

# EpiLog: a novel tool for the qualitative modelling of epithelial patterning

Pedro L. Varela, Pedro T. Monteiro, Nuno D. Mendes,  
Adrien Fauré, Claudine Chaouiya  
Network Modelling Group @IGC

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# Modelling pattern formation in tissues:

*single cell*

network controlling cell fate

*epithelium*

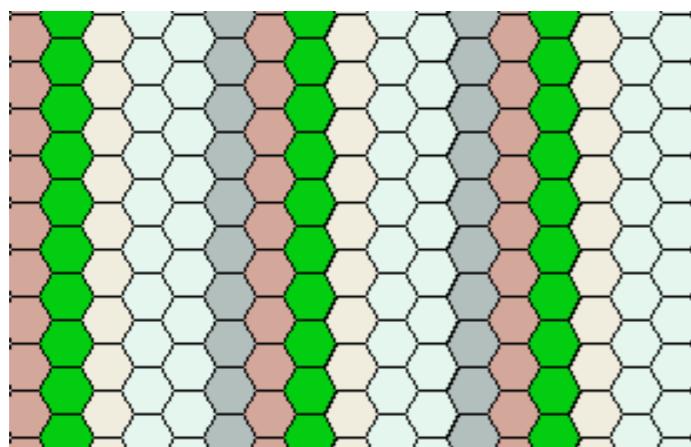
single cell model

cell-cell communication

environment cues

# Introduction

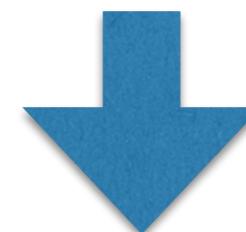
**Celular automata that simulates an epithelium represented by a grid of hexagonal cells in the framework of logical model**



**GINsim exports logical models in the SBML-qual format**



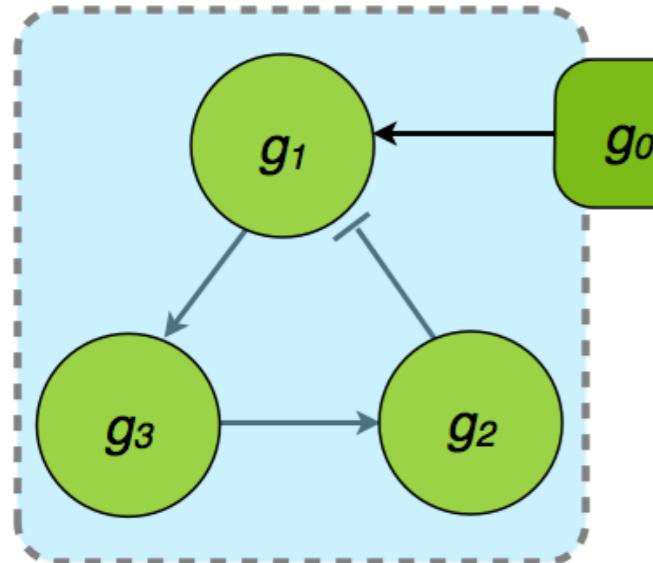
(Naldi et al. 2009)



**SBML**

(Chaouiya et al. 2013)

# Single Cell *logical regulatory module(LRM)*

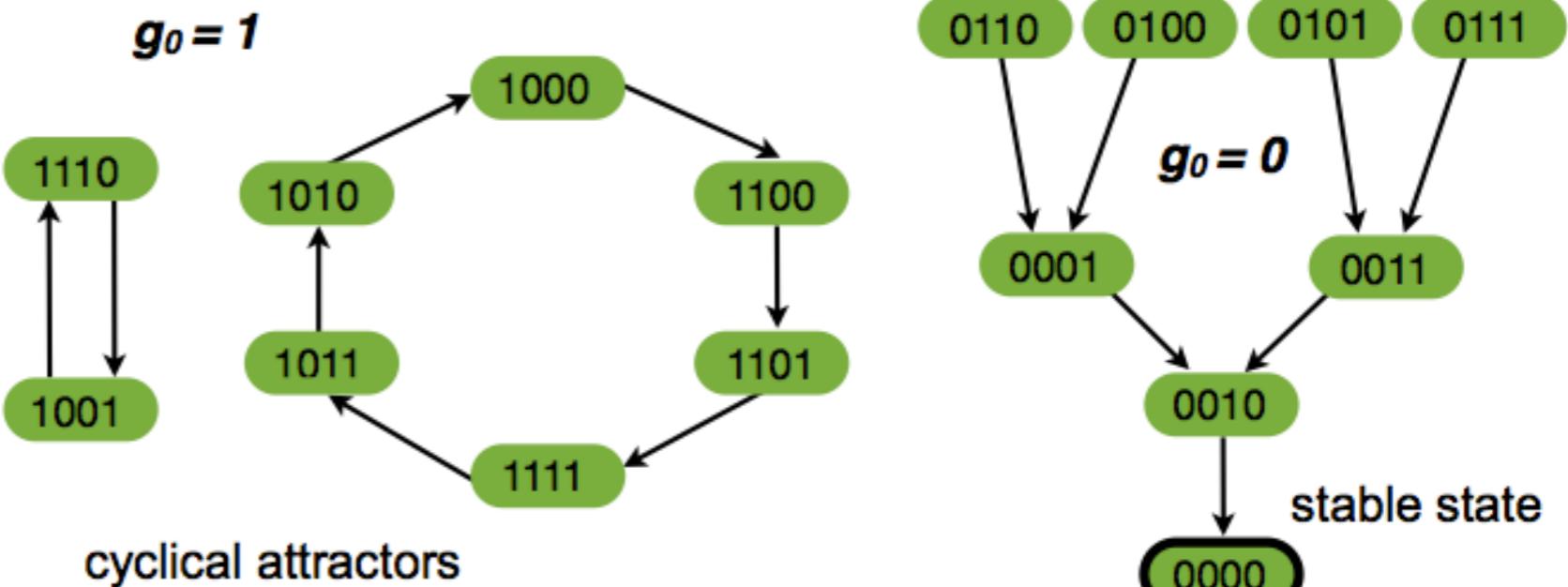


$$K_1(v) = 1 \text{ if } v_2 = 0 \wedge v_0 = 1$$

$$K_2(v) = 1 \text{ if } v_3 = 1$$

$$K_3(v) = 1 \text{ if } v_1 = 1$$

State Transition Graph (synchronous)



