A Proposal for a Language Combining Biochemical Rules and Topological Structure for Systems Biology

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Abstract: For about twenty years, rule-based modelling has been widely used for Systems Biology issues. Most existing languages focus on biochemical reactions primarily, and to a lest extent, on the cell structure in compartments. BIOCHAM and Pathway Logic Assistant (PLA) are representative examples of such rule-based languages. They are equipped with tools providing great analysis capabilities. We propose to provide such biochemical languages with annotations relating to the compartments in which the biochemical reactions take place. We will make sure that biochemical rules always indicate the nature of the compartments involved and the neighbourhood relations between them. At the end, it suffices to specialize the generic rules according to a particular topological structure in order to obtain sets of localized rules. Thus, resulting models can be analysed by using either BIOCHAM or PLA.

1 INTRODUCTION

Systems biology concerns the study of molecular interaction networks at the cellular level by using different disciplinary fields such as biochemistry, cell biology, computer science, mathematics or systems engineering. Cellular biological mechanisms are considered as natural complex systems (Ma'ayan, 2017) mainly characterized by unpredictability, context dependency, emergence and stochasticity (Chen and Crilly, 2016). A lot of aspects participate to this complexity: the dynamic rearrangements of the compartments, related to the movements of membranes; the kinetic parameters characterizing each reaction; the combinatorial complexity due to the possible great numbers of the states of the molecules knowing that for a given molecule M, different states of M can induce different functionalities and thus different reactions involving M. Because of this intrinsic complexity, elucidating or predicting the functioning of biological systems generally proceeds by modelling. This modelling aims at interconnecting the different underlying cellular processes - at the cellular level - and integrating different hierarchies of cells - at a cells population level. In this effort, a lot of modelling approaches, based on a diversity of formalisms (Bartocci and Lio, 2016)) have been defined and used in the study of some phenomenons such as signal transduction (Talcott, 2016; Riesco et al., 2017), gene regulation (Faeder et al., 2009), metabolism and protein-protein interactions (Fages et al., 2004).

The way the coupling between biochemical reactions and compartmentalization is made differs from one approach to another: while the spatio-temporal dynamics-oriented approaches explain the interested phenomenon only by the dynamic of the system's geometry (Regev et al., 2004; Cardelli, 2004; Giannakis and Andronikos, 2017), some others such as BIOCHAM (Fages et al., 2004), pathway Logic (Eker et al., 2002), the first version of BioNetGen (Faeder et al., 2005) focus on the biochemical reactions in an implicit static compartmentalization. The majority of the first models are equation-based and permit quantitative analysis. However, these modellings can be limited by the number of equations to be defined (due to the combinatorial complexity) and the difficulties in the estimation of kinetics. Therefore, other formalisms, inspired by computer science such as process calculi, cellular automata, agents and rule-based languages have been used, and the so designed modelling tools permit quantitative and/or qualitative simulations and analysis (Machado et al., 2011; Pedersen et al., 2015).

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We chose to focus on rule-based modelling of biochemical reactions in a static compartmentalization for the following main reason: a rule-based modelling formalism is generally considered as relatively simple and intuitive: a reaction results in changes in the contents - in terms of present molecules and/or their quantities or concentrations - of some compartments of the considered system. Rules, representing reactions, are then of the form $Left\ Hand \rightarrow Right\ Hand$ to materialize this transition of states. $Left\ Hand$ and $Right\ Hand$ respectively represent the needed molecules for the reaction to occur and the molecules resulting from this occurrence. This form of rules is familiar to biologists because inspired of classical chemical equations. To simplify modelling a little more, molecules are often abstracted by identifiers and if necessary, mechanisms are added to specify sites. For a very classical example, the reaction of water dislocation can be expressed by the rule $2A \longrightarrow B + C$ where A, B et C respectively stand for molecules H_2O, H_3O^+ and HO^-. In the context of biology, the localization of the involved molecules is a key information to be added to this rule. In (Hlavacek et al., 2006), one can find other advantages of rule-based languages for the modelling of biological cells. The remainder of the paper is organized as follows: in Section 2, we present in more details our motivations in the context of rule-based languages for systems biology. In Section 3, we outline our approach emphasizing the role of compartmentalization and the interest of systematically locating biomolecules in compartments in a generic way. In Section 4, we illustrate our approach on some examples issued from the literature. Section 5 gives some concluding remarks.

