Modeling short-term interval-force relations in cardiac muscle

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Rice, J. Jeremy, M. Saleet Jafri, and Raimond L. Winslow. Modeling short-term interval-force relations in cardiac muscle. Am. J. Physiol. Heart Circ. Physiol. 278: H913–H931, 2000.—This study employs two modeling approaches to investigate short-term interval-force relations. The first approach is to develop a low-order, discrete-time model of excitation-contraction coupling to determine which parameter combinations produce the degree of postextrasystolic potentiation seen experimentally. Potentiation is found to increase 1) for low recirculation fraction, 2) for high releasable fraction, i.e., the maximum fraction of Ca\(^{2+}\) released from the sarcoplasmic reticulum (SR) given full restitution, and 3) for strong negative feedback of the SR release on sarcolemmal Ca\(^{2+}\) influx. The second modeling approach is to develop a more detailed single ventricular cell model that simulates action potentials, Ca\(^{2+}\)-handling mechanisms, and isometric force generation by the myofibrils. A slow transition from the adapted state of the ryanodine receptor produces a gradual recovery of the SR release and restitution behavior. For potentiation, a small extrasystolic release leaves more Ca\(^{2+}\) in the SR but also increases the SR loading by two mechanisms: 1) less Ca\(^{2+}\)-induced inactivation of L-type channels and 2) reduction of action potential height by residual activation of the time-dependent delayed rectifier K\(^{+}\) current, which increases Ca\(^{2+}\) influx. The cooperativity of the myofibrils amplifies the relatively small changes in the Ca\(^{2+}\) transient amplitude to produce larger changes in isometric force. These findings suggest that short-term interval-force relations result mainly from the interplay of the ryanodine receptor adaptation and the SR Ca\(^{2+}\) loading, with additional contributions from membrane currents and myofilament activation.

excitation-contraction coupling; calcium handling; mechanical restitution

SHORT-TERM INTERVAL-FORCE (I-F) relations, as defined by Johnson (23), describe the dependence of contraction strength for short interbeat intervals (\(\leq 3\) s) in the physiological range for active mammals. Two phenomena that characterize the short-term I-F relations are restitution and postextrasystolic potentiation. Examples of experimentally obtained I-F relations from Wier and Yue (42) are shown in Fig. 1. The pacing protocol is a priming period, which is followed by variable extrasystolic intervals (ESIs) and then a fixed 3,000-ms postextrasystolic interval (PESI). The family of traces demonstrates restitution by the rise in twitch force (F), rate of force onset (+dF/dt), and aequorin luminescence (L/\(L_{\text{max}}\)) as ESI increases (cf. a and b in Fig. 1). Twitch force in response to a second stimulus applied at a fixed PESI shows the opposite behavior. For example, a small extrasystolic force leads to a potentiated postextrasystolic beat (a and a’ in Fig. 1). Similarly, as extrasystolic force rises with restitution, postextrasystolic force declines (b and b’ in Fig. 1). These data, along with other experimental studies (11, 46), have shown that restitution and postextrasystolic potentiation can be fit to exponentials with similar time constants, suggesting that a common mechanism may underlie both phenomena.

A relatively simple model has been developed to address the general behavior of restitution and postextrasystolic potentiation (12, 42). This model explains these behaviors in terms of the interplay of two features: 1) the total amount of Ca\(^{2+}\) loaded in the sarcoplasmic reticulum (SR) and 2) a feature in which Ca\(^{2+}\) loaded in the SR slowly becomes available for the next release. More specifically, restitution is explained by more Ca\(^{2+}\) becoming available for release as ESI increases. Given a sufficiently long ESI, the saturating plateau level of Ca\(^{2+}\) release at full restitution is assumed to reflect the total amount of Ca\(^{2+}\) in the SR. This plateau level has been shown to increase with the frequency of stimulation during the priming period. Presumably, this increase occurs because of a greater time-averaged influx of Ca\(^{2+}\) that loads the SR to a greater extent. Furthermore, after a small extrasystolic release, postextrasystolic potentiation occurs because 1) there is more Ca\(^{2+}\) remaining in the SR for the next release and 2) additional Ca\(^{2+}\) influx into the cell increases the SR Ca\(^{2+}\) load for the next release. The proposed mechanism for the additional Ca\(^{2+}\) influx is a reduction of negative feedback of the SR Ca\(^{2+}\) release on influx of Ca\(^{2+}\) through L-type Ca\(^{2+}\) channels (42).

Although this model makes accurate predictions of the general behaviors of restitution and postextrasystolic potentiation, it lacks mechanistic detail. The purpose of this study is to develop new models that improve on the results of the previous modeling efforts described above. The first phase of this work entails the development of a discrete-time model of excitation-contraction (E-C) coupling to address how systematic parameter variation affects restitution/postextrasystolic potentiation seen experimentally.
will be reproduced if the underlying biophysical mechanisms are reproduced. A detailed model is developed here by combining a single ventricular cell model simulating action potentials (APs) and Ca\(^{2+}\)-handling mechanisms (20) with a model of the myofilaments simulating isometric force generation (32). The single cardiac cell model incorporates recent experimental findings on the mechanisms of E-C coupling in cardiac cells, including 1) adaptation of the ryanodine receptor (RyR), the SR release channel; 2) a model of the L-type Ca\(^{2+}\) channel with Ca\(^{2+}\)-induced inactivation based on mode switching (18); and 3) a restricted subspace thought to exist between the RyR and L-type Ca\(^{2+}\) channels, where the local Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_{lo}\)) is thought to rise to \(\geq 10\) times the bulk myoplasmic ([Ca\(^{2+}\)]([Ca\(^{2+}\)]\(_{lo}\))) (19, 33). The myofilament model used in this model can reproduce isometric force responses seen experimentally and allows for direct comparison of model output with experimental data on I-F relations.

The “minimum” and “maximum” approaches to model I-F relations in this study are complementary. The low-order discrete-time model is suitable for systematic parameter variation studies. However, this model lacks mechanistic detail, and the physiological plausibility of any given parameter choice is difficult to assess on the basis of simple model results alone. The detailed model can better address such issues. However, the complexity of this model precludes exhaustive exploration of the complete parameter space.

**Glossary**

**General Terms**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-F</td>
<td>Interval-force</td>
</tr>
<tr>
<td>AP</td>
<td>Action potential</td>
</tr>
<tr>
<td>E-C</td>
<td>Excitation-contraction</td>
</tr>
<tr>
<td>SR</td>
<td>Sarcoplasmic reticulum</td>
</tr>
<tr>
<td>NSR</td>
<td>Network SR</td>
</tr>
<tr>
<td>J SR</td>
<td>J functional SR</td>
</tr>
<tr>
<td>RyR</td>
<td>Ryanodine receptor</td>
</tr>
<tr>
<td>SSI</td>
<td>Steady-state interval</td>
</tr>
<tr>
<td>ESI</td>
<td>Extrasystolic interval</td>
</tr>
<tr>
<td>PESI</td>
<td>Postextrasystolic interval</td>
</tr>
<tr>
<td>BCL</td>
<td>Basic cycle length</td>
</tr>
<tr>
<td>F</td>
<td>Isometric force</td>
</tr>
<tr>
<td>(\frac{dF}{dt})</td>
<td>Time derivative of isometric force</td>
</tr>
<tr>
<td>(\frac{L}{L_{max}})</td>
<td>Aequorin luminescence</td>
</tr>
</tbody>
</table>

**Simple Model Variables and Parameters**

**Variables**

- \(I_{NS2}(n)\): Ca\(^{2+}\) influx from SR of beat \(n\) (\(\mu M\))
- \(I_{NS3}(n)\): Ca\(^{2+}\) influx across sarcolemma of beat \(n\) (\(\mu M\))
- \(Out_{SR}(n)\): Ca\(^{2+}\) uptake into SR of beat \(n\) (\(\mu M\))
- \(Out_{SR}(n)\): Ca\(^{2+}\) efflux across sarcolemma of beat \(n\) (\(\mu M\))
- \(Load_{SR}(n)\): Ca\(^{2+}\) load of SR at beat \(n\) (\(\mu M\))
- \(Ca_{transient}(n)\): Ca\(^{2+}\) transient of beat \(n\) (\(\mu M\))
- \(Force(n)\): Force transient of beat \(n\) (N/mm\(^2\))
- \(\alpha(n)\): Restitution function of beat \(n\) (nondimensional)
- \(\Delta t(n)\): Time between beat \(n\) and \(n-1\) (ms)

**Fig. 1.** Original records illustrating restitution and postextrasystolic potentiation from Wier and Yue (42). Top: stimulation protocol. SSI, ESI, and PESI, steady-state, extrasystolic, and postextrasystolic intervals. A: isometric force \(F\); B: rate of force onset \(\frac{dF}{dt}\); C: aequorin luminescence \(\frac{L}{L_{max}}\). Traces are averages of 16–32 sweeps, with records aligned to superimpose steady-state responses. Responses a and a’ are from an extrasystole and accompanying postextrasystole obtained with ESI of 450 ms; b and b’ correspond to ESI of 3,000 ms. In all cases, PESI is fixed at 3,000 ms. Steady-state priming interval is 1,500 ms, and external Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_{i}\)) is 0.7 mM.

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### Glossary (continued)

**SR parameters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N_{fb} )</td>
<td>Forward cooperativity constant for Ca(^{2+})-ATPase</td>
<td>(1.4)</td>
</tr>
<tr>
<td>( \nu )</td>
<td>( \nu ) Ca(^{2+})-ATPase forward rate parameter</td>
<td>(0.292 ( \mu )M/s)</td>
</tr>
<tr>
<td>( \psi )</td>
<td>( \psi ) Ca(^{2+})-ATPase reverse rate parameter</td>
<td>(0.311 ( \mu )M/s)</td>
</tr>
<tr>
<td>( \tau_r )</td>
<td>Time constant for transfer from NSR to SR</td>
<td>(0.5747 ms)</td>
</tr>
<tr>
<td>( \tau_{ext} )</td>
<td>Time constant from subspace to myoplasm</td>
<td>(9.09 ms)</td>
</tr>
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### Detailed Model Variables and Parameters

**Cell geometry parameters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A_{cap} )</td>
<td>Capacitive membrane area</td>
<td>( 1.534 \times 10^{-4} ) cm(^2)</td>
</tr>
<tr>
<td>( V_{myo} )</td>
<td>Myoplasmic volume</td>
<td>(25.84 ( \times 10^{-6} ) µl)</td>
</tr>
<tr>
<td>( V_{JSR} )</td>
<td>Junctional SR volume</td>
<td>(0.16 ( \times 10^{-6} ) µl)</td>
</tr>
<tr>
<td>( V_{SS} )</td>
<td>Subspace volume</td>
<td>(1.40 ( \times 10^{-6} ) µl)</td>
</tr>
<tr>
<td>( V_{NSR} )</td>
<td>Network SR volume</td>
<td>(0.495 ( \times 10^{-9} ) µl)</td>
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</table>