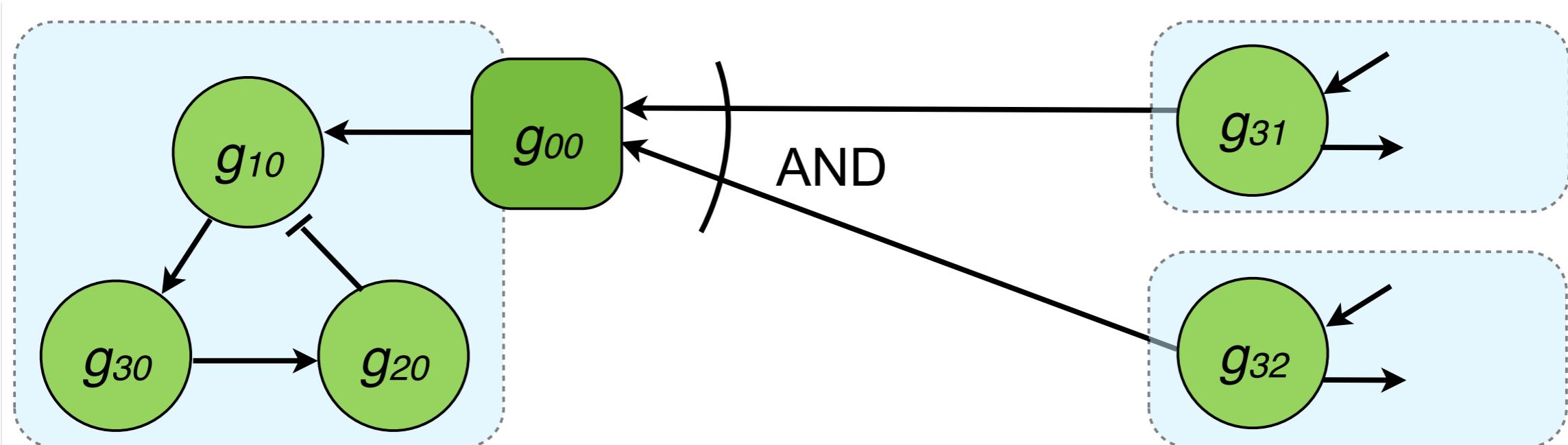
Logical Formalism

Synchronous updating scheme: all components are updated at the same time

Proper components: internal to the module

Input components: external influences (environmental cues, neighbours)

# Epithelial model



**Integration function :**  $K_{00}(v) = 1 \text{ if } v_{31} = 1 \wedge v_{32} = 1$

**Integration inputs** are mapped to proper components (Mendes et al. 2013)

A **logical integration function** sets the relationships between signals

# Neighbourhood relations

We defined a grammar for the neighbourhood relations

t: threshold

m,M: neighbours

d:D: distance

$C(t,m,M,d)$

$C(t,m,M,d:D)$

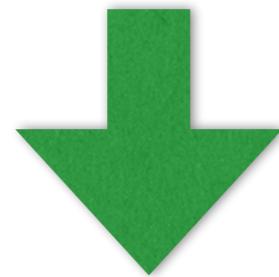
$C(t,m,M)$

logical connectors: ! | &

Integration Function	Description
$G_0=1 \text{ if } G_3(1,1,_,1)$	at least 1 neighbour at distance 1 with $G_3 = 1$
$G_0=1 \text{ if } G_3(1,1,4,2:3)$	at least 1 and at most 4 neighbours at distance 2 or 3 with $G_3 = 1$
$G_0=1 \text{ if } G_3(1,1,_,2) \mid G_2(_,1,1)$	at least 1 neighbour at distance 2 with $G_3=1$ <b>OR</b> exactly one neighbour with $G_2$ at maximum value

# Simulation

Update Input Components



Synchronously update cells

integration functions

using the library  
LogicalModel

Sync due to size of the grid and multivalue leading to a  
combinatorial explosion

# Priorities

The user can select the order a proper component or a set of proper components are updated.

Restriction over priorities classes (Faure et al. 2006)

Each class has at least one component and all classes are synchronous

```
for classSet in priorityClasses:  
    setChanged=false  
    for C in classSet:  
        if vi(C)!=vi+1(C):  
            update C  
            setChanged=true  
    if setChanged:  
        break
```

