Modelling Short-Range Stiffness: a Comparison Between Hill- and Huxley-type Muscle Models

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Preface

I have always had a broad interest in engineering, that is to say, I am not only interested in physics and mathematics but also interested in how to apply them to everyday situations. During my bachelor studies of advanced technology I was taught a large fundamental base for many fields like chemical, electrical and mechanical engineering. Gradually during my bachelors my focus shifted towards more mechanical engineering (which might have to do with the fact that at some point I lived with four mechanical engineers). After my bachelors was finished I choose to continue in mechanical engineering and specialise in bio-mechanical design. Although, I had encountered many fields of engineering already, one managed to elude me until I followed a course called Neuromechanics and Muscular control. The field of biomedical engineering was especially interesting in that it was different in application, not machines, but humans. Biology, although interesting at high school, was a field I never (wrongly) presumed to use (complicated) mathematics and physics. It was the combination of an opportunity to study something new as well as the application of it that led me to contact Frans van der Helm, the professor of the department, when the time came to look for the possible subjects for my thesis. During our conversation the current state of muscle models was brought up and the current shortcomings. What struck me as interesting was the apparent mismatch between the physiologists, the ones who perform experiments, and the modellers, the people that try to model muscle behaviour. This mismatch showed in the fact that often a lot of muscle models were not trying to simulate mechanochemical processes in the muscle. In itself this is not a bad thing, if the model can be simplified without loosing accuracy it is even considered good. However, it appears that that some properties, like short-range stiffness, can play a key-role in muscle behaviour, for instance in postural control. This property is caused by the history dependent behaviour of the mechanochemical processes and thus is not represented accurately. In addition, by using a model that simulates mechanochemical processes in the muscle, the energy expenditure of a muscle can be modelled, which can be used to create a better insight in muscle activation patterns, as well as in why humans walk and move in particular ways. Thus, during my thesis I set out to investigate current muscle models and see if they can be modified to be easy to use and simulate complex processes inside the muscle.
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Abstract
Musculoskeletal models often use Hill-type models to study and simulate muscle behaviour. Due to fast simulation time and ability to simulate large and slow movements, Hill-type models have remained largely unchanged throughout recent years. Large and slow movements spend a large part in steady state behaviour and thus experience limited influence of transitional behaviour. However, during small and fast movements, transitional behaviour has more influence and causes inaccuracies in Hill-type models, which can cause an overestimation of muscle force. One characteristic of transitional behaviour is short-range stiffness (SRS). This property is a result of crossbridge dynamics and causes an increase in stiffness when muscle velocity changes. Huxley-type models are capable of simulating transitional behaviour, but are computationally expensive. The goal of this article is to identify the optimal parameter values for two Hill- and one Huxley-type model using a surrogate optimization algorithm and determine if these models can simulate general behaviour and SRS. The parameters are fitted to one soleus and medial gastrocnemius muscle of a cat. All models were able to simulate the experimental data with an average RMS of 6.6N and 4.8N for the Hill models and 5.5N for the Huxley model. However, all three models were not capable of predicting SRS during isometric contractions and the method of determining SRS during non-isometric contractions proved unusable. Thus, the Huxley model that was used had no advantage over the used Hill-type muscle models. Furthermore, it was concluded that the simplest Hill was the only model viable for real-time application.

Introduction

When studying muscle behaviour, muscle models can greatly contribute to insight in muscle behaviour and musculoskeleton dynamics. In addition, by combining multiple muscle models a musculoskeletal model can be generated which can aid in studying movement patterns (Chumanov et al., 2011), which for instance, can be used to analyse muscle behaviour in cerebral palsy patients and plan treatment (Gooijer-van de Groep et al., 2013)(Arnold and Delp, 2005), predict the impact of surgical operations on patients (Chen et al., 2016) and study the effects of aging muscle in older adults (Thelen, 2003). This is done by fitting the model parameters to a patient and sequentially changing one or more parameters of the model, which can give an indication of the origin of a change in macro behaviour. In addition, musculoskeletal models can aid in optimizing movements in healthy patients, like gait, to reduce the risk of injuries (Heiderscheit et al., 2011). Almost all muscle models used in musculoskeletal models are Hill-type models, a descriptive muscle model that relates macro properties like muscle force, muscle length and muscle velocity (A. Hill, 1938)(Gordon et al., 1966). The Hill-type models are based on two equations: a force-velocity relationship discovered by A. Hill (1938) and a force-length relation, discovered by Gordon et al. (1966). These can be combined into an ordinary differential equation (ODE). In addition, often a relation between excitation and muscle activation is included. Many forms of activation dynamics exist and often consists of one or two first order ODEs. The combination of force-length, force-velocity and activation dynamics give rise to a system of equations that consist of two or three ODEs.

For slow or large motions these relations suffice. However, in fast movements and short movements it has been found that Hill-type models are not able to simulate behaviour (Rack and Westbury, 1974) due to additional dynamics that are not modelled by the Hill-type model (Sandercock and Heckman, 1997). One of the effects not modelled by Hill-type models is the short-range stiffness (SRS), a direct result of crossbridge dynamics in the sarcomere. In literature, various authors use different terminology and definitions of the short-range stiffness. Often the description of SRS is limited and described as a static property that is experienced when a muscle is stretched during an isometric contraction (D. K. Hill, 1968)(Eesbeek et al., 2010), although this is correct, it is too limited. The confusion largely caused by the limitations during experimentation, it is difficult to get in vivo or in situ measurements of stiffness during varying velocities and thus extensive literature is absent. However, crossbridge dynamics are continuously active and time constants influence force and stiffness during every velocity change. Thus, in this article SRS is described as the dynamic increase or decrease in muscle stiffness due to a change in velocity as a consequence of crossbridge dynamics. One of the ways SRS plays a large role in mammalian behaviour is in instantaneous postural control, since it is not dependent on feedback. By neglecting the SRS in muscle models, muscle models compensate for the lack of stiffness by co-contracting antagonistic muscles, which can lead to an incorrect estimation of energy expenditure in the muscle. Huxley-type models, also known as crossbridge models, should be able to simulate short-range stiffness, since these models are based on the physiological behaviour of crossbridges. In literature
Huxley-type models are not often used due to their complexity. The Huxley-type muscle model created by Huxley (1957) is described by a partial differential equation, an equation that is harder to solve. However, Zahalak (1981) has described a way of discretizing the partial differential equation which results in a set of ODEs for every discretized location of the myosin filament, a method that Lemaire et al. (2016) have also utilised.

The primary aim is to find parameters for two Hill-type muscle models and one Huxley-type muscle model. To obtain the parameter values, the model parameters will be optimized to experimental data using a surrogate optimization algorithm. The secondary aim is to validate the models and their respective parameters. The validation of the models consists of three parts. Firstly, the models will be evaluated on their performance during long-range movements. Secondly the models will be validated by their ability to simulate short-range stiffness. Lastly, the model run-time will be evaluated as a measure of ease of use.

For the primary aim it is hypothesized that all three models are able to be fitted to the data, however, it is expected that the Huxley-type model will have a higher RMS error due to the complexity of the model. For the secondary aim, it is expected that all three models are capable of simulating long-range and slow movements, but that the Huxley-type model is the only model capable of simulating SRS. On the other hand, the Hill models are expected to be relatively easy of use compared to the Huxley models, due to faster run-times and therefore, more easily adjusted and tweaked.

The model parameters will be optimized to fit experimental data obtained from a soleus (SOL) and one on a medial gastrocnemius (MG) muscle from a cat. The muscles were chosen due to their difference in fiber composition, soleus muscle predominantly consists of slow-type fibers whereas the MG consists mostly of fast-type fibers. For both muscles the experimental data will be divided into two sets, one to estimate the parameters and one to validate the models. The RMS between experimental data and model data will be used as a fitness measure during estimation of parameters and the validation of long-range movements. Validation of the models with respect to SRS is divided into two measurements. Firstly, the crossbridge stiffness is calculated by applying a triangular wave perturbation of 20Hz and amplitude of 0.1mm around a constant muscle length with constant activation. Secondy, the dynamic crossbridge stiffness is determined by increasing the muscle velocity during an eccentric contraction and decreasing the velocity during an concentric contraction.

