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Metabolic P Systems: A Discrete Model for Biological Dynamics*

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Abstract — A recent methodology to model biochemical systems is here presented. It is based on a conceptual framework rooted in membrane computing and developed with concepts typical of discrete dynamical systems. According to our approach, from data observed at suitable macroscopic temporal scales, one can deduce, by means of algebraic and algorithmic procedures, a discrete model (called Metabolic P system) which accounts for the experimental data, and opens the possibility to understand the systemic logic of the investigated phenomenon. The procedures of such a method have been implemented within a computational platform, a Java software called MetaPlab, processing data and simulating behaviors of metabolic models. In the paper, we briefly describe the theory underlying the modeling of biochemical systems by Metabolic P systems, along with its development stages and the related extensive literature.

Key words — Biological oscillator, Computational modeling, Discrete dynamics, Membrane computing, Metabolic P systems (MP systems), Systems biology markup language (SBML).

I. Introduction

A huge amount of experimental data related to metabolic pathways requires suitable computational tools in order to be stored, retrieved, visualized and analyzed, as well as *ad hoc* mathematical models to be correctly interpreted. Although in the last years there have been several attempts, there is still a big need for modeling tools based on new theories, *ad hoc* developed to understand complex biochemical processes.

Computational modeling[1] is a key approach to understand complex biochemical processes underlying observed data[2], and many software tools have been developed in the field of systems biology (see for example the list in the SBML website `http://sbml.org`). The theory commonly employed to computationally study metabolic systems is based on ODE (Ordinary differential equations) or stochastic modeling, which requires numerical rates, not easy to estimate. In fact, new *ad hoc* methodologies need to be investigated in order to capture the systemic behaviors of biological phenomena, and this work is one step in this sense.

A Metabolic P system (MP system) is a discrete representation of a metabolic system[3]. It is mainly given by a set of substances (each one occurring in many copies) and reactions, each one equipped with a corresponding flux regulation map. Such a map provides, for any state of the system, a (flux) reaction unit ('flux' and 'reaction unit' will be used equivalently) which establishes the molar quantity of reactants transformed by the reaction in the system evolution to the next state.

Let us give a first intuition. A reaction $2a + b \rightarrow c$ identifies a transformation such that, when it is applied to a population of objects where types a and b occur in more than 20000 and 10000 elements respectively, and when its flux regulation map specifies a reaction unit of, say 10000 elements, then, in the passage between two time instants (with a given time distance τ), these 30000 elements are replaced by 10000 new objects of type c. For example, 20000 molecules of Hydrogen, plus 10000 molecules of Oxygen, are transformed into 10000 molecules of water.

The time interval between consecutive instants depends on the macroscopic level which is chosen for considering the dynamics of the system in question. The state, on which reaction units depend, is given by both the value of some magnitudes, called parameters, which are not transformed by reactions, but can influence them (*e.g.*, temperature and pressure), and on the sizes of the different substance populations inside the system. From a mathematical point of view, a (finite) multiset is a collection of elements where the same kind of element may occur in many copies, and a reaction (such as water formation) is a multiset rewriting rule; therefore the whole MP system is essentially a multiset grammar with maps regulating its rules.

The letter P of MP systems comes from the theoretical framework of P systems introduced by Gheorghe Păun[4], in the context of membrane computing. In fact, MP systems are a special class of P systems introduced for expressing metabolism in a discrete mathematical setting, and a peculiar aspect of MP systems is given by the Log-gain theory, specifically devised for them[5−7]. According to this theory, given a number of observation steps (at a specified time interval τ), and the corresponding time series of the states of a real metabolic system (with a known stoichiometry), then it is possible to deduce, by suitable algebraic manipulations, the flux regulation maps of an MP system which, on the observation steps, coincides with the observed real system, with a good approximation. In many cases, this coincidence is an evidence of description adequacy between the systemic logic of the observed real system and the mathematical structure of the deduced MP system. Many phenomena were reconstructed in terms of MP systems (*e.g.*, Goldbeter's mitotic oscillator[8], Belousov-Zhabotinski reaction in the Nicolis and Prigogine's formulation, and Lotka-Volterra's Prey-Predator model), and a complete concordance with the classical models was found. Moreover, some synthetic oscillators with interesting dynamical behaviors were easily discovered[9,10], and some MP models were directly deduced by using the Log-gain theory (for example a part of the photosynthetic NPQ phenomenon of Nonphotochemical quencing, for which no analytical model was known[11]).

