SILICOFCM

Decision Support System for prediction of Heart Failure disease

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3rd CONFERENCE ON NONLINEARITY
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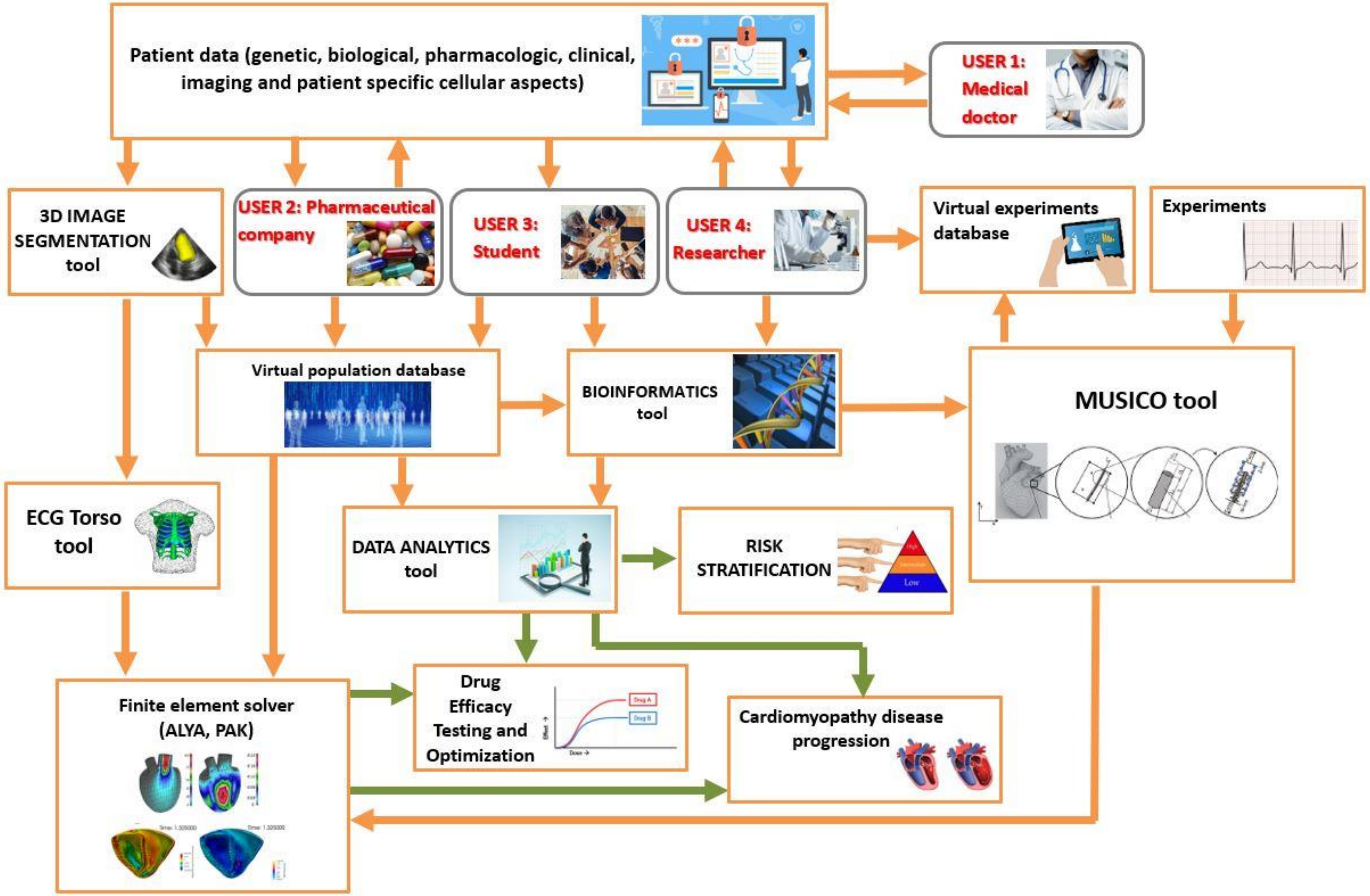
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

SILICOFCM Scope and Concept

- SILICOFCM aims to develop a computational platform for *in silico* clinical trials of Familial cardiomyopathies (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.
- The SILICOFCM platform is based on the integrated multidisciplinary and multiscale methods for analysis of patient-specific data and development of patient-specific models for monitoring and assessment of patient condition from current through the progression of disease.



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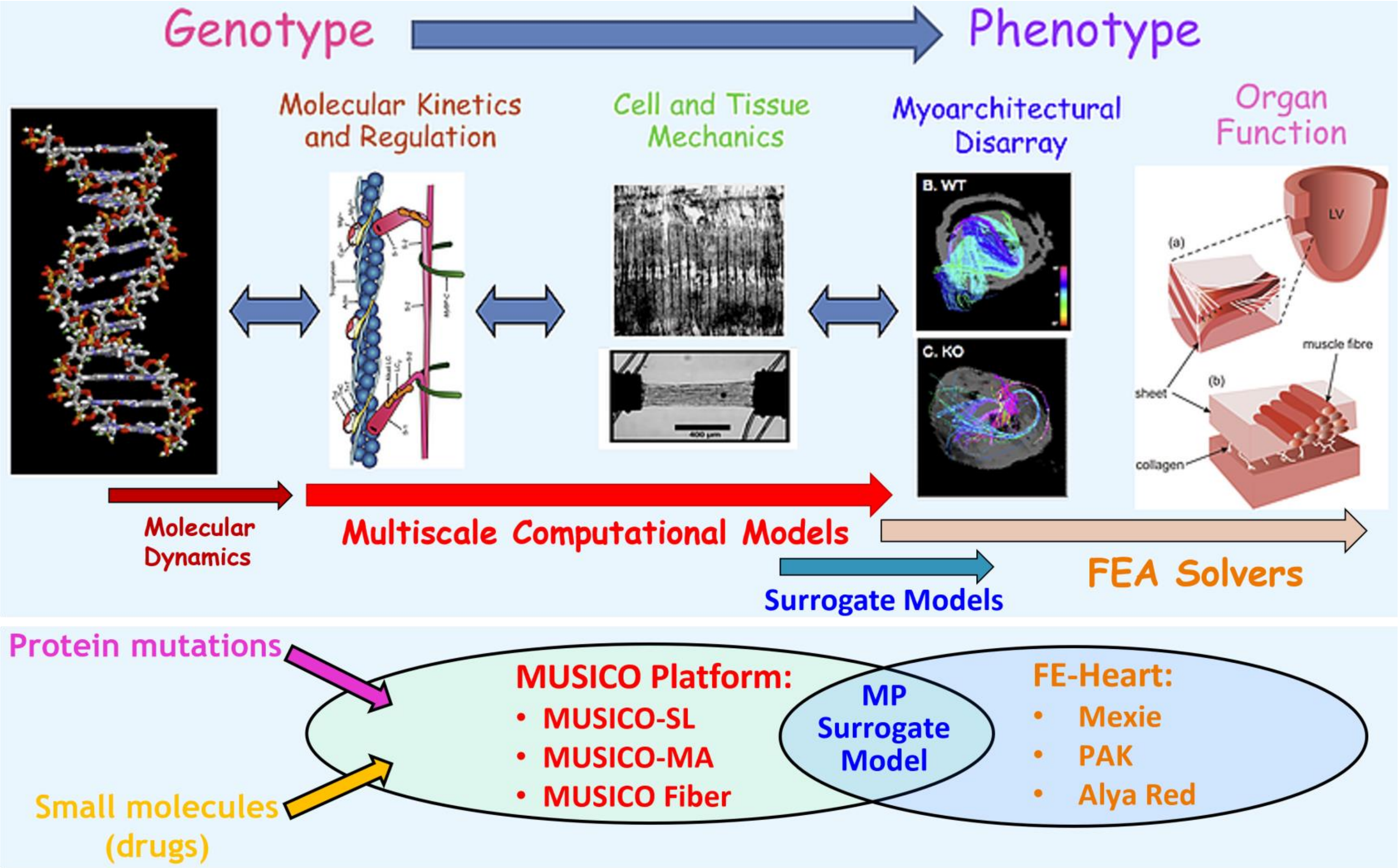
Multiscale Integration of Experiments at Molecular, Cellular and Organ Level



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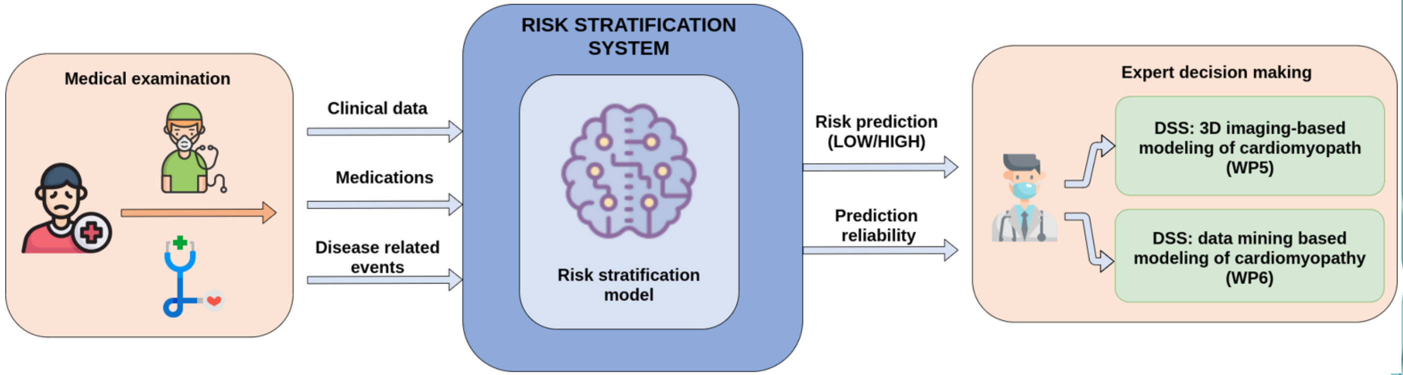
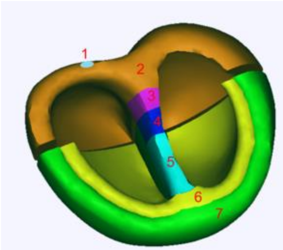
Set up R&D computation pipelines for drug testing

Scenario #5 Data Analytics Tool (Risk Stratification System)

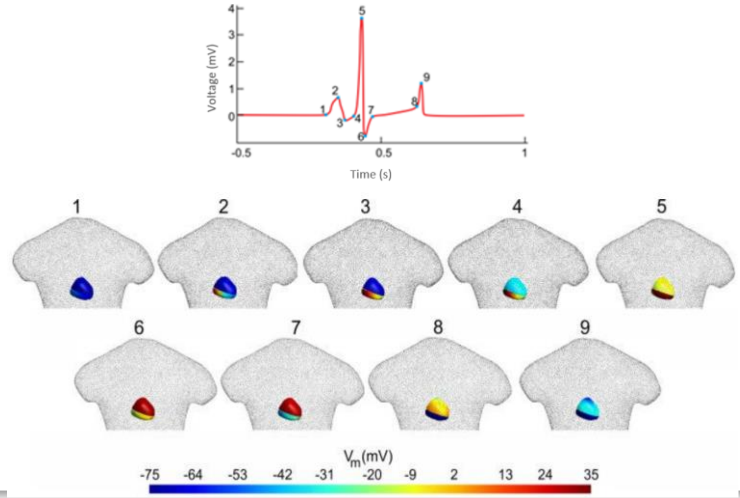


Scenario #4 Electric Field of Heart Model Embedded in Torso



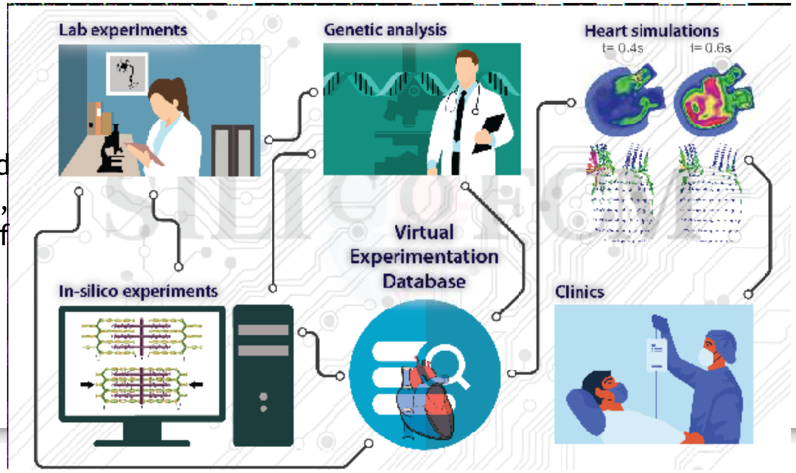
1) Sinoatrial node
2) Atria
3) Atrioventricular node
4) His bundle
5) Bundle fibers
6) Purkinje fibers
7) Ventricular myocardium

PAK
Finite element solver



Scenario #6 From Genetics to Heart Simulations – population of virtual experimentation database

Three case scenarios are being explored using MUSICO tool: Myosin mutations, Mutations of Cardiac troponin C, Effects of drugs on heart function.



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Target \ prediction	Model **MD**	Expert **E**	Consortium **C**	Joint **J**
NYHA	**0.30 ± 0.48**	0.84 ± 0.69	0.56 ± 0.34	0.43 ± 0.29
LA	1.70 ± 0.82	1.69 ± 0.97	**1.66 ± 0.70**	1.68 ± 0.50
LA_vol	**1.00 ± 0.82**	1.25 ± 0.98	1.13 ± 0.63	0.84 ± 0.51
LVIDd	**0.80 ± 0.63**	1.09 ± 0.91	1.00 ± 0.77	0.74 ± 0.49
LVIDs	**0.50 ± 0.71**	1.02 ± 0.86	0.88 ± 0.68	0.69 ± 0.29
LVEF	**0.90 ± 0.88**	1.32 ± 0.90	1.28 ± 0.79	1.09 ± 0.65

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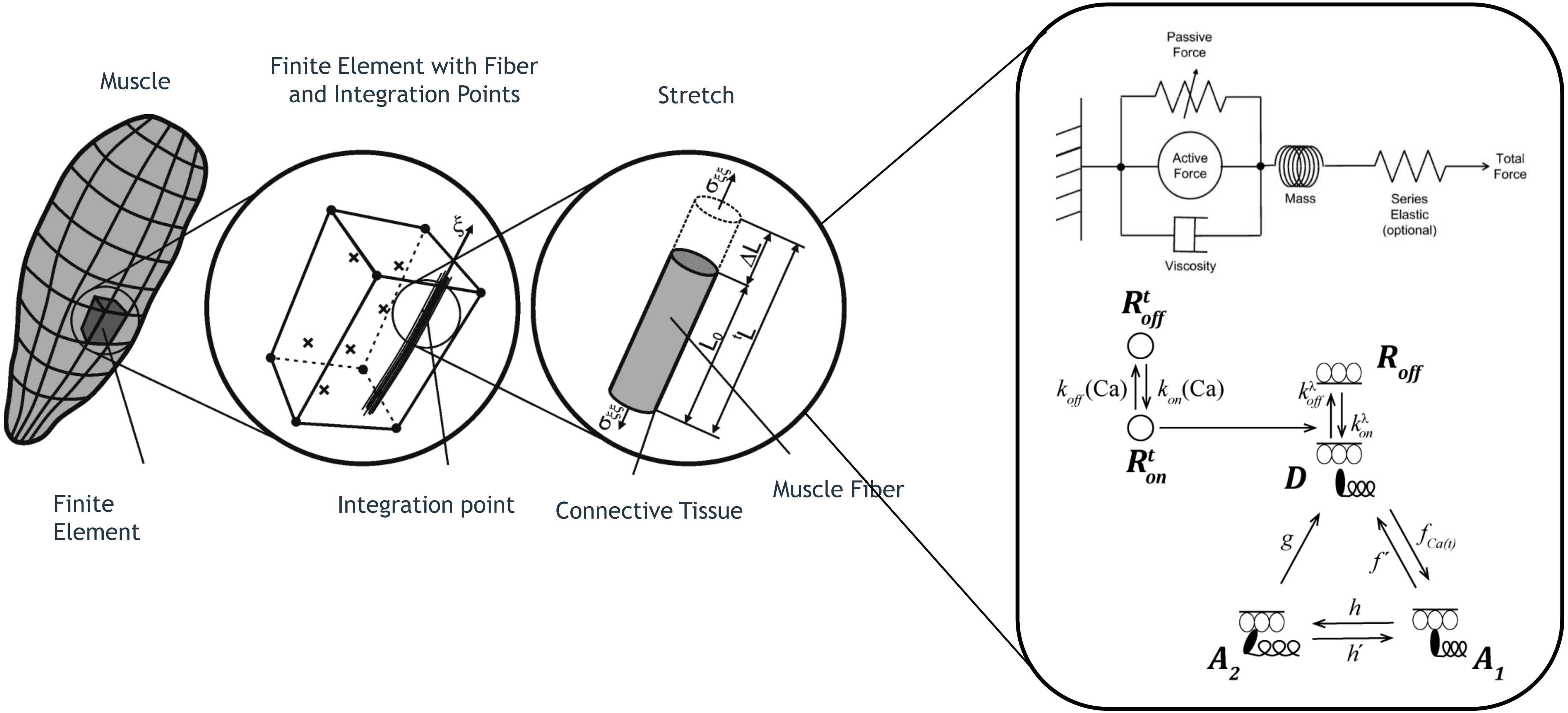
Linking MP Micromodel and FE Biomechanical Simulation TWO-scale Muscle MODEL

MP micromodel and Physiological macromodel:
Different time/space scale Complex computation



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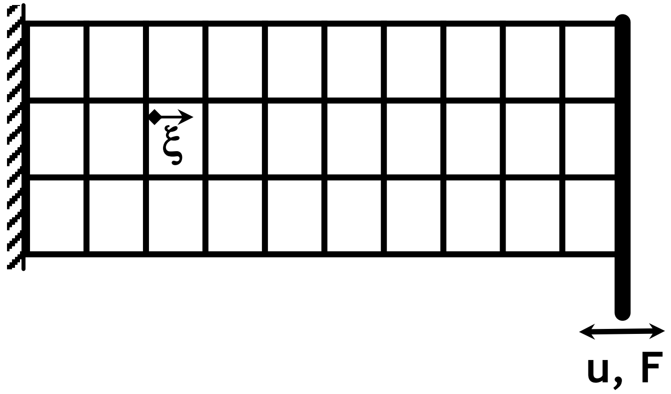
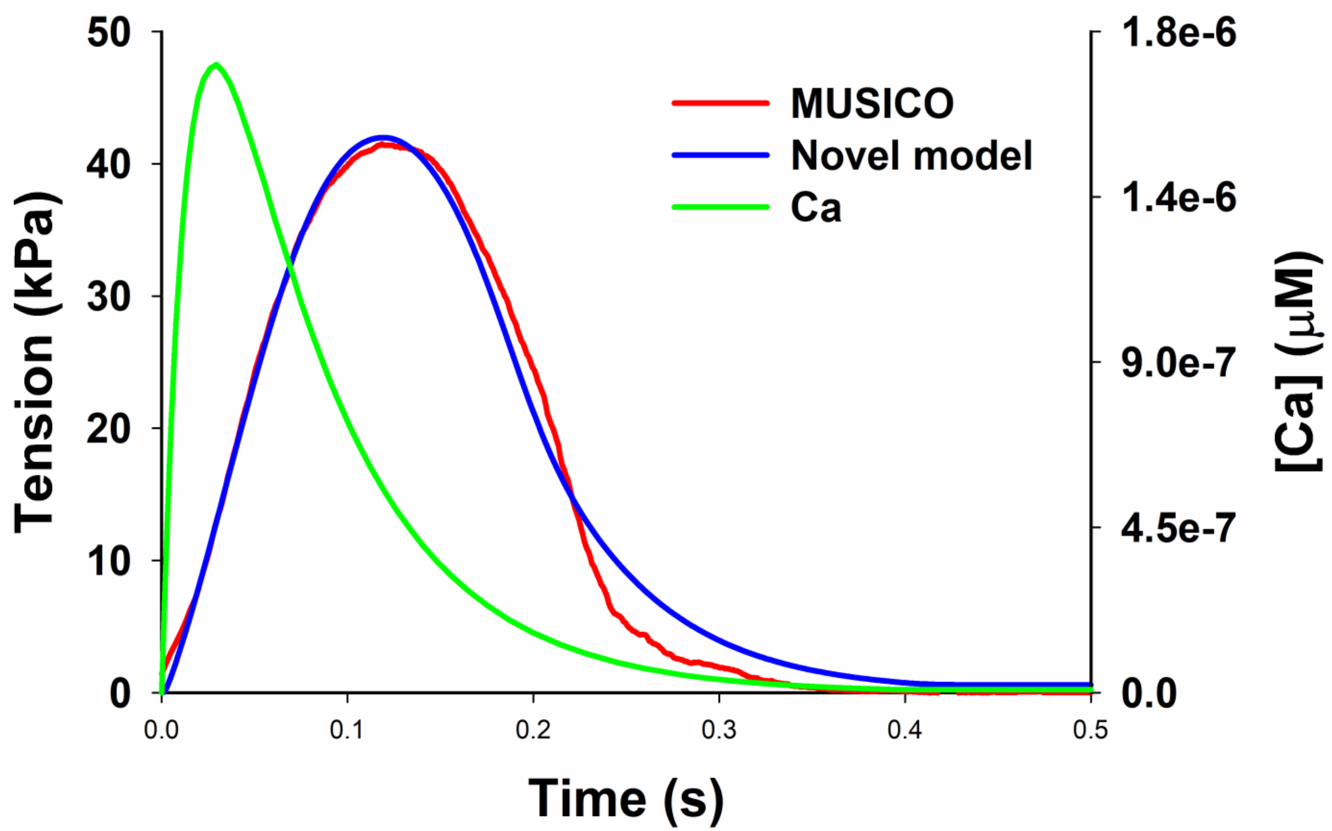
Linking MP Micromodel and FE Biomechanical Simulation of Isometric Twitch



