

Metabolic P systems for biochemical dynamics

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Abstract Metabolic P systems are a special class of P systems which seem to be adequate for expressing biological phenomena, especially, metabolism and signaling transduction. Basic motivations for their introduction are given and their main aspects are explained by means of an example of biological modeling. A new kind of regulation mechanism is outlined, which could be the basis for a more efficient construction of computational models from experimental data of specific metabolic processes.

Keywords: biological dynamics, biochemical reactions, metabolic algorithm, P systems.

P systems were introduced as a new computation model, inspired by biology^[1–3], based on multisets and membranes. The biological roots of this formalism suggested its use for qualitative modeling of several biomolecular phenomena acting at the cellular level, such as trans-membrane transport and communication^[4,5], consumption of energy^[6,7] and even more specific biological processes^[8–12]. Metabolic P systems, shortly MP systems, were introduced for a better understanding of quantitative aspects of biological systems, meanwhile avoiding the use of complex systems of differential equations. Different from the classical P systems which typically based on nondeterministic evolution strategies, MP systems have a discrete deterministic evolution strategy that links their behavior to specific dynamical parameters.

Early attempts of symbolic descriptions of metabolic processes were initiated by the author, approximately, ten years ago^[13,14]. In these papers some primitive notions of membrane systems were considered, but the use of logical formulae driving metabolite concentrations made them too general for expressing biological situations in a significant way. The theory of P systems is crucial in two important steps toward a new symbolic model of a metabolic system. A first step is the dynamical perspective in the study of P systems, introduced in^[15,16], where the dynamical patterns of P systems were the main focus of investigation. A second step is the introduction of a molar perspective, borrowed from chemistry, with an abstract notion of “reaction strength” as a parameter able to regulate the cooperation/competition among the rules of P systems^[17]. In fact, in a very first approximation, a cell is a membrane sys-

tem, and its functioning is determined by all the types of molecules inside it, by the amount of molecules of these types, and by the cell compartments where they are located^[18]. Therefore, it is of great importance to define a method for computing the evolution of a P system that is directly meaningful with respect to biochemical reactions. In this perspective, a transformation $AA \rightarrow BC$ is better read in chemical terms^[19], as something which expresses the following prescription: “two moles of A produce one mole of B and a mole of C ”. Here a mole is a conventional population unit like a battalion, a company, a brigade, which is not conceived in an absolute way, as it happens in the classical chemical setting (1 mole $\approx 6.02 \times 10^{23}$ molecules), but it is relative to the specific system. If we fix the number of objects of a mole, then the dimension of a multiset is expressed, in terms of moles, by a rational number.

The Brusselator, which is a differential model of a chemical oscillator, inspired by the famous Belousov-Zhabotinsky reaction, was modeled in [20, 21] by means of multiset rewriting rules. This model suggested us the idea of defining a general algorithmic procedure on P systems which could provide results comparable with the classical differential models, but using different principles. Three main points emerged in this direction: (i) population multiset rewriting rules, instead of object rewriting rules, (ii) observation (discrete) time, instead of (continuous) reaction time, and (iii) a criterion for computing, at each step, the masses of reactants which the rules need for producing their products.

MP systems^[22–24] formalize these intuitions by

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considering P systems with a particular deterministic procedure for computing their evolution. This procedure, called MP Algorithm, shortly MPA, aims at capturing the salient chemical mechanisms that are responsible of the dynamics of a wide class of biomolecular processes. MP systems provided models of several biochemical processes: the Belousov-Zhabotinsky reaction (Brusselator)^[25,26], the Lotka-Volterra dynamics^[17,19,25,26], a susceptible-infected-recovered epidemic^[25], the leukocyte selective recruitment in the immune response^[8,25], the protein kinase C activation^[26], circadian rhythms^[27], and pseudomonas quorum sensing^[28]. Other phenomena under investigation concern mitotic cycles and Cdc25A degradation in tumor processes^[29], an oscillatory circuit that includes protein kinases ERK2 and PK^[30] and the intercellular communication which occurs in *Dictyostelium discoideum*^[31].

