}$$

in which we have introduced the term $\psi_r(q)$ in place of the summation for notation compactness. In this way, for every $X \in T$ the variation of $q(X)$ at every system transition according to the MP algorithm is equal to

$$\Delta_q(X) = \sum_{r \in R(X)} (g_r(X) - h_r(X)) w_q(r) q(\alpha_r), \tag{11}$$

in fact the property of input closure implies that the rightmost summation in Definition 3 is null, furthermore for a non-cooperative MP system it is

$$\min\left\{ w_{Y,q}(r) \frac{q(Y)}{h_r(Y)} \mid Y \in \alpha_r \right\} = w_q(r) q(\alpha_r). \tag{12}$$

By noticing that for every $r \in R$

$$w_q(r) = \frac{f_r(q)}{\phi + \psi_r(q)} = \frac{1}{\phi} \frac{f_r(q)}{1 + \psi_r(q)/\phi} \tag{13}$$

then from (11) we can immediately compute the limit

$$\begin{aligned} \lim_{\phi \to \infty} \phi \Delta_q(X) &= \lim_{\phi \to \infty} \sum_{r \in R(X)} (g_r(X) - h_r(X)) \frac{f_r(q)}{1 + \psi_r(q)/\phi} q(\alpha_r) \\ &= \sum_{r \in R(X)} (g_r(X) - h_r(X)) f_r(q) q(\alpha_r). \end{aligned} \tag{14}$$

Now, suppose that *our MP system performs a transition every t seconds* and consider it at a given instant t_0. By substituting $q(X)$ with the corresponding real variable x we can write the variation of $q(X)$ between two subsequent transitions as

$$\Delta_q(X) = x(t_0 + t) - x(t_0). \tag{15}$$

Suppose also that *the finer the granularity of the observation, the shorter the transition time*. This relation between time and granularity implies that the portion of objects allocated to a reaction becomes smaller as much as the time between subsequent transitions becomes shorter.

Granularity can be managed in the MP system by tuning the value of ϕ. In particular, we can put the limit to an infinitely fine granularity in relation with the limit to an infinitely short transition time by means of the following equation:

$$\lim_{t\to 0} \frac{x(t_0+t)-x(t_0)}{t} = \lim_{\phi\to\infty} \frac{x(t_0+1/\phi)-x(t_0)}{1/\phi}. \tag{16}$$

By (15), then (16) is equal to

$$\lim_{t\to 0} \frac{\Delta_q(X)}{t} = \lim_{\phi\to\infty} \frac{\Delta_q(X)}{1/\phi} = \lim_{\phi\to\infty} \phi\Delta_q(X). \tag{17}$$

Furthermore, (16) is also equal to

$$\lim_{t\to 0} \frac{x(t_0+t)-x(t_0)}{t} = x'(t_0). \tag{18}$$

Hence, the right member of (18) equals the right member of (14) and this completes the proof, in fact this equivalence matches Eq. (4) in the case of non-cooperative MP systems. □

Theorem 12. *Given an MP system* $M = (T, Q, R, F, q_0)$ *there exists a non-cooperative MP system* $M^* = (T, Q, R^*, F^*, q_0)$ *which is ODE equivalent to* M.

Proof. Every non-cooperative rule $r \in R$ is copied in R^*. Every cooperative rule $r \in R$ is replaced by choosing $Y \in \alpha_r$, then putting in R^* the rules r^*, s^*, and p_X for every $X \in \alpha_r$ such that $X \neq Y$. The reaction maps to be put in F^* are indicated on the right side of the formulas below.