Execution times (s)	
MUSICO	27881.433
FE-MP	37.376



MEXIE Simulations

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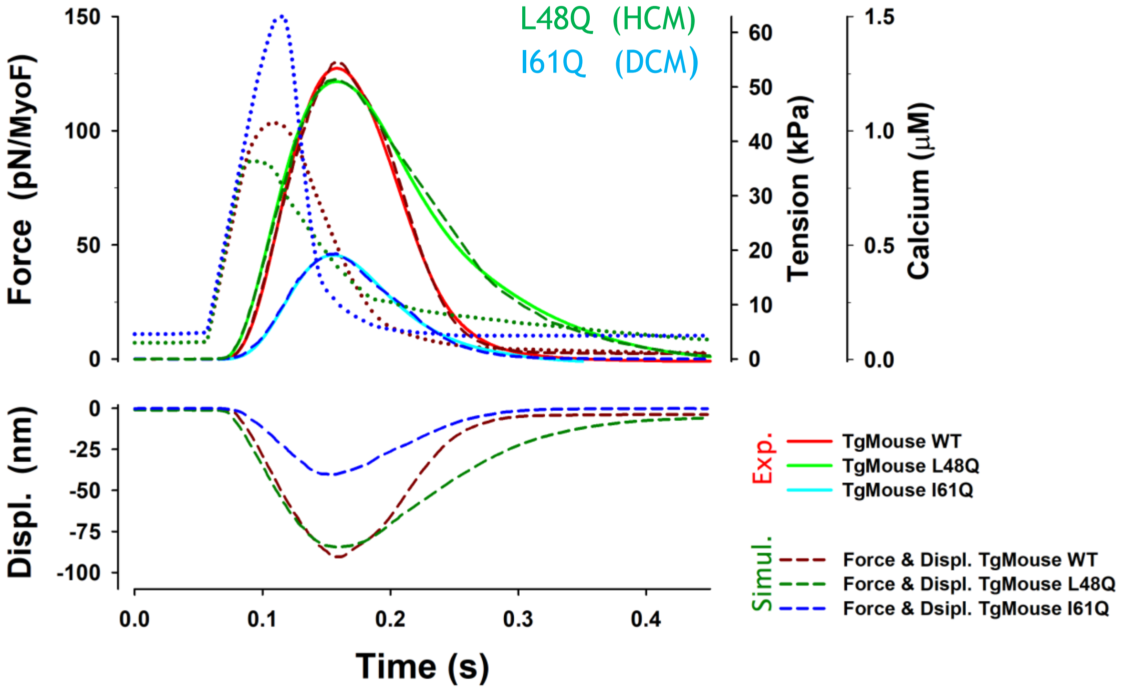
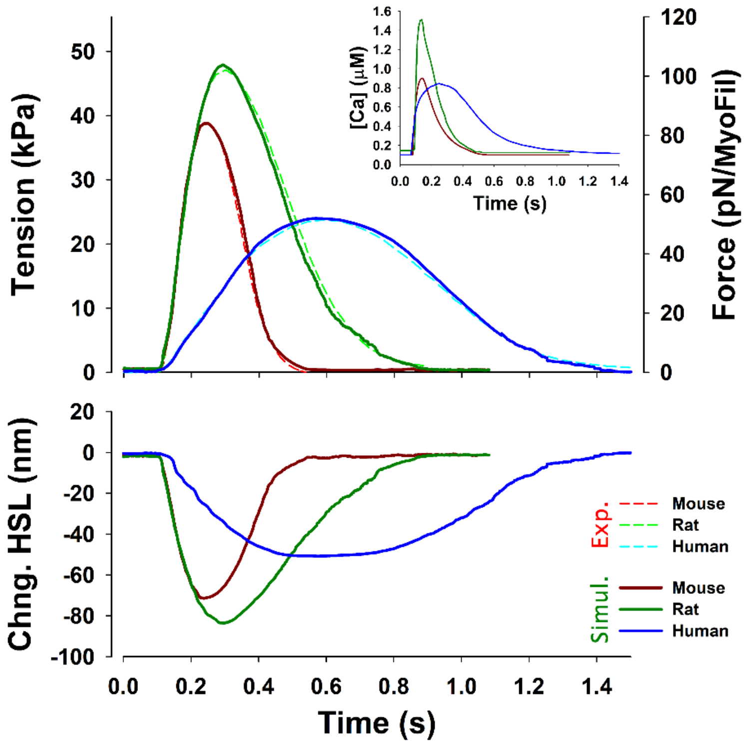
Effect of Mutations in Troponin C (TnC) and Myosin Isoforms from Mouse to Human

TnC Mutations in Mouse



Mijailovich et al., 2021,
J Mol Cell Cardiol, 155:112-124

Myosin Isoforms across the Species



	%α	%β
Mouse	100	0
Rat	75	25
Human	5	95

Prodanovic et al., 2022,
Int. J. Mol. Sci, 23, 1135

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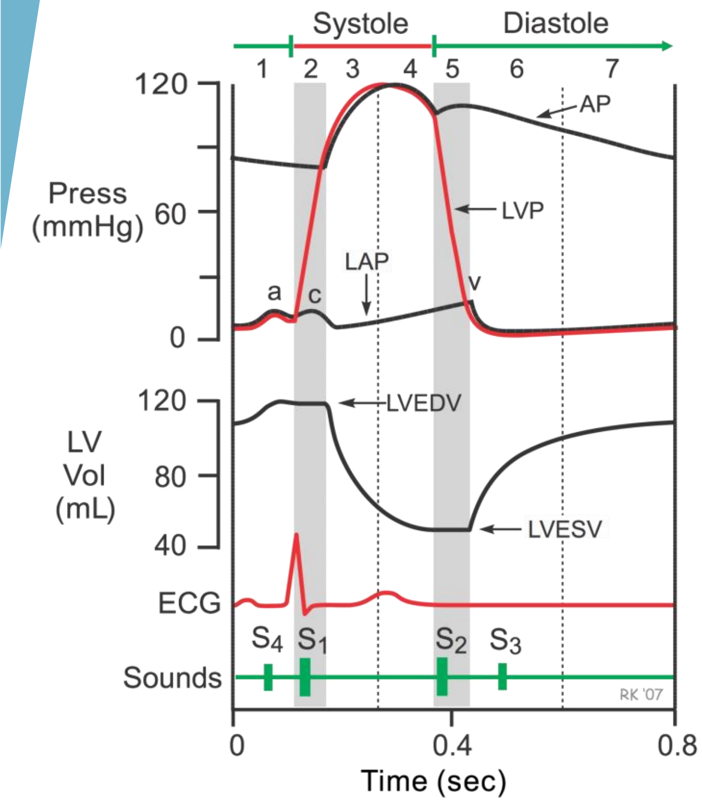
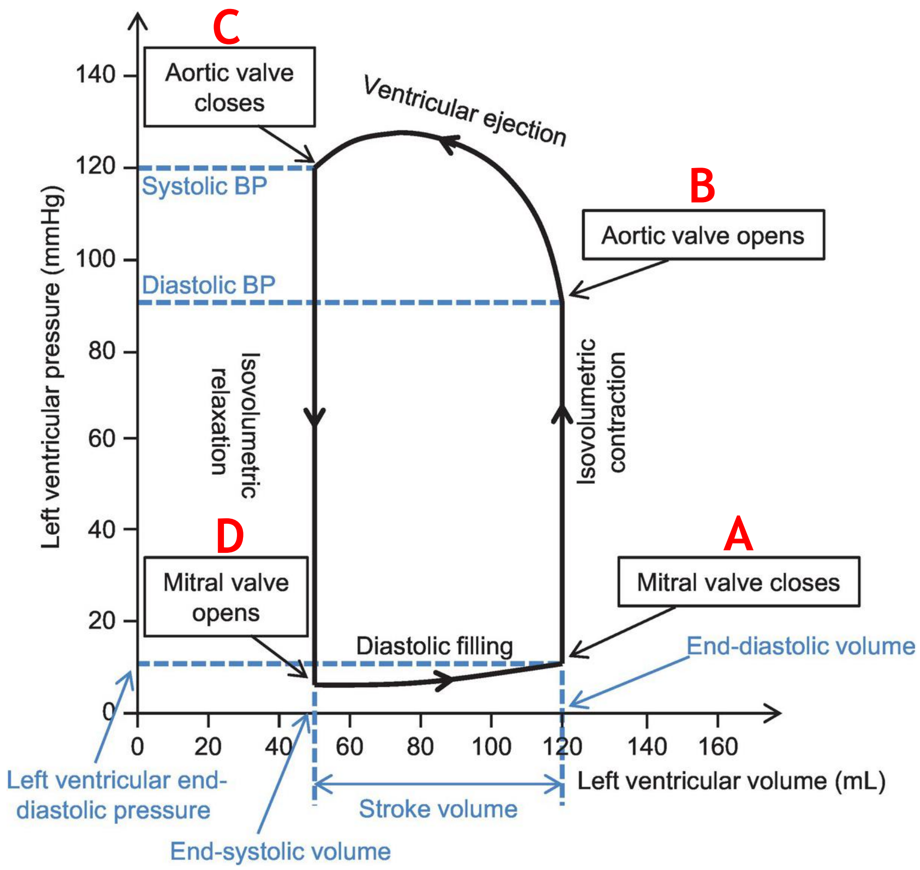
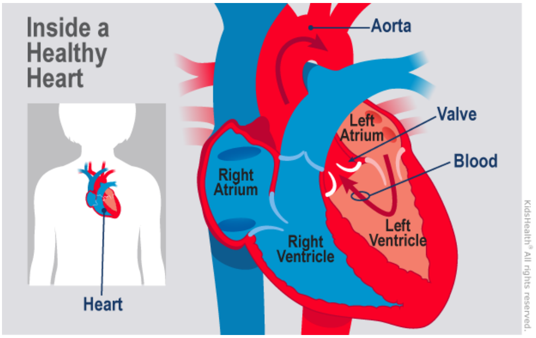
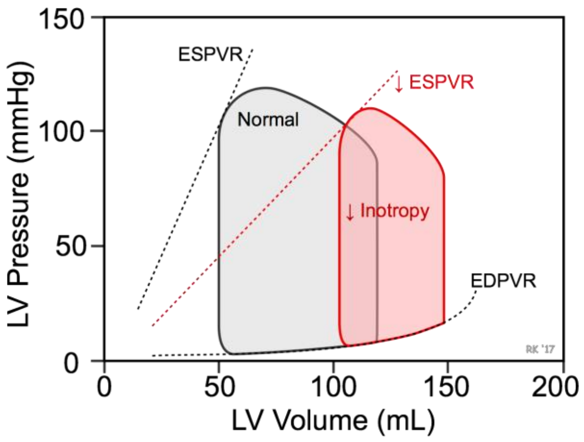
Left Ventricular Pressure-Volume









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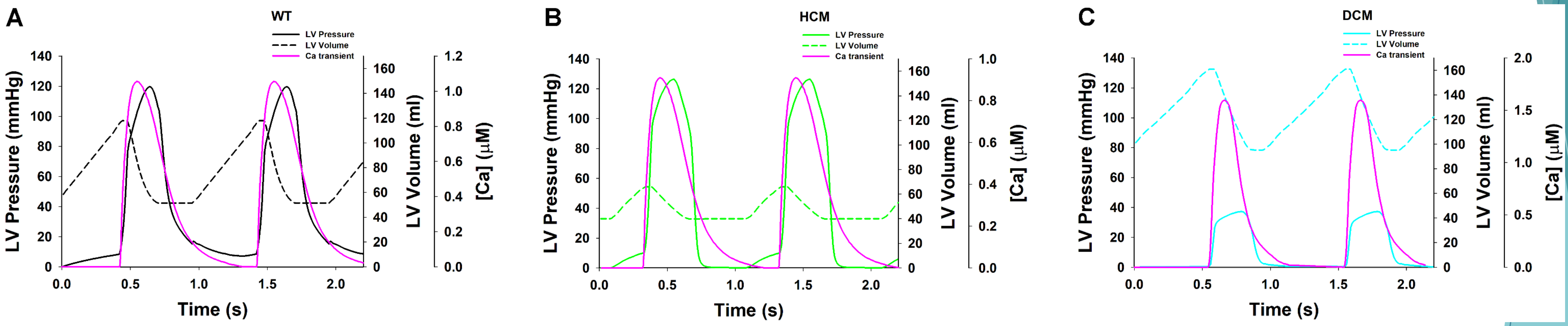
Left Ventricular Calcium, Pressure and Volume Traces During Two Heartbeats

Healthy | **Hypertrophic Cardiomyopathy** | **Dilated Cardiomyopathy**



Mexie Simulations

Human Left Ventricle

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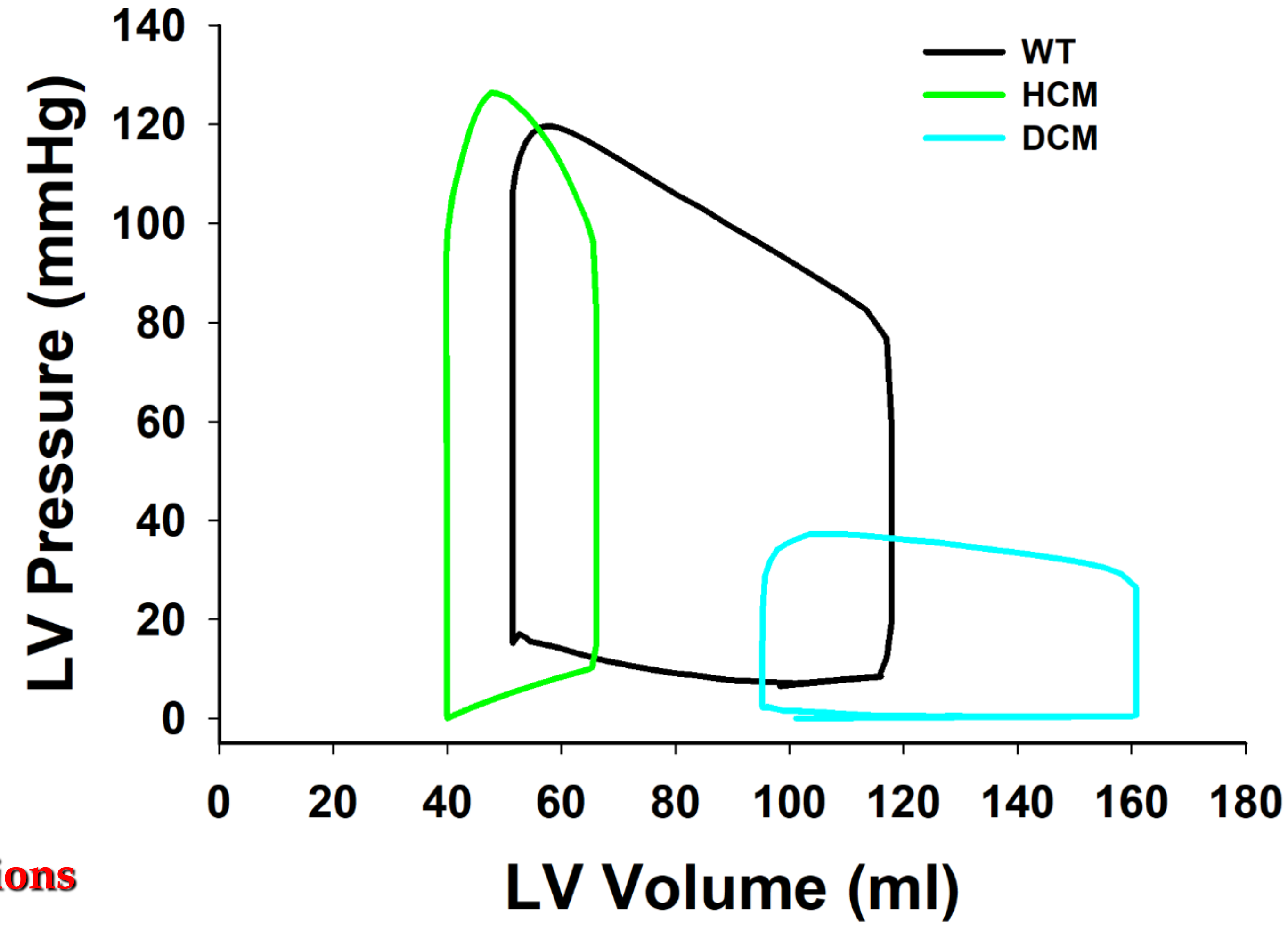
Human Left Ventricular Pressure-Volume



