# Introduction

# Methods

## Calcium activation

The crossbridge kinetic model used to simulate cardiomyocyte crossbridge mechanics was adapted from the previous Tewari et al. [3] and Campbell et al.[3] and Campbell et al. [4] crossbridge and calcium models. The possible states of myosin heads in the model are illustrated in Figure 3, and model variables are defined in Table 1.

The kinetics of attachment and detachment and the dynamics of force development and muscle deformation depend on the fraction of the thick myosin filament that overlaps with the opposite actin-myosin binding sites on the thin actin filament. The overlap function is denoted by *OV*(*SL*) and is a function of half-sarcomere length *SL/2*, as described below. The variable represents the fraction of actin-myosin binding sites on the thin filament that are not calcium bound and not permissive for crossbridge attachment. The variable *P*(*t*)is the fraction of myosin heads that are not attached to the thin filament via a crossbridge but are adjacent to a calcium bound active permissible binding site on the thin filament. The maximal value of *P*(*t*)at a given half sarcomere length *SL/2* is *OV*(*SL*) .

The calcium activation model is adapted from Campbell et al. [4]:

(1)

(2)

(3)

where *Jon* and *Joff* are the the rates of calcium association and dissociation. The term in the *Jon* equation is representative of cooperative activation along the thin filament. Assuming the probability of Ca2+-tropomyosin interaction is independent of location in overlapping versus non-overlapping zones, represents the fraction of total myosin binding sites on actin that are in the calcium-activated state but not in the myosin-attached state. Thus, because it is assumed that calcium does not dissociate from troponin at sites that are associated with attached crossbridges, the calcium unbinding rate is proportional to .



## Kinetics of attachment and attached-states

At a given sarcomere length mysosin heads that are in the thick filament overlap zone may be in a permissive, non-permissive, or one of three attached states (,,). The superscript *T* identifies the attached states that are influenced by cytosolic phosphate metabolite levels and the equations describing this relationship is further described below. The proportioning of myosin heads into these states obeys the conservation property

(4)

where *P*(*t*) is the proportion of myosin-heads that are permissible to binding to actin (associated with corresponding calcium-activated sites in the overlap zone), and , , and are the relative proportion of myosin heads that are in the attached states *A*1, *A*2, and *A*3, as described below. Thus, *P*(*t*) can be calculated

. (5)

The attached states , *A*2, and are associated with the probability density functions , , and , where *s* is the strain, or deformation, associated with attached states. The total fractions of myosin heads in each of the three attached states, , , and , are computed as the zeroth moments of the probability distributions:

(6)

(7)

. (8)

The strain distributions of attached states are governed by one-dimensional hyperbolic equations (Tewari et al. [3]): The strain distributions of attached states are governed by one-dimensional hyperbolic equations (Tewari et al. [3]):

(9)

(10)

. (11)

The left-hand side of Equations (9) -- (11) is the material derivative defining how the velocity of sliding, , influences the evolution of the strain distributions. The right-hand side defines the rate transitions from the permissive state to attached state *A*1, from *A*1 to *A*2, from *A*2 to *A*3, and from *A*3 back to the unattached permissive state.

In the above equations the Tewari et al. model [3] has been modified to include the factor in the attachment term This factor represents the proportion of myosin heads that are not in the super-relaxed state, . The kinetics of super-relaxed/not super-relaxed state transitions are described below.

The rate transitions in Equations (9) -- (11) are also influenced by cytosolic phosphate metabolite levels according to

(12)

as described by Tewari et al. [3].

**Super-relaxed state kinetics**

Unattached myosin heads (permissive P and non-permissive N) are assumed to exist in either a super-relaxed (SR(t)) or not super-relaxed (NR(t)) state. The fractions of unattached myosin heads in the SR and NR states are denoted and . The states PSR(t) and NSR(t) illustrated in Figure 1 represent the fractions of the P(t) and N(t) states in the SR state: and .

