From in-Vitro Models to Patient Specific Cardiac Predictions

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Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease, and remains a leading cause of sudden cardiac death in the young. Its striking clinical heterogeneity reflects complex, multiscale interactions between genetics, cellular dynamics, and cardiac structure. In this context, cardiac digital twins offer a powerful framework to integrate imaging, electrophysiology, and mechanistic modelling, holding promise for refined risk stratification and more targeted clinical management in HCM.

This talk will showcase progress from the EU/UKRI-funded SMASH-HCM project in developing and exploiting multiscale cardiac digital twins for HCM. We will present advances on the construction and validation of biophysically detailed in-silico heart models spanning cellular, tissue, and whole-organ scales. At the cellular level, our patient-specific models capture both primary mutation-driven effects and secondary electrophysiological, mechanobiological, and energetic remodelling during disease progression, enabling systematic in-silico phenotyping under established pro-arrhythmic stressors. At the tissue scale, models informed by in-vitro and clinical imaging data resolve mutation-specific mechanisms of conduction impairment and mechanical dysfunction. At the organ level, personalised whole-heart simulations link genotype-phenotype interactions to ECG biomarkers and arrhythmic risk, also serving as generators of synthetic datasets to support AI-based stratification. Finally, we will demonstrate how these integrated digital twins can provide a unified high-throughput platform for predicting patient-specific responses to established and emerging HCM therapies, elucidating divergent drug effects across genetic variants and supporting precision disease management.

Altogether, the validated multiscale cardiac digital twin models developed within SMASH-HCM advance our understanding of HCM pathophysiology and therapeutic response. By bridging clinical and in-vitro data, they enable deep phenotyping of genetic variants, support the generation of synthetic datasets for AI-based stratification, and provide prototypes of patient-specific simulators, offering an exemplar for future application to other cardiac and multiorgan diseases and comorbidities.