The reactivity of a rule, can be also considered as a measure of the propensity or probability of applying it, in the line of Gillespie's approach^[32]. This perspective was developed in [33] and [34], where some specific kinds of probabilistic approaches to biochemical kinetic were set in P systems frameworks.

1 Metabolic P systems

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, and (ii) the transition to the next state (after some specified interval of time) is calculated according to a mass partition strategy, that is, the available matter of each substance is partitioned among all reactions which need to consume it. The policy of matter partition is regulated at each instant by some real values, call them *reactivities*, which represent the strength of any reaction.

As it is customary in P systems, we will adopt the string notation for discrete multisets, that is, when a string denotes a multiset, the order of its symbols is not relevant. We write $X \in \alpha$ for saying that X is a symbol occurring in the string α (sometimes, the symbol $+$ is used for concatenation, in order to stress that in multisets concatenation is commutative; more details on P systems notations can be found in [2]).

The set Q of states over an alphabet T are the

continuous multisets over T . The passage from discrete to continuous states is motivated by the use of moles for determining the mass associated to each symbol of T .

The notion of MP system we consider here comes from [23] and should be better identified by that of *zero level* MP system, because only one membrane is considered.

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

$$M = (T, R, F, \nu, \mu, \tau, q_0)$$

in which T is a finite set of symbols; R is a finite set of rules, i. e., pairs of discrete multisets over T (represented, as usual, in the arrow notation); F is the set of reaction maps, such that $F = \{f_r \mid r \in R\}$, where $f_r: Q \rightarrow \mathbb{R}$. Very often the reactivity $f_r(q)$ in the state q depends only on the mass associated to some of the symbols of T . For this reason, it is convenient to introduce a real variable $x = q(X)$ to any symbol $X \in T$. We write $f_r(x, y, \dots)$ to make explicit the variables x, y, \dots which f_r depends on, and we denote by γ_r a string where all and only the elements of T occur which may influence the reactivity of the rule r ; ν is a natural number which specifies the value of a (conventional) mole of M ; μ is a function which assigns to each $X \in T$, the mass $\mu(X)$ of a mole of X , with respect to some measure unit; τ is the temporal interval between two consecutive states; q_0 , the initial state of M , 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

$$\Delta_q: Q \rightarrow \mathbb{R}$$

such that, if q' is the state following q in the temporal evolution of M , then $q'(X) = q(X) + \Delta_q(X)$ for every $X \in T$.

Two assumptions are fundamental in the definition of reaction rules and reaction maps used by MPA, which directly relate to the perspective of mass partition strategy adopted for MP systems evolution.

Principle 1 (Inertia). In any MP system, for every $X \in T$, a inertial rule r_X for the substance X is present. The reactivity of r_X , in a given state, is the inertia of the substance X in that state, that is, its tendency to not be transformed into other substances.

Principle 2 (Creativity). Any input rule r of type $\lambda \rightarrow X$ is assumed to be implicitly transformed into a rule $\lambda_r \rightarrow \lambda_r X$ where λ_r is a new symbol in T , called the input symbol of r . This means that a sort of input gate, as a container of a given capacity of X , is assumed to feed the system from the outside, at a rate depending on the reactivity of the input rule. This capacity determines the creativity of the rule $\lambda \rightarrow X$, as the maximum value of elements X that can enter into the system at each evolution step.

The value of inertia of each element of T (possibly extended with input symbols), and the value of the creativity of input rules are very important parameters for the evolution of MP systems according to the strategy we are going to define.

In order to define our MP algorithm, which formalizes the intuition given at beginning of Section 1, we use the following notation, that will be adopted in the rest of the paper and it will be always related to a metabolic system $M = (T, R, F, \nu, \mu, \tau, q_0)$.

Definition 2 (MP notation). Each $r \in R$ is denoted by $r: \alpha_r \rightarrow \beta_r$; α_r identifies the multiset of the substrates of r , and β_r identifies the multiset of the products of 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 ; $R_\alpha(X) = \{r \in R \mid X \in \alpha_r\}$; $R_\beta(X) = \{r \in R \mid X \in \beta_r\}$; $R(X) = R_\alpha(X) \cup R_\beta(X)$; $\Pi(\alpha_r) = \prod_{X \in \alpha_r} q(X)^{h_r(X)}$ ($\Pi(\alpha_r) = 1$ if $\alpha_r = \lambda$).

