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# A computational model of excitation and contraction in uterine myocytes from the pregnant rat

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## Supplement A – Electromechanical model

This supplement details elements of the ion channels, exchangers and pumps that constitute the electrophysiological element of our single uterine cell model that were not included in the main body of this text.

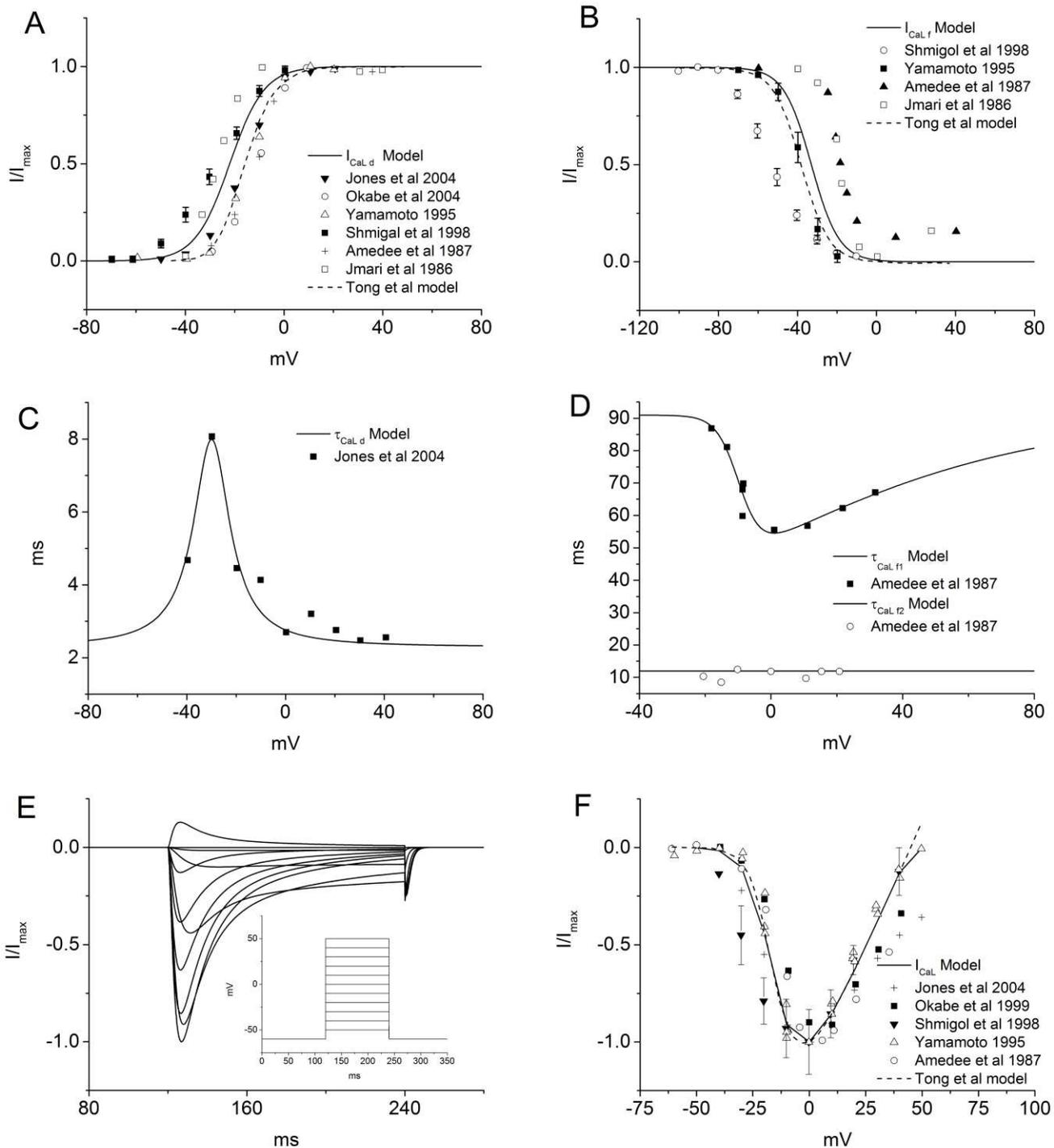
### L-type calcium current - $I_{CaL}$

$I_{CaL}$  is the major contributor to the total inward current and is present in both rat and human uterine smooth muscle cells. It is the main entry route for calcium, acting as the trigger for myometrial contraction [1]–[4]. The voltage-dependence of the steady-state of the activation and inactivation processes in the Tong et al. model has been altered (Fig A1A and A1B). These changes ensure that the I-V relationship for  $I_{CaL}$  (Fig A1F) provide a close fit to the most recent data available (Jones et al 2004) over the physiologically relevant range from -60 to 40 mV. The activation and inactivation curves have been shifted by -7 and + 5mV.

$I_{CaL}$  activates between -40 to -30 mV, peaks between -10 to 10 mV and has a reversal potential  $E_{CaL} \approx 45$  mV to 60 mV at 30-35°C at an extracellular  $Ca^{2+}$  concentration of 1.2-1.5 mM [5], [6]. Currently there is no data specific to myometrial cells, but it has been reported that in other cell types where  $I_{CaL}$  is present, it is permeable to other cations [7]. Therefore, the commonly used Goldman-Hodgkin-Katz formulation is not used here;  $E_{CaL}$  has instead been fixed at 45 mV, in agreement with experimental data [5], [6].

Different steady-state values for activation and inactivation have been reported, possibly reflecting different  $[Ca^{2+}]_o$  employed between studies or differing residual hormonal influences. The half-activation and I-V relationships are right-shifted by  $\approx 15$  mV when  $[Ca^{2+}]_o$  was increased from 3 mM to 30 mM [8]. Yamamoto [6] showed that the I-V relationship was reduced and the half-inactivation left-shifted in myometrial cells exposed to estradiol, which increases near term in rodents. The model uses data sets that are close to the control sets of Yamamoto [6], which are representative of the  $I_{CaL}$  steady-state values from a collection of studies [3], [8].

Due to the lack of available data for voltage-dependent activation time constants, they were extracted from published current tracings, specifically from Jones et al. [9], by fitting the initial few tens of milliseconds of raw data; this is undertaken with the assumption that  $I_{Cl}$  would be slower than  $I_{CaL}$ . The qualification for this assumption is that the activation times for  $I_{CaL}$  and  $I_{Cl}$  in other smooth muscles are 2-8 ms and  $> 50$  ms respectively. The initial fast inward current was blocked by nifedipine, permeable to  $Ba^{2+}$  and increased by L-type calcium channel agonist Bay K8644; thus, it was attributed to  $I_{CaL}$ . The fast inactivation is voltage-independent at  $\approx 12$  ms and the slow inactivation is voltage-dependent with a minimum  $\approx 55$  ms at  $V = 0$  mV.



**Fig A1. Voltage dependence and dynamics of L-type calcium current model –  $I_{CaL}$**  **A:** the activation and **B:** inactivation steady states of  $I_{CaL}$ . **C** and **D:** the activation and inactivation time constants of  $I_{CaL}$ , respectively. **E:** the normalised current-time traces resulting from a voltage-step protocol of -50 mV to 50 mV in steps of 10 mV with a holding potential of -60 mV, used to establish the I-V relationship of  $I_{CaL}$ . **F:** the normalised peak I-V relationship of  $I_{CaL}$ .

### T-type calcium current – $I_{CaT}$

There have been reports of  $I_{CaT}$  in human myometrial cells [4], [10]. Detailed electrophysiological data of cells expressing rat  $\alpha 1G/Cav3.1$  are available [11], [12]. Spontaneous contractions in strips of pregnant rat myometrial tissue were inhibited by the reputed T-type calcium channel blockers mibefradil, NNC 55-0396 (a non-hydrolysable analogue of mibefradil) and  $Ni^{+}$  [13], [14]. In addition Ohkubo et al. [15] showed that the expressions of mRNA encoding for the  $\alpha 1G$  and  $\alpha 1H$  protein subunits of the T-type calcium channel were gestationally regulated in murine

myometrial cells. As a result, this model has been developed from the electrophysiological characteristics of the rat  $\alpha 1G/Cav3.1$  clonal expression cell data, which was recorded at room temperature [11] and adjusted to the human myometrial cell current density [4], [10]. The activation and inactivation steady-state values and the I-V relationships of these different datasets are similar.

$I_{CaT}$  activates at  $V \approx -60$  mV, peaks between  $-20$  to  $-30$  mV and has fast activation, but inactivation varying between 7 to 100 ms [4], [10]–[12]. This might be due to different external divalent cation concentrations used between experiments.

#### **Calcium pump current - $I_{Capump}$**

The calcium pump (plasma membrane  $Ca^{2+}$  ATP-ase) is an ionic transporter that maintains and regulates the calcium concentrations between the cytoplasm, sarcoplasmic and endoplasmic reticulum (SR and ER) in the cells [16]–[18]. There is a disparity between the concentrations of calcium ions in the cytosol ( $0.1 \mu M$ ) and the ER and SR ( $0.1$  to  $1$  mM) [19]; thus  $Ca^{2+}$  ions must be pumped against the concentration gradient, using energy obtained from the ATP chemical energy store. We assume an instantaneous pump with quick bindings resulting in rapid equilibrium using an empirical Hill-type formula.

#### **Sodium/potassium exchanger current – $I_{NaK}$**

This exchanger current plays a major role in regulating intra and extracellular sodium and potassium cations and has been found in late pregnant rat [20], [21] and human [1] myometrial cells. A net negative charge within the cell is achieved by using energy derived from hydrolysed ATP to expel three  $Na^+$  ions for each two  $K^+$  ions brought in.  $I_{NaK}$  reportedly increases during pregnancy in the rat myometrium [21].

This model adopts and modifies the formulae from the Luo-Rudy mammalian ventricular model for  $I_{NaK}$ , due to the absence of information relating to its role in the myometrium [22]. The inhibition of the exchanger changes dynamically, affecting the activities of  $K^+$  and its dependent currents, leading to a bursting AP.

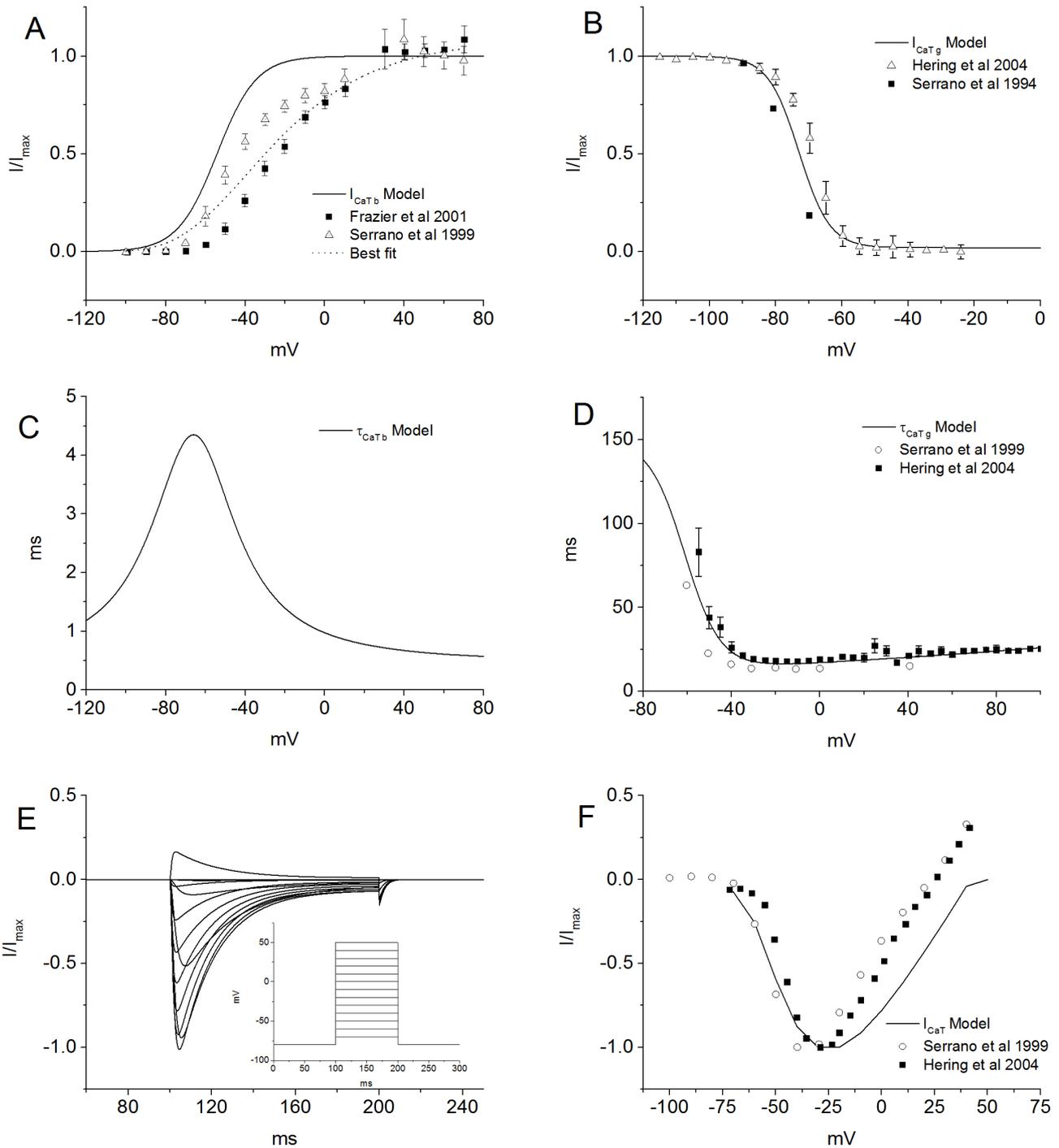
#### **Fast sodium current – $I_{Na}$**

$I_{Na}$  has been found in pregnant human myometrial cells [23] and a fraction of late pregnant rat myometrial cells [4]. This channel is sensitive to tetrodotoxin and sagitoxin. It may be responsible for the fast upstroke of AP generation, the formation of the gap junction and quick excitation propagation during parturition [24]. Studies have found that the number density of sodium channels in the rat increases towards term [25].

