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**Extension of two dimensions morphogenesis
simulation models of the urothelium into three
dimensions within the moduro simulation
environment**

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Mannheim, 11.11.2015

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Abstract

Extension of two dimensions morphogenesis simulation models of the urothelium into three dimensions within the moduro simulation environment

The European languages are members of the same family. Their separate existence is a myth. For science, music, sport, etc, Europe uses the same vocabulary. The languages only differ in their grammar, their pronunciation and their most common words. Everyone realizes why a new common language would be desirable: one could refuse to pay expensive translators. To achieve this, it would be necessary to have uniform grammar, pronunciation and more common words. If several languages coalesce, the grammar of the resulting language is more simple and regular than that of the individual languages. The new common language will be more simple and regular than the existing European languages. It will be as simple as Occidental; in fact, it will be Occidental. To an English person, it will seem like simplified English, as a skeptical Cambridge friend of mine told me what Occidental is.

Einsatz eines Flux-Kompensators für Zeitreisen mit einer maximalen Höchstgeschwindigkeit von WARP 7

Jemand musste Josef K. verleumdet haben, denn ohne dass er etwas Böses getan hätte, wurde er eines Morgens verhaftet. Wie ein Hund! sagte er, es war, als sollte die Scham ihn überleben. Als Gregor Samsa eines Morgens aus unruhigen Träumen erwachte, fand er sich in seinem Bett zu einem ungeheueren Ungeziefer verwandelt. Und es war ihnen wie eine Bestätigung ihrer neuen Träume und guten Absichten, als am Ziele ihrer Fahrt die Tochter als erste sich erhob und ihren jungen Körper dehnte. Es ist ein eigentümlicher Apparat, sagte der Offizier zu dem Forschungsreisenden und überblickte mit einem gewissermaßen bewundernden Blick den ihm doch wohl bekannten Apparat. Sie hätten noch ins Boot springen können, aber der Reisende hob ein schweres, geknotetes Tau vom Boden, drohte ihnen damit und hielt sie dadurch von dem Sprunge ab. In den letzten Jahrzehnten ist das Interesse an Künstlern sehr zurückgegangen. Aber sie überwandten sich, umdrängten den Käfig und wollten sich gar nicht fortrühren.

Contents

1. Introduction	1
1.1. Background	2
1.1.1. Biology of the Urothelium	2
1.1.2. Glazier Graner Hogeweg Model	3
1.1.3. CompuCell3D	5
1.2. Given Task	6
1.3. Outline	6
2. State of the Art	7
2.1. Display and Simulation of the Urothelium	7
2.1.1. Events every Monte Carlo Step (MCS)	8
2.1.2. Events not every MCS	8
2.2. Simulation Properties	9
2.3. Models	9
2.4. Adhesion and cell sorting	11
2.5. Cell Properties	11
2.6. Fitness functions	12
2.6.1. Arrangement fitness function	12
2.6.2. Volume fitness function	13
2.6.3. Overall fitness function	13
2.6.4. Moduro Toolbox	13
2.7. Simulation Scripts	14
2.7.1. Area of stem cells	14
2.7.2. Position of the stem cells	14
2.7.3. Cell Drawing	15
2.7.4. MinMaxVolume	15
2.7.5. Volume and TargetVolume	16
2.7.6. Lambda TargetVolume and TargetSurface	16
3. Method	19
3.1. Draw Cells	19
3.2. Lambda Multiplier	23
3.3. Approximation Error	23
3.4. Area of stem cells on the basal membrane	27

3.5. TargetVolume, Surface after Mitosis	31
4. Results	33
4.1. Draw Sphere Cells	33
5. Conclusion	35
5.1. Draw Sphere Cells	35
5.2. lambda values	35
5.3. Approximation Errors	35
List of Abbreviations	vii
List of Tables	ix
List of Figures	xi
Listings	xiii
Bibliography	xv
Index	xvii
A. Erster Anhang	xvii
B. Zweiter Anhang	xix

Chapter 1

Introduction

Without cell adhesion no complex life would exist **REF** This is a well known and long existing statement in the biology. It describes that if different cells would not stick to each other the only living things would be cells. In humans many organs are made of several cells. This is also the case for the urothelium. For the urothelium it is necessary that the cells stick to each other. Otherwise the functions of the urothelium could not be executed and also it would not be able to growth. In the project we simulate this growth of an urothelium with several different models.

There are several types of tumors. One is the and the other one is the Since bladder cancer is one of the most common cancer types among men it is important to understand how and why the cancer is able to growth. Bladder cancer starts to growth in the urothelium. With the simulation of the urothelium and the different models we hope to be able to predict when bladder cancer occurs.

To understand the functionality of organs observation is necessary. For the urothelium this is already done, as there are a lot of different in vitro experiments about the methodology of the urothelium. After the observation of organs is complete, we are able to predict how the organ will react to different situations. To verify these predictions we need to simulate the behavior of the organ. A simulation is in general an illustration of the reality, but it can also be used to change reality in a for the research specific way to get more knowledge of this organ.

1.1. Background

1.1.1. Biology of the Urothelium

Bladder cancer is one of the most common cancer types among men. It is the 4th most common type regarding to everydayhealth.com¹, where every 36st out of 100.000 men gets it. Bladder cancer usually starts with some cells in the bladder, which growth uncontrolled. From these cells, the tumor can spread further into surrounding areas ². The most common bladder cancer type is the urothelial carcinoma². An illustration of how bladder cancer evolves is displayed in figure 1.1 at page 3.

The bladder is located in the lower urinary tract and consist of several parts, where urothelium coats the bladder [1]. More specifically, it covers the bladder from the renal pelvis to the proximal urethra [2], [3]

Two important tasks of the bladder are the storage and release of urine. To do so the bladder will extend, during the storage, and then shrink again [4]. One task of the urothelium is to form a distensible barrier **WRCross2005**, [1], [5], [6]. That the urothelium ensures its barrier function, it has to growth and downsize its size. This is done by the largest cells of the urothelium – the umbrella cells. Because the umbrella cells are in direct contact with the bladder, it is their task to change size and form during the growth and shrink process of the bladder. Birder described the urothelium as “... a responsive structure capable of detecting physiological and chemical stimuli and releasing a number of signaling mole-cules.” [3]. Another task of the urothelium is to control the movement and passage of macromolecules, ions, water, toxic metabolites and solutes [5], [6]. If the urothelium is damaged, it rapidly generates new cells, to ensure full functionality [2], [5], [6]. In the research there are assumptions, that the quick regeneration is done by a lot of mitosis, i.e. cell division.

To receive a better overview the different cell types are explained in the following paragraph. They are also displayed in figure XY. The umbrella cells, also called superficial cells, they are connected directly with the bladder and have an average diameter of 25 up to 250 µm [2], [6].

Below these cells the intermediate cells are located. With an average diameter of 10 up to 20 µm [2], [6], they are a far bit smaller then the umbrella cells. The middle

¹<https://www.everydayhealth.com/bladder-cancer/guide/> visited: 31.12.2017

²<https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html> visited: 31.12.2017

