Colonic Crypts Modeling: An Exercise with SBML Spatial and VCell

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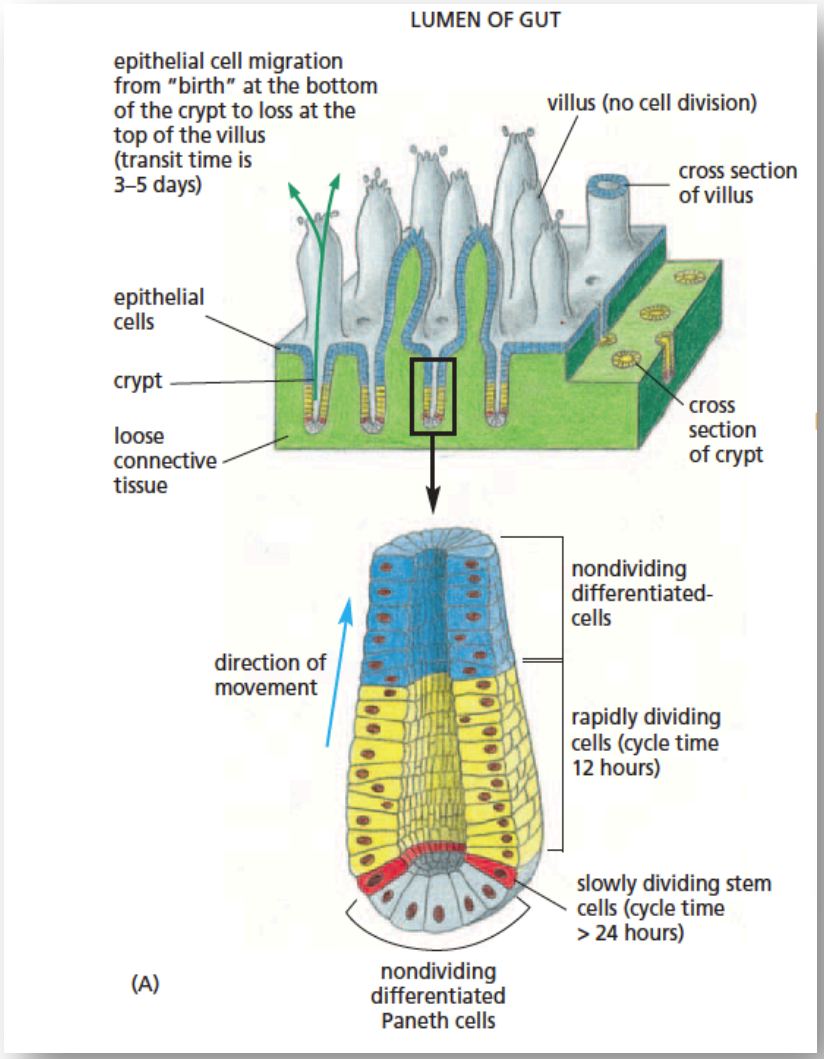
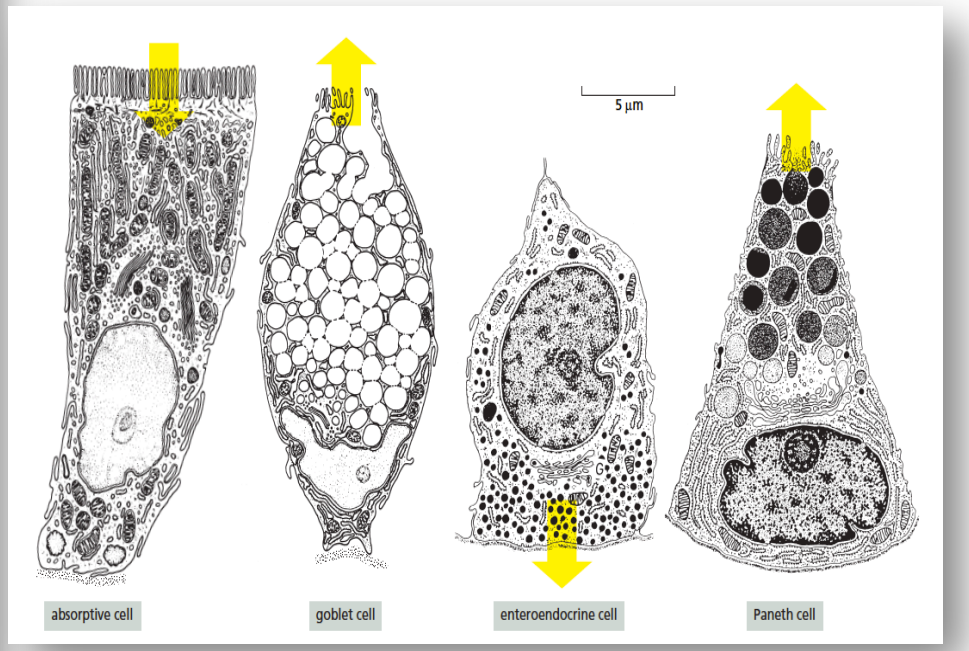
Outline

- A bit of context: Colorectal crypts, colorectal cancer, simulation schemes (in-lattice, off-lattice), multiscale simulations
- The exercise
  - Rendering a crypt with SBML Spatial
  - Using VCell
  - Issues found

