Universität Stuttgart

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Parallelizing a Multiscale Model Of a Skeletal Muscle

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Simulation of Large Systems
Institute for Parallel and Distributed Systems
University of Stuttgart

IPVS

SGS

SimTech Cluster of Excellence

Overview

Overview

Motivation

The musculoskeletal system

- Fitness for different tasks: endurance, fine control, strength



- Enabled by same muscle tissue
- Complex system: skeletal muscles, bones, tendons, motor neurons

Understanding the system

- Experiments difficult

- Need for simulation

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  - Involves tests on human or animals
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  - Hard measurements of inner quantities $\rightsquigarrow$ EMG
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  - Submodels for different phenomena
  - Integrated simulation of muscle physiology - "overall human model"

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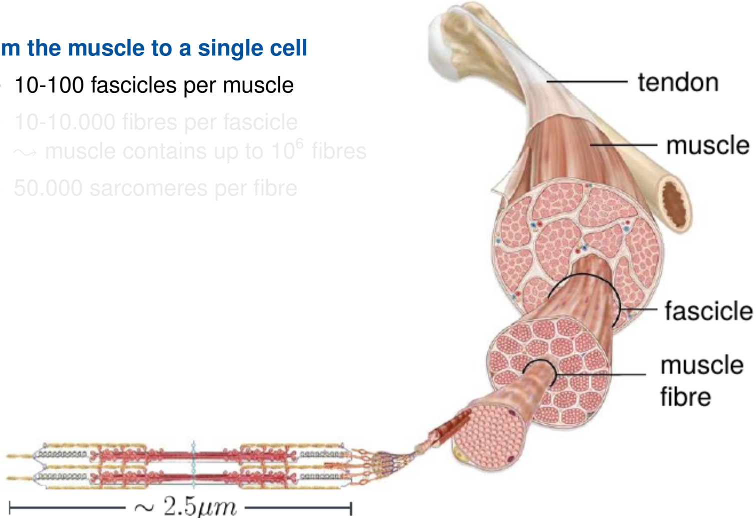
Physiological Introduction

1. Motivation
2. **Physiological Introduction**
3. The Mathematical Model
4. The Computational Framework OpenCMISS

Physiological Introduction

From the muscle to a single cell

- 10-100 fascicles per muscle
- 10-10.000 fibres per fascicle
  ⇝ muscle contains up to 10^6 fibres
- 50.000 sarcomeres per fibre



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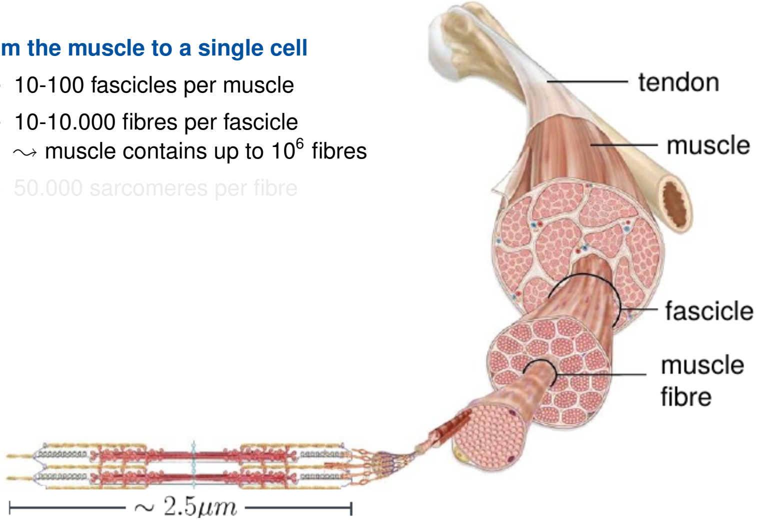

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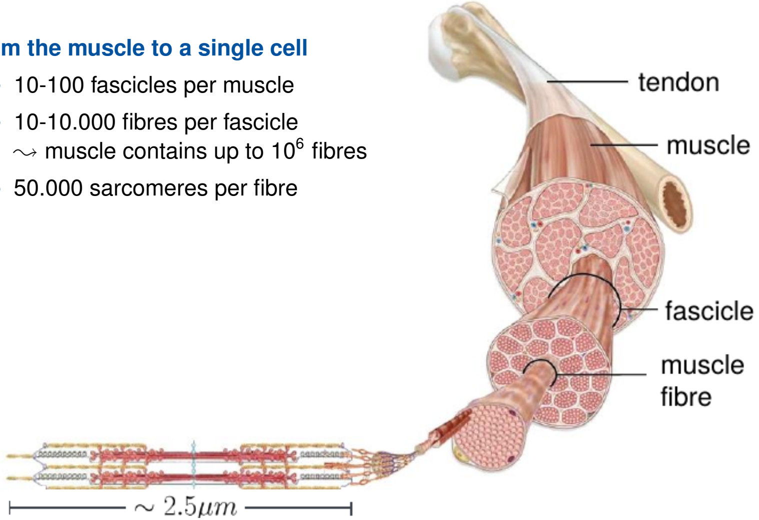

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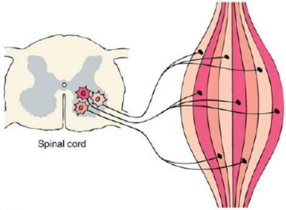
Activation of muscle fibres

- Origin of stimulation is motor neuron pool in spinal cord
- Transport of electrical signals via nerves
- Activation level proportional to frequency of ”spike trains”

- Fibres are adressed as motor units (MU), all fibres of a MU are excited simultaneously
- Exponential MU distribution
- Action potential travels along muscle fibre
- Neighbouring fibres are not electrophysically coupled



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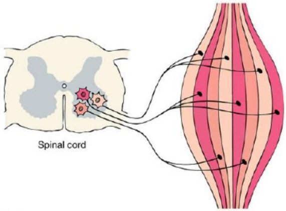

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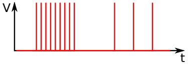

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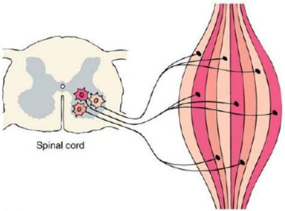

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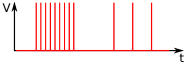

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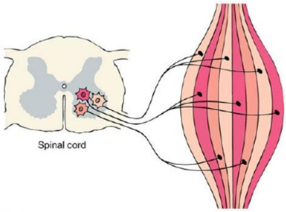

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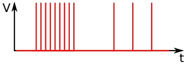

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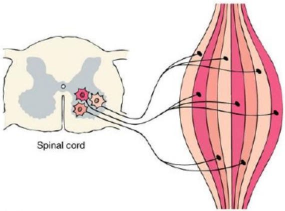

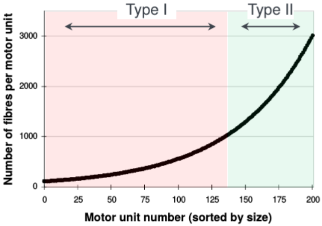

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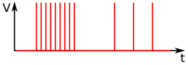

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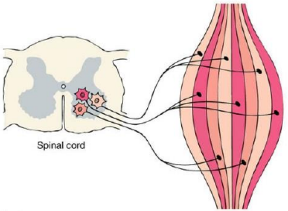

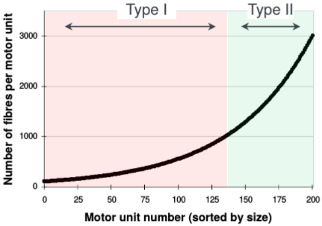

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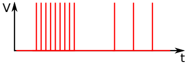

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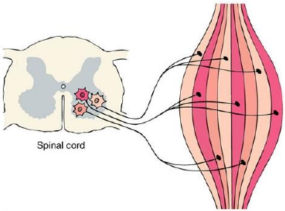

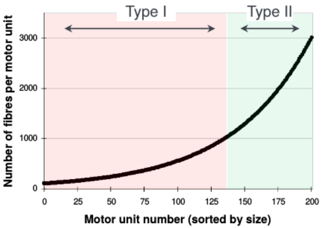

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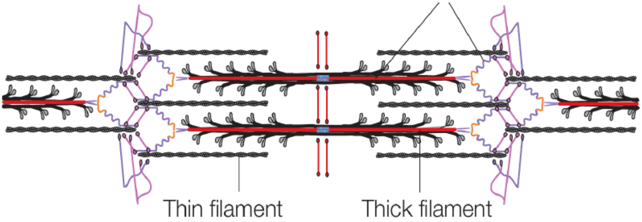
Force generation

- Contractile unit: sarcomere
- Crossbridges attach and detach to thin filament
- Passive behaviour: hyperelastic