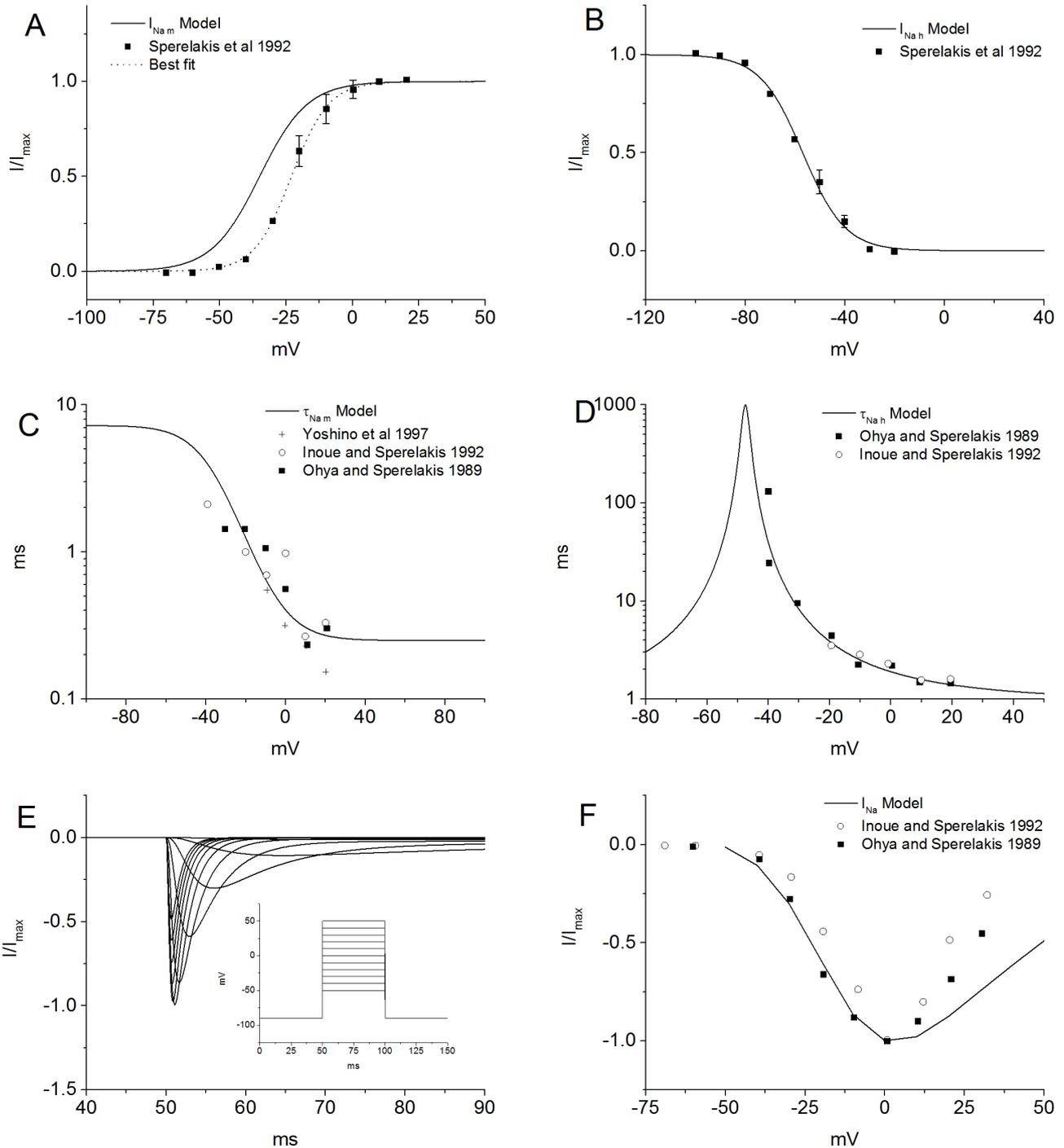
$I_{Na}$  activates at  $V \approx -50$  mV, reaches its peak between  $-10$  to  $10$  mV within  $\approx 1$  ms and is almost completely inactivated after 10 to 20 ms [3], [8].

#### **Sodium/calcium exchanger current – $I_{NaCa}$**

$I_{NaCa}$  expels a  $Ca^{2+}$  ion and brings in three  $Na^+$  ions against the concentration gradient. Abe [26] found that the pre-potential and spontaneous spike discharge disappears at low  $[Na^+]_o$ , but the tissue remains excitable; a depolarising current stimulus causes larger, faster spikes. This confirms the existence of the electrogenic  $I_{NaCa}$  in the rat myometrium. We also borrow from cardiac models for this current, particularly the Hund-Rudy canine ventricular model [27], to make up for the lack of available data.



**Fig A2. T-type calcium current –  $I_{CaT}$**  **A** and **B**: the activation and inactivation steady states of  $I_{CaT}$ , respectively. This is not an ideal fit to the steady state data, but produced a closer reproduction of the  $I_{CaT}$  I-V relationship. **C** and **D**: the activation and inactivation time constants of  $I_{CaT}$ , respectively. **E**: the normalised current-time traces resulting from a voltage-step protocol of -70 mV to 50 mV in steps of 10 mV with a holding potential of -80 mV, used to establish the I-V relationship of  $I_{CaT}$ . **F**: the normalised peak I-V relationship of  $I_{CaT}$ .



**Fig A3. Fast sodium current –  $I_{Na}$**  **A** and **B**: the activation and inactivation steady states of  $I_{Na}$ , respectively. **C** and **D**: the activation and inactivation time constants of  $I_{Na}$ , respectively. **E**: the normalised current-time traces resulting from a voltage-step protocol of -50 mV to 50 mV in steps of 10 mV with a holding potential of -90 mV, used to establish the I-V relationship of  $I_{Na}$ . **F**: the normalised peak I-V relationship of  $I_{Na}$ .

### **Voltage-dependent potassium currents – $I_{K1}$ and $I_{K2}$**

$I_{K1}$  and  $I_{K2}$  play a role in repolarising the cell. We have altered the activation steady state relationship of  $I_{K2}$  from the Tong et al. model in order to provide a better fit to the I-V relationship obtained by Knock and Aaronson (Fig A5A).

Knock et al. [28] separated  $I_{K1}$  and  $I_{K2}$  myometrial potassium currents and categorized them by their inactivation properties and sensitivity to pharmacological blockers of varying channel subtype specificity [28], [29].  $I_{K1}$  and  $I_{K2}$  have rectifying properties and were found in myometrial cells of late pregnant rats [29] and humans [28]; they have very slow dynamics in comparison to other membrane currents and are unevenly distributed between cells. Their primary role appears to be to reset the action potential to its resting state by repolarising the cell membrane.

$I_{K1}$  and  $I_{K2}$  have similar voltage-dependent kinetics.  $I_{K1}$  activates between  $V \approx -50$  to  $-40$  mV and half-inactivates between  $-62$  to  $-68$  mV.  $I_{K2}$  activates between  $V \approx -40$  to  $-30$  mV and half-inactivates between  $-30$  to  $-20$  mV.  $I_{K2}$  inactivates faster than  $I_{K1}$ . Our model took advantage of the more abundant information on the electrophysiological characteristics of human myometrial  $I_{K1}$  and  $I_{K2}$ , complementing them with data from rat myometrium.  $I_{K1}$  and  $I_{K2}$  were separated by their activation thresholds, inactivation properties and current sensitivities to 4-aminopyridine (4-AP) and TEA. The Tong et al fit of the  $I_{K2}$  activation steady state was adjusted to allow a better fit to the unpublished I-V curve data from Knock and Aaronson.

### **A-type transient potassium current – $I_{KA}$**

$I_{KA}$  has very fast activation and inactivation kinetics, is found in both rat and human myometrial cells (though it is rare in pregnant cells), is sensitive to 4-AP and insensitive to TEA [30]. It activates at  $V \approx -40$  mV, peaks within  $\approx 10$  ms and is almost completely inactivated within 50 ms [2], [30]. In human myometrium it has a half-inactivation  $\approx -70$  mV and a slope factor  $\approx 5$  mV [28], [30]. These are similar characteristics to the transient potassium current in myometrial cells isolated from immature rats.

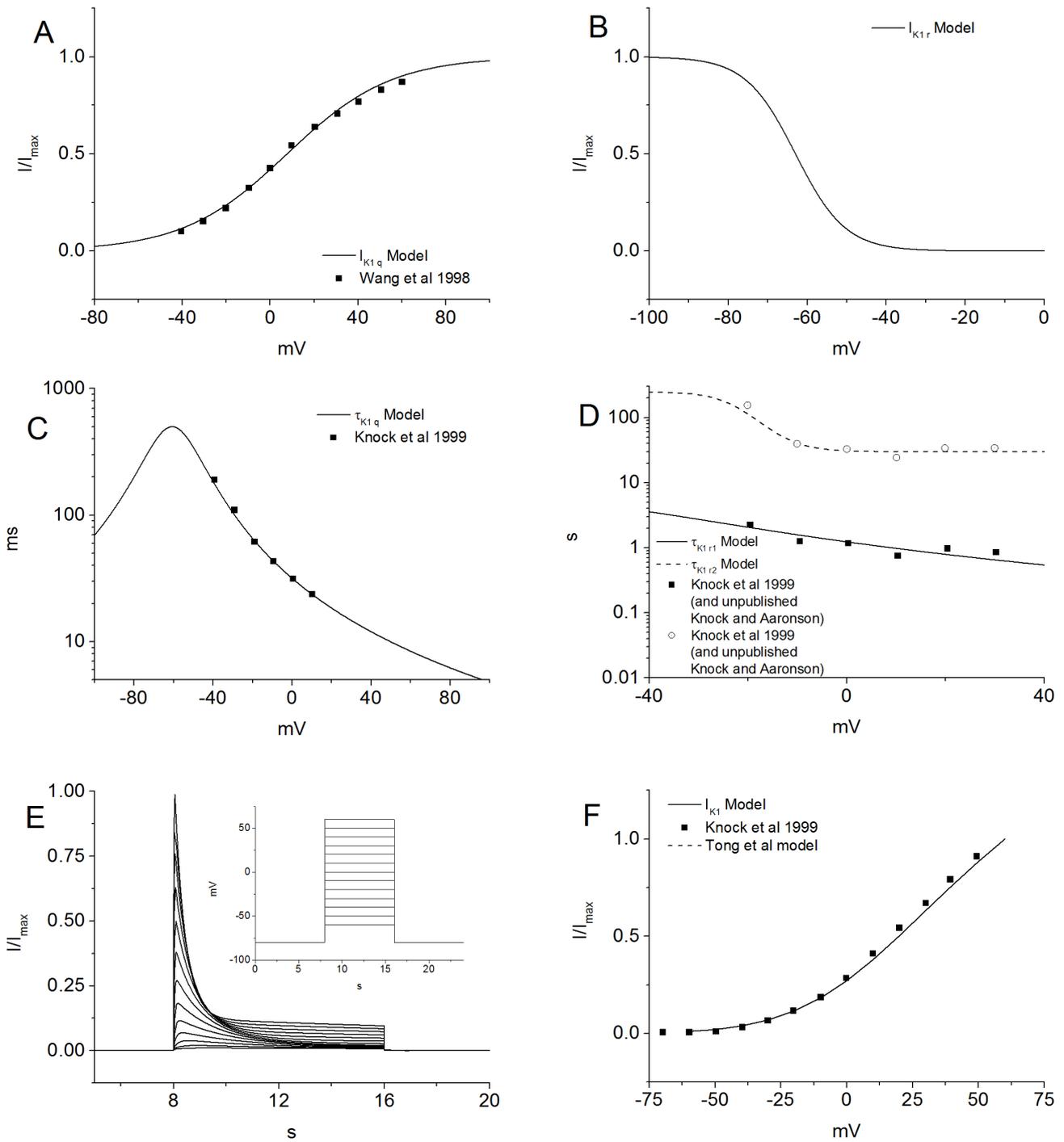
### **Calcium activated potassium current - $I_{K(Ca)}$**

$I_{K(Ca)}$  is associated with setting the resting membrane potential and regulating the shape and duration of the action potential. It may be responsible for up to 10% of the total  $K^+$  current in late pregnant rat myometrial cells [29]. Quantitative data for the dynamics of this channel in the myometrium is lacking and the equations developed for rat mesenteric smooth muscle have been used [31]. Calcium activated potassium currents provide a means of burst termination in pancreatic cells (Chay Keizer model) and neurones (Chay Fan model).