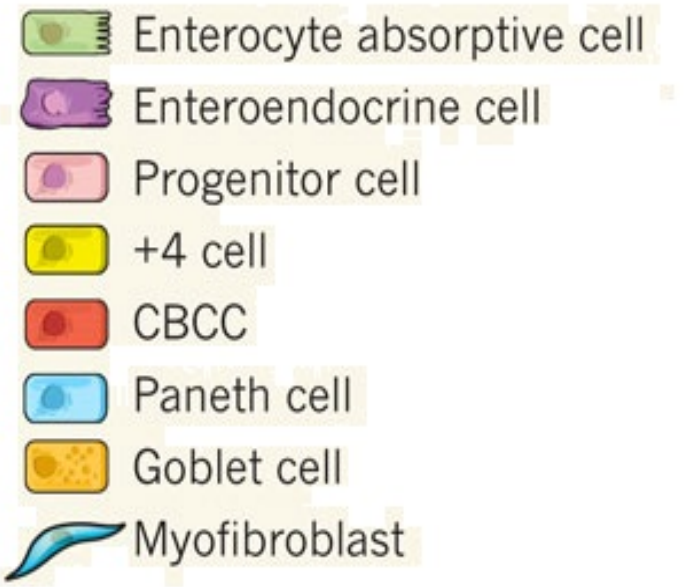
Intestinal crypts

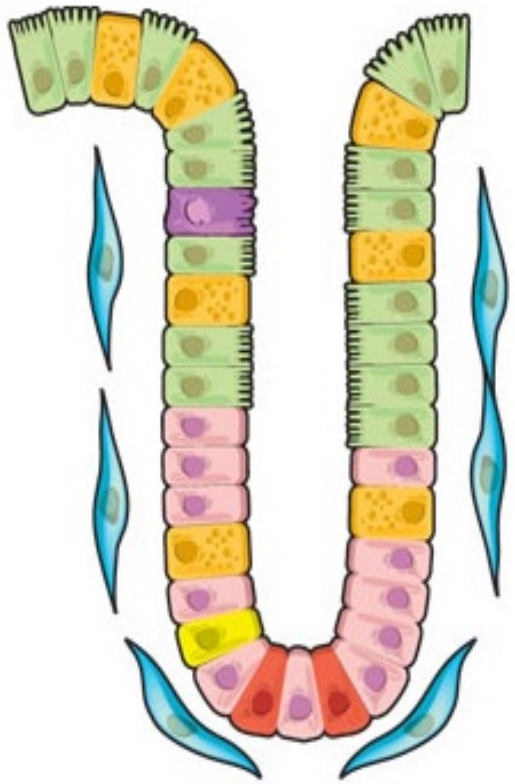




From: Alberts, B. et al. Molecular Biology of the Cell, 5th ed. Garland Science (2007)

