The Moduro-Notebook

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Ongoing thoughts

Overview

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Turnover time and rate

A possible definition by GUM.

Definition

The turnover time is the time it takes to completely label all cells (in the urothelium). At an initial time point t_0 the tissue is exposed to a marker such that all proliferating cells are labelled. Typically, a marker incorpareted during S-Phase is used. Let t_L be the time when all cells in the tissue are labelled. $T_o = t_L - t_0$ is the turnover time. The turnover rate is $1/T_o$.

Turnover time and rate

A possible definition by TOR, based on [Pellettieri and Alvarado, 2007].

Definition

The turnover time is the time it takes to completely replace all the differentiated cells from the tissue in question. Differentiated cells are in this case cells with the most specialized cells in it's cell lineage. The replacement of these cells typically involves adult stem cells and their descendants. Experimentally speaking, markers for superficial urothelial cells, such as cytokeratin 1, 20 and uroplakins can be applied inside the bladder. In this case the initial time point t_0 would represent either the injection or after the absorption "labeling". Let t_L be the time after none of the labeled superficial urothelial cells are present. $T_o = t_L - t_0$ is the turnover time.

Colony

Colony

A colony of cells is a group where each cell has derived from the same progenitor cell (usually a stem cell).

Assume that it is possible to mark a single cell and to propagate the marker (label) to the daughter cells. Then all cells of a colony will be labelled by the same marker.

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Lineage model according to [Ho et al., 2012]

- Note: similar to our approach
- The authors note that there at least two hypotheses how umbrella cells do differentiate.

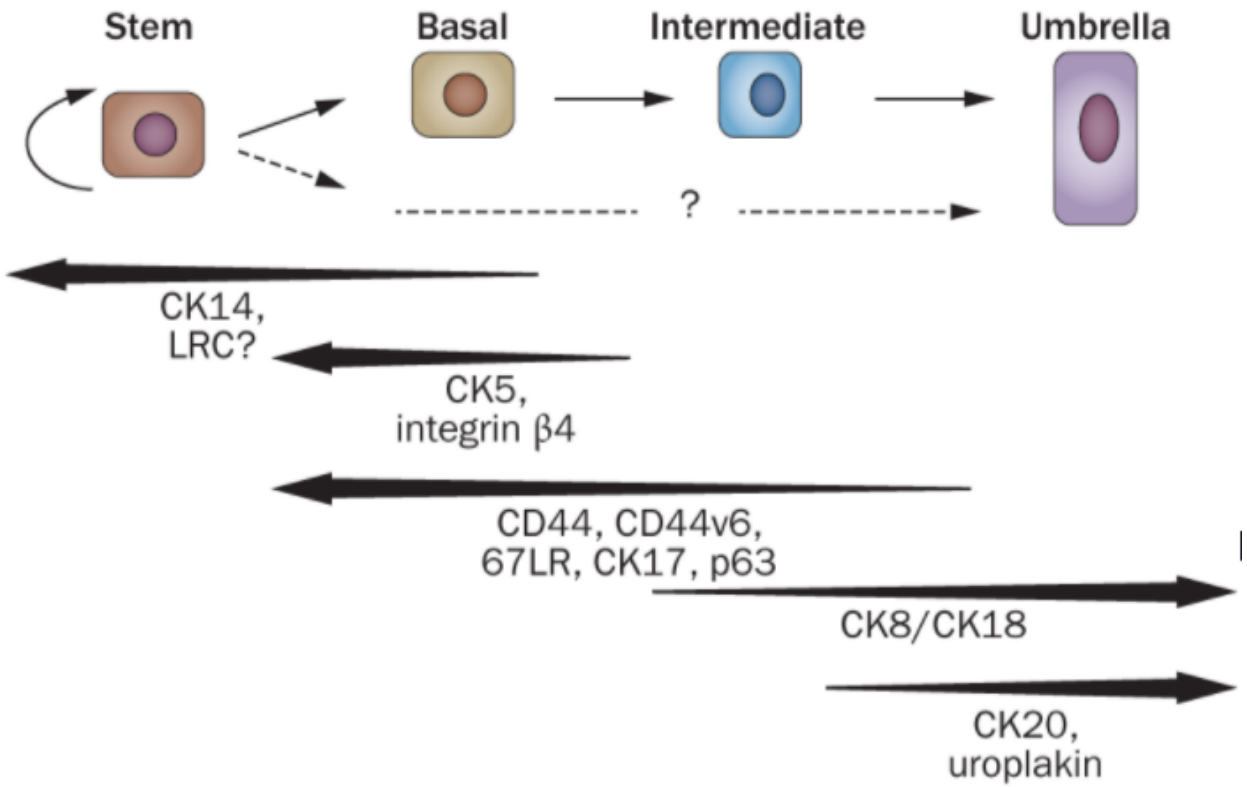

Figure: Proposal for a urothelium lineage according to [Ho et al., 2012].

