A Model Based Analysis of Steady-State versus Dynamic Aspects of the Relationship between Calcium and Force

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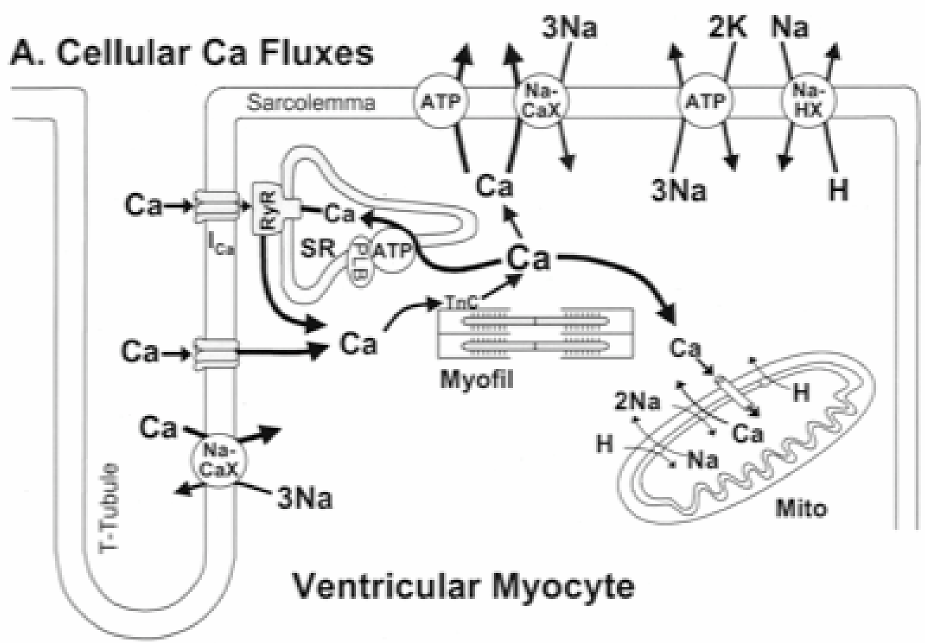
Background

Cardiac Contraction - The Role of Calcium

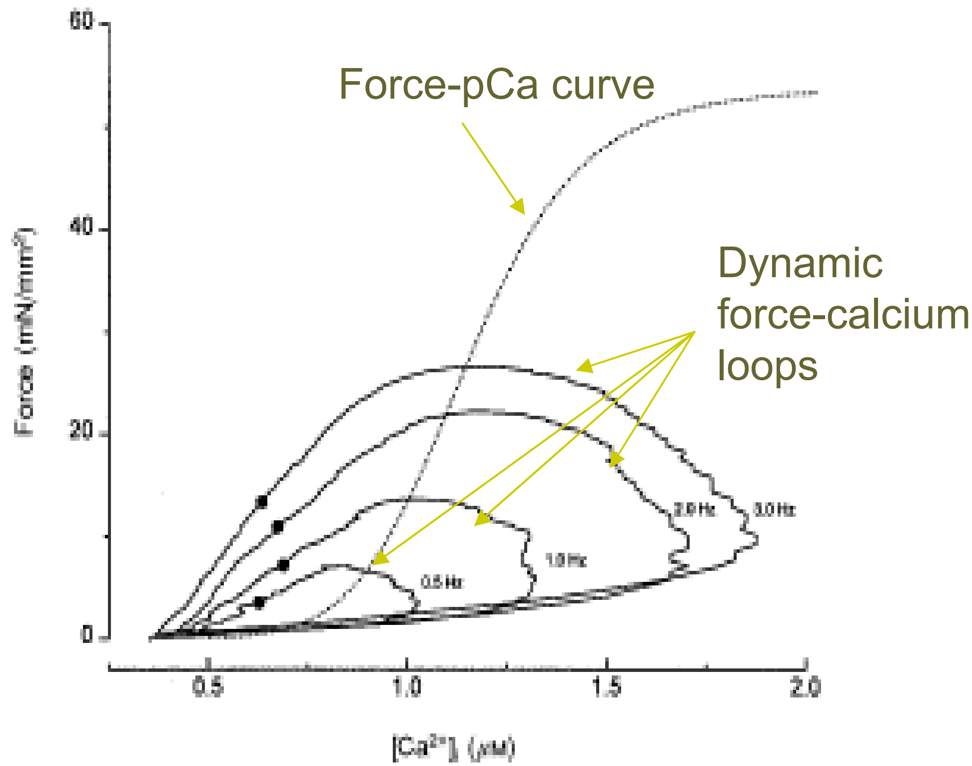
- Calcium is required for contractile activation



