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Introduction

Systems biology aims at understanding biological phenomena at different scales: Intracellular environment, cells, organs, living beings. Modelling and simulation of such systems by means of computational tools are essential research topics. The main issues include the recognition of the relevant parameters of the targeted phenomenon, the choice of the appropriate abstraction level and the ability of the model to bring out discriminating results about the simulated system. Among the possible parameters that the model can take into account (biochemical reactions, regulation networks, etc.), compartmentation of the biological systems is often a key feature [10]. Indeed, a spatial representation of the compartments is needed to describe both static and dynamic characteristics of the systems. In particular, the modifications of the neighbouring relations between compartments influence the evolution of the system parameters (e.g. concentration of molecules or more specifically proteins).

Different approaches have been used in order to model biocellular systems: Differential models for studying the evolution of concentrations (see Virtual Cell [8]), Boolean or discrete modelling for genetic regulatory networks, or rule-based modelling to simulate interacting molecular phenomena. Indeed, transformation rules are well-adapted to represent biochemical reactions (for instance complexation or catalysis). For such kinds of models, formal methods like model checking [1] or symbolic execution [7] have been fruitfully applied to verify that the model under consideration satisfies a known property of the biological system. Nevertheless, many rule-based models do not take compart-

ments into account and consequently consider, unrealistically, the systems as a homogeneous environment. Recently, such formalisms have been extended to take into account different compartments (see BioCham [2], Bioambients [11] and Brane calculi [3]). In these models, the compartmentation only captures simple phenomena (for instance endocytosis or exocytosis) and is not related to geometric aspects (position and shape of the objects).

Topology-based geometric modelling [6] is particularly adapted to represent compartmentation and is widely advocated for computer graphics. It deals with the representation of the structure of the objects (their decomposition into topological units: Vertices, edges, faces and volumes) and of the neighbouring relations that exist between topological units. Since it considers topological structure and geometry separately, it offers a sufficiently high level of abstraction. In particular, the manipulations of compartments and of frontiers between compartments can be handle in the same manner. This allows us to model the role of frontiers in the transport regulation of biochemical elements. In a previous work [9], we have already expressed basic topological operations by means of generic rules which can be applied to a large family of topological objects. In this paper, we explore the capabilities of this topology-based approach for discrimination of models of biological systems. The chosen case study is the Golgi apparatus. This intra-cellular entity is the place where proteins remain for a maturation phase before their excretion to extra-cellular environment. It is widely accepted that excretion of proteins is strongly linked to the spatial dynamics of the Golgi apparatus. However, the precise topology of the apparatus is not well defined and three main hypotheses have been emitted [5].

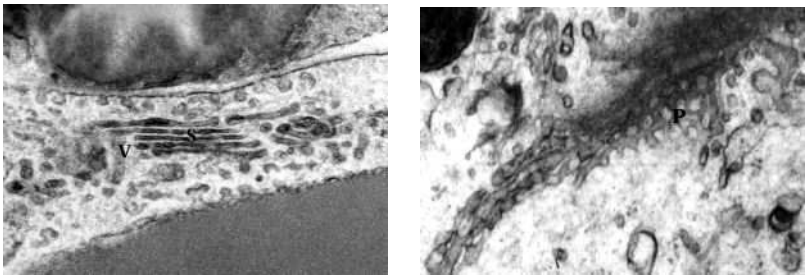
We introduce a computer-aided methodology in order to help biologists in analysing topology and dynamics of their different hypotheses. Our methodology is based on succesive simulations of topological models which implement different hypotheses: At each step, one simulation is done by hypothesis under study and parameters of models are updated according to the analysis of output parameters resulting from previous simulations. The biological knowledge is widely involved for initialisation, analysis and updating of parameter values. Moreover, when it seems to be pertinent to biologists, the same updatings are applied to each simulated model. Finally, an hypothesis can be rejected when biologist experts have the conviction that no additional parameter updating would lead to a model which fits with biological expectations (according to their knowledge).

The paper is organised as follows: The Golgi apparatus and the current hypotheses on its topology are presented in Section 1. Section 2 presents our rule-based topological approach. Section 3 is dedicated to a topology-based implementation of the Golgi apparatus hypotheses. In particular, we introduce two topological models corresponding to ongoing biological hypotheses. We also describe our computer-aided methodology for helping biologists in understanding and discriminating hypotheses about both topology and dynamics of the Golgi apparatus.