- Step 1:

$$r^* : Y \to \beta_r, \quad f_{r^*} = f_r \frac{\Pi(\alpha_r)}{q(Y)}; \tag{19}$$

if other occurrences of Y exist, define

$$s^* : Y \to \lambda, \quad f_{s^*} = \{h_r(Y)-1\} f_r \frac{\Pi(\alpha_r)}{q(Y)}. \tag{20}$$

- Step 2:

$$p_X : X \to \lambda, \quad f_{p_X} = h_r(X) f_r \frac{\Pi(\alpha_r)}{q(X)}. \tag{21}$$

To show the ODE equivalence between M and M', let us gather the positive and negative components in x' in order to form an additive part x'_+ and a subtractive part x'_-, respectively: $x' = x'_+ + x'_-$. The MP-ODE transformation of M' is, by Definition 5 applied to non-cooperative MP systems:

$$x'_+ + x'_- = \sum_{\rho\in R^*_\beta(X)} g_\rho(X) f_\rho(q) q(\alpha_\rho) - \sum_{\rho\in R^*_\alpha(X)} f_\rho(q) q(X). \tag{22}$$

Consider any term of the additive part x'_+ in (22), associated with $\rho \in R^*_\beta(X)$, and compare it with the terms of summation

$$\sum_{r\in R_\beta(X)} g_r(X) f_r(q) \Pi(\alpha_r).$$

For every $\rho \in R^*_\beta(X)$ there are two possibilities: (i) ρ is a non-cooperative rule of $R_\beta(X)$; or (ii) there exists a unique $r \in R_\beta(X)$ such that $\rho = r^*$. In case (i) the terms of the two summations are clearly the same; in case (ii) we have, by (19),

$$f_{r^*}(q)q(\alpha_{r^*}) = f_r(q)\frac{\Pi(\alpha_r)}{q(X)}q(X) = f_r(q)\Pi(\alpha_r), \tag{23}$$

therefore the terms of two summations again are the same, as $g_\rho(X) = g_r(X)$. In conclusion:

$$x'_+ = \sum_{\rho \in R^*_\beta(X)} g_\rho(X) f_\rho(q) q(\alpha_\rho) = \sum_{r \in R_\beta(X)} g_r(X) f_r(q) \Pi(\alpha_r). \tag{24}$$

Now, consider the terms of the subtractive part x'_- in (22), associated with $\rho \in R^*_\alpha(X)$, and compare each one of them with the terms of summation

$$\sum_{r \in R_\alpha(X)} h_r(X) f_r(q) \Pi(\alpha_r).$$

By construction of R^*, every cooperative rule $r \in R_\alpha(X)$ translates either into two rules $r^*, s^* \in R^*_\alpha(X)$ or into one rule $p_X \in R^*_\alpha(X)$. In the former case, by (19) and (20), r^* and s^* provide the following component in x'_-:

$$f_{r^*}(q)q(X) + f_{s^*}(q)q(X) = \{1 + h_r(X) - 1\} f_r(q)\frac{\Pi(\alpha_r)}{q(X)}q(X) = h_r(X) f_r(q)\Pi(\alpha_r). \tag{25}$$

In the latter case p_X results, by (21), in a component in x'_- equal to

$$f_{p_X}(q)q(X) = h_r(X) f_r(q)\frac{\Pi(\alpha_r)}{q(X)}q(X) = h_r(X) f_r(q)\Pi(\alpha_r). \tag{26}$$

This implies that the subtractive part in (22) is equal to (including the contribution of the non-cooperative rules of R, directly copied into R^*)

$$x'_- = \sum_{\rho \in R^*_\alpha(X)} f_\rho(q)q(X) = \sum_{r \in R_\alpha(X)} h_r(X) f_r(q)\Pi(\alpha_r). \tag{27}$$

By summing, member by member, (24) and (27) and comparing to (3) we obtain the ODE equivalence between M and M^*. □

The non-cooperative MP system obtained using Theorem 12 is not uniquely determined. If, on the one hand, by Theorem 11 we know that *all* possible non-cooperative MP systems obtained using Theorem 12 provide solutions that converge, in the sense of Theorem 11, to the same ODE system, on the other hand the speed of this convergence (w.r.t. the values of ϕ) depends on the specific non-cooperative MP system.

In a speculative perspective, Theorems 12 and 11 tell us that an ODE system models not exactly *one* metabolic network but, rather, *all* possible variants of the same network in which every reaction transforms one metabolite into a product, should this transformation be physical or not. The product will be in general made of one or more metabolites, as well as enzymes and effectors [8], their amount depending on the regulatory mechanism provided by the reaction map. We will provide (at least partial) evidence of this speculation in the following examples.