**METHODS**

**Experiment Set-Up**

To acquire the experimental data that will be used to fit the parameters, an experiment will be performed with similar set-up to the experiment from Sandercock and Heckman (1997). The experiment was performed on two cats, one to measure the soleus muscle and one to measure the medial gastrocnemius. Both experiments were approved by the Institutional Animal Care and Use Committee at Northwestern University.

Before and during the experiment the cats remained in a deep state by administering an anesthetic. To monitor well being of the cat, blood pressure, heart rate, body temperature and muscle temperature were monitored. The cat was placed in a harness were the hind-leg was fixed in position in a saline bath. The connection between the soleus and medial gastrocnemius and other muscles was severed as much as possible without damaging the experiment muscle. The soleus and medial gastrocnemius were connected to the puller during their respective experiments by the distal tendon. Once the muscle was connected to the puller, it was completely denervated with the exception of the soleus and medial gastrocnemius nerve, for their respective experiments. After the experiment a lethal dose of pentobarbital was administered (100 mg/kg i.v.).

During the experiments two inputs were used: the puller position, which equals the desired muscle tendon complex (MTC) length and the stimulation of the muscle, which was administered as a pulse train. To account for compliance in the puller, the actual MTC length was measured by placing a length transducer within the puller shaft. The resulting muscle force was measured using a strain gauge in series with the puller.

**Experiment protocol**

Both muscle experiments consists of three series of trials measuring the muscle length and force for different stimulation and length inputs. Between each trial 30s rest is scheduled and after each trial with activation the trial is repeated without activation. Hence, there is at least a minute rest between active trials. Experiment protocols for both experiments can be found in appendix A. Each experiment is divided into an initiation set (TS0), an optimization set (TS1) and a validation set (TS2). The initiation set is used to experimentally determine the maximal isometric force, $F_{isom_{max}}$, and the corresponding muscle tendon complex (MTC) length, $l_{MTC_{max}}$. This is done by performing a set of trials with full activation at different muscle lengths. Afterwards, TS1 is used to identify muscle behaviour and consists of several tetani trials with different frequencies at optimum length, lengthening trials, shortening trials and a passive lengthening trial. The shortening and lengthening trials are performed at full and half activation. The frequency of half activation is experimentally determined during the experiment as the activation frequency where $F_{isom}$ is equal to half $F_{isom_{max}}$ at full activation. To validate the models, the models will be used to simulate TS2. This set consists of two triangular wave patterns, performed at two activation levels and three muscle lengths, resulting in a set of 12 trials per experiment. The first wave pattern consists of activating the muscle at a constant length and perturbing the muscle with a triangular wave with an amplitude of 0.1mm and a frequency of 20 Hz. The second wave
pattern consists of a perturbation administered during constant activation level. The perturbation consists of a triangular wave with a frequency of 2.5 Hz and 1mm amplitude, which results in a perturbation velocity of 10mm/s. During the eccentric part in the second period the MTC velocity is increased after 0.04 seconds to 40mm/s for 0.03 seconds after which it is returned to 10mm/s for another 0.03 seconds. This procedure is repeated with negative velocities during the concentric part.

Model formulation

Hill 1

The trials will be used to characterize the three muscle models as well as validate them. The first model (HILL1) that is investigated is the Hill-type muscle model formulated by Sandercock and Heckman (1997). This model consists of a contractile element (CE) in series with a series elastic (SE) element and is shown in Fig. 1a. The activation of the model is obtained by converting the excitation to muscle activation by modelling calcium uptake, eq.(1), and calcium binding to troponin, eq.(2). Here $C_i$ and $C_t$ represent the available calcium and the amount of calcium bound to troponin, respectively.

$$\frac{dC_i}{dt} = (1-C_i) \cdot a_{release} \cdot a_{amprel} - C_i \cdot a_{Kit} \cdot a_{sc5}$$

$$\frac{dC_t}{dt} = C_t \cdot (1-C_i) \cdot a_{Kit} - C_t \cdot a_{Kit}$$

$$a_{sc5} = \begin{cases} 1 & \text{if } (t-t_{lastpulse}) > \tau_{sc5} \\ \frac{t_{lastpulse}}{\tau_{sc5}} & \text{otherwise} \end{cases}$$

$$a_{release} = \begin{cases} 1 & \text{if } t > t_{pulse} + a_{delay} \\ 0 & \text{otherwise} \end{cases}$$

The resulting bound calcium to troponin is taken as the activation of the muscle, $q(t)$. In these formulas the following parameters need to be determined through optimization: a calcium to troponin binding constant, $a_{Kit}$; a constant that determines the amount of unbinding of calcium to troponin, $a_{Kit}$; a time delay between excitation and activation, $a_{delay}$; a time constant that determines rate of calcium pumped back $a_{Kit}$; the constant that determines the amount of calcium released $a_{amprel}$ during excitation and a constant that determines the time constant of the calcium pump, $\tau_{sc5}$.

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as the product of $F_{\text{isom max}}$, the force-length relationship, force-velocity relationship and activation, see eq.(7). $F_{\text{SE}}$ is shown in eq.(8) and is simulated as a linear spring with spring constant $k_{\text{SE}}$. In all equation forces in upper case denote an absolute value and a variable in lower case denotes a force normalized with respect to $F_{\text{isom max}}$, see eq.(9).

$$F_{\text{MTC}} = F_{\text{CE}} = F_{\text{SE}}$$

$$F_{\text{CE}} = F_{\text{isom max}} \cdot f_1(l_{\text{CE}}) \cdot f_2(v_{\text{CE}}) \cdot q(t)$$

$$F_{\text{SE}} = k_{\text{SE}} \cdot F_{\text{CE}}$$

$$f_2 = \frac{F_{\text{SE}}}{F_{\text{isom max}}}$$

The force-length relationship and force-velocity are given by eq.(10) and eq.(11), respectively. In eq.(10), the optimum contractile element length is denoted by $l_{\text{CE}}$ and $W$ is a parameter that determines the width of the force-length relationship. In eq.(11) $a_0$, $b_0$, $c_0$ and $d_0$ are constants that determine the shape of the force-velocity relationship.

$$f_1(l_{\text{CE}}) = -7.987 + 22.40z - 17.74z^2 + 4.32z^3$$

$$z = \frac{l_{\text{CE}} - l_0}{l_{\text{CE}} + W}$$

$$v_{\text{CE}} = \begin{cases} -b_0 \cdot f_{1} \cdot f_{2} \cdot f_3(ce) & \text{if } F_{\text{ISOM max}} \ \lesssim \ F_{\text{MTC}} + c_0 \\ -d_0 \cdot f_{1} \cdot f_{2} \cdot f_3(ce) & \text{if } F_{\text{ISOM max}} > F_{\text{MTC}} + c_0 \end{cases}$$

Equations 6-11 can be normalized with respect to $F_{\text{ISOM max}}$ and rewritten to give $v_{\text{CE}}$ as a function of $f_{\text{SE}}$, $f_1(ce)$ and $q(t)$.

$$v_{\text{CE}} = \begin{cases} -b_0 \cdot f_{1} \cdot f_{2} \cdot f_3(ce) & \text{if } F_{\text{ISOM max}} \ \lesssim \ F_{\text{SE}} + d_0 \\ -d_0 \cdot f_{1} \cdot f_{2} \cdot f_3(ce) & \text{if } F_{\text{ISOM max}} > F_{\text{SE}} + d_0 \end{cases}$$