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In this paper, we report a definition of MP system and a brief description of the Log-gain theory, together with the MetaPlab software[12], which is a simulator of biochemical dynamics based on this theory. It provides a virtual laboratory for modeling and analyzing metabolic phenomena, and for performing computational experiments relevant to many biological investigations.

II. MP Systems and MP Graphs

Given n substances and m reactions to transform them, each reaction r can be described as a pair of vectors $(\boldsymbol{r}^-, \boldsymbol{r}^+)$ of $\mathbb{N}^n$ ($\mathbb{N}$ is the set of natural numbers), where $\boldsymbol{r}^-$ gives the stoichiometric coefficients of the substances consumed by r and $\boldsymbol{r}^+$ gives the stoichiometric coefficients of substances produced by r. For example, $2a + b \to c$ becomes $((2,1,0),(0,0,1))$, since $2a$, $1b$ and $0c$ are consumed, while $0a$, $0b$ and $1c$ are produced.

Formally, an MP system M of type (n, m, k), that is, with n substances, m reactions, and k parameters, is a discrete dynamical system (any step i of its dynamics belongs to the set $\mathbb{N}$ of natural numbers). It is specified by (1) Reactions, (2) Flux regulation maps, (3) Parameter time series, and (4) Initial substance quantities. In mathematical terms this means: (1) a set $\{r_j = (\boldsymbol{r}_j^-, \boldsymbol{r}_j^+) | \ j = 1, \cdots, m\}$ of reactions of M, (2) a function $\boldsymbol{\Phi} : \mathbb{R}^{n+k} \to \mathbb{R}^m$ giving the reaction units of each reaction in correspondence to the state of the system (which is an $n + k$-dimensional vector of real numbers); (3) a function $\boldsymbol{H} : \mathbb{N} \to \mathbb{R}^k$ providing the time series of the k-dimensional vectors of parameters; (4) a vector $\boldsymbol{X}[0]$ of $\mathbb{R}^n$ giving the values of substance quantities at the time zero. Other three components need to be mentioned, providing the scale factors of the system, that is: (1) a unit population ν specifying the size of a conventional mole, which size depends on the modeled phenomenon (if $\nu = 1000$, 3.2 moles of a are a population of 3200 objects of type a); (2) the weight (according to a suitable measure unit) of a mole, for each substance, and the measure units of parameters; (3) the time unit τ, specifying the time interval between two consecutive instants of time.

The dynamics of such a system is given, for $i > 0$, by the vector recurrence equation (1),

$$\boldsymbol{X}[i+1] = \boldsymbol{R} \times \boldsymbol{U}[i] + \boldsymbol{X}[i] \tag{1}$$

where $\boldsymbol{X}[i] \in \mathbb{R}^n$ is the vector of substance quantities (moles) at step i, $\boldsymbol{R} = \boldsymbol{R}^+ - \boldsymbol{R}^-$ is the stoichiometric matrix of integer numbers, where $\boldsymbol{R}^+$ is constituted by the matrix of the column vectors $\boldsymbol{r}_1^+, \boldsymbol{r}_2^+, \cdots, \boldsymbol{r}_m^+$, $\boldsymbol{R}^-$ is constituted by the matrix of the column vectors $\boldsymbol{r}_1^-, \boldsymbol{r}_2^-, \cdots, \boldsymbol{r}_m^-$, (+ and − are the componentwise sum and difference respectively), and $\boldsymbol{U}[i] = \boldsymbol{\Phi}(\boldsymbol{X}[i], \boldsymbol{H}[i])$, while $\times$ is the usual matrix product.