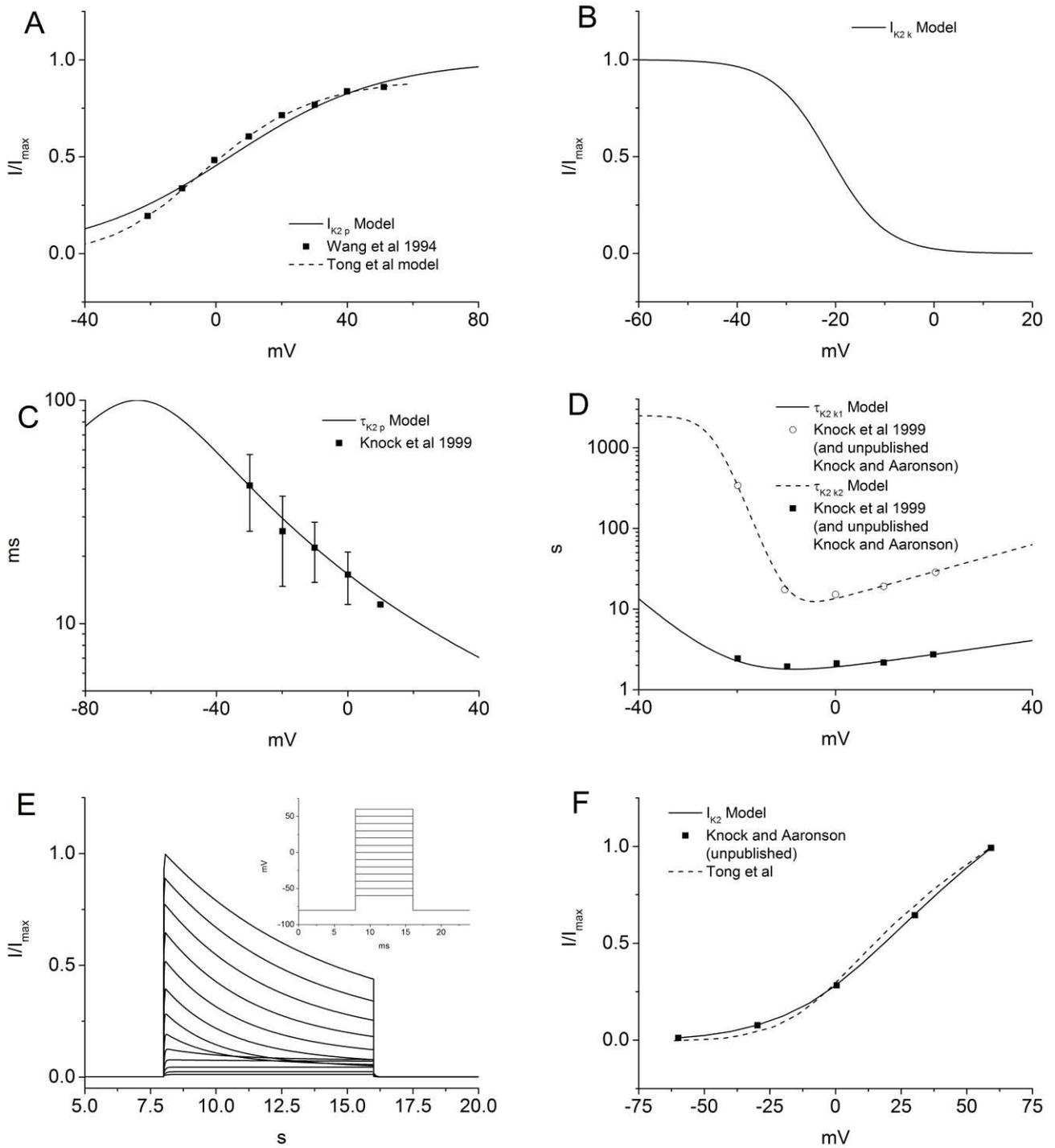
### **Hyperpolarisation-activated current – $I_h$**

This current has reportedly been found in the circular and longitudinal cells of the pregnant murine myometrium [32], [33] and is otherwise known as the funny current ( $I_f$ ) in cardiac cells. It is activated by hyper polarisation of the membrane potential, below  $-60$  mV, has a half-maximal activation around  $-85$  mV and does not inactivate. In voltage clamp experiments the activation is slow, taking  $> 1$  s.  $K^+$  ions permeate this channel more readily than  $Na^+$  ions, with a ratio of  $P_{Na}/P_K = 0.35$ . The reversal potential  $E_h \approx -20$  mV is dependent on the extracellular concentration of  $K^+$  and  $Na^+$ ; and excess of  $K^+$  increases the current amplitude and a low measure of  $Na^+$  decreases it, while  $Cs^+$  blocks the channel. This current is activated at the resting membrane potential and its role is to maintain this potential and spontaneous activity within the myometrium.

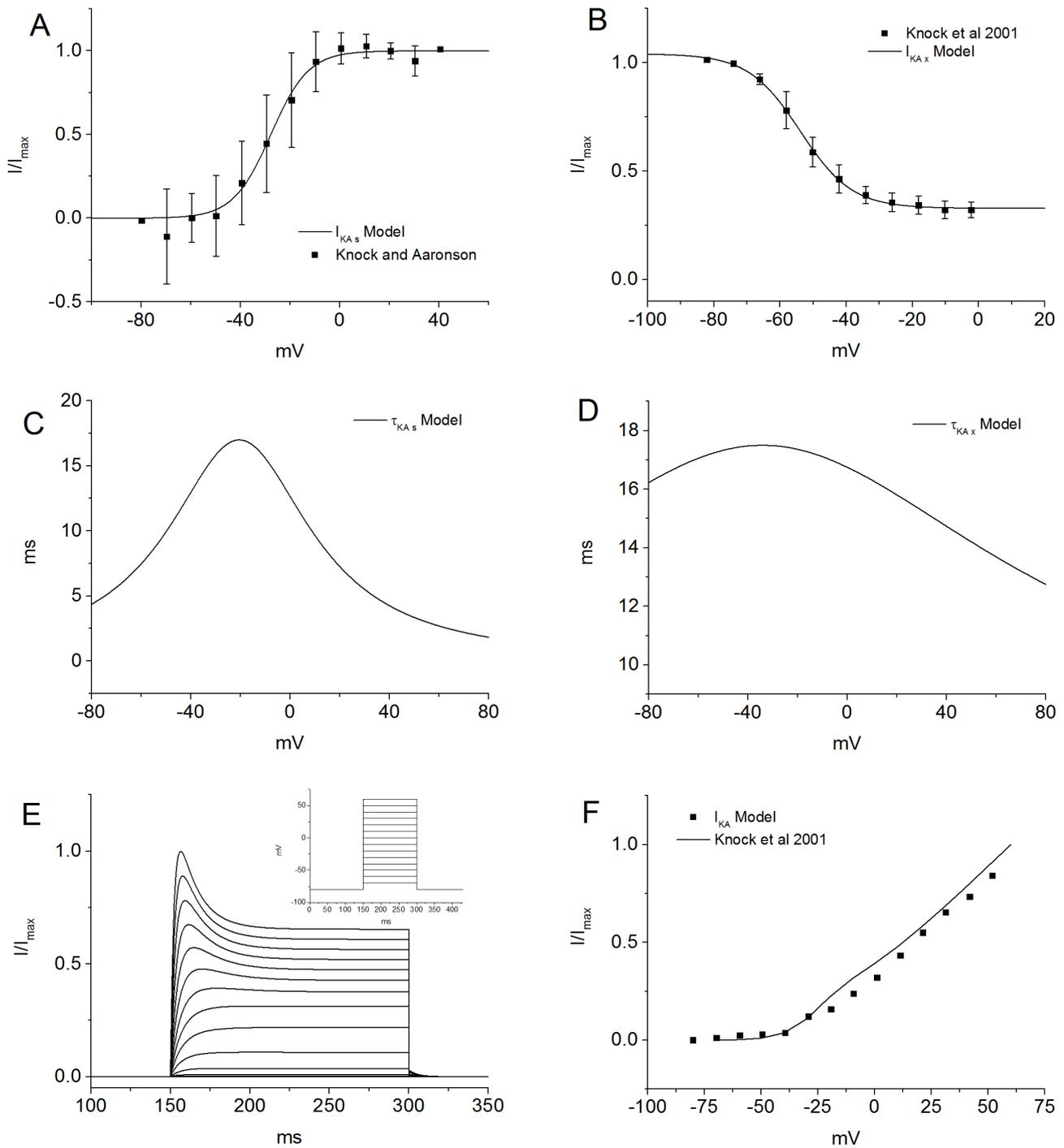
Data for this channel has been found experimentally by Okabe et al. [32] and Satoh [33]. Temperatures ranged from  $24-30^\circ\text{C}$ ; the time constant  $\tau_h$  was adjusted to compensate, with a  $Q_{10}$  value of 3.5. The single cell model was developed for a longitudinal cell. The circular cell half-activation has been shifted by  $-15$  mV to match the longitudinal data. At room temperature, with a holding potential of  $-50$  mV,  $I_h$  has a current density of  $-1.03$  pApF<sup>-1</sup>.



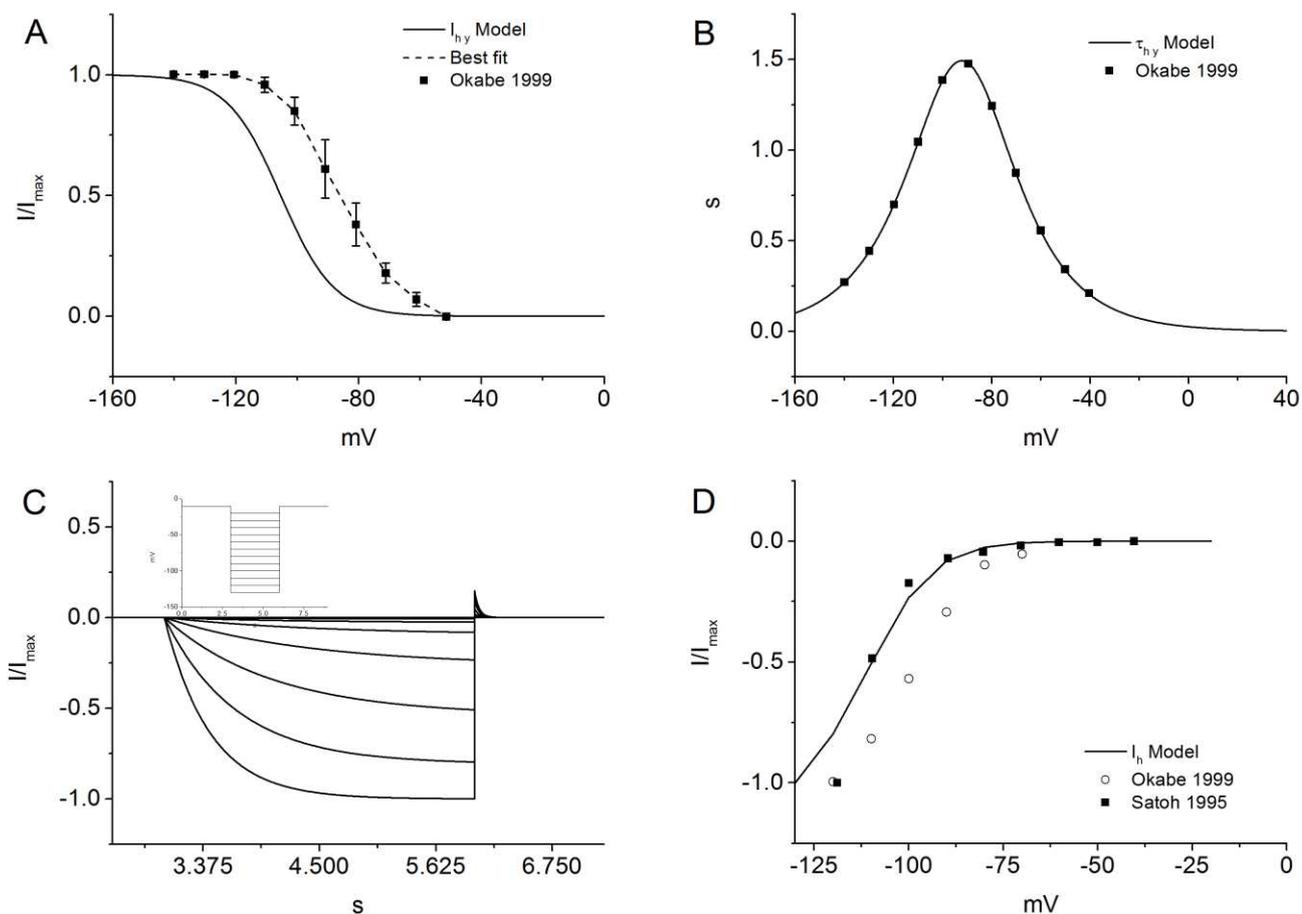
**Fig A4. Voltage-dependent potassium current –  $I_{K1}$**  **A** and **B**: the activation and inactivation steady states of  $I_{K1}$ , respectively. **C** and **D**: the activation and inactivation time constants of  $I_{K1}$ , respectively. **E**: The normalised current-time traces resulting from a voltage-step protocol of -60 mV to 60 mV in steps of 10 mV with a holding potential of -80 mV, used to establish the I-V relationship of  $I_{K1}$ . **F**: the normalised peak I-V relationship of  $I_{K1}$ .