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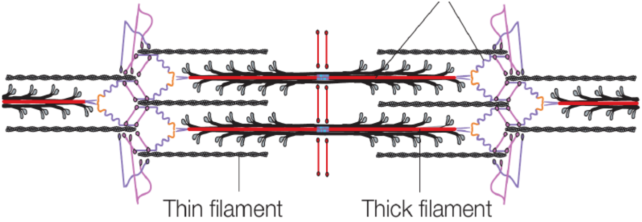

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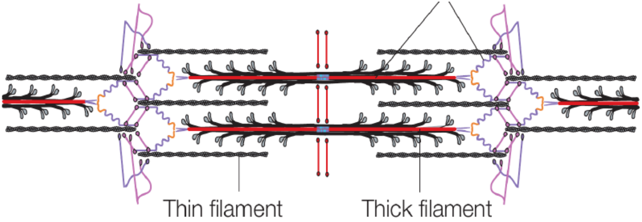
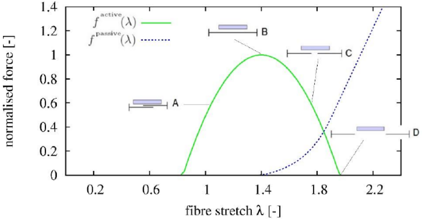


Physiological Introduction

Force generation characteristics

- Force-length relationship



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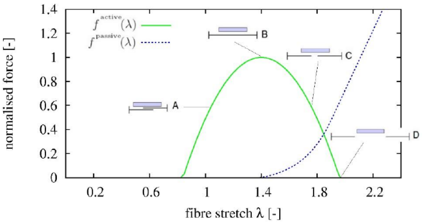

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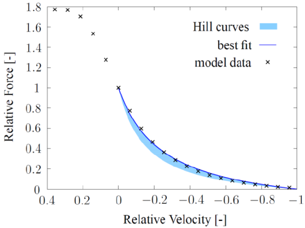
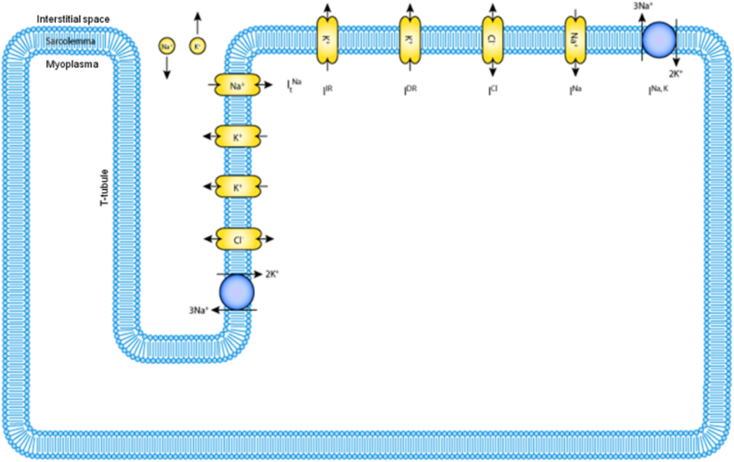


The Mathematical Model

Model on cellular level

Ion currents

- Ionic currents between intracellular and extracellular space
- Different ions pass through dedicated channels and carry charge



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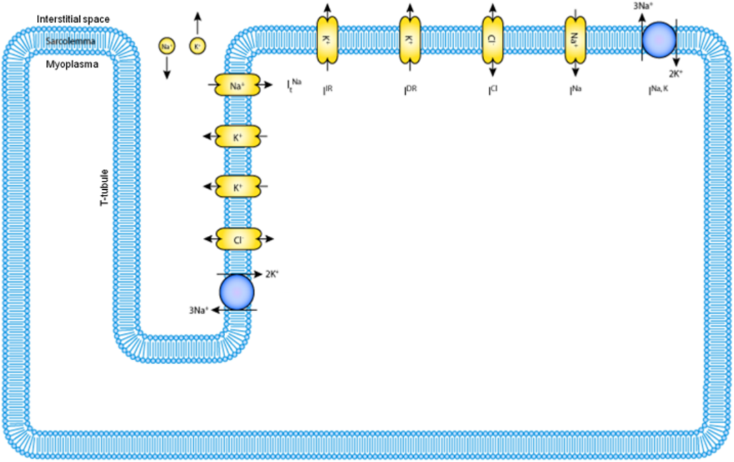

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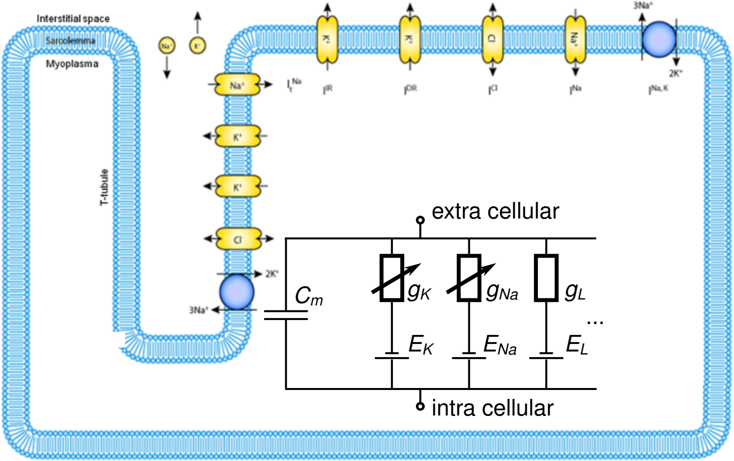

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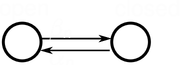
where $g_i(V_m)$ ... conductance of ion channel $i \in \{Cl, Na, ...\}$

Conductances

- Channels open on molecular level



$$g_{Na} = \bar{g}_{Na}\, m^3\, h$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m\,(1-m) + \beta_m\, m, \qquad \frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(1-h) + \beta_h\, h \tag{2}$$

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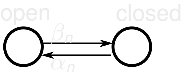

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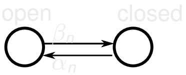

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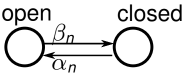

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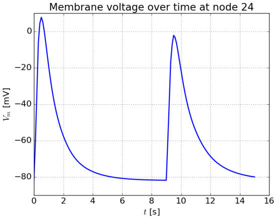
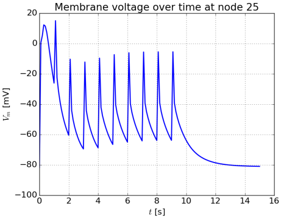
Model on cellular level

Behaviour of electrodynamics model

- Fatigue is included in the model





Force generation

- State model with transition parameters

Model on cellular level

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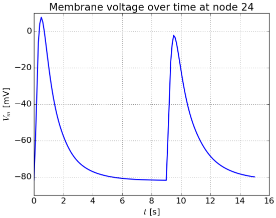

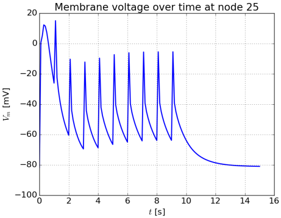

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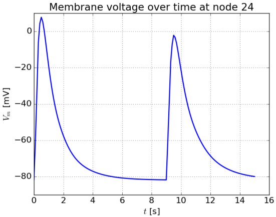

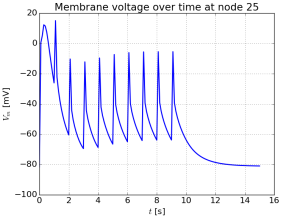

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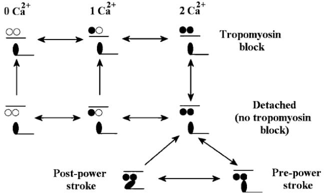

Model on cellular level

Model overview

- System of ordinary differential equations with 56 variables
- Input: I_{Stim}, Output: F

Two compartment model

$I_T = (v_s - v_t)/R_a 10^3\ \mu A/cm^2$ (access current)

$\frac{dv_s}{dt} = -\left(I_s^{ionic} + I_T\right)/C_m$ mV/ms (sarcolemma membrane voltage)

$\frac{dv_t}{dt} = -\left(I_t^{ionic} - I_T/\gamma\right)/C_m$ mV/ms (t - tubule membrane voltage)

$\left[\frac{dh_s}{dt}, \frac{dm_s}{dt}, \frac{dn_s}{dt}, \frac{dh_s^K}{dt}, \frac{dS_s}{dt}, I^{Cl}, I^{IR}, I^{DR}, I^{Na}, I^{NaK}\right] = Z_s\left(v_s, h_s, m_s, n_s, h_s^K, S_s, K_i, K_e, Na_i, Na_e\right)$

$I_s^{ionic} = I^{Cl} + I^{IR} + I^{DR} + I^{Na} + I^{NaK} - I_{app}(t; t_{app})\ \mu A/cm^2$ (sarcolemma current)