Mexie Simulations

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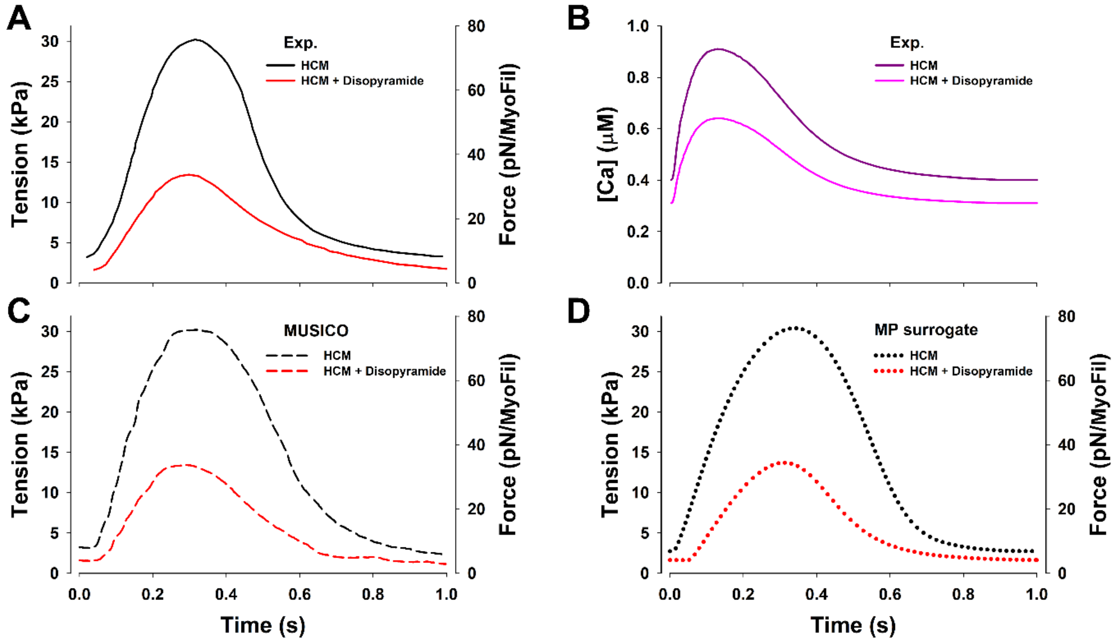
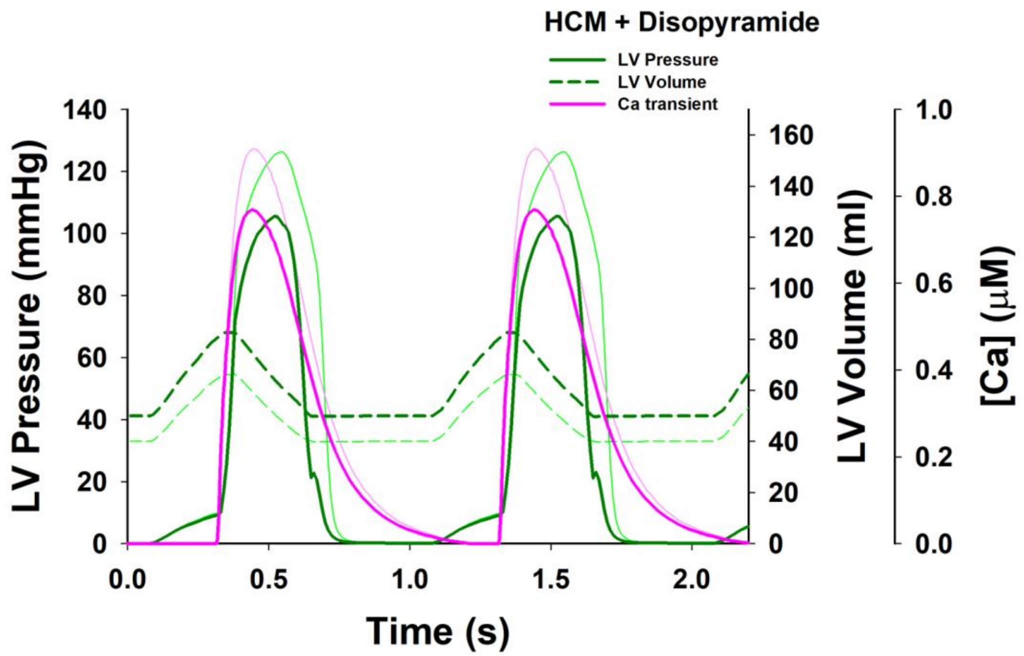
The Effect of Disopyramide on HCM Muscle and Left Ventricle

Modulation of [Ca^{2+}] transients

Human Cardiac Muscle Fiber



Human Left Ventricle



Mexie Simulations

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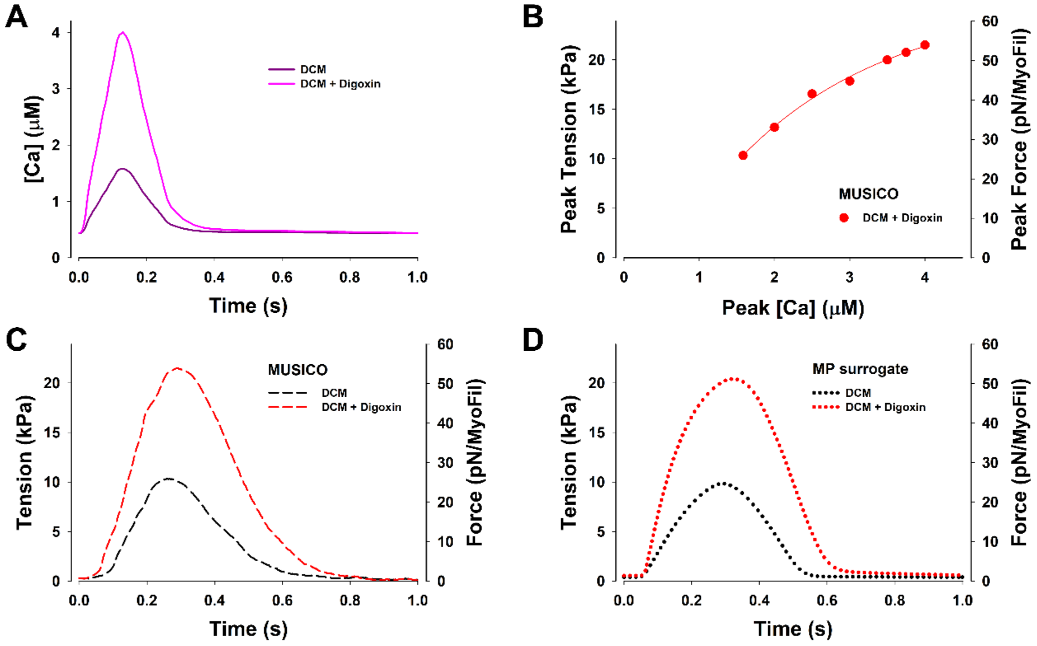
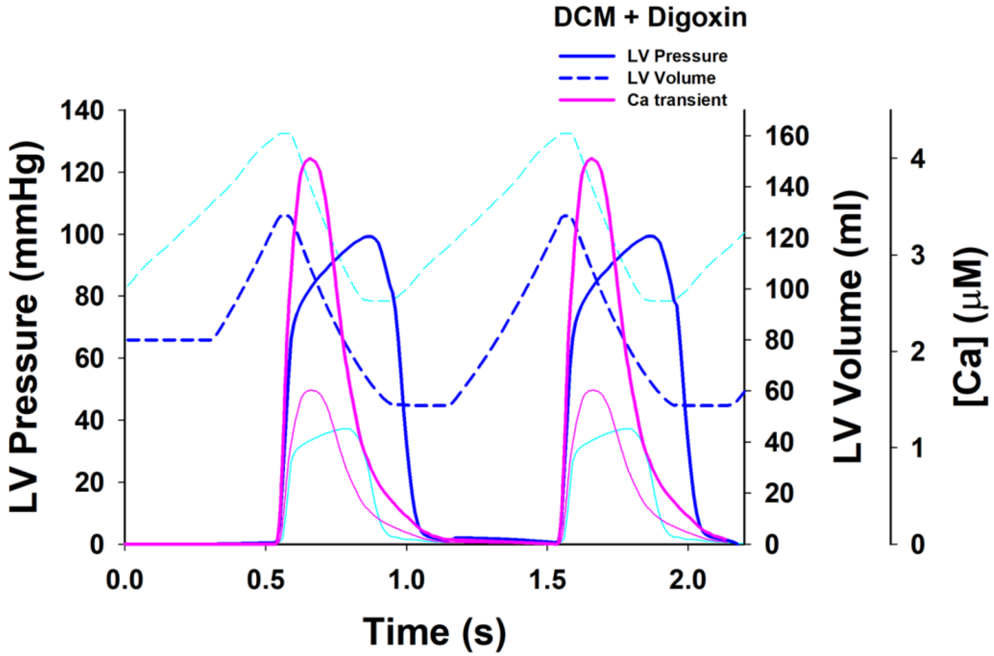
The Effect of Digoxin on DCM Muscle and Left Ventricle

Modulation of [Ca^{2+}] transients

Human Cardiac Muscle Fiber



Human Left Ventricle



Mexie Simulations

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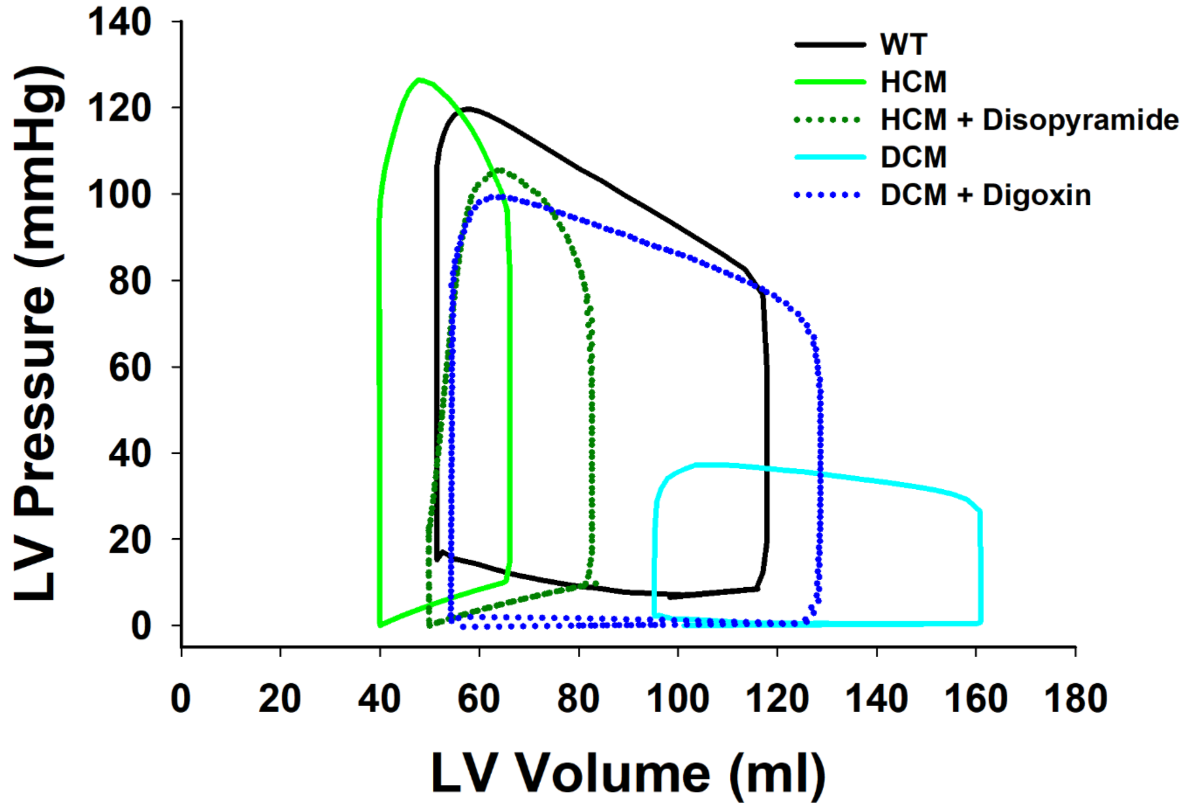
The Effect of Disopyramide and Digoxin on HCM and DCM Left Ventricle Function



Mexie Simulations

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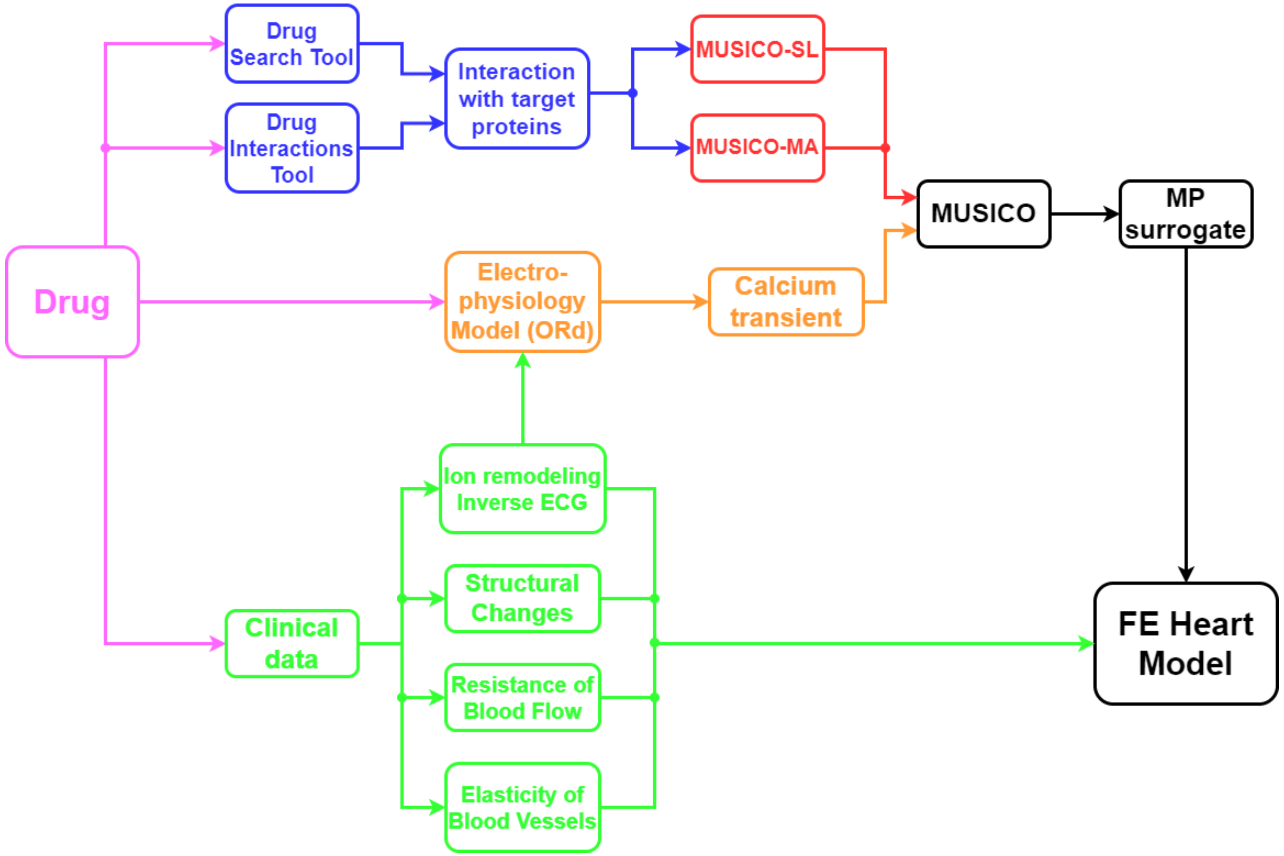
SILICOFCM Workflow for drug testing



3 characteristic pathways of drug flow:

(i) for drugs acting at the level of contractile proteins;

(ii) at the level of regulation of transient intracellular calcium concentration;

(iii) at the level tissue remodeling and/or by modulation of blood vessel elasticity, i.e. resistance to blood flow and cardiac output.

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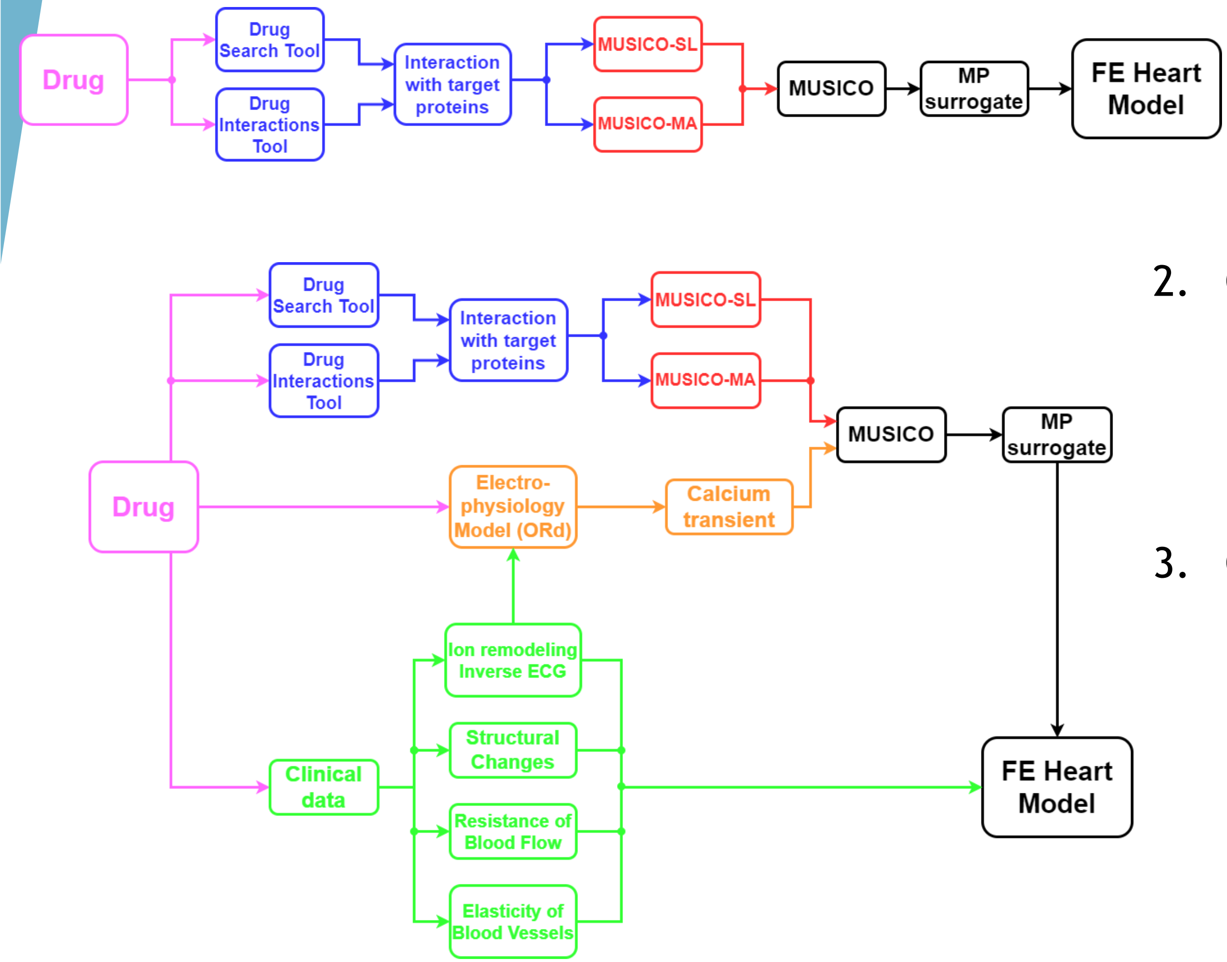
SILICOFCM Workflow for drug testing



1. Modulation of [Ca^{2+}] transients
   - HCM – Disopyramide, which lowers peak and baseline levels of [Ca^{2+}] transient during twitch contractions
   - DCM – Digoxin, which increases peak of [Ca^{2+}] transient during twitch contractions, but does not change time to peak and relaxation time
2. Changes in kinetic parameters
   - HCM – Mavacamten, which is associated with regulation of kinetics rates of transition between disordered myosin detached states and ordered parked state
   - DCM – dATP, which modulates crossbridge cycle rates
3. Changes in macroscopic parameters
   - HCM – Entresto, which acts on remodeling of heart ventricle walls and modulates the elasticity of blood vessels, typically reducing resistance to blood flow and improving cardiac output in HCM

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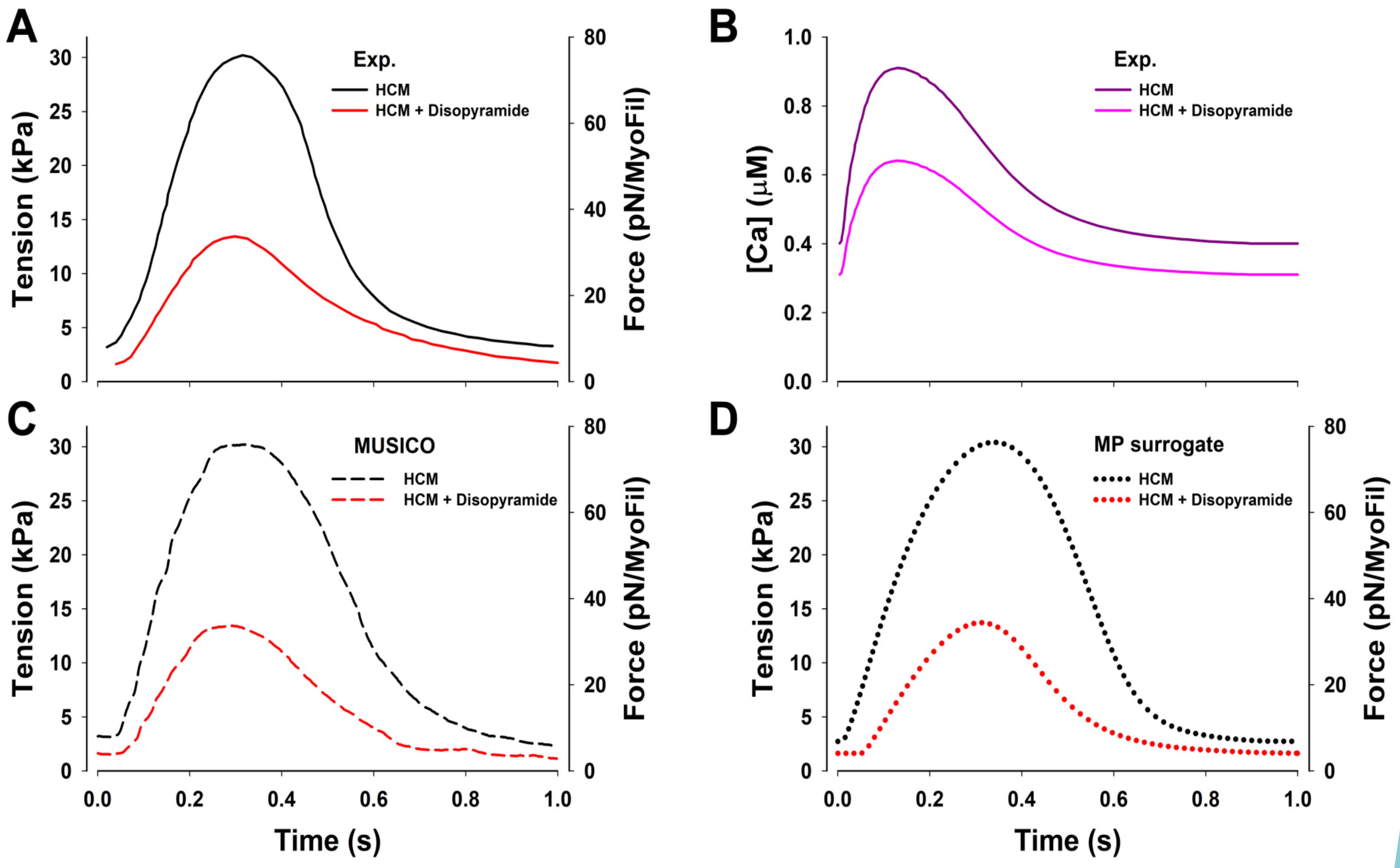
Modulation of [Ca^{2+}] transients - Disopyramide

For treating
Hypertrophic Cardiomyopathy (HCM)

Disopyramide lowers peak and baseline levels of [Ca^{2+}] transient during twitch contractions!