Lineage model according to [Yamany et al., 2014]

They propose a (incomplete) cell lineage for urothelial cells (cf. 2). It says that

- Keratine-5 cells are **not** related or linked to intermediate cells.
- Intermediate cells have a predecessor P-cell during embryogenesis.

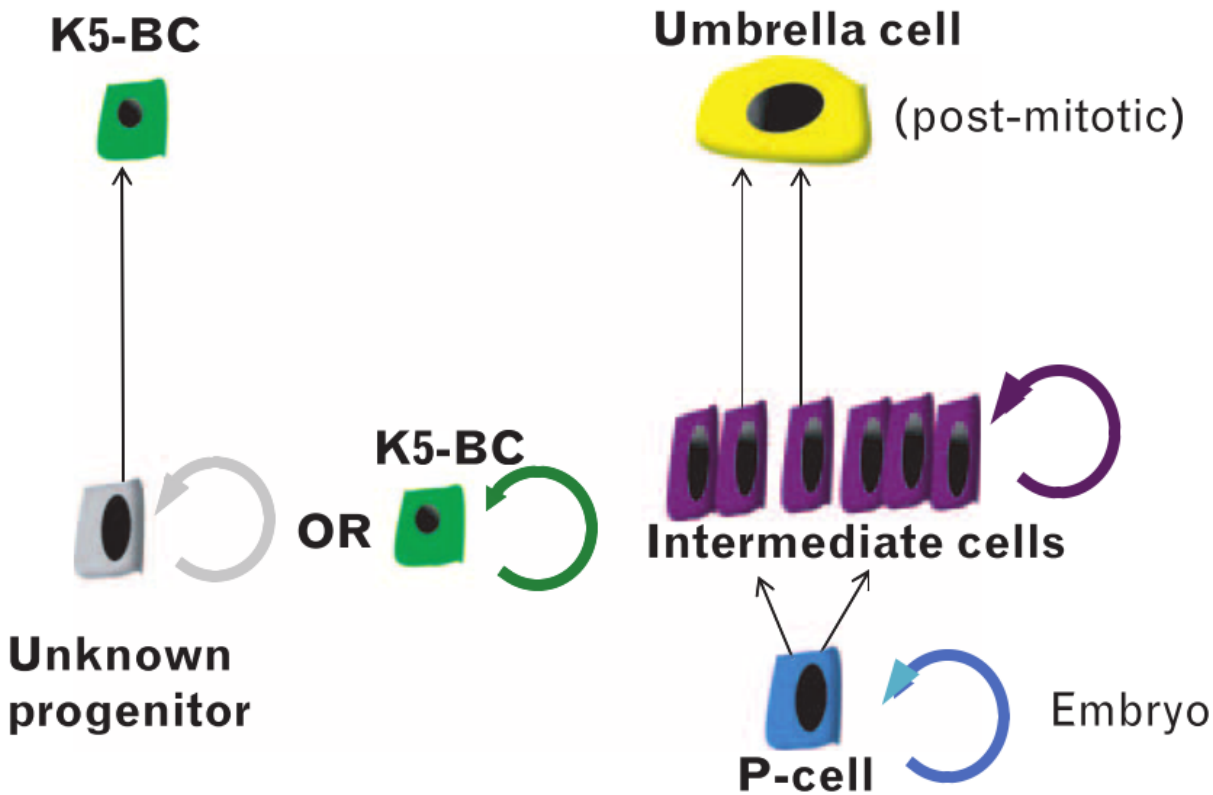

Figure: Proposal for a urothelium lineage according to [Yamany et al., 2014].

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Cell kinetics parameters

Note the "contradiction" in R and R_U.

Parameter	Symbol	Value	Source
turn over time	T_O	3 - 6 months	? referenced in [Ho et al., 2012]
regeneration after complete injury	R	3 d	? referenced in [Ho et al., 2012]
regeneration after removal of umbrella cells	R_U	10 d	? referenced in [Ho et al., 2012]

Table: Cell kinectics parameters. R_U in rat, R in mice

Marker for cell types

Property \ Cell type	S	B	I	U	P
Keratine-5	x	x			
Keratine- 18 and 20				x	
p63	x	x	x		x
uroplakin			x	x	x
CD90	x				
CD44	x	x			
CD49	x	x	x		
Foxa2					x

Table: Marker for cell types. From [Yamany et al., 2014] and [Ho et al., 2012]

Cell shapes

Cell type	diameter	shape
Stem	10-20*, 10+	polygonal+
Basal	10-20*	
Intermediate	10-15*, 10-40+	pyriform+
Umbrella	25-250*, 70-100+	cuboidal+

Table: Morphological properties. Diameter in μm. From *[Yamany et al., 2014] and +[Ho et al., 2012]. Range of umbrella cells is large because of the distension of the bladder.