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_1 )</td>
<td>( k_1 ) RyR ( P_{c1} \otimes P_{o1} ) rate constant</td>
<td>(0.01215 ( \mu )M(^{-4}) s(^{-1}))</td>
</tr>
<tr>
<td>( k_2 )</td>
<td>( k_2 ) RyR ( P_{c1} \otimes P_{c1} ) rate constant</td>
<td>(0.1425 s(^{-1}))</td>
</tr>
<tr>
<td>( k_6 )</td>
<td>( k_6 ) RyR ( P_{o1} \otimes P_{o2} ) rate constant</td>
<td>(0.00405 ( \mu )M(^{-3}) s(^{-1}))</td>
</tr>
<tr>
<td>( k_7 )</td>
<td>( k_7 ) RyR ( P_{o2} \otimes P_{o1} ) rate constant</td>
<td>(1.930 s(^{-1}))</td>
</tr>
<tr>
<td>( K_{p} )</td>
<td>Maximum plateau ( \alpha ) channel conductance</td>
<td>(0.0008 ms(^{-1}))</td>
</tr>
<tr>
<td>( n )</td>
<td>( n ) RyR ( Ca^{2+} ) cooperativity parameter ( P_{c1} \otimes P_{o1} )</td>
<td>(4)</td>
</tr>
<tr>
<td>( m )</td>
<td>( m ) RyR ( Ca^{2+} ) cooperativity parameter ( P_{o1} \otimes P_{o2} )</td>
<td>(3)</td>
</tr>
</tbody>
</table>

### Standard ionic concentrations

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
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<tbody>
<tr>
<td>( [K^+]_o )</td>
<td>Extracellular ( K^+ ) concentration</td>
<td>(5.4 mM)</td>
</tr>
<tr>
<td>( [Na^+]_o )</td>
<td>Extracellular ( Na^+ ) concentration</td>
<td>(140.0 mM)</td>
</tr>
<tr>
<td>( [Ca^{2+}]_o )</td>
<td>Extracellular ( Ca^{2+} ) concentration</td>
<td>(1.8 mM)</td>
</tr>
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### Membrane current parameters

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_m )</td>
<td>Unit membrane capacitance</td>
<td>(1.0 ( \mu )F/cm(^2))</td>
</tr>
<tr>
<td>( F )</td>
<td>Faraday's constant</td>
<td>(96.5 coul/mmole)</td>
</tr>
<tr>
<td>( T )</td>
<td>Absolute temperature</td>
<td>(310 K)</td>
</tr>
<tr>
<td>( R_\text{Na} )</td>
<td>Ideal gas constant</td>
<td>(8.314 ( \times ) ( \cdot ) mol(^{-1}) ( \cdot ) K(^{-1}))</td>
</tr>
<tr>
<td>( \tau_{K,P} )</td>
<td>Maximum plateau ( K^+ ) channel conductance</td>
<td>(12.8 mS/µF)</td>
</tr>
<tr>
<td>( P_{Na,K} )</td>
<td>( Na^+ ) permeability of ( K^+ ) channel</td>
<td>(0.00828 mS/µF)</td>
</tr>
<tr>
<td>( K_{Na,Ca} )</td>
<td>Scaling factor of ( Na^+ /Ca^{2+} ) exchange</td>
<td>(0.01833)</td>
</tr>
<tr>
<td>( K_{Na} )</td>
<td>( Na^+ ) half-saturation constant</td>
<td>(9.000 ( \mu )A/µF)</td>
</tr>
<tr>
<td>( K_{Ca} )</td>
<td>( Ca^{2+} ) half-saturation constant for ( Na^+ /Ca^{2+} ) exchange</td>
<td>(1.38 mM)</td>
</tr>
<tr>
<td>( k_{sat} )</td>
<td>( Na^+ /Ca^{2+} ) exchange saturation factor at negative potentials</td>
<td>(0.1)</td>
</tr>
<tr>
<td>( \tau_{Na} )</td>
<td>( Na^+ ) control's voltage dependence of ( Na^+ /Ca^{2+} ) exchange</td>
<td>(0.35)</td>
</tr>
<tr>
<td>( P_{Na,K} )</td>
<td>Maximum ( Na^+ /K^+ ) pump current</td>
<td>(2.47 ( \mu )A/µF)</td>
</tr>
<tr>
<td>( P_{Na,K} )</td>
<td>( Na^+ ) half-saturation constant for ( Na^+ /K^+ ) pump</td>
<td>(10.0 ( \mu )M)</td>
</tr>
<tr>
<td>( P_{Na,K} )</td>
<td>( K^+ ) half-saturation constant for ( Na^+ /K^+ ) pump</td>
<td>(1.5 ( \mu )M)</td>
</tr>
<tr>
<td>( P_{Na,K} )</td>
<td>( Na^+ ) non-specific current channel</td>
<td>(0.01 ( \mu )A/µF)</td>
</tr>
<tr>
<td>( P_{Na,K} )</td>
<td>( K^+ ) non-specific current channel</td>
<td>(0.01 ( \mu )A/µF)</td>
</tr>
<tr>
<td>( K_{m,K} )</td>
<td>( Ca^{2+} ) half-saturation constant for ( Na^+ /K^+ ) pump</td>
<td>(1.2 ( \mu )M)</td>
</tr>
<tr>
<td>( K_{m,K} )</td>
<td>Maximum ( Ca^{2+} ) pump current</td>
<td>(0.575 ( \mu )A/µF)</td>
</tr>
<tr>
<td>( K_{m,K} )</td>
<td>Half-saturation constant for ( Ca^{2+} ) pump</td>
<td>(0.5 ( \mu )M)</td>
</tr>
<tr>
<td>( \tau_{Na,b} )</td>
<td>Maximum ( Na^+ ) current conductance</td>
<td>(0.006032 mS/µF)</td>
</tr>
<tr>
<td>( \tau_{Na,b} )</td>
<td>Maximum ( Na^+ ) current conductance</td>
<td>(0.00141 mS/µF)</td>
</tr>
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</table>

### SR parameters

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_f )</td>
<td>RyR channel flux constant</td>
<td>(3.6 ms(^{-1}))</td>
</tr>
<tr>
<td>( K_{fb} )</td>
<td>Forward half-saturation constant for ( Ca^{2+})-ATPase</td>
<td>(0.24 ( \mu )M)</td>
</tr>
<tr>
<td>( K_{rb} )</td>
<td>Backward half-saturation constant for ( Ca^{2+})-ATPase</td>
<td>(1.64 ( \mu )M)</td>
</tr>
</tbody>
</table>

### Buffering parameters

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( [LTPRN]_{tot} )</td>
<td>Total troponin low-affinity site concentration</td>
<td>(70.0 ( \mu )M)</td>
</tr>
<tr>
<td>( [HTRPN]_{tot} )</td>
<td>Total troponin high-affinity site concentration</td>
<td>(140.0 ( \mu )M)</td>
</tr>
<tr>
<td>( k_{b,\alpha} )</td>
<td>( Ca^{2+} ) on-rate for troponin high-affinity sites</td>
<td>(1.0 ( \times ) ( 10^{9} ) M(^{-1}) s(^{-1}))</td>
</tr>
<tr>
<td>( k_{b,\alpha} )</td>
<td>( Ca^{2+} ) off-rate for troponin high-affinity sites</td>
<td>(0.33 s(^{-1}))</td>
</tr>
<tr>
<td>( k_{b,\alpha} )</td>
<td>( Ca^{2+} ) on-rate for troponin low-affinity sites</td>
<td>(4.0 ( \times ) ( 10^{7} ) M(^{-1}) s(^{-1}))</td>
</tr>
<tr>
<td>( k_{b,\alpha} )</td>
<td>( Ca^{2+} ) off-rate for troponin low-affinity sites</td>
<td>(40.0 s(^{-1}))</td>
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### Myofilament/force generation parameters

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f )</td>
<td>Conversion factor for normalization to physiological force</td>
<td>(0.1 N/mm(^2))</td>
</tr>
<tr>
<td>( f_{KB} )</td>
<td>Basic transition rate from weak to strong cross bridge</td>
<td>(10 s(^{-1}))</td>
</tr>
<tr>
<td>( g_{KB} )</td>
<td>Minimum transition rate from strong to weak cross bridge</td>
<td>(30 s(^{-1}))</td>
</tr>
<tr>
<td>SL</td>
<td>Sarcomere length</td>
<td>(2.15 µm)</td>
</tr>
</tbody>
</table>
Glossary (continued)

Current and fluxes

\(\dot{I}_{Na}\) Fast Na⁺ current (µA/µF)
\(\dot{I}_{Ca}\) L-type channel Ca²⁺ current (µA/µF)
\(\dot{I}_{Ca,K}\) L-type channel K⁺ current (µA/µF)
\(\dot{I}_K\) Time-dependent delayed rectifier K⁺ current (µA/µF)
\(\dot{I}_{K1}\) Time-independent K⁺ current (µA/µF)
\(\dot{I}_P\) Plateau K⁺ current (µA/µF)
\(\dot{I}_{Na,Ca}\) Na⁺/Ca²⁺ exchanger current (µA/µF)
\(\dot{I}_{Na,K}\) Na⁺-K⁺ pump (µA/µF)
\(\dot{I}_{Ca,Ca}\) Nonspecific Ca²⁺-activated current (µA/µF)
\(\dot{I}_{Ca,Na}\) Sarcoplasmic Ca²⁺ pump current (µA/µF)
\(\dot{I}_{Ca,B}\) Ca²⁺ background current (µA/µF)
\(\dot{I}_{Na,B}\) Na⁺ background current (µA/µF)

\(J_{up}\) SR Ca²⁺-ATPase pump flux (µM/ms)
\(J_{rd}\) SR Ca²⁺ RyR release flux (µM/ms)
\(J_{tr}\) Troponin Ca²⁺ buffer flux (µM/ms)
\(J_{sr}\) Network SR-to-junctural SR flux (µM/ms)
\(J_{xsr}\) Subspace-to-myoplasm Ca²⁺ flux (µM/ms)

Initial conditions

\(t\) Time (0.00 ms)
\(V\) Membrane potential (−80.578 mV)
\(m\) Na⁺ activation gate (0.962369)
\(h\) Na⁺ slow inactivation gate (0.975658)
\(j\) K⁺ activation gate (3.37175 × 10⁻⁴)
\(k\) K⁺ inactivation gate (3.26174 × 10⁻⁴)

\([Ca]\) Intracellular Ca²⁺ concentration (0.0814869 µM)
\([Ca]\) Subsarcolemmal Ca²⁺ concentration (0.637931 µM)
\([Ca]\) Network SR Ca²⁺ concentration (0.228497 mM)

\(P_{C1}\) Fraction of channels in state \(C_{1}\) (0.637931)
\(P_{D1}\) Fraction of channels in state \(D_{1}\) (0.428917 × 10⁻³)
\(P_{C2}\) Fraction of channels in state \(C_{2}\) (0.361643)
\(C_0\) L-type Ca²⁺ current—normal mode (0.998666)
\(C_1\) L-type Ca²⁺ current—normal mode (1.63594 × 10⁻⁴)
\(C_2\) L-type Ca²⁺ current—normal mode (1.0495 × 10⁻⁸)
\(C_3\) L-type Ca²⁺ current—normal mode (2.74371 × 10⁻¹³)
\(C_4\) L-type Ca²⁺ current—normal mode (2.80908 × 10⁻¹⁸)
\(O\) L-type Ca²⁺ channel open—normal mode (4.21370 × 10⁻¹⁹)
\(C_{a0}\) L-type Ca²⁺ channel—normal mode (1.17155 × 10⁻³)
\(C_{a0}\) L-type Ca²⁺ channel—normal mode (7.67674 × 10⁻⁷)
\(C_{a0}\) L-type Ca²⁺ channel—normal mode (1.88635 × 10⁻¹⁰)
\(C_{a0}\) L-type Ca²⁺ channel—normal mode (2.06007 × 10⁻¹⁴)
\(C_{a0}\) L-type Ca²⁺ channel—normal mode (8.43672 × 10⁻¹⁹)
\(C_{a0}\) L-type Ca²⁺ channel—normal mode (0.0)
\(y\) L-type Ca²⁺ inactivation gate (0.0)