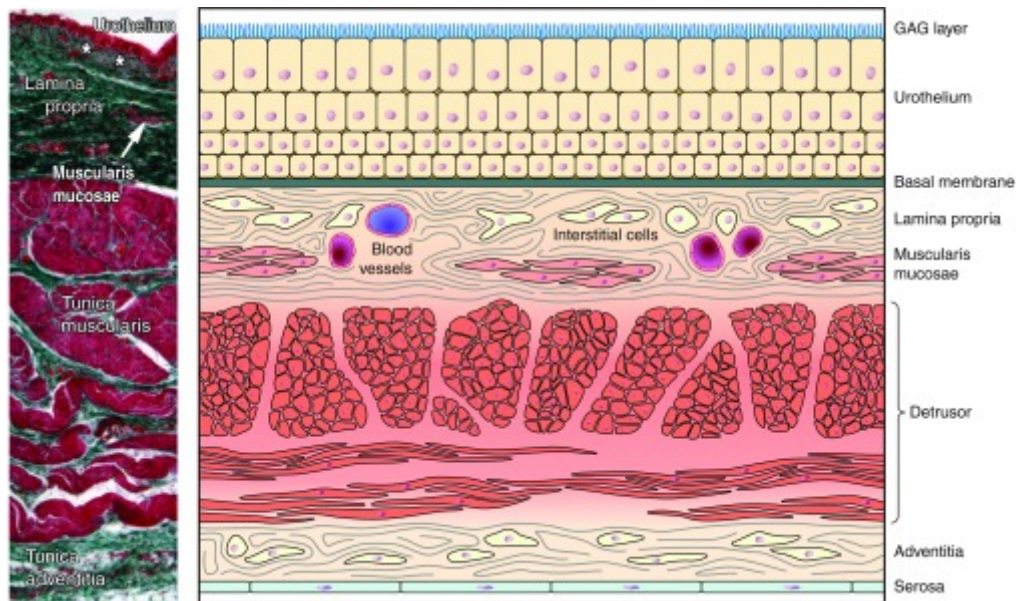


Figure 1.1.: Physiology of the urothelium - <http://000ekkt.myregisteredwp.com/trauma/>
visited: 31.12.2017

layer of the urothelium can consist of several own layers, i.e. there can be several layers in the layer of the intermediate cells.

The smallest and the most common cells in the urothelium are the basal and stem cells. Those cells have a diameter of up to $10\text{ }\mu\text{m}$ [1], [6].

The urothelium has several layers. In the first layer, there are the basal and stem cells. Above them, there are several layers of intermediate cells. On top of the epithelium, i.e. a membranous tissue which consists of one or several layers¹, there is one layer of umbrella cells.

1.1.2. Glazier Graner Hogeweg Model

Since there are several formulas and models developed from Glazier and Graner, this subsection briefly describes these models and formulars.

Glazier-Graner-Hogeweg (GGH) models are widely used in biological simulations, since it provides a good flexibility, extensibility and it is easy to use [7]. Glazier and Graner developed their model as an extension of the large- q Potts model, which itself is an extension of the Ising Model, and called it first the Extended Potts Model (EPM). Nowadays, this model is called Cellular Potts Model (CPM) [7]–

[9]. Glazier and Graner extended their CPM in a way that also volume constraints are considered for the hamiltonian, see following form:

$$\begin{aligned}\mathcal{H}_{CPM} = & \sum_{\vec{i}, \vec{j}} J(\tau(\sigma(\vec{i})), (\tau(\sigma(\vec{j}))) (1 - \delta(\sigma(\vec{i}), (\sigma(\vec{j}))) \\ & + \sum_{\sigma} \lambda_{vol}(\tau)v(\sigma) - V_{target}(\tau(\sigma)))^2\end{aligned}\quad (1.1)$$

This hamiltonian, describes first the adhesion energy between different cell types. Therefor, every cell has a specific cell type $\tau(\sigma)$ [8], [9]. Each cell is placed onto a lattice with a spin $(\sigma(\vec{i}, \vec{i}))$ for every given dimension [7]–[9]. The adhesion energy between cells is only considered if the kroenecker delta is 0. Thus, the surface energy between cells is considered if $\delta(\sigma, \sigma') = 0$ **Scott1999**, [7]–[10]. Second, the volume of each cell is now considered and the user is allowed to add a multiplier to the hamiltonian, which is done by the multiplier λ_{vol} .

Together with Hogeweg they further develop their created extension of the CPM. The further developed model is today called GGH model. The main extension was that the user of GGH model is now able to add surface area constraints [7]–[9] as well as to use a negative boundary energy [7]. With the surface are constraint the formula for the GGH model is:

$$\begin{aligned}\mathcal{H}_{GGH} = & \sum_{\vec{i}, \vec{j}} J(\tau(\sigma(\vec{i})), (\tau(\sigma(\vec{j}))) (1 - \delta(\sigma(\vec{i}), (\sigma(\vec{j}))) \\ & + \sum_{\sigma} \lambda_{vol}(\tau)v(\sigma) - V_{target}(\tau(\sigma)))^2 \\ & + \sum_{\sigma} \lambda_{sur}(\tau)s(\sigma) - S_{target}(\tau(\sigma)))^2\end{aligned}\quad (1.2)$$

The new model also allows the user to model (a): cell growth and proliferation (b): mitosis, i.e. cell division (c): fields, forces and diffusion and (d): chemotaxis and haptotaxis [7].

Glazier et. al. describe their model as:

GGH models define biological structure consisting of the configuration of a set of *generalized cells*, each represented on a *cell lattice* as a domain of latitice sites sharing the same cell index [...], a set of *internal cell states* for each cell [...], and a set of *auxiliary fields* ..." [7].

The GGH model has the advantage that “Initial conditions emulating a particular biological configuration rather than random initial conditions.” [7] and it has now biologically motivated properties instead of physically motivated properties [7].

1.1.3. CompuCell3D

CompuCell3D (CC3D) is an open-source program, which provides a simulation environment for multi- or single-cell-based modeling of tissues, organs and organisms³. To do so, CC3D uses the CPM in its simulation³, which describes cell and Extended Cellular Matrix (ECM) behavior [11]. CC3D provides the possibility to create scripts for the simulation, e.g. cell growth, mitosis, apoptosis or necrosis scripts, in python, C++ or in their own CC3DM, which is their own Markup Language. With such scripts CC3D allows the user to modify the behavior of the simulation for a specific purpose. CC3D uses the GGH approach, explained in section 1.1.2 at page 3. It allows the user to choose between several cell-lattice types, i.e. a presentation of the pixels of a cell at a specific position in the simulation field (see picture XY). By default, it uses a square-lattice of single pixels for each dimension. There is also the possibility to use a hexagonal-lattice, where the pixels would be hexagons in two dimensions, or rhombic dodecahedrons in three dimensions. Since the core of a GGH simulation is the effective energy **IntroCC3D** CC3D tries to minimize this effective energy every MCS, i.e. a calculation step in the simulation. The basic form for the effective energy is:

$$\mathcal{H}_{boundary} = \sum_{\vec{i}, \vec{j}} J(\tau(\sigma(\vec{i})), (\tau(\sigma(\vec{j}))) (1 - \delta(\sigma(\vec{i}), (\sigma(\vec{j}))) \quad (1.3)$$

There are several ways to extend this form, it is possible to add a volume or a surface constraint. During each MCS an index-copy attempt takes place **MaciejH.Swat2017** I.e. a pixel is selected, and it will be tried to overwrite a randomly chosen pixel, next to the current pixel, in order to minimize the effective energy. The index copy attempt succeed and takes place only if this index copy attempt decreases the effective energy **IntroCC3D** Each MCS the program tries to minimize the simulation, e.g. with index copy attempts. The user has the chance to use her/his specific script every MCS, before the simulation starts or at the end of the simulation.

³<http://www.compuCell3d.org/> visited: 13.01.2018

1.2. Given Task

The task of this bachelor thesis is to create a 3D morphogenesis simulation of the urothelium by using CC3D. Since the simulation models and python scripts for a 2D simulation are given and the simulation is done by CC3D the task is to modify the current simulation scripts, of the 2D simulation, in a way that these scripts can be used for a 3D simulation of the different models.

Therefor, first I have to analyse and understand the simulation scripts, in order to modify these for the 3D simulation. In some scripts, I will have to modify the parameters or change complete methods. My results of the 3D simulation has to be presented with at least one model. The results are also presented by prototypes (if there is enough space to present the different configuration). Another important task is to estimate or to calculate, if possible, the time effort and compare this time effort to the time effort of the current 2D simulations.

1.3. Outline

In this chapter the basic knowledge to understand this bachelor thesis is provided. The next chapter provides the process of the project, at the point where I started with the bachelor thesis. Once the basic knowledge and the state of the art are explained, I describe how I worked, i.e. what did I do to understand the project and to find solutions. After these information I reveal the results of this bachelor thesis. Therefor, if it is possible to have a 3D simulation by using CC3D. In the last chapter a conclusion of this bachelor thesis is provided.

