A Model of Colonic Crypts using SBML Spatial

Daniele Ramazzotti
Dipartimento di Informatica, Sistemistica e Comunicazione
Università di Milano-Bicocca
Milan, Italy
daniele.ramazzotti@disco.unimib.it

Carlo Maj
Dipartimento di Informatica, Sistemistica e Comunicazione
Università di Milano-Bicocca
Milan, Italy
carlo.maj@disco.unimib.it

Marco Antoniotti
Dipartimento di Informatica, Sistemistica e Comunicazione
Università di Milano-Bicocca
Milan, Italy
marco.antoniotti@disco.unimib.it

Colonic crypts are invaginations of the connective tissue of human intestine and are supposed to be the site where mutations affecting the stem cells can occur leading to the emergence and progression of Colorectal Cancer (CRC)[3]. See figure 1 for a schematic representation of a colonic crypt from[7].

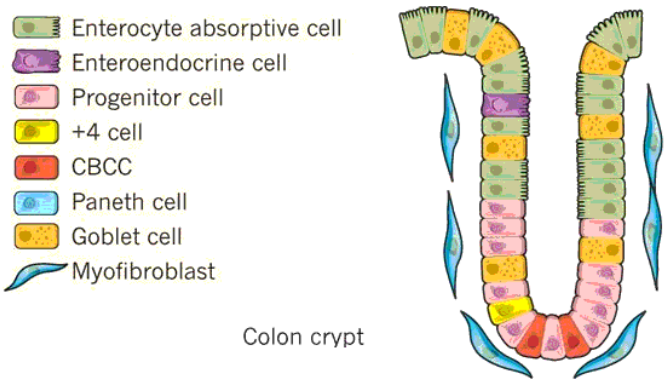

Figure 1: Schematic representation of a colonic crypt from[7]. In the figure, on the left the cellular types present in the crypt are listed, while on the right the shape of the crypt is represented.

Different models aimed at describing the colonic crypt behavior have been defined over the years and can be divided in two groups: *in-lattice models*, [5], [8], and *off-lattice*, [1]. See [3] and further reference therein for a recent review on the subject.

In this work we propose a computational model that implements the most recent SBML format [4] and, in particular, the SBML *Spatial Processes* package. SBML is currently the most used standard for representing computational models in systems biology. It is open and has widespread software support and a community of users and developers.

A. Graudenzi, G. Caravagna, G. Mauri, M. Antoniotti (Eds.):
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The *Spatial Processes* package introduces a new tag, named *geometry*, which enables an explicit definition of a spatial environment for the simulation. The possibility of an explicit representation of spatial dynamics increases the representation power of SBML. The SBML *Spatial Processes* package has been proposed in 2010 and is currently still under development. At March 2013 the latest version of this package is the 0.81 release of July 2012[6]. In this work, we refer to this version of SBML *Spatial Processes*.[1]

Our goal is to model the dynamics and the spatial evolution of the tissue by taking into account both the cellular differentiation and cellular migration processes in specific crypt locations. Our model consists of two main parts: the dynamic component, which models the cellular differentiation process, and the spatial component, which models the positioning and the movement of cells.

The basic dynamic part of the model describes 8 cellular types and 12 cellular transformations. The representation with SBML core has been done by describing the cellular types as species and the cellular transformation as reactions. In addition to these 8 species, an *empty* cell is considered in order to represent the empty space in the colonic crypt.

More in details, the 8 cellular types are Stem cell, Paneth cell, Ta1 (mutated cells of type 1), Ta2a (mutated cells of type 2-a), Ta2b (mutated cells of type 2-b), Goblet cell, Enteroendocrine cell and Enterocyte absorptive cell. The choice of these cellular types has been done to represent the cellular differentiation processes that gradually transforms the stem cell progeny into four different fully differentiated cellular types (paneth, goblet, enteroendocrine and enterocyte). Three types of partially differentiated cellular types are present (ta1, ta2a, ta2b) in our model.

We have defined twelve reactions: seven reactions to represent the cellular differentiations, one reaction regarding the duplication of the stem cells and four reactions to represent the degradation of the final differentiated cell types (paneth, goblet, enteroendocrine and enterocyte). The duplication and the degradation reactions are present in order to assure the attainment of a steady condition. More in detail, the duplication of the stem cells assures that the system does not cease to work as a consequence of the depletion of stem cells, while the degradation of the differentiated cell prevents the unlimited formation of the terminal node of the network. In figure 2 the resulting dynamic network is shown.

Once the spatial system has been defined, it is linked to and guided by the dynamic part of the system to reflect the spatial evolution of the colonic crypts (i.e. downward displacement of the Paneth cells and upward movement of the other cells once they specify from stem cells).

[1] In the *geometry* tag, five new SBML subtags are permitted:

- *ListOfCoordinateCompartments*: in this sub-tag the spatial frame is defined. Different types of reference frames are permitted: in our model it is a 3-dimensional Cartesian System where the x-axis represent the width, the y-axis the height and the z-axis the depth of the geometrical shapes.
- *ListOfDomainTypes*: in this sub-tag, homogeneous spatial zones present in the system should be defined. Each spatial zone is intended as being anatomically and physiologically similar and the domain types defined in this tag can refer to one or multiple concrete domains (defined in the next tag). For instance, in our case the cell domain types have been defined here, while the single concrete cells have been defined in the next tag.
- *ListOfDomains*: the domains represent contiguous regions identified by the same domain type. For each domain a position in the reference frame defined before is assigned. The domains defined here should match the initial condition of the dynamic model.
- *ListOfAdjacentDomains*: adjacent domain types can be defined here two by two. In our case we have a domain type for each cell position in the crypt hence each domain type has multiple adjacent domains.
- *ListOfGeometryDefinitions*: here is defined the geometrical structure of each domain type. This is an abstract structure to be assigned to the real domains linked through the domain types definition. SBML *Spatial Processes* offers four possible ways to define the geometry: in our case the *AnalyticalGeometry* tag has been adopted.

