Patient-specific multi-scale modeling of cardiac resynchronization therapy for dyssynchronous heart failure

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Cardiac resynchronization therapy (CRT) is a cost-effective treatment for dyssynchronous heart failure in which the patient receives a biventricular pacemaker to improve ventricular pumping function. Unfortunately up to 40% of patients are considered non-responders to CRT. CRT has received much attention in clinical and animal studies since its implementation about a decade ago. Recently, it is also receiving much attention from the multi-scale modeling community, in which groups are working on developing mechanistic patient-specific models of the heart for understanding the mechanisms of CRT and to better predict whether or not a patient will respond. Here we address some of the key challenges in developing and using mechanistic patient-specific models of cardiac electromechanics to predict CRT outcomes: Minimal model - How much data should be acquired to make an accurate prediction? In our clinical study we acquire more data than typically is obtained under normal clinical conditions (e.g. invasive catheterization, electroanatomical mapping). This however increases the burden on the patient and the number of (invasive) measurements should be kept as low as possible; Accuracy of model and clinical measurements - The accuracy of for example the geometric model reconstruction depends on the type of imaging technique used. While MRI and CT are higher resolution and frequently used in research studies, they are expensive and exceptional for heart failure patients. Therefore it is worth investigating the effects of different image modalities on model reconstruction. An interesting candidate for heart failure patients is echocardiography since it is routinely performed in these patients. Owing to the lower resolution of ultrasound images, the resulting geometric model can be fitted using fewer degrees of freedom, although there is a corresponding loss of anatomic detail; Mapping myofiber architecture to patient geometries - Myofiber and laminar sheet orientations are required to model the anisotropic electromechanical properties of the myocardium. Diffusion tensor magnetic resonance imaging (DTMRI) can provide regional information on myofiber architecture throughout the ventricular walls. Studies suggest that fiber orientations are remarkably conserved between individuals when geometric variations are taken into account with the exception of sheet orientation. Therefore, the task of including fiber orientations in patient-specific models is focused on mapping fiber architecture from *ex-vivo* studies into patient-specific ventricular geometries and sensitivity of outcome prediction needs to be determined; Estimating regional tissue conductivities from electrocardiographic recordings – it is known that electrical dyssynchrony detrimentally influences cardiac regional mechanical function and recently we have shown that electrical dyssynchrony interacts strongly with ventricular dilation. There are several modalities available to obtain the conductivities for electrophysiology models, such as electroanatomic mapping and inverse methods making use of body surface potentials; Estimating unloaded ventricular reference geometry and mechanical properties - An essential requirement of the mechanical model is an unloaded reference geometric mesh, however the heart is continually loaded *in vivo* and several methods have been proposed in the literature to obtain this; Modeling long-term remodeling and reverse remodeling - comprehensive computational multi-scale models of cardiac electromechanics combined with growth and remodeling will become invaluable in predicting long-term effects of medical devices, surgeries and therapies on the heart. To date, patient-specific heart models are invariably acute, thus ignoring long-term effects.

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