We assume that if $\alpha_r = \lambda$, then $\beta_r \in T$, and if $\beta_r = \lambda$ then $\alpha_r \in T$.

MP systems and their evolution is based on three basic assumptions which generalize well known chemical principles^[35].

Lavoisier Principle: The overall mass consumed by any non-input rule has to equate the overall mass of its products (mass conservation law).

Avogadro Principle: If $X \in \alpha_r$, then $h_r(X)u_r(q)$ moles of X are consumed by r and if $Y \in \beta_r$, then $g_r(Y)u_r(q)$ moles of Y are produced by r . The number $u_r(q)$, called *the reaction unit* of rule r in the state q , is determined by the reactivity of r at that time (stoichiometry law).

Dalton Principle: For any $X \in T$, the global

number of moles of X produced/consumed, in the passage from a state to the next state, is the algebraic sum of moles produced/consumed, according to Avogadro's principle, by all the rules where X occurs (additivity law).

The first principle imposes a constraint to the rules, the second principle defines the role of reaction units, and the third one says that the variation of a substance is the sum of the variations due to all the rules acting on it.

Definition 3 (MPA). 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:

$$\Delta_q(X) = \sum_{r \in R(X)} (g_r(X) - h_r(X)) \cdot u_r(q)$$

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 $K_{Y,q} \neq 0$.

The extension of this algorithm to the case of MP systems with many membranes is obtained by replacing a variables X with the pair of variables (X, i) where i denotes an index of a membrane, and (X, i) means that X is inside the membrane i (by using the membrane boundary notation^[36], this information is explicitly put in each rule).

In an MP system two parts are clearly distinguishable: the *signature* and the *quantities*. The first part (T, R, F) indicates the kinds of objects, the reaction and their regulation structure. The second part specifies the quantitative aspect which give meanings to the numbers which describe the evolution of systems. We represent the signature of metabolic P systems by means of MP graphs. Similar graphical formalisms were developed in the context of complex reaction networks (Stoichiometric Network Analysis and Metabolic Control Analysis^[37–39]; see also^[40, 41]). Fig. 1 is an example of MP graph which translates in graphical terms all the information given in Fig. 2 (the biological meaning will be clarified in the next paragraph): circles are substances, full black circles are rules, squares are reaction maps, and triangles link to rules which feed the system from outside or expel substances ($\lambda \rightarrow X$ or $X \rightarrow \lambda$ for some $X \in T$).

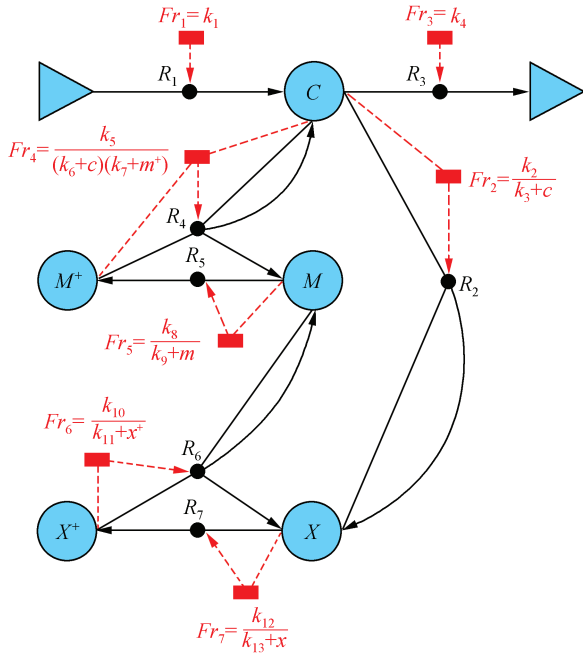


Fig. 1. A model of the mitotic oscillator of Fig. 3 represented by an MP graph. The correspondences with Goldbeter's constants are: $k_1 = v_i$, $k_2 = v_d$, $k_3 = k_d$, $k_4 = K_d$, $k_5 = V_{M1}$, $k_6 = K_c$, $k_7 = K_1$, $k_8 = V_2$, $k_9 = K_2$, $k_{10} = V_3$, $k_{11} = K_3$, $k_{12} = V_4$ and $k_{13} = K_4$, $V_1 = \frac{c}{K_c + c} V_{M1}$.