The intuition behind the previous definition is that (1) reactions transform substances, (2) flux regulation maps establish the amount of matter transformed by each reaction at each step, (3) and parameters influence the flux regulation maps. An MP system can be depicted by means of an MP graph (extending a notion introduced in Ref.[13]) with five kinds of nodes and four kinds of edges, as in Fig.1. Nodes are: substance nodes (light circles), reaction nodes (dark circles), regulation nodes (rectangles with round corners), parameter nodes (rectangles), and gate nodes (triangles) denoting matter fluxes from/to the external environment. Edges are: consumption and production edges (continuous arrows to/from reactions), regulation edges (discontinuous arrows with dark pointer) and dependency edges (discontinuous arrows with light pointer).

1. Log-gain theory for MP systems

Log-gain principle derives from a general biological principle called allometry[14], according to which, in a living organism, the global variation of its typical magnitudes follow a sort of harmonic rule stating that their relative variations have to be proportional to the relative variation of the magnitudes related to them. In differential terms the relative variation in time of a quantity coincides with the variation of its logarithm, therefore the term "log-gain" is used for any law grounded on this assumption. In the specific context of our problem, we assume that the relative variations of a reaction flux is a linear combination of the relative variations of substance quantities and parameters affecting the reaction, and in a more restrict case, it is the sum of the relative variations of the reactants of the reaction. We refer to Ref.[6] for a detailed account of the mathematical log-gain theory of MP systems.

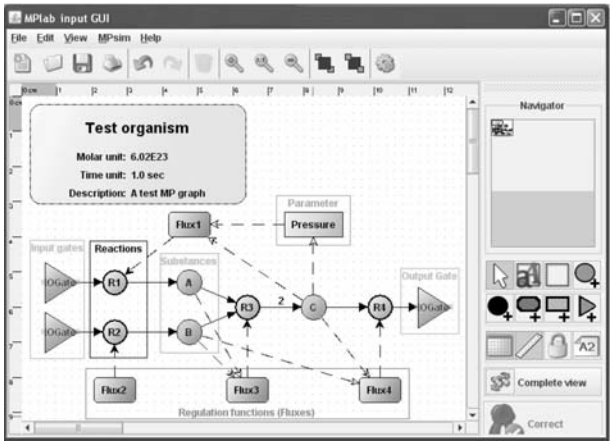

Fig. 1. The MetaPlab's input GUI

The main question, at beginning of the log-gain theory for MP systems, was the following inverse dynamic problem. Given a time series $(\boldsymbol{X}[i], \boldsymbol{H}[i]) \in \mathbb{R}^{n+k}$ (for $i = 0, 1, 2, \cdots, t$) of some consecutive states of a metabolic system (observed at a time interval τ), is it possible to deduce a corresponding time series of vectors $\boldsymbol{U}[i] = (\boldsymbol{\varphi}_i(\boldsymbol{X}[i], \boldsymbol{H}[i]) \, | i = 1, \cdots, m) \in \mathbb{R}^m$ (for $i = 0, 1, 2, \cdots, t-1$), giving the reaction units at any step, which according to Eq.(1) provide the time series $\boldsymbol{X}[i]$ of substance quantities (for $i = 1, 2, \cdots, t$)?

An important remark is due in this context. The approach of regulation maps discovery is essentially observational, macroscopic, and global, in a sense which is opposite to the perspective of differential models, which is infinitesimal, microscopic and local. In fact, we do not even ask to discover the real kinetic, responsible, at a microscopic level, of the biochemical dynamics of each reaction, but we aim at capturing the global pattern of reaction ratios of an observed dynamics. In other words, leaving unknown the real local internal dynamics, we decide to consider the system at an high abstraction level, but sufficiently low to reveal the logic of the behavior we observe. Indeed, this more abstract approach can be less informative, with respect to specific important details, but in many cases it turns out to be discriminating for important aspects of the reality, and often, especially in the case of very complex systems, is the only way for grasping some kind of comprehension of the reality under investigation.