Chapter 2

State of the Art

The current moduro project has a stable 2D simulation of 16 different models using CC3D. With these models it is tried to make predictions about how bladder cancer arises. The simulations are performed by CC3D and then several values, e.g. the fitness of the model or how realistic the model is, etc., are summarized and displayed by the 'Moduro-Toolbox'. The project consists of several models and several scripts, both are written in python, i.e. a programming language. The models include properties of the specific model, e.g. adhesion energy or the possibility of the new cell types after mitosis, i.e. cell division, and the scripts modify the cell behavior, e.g. they check when a mitosis takes place, how fast the cell will growth, etc.. The scripts are also calculating if the current model is a realistic one or not. These evaluating data are later used by the 'Moduro-Toolbox' to provide a overview over these data.

2.1. Display and Simulation of the Urothelium

In CC3D we use simulate an urothel of the size of $200\text{ }\mu\text{m}$ for the x-axis and $100\text{ }\mu\text{m}$ for the y-axis. The simulation of the urothel covers 2 years. At the first calculation step, MCS 0, the simulation is initialized, i.e. the cells are drawn and placed. In order to provide a realistic simulation, i.e. the simulation is not too easy and not too hard, we have to calculate events which occur every MCS and some events which are occur not every MCS. The events, which are performed every MCS are a) cell growth and b) the check for mitosis. Events which are not performed every MCS

2. State of the Art

are c) urination d) cell death e) transformation and f) mutation. These events will occur at some point in the simulation

2.1.1. Events every MCS

Cell Growth

Every MCS we calculate the growth of a cell. In the project currently the maximum possible growth of a cell is calculated. We need this calculation for the relation volume and TargetVolume as well as for the relation volume, surface and TargetSurface. CC3D calculates the volume itself, because the by CC3D calculated volume or surface is a read-only value, i.e. it can not be overwritten. We set every MCS a targetVolume and a λ_{vol} at the initialization of the simulation. If we would not set up a targetVolume the effective energy would be 0 and the simulation would not start. Cell growth is also required to influence the shape of the cell, as we calculate the shape out of the volume and apply the calculated surface as TargetSurface and the lambda λ_{sur} to the effective energy.

Mitosis

The verification if a cell divides or growth further is done every simulation step. Doing so allows us to define a very specific MCS at which a cell divides, as there are 500 MCS per day. The cells which are able to grow and as a result divide are a) stem cells b) basal cells and c) intermediate cells. The umbrella cells are more a product of mitosis than of cell division, if they would divide there would be two instead of one umbrella cell.

2.1.2. Events not every MCS

Urination

Every 12 hours an urination is taken place. This is simulated in a way that for *some specific cells* a necrosis flag is set, i.e. the simulation scripts let the cell shrink and then disappear.

Necrosis

If a cell dies, i.e. necrosis takes place, a flag in the cell dictionary is set. Every 12 hours, 250 MCS, we check if a cell dies or not. If so, the cell will shrink and finally disappear.

Transformation

A transformation can take place if a basal cell divides into a basal and a intermediate cell. Because the intermediate cell has to be inside the strata, it immediately will be transformed to an umbrella cell, which are kind the barrier to the urin in the bladder.

Mutation

In the current project every day it is checked if a cell mutates or not. Every cell type has, dependant on the biological model, a propability if the cell mutates or not. If the mutates, currently the flag for necrosis is set and therfor the cell disappears.

2.2. Simulation Properties

2.3. Models

The 2D simulation of the urothel provided 16 different models. These model differ mostly in which cell types after the mitosis are created. The project divides the models into two domains, one has the id 'SSD', which stands for "stem cell-like division" **Torelli2017** and means that every time a stem cell divides there will be one stem and one basal cell. The second domain has the id 'SPA', which stands for "stem cell population asymmetry" **Torelli2017** In the second domain the stem cell has a propability of 90% that it will be one stem and one basal cells after mitosis. There is also the chance with a probability of 5% that after mitosis there are two stem cells or two basal cells. This two domains and how the different models derive is displayed in figure XY.

2. State of the Art

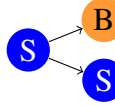
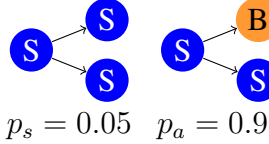
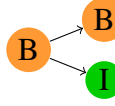
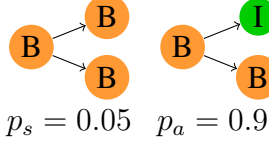
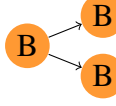
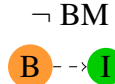
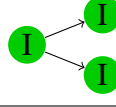
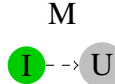
Type	ID	Description	Model
Stem cells	SSD	Stem cell-like division	
	SPA	Stem cell population asymmetry	
Basal cells	BSD	Stem cell-like division in basal cell	
	BPA	Basal cell population asymmetry	
	BPCD	Proliferation and contact differentiation of basal cells	
	BCD	Only contact differentiation of basal cells	
Intermediate cells	IPCD	Proliferation and contact differentiation of intermediate cells	
	ICD	Only contact differentiation of intermediate cells	

Table 2.1.: Possible proliferation and differentiation concepts for the three cell types stem (S), basal (B) and intermediate (I) cell (column Type). Column ID assigns a label for a specific proliferation or differentiation rule which refers to a specific model (column Model). Per cell type group one model can be chosen. In total we have $2 \cdot 4 \cdot 2 = 16$ lineage models. Dividing cells are expressed by a plain line and transformation (differentiation) by a dashed line. Transformation might happen either through contact (see ICD) or the loss of contact (see BCD).

Cell type		V_{min}	d_{min}	V_{max}	d_{max}	Volume	Surface
Stem	S	268	8	523	10	perfect	average
Basal	B	381	9	523	10	important	average
Intermediate	I	905	12	1767	15	important	poor
Umbrella	U	1767	15	3591	19	important	poor

Table 2.2.: Cell properties. Volumes V in μm^3 , diameters d in μm . Columns *Volume* and *Surface* are adjusted with the weights λ_V and λ_A , respectively.

Types		M	BM	S	B	I	U
Medium	M	0	14	14	14	14	4
Basal membrane	BM		-1	1	3	12	12
Stem cell	S			6	4	8	14
Basal cell	B				5	8	12
Intermediate cell	I					6	4
Umbrella cell	U						2

Table 2.3.: Surface tension values for the four cell types, the basal membrane (BM) and the medium (M). The values are according to CompuCell3D conventions: small values represent high adhesion, higher values less adhesion/greater repulsion.

2.4. Adhesion and cell sorting

During morphogenesis of a strata the cells not only growth, they also sort themselves. In order for the cell sorting there have to be different adhesion values **REF** i.e. how strong the surface of two different cell types are holding together. In the project this is done with a matrix, which every of the 16 model has. The cell type 'Medium' is a CC3D specific cell type and describe the space where no cells are in the simulation.

2.5. Cell Properties

Each cell of cell type has several attributes, moreover each cell has an cell dictionary, in which additional attributes are stored. The properties regarding the cell type are likely what every cell in general has, e.g. min- max Diameter, min- max Volume, growth in μm per day or time until apoptosis, i.e. cell death, etc.. Some of the properties are displayed in figure XY. The attributes in the cell dictionary are more likely for the simulation. Therefore, these are some attributes which we are using to make decisions, e.g. the current and expected live time, a flag for necrosis can be set here, etc..

2. State of the Art

Each cell have a cell dictionary, where different values about the cell are saved. These values are a) exp-life-time, i.e. the expected live time of a cell until necrosis, i.e. cell death—in the simulation the cell shrinks and then dissappears—takes place b)necrosis c)DNA d)TurnOver e)colony f)id g)removed h)inhibited i)min-max-volume j)normal-volume k)growth-factor l)life-time.