$r_1: \lambda \rightarrow C$	$f_1 = v_i$
$r_2: XC \rightarrow X$	$f_2 = v_d / kd + c$
$r_3: C \rightarrow \lambda$	$f_3 = K_d$
$r_4: M^+ C \rightarrow MC$	$f_4 = V_{M1} / (K_c + c) (K_1 + m^+)$
$r_5: M \rightarrow M^+$	$f_5 = V_2 / (K_2 + m)$
$r_6: X^+ M \rightarrow XM$	$f_6 = V_3 / (K_3 + x^+)$
$r_7: X \rightarrow X^+$	$f_7 = V_4 / (K_4 + x)$

Fig. 2. An alternative formulation of the MP of Fig. 1. Parameters and their numerical value are defined in [42].

Now we consider an example of biological modeling which highlights the expressive power of MP formalisms and its relationship with classical differential models. Fig. 3 describes the mitotic oscillator in amphibian embryos, which is an important case study reported in [31, 42, 43]. Mitotic oscillations are a mechanism exploited by nature to regulate the onset of mitosis, that is, the process of cell division aimed at producing two identical daughter cells from a single parent cell. More precisely, mitotic oscillations concern the fluctuation in the activation state of a protein produced by *cdc2* gene in fission yeasts or by homologous genes in other eukaryotes. The model here considered focuses on the simplest form of this mechanism, as it is found in early amphibian embryos. Here (see Fig. 3) cyclin is synthesized at a constant rate

and triggers the transformation of inactive (M^+) into active (M) *cdc2* kinase, by enhancing the rate of a phosphatase E_1 . Another kinase reverts this modification. On the other hand a kinase E_3 elicits the transformation from the inactive (X^+) to the active (X) form of a protease that degrades cyclin, and this activation is reverted by a phosphatase E_4 (E_1, E_2, E_3, E_4 are not indicated in the figure, $v_i, v_d, V_1, V_2, V_3, V_4$ denote rates of the processes). The activation of *cdc2* kinase provides the formation of a complex known as M-phase promoting factor (or MPF). The complex triggers mitosis and the degradation of cyclin leads to the inactivation of the *cdc2* kinase that brings the cell back to the initial conditions in which a new division cycle can take place. In yeasts and in somatic cells the cell cycle is subject to the control of many checkpoints, but the mechanism based on the activation-inactivation of *cdc2* kinase remains the same^[18].

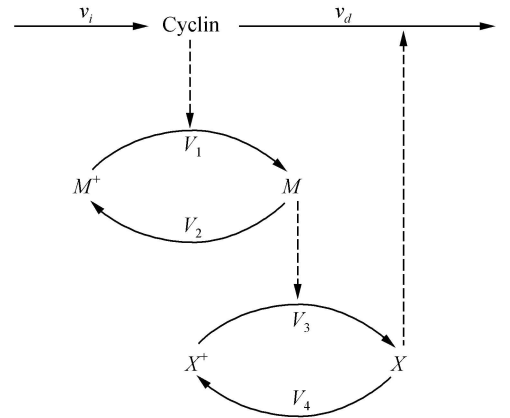


Fig. 3. The model provided by A. Goldbeter, from [42].

The following autonomous system of Ordinary Differential Equations (ODE) where time variable does not explicitly occurs in the right member of equations^[44]) is the differential model of dynamics described in Fig. 3, where c, m, x are the percentages of C, M, X respectively ($1 - m, 1 - x$ are the percentages of M^+, X^+ respectively):

$$\begin{aligned} \frac{dc}{dt} &= v_i - v_d x \frac{c}{K_d + c} - K_d c \\ \frac{dm}{dt} &= V_1 \frac{(1 - m)}{K_1 + (1 - m)} - V_2 \frac{m}{K_2 + m} \quad (1) \\ \frac{dx}{dt} &= V_3 \frac{(1 - x)}{K_3 + (1 - x)} - V_4 \frac{x}{K_4 + x} \end{aligned}$$

Fig. 4 is a solutions of these equations obtained by numerical integration for some value of parameters given in [42].