# Simulation

**Update Input Components**

integration functions



**Check if there are priorities**



**Synchronously update priority  
set components**

using the library  
LogicalModel

# Perturbations

**Full mutants:** all grid is affected by that mutation

**Clones:** one cell or a set of cells

**Set to a single value or to a range of values**

**Use LogicalModel to retrieve the perturbed model**

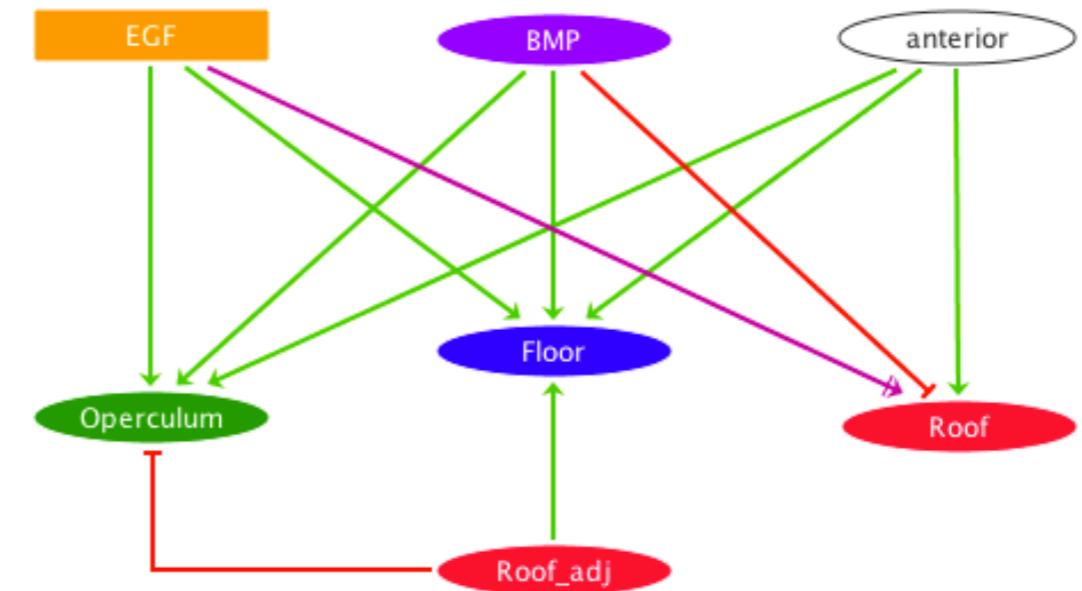
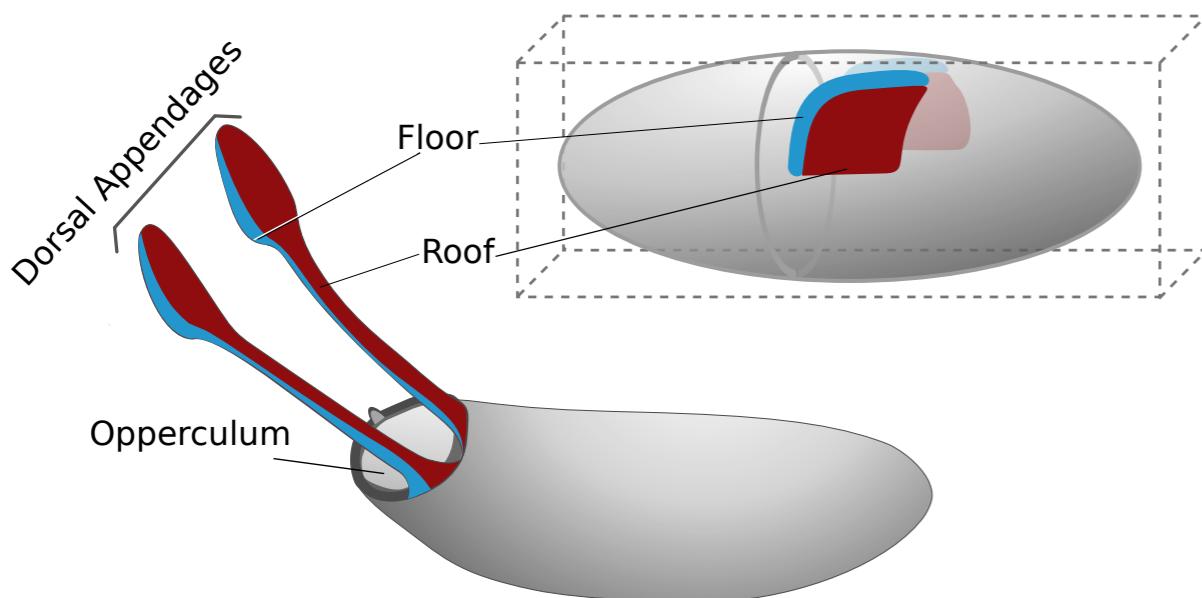
**Perturbations can refer to more than one component (multiple perturbations)**

```
for cell in gridCell:  
    if cellHasPerturbation:  
        PerturbedModel =  
            perturbation.apply(model)
```

# Example

## Drosophila Eggshell Patterning

Node	Level	Logical function
Roof	1	anterior & EGF:1 & !BMP
Floor	1	anterior & (EGF:2   (EGF:1 & BMP)) & Roof_adj
Operculum	1	anterior & (EGF:2   (EGF:1 & BMP)) & !Roof_adj