III. MetaPlab Software

Computational modeling of biochemical dynamics deduced by experimental data is usually based on: (1) discrete and stochastic approaches[15−18], such as the Gillespie's algorithm[19,20], (2) continuous and deterministic approaches[21−24], mainly involving Ordinary differential equations (ODE), and (3) hybrid approaches[15,21,25].

Some tools in particular provide graphical facilities for model design and visualization, and for the discovery of biological properties through the model representation. An example is Cell illustrator$^{\text{TM}}$[22], a software tool which enables to graphically model metabolic, signal transduction and gene regulatory pathways by means of hybrid functional Petri nets[26] and to simulate deterministically their dynamics[27,28]. Other tools for biological modeling aim to analyze fluxes[29] and to manage data and components

integration[30,31]. COPASI (COmplex pathway simulator)[21] combines graphical facilities for editing and visualizing model parameters, with simulation, plotting, analysis, exportation and parameter estimation tools. This software, implemented in C++, can be used through graphical or command line user interfaces and it models concepts of reaction, compartments, metabolites by means of variables and differential equations. Another well known simulator aiming at simulating the whole-cell behavior is E-CELL[23,24]. It is an object-oriented tool implemented in C++ attempting to model cellular processes at several levels, such as protein-protein interactions, protein-DNA interactions, regulation of gene expression and other cellular interactions, with the aim to construct a cell model for in silico experiments. A cell model involves three types of objects: substances, genes and reaction rules, where substances represent molecular species, genes represent DNA sequences, and reaction rules represent typical reactions in metabolic pathways (complex reactions, such as transcription or translation are modeled as series of reactions). Simulations of cell behaviors are performed by numerically integrating differential equations describing the system under investigation.

In the last years, it has been introduced a specific platform entirely developed to compute and represent discrete dynamics of biochemical systems in terms of MP systems. MetaPlab[12], developed starting from the previous PSim project[32], has an extensible Java plugin based architecture, already equipped with several specific plugins, performing representations of MP systems and of their dynamics.

MetaPlab is a stand-alone program which can be used through some Graphical user interfaces (GUIs) whereby MP models can be easily generated, processed, visualized and connected to experimental data. The main MetaPlab graphical user interface is called input GUI since it enables the user to input MP models represented by MP graphs, to import external data, and to visualize them in a "network-oriented" way. Three main areas, displayed in Fig.1, can be identified in the GUI: (1) a menu section, on top, whereby the user can manage model files (opening, closing, saving, printing, *etc.*), edit the related MP graphs (undoing, redoing, deleting, *etc.*), visualize their elements (zooming, grid viewing, *etc.*), check basic correctness requirements and start a new processing session; (2) a central white panel, where MP graphs are visualized; (3) a design toolbar, on the right, containing the tools needed to generate new MP graphs from scratch: substance, parameter, reaction and flux nodes, arches between nodes can be easily created here.

1. Dynamics computation

Given an MP system in which the stoichiometry, the initial state, and the regulation functions are known, one usually wants to compute the dynamics of the system for a specific number of steps, by means of the difference equation system of Eq.(1). The plugin tool we developed to automatically generate the MP dynamics initially asks the user to set a few "simulation parameters" (the number of steps to simulate, the way the fluxes are given, *i.e.*, "by time series" or "by regulation functions", and the choice to save the results into a file). The simulation starts, generating the time series of substances, parameters and fluxes, and storing them into an MP store instance. A first analysis of the simulation results can be performed by updating the MP graph in the input GUI with the new data generated by the plugin, and then clicking on each node to visualize the related dynamics charts. More accurate analysis can be performed by the chart plotting plugin which is presented below.

2. Chart plotting

MetaPlab provides a plugin which automatically loads substance, parameter and flux time series from the MP store instance of the model displayed in the input GUI, and plots their dynamics in a single chart. The graphical interface of this tool, showed in Fig.2, is split in two main areas: a 2D chart, shown on the top, and a control area, at the bottom, where three tabbed panes enable the user to choose the chart type between line chart and phase chart, and to set the main features of the chart.