1 The Golgi Apparatus

1.1 General description

Discovered by Camillo Golgi in 1898, the Golgi apparatus (or dictyosome in plants) is an organelle whose role includes the transport of proteins synthesised by the cell from the endoplasmic reticulum to the plasma membrane or to lysosomes. Not only the Golgi apparatus sorts the proteins in order to transport them into adapted locations, but it is also the place of protein maturation by the means of loss of peptidic sequence and addition of sugars (glycosylation) or sulfate (sulfatation). The Golgi apparatus (see electron micrograph on Fig[4]. 1) is located near the nucleus and the centrosome. It generally appears as a stack of 5 or 6 disconnected cisternaes (the saccules) bounded with a phospholipidic membrane (see **S** on Fig. 1(a)). This stack is usually surrounded by small vesicles that bud out from the saccules (see **V** on Fig. 1(a)). Notice that on some pictures, the saccules appear perforated (see **P** on Fig. 1(b)). At last, the Golgi apparatus is a polarised object: The *cis* face is directed to the endoplasmic reticulum while the *trans* face is directed to the plasma membrane.



(a) Saccules stack (b) Saccules perforation

Fig. 1. The Golgi apparatus

1.2 Three hypotheses on the Golgi apparatus

Because of observation limitations, the complete structure of the Golgi apparatus is not precisely known. Indeed, with optical microscopy techniques, biologists observe the dynamics at the cost of a small resolution that does not allow them to observe the structure. By contrast, electron microscopy provides high resolution pictures but the observation is done on thin and inert section of the Golgi apparatus. Last but not least, those thin sections lead to

[4] We thank Alain Rambourg and Jean-Marc Verbavatz for the electron micrograph pictures of the Golgi Apparatus.

many interpretation mistakes at the time of a 3-dimensional reconstruction (for instance, both sphere and tube section can appear as a disc on a picture).

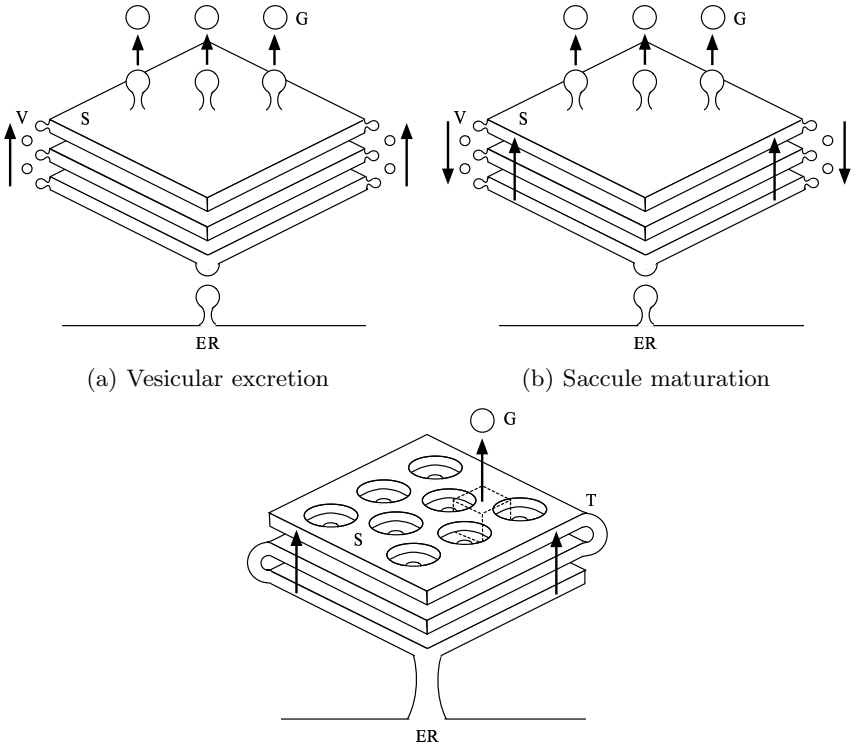
Thus, the path that proteins follow from the endoplasmic reticulum to the plasmic membrane or lysosomes is not well known. Three main hypotheses exist [5]. The two first hypotheses appear quite similar since they both suppose that vesicles play a major role in the excretion of proteins. In the vesicular secretion hypothesis (see Fig. 2(a)), an aggregate of endoplasmic reticulum (**ER**) fragments generates disconnected saccules (**S**). Proteins migrate through the stack by means of vesicles (**V**) that jump from one saccule to another. They are finally evacuated by the means of secretory granules (**G**) that bud out from the *trans* face. We know that enzymes in charge of the activation and the maturation of proteins are located near the *cis* face of the Golgi apparatus. In this first hypothesis, those enzymes may stay in the first saccules that are motionless by definition. In the second hypothesis, namely the saccule maturation (see Fig. 2(b)), saccules are still disconnected but follow an anterograde movement which fully explains the transport of proteins. Here, vesicles move along a retrograde flow in order to return enzymes that function early in the pathway to the *cis* region. The third hypothesis do not relies on any vesicule transporation. On the contrary, it considers a continuous membranes flow (see Fig. 2(c)) emerging from the endoplasmic reticulum. Indeed, observed endoplasmic reticulum fragments and vesicles are interpreted in this hypothesis as small sections of a tubular network that connects the saccules (**T**). In this case, proteins may follow the membrane flow and diffuse from one saccule to another along the tubes while enzymes may diffuse following a retrograde movement. Moreover, this last hypothesis takes into account the saccules perforation. This phenomenon may explain the creation of the secretory granules by the rupture of the junctions resulting from the perforation.