4. Examples

In this section we report a couple of examples, showing the potential of the MP algorithm in describing families of biochemical and also non-biochemical dynamic phenomena. The first example illustrates two different evolutions that a traditional nonlinear dynamics, such as the Lotka–Volterra system, can have according to the set of non-cooperative rules we derive for its description. The latter example is a transposition in terms of MP systems of the well-known Lorenz model.

4.1. Lotka–Volterra model

Due to their well known properties and dynamic behavior, as well as for their (not only historical) importance in the field of biochemistry [1,16], the Lotka–Volterra equations have been frequently used as a test case in the evaluation of algorithms for the simulation of biochemical reactions [13,5].

The traditional formulation of the Lotka–Volterra reaction model [13] involves the auto-catalysis with constant rate c_1 of a reactant X on the (supposed constantly available) substance A, along with the auto-catalysis with constant rate k_2 of a second reactant Y depending on the available concentration of X. Finally, the degradation of Y is accounted for by a third reaction having a constant rate k_3:

$$\begin{aligned} AX &\xrightarrow{c_1} XX \\ XY &\xrightarrow{k_2} YY \\ Y &\xrightarrow{k_3} B. \end{aligned} \tag{28}$$

Here we propose two non-cooperative MP systems modeling the set (28) of coupled reactions depending on the interpretation, of either promoters or reactants, we give to the elements A and X taking part in the first auto-catalytic reaction. It will be straightforward to see that both of them are associated, by MP-ODE transformation, with an ODE system that expresses the traditional differential formulation of the Lotka–Volterra dynamics [13]:

$$x' = c_1 ax - k_2 xy \tag{29a}$$

$$y' = k_2 xy - k_3 y. \tag{29b}$$

Hence, by Theorem 11 their computation will converge to the solution of (29).

As a first choice (see also the upper MP graph of Fig. 4), we assign a promoting role to X in the transformation rule r while maintaining A constant throughout the computation. In the meantime, we assign a regulation role to Y in the rule s as well as accounting for linear degradation of the same element by means of t. In addition to this we include transparent rules for all species:

$$\begin{array}{lll} r: & A \to AX, & f_r = c_1 x \\ s: & X \to Y, & f_s = k_2 y \\ t: & Y \to, & f_t = k_3 \\ \rho_A: & A \to A, & \phi_r = \phi \\ \rho_X: & X \to X, & \phi_s = \phi \\ \rho_Y: & Y \to Y, & \phi_t = \phi. \end{array} \tag{30}$$

Conversely we may think of letting A promote the first reaction in (28) [10]. This can be done by changing the rule r in the MP system, hence coming up with the following alternative rule set (see also the lower MP graph of Fig. 4):

$$\begin{array}{lll} r: & X \to XX, & f_r = c_1 a \\ s: & X \to Y, & f_s = k_2 y \\ t: & Y \to, & f_t = k_3 \\ \rho_X: & X \to X, & \phi_s = \phi \\ \rho_Y: & Y \to Y, & \phi_t = \phi. \end{array} \tag{31}$$

Note that this time A is no longer transformed and, hence, the corresponding transparent rule (formerly ρ_A) can be avoided. Furthermore this choice implies the constancy of f_r.

As specified by (14), the behavior of both MP systems (30) and (31) converges, for increasing values of ϕ, to the solution of (29a) and (29b). However, according to the values plotted in Fig. 5, we observe two different dynamics for X, depicted in a light line and dark line respectively. The first MP system (30, light line) reaches a fixed point via damped oscillations. Conversely, in the second MP system (31, dark line), the amount of X oscillates forever. In the latter case, the evolution obtained using the last rule set is almost identical to the solution obtained by applying a Runge–Kutta integration method to (29) [10]. This means that even if two non-cooperative ϕ-uniformly transparent MP systems are ODE-equivalent, their computations can evolve differently, exactly as happens when applying to the same ODE system numerical integration methods having different degrees of accuracy. In Fig. 6 the evolution of X in three different systems is given having the same initial conditions of 5, but different values of transparency. However,

