# Expansion of cardiac chambers : role of physical constraints

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## Description of the project

Effective heart contraction depends on the architecture of the cardiac muscle, the myocardium. This is not only a question of size, underlying contractile power, but also a question of orientation determining specific patterns of contraction in the adult heart. The adult myocardium has an oriented cellular architecture (myofibres) which underlies the twisted pattern of contraction in the left ventricle. The team of S. Meilhac has identified and mapped in 3D oriented tissue growth (Meilhac et al., 2004) and oriented cardiomyocyte division (Le Garrec et al., 2013) early in development, during the expansion of the embryonic ventricles. This correlates with the specific geometry of cardiac chambers (Meilhac et al., 2004), as well as with the establishment of the oriented myofibre architecture (Meilhac et al., 2003). However, how such orientation of myocardial growth is regulated remains enigmatic. We aim to uncover regulators of myocardial growth orientation. Taking into account the fine 3D geometry of the organ raises novel challenges for imaging and quantitative image analysis, that we address in collaboration with computational scientists.

In other tissues, oriented cell division has been shown to occur as a result of the physical constraints imposed by the geometry of the cell. Following Hertwig's rule (1884), cells divide perpendicular to their long axis to minimise tissue stress. In this context, the orientation of cell division is expected to be predicted from the cellular architecture. We have already established conditions to image the entire cellular architecture of the embryonic myocardium, together with the orientation of cell division, by CUBIC aqueous clearing and lightsheet microscopy of fluorescent markers. 3D segmentation tools are being developed in collaboration with JC Olivo-Marin at the Institut Pasteur, to test whether Hertwig's rule applies to embryonic cardiomyocytes.

Physical forces exerted on cells have also been shown to bias cell division orientation (ex Scarpa et al., 2018). This is relevant to the myocardium, given its contractile nature. We will test the importance of heart mechanics in oriented growth, by drug interference with cardiac contractions in embryo cultures. The impact on oriented cell division and tissue growth will be assessed by quantitative 3D imaging of sister cells and of cell mosaics.

The project, which can be extended for a PhD, is expected to provide novel insight into the mechanisms of heart growth and is relevant to heart repair.

## Selected team publications

Oriented clonal cell growth in the developing mouse myocardium underlies cardiac morphogenesis.S. Meilhac, M. Esner, M. Kerszberg, J. Moss and M. Buckingham, The Journal of Cell Biology 2004, 164(1) : 97-109.

Extracting 3D cell parameters from dense tissue environments: Application to the development of the mouse heart, S. Pop, A. Dufour, J-F. Le Garrec, C. Ragni, C. Cimper, S. Meilhac and J-C. Olivo-Marin, Bioinformatics 2013, 29(6):772-9.

Quantitative analysis of polarity in 3D reveals local cell coordination in the embryonic mouse heart, J-F. Le Garrec, C. Ragni, S. Pop, A. Dufour, J-C. Olivo-Marin, M. Buckingham and S. Meilhac, Development 2013, 140(2):395-404.

A predictive model of asymmetric morphogenesis from 3D reconstructions of mouse heart looping dynamics. Le Garrec JF, Domínguez JN, Desgrange A, Ivanovitch KD, Raphaël E, Bangham JA, Torres M, Coen E, Mohun TJ, Meilhac SM. Elife. 2017 Nov 28;6. pii: e28951.