All MUSICO parameters are the same!
The only change is in the peak of [Ca^{2+}] transient in the presence of 5 μM of disopyramide



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Modulation of $[Ca^{2+}]$ transients - Digoxin

For treating
Dilated Cardiomyopathy (DCM)

Digoxin increases peak of $[Ca^{2+}]$ transient during twitch contractions but does not change time to peak and relaxation time!

All MUSICO parameters are the same, and the only change is in the peak of $[Ca^{2+}]$ transients

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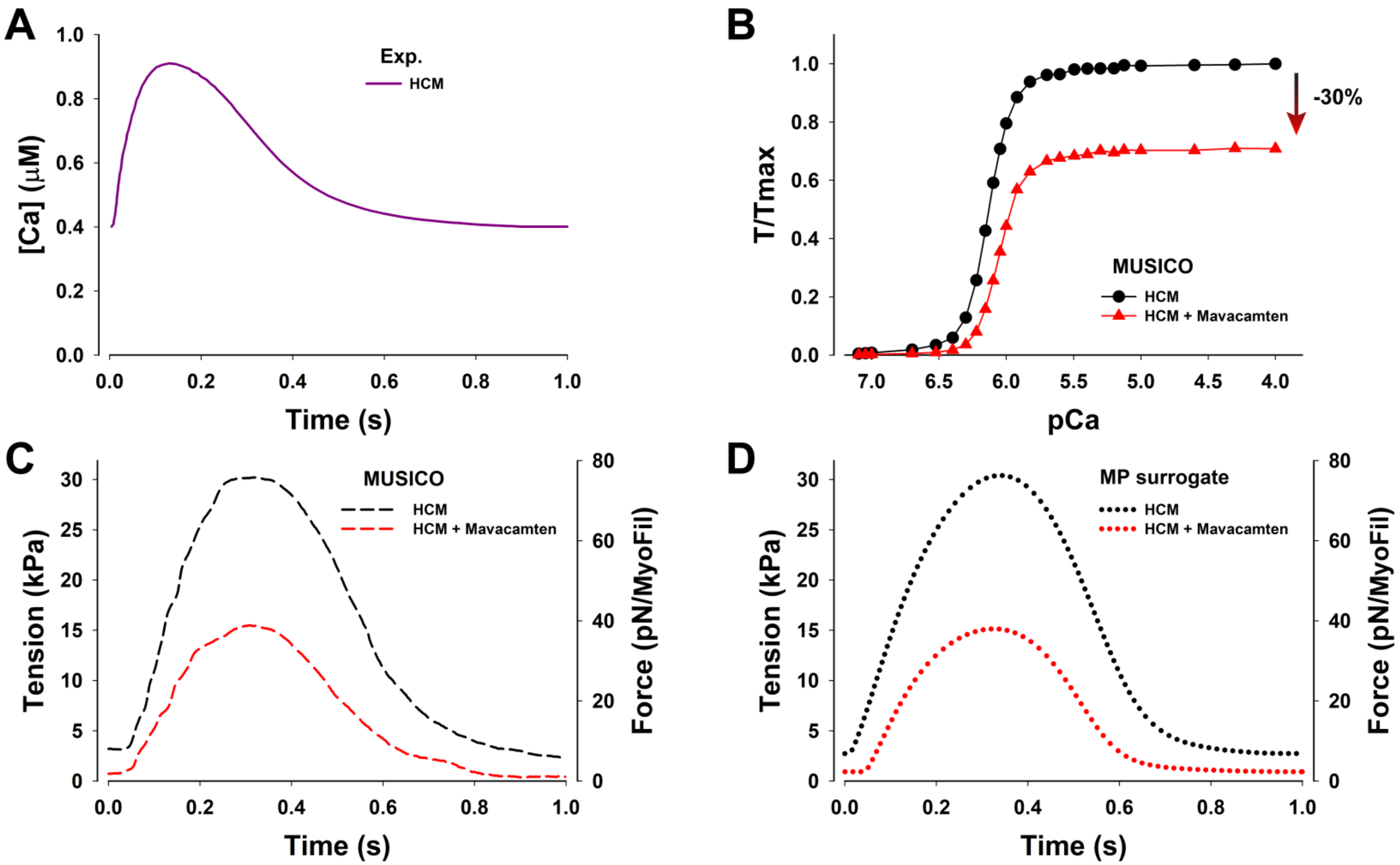
Changes in kinetic parameters - Mavacamten

For treating
Hypertrophic Cardiomyopathy (HCM)

Mavacamten is associated with regulation of kinetics rates of transition between disordered myosin detached states and ordered parked state!

The 1μm Mavacampten decreases tension at full Ca^{2+} activation by 30% and twitch peak for ~ 50 %.

This was achieved by 3.5-fold increase in the transition rate from M.D.Pi to "Parked state"



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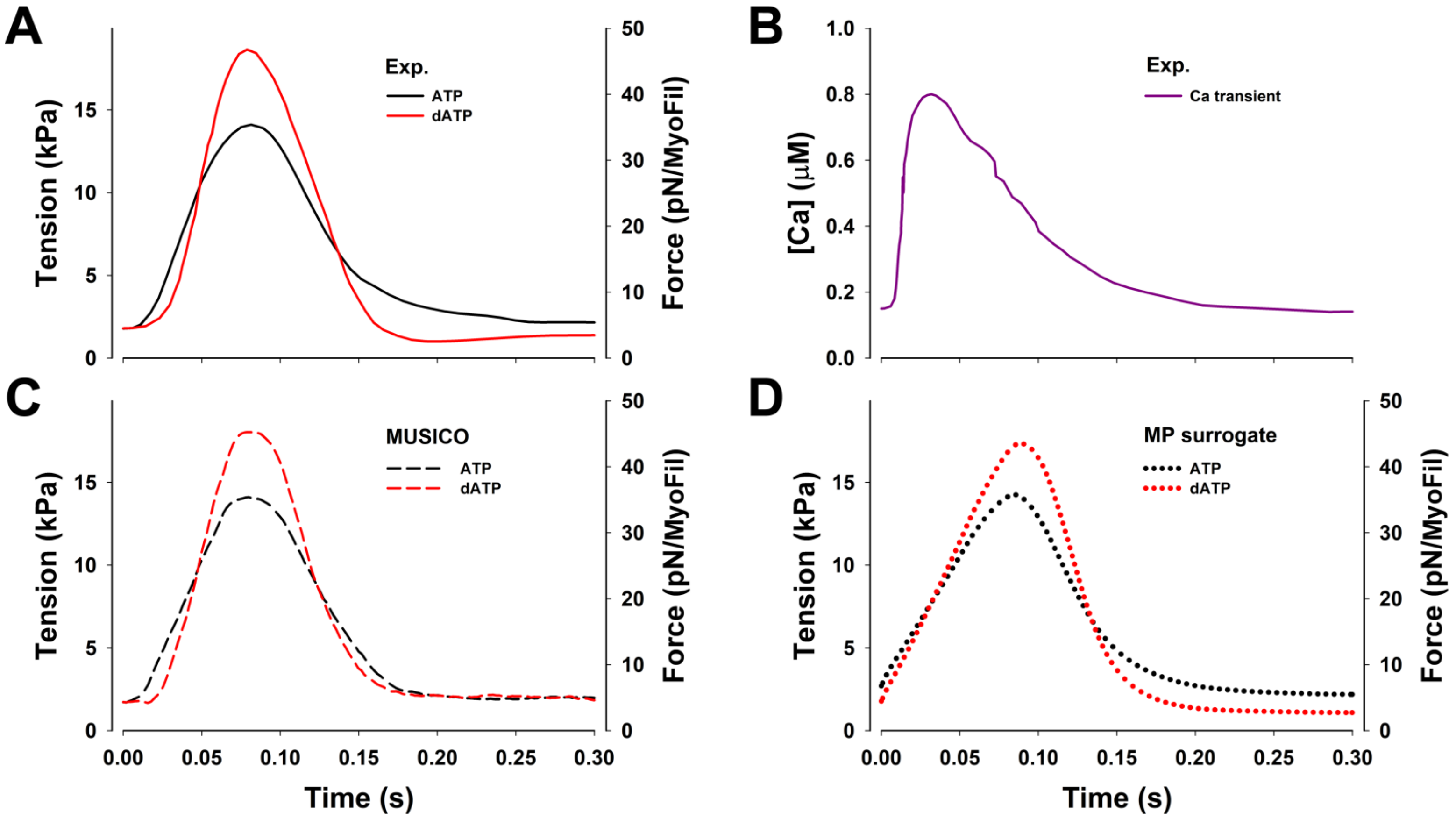
Changes in kinetic parameters - dATP

For treating
Dilated Cardiomyopathy (DCM)

dATP modulates crossbridge cycle rates!

The observed increase it twitch tension peak is achieved by ~3-fold increase in binding rate but keeping binding equilibrium rate constant, and 2-fold increase in ADP release rate.



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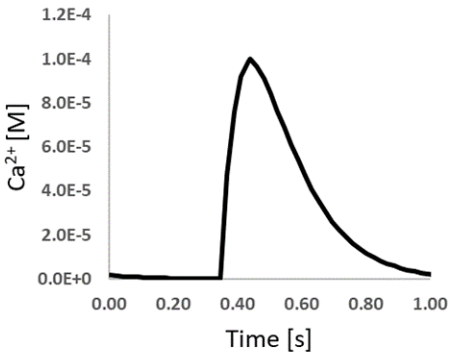
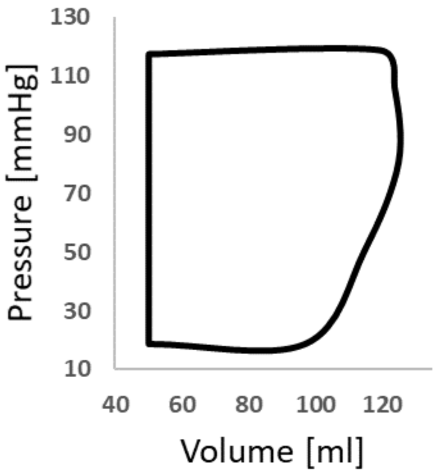
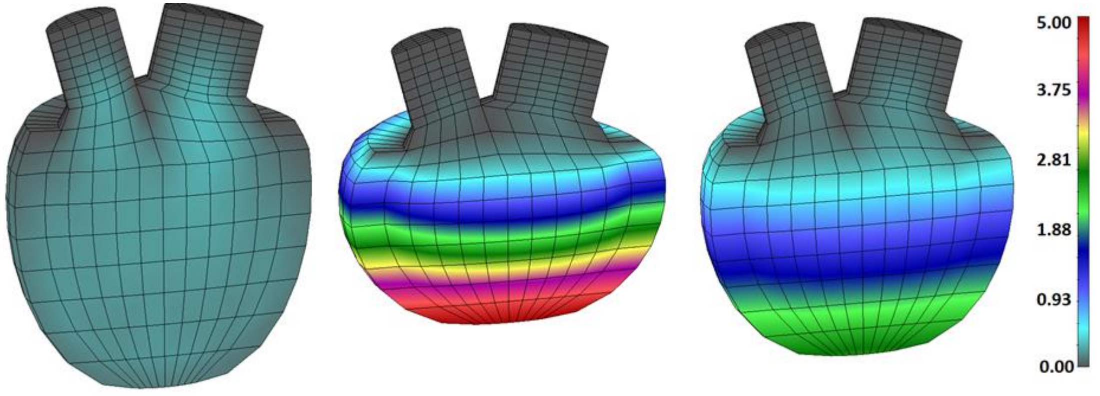
Effects of calcium change

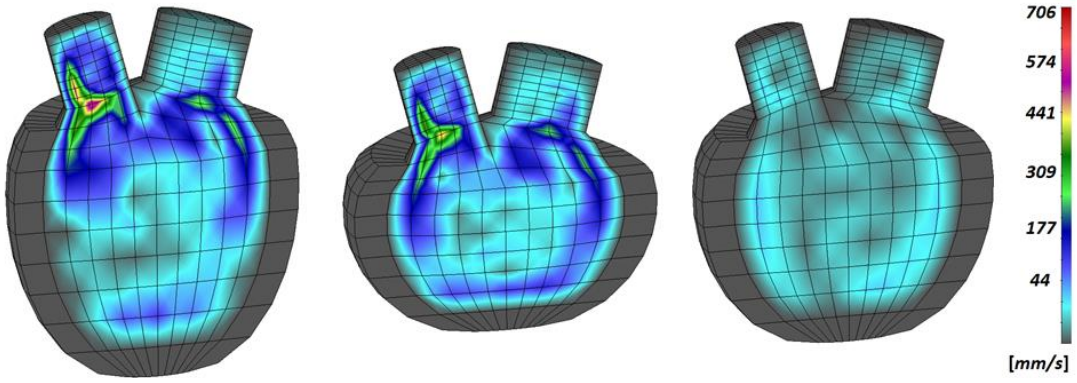


Calcium concentration

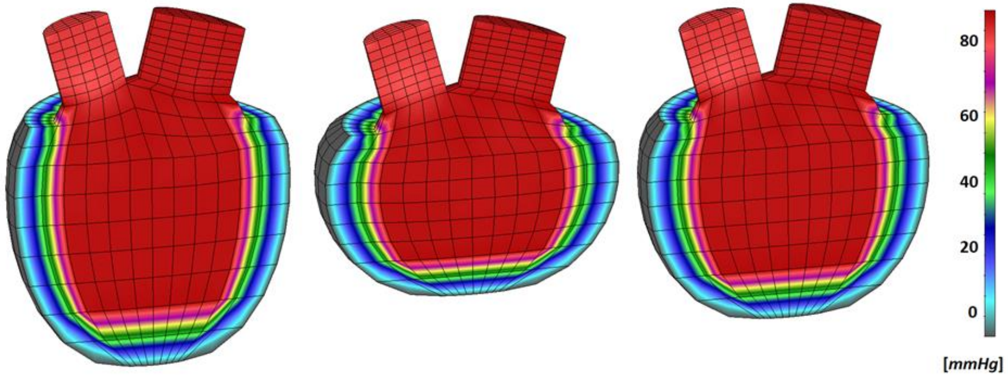




Displacement field at 0.2s, 0.5s and 0.6s



Velocity field at 0.2s, 0.5s and 0.6s



Pressure field at 0.2s, 0.5s and 0.6s

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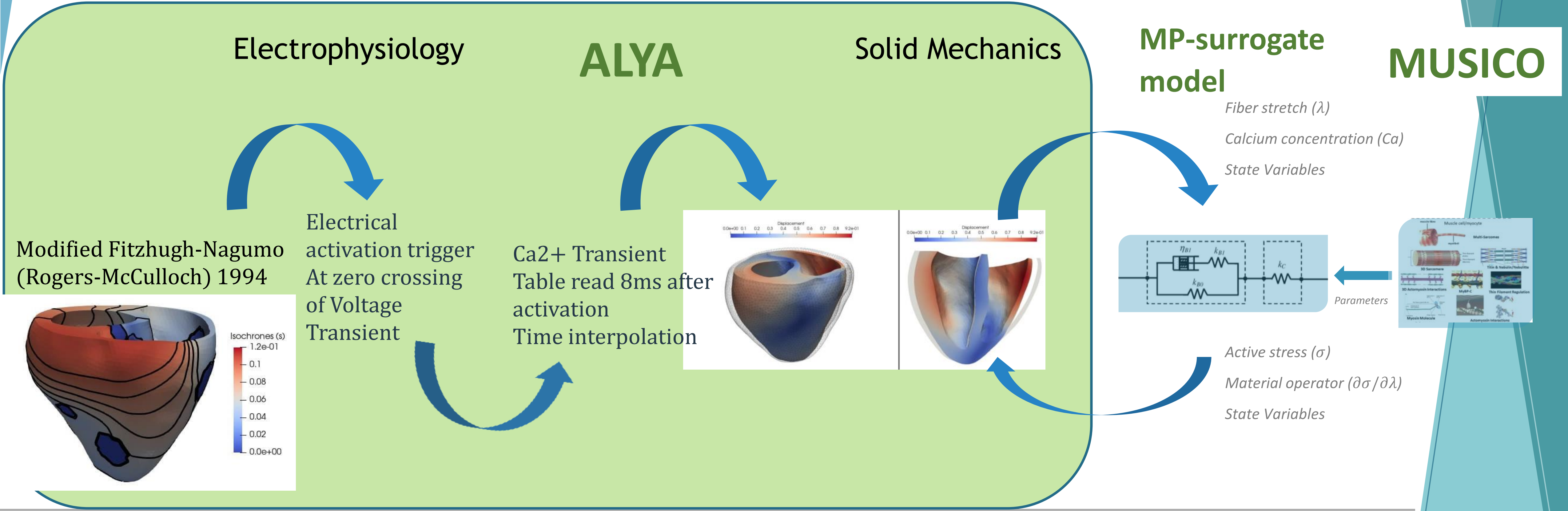
Linking MUSICO and FE simulation ALYA

- The coupling of Alya and MP-surrogate was extended to a human heart biventricular anatomy



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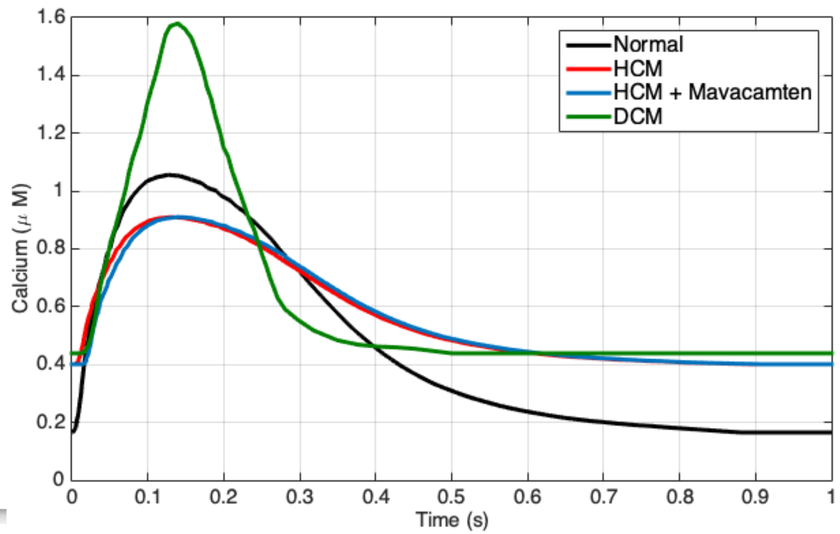
Integration of MP-surrogate into Alya finite element solver

WP5 Alya – MP surrogate Coupling

Data input to both Calcium Transients and MP-surrogate parameters are read and integrated within the ALYA FEM solver

With this setup, any normal, diseased or drug-treatment condition can be simulated in any given anatomy or geometry




```
slab.dat
slab.dom.dat          slab.post.alyadat
slab.ker.dat          MP-params.dat
slab.exm.dat          MP-Ca.dat
slab.sld.dat          msh
```

```
PHYSICAL_PROBLEM
  ECCOUPLING
    MATERIAL:   1
    MODEL: MUSICO
    MUSICO_OPTIONS
      CALCIUM_FILE: MP-Ca.dat
      PARAMETERS_FILE: MP-params.dat
    END_MUSICO_OPTIONS
  END_ECCOUPLING
END_PHYSICAL_PROBLEM
```

a) Alya's configuration files and ket.dat.

```
38                  ! Number parameters
1.0e-6              ! TimeStep
5000                ! IterMax
1.6                 ! SL_0
2.2                 ! SL_isom
1.1                 ! LA
1.6                 ! LM
0.176               ! B
1.62e5              ! R_T_0
0.007               ! x0
0.915               ! Ca_50 (uM)
0.0                 ! K_on_0
553.701             ! K_on_Ca
100.0               ! K_off_0
150.0               ! K_off_Ca
64.1084910194011    ! f_0_p
...
```

b) MP input parameters (params.dat).