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Hypotheses on epidermis cell lineages

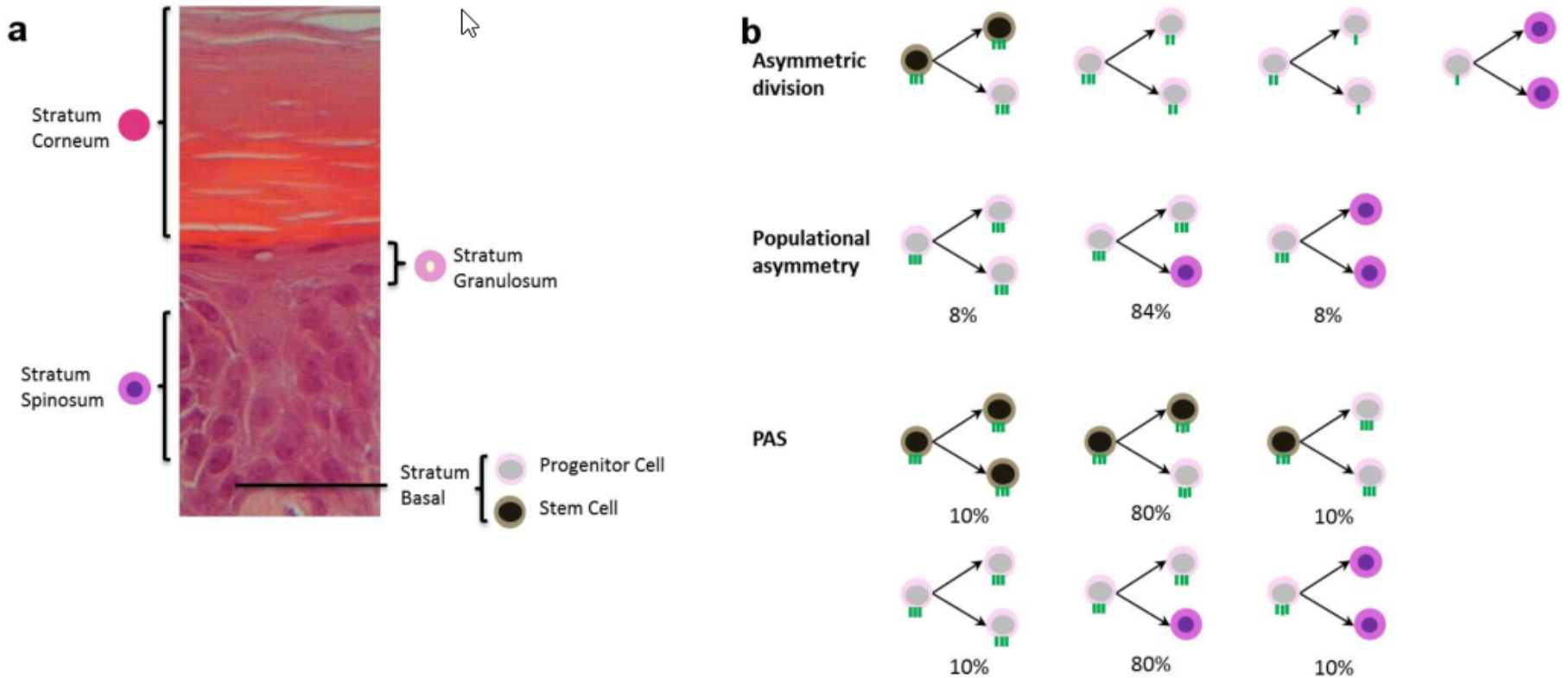

Figure: Three hypotheses on epidermis cell lineages (taken from [Li et al., 2013]). The other celltypes Stratum Granulosum and Stratum Corneum are derived directly from Stratum Spinosum.

Epidermis lineage according to [Grabe and Neuber, 2005]

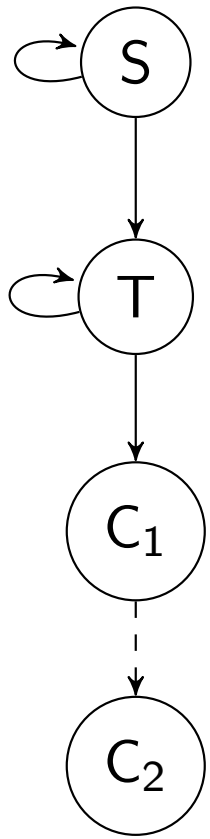

Figure: Epidermis lineage according to [Grabe and Neuber, 2005]. S: stem cell, T: transition amplifying cell, C_1: stratum spinosum, C_2: Late stratum spinosum (needs to be verified)

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Invasive bladder cancer

Umbrella and intermediate cells are represented as one cell.