2.6. Fitness functions

In order to validate the simulated models, there are several scripts which check if the model is realistic or not. These scripts will check every day, every 500, MCS if the model is realistic or not **Torelli2017** The result of these two fitness functions will be written into a file, and later read out by the moduro toolbox.

2.6.1. Arrangement fitness function

The arrangement fitness function ensure that the strata of the simulated urothelium has the correct order **Torelli2017** i.e. that the first layer on the basal membrane consits only of stem and basal cells **REFS** the next three to five layers consits only of intermediate cells **REFS** and that there is one layer of umbrella cells **REFS**

$$f_a^* = \begin{cases} \frac{1}{(1 - L_B) + (lib - L_I) + (1 - L_U) + 1} & \text{if amount of layers} > 0 \\ 0 & \text{else } 0 \end{cases} \quad (2.1)$$

In this equation L_B and L_U are boolean values, i.e. they have the value 0 or 1 **Torelli2017** They are 1 if the the first layer of cells consits only of basal or stem cells and if the most upper layer consits only of umbrella cells, otherwise they will be 0 **Torelli2017** lib is the amount of layers in betwenn the first and the last layers **Torelli2017** L_I contains the amount of layers, which consits only intermediate cells **Torelli2017** Therefore, $lib - L_I$ describes the amount cells which are not in there intended layer **Torelli2017**

The arrangement fitness function is calculated columnwise, every 25 μm . After this calculation the average of all calculations of this function is calculated **Torelli2017**

2.6.2. Volume fitness function

This function calculates the relative volume regarding the current volume of the different cell types in the urothel. The relative amount of the different cell types should be: stem and basal cell = 10%, intermediate cells = 67% and umbrella cells = 23% considering an average thickness of 85 μm **Torelli2017** Therefore the formula is:

$$f_{V_i} = \frac{1}{4\left(\frac{V_{Si} - V_{Ii}}{V_{Si}}\right)^2 + 1} \quad (2.2)$$

V_{Si} and V_{Ii} describes the *should* and the actual *is* volume of a specific cell type i **Torelli2017**

2.6.3. Overall fitness function

The overall fitness function calculates the total fitness out of the volume and the arrangement fitness function. Therefore the average of both functions is calculated **Torelli2017** The function is the following:

$$f(t_i) = \frac{f_V(t_i) + f_a^*(t_i)}{2} \quad (2.3)$$

t_i describes a specific time point, in MCS, at which this calculation could be done. At the end of the simulation is calculated as the average of the overall fitness function **Torelli2017** Therefore, the formula is:

$$f = \frac{1}{e+1} + \sum_{i=0}^e f(t_i) \quad (2.4)$$

$e+1$ indicating the amount of calculations of the overall fitness function **Torelli2017**

2.6.4. Moduro Toolbox

The purpose of the moduro toolbox is that we are able to evaluate a simulation. The toolbox itself was an bachelor thesis. All the data, which are written in to a file, e.g. cell birth and death by mitosis, data about the volume and arrangement fitness, etc., can be read out and analyzed with the moduro toolbox. It is possible to create

a short video out of the simulation screenshots. This video is able to display the complete simulation within a few minutes. Therefore an extra program is required.

2.7. Simulation Scripts

In order to not overload this chapter by presenting all scripts, I will present parts of the scripts which are important for the given task. A complete overview of the scripts is displayed at figure XY.

2.7.1. Area of stem cells

To provide optimal proliferation, i.e. to grow and multiply, of the cells, around 12% of the basal membrane are used for the stem cells **Torelli2017**. Of these 12% the amount of stem cells is calculated and then they will be drawn. In the current project there is no specific calculation of the percentage area of stem cells on the basal membrane. Moreover, the calculation is done with a magic number, i.e. a number in the code without any explanation. So there is no mathematical evidence that the calculation is correct and it would be additional work to change the calculation if the area of the stem cells on the basal membrane changes. This calculation works fine for two dimensions, since the result is around 12%. For the third dimension there have to be adjustments made.

```
# Adds the stem cells throughout the basal membrane:
cellDiameter = self.cellTypes[2].getAvgDiameter()
stemCellFactor = 8 * cellDiameter
if self.execConfig.dimensions == 2:
    noStemCells = int(self.execConfig.xLength / stemCellFactor)
else:
    noStemCells = int(self.execConfig.xLength * self.execConfig.yLength /
                      (stemCellFactor * stemCellFactor))
```

Listing 2.1: cell Area

2.7.2. Position of the stem cells

After the amount of stem cells on the basal membrane is calculated, the cells will be positioned randomly on it. To do so a random value for the x and z Position is calculated in a way, that the cell will not be at the edge of the lattice. If the stem

cell would be close to the lattice, than the proliferation could not take place in an optimal way.

```
for s in range(1, noStemCells + 1, 1):
    xPos = random.uniform(cellDiameter, self.execConfig.xLength -
        cellDiameter)
    zPos = random.uniform(cellDiameter, self.execConfig.zLength -
        cellDiameter)
    if self.execConfig.dimensions == 2:
        self._addCubicCell(2, xPos, 2, 0, cellDiameter, cellDiameter, 0,
            steppable)
    else:
        self._addCubicCell(2, xPos, 2, zPos, cellDiameter, cellDiameter,
            cellDiameter, steppable)
```

Listing 2.2: stem cell position

2.7.3. Cell Drawing

The cells are drawn in a cubic way. For every of the three dimensions a start and endpoint is defined, see the following listing:

```
steppable.cellField[xPosDim:xPosDim + xLengthDim - 1,
    yPosDim:yPosDim + yLengthDim - 1,
    zPosDim:zPosDim + zLengthDim - 1] = cell
```

Listing 2.3: cell Draw

In this listing 'x,y,zPosDim' defines the start points and 'x,y,zPosDim + x,y,zLengthDim - 1' defines the end points of the cell.

2.7.4. MinMaxVolume

In order that we are able to simulate mitosis a minimum and a maximum value regarding cell size is necessary. This is done by the 'MinMaxVolume' in the cell Dictionary. This is done with a one dimensional array with two values, as it is displayed in the listing below:

```
cellDict['min_max_volume'] = [self.execConfig.calcVoxelVolumeFromVolume(cellType.
    minVol),
    self.execConfig.calcVoxelVolumeFromVolume(cellType.maxVol)]
```

Listing 2.4: MinMaxVolume

Every cell type has its own minimum and maximum volume **Torelli2017** Since these values are saved in μm , they have to be converted to the voxel unit. With these

2. State of the Art

values, in voxel, it is possible to set boundaries for the specific cell, e.g. to calculate the volume when mitosis takes place or the maximal volume of a cell of a specific cell type.

2.7.5. Volume and TargetVolume

As explained earlier, in order that the simulation starts the effective energy is not allowed to be 0. As we are initializing every cell, we set the target volume of every cell to be 1 larger than the current volume. This has the effect, that the simulation starts. During the simulation we calculate the target volume out of the possible growth volume and the current volume.

```
cell.targetVolume = cell.volume + 1 # At the beginning, the target is the actual
    size.
# cell.targetVolume = cellDict['normal_volume'] # At the beginning, the target is
    the actual size.
cell.targetSurface = self.execConfig.calcVoxelSurfaceFromVoxelVolume(cell.
    targetVolume)
```

Listing 2.5: set target Volume and Surface of a cell

In the same context we calculated the target surface as well. This has the same reason as for the target volume.

2.7.6. Lambda TargetVolume and TargetSurface

The lambda values for the volume and for the surface describe how much the deviation between the current and the should value is considered in the effective energy, see section 1.GGH. In the project there are several places where these values are set. One place is just behind the target volume and target surface is set.

```
cell.lambdaVolume = self.execConfig.calcVollambdaFromVolFit(cellType.volFit)
cell.lambdaSurface = self.execConfig.calcSurLambdaFromSurFit(cellType.surFit)
```

Listing 2.6: set lambda volume and lambda surface

At this place for each lambda value a function is called, these are displayed below, which has itself a multiplier for the multiplier of the specific volume or surface energy.

```
def calcSurLambdaFromSurFit(self, surFit):
    return 0.05 * surFit
```



```
def calcVollambdaFromVolFit(self, volFit):  
    return 1.0 * volFit
```

Listing 2.7: functions to calculate the lambda multiplier for the effective energy of the volume and surface

The values for the volume and surface fitness are also set in every cell. Since these values are never used as a cell property, I not go further into detail of these two values.