Cellular Types

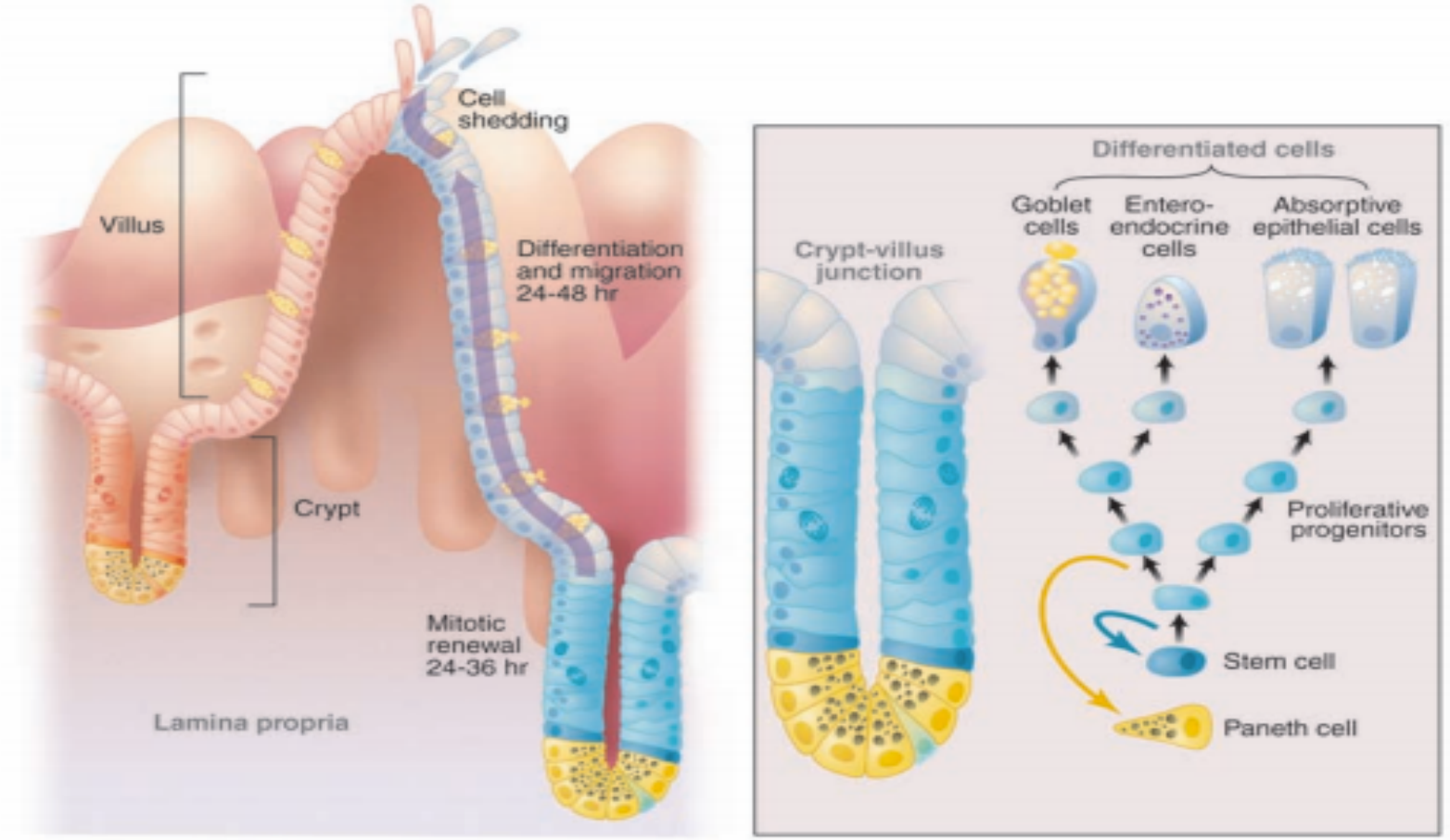




Colon crypt

Cfr. Microenvironmental regulation of stem cells in intestinal homeostasis and cancer
doi:10.1038/nature10212
Jan Paul Medema & Louis Vermeulen

Lineage Commitment Tree



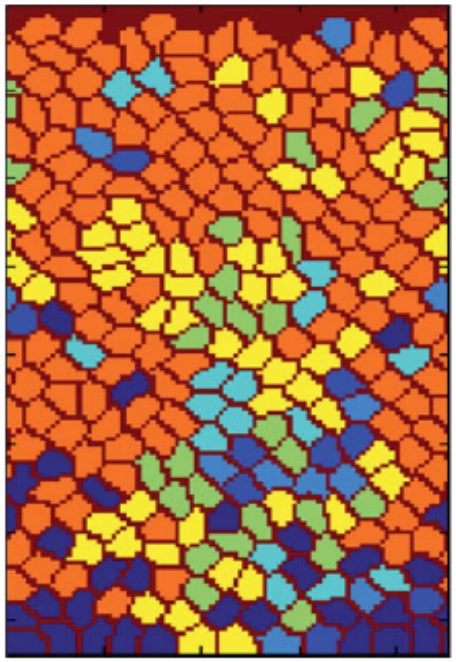
Potential for in Vitro Experimental Validation

- Recently, several researchers interested in cancer (especially in CSCs) have looked at the potential of growing “mini-guts” in vitro

- As an example:
  Growing Self-Organizing Mini-Guts from a Single Intestinal Stem Cell: Mechanism and Applications
  Toshiro Sato and Hans Clevers
  Science **340**, 1190 (2013);
  DOI: 10.1126/science.1234852

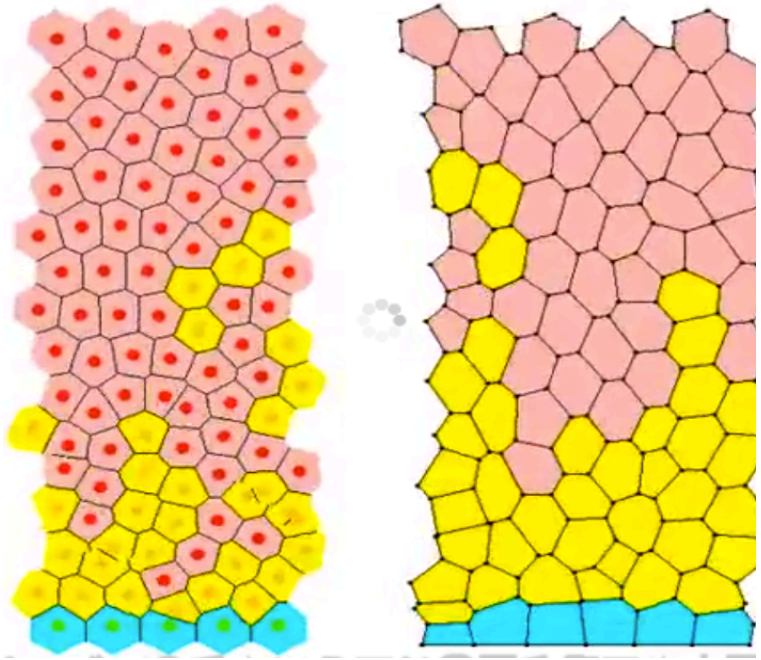
Spatial Models for Intestinal crypt Simulations

In lattice – CPM
(e.g., CompuceII3D)



From: Wong et al. Journal of The Royal Society Interface 7(Suppl 3), S351-S363 (2010).