A general relationship between MP graphs and ODE holds. In fact, MP graphs transform naturally into ODE systems according to the mass principle, on which differential models are based. The amount of a product generated by a reaction is proportional to the product of quantities of substrates (considered with their multiplicity). This idea is formalized by the following definition where the MP notation 4 is assumed, x is the real variable $q(X)$, and x' denotes the derivative of variable x with respect to time.

Definition 4 (MP-ODE transformation). Let $G = (T, R, F)$ be an MP graph. For every $X \in T$, let x be the real variable associated to X ; then the following is the ODE-transformed of G :

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

Fig. 1 shows an MP graph which provides the dynamical structure of an MP system. It is directly related to Goldbeter's model. It is obtainable by means of the following procedure¹⁾, which is completely motivated by the theorems we give at the end of this section. Consider an MP graph H where all the known biochemical reactions involving the mitotic phenomenon in amphibian embryos are indicated as rules, while reaction maps are unknown. Consider the ODE-transform $ODE(H)$ of H , defined in Definition 4, and equate the right members of (1) and $ODE(H)$. Of course, these equations determine the values of the reaction maps of H such that its ODE-transform coincides with (1).

Fig. 2 is an alternative way to represent the MP graph in Fig. 1, where constants were put in the original format given in [42].

The following classes of MP systems play an important role in the relationship between ODE and MP systems.

Definition 5 (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 rule r of the system.

Definition 6 (Uniformly inertial MP system). For some $\phi \in \mathbb{R}$, an MP system is ϕ -uniformly inertial if the reaction map of any inertial rule of the system has the same constant value ϕ in any possible state. In this case ϕ is the (uniform) inertia of the system.

The following results can be proved as generalizations of those proved in the forthcoming author's paper, already mentioned, on discrete solutions of differential equations by metabolic P systems.

Theorem 1. Given an ODE, we can find (in many possible manners) an MP graph having the given ODE as its ODE transform.

Theorem 2. The computation of a non-cooperative ϕ -uniformly inertial MP system converges, as $\phi \rightarrow \infty$, to the solution provided by the ODE system obtained by using MP-ODE transformation.

Theorem 3. For any MP system M , there exists a non-cooperative MP system M' having the same ODE transform of M .

Corollary 1. Approximate solutions of autonomous ODE which describes metabolic systems can be solved by computing the evolution of suitable MP systems.

The system of Fig. 2 does not fulfill the non-cooperativity requirement, while Fig. 5 describes a non cooperative MP graph which is obtained by a procedure relative to Theorem 3 and which has the same ODE-transform, according to Definition 4, of the MP graph in Fig. 2, that is, the equations (1).

As it is asserted by Theorem 2, if we consider an uniform inertia acting in the system of Fig. 5, then the MP evolution of this system approximates, for increasing inertia, the differential solution of Goldbeter's model. The evolution of the system given in Fig. 5, for a suitable value of its inertia, is shown in Fig. 6. The similarity with Goldbeter's solution described in Fig. 4 is really impressive and confirms the validity of the previous theorems, in a very significant biological model.

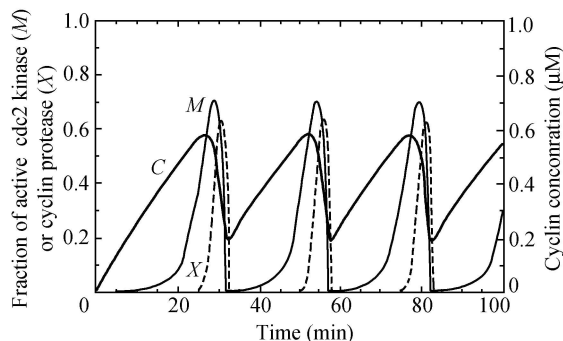


Fig. 4. A numerical solution of the set of differential equations (1) implementing the model provided by A. Goldbeter, from [42].

