In the developing organism cells proliferate, rearrange, and physically interact with other cells in the growing tissue. The specific chemical signals spread through the tissue forming gradients of concentration. Despite the noisy nature of the signals and dynamics of cellular processes, cells interpret the chemical signals to form spatial patterns of gene expression that are remarkably precise and reproducible between individuals. Intuitively, cells are instructed about their position in the tissue and based on these instructions cells commit to specific cell fates forming a spatial pattern of different cell types at the tissue level. What is remarkable in this specification process is that this pattern is established with striking precision of one cell diameter in fruit fly and three cell diameters in the developing mouse spinal cord. This raises the question of how patterning precision is established in a growing tissue? This is a fundamental question in biology that remains unresolved. We still lack an understanding of how growth, cellular dynamics, biomechanical feedbacks and global mechanical constraints together limit patterning precision in the developing tissues.

The importance of patterning precision for achieving correct tissue function is well illustrated in the developing heart. The narrow pacemaker region is formed of slowly proliferating cells of specific type, whereas highly proliferative cells of different type form chamber tissue. The high precision of spatiotemporal pattern of pacemaker-like cells that establish cardiac conductive system is required to correctly set the heartbeat. Conversely, the chamber tissue can presumably tolerate lower patterning precision. In simple terms, the region of heart that is responsible for accurate timing of heartbeat is formed slowly whereas parts of heart that presumably can be more imprecise grow at a faster rate. Hence, there is evidence that in developing tissues the patterning precision is altered to meet different functional goals and that growth can be important factor that limits patterning precision.

Taking a broader perspective, in growing tissues, the rate of cell division can change significantly in space and time, as in the above heart example, or in the developing spinal cord in which cells that will become neurons proliferate slower and slower as spatial pattern is being formed. These observations open the possibility that relation between growth and patterning precision can be overarching for different types of growing tissues. I will investigate this relation by posing the following research hypothesis: The pattern formation in a growing tissue is governed by an optimal limit of patterning precision and growth. I will refer to this hypothesis, as precision limiting hypothesis. For instance, if sharp straight domain boundary preserves its shape due to growth, the patterning precision is high. Conversely, if the same sharp domain boundary gets fragmented or wiggled, the patterning precision is low. One of the important consequences of the precision limiting hypothesis is that the patterning precision in a growing tissue is as high as possible for a given proliferation rate.

The verification of the proposed precision limiting hypothesis is challenging as patterning process in growing tissue potentially depends on multiple cellular and mechanical aspects of tissue dynamics. In the proposed project I want to conceptually disentangle cellular and mechanical factors, by addressing the following research questions: (1) how is growth related to patterning precision? (2) how are cellular dynamics and biomechanical feedbacks affecting the patterning precision? (3) how are global mechanical constraints acting on growing tissue to limit patterning precision? To verify this relation, I will build on my expertise with biophysical and computational modelling as well as take advantage of collaborations with experimentalists. I will develop a new framework for understanding precision in a cell-based model. Understanding the limits for patterning precision as a function of growth will advance our understanding of patterning in a broad range of tissues.

Understanding patterning precision could also help to identify cases of abnormal cell divisions. For instance, patterning precision could deteriorate when highly proliferating cancer cells are considered. In practice, the identified relation between patterning precision and biomechanical feedbacks that control cell size variation and motility of cells might be of importance when designing diagnostic criteria for cancer patients. Further, the cell-based description of growing tissue that is consistent with high-resolution experimental data for spinal cord development or pacemaker region formation will determine the relation between patterning precision and growth in these tissues. This relation between patterning precision and growth in long-term can be utilized in designing optimal growth conditions for neuroregenerative therapies, or stem cell guided therapies of heart defects. Taken together, identified mechanisms are likely to be generally relevant and broadly influential for both experimental and theoretical groups working in the field of developmental, systems and medical biology.