$\left[\frac{dh_t}{dt}, \frac{dm_t}{dt}, \frac{dn_t}{dt}, \frac{dh_t^K}{dt}, \frac{dS_t}{dt}, I_t^{Cl}, I_t^{IR}, I_t^{DR}, I_t^{Na}, I_t^{NaK}\right] = Z_t\left(v_t, h_t, m_t, n_t, h_t^K, S_t, K_i, K_t, Na_i, Na_t\right)$

$I_t^{ionic} = I_t^{Cl} + I_t^{IR} + I_t^{DR} + I_t^{Na} + I_t^{NaK} \mu A/cm^2$ (t - tubule current) (1)

$\frac{dK_i}{dt} = -f_T\left(I_t^{IR} + I_t^{DR} - 2I_t^{NaK} + I_{rest}^K\right)/(1000F\xi) - \left(I^{IR} + I^{DR} - 2I^{NaK} + I_{rest}^K\right)/(1000F\xi_2)$ mM/ms (intracellular $[K^+]$)

$\frac{dK_t}{dt} = \left(I_t^{IR} + I_t^{DR} - 2I_t^{NaK} + I_{rest}^K\right)/(1000F\xi) - (K_t - K_e)/\tau_K$ mM/ms (t - tubule $[K^+]$)

$\frac{dK_e}{dt} = \left(I^{IR} + I^{DR} - 2I^{NaK} + I_{rest}^K\right)/(1000F\xi_3) + (K_t - K_e)/\tau_{K_2}$ mM/ms (interstitial $[K^+]$)

$dNa_i/dt = -f_T\left(I_t^{Na} + 3I_t^{NaK} + I_{rest}^{Na}\right)/(1000F\xi) - \left(I^{Na} + 3I^{NaK} + I_{rest}^{Na}\right)/(1000F\xi_2)$ mM/ms (intracellular $[Na^+]$)

$dNa_t/dt = \left(I_t^{Na} + 3I_t^{NaK} + I_{rest}^{Na}\right)/(1000F\xi) - (Na_t - Na_e)/\tau_{Na}$ mM/ms (t - tubule $[Na^+]$)

$dNa_e/dt = \left(I^{Na} + 3I^{NaK} + I_{rest}^{Na}\right)/(1000F\xi_3) + (Na_t - Na_e)/\tau_{Na_2}$ mM/ms (interstitial $[Na^+]$)

where the function Z_s is defined by

$\left[\frac{dh}{dt}, \frac{dm}{dt}, \frac{dn}{dt}, \frac{dh^K}{dt}, \frac{dS}{dt}, I^{Cl}, I^{IR}, I^{DR}, I^{Na}, I^{NaK}\right]$

$= Z_s(V, h, m, n, h^K, S, K_i, K_o, Na_i, Na_o)$

$\alpha_h = \bar{\alpha}_h \exp(-(V - V_h)/K_{\alpha_h})\ ms^{-1}$

$\beta_h = \bar{\beta}_h/(1 + \exp(-(V - V_h)/K_{\beta_h}))\ ms^{-1}$

$\alpha_m = \bar{\alpha}_m(V - V_m)/(1 - \exp(-(V - V_m)/K_{\alpha_m}))\ ms^{-1}$

$\beta_m = \bar{\beta}_m \exp(-(V - V_m)/K_{\beta_m})\ ms^{-1}$

$\alpha_n = \bar{\alpha}_n(V - V_n)/(1 - \exp(-(V - V_n)/K_{\alpha_n}))\ ms^{-1}$

$\beta_n = \bar{\beta}_n \exp(-(V - V_n)/K_{\beta_n})\ ms^{-1}$

$h_\infty^K = 1/(1 + \exp((V - V_{h_K^\infty})/A_{h_K^\infty}))$

$S^\infty = 1/(1 + \exp((V - V_{S^\infty})/A_{S^\infty}))$

$\tau_{h^K} = 1000 \times \exp(-(V + 40)/25.75)$ ms

$\tau_S = 8571/(0.2 + 5.65((V + V_\tau)/100)^2)$ ms

$a = 1/(1 + \exp((V - V_a)/A_a))$ (2)

$E_K = RT/(+F)\log(K_o/K_i)$ mV (K^+ Nernst potential)

$E_{Cl} = E_K(Cl^-$ Nernst potential)

$E_{Na} = RT/(+F)\log(Na_o/Na_i)$ mV (Na^+ Nernst potential)

$Cl_i = (128 + 5 \times 5.7)$
$/(5 + \exp((-FE_K)/(RT)))$ (Intracellular $[Cl^-]$)

$Cl_o = (128 + 5 \times 5.7) - 5Cl_i$ (Extracellular $[Cl^-]$)

$J_{Cl} = V(Cl_i - Cl_o\exp((FV)/(RT)))/(1 - \exp((FV)/(RT)))$

$J_K = V(K_i - K_o\exp(-(FV)/(RT)))/(1 - \exp(-(FV)/(RT)))$

$J_{Na} = V(Na_i - Na_o\exp(-(FV)/(RT)))/(1 - \exp(-(FV)/(RT)))$

$g_{Cl} = \bar{g}_{Cl} a^4\ mS/cm^2$

$K_R = K_o\exp(-\delta E_K F/(RT))$ mM

$\bar{g}_{IR} = G_K K_R^2/(K_K + K_R^2)\ mS/cm^2$

$y = 1 - (1 + (K_S/(S_i^2\exp(2(1-\delta)VF/(RT)))) \times (1 + K_R^2/K_K))^{-1}$

$g_{IR} = \bar{g}_{IR} y\ mS/cm^2$

$g_{DR} = \bar{g}_K n^4 h^K\ mS/cm^2$

$g_{Na} = \bar{g}_{Na} m^3 hS\ mS/cm^2$

$I_{Cl} = g_{Cl}(J_{Cl}/45)\ \mu A/cm^2$ (Cl^- current)

$I_{IR} = g_{IR}(J_K/50)H(J_K/50)\ \mu A/cm^2$ (K^+ IR current)

$I_{DR} = g_{DR}(J_K/50)\ \mu A/cm^2$ (K^+ DR current)

$I_{Na} = g_{Na}(J_{Na}/75)\ \mu A/cm^2$ (Na^+ current)

$H(t) = \begin{cases} 1, t > 0 \\ 0, t < 0 \end{cases}$ (3)

$\sigma = \frac{1}{7}(\exp(Na_o/67.3) - 1)$

$f_1 = (1 + 0.12\exp(-0.1VF/(RT)) + 0.04\sigma\exp(-VF/(RT)))^{-1}$

$\bar{I}_{NaK} = F\bar{J}_{NaK}/((1 + K_{mK}/K_o)^2 \times (1 + K_{mNa}/Na_i)^3)\mu A/cm^2$

$I_{NaK} = \bar{I}_{NaK} f_1\ \mu A/cm^2$ (Na-K exchanger)

$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h$ (Na inactivation gating variable)

$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m$ (Na activation gating variable)

$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n$ (K-DR activation gating variable)

$\frac{dh^K}{dt} = (h_\infty^K - h^K)/\tau_{h^K}$ (K-DR inactivation gating variable)

$\frac{dS}{dt} = (S_\infty - S)/\tau_S$ (Na very slow inactivation gating variable)

and the function Z_t is defined by

$\left[\frac{dh_t}{dt}, \frac{dm_t}{dt}, \frac{dn_t}{dt}, \frac{dh_t^K}{dt}, \frac{dS_t}{dt}, I_t^{Cl}, I_t^{IR}, I_t^{DR}, I_t^{Na}, I_t^{NaK}\right] = Z_t(v_t, h_t, m_t, n_t, h_t^K, S_t, K_i, K_t, Na_i, Na_t)$

$\left[\frac{dh_t}{dt}, \frac{dm_t}{dt}, \frac{dn_t}{dt}, \frac{dh_t^K}{dt}, \frac{dS}{dt}, I^{Cl}, I^{IR}, I^{DR}, I^{Na}, I^{NaK}\right] = Z_s(v_t, h_t, m_t, n_t, h_t^K, S_t, K_i, K_t, Na_i, Na_t)$

$\eta_{Cl} = 0.1$ (Cl channel density in t-tubules relative to sarcolemma)

$\eta_{IR} = 1.0$ (K-IR channel density in t-tubules relative to sarcolemma)

$\eta_{DR} = 0.45$ (K-DR channel density in t-tubules relative to sarcolemma)

$\eta_{Na} = 0.1$ (Na channel density in t-tubules relative to sarcolemma)

$\eta_{NaK} = 0.1$ (Na/K exchanger density in t-tubules relative to sarcolemma)