\([LTRPNCa]\) Concentration of Ca²⁺ bound to low-affinity troponin sites (0.4068232 µM)
\([HTRPNCa]\) Concentration of Ca²⁺ bound to high-affinity troponin sites (0.132944 mM)
\(N_0\) Nonpermissive tropomyosin with 0 cross bridges (0.99999027)
\(N_1\) Nonpermissive tropomyosin with 1 cross bridge (3.88506 × 10⁻⁶)
\(N_2\) Nonpermissive tropomyosin with 2 cross bridges (1.46758 × 10⁻⁶)
\(N_3\) Nonpermissive tropomyosin with 3 cross bridges (1.47026 × 10⁻⁶)
\(N_4\) Nonpermissive tropomyosin with 4 cross bridges (1.83527 × 10⁻⁶)
\(N_5\) Nonpermissive tropomyosin with 5 cross bridges (1.06786 × 10⁻⁶)

Initial conditions (continued)

\(P_0\) Permissive tropomyosin with 0 cross bridges
\(P_1\) Permissive tropomyosin with 1 cross bridge
\(P_2\) Permissive tropomyosin with 2 cross bridges
\(P_3\) Permissive tropomyosin with 3 cross bridges

METHODS

Simple Model Construction

A simple model is developed as shown in Fig. 2. The model assumes two sources of intracellular Ca²⁺ per AP: one from across the sarcolemma (\(I_{Na}\)) and one from the SR release (\(I_{Ca}\)). Ca²⁺ is removed from the cell by efflux across the sarcolemma (\(Out_{SR}\)) and uptake into the SR (\(Out_{SC}\)). Each of the four variables just described is calculated at each iteration [denoted by \(n\)]. Additional equations governing the system are given below.

The amount of Ca²⁺ released from the SR during each AP is assumed to depend on the amount of Ca²⁺ in the SR and the state of restitution. The governing equation for the SR release is given by

\[\dot{I}_{Ca} = \alpha(n)[\beta \cdot Load_{SR}(n-1)]\] (1)

where \(Load_{SR}(n-1)\) is the total Ca²⁺ load of the SR computed from the last iteration, \(\beta\) is the fraction of the total load that can be released with the assumption of full restitution, and \(\alpha(n)\) is the restitution function that assumes a value between 0 and 1. The restitution function is

\[\alpha(n) = [1 - \exp(-\Delta t(n)/\tau)]\] (2)

where \(\Delta t(n)\) is the time difference between the last AP and the present AP and \(\tau\) is the time constant of restitution.

The simple model assumes that transsarcolemmal influx (\(I_{Na}\)) does not contribute directly to the Ca²⁺ transient but is, instead, sequestered by the SR and is made available for release only on the subsequent beat. Hence, the total Ca²⁺ transient is produced by the SR release alone

\[Ca_{Transient}(n) = I_{Na}(n)\] (3)

A similar formulation has been used previously (46). Clearly, this is an approximation; influx through L-type channels initiates the SR release and, therefore, must contribute to the Ca²⁺ transient to some extent. However, the initial influx that triggers the SR release may be small, and the subsequent Ca²⁺ influx may play a larger role in the SR loading (9, 16).

In the simple model the SR uptake [\(Out_{SR}(n)\)] contains a component from the recirculation fraction (\(r\)) of the Ca²⁺ transient and a component from the sarcolemmal influx

\[Out_{SR}(n) = r \cdot Ca_{Transient}(n) + I_{Na}(n)\] (4)

The fraction of Ca²⁺ transient that is not sequestered into the SR is assumed to be extruded from the cell across the sarcolemma. Therefore

\[Out_{SC}(n) = (1 - r) \cdot Ca_{Transient}(n)\] (5)

The load of Ca²⁺ in the SR is updated at each iteration by the governing equation

\[Load_{SR}(n) = Load_{SR}(n-1) - I_{SR}(n) + Out_{SR}(n)\] (6)
The sarcolemmal influx \( (I_{nSC}) \) is assumed to be a decreasing function of the Ca\(^{2+}\) transient to account for Ca\(^{2+}\)-induced inactivation of L-type channels. The effect of Ca\(^{2+}\)-induced inactivation is that a small Ca\(^{2+}\) release from the SR on the current beat produces a greater influx of Ca\(^{2+}\), which in turn increases the SR load for the next beat. The input across the sarcolemma is given by

\[
I_{nSC}(n) = \gamma(1 - h \cdot \alpha(n)) \tag{7}
\]

where \( \gamma \) is a constant, \( \alpha(n) \) is defined in Eq. 2, and \( h \) is a constant between 0 and 1 that corresponds to the amount of Ca\(^{2+}\)-induced inactivation. A value of \( h \) near 1 produces a large dependence of sarcolemmal influx on the Ca\(^{2+}\) transient, whereas a value of 0 corresponds to a constant sarcolemmal influx with no dependence on the Ca\(^{2+}\) transient. Although the formulation of Eq. 7 does not appear to depend on the Ca\(^{2+}\) transient, there is an implicit dependence through the term \( \alpha(n) \) (SR release and Ca\(^{2+}\) transient are directly proportional to \( \alpha(n) \), see Eqs. 1 and 7).

The model just described produces Ca\(^{2+}\) transients for each beat. The Ca\(^{2+}\) transients must be converted to force transients for every beat to compare the model predictions more directly with experimental results. This is accomplished with the following conversion

\[
\text{Force}(n) = \eta \cdot [\text{Ca}_{\text{Transient}}(n) - \epsilon] \quad \text{if } \text{Ca}_{\text{Transient}}(n) > \epsilon
\]

\[
= 0 \quad \text{otherwise} \tag{8}
\]

where \( \eta \) and \( \epsilon \) are empirically determined constants. This relation follows directly from the work of Wier and Yue (42) that demonstrates that peak force is linearly correlated with peak [Ca\(^{2+}\)]. The average values from this study are \( \eta = 0.03 \) N·mm\(^{-2}\)·μM\(^{-1}\) and \( \epsilon = 0.51 \) μM. Empirical data also determine the time constant of restitution (in Eq. 2) to be equal to 765 ms. With these parameters constrained, the simple model is run with the following free parameters: \( r, \beta, \) and \( h \).

**Simple Model Simulation Protocol**

The simulation protocol is based on the experimental work of Wier and Yue (42) and is shown schematically in Fig. 1. In the original experiment, 12–20 priming beats were used to load the SR and produce a near steady-state output. In the simulations the number of priming beats is increased to 60 to ensure a near-steady output for all choices of model parameters. The influx constant \( \gamma \) in Eq. 7 is adjusted to generate a standard force level by the 60th priming beat. The standard level of force is arbitrarily chosen to be 12.5 ± 0.1 mN/mm\(^2\), a level similar to the last steady-state beat in Fig. 1. The priming beats are delivered at 1,500-ms intervals. The ESI is varied between 150 and 3,000 ms in 150-ms increments. The PESI is fixed at 3,000 ms.

The initial conditions are chosen to yield a force close to the standard value of 12.5 ± 0.1 mN/mm\(^2\). The initial conditions are

\[
\begin{align*}
I_{nSC}(0) &= I_{\text{InfluxPriming}} \\ I_{nSR}(0) &= 1 - I_{\text{InfluxPriming}} \\ \text{Out}_{SC}(0) &= 1 - r \\ \text{Out}_{SR}(0) &= r \\ \text{Load}_{SR}(0) &= 1 - \exp(-1,500 \text{ ms}/r)
\end{align*} \tag{9-13}
\]

**Detailed Model Construction**

The detailed model is derived from two models developed previously. Briefly, membrane currents and Ca\(^{2+}\) handling are described using a modified version of a single cardiac cell model described previously (20). This model lacked force generation, which is now provided by a model of the myofilaments (model 5 in Ref. 32). The two models are linked as follows. The cardiac cell model provides the Ca\(^{2+}\) transient to drive the myofilament model. This is a feedforward pathway by which the Ca\(^{2+}\) transient produces binding to troponin and subsequent force generation by the myofilaments. A feedback pathway also exists, because the affinity of troponin for Ca\(^{2+}\) is a function of developed force. Specifically the off-rate of Ca\(^{2+}\) from troponin is assumed to be a decreasing function of normalized force. Thus the level of developed force can alter the amount of Ca\(^{2+}\) bound to troponin and, subsequently, alter the activator Ca\(^{2+}\) transient (in the original cardiac cell model, troponin was assumed to be a simple buffer).

The full set of equations for the detailed model is provided in the Appendix. The description here will focus on a number of critical differences between the new formulation and the previous model (20) from which it was derived.

RyRs. The original formulation of RyRs was modified to increase the forward rate to and reverse rate from the adapted state (\( P_{C2} \) in Eqs. A71–A74). The forward rate was increased to 100 s\(^{-1}\) to make the time constant of adaptation ~10 ms. A similar value of 15 ms is found experimentally for the rat at room temperature (45). The model assumes a slightly higher rate at a physiological temperature. The increase in forward rate makes adaptation a more important modulatory factor in shaping SR release than in the original model (20). These roles can justified by recent experimental findings that suggest an important role of RyR inactivation in terminating release (36).

Network SR-to-junctional SR transfer rate. The SR is assumed to consist of two compartments: the uptake compartment [network SR (NSR)] and the release compartment [junctional SR (J SR)]. The transfer rate between these compartments is set by \( J_{TR} \). In the original model (20), \( J_{TR} \) was a
relatively small value, resulting in the depletion of JSR during each AP, hastening the termination of the SR release. In the present model, J_{TR} is made sufficiently large so that NSR and JSR vary by only a small amount. A large value of J_{TR} is consistent with estimates that Ca^{2+} diffusion between these compartments should be quite rapid, requiring only a few milliseconds at most (9).

Ca^{2+}-ATPase pump. The formulation of the SR Ca^{2+}-ATPase pump was modified to be similar to a model proposed by Shannon et al. (38) that includes both forward and reverse modes, each with its own binding constant and maximum rate. The forward mode exhibits slight cooperativity, with an experimentally determined value of 1.2 (38). In the original Ca^{2+}-handling model (20), forward cooperativity of 2 was assumed, which is consistent with other estimates (28). In the present model, a value of 1.4 is chosen as a compromise between these two conflicting estimates. In general, the choice of this parameter was limited by two extremes. Low cooperativity values cause the Ca^{2+}-ATPase pump to run at relatively high rates during diastole, producing unphysiologically low [Ca^{2+}]. High cooperativity values cause a rapid increase in pump rate as [Ca^{2+}] increases. This leads to Ca^{2+} transients with narrow peaks. This is a consequence of the large SR uptake at peak [Ca^{2+}].

A final change is the removal of a Ca^{2+} leak from the SR. In the original model, the leak kept [Ca^{2+}]_{NSR} from rising too high by counterbalancing the Ca^{2+}-ATPase pump, which had no reverse rate. This SR leak is no longer necessary, inasmuch as the Ca^{2+}-ATPase has a reverse rate that counterbalances the forward rate as [Ca^{2+}]_{NSR} increases.

**Detailed Model Simulation Protocol**

The model comprises 36 ordinary differential equations that are solved using the methods described in our previous modeling work (20). The equations, standard parameters, and initial conditions are provided in the Appendix. The pacing stimulus is a square pulse of 100 mA with a 0.5-ms duration.