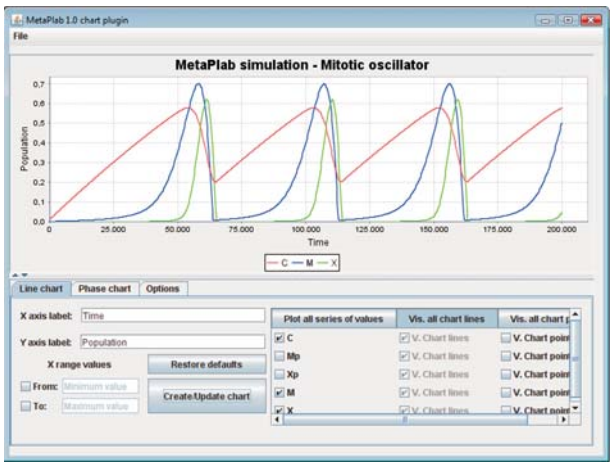

Fig. 2. Oscillations of the mitotic cycle in early amphibian embryos showed by the chart plotting plugin (see also Fig.5)

3. Regulation function synthesis

The synthesis of MP regulation functions (also called regulators), from datasets of observed substance time series and of flux time series deduced by the flux discovery plugin, is basically a regression problem. The choice of a good regression technique for this question deeply depends on the knowledge one has about the form of the expected functions[33]. The MP modeling process of a metabolic system can be reduced to an inverse dynamical problem. In fact, in the MP framework, it corresponds to the discovery of the regulation maps $\boldsymbol{\Phi}$ of a given biological dynamics, described as an MP system. The most recent mathematical development of MP theory is an algorithm, called LGSS (Log gain stoichiometric stepwise algorithm) that systematically solves this problem. In fact, starting from the dynamics (time series) of a given dynamical system S, the LGSS algorithm provides an MP system generating (with some approximations) the dynamics of S. In particular, the regulators of the MP system are deduced from: (1) the time series, (2) the rewriting rules (stoichiometry is usually deduced from basic information about S), and (3) a set of primitive functions called regressors (constants, polynomials, rational functions, and so on). The LGSS algorithm combines: (1) an algebraic manipulation (based on matrix Kronecker product) of matrices deduced from time series, regressors, and stoichiometry, (2) the method of least square evaluation, (3) regressor scores (computed by the Log-gain method), and (4) stepwise statistical regression based on Fisher tests (see Refs.[34–36] for technical details and Refs.[37–39] for some successful applications). Though, this recent development of the MP theory is not implemented in MetaPLab, because it is is based on MATLAB functions integrating all the components of the algorithm.

IV. Integration with SBML

In order to have a textual rather than a graphical representation of MP systems, in Ref.[40] a way to export MP systems into suitable XML documents is defined, and a way to validate these representations through the definition of an XML schema document is studied. In that work, the attention has been focused on the definition of an XML document which permits the exportation of MP models as they are, without important modifications. However, a main format used in biological contexts is the Systems biology markup language (SBML website `http://sbml.org`), which is an XML-based language designed for representing biological models in widely distributed simulation/analysis tools.

MetaPlab is equipped by a plugin which permits to automatically map an MP model to its SBML representation, giving an SBML document which can be imported by any software supporting SBML models importation.

Each type of component in a model is described in SBML by

using a specific type of data object that organizes the relevant information. An high level SBML model definition consists of the following optional lists of: (1) function definitions, (2) unit definitions, (3) compartment types, (4) species types, (5) compartments, (6) species, (7) parameters, (8) initial assignments, (9) rules, (10) constraints, (11) reactions, (12) events. Since an MP system has an elementary membrane structure, the resulting SBML model, after an exportation procedure, gives a model with only one compartment (the skin membrane) where (1) constants are mapped into SBML parameters, (2) substances are mapped into SBML species; (3) parameters are mapped into SBML parameters whose evolution in time is specified by an SBML assignment rule (if the MP parameter is defined by an evolution formula) or by a list of SBML events (if the MP parameter is definited by a time series of values); and (4) reactions are mapped into SBML reactions with kinetic laws expressed by the corresponding formulae of the flux regulation maps.

