STSE: a microscopy image based spatial modelization framework

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1 Introduction

This document describes the user case of Spatio-Temporal Simulation Environment (STSE) [1] in the context of system biology. STSE is set of *open-source* tools used to perform spatio-temporal simulations in discrete structures. The framework contains modules to *digitize, represent, analyze*, and *model* spatial distributions of species in static and dynamic structures (e.g. growing).

The user case described in this document is inspired on the modelization of *Aquaglyceroporins*[2]. However, we resigned from any biological references to present rather a *protocol*, then a particular study. Our main motivation is to give an intuitive description of what can be expected of so-called *spatial modeling* and we are open to any comments, discussions and suggestions.

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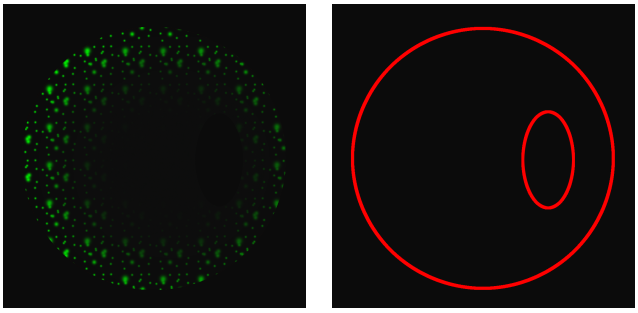
[1] STSE is a framework started by *Szymon Stoma* and other members of Virtualplants team in INRIA (The National Institute for Research in Computer Science and Control, France) under the name `mersim` and now being developed in HU (Humboldt University, Berlin). It is a package of Openalea (`http://openalea.gforge.inria.fr/`), a collaborative effort to develop Python libraries and tools which address the needs of code *quality, standarization* and *reuse* in modeling. The official webpage of the STSE projecte is: `http://stoma.name/stse/`

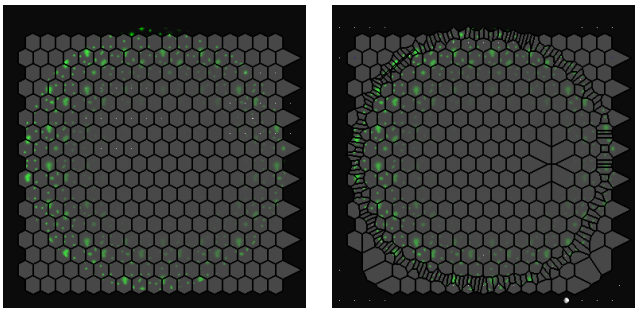
[2] Another example of the use of STSE was the study of *auxin fluxes* in the vegetal tissues (*Flux-Based Transport Enhancement as a Plausible Unifying Mechanism for Auxin Transport in Meristem Development*, Stoma S, Lucas M, Chopard J, Schaedel M, Traas J, Godin C, PLoS Computational Biology 4(10), 2008). The main differences were: the study was at the level of *tissue* (and not the *cell* as in the example below); the structure was *dynamic* (and not *static* as in the example below); the expression levels were assumed to be *present/absent* (and not *continous* as in the example below).

2 Spatial quantitative study

The general goal of this abstract example is to provide more detailed data describing location of molecule A in a cell/tissue. Let us assume that we have images containing information about localization of molecule A in a cell/tissue (and for completeness, another channel of each image is showing the cell/nucleus membranes). An example of such an image may look like:



STSE allows us to divide the image into abstract compartments used to *digitize* the image, and as a result to prepare it for a *quantitative* study. STSE allows for editing the compartments in an *automatic* or *manual* way, leading thus to *custom geometries* describing the image. Images below show *regular* (left image) or *custom* geometry (right image):

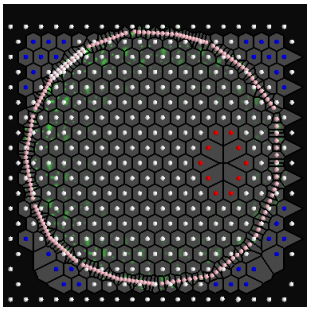


Each compartment may have its *type*, which defines the physiological function of the compartment (e.g. sample compartment types at cellular scale are: *cell membrane, nucleus, mitochondria, cytoplasm*, etc.). The compartments are used to:

