credible enough?
perspectives from cardiac growth and remodeling

ELLEN KUHL

credible practice of modeling and simulation in healthcare

Stanford University

Credible Practice of Modeling & Simulation in Healthcare

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CFMS

TEN “SIMPLE” RULES?

- R1 - define context clearly
- R2 - use appropriate data
- R3 - evaluate within context
- R4 - list limitations explicitly
- R5 - use version control
- R6 - document adequately
- R7 - disseminate broadly
- R8 - get independent reviews
- **R9 - test competing implementations**
  use contrasting modeling and simulation execution strategies to check the conclusions of the different execution strategies against each other
- R10 - conform to standards

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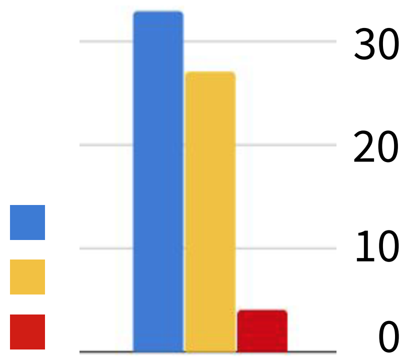
R9 - testing "competing" implementations

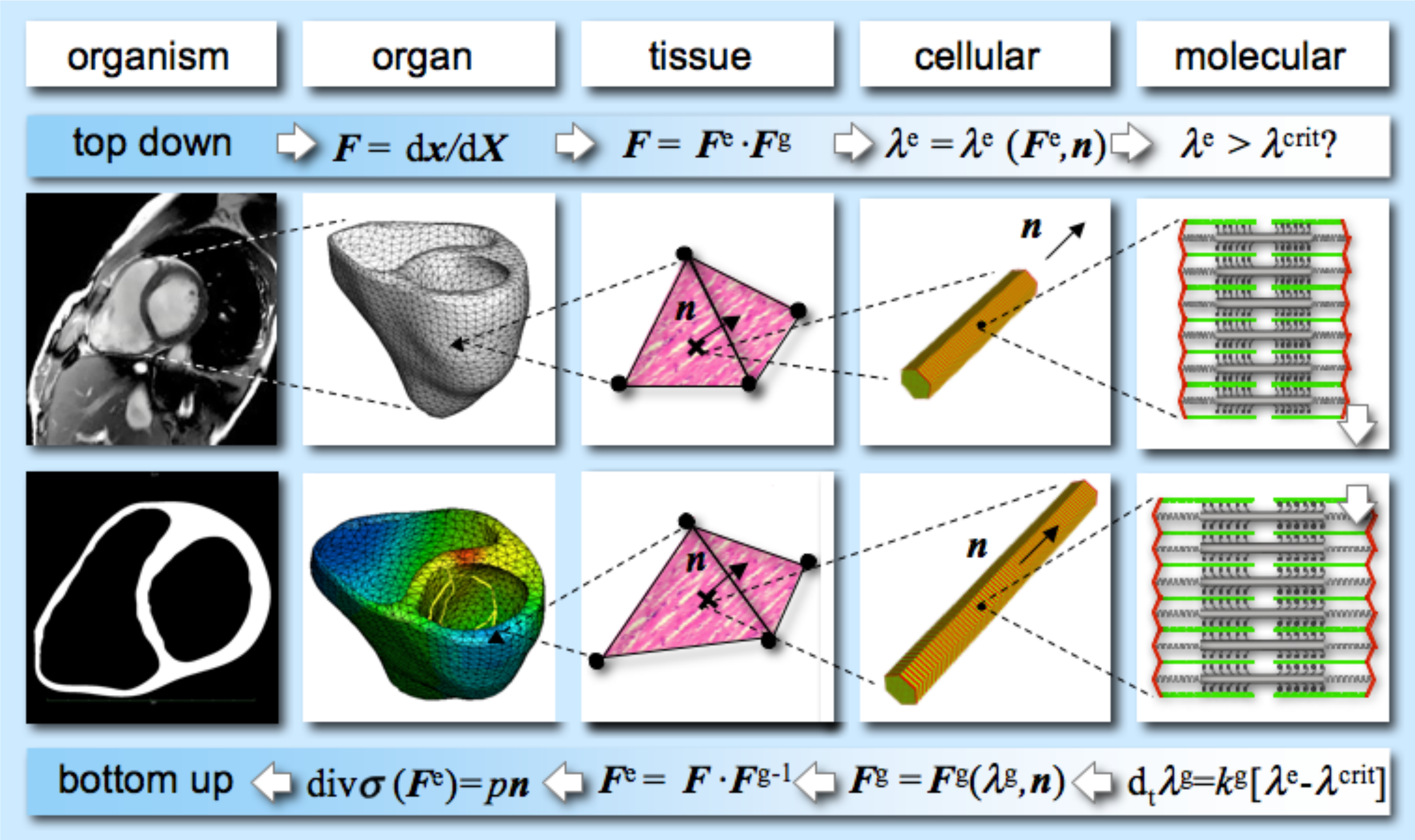
reports n = 35
reviews n = 64

sufficient
insufficient
n/a



“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**.“

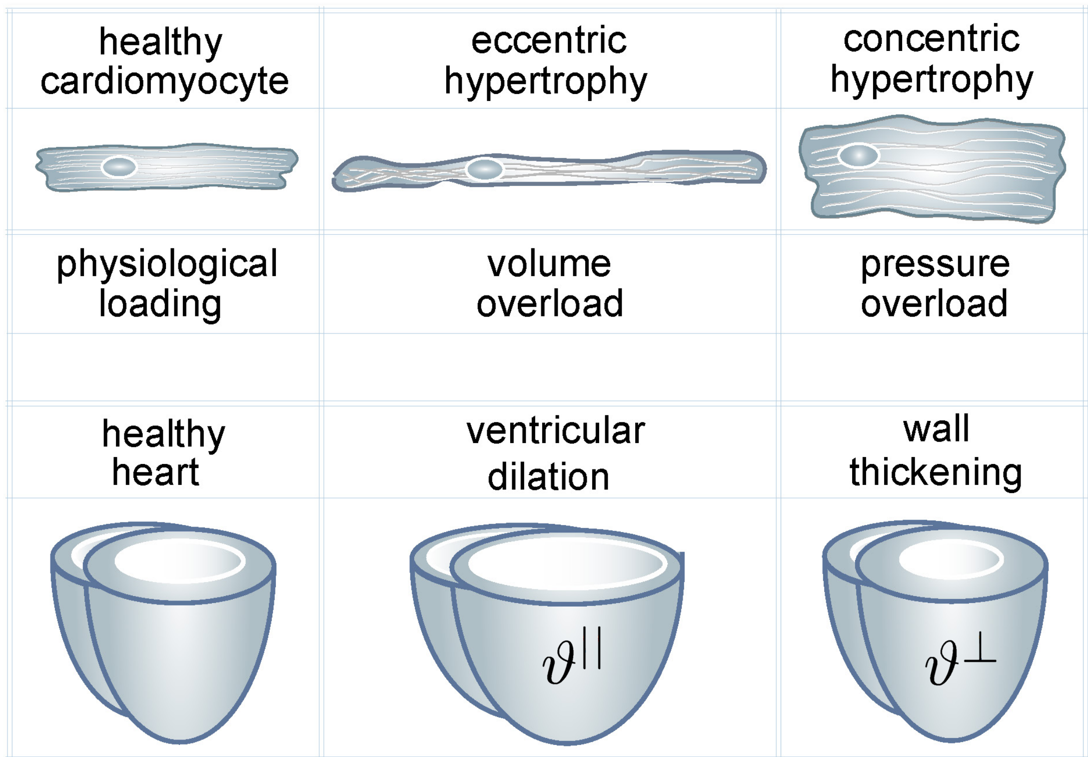
multiscale modeling of heart failure



multiscale modeling of heart failure

$$\boldsymbol{F}^{\mathrm{g}} = \vartheta^{||}\,\boldsymbol{n}\otimes\boldsymbol{n} + \vartheta^{\perp}\,[\,\boldsymbol{I} - \boldsymbol{n}\otimes\boldsymbol{n}\,]$$

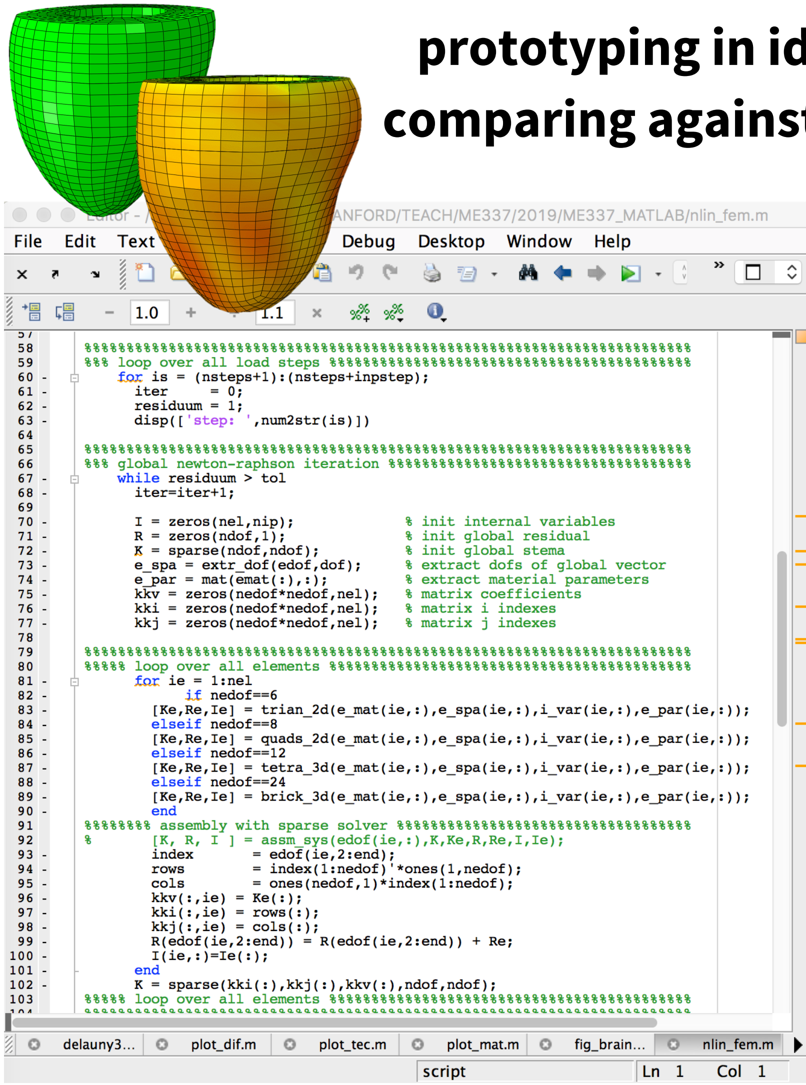
eccentric & concentric & growth

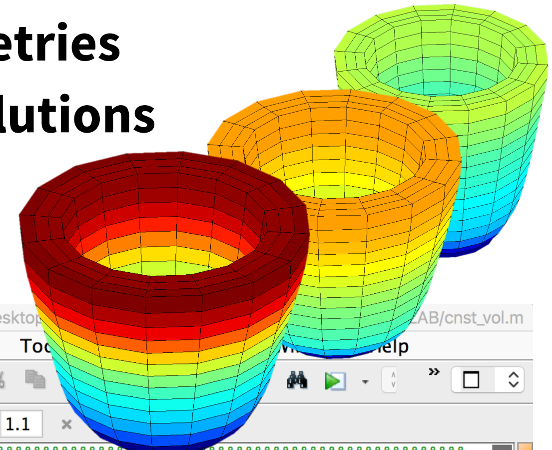


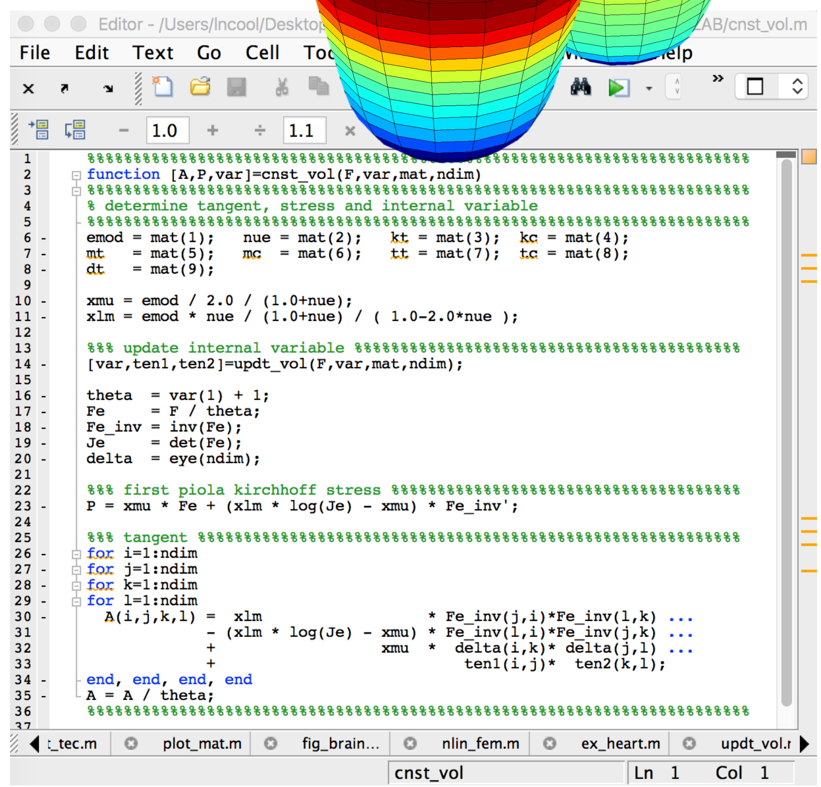
implementation #1 • matlab / elliptical model

