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Parameter estimation of the Huxley cross-bridge muscle model in humans

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***Abstract*—The Huxley model has the potential to provide more accurate muscle dynamics while affording a physiological interpretation at cross-bridge level. By perturbing the wrist at different velocities and initial force levels, reliable Huxley model parameters were estimated in humans in vivo using a Huxley muscle-tendon complex. We conclude that these estimates may be used to investigate and monitor changes in microscopic elements of muscle functioning from experiments at joint level.**

I. Introduction

MUSCULOSKELETAL models are increasingly used in biomechanical analysis. Many experiments at both joint level as well as endpoint level rely on stiffness and damping properties of muscles to describe and investigate questions into motor control. These properties ultimately depend on how the muscle is modeled, and it is therefore essential to have correct muscle models. Currently, most studies use the ubiquitous Hill muscle model [1] The Hill model is computationally fast and easy to implement. However, it descriptive in nature and therefore lacks a clear physiological interpretation of the underlying contractile process. In addition, the Hill-model fails to describe the stiffness and damping properties correctly under several conditions [2, 3], most notably, fast eccentric contractions [4]. Moreover, the Hill model does not account for short-range stiffness (SRS), the property of muscle tissue undergoing eccentric contraction exhibiting an initial high level of stiffness followed by a marked drop in stiffness when subjected to further elongation [5, 6]. It is thought that SRS provide joint stabilization before reflexive or conscious control is possible.

To address these issues, we propose the Huxley cross-bridge model [7], which is based on the binding and unbinding of the microscopic protein filaments that are ultimately responsible for muscle contraction.

The Huxley model affords an interpretation of stiffness and damping of muscle through the cross-bridge cycle. The binding and unbinding of cross-bridges is explicitly modeled and stiffness is readily available through the population of bound cross-bridges. Indeed, the Huxley model models each cross-bridge as a detachable linear spring and muscle stiffness is the combined effect of all cross-bridges together.

However, Huxley model parameters for humans are currently unknown. Although some attempts have been made to identify Huxley model parameters, most research has been confined to *in vitro* animal studies (see e.g. [4]). For human research, *in vivo* estimation is required, which has remained problematic as the Huxley model only models the contractile element.

In this paper, we propose a method of identifying Huxley model parameters based on experimental data at joint level. To this end, we performed short and fast muscle stretches on the wrist flexors and optimized the Huxley model parameters to fit resulting force responses. Dependency of the parameters on force and velocity was investigated.

In a previous study [8], we estimated parameters based on a simplified Huxley model without a tendon. Here, for an accurate physiological representation, the Huxley model is embedded into a muscle-tendon model [9]. The Huxley model was rewritten as a non-linear first-order state space model that includes length-dependent pennation angle, activation dynamics, series- and elastic elements, and a force-length relationship. As such, current efforts describe the state of the art regarding Huxley model parameter estimation in humans. If Huxley model parameters can indeed be estimated correctly, the use of the Huxley model affords the study of binding and unbinding properties of cross-bridge populations *in vivo* in human, and may provide a better description of joint stiffness and damping. In this paper, we evaluate the accuracy of the model describing force responses during fast eccentric contractions around the wrist joint and attempt to quantify SRS for the Huxley model.

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II. METHODS AND MATERIALS

A. Experimental design

Eight healthy subjects (age 25±4 years, 4 males) participated in the experiment after signing an informed consent form. The study was approved by the local ethics committee. Subjects were seated upright with their right arm fixated at the elbow and wrist (Fig. 1). Ramp-and-hold (0.15 rad) angular displacements of the wrist joint were imposed from the neutral position at 5 different speeds (0.65, 1.30, 1.95, 2.60, and 3.25 rad/s) and for 3 initial flexion torques (0.9, 1.5, and 2.1 Nm) yielding a total of 15 conditions. Subjects were instructed to relax their wrist extensors to eliminate co-contraction. Visual feedback of extensor muscle activity (measured by electromyograms) was provided to ensure that wrist extensors were indeed relaxed. The perturbation was given when subjects provided a stable initial torque level lasting 0.5 s (see also [6] for more details). Each condition was repeated 3 times yielding 45 trials for each subject; initial torque level and perturbation velocity were counterbalanced.

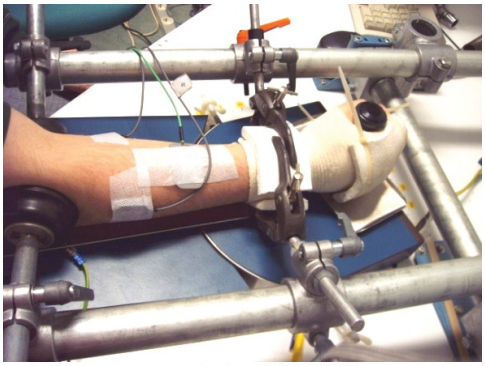

Fig. 1. Experimental setup. The hand and distal part of the lower arm are fixated. A robotic manipulator provides short angular deviations around the wrist.