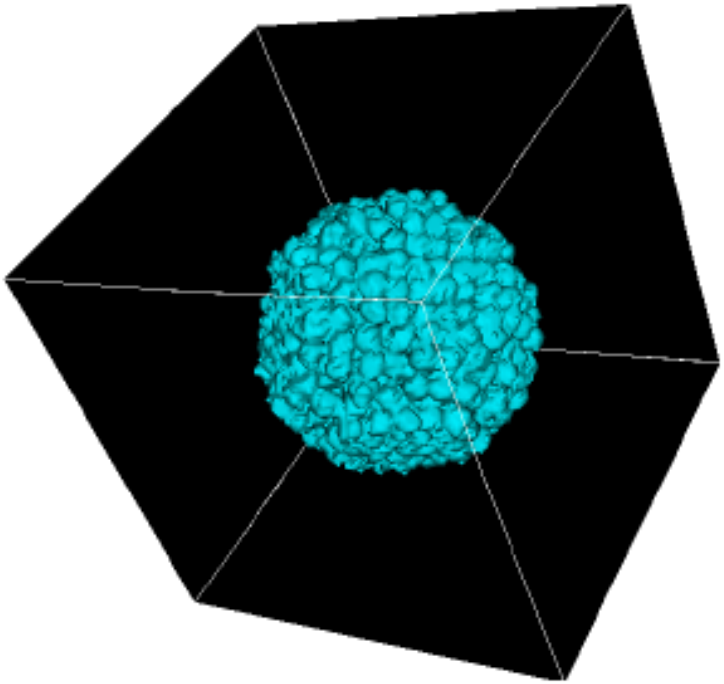
Off lattice
(e.g. CHASTE, CellSys)



From: Pitt-Francis, J. et al. Computer Physics Communications 180(12), 2452 - 2471 (2009).

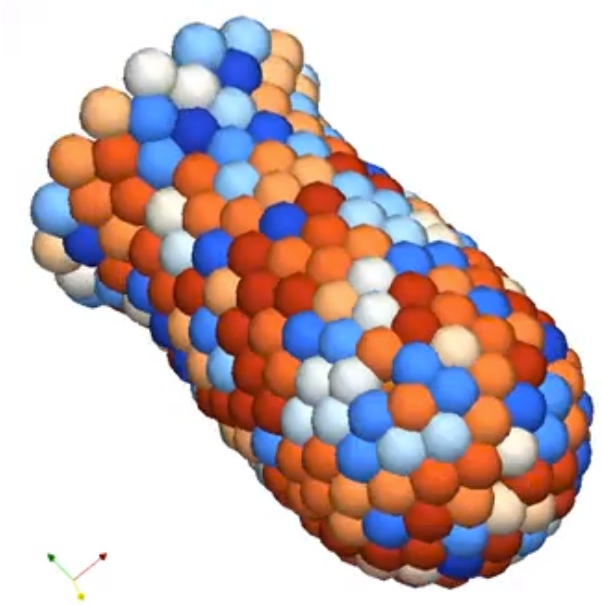
Extensions in 3D

In lattice (e.g. CPM)



http://www.compucell3d.org/

Off lattice (e.g. CHASTE, CellSys)



From: Pitt-Francis, J. et al. Computer Physics Communications 180(12), 2452 - 2471 (2009).

A multiscale model of intestinal crypts

- Intestinal crypts are a clear example of multiscale system:
  - Low-level processes:
  - Gene regulatory networks
  - Signaling pathways
  - Intercellular communication
- High-level "hallmark" phenomena
  - Angiogenesis
  - Enabling replicative immortality
  - Metastasis
  - Evading growth suppressors
  - Sustaining proliferative signaling
  - Resisting cell death
- Tumor microenvironment
  - Stroma interaction

Model of Gene Regulatory Network (GRN):
Noisy Random Boolean Networks (RBN)

+

Spatial/morphological model of crypt dynamics:
Cellular Potts Model (CPM)

MULTISCALE MODEL

SBML SPATIAL

SBML 3 Spatial Extension:

- the current version of the extension is the 0.81 release of July 2012*.

- a new tag, named *geometry*, has been introduced and it enables an explicit definition of a spatial environment for simulation.

*James Schaff.SBML Spatial Extension proposal – Oct 9, 2010 – COMBINE meeting, Version 0.81 release on 15 August 2012.

SBML3 Spatial Tags 1/2

- **`ListOfCoordinateCompartments`**: Definition of the spatial reference frame .
  - In our case 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.

- **`ListOfDomainTypes`**: Definition of homogeneous spatial zones present in the system.
  - In our case the domain type is a cell in the colonic crypt.

