

EpiLog:

a novel tool for the qualitative modelling
of epithelial patterning

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Modelling pattern formation in tissues:

single cell

network controlling cell fate

epithelium

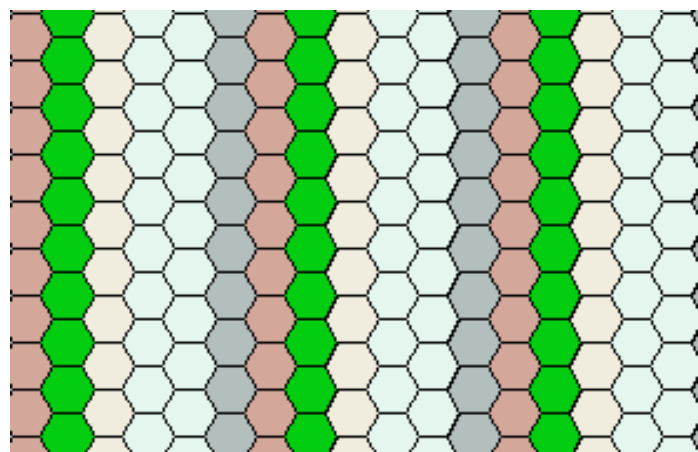
single cell model

cell-cell communication

environment cues

Introduction

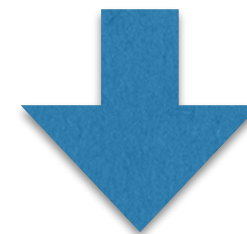
Cellular automata that simulates an epithelium represented by a grid of hexagonal cells in the framework of logical model



GINsim exports logical models in the SBML-qual format

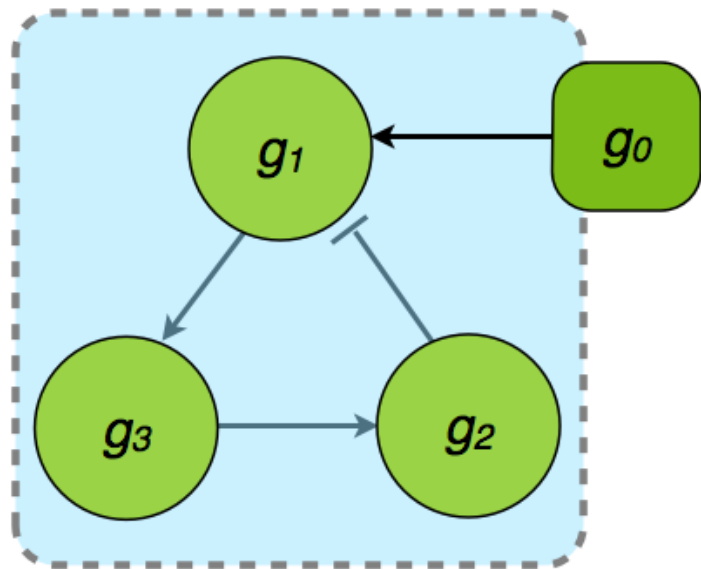


(Naldi et al. 2009)



(Chaouiya et al. 2013)