$r_1: \lambda \rightarrow C$	$f_1 = v_i$
$r_2': C \rightarrow X$	$f_2 = v_d \cdot x / k_d + c$
$r_2'': X \rightarrow \lambda$	$f_2 = v_d \cdot c / k_d + c$
$r_3: C \rightarrow \lambda$	$f_3 = K_d$
$r_4': C \rightarrow MC$	$f_4 = V_{M1} \cdot m / (K_c + c) \wedge (K_1 + m^+)$
$r_4'': M^+ \rightarrow \lambda$	$f_4 = V_{M1} \cdot c / (K_c + c) \wedge (K_1 + m^+)$
$r_5: M \rightarrow M^+$	$f_5 = V_2 / (K_2 + m)$
$r_6': X^+ \rightarrow XM$	$f_6 = V_3 \cdot m / (K_3 + x^+)$
$r_6'': M \rightarrow \lambda$	$f_6 = V_3 \cdot x^+ / (K_3 + x^+)$
$r_7: X \rightarrow X^+$	$f_7 = V_4 / (K_4 + x)$

Fig. 5. A non-cooperative model equivalent to the model of Fig. 2.

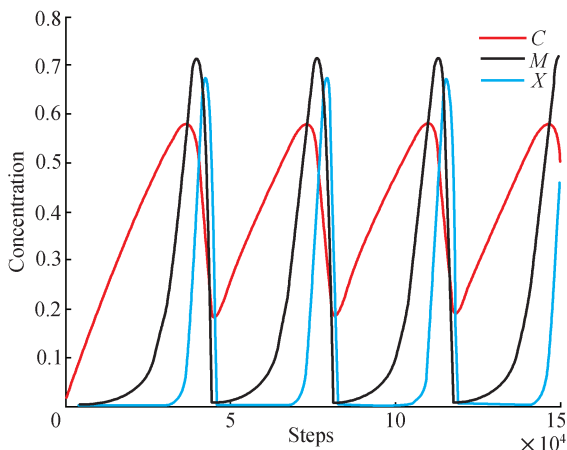


Fig. 6. The mitotic oscillator of Fig. 3 computed by means of noncooperative MP systems having equations (1) as ODE-transformation.

2 Metabolic P systems with log-gain regulation

In the definition of MPA it appears completely clear that what is essential in the evolution of an MP system is the knowledge of the reaction unit of each rule at each evolution step. A simple argument proves that reaction units determine completely the variation concentration of substances in the passage from a state to the next one. In fact, if we know the rules which produce and consume a given substance X , from the stoichiometry of these rules, given the value (number of moles) or their reaction units, we can deduce exactly the mole variation of X in the step. In other words, the knowledge of the number of objects transformed by any rule in the time unit is what we need for derive the new concentrations of substances at the next step.

The reaction maps allow us to evaluate these values by computing some ratios and by choosing a suitable minimum, according to Avogadro's principle.

However, we could follow a different strategy, by reversing the relationship between reactivities and reaction maps. If the reaction unit of a rule depends on the state of the system, it is reasonable to assume that really only a subset of all substance types influence this reactivity. The types such that a variation of their concentration determine a variation of reactivity of r are called *regulators* of rule r . We denote by a string γ_r the regulators of r (the order of symbols of γ_r is not relevant). In a perspective of population phenomena, another assumption 8 seems to be perfectly natural: a proportion should exist among the relative variation of a regulator of a rule r and the relative variation of reactivity of r . The relative variation of a substance X is defined as the ratio between the variation $\Delta(x)$ and x . In differential notation (using derivative with respect a continuous time) this ratio corresponds to $\frac{dx}{x}$, but from elementary calculus we know that $\frac{dx}{x} = d(\lg x)$. This equation explains the term "log-gain" for expressing relative variations^[41].