Interface defining the Alya-MP surrogate model

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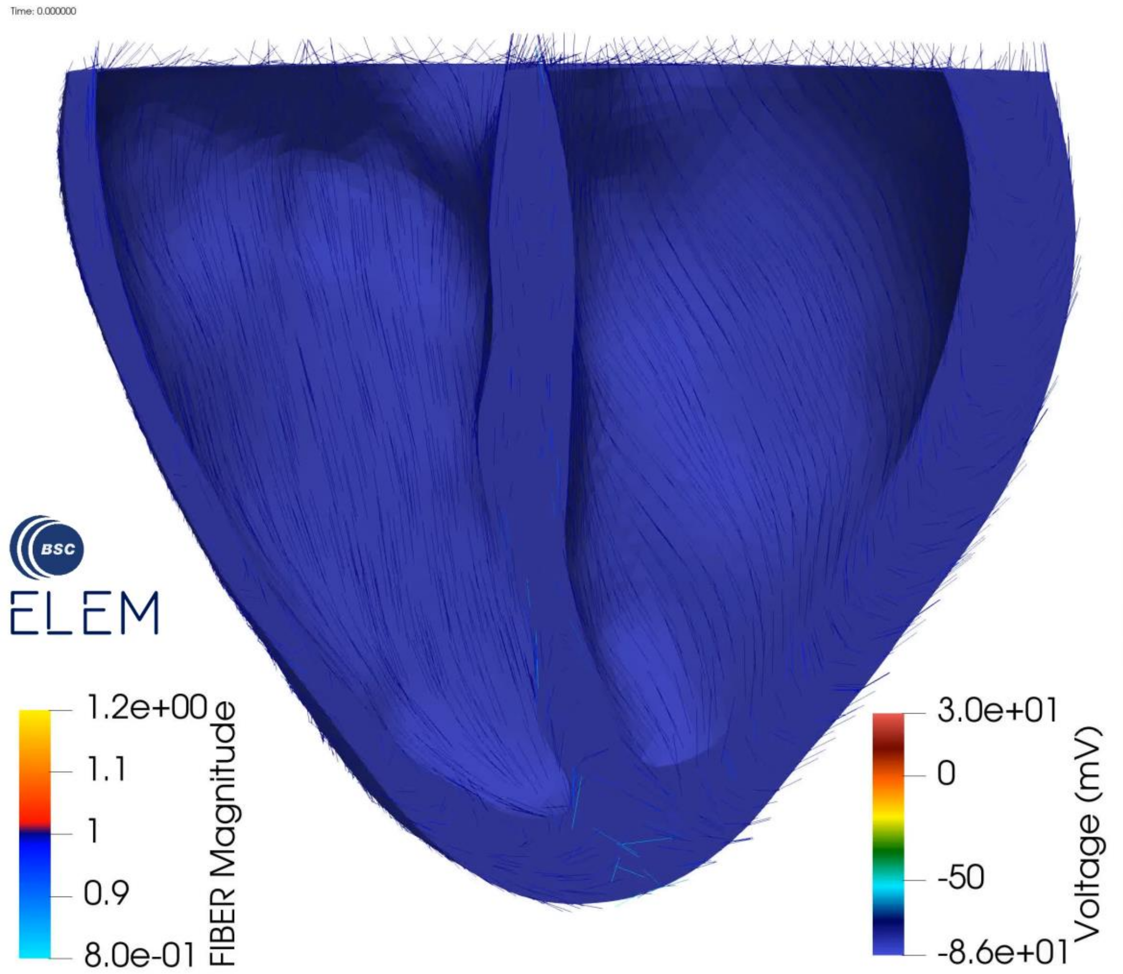
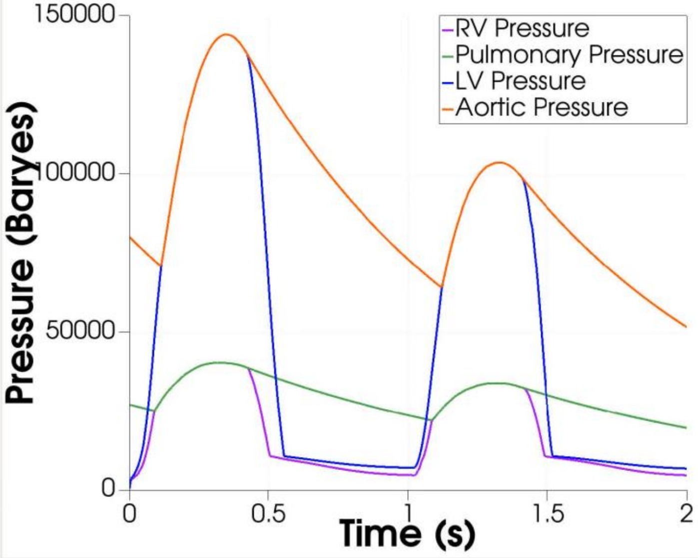
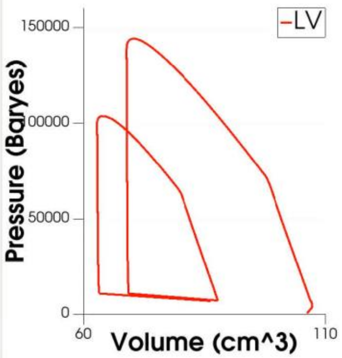
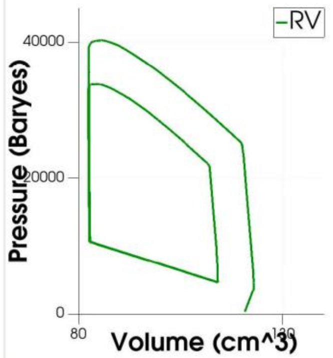
Normal Human Heart









	LV	RV
WK resistance (dyn s/cm^5)	3400	750
WK capacitance (cm^5/dyn)	0.00027	0.00156
Diastolic P (baryes)	8000 (6 mmHg)	4000 (3 mmHg)
Valve Opening P (baryes)	80000 (60 mmHg)	27000 (20 mmHg)

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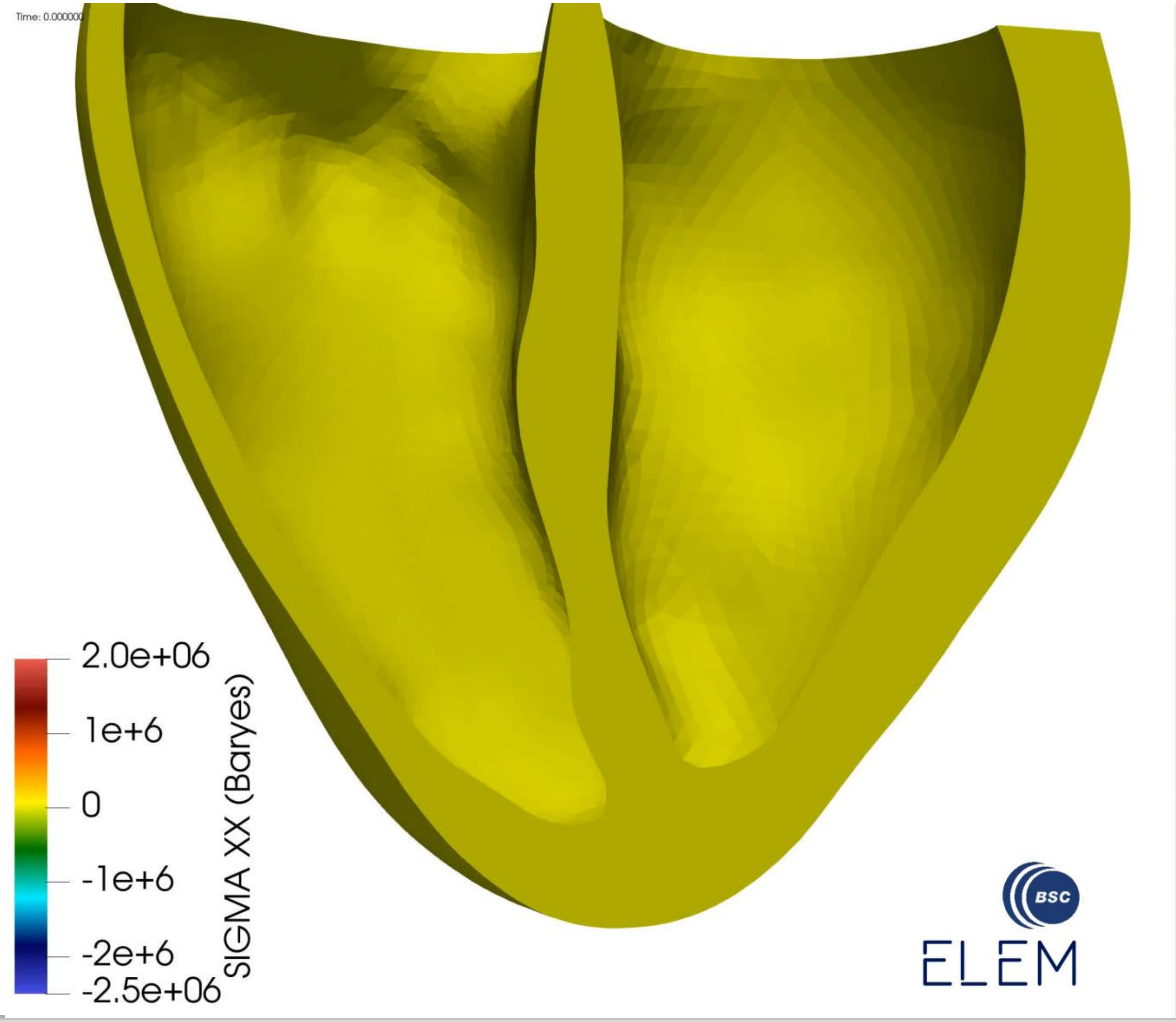
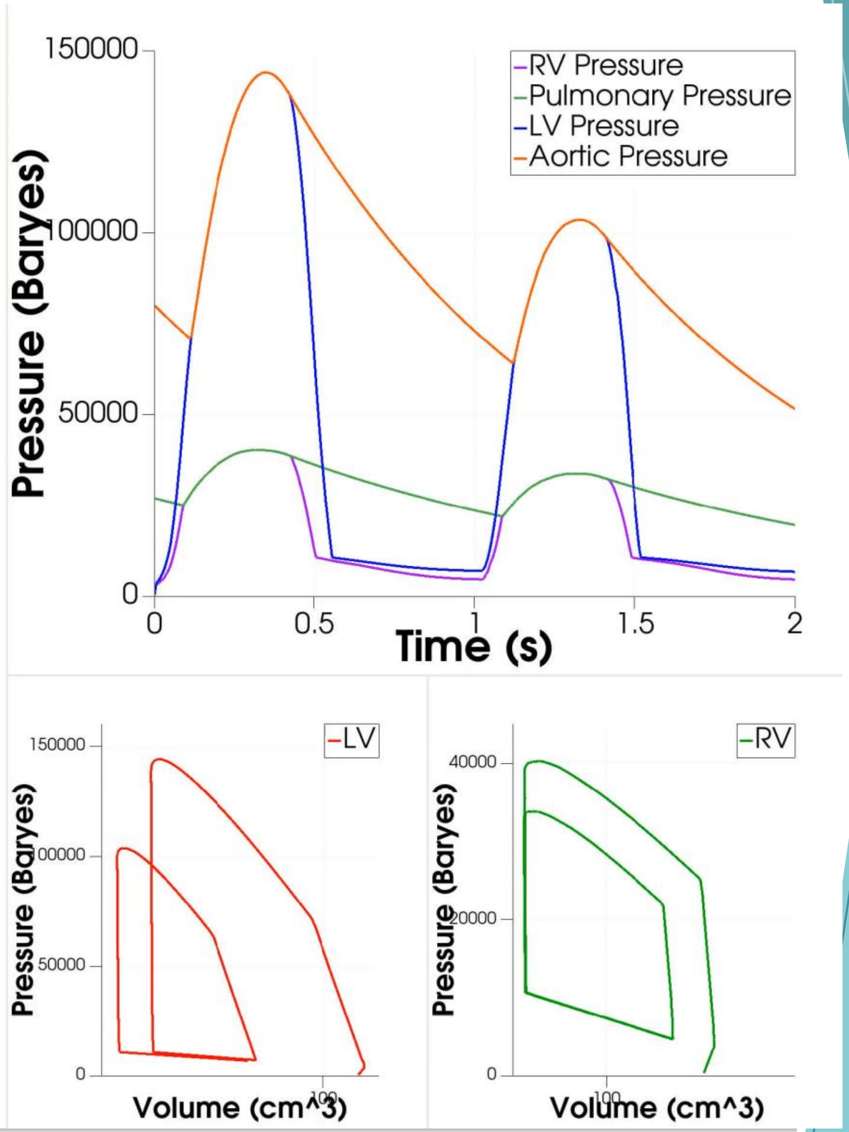
Normal Human Heart - Stress





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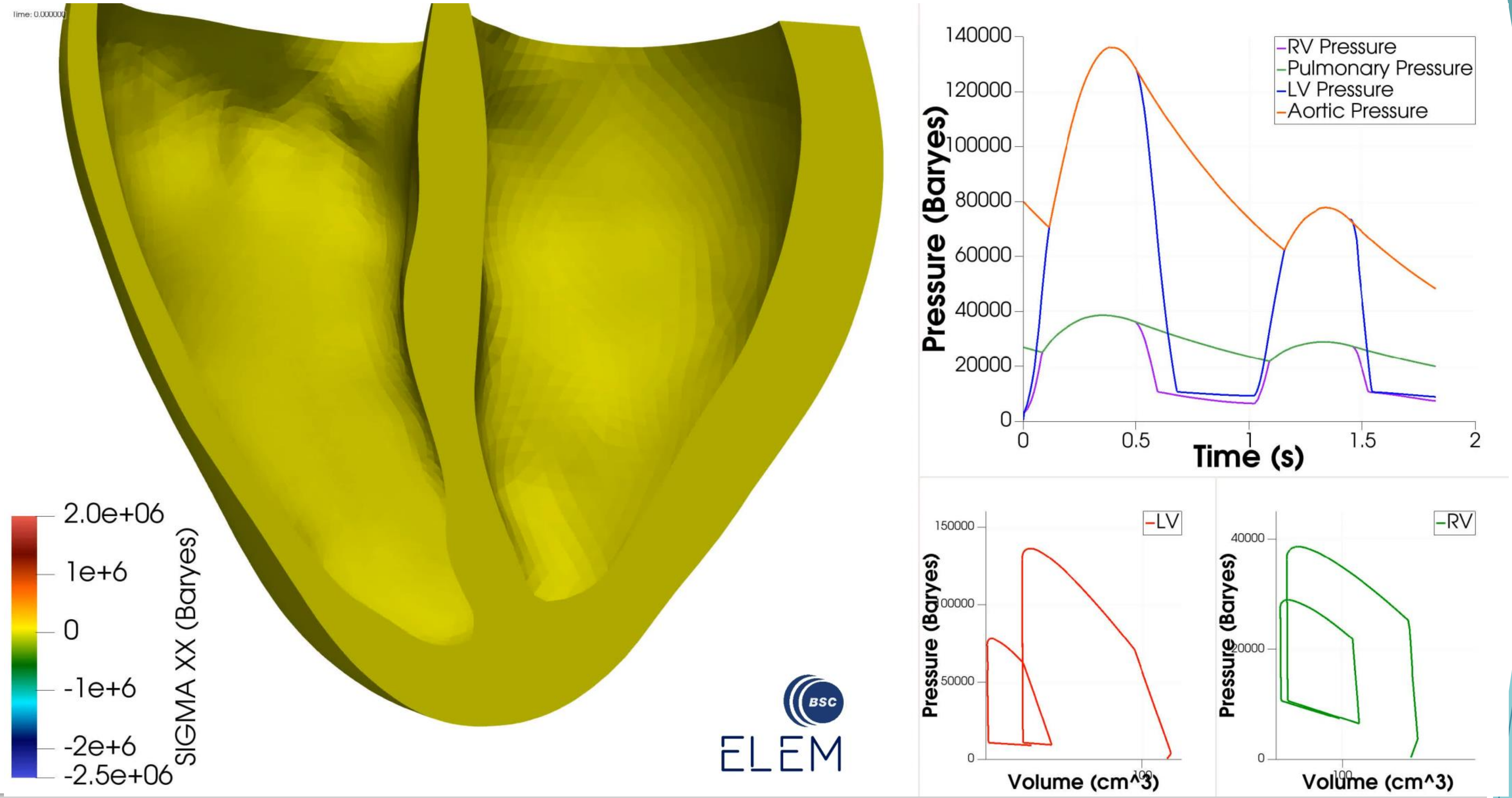
Hypertrophic Cardiomyopathy



