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A multivariate statistical strategy to adjust musculoskeletal models

Santiago Arroyave-Tobón^{a,*}, Guillaume Rao^a, Jean-Marc Linares^a

^a*Aix Marseille Univ, CNRS, ISM, Marseille, France*

Abstract

In musculoskeletal modelling, adjusting model parameters is challenging. This paper proposes a multivariate statistical methodology to adjust muscle force-generating parameters optimally. Dynamic residuals are minimized as muscle force-generating parameters are varied (maximal isometric force, optimal fiber length, tendon slack length and pennation angle). First, a sensitivity and a Pareto analyses are carried out in order to sort out and screen the set of parameters having the greatest influence regarding the dynamic residuals. These parameters are then used to create a response surface following a Design of Experiments (DoE) approach. Finally, this surface is used to determine the optimum levels of the design variables (muscle force-generating parameters). The proposed methodology is illustrated by the adjustment of a three-dimensional musculoskeletal model of a sheep forelimb. After adjustment, the reserve actuator values of the elbow and wrist joints were reduced, on average, by 18%, and 16%, respectively. These results demonstrate that the use of multivariate statistical strategies is an effective way to adjust model parameters optimally while reducing dynamic inconsistencies. This study constitutes a step towards a more robust methodology in musculoskeletal modelling, focusing on muscular parameter tuning.

Keywords: Musculoskeletal modelling, Force-generating parameters, Optimization, Multivariate, Response surface

1. Introduction

*Corresponding author: santiago.arroyave-tobon@univ-amu.fr

23 Musculoskeletal modelling allows estimating physical quantities that can be difficult to
24 measure (for instance muscle forces and joint reaction forces) or even studying what-if scenar-
25 ios. A major challenge in this field is to adjust model parameters reliably, namely geometric
26 parameters, segment inertial parameters and muscle parameters. Geometric parameters can
27 be determined by scaling procedures (from generic models [23]), optimization-based pro-
28 cedures (contact surfaces best-fit [20, 2]) or by functional movement analysis [31, 19, 32].
29 There exist several methods in the literature either to experimentally estimate [1, 9, 18] or
30 to scale inertial parameters from anatomical datasets [23, 30]. Muscle parameters are typ-
31 ically scaled from generic models [12, 34, 16] or estimated by functional approaches. Func-
32 tional approaches require isometric trials using isokinetic ergometers or experimental ones
33 [27, 15, 13], which can be expensive, prone to modeling and experimental errors and difficult
34 to apply when dealing with animals. Modenese *et al.* [25] proposed a numerical method
35 for estimating the optimal fiber length and tendons slack length of the muscle-tendon units
36 by optimizing the operating range of the muscles simultaneously. In that approach, muscle
37 contraction dynamics are not required to be solved, making the method fast to compute.
38 However, in this approach, each muscle is solved independently, hindering the possibility to
39 solve the whole optimization problem as a multivariate one (pennation angle, tendon slack
40 length, optimal fiber length, maximal isometric force).

41 The effect of the uncertainty of musculoskeletal parameters has been evaluated by means
42 of uncertainty propagation analysis [28, 29] and sensitivity analysis [4, 24, 11, 5]. These
43 studies reveal a high influence of the force-generating parameters (FGPs) in muscle force
44 prediction (MFP). However, these parameters (pennation angle, tendon slack length, optimal
45 fiber length, maximal isometric force) are difficult to measure or estimate [3, 25]; therefore,
46 the use of numerical methods could be further explored as an option to adjust them.

47 Using conventional optimization methods to adjust musculoskeletal models may become
48 extremely time consuming due to the large number of optimization variables together with

49 the complexity of the MFP process (nonlinearities). Additionally, conventional optimization
50 methods typically vary one parameter at a time, thus the interdependence of variables is not
51 considered. Multivariate statistical approaches, such as Design of Experiments (DoE), offer
52 means for understanding the contribution of individual factors of a process to determine
53 the optimal operating conditions at low computational cost. This methodology consists in
54 fitting a multidimensional surface to the response variables through sequential variations of
55 the design variables over a specific region of interest. The parameters defining the response
56 surface can be determined by a least-squares regression. This surface can then be used
57 to determine the optimum levels of the design variables regarding the response variables.
58 DoE and response surface methodologies have been used in biomechanics [22, 8] but, to the
59 knowledge of the authors, it has not been explored as a possibility to adjust musculoskeletal
60 models.

61 Consequently, the focus of this paper is on the adjustment of the FGPs of the muscles
62 using a multivariate statistical methodology based on the DoE approach. Two algorithms are
63 proposed in this work: one for screening the most influencing parameters, and a second aimed
64 at creating the response surface and determining the optimum levels of the design variables.
65 In the next section, the methodology to adjust FPGs is detailed. This methodology is
66 applied to a musculoskeletal model of a sheep forelimb. The results are presented in Section
67 3 and discussed in Section 4.

68 **2. Methods**

69 The methodology proposed in this paper to adjust FGPs of the muscles is depicted in
70 Figure 1. The methodology is based on three steps. The first step consists in screening the
71 parameters by means of sensitivity analysis to identify those having the greatest impact on
72 the performance of a given MFP. The performance of a simulation, as explained below, is
73 defined in function of the dynamic residuals (reserve actuators). The second step consists

Figure 1: Flow chart of the main steps of the proposed methodology to adjust musculoskeletal models. The methodology is based on three steps. The parameter screening step consists in computing the sensibility index S_k of the parameter P_k regarding the metric $\epsilon_{res}(t, \mathbf{P})$ (dynamic residuals). The response surface regression consist in fitting a multidimensional surface to the response variables by sequential variations of the influencing parameters. The model optimization step consists in finding the parameter values that minimizes the response variable (dynamic residuals).