Background

Static vs. Dynamic calcium-force relationship

- Myofilament response to calcium is often studied in skinned fibers
- Data produced using this technique is presented as force-pCa curves
- May exist characteristics of the calcium-force relationship not described well by a force pCa curve



Gao W D, Perez N G, Marban E:
Calcium cycling and contractile activation in intact mouse cardiac muscle.
J of Physiol (1998), 507.1, pp. 175-184

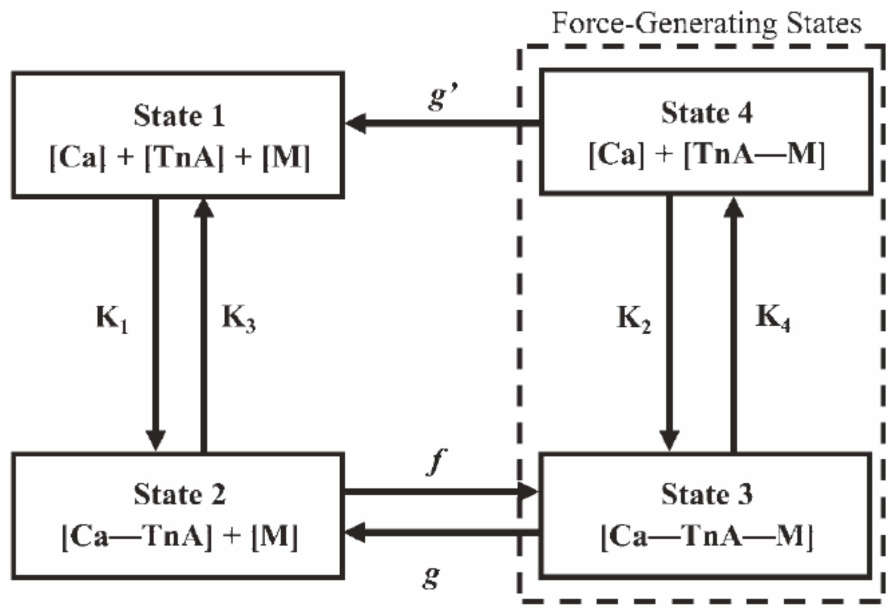
Purpose

- Interested in studying both dynamic and steady-state aspects of the calcium-force relationship simultaneously
- Interested in studying how changing different cellular processes affect steady-state and dynamic characteristics
- Cellular processes: calcium binding kinetics, crossbridge kinetics, and cooperativity feedback mechanism

Methods

The Four State Model – Determining Parameter Sets

[Ca](t) → Model Parameters → F(t)



MacGowan, Kirk, Evans, Shroff. The four-state model.
(Am J Physiol Heart Circ Physiol . 290: H2614-H2624. 2006)

Process	Parameter Set
Calcium-Troponin interaction	K_1, K_2, K_3, K_4
Crossbridge cycling	f, g, g'
Cooperativity feedback mechanism	α_1, α_f, β_1, β_f

