



Part of the MorphogenetiX team (from left): David Dreher, Marisa Oliveira and project leader Damian Brunner.

### Three-dimensional tissue shaping (MorphogenetiX)

## The mechanics of life

Recent research findings show that tissue shaping is a particularly dynamic feedback process during which cells not only exert their own mechanical forces, but are also heavily influenced by external forces acting upon them and can even differentiate into different cell types as a result. This sounds like a case for systems biology.

When the liver of a small dog is transplanted into the body of a larger dog, the organ grows until it reaches the appropriate dimensions for the larger animal. This happens despite the fact that the liver cells were originally “programmed” for the volume of the smaller dog. But how does the donated liver “know” that it has to alter its shape, and what stops it from growing further after it has reached the ideal size? “No one is able to explain this phenomenon. The molecular interconnections involved in tissue shaping are still, to a large extent, a black box,” says Damian Brunner, project leader of MorphogenetiX. The aim of the project is to study the spatial organization of cell systems, examining genetic factors, signaling networks and the physics behind these processes.

Although basic research in this field is still in its infancy, Brunner is sure of one thing: “Mechanical forces play a critical role in tissue shaping.” This fact was only uncovered a few years ago, after scientists observed the fate of embryonic stem cells placed onto supports of differing stiffness, but which received the same molecular signals. Astonishingly, the cells first examined their surroundings before beginning to differentiate. “The stem cells placed on a soft substrate started developing towards a nerve cell fate, those on a semi-hard medium towards muscle cells, whereas bone cell development was initiated on the hardest surfaces,” explains Brunner.

The experts therefore think that although molecular signals initiate cell differentiation, the physical properties of the stem cells’ environment, along with the external forces acting on the cells,

significantly influence what tissue type the cells will develop into. This is just one aspect that makes the exploration of the mechanical processes in morphogenesis so exciting, but also complex. “In order to really understand the development of tissues, we need to study them under as natural conditions as possible, and in three dimensions,” states Brunner. This is why MorphogenetiX employs the most modern equipment, innovative technologies and ingenious mathematical models in search of this understanding.

### High-quality images

One of these pieces of equipment is the light sheet fluorescence microscope (LSFM). It allows the scientists to examine tissue shaping either in an intact organism, or in tissue elements cultured *in vitro*. It does this with an unprecedented image quality and over a relatively long time period. A picture of the subject is taken every 30 seconds, and the images are subsequently assembled into a movie in which the tissue development can be analyzed in three dimensions. To further optimize the image quality and measurement accuracy, the MorphogenetiX team is setting up an improved prototype LSFM. With this new device, the sample can be simultaneously illuminated by two sheets of light, and observed through two objectives perpendicular to the light sheets, resulting in a considerable improvement in the image quality.

But there is a down side to this new technology, as Damian Brunner explains. “We generate around eight terabytes of data within four hours.” To avoid drowning in a flood of data, the re-

searchers implement a processing pipeline before each LSFM experiment, where they define what data should be gathered, and which cells analyzed. The scientists then filter out these results from the mountain of data, deleting the rest. This step isn't easy for any scientist, but Brunner emphasizes the sheer impossibility of holding on to all of the data. Thankfully, there is a saving grace: "The movies of the tissue development can be easily reproduced at any time with the help of standardized methods."

### Targeted manipulation of proteins

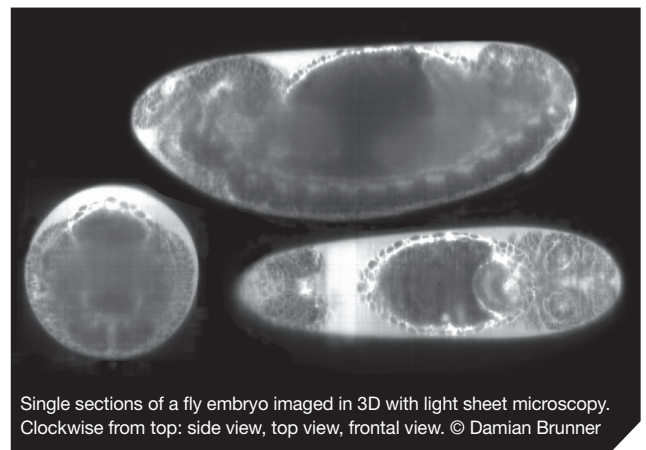
The LSFM is not the only state-of-the-art technology that Brunner and his team are making use of. "Markus Affolter has developed a method with which proteins in the cells can be turned on and off with remarkable accuracy and speed. We can even relocate proteins within the cells," reports the project leader. These methods enable the team to acutely and selectively manipulate these extremely dynamic processes and analyze the immediate consequences in the living organism, for instance during embryonic development.

Yet another innovative method involves staining each individual cell, making it easily distinguishable from its neighbors. "This gives us previously unseen insight into the behavior of cellular processes during tissue shaping," explains Brunner excitedly. The MorphogenetiX team now wants to look at the changes occurring in individual cells from each tissue type, for example in the larval wing disc, from different perspectives over a longer time period.

### Finite element method

In order to use the collected data efficiently and try to understand the complex molecular processes at play, suitable mathematical models must be implemented. Here, the MorphogenetiX team is again opting for an innovative approach. "We are using models based on the finite element method, which is a routinely used approach in architecture or engineering," explains the project leader.

The finite element method allows the simulation of physical processes that would otherwise involve an enormous computational cost. A complex form is divided up into many smaller elements with simpler forms. The physical behavior of these elements can be easily calculated thanks to their simpler geometry. Both Damian Brunner's and Christof Aegerter's teams have adapted this model to meet their needs. Now the researchers are able to incorporate the third dimension in their simulations of tissue shaping and can also take into account variability amongst similar cells. "The predictive power of these models has significantly increased as a result, which in turn helps us optimize the experimental studies," says Brunner.



The clever interplay of interdisciplinary research approaches with customized models and innovative technologies makes MorphogenetiX an exemplary large-scale systems biology research project. And who knows? In the near future, it might just unravel the mystery of the mechanics of life.

### MorphogenetiX at a glance

Principal investigator: Prof. Damian Brunner

#### Research groups:

- Prof. Damian Brunner, Institute of Molecular Life Sciences, University of Zurich – 4D tissue morphogenesis, finite element modeling
- Prof. Lucas Pelkmans, Institute of Molecular Life Sciences, University of Zurich – 4D tissue morphogenesis
- Prof. Christof Aegerter, Physik-Institut, University of Zurich – Biophysics, finite element modeling
- Prof. Markus Affolter, Biozentrum, University of Basel – Development of molecular tools
- Prof. Richard Smith, Max Planck Institute for Plant Breeding Research, Cologne, Germany – Finite element modeling

Total budget (2014–2018): CHF 6.2 million, including CHF 3.0 million from SystemsX.ch

Project type: Research, Technology and Development (RTD) Project



**MorphogenetiX**  
Modeling the  
3-Dimensional Shaping  
of Tissue Systems