Finding the tipping point in dilated cardiomyopathies: A dynamical systems' analysis of single cardiomyocytes functional and morphological long-term trajectories using big data

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Heart failure is a major cause of human morbidity and mortality, affecting 1-2 % of the European population. Yet, the time-course of genetic heart muscle related diseases as dilated cardiomyopathy, a disease that appears during adulthood, is barely understood. Heart failure is a major cause of human morbidity and mortality, affecting 1-2 % of the European population. Yet, the time-course of genetic heart muscle related diseases as dilated cardiomyopathy, a disease that appears during adulthood, is barely understood. The motion of heart muscle emerges from the ATP-driven molecular motors, collectively creating the reversible contraction of sarcomeres, the basic mesoscopic building block with lengths of around 2 µm. In cardiomyocytes, many sarcomeres in series and in parallel enable a rapid and strong anisotropic contraction. On an organ scale, a tissue of aligned heart muscle cells then creates the high macroscopic forces necessary to pump blood throughout our bodies. This functional hierarchy, however, renders our heart muscles vulnerable to defects of individual sarcomere proteins caused by genetic mutations.

To better comprehend the emergence of cardiac diseases, I study the morphogenetic trajectories of single stem-cell derived cardiomyocytes during sarcomeregenesis and maturation using an automated microscope that records thousands of cells over multiple days. This in-vitro model allows us to introduce adverse pathological conditions and common mutations of genes encoding sarcomere proteins, here the giant protein titin. Recently, I developed SarcAsM (Sarcomere Analysis Multitool), a deep-learning based software for automated morphological and functional analysis of sarcomeres in cardiomyocytes. With the various features extracted by SarcAsM, one can follow the temporal evolution of cells in a high-dimensional phase space. I then construct a dynamic embedding using machine learning techniques to identify relevant degrees of freedom in a hypothesis-free manner. In this low-dimensional space, I aim to understand the trajectories of individual cardiomyocytes from a non-linear dynamic systems' viewpoint, and identify stable fix points (mature cardiomyocytes or cell death) and tipping points (dilated cardiomyopathy). By combining medical biology, big data, machine learning, and complex systems theory, this project will create novel insights into the self-organization and pathogenesis of sarcomeres in cardiomyocytes.