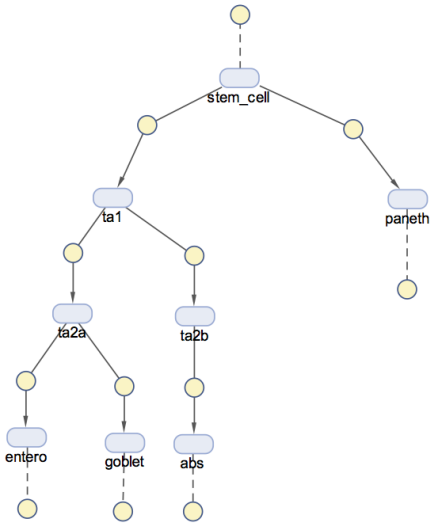

Figure 2: Model Network: the resulting network generated by the model. It involves the differentiated cell types (paneth, goblet, enteroendocrine and enterocyte) and three partially differentiated cells (ta1, ta2a, ta2b).

The spatial part of the model exploits an in-lattice representation where the colonic crypt is described with a series of cubic cells which can be empty or filled with one of the 8 species defined in the dynamic model. The colonic crypt has been represented as a hollow parallelepiped placed in a 3-dimensional xyz Cartesian reference frame. The width and depth of the parallelepiped are represented respectively by the x and z axis. The y-axis represents the height of the parallelepiped. The spatial dynamics of the system consists in upward and downward movements, hence the y-values can be within a certain range defined by the dynamic itself. See figure 3.

Figure 4 shows a section of the crypt as represented in our model with a view from above.

Finally, three special layers have been defined in the crypt. The first one is located in the middle-lower part of the crypt and here new stem cells are created in order to feed the system and avoid the possibility of completly consume all the stem cells. Then two more special layers are defined at the lower and upper border of the system in order to consume the cells that are leaving the crypt.

This work is a first attempt to attach the task of using SBML *Spatial Processes* to model colonic crypts. The latest *VCell* release[2], which is the first modeling software implementing the extension package, has been adopted to define and import the model.

Currently, *VCell* is under developement and its spatial simulation capabilities will be improved in order to allow more powerfull simulations and parameter tuning, which will be the next steps of this work.

Ongoing simulations are aimed at defining the parameter tuning for the model parameters such, i.e. the initial conditions and the reaction rates that better represents the colonic crypt dynamics and allows

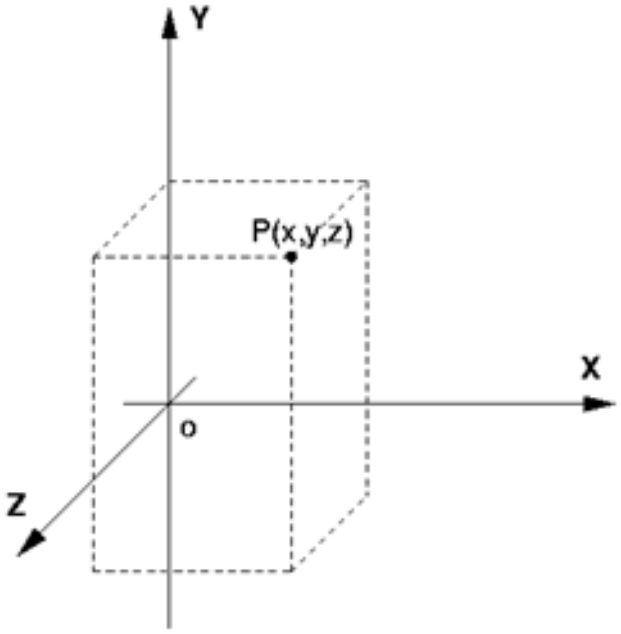

Figure 3: In our model the space is discretized in a finite number of cells following an in-lattice approach.

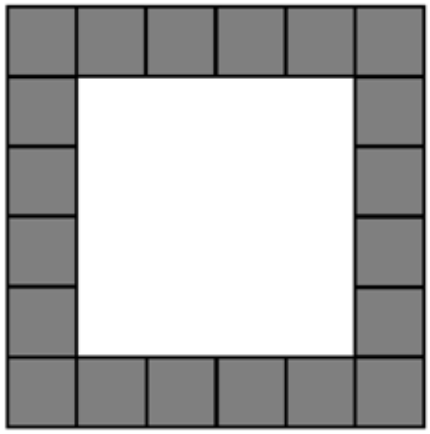

Figure 4: A Section of the Colonic Crypt from above, showing the positioning of the cells and that the interior area is empty.

the maintenance of a stable dynamic state, i.e. homeostasis.

Besides, further simulations will be performed in order to verify the robustness and the homeostasis of the system. This will be accomplished by analysing the influence of a variation of the initial conditions, as well as perturbations of other key parameters of the model.

References

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[2] *Virtual Cell Modeling and Analysis Software*. `http://www.nrcam.uchc.edu/`.

[3] Giovanni De Matteis, Alex Graudenzi & Marco Antoniotti (2012): *A review of spatial computational models for multi-cellular systems, with regard to intestinal crypts and colorectal cancer development*. Journal of Mathematical Biology, pp. 1–54, doi:10.1007/s00285-012-0539-4.

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