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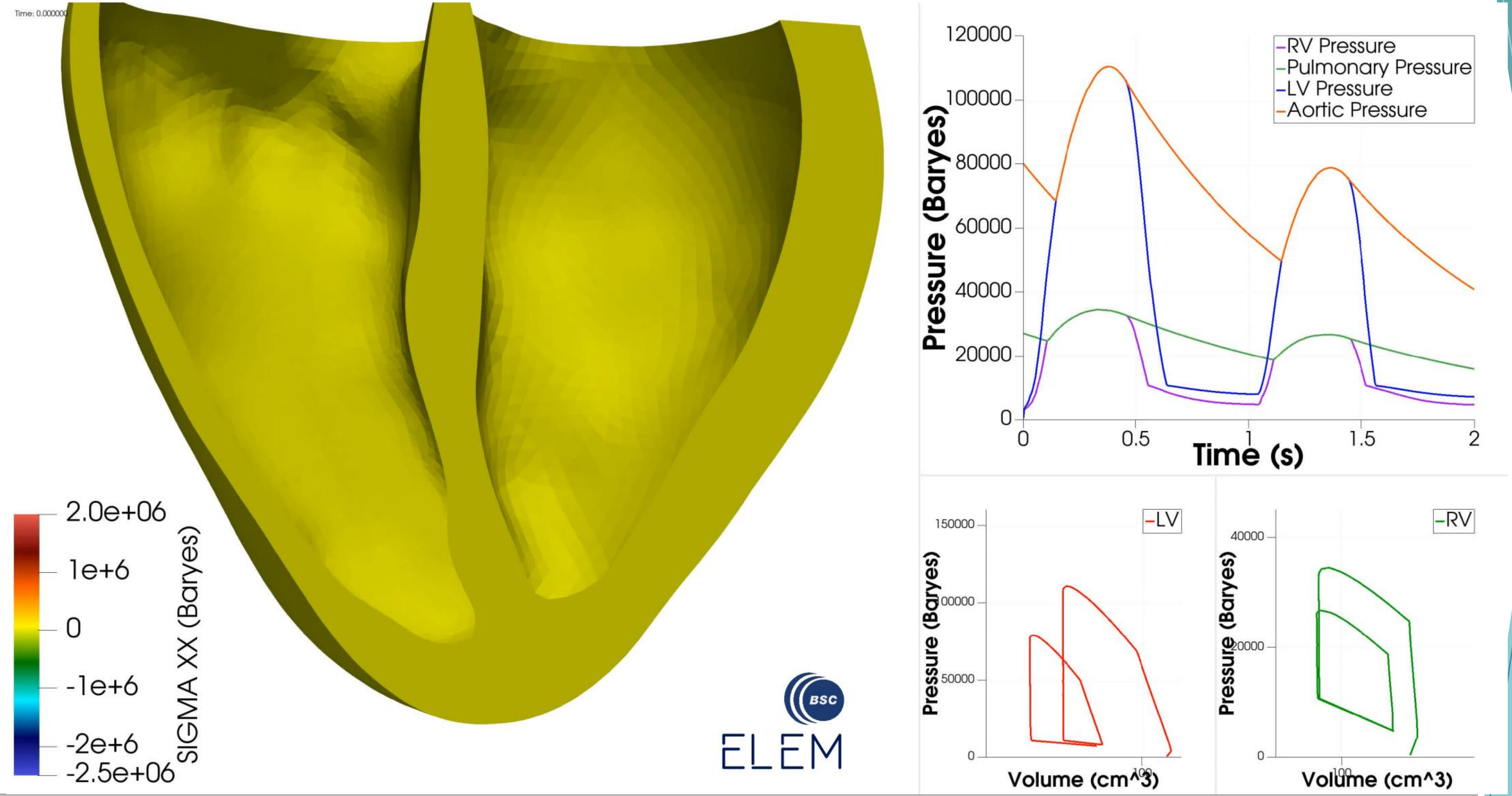
HCM + Mavacamten



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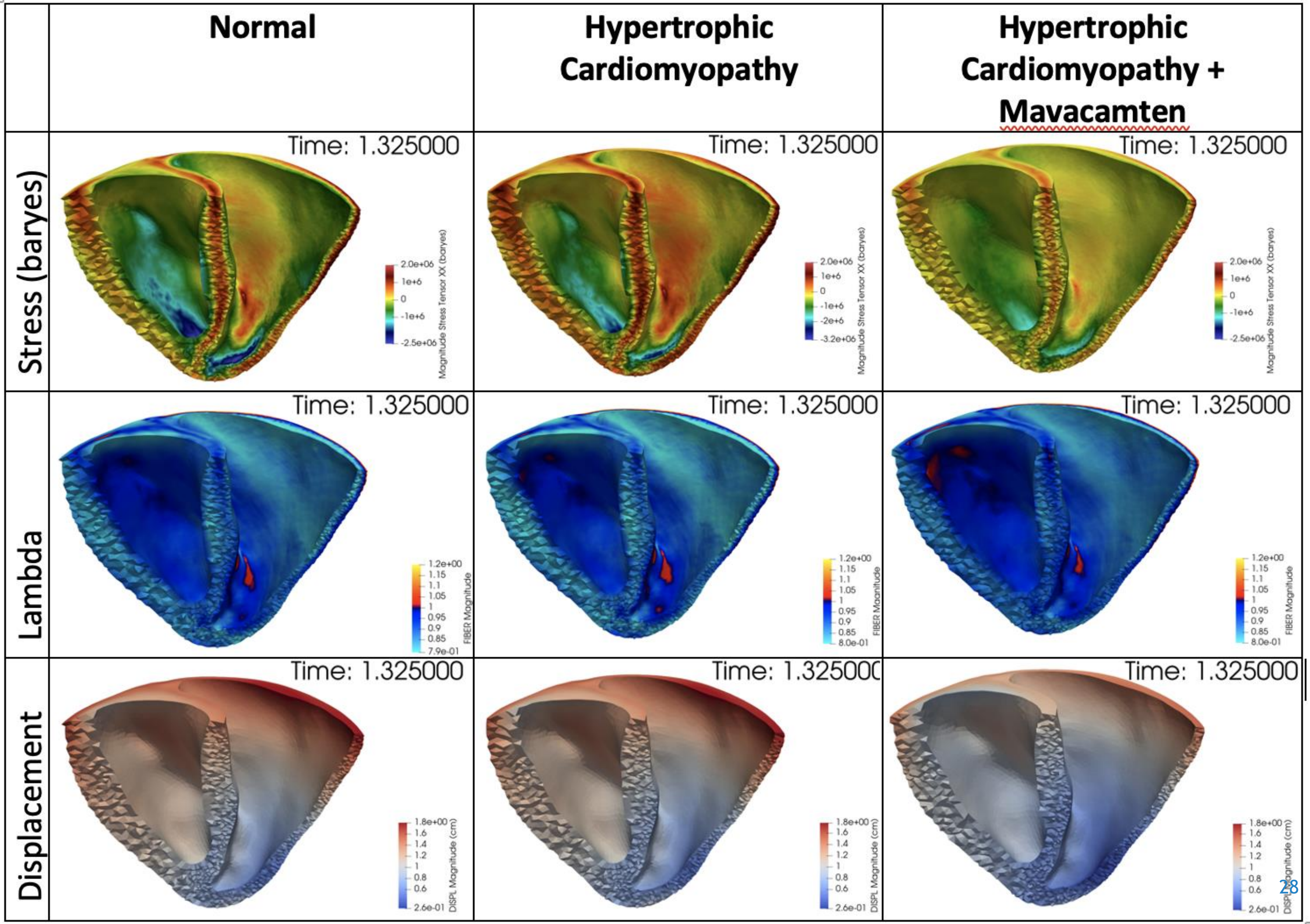
Mavacamten reduced the myocardial stress



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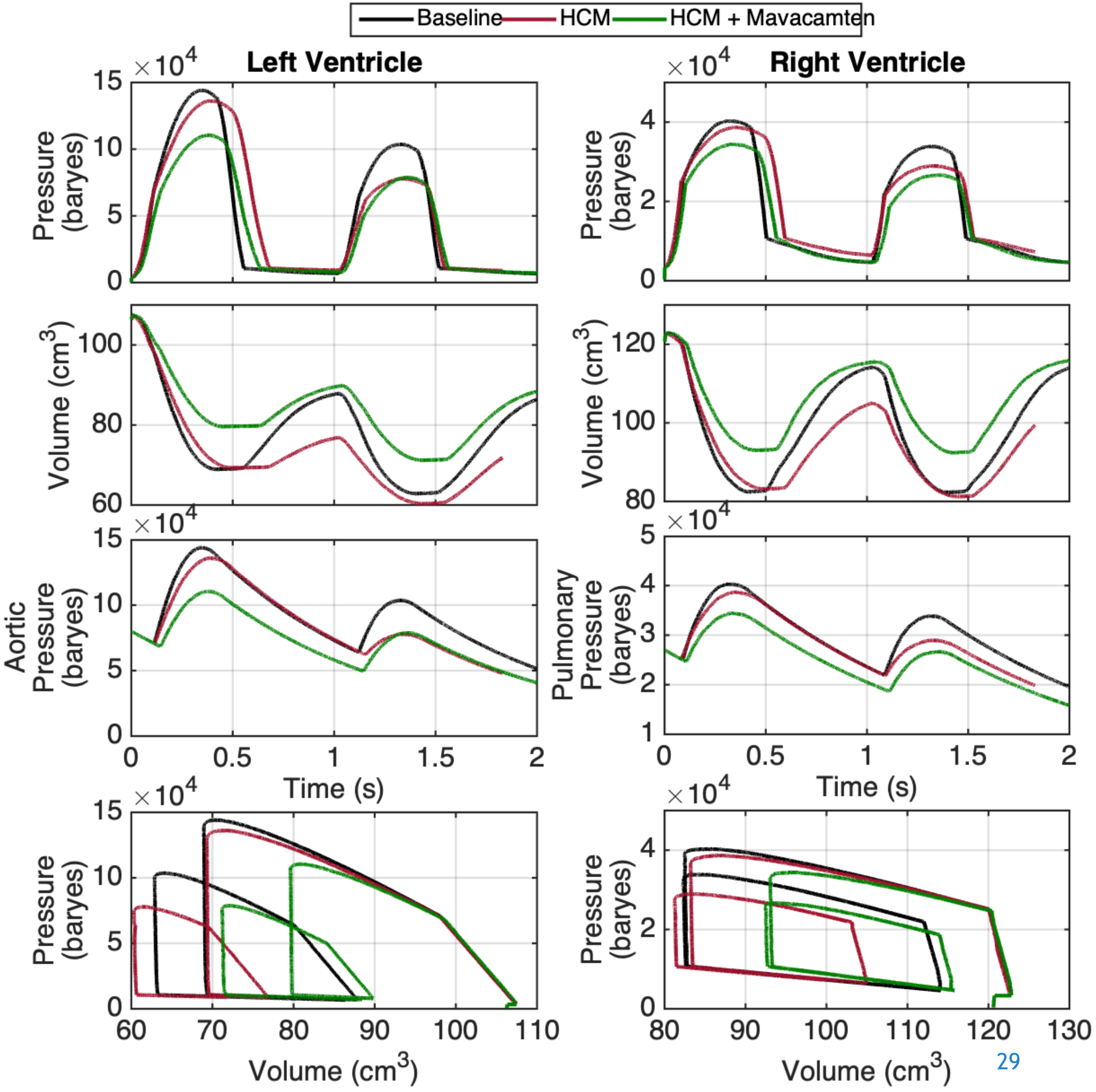
Pressure-Volume Loop Comparison between models

- Full heartbeat simulations require simulation of more than one beat to reach a steady state
- Baseline calcium transient magnitude pre-stresses the anatomy
- There is a need to pre-stress the anatomy so as to preserve initial diastolic volume
- Mavacamten slightly reduced arterial pressure

Percentage change from Normal	LV EF(%)	RV EF(%)
HCM	-25%	-15%
HCM + Mavacamten	-29%	-26%



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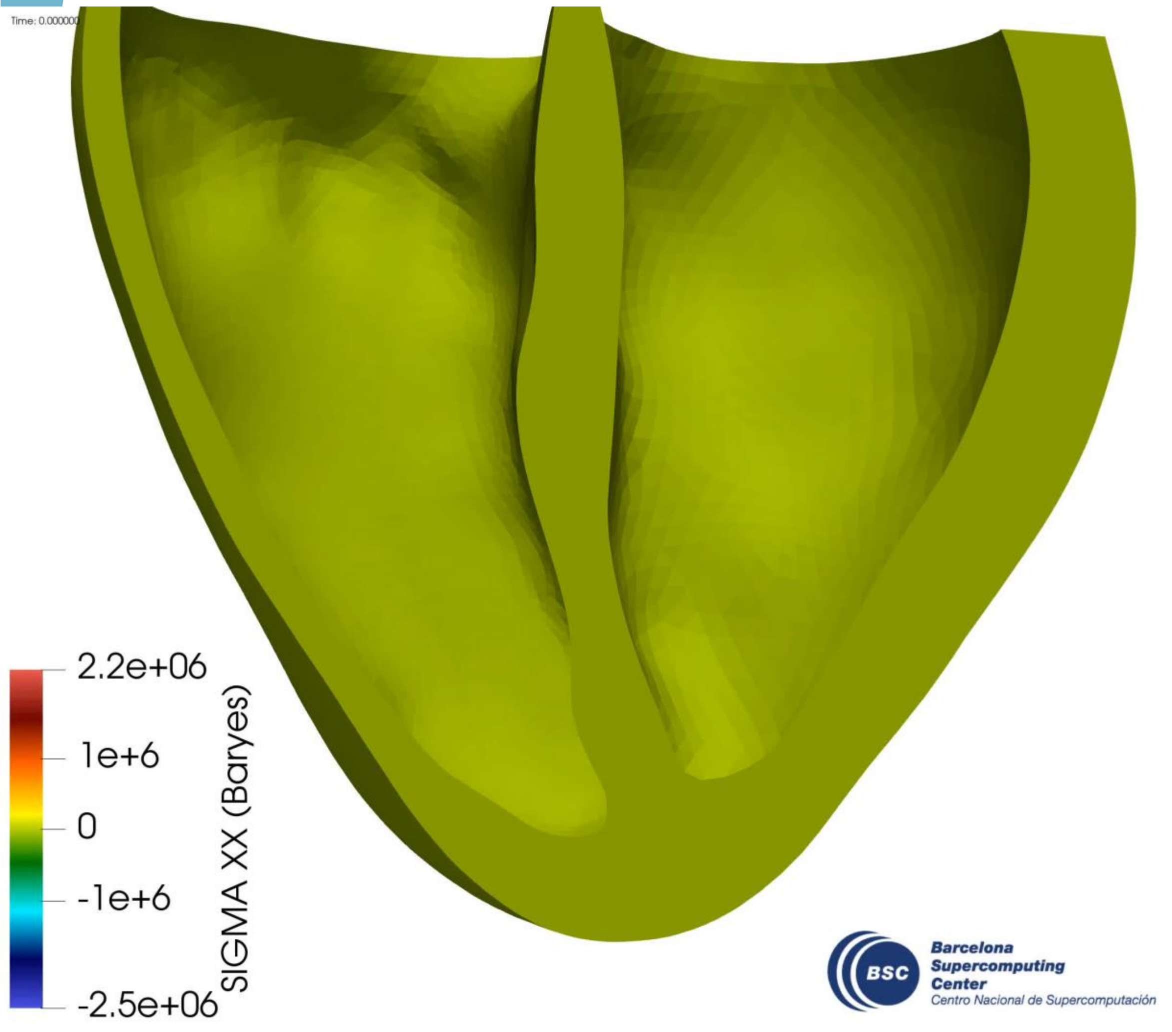
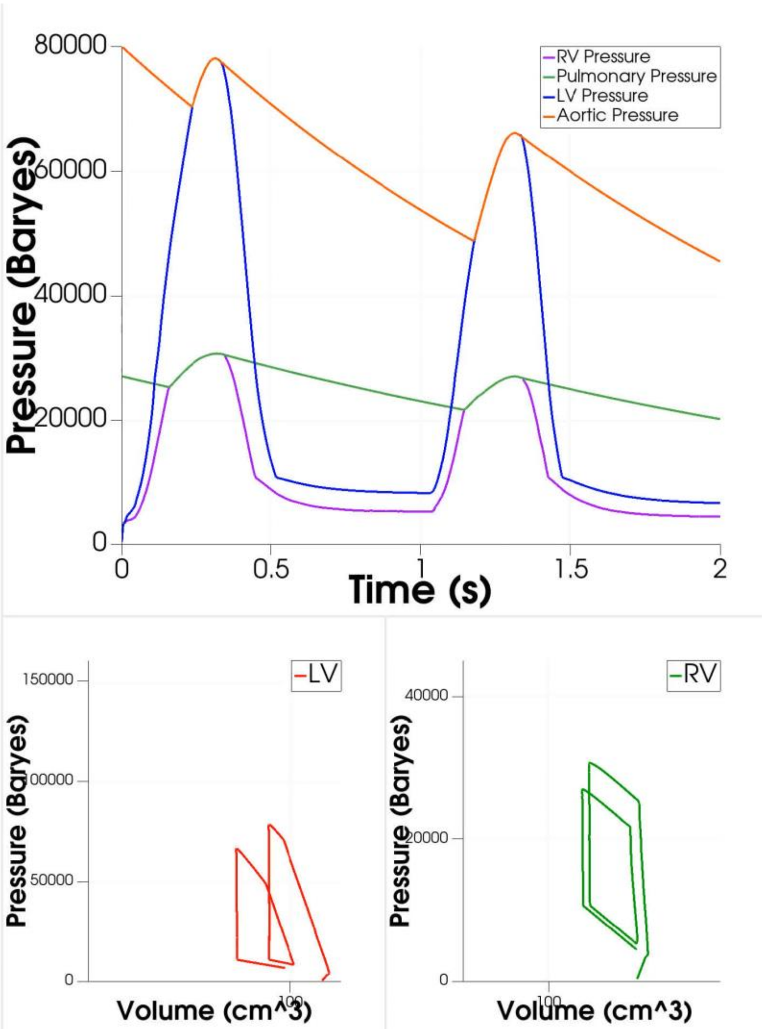
Dilated Cardiomyopathy





	LV	RV
WK resistance (dyn s/cm^5)	6800	1500
WK capacitance (cm^5/dyn)	0.00027	0.00156
Diastolic P (baryes)	8000 (6 mmHg)	4000 (3 mmHg)
Valve Opening P (baryes)	80000 (60 mmHg)	27000 (20 mmHg)