$I_t^{Cl} = \eta_{Cl} I^{Cl}\ \mu A/cm^2$

$I_t^{IR} = \eta_{IR} I^{IR}\ \mu A/cm^2$

$I_t^{DR} = \eta_{DR} I^{DR}\ \mu A/cm^2$

$I_t^{Na} = \eta_{Na} I^{Na}\ \mu A/cm^2$

$I_t^{NaK} = \eta_{NaK} I^{NaK}\ \mu A/cm^2$

PDE model

$\bar{G}_L = G_L \tau f_T$ mS/cm

$D_s = 1000 \times (R_s/(2(R_i + R_e)))/C_m$ cm^2/ms

$D_t = \bar{G}_L/(C_m f_T/\xi)$ cm^2/ms

$\left[\frac{dh_s}{dt}, \frac{dm_s}{dt}, \frac{dn_s}{dt}, \frac{dh_s^K}{dt}, \frac{dS_s}{dt}, I^{Cl}, I^{IR}, I^{DR}, I^{Na}, I^{NaK}\right] = Z_s(v_s, h_s, m_s, n_s, h_s^K, S_s, K_i, K_e, Na_i, Na_e)$

$I_s^{ionic} = I^{Cl} + I^{IR} + I^{DR} + I^{Na} + I^{NaK} - I_{app}(t; t_{app})\ \mu A/cm^2$ (sarcolemma current)

$\left[\frac{dh_t}{dt}, \frac{dm_t}{dt}, \frac{dn_t}{dt}, \frac{dh_t^K}{dt}, \frac{dS_t}{dt}, I_t^{Cl}, I_t^{IR}, I_t^{DR}, I_t^{Na}, I_t^{NaK}\right] = Z_t(v_t, h_t, m_t, n_t, h_t^K, S_t, K_i, K_t, Na_i, Na_t)$

$I_t^{ionic} = I_t^{Cl} + I_t^{IR} + I_t^{DR} + I_t^{Na} + I_t^{NaK}\ \mu A/cm^2$ (t-tubule current)

$\frac{\partial v_t(r,x)}{\partial t} + \frac{I_t^{ionic}}{C_m} = D_t\left(\frac{\partial^2 v_t}{\partial r^2} + \frac{1}{r}\frac{\partial v_t}{\partial r}\right)$ mV/ms (t-tubule membrane voltage)

$\left.\frac{\partial v_t}{\partial r}\right|_{r=0} = 0$

$\frac{dO_1}{dt} = k_L/fC_1 - k_{Lm}fO_1 + 4k_C/fO_0 - fk_{Cm}O_1 - 3k_C/fO_1 + 2fk_{Cm}O_2$

$\frac{dC_2}{dt} = 3k_C C_1 - 2k_{Cm}C_2 - k_L/f^2C_2 + k_{Lm}f^2O_2 - 2k_C C_2 + 3k_{Cm}C_3$

$\frac{dO_2}{dt} = 3k_C/fO_1 - 2fk_{Cm}O_2 + k_L/f^2C_2 - k_{Lm}f^2O_2 - 2k_C/fO_2 + 3fk_{Cm}O_3$

$\frac{dC_3}{dt} = 2k_C C_2 - 3k_{Cm}C_3 - k_L/f^3C_3 + k_{Lm}f^3O_3 - k_C C_3 + 4k_{Cm}C_4$

$\frac{dO_3}{dt} = k_L/f^3C_3 - k_{Lm}f^3O_3 + 2k_C/fO_2 - 3fk_{Cm}O_3 - k_C/fO_3 + 4fk_{Cm}O_4$

$\frac{dC_4}{dt} = k_C C_3 - 4k_{Cm}C_4 - k_L/f^4C_4 + k_{Lm}f^4O_4$

$\frac{dO_4}{dt} = k_C/fO_3 - 4fk_{Cm}O_4 + k_L/f^4C_4 \text{-} k_{Lm}f^4O_4$

$I_T = 1000 \times [v_s(x) - v_t(r = R_s, x)]/R_a = \bar{G}_L \left.\frac{\partial v_t}{\partial r}\right|_{r=R_s}$ $\mu A/cm^2$ (access current)

$\frac{\partial v_s(x)}{\partial t} + \frac{I_s^{ionic}}{C_m} = D_s\frac{\partial^2 v_s}{\partial x^2}$, mV/ms (sarcolemma membrane voltage)

$\left.\frac{\partial v_s}{\partial x}\right|_{x=0} = 0, \left.\frac{\partial v_s}{\partial x}\right|_{x=l_s} = 0$

$\frac{\partial K_t(r,x)}{\partial t} = D_K\left(\frac{\partial^2 K_t}{\partial r^2} + \frac{1}{r}\frac{\partial K_t}{\partial r}\right) + (I_t^{IR} + I_t^{DR} - 2I_t^{NaK} + I_{rest}^K)/(1000F\xi)$

$\left.\frac{\partial K_t}{\partial r}\right|_{r=0} = 0$

$K_t(r = R_s, x) = K_e(x)$ mM/ms (t-tubule $[K^+]$)

$\frac{\partial Na_t(r,x)}{\partial t} = D_{Na}\left(\frac{\partial^2 Na_t}{\partial r^2} + \frac{1}{r}\frac{\partial Na_t}{\partial r}\right) + (I_t^{Na} + 3I_t^{NaK} + I_{rest}^{Na})/(1000F\xi)$

$\left.\frac{\partial Na_t}{\partial r}\right|_{r=0} = 0$

$Na_t(r = R_s, x) = Na_e(x)$ mM/ms (t-tubule $[Na^+]$)

$\frac{\partial K_e(x)}{\partial t} = (I^{IR} + I^{DR} - 2I^{NaK} + I_{rest}^K)/(1000F\xi_3)$ mM/ms (extracellular $[K^+]$)

$\frac{\partial Na_e(x)}{\partial t} = (I^{Na} + 3I^{NaK} + I_{rest}^{Na})/(1000F\xi_3)$ mM/ms (extracellular $[Na^+]$)

$\frac{\partial K_i(r,x)}{\partial t} = -f_T(I_t^{IR} + I_t^{DR} - 2I_t^{NaK} + I_{rest}^K)/(1000F\xi)$ mM/ms (intracellular $[K^+]$)

$\frac{\partial Na_i(r,x)}{\partial t} = -f_T(I_t^{Na} + 3I_t^{NaK} + I_{rest}^{Na})/(1000F\xi)$ mM/ms (intracellular $[Na^+]$)

Ca^{2+} release from RyR's

$k_C = 0.5\alpha_1\exp((v_t - \nabla/(8K))$ (activation rate between closed states)

$k_{Cm} = 0.5\alpha_1\exp(-(v_t - \nabla/(8K))$ (inactivation rate between closed states)

$\frac{dC_0}{dt} = -k_L C_0 + k_{Lm}O_0 - 4k_C C_0 + k_{Cm}C_1$ ($C_0 - C_4$ are RyR closed states)

$\frac{dO_0}{dt} = +k_L C_0 - k_{Lm}O_0 - 4k_C/fO_0 + fk_{Cm}O_1$ ($O_0 - O_4$ are RyR open states)

$\frac{dC_1}{dt} = +4k_C C_0 - k_{Cm}C_1 - k_L/fC_1 + k_{Lm}fO_1 - 3k_C C_1 + 2k_{Cm}C_2$

Model on cellular level

Model overview

- System of ordinary differential equations with 56 variables
- Input: I_{Stim}, Output: F