2 MOTIVATIONS

2.1 Context

Rule-based modelling is widely used in Systems Biology as evidenced by the important number of tools such as Kappa (Danos and Laneve, 2004; Boutillier et al., 2018), Virtual Cell (VCell) (Blinov et al., 2017) and BioNetGen (Faeder et al., 2009) issued from studies dealing with the explicitation of biological phenomena by the mean of this formalism. The rule-based languages underlying these three tools are designed for the definition of models that especially track biomolecular sites dynamics. Generally, the expressible reactions are reversible and consist in the synthesis of a molecule, the binding of two molecules and the modification of the form of a molecule. Those of the languages that take into account compartments can express the transport of a molecule from one compartment to another and species spanning multiple compartments. Figure 1 gives a schematic representation of some localized reactions. More or less similar schematics can be found in the literature of most of the aforementioned languages and their understanding is intuitive.

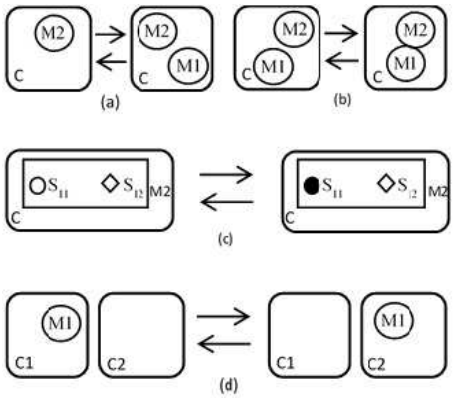

Figure 1: Representation of some rules. (a): Synthesis ($\rightarrow$) and Degradation ($\leftarrow$) of M1 catalysed by M2 in C. (b): Binding ($\rightarrow$) and Unbinding ($\leftarrow$) of M1 and M2 in C. (c): Phosphorylation ($\rightarrow$) and Dephosphorylation ($\leftarrow$) of M2 on site S_{11} in C. (d): Transport of M1 from C1 to C2 ($\rightarrow$) and from C2 to C1 ($\leftarrow$).

Each of the tool-sets provide capabilities to simulate, analyse and visualize networks generated from the models and the graphs issued from simulation. Currently, more and more initiatives are working to enable modellers to easily take advantage of the functionality of different tools. That results either in translators like the Kappa-BioNetGen one introduced by (Suderman and Hlavacek, 2017) that enables translation in the two senses or in provided capabilities of inferring from a given model, another model based on a different formalism.

Most of the rule-based approaches first focused on biochemical reactions before proposing extensions to highlight the topology a little more. BioNetGen Language (BNGL) has therefore been extended, resulting in compartmental BNGL (cBNGL) (Harris et al., 2009) that makes it possible to explicit topology as an inclusion graph. Similarly, the modeling of compartments and space within the cell is possible in Virtual Cell (VCell) since the extension presented in (Blinov et al., 2017).

The approach we propose in this paper depends on BIOCHAM (Fages and Soliman, 2008) and Pathway Logic (PL) (Eker et al., 2002; Talcott, 2016). BIOCHAM is an environment to modelling biochemical interactions which provides a rule-based language for the definition of the models and a tempo-

ral logic based language to express properties that are supposed to be checked by the system. It offers different semantics, the boolean one being based on rewriting logic, and the carrying out of both qualitative and quantitative analysis. It also enables the checking (and the learning (Calzone et al., 2005)) of the properties of the models by the using of NuSMV model-checker. BIOCHAM has been extended to provide the capability of infering rule-based models from ODE-based one (Fages et al., 2015). This is useful when kinetics parameters value are not totally defined. PL is another rule-based approach to modelling cellular processes, that uses the rewriting language MAUDE (Clavel et al., 2000) to write the algebraic specification underlying its models. It queries its models by using Pathway Logic Assistant (PLA) (Talcott and Dill, 2005) that offers a graphical interface and accesses to some formal tools such as Pathanalyser (Dill et al., 2005) and the simulation and model-checking features of MAUDE. These tools materialize localizations by attaching simple labels to molecules, with a difference for PL that can write models from which one can deduce the hierarchical organization of cells found in Biomodels (Li et al., 2010). A model in these languages is not explicitly guaranteed to be coherent with a specific topology. It is this aspect of combining rules with formal topological structure that we address in this paper.