Similar to the experimental work of Wier and Yue (42), a priming period of 30 s is sufficient to bring the detailed model to approximately steady state. The priming beats are delivered at a fixed interval of 1,500 ms in the simulations, unless otherwise noted in Results. The ESI is varied between 236.6 and 2,942.1 ms in 236.6-ms increments. The PESI is fixed at 3,000 ms. It is emphasized that the detailed model simulation involves only changes in the stimulus pattern, and otherwise no parameters are varied to alter the restitution/postextrasystolic behavior.

**RESULTS**

**Simple Model**

Sample simulation results for the simple, discrete-time model are shown in Fig. 3. The parameter choices for this run are r (recirculation fraction) = 0.75, β (releasable fraction) = 0.5, and h (feedback parameter) = 0.27. Figure 3A shows Ca^{2+} transients, and Fig. 3B shows the corresponding force transients. The last two priming beats are shown in Fig. 3, A and B, left, and demonstrate that the model has reached steady state. The plots show a composite of 10 runs with ESI ranging from 300 ms (a in Fig. 3) to 3,000 ms (b in Fig. 3), a range similar to that of the experimental data in Fig. 1. As in the experimental data, as ESI increases, restitution of Ca^{2+} transients and force transients occurs. Note that force is 0 at the shortest ESI, because the Ca^{2+} transient is less than ε (see Eq. 8). For ESI equal to the priming interval (1,500 ms), there is incomplete restitution because of the long time constant of restitution (τ = 765 ms, see Eq. 2). Restitution is nearly complete when ESI is maximal at 3,000 ms (b in Fig. 3).

The postextrasystolic beats show behavior that is opposite from that of the extrasystolic beats; i.e., the least amount of restitution (a in Fig. 3) corresponds to the greatest level of potentiation (a' in Fig. 3). In contrast, the force at full restitution (b in Fig. 3) corresponds to the lowest level of postextrasystolic potentiation (b' in Fig. 3). This behavior is qualitatively consistent with experimental data from a number of studies in whole heart (11) and muscle preparations (24, 29, 42). However, the simulated and experimental results differ quantitatively in the degree of postextra-
In the experimental data, postextrasystolic force can be two or more times greater than the steady-state force from the last priming beat (29, 42, 44, 46). The level of postextrasystolic potentiation is smaller in this simulation. A potentiation ratio can be computed as the ratio of force at the greatest level of potentiation \((a_8\) in Fig. 3 corresponding to the shortest ESI) to the force in response to the last priming beat \((ss\) in Fig. 3). The potentiation ratio is 1.53, which falls short of experimental data \((\geq 2)\) at least for the parameters chosen for this simulation.

The next set of simulations addresses the question of whether another choice of \(r\), \(\beta\), and \(h\) can produce a high level of postextrasystolic potentiation. The simulation protocol used in Fig. 3 is repeated for \(r\) in the range 0.5–0.975 and \(h\) in the range 0.0–1.0; \(\beta\) is fixed at 0.25, 0.5, and 0.75 in Fig. 4, A, B, and C, respectively. The resulting potentiation ratios are plotted as a surface plot and as a contour plot. The contour plots show the isoclines for parameter combinations that produce potentiation ratios of 1.5, 2, 3, and 4, as labeled.

In a comparison of Fig. 4, A–C, the potentiation ratio increases as \(\beta\) increases for any given choice of \(r\) and \(h\). A small \(\beta\) means that only a small fraction of the total SR \(\text{Ca}^{2+}\) is released (and resequestered) on each AP. The net effect is that the SR loading shows little beat-to-beat variation. In contrast, a high level of postextrasystolic potentiation requires a large change in the SR load after the extrasystole. Recall that the SR release is a function of restitution and the SR load (see Eq. 1). For the simulations, the PESI is long (3,000 ms), so there is full restitution \((\lambda \sim 1)\). Hence, the SR load is the only variable that changes the level of postextrasystolic potentiation. For example, the difference between \(a_8\) and \(b_8\) in Fig. 3A can be attributed solely to differences in the SR loading.

The potentiation ratio increases for decreasing \(r\) at any given choice of \(\beta\) and \(h\). Intuitively, decreasing \(r\) means that less of the \(\text{Ca}^{2+}\) released is being recycled back into the SR. The net effect is to increase the beat-to-beat variation in the SR load that is crucial for high levels of postextrasystolic potentiation. In contrast, a large \(r\) means that most of the \(\text{Ca}^{2+}\) released is being recycled back into the SR. Hence, each beat has almost the same SR load, a feature incompatible with a large degree of postextrasystolic potentiation.

The potentiation ratio increases with \(h\) at any given choice of \(\beta\) and \(r\). The feedback parameter \(h\) controls the degree to which the \(\text{Ca}^{2+}\) transient has a negative-feedback effect on the sarcolemmal influx. Recall that sarcolemmal influx goes directly to loading the SR for the next beat. Therefore, the negative feedback increases the beat-to-beat variation in sarcolemmal influx.

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Fig. 4. Simple model potentiation ratios are computed for \(r\) in range 0.5–0.975 and \(h\) in range 0.0–1.0; \(\beta\) is fixed at 0.25 in A, 0.5 in B, and 0.75 in C. Resulting potentiation ratios are plotted as surface (bottom) and contour (top) plots. Contour plots show isoclines for parameter combinations that produce potentiation ratios of 1.5, 2, 3, and 4, as labeled. For any given choice of \(r\) and \(h\), potentiation ratios increase as \(\beta\) increases (cf. A, B, and C). For any given \(\beta\), potentiation ratios increase as \(r\) increases and \(h\) decreases.
flux and also the SR loading. For example, a short ESI produces a small extrasystolic Ca\(^{2+}\) transient, which in turn produces little negative feedback. With a large h, the result is a relatively larger sarcoplasmic influx that increases SR load and potentiation.

In Fig. 4, the potentiation ratio is <2 for small h. Moreover, if h = 0, then the potentiation ratio is <2 for all choices of r (range 0.5–0.95) and β (0.05–1.0, all data are not shown). Hence, the simulation results suggest that negative feedback on sarcoplasmic influx plays a critical role in producing the large degree of postextrasystolic potentiation observed in the cardiac muscle.

**Detailed Model**

Figure 5 shows simulation results for the detailed model with use of the experimental protocol of Wier and Yue (42). Similar to the experimental data, the last priming beat is shown to demonstrate the steady-state output level. After the last priming beat, a family of traces is shown for different ESIs, each of which is accompanied by a postextrasystolic beat 3,000 ms later. [Ca\(^{2+}\)] is shown in Fig. 5A, and the corresponding isometric twitch force is shown in Fig. 5B. Only the force results can be directly compared with experimental results in Fig. 1.

**Detailed Model**

**Figure 6.** A: simulated force data from detailed model plotted as rate of force onset (+\(dF/dt\)). B: simulated \(L/L_{\text{max}}\). This signal is derived from [Ca\(^{2+}\)] according to fit to calibration data in Wier and Yue (42). These results can be directly compared with experimental results in Fig. 1.

When corresponding traces are compared, the experimental and model results are similar in extrasystolic restitution and postextrasystolic potentiation. The potentiation ratio is slightly >2 for force (a' = 0.0326 and ss = 0.0157 in Fig. 5B). The relative changes in peak [Ca\(^{2+}\)] levels (Fig. 5A) are considerably smaller than those for peak force, similar to the experimental results. The peak [Ca\(^{2+}\)] of the last priming beat is

\[
L/L_{\text{max}} = 3.61 \times 10^{-5} \times [\text{Ca}^{2+}](\mu\text{M})^{2.37} \tag{14}
\]
uptake occurs, whereas that of the maximally potentiated beat is 1.11 μM.

We hypothesize that the short-term I-F relations are produced from an interplay of RyR adaptation and the SR loading. This hypothesis is investigated using the detailed model. In Fig. 7A, RyR open probabilities are plotted for the same sequence as in Fig. 5. As ESI increases, the peak open probability increases from 0.269 for the shortest ESI (a in Fig. 7) to 0.853 for the longest ESI (b in Fig. 7). In contrast, the peak open probability is a constant value of 0.869 for each of the postextrasystolic beats. In this case, the SR release depends mainly on the SR load. This hypothesis is investigated using the model for same sequence as in Fig. 5. The peak open probability increases from 0.825 μM, whereas that of the maximally potentiated beat is 1.11 μM.

For postextrasystolic potentiation, the important variable is the degree of the SR loading after the restitution beat. For the shortest ESI (a in Fig. 7B), there is a relatively small decrease in [Ca\(^{2+}\)]\(_{SR}\) that recovers to a higher value. The small release occurs because most of the RyRs are in the adapted state, and not from a slow transfer from NSR to JSR. [Ca\(^{2+}\)]\(_{SR}\) has reached its peak value for a in Fig. 7 compared with larger ESIs so that a lack of available Ca\(^{2+}\) for release is not an issue in restitution for this model (i.e., there is no component of restitution from a slow transfer of Ca\(^{2+}\) from NSR to JSR). Also there is a slow decrease in [Ca\(^{2+}\)]\(_{NSR}\) and [Ca\(^{2+}\)]\(_{JSR}\) when no APs are occurring (i.e., in the period between a and a’ in Fig. 7). The slow decrease is produced by two features. First, after the AP, there is still release from the SR, because the RyR open probability is small but nonzero. Consider that, after an AP, most of the RyRs are in the adapted state (P\(_{C_2}\)). The RyRs revert back to the resting closed state (P\(_{C_1}\)), but this transition requires a sojourn through an open state (P\(_{O_1}\)). This transition through the open state causes the nonzero open probability. A second feature that produces a slow unloading of the SR is that the Ca\(^{2+}\)-ATPase pump can run in a reverse mode. The balance between the forward mode (that fills NSR) and the reverse mode (that empties NSR) depends on [Ca\(^{2+}\)] and [Ca\(^{2+}\)]\(_{NSR}\) (see Eqs. A76–A78). During diastole, when [Ca\(^{2+}\)] is small and [Ca\(^{2+}\)]\(_{NSR}\) is larger, the reverse mode is more favored, so some degree of SR emptying occurs.

Figure 7B shows that the potentiation at a’ occurs because the SR [Ca\(^{2+}\)] recovers to a higher level than the steady-state value achieved after the priming period (ss in Fig. 7B). The small release (a in Fig. 7B) leaves more residual Ca\(^{2+}\) in the SR to help potentiate the next beat. Recall from the simple model results that a strong feedback on sarcolemmal influx is required to achieve a high level of potentiation. This effect is shown in Fig. 8A, where L-type Ca\(^{2+}\) currents (top traces, right axis) are plotted for the same sequence as in Fig. 5. The L-type Ca\(^{2+}\) current is largest at the shortest ESI (a in Fig. 8). The reasons are twofold. First, the small SR release produces less Ca\(^{2+}\)-induced inactivation of the L-type Ca\(^{2+}\) current. Second, the AP (Fig. 8A, bottom traces, left axis) has reduced amplitude, because the time-dependent K\(^+\) membrane current has not yet fully recovered and is still partially activated. The result is that the peak membrane potential is substantially lower than the reversal potential for the L-type Ca\(^{2+}\) current (≈50 mV, see Fig. 3 in Ref. 20) that increases the net driving force for Ca\(^{2+}\) entry. Hence, the low AP amplitude produces increased Ca\(^{2+}\) influx.