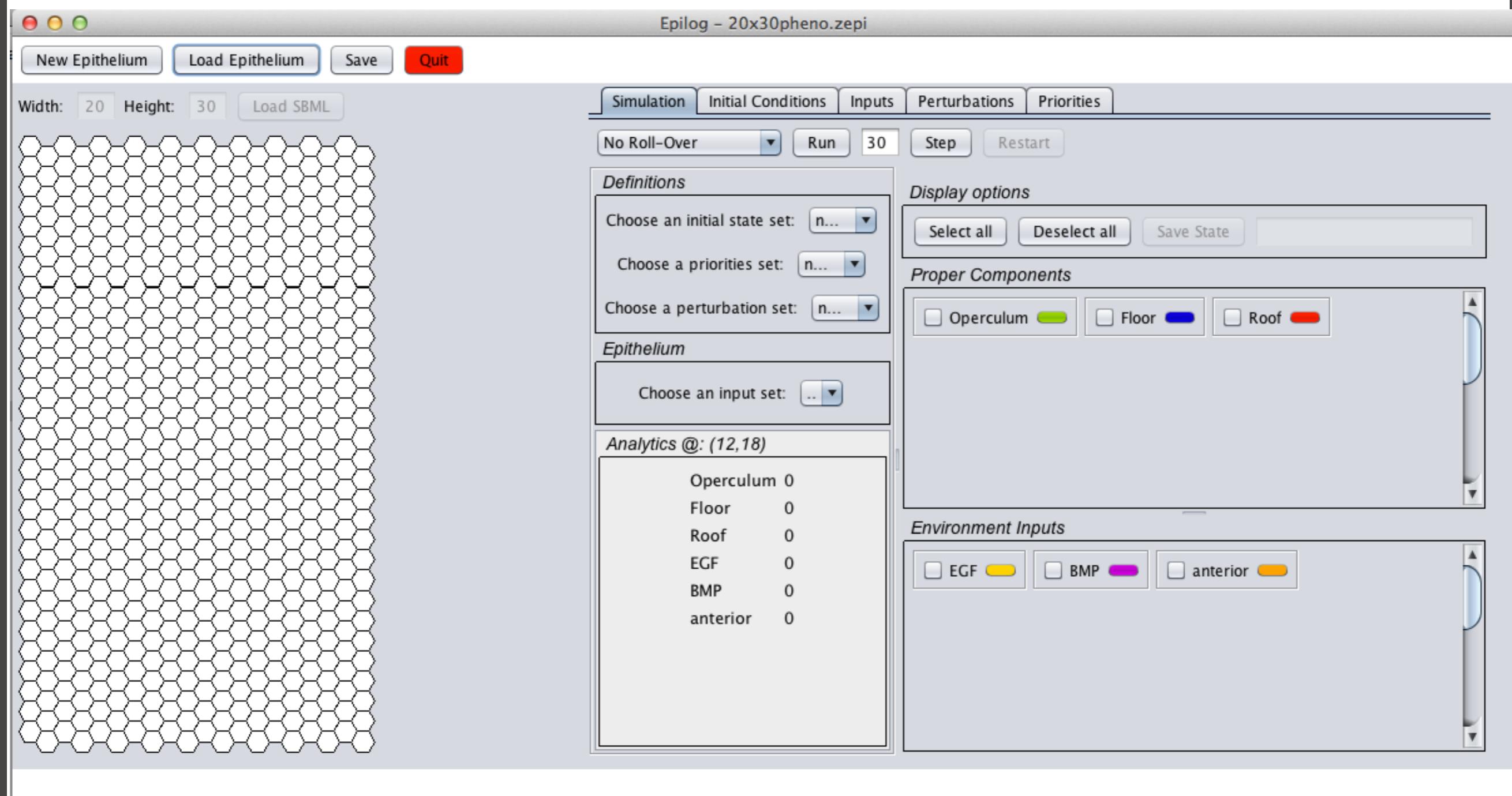


Integration Input: Roof\_adj

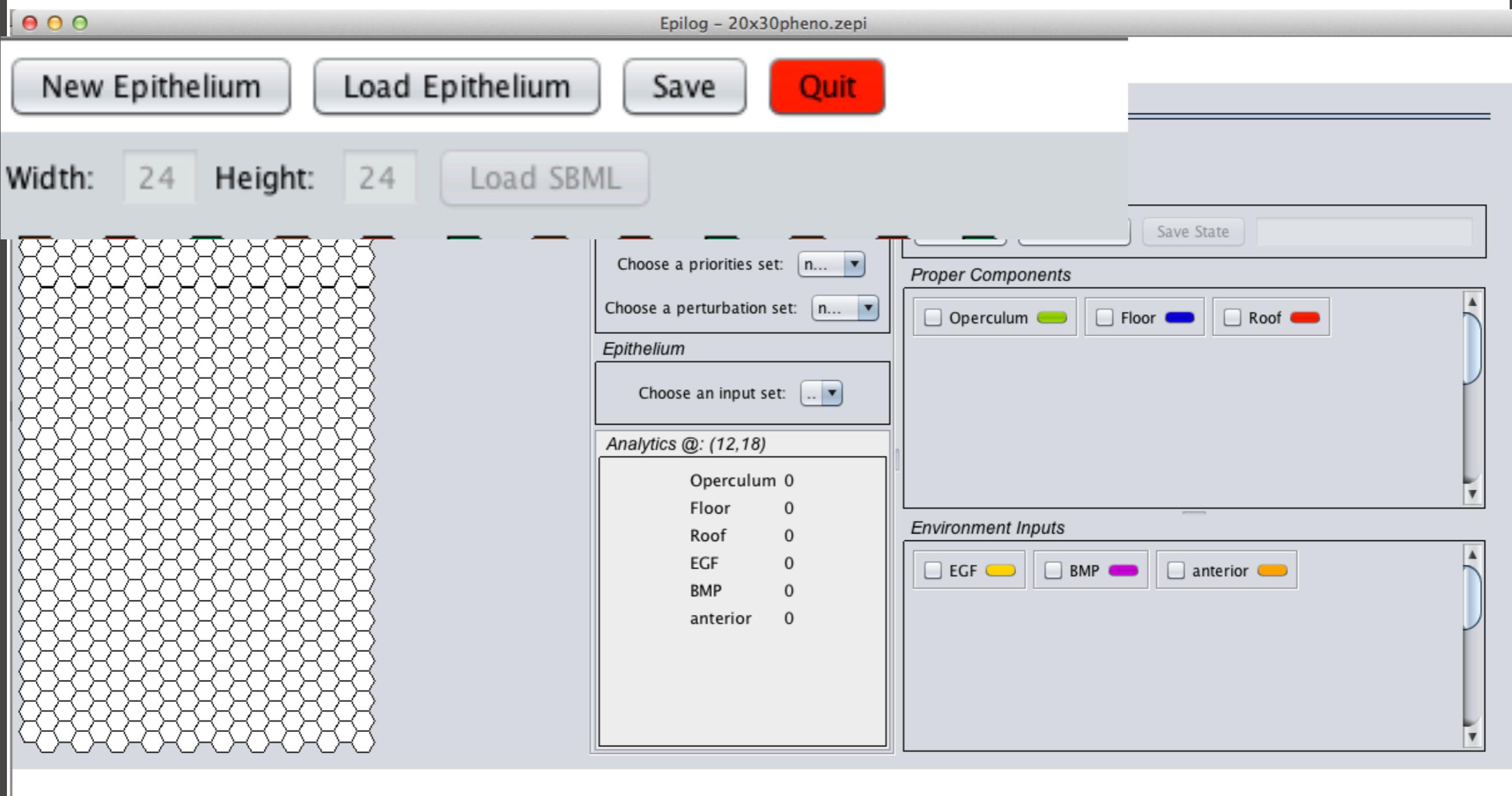
Fauré, A., Vreede, B. M., Sucena, É., & Chaouiya, C. (2014). A Discrete Model of Drosophila Eggshell Patterning Reveals Cell-Autonomous and Juxtacrine Effects. *PLoS computational biology*, 10(3), e1003527.