2.2 Motivations

Living organisms are highly compartmentalized biological systems whose functioning depends on the coordination of the isolated behaviours of each compartment. Then, topology, i.e the nature of compartments composing the system and their relative position in the system, as well as biochemical reactions are determinant for the life of the system. The importance of topology is directly related to the role of compartmentalization. On one hand, compartments of same nature are entities sharing the same functionalities and the same behaviour. On the other hand, by grouping in each compartment the appropriate molecules (due to the selective permeability of membranes), it improves systems efficiency by speeding up the molecular interactions given that their occurrences are location-dependant. This role of compartmentalization is highlighted by (Harris et al., 2009) that presents a compartmental model of an eukaryotic cell in which a signalling process results from interactions between molecules from four distinct compartments each containing specific molecules and transport reactions concerning neighbouring compartments.

Despite its importance, a relative weakness in the taking into account of the topology can be noticed in most formalisms for rule-based modelling of biological processes. Our motivation is then to reinforce in these modellings, the place of the topology by enabling its separate representation. A particular regard is put on the neighbouring relationships to take into account the location-dependency of reactions, and on the types of compartments to respect the specific potential behaviour of each compartment. Moreover, the organels are not abstracted by a generic one (if a system has n compartments of type T, all the n compartments are represented), to make possible the simultaneous occurrences of concurrent reactions. The resulted models are guaranteed to be coherent with the static topological structure of the system under consideration: all the rules are contextualized with regard to the compartments. Then, our models can be used through existing tools. We have chosen BIOCHAM and PL as privileged target tools because they have a lot of similarities.

3 THE MODELLING APPROACH

3.1 General Overview

Classically, in rule-based modelling of biological processes, topology and biochemical reactions are taken into account in an integrated manner. Unlike these approaches, our rule-based modelling approach focuses on an explicit specification of the topological structure. We propose to separate the two following complementary aspects: a static topology of the system and biochemical reactions. Our approach can then be considered as a topology-driven rule-based modelling approach as shown in Figure 2. We propose to take as input data firstly a graph, that we call as *exchange graph* and that abstracts the topology of the system and secondly, a set of generic rules that describe the biochemical reactions that can occur in the system provided that there is some correspondence between compartments mentioned in the topological structure and indications of localization w.r.t types of compartments given in the rules. Then, we automatically elaborate a concrete model which can be translated in such a way that it can be handled by the target tool chosen by the modeller.

3.2 The Exchange Graph

Generally speaking, a compartment of a biological system is of a certain type and is delimited by a double-layered membrane. Molecules may be localized more precisely in one of the four locations related

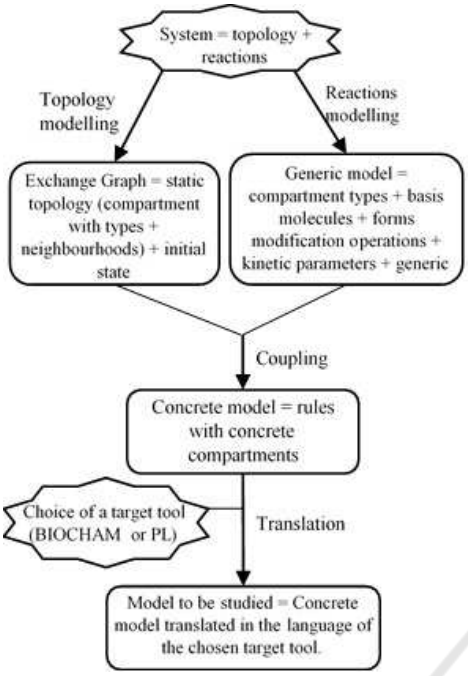

Figure 2: Schematic representation of the approach.

to a given compartment: from the most external to the most internal, we name these locations *EM* (molecule is tethered to the external membrane), *TM* (molecule is in the trans-membrane space), *IM* (molecule is tethered to the internal membrane) and *IC* (molecule is inside the compartment). *IC* is the default location for a given compartment. Two kinds of neighbourhoods for localisations are considered: the neighbourhood by inclusion in which one compartment is included in another one and the neighbourhood by adjacency in which two compartments stuck each other by portions of their membranes. Figure 3 is an example of such a topology. The particular compartment of type *Env* stands for the outer compartment of any system. Its role is to delimit the system of interest. Generally speaking, the rules will bring into play molecules that are in localities connected by neighbourhood relations.