Now, another kind of Dalton's principle claims that the effects of regulators are cumulative, therefore the passage from the value of the reactivity of a rule r to its value in the next step can be computed as a linear combination of the relative variations of concentrations of the regulators of r . The coefficients of this linear form are called the log-gain parameters of the reaction (shortly LG parameters). In this way, starting from some initial values of reactivities we can derive their values in time, therefore, these parameters determine the reaction maps of rules.

MP systems with log-gain regulation, shortly MP systems with LG regulation or MP-LG systems, are similar to the systems previously defined, but their states have two components (q, u); the first one coincides with the state of a simple MP system, the second one is the reactivity function $u: R \rightarrow \mathbb{R}$ where, for each rule r , $u(r)$ is the reactivity of r . LG parameters determine a new evolution strategy which is defined in the next Definition 7. In simple words, the state of an MP-LG system, having n substances and m rules, is determined by a real vector of $n + m$ values giving the mass of each substance and the strength of each rule. At each step an MP rule r changes the substance masses and its LG parameters p_r and $(p_{(r, Y)} | Y \in \gamma_r)$ change the reactivities according to the principle that the log-gain of each rule

has to be a linear combination of the log-gains of substances regulating the rule.

Definition 7 (MPA-LG). The value of the metabolic difference operator, in a state (q, u) , for an MP-LG system $(T, R, P, \nu, \mu, \tau, q_0, u_0)$ (reaction maps were replaced by parameters P , and the vector u_0 of initial reactivities was added) consists of two parts, the variation $\Delta_{q(X)}$ of substance concentrations and the variation $\Delta_{u(r)}$ of reactivities, where, for any $X \in T$ and $r \in R$:

$$\Delta_{q(X)} = \sum_{r \in R(X)} (g_r(X) - h_r(X)) \cdot u(r) \quad (2)$$

$$\Delta_{u(r)} = u(r) \cdot$$

$$\left[\sum_{Y \in \mathcal{Y}_r} (p_{(r, Y)} \Delta_{q(Y)} / q(Y)) + p_r \right] \quad (3)$$

Assume that log-gain parameters remain constants, or with very small variations for a number of steps. The following theorem provides the theoretical possibility of deducing the regulation parameters from the experimental observation of the evolution of a real system.

Theorem 4. For any MP-LG system, there exists a sequence of steps of its evolution (each step being the next of the previous one) which univocally determines the value of log-gain regulation parameters.

Proof. Consider a metabolic system with n substances, m rules and having globally k regulation parameters for all the m rules. Observe this system for s steps and put the step as index in concentrations and reactivities. From the first equation of Definition 7, by evaluating the concentrations in the first two steps we get n equations with m unknown quantities: $u_1(r_1), u_1(r_2), \dots, u_1(r_m)$. In each of the following steps, by using both equations of Definition 7, we add other $m + n$ equations with m unknown quantities (the reactivities of each step) and k unknown quantities of regulation parameters that are the same for any step. In conclusion, in s steps we get $(s - 2)(n + m) + n$ equations and $(s - 1)m + k$ unknown quantities. This means that in order to have a sufficient number of equations for solving the system we need to proceed a number s of steps which solves the following equation:

$$(s - 2)(n + m) + n = (s - 1)m + k$$

which, after simple manipulations, provides the solution ($\lceil x \rceil$ denotes the minimum integer $\geq x$):

$$s = \lceil \frac{m + k}{n} \rceil$$

3 Conclusions

MP systems have several computational advantages with respect to the differential models, but their most important aspect is their direct biological meaning and their structure, where the reaction level and the regulation level are clearly interconnected but separated.

The search for MP systems where reaction maps can be deduced in some way from experimental data is the main problem to solve for a systematic applications of MP systems to complex dynamics. Without this possibility the construction of models is a very difficult task, which can be developed only with specific strategies depending on the particular cases.

Maybe other difference operators for MP-LG systems will be more appropriate in some specific cases. However, the main idea of this approach seems to indicate real possibilities to overcome many difficulties of differential models. In fact, MP systems with log-gain regulation seem to be structures which could allow us to directly build models from the data of biological phenomena. The future developments in theoretical investigation, in suitable biological experiments, and in related computational tools will be focused on this main objective.

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