**Fig A5. Voltage-dependent potassium current –  $I_{K2}$**  **A** and **B**: the activation and inactivation steady states of  $I_{K2}$ , respectively. **C** and **D**: the activation and inactivation time constants of  $I_{K2}$ , respectively. **E**: The normalised current-time traces resulting from a voltage-step protocol of -60 mV to 60 mV in steps of 10 mV with a holding potential of -80 mV, used to establish the I-V relationship of  $I_{K2}$ . **F**: the normalised peak I-V relationship of  $I_{K2}$ .



**Fig A6. A-type transient potassium current –  $I_{KA}$**  **A** and **B**: the activation and inactivation steady states of  $I_{KA}$ , respectively. **C** and **D**: the activation and inactivation time constants of  $I_{KA}$ , respectively. **E** and **F**: the normalised current-time traces and current-voltage relationship of  $I_{KA}$ , respectively. **E**: the normalised current-time traces resulting from a voltage-step protocol of -80 mV to 60 mV in steps of 10 mV with a holding potential of -80 mV, used to establish the I-V relationship of  $I_{KA}$ . **D**: the normalised peak I-V relationship of  $I_{KA}$ .



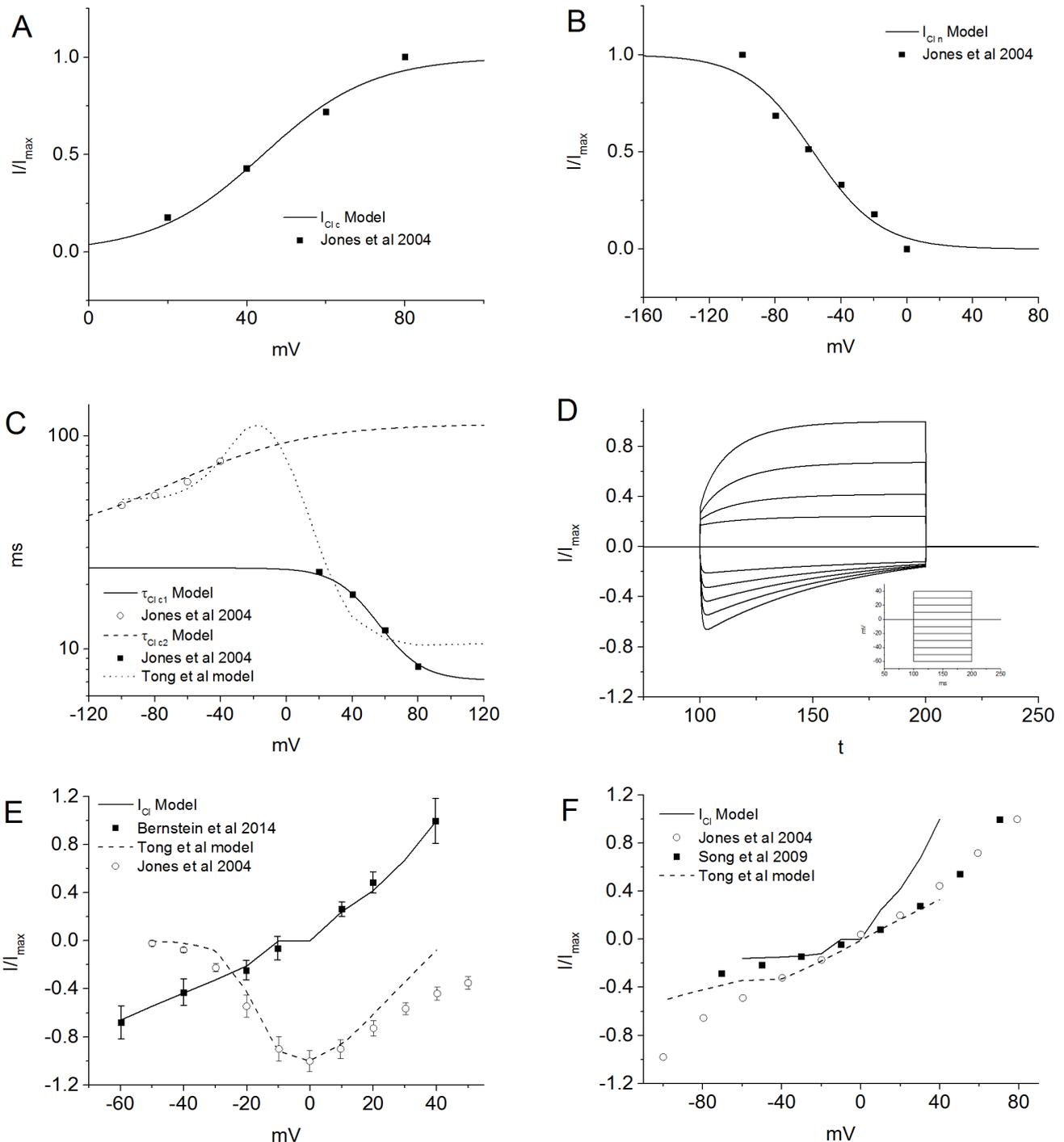
**Fig A7. Hyperpolarisation-activated current –  $I_h$**  **A:** the activation steady state of  $I_h$ . The experimental data was taken at temperatures of 24 °C and 30 °C; to compensate a  $Q_{10}$  factor of 3.5 was introduced, negatively shifting the activation curve. **B:** the activation time constant of  $I_h$ . **C:** the normalised current-time traces resulting from a voltage-step protocol of -20 mV to -130 mV in steps of 10 mV with a holding potential of -10 mV, used to establish the I-V relationship of  $I_h$ . **D:** the normalised peak I-V relationship of  $I_h$ .

### Calcium-activated chloride current – $I_{Cl}$

Spontaneous transient inward currents (STICs) are pro-contractile currents that exhibit the characteristics of calcium-activated channels (CaCCs) and have been observed in murine and human uterine smooth muscle cells, and in putative pacemaking interstitial cells of Cajal in the intestine [34]. They are blocked by Cl<sup>-</sup> inhibitors such as niflumic acid and flufenamic acid and are greatly diminished in calcium-free buffers, consistent with their being calcium-activated channels (CaCCs), showing calcium activation, voltage dependence and a reversal potential of -15 mV [35], [36]. The anoctamin 1 and 2 (ANO1, ANO2) channels are responsible for these currents [36], and their kinetics were formulated from experimental data in Jones et al 2004 [9].

It is believed that CaCCs prolong the duration of contraction in pregnant tissue [9], [37]. They may play a role in depolarising the membrane, leading to increased Ca entry [38], [39]. In the interstitial cells of Cajal (ICC) of the intestines they play a role in pace making; ICC-like cells have been described in the myometrium [40] and Bernstein et al suggest there may be evidence of this role in the myometrium [36]. The contribution of  $I_{Cl}$  to the total inward current is a matter for debate, with contrasting reports indicating it is responsible for up to 30% [9] or unimportant [41].

Jones et al [9] assessed the electrophysiology of  $I_{Cl}$  in the single cell using two distinct voltage clamp experiments. The activation time relationship of  $I_{Cl}$  is relatively complex. In order to provide a more representative activation model for  $I_{Cl}$ , its time coefficient relationship has been split into two functions (Fig A8C); the current is calculated differently for voltages above and below 0 mV. The Tong model used an alternative continuous function for the activation time constant and fitted I-V data from Jones 2004. I-V curves for  $I_{Cl}$  for our model reproduce those seen in the more recent Bernstein 2014 [36], [42]–[44].



**Fig A8. Modifications to the calcium-activated chloride channel –  $I_{Cl}$**  **A** and **B**: the activation and inactivation steady states of  $I_{Cl}$ , respectively. This updated model includes the inactivation properties. **C**: the activation time constant of  $I_{Cl}$  was split into two components. The inactivation time constant was fixed at 0.69 ms (not shown here) **D**: the normalised current-time traces resulting from a voltage-step protocol of -60 mV to 40 mV in steps of 10 mV with a holding potential of 0 mV, used to establish the I-V relationship of  $I_{Cl}$ . **E** and **F**: the peak and tail I-V relationships of  $I_{Cl}$  respectively. This channel was reformulated to account for new data describing the peak I-V values [36].

### Ionic concentration dynamics

$[Ca^{2+}]_i$  increases as the calcium channels respond to a depolarising cell membrane.  $Na^+$ ,  $K^+$  and  $Cl^-$  ion regulation are also regulated by the intracellular ion handling component. Additional  $Ca^{2+}$  is also released by the sarcoplasmic reticulum store (SR), by the process of calcium-induced calcium-release (CICR). The  $[Ca^{2+}]_i$  –dependent kinetics

respond to this influx of  $\text{Ca}^{2+}$  into the cytoplasm, leading to the development of contractile forces. Calsequestrin (CSQN) binds to  $\text{Ca}^{2+}$  in the SR, storing it despite the higher concentration within the SR relative to the cytosol.

The Tong et al. model calculates the calcium current using a simple formula consisting of three components: contributions from the L-type calcium current, the T-type calcium current and the sodium-calcium exchanger. Notably absent from this description are contributions from the non-selective cation current (NSCC), the store-operated non-selective cation current, the calcium pump and the SR currents. We included these factors for a more complete description of the calcium dynamics (B17.1).

Another advance from the previous Tong et al. model was the inclusion of formulae describing the sodium, potassium and chloride ion currents. Changes in the concentration of these ions contribute less significantly to contraction than calcium ions; however their effects are not negligible and should be accounted for in a comprehensive model. We modelled the changes to intracellular ionic concentrations of  $\text{Ca}^{2+}$ ,  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cl}^-$  with a series of first order differential equations (B17.2, B17.4, B17.6, and B17.8, respectively). A calcium buffer was implemented to reduce sensitivity to  $[\text{Ca}^{2+}]_i$  (B17.2).

Changes to intracellular ionic concentrations of  $\text{Ca}^{2+}$ ,  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cl}^-$  are described by a series of first order differential equations (B17.2, B17.4, B17.6, and B17.8, respectively). A calcium buffer was implemented to reduce sensitivity to  $[\text{Ca}^{2+}]_i$  (B17.2).

The calcium currents include contributions from the L-type calcium current, the T-type calcium current, the sodium-calcium exchanger, the non-selective cation current, the store-operated non-selective cation current, the calcium pump and the SR currents in (B17.1). Changes in the concentration of  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cl}^-$  do not directly contribute to contraction, but they do influence the behaviour of several ionic currents: the fast sodium current, the voltage-dependent potassium currents, the A-type transient potassium current, the calcium-activated potassium current, the background potassium leakage current, the hyperpolarisation-activated current, the sodium/potassium exchanger current, the sodium/calcium exchanger current, the sodium-potassium-chloride co-transport current, the store-operated non-selective cation current and the non-selective cation current. The feedback from changes to these currents can in turn affect the morphology of the AP, calcium transients and ultimately contractile force. The intracellular ionic concentration dynamics are measurable in in vitro experiments and provide additional constraints on the behaviour of the cell model [45].

### **Cell contraction**

In order to model the contractile activity in the cell we must couple the electrical systems to mechanical systems (Fig 1), using the intracellular calcium concentration as a mediator.

Calcium plays a key role in the mechanical contraction and relaxation of myometrial tissue.  $\text{Ca}^{2+}$  enters the cell through voltage-gated channels, primarily through the L-type Calcium channel. It can also be released from its store in the sarcoplasmic reticulum (Fig A9) via  $\text{IP}_3$  and the ryanodine receptors. Some experimental evidence suggests the SR makes a minimal contribution [46]–[48] to contractile activity; though other findings suggest it may be more significant [49], [50]. Optical measures of intracellular  $[\text{Ca}^{2+}]_i$  in tissue preparations have been used as a surrogate measure of myometrial cell excitation [51].