Single Cell *logical regulatory module (LRM)*

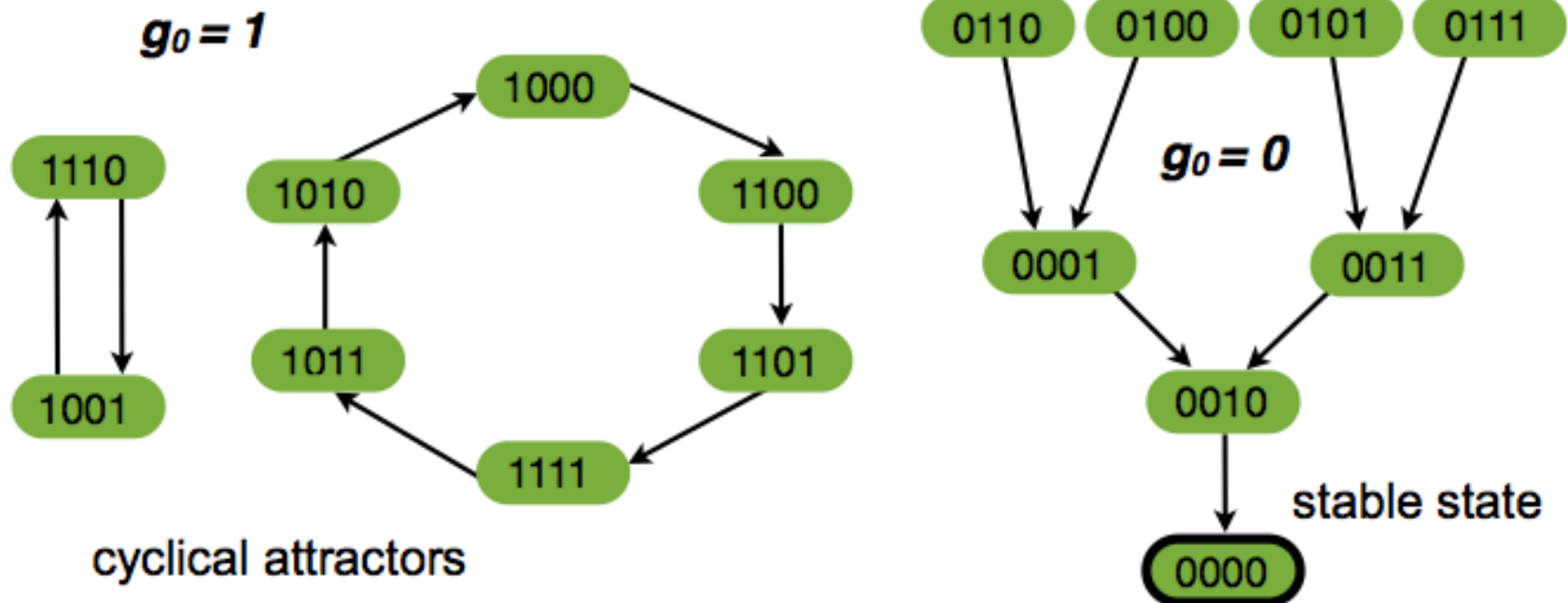


$$K_1(v) = 1 \text{ if } v_2 = 0 \wedge v_0 = 1$$

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

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

State Transition Graph (synchronous)



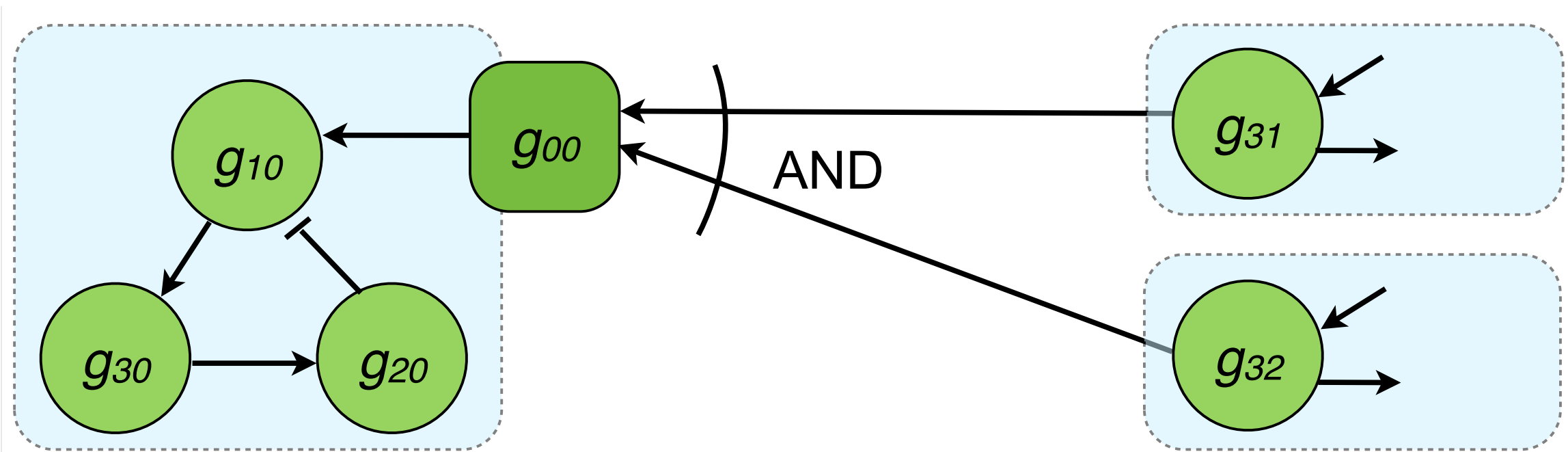
Logical Formalism

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 : $K_{00}(v) = 1$ 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

