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Electromechanical model of hiPSC-derived ventricular cardiomyocytes co-cultured with fibroblasts

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Healthy cardiac tissue includes approximately 75% of cardiomyocytes by volume but cardiomyocytes account for only 30-40% of cell numbers [1]. The majority of the other cells are fibroblasts whose number even increases in aged tissue and in many forms of diseases. Fibroblasts do not only contribute to the tissue structure but it has been shown in both experimental and computational studies that they alter cardiomyocyte electrophysiology [2,3]. Furthermore, a numerical study by Zhan *et al*. [4] suggests that also the mechanical contraction of ventricular cardiomyocytes is influenced by fibroblasts. This is reasonable since the membrane potential triggers contraction via calcium currents. Calcium currents in fibroblasts on the other hand have not been found yet which suggests that they cannot actively contract by themselves. Mechanical analyses of cardiac tissue are possible with the *CellDrum* device which was developed in our institute [5]. The *CellDrum* is a well with a bottom formed by an ultra-thin circular silicone membrane on which cardiac tissue is cultivated. Clamped in a fixed ring, the displacement and contraction frequency of the auto-contractile tissue construct can be measured using a capacitive sensor. Experimental and computational studies are being performed to get a more detailed insight into the role of fibroblasts in the electromechanics of ventricular cardiac tissue. For the experiments human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) with a content of about 90% ventricular cells are used. They are co-cultured with various cell amounts of fibroblasts. For a better interpretation of the experiments, FEM based electromechanical multi-scale models are being developed. They are based on existing models [6,7] and can be partly tailored to the specific sample. Numerous models exist which describe ventricular cell electrophysiology. Intercellular coupling with fibroblasts can be realized by the connection with a model published by MacCannel *et al*. [3]. This model is an “active” representation of mammalian fibroblasts which includes four membrane ionic currents. The coupled cell model is embedded into the reaction-diffusion type monodomain model to compute the propagation of the action potential throughout the tissue. Controlled by the membrane potential, the calcium concentration in the ventricular cardiomyocyte varies with time. Excitation-contraction cell models relate the calcium concentration to the active stress during contraction. The active is added to the passive stress to derive the total mechanical response of the tissue construct.

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