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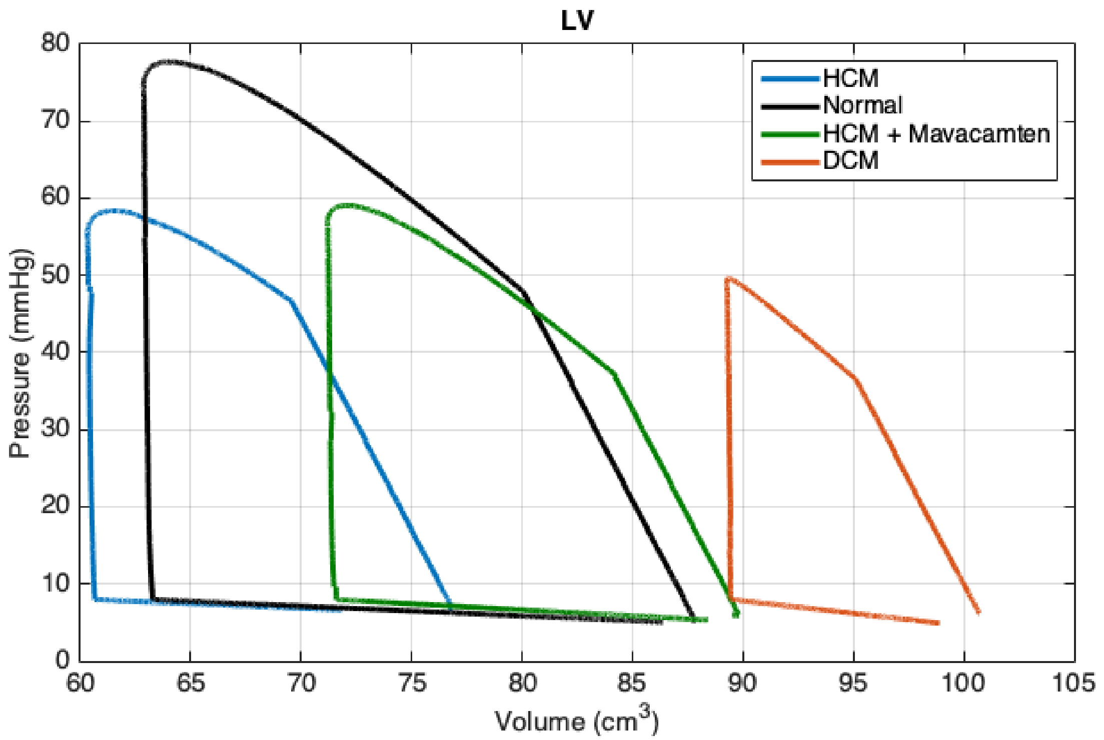
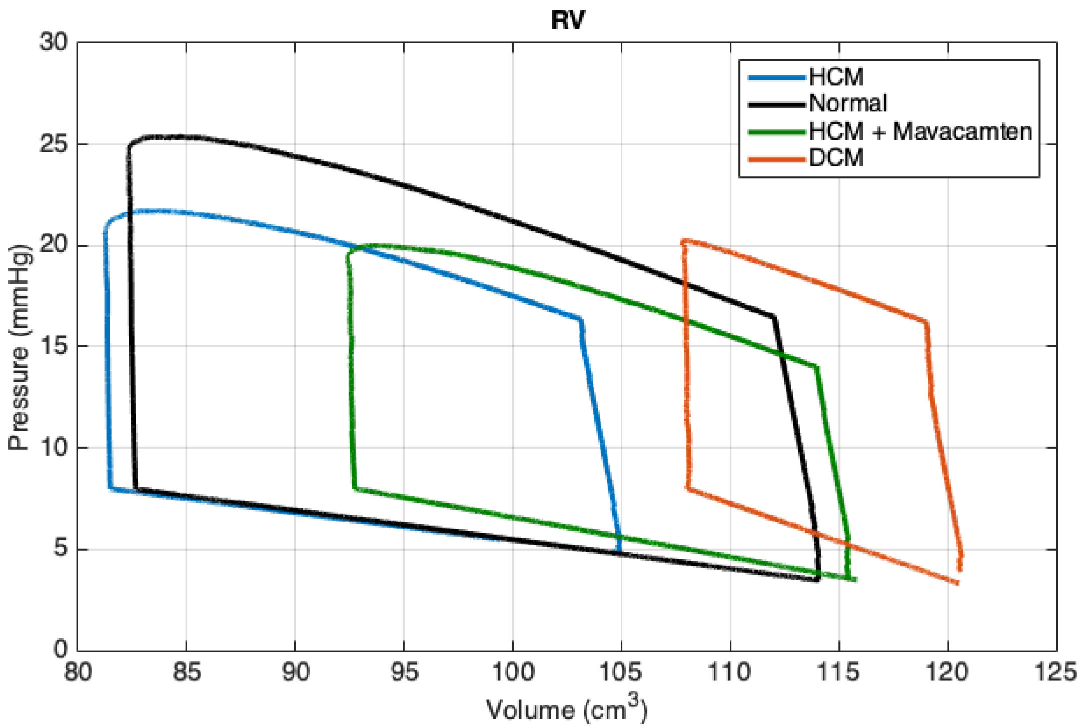
SILICOFCM

Pressure-Volume loops





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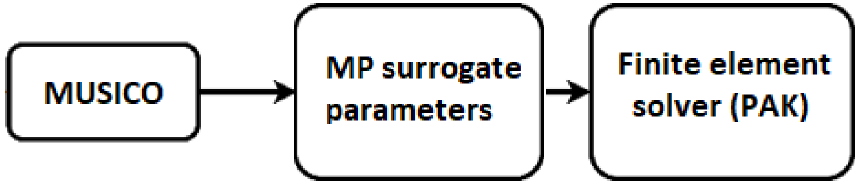
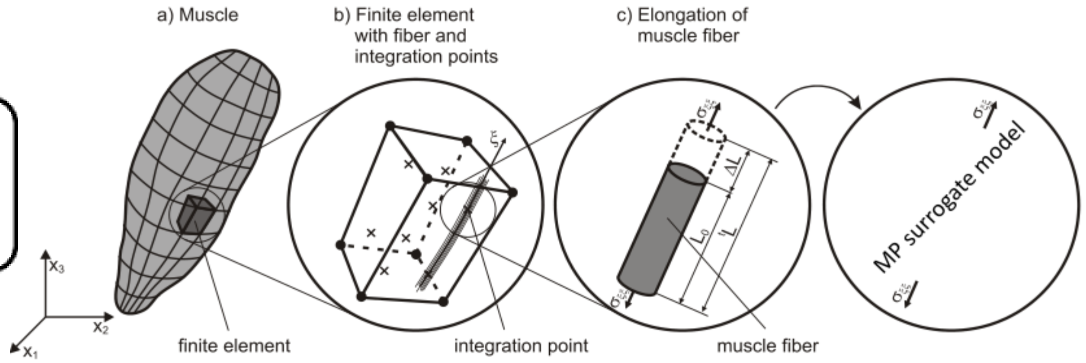
PAK FE solver tool with linked MP surrogate model



Data flow of the pak-musico integration



Multi-scale model of muscle contraction.
a) Muscle discretized into finite elements,
b) Muscle fiber within the finite element and integration points,
c) deformation of the muscle

- MP surrogate was built into our finite element solver PAK as a new muscle material model. MP surrogate consists of parameters, states, and calculator.
- Based on input parameters, the current state of the material model and provided stretch, MP surrogate calculates stress and instantaneous stiffness along muscle fiber and it produces a new state of the MP

D5.4 Software: Linking MUSICO and FE simulation

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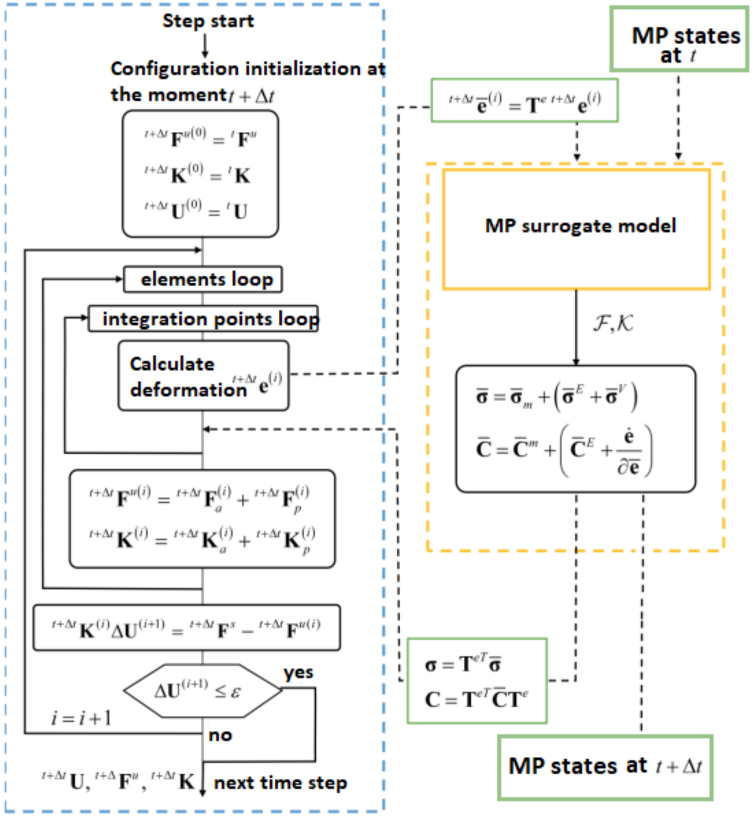
PAK FE solver tool with linked MP surrogate model



Algorithm: Finite element analysis and MP surrogate model

- Finite element solver maintains and updates states of the MP model. We accept the new state of the model if the finite elements achieved convergence. We neglect the new state and use the state from the previous time step if convergence is not achieved.
- In our code, we incorporated openMP, which is typically used for loop-level parallelism, to speed up the calculations of integrated PAK-MP simulations.
- OpenMP introduces parallelism into the application by launching a set of threads that execute portions of code concurrently. Since MP calculations are computationally intensive we created one thread per integration point, so that the calculations done at each integration point are done in parallel.

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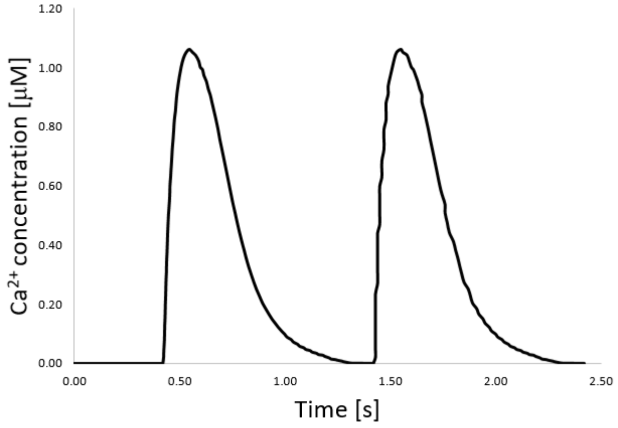
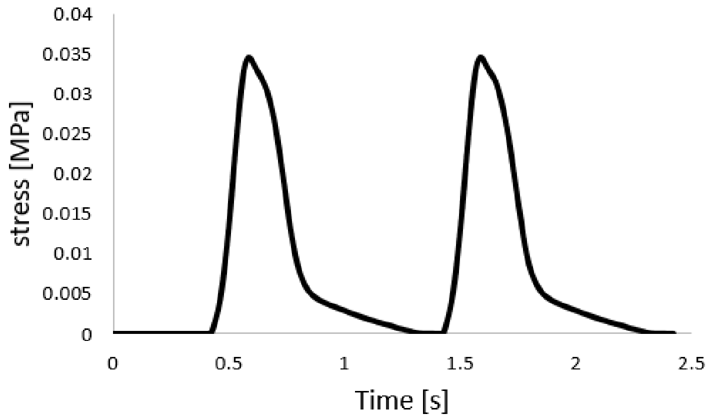
SILICOFCM

PAK linked with MP - Use cases

- Cube model – Healthy muscle



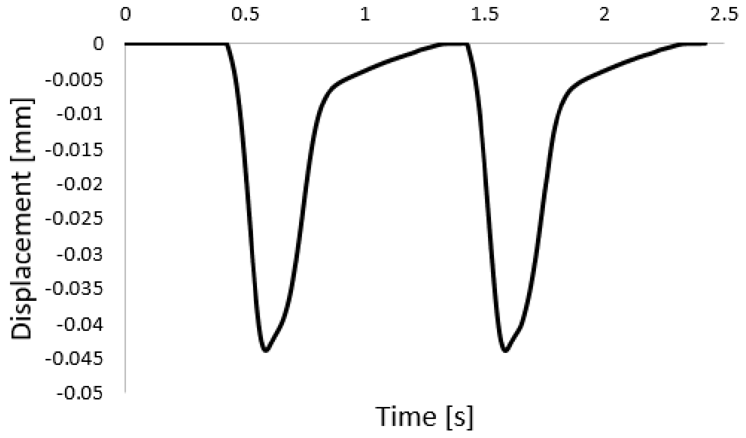
Prescribed calcium concentration for a healthy heart



Active stress generated within muscle fiber during contraction

Table MP model parameters for a healthy heart

Parameter	Value	Parameter	Value	Parameter	Value
TimeStep	1.00E-05	*k_off_Ca*	50	*ErrFlag*	0
IterMax	100	*f_0_p*	1000	*Stiff_Eq_P1*	197.5442
SL_0	1.6	*h_0*	5000	*Stiff_Eq_P2*	3434.963
SL_isom	1.9	*h_0_p*	550	*Stiff_Eq_P3*	0
LA	1.1	*g_0*	450	*Ca_amp*	3.380394
LM	1.6	*u*	1.1	*tau1*	0.065917
B	0.176	*w*	1	*tau2*	0.014666
R_T_0	1.62E+05	*v*	1	*k_PS_0*	50
x0	0.007	*beta*	0	*k_PS_max*	700
Ca_50	0.915	*eta*	0.396	*b_param*	5
k_on_0	0	*sigma_p*	7.2	*Ca_50_PS*	1
k_on_Ca	120	*sigma_n*	1	*k_lambda_on_0*	3750
k_off_0	100	*ErrorEps*	1.0E-7	*k_lambda_off_0*	375



Displacement at the free node of the 3D model during muscle contraction

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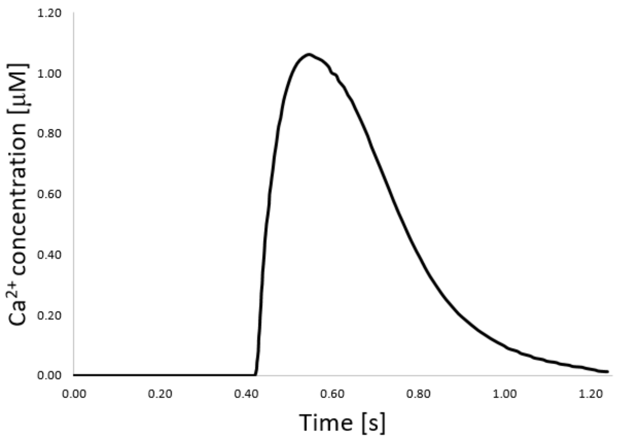
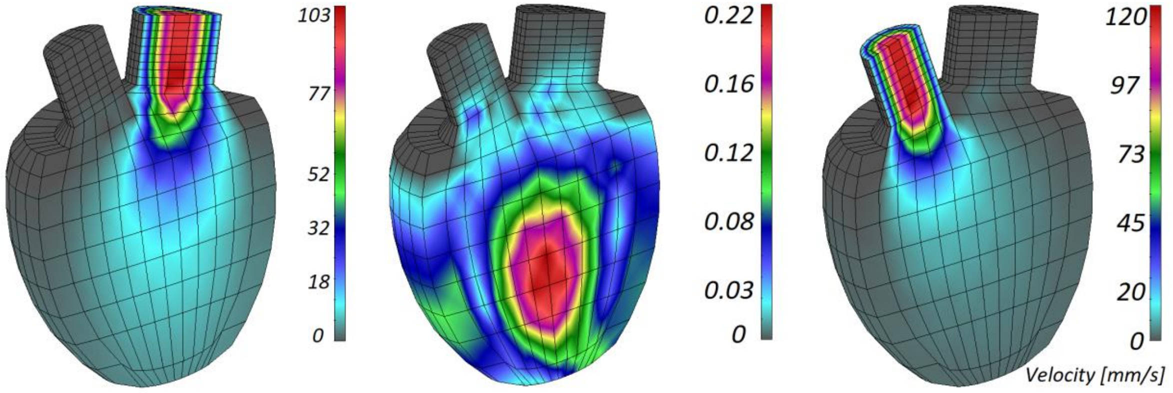
PAK linked with MP - Use cases

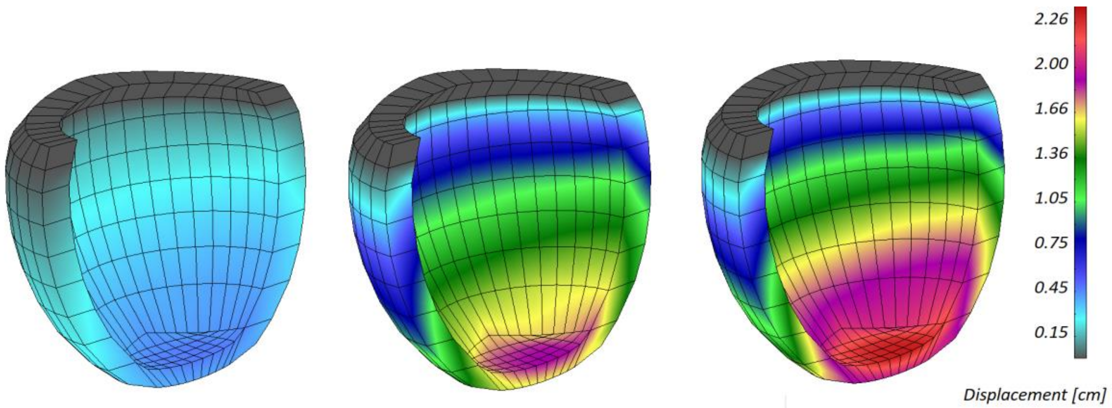
- **LV parametric model**



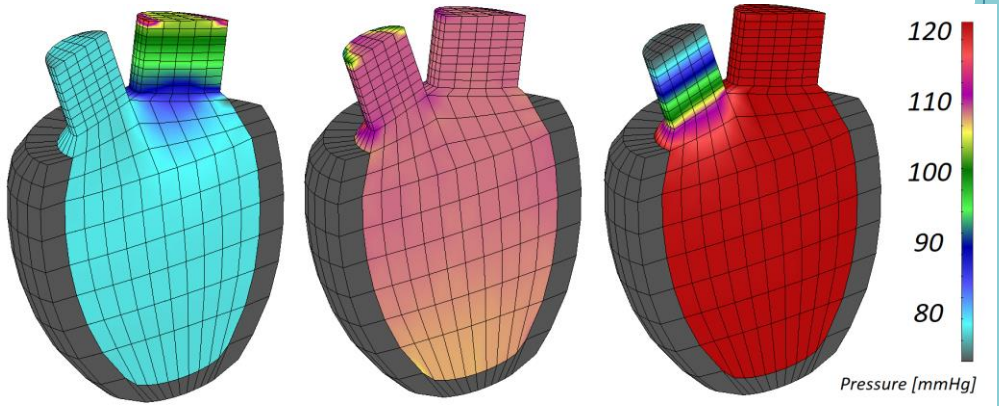
Prescribed calcium concentration



Velocities at start of diastole, end of diastole and middle of systole



Solid displacements at start of diastole, end of diastole, and middle of systole



Pressures at start of diastole, end of diastole and middle of systole

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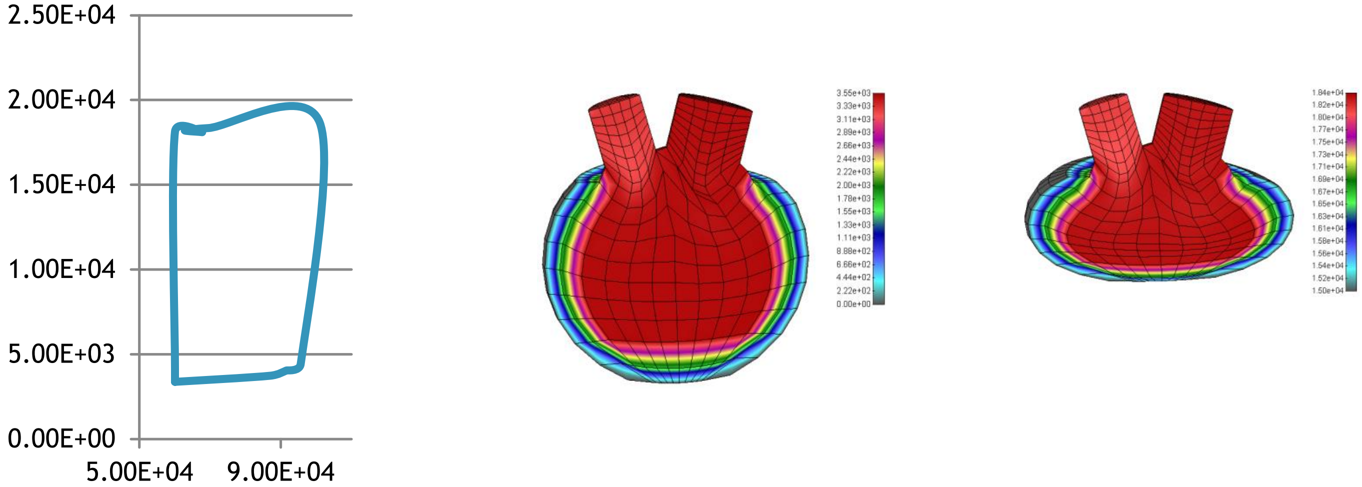
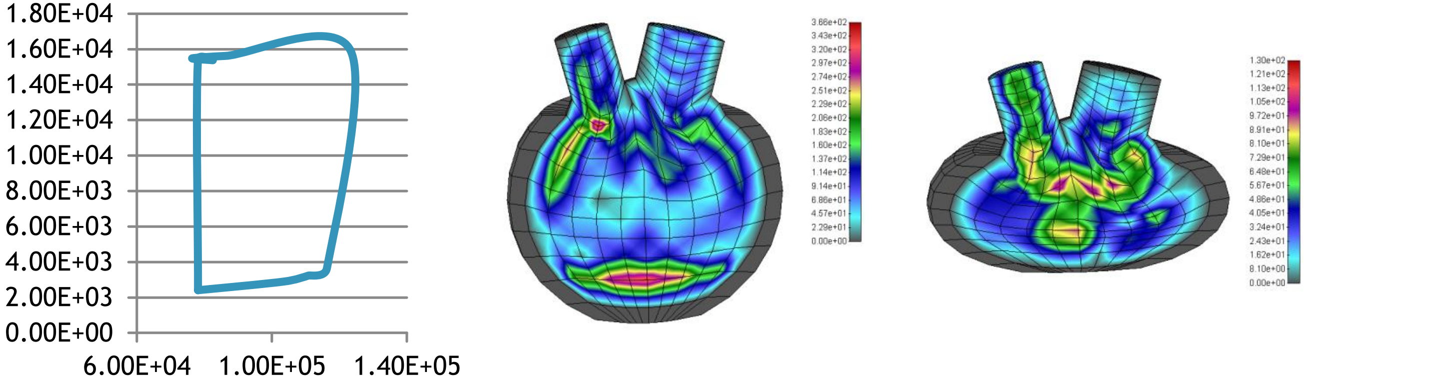
SILICOFCM