Chapter 3

Method

für die reproduzierbarkeit der BA

was habe ich wie gemacht -> warum habe ich es so gemacht

In order to get familiar with this topic I first needed some background knowledge. To receive this knowledge I did use keyword searches on 'GoogleScholar' and then read the papers I found about the topic. To solve the problem, I also needed knowledge about CC3D. I received this by reading their manuals and by trying out different settings, since there is no detailed documentation about their simulation.

To analyze the simulation scripts I used papers and a pen. Since, in this project it is not possible to use a compiler to debug the scripts, because the computation is done by CC3D, to draw the the different function calls per hand was one of two ways to understand the scripts. The second way was to use print commands, i.e. an output at the console (another i.e.), to see at which point which function in which script is called.

For this bachelor thesis I used a constructive research, i.e. develop a solution to a given problem.

3.1. Draw Cells

Since the program so far draws cubic cells and overgives the same parameter three times, a modification for this function was necessary. In the following the function call and the method of the old cell drawing method are displayed.

3. Method

```
self._addCubicCell(2, xPos, 2, zPos, cellDiameter, cellDiameter, cellDiameter,
    steppable)
```

Listing 3.1: function call of the cell drawing method addCubicCell for a 3D cell

```
def _addCubicCell(self, typename, xPos, yPos, zPos, xLength, yLength, zLength,
    steppable):
    cell = steppable.newCell(typename)
    xPosDim = self.execConfig.calcPixelFromMuMeter(xPos)
    yPosDim = self.execConfig.calcPixelFromMuMeter(yPos)
    zPosDim = self.execConfig.calcPixelFromMuMeter(zPos)
    xLengthDim = self.execConfig.calcPixelFromMuMeter(xLength)
    yLengthDim = self.execConfig.calcPixelFromMuMeter(yLength)
    zLengthDim = self.execConfig.calcPixelFromMuMeter(zLength)
    # size of cell will be SIZExSIZEx1
    steppable.cellField[xPosDim:xPosDim + xLengthDim - 1,
        yPosDim:yPosDim + yLengthDim - 1,
        zPosDim:zPosDim + zLengthDim - 1] = cell
```

Listing 3.2: method to draw cubic cells

In the function 'addCubicCell' the parameters are converted into pixels, using the 'calcPixelFromMuMeter' function and then the cube will be drawn. To provide a deeper understanding of the of CC3D provided method, to draw the cell, the boundaries for the cube are displayed more generell in the following listing:

```
steppable.cellField[xStart:xEnd,
    yStart:yEnd,
    zStart:zEnd] = cell
```

Listing 3.3: boundaries of a drawn cuboid

In the listing above x,y,zStart defines the start and x,y,zEnd the end point of the to drwan area for each axis.

In order to be able to draw a cell as a sphere, CC3D has to be able to draw all the different pixels containing to one cell. Because CC3D allows the user to draw several pixels containing to one cell, a solution for this problem is possible. It is possible to lay a cuboid around the sphere, as it is displayed in fiugre 3.1 at page 21 and then decide if a point of the cuboid is in the sphere or not.

As long as both, the cuboid and the sphere, have the same center it is possible to calculate every point inside or outside the sphere^{REF} To do so, for every point within the cuboid it is necessary to calculate if the distance to the center is smaller or equal to the radius of the sphere. If this is the case, the point is inside of the

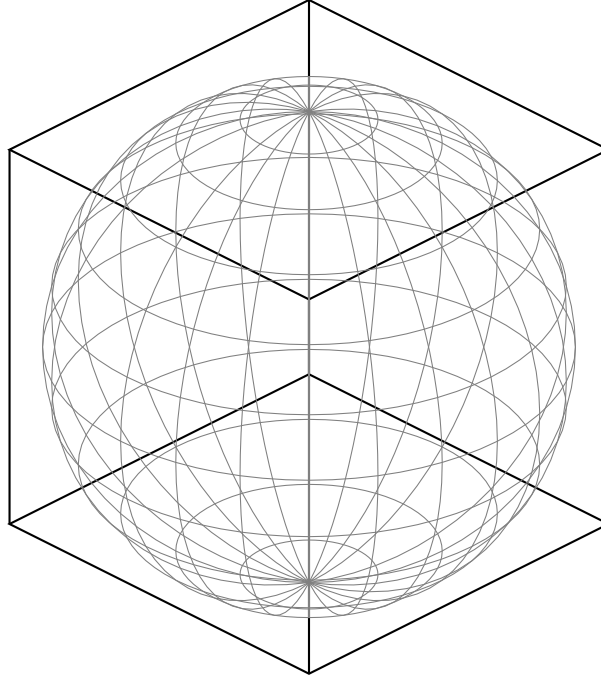


Figure 3.1.: A cuboid layed around a sphere

sphere, otherwise it is outside of the sphere. Thus, the formula to determine if a point is inside of the sphere is the following:

$$\sqrt{(x_r - x_0)^2 + (y_r - y_0)^2 + (z_r - z_0)^2} \leq radius \quad (3.1)$$

In this formula x_r, y_r, z_r contains the current point of the specific axis and x_0, y_0, z_0 is the center of the cuboid and the sphere. Whenever the distance of the current point in the cuboid to the center is smaller or equal the radius of the sphere, than this point is inside of the sphere.

In order that it is possible to draw the cells in this way, the iteration over all points of the cuboid is necessary. Because to do this is computational more expensive than to just draw a cube, the cuboid should be as small as possible. Still, the cuboid has to be at least as large as $2 * radius$ of the sphere, as it is displayed figure 3.2 at page 22.

Since we need the old method to draw the basal membrane throughout the whole area, a new function is required. The old function is refactored into 'addMembrane', i.e. renamed and every time the function name appears within the project, within a comment or the function is called, this appearance is also change. With the new method name it clear that this function is now, in the 3D simulation, only required

3. Method

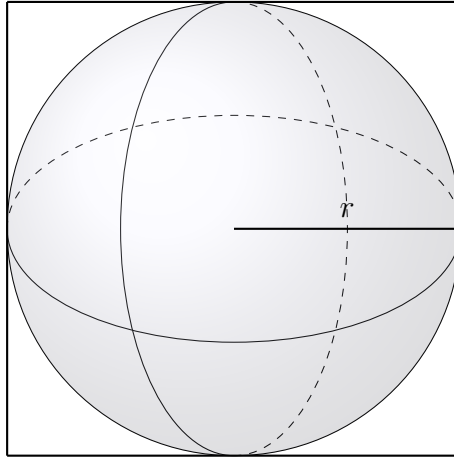


Figure 3.2.: A cuboid with minimal size layed around a sphere

for the basal membrane, since it is a cubic cell, and if some simulations in two dimensions are made.

The created function 'add3DCell', it is displayed in the listing below, is similar to the old one, as it also has to convert the used points, i.e. the start and end point of the cuboid and the center of the cuboid and the sphere, into pixels. Then the iteration of all three axis as well as the calculation to decide if the pixel is inside the sphere or not takes place.

```
def _add3DCell(self, typename, xPos, yPos, zPos, radius, steppable):
    '''The parameters are all in micro meter
    whereas the calculated variables are in px'''

    cell = steppable.newCell(typename)
    xStart = self.execConfig.calcPixelFromMuMeter(xPos - radius)
    x0 = self.execConfig.calcPixelFromMuMeter(xPos)
    xEnd = self.execConfig.calcPixelFromMuMeter(xPos + radius)
    yStart = self.execConfig.calcPixelFromMuMeter(yPos - radius)
    y0 = self.execConfig.calcPixelFromMuMeter(yPos)
    yEnd = self.execConfig.calcPixelFromMuMeter(yPos + radius)
    zStart = self.execConfig.calcPixelFromMuMeter(zPos - radius)
    z0 = self.execConfig.calcPixelFromMuMeter(zPos)
    zEnd = self.execConfig.calcPixelFromMuMeter(zPos + radius)

    radiusPx = self.execConfig.calcPixelFromMuMeter(radius)

    for xr in range(xStart, xEnd):
        for yr in range(yStart, yEnd):
            for zr in range(zStart, zEnd):
                rd = sqrt((xr - x0) ** 2 + (yr - y0) ** 2 + (zr - z0) ** 2)
                if (rd <= radiusPx):
                    steppable.cellField[xr, yr, zr] = cell
```

Listing 3.4: created method to draw a sphere cell

With this created function it is now possible to draw a cell as a sphere, as it is displayed at figure XY XY This has several advantages, as we are now able not to increase the λ_{sur} in a way that the volume constraint does not count as it will be really consider.....