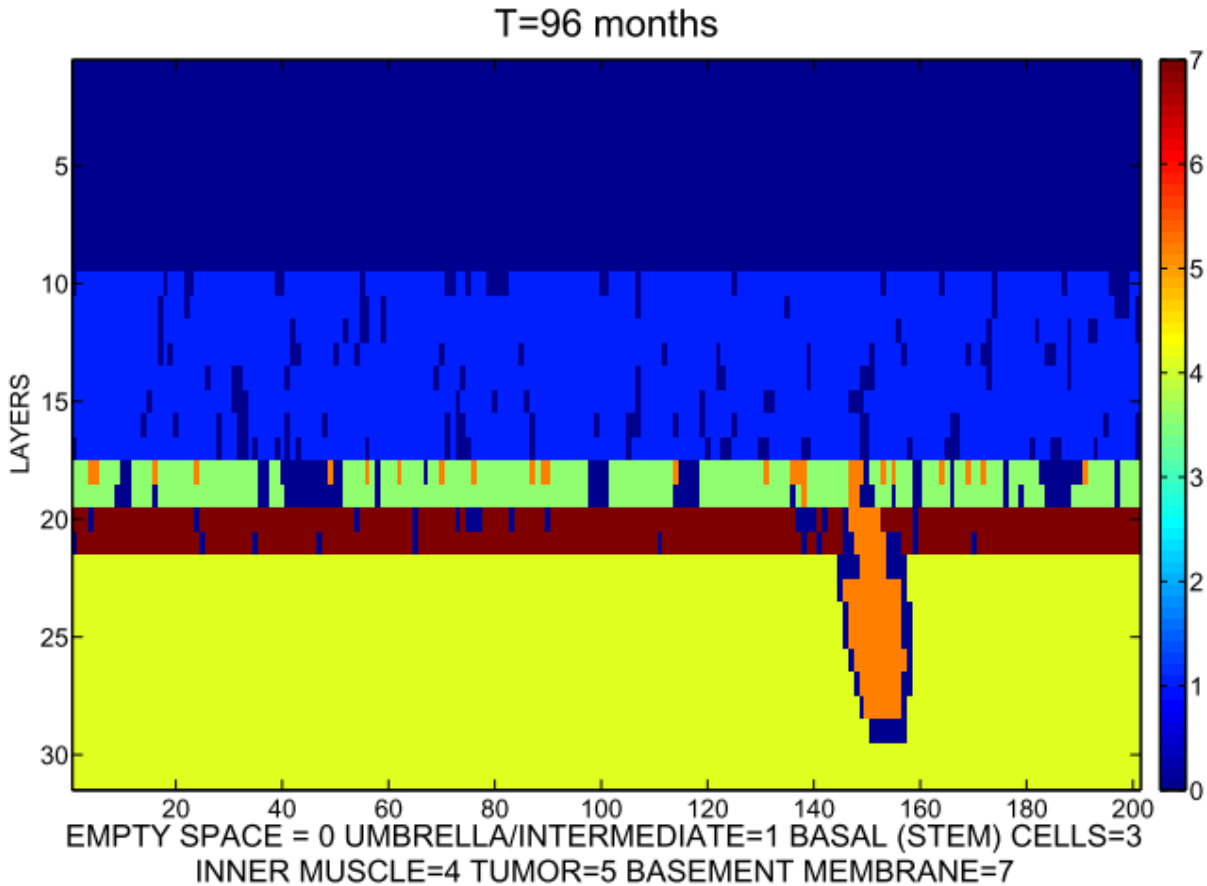

Figure: Invasive bladder cancer simulation [Kashdan, 2013].

Epidermis simulation with CC3D

[Savill and Sherratt, 2003] analyze the differentation of epidermal cells with CompuCell3D. More to come.