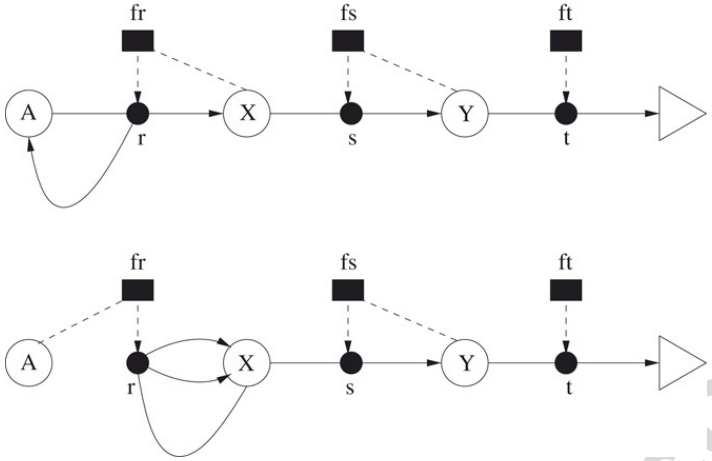

Fig. 4. MP graphs of the Lotka–Volterra Model. Above: from rule set (30); below: from rule set (31).

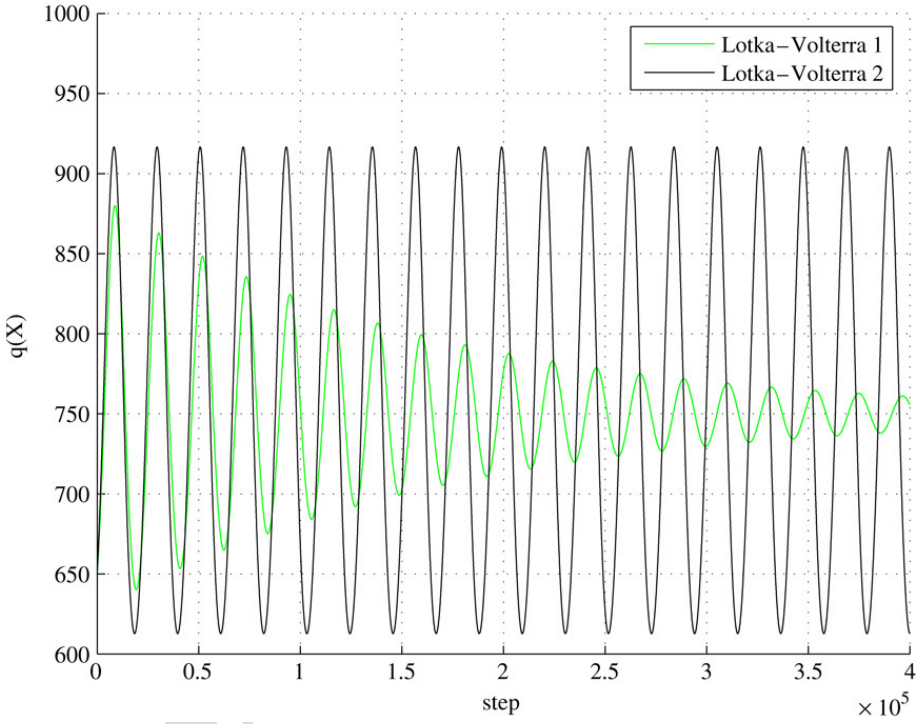

Fig. 5. Evolution of X in the MP system with $q_0(A) = 100$, $c_1 = 3 \times 10^{-4}$, $k_2 = 4 \times 10^{-5}$, $k_3 = 3 \times 10^{-2}$, $\phi = 5$, and $q_0(X) = q_0(Y) = 650$. Light line: rule set given by (30). Dark line: rule set given by (31).

we observe that when the transparency of the first MP system increases, from the value 5 to the value 100, then the two systems behave in a more similar way, in accordance with the Theorems 11 and 12.