The *exchange graph* of a biological system S captures all the neighbourhood relations between the compartments of S and only these ones. It will also store the contents of these compartments. We note V_S the set of the compartments of S, T_S the set of the types of the compartments of S and E the unique external compartment of type *Env*. The *exchange graph* GE_S associated to S is an undirected graph in which a vertex represents an element of $V_S \cup E$ and an edge represents either the adjacency between two compartments, or the inclusion of a compartment in another one. Each compartment is associated with its type, an element of $T_S \cup Env$ and its content in terms of

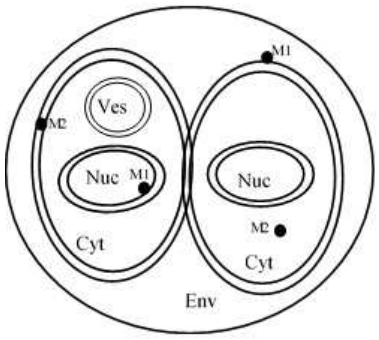

Figure 3: A topological structure S_1. It has two adjacent compartments of type *Cyt*: each of them contain a compartment of type *Nuc* while only one of them contains in addition a compartment of type *Ves* (for vesicle). The localizations of molecules are *TM* for the first compartment of type *Cyt*, *EC* and *IC* for the second one and *IM* for the first compartment of type *Nuc*.

molecules. To sum up, we impose the following conditions on the *exchange graphs*: i) exactly one compartment is of type *Env* and ii) for each element t of T_S, there is at least one element of V_S whose type is t. For example, when considering the topology S_1 (Figure 3), we have $V_{S_1} = \{C1, C2, N1, N2, V1\}$ and $T_{S_1} = \{Cyt, Nuc, Ves\}$ by naming C_1 and C_2 ...the compartments of S_1. Figure 4 gives the schematic representation of GE_{S_1}.

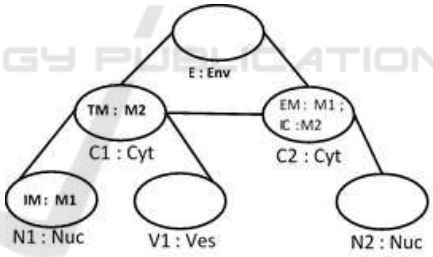

Figure 4: *Exchange Graph* GE_{S1} for to S_1 (Figure 3).

In practice, there are essentially two ways for obtaining an *exchange graph*: the first one is to directly construct it by manually designing it while respecting basic topological and biological conditions. This method is clearly sufficient when the topology to be abstracted is simple enough not to be mistaken.

The second way consists in extracting the graph from geometric models, called the bio-geometric models and handled by some geometric 3D-modellers. For our part, we build bio-geometric models using a specialization of MOKA (Vidil et al., 2002), a topology-based geometric modeller implementing 3-Generalized-Maps. For modelling an object as Generalized-Map, the topology of the object is first modelled by as a set of darts (obtained by decomposing the objects along their topological structure until

getting elements of smaller dimensions, called darts). Then embeddings, that is pieces of information such as forms, colors, dimensions or molecule concentrations, ... are associated to main elements (such as volumes, faces, vertices) composing the topology in order to obtain a full geometric object.
In our specialization of MOKA, we represent compartments as double-cubes (representing respectively the inner membrane and the outer membrane of the compartment) linked by a 3-dimensional neighbourhood relation. A compartment has then forty-eight darts (eight for each face). In our setting, the embeddings consist in the name, the type and the content of compartment attached to the 3-cells (volumes) of the topology. In addition to the creation of the environment, we offer two other creation operations: i) the creation of a compartment $C1$ in a compartment $C2$: the name $C2$ is associated to the outer membrane of $C1$; ii) the creation of a compartment $C1$ stuck to a compartment $C2$: the bonding surface on $C2$ must be defined and 3-dimensional links are established between corresponding surfaces of $C1$ and $C2$. An illustration of the bonding surface is given by Figure 5 where the 3-dimensional links are the horizontal black lines between two darts (points).

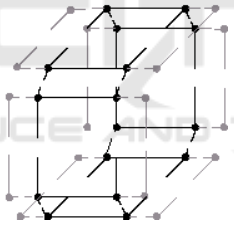

Figure 5: Bonding surface of two volumes.

Figure 6 represents the bio-geometric model of S_1 (Figure 3). Five compartments are visible and we use colors for distinguishing compartments.