Two compartment model

$$I_T = (v_s - v_t)/R_a 10^3\ \mu A/cm^2 \text{ (access current)}$$
$$\frac{dv_s}{dt} = -\left(I_s^{ionic} + I_T\right)/C_m \text{ mV/ms (sarcolemma membrane voltage)}$$
$$\frac{dv_t}{dt} = -\left(I_t^{ionic} - I_T/\gamma\right)/C_m \text{ mV/ms (t - tubule membrane voltage)}$$
$$\left[\frac{dh_s}{dt}, \frac{dm_s}{dt}, \frac{dn_s}{dt}, \frac{dh_s^K}{dt}, \frac{dS_s}{dt}, I^{Cl}, I^{IR}, I^{DR}, I^{Na}, I^{NaK}\right] = Z_s\left(v_s, h_s, m_s, n_s, h_s^K, S_s, K_i, K_e, Na_i, Na_e\right)$$
$$I_s^{ionic} = I^{Cl} + I^{IR} + I^{DR} + I^{Na} + I^{NaK} - I_{app}(t; t_{app})\ \mu A/cm^2 \text{ (sarcolemma current)}$$
$$\left[\frac{dh_t}{dt}, \frac{dm_t}{dt}, \frac{dn_t}{dt}, \frac{dh_t^K}{dt}, \frac{dS_t}{dt}, I_t^{Cl}, I_t^{IR}, I_t^{DR}, I_t^{Na}, I_t^{NaK}\right] = Z_t\left(v_t, h_t, m_t, n_t, h_t^K, S_t, K_i, K_t, Na_i, Na_t\right)$$
$$I_t^{ionic} = I_t^{Cl} + I_t^{IR} + I_t^{DR} + I_t^{Na} + I_t^{NaK} \mu A/cm^2 \text{ (t - tubule current)} \tag{1}$$
$$\frac{dK_i}{dt} = -f_T\left(I_t^{IR} + I_t^{DR} - 2I_t^{NaK} + I_{rest}^K\right)/(1000F\xi) - \left(I^{IR} + I^{DR} - 2I^{NaK} + I_{rest}^K\right)/(1000F\xi_2) \text{ mM/ms (intracellular } [K^+])$$
$$\frac{dK_t}{dt} = \left(I_t^{IR} + I_t^{DR} - 2I_t^{NaK} + I_{rest}^K\right)/(1000F\xi) - (K_t - K_e)/\tau_K \text{ mM/ms (t - tubule } [K^+])$$
$$\frac{dK_e}{dt} = \left(I^{IR} + I^{DR} - 2I^{NaK} + I_{rest}^K\right)/(1000F\xi_3) + (K_t - K_e)/\tau_{K_2} \text{ mM/ms (interstitial } [K^+])$$
$$dNa_i/dt = -f_T\left(I_t^{Na} + 3I_t^{NaK} + I_{rest}^{Na}\right)/(1000F\xi) - \left(I^{Na} + 3I^{NaK} + I_{rest}^{Na}\right)/(1000F\xi_2) \text{ mM/ms (intracellular } [Na^+])$$
$$dNa_t/dt = \left(I_t^{Na} + 3I_t^{NaK} + I_{rest}^{Na}\right)/(1000F\xi) - (Na_t - Na_e)/\tau_{Na} \text{ mM/ms (t - tubule } [Na^+])$$
$$dNa_e/dt = \left(I^{Na} + 3I^{NaK} + I_{rest}^{Na}\right)/(1000F\xi_3) + (Na_t - Na_e)/\tau_{Na_2} \text{ mM/ms (interstitial } [Na^+])$$

where the function Z_s is defined by

$$\left[\frac{dh}{dt}, \frac{dm}{dt}, \frac{dn}{dt}, \frac{dh^K}{dt}, \frac{dS}{dt}, I^{Cl}, I^{IR}, I^{DR}, I^{Na}, I^{NaK}\right]$$
$$= Z_s(V, h, m, n, h^K, S, K_i, K_o, Na_i, Na_o)$$
$$\alpha_h = \bar{\alpha}_h \exp(-(V - V_h)/K_{\alpha_h})\ ms^{-1}$$
$$\beta_h = \bar{\beta}_h/(1 + \exp(-(V - V_h)/K_{\beta_h}))\ ms^{-1}$$
$$\alpha_m = \bar{\alpha}_m(V - V_m)/(1 - \exp(-(V - V_m)/K_{\alpha_m}))\ ms^{-1}$$
$$\beta_m = \bar{\beta}_m \exp(-(V - V_m)/K_{\beta_m})\ ms^{-1}$$
$$\alpha_n = \bar{\alpha}_n(V - V_n)/(1 - \exp(-(V - V_n)/K_{\alpha_n}))\ ms^{-1}$$
$$\beta_n = \bar{\beta}_n \exp(-(V - V_n)/K_{\beta_n})\ ms^{-1}$$
$$h_\infty^K = 1/(1 + \exp((V - V_{h_K^\infty})/A_{h_K^\infty}))$$
$$S^\infty = 1/(1 + \exp((V - V_{S^\infty})/A_{S^\infty}))$$
$$\tau_{h^K} = 1000 \times \exp(-(V + 40)/25.75)\ ms$$
$$\tau_S = 8571/(0.2 + 5.65((V + V_\tau)/100)^2)\ ms$$
$$a = 1/(1 + \exp((V - V_a)/A_a)) \tag{2}$$

$$E_K = RT/(+F)\log(K_o/K_i)\ mV\ (K^+ \text{ Nernst potential})$$
$$E_{Cl} = E_K(Cl^- \text{ Nernst potential})$$
$$E_{Na} = RT/(+F)\log(Na_o/Na_i)\ mV\ (Na^+ \text{ Nernst potential})$$
$$Cl_i = (128 + 5 \times 5.7)/(5 + \exp((-FE_K)/(RT))) \quad (\text{Intracellular } [Cl^-])$$
$$Cl_o = (128 + 5 \times 5.7) - 5Cl_i \quad (\text{Extracellular } [Cl^-])$$

$$J_{Cl} = V(Cl_i - Cl_o\exp((FV)/(RT)))/(1 - \exp((FV)/(RT)))$$
$$J_K = V(K_i - K_o\exp(-(FV)/(RT)))/(1 - \exp(-(FV)/(RT)))$$
$$J_{Na} = V(Na_i - Na_o\exp(-(FV)/(RT)))/(1 - \exp(-(FV)/(RT)))$$
$$g_{Cl} = \bar{g}_{Cl} a^4\ mS/cm^2$$
$$K_R = K_o\exp(-\delta E_K F/(RT))\ mM$$
$$\bar{g}_{IR} = G_K K_R^2/(K_K + K_R^2)\ mS/cm^2$$
$$y = 1 - (1 + (K_S/(S_i^2\exp(2(1-\delta)VF/(RT)))) \times (1 + K_R^2/K_K))^{-1}$$
$$g_{IR} = \bar{g}_{IR} y\ mS/cm^2$$
$$g_{DR} = \bar{g}_K n^4 h^K\ mS/cm^2$$
$$g_{Na} = \bar{g}_{Na} m^3 hS\ mS/cm^2$$
$$I_{Cl} = g_{Cl}(J_{Cl}/45)\ \mu A/cm^2\ (Cl^- \text{ current})$$
$$I_{IR} = g_{IR}(J_K/50)H(J_K/50)\ \mu A/cm^2\ (K^+ \text{ IR current})$$
$$I_{DR} = g_{DR}(J_K/50)\ \mu A/cm^2\ (K^+ \text{ DR current})$$
$$I_{Na} = g_{Na}(J_{Na}/75)\ \mu A/cm^2\ (Na^+ \text{ current})$$
$$H(t) = \begin{cases} 1, t > 0 \\ 0, t < 0 \end{cases} \tag{3}$$
$$\sigma = \frac{1}{7}(\exp(Na_o/67.3) - 1)$$
$$f_1 = (1 + 0.12\exp(-0.1VF/(RT)) + 0.04\sigma\exp(-VF/(RT)))^{-1}$$
$$\bar{I}_{NaK} = F\bar{J}_{NaK}/((1 + K_{mK}/K_o)^2 \times (1 + K_{mNa}/Na_i)^3)\mu A/cm^2$$
$$I_{NaK} = \bar{I}_{NaK} f_1\ \mu A/cm^2 \text{ (Na-K exchanger)}$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h \text{ (Na inactivation gating variable)}$$
$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \text{ (Na activation gating variable)}$$
$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \text{ (K-DR activation gating variable)}$$
$$\frac{dh^K}{dt} = (h_\infty^K - h^K)/\tau_{h^K} \text{ (K-DR inactivation gating variable)}$$
$$\frac{dS}{dt} = (S_\infty - S)/\tau_S \text{ (Na very slow inactivation gating variable)}$$

and the function Z_t is defined by

$$\left[\frac{dh_t}{dt}, \frac{dm_t}{dt}, \frac{dn_t}{dt}, \frac{dh_t^K}{dt}, \frac{dS_t}{dt}, I_t^{Cl}, I_t^{IR}, I_t^{DR}, I_t^{Na}, I_t^{NaK}\right] = Z_t(v_t, h_t, m_t, n_t, h_t^K, S_t, K_i, K_t, Na_i, Na_t)$$
$$\left[\frac{dh_t}{dt}, \frac{dm_t}{dt}, \frac{dn_t}{dt}, \frac{dh_t^K}{dt}, \frac{dS}{dt}, I^{Cl}, I^{IR}, I^{DR}, I^{Na}, I^{NaK}\right] = Z_s(v_t, h_t, m_t, n_t, h_t^K, S_t, K_i, K_t, Na_i, Na_t)$$
$$\eta_{Cl} = 0.1 \text{ (Cl channel density in t-tubules relative to sarcolemma)}$$
$$\eta_{IR} = 1.0 \text{ (K-IR channel density in t-tubules relative to sarcolemma)}$$
$$\eta_{DR} = 0.45 \text{ (K-DR channel density in t-tubules relative to sarcolemma)}$$
$$\eta_{Na} = 0.1 \text{ (Na channel density in t-tubules relative to sarcolemma)}$$
$$\eta_{NaK} = 0.1 \text{ (Na/K exchanger density in t-tubules relative to sarcolemma)}$$
$$I_t^{Cl} = \eta_{Cl} I^{Cl}\ \mu A/cm^2$$
$$I_t^{IR} = \eta_{IR} I^{IR}\ \mu A/cm^2$$
$$I_t^{DR} = \eta_{DR} I^{DR}\ \mu A/cm^2$$
$$I_t^{Na} = \eta_{Na} I^{Na}\ \mu A/cm^2$$
$$I_t^{NaK} = \eta_{NaK} I^{NaK}\ \mu A/cm^2$$