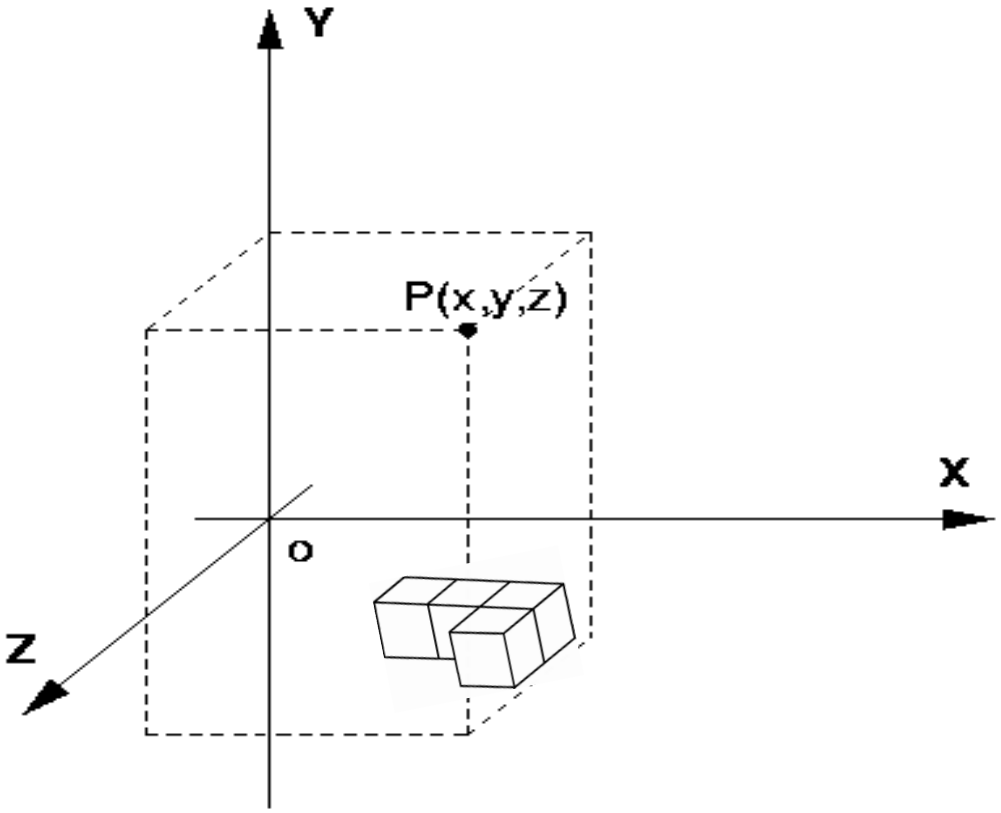
- **`ListOfDomains`**: Definition of contiguous regions identified by the same domain type.
  - In our case the specific cells in the colonic crypt.

SBML3 Spatial Tags 2/2

- **`ListOfAdjacentDomains`**: Definition of adjacent domain types.
  - In our case the adjacent cells in the colonic crypt.

- **`ListOfGeometryDefinitions`**: Definition of the geometrical structure of each domain type (i.e., analytic, sampledField, constructive solid geometry, and parametric shapes).
  - In our case the `AnalyticalGeometry` tag has been adopted, which, in our case, was a stop-gap measure

Spatial Structure



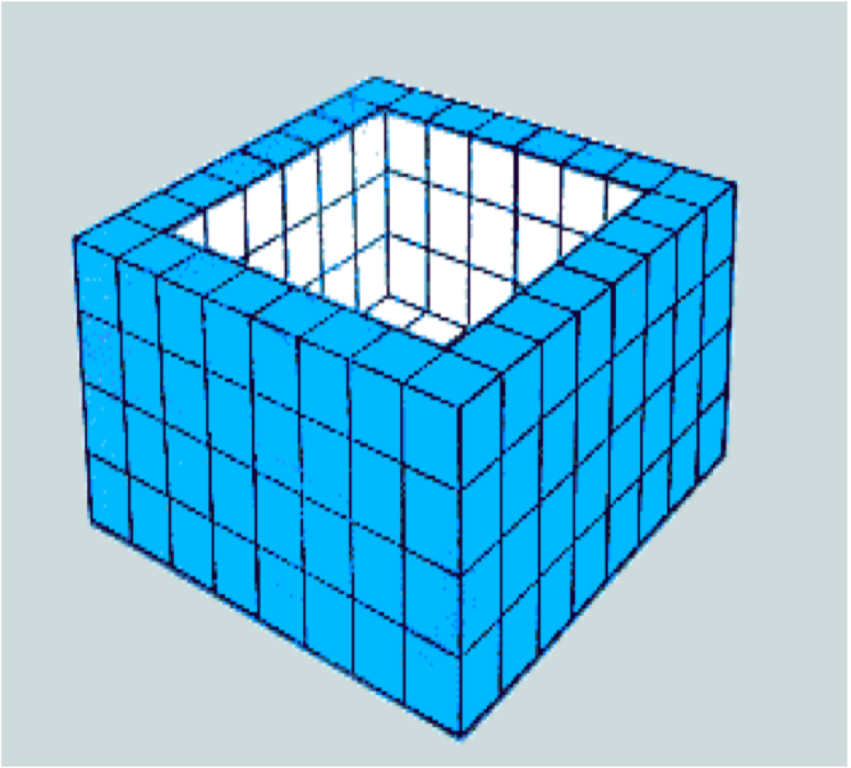
- The crypt as a hollow parallelepiped
- The cells as cubes

Spatial Initial Condition

- A set of stem cellular types (no cells of other types).
- Located in the bottom of the colonic crypt.
- The cells above and below the layer of stem cellular types are empty

Crypt SBML Spatial 1/3

- **Dynamic model:** cellular differentiation
- **Spatial model:** the movement is simulated by consuming a cellular type in a given cell and creating a new one in the upper or lower cell