The increase in L-type Ca\(^{2+}\) current at short ESI helps produce a high level of potentiation. This effect is explored further in Fig. 8B, where the time-integrated flux of Ca\(^{2+}\) is computed for the influx through L-type
channels (middle traces), SR release through RyRs (top traces), and the sum of the other membrane Ca\(^{2+}\) currents (bottom traces). The combined fluxes of other membrane Ca\(^{2+}\) currents (Na\(^+\)/Ca\(^{2+}\) exchanger, sarcolemmal Ca\(^{2+}\) pump, and background Ca\(^{2+}\) leak) can be added to the influx through L-type channels to compute the net change in cellular Ca\(^{2+}\) load. The integrated fluxes are presented as concentrations that are computed with respect to the volume of the myoplasm. This method facilitates direct comparisons of membrane currents (both sets of bottom traces) and intracellular fluxes (top traces). Also the fluxes into the myoplasm are positive, whereas extrusion from the myoplasm is negative.

For the shortest ESI (a in Fig. 8), the total Ca\(^{2+}\) release is smaller than for the last priming beat (ss in Fig. 8). The corresponding postextrasystolic beat (a' in Fig. 8) produces the largest release. The other traces show data for the longest ESI (b in Fig. 8) and an intermediate value (c in Fig. 8) and correspond to the labeled transients in Fig. 8A. Figure 8B also illustrates some key characteristics of Ca\(^{2+}\) handling. First, the time-integrated SR release flux has a fairly stairlike waveform, indicating that the majority of Ca\(^{2+}\) is released over a short period of time. In contrast, the integrated L-type Ca\(^{2+}\) flux has a sloping appearance that indicates a smaller-magnitude flux over a longer time interval. The contribution of the cellular Ca\(^{2+}\) extrusion mechanisms is shown by the sum of the Na\(^+\)/Ca\(^{2+}\) exchanger, sarcolemmal Ca\(^{2+}\) pump, and background Ca\(^{2+}\) leak fluxes. The contribution of the background Ca\(^{2+}\) leak flux is included, because this current counterbalances the other currents so that the net cellular Ca\(^{2+}\) load does not deplete too quickly during diastole. The summed flux (bottom traces in Fig. 8B) first has a positive-going deflection after an AP as a result of the Na\(^+\)/Ca\(^{2+}\) exchanger running in reverse mode. The positive-going deflection is slightly larger for the shortest ESI (a in Fig. 8), indicating that more Ca\(^{2+}\) enters the cell during the small Ca\(^{2+}\) transient (favoring the reverse Na\(^+\)/Ca\(^{2+}\) exchanger mode). This suggests some contribution of extrusion mechanisms to increased SR loading and potentiation. However, by the postextrasystolic release, the total Ca\(^{2+}\) extruded from the cell (indicated by the downward deflection of the trace) is very similar for a', b', and c'. This shows that total extrusion Ca\(^{2+}\) is fairly independent of the stimulus pattern and suggests a fairly minor role in beat-to-beat changes in cellular (and hence SR) Ca\(^{2+}\) load, at least for the pattern tested.

Recirculation fraction can be estimated from Fig. 8B. One way to estimate this quantity is

$$r/(1 - r) = \frac{(\text{Integrated Ca}^{2+} \text{ resequestered into SR})}{(\text{Integrated Ca}^{2+} \text{ extruded from cell})}$$  \hspace{1cm} (15)$$

The uptake and release from the SR must balance to maintain no net change after each beat. With use of this fact, recirculation fraction can be estimated by setting

$$r/(1 - r) = \frac{(\text{Integrated Ca}^{2+} \text{ released from SR})}{(\text{Integrated Ca}^{2+} \text{ extruded from cell})}$$  \hspace{1cm} (16)$$

From the RyR release trace (ss in Fig. 8B), integrated Ca\(^{2+}\) released from SR is 8.9 \(\times\) 10^{-7} M. The total extrusion is computed from the combined fluxes of other membrane Ca\(^{2+}\) currents. The amount of extrusion in the bottom trace (c in Fig. 8B), just before the extrasystole, shows that integrated Ca\(^{2+}\) extruded from the cell is 2.3 \(\times\) 10^{-7} M. With use of these values and Eq. 15, r is calculated to be 0.79.
In summary, the detailed model has been shown to reproduce experimental findings that show slow recovery of force during restitution, with similar results found for the rate of force onset (+dF/dt) and the Ca\(^{2+}\) transient. There has not yet been any examination of the temporal details of restitution. Many experimental findings show that restitution can be fit by an exponential (2, 11, 42, 46). For example, the data in Fig. 1 have time constants on the order of 700–800 ms (42). Other sets of experimental findings show that as the priming rate increases, the plateau at full restitution increases while the time constant of the exponential rise is unchanged (11).

The ability of the detailed model to reproduce these experimental findings is now examined in Fig. 9A, where the priming rate is increased from the original basic cycle length (BCL) of 1,500 ms to 1,250 and 1,000 ms. Here the peak rates of force onset (peak dF/dt) are shown for the range of ESIs in Fig. 5, and an exponential fit is shown with \( \tau \) as labeled. Consistent with experimental observations, the higher priming rate increases the plateau level but produces little change in the time constant of restitution. Although only data for peak rate of force onset are shown, similar results are obtained for force, a result also consistent with experimental findings (22, 42). The lowest ESI produced peak force or dF/dt values that are not well fit by the exponentials; hence, they are not included in the fits shown. These points are larger than predicted by an exponential curve fit and, if included, would give the restitution curves a sigmoidal shape. However, this deviation should not be considered to be significant, because this trend can also be seen in some experimentally determined restitution curves (see Fig. 3A in Ref. 12).

The peak rate of force onset for postextrasystolic data is plotted in Fig. 9B. These results show that postextrasystolic data are also well fit by exponential curves with time constants on the order of 700 ms, consistent with experimental findings (42). Very similar exponential fits and time constants are obtained for force data. The close similarity between time constants for restitution and postextrasystolic potentiation is seen in experimental results and has been interpreted to suggest a common mechanism (42, 46).

**DISCUSSION**

The simple, discrete-time model produces restitution but is only able to generate high levels of potentiation with appropriate parameter choices. Specifically, potentiation ratio increases with increase in the release fraction \( b \), decrease in the recirculation fraction \( r \), and increase in the feedback parameter \( h \). The effects of varying these three parameters are now considered separately.

**Release Fraction**

The release fraction is the maximum fraction of Ca\(^{2+}\) in the SR that can be released, given full restitution. Some experimental estimates suggest that about one-half of the total amount of Ca\(^{2+}\) in the SR is released on each beat in the guinea pig (14). Similar values are reported for the rabbit, rat, and ferret, although some variation can occur with the degree of SR loading (4, 5). If it is assumed that these estimates correspond to a release that is characterized by full restitution, then a releasable fraction of 50% can be inferred. Behavior of the simple model suggests that such a small release fraction would make high levels of potentiation difficult to achieve. Recall that in the simple model results, only large release fractions near 1 produce high levels of potentiation.

The discrepancy between the modeling results and the experimental work may result from the release fraction being an increasing function of the SR load (5, 39). This experimental finding invalidates the constant release fraction assumption in the simple model. A likely consequence of the variable release fraction would be an increase in potentiation, because any increase in the SR loading (from an extrasystole at a short ESI) will also produce release of a greater fraction of the increased load. An alternative explanation for the
discrepancy could be that experimental methods underestimate the release fraction. The experiments compared Ca\(^{2+}\) released from the SR during an AP with Ca\(^{2+}\) released during caffeine application. However, the possibility exists that some Ca\(^{2+}\) in the SR may not be involved in normal E-C coupling but is only released with caffeine (14), leading to underestimation of the release fraction.

Recirculation Fraction

The recirculation fraction is the fraction of Ca\(^{2+}\) released from the SR during each Ca\(^{2+}\) transient that is resequestered back into the SR. Large values of this parameter reduce postextrasystolic potentiation, because most of the released SR Ca\(^{2+}\) is recycled back into the SR on each beat. This in turn leads to smaller beat-to-beat variability in the SR load. In this modeling study, only values of recirculation fraction >0.5 were considered. The rationale for this is that smaller values are unlikely to occur in real myocardium. The argument for this is as follows. Assume a minimum value of recirculation fraction of 0.5. From Eq. 5, the remainder of the Ca\(^{2+}\) in the transient must be extruded across the sarcolemma on each beat. These conditions imply that

\[
\text{Out}_{SR}(n) = \text{Out}_{SC}(n) = 0.5 \quad (17)
\]

Also assume that the myocardium is driven at a constant rate and has achieved steady state. To prevent long-term loading or unloading of Ca\(^{2+}\) in the cell or the SR, there must be a net balance of Ca\(^{2+}\) fluxes across the sarcolemma and across the SR, yielding

\[
\text{In}_{SC}(n) = \text{Out}_{SC}(n) \quad (18)
\]

and

\[
\text{In}_{SR}(n) = \text{Out}_{SR}(n) \quad (19)
\]

Combining the above results, one finds that

\[
\text{In}_{SC}(n) = \text{In}_{SR}(n) = \text{Out}_{SR}(n) = \text{Out}_{SC}(n) = 0.5 \quad (20)
\]

This result implies that a recirculation fraction of 0.5 requires that the same amount of Ca\(^{2+}\) that enters the cell is also released from the SR.

Estimates from experimental studies indicate that sarcolemmal influx provides only 20% of the Ca\(^{2+}\) necessary to produce a typical transient (8, 10, 13) (these estimates are from rat and are most likely lower than that for guinea pig, which has a less-developed SR). Now consider the steady-state assumptions, developed above, where sarcolemmal influx equals the SR release [\(\text{In}_{SC}(n) = \text{In}_{SR}(n)\)]. In the simple model the total Ca\(^{2+}\) in the transient is assumed to be the SR release alone, which would be 20% of the necessary Ca\(^{2+}\). Hence, these results suggest that a recirculation fraction of 0.5 (or less) is incompatible with the experimental estimates of sarcolemmal influx per AP and the Ca\(^{2+}\) necessary to produce a typical myoplasmic Ca\(^{2+}\) transient.

Feedback on the Sarcolemmal Influx

In the simple model, strong feedback on the sarcolemmal influx is necessary to reproduce potentiation ratios \(\geq 2\), as seen experimentally. For example, as described above, a reasonable estimate of \(\alpha = 0.6\) and \(\beta = 0.5\). However, with use of these estimates, a potentiation ratio of 2 requires that \(h = 0.7\) (Fig. 4B). This value is large considering that experimental data suggest that \(h\) should only be \(\approx 0.25\), as inferred from the effects of Ca\(^{2+}\)-induced inactivation of L-type current (17). This discrepancy will be addressed in the discussion of the detailed model results.

Although the simple model allows for complete freedom in setting \(h\), there is an upper limit for plausibility. The simple model assumes that influx does not contribute directly to the Ca\(^{2+}\) transient. This is only an approximation, because the Ca\(^{2+}\) influx through the L-type channels must contribute to the Ca\(^{2+}\) transient, at least to some degree. With preliminary versions of the simple model, the Ca\(^{2+}\) transient was assumed to be the sum of the SR release and influx through the L-type channels. However, this construction produced blunted restitution because of a negative-feedback effect. Consider that a small SR release at a short ESI would be bolstered by a large L-type influx. Hence, when these two components are summed, the resulting Ca\(^{2+}\) transient is increased at short ESI, effectively reducing restitution behavior. Similarly, the detailed model results indicate that L-type current does produce a noticeable increase in the Ca\(^{2+}\) transient, especially when the SR release is small at short ESIs (a in Fig. 5A). Hence, there is likely a practical limit on how large \(h\) can be without counteracting the restitution behavior produced by the slow recovery of the SR release.