Hill 2

The second model (HILL2) was provided by the Delft University of Technology and is also a Hill-type model. However, in addition to SE and CE an additional parallel elastic element (PE) is included,
see Fig. 1b. The total force of the model is equal to the sum of
\( F_{SE} \) and \( F_{PE} \), see eqs.(13-14).

\[
F_{CE} = F_{max} \cdot f_l \cdot f_v \cdot q
\]

(13)

\[
F_{mtc} = F_{SE} + F_{PE} = F_{CE} + F_{PE}
\]

(14)

Similarly to HILL1, HILL2 uses a force-velocity and force-length relationship, however the force-length relation is a Gaussian function and the force-velocity function is derived form Winters and Stark (1987). In addition the force-length relationship and force-velocity are a function of \( l_{CE} \) and \( v_{CE} \) normalized with respect to \( l_{CE}^0 \), resulting in \( \tilde{l}_{CE} \) and \( \tilde{v}_{CE} \), respectively.

\[
f_l(\tilde{l}_{CE}) = e^{-\left(\frac{\tilde{l}_{CE} - 1}{L_{cosh}}\right)^2}
\]

(15)

\[
f_v(\tilde{v}_{CE}) = \begin{cases} 0, & \text{if } \tilde{v}_{CE} \leq \tilde{v}_{max} \\ \frac{V_{sh} \tilde{v}_{max} + V_{sh} \tilde{v}_{CE}}{V_{sh} \tilde{v}_{max} - \tilde{v}_{CE}}, & \text{if } -\tilde{v}_{max} < \tilde{v}_{CE} \leq 0 \\ \frac{V_{sh} \tilde{v}_{sh} \tilde{v}_{max} + V_{ml} \tilde{v}_{CE}}{V_{sh} \tilde{v}_{sh} \tilde{v}_{max} + \tilde{v}_{CE}}, & \text{if } \tilde{v}_{CE} > 0 \end{cases}
\]

(16)

\[
\tilde{v}_{max} = V_{vm}(1-V_{el}(1-q(t) \cdot f_l(\tilde{l}_{CE})))
\]

(17)

The shape of the force-length relationship is determined by \( L_{cosh} \) in eq.(15). In eq.(16) \( V_{sh} \) and \( V_{sh} \) determining the shape of the force-velocity relationship for the concentric and eccentric contractions, respectively. The maximum velocity for concentric and eccentric contractions are determined by \( V_{vm} \) and \( V_{ml} \), respectively, and \( V_{el} \) relates the maximum velocity to the \( q(t) \) and \( f_l(\tilde{l}_{CE}) \). The activation is given by two first order differential equations. In addition, the pulses that are administered to the cat are recorded as a time stamp with no duration. These will be converted into a square pulse signal, \( stim(t) \) where the duration of a single pulse is equal to the period of the minimum frequency for which \( F_m = 0.95 \cdot F_{max} \) at \( l_{CE}^0 \). These pulses are converted to an excitation \( e(t) \), see eq.(18), and the excitation is converted to activation or deactivation by eq.(19). Depending on whether the excitation level is higher or lower than the activation level, the activation or deactivation time constant is used, respectively.

\[
\dot{e}(t) = \frac{e(t) - stim(t)}{\tau_{ne}}
\]

(18)

\[
\dot{q}(t) = \begin{cases} \frac{q(t) - e(t)}{\tau_{act}}, & \text{if } e(t) \geq q(t) \\ \frac{q(t) - e(t)}{\tau_{deact}}, & \text{if } e(t) < q(t) \end{cases}
\]

(19)

The forces of PE and SE are given by eq.(20) and eq.(21), respectively. \( SE_{shape}, SE_{exm}, PE_{shape} \) and \( PE_{shape} \) are parameters that determine the shape and dependency on \( l_{SE} \) and \( l_{PE} \).

\[
F_{PE} = \frac{1}{e^{\frac{l_{PE}}{c_{PE}}}} e^{\frac{l_{PE}_{shape}}{c_{PE_{exm}}} - l_{SE} - 1)}
\]

(20)

\[
F_{SE} = \frac{1}{e^{\frac{l_{SE}}{c_{SE}}}} e^{\frac{l_{SE}_{shape}}{c_{SE_{exm}}} - l_{SE} - 1)}
\]

(21)

The resulting system of equations is shown in eqs.(22-24).

\[
\dot{e}(t) = e(t) - stim(t)
\]

(22)

\[
\dot{q}(t) = \begin{cases} \frac{q(t) - e(t)}{\tau_{act}}, & \text{if } -\tilde{v}_{max} \\ \frac{q(t) - e(t)}{\tau_{deact}}, & \text{if } \tilde{v}_{max} \end{cases}
\]

(23)

\[
\tilde{v}_{CE} = \begin{cases} f_{rel} + \frac{V_{sh}}{V_{sh} V_{ml}(f_{rel} - 1)} & \text{if } 0 \leq f_{rel} \leq 1 \\ f_{rel} + (1-V_{el} V_{sh}(f_{rel} - 1)) & \text{if } 1 \leq f_{rel} \leq V_{ml} \end{cases}
\]

(24)

where,

\[
f_{rel} = \frac{f_{SE}}{\tilde{v}_{CE}}
\]

(25)

**Huxley**

The Huxley model, replicated from Lemaire et al. (2016), consists of a contractile element, a series elastic element and a parallel element. \( F_{CE}, F_{SE} \) and \( F_{PE} \) are shown in eqs.(27-28), where \( c_{PE} \) and \( c_{SE} \) are constants that determine the shape of the function. In addition, the slack lengths, \( l_{PE}^0 \) and \( l_{SE}^0 \), are included, which represent the minimum length of the respective element at which force is generated.

\[
F_{CE} = C_{CE} \cdot (\tilde{l}_{CE} - 1)^4 + 1
\]

(26)

\[
F_{PE} = \begin{cases} c_{PE} (l_{PE} - l_{PE}^0)^2 & \text{if } l_{PE} \geq l_{PE}^0 \\ 0 & \text{otherwise} \end{cases}
\]

(27)

\[
F_{SE} = \begin{cases} c_{SE} (l_{SE} - l_{SE}^0)^2 & \text{if } l_{SE} \geq l_{SE}^0 \\ 0 & \text{otherwise} \end{cases}
\]

(28)
HILL2, where the pulse timestamp is converted into a square pulse with a on time of $t_{\text{pulse}}$. The pulse is converted to a excitation using the differential equation from HILL2. The final activation, $q(t)$, is dependent on a sigmoid relationship, see eq.(30), where gamma is equal to a first order differential equation with different time constants depending on activation and deactivation. The constants $n$ and $k$ are used to change the dependency of $q(t)$ on gamma.

$$q(t) = (1 + n'' \cdot \frac{\gamma}{\gamma + n''})$$

$$\gamma = \begin{cases} \frac{e(t) - \gamma(t)}{\tau_{\text{act}}} & \text{if } e \geq \gamma \\ \frac{e(t) - \gamma(t)}{\tau_{\text{deact}}} & \text{otherwise} \end{cases}$$

$$\dot{e} = \frac{e(t) - \text{stim}(t)}{\tau_{\text{ne}}}$$

Lemaire et al converted the original Huxley partial differential equation in a set of ODEs by method of discretization (Zahalak, 1981), resulting in a set of ODEs for the discretized crossbridge distribution shown in eqs.(32-33). The rate of change of the amount of crossbridges $n$ is dependent on the attachment rate, $f(x)$ and detachment rate $g(x)$, which depend on the current crossbridge length, $x$. The change in crossbridge length, $dx$ is equal to the relative sliding velocity between the actin and myosin filament, $u$, which is linearly dependent on $v_{CE}$ according to eq.(34).