4.2. Lorenz model

Another ODE system, which has become quite famous due to the richness of its dynamics, was proposed by Lorenz [15]. Although defined by simple nonlinear equations, within specific parameter ranges, it exhibits a chaotic behavior and its *strange attractor* was the first case where the possibility of deterministic chaos was recognized.

In its traditional formulation the Lorenz model is defined by the following equations [15]:

$$x' = py - px \tag{32a}$$

$$y' = rx - xz - y \tag{32b}$$

$$z' = xy - bz. \tag{32c}$$

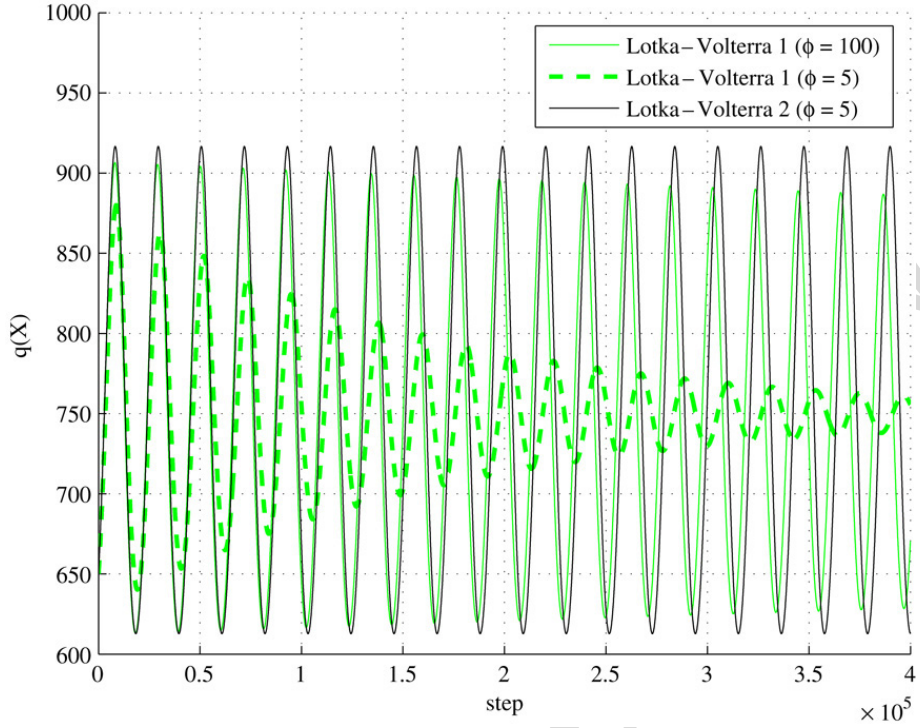

Fig. 6. Evolution of X in the two MP systems for Lotka–Volterra dynamics with different values of transparency.

A quick look at these equations tells us that the Lorenz model has little in common with a metabolic system since it does not account for any mass transfer, as opposed to the Lotka–Volterra model in which X is transformed into Y. Despite this, investigating the way we can represent the equation set (32) by means of an MP system sheds light on the potential of such constructs to simulate complex dynamics even when these dynamics are not tailored for MP system-based simulation.

Another drawback with the use of MP systems for non-metabolic networks is given by the fact that they cannot deal with negative state values. In particular, the Lorenz model shows the most interesting dynamics when its variables $x(t)$ and $y(t)$ become also negative along time.

We can account for trajectories assuming finite negative values of the x and/or y component by shifting such variables of two offsets x_0 and y_0, respectively:

$$\tilde{x} = x + x_0, \qquad \tilde{y} = y + y_0. \tag{33}$$

In this way we obtain a modified version, in the new variables $(\tilde{x}, \tilde{y}, z)$, of the ODE system (32). Since $\tilde{x}' = x'$ and $\tilde{y}' = y'$ then the modified system is:

$$\tilde{x}' = p\tilde{y} + px_0 - p\tilde{x} - py_0 \tag{34a}$$
$$\tilde{y}' = r\tilde{x} - \tilde{x}z - \tilde{y} + x_0 z - rx_0 + y_0 \tag{34b}$$
$$z' = \tilde{x}\tilde{y} - bz - y_o\tilde{x} - x_o\tilde{y} + x_0 y_0. \tag{34c}$$

Since there is no mass transfer, the rule set must be associated with an MP graph whose element nodes are connected to each other via only regulation nodes. For this reason the transformation rules will account only for substance creation or degradation.