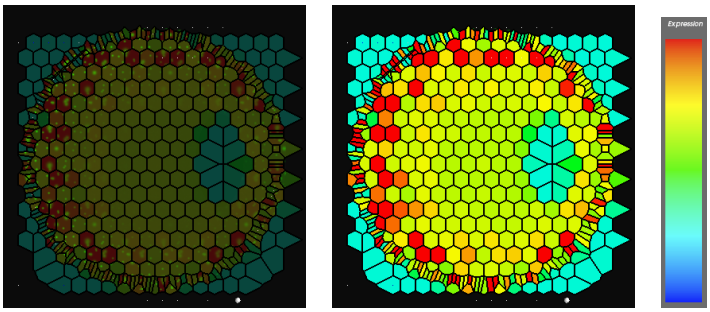
1. Allow for answering questions for given *image* or *series of images* e.g.
   (a) What is the average concentration of molecule A in the given compartment (e.g. vesicles/membrane/nucleus)?
   (b) What are the ratios between the average concentration of A in different compartments (e.g. vesicles/membrane/nucleus)?

2. Allow for comparing the *real images* with *simulation results* (explained in the next section).

Image below shows tagged compartments (a *type* of the compartment is depicted using a sphere *color*) for the custom geometry image above:



STSE allows us to compute the average *expression* levels of A in different compartments. The image below shows us the map of A expression (left image: an overlap of the original image and computed expression map; middle image: expression map alone; right image: color map used to depict expression level - red depicts high values):

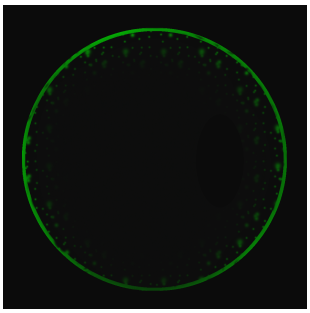


We can use such a protocol to *quantitatively* describe the location of A with respect to different tissues, organisms, etc. STSE allows us to *store* the geometries, enabling an easy *reproduction* of the results in the future (contrary to many other tools based on *selection*).

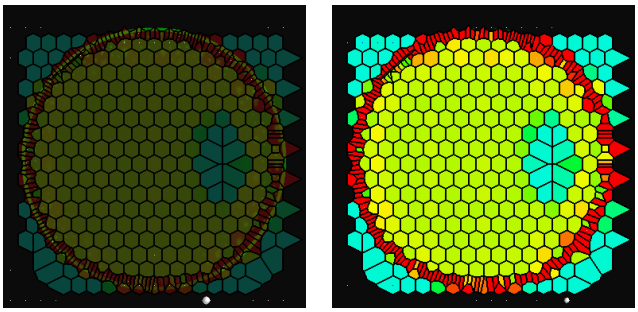
3 Quantifying the process of A trafficking

Another application might be a usage of such a framework to describe trafficking of A. By trafficking we understand here the dynamical cycling of A molecules between the cell membrane and the vesicles inside the cell. Here we assume, that we have also *in vivo* data showing a cell reaction to the stimulus triggering the trafficking of A. It is important to note, that the *in vivo* observation is an ideal method, however different scenarios are also possible (for the sake of

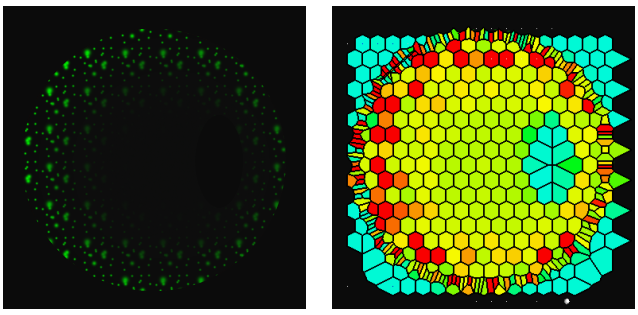
simplicity we focus here only on *in vivo* techniques). A sample image showing trafficking of A after stimulus may look like this one (we assume that this is the same cell as on the previously studied image just after "reacting" for the stimulus S):