As we can see, by a first look at the graphs of Fig.3, an SBML model has components which seem to suggest a natural mapping into an MP model. However, MP systems have been developed for discrete simulations while SBML have been designed to represent ODE systems. Hence, in order to guarantee an adequate mapping of the dynamics, MetaPlab SBML plugin assumes that the resulting SBML model will be simulated with a numerical integration time step equal to the MP model interval time.

MP parameters given by time series are mapped into an appropriate list of SBML events without delay. Each event must have a trigger condition which permits to fire at the sound simulation time. To implement this feature, the SBML plugin adds to the MP model a reaction increasing a time "counter" substance T of one unit at each step. More technically, each value e_i of a parameter time series is mapped by the SBML plugin into an event which assigns the value e_i to the parameter whenever the trigger condition $T = i$ holds. This method might be also employed to map substance time series, but it does not work for flux time series, because SBML events cannot modify kinetic laws. In this case, the SBML plugin first creates a new SBML parameter which will be used to define the kinetic law and then modifies the parameter by means of the above method.

Here we have considered the exportation of an MP model in SBML. The inverse process, consisting in the importation in MetaPlab of a differential model from an SBML specification, assumes a greater importance. To this aim, MetaPlab has been recently extended to compute the model dynamics not only according to EMA system of Eq.(1), but also as a numerical integrator, with respect to some standard algorithms (such as Euler and Runge-Kutta), in order to study the dynamics of a differential model.

V. MP Goldbeter's Mitotic Oscillator

In the following, an applications of MP systems is shortly introduced for discovering the internal regulation logic of a phenomena relevant in systems biology: the Goldbeters mitotic oscillator[8]. Such kind of oscillator represents the simplest form of mitotic trigger mechanism found in early amphibian embryos. Rhythmic phenomena represent one of the most striking manifestations of dynamic behaviour in biological systems. Understanding the molecular and cellular mechanisms responsible for oscillations is crucial for unravelling the dynamics of life[42].

The fundamental mechanism of mitotic oscillations concerns the periodic change in the activation state of a protein produced by the cdc2 gene in fission yeast or by homologous genes in other eukaryotes. The simplest form of this mechanism is found in early amphibian embryos. Here (see the picture in the left part of Fig.4(a)) cyclin (C) is synthesized at a constant rate and triggers the transformation of inactive (M^+) into active (M) cdc2 protein, which leads to the formation of a complex known as M-phase promoting factor (MPF). MPF triggers mitosis, but at the same time M elicits the activation of a protease from state X^+ to X. The active protease then degrades cyclin resulting in the inactivation of cdc2. This brings the cell back to initial conditions and a new division cycle can take place. The ODE presented in Fig.4 is the differential model of dynamics described in the right part of Fig.4(b), where C, M, X are the concentrations of C, M, X respectively and $1-M, 1-X$ are the concentrations of M^+, X^+ respectively (the definitions of the parameters of the ODE model are not simple and are not relevant for our further discussion, however they can be found in Ref.[8]).

In Ref.[37] MP theory has been applied to Goldbeter's oscillator for showing that MP systems yield a robust method for biological modelling. In this manner, were automatically generated 700 models of this oscillator, which, for the most part, provide the same order of approximation of Goldbeter's model (see Fig.5 andFig.6 for an example). Moreover, by considering the phenomenon at different values of τ, different models have been obtained and in many cases the analytical form of these models is simpler than Goldbeter's model. These models have been also categorised with respect to the analytical form of their regulators. In this way a set of grammatical schemata was obtained which express the regulation relationship acting on the systems in different intervals of the temporal interval τ.