$$\frac{dn}{dt} = f(x) - [f(x) + g(x)]n$$

$$\frac{dx}{dt} = \frac{s}{2h \cdot \dot{v}_{CE}} \cdot v_{CE}$$

$$f(x) = \begin{cases} f1 \cdot x & \text{if } 0 \leq x \leq h \\ 0 & \text{otherwise} \end{cases}$$

$$g(x) = \begin{cases} g2 \cdot x^2 + g2 & \text{if } x \leq 0 \\ g1 \cdot x & \text{if } 0 \leq x \leq h \\ g3 \cdot (x-h)^2 + g3 & \text{if } h \leq x \end{cases}$$

To include the force-length relationship and activation in the crossbridge model, Lemaire et al. (2016) scaled the number of crossbridges that can attach by the force-length relation and activation. In eqs.(37-38) the amount of crossbridges that can attach is dependent on the activation and length of contractile element.

$$\frac{dn}{dt} = q \cdot \dot{f} \cdot f(x) - [f(x) - [f(x) + g(x)]n$$

$$\frac{dx}{dt} = u \cdot \dot{1}$$

By calculating first and second order distribution moments (Zahalak, 1981) and substituting those in the differentiated force equations Lemaire et al rewrite the equations to obtain an equation for the contractile element velocity see eq.(39).

$$l_{CE} = \frac{k_{SE}(l_{CE}) \cdot l_{\text{int}} - l_{\text{ax}}}{I_{\text{h}} \cdot (s/(2h \cdot \dot{v}_{\text{CE}})) + k_{PE}(l_{PE} + k_{SE}(l_{SE}))}$$

### Parameter estimation

All parameters are determined by means of global simultaneous optimization, with the exception of sarcomere length, $s$, which was set at 2.43µm (Burkholder and Lieber, 2001), $f_{\text{max}}$ which is determined using TS0 and the duration of stimulation pulses, $t_{\text{pulse}}$, which is determined using TS1. Several optimization algorithms were compared and it was determined that for all models a surrogate optimization algorithm will be used, see appendix B. After the global optimization is finished the resulting parameters are used as a starting point for local optimisation using a interior-point algorithm. The surrogate optimization will be run with a time limit of 1 hour per second of experimental data, resulting in a maximal optimization time of 15 hours for the SOL experiment and 14.5 hours for the MG experiment. The measured MTC length and activation pulse times are used as an input for the models. The cost function of the optimization routine is derived by calculating the RMS of the difference between experimental and simulated force for 10000 linearly spaced points throughout every trial.

### Validation

To validate the different muscle models, three measures of performance will be compared between models. Firstly, the models will simulate the perturbation trials from TS2. The resulting RMS will give an indication of how well the muscle models are applicable to experiments for which they have not been optimized. Since trials for parameter estimation and validation differ, the RMS can not be compared between estimation and validation trials, however, the RMS can still be compared between different muscle models.

As a secondary validation step the SRS will be calculated for the muscle models and compared with the experimental data. The crossbridge stiffness will be determined by subtracting constant force from the 0.1mm amplitude perturbation trials. The resulting difference in force will be divided by the change in length to obtain the stiffness. It is assumed that due to the small difference in MTC length the influence of force-length and force-velocity dependencies will be negligible. During non-isometric contractions it is expected that the force due to SRS will not increase linearly with length due to dynamic behaviour of crossbridges. Therefore, it is chosen to illustrate the SRS during non-isometric contractions to visualize the effect of SRS on the magnitude of muscle force during a change in velocity. The force increase due to SRS will be obtained for a velocity change from 10mm/s to 40mm/s, from 40mm/s to 10mm/s, from -10mm/s to -40mm/s and from -40mm/s to -10mm/s.
The computation time will be used as the last measure of performance. The models with optimal parameters will be used to simulate a set of 27 active and 17 passive trials for SOL and 54 active and 54 passive trials for the MG. The resulting computation time will calculated as a fraction of the combined trial time. A result lower than one indicates that the model will be suitable for real-time applications.

**RESULTS**

**Environment**

Fig. 3 shows two typical trials that were used during the parameter optimization. Although constant length was applied during the trial shown in Fig. 3a, the resulting puller position was not constant during the trial. To identify the stiffness of the puller 26 data-points were analysed from 26 trials with constant force and MTC length, 11 from SOL and 15 from MG. Using regression analysis the linear relationship shown in eq.(40) was obtained, which has an R-squared value of 0.987.

\[
\Delta L_{\text{mtc}} = 5.3 \cdot 10^{-6} \cdot F_{\text{mtc}} - 4.4 \cdot 10^{-5} \quad (40)
\]

Although the correlation is quite high, this is only valid in static conditions with constant length and force. During dynamic trials the displacement was found to be dependent on position history, velocity and acceleration. Using linear regression on all data-points resulted in eq.(41) with R-squared value of 0.778.

\[
\Delta L_{\text{mtc}} = 5.2 \cdot 10^{-6} \cdot F_{\text{mtc}} - 2.5 \cdot 10^{-5} \quad (41)
\]

The maximal displacement reached was slightly below 1mm during a lengthening trial of MG when a force of 160 was reached. Although this is less than 10% of the displacement applied during the trial, it was chosen to minimize environmental effects during modeling by using measured MTC length as model input rather than puller position input.

**Parameter estimation**

Before optimization of the muscle model parameter values, two parameters had to be determined: \( F_{\text{isom}}^{\text{max}} \) and \( t_{\text{pulse}} \). \( F_{\text{isom}}^{\text{max}} \) was found to be 18 N for SOL, while \( F_{\text{isom}}^{\text{max}} \) of MG declined over time. In addition, the decline of \( F_{\text{isom}}^{\text{max}} \) of MG was dependent on muscle length, where \( F_{\text{isom}} \) declined faster at muscle lengths shorter than \( F_{\text{isom}} \) at optimum muscle length, see eq.(42). In eq.(42) \( T_{\text{nr}} \) represents the trial number, which started for the MG experiment at 193 and ended with 302, which resulted in a \( F_{\text{isom}}^{\text{max}} \) of 154.2 N and 56.3 N, respectively.

\[
F = \begin{cases} 3.3 \cdot 10^6 \cdot e^{(-0.054\cdot T_{\text{nr}})} + 55.6 & \text{if } L = L_{\text{opt}} \\ 1.4 \cdot 10^6 \cdot e^{(-0.16\cdot T_{\text{nr}})} + 81.4 & \text{if } L = L_{\text{opt}} - 4 \text{mm} \end{cases} \quad (42)
\]

Although, \( F_{\text{isom}}^{\text{max}} \) declined faster at muscle lengths shorter than optimum length, the data was insufficient to establish a continuous relationship between the muscle length and force decline. Therefore, \( F_{\text{isom}}^{\text{opt}} \) of MG for all muscle lengths was set as eq.(42) for \( L = L_{\text{opt}} \).

The secondary input of the model, stimulation, was recorded as time-stamp without duration. To convert the pulse train to a stimulation that can be used as input for HILL2 and HUXLEY the signal was given duration \( t_{\text{pulse}} \) that was determined by fitting maximal muscle force to pulse frequency. The frequency where \( F_{\text{isom}} = 0.95 \cdot F_{\text{isom}}^{\text{max}} \) was used to determine \( t_{\text{pulse}} \). The resulting \( t_{\text{pulse}} \) for SOL and MG were 0.029 s and 0.0195 s, respectively.