Section overview

Comparison

Tumor / Angiogenesis	3D	Framework / Simulation type	cell shape	diffusion	inhibition	adhesion
Tumor [Anderson et al., 2006]		Hybrid discrete-continuum	1 pixel / space-less	yes	no	yes
Avascular Tumor [Jiang et al., 2005]		Cellular Automata (CA)	1 pixel	yes	no	yes
Tumor Angiogenesis [Tang et al., 2014]	✓	CA with MatLab (Code)	1 pixel	yes	no	no
Brain Tumor [Gevertz and Torquato, 2006]		Voronoi Tesselation	voronoi	yes	no	no
Blood Vessel [Kleinstreuer et al., 2013]		CompuCell3D / AngioTool	arbitrary	yes	chemical	yes
Epidermis	**3D**	**Framework / Simulation type**	**cell shape**	**diffusion**	**inhibition**	**adhesion**
Epidermis [?]	✓	FLAME	sphere	no	yes	no
Epidermis [Grabe and Neuber, 2005]		MASON	exagonal	yes	no	yes
Psoriasis [Grabe and Neuber, 2007]		MASON	exagonal	yes	no	yes
Epidermis [Sutterlin et al., 2009]		MASON	exagonal	yes	no	yes
Epidermis [Savill and Sherratt, 2003]		CompuCell3D	arbitrary	yes	no	yes
Urothelium	**3D**	**Framework / Simulation type**	**cell shape**	**diffusion**	**inhibition**	**adhesion**
Urothelium [Kashdan, 2013]		Cellular Automata (CA)	1 pixel	yes	no	no
Urothelium [?]		Cellular Automata (CA)	1 pixel	yes	indirect	no
Moduro 2014		CompuCell3D	arbitrary	yes	nutrition	yes
Moduro (in general)	✓	CompuCell3D	arbitrary	yes	nutrition	yes

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Model domain

Definition

Let $x \in I$ be a value that can can be observed or measured directly in the real world and I is its domain, i. e. a set of all observable values. I is called a model domain.

Examples are

- a pixel (voxel) with i, j (i, j, k) coordinates (a position) that is part of a cell
- cell-ID of a pixel
- cell type of pixel
- nutrient value of a pixel etc.

Note: The size $(x \times y)$ of a simulation is implicitely defined via the pixel set.

Parameter domain

Definition

Let $\varphi \in P$ be a value that *cannot* be observed or measured directly in the real world and P is its domain, i. e. a set of all values. P is called a paramter domain.

Examples are properties of a cell like

- target size (volume)
- cell life time
- etc.

Input, output and parameters

Definition

Let I_i be a model domain and P_i a parameter domain. A n-tuple $(x_1, x_2, \ldots, x_n) \in I_1 \times I_2 \ldots \times I_n$ is a called an **input list** (for a model and $I = I_1 \times I_2 \ldots \times I_n$ is the input range. A m-tuple $(\varphi_1, \varphi, \ldots, \varphi_m) \in P_1 \times P_2 \ldots \times P_m$ is a called a **parameter list** for a model and $P = P_1 \times P_2 \ldots \times P_m$ is the paramter range.

Remark

$(x_1, x_2, \ldots, x_n)$ and $(\varphi_1, \varphi, \ldots, \varphi_m)$ could be considered as vectors $\vec{x}$ and $\vec{\varphi}$ – however, this is only correct if all elements are of the same type which is not necessarily the case.

Modeling

A model is a function that maps the input and time but also parameters to an output value. The output itself is of the same type as the input.

$$f : (\mathbb{R} \times I \times P) \to I$$

$$\text{Input } x \longrightarrow \begin{array}{l}\text{Nature or System:} \\ y = f_r(t, x)\end{array} \longrightarrow \text{Output } y$$

$$\text{Input } x \longrightarrow \begin{array}{l}\text{Model:} \\ \hat{y} = f(t, x, \varphi)\end{array} \longrightarrow \text{Output } \hat{y}$$

Figure: Overview of Modelling. top: a real world system maps an input (vector) to an output (vector) y depending on the time t and the input x. bottom: a model estimates the output value $\hat{y}$ depending on the on the time t, the input x and the parameters φ.

State

The state of a simulation is $S = \mathbb{R} \times I \times P$, i. e. point in time, and a combination of observable values (input) and parameters.
Example for 2×2-field:

$$S = (1.0, \underbrace{(\overbrace{2,2}^{\textit{lattice size}}, \overbrace{1,1,2,3}^{\textit{cell id}}, \overbrace{1,1,2,2}^{\textit{cell type}})}_{I}, \underbrace{(\overbrace{2.0,1.0}^{\textit{Target volume}}, \overbrace{30.5,35.0}^{\textit{Cell cycle times}})}_{P})$$

Note that S contains redundant data (here type). This would be different in a data structure.

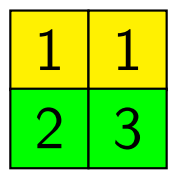

Figure: Example for a state. Number: cell ID, color: cell type 1 is yellow, cell type 2 green.

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Optimum

Let m be metric (a fitness function) that compares the real word data with the model estimation.

$$m : I \times I \rightarrow [0, 1] \subset \mathbb{R}$$

$m = 0$ indicates the worst and $m = 1$ the best match.
Let $I_S \subset I$ be the set of possible start configurations and $T = \{t_1, t_2, \ldots\}$ a series of points in time for which an output y is known for any $x \in I_S$.

$$M(\varphi) = \sum_{x \in I_S} \sum_{t \in T} m\left(f(t, x, \varphi), f_r(t, x)\right)$$

The optimal parameter (set/vector) is φ^* where $M(\varphi)$ is maximal.