Transitions between the SR and NR states are governed by:

(13)

. (14)

In the Campbell et al. model the rate of transition from the SR to NR state is linearly dependent on active muscle tension, while here we assume that transition from SR to NR state is linearly dependent on active tension and a function of ATP concentration *ksr*. Thus Equation (13) assumes a linear mass-action decay of unattached myosin heads in the NR state into the SR state.

**Sarcomere geometry and filament overlap**

The overlap function *OV*(*SL*) represents the fraction of myosin heads that are adjacent to or attached to corresponding actin-myosin binding sites on the thin filament, ranges from 0 at SL of 1.2 to 1 at SL 2.3 and higher. The function is constructed based on the idealized sarcomere geometry illustrated in Figure 5, based on the formulation of Rice et al. [5]. The thick myosin filament is assumed to have constant length, *Lthick* = 1.65 m. The constant length of the stretch of the thick filament not populated by myosin heads is denoted *Lbare* = 0.1 m. The stretch of the thin filament with myosin head binding sites is also assumed to have a constant length, denoted *Lthin* = 1.2 m.

The length of thick filament occupying a half sarcomere is calculated

where *SL*(*t*) is the half-sarcomere length. The length of myosin thick filament in a half sarcomere that may not form crossbridges with adjacent actin thin filament binding sites is computed

Thus, the length of thick filament that has adjacent actin thin filament binding sites is calculated

and the total fraction of thick filament overlapping with accessible thin filament is calculated:

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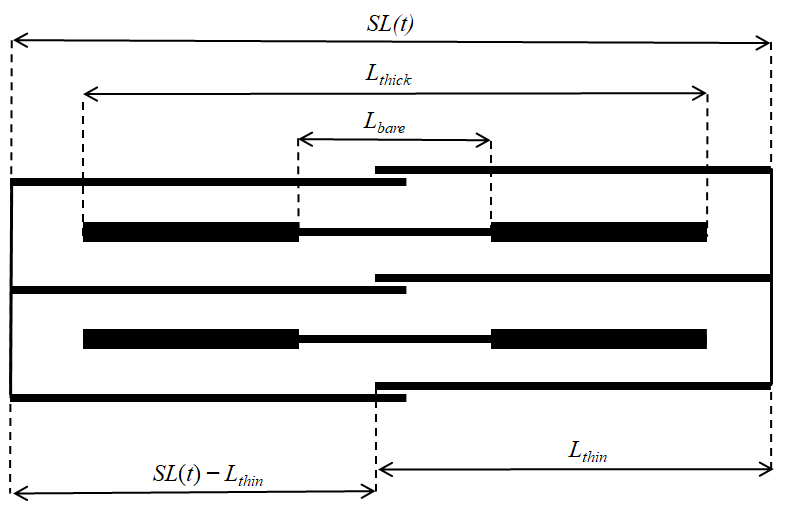


Figure 5: Schematics of overlap of thin and thick filaments.

## Active and passive forces

The force associated with cross bridges is computed from contributions from pre- and post-ratcheted states:

(11)

The passive tension is a function of sarcomere length and is calculated

(14)

where is a stiffness parameter and is the sarcomere length at rest. The term  is an adjustable parameter.

where and are stiffness constants.

The full muscle model (Figure 4) includes contributions from the active tension generated by the crossbridge mechanics, viscous () and passive (p) tensions associated with the muscle and a series element force . Overall force balance for the model yields

(12)

The tension contributed from the dashpot (viscous) is determined from the rate of change of sarcomere length

= (13)

## Simulation method

The kinetics of the attached-state strain distributions (Equations (9) -- (11)) are simulated by…

## Model calibration

**Works cited**

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7. Tewari, S.G., et al., *Influence of metabolic dysfunction on cardiac mechanics in decompensated hypertrophy and heart failure.* J Mol Cell Cardiol, 2016. **94**: p. 162-175.

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. (12)

The passive tension is not considered at the moment.a function of sarcomere length and is calculated

(14)

where is a stiffness parameter and is the sarcomere length at rest. The term  is an adjustable parameter.