B. Model

The total model consisted of two mass-spring-dampers describing the dynamics of the wrist perturbator and those of the hand and tissue in series with a muscle-tendon complex (Fig. 2). The perturbator parameters were known. The hand-handle interaction was modeled by a spring-damper system and its parameters estimated along with the Huxley model parameters. Parameter optimization is discussed in section III. DATA ANALYSIS.

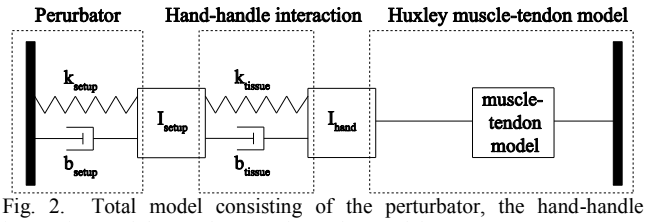

Fig. 2. Total model consisting of the perturbator, the hand-handle interaction, and the Huxley muscle-tendon model.

Tendon dynamics were taken from Thelen [10], but other tendons (e.g., [11]) can also be used. Perturbator properties were known (mass: 0.0015 kg, stiffness: 0.14 N/m, and damping: 2570 Ns/m). Tendon parameters for the model by Thelen [10] consisted of a shape factor (2.9), strain at maximal isometric force (1%), and the normalized length indicating the transition from non-linear to linear force-length behavior (0.33). Parallel elasticity was omitted as the angular displacement of the wrist was only 0.15 rad starting from the neutral wrist position.

The muscle-tendon complex was modeled using a Huxley cross-bridge model in series with a tendon. The classical two-stage cross-bridge model as described by [7] was used with an extension by Zahalak [12] (see below).

Many muscles in the wrist contribute to wrist flexion. These muscles (and their tendons) were modeled by a single lumped muscle-tendon model. Using existing parameters [13, 14], optimal CE length and tendon lengths were averaged and maximal isometric force levels (F_{max}) summed wrist flexor muscles. The Huxley cross-bridge model is based on a first-order partial differential equation based describing the population of bound cross-bridges. The cross-bridges cycle of binding and unbinding is governed by the binding rate function $f(x)$ and unbinding rate function $g(x)$. The contractile element is essentially modeled as a single sarcomere with as input the stretch velocity v_m:

$$n_t + v_m n_x = f(x) + \big(f(x) + g(x)\big) n$$

where

$$f(x) = \begin{cases} 0 & x < 0 \\ f_1 \cdot \dfrac{x}{h} & \text{for} \quad x \le 0 \le h, \\ 0 & x > h \end{cases}$$

$$g(x) = \begin{cases} g_2 & x < 0 \\ g_1 \cdot \dfrac{x}{h} & \text{for} \quad x \le 0 \le h \\ g_1 \cdot \dfrac{x}{h} + g_3 \cdot \left(\dfrac{x}{h} - 1\right) & x > h \end{cases}$$

The unbinding rate function was extended from the original formulation by introducing the parameter g_3 to account for the yielding effect [12]. The initial condition, $v_m = 0$, is given by:

$$n_0(x) = \begin{cases} \dfrac{f_1}{f_1 + g_1} & 0 \le x \le h \\ 0 & \text{otherwise} \end{cases}$$

The Huxley model has 5 parameters which govern the binding and unbinding of cross-bridges. The parameter h denotes the maximal bond length. As we only consider stretch, the parameter g_2 is unused. The optimization therefore included the 3 hand-handle interaction parameters (m_{hand}, k_{hand}, b_{hand}), which were held equal across conditions, and 4 Huxley model parameters (h, f_1, g_1, and g_3).

The addition of a tendon was implemented by relating the muscle velocity to the cross-bridge distribution $n(x,t)$, the muscle tendon velocity v_{MTC}, maximal isometric force $F_{\max}$, activation level a, and the tendon stiffness K_{SE}. This relationship is given by

$$v_m = \frac{v_{MTC} \cdot K_{SE} - F_{\max} \cdot a \cdot (I_f + I_H) \cdot \cos(\alpha)}{K_{SE} + F_{\max} \cdot a \cdot I_n \cdot \cos(\alpha)}$$

where the integrals I_n, I_f, and I_H are given by:

$$I_n = \int n(x,t)dx, \quad I_f = \int x \cdot f(x)dx,$$
$$I_H = -\int x \cdot \big(f(x) + g(x)\big) \cdot n(x,t)dx$$

Note that the pennation angle was set to zero and that muscle activation a and $F_{\max}$ were chosen as to match the initial torque level in each trial. No force-length relationship or parallel elastic (PE) component was used as the perturbations were small and the force-length relationship is flat around the neutral position. The experimental design ensured that the muscle activation level was constant for the duration of the trial.