2 Topology-based geometric modelling for biological cellular processes

2.1 Topology-based geometric modelling

In order to take into account the biological compartments into our model, we base our work on the topology-based geometric modelling (topological modelling for short). This field of the computer graphics deals with the representation of the objects structure (their decomposition into topological units: Vertices, edges, faces and volumes) and of the neighbouring relations that exist between topological units. Among numerous topological models, we choose the n-dimensional generalised map [6] (n-G-maps for short). It defines the topology of an n-dimensional space subdivision and allows the representation of a large class of objects[5]. This topological model has the advantage of provid-

[5] quasi-varieties, orientable or not



(a) Vesicular excretion (b) Saccule maturation

(c) Continuous membrane flow

Fig. 2. Three hypotheses on the Golgi apparatus

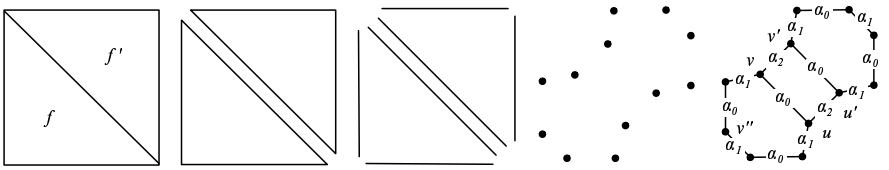


Fig. 3. 2-G-map intuition

ing a homogeneous mathematical definition for all dimensions. This genericity allows one to easily develop robust softwares.

On Fig. 3, a 2-dimensional object (see Fig. 3(a)) is successively decomposed into topological units: Faces (see Fig. 3(b)), edges (see Fig. 3(c)) and vertices (see Fig. 3(d)). These vertices, also called darts or half-edges, are the basic elements of the n-G-maps. Labelled graph edges are used in order to recover the neighbouring relations (see Fig. 3(e)). The label of an edge depends on

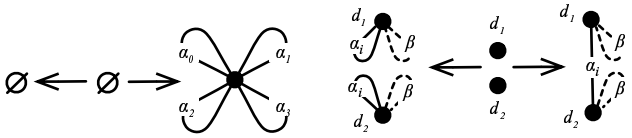
the nature of the neighbouring relation that is symbolised by the edge. For instance, the α_2-edge between v and v' illustrates the sticking of the two faces that include v and v' on the original picture (see faces f and f' on Fig. 3(a)). Here is the mathematical definition of an n-G-map:

Definition 1 (n-G-map). *Let $n \geq 0$. An n-G-map is an edge-labelled graph $G = (V_G, E_G)$ with labels in $\Sigma_E = \{\alpha_0, \ldots, \alpha_n\}$, s. t.:*