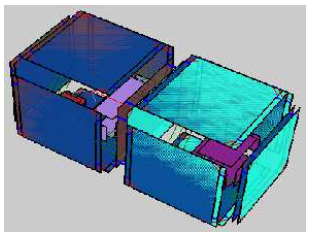

Figure 6: Bio-Geometric model of S_1 (Figure 3).

Using geometric modellers becomes particularly convenient for situations involving a significant number of compartments (e.g. Figure 7)
The extraction of the *exchange graph* is done by browsing the darts of the bio-geometric model. For a compartment $C1$, the set of its neighbours contains all the compartments which have at least one dart linked with a dart of $C1$ by an 3-dimensional link.

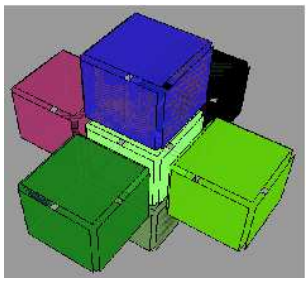

Figure 7: Bio-Geometric model of a system that has a compartment (the central one) which has no direct neighbourhood with its container, because it is adjacent on all its faces to another compartment.

3.3 The Generic Model

The *generic model* is the transcription in our rule-based language, of the reactions. As shown by Listing 1 that gives an extract of the grammar of the language, a generic model (*GM*) is organized in five sections (line 1) each delimited by *BEGIN_section-name* and *END_section-name*.
The first section *CTypes* that lists the compartment types is original to our approach while the others respectively listing the basis molecules (*BMols*), the molecules forms transformations (*Modifs*), the kinetic parameters identifiers (*KPS*) and the generic reaction rules (*GRS*) are classically found in the other languages. The syntax allows association of particular sites to a basis molecule (lines 8 and 9) and kinetic parameters are valued (line 16).

Listing 1: Syntax of *generic model*.

```
1  GM      ::= CTypes BMols Modifs KPS GRS
2
3  CTypes  ::= BEGIN_CTypes LCT END_CTypes
4  LCT     ::= idCT | idCT;LCT
5
6  BMols   ::= BEGIN_BMols LBM END_BMols
7  LBM     ::= BM | BM; LBM
8  BM      ::= idBM | idBM (LSites)
9  LSites  ::= idSite | idSite, LSites
10
11 Modifs  ::= BEGIN_Modifs LMod END_Modifs
12 LMod    ::= idMod | idMod, LMod
13
14 KPS     ::= BEGIN_KPS LKP END_KPS
15 LKP     ::= KP | KP, LKP
16 KP      ::= idKP(reel)
17
18 GRS     ::= BEGIN_GRS LGR END_GRS
19 LGR     ::= GR | GR LGR
20
21 GR      ::= idGR : PREC KParam
22               State => State
23               CondMolVar.
24 State   ::= []@CVar | LocSol
```

```
25  LocSol::= [MolSet]@CVar |
26            [MolSet]@CVar & LocSol
27  MolSet::= Molec | Molec + MolSet
28  Molec ::= idBM | (Molec:Modif) |
29            Molec-Molec
30  Modif ::= idMod <LSites> | idMod
31  CVar  ::= idCV : idCT TCPart | idCV |
32            idCT TCPart | AnyW
33  TCPart::= (EM) | (TM) | (IM) | (IC) |_
34  PREC  ::= [PreC : LCond]
35  LCond ::= {CVar,CVar} | {CVar,CVar}LCond
```

The *generic rules language* is widely inspired from BIOCHAM and PL in the sense that it has been designed to be able to express what is expressible in the rule-based languages of these environments. Listing 1 gives from line 21 the syntax of (the transition part of) a generic rule which consists in two mandatory components (rule identifier (idGR) and transition part (line 22)), the others being optional. A molecule (*Molec* is a basis one, an altered form of a molecule or a complex). The localizations of molecules are expressed using @ (line 24 to 26) that attaches a *compartment variable* (*CVar*) to a set of molecules (solution, *MolSet*) or to *[]* (empty solution). The *compartment-variable* gives the type of compartment in which the molecules are localized. It can be abbreviated (line 30, options 2 and 3) when there is no possibility of confusion and *AnyW* is used to express that all the types of compartment can be concerned.
Concerning the optional components of a rule, a specificity of our language is the *neighbourhood preconditions* (*PREC*) that give the possibility to make explicit some conditions to the occurrence of a reaction. They consists in a list of pairs of *compartment variables* to signify that instances of these variables must have a direct neighbourhood. Kinetic parameters (*KParam*) are inspired of BIOCHAM. They consist in some arithmetic terms ranging from constant values to more complex expressions based on the identifiers given in the *KPS* section and the concentrations of molecules.