PDE model

$$\bar{G}_L = G_L \tau f_T \quad mS/cm$$
$$D_s = 1000 \times (R_s/(2(R_i + R_e)))/C_m \quad cm^2/ms$$
$$D_t = \bar{G}_L/(C_m f_T/\xi) \quad cm^2/ms$$
$$\left[\frac{dh_s}{dt}, \frac{dm_s}{dt}, \frac{dn_s}{dt}, \frac{dh_s^K}{dt}, \frac{dS_s}{dt}, I^{Cl}, I^{IR}, I^{DR}, I^{Na}, I^{NaK}\right] = Z_s(v_s, h_s, m_s, n_s, h_s^K, S_s, K_i, K_e, Na_i, Na_e)$$
$$I_s^{ionic} = I^{Cl} + I^{IR} + I^{DR} + I^{Na} + I^{NaK} - I_{app}(t; t_{app})\ \mu A/cm^2 \text{ (sarcolemma current)}$$
$$\left[\frac{dh_t}{dt}, \frac{dm_t}{dt}, \frac{dn_t}{dt}, \frac{dh_t^K}{dt}, \frac{dS_t}{dt}, I_t^{Cl}, I_t^{IR}, I_t^{DR}, I_t^{Na}, I_t^{NaK}\right] = Z_t(v_t, h_t, m_t, n_t, h_t^K, S_t, K_i, K_t, Na_i, Na_t)$$
$$I_t^{ionic} = I_t^{Cl} + I_t^{IR} + I_t^{DR} + I_t^{Na} + I_t^{NaK}\ \mu A/cm^2 \text{ (t-tubule current)}$$
$$\frac{\partial v_t(r,x)}{\partial t} + \frac{I_t^{ionic}}{C_m} = D_t\left(\frac{\partial^2 v_t}{\partial r^2} + \frac{1}{r}\frac{\partial v_t}{\partial r}\right) \text{ mV/ms (t-tubule membrane voltage)}$$
$$\left.\frac{\partial v_t}{\partial r}\right|_{r=0} = 0$$

$$\frac{dO_1}{dt} = k_L/fC_1 - k_{Lm}fO_1 + 4k_C/fO_0 - fk_{Cm}O_1 - 3k_C/fO_1 + 2fk_{Cm}O_2$$
$$\frac{dC_2}{dt} = 3k_C C_1 - 2k_{Cm}C_2 - k_L/f^2C_2 + k_{Lm}f^2O_2 - 2k_C C_2 + 3k_{Cm}C_3$$
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$$\frac{dO_4}{dt} = k_C/fO_3 - 4fk_{Cm}O_4 + k_L/f^4C_4\text{-}k_{Lm}f^4O_4$$

$$I_T = 1000 \times [v_s(x) - v_t(r = R_s, x)]/R_a = \bar{G}_L\left.\frac{\partial v_t}{\partial r}\right|_{r=R_s}\ \mu A/cm^2 \text{ (access current)}$$
$$\frac{\partial v_s(x)}{\partial t} + \frac{I_s^{ionic}}{C_m} = D_s\frac{\partial^2 v_s}{\partial x^2}, \text{ mV/ms (sarcolemma membrane voltage)}$$
$$\left.\frac{\partial v_s}{\partial x}\right|_{x=0} = 0, \left.\frac{\partial v_s}{\partial x}\right|_{x=l_s} = 0$$
$$\frac{\partial K_t(r,x)}{\partial t} = D_K\left(\frac{\partial^2 K_t}{\partial r^2} + \frac{1}{r}\frac{\partial K_t}{\partial r}\right) + (I_t^{IR} + I_t^{DR} - 2I_t^{NaK} + I_{rest}^K)/(1000F\xi)$$
$$\left.\frac{\partial K_t}{\partial r}\right|_{r=0} = 0$$
$$K_t(r = R_s, x) = K_e(x) \text{ mM/ms (t-tubule } [K^+])$$
$$\frac{\partial Na_t(r,x)}{\partial t} = D_{Na}\left(\frac{\partial^2 Na_t}{\partial r^2} + \frac{1}{r}\frac{\partial Na_t}{\partial r}\right) + (I_t^{Na} + 3I_t^{NaK} + I_{rest}^{Na})/(1000F\xi)$$
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$$Na_t(r = R_s, x) = Na_e(x) \text{ mM/ms (t-tubule } [Na^+])$$
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Ca^{2+} release from RyR's

$$k_C = 0.5\alpha_1\exp((v_t - \nabla/(8K)) \text{ (activation rate between closed states)}$$
$$k_{Cm} = 0.5\alpha_1\exp(-(v_t - \nabla/(8K)) \text{ (inactivation rate between closed states)}$$
$$\frac{dC_0}{dt} = -k_L C_0 + k_{Lm}O_0 - 4k_C C_0 + k_{Cm}C_1 \text{ } (C_0 - C_4 \text{ are RyR closed states})$$
$$\frac{dO_0}{dt} = +k_L C_0 - k_{Lm}O_0 - 4k_C/fO_0 + fk_{Cm}O_1 \text{ } (O_0 - O_4 \text{ are RyR open states})$$
$$\frac{dC_1}{dt} = +4k_C C_0 - k_{Cm}C_1 - k_L/fC_1 + k_{Lm}fO_1 - 3k_C C_1 + 2k_{Cm}C_2$$

Propagation of electrical signals

Overview

- Model the propagation of electric stimuli along the muscle fibres
- Extend the existing local model
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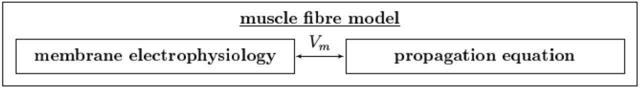

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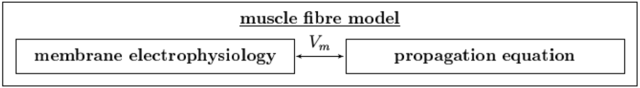

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- 2 domains: intra-, extracellular
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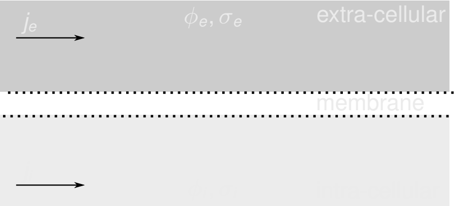

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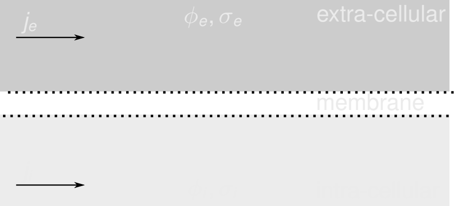

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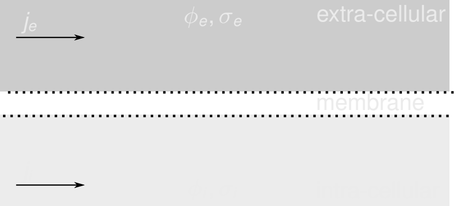

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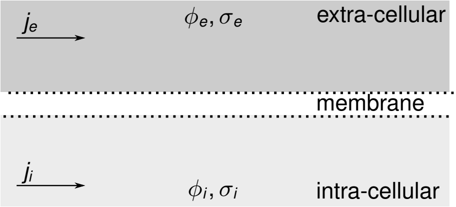

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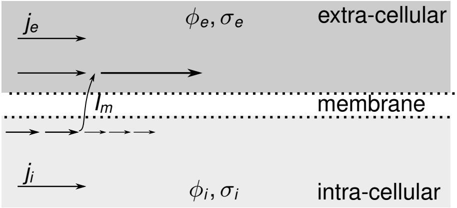

- Conservation of charges: local changes in current density affect other domain

$$\frac{\partial}{\partial x} j_i = -\frac{\partial}{\partial x} j_e$$

$$\Leftrightarrow \quad \frac{\partial}{\partial x}\left(\sigma_i \frac{\partial \phi_i}{\partial x}\right) = -\frac{\partial}{\partial x}\left(\sigma_e \frac{\partial \phi_e}{\partial x}\right) \quad = I_m$$

$$= A_m\left(C_m \frac{\partial V_m}{\partial t} + I_{ionic}(V_m)\right)$$

Propagation of electrical signals

- Substitute $V_m = \phi_i - \phi_e$ to eliminate ϕs:

$$\frac{\partial}{\partial x}\left(\sigma_{eff}\,\frac{\partial V_m}{\partial x}\right) = A_m\left(C_m \frac{\partial V_m}{\partial t} + I_{ionic}(V_m)\right), \qquad \text{with } \sigma_{eff} := \sigma_i || \sigma_e$$

