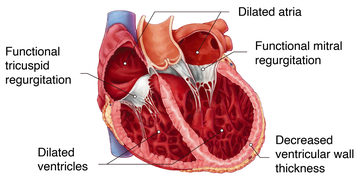
A Coupled Multiscale Electromechanical Myocyte Model to Assess the Effects of 2-Deoxy-ATP on Contractile Function in the Heart

[1]Abigail Teitgen, [2]Kimberly McCabe, [3]Michael Regnier, [1]Andrew D McCulloch
[1]Department of Bioengineering, University of California, San Diego, [2]Simula Research Laboratory,
[3]Department of Bioengineering, University of Washington

INTRODUCTION

- **Heart failure** remains a significant cause of **morbidity, mortality, and medical costs**

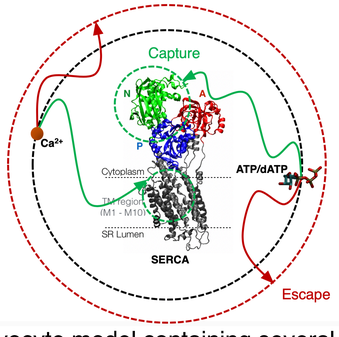
Dilated cardiomyopathy: reduced contractile function, heart is unable to pump sufficient blood to meet body's demands



- **2-deoxy-ATP (dATP):** a **novel heart failure therapeutic** shown to improve contractile function without impairing relaxation [1]
- dATP acts on myosin to increase the rate of crossbridge cycling, and has been shown to increase the rate of Ca^{2+} transient decay [2, 3]
- We hypothesized that dATP acts on the sarcoplasmic reticulum ATPase (SERCA), the pump responsible for removing Ca^{2+} from the cytosol following contraction, which could explain this increased Ca^{2+} decay
- Mechanisms of dATP still not fully understood, may have multiple targets in the myocyte
- Difficult to fully assess the mechanisms of dATP experimentally
- **We developed a novel multiscale modeling approach to investigate whether the effects of dATP on myosin and SERCA are sufficient to explain its therapeutic effects**

METHODS

- Gaussian Accelerated Molecular Dynamics (GaMD) simulations were used to assess the effects of dATP on SERCA conformation
- Brownian Dynamics (BD) simulations were used to obtain association rates for ATP/dATP binding to SERCA and Ca^{2+} binding to dATP-SERCA and ATP-SERCA using lowest energy structures from GaMD (Figure 1)



$$d\vec{x} = \underbrace{\frac{1}{k_B T}}_{\text{Movement}} \underbrace{\boldsymbol{D}\cdot\vec{F}\,dt}_{\text{Forces (electrostatic, short-ranged)}} + \underbrace{\sqrt{2\,dt}\,\boldsymbol{S}\cdot\vec{w}}_{\text{Diffusion (Brownian Motion)}}$$

Figure 1: Overview of Brownian Dynamics simulations performed on SERCA

- A myocyte model containing several ion channels including SERCA was utilized to assess the effects of dATP on Ca^{2+} handling; model was first optimized to match experimental data for ATP [3]
- The myocyte model was coupled to a Markov model of crossbridge cycling: state occupancies were input into the myocyte model to compute Ca^{2+} buffering and Ca^{2+} concentration determined from the myocyte model was input into the sarcomere model (Figure 2)
- Rates from BD were input as association rates in the SERCA model within the myocyte model, and crossbridge cycling parameters were altered based on previous study to simulate dATP treatment [2] (Table 1)

METHODS

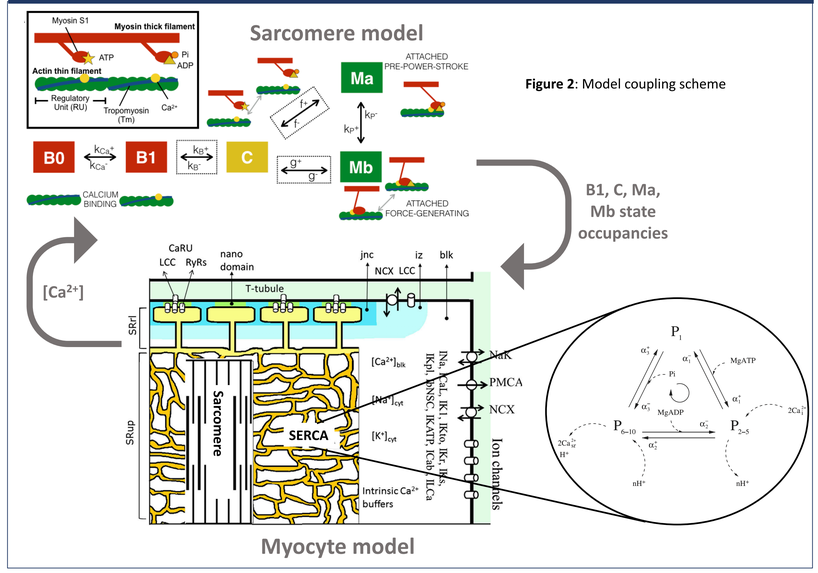


Figure 2: Model coupling scheme

RESULTS

- GaMD simulations show dATP causes separation of cytosolic domains of SERCA, which suggests increased pump speed
- Association rate for dATP binding to SERCA is 80% higher than the association rate for ATP (Table 1)
- Association rate for Ca^{2+} binding to SERCA is increased due to altered electrostatics in transmembrane region (Table 1)