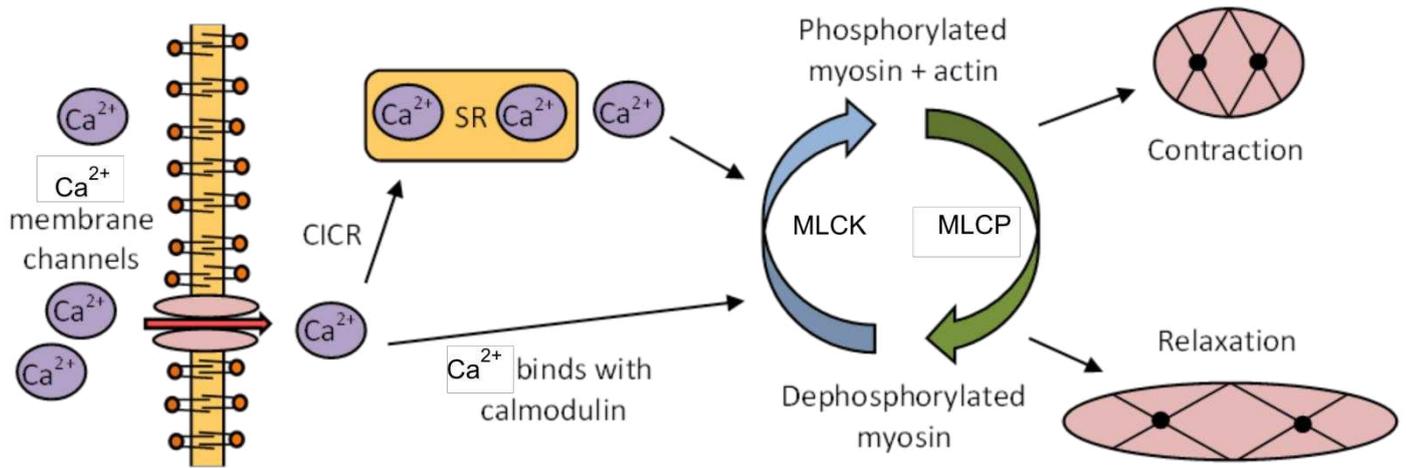
### **The sarcoplasmic reticulum (SR)**

The SR is a calcium store within the cell. Noble et al state that the myometrial SR contributes to sustained depolarisation, bursts of APs and phasic contractions [50]. They remark that the model of the SR developed in cardiac muscle, whereby a small amount of L-type  $\text{Ca}^{2+}$  entry triggers a substantial rise of cytoplasmic  $\text{Ca}^{2+}$  via RyR-mediated SR  $\text{Ca}^{2+}$  release leading to contraction is not substantiated by their findings. Rather the  $\text{Ca}^{2+}$  released from the SR stimulates store-operated calcium entry (SOCE), meaning that although the SR plays an important role, the greater contribution to contraction in myometrial cells comes from the membrane channels, unlike cardiac myocytes.

We modelled the SR as a two-compartment system; an uptake compartment and a release compartment, as described for vascular smooth muscle cells by Yang et al [52]. Calcium enters the SR via the SERCA pump ( $I_{\text{up}}$ ); the release mechanism is governed by a Hai and Murphy four-state ryanodine receptor model (Fig A10) via the process of CICR ( $I_{\text{rel}}$ ) [53]. The three currents  $I_{\text{up}}$ ,  $I_{\text{tr}}$  and  $I_{\text{rel}}$  (B18.1 – B18.3) describe the uptake into the SR, transfer between compartments and release of calcium ions into the cytoplasm.

The Michaelis constant of  $1\mu\text{M}$  suggested by Kapela et al [31] was used rather than the  $80\mu\text{M}$  used by Yang et al, as it is closer to physiological values. To avoid excessive loading of the SR a leakage component was included,  $R_{\text{leak}}$ .

This and the release time constant  $\tau_{rel}$  were adjusted from the Kapela et al model to better fit myometrial  $[Ca^{2+}]_i$  data.  $F_{rel}$  is a scaling factor used to adjust the magnitude of the release current.



**Fig A9. Cell contraction mechanisms in the uterine myocyte** [54]. Calcium enters the cell through the membrane channels. This begins the process of Calcium Induced Calcium Release (CICR) from the SR. The  $Ca^{2+}$  then bonds with calmodulin, activating the Myosin Light-Chain Kinase (MLCK). Phosphorylated myosin can then form cross-bridges with actin, causing the cell to contract. Myosin Light-Chain Phosphatase (MLCP) dephosphorylates the myosin leading to relaxation.

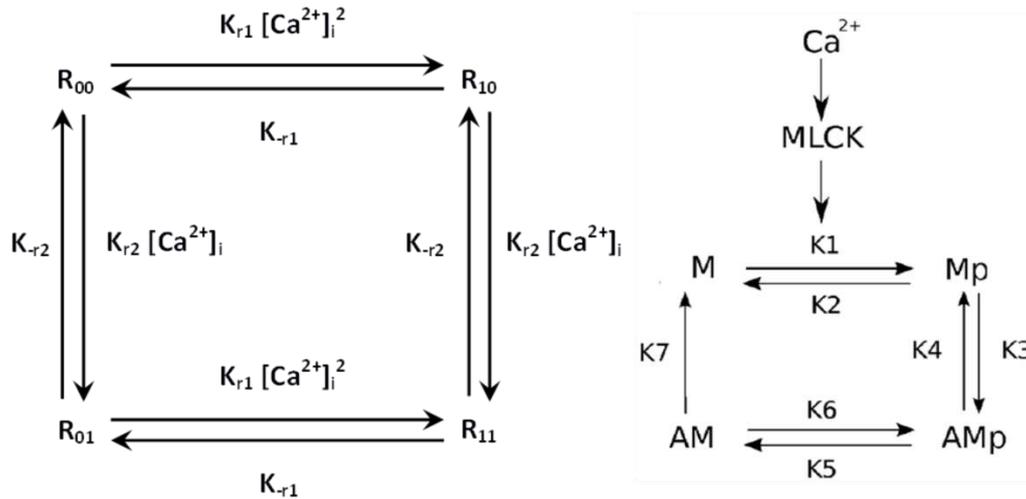
### The ryanodine receptors (RyR)

In the process of CICR  $[Ca^{2+}]_i$  binds to the RyR; they open, allowing calcium from inside the SR store to enter the intracellular space. In order to simulate CICR we have incorporated the model described by Yang et al [52]; the states of the ryanodine receptors are  $R_{00}$  (free receptors),  $R_{10}$  (activation sites with bound calcium),  $R_{01}$  (inactivation sites with bound calcium) and  $R_{11}$  (activation and inactivation sites with bound calcium) [52]. Transitions between these states were controlled by the activation and inactivation rate constants,  $K_{\pm r1}$  and  $K_{\pm r2}$ .

### The kinetic cross-bridge cycle (KCBC)

We modelled the kinetic cross-bridge cycle using the four-state hypothesis described by Hai and Murphy [53] (Fig A10). Unlike striated and cardiac muscles, smooth muscles do not contain troponin for the calcium to bind to; instead  $[Ca^{2+}]_i$  binds with calmodulin and activates the myosin light-chain kinase (MLCK), forming cross-bridges between actin and myosin filaments, via the attached phosphorylated and attached de-phosphorylated non-cycling cross-bridges (AMP and AM) [55], [56], leading ultimately to muscle contraction. There are also free cross-bridges and phosphorylated cross-bridges (M and Mp). The flow between states was determined by the rate constants,  $K_{1-6}$ , which are  $[Ca^{2+}]_i$  dependent.  $K_7$  was the slow detachment rate constant, which leads to relaxation.

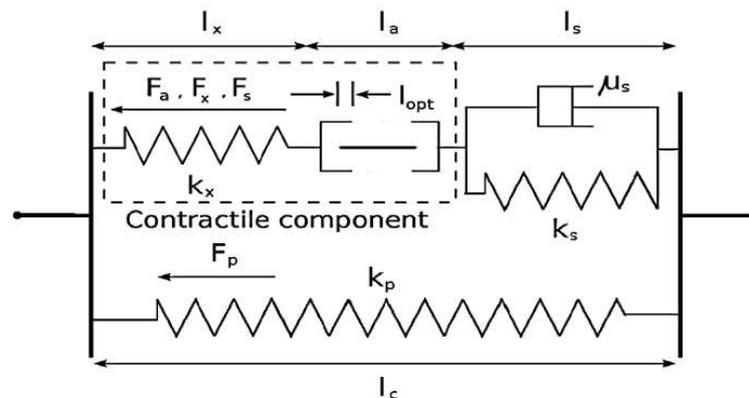
Hai and Murphy established the values for the rate constants by first fitting phosphorylation kinetic data for  $K_1$ ,  $K_2$ ,  $K_5$  and  $K_6$ . These were then held constant while  $K_3$ ,  $K_4$  and  $K_7$  were fitted to stress data. The rate-limiting step was revealed to be  $K_7$ , the latch-bridge detachment rate.



**Fig A10. Ryanadine receptor and kinetic cross-bridge cycling models in smooth muscle.** **Left:** Four-state kinetic model of ryanodine receptors from Hai and Murphy [53] and Yang et al [52]. The states are defined as being bound or unbound to  $\text{Ca}^{2+}$  and if bound, whether the calcium is attached to activation sites, inactivation sites or both. The rate constants  $K_{r1}$  and  $K_{r2}$  represent the speed that  $\text{Ca}^{2+}$  binds to the activation and inactivation sites, respectively. Unbinding rates are indicated with a minus sign. **Right:** Four-state kinetic cross-bridge cycling model in smooth muscle adapted from Yang et al [52]. The states are differentiated by their status as attached or detached, and phosphorylated or dephosphorylated. Cycling between the states is described by the various rate constants,  $K$ .

### Force production

We modelled force production in the cell as described by Yang et al (Fig A11) [52], using a modification of the three-component Hill model. The cross-bridges in smooth muscles are arranged in parallel with equal spacing; hence force production by the muscles is proportional to the length of the myosin fibre. The total myometrial force is comprised of four components; they are the passive force  $F_p$ , cross-bridge elastic force  $F_x$ , active force  $F_a$  and series visco-elastic force  $F_s$ .



**Fig A11. The mechanical model of a smooth muscle cell from Yang et al [52].** The four force components  $F_p$ ,  $F_a$ ,  $F_x$  and  $F_s$  couple together to generate tension and stress in the cell. The  $k$  values are spring constants and  $\mu_s$  is the coefficient of viscoelasticity of the dashpot, tasked with absorbing shock from impacts caused by the spring.

$F_p$  (B21.5) is dependent on the length of the cell  $l_c$ , taken to be  $123 \mu\text{m}$ . The myometrial cell length for the late pregnant rat can range from  $80$  to  $700 \mu\text{m}$  [3], [25], [57], [58]. Other parameters necessary to calculate  $F_p$  that were not available experimentally for the uterine cell have been substituted for values found in the Yang et al arterial smooth muscle model.

$F_x$  (B21.6) is dependent on the length of the cross-bridge  $l_x$  and the length of the active force component  $l_a$ .  $l_{opt}$  represents the optimal muscle length, i.e. when the maximum force is achieved from the overlapping of the myosin and actin filaments.  $F_x$  and  $F_a$  coupled to describe the sliding of the myosin and actin filament.

$F_a$  (B21.7) is the component of the force generated by the activity of the cross-bridges. It is characterised by the friction coefficients for the attached phosphorylated (AMp) and attached dephosphorylated (AM) cross-bridges.

$F_s$  (B21.8) is described by a spring and dashpot working in parallel. The force produced by the spring can deform the element and so the dashpot is included as a shock absorber to compensate for the effect. The displacement for the two components is the same and the total force produced by this element is a combination of the elastic and viscous forces. The total force produced by the cell is the sum of  $F_a$  and  $F_p$  (1.5).

## Supplement B – Formulations and parameters

This supplement contains all of the equations and parameters used in our single cell model. Formulae that are not present in Tong et al or have been altered are highlighted in red.