Numerical treatment

- Equation solved for $\dfrac{\partial V_m}{\partial t}$:

$$\frac{\partial V_m}{\partial t} = -\frac{1}{C_m} I_{ionic}(V_m) + \frac{1}{A_m C_m}\frac{\partial}{\partial x}\left(\sigma_{eff}\frac{\partial}{\partial x} V_m\right)$$

- Employ finite differences in t and Godunov operator splitting:

$$\frac{V_m^* - V_m^{(k)}}{\Delta t} = -\frac{1}{C_m} I_{ionic}(V_m^{(k)}),$$

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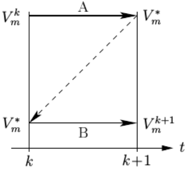

Continuum mechanics model

Basics in continuum mechanics

- Consider muscle in reference configuration, $\mathbf{X} \in \mathcal{B}_0$ and in deformed state at time t, $\mathbf{x} \in \mathcal{B}_t$
- Mapping is called placement function $\mathbf{x} = \chi(\mathbf{X}, t)$
- Deformation gradient: $\mathbf{F} = \dfrac{\partial \chi(\mathbf{X}, t)}{\partial \mathbf{X}}$, right Cauchy-Green tensor: $\mathbf{C} = \mathbf{F}^\top \mathbf{F}$
- Strain: Green-Lagrangian strain tensor: $\mathbf{E} = 1/2(\mathbf{C} - \mathbf{I})$
- Stress: 2nd Piola-Kirchhoff stress tensor: $\mathbf{S} = (\det \mathbf{F})\mathbf{F}^{-1}\mathbf{T}\mathbf{F}^{-T}, \quad \mathbf{t} = \mathbf{T}\,\mathbf{n}$
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Model assumptions of muscle

- Incompressibility, i.e. $\det(\mathbf{F}) = 1$
- Quasi-static condititons: no inertial terms
- No external body forces: no gravity, no contact e.g. to bones
- Isothermal conditions: no balance of energy
- Stress tensor can be additively composed into active and passive part:

$$\mathbf{S} = \mathbf{S}_{pass} + \mathbf{S}_{act} - p\,\mathbf{C}^{-1}$$

Passive stresses

- Modelled as fibre reinforced material with isotropic and anisotropic part:

$$\mathbf{S}_{pass} = \mathbf{S}_{iso} + \mathbf{S}_{ani}$$

- Isotropic part, "ground matrix" modelled by *Mooney-Rivlin* material:

$$\mathbf{S}_{iso} = 2\,c_{10}\,\mathbf{I} + 2\,c_{01}\,(tr(\mathbf{C})\mathbf{I} - \mathbf{C})$$

- Anisotropic part acts in fibre direction $\mathbf{a}_0$ with fibre stretch λ_f:

$$\mathbf{S}_{ani} = b_1\,(\lambda_f^{d_1-2} - \lambda_f^{-2})\,\mathbf{a}_0 \otimes \mathbf{a}_0$$

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Continuum mechanics model

Model assumptions of muscle

- Incompressibility, i.e. $\det(\mathbf{F}) = 1$
- Quasi-static condititons: no inertial terms
- No external body forces: no gravity, no contact e.g. to bones
- Isothermal conditions: no balance of energy
- Stress tensor can be additively composed into active and passive part:

$$\mathbf{S} = \mathbf{S}_{pass} + \mathbf{S}_{act} - p\,\mathbf{C}^{-1}$$

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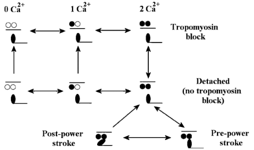
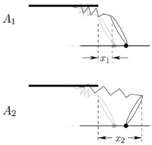
Continuum mechanics model

Active stresses

- From crossbridge dynamics to a stress tensor field
  ℓ_S: sarcomere length, f_s: stimulation frequency
  $\lambda_f = \ell_S / \ell_S^0$: fibre stretch





$$\frac{\partial x_1}{\partial t} = -\left(f_0 \frac{[D_2]}{[A_1]} + h' \frac{[A_2]}{[A_1]}\right) x_1 + h' \frac{[A_2]}{[A_1]} (x_2 - x_0) + \frac{\dot{\ell}_S}{2}$$

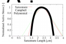
$$\frac{\partial x_2}{\partial t} = -h_0 \frac{[A_1]}{[A_2]} (x_2 - (x_1 + x_0)) + \frac{\dot{\ell}_S}{2}.$$

$$f_0 = \bar{f}\left(1 + \frac{[A_1]}{T_{tot}}\left[\exp\left(\frac{x_1}{x_0}(\nu - 1)\right) - 1\right] + \frac{[A_2]}{T_{tot}}\left[\exp\left(\frac{x_2}{x_0}(\nu - 1)\right) - 1\right]\right),$$

$$g_0 = \bar{g} \exp\left(\vartheta (x_2 - x_0)^2\right),$$

$$B(f_s, \dot{\ell}_s) = [A_1]\, x_1 + [A_2]\, x_2$$

Λ :



$$\gamma = \Lambda(\ell_S) \frac{B(f_s, \dot{\ell}_S) - B(0,0)}{B(f_s^{max}, 0) - B(0,0)}$$

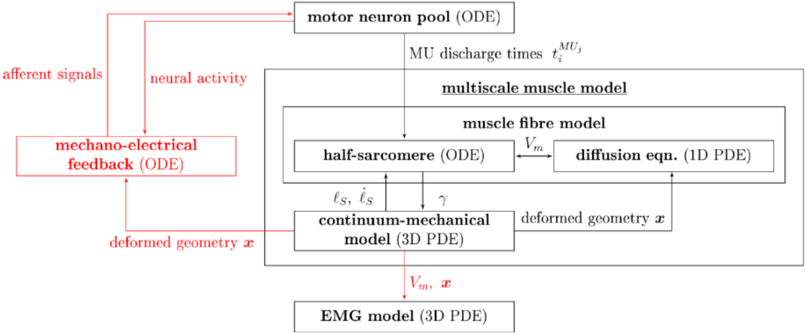
$$\bar{\gamma} = \Gamma(\gamma)$$

$$P^{act} = P^{max}\, \bar{\gamma}(f_s, \lambda_f, \dot{\lambda}_f)$$

$$\mathbf{S}_{act} = \lambda_f^{-1}\, P^{act}\, \mathbf{a}_0 \otimes \mathbf{a}_0$$

The Mathematical Model

The full multiscale model



Timestepping scheme

Discretization and solver types

- ODE: finite differences, forward Euler
- 1D PDE: 1D finite elements, Crank-Nicholson ($\theta = \frac{1}{2}$) $\rightsquigarrow$ nonlinear system, solved using newton search, linear system in each step: GMRES (PETSc)
- 3D PDE: 3D finite elements, backtracking line search (PETSc)
- The solvers have different time steps according to characteristic sizes of the scales
- Typical values: $h^{ODE} = 10^{-4} ms, \quad h^{DEQ} = 50 \cdot 10^{-4} ms, \quad h^{CMM} = 10^{-1} ms$

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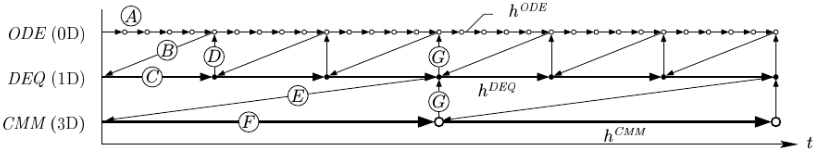

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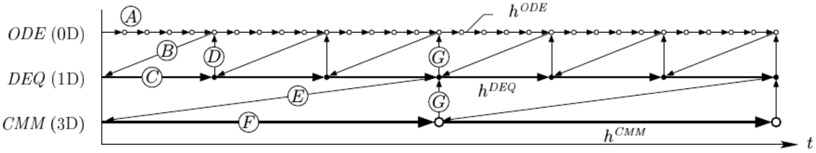

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The Computational Framework OpenCMISS

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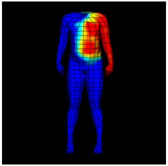

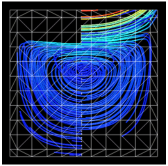

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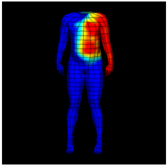  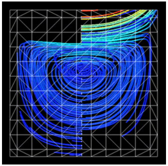

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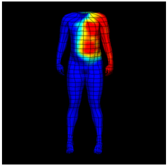

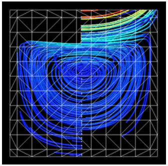

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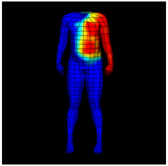

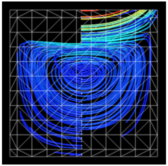

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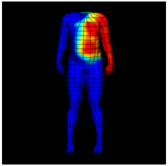