III. Data Analysis

For each trial, the first 60 ms after perturbation onset was used to fit model parameters. This time frame was chosen to ensure that no reflex components were present. Data were smoothed using a Savitzky-Golay filter prior to parameter estimation. Huxley model parameters were optimized for each condition separately using a nonlinear least square optimization. Hand mass and tissue stiffness and damping were included in the optimization and assumed to be constant over conditions. Model parameter estimates for each subject and condition were averaged over the three repetitions.

IV. Results

For sake of completion, Table 2 contains the mean and standard deviations of the hand and tissue parameters. Huxley model parameter were grouped for each initial torque level and shown for each perturbation velocity. Model fits were evaluated using the variance accounted for (VAF) averaged over subjects. For the 15 conditions, the VAF was similar (96.8±1.2). Averaged model estimates are given in Fig. 3.

Model parameters h, g_1, increased, and f_1, and g_3 with decreased with initial torque level. There was no influence of perturbation velocity, only the lowest perturbation level deviated from the other levels for g_3 (see Fig. 4). Parameters were robust across subjects.

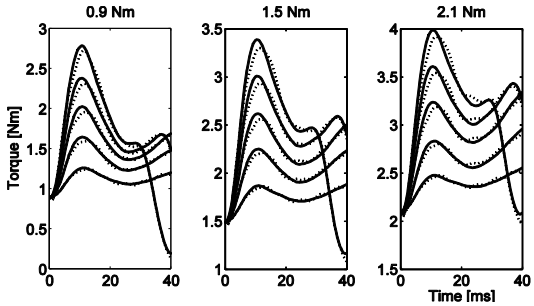

Fig. 3. Measured (solid) and estimated (dashed) wrist torques averaged over subjects. Model fits exhibited a high variance accounted for; at least 95% for all conditions.

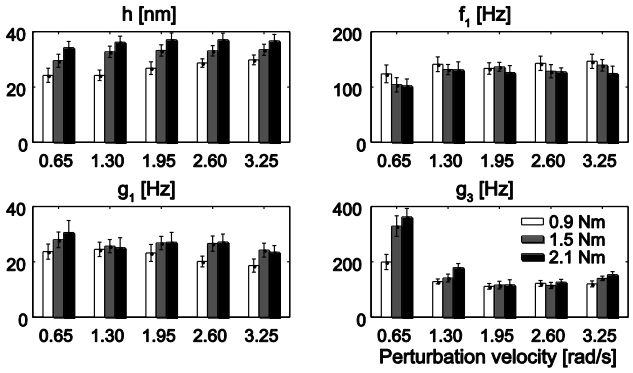

Fig. 4. Model parameter estimates; bond length *h*, binding rate parameter f_1, and unbinding rate parameters g_1 and g_3. Estimates were dependent on initial torque level as well as on perturbation speed. Error-bars represent the standard error of the mean.

TABLE 2
ESTIMATED HAND PARAMETERS

Parameter	Value
Hand mass (m_{hand})	0.0024 ± 0.0005 [kg]
Tissue stiffness (k_{tissue})	5.7401 ± 0.6378 [Ns/m]
Tissue damping (b_{tissue})	0.9256 ± 0.0625 [N/m]

V. Discussion

This paper demonstrated the estimation of Huxley model

parameters in humans *in vivo*. The proposed estimation technique is useful for studying the microscopic functioning of the contractile machinery of skeletal muscles and, as such, is a valuable tool for both fundamental and clinical research.

Using a Huxley muscle-tendon complex, we were able to robustly estimate model parameters for different muscle loads and stretch velocities. Moreover, model parameters were very consistent among subjects. Model parameters depended on initial torque level as well as perturbation velocity.

The dependency of model parameters on muscle velocity agrees with an earlier simulation study where a linear relationship for unbinding rate with velocity was demonstrated [15]. In addition, [4] found that estimates for the maximum bond length h differed for low and high contraction velocities. It is currently unclear why muscle velocity may have such a profound effects on cross-bridge kinetics and therefore requires further study.

The dependency of the model parameters on initial torque may be related to motor unit recruitment, where recruitment of smaller units precede the larger ones for increasing excitation [16]. Smaller motor units typically contain more slow-twitch fibers, and larger ones more fast-twitch fibers [17]. Studies suggest that fast and slow muscle fibers contain different types of myosin, one of two proteins directly involved in cross-bridge dynamics [18].

VI. Conclusion

Huxley model parameters can be reliably estimated from *in vivo* experiments at joint level. As such, the technique is important for multi-scale analysis relating macroscopic mechanical features on the joint level to underlying microscopic properties on the muscle level.

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