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

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

$C(t,m,M)$

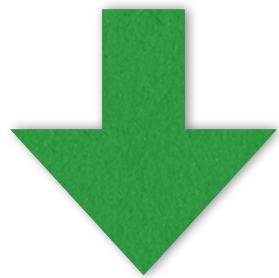
logical connectors: ! | &

Integration Function	Description
$G_0=1$ if $G_3(1,1,_,1)$	at least 1 neighbour at distance 1 with $G_3 = 1$
$G_0=1$ if $G_3(1,1,4,2:3)$	at least 1 and at most 4 neighbours at distance 2 or 3 with $G_3 = 1$
$G_0=1$ if $G_3(1,1,_,2) G_2(.,1,1)$	at least 1 neighbour at distance 2 with $G_3=1$ OR exactly one neighbour with G_2 at maximum value

Simulation

Update Input Components

integration functions



Synchronously update cells

using the library
LogicalModel

Sync due to size of the grid and multivalued 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  $v_i(C) \neq v_{i+1}(C)$ :  
            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

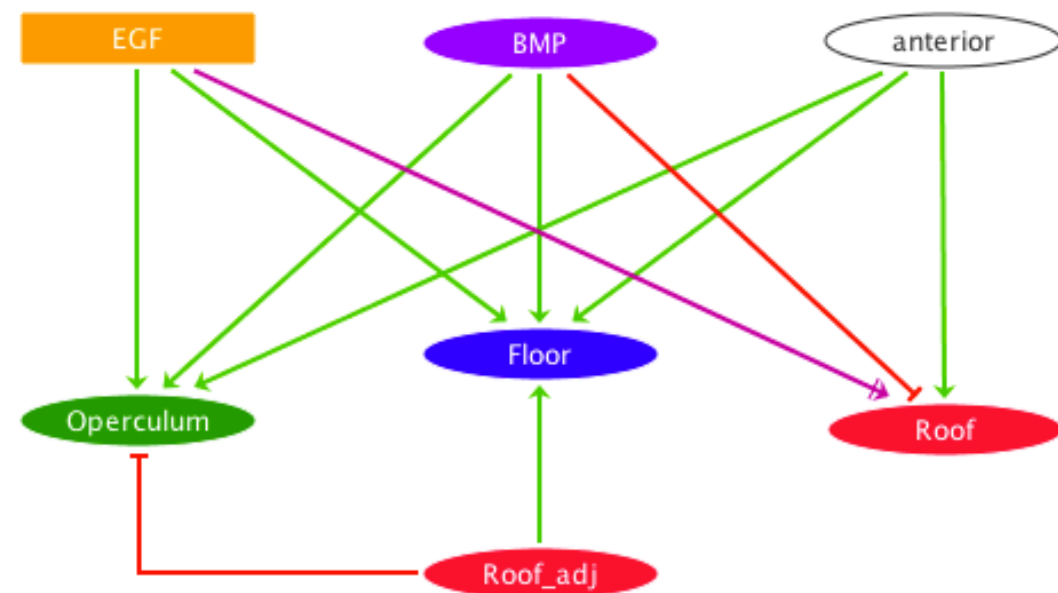
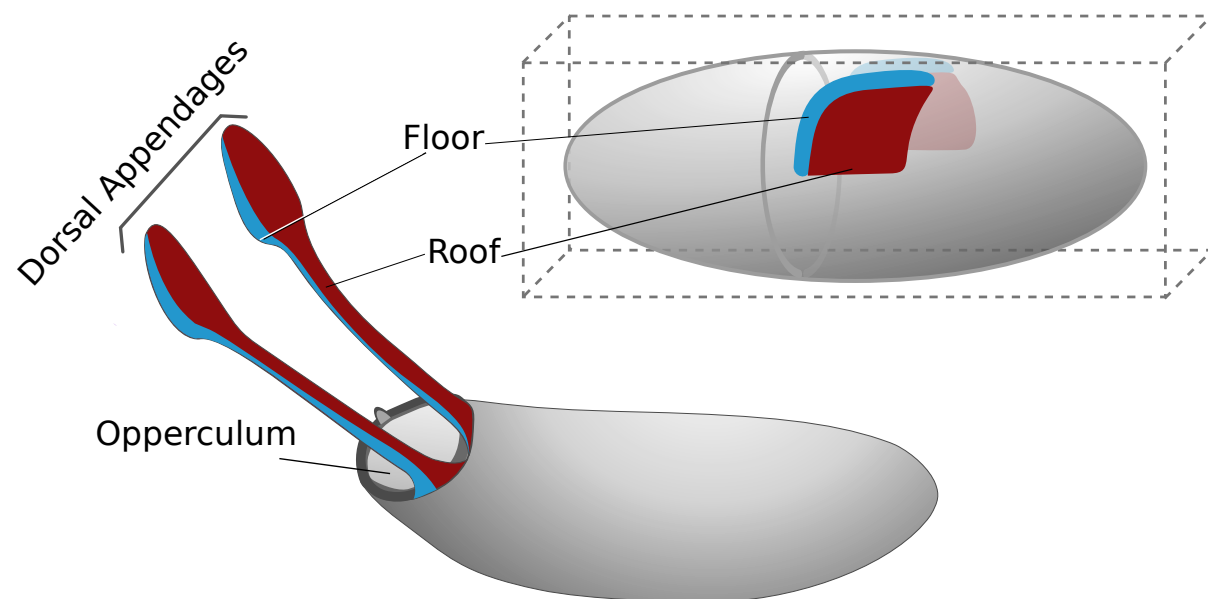
Perturbations can refer to more than one component (multiple perturbations)

```
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*

The screenshot displays the EpiLog software interface for a simulation titled "Epilog - 20x30pheno.zepi". The interface is divided into several sections:

- Top Bar:** Contains buttons for "New Epithelium", "Load Epithelium", "Save", and "Quit".
- Grid Parameters:** Shows "Width: 20" and "Height: 30", with a "Load SBML" button.
- Simulation Controls:** Includes a "No Roll-Over" dropdown, "Run" and "Step" buttons, and a "30" value field. A "Restart" button is also present.
- Definitions:** Contains three dropdown menus for "Choose an initial state set:", "Choose a priorities set:", and "Choose a perturbation set:", each with a "n..." label.
- Epithelium:** Features a "Choose an input set:" dropdown with a ".." label.
- Analytics @: (12,18):** A table showing the current state of various components:

Operculum	0
Floor	0
Roof	0
EGF	0
BMP	0
anterior	0
- Display options:** Includes "Select all", "Deselect all", and "Save State" buttons.