### L-type calcium current – $I_{CaL}$

$$I_{CaL} = \bar{g}_{CaL} d^2 f_{Ca} (0.8f_1 + 0.2f_2)(V - E_{CaL}) \quad B1.1$$

$$f_{Ca} = \frac{1}{1 + \frac{[Ca^{2+}]_i}{K_{m,CaL}}} \quad B1.2$$

$$d_{\infty} = \frac{1}{1 + e^{\frac{-V-22}{7}}} \quad B1.3$$

$$f_{\infty} = \frac{1}{1 + e^{\frac{V+33}{7}}} \quad B1.4$$

$$\tau_d = 2.29 + \frac{5.7}{1 + \left(\frac{V+29.97}{9}\right)^2} \quad B1.5$$

$$\tau_{f_1} = 12 \text{ ms} \quad B1.6$$

$$\tau_{f_2} = 90.97 - \frac{90.97}{\left(1 + e^{\frac{V+13.96}{45.38}}\right) \left(1 + e^{\frac{-V-9.5}{3.39}}\right)} \quad B1.7$$

$$\frac{dd}{dt} = \frac{d_{\infty} - d}{\tau_d} \quad B1.8$$

$$\frac{df_1}{dt} = \frac{f_{\infty} - f_1}{\tau_{f_1}} \quad B1.9$$

$$\frac{df_2}{dt} = \frac{f_{\infty} - f_2}{\tau_{f_2}} \quad B1.10$$

Parameter	Value	Definition
$\bar{g}_{CaL}$	0.318 nS pF <sup>-1</sup>	Maximum conductance of $I_{CaL}$
$E_{CaL}$	45 mV	Reversal potential of $I_{CaL}$
$K_{m,CaL}$	0.6 $\mu$ M	Half saturation concentration of $I_{CaL}$

Table B1. L-type calcium current parameters

### T-type calcium current – $I_{CaT}$

$$I_{CaT} = \bar{g}_{CaT} b^2 g(V - E_{CaT}) \quad B2.1$$

$$b_{\infty} = \frac{1}{1 + e^{\frac{-V-43}{6}}} \quad B2.2$$

$$g_{\infty} = 0.02 + \frac{0.98}{1 + e^{\frac{V+72.98}{4.64}}} \quad B2.3$$

$$\tau_b = 0.45 + \frac{3.9}{1 + \left(\frac{V+66}{26}\right)^2} \quad B2.5$$

$$\tau_g = 150 - \frac{150}{\left(1 + e^{\frac{V-417.43}{203.18}}\right) \left(1 + e^{\frac{-V+61.11}{8.07}}\right)} \quad \text{B2.5}$$

$$\frac{db}{dt} = \frac{b_\infty - b}{\tau_b} \quad \text{B2.6}$$

$$\frac{dg}{dt} = \frac{g_\infty - g}{\tau_g} \quad \text{B2.7}$$

Parameter	Value	Definition
$\bar{g}_{CaT}$	0.02319 nS pF <sup>-1</sup>	Maximum conductance of I <sub>CaT</sub>
$E_{CaT}$	42 mV	Reversal potential of I <sub>CaT</sub>

**Table B2. T-type calcium current parameters**

**Fast sodium current – I<sub>Na</sub>**

$$I_{Na} = \bar{g}_{Na} m^3 h (V - E_{Na}) \quad \text{B3.1}$$

$$E_{Na} = \frac{RT}{F} \ln \left( \frac{[Na]_o}{[Na]_i} \right) \quad \text{B3.2}$$

$$m_\infty = \frac{1}{1 + e^{\frac{-V+35}{9}}} \quad \text{B3.3}$$

$$h_\infty = \frac{1}{1 + e^{\frac{V+57}{8}}} \quad \text{B3.4}$$

$$\tau_m = 0.25 + \frac{7}{1 + \left(\frac{V+38}{10}\right)} \quad \text{B3.5}$$

$$\tau_h = 0.9 + \frac{1002.85}{1 + \left(\frac{V+47.5}{1.5}\right)^2} \quad \text{B3.6}$$

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \quad \text{B3.7}$$

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h} \quad \text{B3.8}$$

Parameter	Value	Definition
$\bar{g}_{Na}$	0.1152 nS pF <sup>-1</sup>	Maximum conductance of I <sub>Na</sub>

**Table B3. Fast sodium current parameters**

**Voltage-dependent potassium current – I<sub>K1</sub>**

$$I_{K1} = \bar{g}_{K1} q (0.38r_1 + 0.62r_2) (V - E_K) \quad \text{B4.1}$$

$$E_K = \frac{RT}{F} \ln \left( \frac{[K]_o}{[K]_i} \right) \quad \text{B4.2}$$

$$q_\infty = \frac{1}{1 + e^{\frac{-V-7.7}{23.7}}} \quad \text{B4.3}$$

$$r_{\infty} = \frac{1}{1+e^{\frac{V+63}{6.3}}} \quad \text{B4.4}$$

$$\tau_q = \frac{500}{1+\left(\frac{V+60.71}{15.79}\right)^2} \quad \text{B4.5}$$

$$\tau_{r_1} = \frac{5 \times 10^3}{1+\left(\frac{V+62.71}{35.86}\right)^2} \quad \text{B4.6}$$

$$\tau_{r_2} = 3 \times 10^4 + \frac{2.2 \times 10^5}{1+e^{\left(\frac{V+22}{4}\right)}} \quad \text{B4.7}$$

$$\frac{dq}{dt} = \frac{q_{\infty}-q}{\tau_q} \quad \text{B4.8}$$

$$\frac{dr_1}{dt} = \frac{r_{\infty}-r_1}{\tau_{r_1}} \quad \text{B4.9}$$

$$\frac{dr_2}{dt} = \frac{r_{\infty}-r_2}{\tau_{r_2}} \quad \text{B4.10}$$

Parameter	Value	Definition
$\bar{g}_{K1}$	0.2048 nS pF <sup>-1</sup>	Maximum conductance of I <sub>K1</sub>

**Table B4. Type-1 Voltage-dependent potassium current parameters**

#### Voltage-dependent potassium current – I<sub>K2</sub>

$$I_{K2} = \bar{g}_{K2} p (0.75k_1 + 0.25k_2) (V - E_K) \quad \text{B5.1}$$

$$E_K = \frac{RT}{F} \ln \left( \frac{[K]_o}{[K]_i} \right) \quad \text{B5.2}$$

$$p_{\infty} = \frac{1}{1+e^{\frac{-V+4.2}{23}}} \quad \text{B5.3}$$

$$k_{\infty} = \frac{1}{1+e^{\frac{V+21.2}{5.7}}} \quad \text{B5.4}$$

$$\tau_p = \frac{100}{1+\left(\frac{V+64.1}{28.67}\right)^2} \quad \text{B5.5}$$

$$\tau_{k_1} = 1 \times 10^6 - \frac{1 \times 10^6}{\left(1+e^{\frac{V-315}{50}}\right) \left(1+e^{\frac{-V-74.9}{8}}\right)} \quad \text{B5.6}$$

$$\tau_{k_2} = 2.5 \times 10^6 - \frac{2.5 \times 10^6}{\left(1+e^{\frac{V-132.87}{25.4}}\right) \left(1+e^{\frac{-V-24.92}{2.68}}\right)} \quad \text{B5.7}$$

$$\frac{dp}{dt} = \frac{p_{\infty}-p}{\tau_p} \quad \text{B5.8}$$

$$\frac{dk_1}{dt} = \frac{k_{\infty}-k_1}{\tau_{k_1}} \quad \text{B5.9}$$

$$\frac{dk_2}{dt} = \frac{k_\infty - k_2}{\tau_{k_2}}$$

B5.10

Parameter	Value	Definition
$\bar{g}_{K2}$	0.0315 nS pF <sup>-1</sup>	Maximum conductance of I <sub>K2</sub>

Table B5. Type-2 Voltage-dependent potassium current parameters

**A-type transient potassium current – I<sub>KA</sub>**

$$I_{KA} = \bar{g}_{KA} s x (V - E_K) \quad \text{B6.1}$$

$$E_K = \frac{RT}{F} \ln \left( \frac{[K]_o}{[K]_i} \right) \quad \text{B6.2}$$

$$s_\infty = \frac{1}{1 + e^{\frac{-V - 27.79}{7.57}}} \quad \text{B6.3}$$

$$x_\infty = 0.3293 + \frac{0.71165}{1 + e^{\frac{V + 53.919}{7.8111}}} \quad \text{B6.4}$$

$$\tau_s = \frac{17}{1 + \left( \frac{V + 20.52}{35} \right)^2} \quad \text{B6.5}$$

$$\tau_x = 7.5 + \frac{10}{1 + \left( \frac{V + 34.18}{120} \right)^2} \quad \text{B6.6}$$

$$\frac{ds}{dt} = \frac{s_\infty - s}{\tau_s} \quad \text{B6.7}$$

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x} \quad \text{B6.8}$$

Parameter	Value	Definition
$\bar{g}_{KA}$	0.001418 nS pF <sup>-1</sup>	Maximum conductance of I <sub>KA</sub>

Table B6. A-type transient potassium current parameters

**Calcium-activated potassium current – I<sub>KCa</sub>**

$$I_{KCa} = \frac{A_c N_{BKCa} P_{KCa} i_{KCa}}{C_{est}} \quad \text{B7.1}$$

$$P_{KCa} = 0.17 p_f + 0.83 p_s \quad \text{B7.2}$$

$$i_{KCa} = 10^4 P_{BKCa} V \frac{F^2 [K]_o - [K]_i e^{\frac{VF}{RT}}}{RT (1 - e^{\frac{VF}{RT}})} \quad \text{B7.3}$$

$$\bar{p}_o = \left( 1 + e^{\frac{V_{1/2KCa} - V}{18.25}} \right)^{-1} \quad \text{B7.4}$$

$$V_{1/2KCa} = -41.7 \log_{10} [Ca^{2+}]_i - 128.2 \quad \text{B7.5}$$

$$\frac{dp_f}{dt} = \frac{\bar{p}_o - p_f}{\tau_{p_f}} \quad \text{B7.6}$$

$$\frac{dp_s}{dt} = \frac{\bar{p}_o - p_s}{\tau_{p_s}} \quad \text{B7.7}$$

Parameter	Value	Definition
$N_{BKCa}$	$5.94 \times 10^6 \text{ cm}^{-2}$	Channel density
$C_{est}$	100 pF	Estimated cell capacitance of late pregnant rat
$\tau_{p_f}$	0.84 ms	Fast activation time constant
$\tau_{p_s}$	35.9 ms	Slow activation time constant
$P_{BKCa}$	$3.9 \times 10^{-12} \text{ cm}^3 \text{ s}^{-1}$	Single channel permeability

**Table B7. Calcium-activated potassium current parameters**

**Background potassium leakage current –  $I_{Kleak}$**

$$I_{Kleak} = g_{K-leak}(V - E_K) \quad \text{B8.1}$$

Parameter	Value	Definition
$g_{K-leak}$	0.0004 nS pF <sup>-1</sup>	Conductance of $I_{Kleak}$

**Table B8. Background K<sup>+</sup> leakage current parameters**

**Hyperpolarisation-activated current –  $I_h$**

$$I_h = \bar{g}_h y (V - E_h) \quad \text{B9.1}$$

$$E_h = \frac{RT}{F} \ln \left( \frac{[K]_o + (P_{Na}/P_K)[Na^+]_o}{[K]_i + (P_{Na}/P_K)[Na^+]_i} \right) \quad \text{B9.2}$$

$$y_\infty = \frac{1}{1 + e^{\frac{V + 105.39}{8.66}}} \quad \text{B9.3}$$

$$\tau_y = \frac{1}{3.5 \times 10^{-6} e^{-0.0497V} + 0.04 e^{0.0521V}} \quad \text{B9.4}$$

$$\frac{dy}{dt} = \frac{y_\infty - y}{\tau_y} \quad \text{B9.5}$$

Parameter	Value	Definition
$\bar{g}_h$	0.04065 nS pF <sup>-1</sup>	Maximum conductance of $I_h$
$P_{Na}/P_K$	0.35	Na <sup>+</sup> and K <sup>+</sup> permeability ratio

**Table B9. Hyperpolarisation-activated current parameters**

**Calcium-activated chloride current –  $I_{Cl}$**

$$I_{Cl} = \begin{cases} g_{Cl} g_{fca} \sqrt{c1} (V - E_{Cl}) & \text{if } V > 0 \\ g_{Cl} g_{fca} (c2)n (V - E_{Cl}) & \text{otherwise} \end{cases} \quad \text{B10.1}$$

$$E_{Cl} = \begin{cases} -30 & \text{if } V > 0 \\ -5 & \text{otherwise} \end{cases} \quad \text{B10.2}$$

$$g_{Cl} = \begin{cases} \bar{g}_{Cl}(19.26 + 365.8e^{0.0564V}) & \text{if } V \leq -20 \\ \bar{g}_{Cl}(0.752 + 0.0349e^{-0.414V}) & \text{otherwise} \end{cases} \quad \text{B10.3}$$

$$g_{fCa} = \frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + K_{d,Cl}} \quad \text{B10.4}$$

$$c_{\infty} = \frac{1}{1 + e^{\frac{44.08 - V}{13.7}}} \quad \text{B10.5}$$

$$n_{\infty} = \frac{1}{1 + e^{\frac{V + 56.97}{20.29}}} \quad \text{B10.6}$$

$$\tau_{c1} = 24 - \frac{16.88}{1 + e^{\frac{48.14 - V}{13}}} \quad \text{B10.7}$$

$$\tau_{c2} = 32 + \frac{81.54}{1 + e^{\frac{43.51 - V}{39.5}}} \quad \text{B10.8}$$

$$\tau_n = 0.69 \text{ ms} \quad \text{B10.9}$$

$$\frac{dc1}{dt} = \frac{c_{\infty} - c1}{\tau_{c1}} \quad \text{B10.10}$$

$$\frac{dc2}{dt} = \frac{c_{\infty} - c2}{\tau_{c2}} \quad \text{B10.11}$$

$$\frac{dn}{dt} = \frac{n_{\infty} - n}{\tau_n} \quad \text{B10.12}$$

Parameter	Value	Definition
$\bar{g}_{Cl}$	0.1406 pA pF <sup>-1</sup>	Maximum conductance of I <sub>Cl</sub>
$K_{d,Cl}$	257 μM	Calcium required for half-activation in I <sub>Cl</sub>

