1. Project title.
MULTISCALE LAWS OF MYOCARDIAL GROWTH AND REMODELING

2. Brief summary of the project topic.
Heart failure is a worldwide epidemic that contributes considerably to the overall cost of health care in developed nations. The overall objectives of this project are to identify the mechanical culprits that dictate the bifurcation of the system from the stable healthy state into the instable state of heart failure and to determine the borderline between physiological and pathophysiological growth and remodeling. To address these goals, our research approach is to experimentally inform and validate multiscale laws of myocardial growth and remodeling using three different large animal models to predict the propensity of developing heart failure.

3. Details regarding Model Credibility plan following the CPMS Ten Simple Rules format.

Rule 1 – Define context clearly.
The goals of our models are clearly defined by the *Specific Aims* of the project: *Aim 1* is to elucidate a predictive validated multi-scale law of myocardial growth and remodeling in eccentric hypertrophy associated with cardiac dilation. *Aim 2* is to validate a predictive multi-scale law of myocardial growth and remodeling in concentric hypertrophy associated with wall thickening. *Aim 3* is to use the strain growth and remodeling laws from Aims 1 and 2 to predict the propensity for heart failure in ischemic heart disease based on specific mechanical indices of myocardial function.

Rule 2 – Use appropriate data.
In iterative cycles of experiment and modeling, we generate our own appropriate data for model calibration, validation, and verification. In *Aim 1*, we induce eccentric hypertrophy in a chronic porcine model using volume overload, we collect longitudinal biopsy samples of myocardial tissue every two weeks for a period of eight weeks to determine sarcomere numbers and myocyte lengths using immunohistochemistry, and we perform bi-weekly echocardiography to determine end diastolic volumes. In *Aim 2*, we induce concentric hypertrophy in a chronic porcine model using pressure overload, we collect longitudinal biopsy samples of myocardial tissue every two weeks for a period of eight weeks to determine sarcomere numbers and myocyte widths using immunohistochemistry, and we perform bi-weekly echocardiography to determine end diastolic and end systolic volumes and ejection fractions. In *Aim 3*, we induce infarcts and potential heart failure in a chronic porcine model using multiple coil occlusion, we collect longitudinal biopsy samples of myocardial tissue every two weeks for a period of eight weeks to determine sarcomere numbers and myocyte morphologies using immunohistochemistry, and we perform bi-weekly echocardiography to determine end diastolic and end systolic volumes and ejection fractions.

Rule 3 – Evaluate within context.

For each *Specific Aim*, we collect data on the subcellular, cellular, and organ level and correlate those data using multiscale computational modeling. Specifically, we use the subcellular and cellular level data as input to our model and make predictions on the organ level. We then compare these predictions to our organ level data. At the same time, we perform an inverse approach and use our organ level data as input to our model and make predictions on the cellular and subcellular level. We then compare these predictions to our cellular and subcellular level data. We adopt this approach throughout all three aims using data of the same format, but collected from three different chronic animal models and evaluated with three different growth and remodeling models. This independent bottom up and top down approach validates our models. Using the same approach for all three aims validate our overall approach.

Rule 4 – List limitations explicitly.

Simplifying assumptions and limitations of our methods are explicitly described in publications. Our approach has three conceptual limitations: *First*, we only monitor our animals throughout a period of eight weeks. A unique aspect of our study is that we collect biopsy samples and echocardiography images of the same heart at five points in time. In retrospect, we should probably have continued the study for an additional two or even four weeks to allow these alterations to become more pronounced. *Second*, in our initial cohort, we have only studied six animals. In retrospect, we observed a relatively large inter-animal variation, and this number of animals seems rather low. We should probably increase the number of subjects in the future to explore how robustly our findings extent to a larger group. For now, to analyze and interpret our relatively sparse data, we have consulted novel machine learning techniques to interpret the individual behavior of each animal in view of the collective behavior of all animals. *Third*, our study induced controlled heart failure in porcine models as a surrogate model for heart failure in humans. While sarcomere lengths and numbers, myocyte lengths and widths, and ventricular volumes are relatively comparable between pigs and humans, it remains to be shown how the timeline of cellular and ventricular adaptation in pigs translates into the timeline of heart failure in humans.

