In Silico trials for drug tracing the effects of sarcomeric protein mutations leading to familial cardiomyopathy- SILICOFCM project

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Familial cardiomyopathies (FCM) are most commonly diagnosed, or progress of the disease is monitored, through in vivo imaging, with either echocardiography or, increasingly, cardiac magnetic resonance imaging (MRI). The treatment of symptoms of FCM by established therapies could only in part improve the outcome, but novel therapies need to be developed to affect the disease process and time course more fundamentally. In SILICOFCM project we are doing in silico multiscale modeling of FCMs that would take into consideration comprehensive list of patient specific features (genetic, biological, pharmacologic, clinical, imaging and patient specific cellular aspects) capable of optimizing and testing medical treatment strategy with the purpose of maximizing positive therapeutic outcome, avoiding adverse effects, avoiding drug interactions, preventing sudden cardiac death, shortening time between the drug treatment commencement and the desired result.

There are currently no interventions available that specifically treat or prevent cardiomyopathies resulting from mutations in sarcomere proteins. Current standard of care is designed to manage progression of heart failure, thus novel therapies are needed to affect the disease process and time course more fundamentally. Here, we emphasize potential novel therapies and approaches which may prevent, delay, or even reverse FCM that involves genetic defects, altered sarcomere function, perturbed intracellular ion homeostasis, and impaired myocardial energetics