- *for all $v \in V_G, l \in \Sigma_E$, there exists a unique $v' \in V$ s. t. $(v, l, v') \in E_G$;*
- *for each $v \in V_G$, for all $\alpha_i, \alpha_j \in \Sigma_E$ such that $0 \leq i < i+2 \leq j \leq n$, there exists a cycle $(\alpha_i, \alpha_j, \alpha_i, \alpha_j)$ that reaches v.*

On the border of the objects, some darts do not have all of its neighbours. For instance, on Fig. 3(e) the dart v'' is not linked to another dart by an α_2-edge. However, according to the first point of definition all darts must have one incident label for each dimension. Thus, if a dart is not linked to another dart by an α_i-edge ($0 \leq i \leq n$), it exists an implicit α_i-loop that links the dart to itself. For instance, on Fig. 3(e), there is an implicit α_2-loop incident to vertex v''. The second point of the definition means that if two i-dimensional units are stuck, they must be stuck along a $(i-1)$-dimensional unit (this is a quasi-variety condition). For instance, on Fig. 3(a), the faces (2-dimensional units) f and f' are stuck along an edge (1-dimensional unit). In the corresponding 2-G-map, this property is translated into the presence of a cycle $(\alpha_0, \alpha_2, \alpha_0, \alpha_2)$ that reaches v on Fig. 3(e). Thus, since darts v and v' are linked with an α_2-edge, then darts u and u' are linked too.

2.2 Topological transformation rules



(a) addition rule (b) i-sew meta-rule

Fig. 4. rules and meta-rules

In order to build and modify topological objects, computer scientists have defined many topological operations on the n-G-maps. Moreover, it has been established that all of these operations can be decomposed into four basic operations: Dart addition, dart suppression, dart i-sew and dart i-unsew (these two last operations consist in, respectively, sticking and unsticking two i-

dimensional topological units along two isomorphic[6] $(i-1)$-dimensional topological units).

In [9], we have expressed the basic operations into graph transformation rules [4]. Classical rules are sufficient to express the dart addition (see Fig. 4(a)) and dart suppression (this new rule is obtained by swaping the left-hand and right-hand sides of the dart addition rule). Nevertheless, they are not sufficient to represent the dart i-sew and i-unsew operations. Indeed, the graph transformation to perform for sticking (resp. unsticking) two topological units depends on the size of these units. For instance, sticking two triangular faces implies to add 6 α_2 edges while sticking two square faces implies to add 8 α_2 edges. As it is clearly unreasonable to introduce as many rules as all the potential sizes of the topological units, we introduce the notion of graph transformation meta-rule that abstracts this infinite set of classical rules.

Definition 2 (meta-rule definition). *Let us consider Σ_E a set of labels and $\beta \notin \Sigma_E$ a new label. A graph transformation meta-rule on β, noted $L \leftarrow K \rightarrow R$, is a graph transformation rule where L, K and R are edge-labelled graphs with labels in $\Sigma_E \cup \{\beta\}$ and satisfying both following properties:*

- *for each edge in L (resp. R) of the form (v, β, v'), then $v = v'$;*
- *there exists at least in L an edge of the form (v, β, v). Graphically β-edges are noted with dotted lines.*

In [9], we define the translation of such a meta-rule into a set of classical rules. The dart i-sew meta-rule is introduced in Fig. 4(b) (the i-unsew meta-rule is obtained by simply swapping the left-hand and right-hand side of the i-sew meta-rule). On this figure, the β-edges represent the topological units that parameterise the meta-rule. In short, the i-sew meta-rule may be understood as follows: It matches two isomorphic i-dimensional topological units such that all α_i-edges are loops and links the vertices of both units with an α_i-edge.