Previously Published Detailed Models

Previously published detailed models have failed to reproduce accurately restitution and postextrasystolic potentiation behavior. For example, the OxsoftHeart ventricular model fails to show restitution behavior (31). The Luo-Rudy phase II ventricular cell model does produce restitution behavior, as assessed by changes in (Ca\(^{2+}\)) transient amplitude (force is not computed). In this model, the restitution results from a different mechanism, a slow transfer of Ca\(^{2+}\) from the NSR to the JSR (27), instead of from refractoriness of the SR release channels, as in the detailed model developed here. The Luo-Rudy phase II model fails to show clear postextrasystolic potentiation behavior as a result of insufficient extra loading of the SR to potentiate the postextrasystolic (31).

Modifications to Improve Short-Term I-F Relations

The present model is based on a single cardiac cell model described previously (20). Besides the addition of myofilaments, the earlier Ca\(^{2+}\)-handling model is modified in specific ways to improve the ability to reproduce short-term I-F relations. For example, the rate of adaptation of the RyRs is increased (see methods),
which in turn makes adaptation a more important factor in terminating the SR release. This approach is justified by recent experimental findings that suggest that inactivation strongly modulates RyR release (36).

In the models the recovery of release during restitution relies on the slow recovery of the RyR channels (Fig. 7A). This construction is consistent with recent data showing that restitution at the level of the Ca\(^{2+}\) sparks (fundamental E-C coupling events) depends on a slow recovery process with a time constant of 550 ms in rat (37).

In contrast, our previous model (20) incorporated a long time constant for Ca\(^{2+}\) transfer from NSR to J SR to produce greater depletion of J SR. This long time constant is not maintained in the new version of the model, because it produces a number of undesirable behaviors. First, the restitution curves are very sigmoidal instead of exponential (the present model produces only slightly sigmoidal restitution curves, see leftmost points in Fig. 9A). Second, a long time constant, coupled with a high stimulus rate, could produce situations where \([\text{Ca}^{2+}]_{\text{NSR}}\) far exceeds \([\text{Ca}^{2+}]_{\text{SR}}\). This often leads to spontaneous SR release and ectopic beating on return to a lower stimulus rate. Finally, a long time constant allows J SR to empty while NSR simultaneously fills. This effectively limits the releasable fraction of Ca\(^{2+}\) from the SR (the previous model has a releasable fraction of \(\sim 0.3\) (20)). In the present version the decreased time constant produces greater emptying of the SR and effectively gives a higher releasable fraction of Ca\(^{2+}\). Recall from the simple model results that a high releasable fraction (\(h\)) improves the potentiation ratio by increasing the beat-to-beat variation in the SR load.

Another change in the present model, as suggested by the simple model, is to decrease the recirculation fraction. Recall that a high recirculation fraction decreased the potentiation ratio by decreasing the beat-to-beat variation in the SR Ca\(^{2+}\) load. In the detailed model the recirculation fraction is reduced mainly by increasing the Na\(^+\)/Ca\(^{2+}\) exchanger rate, which favors extrusion of Ca\(^{2+}\) across the sarcolemma rather than resequstration into the SR. However, the precise value of the recirculation fraction is constrained by a number of biophysical factors. As argued earlier, the influx of Ca\(^{2+}\) across the sarcolemma must be in net balance with the efflux to be in steady state. The first quantity can be estimated from experimental measurements of L-type Ca\(^{2+}\) current, whereas the second quantity is mainly the contribution from the Na\(^+\)/Ca\(^{2+}\) exchanger current. This effectively limits efflux from the cell. Likewise, there must be a net balance of influx and efflux from the SR in the steady state. Given that enough Ca\(^{2+}\) must be released to activate the myofilaments, then efflux from and influx to the SR must be relatively large.

In the detailed model the recirculation fraction was found to be \(\sim 0.79\). This value is consistent with experimental estimates for recirculation fraction as computed by comparing efflux of the myoplasmic Ca\(^{2+}\) via the competing pathways of the SR Ca\(^{2+}\)-ATPase and Na\(^+\)/Ca\(^{2+}\) exchange. These pathways are considered to be the major pathways, with the SR Ca\(^{2+}\)-ATPase removing \(\sim 70\%\) and the Na\(^+\)/Ca\(^{2+}\) exchangers \(\sim 20\% - 30\%\) of Ca\(^{2+}\) released from SR (9). With the assumption of such a ratio, the recirculation fraction is \(\sim 0.7\). Other researchers have suggested smaller values. Calculations using the beat-to-beat decay of potentiation (i.e., negative staircase) place the lower value of the recirculation fraction at 0.45 (41). However, this value contained a component from feedback on sarclemmal input (analogous to \(h\)), which could potentially introduce considerable error.

An important finding from the simple model is that a large value of \(h\) is required to produce potentiation ratios of \(\sim 2\), as shown in experimental results. The feedback is found to be relatively large in the detailed model. In Fig. 8A, the L-type channel Ca\(^{2+}\) current trace for \(a\) is roughly twice as large as has that for \(a'\). The corresponding \(h\) can then be estimated to be on the order of 0.5. This value is actually larger that what might be estimated by comparing experimentally measured L-type currents with and without the SR releases (17). These data show an \(\sim 25\%\) increase in L-type current when Ca\(^{2+}\)-induced inactivation is effectively removed by depleting the SR. However, these data were collected with an AP clamp. In contrast, the detailed model, running without an AP clamp, predicts that a small change in AP shape at short ESIs may increase influx and effectively increase \(h\). Recall from Fig. 8A that the short ESI produced APs with reduced amplitude, which in turn increased the driving force for Ca\(^{2+}\) influx. Finally, this is an example in which interaction between the membrane currents and the Ca\(^{2+}\) handling required a detailed model approach and could not have been predicted by the simple model alone.

Effects of Low External [Ca\(^{2+}\)] on Potentiation

The detailed model, with changes outlined above, produced potentiation ratios of 2. This level is appropriate for that seen in the guinea pig (2, 29, 44) and the dog (12, 46). Interestingly, the data in Fig. 1, on which most of this study is based, are from ferret muscle with low external Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_o\)). In normal [Ca\(^{2+}\)]\(_o\), the potentiation ratios were much reduced (42). The findings of this study offer a possible explanation for this disparity. The simple model results suggest that the potentiation ratio can be increased by a low recirculation fraction. One effect of low [Ca\(^{2+}\)]\(_o\) is to favor the forward mode of the Na\(^+\)/Ca\(^{2+}\) exchanger, which results in greater extrusion of Ca\(^{2+}\) across the sarcolemma and decreases the recirculation fraction.

Contribution of Myofilaments

Most of the discussion of the detailed model has focused on features that modify the magnitude of Ca\(^{2+}\) transients. This is justified, because Wier and Yue (42) showed that mechanical restitution and postextrasystolic potentiation depend directly on the SR release and the Ca\(^{2+}\) transient. However, the model suggests that the myofilaments may also make an important contribu-
tion to the observed phenomena. Recall that the relative changes in the peak Ca\(^{2+}\) transient are smaller (Fig. 5A) than for peak force (Fig. 5B) or peak rate of force onset (Fig. 6A). In the detailed model the relatively small change in the Ca\(^{2+}\) transient translates into a much larger change in force because of the highly cooperative force generation model. The myofilament model has a steady force-Ca\(^{2+}\) (F-Ca\(^{2+}\)) relation with a Hill coefficient of \(\sim 6\) for the sarcomere length used in the simulations (i.e., 2.15 \(\mu\)m). Although this value is consistent with numerous experimental estimates with intact muscle preparations (3, 15, 47), it is somewhat steeper than that of the simple model (based on the work of Weir and Yue). The steeper dependence in the detailed model allows for peak force to double (potentiation ratio = 2) with a total change in peak [Ca\(^{2+}\)], of only 0.3 \(\mu\)M (cf. ss and a’ in Fig. 5A).

In the development of the force generation model, the contribution of end-to-end troponin-tropomyosin interactions is assumed to produce the steady-state F-Ca\(^{2+}\) relations with high apparent cooperativity, as observed in real myocardium (32). For twitches, the highly cooperative behavior produces a steep dependence of peak force on the peak of the [Ca\(^{2+}\)] transient. Another feature of the myofilament model is that troponin/tropomyosin is assumed to shift rapidly to a permissive state, whereas slower cross-bridge dynamics determine the rise of force. Such a construction makes the time to peak force relatively independent of level of peak force, consistent with experimental data (see data in Refs. 6, 21, and 41). Considered another way, the rate of rise of force is proportional to the peak level of force. This leads to the behavior seen in the detailed model, where peak force and the peak rate of force onset behave in a similar fashion (cf. Figs. 5B and Fig. 6A). These results are consistent with experimental findings that I-F relations are virtually identical for peak force and the peak rate of force onset in a variety of isolated muscle preparations (42, 44). Similarly, restitution behavior is equivalent for peak pressure and rate of pressure rise in the whole ventricle (12).

Limitations of the Detailed Model

Although adequately reproducing restitution and postextrasystolic potentiation behavior, the detailed model has limitations that should be addressed. In real cardiac cells, postextrasystolic potentiation may be augmented by three mechanisms not included in the detailed model. The first mechanism, as previously mentioned, is that the release fraction may be an increasing function of the SR load (5, 39). This mechanism could potentially increase potentiation, because any increase in the SR loading (such as occurs after a extrasystole) will also produce a greater fraction of the increased load being released. A second mechanism is that the SR uptake may be augmented for a short time after an AP that could preferentially increase the SR uptake for a short ESI. A proposed mechanism is the following sequence of events: the Ca\(^{2+}\) transient produces binding to calmodulin, activation of protein kinase C, phosphorylation of phospholamban, and increased SERCA uptake. A similar mechanism has been suggested by Schouten (34) to account for increased relaxation rates for short stimulus intervals. A third mechanism is that short ESIs could produce increased Ca\(^{2+}\) influx via L-type channels. Data from the dog and the guinea pig (40) show that L-type currents can overshoot the control level for interpulse intervals in a range similar to the range of ESIs studied here (i.e., the overshoot peaked at 30–100 ms after the repolarization of the initial pulse). The mechanism of the enhancement is unclear but may involve a dual modulation of the L-type channel. As proposed by some researchers (25, 30), slightly increased [Ca\(^{2+}\)] may enhance L-type current (not included in the detailed model), whereas higher [Ca\(^{2+}\)] will inactivate the channel (included in the detailed model).

Another limitation of the detailed model involves species- and tissue-based differences in membrane currents and E-C coupling mechanisms. For example, the experimental data most used in this study (Fig. 1) are from ferret papillary muscle with low [Ca\(^{2+}\)]. Such a choice is justified given the completeness of this data set and the similarity to restitution/postextrasystolic potentiation behavior in other species. However, the detailed model was developed to correspond most closely to the guinea pig under physiological [Ca\(^{2+}\)]. Hence, one could question the validity of such an approach.

In defense of the study, we note that the most important behaviors we have sought to replicate in Fig. 1 are similar to those measured in guinea pig tissue. For example, restitution follows an exponential time course (2, 29, 44), although the rate of recovery may be somewhat faster than that in Fig. 1. Also similar to the data in Fig. 1, restitution and postextrasystolic potentiation follow similar time courses in the guinea pig (29). In this study the targeted level of the potentiation ratio is 2, a reasonable value for guinea pig ventricular (29) and papillary muscle (44). Even larger potentiation ratios are measured in other species, such as dog (46) and rabbit (43), so the mechanisms explored in this study may prove useful in generating models of these tissues.