Crypt SBML Spatial 2/3

The dynamic model based on SBML core and the geometry based on SBML spatial are connected by the **`compartmentMapping`** tag

```
<listOfCompartments>
  <compartment id="id_comp_cel_1" name="comp_cel_1" size="1" spatialDimensions="3" constant="false">
      <spatial:compartmentMapping compartment="id_comp_cel_1" spatial:domainType="colonic_crypt_cell_1" spatial:unitSize="1" spatial:spatialId="com_dom_mapping_1"/>
  </compartment>
```

```
<spatial:geometry spatial:coordinateSystem="XYZ">
   <spatial:listOfCoordinateComponents>
      <spatial:coordinateComponent spatial:spatialId="x" spatial:componentType="cartesianX" spatial:index ="0" spatial:sbmlUnit="microns">
         <spatial:boundaryMin spatial:spatialId ="x_min" spatial:value="0"></spatial:boundaryMin>
         <spatial:boundaryMax spatial:spatialId ="x_max" spatial:value="2"></spatial:boundaryMax>
      </spatial:coordinateComponent>
      <spatial:coordinateComponent spatial:spatialId="y" spatial:componentType="cartesianY" spatial:index ="1" spatial:sbmlUnit="microns">
         <spatial:boundaryMin spatial:spatialId ="y_min" spatial:value="0"></spatial:boundaryMin>
         <spatial:boundaryMax spatial:spatialId ="y_max" spatial:value="6"></spatial:boundaryMax>
      </spatial:coordinateComponent>
      <spatial:coordinateComponent spatial:spatialId="z" spatial:componentType="cartesianZ" spatial:index ="2" spatial:sbmlUnit="microns">
         <spatial:boundaryMin spatial:spatialId ="z_min" spatial:value="0"></spatial:boundaryMin>
         <spatial:boundaryMax spatial:spatialId ="z_max" spatial:value="2"></spatial:boundaryMax>
      </spatial:coordinateComponent>
   </spatial:listOfCoordinateComponents>
```