prototyping in idealized geometries

comparing against analytical solutions







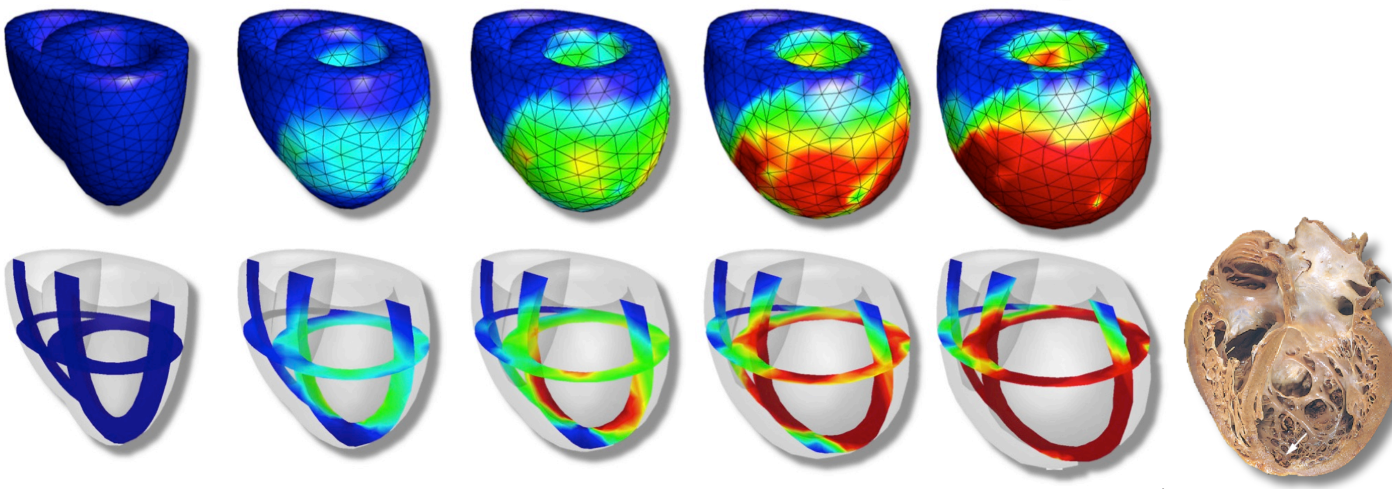
rule 9 • testing competing implementations • crowdsourcing for grades

me337 mechanics of growth • 2007-2019 • ~30 students per year

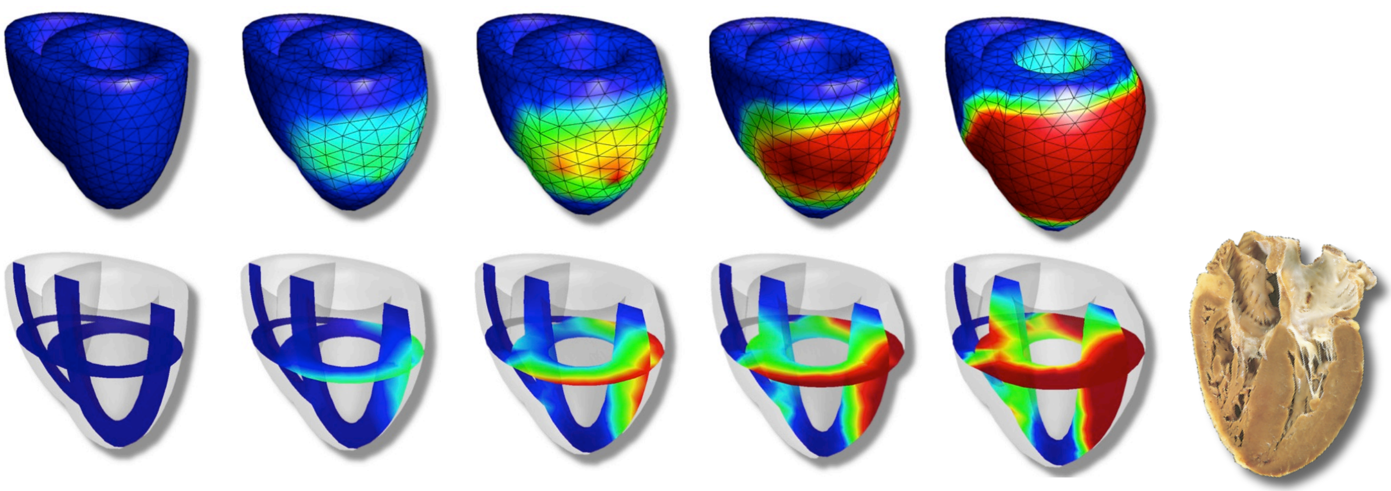
MATLAB

implementation #2 • feap / biventicular model

systolic heart failure / eccentric growth $\vartheta^{||}$



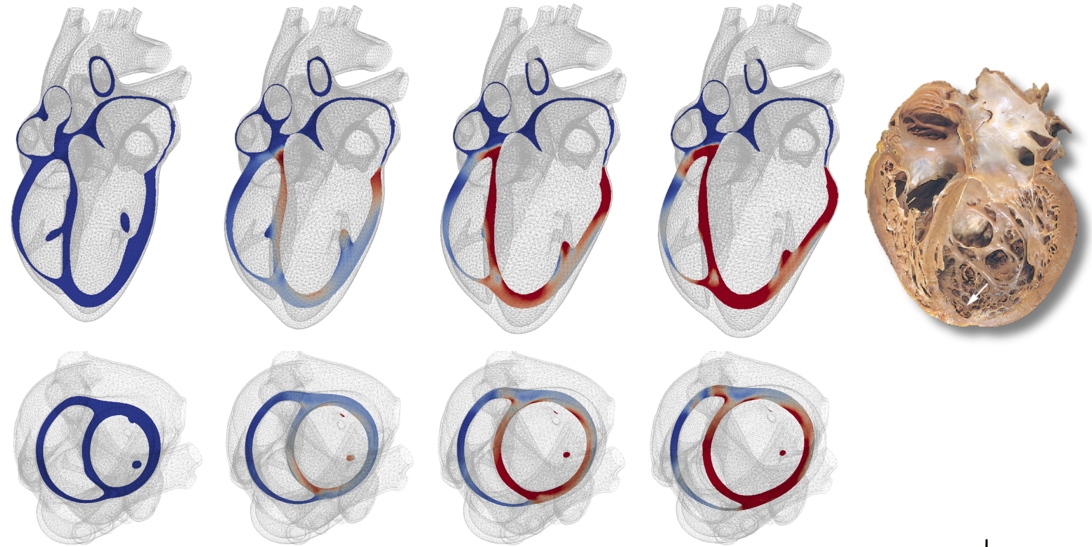
diastolic heart failure / concentric growth $\vartheta^{\perp}$