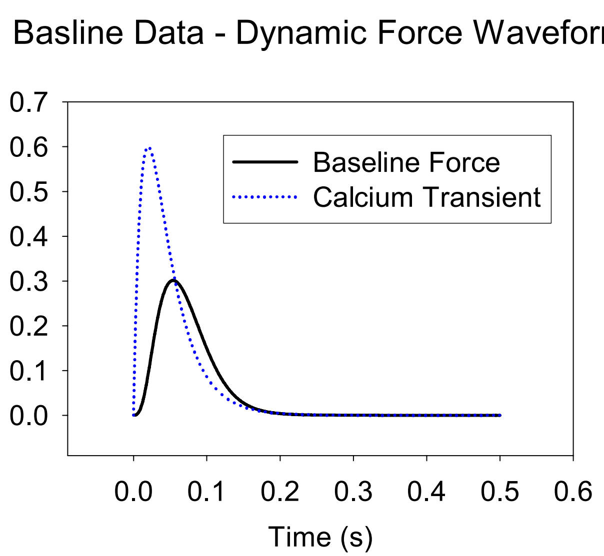
Methods

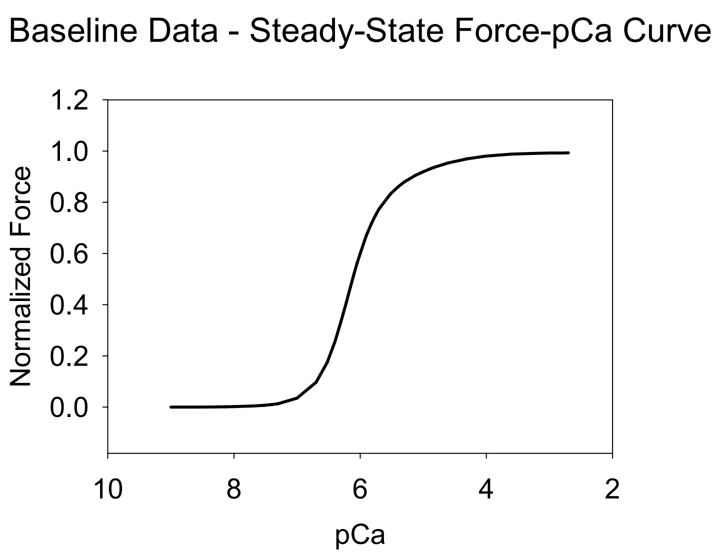
Determination of Baseline values

- Used time-varying and constant calcium inputs to represent dynamic and steady-state calcium input

- Model produces graphs based off of chosen baseline parameters

- Adjust values until fit experimental data in the literature





Methods

Evaluation of Force Response Waveforms

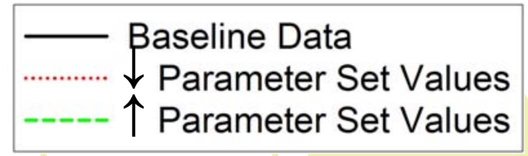
- Indices describing steady-state and dynamic aspects

Steady State Indices	**Description**
F_{max}	Force at maximum activation.
pCa_{50}	The $[Ca^{2+}]$ at which force is 50% of F_{max} and represents a compound affinity constant (i.e., the calcium sensitivity index).
nH	The Hill coefficient is the maximal slope of pCa_{50} and a quantitative measure of cooperativity.

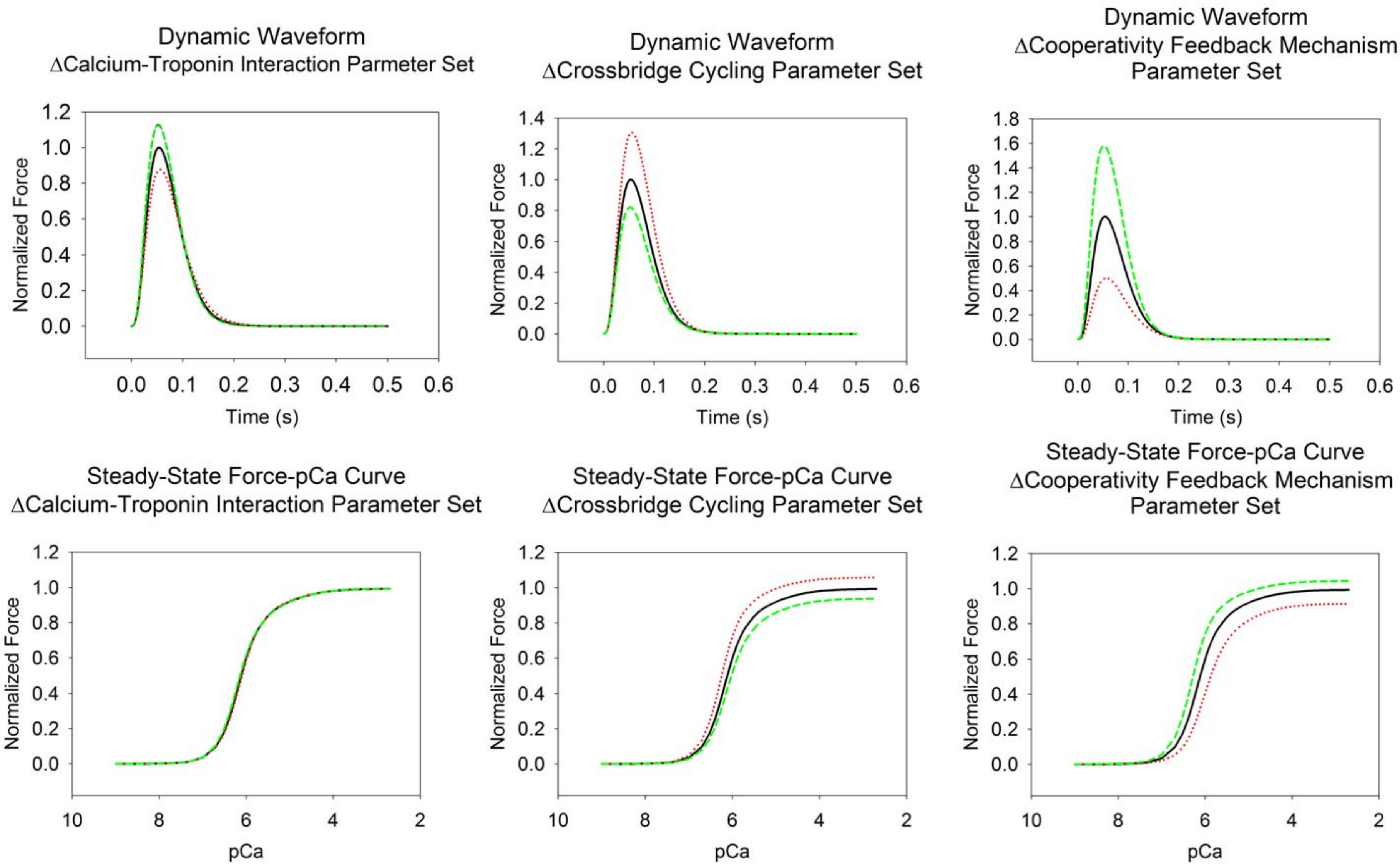
Dynamic Indicies	**Description**
F_{max}	The maximum force for the full range of calcium concentrations
T_{rise}	The time to rise from baseline to F_{max}
T_{relax}	The time to relax from F_{max} to baseline
dF/dt_{min}	The maximal rate of falling force (during relaxation)
dF/dt_{max}	The maximal rate of rising force (during contraction)