The rest of the model parameters were fitted to the muscle experimental data using TSI, see appendix A. Typical results of the optimization routine are shown for a tetanus trial and a lengthening trial in Fig. 3a and 3b, respectively. These two figures show the general trend between models: HILL1 outperforms the other two, yet HILL1 and HUXLEY are still able to show behaviour quite well. This is confirmed by calculating the RMS for the models. The RMS for all parameter estimation trials are shown in table 1. The RMS for obtaining the parameters for SOL is 2.4N, 1.7N and 2.5N for HILL1, HILL2 and Huxley, respectively. Although, the RMS of HILL1 seems rather high in contrast to HILL2, this is caused by the inclusion of passive trials and since HILL1 has no parallel element these trials contributed relatively much to the RMS. The main reason for the higher value of HUXLEY can be attributed to slower optimization routine of Huxley, which caused the algorithm to perform less function evaluations. It is assumed that with a longer optimization period the result can be improved. Similar results were obtained for the MG experiment, however the RMS values were higher: 12.6N, 9.2N and 9.4N for HILL1, HILL2 and HUXLEY, respectively. The higher RMS values are suspected to arise because of two reasons. Firstly, the forces of the MG were higher, thus relative differences between experimental and modeled force cause an absolute increase in RMS. Secondly, to compensate for the optimum force decline in MG the es-
Fig. 4. Typical examples of experimental and simulated data used for parameter validation: (a) shows the response to a pulse train stimulation input of 10 Hz at with a small perturbation around constant length and (b) shows the response to a triangular wave perturbation. The top plot shows the measured MTC length, the thick black bar between graphs indicates the period of stimulation and the bottom plot shows the MTC force as a function of time of the experimental data and the model output.

Table 1. RMS error of HILL1, HILL2 and HUXLEY during parameter estimation and validation for Soleus (SOL) and medial gastrocnemius (MG)

<table>
<thead>
<tr>
<th>model</th>
<th>RMS SOL estimation</th>
<th>validation</th>
<th>RMS MG estimation</th>
<th>validation</th>
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<td>HILL1</td>
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<td>12.6 N</td>
<td>7.3 N</td>
</tr>
<tr>
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<td>9.2 N</td>
<td>5.9 N</td>
</tr>
<tr>
<td>HUXLEY</td>
<td>2.6 N</td>
<td>2.6 N</td>
<td>9.6 N</td>
<td>7.3 N</td>
</tr>
</tbody>
</table>

Fig. 5. Typical trials used to determine SRS (obtained from MG): (a) was performed at optimum length and half activation and (b) was performed at optimum length and full activation. The top plots shows the length input, L_opt and the measured length, L_exp, over time. Note that the perturbation was applied around optimum length, L_0, and the difference between L_in and L_exp, comes form compliance in the puller. The middle plots shows the measured force of the perturbed muscle in blue and the red dotted line is the estimation of the muscle force in similar conditions without perturbation. The bottom plots shows the difference of the forces in the middle plots, which are used in combination with the measured length to determine the SRS. In both trials the muscle force was still increasing while the muscle was perturbed, which causes the increase of muscle force over time.

Validation

To validate the models, three separate measures where used: overall performance, SRS performance and optimization and computation time. Overall performance was calculated as the RMS for the validation trials, which consist of the trials shown in Figs. 4a and 4b, performed at three muscle lengths for full and half activation. The results are shown in table 1 in the columns with the validation header. The three models have similar RMS for SOL, however, for MG the RMS of HILL2 is significantly lower, which is in line with the better results during parameter estimation. The decrease in RMS between parameter estimation and validation can be contributed to the absence of lengthening trials in the validation trials. During lengthening trials the forces are greatest, which causes the relative contribution to RMS to be large as well.

To obtain SRS during isometric contraction Fig. 5a was analysed to obtain the force due to perturbation, \( F_{pert} \). This was done by subtracting an estimated force, \( F_{est} \), form the muscle force, see Fig. 5. The estimated force is based on other trials where the muscle was activated exactly the same at exactly the same length. By dividing \( \Delta F_{pert} \) by \( \Delta L_{exp} \) the SRS was obtained. This is possible due to the linear dependence of perturbation force on MTC length, see Fig. 5.

The resulting SRS for SOL and MG are shown in Fig. 6 for the experimental data, HILL1, HILL2 and HUXLEY for three muscle lengths and two activation levels per muscle. The SRS of the experimental data reduced in both MG and SOL when activation was halved. In SOL the stiffness at half activation was half the stiffness at full activation when \( L = L_{opt}-5 \text{mm} \) and \( L = L_{opt} \), and 75% the stiffness of full activation at \( L = L_{opt} + 5 \text{mm} \). However, in MG the stiffness was relatively high at half activation, when \( L = L_{opt}-5 \text{mm} \) and \( L = L_{opt} \) stiffness was around 80% the stiffness at full activation. When \( L = L_{opt}-5 \text{mm} \) the SRS was even 105% of stiffness at full activation, however, this could be a fluke caused due to the high standard deviation of the SRS at full activation. In both MG and SOL the stiffness increases with longer muscle lengths, with the exception of MG at full activation. However, the standard deviation is quite large and thus is not a reliable indicator. Furthermore, stiffness of MG is approximately twice as high as SOL, which was to be expected due to higher maximal isometric force. However, the difference is only a factor two, while \( \frac{F_{isom}}{F_{max}} \) is three times larger for MG compared to SOL.

All three models are not capable of generating the same SRS as in the experimental data and have significantly less stiffness. Furthermore, it was not possible to determine SRS in HUXLEY at optimum length and half activation for both SOL and MG, due to too much noise. Despite the shortcomings other observations can be made. For the soleus muscle SRS in HILL2 and HUXLEY...
declines with activation, similarly to the experimental data. HILL1 shows no clear decline of stiffness with activation.

To simulate the SRS during contraction an estimation of muscle force is used, see Fig. 7. This estimation was supposed to take into account force-length and force-velocity dependence. Although the force-length dependence can be obtained from the first period of Fig. 4b, the trials that would determine the force-velocity relation were unsuccessful. Therefore, the perturbation force is expected to not only be caused due to SRS, but also have a contribution of force-velocity dependence. The bottom plot of Fig. 7 shows a drop in force after the muscle velocity increases which is likely caused by the force-velocity dependence. Nevertheless, the result of the perturbation force is shown during isometric contraction at optimum length for SOL and MG are shown in Fig. 8 to give some insight in model behaviour. As expected the Hill-type models seem only to simulate relative low perturbation force, which would indicate that the SRS is not modelled accurately. There is however, a small perturbation force of similar shape to the experimental data with smaller magnitude, which is most likely an effect of the used input. The input in the models is the experimental MTC length output of the experimental data. This length input is dependant on the force generation of the muscle during the experiment and thus, introduces SRS in the models artificially. When comparing the magnitude of the SRS, HILL1 and HILL2 show only little variation in force compared to the experimental data. Unexpectedly, Huxley has similar perturbation force, which indicates that HUXLEY would also not capable of simulating SRS. However, Fig. 4b shows that the muscle force is not sensitive enough for extension and shortening, which would indicate that PE or SE stiffness is too low, which causes the perturbation force also to be low. In addition, Fig. 8 shows that the behaviour is not symmetrical, this could be caused by dynamic environmental effects, since the model is only corrected for the static compliance of the puller, dynamic effects are not compensated. The dynamic effects, the force-velocity dependence and measured length input make this method not a valid measure of performance. Therefore, it is not possible to make quantitative statements and qualitative statements on SRS during eccentric or concentric contraction.

Optimization and computation time
Since the optimization was only limited by a time constraint, the optimization times were equal for all three models. However, to determine the speed of optimization a comparison was made between the three models by identifying the time it took to reach the lowest cost function value. This showed that both Hill1 is the fastest optimization routine with an optimization time of 11949 seconds, followed by Hill2 with 26618 seconds and the slowest was HUXLEY with 53321 seconds. Furthermore, the optimization routine had 100 surrogate resets for HILL1, around 10 surrogate resets for HILL2 and 1 or 2 for HUXLEY. This indicates that it is unlikely for the HUXLEY model that its parameter set is close to optimal.