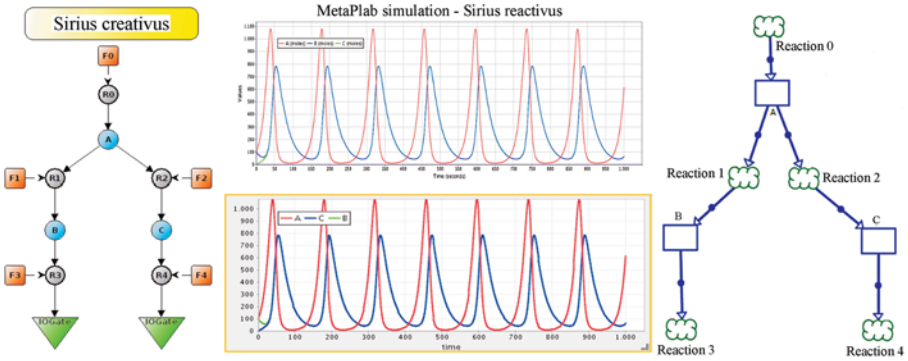

Fig. 3. An example of successful SBML exportation of the Sirius MP oscillator (defined in Table 1). In the left part of the picture is depicted the MP graph of the model, while in the right one is depicted the network obtained from its SBML specification by using the standard software Narrator[41] which supports the SBML importation. In the center part of the picture are represented two graphs which display the dynamics calculated by MetaPlab (on the top) and the dynamics calculated by the SBML specification using the Euler algorithm with unitary time step (on the bottom)

Even if computational tools are available for evaluating unknown parameters of ODE models[43,21], MP theory seems to point out a general methodology for solving dynamical inverse problems[44]. In fact, in this case we do not only discover unknown parameters, but we suggest also the form of regulators as a combination of basic functions. This possibility could be very important in the case where the knowledge about the phenomenon under investigation is so poor that no clear idea is available about the kind of model underlying the observed behaviour. Moreover, since the integration of differential equations may be very time consuming, especially when the system is stiff* the discrete nature of MP systems becomes even more important. In fact, MP models can be

*In this case it generally requires 95% or more of the entire estimation time[45].

Table 1. The specification of the Sirius MP oscillator used by the example presented in Fig.3. This oscillator was found within MP theory, and resulted to be very helpful in the development of this theory[9]

$r_1 : \emptyset \to A$	$f_1 = 0.047 + 0.087A$
$r_2 : A \to B$	$f_2 = 0.002A + 0.0002AC$
$r_3 : A \to C$	$f_3 = 0.002A + 0.0002AB$
$r_4 : B \to \emptyset$	$f_4 = 0.04B$
$r_5 : C \to \emptyset$	$f_5 = 0.04C$

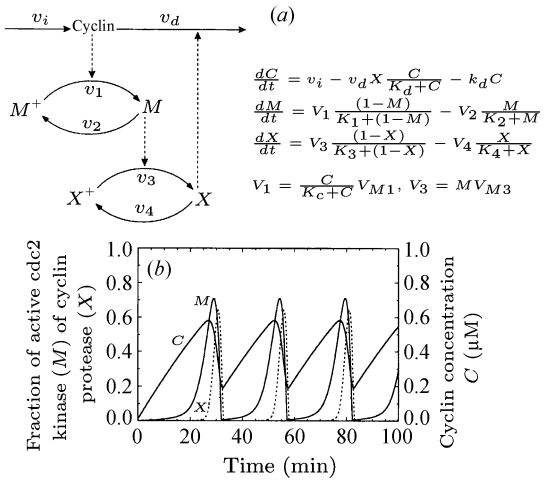

Fig. 4. Goldbeter's oscillator, which has a cycle of about 25 min[8] simulated without integration with a big saving of time and resources.

VI. Conclusion

There are numerous algorithms and platforms in literature to compute biological dynamics and to simulate behaviors, mainly based on either differential equations or stochastic theories, mostly following Gillespie's track[19,20,46–49]. However, along with these approaches, there is the common problem to estimate suitable numerical coefficients, that is a difficult and often unreliable task[50]. In this paper we have outlined a possible solution to this problem, to further verify, develop and deepen, which is based on a conceptual framework where membrane systems benefit from a viewpoint typical of discrete dynamical systems[10,51]. According to this perspective, from data observed at suitable macroscopic temporal scales, we can deduce, by means of algebraic and algorithmic procedures,