Table B10. Chloride current parameters

### Calcium pump current - I<sub>Capump</sub>

$$I_{Capump} = \frac{z_{Ca} F V_c}{C_m B_{Ca} A_c} \cdot \frac{J_{pCa}}{1 + \left( \frac{K_{m,pCa}}{[Ca^{2+}]_i} \right)^{hpCa}} \quad \text{B11.1}$$

Parameter	Value	Definition
$J_{pCa}$	3.5 x 10 <sup>-6</sup> mM ms <sup>-1</sup>	Maximum flux of I <sub>Capump</sub>
$K_{m,pCa}$	0.5 μM	Half saturation of [Ca <sup>2+</sup> ] <sub>i</sub>
$hpCa$	2	Hill coefficient

Table B11. Plasma membrane Ca<sup>2+</sup>-ATPase current parameters

### Sodium/potassium exchanger current – I<sub>NaK</sub>

$$I_{NaK} = g_{NaK} f_{NaK} k_{NaK} n_{NaK} \quad B12.1$$

$$f_{NaK} = \frac{1}{1 + 0.125 e^{\frac{-0.1VF}{RT}} + 0.00219 e^{\frac{49.71}{49.71} \cdot e^{\frac{-1.9VF}{RT}} [Na^+]_o}} \quad B12.2$$

$$k_{NaK} = \frac{1}{1 + \left( \frac{K_{d,K}}{[K^+]_o} \right)^{n_K}} \quad B12.3$$

$$n_{NaK} = \frac{1}{1 + \left( \frac{K_{d,Na}}{[Na^+]_i} \right)^{n_{Na}}} \quad B12.4$$

Parameter	Value	Definition
$g_{NaK}$	3.4 nS pF <sup>-1</sup>	Maximum conductance of I <sub>NaK</sub>
$K_{d,K}$	2 mM	Half saturation of K <sup>+</sup> in I <sub>NaK</sub>
$n_K$	1.5	Hill coefficient of K <sup>+</sup> in I <sub>NaK</sub>
$K_{d,Na}$	22 mM	Half saturation of Na <sup>+</sup> in I <sub>NaK</sub>
$n_{Na}$	2	Hill coefficient of Na <sup>+</sup> in I <sub>NaK</sub>

**Table B12. Sodium/potassium exchanger current parameters**

### Sodium/calcium exchanger current – I<sub>NaCa</sub>

$$I_{NaCa} = \frac{J_{NaCa} z_{Ca} V_c F}{A_c C_m} \quad B13.1$$

$$J_{NaCa} = (Allo)(\Delta E) \quad B13.2$$

$$\Delta E = \frac{E_1}{E_2(E_3 + E_4)} \quad B13.3$$

$$Allo = \frac{1}{1 + \left( \frac{K_{m,Allo}}{[Ca^{2+}]_i} \right)^{n_{Allo}}} \quad B13.4$$

$$E_1 = \bar{J}_{NaCa} \left( [Na^+]_i^3 [Ca^{2+}]_o e^{\frac{\gamma VF}{RT}} - [Na^+]_o^3 [Ca^{2+}]_i e^{\frac{(\gamma-1)VF}{RT}} \right) \quad B13.5$$

$$E_2 = 1 + k_{sat} e^{\frac{(\gamma-1)VF}{RT}} \quad B13.6$$

$$E_3 = K_{m,cao} [Na^+]_i^3 + K_{m,nao}^3 [Ca^{2+}]_i + K_{m,cai}^3 [Ca^{2+}]_o \left( 1 + \frac{[Ca^{2+}]_i}{K_{m,cai}} \right) \quad B13.7$$

$$E_4 = [Ca^{2+}]_o [Na^+]_i^3 + [Na^+]_o^3 [Ca^{2+}]_i + [Na^+]_o^3 K_{m,cai} \left( 1 + \frac{[Na^+]_i^3}{K_{m,cai}} \right) \quad B13.8$$

Parameter	Value	Definition
$\bar{J}_{NaCa}$	$1.75 \times 10^{-5} \text{ mM ms}^{-1}$	Maximum flux of $\text{Na}^+ / \text{Ca}^{2+}$ exchanger
$K_{m,Allo}$	$0.3 \text{ }\mu\text{M}$	Calcium activation of $I_{NaCa}$
$n_{Allo}$	4	Hill coefficient of $I_{NaCa}$
$k_{sat}$	0.27	Saturation of $I_{NaCa}$ at negative potentials
$\gamma$	0.35	Electric field energy barrier of $\text{Na}^+ / \text{Ca}^{2+}$ exchanger
$K_{m,Nai}$	30 mM	Saturation concentration of $[\text{Na}^+]_i$
$K_{m,Cai}$	$7 \text{ }\mu\text{M}$	Saturation concentration of $[\text{Ca}^{2+}]_i$
$K_{m,NaO}$	87.5 mM	Saturation concentration of $[\text{Na}^+]_o$
$K_{m,CaO}$	1.3 mM	Saturation concentration of $[\text{Ca}^{2+}]_o$

**Table B13. Sodium/calcium exchanger current parameters**

**Sodium-potassium-chloride co-transport current –  $I_{NaKCl}$**

$$I_{NaKCl} = -R_{NaKCl} z_{Cl} A_c L_{NaKCl} RFT \times \ln \left( \frac{[\text{Na}^+]_o [\text{K}^+]_o}{[\text{Na}^+]_i [\text{K}^+]_i} \left( \frac{[\text{Cl}^-]_o}{[\text{Cl}^-]_i} \right)^2 \right) \quad \text{B14.1}$$

$$I_{NaKCl-Na} = I_{NaKCl-K} = -0.5 I_{NaKCl-Cl} \quad \text{B14.2}$$

Parameter	Value	Definition
$L_{NaKCl}$	$3.58 \times 10^{-10} \text{ nmol}^{-2} \text{ J}^{-1} \text{ s}^{-1} \text{ cm}^2$	Cotransport coefficient
$R_{NaKCl}$	1	Cotransport regulation

**Table B14. Sodium-potassium-chloride co-transport current parameters**

**Store-operated non-selective cation current –  $I_{SOC}$**

$$I_{SOC} = I_{SOCCa} + I_{SOCNa} \quad \text{B15.1}$$

$$I_{SOCNa} = g_{SOCNa} P_{SOC} (V - E_{Na}) \quad \text{B15.2}$$

$$I_{SOCCa} = g_{SOCCa} P_{SOC} (V - E_{Ca}) \quad \text{B15.3}$$

$$P_{SOC} = \left( 1 + \frac{[\text{Ca}^{2+}]_i}{K_{m,SOC}} \right)^{-1} \quad \text{B15.4}$$

Parameter	Value	Definition
$g_{SOCNa}$	$5.75 \times 10^{-4} \text{ nS pF}^{-1}$	Maximum conductance of the $\text{Na}^+$ component of $I_{SOC}$
$g_{SOCCa}$	$8.3 \times 10^{-5} \text{ nS pF}^{-1}$	Maximum conductance of the $\text{Ca}^{2+}$ component of $I_{SOC}$
$K_{m,SOC}$	$0.1 \text{ }\mu\text{M}$	Half activation constant of $I_{SOC}$

**Table B15. Store-operated non-selective cation current parameters**

**Non-selective cation current –  $I_{NSCC}$**

$$I_{NSCC} = I_{NSCa} + I_{NSNa} + I_{NSK} + I_{NSleak} \quad \text{B16.1}$$

$$I_{NSCa} = 0.15f_{Mg}g_{[Ca^{2+}]_o}\bar{g}_{NS}(V - E_{NS}) \quad B16.2$$

$$I_{NSNa} = f_{Mg}g_{[Na^+]_o}\bar{g}_{NS}(V - E_{NS}) \quad B16.3$$

$$I_{NSK} = 1.19f_{Mg}g_{[K^+]_o}\bar{g}_{NS}(V - E_{NS}) \quad B16.4$$

$$I_{NSleak} = f_{Mg}\bar{g}_{leak}(V - E_{NS}) \quad B16.5$$

$$g_{[X]_o} = \frac{1}{g_s} \frac{0.03}{1 + \left(\frac{150}{[X]_o + 10^{-8}}\right)^2} \quad B16.6$$

$$g_s = \begin{cases} 0.000525 & \text{for } Ca^{2+} \\ 0.0123 & \text{otherwise} \end{cases} \quad B16.7$$

$$f_{Mg} = 0.1 + \frac{0.9}{1 + \left(\frac{[Mg^{2+}]_o}{K_{d,Mg}}\right)^{1.3}} \quad B16.8$$

$$E_{NS} = \frac{RT}{F} \cdot \ln \left( \frac{\frac{P_{Na}}{P_{Cs}}[Na^+]_o + \frac{P_K}{P_{Cs}}[K^+]_o + P'_{Ca} \frac{4P_{Ca}}{P_{Cs}}[Ca^{2+}]_o}{\frac{P_{Na}}{P_{Cs}}[Na^+]_i + \frac{P_K}{P_{Cs}}[K^+]_i + P'_{Ca} \frac{4P_{Ca}}{P_{Cs}}[Ca^{2+}]_i} \right) \quad B16.9$$

$$P'_{Ca} = \frac{P_{Ca}}{1 + e^{\frac{VF}{RT}}} \quad B16.10$$

Parameter	Value	Definition
$\bar{g}_{NS}$	0.0123 nS pF <sup>-1</sup>	Maximum conductance of I <sub>NSCC</sub>
$\bar{g}_{leak}$	0.009685 nS pF <sup>-1</sup>	Maximum conductance of leakage component of I <sub>NSCC</sub>
$K_{d,Mg}$	0.28	Half saturation concentration
$P_{Na}/P_{Cs}$	0.9	Permeability ratio of Na <sup>+</sup> : Cs <sup>+</sup>
$P_K/P_{Cs}$	1.3	Permeability ratio of K <sup>+</sup> : Cs <sup>+</sup>
$P_{Ca}/P_{Cs}$	0.89	Permeability ratio of Ca <sup>2+</sup> : Cs <sup>+</sup>

**Table B16. Store-operated non-selective cation current parameters**

### Ionic balance currents

$$I_{Ca-tot} = I_{CaL} + I_{CaT} + I_{NSCa} + I_{SOCCA} - 2I_{NaCa} + I_{Capump} + I_{up} - I_{rel} \quad B17.1$$

$$\frac{d[Ca^{2+}]_i}{dt} = -\frac{A_c C_m}{V_c z_{Ca} F} (I_{Ca-tot}) \times F_{BCa} \left( 1 + \frac{[SCM]K_d}{(K_d + [Ca^{2+}]_i)^2} + \frac{[B_F]K_{d,B}}{(K_{d,B} + [Ca^{2+}]_i)^2} \right)^{-1} \quad B17.2$$

$$I_{Na-tot} = I_{Na} + I_{NSNa} + I_{SOCNa} - 3I_{NaK} + 3I_{NaCa} + P_{Na}I_h - 0.5I_{NaKCl} \quad B17.3$$

$$\frac{d[Na^+]_i}{dt} = -\frac{A_c C_m}{V_c z_{Na} F} (I_{Na-tot}) \quad B17.4$$

$$I_{K-tot} = I_{K1} + I_{K2} + I_{KA} + I_{KCa} - 2I_{NSK} + I_{Kleak} + I_{NaKCl} - 2I_{NaK} \quad B17.5$$

$$\frac{d[K^+]_i}{dt} = -\frac{A_c C_m}{V_c z_K F} (I_{K-tot}) \quad B17.6$$

$$I_{Cl-tot} = I_{Cl} + I_{NaKCl} \quad B17.7$$

$$\frac{d[Cl^+]_i}{dt} = -\frac{A_c C_m}{V_c z_{Cl} F} (I_{Cl-tot}) \quad \text{B17.8}$$

$$I_{tot} = I_h + I_{CaL} + I_{CaT} + I_{Na} + I_{K1} + I_{K2} + I_{KA} + I_{KCa} + I_{NSCC} + I_{Cl} \\ + I_{Capump} + I_{NaK} + 0.5I_{NaCa} + I_{sus} + I_{soc} + I_{Kleak} + I_{NaKCl} \quad \text{B17.9}$$

$$\frac{dV}{dt} = \frac{I_{tot} + I_{stim}}{C_m} \quad \text{B17.10}$$

Parameter	Value	Definition
$C_m$	1.4 $\mu\text{F cm}^{-2}$	Specific membrane capacitance
$A_c$	$7.422 \times 10^{-5} \text{ cm}^2$	Area of the cell
$V_c$	$2.65 \times 10^{-8} \text{ cm}^3$	Volume of the cell
$z_{Ca}$	2	Valency of $\text{Ca}^{2+}$
$z_{Na}$	1	Valency of $\text{Na}^+$
$z_K$	1	Valency of $\text{K}^+$
$z_{Cl}$	-1	Valency of $\text{Cl}^-$
$F$	96485 $\text{C M}^{-1}$	Faraday's constant
$P_{Na}$	0.35	Permeability of sodium ions
$I_{sus}$	0.6 pA	Sustained stimulus
$I_{stim}$	Various	Stimulus current
$F_{BCa}$	20	Buffer fractional strength factor
$[S_{CM}]$	0.3	Total concentration of calmodulin sites for $\text{Ca}^{2+}$
$[B_F]$	0.2	Total concentration of other buffer sites for $\text{Ca}^{2+}$
$K_d$	$2.6 \times 10^{-4}$	Dissociation constant
$K_{d,B}$	$5.3981 \times 10^{-4}$	Dissociation constant in buffer