Running the optimization for all available trials with the optimized parameters resulted in a average computation time of 0.12 s, 7.94 s and 18.29 s for HILL1, HILL2 and HUXLEY, respectively. Moreover, the ratio between trial duration and computation time is 0.085, 5.42 and 18.3 for Hill1, Hill2 and HUXLEY, respectively.
DISCUSSION

The primary aim was to identify model parameters for two Hill-type muscle models and one Huxley-type muscle model. One Hill-type muscle model, HILL1, was obtained from Sandercock and Heckman (1997) and consisted of a contractile element (CE) and series elastic element (SE). The other Hill-type model, HILL2, was obtained from TUDelft, is based on Winters and Stark (1987) and consists of a CE, SE and parallel elastic element (PE). The Huxley-model was reproduced from Lemaire et al. (2016) and also consisted of a CE, SE and PE. The models were fitted to experimental data obtained from the soleus (SOL) and medial gastrocnemius (MG) muscle of a cat. All models were able to be fitted to the data. However, none was able to predict all the behaviour completely, when compared to work by Lemaire et al. (2016) it seems all these three models have higher RMS. Although this could be caused by differences in model architecture in the case of Hill-type models this can not be the case for the Huxley model since it is the same model. Most likely, this is caused due to several factors, of which four will be discussed further. Firstly, the models were fitted to a varying set of situations, with different activation levels, different muscle lengths and different velocities. Most likely, by optimizing for a specific type of trials, e.g. lengthening, the muscle model performance could be improved. Secondly, the activation dynamics and rest of the model were decoupled. Although this is widely used in literature, it is most likely not correct, as Lakatta and Jewell (1977) showed activation and length are coupled. Thirdly, the optimization routine was the same for every model, i.e. the same optimization trials and optimization algorithm were used. Since, optimization of HUXLEY was quite slow, the amount of trials was limited, which thus also limited the data for Hill-type model optimization. Although, this gives a fair comparison between models, it does not necessarily gives the best outcome for each individual model. Lastly, the amount of experiments was limited (n=2) and were performed on different cats and different muscles. Although this limits the ability to generalize, the performance of the models shows that it is possible to model the behaviour for the different types of muscle of cats.

To validate the models with parameters three measures of performance were created. Firstly, the performance was measured for overall behaviour, which was calculated as the RMS for trials for which they had not been optimized. These trials were selected to measure overall performance as slow and fast perturbations were applied with full and half activation at three different muscle lengths. The results in table 1, show similar behaviour between HILL1 and HUXLEY, while HILL2 has a lower RMS value (5.9N vs 7.3N). This indicates that for general behaviour HILL2 is the most suited. Similar to parameter estimation it seems that parameter tuning quite a lot of performance could have been gained by Huxley, but this would involve manual calibration and optimization.

The second measure of performance was the ability of the muscle models to simulate short-range stiffness (SRS). For the experimental data, the increase in force was found to be linear for perturbations with 0.1mm amplitude and frequency of 20 Hz around a constant length in the experimental data. The SRS was obtained by dividing the linear force increase by the measured linear length difference. However, the estimation of the SRS had quite a large variance due to...
the limited trials to determine SRS. Due to limited time during the experiment every trial was performed only once. Ideally, the small perturbations would be repeated over multiple trials to give a more reliable estimate. In addition, SOL did not reach maximal force before perturbations were applied, presumably due to a high activation time constant. As a consequence extrapolating experimental data was necessary. Nevertheless, the method of estimating the stiffness proved useful and gave an indication of SRS and showed the difference between the SOL and MG; MG generated more force and had a higher stiffness. This was to be expected since slow type muscle fibers often have a lower, but more constant force. The difference in relative magnitude of SRS between SOL and MG was significantly lower than the relative difference in optimum muscle force, as was also reported by Cui et al. (2007). The simulated forces due to SRS were also linear which made the calculation of SRS possible. However, the magnitude of the resulting SRS of all three models was significantly lower and thus it appears that none of the models are capable of modelling SRS. Although, this was to be expected of the Hill-type models, it was unexpected of the Huxley-type model. The most likely explanation can be found in a too low stiffness constant for SE or PE of the model, resulting less force generation under extension, which is observed in Figs. 3b and 4b. Other effect which may have caused the lack of perturbation force are sub-optimal model parameters, a low amount of data points, environmental effects and fatigue. An effort to illustrate SRS during muscle velocity changes from 10mm/s to 40mm/s, 40mm/s to 10mm/s, -10mm/s to -40mm/s and -40mm/s to -10mm/s proved unsuccessful and hence does not provide any useful information on the performance of the models.

The last measure of performance was the optimization time and computation time of the models to investigate if they have merit in real-time applications. During optimization of the models differences in model architecture affected the optimisation time. HILL1, was the simplest and thus the fastest, HILL2, was slower by a factor of 2.3 and HUXLEY was the most complicated and proved the slowest to optimize, using almost the maximum optimization time of 54000 seconds to reach its optimal value. However, all models were able to get reasonable results within the maximum optimization time. However, the slower optimization meant less function evaluations and surrogate resets could be made. Slower function evaluations causes the optimization routine to take a long time to find the optimum function value given the current surrogate function. Less surrogate resets, decreases the amount of times the optimization routine restarts itself with different random starting points, thus decreasing the possible paths the optimization algorithm can take through the solution manifold. This has as a result that the chance of ending in a local minima instead of a global minima is increased. However, once a set of parameters was obtained all three muscle models could model behaviour within reasonable time, but only HILL1 was able to simulate the data faster than the runtime of the trials. Thus, HILL1 is the only one of the three models that were tested that is suitable to be used in real-time applications.

Conclusion
The primary aim was to measure force output of cat soleus medial gastrocnemius muscle during varying trials and model this behaviour with two Hill-type models and one Huxley-type muscle model. This was successful, all three models were able to simulate behaviour consisting of pulse trains, lengthening and shortening trials. As the secondary aim, the models were validated by testing three types of performance, the ability to simulate general behaviour, the ability to simulate short-range stiffness (SRS) and the optimization and computation time of the model. To verify general behaviour the models were used to simulate trials for which they had not been optimized, which succeeded. For the secondary validation step a method was developed to determine SRS during isometric contraction and a method was developed to illustrate SRS during non-isometric contraction. The latter method proved unsuitable due to high levels of noise and uncertainty and thus was not used as a performance measure. The SRS during isometric contraction proved useful and indicated that none of the models were able to predict SRS. Although this was expected from Hill-type muscle models, this was unexpected for the Huxley model. However, this could be caused by the low amount of experiments, low amount of repetition in trials and long optimization time. It is expected that with longer optimization time Huxley is able to perform better. Improvement with Hill-type models is less likely due to the high amount of starting points of the surrogate optimization algorithm. On the other hand, Hill-type models performed much faster and as expected performed the simplest Hill-model the fastest. This was also the only model that simulated the experiments faster than the experiment duration, thus making it eligible for use in real-time applications. The models with optimized parameters indicate that the Huxley-type muscle model as it is now can be used to model similar behaviour as Hill-type muscle models, but is more difficult to optimize. Moreover, the more complicated Hill-model has a better performance and lower RMS during large and slow movements with shorter computation time. However, none of the models are capable of modelling SRS and the Huxley type muscle model has the highest margin of improvement since the current optimization method is limited by time constraint, which effects the Huxley model the most.