2.3 Embedding

In order to model biological cellular processes we may want to associate different kinds of information to the topological units, that is to say to embed them. For instance, we may want to attach geometric or biochemical data to the volumes that abstract the biological compartments. Thus, we may want to write transformation rules whose application depends on embedding and which modify embedding information. In [9], we introduce a language in order to write embedding expressions. Here is an example of expressions (here, we give a simplified syntax whose meaning can be easily understood from the convention) which can be related to the sew meta-rule (see Fig. 4(b)):

$$3\_distance(d_1, d_2) \leq \epsilon \tag{1}$$

[6] Roughly speaking, two topological structures are said to be isomorphic if they are superposable.

$$3\_update\_position(d_1) \wedge 3\_update\_position(d_2) \quad (2)$$

Pre-condition (1) is used to restrict the application of the rule. The prefix 3 of 3_*distance* means that we consider the distance between 3-dimensional topological units (*i.e.* volumes). Thus, the condition means that the volumes which contain the darts d_1 and d_2 may be glued only if they are sufficiently close to each other according to a small distance, denoted ϵ here. Finally, the post-condition (2) updates the position of two volumes that have been glued.

3 Towards a topological discrimination of Golgi Apparatus models

3.1 Iterative approach for modelling biological systems

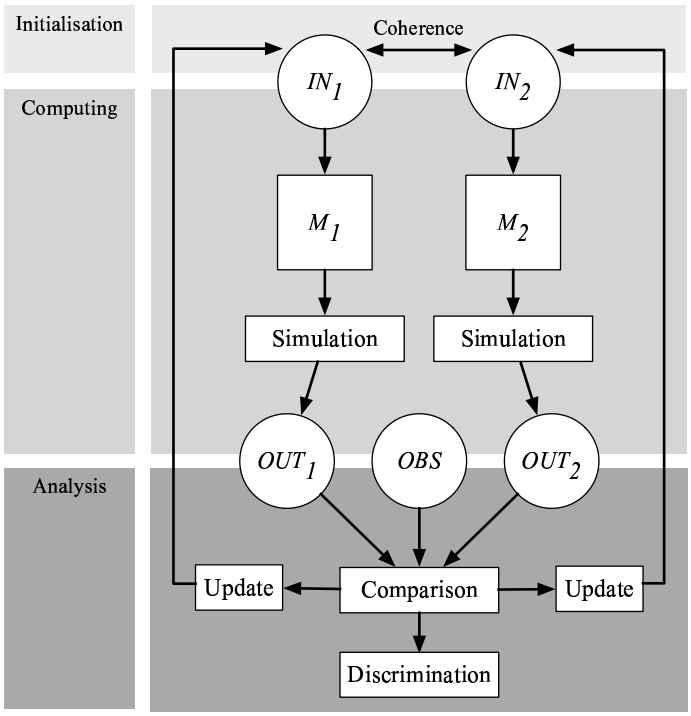


Fig. 5. Models discrimination loop

In Section 1.2, we have introduced three hypotheses that have been investigated by the biologists to explain the behavior of the Golgi apparatus. Our main goal consists in providing a framework to help biologists in discriminating which one better corresponds to the biological knowledge. We base our

approach on a topology-based geometric modelling of the hypotheses. Discriminating parameters may be highlighted by expert analyses of simulation processes.

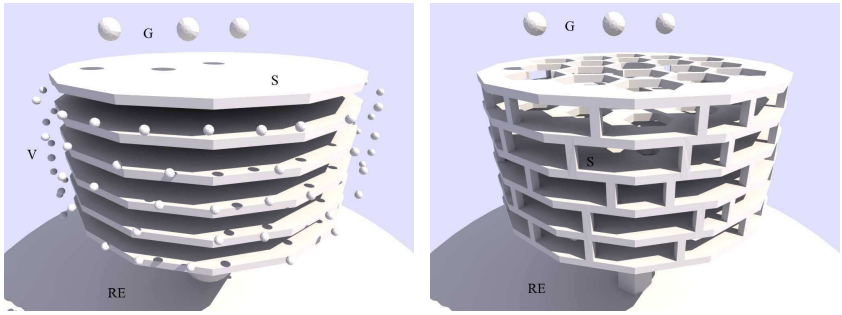
We choose to confront the third hypothesis, namely the continuous membrane flow, to one vesicular hypothesis. We focus on the saccule maturation hypothesis, which implies several different phenomena (both saccules and vesicles movements) and is therefore more subtle than the vesicular excretion hypothesis. Moreover, the vesicular hypotheses are strictly identical from the topological point of view (only dynamics differ) while the third one introduces significant topological differences (connected and perforated saccules).