# EpiLog *defining and simulating epithelial models*

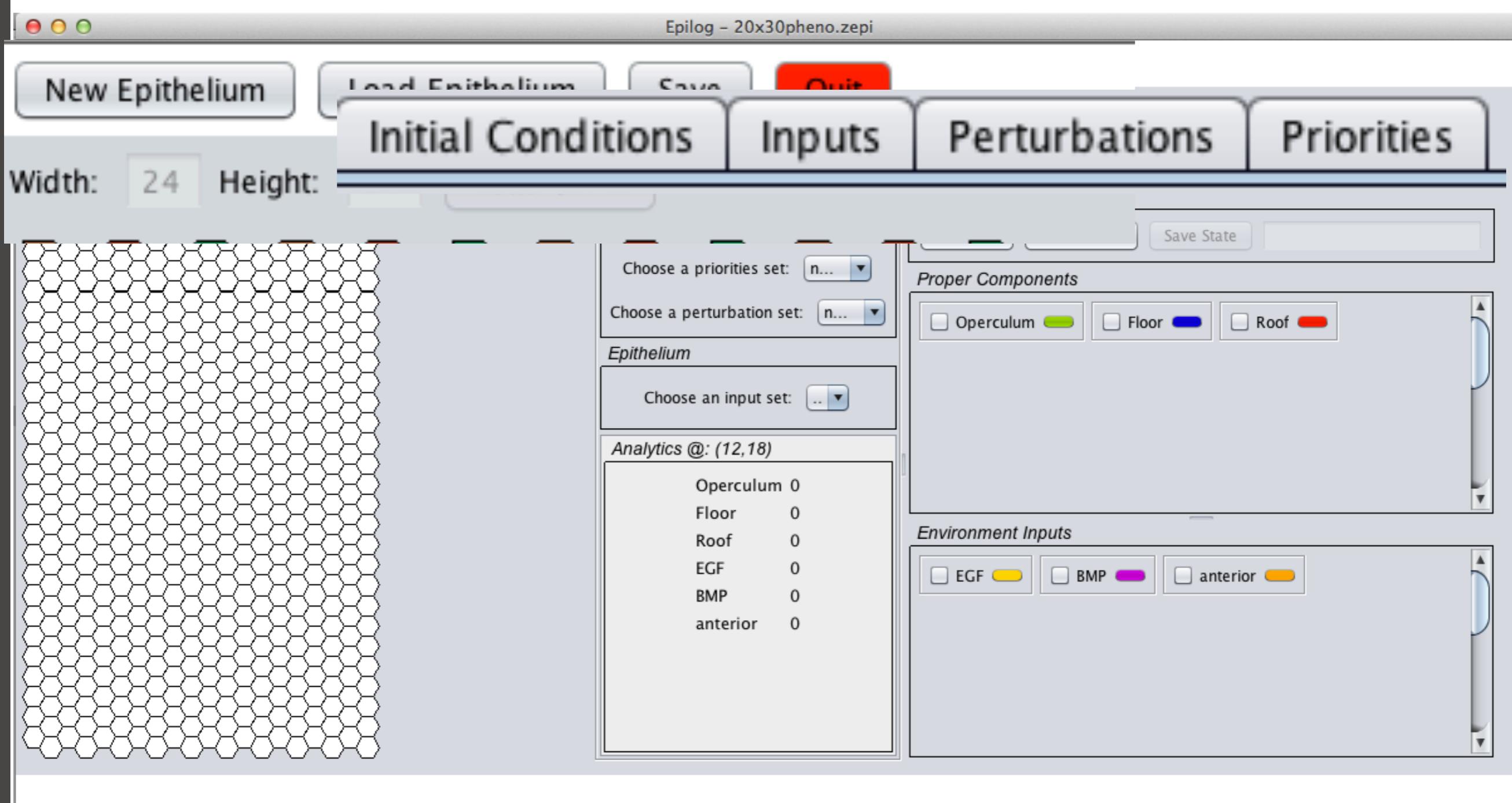
# EpiLog *defining and simulating epithelial models*