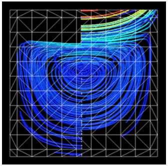

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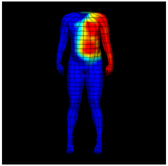

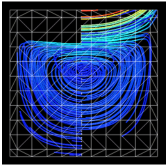

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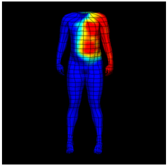

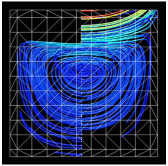

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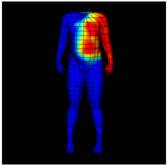

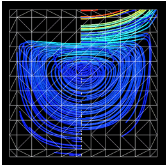

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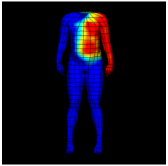
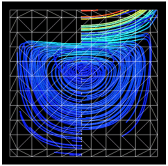
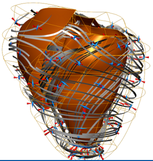


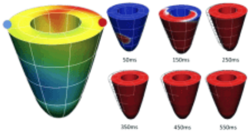


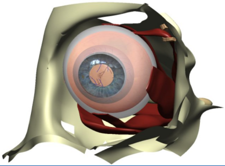
The computational framework OpenCMISS

Features

- Finite elements calculations in different dimensions
- Different general components from which the desired problem can be build: regions with possibly multiple overlayed meshes, basis functions, interpolation methods, solvers
- The structure of control loops can be arbitrarily composed, subloops with fixed time stepping, load increment stepping, conditional break
- Parallelization requirements like ghost cells can be automatically created, MPI communication is transparent from user
- Some external dependencies can be interfaced: PETSc (solvers), SUNDIALS (for DAE solver), Hypre (preconditioners), SLEPc (eigenproblems), ScaLAPACK (linear algebra)
- The XML-based description standards *CellML* and *FieldML* are supported.
- Offline-visualization tools







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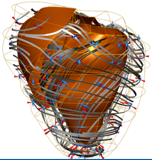

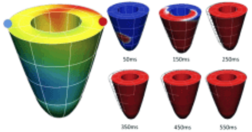

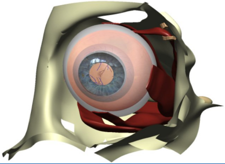

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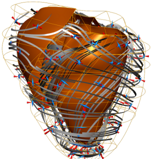

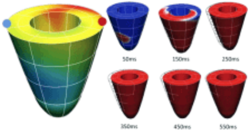

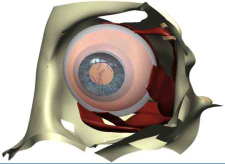

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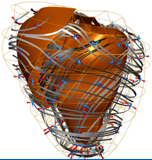
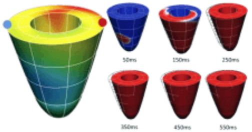
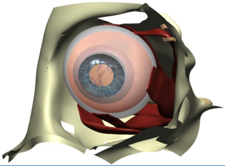
- Finite elements calculations in different dimensions
- Different general components from which the desired problem can be build: regions with possibly multiple overlayed meshes, basis functions, interpolation methods, solvers
- The structure of control loops can be arbitrarily composed, subloops with fixed time stepping, load increment stepping, conditional break
- Parallelization requirements like ghost cells can be automatically created, MPI communication is transparent from user
- Some external dependencies can be interfaced: PETSc (solvers), SUNDIALS (for DAE solver), Hypre (preconditioners), SLEPc (eigenproblems), ScaLAPACK (linear algebra)
- The XML-based description standards *CellML* and *FieldML* are supported.
- Offline-visualization tools

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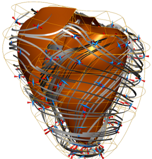
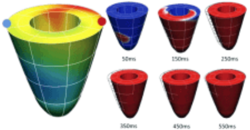
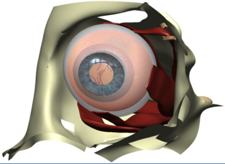

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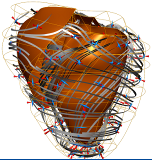

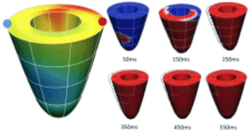

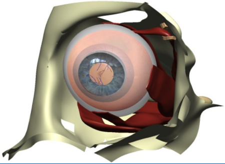

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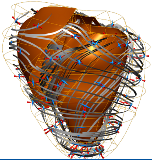

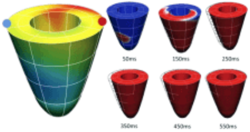

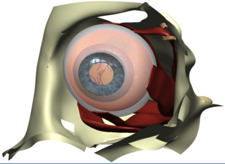

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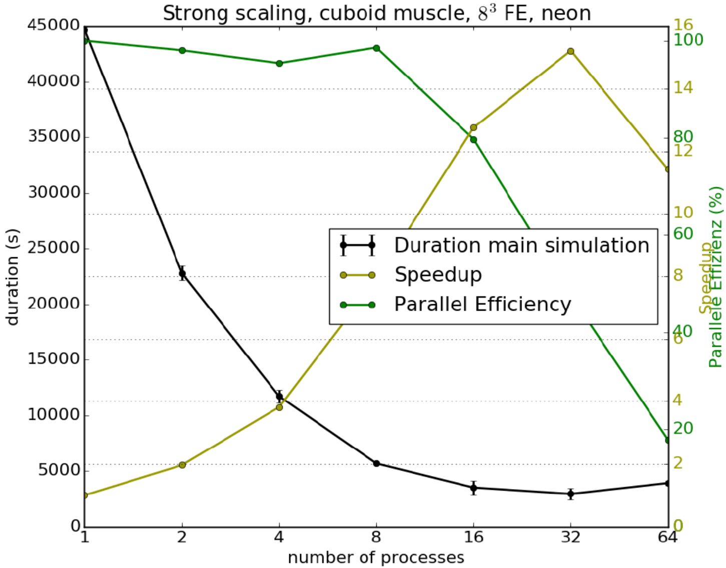
Simulation

Scaling Properties



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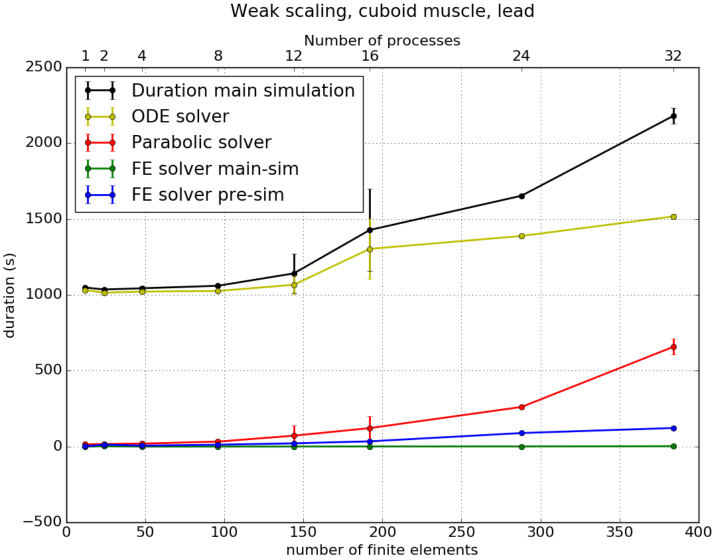

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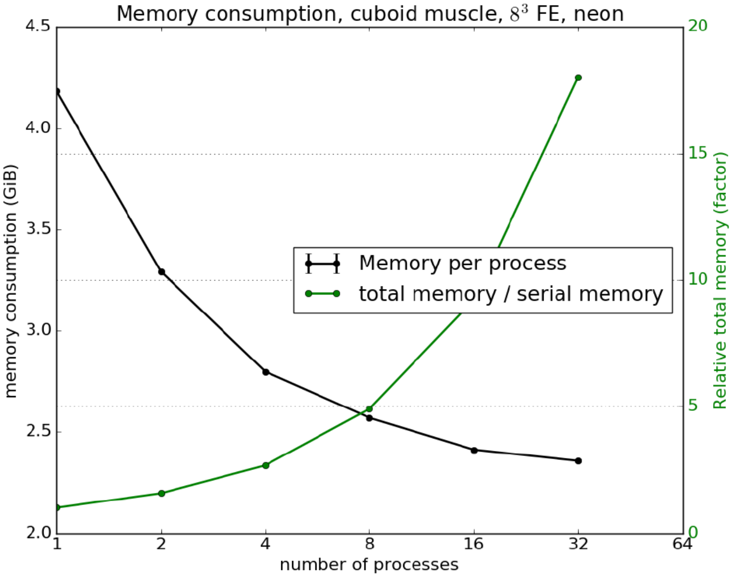

Thank you for your attention!