Fig. 5 illustrates the loop of topological model discrimination. Two kinds of parameters appear on the figure. The input parameters (IN_1 and IN_2) are realistic values given by the biologists to initialise the simulations of, respectively, topological models M_1 and M_2 that implement the selected hypotheses. Even if some parameters are specific to only one model (for instance, the vesicle diameter is only related to the vesicular hypothesis), they are correlated to parameters of the other model (for instance, to be compatible with same electron micrograph pictures, the vesicle diameter should be linked to the diameter of tubes connecting saccules in the continuous membrane flow hypothesis). This coherence between parameters of M_1 and M_2 is necessary for the models discriminating process. Indeed, a decision which discriminates a model with respect to another one only holds up to some common biological observations taken into account in both models. OUT_1 and OUT_2 parameters result from the simulations of, respectively, M_1 and M_2 (for instance, the flux of excreted proteins are output parameters for both models). After each iteration, results of the simulations are compared with biological experimental observations (OBS on the figure). Different situations result from this comparison:

- Both models are not coherent with observations. If an updating of input parameters seems to lead to a more accurate simulation for at least one of both models, both IN_1 and IN_2 parameters are updated (preserving coherence between them) and new simulations are performed. Otherwise, the topological models have to be called into question.
- Both models are coherent with observations. They have to be refined: The models are detailed by, for instance, adding new parameters, likely to refine informations manipulated by both models.
- Only one model is coherent with observations. If an updating of input parameters seems to lead to a more accurate simulation for the incoherent model, the associated input parameters are updated (the coherence between parameters leads us to update also the input parameters of the other model) and new simulations are performed. Otherwise, the discrimination process is completed since no updating of the incoherent model seems to make it coherent with observations.

The static definition of topological models (M_1 and M_2 on the figure) is complete. Intuitively, such a static model serves as initial state of the dynamic process and represents a topological description of the steady state for each of the considered hypotheses. The dynamic processes (model simulation and discrimination) are initiated. The first results are presented in the following subsections.

3.2 Topological models of the Golgi Apparatus



(a) Plate stack model (b) Tower model

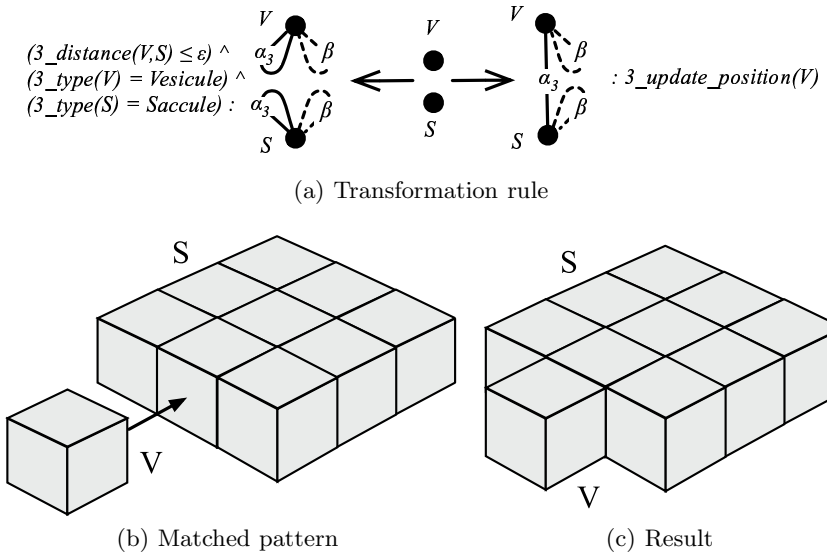
Fig. 6. 3-G-map topological representation of Golgi Apparatus

Fig. 6 illustrates 3-G-map topological representations of the Golgi apparatus. The plate stack model (see Fig. 6(a)) represents the saccule maturation hypothesis and the tower model (see Fig. 6(b)) represents the continuous membrane flow hypothesis.