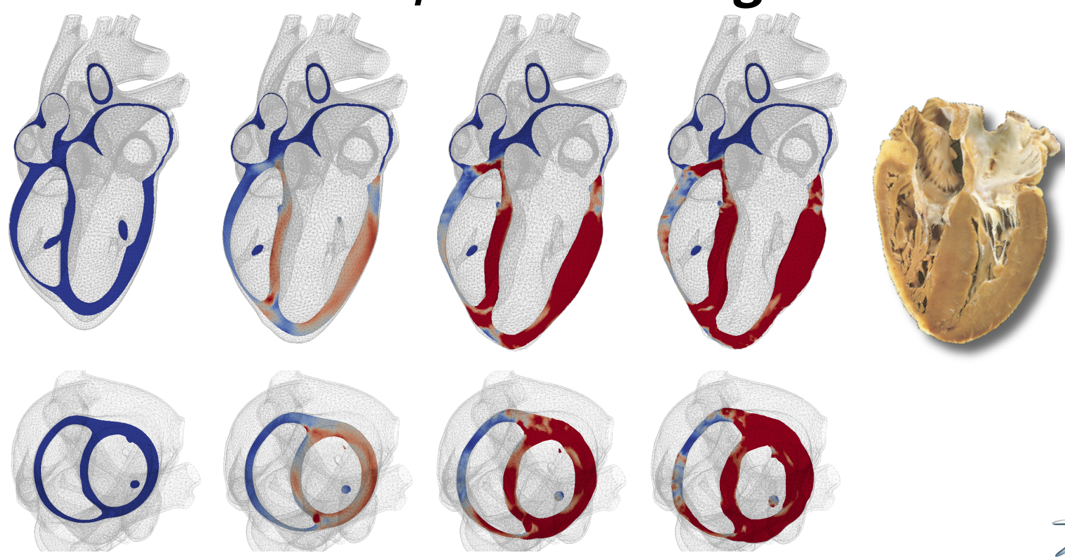
goktepe, abilez, parker, kuhl [2010], goktepe, abilez, kuhl [2010]

implementation #3 • abaqus/living heart model

systolic heart failure / eccentric growth $\vartheta^{||}$



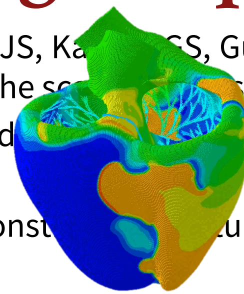
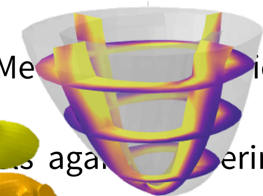
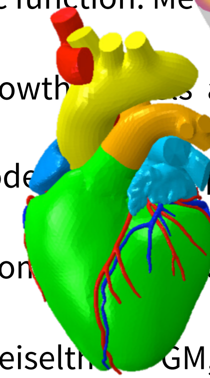
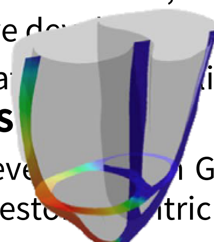
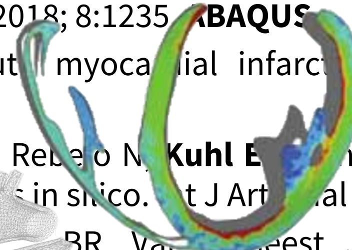
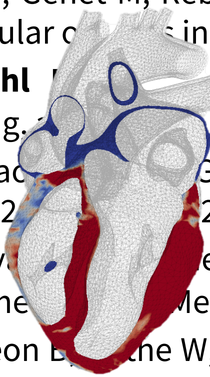
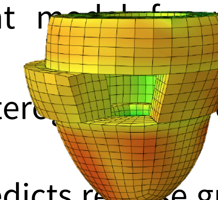
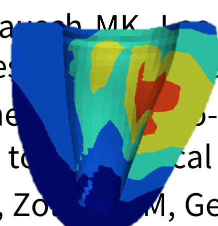
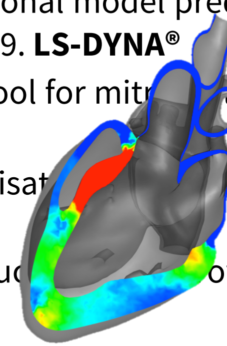
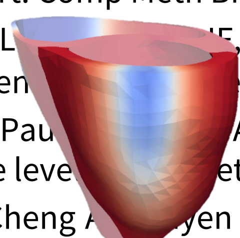
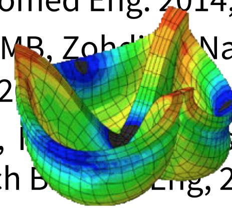
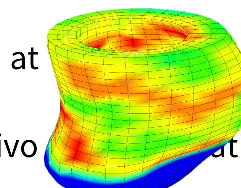
diastolic heart failure / concentric growth $\vartheta^{\perp}$



genet, lee, baillargeon, guccione, kuhl [2015]

DASSAULT SYSTEMES

testing ”competing” implementations

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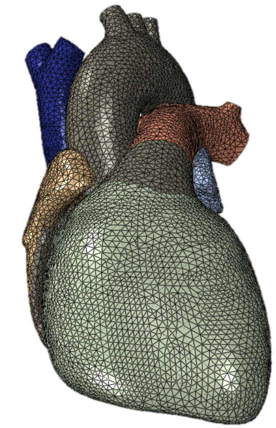
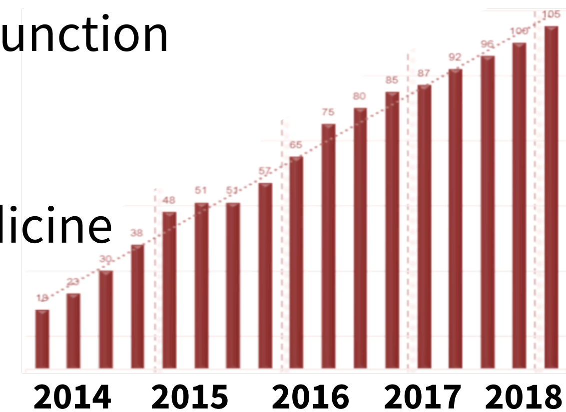
testing ”competing” implementations



THE LIVING HEART PROJECT

a **translational research initiative** to revolutionize cardiovascular science through realistic simulation