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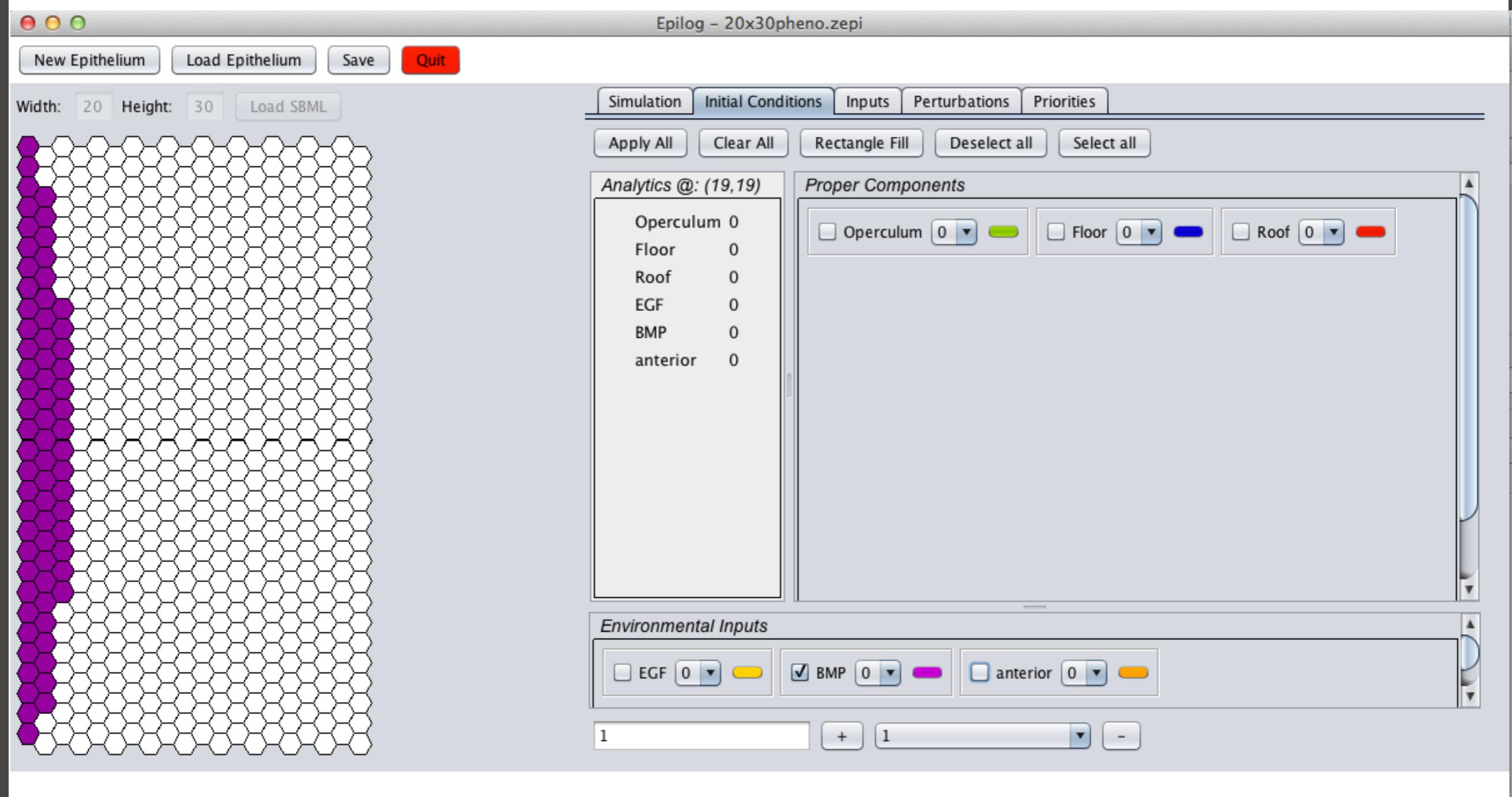