Rule 5 – Use version control.

We share all our models on Github and use the built-in Github version control system.

Rule 6 – Document adequately.

While developing model code, we simultaneously write drafts of publications that precisely describe our eccentric and concentric growth models. This allows us to iterate between the mathematical model and the computational simulation tool. To document the simulation tools, we utilize the documentation control system provided by Github.

Rule 7 – Disseminate broadly.

All mathematical models and computational tools are disseminated through peer-reviewed journal publications and conference presentations. All algorithms will be made available in multiple formats on Github.

Rule 8 – Get independent reviews.

We independently develop our models in our three contributing groups and exchange and test the algorithms between our different labs. Our work is continuously assessed and evaluated through third-party users and developers via peer review of our manuscripts to establish model credibility. We closely collaborate with different groups that use and adopt modules of our software. We are highly responsive to requests and problems of other end users. This interaction is facilitated via GitHub and freely available software tools.

Rule 9 – Test competing implementations.

We implement our models into different finite element platforms and perform independent simulations to compare individual implementations. We test our algorithms using simple model problems and benchmark our codes against established model problems with known solutions to identify discrepancies and estimate numerical error tolerances.

Rule 10 – Conform to standards.

Models and Software sharing plan: We will make all tools that are developed as part of this project freely available and transferable upon publication. We will take full responsibility for creating the original and subsequent versions of the computational tools outlined in our proposal.

Sharing and reproducibility of published simulation works: Following publication of all work supported through this grant, specific standards for reproducibility of results will be imposed by source code sharing through shared resources.

Software dissemination and distribution plan: Our algorithms will be made available in GitHub. All packages will be tested prior to public dissemination.

Dissemination and distribution through other shared resources: In addition to the core models, we will also share other tools and resources relevant to our project. These include, for example, a tool to generate Purkinje fiber networks, or algorithms for sensitivity analyses.

Other terms of use: To ensure continued utility to the wider scientific and academic community, all software developed within this project will transferable such that another individuals or teams can continue development.

Description of how the planned activities lead to a credible model

Throughout all three *Specific Aims*, we collect our own data that are tailored to calibrate, validate, and verify our models. Specifically, we experimentally characterize sarcomere numbers and length, myocyte widths and lengths, and end diastolic and systolic volumes in three longitudinal studies of volume overload in *Aim 1*, pressure overload in *Aim 2*, and myocardial infarction in *Aim 3* using histology and echocardiography. In each *Specific Aim*, we quantify the agreement between simulation and experiment in terms of

myocyte lengths and end diastolic volumes recorded in six animals throughout a period of eight weeks with bi-weekly data collection, see Figure 1.