3.2. Lambda Multiplier

In the project there were several places, where a lambda multiplier for the effective energy, see section 1.X, is calculated, but it is only set once. There are two additional multipliers, for the surface and volume constraints, saved in within each cell object. Since we are not using these values in the programm and they do not influence or set the λ_{vol} or λ_{sur} which CC3D uses, these two values were outcommented in the first step and later deleted.

Also in one place there were methods to calculate the lambda values. Since this methods are not used in the project and moreover they had a multiplier itself to calculate the multiplier for the specific effective energy, as it is displayed in the following listing, these were also first outcommented and later deleted.

```
def calcSurLambdaFromSurFit(self, surFit):
    return 100.0 * surFit

def calcVollLambdaFromVolFit(self, volFit):
    return 1.0 * volFit
```

Listing 3.5: methods to calculate the λ_{vol} and λ_{sur} for the effective energy

In the project the multipliers for the effective energy are now set each time when a cell is initialized. A second time the multiplier λ_{vol} is set, is during necrosis, in generell if a cell dies. Thus, there is now the advantage that at a specific point in the coding these values are set.

3.3. Approximation Error

Since the project includes conversions from μm to pixels and the amount of pixels, e.g. for the surface of a cell, have to be set in integer, i.e. a whole number, it is possible that in some places in the program there are approximation errors. In the project, the values of μm are saved either with the data type double or float – both allow several decimal digits. To set these values as a whole number the values are

3. Method

casted, i.e. the datatype of a variable, i.e. a placeholder, will be changed – in this context the values of type double or float will be transformed to a whole number by cutting of the decimal digits. At some points in the project the values of μm are converted to a whole number and then it is further calculated with this casted value. To cast the value should always be the last step in order to avoid approximation and calculation errors. In the following listings an example of too early casting is displayed:

```
def calcVoxelVolumeFromVolume(self, volume):  
  
    r = (3 * volume / (4.0 * PI)) ** (1.0 / 3.0) # Radius of a sphere with  
        known volume.  
    rDimension = self.calcPixelFromMuMeter(r) # Convert it to a pixel unit.  
  
    if self.dimensions == 2:  
        return self.__truncate(PI * (rDimension ** 2)) # Area of a circle.  
    else:  
        return self.__truncate(4.0 / 3.0 * PI * (rDimension ** 3)) # Volume of a  
            sphere.
```

Listing 3.6: example of an calculation error because of an too early executed cast

```
def calcPixelFromMuMeter(self, mum):  
    return int(self.voxelDensity * mum + 0.000001)
```

Listing 3.7: function to convert values of μm into pixel

In this example the second command of the 'calcVoxelVolumeFromVolume' function calls the function of the second listing, in which the approximation error happens. Since the decimal digits are just cut off, the further calculation contains a wrong value and as a consequence the result of the calculation is incorrect.

In order to solve the problem the complete calculation is calculated with decimal digits. After the calculation is done it will be checked if the first decimal digit is larger or equal to 5. If this condition is true the result is increased by 1 otherwise not, as a last step the result is casted. This technique has the advantage that calculation errors due to casting are decreased, because the cast is the very last step. It is possible that in the program still have some rounding errors, but these are not as dramatic as an casting error in the calculation. To remove this casting error, the function 'calcVoxelVolumeFromVolume' is extended in the following way.

```
def calcVoxelVolumeFromVolume(self, volume):  
    r = (3 * volume / (4.0 * PI)) ** (1.0 / 3.0) # Radius of a sphere with  
        known volume.  
    rDimension = r * self.voxelDensity  
    if self.dimensions == 2:  
        return int(self.__truncate(PI * (rDimension ** 2))) # Area of a circle.  
    else:  
        return int(self.__truncate(4.0 / 3.0 * PI * (rDimension ** 3))) # Volume of a  
            sphere.
```



```

result = 4.0 / 3.0 * PI * (rDimension ** 3)
if result % 1.0 >= 0.5:
    result += 1

return int(result)

```

Listing 3.8: the same function as before but without approximation errors because the cast and the rounding is done after the calculation

One use of the function is to calculate the volume constraints of a specific cell type. In the simulation a minimum and a maximum volume for each cell type is calculated by the function 'calcVoxelVolumeFromVolume'. These value are used in the calculation to determine if mitosis takes place or not.

For the basal cell the minimum volume is 381 μm and the maximal volume is 523 μm . With the old calculation the minimum volume constraint would be the same as for the stem cells –905vx. Since the current calculation only casts and round at the very last step, the result is now 1286vx, which is a more precise and correct result. In the following table 3.2 an example of to early rounding and casting is displayed:

Table 3.1.: Stakeholders' motivations to use **SW CS!**

Volume in μm	radius in μm	rounded casted to	or not result in vx	rounded result in vx
381	4.497	not rounded or casted	1285.67	1286
381	4.497	4	904.779	905
381	4.497	5	1767.15	1767

This table provide three possible solutions to calculate the volume in voxel of a given volume in μm . The first row calculates the voxel volume with the modified function. The second row is the calculation of the program without the modification. Thus, the calculated radius is casted and then used in the further calculation. The third row provides a possible calculation in which the radius is rounded and then used for the further calculation.

A similiar calculation error is done in the calculation of the target surface of each cell. The calculation of the target surface is done once by initalizing the simulation and every MCS. This calculation is necessary that CC3D is able to calculate the effective energy and that it is able to determine how the cell should look like, what shape it should have.

3. Method

Because, in the simulation the volume is calculated in every MCS, a calculation of the surface of a sphere with a given volume is more precise than the calculation with the radius. We use the of CC3D calculated volume to calculate the target surface. To calculate the surface with a given volume the formula 3.2 has to be modified, as it is displayed in the formula 3.4 below:

$$Surface_{sphere} = 4 * \pi * r^2 \quad (3.2)$$

To calculate the radius out of a given volume of a sphere, the formula to calculate the volume of a sphere has to be shifted as it is displayed in formula 3.3.

$$\begin{aligned} Volume_{sphere} &= \frac{4}{3} * \pi * r^3 \\ 3 * Volume_{sphere} &= 4 * \pi * r^3 \\ r^3 &= \frac{3 * Volume_{sphere}}{4 * \pi} \\ r &= \sqrt[3]{\frac{3 * Volume_{sphere}}{4 * \pi}} \\ r &= \left(\frac{3 * Volume_{sphere}}{4 * \pi} \right)^{\frac{1}{3}} \end{aligned} \quad (3.3)$$

If the formula 3.3 is inserted in the formula 3.2 the following formula to calculate the surface out of the volume of a sphere is the result:

$$\begin{aligned} Surface_{sphere} &= 4 * \pi * r^2 \\ &= 4 * \pi * \left(\frac{3 * Volume_{sphere}}{4 * \pi} \right)^{\frac{1}{3}^2} \\ &= 4 * \pi * \left(\frac{3 * Volume_{sphere}}{4 * \pi} \right)^{\frac{2}{3}} \end{aligned} \quad (3.4)$$

The following listings displays how the target surface is calculated, with the formula of 3.4 in the program. To calculate the target surface, the current target volume of the cell is given as parameter 'voxelVolume'. The formula to calculate the surface of a sphere, with the radius, is:

```
def calcVoxelSurfaceFromVoxelVolume(self, voxelVolume):
    if self.dimensions == 2:
        # some fractal factor!
        return self.__truncate(1.5 * 2 * (PI * voxelVolume) ** (1.0 / 2.0)) #
        Circumference.
    else:
```

```

return self.__truncate(2.0 * 4 * PI * (3 * voxelVolume / (4 * PI)) ** (2.0 /
3.0)) # Surface.