Finally, difference in AP morphologies should be considered. The guinea pig has a relatively depolarized plateau phase. With such an AP morphology, residual activation of the delayed rectifier current could lower the AP amplitude at short ESI, thereby increasing the Ca\(^{2+}\) influx, SR loading, and potentiation. However, this finding may not carry over to other tissues with different AP morphologies or electrical restitution properties. For example, rabbit ventricle shows a less depolarized AP that increases in amplitude and duration at short ESIs (43), presumably as a result of reduced L-type channel inactivation. This AP change may contribute to increased Ca\(^{2+}\) influx and the high potentiation ratio in this tissue. Different behaviors are also likely to occur in tissues with a prominent transient outward current (I\(_{to}\)), a current that is absent in the guinea pig. A large I\(_{to}\) in species such as rat and mouse produces a very short AP that does not rely on the delayed rectifier current for repolarization (7). A
somewhat smaller $I_{Na}$ in species such as dog and human induces a prominent notch and the spike-and-dome AP morphology in epicardial and midmyocardial ventricular cells (26). In these tissues the plateau membrane potential is already closer to the optimum voltage for L-type Ca$^{2+}$ influx (near 0 mV), so the effect of residual activation of the delayed rectifier current may not be as prominent.

**Summary**

Results with the simple, discrete-time model show uniformly that postextrasystolic potentiation is increased for a low recirculation fraction and a high releasable fraction. Strong feedback of the SR release on sarcolemmal Ca$^{2+}$ influx is also necessary to reproduce potentiation ratios of $\approx 2$, as shown in many experimental results. This suggests that feedback of the SR release on sarcolemmal Ca$^{2+}$ influx plays an important role in postextrasystolic potentiation. The detailed model includes more complete descriptions of cellular mechanisms, including membrane currents, Ca$^{2+}$ handling, and myofilaments. The detailed model is capable of quantitatively predicting restitution and postextrasystolic potentiation, unlike previously published detailed models. The restitution behavior results from a slow recovery of RyRs from the adapted state. For a small extrasystolic beat, potentiation occurs on the postextrasystole because of an increase in the SR Ca$^{2+}$ load. The loading of the SR increases because 1) less Ca$^{2+}$ is released, so more remains in the SR, and 2) more Ca$^{2+}$ enters the cell and loads the SR. Influx of Ca$^{2+}$ into the cell increases because 1) a small SR release produces less Ca$^{2+}$-induced inactivation of the L-type channels and 2) residual activation of the time-dependent K$^+$ membrane current lowers the AP amplitude, thereby increasing the driving force for Ca$^{2+}$ influx. If possible, the initial parameter choices for the detailed model have been guided by experimental results. However, the ability to reproduce short-term I-F relations helps further constrain model parameters. The effects of any given change in parameters may be hard to interpret because of the highly interactive nature of the detailed model. In many cases, the effects can often be more easily interpreted when considered in the context of the simple, discrete-time model results.

**APPENDIX**

**Ionic currents**

Membrane potential

$$\frac{dV}{dt} = \frac{-1}{C_m} [I_{Na} + I_{Ca} + I_{Ca,K} + I_K + I_{K1} + I_{Kp} + I_{NaCa} + I_{NaK} + I_{Na(Ca)} + I_p(Ca) + I_{Ca,b} + I_{Na,b}]$$  

(A1)

Fast Na$^+$ current ($I_{Na}$)

$$I_{Na} = \zeta_{Na} m^3 h j (V - E_{Na})$$  

(A2)

$$E_{Na} = \frac{RT}{F} \ln \left[ \frac{[Na^+]_o}{[Na^+]_i} \right]$$  

(A3)

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m$$  

(A4)

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h$$  

(A5)

$$\frac{dj}{dt} = \alpha_j (1 - j) - \beta_j j$$  

(A6)

$$\alpha_m = 0.32 \frac{V + 47.13}{1 - e^{-0.1(V+47.13)}}$$  

(A7)

$$\beta_m = 0.08e^{-V/11}$$  

(A8)

For $V = -40$ mV or more

$$\alpha_h = 0.0$$  

(A9)

$$\alpha_j = 0.0$$  

(A10)

$$\beta_h = \frac{1}{0.13[1 + e^{V+10.66V^2/11.1}]}$$  

(A11)

$$\beta_j = 0.3 \frac{e^{-2.535 \times 10^{-7} V}}{1 + e^{-0.1(V+32)}}$$  

(A12)

For $V$ less than $-40$ mV

$$\alpha_h = 0.135e^{0.01V} - 6.8$$  

(A13)

$$\alpha_j = (-127.140e^{0.2444V} - 3.474 \times 10^{-5}e^{-0.04391V})\frac{V + 37.78}{1 + e^{0.311(V+79.23)}}$$  

(A14)

$$\beta_h = 3.56e^{0.079V} + 3.1 \times 10^2 e^{0.35V}$$  

(A15)

$$\beta_j = 0.1212 \frac{e^{-0.01052V}}{1 + e^{-0.1378(V+40.14)}}$$  

(A16)

Time-dependent delayed rectifier K$^+$ current ($I_{K}$)

$$I_{K} = \zeta_{K} X_t X^2 (V - E_{K})$$  

(A17)

$$E_{K} = \frac{RT}{F} \ln \left[ \frac{[K^+]_o + P_{NaK}[Na^+]_o}{[K^+]_i + P_{NaK}[Na^+]_i} \right]$$  

(A18)

$$\zeta_{K} = 0.1128 \sqrt{\frac{[K^+]_o}{5.4}}$$  

(A19)

$$X_t = \frac{1}{1 + e^{V-40/40}}$$  

(A20)

$$\frac{dX}{dt} = \alpha_X (1 - X) - \beta_X X$$  

(A21)

$$\alpha_X = 7.19 \times 10^{-5} \frac{V + 30}{1 - e^{-0.148(V+30)}}$$  

(A22)

$$\beta_X = 1.31 \times 10^{-4} \frac{V + 30}{1 - e^{0.0687(V+30)}}$$  

(A23)
Time-independent $K^+$ current ($I_{K_1}$)

$$I_{K_1} = C_{K_1}K_1(V - E_{K_1})$$  \hspace{1cm} (A24)

$$E_{K_1} = \frac{RT}{F} \ln \frac{[K^+]_o}{[K^+]_i}$$  \hspace{1cm} (A25)

$$C_{K_1} = 0.75 \sqrt{\frac{[K^+]_o}{5.4}}$$  \hspace{1cm} (A26)

$$K_{1-} = \frac{\alpha_{K_1}}{\alpha_{K_1} + \beta_{K_1}}$$  \hspace{1cm} (A27)

$$\alpha_{K_1} = \frac{0.4912e^{0.08032(V - E_{K_1}) - 5.476} + e^{0.06175(V - E_{K_1}) - 5.9431}}{1 + e^{0.5348(V - E_{K_1}) - 4.753}}$$  \hspace{1cm} (A28)

$
\beta_{K_1} = \frac{0.4912e^{0.08032(V - E_{K_1}) - 5.476} + e^{0.06175(V - E_{K_1}) - 5.9431}}{1 + e^{0.5348(V - E_{K_1}) - 4.753}}$

Plateau $K^+$ current ($I_{K_p}$)

$$I_{K_p} = C_{K_p}K_p(V - E_{K_p})$$  \hspace{1cm} (A30)

$$E_{K_p} = E_{K_1}$$

$$K_p = \frac{1}{1 + e^{7.4888(V - E_{K_1}) - 5.98}}$$  \hspace{1cm} (A31)

$Na^+ / Ca^{2+}$ exchanger current ($I_{NaCa}$)

$$I_{NaCa} = k_{NaCa} \frac{1}{K_{mNa}^3 + [Na^+]^3 + K_{mCa} + [Ca^{2+}]_0} \cdot \frac{1}{1 + k_{Na}e^{eVF/RT}[Na^+]_o + [Ca^{2+}]_0}$$

$$- e^{eVF/RT}[Na^+]_o[Ca^{2+}]_0$$  \hspace{1cm} (A33)

$Na^+ - K^+$ pump current ($I_{NaK}$)

$$I_{NaK} = I_{NaK} \cdot f_{NaK} \frac{1}{1 + \left(\frac{K_{mNa}[Na^+]_o}{[Na^+]_o}\right)^{1.5} + \left(\frac{K_{mK_0}[K^+]_o}{[K^+]_o}\right)^{1.5}}$$

$$f_{NaK} = \frac{1}{1 + 0.1245e^{0.1VF/RT} + 0.0365se^{-VF/RT}}$$

$$\sigma = \frac{1}{2}(e^{[Na^+]_o/67.3} - 1)$$  \hspace{1cm} (A35)

Nonspecific $Ca^{2+}$-activated current ($I_{ns(Ca)}$)

$$I_{ns(Ca)} = I_{ns(Na)} + I_{rel(K)}$$  \hspace{1cm} (A37)

$$I_{rel(K)} = \frac{1}{1 + \left(\frac{K_{mns(Ca)}}{[Ca^{2+}]_o}\right)^3}$$  \hspace{1cm} (A38)

$$I_{ns(Na)} = \frac{VF}{RT} \frac{0.75[Na^+]_0 e^{VF/RT} - 0.75[Na^+]_o}{e^{eVF/RT} - 1}$$

$$\Gamma_{ns(Na)} = P_{ns(Na)} \frac{VF}{RT} \frac{0.75[Na^+]_0 e^{VF/RT} - 0.75[Na^+]_o}{e^{eVF/RT} - 1}$$  \hspace{1cm} (A39)

Sarcolemmal $Ca^{2+}$ pump current ($I_{pl(Ca)}$)

$$I_{pl(Ca)} = \frac{\Gamma_{pl(Ca)}}{K_{m(Ca)} + [Ca^{2+}]_o}$$  \hspace{1cm} (A42)

$Ca^{2+}$ background current ($I_{Ca,b}$)

$$I_{Ca,b} = \frac{\Gamma_{Ca,b}}{K_{m(Ca)} + [Ca^{2+}]_o}$$  \hspace{1cm} (A43)

$Na^+$ background current ($I_{Na,b}$)

$$I_{Na,b} = \frac{\Gamma_{Na,b}}{K_{m(Ca)} + [Na^+]_o + [Ca^{2+}]_0}$$  \hspace{1cm} (A45)