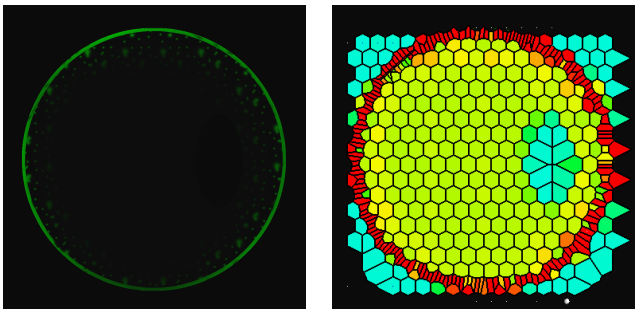


Using the previously described protocol it is possible to create expression maps for the "after stimulus" image (left image: an overlap of original image and computed expression map; right image: expression map alone):



Together with the previous analysis it opens the possibility to describe *quantitatively* the dynamics of spatial trafficking of molecule A:





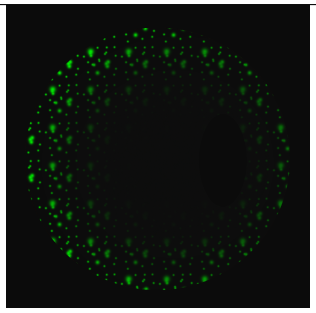
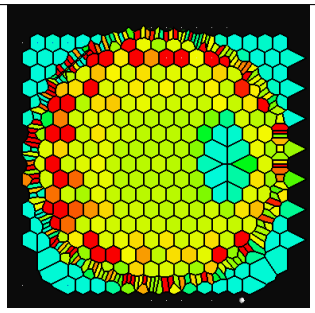
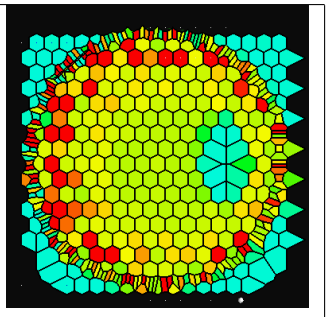
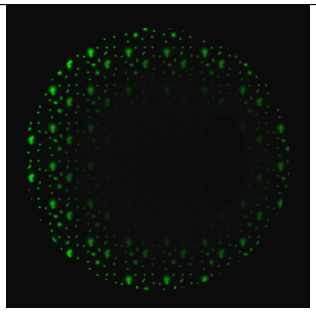
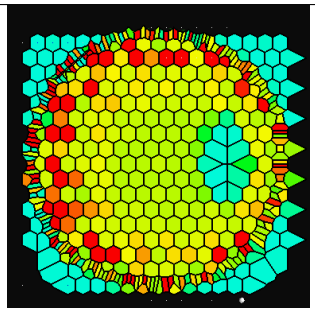
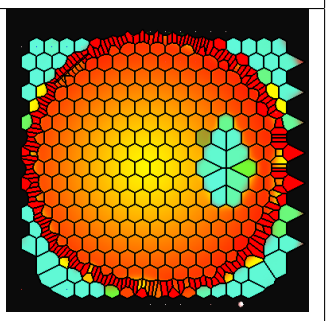
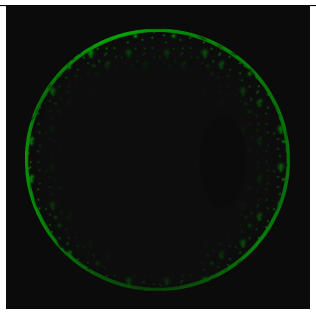
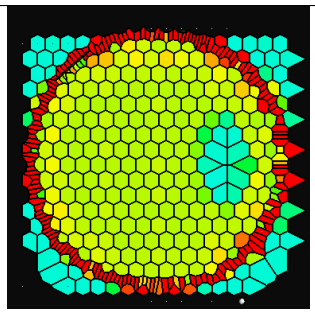
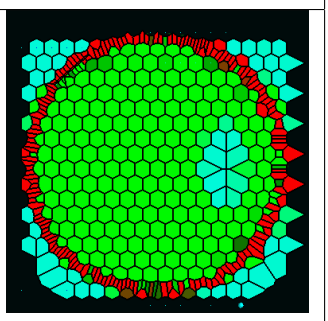
4 Spatial modeling of A trafficking

This is a consecutive step of the previously described protocol. Having a *digitized* and *quantified* data concerning molecule A distribution in a *real* tissue, we can build a spatial model of A trafficking. The spatial model describes how different compartment *types* interact with each other and is defined by a set of axioms (which are translated into mathematical equations by the modeler using STSE). Here we gathered a set of sample hypothesis describing the A dynamics, which form a model 1:

- There is a *fixed* amount of molecules A in the cell,
- A diffuses freely in the *cytoplasm compartments*,
- A cannot cross *cell/nucleus membrane compartments*,
- A is constantly inserted and removed from the *cell membrane compartments*,
- The efficiency of the A insertion in the *cell membrane compartments* is regulated by the amount of stimulus S sensed by the *cell membrane compartments*.