Normalized optimum

$$M(\varphi) = \frac{M(\varphi)}{|I_S| \cdot |T|} \in [0, 1]$$

Statistics

Let

$$m_i(x, \varphi) = m\left(f(t_i, x, \varphi), f_r(t_i, x)\right)$$

be the i-th metric for time point $t_i \in T$ and $f()$ is a random variable. The series

$$m(x, \varphi) = m_1(x, \varphi), m_2(x, \varphi), \ldots, m_{|T|}(x, \varphi)$$

can be described via descriptive statistics.

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Arrangement Fitness Function

$$f_a = \begin{cases} \frac{1}{(1-L_B)+(lib-L_I)+(1-L_U)+1} & \textit{if layers} > 0 \\ 0 & \textit{otherwise.} \end{cases}$$

$L_B = 1$ if the first layer is made of cell type basal or stem otherwise 0.
$L_U = 1$ if the last layer is made of cell type umbrella otherwise 0.
$lib = \textit{layersInBetween}$ is the number of strata in between the first and last layer. L_I is the number of layers made of intermediate cells. $lib - L_I$ results in the number of cells wandering away from their intended layer. The function f_a is then calculated column by column on n different locations on the tissue. Out of these values, the average is taken as follow:

$$\bar{f}_a = \frac{1}{n}\sum_{i=1}^{n} f_a(i)$$

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Volume Fitness Function

$$f_{V_i} = \frac{1}{4\left(\frac{V_{S_i} - V_{I_i}}{V_{S_i}}\right)^2 + 1}$$

V_S and V_I is the desired (should) and actual (is) volume of all cells of a specific type i.The overall fitness volume function is the arithmetic mean for all cell types:

$$f_V = \frac{1}{|C|} \sum_{i \in C} f_{V_i}$$

where C is the set of all cell types in mind. With the urothelium cells this is

$$f_V = \frac{f_{V_B} + f_{V_I} + f_{V_U}}{3}$$

with $C = \{B, I, U\}$.

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Cell cycle times

For every interval of two days the mean cell cycle times for all cells and cell types is calculated. Any time a cell is removed by either dividing or changing their cell type due to differentiation an event is triggered that contains the life time of the removed cell. This event is added to the interval and finally the mean value and standard deviation is computed.

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Nomen clature for *a* model

- Module (or package) concept
- We need at least statements on
  - Differentation process (CM: contact model, PAS: population asymmetry with stem cells)
  - Birth process (NU: mitosis via size via nutrients, IN: infinite growth)
  - Death process (AP: apoptosis, VO: voiding)
  - Sort process (DA: differential adhesion)
- Example: CM-NU-AP-VO-DAE or PASCM-IN-AP-VO
- A Parameter set is defined for each process

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Prerequisites

Software

- Windows 7 or 8 / Linux ?
- Python 2.7.x (tested with 2.7.?)
- CompuCell3D 2.7.x (tested with 2.7.1)

Hardware

- CPU $\geq$ 2 GHz
- $\geq$ 4 GB RAM
- $\geq$ 5 GB disk space

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Proposal for model representation

A model is a set of parameters. Parameters are solely represented as Python code. They can be

- regular variables (primitive data types like integer, float; vectors or matrices etc.)
- functions that can be passed to other objects

Proposal: Class Main starts the program. It requires the parameters

1. Execution parameters (reference to ExecConfig instance)
2. Model parameters (reference to ModelConfig instance)
3. Optional parameters (reference to OptConfig instance)

A ModelConfig can be created on the fly or read from a ModelConfig.py singleton object that represents the model. Ideally, there exist as many model-config files as there are models.