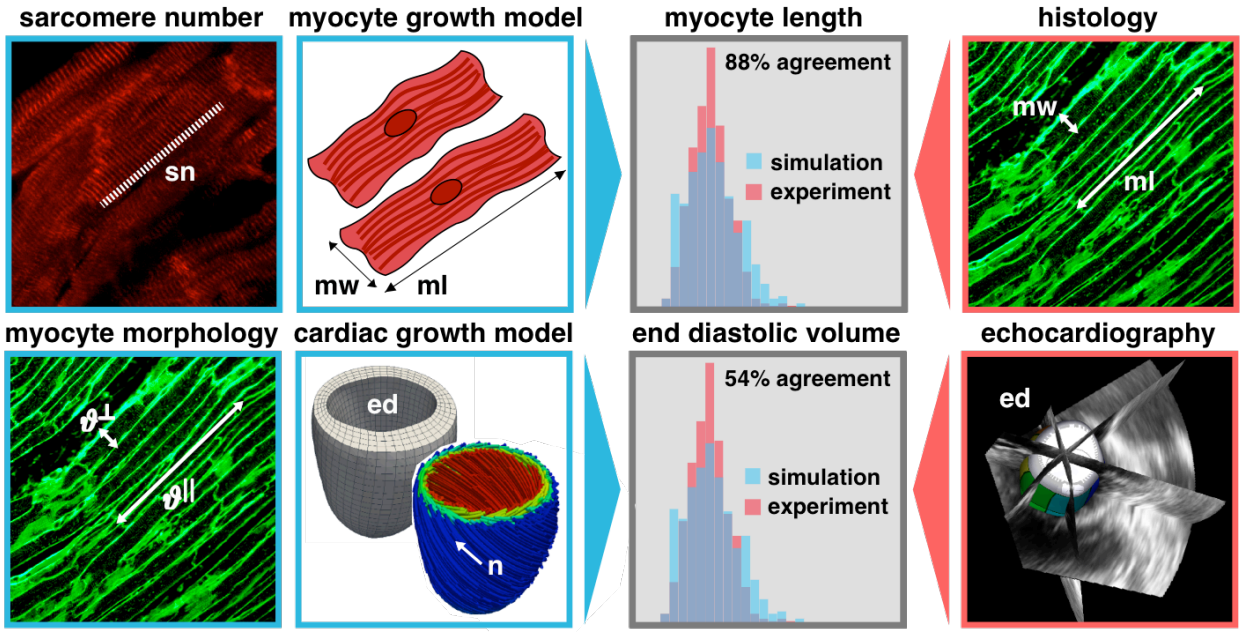

Figure 1. Bridging the subcellular, cellular, and tissue levels using our multiscale continuum growth model. We experimentally characterize sarcomere numbers and length, myocyte widths and lengths, and end diastolic and systolic volumes in three longitudinal studies of volume overload (Aim 1), pressure overload (Aim 2), and myocardial infarction (Aim 3) using histology and echocardiography. For each model, we quantify the agreement between simulation and experiment in terms of myocyte lengths and end diastolic volumes recorded in six animals throughout a period of eight weeks.

Data Analysis. To analyze the changes in both microscopic and macroscopic variables in all subjects, we employ Bayesian inference. For all recorded samples, we postulate that these measurements are drawn from distributions that evolve over time. Specifically, we assume that the measurements of sarcomere number and length, myocyte length and width, and end diastolic and systolic volumes are log-normally distributed at any point in time. To take into account the variability between subjects and, at the same time, take advantage of the entire dataset acquired, we postulate a hierarchical model. We compute posterior distributions for our model parameters using Bayes' theorem. We perform the statistical inference using a Hamiltonian Monte Carlo method. We then compute new samples of our quantities of interest from a predictive posterior distribution at different time points and analyze the discrete measurement points, their medians, their 95% confidence intervals, and their inferred probability density functions throughout our study interval of eight weeks.

Uncertainty propagation. To correlate the cellular and organ levels, we propagated the uncertainty of our experimental measurements through our models. For each subject, we take the 500 samples of myocyte lengths and myocyte widths from our Hamiltonian Monte Carlo chain. Instead of performing a single simulation for each of the 500

samples, we train a Gaussian process regression to predict the end diastolic volume of the simulation. For each subject, in the expected range of uncertainty, we perform n = 10 simulations for training and an additional n = 5 simulations for validation. Since intermediate steps towards the final solution are also valid data points, we gather 301 unique points for training and 151 for validation for each subject. Once the Gaussian process regression is trained and validated, we use the 500 samples and evaluate the longitudinal and transverse growth factors at 101 time points between weeks zero and eight to generate a total of 50,500 longitudinal and transverse growth factors for each subject. We propagate these growth factors through a Gaussian process regression and obtain a simulated distribution of end diastolic volumes, which we compare against the experimentally measured end diastolic volumes from echocardiography. To quantify the agreement between the simulated and experimental end diastolic volumes, we use the percentage agreement between both histograms. Figure 1, bottom row, illustrates this process with a percentage agreement between simulated and experimental end diastolic volumes of 54%.

E. Progress to-date and plans for the next reporting cycle (6 months).

[1] Sahli Costabal F, Choy JS, Sack KL, Guccione JM, Kassab GS, Kuhl E. Multiscale characterization of heart failure, submitted for publication.

4. Issues/Concerns identified.

We have not identified any critical or problematic issues to achieve the standard of credibility set by the MultiScaleModeling Consortium.

5. Other Factors.

We have not identified any other factors that are not covered by the CPMS ‘Ten not-so-simple rules.’