Modelling epidermal homeostasis as an approach for clinical bioinformatics

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Abstract. Modelling in systems biology currently lacks clinical applications. As a possible approach leading to clinical relevance the modelling of tissue homeostasis is proposed. As an example a model of epidermal homeostasis is presented which reproduces central morphological and kinetic characteristics of epidermal tissue. Each individual cell is modelled as an agent. The tissue arises as an emergent phenomenon from the interactions of agents. Each agent's behaviour is qualitatively modelled by a simple differentiation state-flow program. Epithelialisation under the influence of parameters concerning stem-cell location is briefly demonstrated.

1. Introduction

Systems-Biology aims at the systematic analysis and modelling of as large and complex biological networks as possible. Today, systems-biology already has become an important discipline [1, 2] although its modelling side lacks still a clear link to clinical applications. To limited intracellular systems the toolbox of non-linear dynamics has been successfully applied [3, 4]. Nevertheless, the construction of larger systems is the more difficult the larger these systems get. Therefore, here a new approach is suggested. Clinical relevance for modelling could be much better gained by switching to a higher abstraction level by modelling tissue homeostasis instead of only focusing at quantitative intracellular biochemical networks. This approach has major advantages.

Firstly, genomics and proteomics technologies work with homogenized tissue. So the spatial resolution of molecular processes in high-throughput technologies is rather neglected. In the contrary to this, in a clinical setting the morphological analysis of tissue is the prevailing criteria for defining and diagnosing diseases.

Secondly, modelling tissue homeostasis is concerned with rather slow biological processes. An average regeneration of human epidermis takes 20-25 days while signal transduction processes are executed in milli- and microseconds [5]. Slow processes have the advantage of opening the possibility of qualitative modelling. Most biological knowledge published in literature today describe biological phenomena in a qualitative way.

So, can tissue be functionally modelled today? According to the reductionist paradigm systems should be reconstructed bottom-up. Unfortunately, modelling at the

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tissue level on the basis of completely reconstructed intracellular networks exceeds our technological capacity by far in the coming time. On the other hand, the analysis of tissue morphology is a corner-stone of clinical diagnosis – actually it’s the gold-standard. Concluding, it is not the question if tissue functionality can be modelled. Rather it is the question of how it can be done as it will become mandatory for clinical bioinformatics and systems biology to gain a substantial understanding of many critical diseases.

Different approaches for tissue modelling are known [6, 7]. Simulation of tissue homeostasis per definitionem has to model the proliferation and differentiation activity of major parts of the tissue in order to simulate the regenerative capacity of the tissue. Until today only few works model aspects of tissue homeostasis [8-11]. Recently a first prototype has been presented for modelling both, proliferation and differentiation, while maintaining an intact tissue morphology and tissue kinetics [12].

The epidermis is an excellent example for this kind of modelling as it represents the most complex epithelium. Epithelial tissue covers all body organs like skin, liver, bladder, lung, small intestine, kidney and lines the body’s cavities. Over 85% of all cancers arise from a disturbed epithelial homeostasis. Carcinomas are characterized by a loss of spatial tissue integrity. This can be generally described as an unbalance of epithelial proliferation and differentiation. Thus modelling the tissue homeostasis in epidermis may be a good field for studying systems biological modelling in a clinically relevant setting.

We here describe how qualitative modelling has been used to develop a simple agent based discrete differentiation program for epidermal keratinocytes. This discrete differentiation program is used to control the fate of individual agents in a multi-agent environment. A biomechanical model of interacting cells allows the passive spatial movement of cells by proliferative activity inside the tissue. In the following it is shown how from the interaction of all agents different morphologies of a human epidermis arise as emergent phenomena. This emergent behaviour of the agent-society can produce different epidermal homeostatic morphologies.

2. Method

The model has been implemented in the java software environment MASON [13] supporting the efficient simulation of agent societies. All agents have one common source-code implementation. The simulation environment executes the agents in a semi-parallel manner.

2.1. Biomechanical Model

The model consists of a biomechanical and a biochemical component. The biomechanical component reflects the spatial part of the simulation while the biochemical component controls each participating cell’s internal program. Emergent behaviour of the simulation is enabled by simulating the tissue as a multi-agent society where each single cell is represented by an agent. The individual agents cannot move by their own force (cell migration). They can only be moved if necessary to minimize structural forces inside the tissue. As a simple biomechanical model for each cell a force linear to the distance of the cells is assumed. To allow an interactive simulation cells move heuristically in limited fractions of the forces exerted on it. If two cells overlap they try
to partially restore their appropriate distance. If two cells are in a short limited distance they adhere to another. In this way both, adhesion and passive cellular movement are implemented. To avoid artificial side effects the available space for cells is the unwinded surface of a cylinder. Towards the bottom the cell’s movement is restricted by a constant basal membrane. At the beginning the simulation consists only of an undulated basal membrane and a small set of stem-cells. Figure 1 shows the constants available for determining the layout of the basal membrane and the seeding of the virtual stem-cells in the simulation.

Basal Opening (BO)

Basal Amplitude (BA)

Depth Fraction (DF), above or below stem cells are seeded.

Distance between stem cells (SD)

Figure 1: Constant parameters determining the basal layout of the simulations

2.2. Biochemical Model

The biochemical model of the simulation is qualitatively described by a flow of states as depicted in figure 2. Although the epidermis consists of further cell types like Langerhans-cells and melanocytes 95% of the cells are keratinocytes. Therefore, all cells included in the simulation are keratinocytes. Each agent executes the same differentiation program which is therefore common to all in-silico keratinocytes.