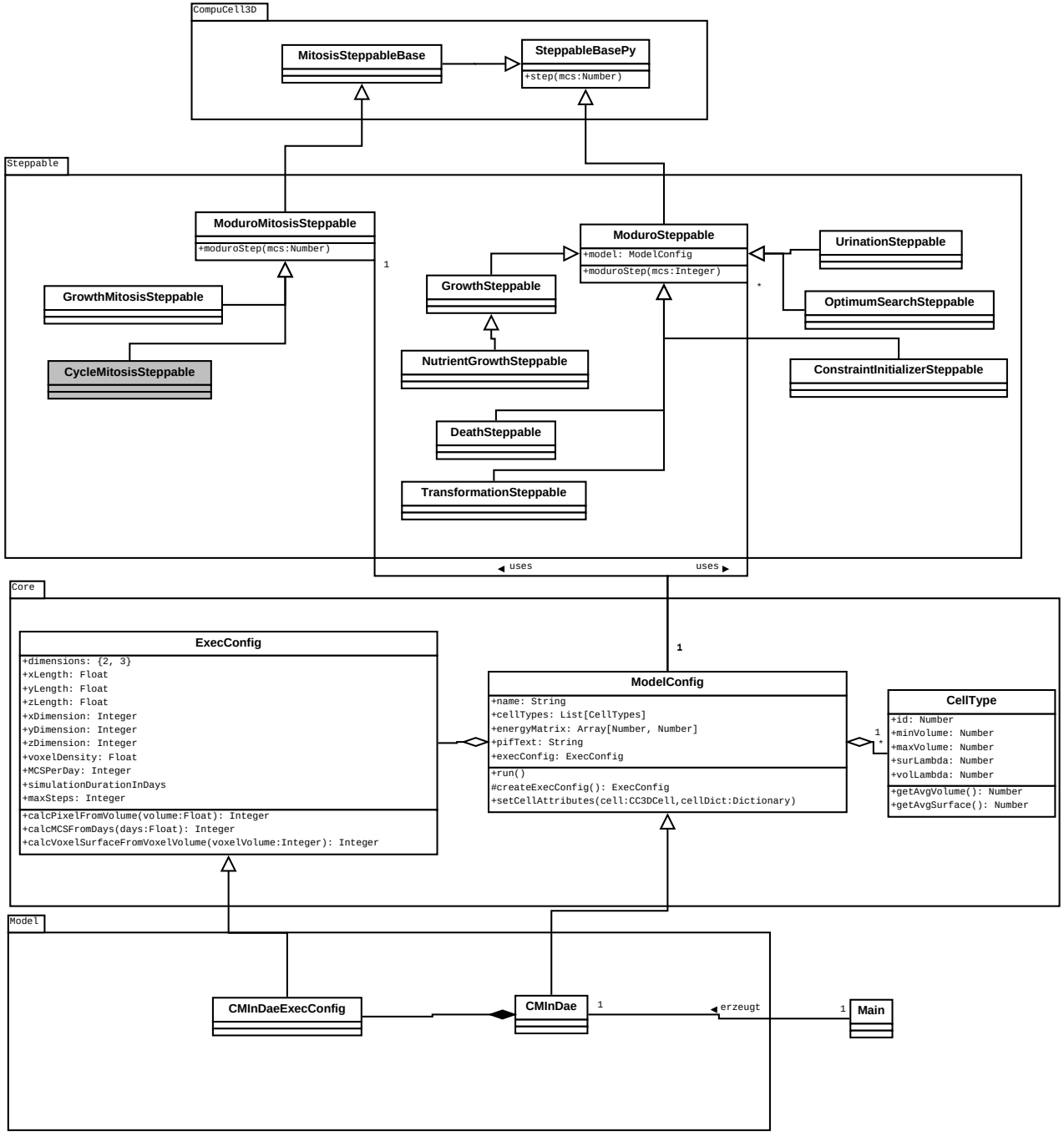

Figure: Package and class design.

CC3D: Cell class

CC3D has objects of type `Cell` which can be accessed from Python via `self.cells`. CC3D `Cell` cannot be derived. Moduro extends a `Cell` by adding new attributes to a `Cell`'s dictionary.

Units in cell are CC3D specific

All values stored in a cell and the associated cell dictionary are CC3D specific. In particular:

- Volume or surface depends on a 2D or 3D lattice.
- Dictionary attributes like 'targetVolume' are lattice dependent.

Attributes of a Moduro-Cell class

A Moduro-cell-class has the following attributes:

min_max_volume The minimal and maximal volume/area this cell can have.

target_Volume The optimal volume/area of this cell.

life_time The life time of this cell in MCS.

exptected_life_time A random number indicating how long a cell will live.

necrosis If true this cell will die.

DNA ???

TurnOver ???

CellType class

A CellType-class contains attributes for a specific type of a cell, e. g. a stem cell. Any cell object instantiated at run-time will obtain those attributes by default.

CellType is CC3D independent

All units in CC3D are physical units. Defaults for volume is μm^3 and for time is a day.

CellType attributes

A CellType-class has the following attributes:

minDiameter The minimal diameter in μm this celltype have have.

maxDiameter The maximal diameter in μm this celltype have have.

surFit A factor indicating how important a correct surface is. Range from 0 (does not matter) to 1 (perfect).

volFit A factor indicating how important a correct volume is. Range see surLambda.

apoptosisTimeInDays The expected life time of this cell in days.

growthVolumePerDay The growth of this celltype in μm^3 per day. Example: a stem cell with a volume of 400 μm^3 growths (in average) 4000 $\mu m^3/d$.