References
Chumanov, E.S., B.C. Heiderscheit, and D.G. Telen (2011). “Hamstring Muscle stiff-
Modelling short range stiffness • May 2019 • Thijs Franzen

don Dynamics during Stance and Swing Phases of High Speed Running”. In: Medicine & Science in Sports & Exercise 43.3, pp. 525–532.
A. Experiment protocol

Experimental trials
In this appendix the experiments are described to characterize model behaviour as well as to verify it. Before the set of optimization trials will be performed, a set of trials will be performed to find the force-length relationship and determine the position of the puller where \( l_{ce} = L_{ce}^{opt} \) and the resulting maximal isometric force \( F_{max}^{isom} \). These trials consists of measuring force during full activation at different muscle lengths. To start these trials, first the muscle will be brought under the minimal tension and simulated at 100Hz. After 60 seconds the length is shortened 2mm and activated again, this is repeated until \( F_{isom} = 0.5 \cdot F_{max}^{isom} \). Sequentially the puller position will be increased 2mm, thus lengthening the muscle before activating it again. This process is repeated until the \( F_{isom} = 0.5 \cdot F_{max}^{isom} \) on the descending slope of the force-length relationship. Afterwards the experiment is repeated around \( l_{ce} = L_{ce}^{opt} \) with steps of 0.2mm, to find optimum length.

Optimization, TS1
Since optimization time of the muscle models increases linearly with the amount of models, it is beneficial to find the minimum amount of different trials that include the most aspects of the models. Firstly, it is important to model the activation, which can be done by stimulating the muscle with different frequencies. Since the activation is decoupled from other equations in both types of models, these trials are performed at optimum length, where active force is largest. Both muscles are stimulated with a pulse train of 10Hz, 20Hz, 40Hz and 100Hz, see figures 9a-9d. To determining SE and PE parameter values, a passive lengthening trial is included. During this trial the muscle is increased with 0.5mm length every 0.1 seconds for a total of 1 seconds, see figure 9e. However, this by itself is not enough to characterize the SE ad PE elements. In the case of HILL2, during a purely passive lengthening \( F_{CE} = 0 \) and the remaining elements are in parallel. As a result the force is equal to the sum of the individual elements, therefore, there are a infinite solutions where \( F_{SE} = F_{exp} - F_{PE} \). In HUXLEY this causes a similar problem, during passive trials the SE and PE act in series and thus have equal force. By optimizing for a purely passive trial this would mean that SE and PE would obtain similar parameters, which is highly unlikely to be right. To find the right parameters the contractile elements should also be active. Therefore, trials are included where the muscle is activated at different lengths. Lastly, trials have to be included to determine the force-velocity relation in the Hill-type models and the rate parameters in the Huxley-type models. To do so 2 lengthening trials are used and 2 shortening trials, see figures 9f-9i.

Validation, TS2
To validate the model parameters two types of trials are performed at 3 lengths and two activation levels. The first set of trials consists of a isometric contraction with a triangular perturbation with amplitude of 0.1mm and frequency of 20 Hz, see figures 10a-10c. The second set of trials will start as an isometric contraction, followed by a triangular perturbation with an amplitude of 1 mm and frequency of 2.5 Hz, see figures 10d-10f. All trials will be repeated with half activation, see figures 10g-10l.
Fig. 9. Trials used to optimized model parameters. The blue striped line is the puller position input, the red line is the experimental output. The black line indicates muscle stimulation $q$. 

Fig. 10. Trials used to validate the models. In (a)-(f) the trials are shown with full activation and in figures (g)-(i), the trials with half activation are shown. The left figures have a start length of $l_{opt} - 5\text{mm}$, the figures in the middle start at $l_{opt}$ and the right figures start with $l_{mtc} = l_{opt} - 5\text{mm}$. Figures (a)-(c) and (g)-(i) show trial with a $0.1\text{mm}$ amplitude perturbation during an isometric contraction. Figures (d)-(f) and (j)-(i) show the trials with a triangular wave perturbation of $2.5\text{Hz}$ and $1\text{mm}$ amplitude. The blue line, red line and black line represent desired puller position, actual puller position and activation, respectively.
B. Optimization Routines

Choosing an Algorithm
To obtain the optimal values for the parameters muscle models an optimization algorithm is used. The models consists of several characteristics which should be taken into account when choosing an optimization algorithm.

1. The models are nonlinear
2. Activation input is noncontinuous (0 or 1)
3. The cost functions are continuous when no errors occur
4. The cost functions are discontinuous when an error occurs
5. The Huxley model consists of more than a 1000 ODEs (slow)
6. The Hill-type models consists of upto three ODEs
7. The model parameters are bound and continuous
8. There are no constraints
9. There are many local minima in every models solution space

\[
\min \text{ MuscleModel}(Par)
\]

\[
\text{Subject to: } Par X \subset \mathbb{R}
\]

\[
(Par \leq Par \leq Par)
\]

\[
(Par \leq Par \leq Par)
\]

The focus is on optimizing the model rather than writing an algorithm, hence the optimization algorithm is chosen from the pre-programmed Matlab optimization algorithms. Four different optimization routines are used: Global Search, Multistart, Genetic Algorithm and Surrogate optimization.

Global Search
The global search algorithm is a global solver that looks for the global optimum by using a local solver at each iteration. The local solver uses the start point and end point of the optimization to estimate the solution space around the local minima, called a basin. The global search algorithm is able to escape the local basin by accepting a set of parameters that results in a worse function value. Although, the global optimization routine can not be run in parallel, the local optimization routine can.

Multistart
Multi start is different from the Global search algorithm since it does not have the ability to search for points outside the current basin. However, to compensate the multi start algorithm used multiple starting points from which a local solver is used. Consequently, the success of the multi-start solver lies in the complexity of the problem and the amount of starting points. If the amount of starting points is lower than the amount of local minima, the multistart solver will not be able to evaluate all local minima. The larger the difference between the amount of local minima and staring points the larger the risk of not finding the optimal solution. In addition, two or more starting points can lie in the same basin, thus increasing the amount of starting points necessary.

Genetic Algorithm
The genetic algorithm looks for the optimum value by emulating evolutionary behaviour. The algorithm evaluates during one generation a sets of different parameter values called a population. After a generation is completed, the algorithm constructs a new population based on the previous population. The new population will be constructed as the sum of three sets. The first part consists of the most fit parameter sets of the previous generation. The second part consists of crossover sets between parameter sets, analogous to parents passing down genes to children. The last part consists of mutated sets, parameter sets where individual parameters are changed according to a Gaussian distribution function.
Surrogate optimization

Surrogate optimization consists of two phases. During the first phase a random set of parameters sets is evaluated. The function values are then used to create a surrogate function to estimate the candidates where local and global minima are the most likely to occur. During the second phase the candidates are evaluated. The function values of the candidates are then used to update the surrogate function, which will in turn create new candidates. If all candidates are expected to have a function value less than than the optimum value, the surrogate will be reset and phase 1 will start again with a different random sets of parameters.

Local solver

Both the Multistart and Globalsearch algorithm require a local solver. Since the problem is bound, `fmincon` was used, as this can handle constraints and bounds. However, since the optimization problems does not have equality and inequality constraints, the problem can be considered large scale. Thus, the interior-point algorithm was used in the local solver as this algorithm is the only algorithm that can solve a large-scale problem without a provided gradient.

Optimization set-up

Every model is optimized for the optimization trial set of the Soleus experiment. The default settings of each optimization routine are used, in addition with a time constraint of 12 hours (43200 seconds). The computer used for comparison of HILL1 and HUXLEY is shown below in table 2 and the computer used for comparison of HILL2 is shown in table 3. Parallel processes were enabled for all functions, but limited to 6 logic cores.

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Results

The results of each optimization are shown in table 4. The fastest optimization routine in all three cases is the surrogate optimization method. It is observed that surrogate optimization in all three models is the fastest, while the genetic algorithm has the best results. For all three models the multi-start and global-search algorithm were stopped because the maximum time was reached. The surrogate optimization on the other hand finished optimization with the standard settings within the time limit of 12 hours. The genetic algorithm also reached the maximal time for the Hill2 and HULXLEY model. The optimization of HILL1 took approximately 8 hours and 15 minutes.