In purely topological modelling, we do not deal with the geometry (the shape) of the objects. First of all, we have to pay attention to their topological characteristics. Indeed, geometric data can be embedded later into the topological units. Thus, the main interest of the plate stack model and the tower model is to point out the topological distinction that exists between the Golgi apparatus hypotheses. The first distinction is the saccules (**S**) connection. The proteins are transported through vesicles (**V**) in the plate stack while they diffuse into tubes (**T**) which connect the saccules in the tower model (the proteins do not appear explicitly on the models, they are abstracted by concentrations which appear as embedding information associated to the compartments). Moreover, small parts of the endoplasmic reticulum aggregate into saccules in the first model while the endoplasmic reticulum is connected to the *cis* face in the second one. Finally, secretory granules (**G**) bud out from the *trans* face of the plate stack while they result from the rupture of the bee nest structure which appears progressively (from the *cis* face to the *trans* face) in the tower model.

Both models have been elaborated by following a loop of topological model refinements. Biologists have deeply analysed intermediate models by proposing either topological modifications or parameter updating. This is particulary true for the most recent hypothesis (the continuous membrane flow) for which the tower model presented in Fig. 6(b) gives a new insight on its possible topological structure.

3.3 Simulating and discriminating the models



(a) Transformation rule

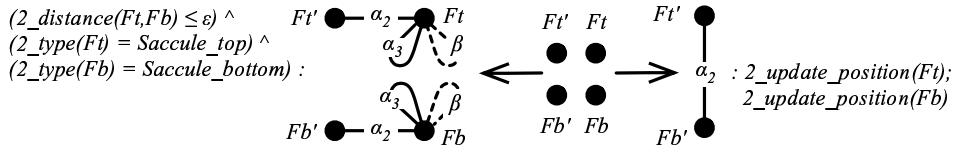
(b) Matched pattern

(c) Result

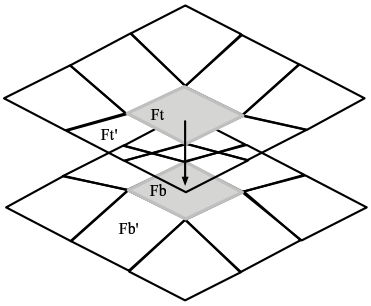
Fig. 7. Gluing a vesicle with a saccule

The interaction with biologists experts of the Golgi apparatus has yet been fructuous. Indeed, as stated in Section 3.2, the conception of the static topological models that abstract the second and third Golgi apparatus hypotheses is now complete. Our next goal consists in providing transformation rules which animate the models. In Section 2, we have introduced a mean to write rules that transform topological objects. Here, we give two examples of rules that may be used in order to transform dynamically, *i.e.* to simulate, the plate stack and tower models.

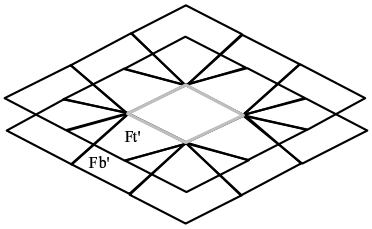
Fig. 7 and Fig. 8 introduce two transformation rules which animate models. The first one is dedicated to the plate stack model. It models the gluing of a vesicle with a saccule which initiates their fusion. Fig. 7(b) introduces a simplified representation of the matched pattern, it contains a vesicle (**V**) close to a saccule (**S**). The transformation rule (see Fig. 7(a)) glues them



(a) Transformation rule



(b) Matched pattern



(c) Result

Fig. 8. Perforating a saccule

(using a 3-sew operation) and updates the position of the glued vesicle (see Fig. 7(c)). On the rule, V and S are respectively dart of vesicule and saccule (β-edges match the volumes). The second rule is dedicated to the tower model, it models the saccule perforation. The matched pattern (see Fig. 8(b)) contains two close faces (**Ft**) and (**Fb**) that belong to the same saccule (one is on the top, the other on the bottom). The rule (see Fig. 8(a)) executes the perforation removing faces (**Ft**) and (**Fb**) and linking their neighbours (see Fig. 8(c)). On the rule, Ft and Fb are respectively darts of removed top and bottom faces, Ft' and Fb' are neighbour faces, and β matches faces.

The definition of such graph transformation meta-rules is mandatory for animating the topological models and constitutes the first stage for simulations of such complex systems. They define the syntactic part of the simulations, in other words, they define what kind of transformations the simulator can implement. But this definition does not explain how these transformation rules are applied. Now, we have to explore what kind of strategies of application of transformation rules have to be taken into consideration in order to simulate biological processes.