- first **four-chamber simulator** for human heart function
- launched in may 2014
- **378 project participants** from **24 countries**
- **163 licensed users** from research, industry, medicine
- **111 organizations** in the **living heart project**
- **research agreement** with **FDA** until **2023**



advance development of safe and effective cardiovascular products and treatments by **uniting engineering, scientific, and biomedical experts** to **deliver validated models** and translate simulation technology into improved patient care

DASSAULT SYSTEMES

collaborative
testing ~~competing~~ implementations

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FEops
simpleware
Pfizer
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inSilicoMED
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Medtronic
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Materialise
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St. Jude Medical
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regulatory agencies

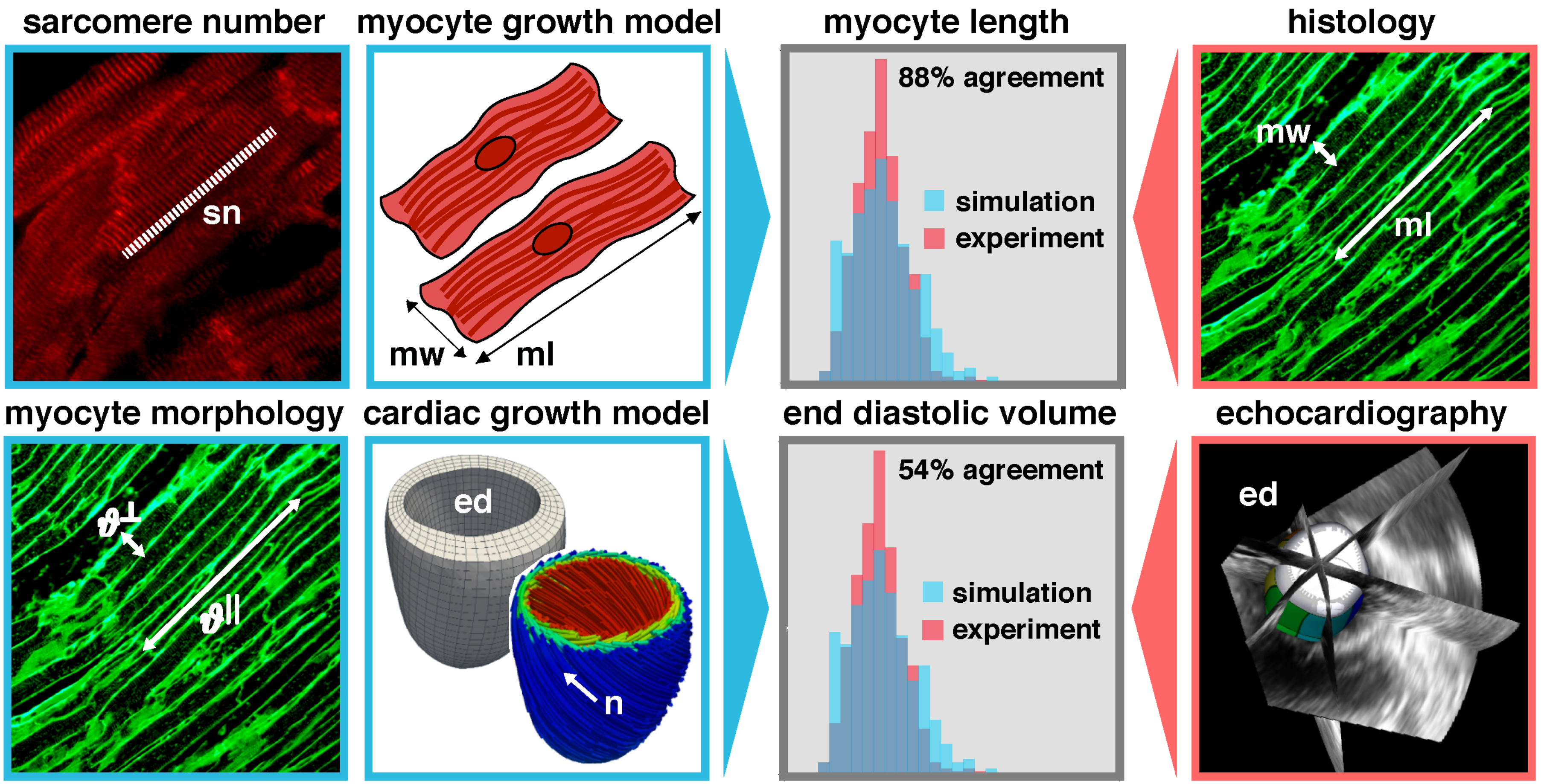
Regulators / Associations

FDA
MDIC

joint mission to translate simulation technology into improved patient care

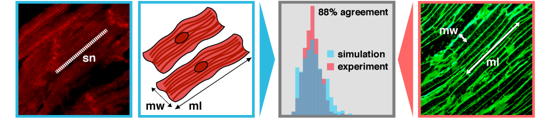
machine learning to characterize heart failure