- Proper Components:** Contains three checkboxes: "Operculum" (green), "Floor" (blue), and "Roof" (red).
- Environment Inputs:** Contains three checkboxes: "EGF" (yellow), "BMP" (purple), and "anterior" (orange).

EpiLog *defining and simulating epithelial models*

The screenshot displays the EpiLog software interface. At the top, the window title is "EpiLog - 20x30pheno.zepi". Below the title bar are four buttons: "New Epithelium", "Load Epithelium", "Save", and "Quit".

Below the buttons, there are input fields for "Width: 24" and "Height: 24", followed by a "Load SBML" button. To the right of these fields is a "Save State" button and an empty text input field.

The main workspace is divided into several panels:

- Left Panel:** A 24x24 grid of hexagonal cells representing an epithelial layer.
- Center Panel:** Contains three dropdown menus: "Choose a priorities set:", "Choose a perturbation set:", and "Choose an input set:". Below these is a section titled "Epithelium" and another titled "Analytics @: (12,18)" which contains a table of values:

Operculum	0
Floor	0
Roof	0
EGF	0
BMP	0
anterior	0

- Right Panel:** Contains two sections of controls:
 - Proper Components:** Three checkboxes with colored indicators: "Operculum" (green), "Floor" (blue), and "Roof" (red).
 - Environment Inputs:** Three checkboxes with colored indicators: "EGF" (yellow), "BMP" (purple), and "anterior" (orange).

EpiLog *defining and simulating epithelial models*

The screenshot displays the EpiLog software interface for a 20x30 phenotypic epithelial model. The window title is "EpiLog - 20x30pheno.zepi". The interface includes a top menu bar with "New Epithelium", "Load Epithelium", "Save", and "Quit" buttons. Below this is a tabbed interface with "Initial Conditions", "Inputs", "Perturbations", and "Priorities" tabs. The "Initial Conditions" tab is active, showing a 24x30 hexagonal grid on the left. The "Width" is set to 24 and "Height" is 30. A "Save State" button is visible in the top right of the main panel. The central configuration area contains several sections:

