2015 Highlights

The StemPhys CoE was initiated in April 2015 and constitutes a novel interdiscliplinary collaboration between stem cell biologists and physicists targeted at increasing our understanding of the fundamental mechanisms underlying stem cell differentiation. As stem cells can differentiate to any specialized cell in an organism, stem cells show great therapeutic potential for regenerative medicine. However, to exploit their potential an understanding, or control, of stem cell decision making mechanisms is of crucial importance.

Liver differentiation is a core focus of interest for StemPhys, in particular the mechanics governing organ development and regenerative mechanisms. In 2015 a StemPhys study published in PNAS (Leijnse et al., 2015) showed how helical coiling of actin inside cellular protrusions promotes cell migration. This result is relevant for our ongoing studies of liver progenitor migration, because unpublished StemPhys work on liver development indicates that dynamic stem cell protrusions play a crucial role for positioning liver progenitors at the right place.

A tight collaboration between theorists and experimentalists is a cornerstone of StemPhys. A genome-wide StemPhys study published in Cell Reports (Hamilton and Brickman, 2014) showing how the duration of Map Kinase/Erk signaling relates to progressive changes in embryonic stem cell (ESC) transcriptome has served as inspiration of a novel model; a focus this model is to understand this emergent network and how it regulates the exit of ESCs from pluripotency to generate primitive endoderm. In another important piece of work for StemPhys published in PLOS Biology in 2015 (Kim et al., 2015) live imaging was used to follow the dynamics of the progeny of individual cells and showed a stochastic conversion of pancreas progenitors into endocrine cells. This work is forming the basis of our mathematical modelling of pancreatic development.

The early mammalian embryo develops in a remarkable dynamic and self-organizing fashion. Recent results on embryonic cells (Morgani and Brickman 2015) served as inspiration for a novel model of blastocyst development. Normal development to the blastocyst starts from fertilization (illustrated in Fig. 1) and mammals are able to form normal embryos despite the removal of cells, cells being cut in half, or recombined. To understand how this information could be recovered, we implemented experimentally-reported mechanisms as a set of developmental rules in an agent-based *in silico* model of physically interacting cells. We found that with only four rules, the model recapitulated development and the ability of embryos to scale following manipulation. This model also supports our experimental observations suggesting that apoptosis of misplaced cells is used as a proofreading mechanism,

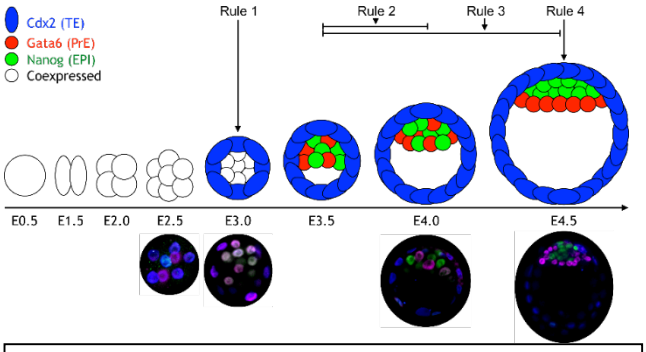

Figure 1: Early embryonic development. The upper part illustrates our model based on 4 simple rules. The lower part shows images from fetus development.

Using optical tweezers, we initiated a mechanical investigation of ESCs. Our hypotheses that the mechanical properties of stem cells change during lineage specification was confirmed; it was proven that endodermal primed ESCs (red in Fig. 1) were significantly more elastic that epiblast primed ESCs (green in Fig. 1), suggesting that physical properties may play a role in lineage segregation during development. Furthermore, we are currently investigating the possibility that cytoskeletal elements may also be important for the decision making process, and for this we use several of the reporter strains developed within StemPhys.