bottom up: comparing predicted myocyte and cardiac geometries

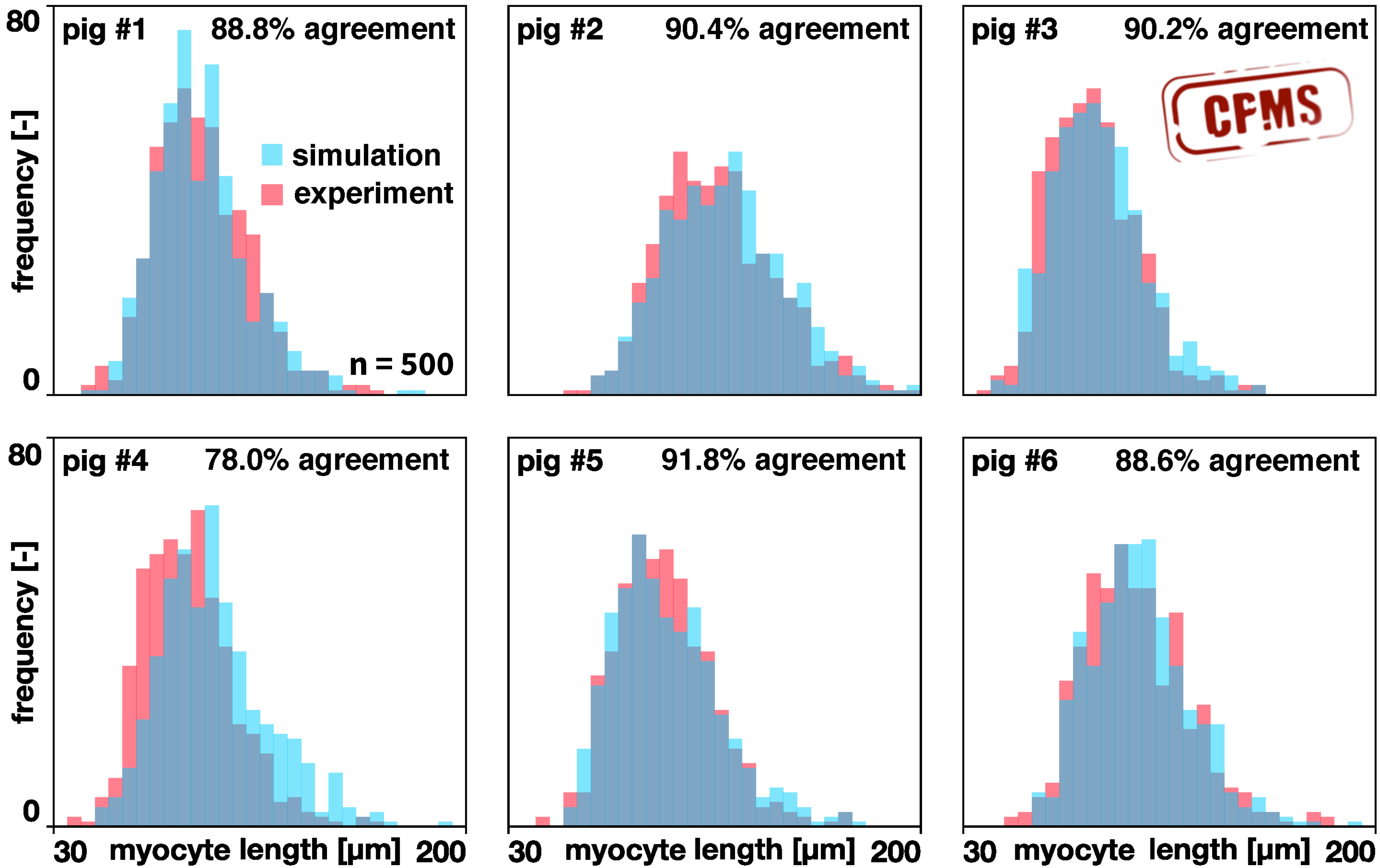


multiscale modeling • hierarchical modeling • bayesian inference • gaussian process regression • uncertainty quantification

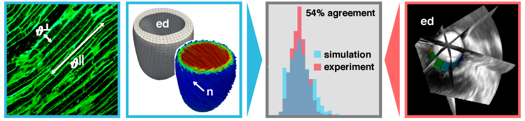
sahli costabal, choy, sack, guccione, kassab, kuhl [2019]



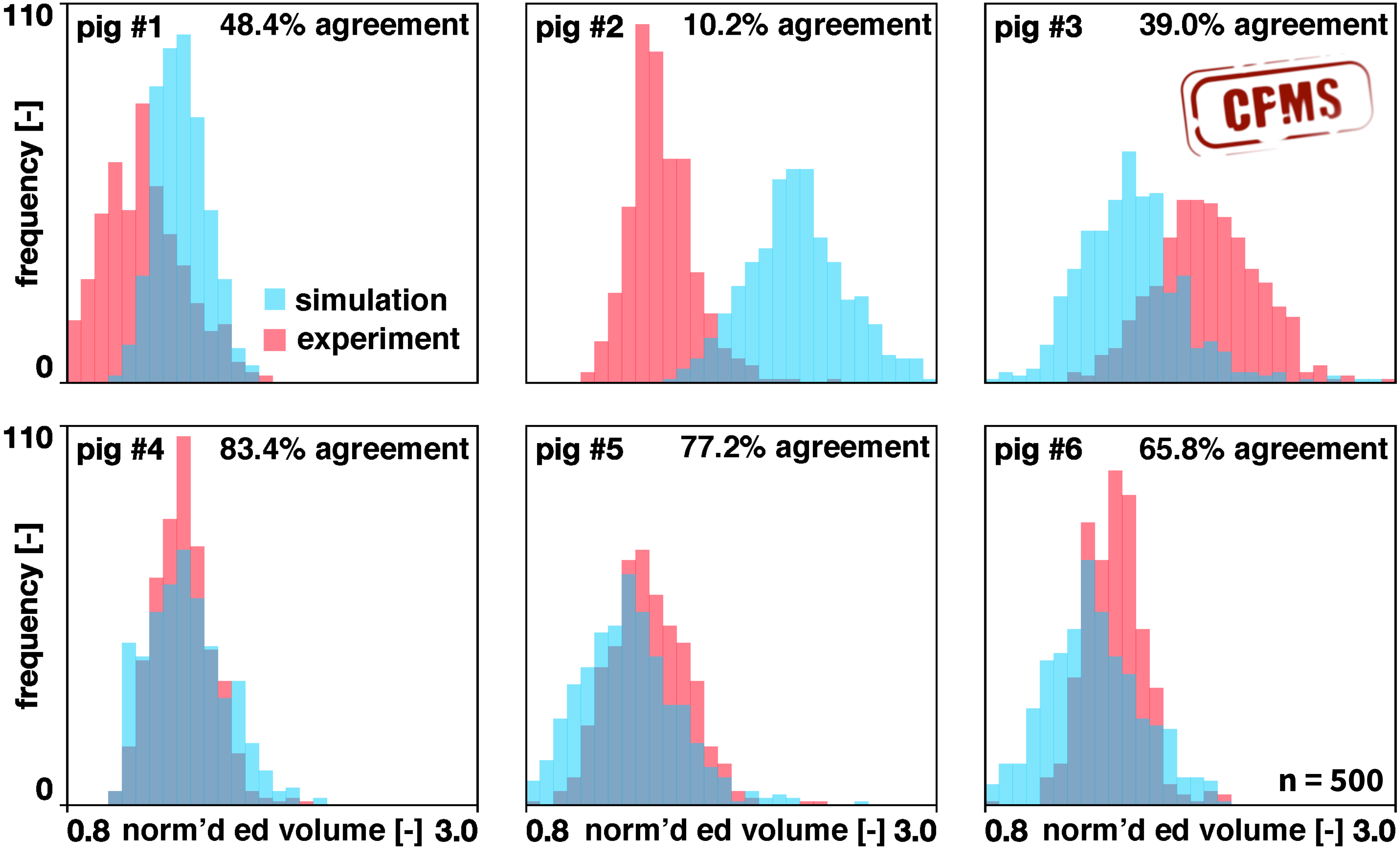
can sarcomere numbers explain myocyte length?