Stem cells are assumed to be proliferating asymmetrically which means that after completion of the cell cycle the stem cell remains a stem-cell, but has produced a differentiating daughter cell. This is consistent with a recent report [14] which shows that asymmetric proliferation is important for building a stratified epithelium. Cells which have been produced by stem cells are assumed to be transit-amplifying (TA) cells which possess a limited proliferation capacity. Proliferating TA-Cells asymmetrically produce differentiating “early spinosum cells” named after the layer stratum spinosum as described in figure 3. Under the influence of high extracellular Ca$^{2+}$ Concentration these cells differentiate in the model into „Late Stratum Spinosum Cells“.

![Figure 2: Qualitative differentiation model of a healthy single cell](image-url)
Healthy epidermis is characterized by a Ca\textsuperscript{2+}-Gradient which is assumed to play a central role in regulating epidermal homeostasis. The passive transportation theory assumes that the trans-epidermal waterflow transports Ca\textsuperscript{2+} towards the stratum corneum under which Ca\textsuperscript{2+} is accumulated.

The transepidermal water flux is realised implicitly in the model. When two cells collide, the lower cell transports a fraction of its calcium environment to the upper cell. In the same way further objects like lamellar bodies are transported upwards. Lipids are produced in the model beginning from the stratum spinosum on where they are enclosed in lamellar bodies. These bodies are later secreted at the surface of the epidermis where they are secreted as a central component for building the stratum corneum. Visualising the stratum corneum requires the graphical modelling of corneocytes which has not been addressed here. Therefore in this simulation only the building of the two basic components of the stratum corneum through the underlying epidermal strata from stratum basale to stratum granulosum has been modelled.

![Epidermal strata](image)

Figure 3: Section of human epidermis

The successful establishment of a stratum granulosum is set equal to successfully establishing an epidermal barrier which reduces the transepidermal waterflow. In this way a feedback of the whole system is achieved. Cells are taken out of the simulation after they reach a certain constant age independent of where they are at this moment localized in the tissue.

3. Results

Epithelialisation is shown in Figure 4. The resulting morphology represents the behaviour of the total agent society. We varied the basal parameter settings of the simulation according to table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>BO</td>
<td>150 µm</td>
<td>150 µm</td>
<td>150 µm</td>
<td>150 µm</td>
</tr>
<tr>
<td>BA</td>
<td>40 µm</td>
<td>10 µm</td>
<td>40 µm</td>
<td>40 µm</td>
</tr>
<tr>
<td>DF</td>
<td>2%</td>
<td>2%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>BD</td>
<td>8 µm</td>
<td>8 µm</td>
<td>8 µm</td>
<td>8 µm</td>
</tr>
<tr>
<td>Above/Below</td>
<td>Below</td>
<td>Below</td>
<td>Below</td>
<td>Above</td>
</tr>
</tbody>
</table>

Table 1: Behavioral scenarios of the simulated epidermis defined by modifications of basal membrane related parameters.
Figure 4: Intact morphology of the tissue emerges after epithelization of the model-space.

The evaluation of the four different scenarios (1, 2, 3, 4) shows four examples of morphologies obtained with the simulation (Figure 5). The standard scenario 1 shows a basal opening of 150 µm and a basal amplitude of 40 µm as shown in figure 1. The depth fraction of 2% means in combination with the parameter below means that stem cells are seeded in the lower 98% of the rete ridges. In this are stem cells are seeded with a distance of 8 µm. The other three scenarios show three different modifications of these settings. In scenario 2 the basal amplitude is reduced to create an epidermis with shallow rete ridges. In scenario 3 stem cells are only seeded in the in the upper parts of the rete ridges while in scenario 4 stem cells are exclusively seeded in the bottom of the ridges.

Figure 5: Different morphologies at the same timepoint $t=2100$ h right after obtaining tissue homeostasis. Parameters are set according to table 1. Compared to Figure 4 a slightly lower transepidermal waterflux has been chosen to produce pronounced layers.
4. Discussion

The standard-scenario 1 reflects rather strong rete ridges as this a difficult situation for the simulation. This scenario makes clear that the differentiation of the cells may not be simply related to the aging of the cells as it could be the case with just a flat basal membrane. Instead the cells at the bottom of the rete ridges need a time-space behaviour different from the ones at the edges of the rete ridges. The well layered morphology shows that the described differentiation program can achieve this. In scenario 2 shallower rete ridges are produced similar to aged epidermis. In scenario 3 there are too few stem-cells to obtain a fully populated epidermal morphology. In scenario 4 stem-cells are located at the top of the rete ridges. The differences between scenarios 1 and 4 reflect a rather historical dispute of where epidermal stem-cells are located. It is interesting to see that the higher stem-cells seem to lead to low density populated low rete ridges, a thicker epidermis, a changed tissue differentiation pattern, and a more irregular epidermal surface.

5. Conclusion

It was shown that simulation of epidermal homeostasis with a limited and rather simple qualitative differentiation program is feasible and may yield interesting results. The approach opens the possibility to include more detailed knowledge about the behaviour of individual cells. This integration of more biomolecular knowledge in the present prototype could show a way of how the systems-biology approach could contribute to clinically relevant bioinformatics.

References