Parameter	Myocyte model alone			Coupled myocyte and sarcomere model	
	WT optimized values	Optimized dATP values (SERCA only)	Optimized values for other pumps (calculated individually)	Altering just crossbridge parameters	Altering crossbridge and SERCA parameters
Amp_{NaK} (mM/ms)	17.77	17.77	170.5	17.77	17.77
Amp_{PMCA} (mM/ms)	0.19	0.19	2.1	0.19	0.19
k_1^+ (1/(M*s)) *from BD d(ATP)-SERCA association*	2.59E6	4.72E6	4.72E6	2.59E6	4.72E6
k_2^+ (1/(mM*s)) ADP-SERCA dissociation	2540	3716	2540	2540	3716
$k_{4,Ca}$ (mM) *from BD* Ca^{2+}-SERCA association	0.0027	0.0023	0.0023	0.0027	0.0023
f^+ (1/uM*ms) *from BD* C → Ma	0.1	0.1	0.1	0.448	0.448
k_P^+ ((1/uM*ms) Ma → Mb	0.754	0.754	0.754	2.6	2.6
g^+ (1/ms) Mb → C	1	1	1	3.45	3.45

Table 1: Parameters altered to simulate dATP treatment

- Unable to fully predict experimental dATP Ca^{2+} transient by modifying SERCA parameters from BD alone, dATP may have downstream effects on SERCA pump function (e.g. ADP dissociation rate) (Figure 3)
- Optimizing NaK and PMCA fluxes suggests dATP may affect other ATPases (Figure 3)

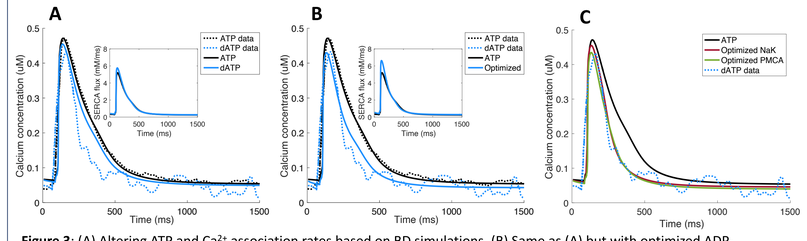


Figure 3: (A) Altering ATP and Ca^{2+} association rates based on BD simulations. (B) Same as (A) but with optimized ADP-SERCA dissociation rate. (C) Same as (A) but with optimized NaK and PMCA fluxes.

RESULTS

- Altering crossbridge cycling parameters in coupled model to simulate dATP treatment shows increased force but minimal changes in Ca^{2+} transient
- Altering both SERCA and crossbridge parameters to simulate dATP treatment shows smaller increase in force and increased Ca^{2+} decay

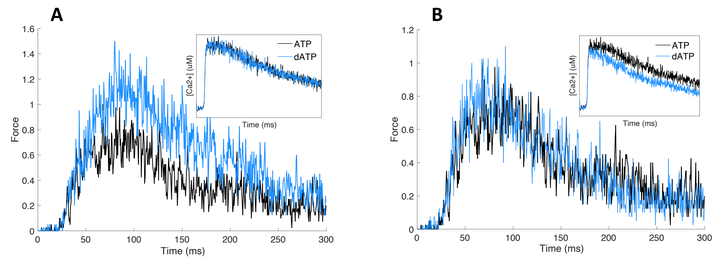


Figure 4: Coupled model altering (A) just crossbridge cycling parameters. (B) both crossbridge cycling and SERCA parameters.

CONCLUSIONS

- dATP is a promising therapeutic for treating heart failure
- dATP enhances SERCA pump function via increased rates of dATP and Ca^{2+} association due to altered electrostatic interactions, leading to faster Ca^{2+} decay
- Mechanism may be generalizable to other ATPases, additional work is needed
- Therapeutic effects of dATP likely depend on its effects on both myosin and SERCA
- Changes in Ca^{2+} buffering on sarcomere with dATP alone are insufficient to explain changes in Ca^{2+} transient, must account for effects of dATP on SERCA to accurately predict force
- Novel multiscale modeling framework allows for assessment of function from atomic to cellular levels
- Limitations: no lipids in BD simulations, Monte Carlo results are noisy, additional experimental data needed for validation

FUTURE WORK

- Couple to mitochondria model to assess effects of dATP on energetics
- Extend model to simulate both healthy and heart failure conditions
- Solve coupled electromechanical myocyte model in a finite element framework to assess effects of dATP on regional stress and strain

REFERENCES

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