Conclusion

In this paper, we present a computer-aided methodology to better understand the dynamics of biocellular processes that strongly depend on compartmentation. Our framework is based on the use of topology-based geometric modelling

in order to represent compartments with their neighbouring relations and on transformation rules which allow us to simulate at the same time topological, geometric and biochemical mechanisms. We define two topological models, called the plate stack model and the tower model, and give examples of rules useful for their animation. The topological models implement two ongoing Golgi apparatus hypotheses. They strongly differ by their topology: in the plate stack model, saccules are disconnected and proteins move from one saccule to another by the mean of vesicles, while in the tower model, saccules are connected with tubes that allow proteins to cross the apparatus. Both these static toplogical models fit with the available biological knowledge. Simulations for each model are simultaneously iterated within our methodological framework. At each step, input parameters are updated in a coherent way between the two models and in accordance to the biological knowledge. Indeed, the modification of a particular parameter for a given model implies to modify in the same way the correlated parameters in the other model. A model is given up when one can no more update parameters in a satisfactory manner.

Another way to discriminate models is to study wich properties are preserved or reached by simulations. Model-checking technics have already been used to analyse discrete models representing biocellular phenomena (e.g. genetic regulatory networks) and to predict some properties about them. Since our underlying theoretical models are also discrete (they are derived from n-G-maps and transformation rules), we plan to associate such kind of technics to exhibit properties that seem to emerge (according to biologists'observations) from the simulations. If such new properties can be studied *in vivo* by biologists, then biological experiments inspired by such emerging computed properties would enrich our discrimination methodology: In the same way as the biological knowledge already guides the updating of simulation parameters, properties issued from simulation would also guide biological experiments. Such a mutual interaction between experiments and simulations would help the biologists in better understanding the biocellular phenomena under interest.

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References

1. G. Bernot, J.-P. Comet, A. Richard, and J. Guespin. Application of formal methods to biological regulatory networks: Extending Thomas' asynchronous logical approach with temporal logic. *Journal of Theoretical Biology*, 229(3):339–347, 2004.
2. L. Calzone, F. Fages, and S. Soliman. Biocham: an environment for modeling biological systems and formalizing experimental knowledge. *Bioinformatics*, 22(14):1805–1807, 2006.
3. L. Cardelli. Brane calculi. interactions of biological membranes. In *Proc. Computational Methods in Systems Biology*, volume 3082 of *Lecture Notes in BioInformatics*, pages 257–280. Springer, 2005.
4. H. Ehrig, K. Ehrig, U. Prange, and G. Taentzer. *Fundamentals of Algebraic Graph Transformation (Monographs in Theoretical Computer Science. An EATCS Series)*. Springer, Secaucus, NJ, USA, 2006.
5. F. Képès, A. Rambourg, and B. Satiat-Jeunemaître. Morphodynamics of the secretory pathway. *International review of cytology*, 242:55–120, 2004.
6. P. Lienhardt. Subdivision of n-dimensional spaces and n-dimensional generalized maps. In *SCG'89*, pages 228–236. ACM Press, 1989.
7. D. Mateus, J.-P. Gallois, J.-P. Comet, and P. Le Gall. Symbolic modeling of genetic regulatory networks. *Journal of Bioinformatics and Computational Biology*, 2007 [to appear].
8. University of Connecticut Health Center NRCAM. Virtual cell. www.vcell.org.
9. M. Poudret, J.-P. Comet, P. Le Gall, A. Arnould, and P. Meseure. Topology-based geometric modelling for biological cellular processes. In *LATA'07*, to appear in LNCS, April 2007. Preliminary version available at: www.ibisc.univ-evry.fr/ comet/MESPAGES/2007LATA.pdf.
10. J. F. Presley, T. H. Ward, A. C. Pfeifer, E. D. Siggia, R. D. Phair, and J. Lippincott-Schwartz. Dissection of COPI and Arf1 dynamics in vivo and role in Golgi membrane transport. *Nature*, 417:187–193, May 2002.
11. A. Regev, E. M. Panina, W. Silverman, L. Cardelli, and E. Shapiro. Bioambients: an abstraction for biological compartments. *Theor. Comput. Sci.*, 325(1):141–167, 2004.