Results

Force Response Waveforms



- Shows how ↑ and ↓each set of parameters by 30% affect steady-state and dynamic wave form characteristics

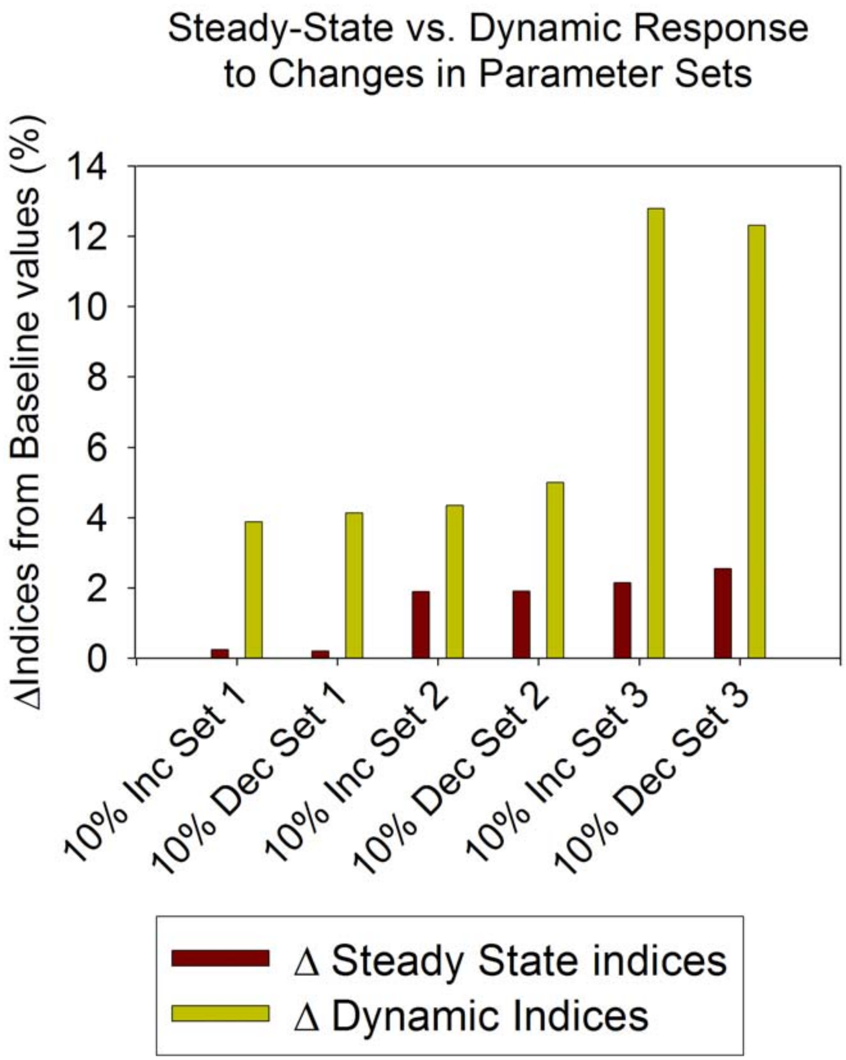


Results

Effect on Steady-State vs. Dynamic Indices

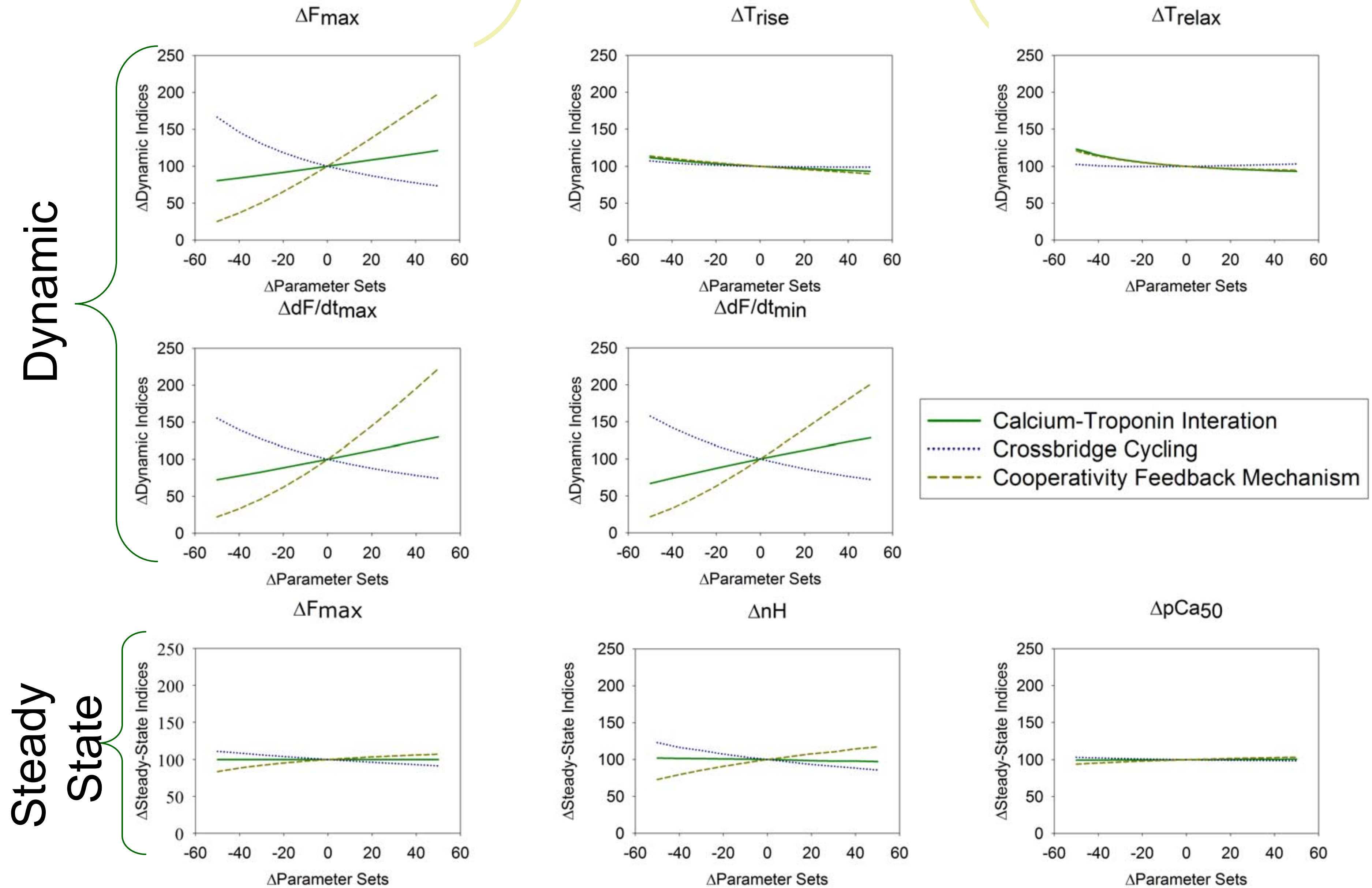
Set #	Process
Set 1	Calcium-Troponin Interaction
Set 2	Crossbridge cycling
Set 3	Cooperativity feedback mechanism

- Recognized a 2.3 to 21.4 fold increase (P = 0.011) in sensitivity to change in dynamic indices compared to steady-state indices



Results

Systematic Varying of Parameters



Conclusions

- Changes in all three processes (calcium binding kinetics, crossbridge kinetics, and cooperativity) affected both steady-state and dynamic aspects
- Relative sensitivity of changes in dynamic aspects were significantly greater
- Dynamic aspects of calcium-force relationship is physiologically important in cardiac contraction
- Model-based analysis may help guide future experimental work

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Thank You!!