```

Listing 3.9: calculation of the target surface of a cell

```

def __truncate(self, value):
    res = int(value + 0.00001)
    if res <= 1:
        return 1 # Ensure that size is at least 1.
    else:
        return res

```

Listing 3.10: calculation of the target surface of a cell

In order that the cell will growth it is required to set a factor, which increases the calculated target surface of the cell. After the calculation of the target surface is done the function 'truncate' is called. This function simply casts the result of the calculation. Also, if the given parameter is smaller than 1 it will be increased to 1, this is for a different functionality of the program and will not be further noticed. To do cast as the last step is correct, but a rounding is required before. With this functions it is possible that a target surface of 623,873 is set to 623 instead of to 624. There are several ways to solve this problem. I choosed to because.....

3.4. Area of stem cells on the basal membrane

In earlier version of the project it was evidenced that around 12% of the area of the basal membrane are required to be filled with stem cells in order to have an optimal proliferation during the morphogenesis of the cells **Torelli2017** In the project the calculation of the amount of stem cells for two dimensions were correct but without an mathematical evidence, as it is shown in the following listing:

```

def _initCells(self, steppable):
    ...
    cellDiameter = self.cellTypes[2].getAvgDiameter()
    stemCellFactor = 8 * cellDiameter

    if self.execConfig.dimensions == 2:
        noStemCells = int(self.execConfig.xLength / stemCellFactor)
    else:
        noStemCells = int(self.execConfig.xLength * self.execConfig.yLength /
                           (stemCellFactor * stemCellFactor))
    ...

```

Listing 3.11: calculation of the amount of stem cells on the basal membrane without a mathematical evidence

3. Method

Since the y-axis is negligible in the calculation of an area, the calculation for two dimensions considers the x-axis and the calculation for three dimensions considers the x- and z-axis. Therefore, in two dimensions, only considering the x-axis, the area of the stem cells should be calculated by using the cell diameter. This situation is displayed in figure 3.3 at page 28. For three dimensions it is possible to calculate the area of a circle with the formula $\pi * radius^2$, since a circle is in two dimensions, and use this calculation to further determine the amount of stem cells on the basal membrane. An example for the basal membrane and a stem cell in three dimensions is displayed in figure 3.4 at page 28.

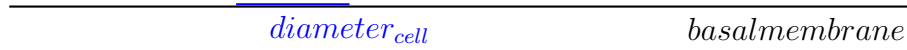


Figure 3.3.: considered area to spread the stem cells in two dimensions with an example of one stem cell placed on the basal membrane. Because only the x-axis is displayed we need to calculate the diameter of a cell

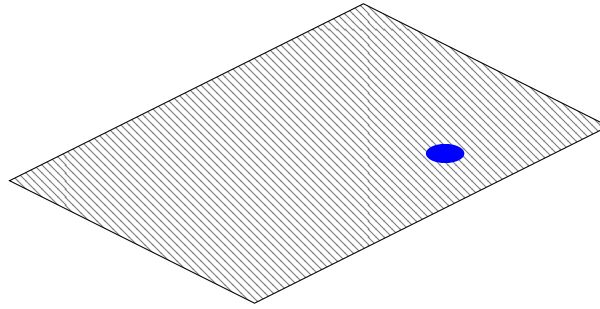


Figure 3.4.: considered area to spread the stem cells in three dimensions with an example of one stem cell placed on the basal membrane. This stem cell is a circle, because for the calculation we use two dimensions

The following formulas calculate the amount of stem cells in two dimensions:

$$A_{stemcells} = xLength * 0.12 \quad (3.5)$$

$$Amount_{StemCells} = \frac{A_{stemcells}}{diameter} \quad (3.6)$$

Formula 3.5 ensures that only 12% of the given area is used. Formula 3.6 then calculates the amount of stem cells on this given area. Since the result of the calculation is often not a whole number, the result is checked if the first decimal digit is larger or equal than 5 and then it is rounded up or down. This has a significant difference in the result, as it is displayed in table 3.2 at page 29.

Table 3.2.: Possible approximation error by not rounding the result of formula 3.6

XLength μm	in $Amount_{StemCells}$	Result of rounded or casted result	Area used of Stem cells in μm	relative used area
200	~ 2.66	3	27	13.5%
200	~ 2.66	2	18	9%

As the table displays, it is important to round the result. Otherwise there would be an approximation error which is to avoid.

For three dimensions the formulas 3.5 and 3.6 have to be extended, because the z-axis is now also considered in the calculation of the amount of stem cells on the basal membrane. Therefore, the extended formulas for three dimensions are:

$$A_{stemcells} = xLength * zLength * 0.12 \quad (3.7)$$

$$Amount_{StemCells} = \frac{A_{stemcells}}{\pi * r^2} \quad (3.8)$$

The result of formula 3.8 has to be rounded as well, otherwise the program would again include rounding errors, as it is shown in table 3.2. That the formulas are correct is shown with the following example. In order to keep a good overview of the results and the parameters in the formulas, the decimal digits are rounded after the third decimal digit.

For a simulation with a length of $200 \mu\text{m}$ at the x-axis and a length of $50 \mu\text{m}$ at the z-axis, the overall area is $10\,000 \mu\text{m}^2$ and the for the stem cells reserved 12% of the membrane are $1200 \mu\text{m}^2$. With an average diameter of $9 \mu\text{m}$, the minimum and maximum diameter of the different cells are displayed in table 2.2 at page 11, the result of the amount of stem cells is ~ 18.863 which is rounded up to 19 stem cells on an area of $10\,000 \mu\text{m}^2$.

$$\begin{aligned}
 Amount_{StemCells} &= \frac{200 \mu\text{m} * 50 \mu\text{m} * 0.12}{\pi * r^2} \\
 &= \frac{1200 \mu\text{m}^2}{63.617 \mu\text{m}^2} \\
 &\sim 18.863 \\
 &= 19
 \end{aligned} \quad (3.9)$$

3. Method

To validate this result, the area of 19 circles with a radius of $\frac{9\mu\text{m}}{2}$ has to be calculated. To then get the relative amount of stem cells on the basal membrane it is required to divide the result of $Amount_{StemCells}$ with the overall possible area of the urothel. As the calculations show, on an area with $10\,000\mu\text{m}^2$ to draw 19 cells uses 12% of the given area.

$$\begin{aligned} A_{StemCells} &= 19 * \pi * cellradius^2 \\ &= 19 * \pi * 4.5\mu\text{m}^2 \\ &\sim 1208.728\mu\text{m}^2 \end{aligned} \tag{3.10}$$

$$\begin{aligned} A_{StemCells} &= \frac{A_{StemCells}}{10\,000\mu\text{m}^2} \\ &= \frac{1208.728\mu\text{m}^2}{10\,000\mu\text{m}^2} \\ &= 0.120 \\ &= 12\% \end{aligned} \tag{3.11}$$

In the following listing the new calculation to figure out the amount of stem cells on the basal membrane at the start of the simulation is shown. The calculation is for two as well as for three dimensions modified, since both did not have a mathematical evidence.

```
def _initCells(self, steppable):
...
    cellDiameter = self.cellTypes[2].getAvgDiameter() # cell diameter is of
        type float

    if self.execConfig.dimensions == 2:
        noStemCells = int(self.execConfig.xLength * 0.12 / cellDiameter)
    else:
        noStemCells = ((self.execConfig.xLength * self.execConfig.zLength) *
            0.12) / (PI * (cellDiameter / 2.) ** 2)

    if noStemCells % 1 > 0.5:
        noStemCells += 1

    noStemCells = int(noStemCells)
...
```