Numerical results from SILICOFCM platform for patients before and after Entresto treatment



PV diagram, pressure diastolic distribution, pressure systolic distribution for case before Entresto treatment



PV diagram, velocity distribution in the diastolic phase, velocity distribution in the systolic phase for case after Entresto treatment

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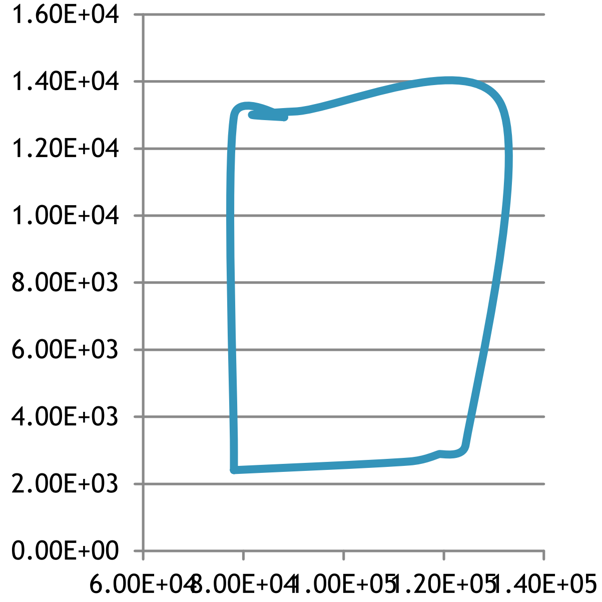
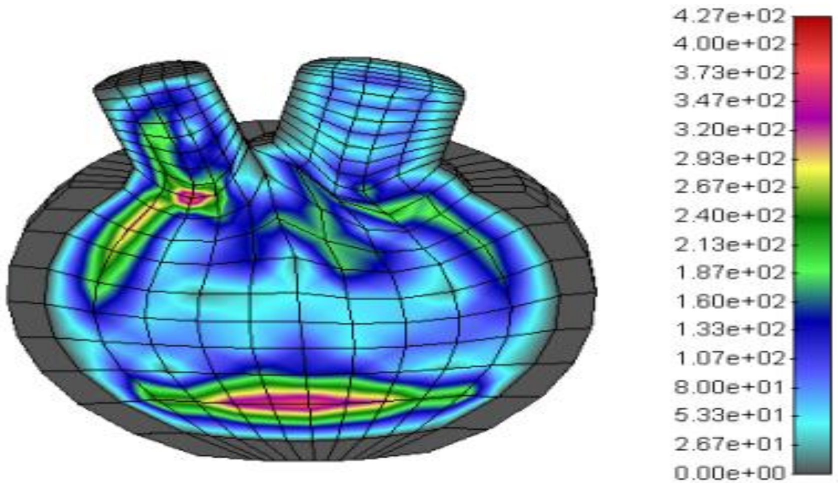
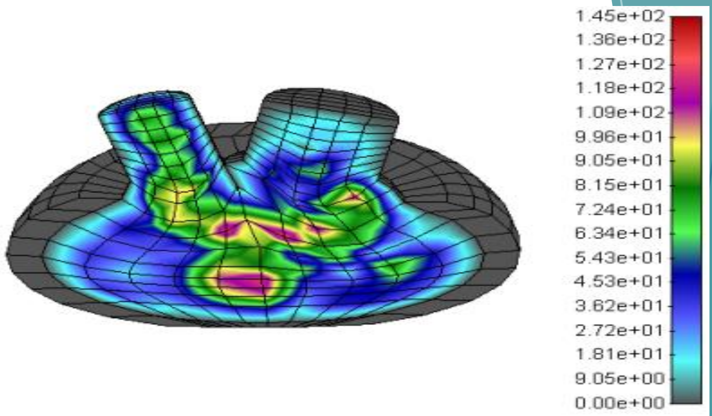
SILICOFCM

Numerical results from SILICOFCM platform for patients after DIGOXIN treatment







PV diagram, velocity distribution in the diastolic phase, velocity distribution in the systolic phase for case after Digoxin treatment

It was found that mean left ventricular ejection fraction increased from 74 ± 2 to 79 ± 1 percentage for 10 patients. In the simulation results ejection fraction was increased from 75 to 80 percentages which is correlated with the observed clinical measurements. Also, we found that velocity field gives increased values after digoxin treatment which may results as consequence of increased ejection fraction.

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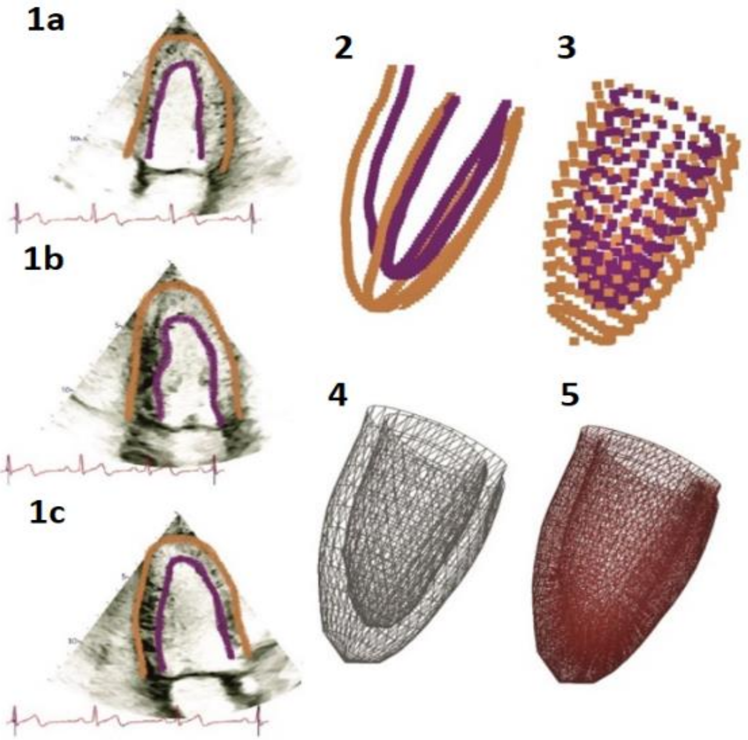
SILICOFCM

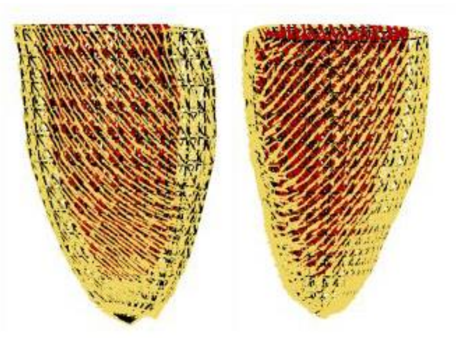
Upgrade FE biomechanical simulation (PAK Solver)

Solid and fluid left ventricle model generated from echocardiography

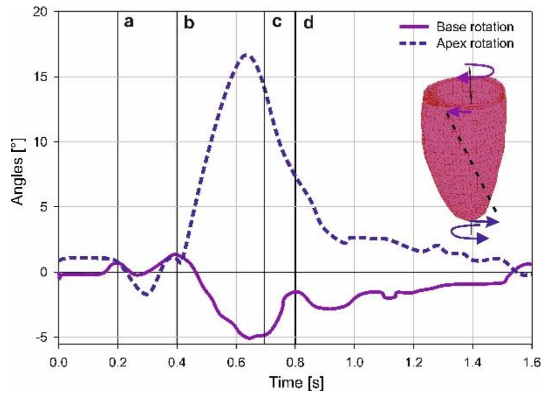
- **Solid echo model**



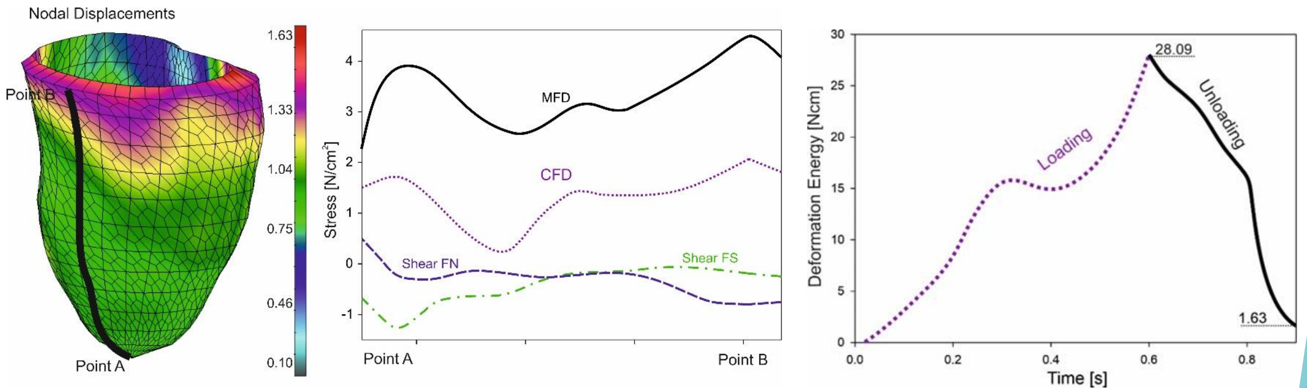
Model generation algorithm



Fibers



Prescribed rotation angles



Solid displacements, stresses and deformation energy

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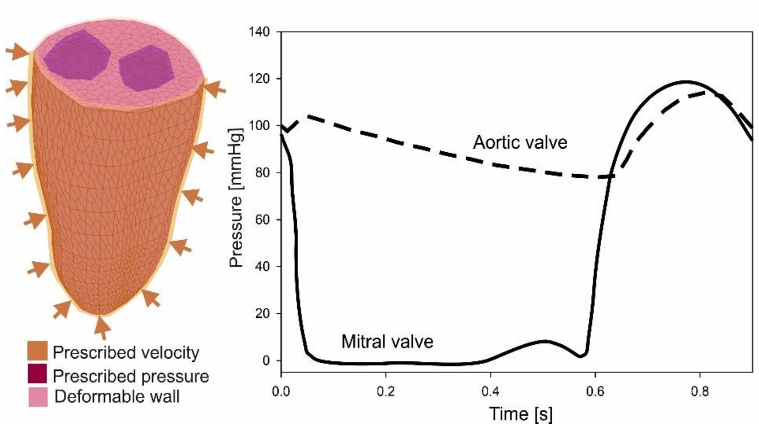
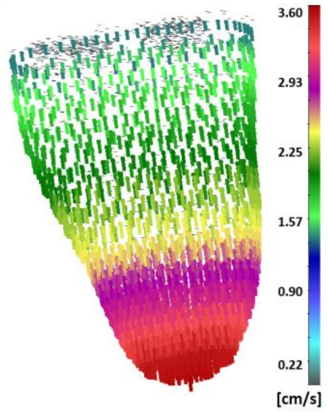
Upgrade FE biomechanical simulation (PAK Solver)

Solid and fluid left ventricle model generated from echocardiography

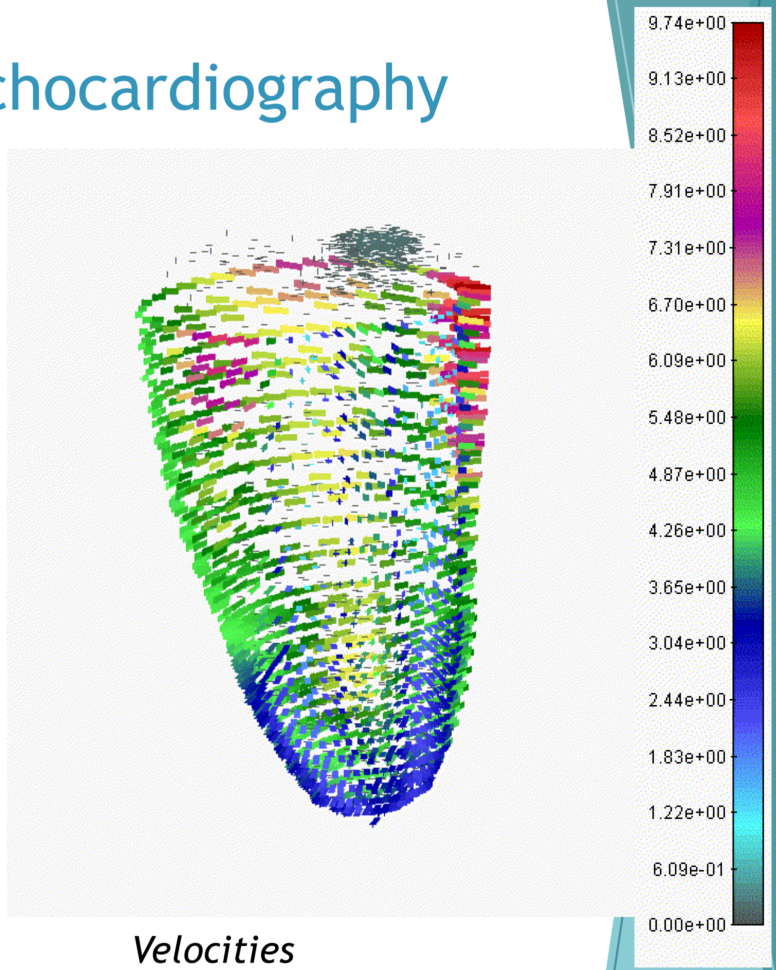
- **Fluid echo model**



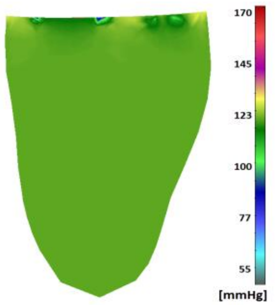
Fluid boundary conditions



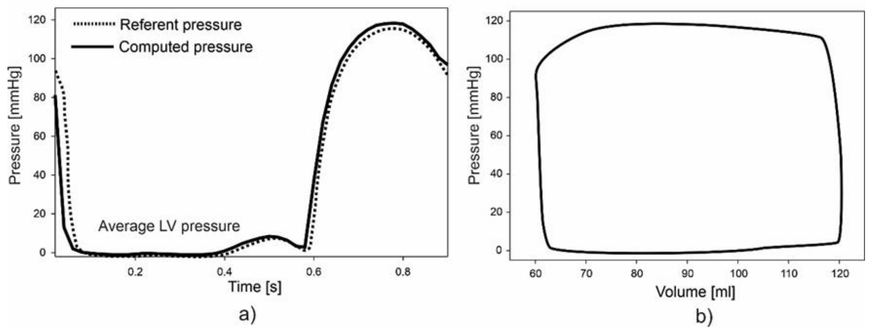
Velocities at the middle of systole



Velocities



Pressures at the middle of systole



Pressure and p-V diagram

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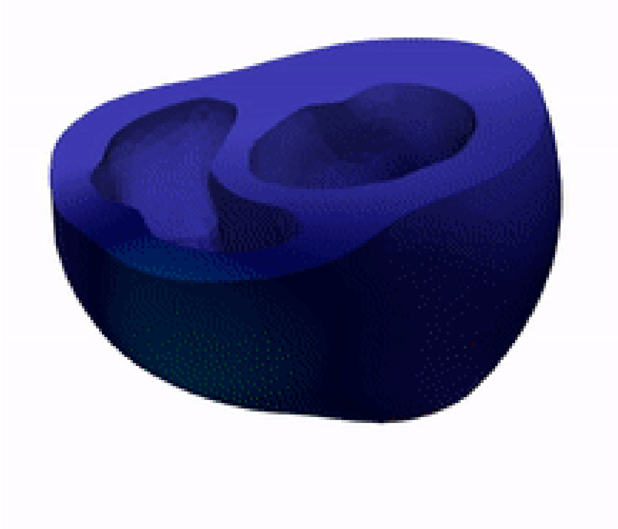
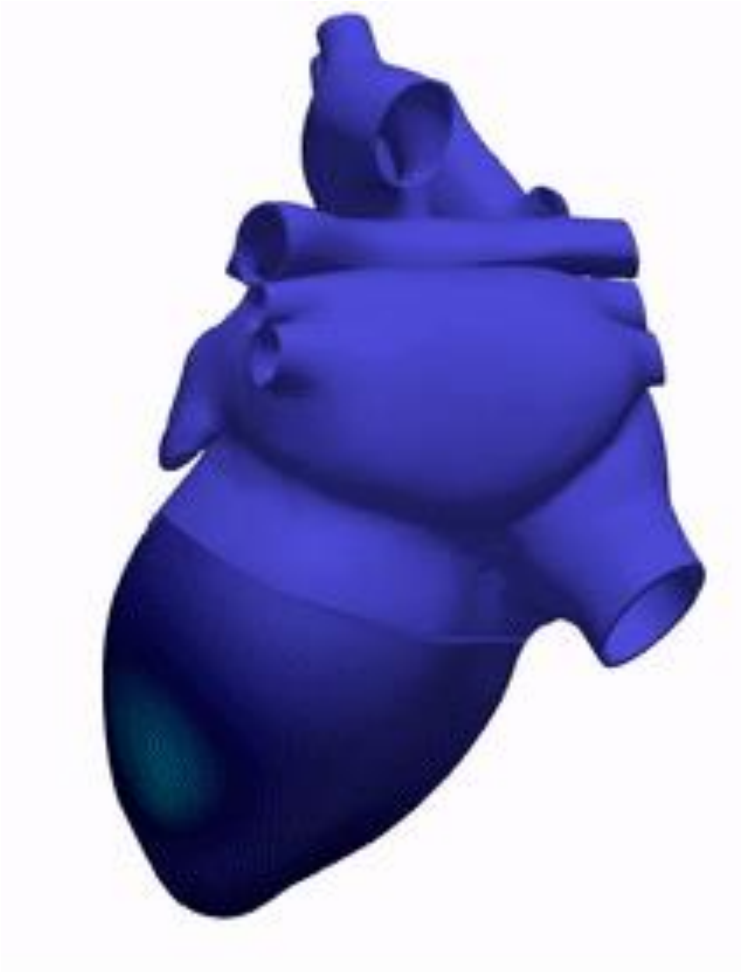
Animations of total heart deformation





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Conclusions

- The full human heart simulations using the Multiscale model and Decision Support System can provide physiologically relevant assessment of the familial cardiomyopathies simulated and the effect of drugs.
- These results can provide insights into clinically relevant observations of the disease and provide better insights on detailed drug effects.
- Future research challenges :
  - A pre-stress algorithm will be added to the simulations in order to achieve higher ejection fractions
  - The application of these methodologies to patient-specific anatomies for high throughput assessment for clinical purposes

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