increase in sarcomere number alone explains myocyte lengthening by 88%



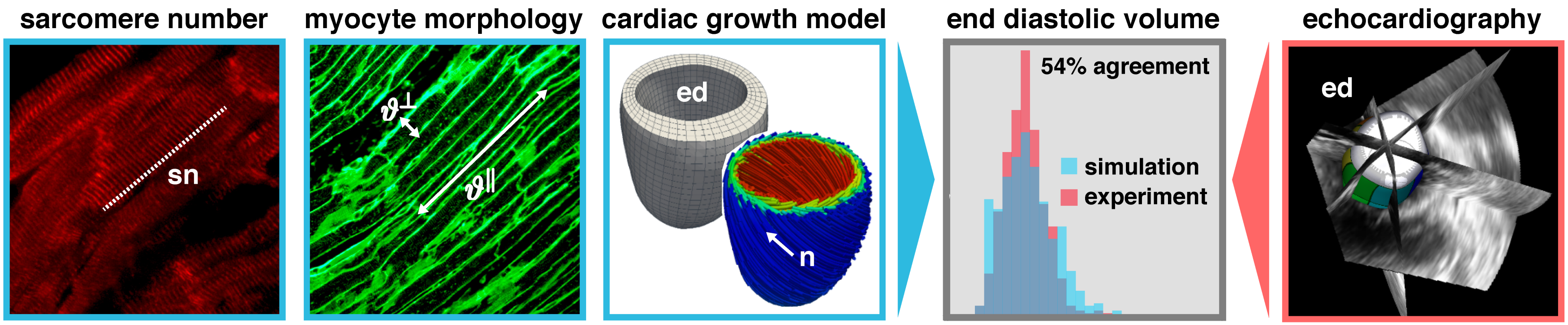
can myocyte lengthening explain cardiac dilation?



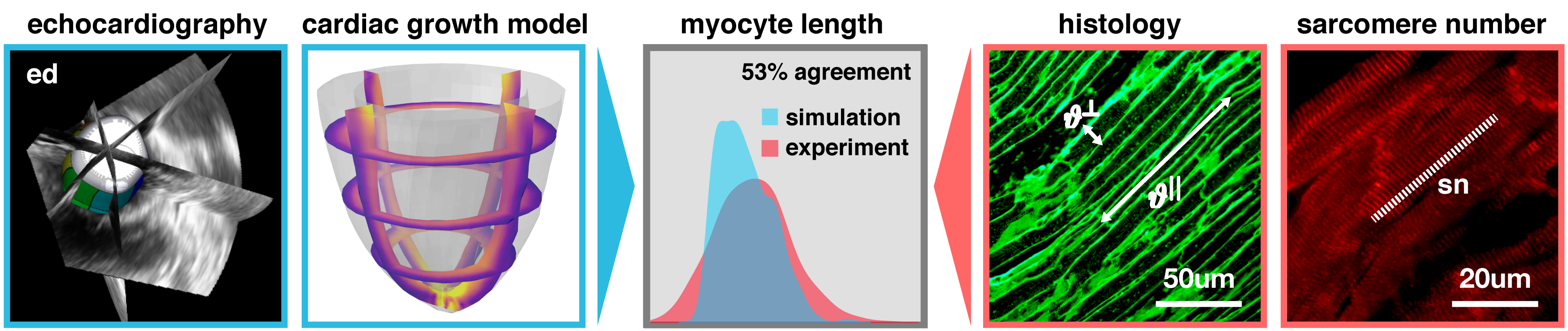
alterations in myocyte length alone explain left ventricular dilation by 54%

machine learning to characterize heart failure

bottom up: comparing predicted cardiac geometries

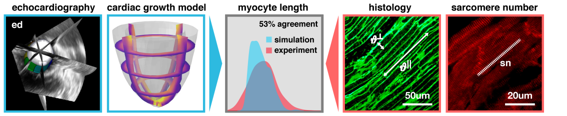


top down: comparing predicted myocyte morphologies

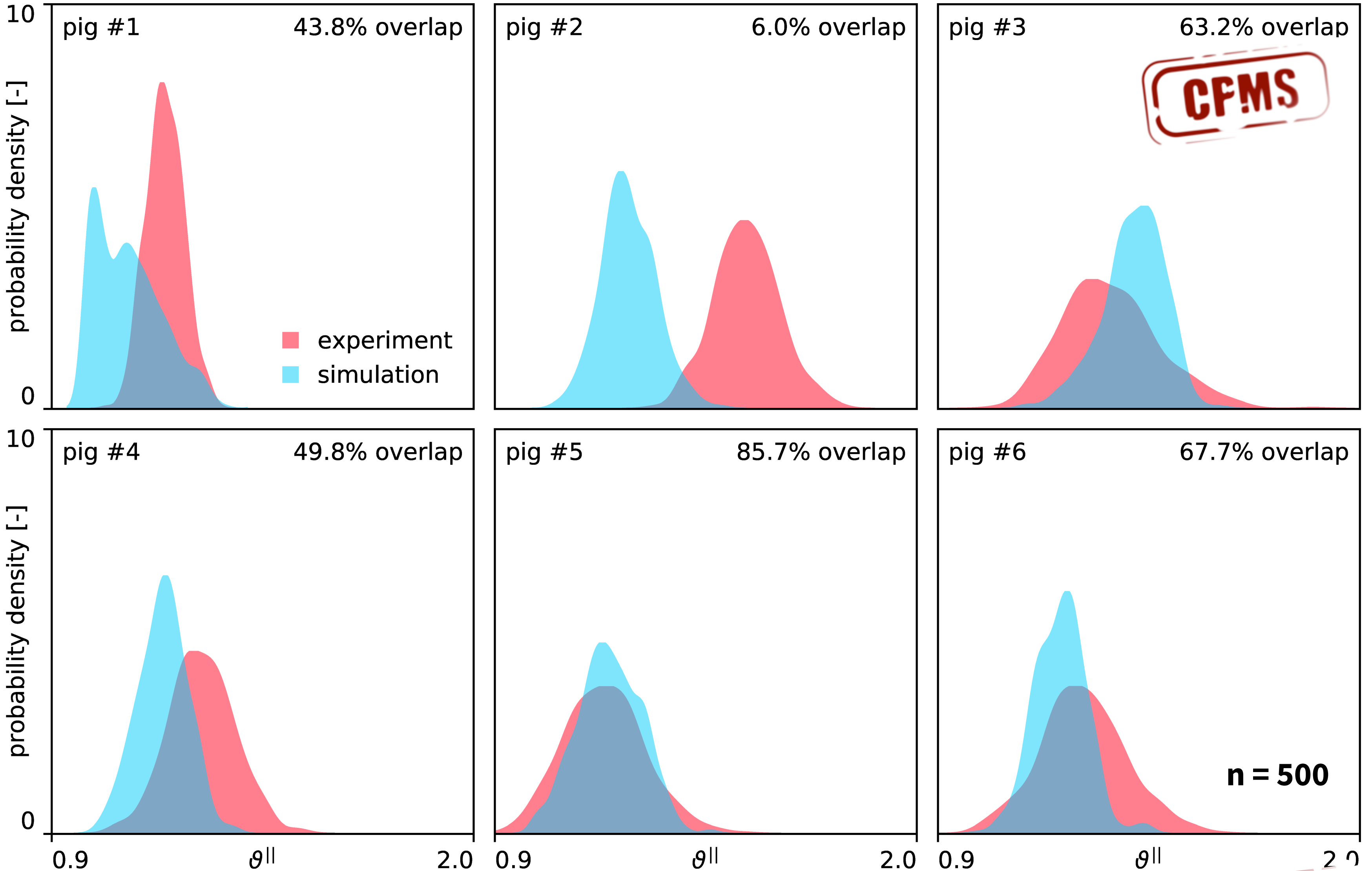


multiscale modeling, hierarchical modeling, Bayesian inference, gaussian process regression, uncertainty quantification

sahli costabal, choy, sack, guccione, kassab, kuhl [2019]
peirlinck, sahli costabal, sack, choy, sack, kassab, guccione, debeule, segers, kassab, kuhl [2019]