Crypt SBML Spatial 3/3

In the **`domainType`** tags homogeneous spatial zones are defined. The specific zone associated with a **`domainType`** are then instantiated by the **`domain`** tag

```
<spatial:listOfDomainTypes>
   <spatial:domainType spatial:spatialId="colonic_crypt_cell_1" spatial:spatialDimension="3"></spatial:domainType>
   <spatial:domainType spatial:spatialId="colonic_crypt_cell_2" spatial:spatialDimension="3"></spatial:domainType>
   <spatial:domainType spatial:spatialId="colonic_crypt_cell_3" spatial:spatialDimension="3"></spatial:domainType>
   <spatial:domainType spatial:spatialId="colonic_crypt_cell_4" spatial:spatialDimension="3"></spatial:domainType>
   <spatial:domainType spatial:spatialId="colonic_crypt_cell_5" spatial:spatialDimension="3"></spatial:domainType>

<spatial:listOfDomains>
    <spatial:domain spatial:spatialId ="colonic_crypt_cell_domain_1" spatial:domainType="colonic_crypt_cell_1">
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          <spatial:interiorPoint spatial:coord1="0" spatial:coord2="0" spatial:coord3="0"></spatial:interiorPoint>
          <spatial:interiorPoint spatial:coord1="1" spatial:coord2="1" spatial:coord3="1"></spatial:interiorPoint>
       </spatial:listOfInteriorPoints>
    </spatial:domain>
    <spatial:domain spatial:spatialId ="colonic_crypt_cell_domain_2" spatial:domainType="colonic_crypt_cell_2">
       <spatial:listOfInteriorPoints>
          <spatial:interiorPoint spatial:coord1="0" spatial:coord2="0" spatial:coord3="1"></spatial:interiorPoint>