Creation can be realized in a non-cooperative, closed-input MP system by means of rules of the type $r : A \to AX$, which, as we have already seen in the previous example, guarantee the ingress of metabolite X into the system through the regulated transformation of a constant amount of "source metabolite" A. In this way the resulting MP system respects the hypotheses of Theorem 11.

Since the element nodes of the MP graph of the Lorenz model are joined together only via regulation nodes, we have to provide one source metabolite for every variable acting within the system. Hence, we need three source

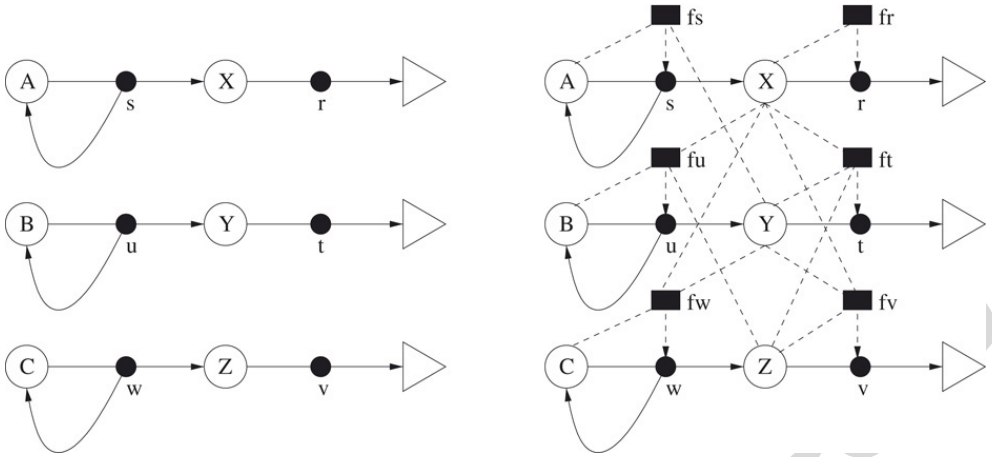

Fig. 7. MP graphs of the Lorenz model. Left: only metabolic reactions; right: metabolic reactions plus map regulations.

metabolites, say A, B, and C, respectively associated with X, Y, and Z. We, then, decide for the following rules and associated MP graph (see Fig. 7, left) over the alphabet $\mathcal{A} = \{X, Y, Z, A, B, C\}$:

$$\begin{array}{ll} r : X \to, & f_r \\ s : A \to AX, & f_s \\ t : Y \to, & f_t \\ u : B \to BY, & f_u \\ v : Z \to, & f_v \\ w : C \to CZ, & f_w. \end{array} \tag{35}$$

Moreover we add six uniform transparent rules, one for each symbol in the alphabet:

$$\rho_S : S \to S, \qquad \phi_S = \phi \quad \text{with } S \in \mathcal{A}. \tag{36}$$

By Proposition 6 we can write the following equations, which put the unknown reaction maps f_S, $S \in \mathcal{A}$, in relationship with the ODE system (34):

$$\begin{aligned} \tilde{x}' &= f_s a - f_r \tilde{x} \\ \tilde{y}' &= f_u b - f_t \tilde{y} \\ z' &= f_w c - f_v z. \end{aligned} \tag{37}$$

Hence, immediately from (34) and (37),

$$\begin{aligned} f_r &= p\frac{\tilde{x} + y_0}{\tilde{x}} \\ f_s &= p\frac{\tilde{y} + x_0}{a} \\ f_t &= \frac{\tilde{x}z + \tilde{y} + rx_0}{\tilde{y}} \\ f_u &= \frac{r\tilde{x} + x_0 z + y_0}{b} \\ f_v &= \frac{y_0\tilde{x} + x_0\tilde{y} + bz}{z} \\ f_w &= \frac{\tilde{x}\tilde{y} + x_0 y_0}{c}. \end{aligned} \tag{38}$$