3.4 The Target Model

Once an *exchange graph* and a *generic model* have been designed, the next step consists in instantiating the generic reaction rules with topological informations given by the exchange graph in order to build a *concrete model*. This last one is defined by all valid instances of generic rules, obtained by replacing *compartment variables* by compartments of the exchange graph, provided that conditions on compartment types and compartments neighbourhoods are satisfied in the exchange graph. For an exchange graph $EG = (V_{EG}, E_{EG})$, a *concrete rule cr* is valid if the three following conditions are met where SL_{cr} and SR_{cr} represent the sets of compartments appearing in respectively the left hand and the right hand of *cr*: i) the neighbourhood preconditions associated to the rule are verified ; ii) the sub-graph resulting from the restriction of EG to SL_{rc} is connex or reduced to one vertex ; and iii) each element SR_{cr} is an element of SR_{rc} or has a direct neighbour in SL_{cr}. For example, the instantiation of

$$gr_1 : [M1 + M2]@Cyt => [M1]@Cyt\&[M2]@Nuc.$$

relatively to GE_{S_1} (Figure 4) gives two concrete rules cr_{11} and cr_{12}, instances of gr_1 in which the couple (Cyt, Nuc) has been respectively replaced by $(C1, N1)$ and $(C2, N2)$.
The *concrete model* can then be exploited for simulation and/or analysis issues, by using features provided by BIOCHAM and/or Pathway Logic. It suffices to translate the *concrete model* in the concrete syntax used by the targeted tool.

4 CASE STUDIES

In this section, we apply our approach on two processes that have already been modelled in the languages of BIOCHAM or PL. The application proceeds in three steps: considering the model from BIOCHAM or PL, we firstly infer from it information about the involved localizations and the modelled reactions. This information is used to elaborate the *exchange graph* and the *generic model* to be used in the coupling process. Then, we proceed to the coupling and finally, the resulted *concrete model* is translated in BIOCHAM and PL and the obtained *target models* can be compared to the initial one. The models we have chosen to consider are the model of the simplified cell cycle of Tyson ($Model_1$) and the the model of the delta-notch signalization pathway ($Model_2$). They are issued from BIOCHAM.
From $Model_1$ that contains ten reaction rules and no mention of localization, we infer that the process is concerned by ten different reactions, occurring in the system seen as a whole. This information induce a one-vertex (namely E of type *Env*) *exchange graph* and a *generic model* whose rules are the transcription in *generic rules language* of the ten reactions.
$Model_2$ contains one hundred and forty-four (abbreviated in seventy-two) reaction rules implicating thirty six cells arranged in a 6x6 matrix, each cell being identified by using its line and column numbers (C_{11}, C_{12} ... C_{66}). Each of the rules of the model concerns the synthesis or the degradation of one the two involved molecules, *Delta* and *Notch*. That allows that the system is about four biochemical reactions occurring in a population cells of of thirty six (36) the same

type. Conditions attached to the rules show that the synthesis of *Notch* is juxtacrine (the occurrence of the reaction in a given compartment depends on the contents of the juxtaposed compartments) When adopting the same topology as BIOCHAM, we can elaborate the bio-geometric model of Figure 8. The *exchange graph* extracted from this geometric model exactly conforms what was expected : Except the neighbouring with E, all the cells have between two and four neighbours. The *generic model* contains four rules corresponding to the transcription of the four reactions in the *generic rules language*.

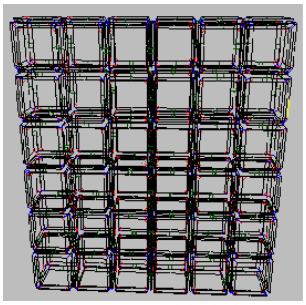

Figure 8: Bio-geometric model of a system consisting in a population of thirty six (36) cells arranged in a 6x6 matrix.