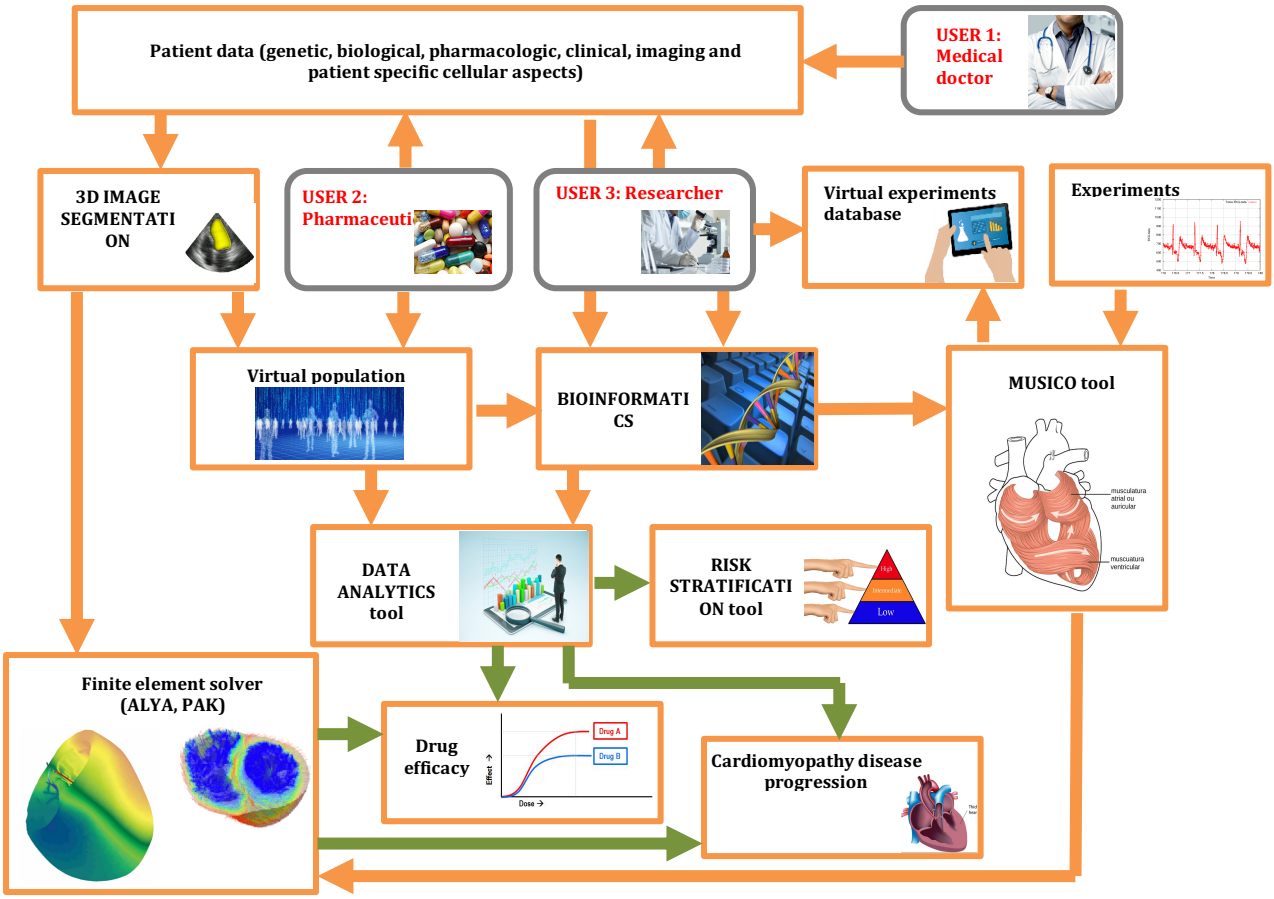

Figure 1 *SILICOFCM project scenario of using*

SILICOFCM platform is a cloud based ICT platform that combines detailed heart reconstructed and computable geometries with state-of-the-art multiphysics solvers (MUSICO, BIOINFORMATICS, DATA ANALYTICS, ALYA and PAK) to directly simulate the heart function and performance of complex biomedical products. This approach could significantly enhance the development of novel therapies which may prevent, delay, or even reverse familial cardiomyopathies caused by sarcomeric gene mutations, altered sarcomere function, perturbations in intracellular ion homeostasis, and impaired myocardial energetics at largely reduced cost of drug development. Flexible modular structure of SILICOFCM platform also allows *in-silico* trials that can be performed on individualised sets of data, specific for particular patient. It is architected with a high performance computing (HPC) scalable system framework for optimal performance. Possible scenario for using SILICFCM platform is presented in Fig. 1. Medical doctors, pharmaceutical companies, researchers collect data to or from patient data, then using 3D image segmentation tool to update the Virtual population database. MUSICO build micro level behavior on the sarcomere level and use very complex 3D finite element solvers ALYA and PAK to make in silico drug efficacy and cardiomyopathy disease progression.

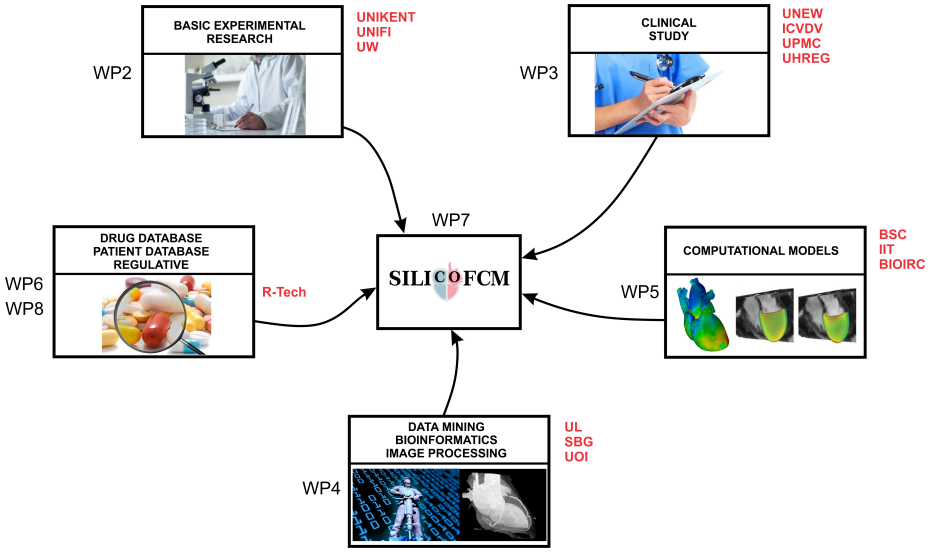

Figure 2 Workpackages and their connection

Distribution of workpackages has been presented in the Fig. 2. Systems biology has introduced new paradigms in science by switching to a more integrative approach toward the study of complex systems. Over the past years, researchers have produced an extraordinary wealth of knowledge on human physiology. The aim of SILICOFCM is to integrate this knowledge and reveal the relationships between the different components and scales that form and balance cardiac systems. In order to integrate this knowledge, a number of mathematical models and ICT (Information and Communication Technologies) are to be developed and used.

Extensive research in the last few decades provided large amount of data from animal and human studies related to many complex diseases. The data were collected at different length scales spanning genetics, protein interactions and structure, and cell, tissue and organ function. Most of the findings at any scale were directly connected to particular disease, neglecting processes at different scales that can significantly distort outcome at organ function. This partial approach led to expensive and frequently unsuccessful development of new drugs and therapies.

We believe that with SILICOFCM project we will connect basic experimental research with clinical study and bioinformatics, data mining and image processing tools using very advanced computer models of FCM and drug and patient database and regulative in order to reduce animal and clinical studies.