          <spatial:interiorPoint spatial:coord1="1" spatial:coord2="1" spatial:coord3="2"></spatial:interiorPoint>
       </spatial:listOfInteriorPoints>
    </spatial:domain>
```
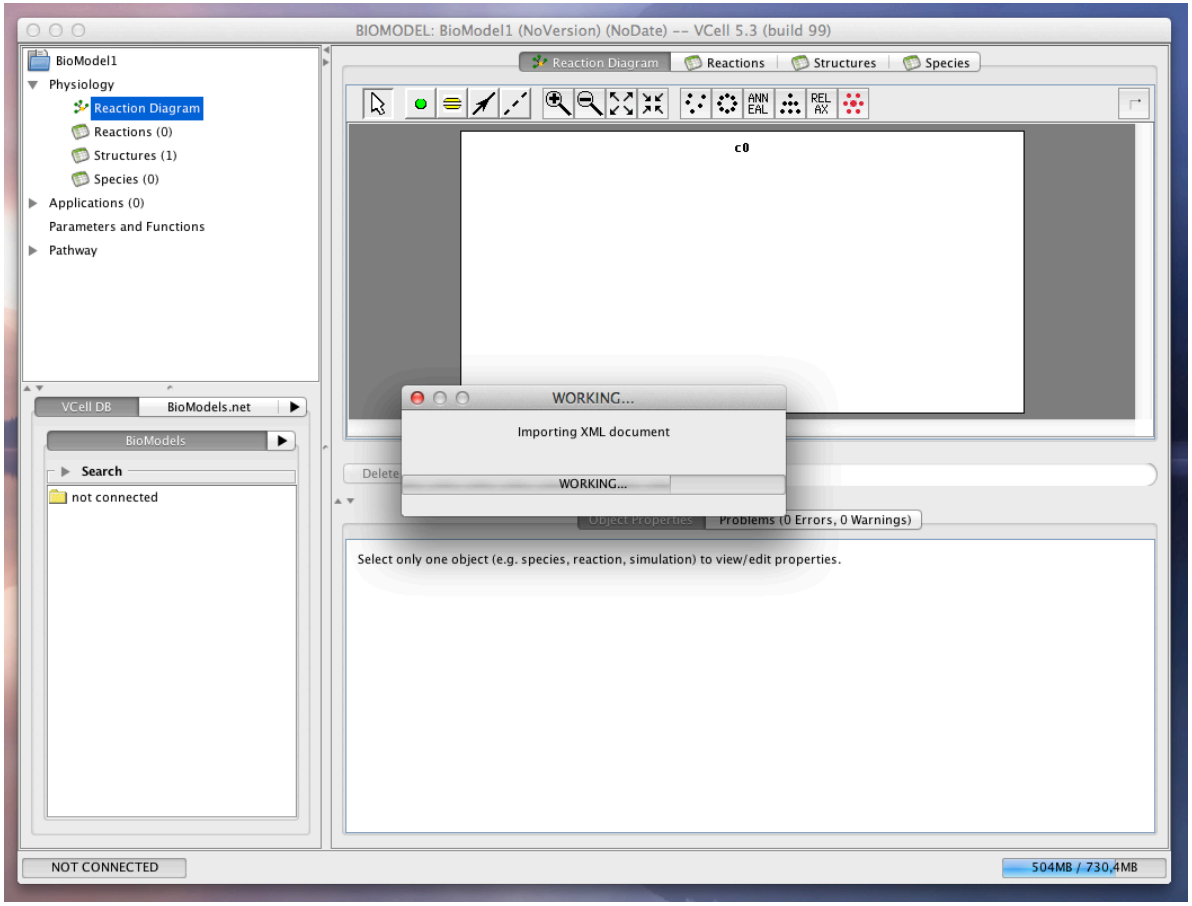
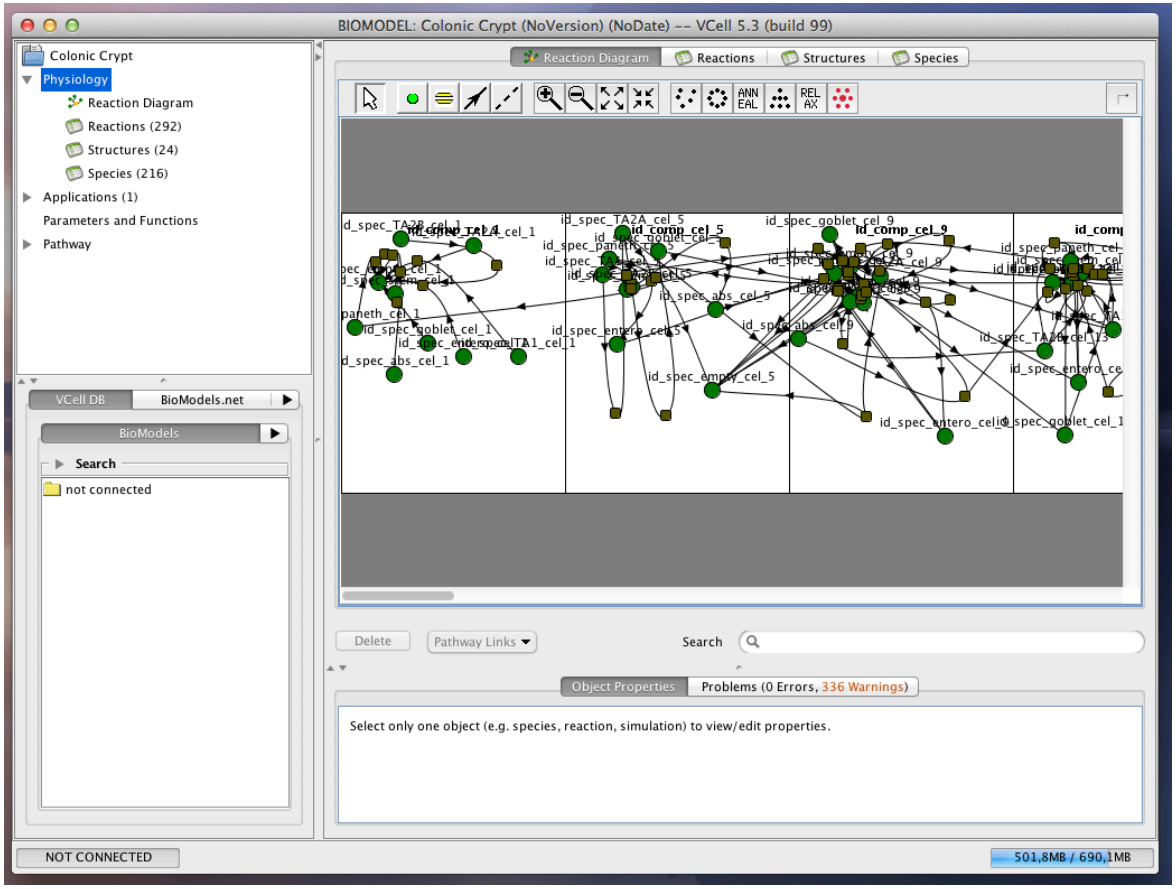
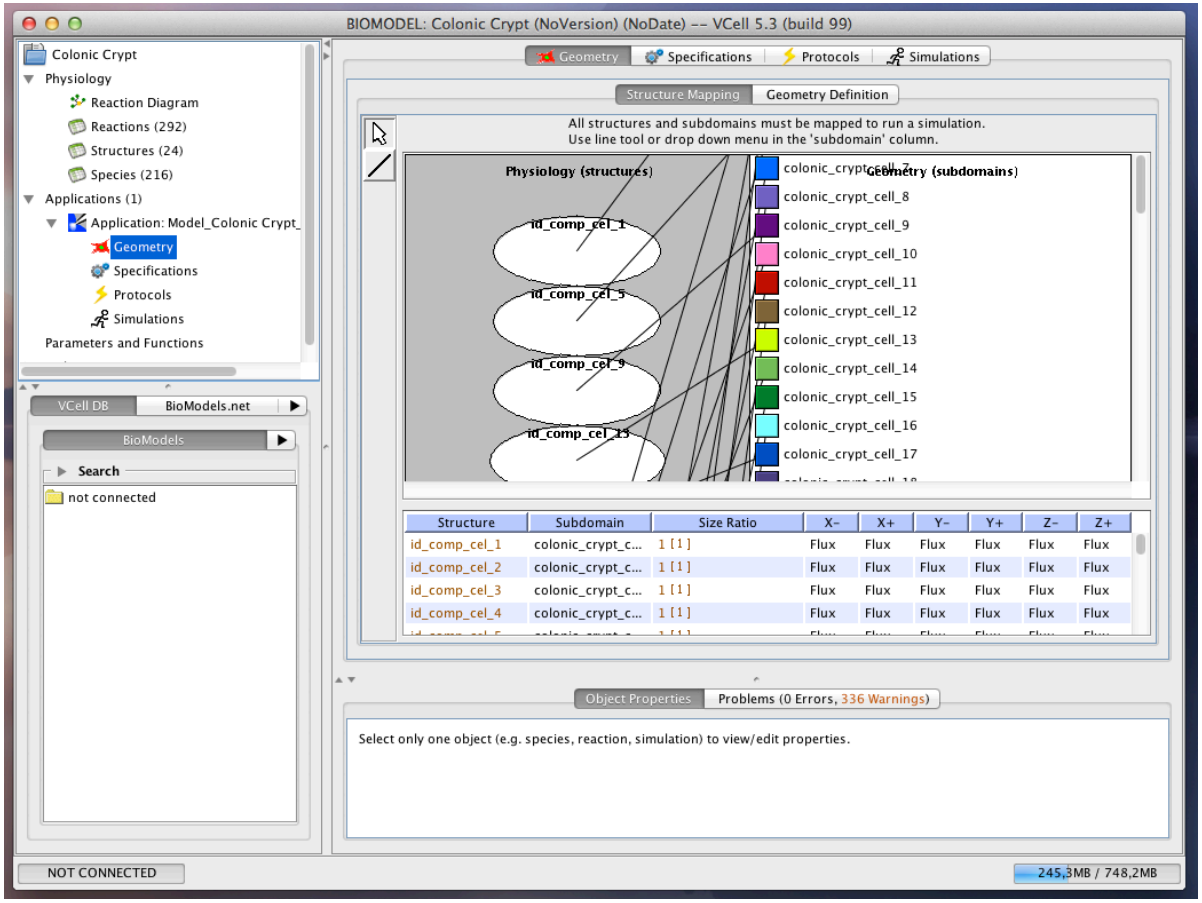

Using VCell 1/3



Using VCell 2/3



Using VCell 3/3



Open Issues

- Link between dynamic and spatial components into an unique model of kinematic evolution of the colonic crypt.
  - Associate to each cellular transformation a spatial movement (i.e., stem to paneth → downward movement)
  - Properly defining cell division (mitosis and cytokinesis)
  - Defining the initial conditions of a given simulation run
  - … and more.

Conclusions

- As usual the interplay between static and dynamic representation poses several problems, as revealed, in our case, by the issue of "events"
- The interplay of SBML Spatial with other SBML packages should be clarified: SBML Multi (and SBML Dynamic?) being an example
- Another issue, as far as we could tell, is that the `ListOfGeometryDefinitions` does not take into account the simple "in-lattice/cellular-automata" simulation schemes
  - Could we just have a 'set-of-voxels' definition?
  - As usual, how much of the "simulation engine" should be represented in SBML
- Finally, spatial simulations should be replicable, which is another topic for SED-ML

Acknowledgements

- BIMIB Lab, Dipartimento Informatica Sistemistica Comunicazione Milano-Bicocca `bimib.disco.unimib.it`
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- **Regione Lombardia**
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