The coupling step in the case of $Model_1$ consists in just eliminating the information about localization, because it's the default compartment *Env*. The *concrete model* is then equivalent to the generic one when considering the number of rules. The *target model*, obtained by syntax adaptation, conserves the semantic and have the same number of rules.
The coupling of the *generic model* and the *exchange graph* issued from the decoupling of $Model_2$ generates a concrete model with one hundred and forty four (144) rules: four rules by cell. That means that each *generic rule* has been instanciated for each cell, regardless of the number of the neighbouring cells it has. latter. The translation of the *concrete model* in BIOCHAM conserves the semantic.
The presented approach intends to model processes in BIOCHAM and PL languages with the guarantee that the obtained models are respectful from the topology of the system. Such models can be directly defined in the targeted tools considering an implicit topology. However, applying the proposed approach presents some advantages: It allows the modeller to have a directory of generic models and another of topology specifications. As a consequence it is possible to him to easily study a set of biochemical reactions modelled as a set of *generic rules* relatively to different topologies and inversely: any combination of an *exchange graph* and a *generic model* defines a model. The *generic rules*, by characterizing the types of compartments involved, contribute to inform a little more on the role of the different types of compartment. Another advantage of the approach is the provided capability to study the same model thought the two target tools: even if these tools presents a lot of similarities, the analysis they carry out are not exactly the same. Different analysis results may be interesting. Naturally, because *generic models* are concise, they are easier to edit.
Based on the cases presented above, we can say that these interests are diversely relevant according to the considered topology. For a system with just one compartment like $Model_1$, just the second point is relevant because the topology cannot change in any way. For cases like $Model_2$ which concerns a topology characterized by an important number of compartments of the same type, and reactions largely depending on neighbourhoods, all the interests are relevant.

5 CONCLUSION

In this paper, we have introduced an approach to modelling biological processes by decoupling the topology of the system and the biochemical reactions occurring in the system. The topology is abstracted by an *exchange graph* that contains the relevant information on each compartment of the system : its name, its type, its content and its neighbourhoods. The reactions in turn are modelled as rules characterizing the types of compartments involved. Our approach can be considered generic at tow levels. First of all, it is generic with regard to the topology: a generic model can be declined according to several graphs of exchange, giving rise to as many concrete models. These concrete models can then be studied through different analysis tools (two in our case: BIOCHAM and PL): this constitutes the second aspect of genericity of our approach.
The use of geometric modelling to represent topological pieces of information is a second trait of originality of our approach. This allows us to design generic models that are at least as concise as resulting concrete models and that are consistent models from a topological point of view.

REFERENCES

Bartocci, E. and Lio, P. (2016). Computational modeling, formal analysis, and tools for systems biology. *PLOS Computational Biology*, 12(1):1–22.

Blinov, M. L., Schaff, J. C., Vasilescu, D., Moraru, I. I., Bloom, J. E., and Loew, L. M. (2017). Compartmen-

tal and spatial rule-based modelling with virtual cell. *Biophysical Journal*, 113(8):1365–1372.

Boutillier, P., Maasha, M., Li, X., Medina-Abarca, H. F., Krivine, J., Feret, J., Cristescu, I., Forbes, A. G., and Fontana, W. (2018). The kappa platform for rule-based modeling. *Bioinformatics*.

Calzone, L., Chabrier-Rivier, N., Fages, F., and Soliman, S. (2005). Apprentissage de règles de réactions biochimiques à partir de propriétés en logique temporelle. In Guy Perrière, A. G. e. C. G., editor, *Actes de JOBIM'05*, pages 183–192, Lyon.

Cardelli, L. (2004). Brane calculi. In *Computational Methods in Systems Biology, International Conference, CMSB 2004*, volume 3082 of *Lecture Notes in Computer Science*, pages 257–278. Springer.

Chen, C.-C. and Crilly, N. (2016). Describing complex design practices with a cross-domain framework : learning from synthetic biology and swarm robotics. *Res Eng Design*, 27:291–305. 10.1007/s00163-016-0219-2.

Clavel, M., Duran, F., Eker, S., Lincoln, P., Marti-Oliet, N., Meseguer, J., and Quesada, J. (2000). Towards Maude 2.0. In *3rd International Workshop on Rewriting Logic and its Applications (WRLA'00)*, volume 36 of *Electronic Notes in Theoretical Computer Science*. Elsevier.

Danos, V. and Laneve, C. (2004). Formal molecular biology. *Theoretical Computer Sciences*, 325(1):69–110.

Dill, D. L., Merrill, K. A., Pamela, G., Talcott, C. L., Laderoute, K., and Lincoln, P. (2005). The pathalyzer: A tool for analysis of signal transduction pathways. In *Proceedings of the First Annual Recomb Satellite Workshop on Systems Biology*, pages 11–22.