For low values of the parameter r the Lorenz model exhibits convergence to a stable fixed point. By choosing [15] $r = 0.5$, $p = 10$, and $b = 8/3$, the MP system computes this kind of evolution with very good accuracy once we set, in the unshifted system (i.e., $x_0 = y_0 = 0$), for instance $\phi = 3 \times 10^5$ along with nominal unit values for the source metabolite amounts, i.e., $q(A) = q(B) = q(C) = 1$. This choice leads to the plots of Fig. 8, obtained using $q_0(X) = 0$, $q_0(Y) = 1$, and $q_0(Z) = 0$ as initial conditions of the system. Note that in this case we have avoided shifting x and y since the evolution proceeds along positive or null state values.

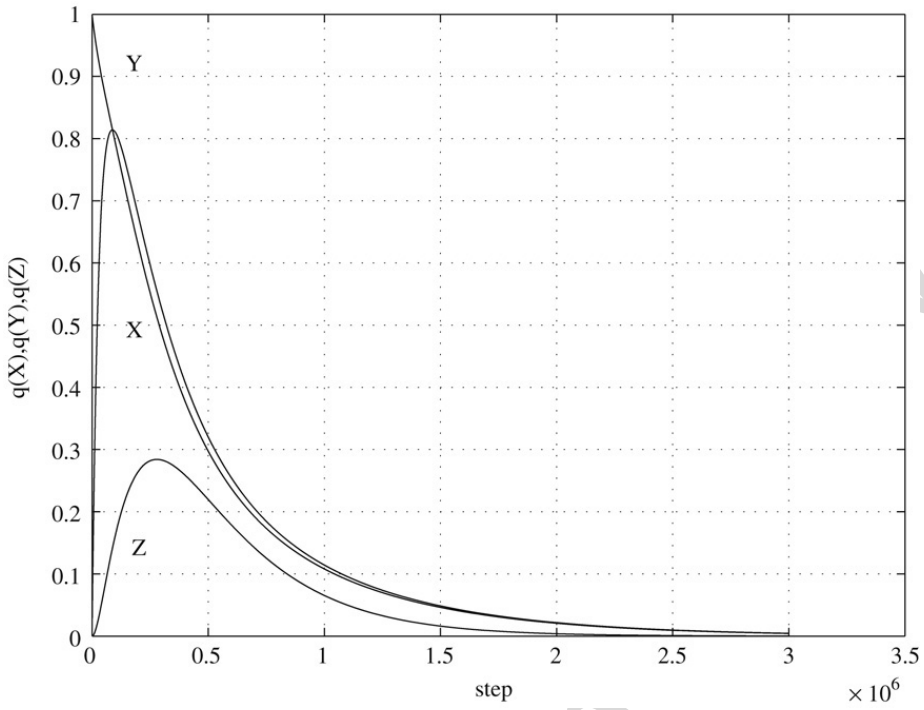

Fig. 8. Unshifted Lorenz model with $r = 0.5$, $p = 10$ and $b = 8/3$. Plots of X, Y, Z as functions of the number of steps, with $\phi = 3 \times 10^5$, $q(A) = q(B) = q(C) = 1$, and initial conditions $q_0(X) = 0$, $q_0(Y) = 1$, $q_0(Z) = 0$.