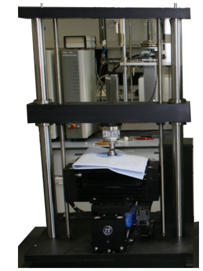
can cardiac dilation explain myocyte lengthening?



alterations in ventricular volume alone explain myocyte lengthening by 53%

last… disagreement is not always bad

gold standard: holzapfel-ogden model



$$\psi = \frac{a}{2b}\exp(b[I_1^{\mathrm{e}} - 3]) + \frac{a_{\mathrm{f}}}{2b_{\mathrm{f}}}[\exp(b_{\mathrm{f}}[I_{4\mathrm{f}}^{\mathrm{e}} - 1]^2) - 1]$$
$$+ \frac{a_{\mathrm{s}}}{2b_{\mathrm{s}}}[\exp(b_{\mathrm{s}}[I_{4\mathrm{s}}^{\mathrm{e}} - 1]^2) - 1] + \frac{a_{\mathrm{fs}}}{2b_{\mathrm{fs}}}[\exp(b_{\mathrm{fs}}(I_{8\mathrm{fs}}^{\mathrm{e}})^2) - 1]$$

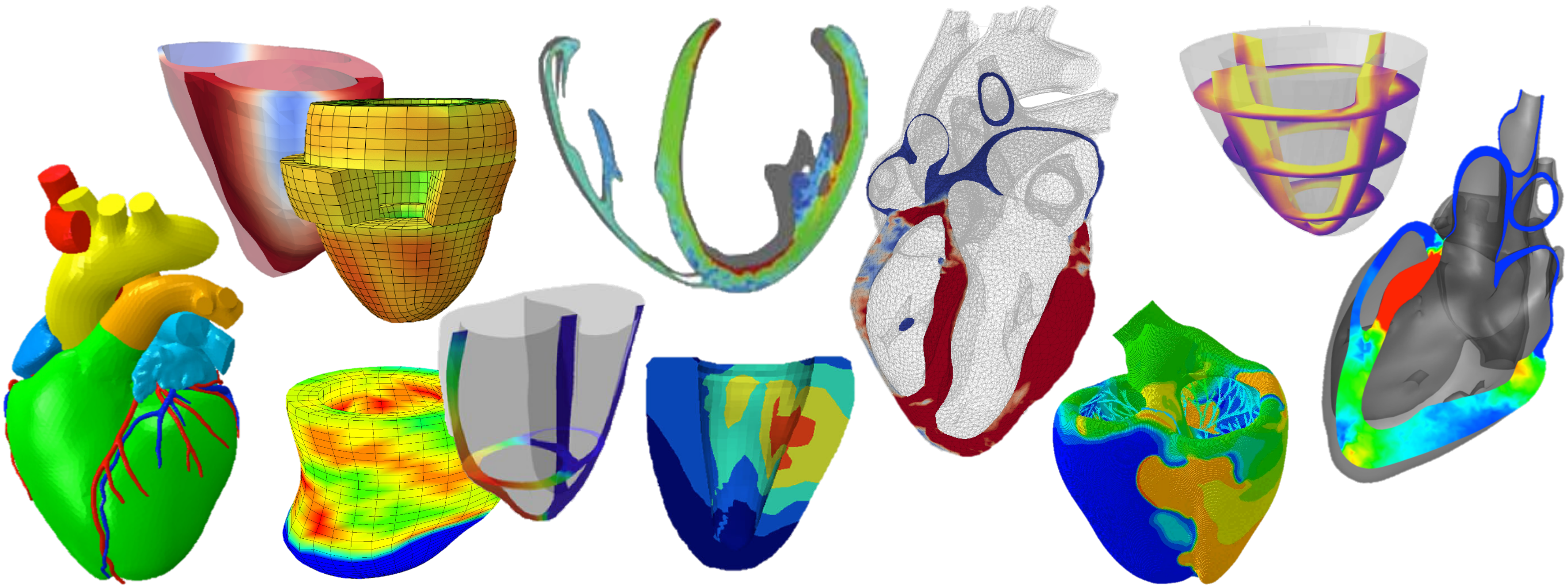
	a [Pa]	b [-]	a_{f} [Pa]	b_{f} [-]	a_{s} [Pa]	b_{s} [-]	a_{fs} [Pa]	b_{fs} [-]
original	798.7	8.61	13886.7	15.87	4661.0	9.04	216.0	9.47
pig #1	69.6	4.34	229.6	8.34	31.8	7.23	18.7	1.78
pig #2	89.5	5.17	295.0	9.93	40.9	8.61	24.0	2.11
pig #3	74.9	4.34	247.1	8.34	34.3	7.23	20.1	1.78
pig #4	62.9	4.32	207.4	8.29	28.8	7.19	16.9	1.77
pig #5	101.1	5.80	333.4	11.13	46.3	9.65	27.2	2.37
pig #6	83.2	4.40	274.5	8.44	38.1	7.32	22.3	1.80
mean	80.2	4.73	264.5	9.08	36.7	7.87	21.5	1.94
std	±13.9	±0.62	±46.0	±1.19	±6.4	±1.03	±3.8	±0.25
discrepancy	0.10	0.55	0.02	0.57	0.01	0.87	0.10	0.17

discrepancies of one-two orders of magnitude have initiated paradigm shift
now it is generally accepted that ex vivo testing overestimates stiffnesses

holzapfel, ogden [2010], sahli costabal, choy, sack, guccione, kassab, kuhl [2019]

credible enough?

perspectives from cardiac growth and remodeling



- testing ”**competing**” **implementations** increases **credibility.**
- a true **metric for credibility** is how many people **use the model.**
- to establish **credibility**, we should **collaborate** and **not compete.**

FRANCISCO SAHLI COSTABAL • MATHIAS PEIRLINCK • KEVIN SACK • SUSY CHOY • JULIUS GUCCIONE • GHASSAN KASSAB • TOM BATTISTI • STEVE LEVINE

NIH U01HL119578 - multiscale laws of myocardial growth and remodeling