# EpiLog *defining and simulating epithelial models*



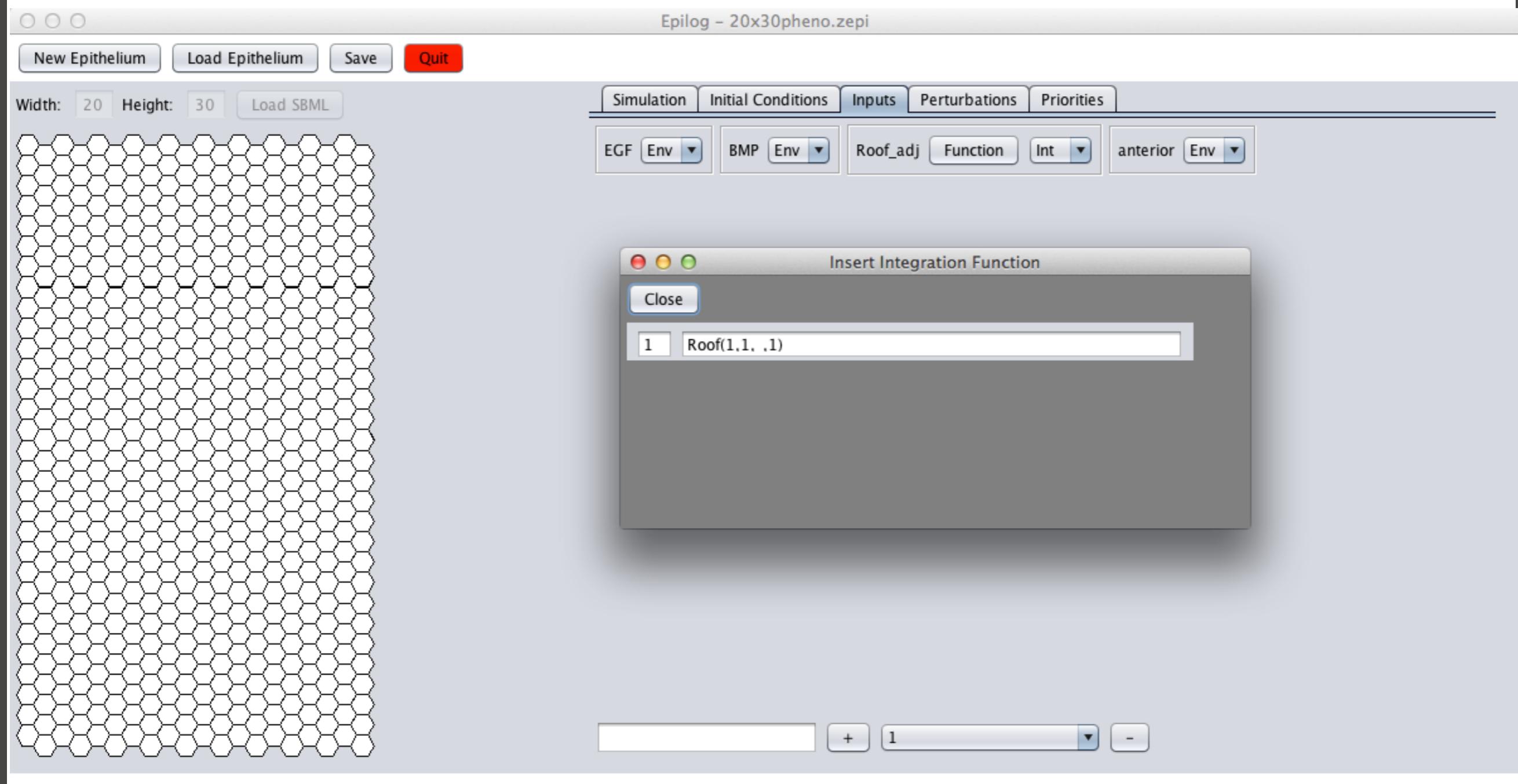
# EpiLog

## Initial Conditions Panel



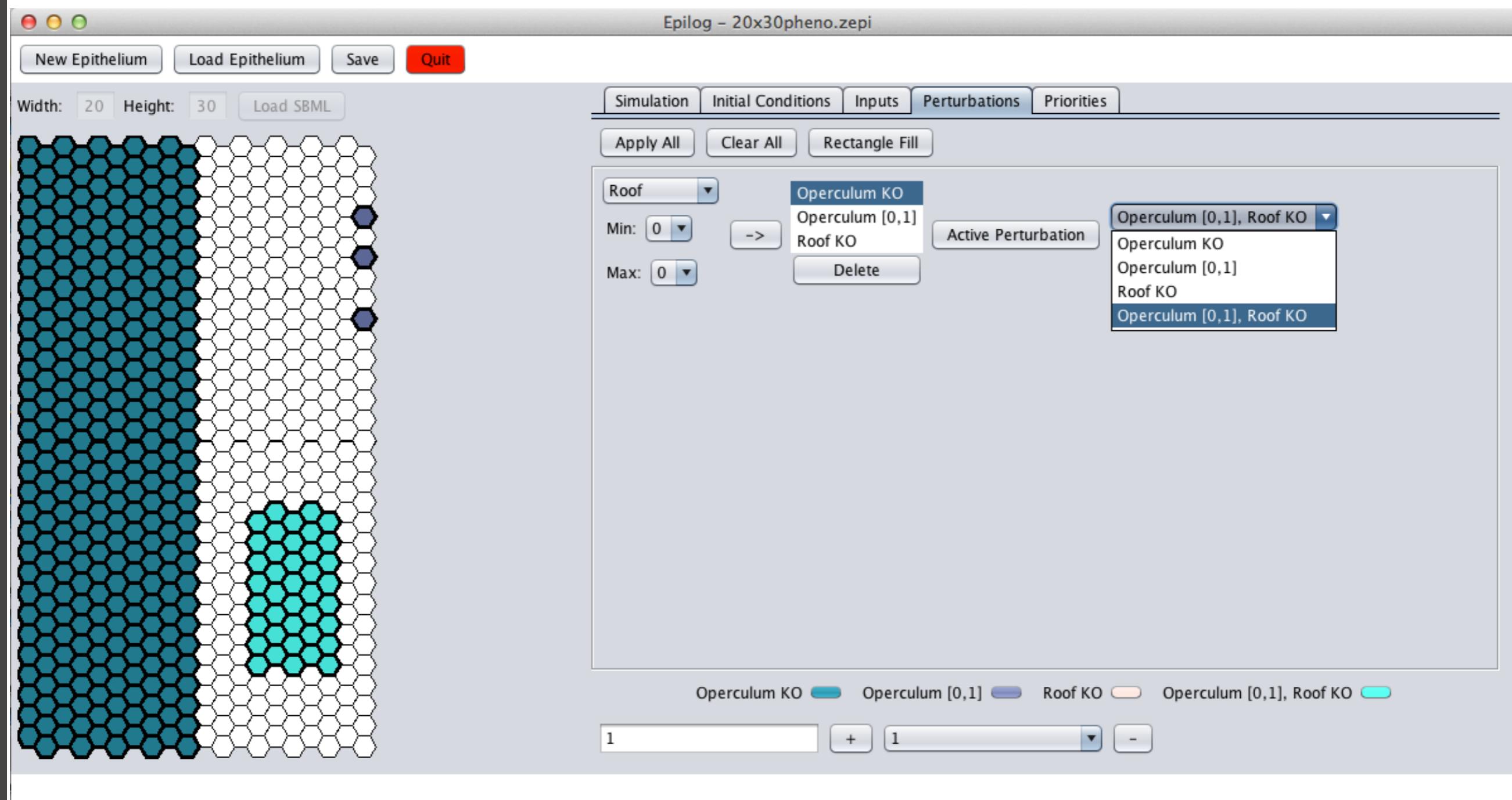
# EpiLog

## *Inputs Definitions Panel*



# EpiLog

## Perturbations Panel



# EpiLog

## Priorities Panel

Epilog - 20x30pheno.zepi

New Epithelium Load Epithelium Save Quit

Width: 20 Height: 30 Load SBML

Simulation Initial Conditions Inputs Perturbations Priorities

Split Unsplit Reset -> <-

Operculum < Floor  
Roof- < Roof+

Selected Priority Display

[ Operculum ] < [ Floor Roof- ] < [ Roof+ ]

1 + 1 ▾

The image shows the EpiLog software interface. On the left is a large hexagonal grid representing a simulation area, 20 units wide by 30 units high. Above the grid are buttons for creating new epithelium, loading existing ones, saving, and quitting. Below the grid are input fields for width (20) and height (30), and a button to load SBML models. To the right of the grid is a tabbed panel with tabs for Simulation, Initial Conditions, Inputs, Perturbations, and Priorities. The Priorities tab is selected, indicated by a blue border. Within this panel, there are buttons for Split, Unsplit, Reset, and navigation arrows (-> and <-). Below these buttons is a priority chain: Operculum < Floor < Roof+. At the bottom of the panel is a section labeled "Selected Priority Display" containing the same priority chain in brackets: [ Operculum ] < [ Floor Roof- ] < [ Roof+ ]. Below this display are numerical input fields for "1", a plus sign, another "1", and a down arrow.