Discussion

Form the results it becomes quite clear that multi-start and global search algorithm are unfeasible, the genetic algorithm has the best results and the surrogate optimization is the fastest. As mentioned before, the reason multi-start performed poorly can be explained by the randomization of starting points and the lack of ability to search outside the basins surrounding the starting points. It is apparent that all three models have a too large amount of local minima for the solver get proper results. The global algorithm has the same difficulty and is
Table 4. Comparison of final function values and optimization times for different optimization algorithms. These values are generated by optimizing the muscle models to the optimization trial set of the SOL experiment.

<table>
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<td>2.4838</td>
<td>43200</td>
<td>2.186</td>
<td>43200</td>
<td>2.3678</td>
<td>29496</td>
</tr>
</tbody>
</table>

dependent on the initial starting point. In addition, the solvers global optimization routine was not able to run in parallel, causing the algorithm the severely slow down, leading to poorer results. The fast optimization time of the surrogate optimization routine can be explained by the fact that the least amount of function evaluations are used. In the default settings the amount of function evaluations is determined as 50 times the amount of variables used, resulting in either 650 (Hill) or 700 function evaluations (Huxley). In contrast the genetic algorithm, which uses a population size of 200 function evaluations for one generation. In addition, the maximum amount of generations is 100 times the amount of variables and the maximum amount of stall generations is 50. Even if the optimum is reached quite quickly, within 50 generations the amount function evaluations would be around 10000. Nevertheless, the genetic algorithm leads to better results with standard settings. However, to see if the surrogate optimization could perform as well as the genetic algorithm the surrogate optimization was repeated with no limit on function evaluations. It was found that after 43200 seconds the function value was equal to 2.1434, even better than the genetic algorithm, albeit slightly. Although, the genetic algorithm can be adjusted and optimized to be better suited for the scale of this particular problem, the difference in function evaluations is too large. It is unlikely that much better results will be obtained within the same time period. Therefore, it is decided that all three muscle models will be optimized using the surrogate optimization algorithm.

C. results
The resulting parameters after the optimization algorithm are shown in table 5-7. The resulting plots and trials of TS1 and TS2 are shown in Figs. 11a-14l.

Table 5. The optimal parameter set of parameters for the HILL1 model, determined by global parameter optimization using a surrogate optimization algorithm

<table>
<thead>
<tr>
<th>HILL1</th>
<th>L_opt</th>
<th>W</th>
<th>a_h</th>
<th>b_h</th>
<th>a_m</th>
<th>b_m</th>
<th>k</th>
<th>a_amprel</th>
<th>a_Kis</th>
<th>a_Kit</th>
<th>a_Kii</th>
<th>a_ljst</th>
<th>t_delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOL</td>
<td>108</td>
<td>77.8</td>
<td>1.13</td>
<td>93.7</td>
<td>-0.015</td>
<td>36.8</td>
<td>0.103</td>
<td>0.512</td>
<td>66.3</td>
<td>261.0</td>
<td>10.87</td>
<td>0.290</td>
<td>0.060</td>
</tr>
<tr>
<td>MG</td>
<td>77.8</td>
<td>75.2</td>
<td>1</td>
<td>100.0</td>
<td>-0.0089</td>
<td>9.71</td>
<td>0.1</td>
<td>0.200</td>
<td>129.6</td>
<td>631.2</td>
<td>10.13</td>
<td>0.105</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

Table 6. The optimal parameter set of parameters for the HILL2 model, determined by global parameter optimization using a surrogate optimization algorithm

<table>
<thead>
<tr>
<th>HILL2</th>
<th>τ_ne</th>
<th>τ_act</th>
<th>τ_deact</th>
<th>L_cosh</th>
<th>S_Esh</th>
<th>S_Exml</th>
<th>P_Esh</th>
<th>P_Exml</th>
<th>mvvm</th>
<th>mver</th>
<th>mvml</th>
<th>mvsh</th>
<th>vmvsh</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOL</td>
<td>0.0031</td>
<td>0.080</td>
<td>0.11</td>
<td>0.71</td>
<td>1.50</td>
<td>0.24</td>
<td>3.50</td>
<td>0.16</td>
<td>5.27</td>
<td>0.77</td>
<td>3.13</td>
<td>0.63</td>
<td>0.40</td>
</tr>
<tr>
<td>MG</td>
<td>0.0030</td>
<td>0.036</td>
<td>0.10</td>
<td>0.80</td>
<td>0.71</td>
<td>0.10</td>
<td>1.50</td>
<td>0.24</td>
<td>4.25</td>
<td>0.014</td>
<td>2.16</td>
<td>0.46</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Table 7. The optimal parameter set of parameters for the Huxley model, determined by global parameter optimization using a surrogate optimization algorithm

<table>
<thead>
<tr>
<th>HUXLEY</th>
<th>h</th>
<th>k</th>
<th>width</th>
<th>τ_ne</th>
<th>τ_act</th>
<th>τ_deact</th>
<th>l_PH</th>
<th>l_Pe</th>
<th>l_sc</th>
<th>ε_sc</th>
<th>ε_se</th>
<th>ε_g1</th>
<th>f1</th>
<th>g2</th>
<th>g3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOL</td>
<td>0.81·10^{-8}</td>
<td>0.56</td>
<td>0.51</td>
<td>0.075</td>
<td>0.145</td>
<td>0.0094</td>
<td>0.094</td>
<td>0.074</td>
<td>0.014</td>
<td>1.175</td>
<td>2.99</td>
<td>97.79</td>
<td>124.8</td>
<td>477.7</td>
<td>100.0</td>
</tr>
<tr>
<td>MG</td>
<td>1.79·10^{-8}</td>
<td>0.55</td>
<td>0.53</td>
<td>0.063</td>
<td>0.175</td>
<td>0.0052</td>
<td>0.085</td>
<td>0.040</td>
<td>0.027</td>
<td>0.100</td>
<td>0.98</td>
<td>284.95</td>
<td>953.0</td>
<td>998.3</td>
<td>220.5</td>
</tr>
</tbody>
</table>
Fig. 11. SOL Optimization trials (TS1)
Fig. 12. MG Optimization trials (TS1)
Fig. 13. SOL validation trials (TS2)
Fig. 14. MG validation trials (TS2)
D. Determining Short Range Stiffness

Isometric contraction
To identify short-range stiffness (SRS) during isometric contractions the muscle was first activated after which a triangular wave perturbation was applied with a frequency of 20 Hz and an amplitude of 0.2mm. So isolate the effects due to perturbation another trial was performed at the same muscle length and activation level without the perturbation. Since the maximal isometric force, $F_{\text{isom}}^{\text{max}}$, changes during the MG experiment the unperturbed force is scaled to match perturbed force. The force due to perturbation was taken as the difference between the perturbed and unperturbed trial, see figure 15b. Sequentially, the stiffness for each half period was identified, see figure 15a and the resulting stiffness was taken as the arithmetic and as a measure of accuracy the standard deviation was calculated using a students T-distribution function.

![Fig. 15. Force due to triangular wave perturbation of 20Hz and 0.1mm amplitude during isometric contraction, for (a) the soleus muscle and (b) the medial gastrocnemius.](image)

Determining stiffness
Eccentric and concentric contraction
To illustrate the short-range stiffness during eccentric and concentric contractions, the validation trials with 2.5 Hz perturbation will be analysed. Firstly, a tetanus is estimated from fully activated trials with the same muscle length. To fit the estimate to the SRS trial the tetanus is scaled to fit the SRS trial. Sequentially force of the tetanus trial is subtracted from the SRS trial. At this point the force due to perturbation is left. However, the change is force is not only due to SRS. In addition to SRS, the length of the muscle also play an important role. The account for this the first part of the perturbation is used to account for the change due to the change in length. The velocity also plays a role, however, the data was not sufficient to estimate the change in force due to the change in velocity. Although this introduces error in the model and makes the results not quantitatively valid, the illustration can still give insight in overall behaviour.