Ca$^{2+}$-Handling Mechanisms

L-type $Ca^{2+}$ channel current

$$\alpha = 0.4e^{(V - 12)/10}$$  \hspace{1cm} (A47)

$$\beta = 0.05e^{(V - 12)/13}$$  \hspace{1cm} (A48)

$$\alpha' = \alpha \beta$$  \hspace{1cm} (A49)

$$\gamma = 0.5625[Ca^{2+}]_o$$  \hspace{1cm} (A51)

$$\frac{dC_1}{dt} = \beta C_1 + \omega C_{Ca0} - (4\alpha + \gamma)C_0$$  \hspace{1cm} (A52)

$$\frac{dC_1}{dt} = 4\alpha C_0 + 2\beta C_2 = \frac{\omega}{b} C_{Ca1} - (\beta + 3\alpha + \gamma)C_1$$  \hspace{1cm} (A53)

$$\frac{dC_2}{dt} = 3\alpha C_1 + 3\beta C_3 + \frac{\omega}{b^2} C_{Ca2} - (2\beta + 2\alpha + \gamma\beta^2)C_2$$  \hspace{1cm} (A54)

$$\frac{dC_1}{dt} = 2\alpha C_1 + 4\beta C_4 + \frac{\omega}{b^4} C_{Ca3} - (3\beta + + \gamma\beta^3)C_3$$  \hspace{1cm} (A55)

$$\frac{dC_4}{dt} = \alpha C_1 + gO + \frac{\omega}{b^4} C_{Ca4} - (4\beta + f + \gamma\beta^4)C_4$$  \hspace{1cm} (A56)

$$\frac{dO}{dt} = fC_4 - gO$$  \hspace{1cm} (A57)

$$\frac{dC_{Ca0}}{dt} = \beta' C_{Ca1} + \gamma C_0 - (4\alpha' + \omega)C_{Ca0}$$  \hspace{1cm} (A58)

$$\frac{dC_{Ca1}}{dt} = 4\alpha' C_{Ca0} + 2\beta' C_{Ca2} + \gamma aC_1$$  \hspace{1cm} (A59)
MODELING INTERVAL-FORCE RELATIONS

\[
\frac{dC_{Ca2}}{dt} = 3\alpha'C_{Ca1} + 3\beta'C_{Ca3} + \gamma a^2C_2
\]
\[
- \left(2\beta' + 2\alpha' + \frac{\omega}{b^3}\right)C_{Ca2}
\]  
(A60)

\[
\frac{dC_{Ca3}}{dt} = 2\alpha'C_{Ca2} + 4\beta'C_{Ca4} + \gamma a^3C_3
\]
\[
- \left(3\beta' + \alpha' + \frac{\omega}{b^3}\right)C_{Ca3}
\]  
(A61)

\[
\frac{dC_{Ca4}}{dt} = \alpha'C_{Ca3} + g'O_{Ca} + \gamma a^4C_4
\]
\[
- \left(4\beta' + \alpha' + \frac{\omega}{b^3}\right)C_{Ca4}
\]  
(A62)

\[
\frac{dO_{Ca}}{dt} = f'C_{Ca4} - g'O_{Ca}
\]  
(A63)

\[
l_{Ca_{max}} = \frac{P_{Ca}V^2}{RT} \frac{0.001e^{V_{F/R}-RT}-0.341[C^{2+}]_b}{0.001e^{V_{F/R}-RT}-1}
\]  
(A64)

\[
l_{Ca} = l_{Ca_{max}} yO + O_{Ca}
\]  
(A65)

\[
l_{CaK} = P_k yO + O_{Ca} \frac{V^2}{RT} \frac{[K^+]_b}{0.001e^{V_{F/R}-RT}-1}
\]  
(A66)

\[
p_k = \frac{P_k}{1 + l_{Ca_{max}}}
\]  
(A67)

\[
\frac{dy}{dt} = \frac{y_\infty - y}{\tau_y}
\]  
(A68)

\[
y_\infty = \frac{1}{1 + e^{V+55(7.5 + \frac{0.5}{1 + e^{V+21}})}}
\]  
(A69)

\[
\tau_y = 20 + \frac{600}{1 + e^{V+309.5}}
\]  
(A70)

RyR channel states

\[
\frac{dP_{C1}}{dt} = -k_a^+[Ca^{2+}]_{SS}P_{C1} + k_aP_{O1}
\]  
(A71)

\[
\frac{dP_{O1}}{dt} = k_\infty^+[Ca^{2+}]_{SS}P_{C1} - k_aP_{O1} - k_aP_{O1}
\]  
(A72)

\[
+ k_b P_{O2} - k_c^+[Ca^{2+}]_2P_{C2}
\]  
(A73)

\[
\frac{dP_{O2}}{dt} = k_b[Ca^{2+}]_{SS}P_{O1} - k_bP_{O2}
\]  
(A74)

\[
\frac{dP_{C2}}{dt} = k_cP_{O1} - k_cP_{C2}
\]  
(A75)

SERCA pump

\[
f_b = \frac{\left([Ca^{2+}]_{i}\right)^{1/3}/\left(k_b\right)}{\gamma_s}
\]  
(A76)

\[
r_b = \frac{\left([Ca^{2+}]_{i}\right)^{1/3}/\left(k_b\right)}{\gamma_s}
\]  
(A77)

Intracellular Ca\(^{2+}\) fluxes

\[
J_{up} = \frac{V_{max} f_b - V_{max} f_b}{1 + f_b + r_b}
\]  
(A78)

\[
J_{tr} = \frac{[Ca^{2+}]_{NSR} - [Ca^{2+}]_{SR}}{\tau_{tr}}
\]  
(A79)

\[
J_{tr} = \frac{d[HTRPNCa]}{dt} + \frac{d[LTRPNCa]}{dt}
\]  
(A80)

Intracellular ionic concentrations

\[
\beta_i = \frac{1 + [CMDF]_{NSR}[K_{m}^{CMDF}]}{[K_{m}^{CMDF} + [Ca^{2+}]]}
\]  
(A81)

\[
\beta_{SS} = \frac{1 + [CMDF]_{SS}[K_{m}^{CMDF}]}{[K_{m}^{CMDF} + [Ca^{2+}]]}
\]  
(A82)

\[
\beta_{SR} = \frac{1 + [CSQ]_{SS}[K_{m}^{CSQ}]}{[K_{m}^{CSQ} + [Ca^{2+}]_{SR}}
\]  
(A83)

\[
\frac{d[Ca^{2+}]_{SS}}{dt} = \beta_{SS} J_{xfer} - J_{up} - J_{tr}
\]  
(A84)

\[
\frac{d[Ca^{2+}]_{SS}}{dt} = \beta_{SS} J_{xfer} - J_{up} - J_{tr} - \frac{[Ca^{2+}]_{SS}}{[Ca^{2+}]_{SS}}
\]  
(A85)

\[
\frac{d[Ca^{2+}]_{SR}}{dt} = \beta_{SR} J_{tr} - J_{rel}
\]  
(A86)

\[
\frac{d[Ca^{2+}]_{SR}}{dt} = \frac{V_{myo} V_{SS} - J_{xfer} V_{myo} V_{SS} - (l_{Ca}) A_{cap} V_{myo}}{2 V_{myo} V_{SS}}
\]  
(A87)

\[
\frac{d[Ca^{2+}]_{SR}}{dt} = \frac{V_{myo} V_{SR} - J_{tr} V_{SR} V_{NSR}}{2 V_{myo} V_{SS}}
\]  
(A88)

\[
\frac{d[Na^+]_{i}}{dt} = -(l_{Na} + l_{Na,b} + l_{rs,Na} + 3l_{NaCa} + 3l_{NaK}) A_{cap} V_{myo}
\]  
(A89)

\[
\frac{d[K^+]_{i}}{dt} = -(l_{K} + l_{K,K} + l_{K,p} + l_{K,S} - 2l_{NaK} + 1l_{Ca,K}) A_{cap} V_{myo}
\]  
(A90)

Myofilaments

Troponin

\[
\frac{d[HTRPNCa]}{dt} = k_{htr}[Ca^{2+}][HTRPNCa]
\]  
(A91)

\[
- [HTRPNCa] - k_{htr}[HTRPNCa]
\]  
(A92)

\[
\frac{d[LTRPNCa]}{dt} = k_{ltr}[Ca^{2+}][LTRPNCa] - [LTRPNCa]
\]  
(A93)

\[
- k_{tr}[Ca^{2+}][LTRPNCa]
\]  
(A94)

\[
- k_{tr}[Ca^{2+}][LTRPNCa]
\]  
(A95)
Tropomyosin/cross bridges

\[ f_{01} = 3 \times f_{XB} \]  
\[ f_{12} = 10 \times f_{XB} \]  
\[ f_{23} = 7 \times f_{XB} \]  
\[ g_{01}(SL) = 1 \times g_{r0}(SL) \]  
\[ g_{12}(SL) = 2 \times g_{r0}(SL) \]  
\[ g_{23}(SL) = 3 \times g_{r0}(9\mu m) \]  
\[ g_{r0}(SL) = g_{r0}^*(2 - SL_{norm})^{1/6} \]  
\[ SL_{norm} = (SL - 1.7 \mu m)/0.7 \mu m \]  
\[ K_{r0}^{\text{trp}} = k_{r0}^{\text{trp}} \times \frac{[\text{LTPN}^{\text{Ca}}]/[\text{LTPN}]_{\text{tot}}}{(K_{r0}^{\text{trp}})^{N_{\text{trp}}}} \]  
\[ N_{\text{trp}} = 3.5 + 2.5 \times SL_{\text{norm}} \]  
\[ K_{r0} = \left( 1 + \frac{K_{r0}^{\text{Ca}}}{1.7 \mu M - 0.9 \mu M \times SL_{\text{norm}}} \right)^{-1} \]  
\[ \frac{dN0}{dt} = k_{r0}^{\text{trp}} P0 - k_{r0}^{\text{trp}} N0 + g_{01}(SL) \times N1 \]  
\[ \frac{dP0}{dt} = -(k_{r0}^{\text{trp}} + f_{01}) P0 + k_{r0}^{\text{trp}} N0 + g_{01}(SL) \times P1 \]  
\[ \frac{dP1}{dt} = -(k_{r0}^{\text{trp}} + f_{12} + g_{01}(SL)) P1 \]  
\[ + k_{r0}^{\text{trp}} N1 + f_{01} P0 + g_{12}(SL) P2 \]  
\[ \frac{dP2}{dt} = -(f_{23} + g_{12}(SL)) P2 + f_{12} P1 + g_{23}(SL) P3 \]  
\[ \frac{dp}{dt} = -g_{23}(SL) \times P3 + f_{23} P2 \]  
\[ \frac{dN1}{dt} = k_{r0}^{\text{trp}} P1 - [k_{r0}^{\text{trp}} + g_{01}(SL)] N1 \]  

**Force computation**

\[ \text{Force} = \zeta \times \text{Force}_{\text{norm}} \]  
\[ \text{Force}_{\text{norm}} = \phi(SL) \times \frac{(P1 + N1 + 2 \times P2 + 3 \times P3)}{\text{Force}_{\text{max}}} \]  

\[ \phi(SL) = \begin{cases} 1 & \text{if } 1.7 \mu m \leq SL \leq 2.0 \mu m \\ 1 & \text{if } 2.0 \mu m < SL \leq 2.2 \mu m \\ (3.6 \mu m - SL)/1.4 \mu m & \text{if } 2.2 \mu m < SL \leq 2.3 \mu m \end{cases} \]  
\[ \text{Force}_{\text{max}} = P_{1_{\text{max}}} + 2 \times P_{2_{\text{max}}} + 3 \times P_{3_{\text{max}}} \]  
\[ P_{1_{\text{max}}} = \frac{(f_{01}) (2 \times g_{r0}^*) (3 \times g_{r0}^*)}{\Sigma \text{paths}} \]  

\[ P_{2_{\text{max}}} = \frac{(f_{01})(f_{12})(3 \times g_{r0}^*)}{\Sigma \text{paths}} \]  
\[ P_{3_{\text{max}}} = \frac{(f_{01})(f_{12})(2 \times g_{r0}^*) (3 \times g_{r0}^*)}{\Sigma \text{paths}} \]  
\[ \Sigma \text{paths} = (g_{r0}^*)(2 \times g_{r0}^*) (3 \times g_{r0}^*) \]  
\[ + (f_{01})(2 \times g_{r0}^*) (3 \times g_{r0}^*) \]  
\[ + (f_{01})(f_{12})(3 \times g_{r0}^*) + (f_{01})(f_{12})(f_{23}) \] 

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**REFERENCES**