# EpiLog

Drosophila Eggshell Patterning *WT simulation*

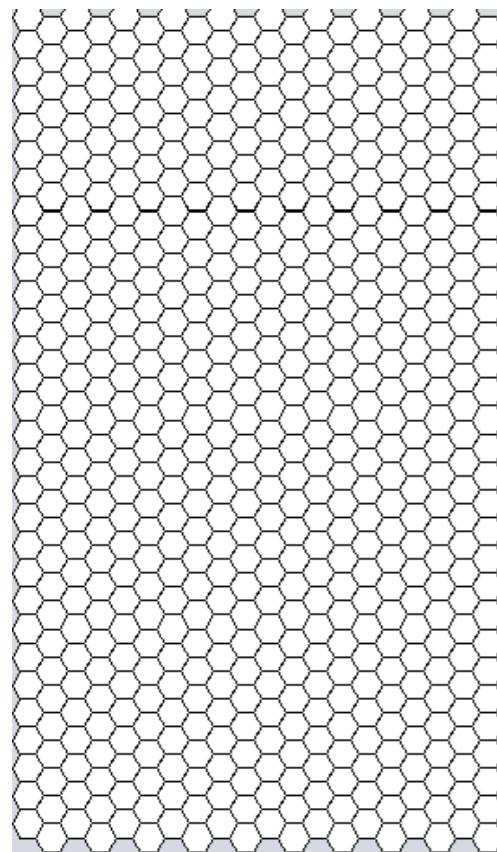
**Image of grid can be saved  
at any step**

**An iteration state can be  
saved as an initial state**

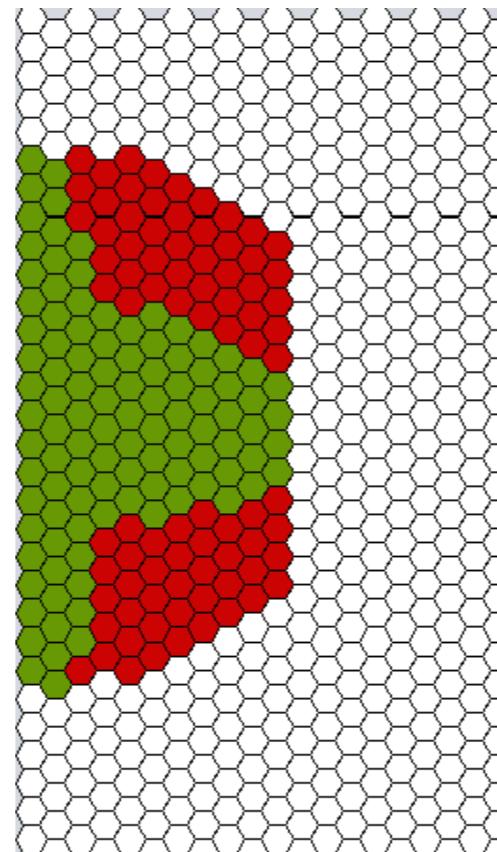
# EpiLog

Drosophila Eggshell Patterning *WT simulation*

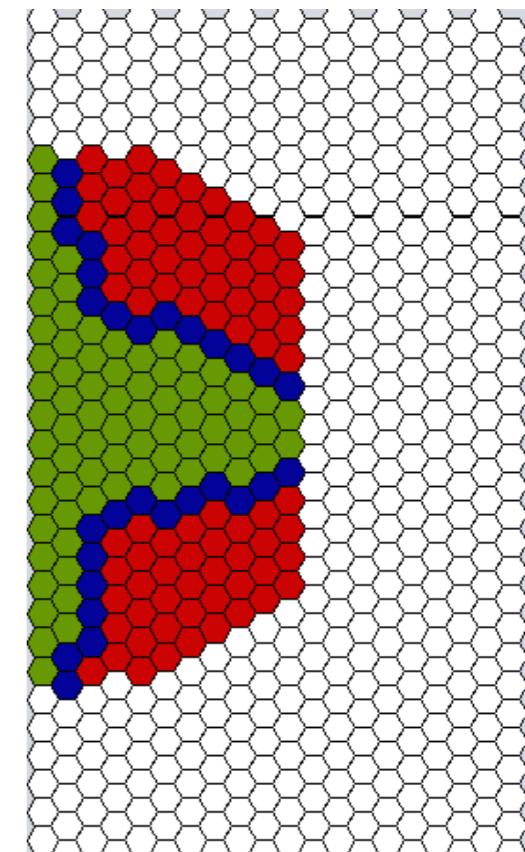
**Iteration 0**



**Iteration 1**



**Iteration 2**



**Image of grid can be saved  
at any step**

**An iteration state can be  
saved as an initial state**

# EpiLog

the new version

New version of EpiLog under development

# EpiLog

the new version

New version of EpiLog under development

Workspace with several Epithelia

An epithelium consists of a grid (fixed dimensions), regulatory rules, and integration functions

Each epithelium can be cloned to create a new epithelium

An epithelium supports cells with different models

**Alternative updating schemes**

**Relaxing grid configurations**

**Cell movement**

**Proliferation and cell death**

EpiLog is available at [www.ginsim.org/epilog](http://www.ginsim.org/epilog)

# Q & A

Thank you!