**Table B17. Ionic balance parameters**

**Sarcoplasmic reticulum currents –  $I_{up}$ ,  $I_{tr}$ ,  $I_{rel}$**

$$I_{up} = \bar{I}_{up} \frac{[Ca^{2+}]_i}{([Ca^{2+}]_i + K_{m,up})} \quad \text{B18.1}$$

$$I_{tr} = \frac{([Ca^{2+}]_u - [Ca^{2+}]_r) z_{Ca} F vol_u}{\tau_{tr}} \quad \text{B18.2}$$

$$I_{rel} = F_{rel} \frac{(R_{10}^{-2} + R_{leak})([Ca^{2+}]_r - [Ca^{2+}]_i) z_{Ca} F vol_r}{\tau_{rel}} \quad \text{B18.3}$$

$$\frac{d[Ca^{2+}]_u}{dt} = \frac{I_{up} - I_{tr}}{z_{Ca} F vol_u} \quad \text{B18.4}$$

$$\frac{d[Ca^{2+}]_r}{dt} = \frac{I_{tr} - I_{rel}}{z_{Ca} F vol_r} \left( 1 + \frac{[CSQN] K_{CSQN}}{(K_{CSQN} + [Ca^{2+}]_r)^2} \right)^{-1} \quad \text{B18.5}$$

Parameter	Value	Definition
$\bar{I}_{up}$	0.668 pA	Max SR uptake current
$K_{m,up}$	10 $\mu$ M	Michaelis constant of SERCA pump
$vol_u$	$1.33 \times 10^{-9}$ cm <sup>3</sup>	Volume of uptake compartment
$vol_r$	$1.33 \times 10^{-11}$ cm <sup>3</sup>	Volume of release compartment
$\tau_{tr}$	180 ms	Time constant of $I_{tr}$
$\tau_{rel}$	0.015 ms	Time constant of $I_{rel}$
$[CSQN]$	15 mM	Concentration of calsequestrin in release compartment
$K_{CSQN}$	0.8 mM	Binding affinity of calsequestrin
$R_{leak}$	$75.07 \times 10^{-4}$	Release compartment calcium leak rate

**Table B18. SR parameters  
Ryanodine receptors**

$$\frac{dR_{00}}{dt} = -(K_{r1}Ca_i^2 + K_{r2}Ca_i)R_{00} \quad B19.1$$

$$\frac{dR_{10}}{dt} = K_{r1}Ca_i^2R_{00} - (K_{-r1} + K_{r2}Ca_i)R_{10} + K_{-r2}R_{11} \quad B19.2$$

$$\frac{dR_{01}}{dt} = K_{r2}Ca_iR_{00} + K_{-r1}R_{11} - (K_{-r2} + K_{r1}Ca_i^2)R_{01} \quad B19.3$$

$$\frac{dR_{11}}{dt} = K_{r2}Ca_iR_{10} - (K_{-r1} + K_{-r2})R_{11} + K_{r1}Ca_i^2R_{01} \quad B19.4$$

Parameter	Value	Definition
$K_{r1}$	$2500 \text{ mM}^{-2} \text{ ms}^{-1}$	Binding activation rate constant
$K_{-r1}$	$0.0076 \text{ mM}^{-1} \text{ ms}^{-1}$	Unbinding activation rate constant
$K_{r2}$	$1.05 \text{ ms}^{-1}$	Binding inactivation rate constant
$K_{-r2}$	$0.084 \text{ ms}^{-1}$	Unbinding inactivation rate constant

**Table B19. RyR parameters**

### Kinetic cross-bridge cycling model

$$\frac{dM}{dt} = -K_1M + K_2Mp + K_7AM \quad B20.1$$

$$\frac{dMp}{dt} = K_4AMp + K_1M - (K_2 + K_3)Mp \quad B20.2$$

$$\frac{dAMp}{dt} = K_3Mp + K_6AM - (K_4 + K_5)AMp \quad B20.3$$

$$\frac{dAM}{dt} = K_5AMp - (K_7 + K_6)AM \quad B20.4$$

$$MLCK = \frac{MLCK_{max}}{1 + \left(\frac{[Ca^{2+}]_i}{K_{MLCK}}\right)^{PM}} \quad B20.5$$

$$K_1 = C_{ms} \frac{MLCK}{1 + \left(\frac{K_{Ca,MLCK}}{[Ca^{2+}]_i}\right)^{n_M}} \quad B20.6$$

$$K_6 = K_1$$

B20.7

$$\text{Phosphorylation fraction} = AMp + Mp$$

B20.8

$$\text{Stress fraction} = AMp + AM$$

B20.9

Parameter	Value	Definition
$MLCK_{max}$	0.84	Maximum fraction of MLCK
$K_{MLCK}$	721.746 nM	Half-activation of MLCK
$K_{Ca,MLCK}$	1.080 $\mu\text{M}$	Half-activation of MLCK set by $[\text{Ca}^{2+}]_i$
$p_M$	1	Hill coefficient for MLCK
$n_M$	8.7613	Hill coefficient for $K_1$
$K_2$	0.4 $\text{ms}^{-1}$	Myosin dephosphorylation rate constant
$K_3$	1.8 $\text{ms}^{-1}$	Cross-bridge formation rate constant
$K_4$	0.1 $\text{ms}^{-1}$	Cross-bridge detachment rate constant
$K_5$	0.4 $\text{ms}^{-1}$	Attached myosin dephosphorylation rate constant
$K_7$	0.045 $\text{ms}^{-1}$	Latch state detachment rate constant

**Table B20. Kinetic cross-bridge cycling parameters**

### Mechanical production model

$$\frac{dl_s}{dt} = \frac{1}{\mu_s} \left( F_s - k_s e^{\frac{\alpha_s(l_s - l_{s0})}{l_{s0}}} - 1 \right)$$

B21.1

$$\frac{dl_a}{dt} = \frac{F_a e^{\beta \frac{(l_a - l_{opt})^2}{l_{opt}}} - f_{AMp} AMp v_x}{f_{AM} AM + f_{AMp} AMp}$$

B21.2

$$\frac{dl_x}{dt} = \frac{(k_{x1} AMp + k_{x2} AM)(l_c - l_a - l_s) - (f_{AMp} AMp v_x)}{f_{AM} AM + f_{AMp} AMp}$$

B21.3

$$l_x = l_c - l_a - l_s$$

B21.4

$$F_p = k_p \left( e^{\frac{\alpha_p(l_c - l_{c0})}{l_{c0}}} - 1 \right)$$

B21.5

$$F_x = (k_{x1} AMp + k_{x2} AM) l_x e^{-\beta \left( \frac{l_a - l_{opt}}{l_{opt}} \right)^2}$$

B21.6

$$F_a = \left( f_{AMp} AMp \left( v_x + \frac{dl_a}{dt} \right) + f_{AM} AM \frac{dl_a}{dt} \right) e^{-\beta \left( \frac{l_a - l_{opt}}{l_{opt}} \right)^2}$$

B21.7

$$F_s = F_a$$

B21.8

$$F_t = F_a + F_p$$

B21.9

Parameter	Value	Definition
$l_c$	120 $\mu\text{m}$	Length of whole cell
$l_{c0}$	40 $\mu\text{m}$	Length of cell at zero passive force
$l_{s0}$	30 $\mu\text{m}$	Length of series viscoelastic component at zero force
$l_{opt}$	100 $\mu\text{m}$	Optimal length of active contractile component
$k_{x1}$	12.5 $\mu\text{N } \mu\text{m}^{-1}$	Phosphorylated cross-bridge stiffness constant
$k_{x2}$	8.8 $\mu\text{N } \mu\text{m}^{-1}$	Latch bridge stiffness constant
$k_s$	0.2 $\mu\text{N}$	Series element stiffness constant
$k_p$	0.1 $\mu\text{N}$	Parallel element stiffness constant
$v_x$	5 $\mu\text{m ms}^{-1}$	Cross-bridge cycling velocity
$f_{AMP}$	1.3 $\mu\text{N ms } \mu\text{m}^{-1}$	Friction constant for phosphorylated cross-bridges
$f_{AM}$	85.5 $\mu\text{N ms } \mu\text{m}^{-1}$	Friction constant for latch bridges
$\mu_s$	0.01 $\mu\text{N ms } \mu\text{m}^{-1}$	Viscosity coefficient of series element
$\alpha_s$	4.5	Length modulation for series viscoelastic element
$\alpha_p$	0.1	Length modulation for passive element
$\beta$	7.5	Length modulation constant for active and cross-bridge elements

**Table B21. Force production parameters**

Parameter	Value	Definition
T	308 K	Model temperature
F	96485 mC mmol <sup>-1</sup>	Faraday constant
R	8314 $\mu\text{J K}^{-1} \text{mmol}^{-1}$	Molar gas constant
$z_{\text{Na}}$	1	Valency of Na <sup>+</sup>
$z_{\text{K}}$	1	Valency of K <sup>+</sup>
$z_{\text{Ca}}$	2	Valency of Ca <sup>2+</sup>
$z_{\text{Cl}}$	-1	Valency of Cl <sup>-</sup>
$[\text{Na}^+]_o$	140 mM	Na <sup>+</sup> extracellular concentration
$[\text{K}^+]_o$	5.4 mM	K <sup>+</sup> extracellular concentration
$[\text{Ca}^{2+}]_o$	2.5 mM	Ca <sup>2+</sup> extracellular concentration
$[\text{Mg}^{2+}]_o$	0.5 mM	Mg <sup>2+</sup> extracellular concentration
$[\text{Cl}^-]_o$	146.4 mM	Cl <sup>-</sup> extracellular concentration
$C_m$	1.4 $\mu\text{F cm}^{-2}$	Specific membrane capacitance
$A_c$	$7.422 \times 10^{-5} \text{cm}^2$	Area of the cell
$V_c$	$2.65 \times 10^{-8} \text{cm}^3$	Volume of the cell

**Table B22. Other parameters**

## Supplement C – Initial Conditions

This supplement contains the initial conditions used in our single cell model.

Parameter	Value	Definition
$[Ca^{2+}]_i$	$9.43 \times 10^{-5}$ mM	Intracellular calcium concentration
$[Ca^{2+}]_o$	2.5 mM	Extracellular calcium concentration
$[Na^+]_i$	4 mM	Intracellular sodium concentration
$[Na^+]_o$	140 mM	Extracellular sodium concentration
$[K^+]_i$	140 mM	Intracellular potassium concentration
$[K^+]_o$	5.4 mM	Extracellular potassium concentration
$[Cl^-]_i$	130 mM	Intracellular chloride concentration
$[Cl^-]_o$	146.6 mM	Extracellular chloride concentration
$[Mg^{2+}]_o$	0.5 mM	Extracellular magnesium concentration

**Table C1. Ionic concentrations**

Parameter	Value	Definition
$d$	0.0133195	$I_{CaL}$ activation gate
$f1$	0.938986	$I_{CaL}$ inactivation gate, fast
$f2$	0.938986	$I_{CaL}$ inactivation gate, slow
$b$	0.179073	$I_{CaT}$ activation gate
$g$	0.0308496	$I_{CaT}$ inactivation gate
$m$	0.129659	$I_{Na}$ activation gate
$h$	0.360711	$I_{Na}$ inactivation gate
$q$	0.0741461	$I_{K1}$ activation gate
$r1$	0.151067	$I_{K1}$ inactivation gate, fast
$r2$	0.108987	$I_{K1}$ inactivation gate, slow
$p$	0.0794842	$I_{K2}$ activation gate
$k1$	0.995353	$I_{K2}$ inactivation gate, fast
$k2$	0.954862	$I_{K2}$ inactivation gate, slow
$s$	0.0385646	$I_{KA}$ activation gate
$x$	0.644685	$I_{KA}$ inactivation gate
$y$	0.00212991	$I_h$ activation gate
$c1$	0.00089031	$I_{Cl}$ activation gate, fast
$c2$	0.00089031	$I_{Cl}$ activation gate, slow
$n$	0.440717	$I_{Cl}$ inactivation gate

**Table C2. Gating variables**

Parameter	Value	Definition
$l_s$	30.08 $\mu$ m	Length of spring component of cell
$l_a$	25.3 $\mu$ m	Length of active component of cell
$M$	0.97	Detached dephosphorylated cross-bridge fraction
$Mp$	0.01	Detached phosphorylated cross-bridge fraction
$AMp$	0.01	Attached phosphorylated cross-bridge fraction
$AM$	0.01	Attached dephosphorylated cross-bridge fraction

**Table C3. Kinetics**

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