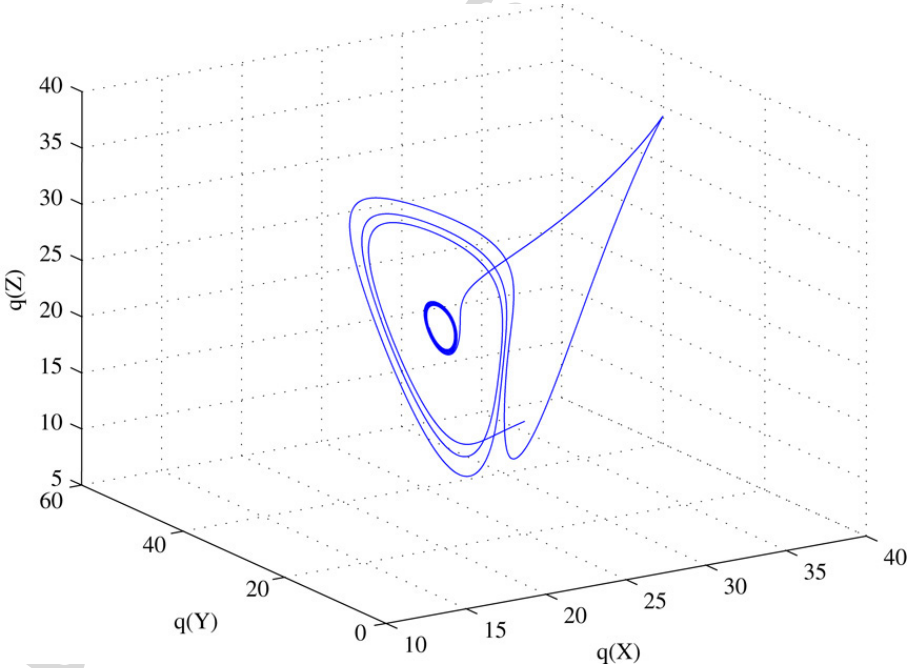

Fig. 9. Shifted ($x_0 = y_0 = 25$) Lorenz model with $r = 25$, $p = 10$ and $b = 8/3$. 3D phase plot of X, Y, Z computed along 3×10^6 transitions of the MP system, with $\phi = 3 \times 10^5$, $q(A) = q(B) = q(C) = 1$ and initial conditions $q_0(X) = 0$, $q_0(Y) = -5$, and $q_0(Z) = 15$.

The behavior of the system becomes more interesting when r is increased. Therefore, we set, in the shifted model ($x_0 = y_0 = 25$), the initial conditions equal to $q_0(X) = 0$, $q_0(Y) = -5$, and $q_0(Z) = 15$, choosing $r = 25$ and leaving all other parameters untouched. Fig. 9 shows the 3D phase plot computed along 3×10^6 transitions of the MP system. In this case the solution provided by the MP system is not so accurate compared to that exhibited by other numerical schemes, but still captures the salient features of the system, showing the beginning of its famous chaotic shape.

5. Conclusions

A systematic approach has been devised which relates MP systems and MP graphs to ODE systems. If on the one hand MP graphs have been shown to completely describe an ODE system, on the other hand MP systems are the machines for computing these graphs and, ultimately, ODE systems.

As for any discrete scheme, such a computation cannot be but an approximation of the ODE system solution. We have shown that a specific class of MP systems (e.g., the non-cooperative ones) exists which, in the limit of an infinitely fine population partitioning, approximate this solution with infinite precision. Since infinitely fine partitioning of populations corresponds to infinitely dense temporal granularity of the computation, non-cooperative MP systems can be equivalently seen as a configurable family of numerical schemes for the solution of ODE systems. As is usual for these families it happens that a variety of non-cooperative MP systems, in the limit all infinitely accurate, can be chosen to solve a given ODE system. However, only some of them provide sufficient accuracy at computationally feasible granularity. In practice, the choice and parameterization of a good MP system solver are driven by the problem itself and often left to the skill of the experimenter, this situation being quite common when handling numerical schemes. We have given evidence of this fact in a simple system based on the Lotka–Volterra model.

Apart from the idiosyncrasies of the specific problem and its peculiar numerical solvers, overall MP systems are inherently well suited to compute models of biochemical processes, particularly metabolic networks, by their own definition. In this paper we have shown, in an application example to the Lorenz model, that MP systems exhibit some limits when they are used to compute evolutionary dynamics which are not elicited by mass transformation. Whether MP systems provide a novel, powerful tool for the computation of biochemical dynamics is a question which we have partially answered in our previous works, and which will keep us busy in the future.

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