- Choose a priorities set:** n... (dropdown)
- Choose a perturbation set:** n... (dropdown)
- Epithelium**
 - Choose an input set:** .. (dropdown)
- Analytics @: (12,18)**

Operculum	0
Floor	0
Roof	0
EGF	0
BMP	0
anterior	0
- Proper Components**
 - Operculum (green)
 - Floor (blue)
 - Roof (red)
- Environment Inputs**
 - EGF (yellow)
 - BMP (purple)
 - anterior (orange)

EpiLog

Initial Conditions Panel

Epilog - 20x30pheno.zepi

New Epithelium Load Epithelium Save Quit

Width: 20 Height: 30 Load SBML

Simulation Initial Conditions Inputs Perturbations Priorities

Apply All Clear All Rectangle Fill Deselect all Select all

Analytics @: (19,19)

Operculum	0
Floor	0
Roof	0
EGF	0
BMP	0
anterior	0

Proper Components

Operculum 0 Floor 0 Roof 0

Environmental Inputs

EGF 0 BMP 0 anterior 0

1 + 1 -

EpiLog

Inputs Definitions Panel

The screenshot shows the EpiLog software interface. The main window title is "EpiLog - 20x30pheno.zepi". At the top, there are buttons for "New Epithelium", "Load Epithelium", "Save", and "Quit". Below these are input fields for "Width: 20" and "Height: 30", along with a "Load SBML" button. The main area displays a hexagonal grid of cells. On the right, there are tabs for "Simulation", "Initial Conditions", "Inputs", "Perturbations", and "Priorities". Below the tabs are several control elements: "EGF Env", "BMP Env", "Roof_adj Function Int", and "anterior Env". A dialog box titled "Insert Integration Function" is open, showing a list with one entry: "1 Roof(1.1, .1)". At the bottom of the main window, there is a numerical input field with a "+" button, the value "1", a dropdown arrow, and a "-" button.

EpiLog

Perturbations Panel

Epilog - 20x30pheno.zepi

New Epithelium Load Epithelium Save Quit

Width: 20 Height: 30 Load SBML

Simulation Initial Conditions Inputs Perturbations Priorities

Apply All Clear All Rectangle Fill

Roof
Min: 0
Max: 0

Operculum KO
Operculum [0,1]
Roof KO
Delete

Active Perturbation

Operculum [0,1], Roof KO
Operculum KO