Eker, S., Knapp, M., Laderoute, K., Lincoln, P., and Talcott, C. (2002). Pathway Logic: Executable models of biological networks. In *Proceedings of Fourth International Workshop on Rewriting Logic and Its Applications (WRLA)*.

Faeder, J. R., Blinov, M. L., Goldstein, B., and Hlavacek, W. S. (2005). Rule-based modeling of biochemical networks. *Complexity*, 10(4):22–41.

Faeder, J. R., Blinov, M. L., and Hlavacek, W. S. (2009). Rule-based modeling of biochemical systems with bionetgen. *Systems Biology*, 10(4).

Fages, F., Gay, S., and Soliman, S. (2015). Inferring reaction systems from ordinary differential equations. *Theoretical Computer Science*, 599:64 – 78. Advances in Computational Methods in Systems Biology.

Fages, F. and Soliman, S. (2008). Formal cell biology in biocham. In *Formal Methods for Computational Systems Biology, 8th International School on Formal Methods for the Design of Computer, Communication, and Software Systems, SFM 2008, Bertinoro, Italy, Advanced Lectures*, volume 5016 of *Lecture Notes in Computer Science*, pages 54–80. Springer.

Fages, F., Soliman, S., and Chabrier-Rivier, N. (2004). Modelling and querying interaction networks in the biochemical abstract machine biocham.

Giannakis, K. and Andronikos, T. (2017). Membrane automata for modeling biomolecular processes. *Natural Computing*, 16(1):151–163.

Harris, L. A., Hogg, J. S., and Faeder, J. R. (2009). Compartmental rule-based modeling of biochemical systems. In *Proceedings of the 2009 Winter Simulation Conference*. M. D. Rossetti, R. R. Hill, B. Johansson, A. Dunkin, and R. G; Ingalls, eds.

Hlavacek, W. S., Faeder, J. R., Blinov, M. L., Posner, R. G., Hucka, M., and Fontana, W. (2006). Rules for modeling signal-transduction systems. *Sciences STKE*, 344(6).

Li, C., Donizelli, M., Rodriguez, N., Dharuri, H., Endler, L., Chelliah, V., Li, L., He, E., Henry, A., Stefan, M., Snoep, J., Hucka, M., NovÃ¨re, N. L., and Laibe, C. (2010). Biomodels database: An enhanced, curated and annotated resource for published quantitative kinetic models. *BMC Syst Biol*, 4(92).

Ma'ayan, A. (2017). complex systems biology. *J. R. Soc Interface*, 14(20170391).

Machado, D., Costa, R. S., Rocha, M., Ferreira, E. C., Tidor, B., and Rocha, I. (2011). Modeling formalisms in systems biology. *AMB Express a SpringerOpen Journal*.

Pedersen, M., P.hillips, A., and Plotkin, G. D. (2015). A high-level language for rule-based modelling. *PLoSONE10(6):e0114296.doi:10.1371/journal.pone.0114296*.

Regev, A., Panina, E. M., Silverman, W., Cardelli, L., and Shapiro, E. Y. (2004). Bioambients: an abstraction for biological compartments. *Theor. Comput. Sci.*, 325(1):141–167.

Riesco, A., Santos-Buitrago, B., Rivas, J. D. L., Knapp, M., Santos-Garcia, G., and Talcott, C. (2017). Epidermal growth factor signaling towards proliferation: Modeling and logic inference using forward and backward search. *BioMed Research International*, 2017:11. https://doi.org/10.1155/2017/1809513.

Suderman, R. and Hlavacek, W. S. (2017). Truml: A translator for rule-based modeling languages. In *Proceedings of the 8th ACM International Conference on Bioinformatics, Computational Biology,and Health Informatics*, ACM-BCB '17, pages 372–377, New York, NY, USA. ACM.

Talcott, C. (2016). The pathway logic formal modeling system: Diverse views of a formal representation of signal transduction. In *Workshop on Formal Methods in Bioinformatics and Biomedicine*.

Talcott, C. and Dill, D. L. (2005). The pathway logic assistant. In *Proceedings of the Workshop Computational Methods in Systems Biology (CMSB, G. Plotkin, Ed., 2005*, pages 228–239.

Vidil, F., Damiand, G., Dexet-Guiard, M., Guiard, N., Ledoux, F., Fousse, A., Fradin, D., Liang, Y., Meneveaux, D., and Bertrand, Y. (2002). Moka: 3d topological modeler.