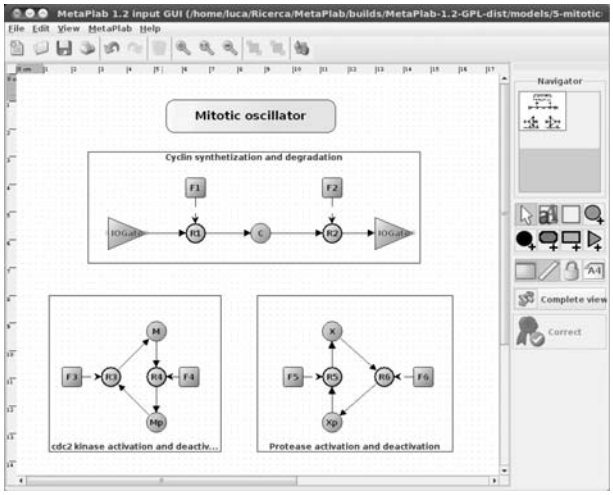

Fig. 5. The main window of MetaPlab loading the MP model of Golbeter's mitotic oscillator. The simulation of the model by MetaPlab is depicted in Fig.2

a discrete mathematical model which accounts of the experimental data, and then opens the possibility to understand the systemic logic of the investigated phenomenon. The procedures of such a method have been realized on a unified platform, whose development allows to apply and study the method here proposed. Indeed, there is a series of open problems related to the MP theory, including the classification of oscillating behaviors in biochemical systems[52], and the determination of systemic features emerging by modeling the biochemical system at a suitable macroscopic scale[44].

Our initial results of modeling[37–39,53,54] seem to confirm the expectations of the developed methodology. Furthermore, several results of mathematical representation of MP systems[7] and of equivalence with other methods (such as ODE[55] and Petri Nets[27,28]) open perspectives of integration and strengthening of our method.

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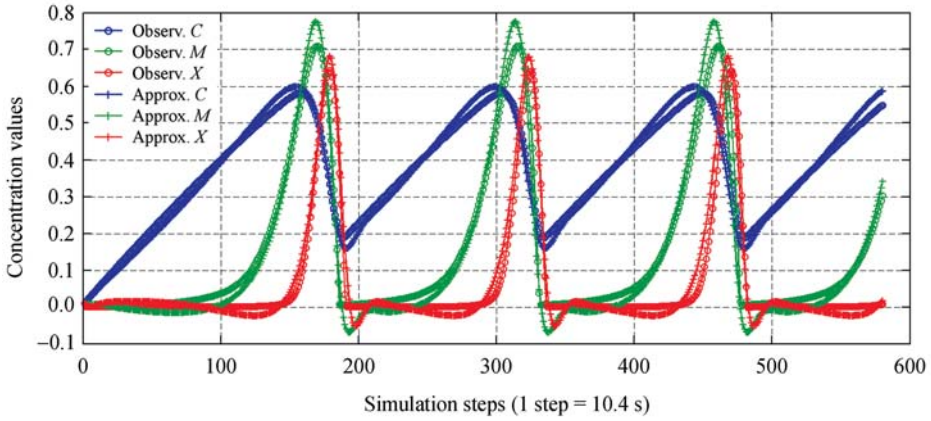

$r_1 : \emptyset \to C$ $\quad \varphi_1 = v_i$

$r_2 : C \to \emptyset$ $\quad \varphi_2 = k_1 + k_2\, M + k_3\, X - k_4\, CM$

$r_3 : M^+ \to M$ $\quad \varphi_3 = k_5 + k_6\, CM$

$r_4 : M \to M^+$ $\quad \varphi_4 = k_7\, M + k_8\, X$

$r_5 : X^+ \to X$ $\quad \varphi_5 = k_9\, C + k_{10}\, M$

$r_6 : X \to X^+$ $\quad \varphi_6 = k_{11} + k_{12}\, X + k_{13}\, C^2 + k_{14}\, C$

Fig. 6. Example of MP mitotic oscillator ($\tau = 10.4$ s). Constants and initial values as in Ref.[37]

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