Listing 3.12: new calculation of the amount of stem cells on the basal membrane with a mathematical evidence

3.5. TargetVolume, Surface after Mitosis

Mmitosis is done by CC3D, i.e. CC3D decides where the cell splits and calculates the volumes and the surface of the two new cells. In our program we calculate and set attributes of the new cells, e.g. the target volume or the target surface. The target volume is simply calculated by dividing the target volume of the cell before mitosis by 2. This value is applied for both new created cells. The problem with this technique is that it is possible that the cell does not split completely in the middle. Therefore, it is not possible to set the target volume of the two created cells without the knowledge of the volume of both cells. Moreover, the function 'initCellAttributes' calls the function 'setCellAttributes', in which the targetVolume of the specific cell is set to be 1 larger than the current volume. If the commands of the function 'initCellAttributes' are complete and the program is again in the below listet function, then the target volume of both cells is set to a value which has no evidence to be correct.

```
def updateAttributes(self):
    parentCell = self.mitosisSteppable.parentCell
    childCell = self.mitosisSteppable.childCell

    #Has to be done this way otherwise if cell.volume is chosen than it
    disappears
    newVol = parentCell.targetVolume / 2

    descendents = self.model.cellTypes[parentCell.type].getDescendants()
    parentCell.type = descendents[0]
    childCell.type = descendents[1]

    # Now set the attributes for the two daughter cells:
    cellDictChild = self.getDictionaryAttribute(childCell)
    self.model.initCellAttributes(childCell, cellDictChild)
    cellDictParent = self.getDictionaryAttribute(parentCell)
    self.model.initCellAttributes(parentCell, cellDictParent)

    parentCell.targetVolume = newVol
    childCell.targetVolume = newVol

    # Register events
    self._cellLifeCycleBirth(parentCell)
    self._cellLifeCycleBirth(childCell)
    cellDictChild['colony'] = cellDictParent['colony']
```

Listing 3.13: two cells are created by mitosis where the target volume is set at a wrong place

```
def setCellAttributes(self, cellDict, cell, lifeTimeParent):
    ...
    cell.targetVolume = cell.volume + 1 # At the beginning, the target is the
    actual size.
```

3. Method

```
cell.targetSurface = self.execConfig.calcVoxelSurfaceFromVoxelVolume(cell.  
    targetVolume)  
...
```

Listing 3.14: set the target volume as well as the target surface in the intended function

Since CC3D calculates the new volume of both created cells and the cell attributes are initialized and set in the functions 'initCellAttributes' and 'setCellAttributes', which is called by 'initCellAttributes', setting the target volume for both cells like it is in 3.5 is not correct. Thus, these commands are deleted and the target volume will now only be set at the function 'setCellAttributes'. There the target volume is 1 larger than the current volume, because the cells are just created. With the next MCS, and then every MCS, the target volume will be calculated regarding the growth per day of the specific cell type. Thus, no changes in the function 'setCellAttributes' were required, the actual code of the function 'updateAttributes' is the following:

```
def updateAttributes(self):  
    print 'GrowthMitosisSteppable.updateAttributes()'  
    parentCell = self.mitosisSteppable.parentCell  
    childCell = self.mitosisSteppable.childCell  
  
    # return cell types based on the probability (in ****Ua) two descendents of  
    # the current cell  
    descendents = self.model.cellTypes[parentCell.type].getDescendants()  
    parentCell.type = descendents[0]  
    childCell.type = descendents[1]  
  
    # Now set the attributes for the two daughter cells:  
    cellDictChild = self.getDictionaryAttribute(childCell)  
    self.model.initCellAttributes(childCell, cellDictChild)  
    cellDictParent = self.getDictionaryAttribute(parentCell)  
    self.model.initCellAttributes(parentCell, cellDictParent)  
  
    print 'parentCell.volume {} >= parentCell.targetVolume {}'.format(parentCell  
        .volume, parentCell.targetVolume)  
    print 'childCell.volume {} >= childCell.targetVolume {}'.format(childCell.  
        volume, childCell.targetVolume)  
  
    # Register events  
    self._cellLifeCycleBirth(parentCell)  
    self._cellLifeCycleBirth(childCell)  
    cellDictChild['colony'] = cellDictParent['colony']
```

Listing 3.15: two cells are created due to mitosis

Chapter 4

Results

ergebnisse (screenshots / source code)

4.1. Draw Sphere Cells

Chapter 5

Conclusion

Final words

5.1. Draw Sphere Cells

It is also possible to use only the effective energy

5.2. λ values

This was the only way to do it

5.3. Approximation Errors

Find a more elegant way to do it

List of Abbreviations

GGH Glazier-Graner-Hogeweg

CC3D CompuCell3D

ECM Extended Cellular Matrix

MCS Monte Carlo Step

CPM Cellular Potts Model

EPM Extended Potts Model

List of Tables

2.1.	Possible proliferation and differentiation concepts for the three cell types stem (S), basal (B) and intermediate (I) cell (column Type). Column ID assigns a label for a specific proliferation or differentiation rule which refers to a specific model (column Model). Per cell type group one model can be chosen. In total we have $2 \cdot 4 \cdot 2 = 16$ lineage models. Dividing cells are expressed by a plain line and transformation (differentiation) by a dashed line. Transformation might happen either through contact (see ICD) or the loss of contact (see BCD).	10
2.2.	Cell properties. Volumes V in μm^3 , diameters d in μm . Columns <i>Volume</i> and <i>Surface</i> are adjusted with the weights λ_V and λ_A , respectively.	11
2.3.	Surface tension values for the four cell types, the basal membrane (BM) and the medium (M). The values are according to Compu-Cell3D conventions: small values represent high adhesion, higher values less adhesion/greater repulsion.	11
3.1.	Stakeholders' motivations to use SW CS!	25
3.2.	Possible approximation error by not rounding the result of formula 3.6	29

List of Figures

1.1. Physiology of the urothelium - http://000ekkt.myregisteredwp.com/trauma/visited: 31.12.2017	3
3.1. A cuboid layed around a sphere	21
3.2. A cuboid with minimal size layed around a sphere	22
3.3. considered area to spread the stem cells in two dimensions with an example of one stem cell placed on the basal membrane. Because only the x-axis is displayed we need to calculate the diameter of a cell	28
3.4. considered area to spread the stem cells in three dimensions with an example of one stem cell placed on the basal membrane. This stem cell is a circle, because for the calculation we use two dimensions .	28

Listings

2.1. cell Area	14
2.2. stem cell position	15
2.3. cell Draw	15
2.4. MinMaxVolume	15
2.5. set target Volume and Surface of a cell	16
2.6. set lambda volume and lambda surface	16
2.7. functions to calculate the lambda multiplier for the effective energy of the volume and surface	16
3.1. function call of the cell drawing method addCubicCell for a 3D cell	19
3.2. method to draw cubic cells	20
3.3. boundaries of a drawn cuboid	20
3.4. created method to draw a spere cell	22
3.5. methods to calculate the λ_{vol} and λ_{sur} for the effective energy	23
3.6. example of an calculation error because of an too early executed cast	24
3.7. function to convert values of μm into pixel	24
3.8. the same function as before but without approximation errors be- cause the cast and the rounding is done after the calculation	24
3.9. calculation of the target surface of a cell	26
3.10. calculation of the target surface of a cell	27
3.11. calculation of the amount of stem cells on the basal membrane with- out a mathematical evidence	27
3.12. new calculation of the amount of stem cells on the basal membrane with a mathematical evidence	30
3.13. two cells are created by mitosis where the target volume is set at a wrong place	31
3.14. set the target volume as well as the target surface in the intended function	31
3.15. two cells are created due to mitosis	32

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Appendix A

Erster Anhang

Hier ein Beispiel für einen Anhang. Der Anhang kann genauso in Kapitel und Unterkapitel unterteilt werden, wie die anderen Teile der Arbeit auch.

Appendix B

Zweiter Anhang

Hier noch ein Beispiel für einen Anhang.