Such a model can be *simulated* using STSE. The *initial state* of the system can be directly acquired from the *digitized images*. The *results* of the simulation can be again compared with the *digitized images*.

If the results of the simulation are *similar* to the real data, we can assume that the proposed model is *plausible*. If not, we can *change* our set of hypothesis, and simulate the system again, what can possibly lead to new findings. A sample output of the model 1 is provided in the image below:

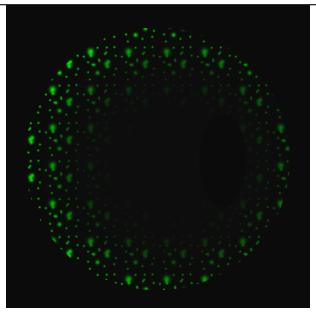
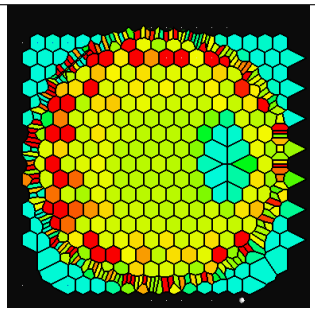
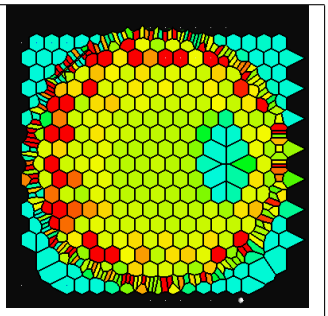
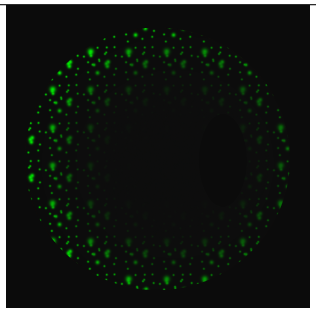
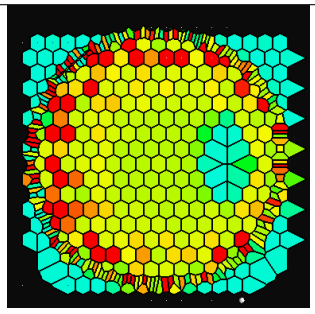
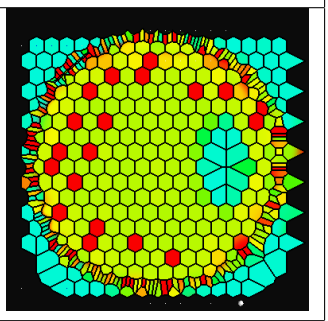
Time	Real data	Digitized data	Simulated data (model 1)
$t = -900s$ (init)			
$t = 0s$ (stimulus)			
$t = 900s$ (stable)			

Comparing the result of the simulation with the real data we can observe, that the simulated state before the stimulus ($t = 0$) differs not only *quantitatively* but also *quantitatively* from the *digitized image* (i.e. *in vivo* the molecules A are clustered, whereas *in silico* they are creating a gradient distribution). If we know, that the real cells contain vesicles in which molecules A are stored, we can suspect that they are *required* to reproduce the *observed pattern*. This can lead to the refinement of one of the hypothesis of model 1 (model 2):

- There is a *fixed* amount of molecules A in the cell,
- A diffuses freely in the *cytoplasm compartments*,
- A cannot cross *cell/nucleus membrane compartments*,
- A is constantly inserted and removed from the *cell membrane/vesicle compartments*,

- The efficiency of the A insertion in the *cell membrane compartments* is regulated by the amount of stimulus S sensed by the *cell membrane compartments*.

Which can be then again tested *in silico* leading to better agreement with *real image* data*:*

Time	Real data	Digitized data	Simulated data (model 2)
$t = -900s$ (init)			
$t = 0s$ (stimulus)			
$t = 900s$ (stable)