Operculum [0,1]
Roof KO
Operculum [0,1], Roof KO

Operculum KO Operculum [0,1] Roof KO Operculum [0,1], Roof KO

1 + 1 -

EpiLog

Priorities Panel

The screenshot displays the EpiLog software interface. At the top, the window title is "EpiLog - 20x30pheno.zepi". Below the title bar, there are four buttons: "New Epithelium", "Load Epithelium", "Save", and "Quit".

On the left side, there are input fields for "Width: 20" and "Height: 30", along with a "Load SBML" button. Below these is a large grid of 20x30 hexagonal cells representing an epithelial sheet.

The right side of the interface features a tabbed menu with "Simulation", "Initial Conditions", "Inputs", "Perturbations", and "Priorities". The "Priorities" tab is active. Below the tabs are buttons for "Split", "Unsplit", "Reset", and two arrow buttons ("->" and "<-").

The main area of the "Priorities" panel shows a hierarchy of priority levels: "Operculum < Floor Roof- < Roof+".

Below this, there is a section labeled "Selected Priority Display" containing a text box with the expression "[Operculum] < [Floor Roof-] < [Roof+]".

At the bottom, there are two input fields, each containing the number "1", separated by a "+" button. The rightmost input field has a dropdown arrow.

EpiLog

Drosophila Eggshell Patterning *WT simulation*

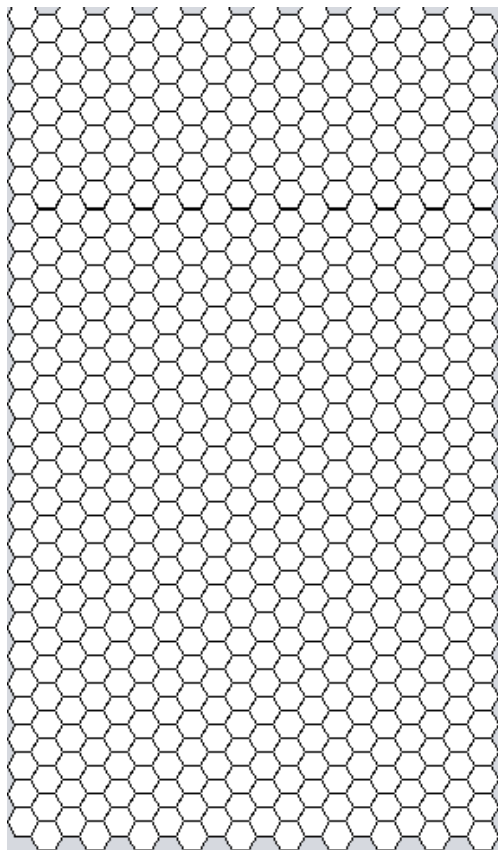
Image of grid can be saved
at any step

An iteration state can be
saved as an initial state

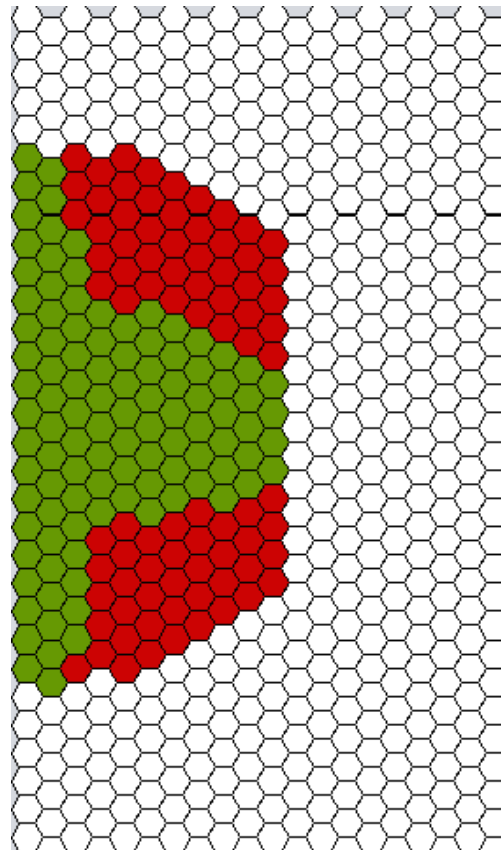
EpiLog

Drosophila Eggshell Patterning *WT simulation*

Iteration 0



Iteration 1



Iteration 2

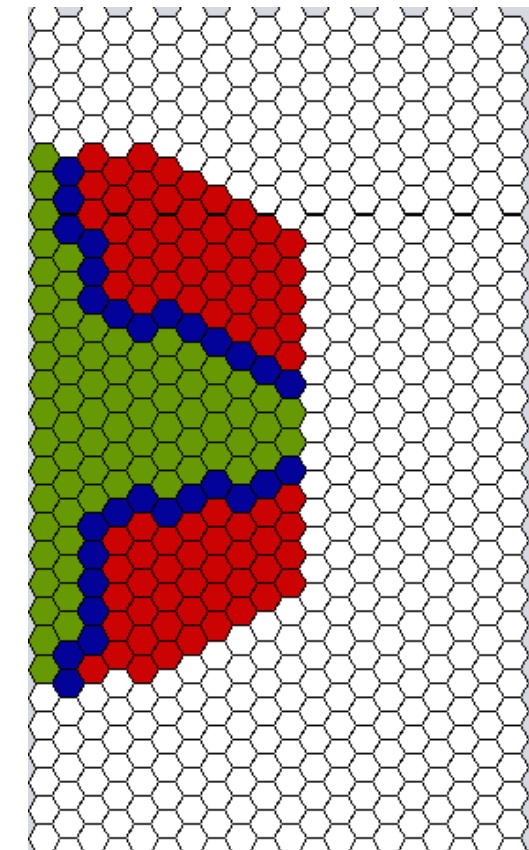


Image of grid can be saved
at any step

An iteration state can be
saved as an initial state

EpiLog

the new version

New version of EpiLog under development

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

EpiLog

open questions

Alternative updating schemes

Relaxing grid configurations

Cell movement

Proliferation and cell death

EpiLog is available at www.ginsim.org/epilog

Q & A

Thank you!