Core concepts and their extensions

CC3D knows several concepts which are helpful for cell simulations. These are

Initializer A method that initializes the area or space with cells. Example: BlobInitializer.

Copy Attempt A callback after each MCS copy attempt.

Stepables A callback after each MCS.

However, some concepts are missing, which are introduced here:

Sampler A callback that occurs after a specific time step. Usually the time intervals are equal.

File formats

Moduro knows the following file formats:

1. Arrangement fitness function (file: `FitnessArrangement.dat`)
2. Volume fitness function (file: `FitnessVolume.dat`)
3. Cell times (file: `Celltimes.dat`) (`.daz` right now because of Toolbox constraints)
4. Colony (TODO)
5. Fitness function (redundant, deprecated)

Log file for cell times

A text file containing an event for each line. Events are

1. Birth of a cell
   <time> B <cellID> <cellTypeID>
2. Death (or removal) of a cell
   <time> D <cellID> <cellTypeID> <cycletime>

```
timescale = h
2440.5 B 1272 B        # 100 Tage
2440.8 B 1234 I
2450.5 D 1272 B 10.0
...
```

Colony

A text file containing an entry for each sample point.

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Command Line Options

You need the full path of the compucell3d.bat (with the GUI) or the runscript.bat (without the GUI) file and the option -i followed by the full path of the simulation which should be started:

- *C:\...\CompuCell3d\compucell3d.bat -i C:\...\Demos\Moduro\Contact\Urothelium .cc3d*

Other options are:

- *-o, –noOutput, –exitWhenDone, -h, –help, -c, -f*

[Swat et al., , p.82-83]

Chapter overview

Simulation power

Platzhalter für Machbarkeitsanalysen

Model	Pixel size	# of Cells	HW	Model time	Exec. time	Problem
CM-NU-AP-VO-DAE	400 x 400		CUDA	500 d	7 d	
PAS-IN-AP-VO	400 x 400		CUDA	500 d	5 d	
Klein Tumor (CC3D)	1000 x 1000	500	CUDA	3 MCS	15 min.	crashed
Klein Tumor (Morpheus)	5000 x 5000	5k to 10k	Laptop	12 700 MCS	5 h	not our model
Klein Tumor (Morpheus)	5000 x 5000	5k to 10k	CUDA	13 400 MCS	6 h 47 min.	not our model
Klein Tumor (Morpheus)	5000 x 5000	5k to 10k	Laptop	720k MCS	16 days	estimation

Table: Simulation power: an overview

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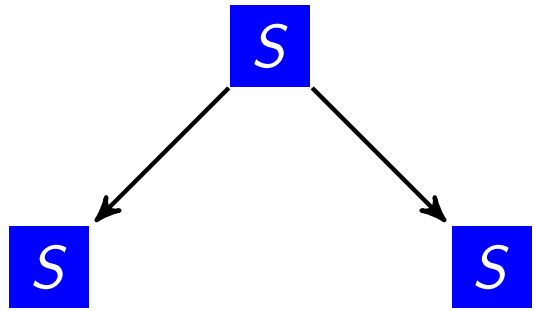
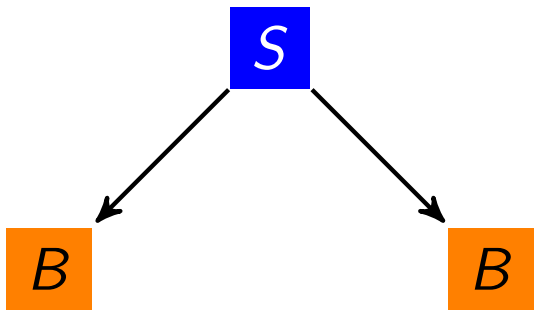
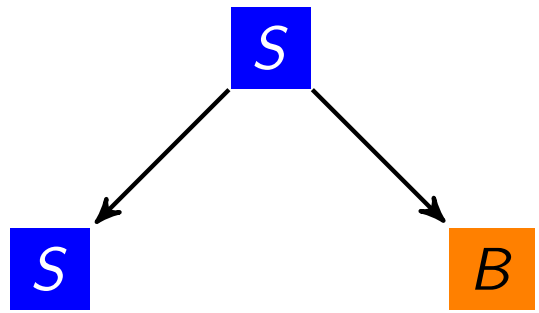
Example with figure



(a) Symmetrical division stem to stem



(b) Symmetrical division stem to basal



(c) Asymmetrical division to stem and basal

Figure: Packages of stem to basal transition

Cellsorting hypothesis

- Cell lineage is autonomous and cells are arragment by a sorting mechanisms

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The End

Thank you very much!