74 in constructing a response surface by means of the DoE approach. This surface represents
 75 the response of the simulation in terms of dynamic residuals to the variation of the model
 76 FGPs. The third step consists on the FGPs adjustment, looking for the minimum value of
 77 the response surface. This corresponds to find the values of the FGPs that minimize the
 78 dynamic residuals. In the following sections, the performance metric chosen to evaluate a
 79 MFP is presented, and then the three steps of the adjustment methodology are detailed.

80 2.1. MFP performance metric

81 For a given MFP process, let $\tau_j(t)$ be the net joint torque of the j -th joint (with $j =$
 82 $1 : N_joints$). Due to dynamic inconsistencies, the model would not be able to follow the
 83 desired kinematics with muscle actuators alone at a given time instant t . In order to allow
 84 the simulation to run, it is a common practice (which is the case of OpenSim, for example)
 85 to include additional actuators at each joint of the model R_j to reach the net joint torque.
 86 These are non-physical actuators that absorb dynamics residuals of the simulation. These
 87 actuators are added to each joint to reach the joint net torque:

$$\tau_j(t) = R_j + \sum_{i=1}^{N_muscles} F_{0,i} r_{ij}(t) a_i(t) f(l_i(t)) g(v_i(t)) \cos(\phi_i(t)) \quad \forall j \in [1; N_joints] \quad (1)$$

88 where $F_{0,i}$ is the maximal isometric force of the i -th muscle (which is proportional to the
 89 physiological cross sectional area), r_{ij} is the moment arm of the i -th muscle about the j -th
 90 joint, $a_i(t)$ is the activation level (0 to 100%) of the i -th muscle at the time instant t , $f(l_i(t))$
 91 is the force-length related coefficient, $g(v_i(t))$ is the force-velocity related coefficient and ϕ_i

92 is the pennation angle.

93 For each time instant of the simulation, these residuals R_j should be null if the MFP
94 problem were perfectly solved. In consequence, it is beneficial to keep these values R_j at
95 minimum levels. For each time instant t , the sum of the squares of reserve actuators of all
96 joints of the model $\epsilon_{res}(t, \mathbf{P})$ has been chosen as the metric to evaluate the performance of
97 an MFP:

$$\epsilon_{res}(t, \mathbf{P}) = \sum_{j=1}^{N_joints} R_j^2 \quad (2)$$

98 where \mathbf{P} is the vector containing all the FGPs of the model. This metric is used in this
99 work to:

- 100 1. define the MFP sensitivity regarding variations in FGPs of the muscles,
- 101 2. define the cost function used for the adjustment of the model.

102 2.2. Parameter screening

103 As it would be very time-consuming to adjust the complete set of FGPs of a musculoskele-
104 tal model, we propose first, by means of a sensitivity analysis, to screen the parameters hav-
105 ing the greatest influence on the MFP performance. This process consists on quantifying the
106 effects of varying each parameter value on the simulation performance. This performance is
107 defined by means of the metric $\epsilon_{res}(t, \mathbf{P})$, as explained in the previous section. This process
108 is summarized in Algorithm 1.

Algorithm 1 Parameter screening

Require: Musculoskeletal model, kinematic data, external forces

Ensure: Parameter sensibility

```
1: for each muscle  $M_i$  (with  $i = 1 : N\_muscles$ ) of the model do
2:   for each parameter  $P_k$  (with  $k = 1 : d$ ) of  $M_i$  do
3:     for each increment step do
4:       Increment the value of  $P_k$ 
5:       Estimate muscle forces for time  $t = t_{start} : t_{end}$ 
6:       Get joint reserve values for time  $t = t_{start} : t_{end}$ 
7:       for ( $t = t_{start}; t < t_{end}; t = t + t_{step}$ ) do
8:         Compute the metric value  $\epsilon_{res}(t, \mathbf{P})$  (Eq. 2)
9:       end for
10:    end for
11:    for ( $t = t_{start}; t < t_{end}; t = t + t_{step}$ ) do
12:      Compute the numerical derivative  $\frac{\partial \epsilon_{res}(t, \mathbf{P})}{\partial P_k}$  (Eq. 3)
13:    end for
14:    Compute sensitivity index  $S_k$  (Eq. 4)
15:    Found the 20% of parameters that produce, at least, 80% of effects
16:  end for
17: end for
```

109 The number of sensitivities to calculate is equal to the number of parameters to consider
110 per muscle times the number of muscles in the model. Each sensitivity calculation requires
111 estimating as many muscle force solutions as the number of points considered for the numer-
112 ical differentiation. From a numerical point of view, using four points allows to smooth local
113 variations, improving the general estimate of the derivative value. In order to avoid this, we
114 used a four-point strategy (see Figure 2). The value of the k -th parameter of the model is
115 moved around its initial value P_k^* four times: $P_k^* - 2q_k$, $P_k^* - q_k$, $P_k^* + q_k$ and $P_k^* + 2q_k$. The
116 value of $2q_k$ corresponds to the variation coefficient and it has been chosen equal to 10%, as
117 in other works [35, 14].

118 From the results of the four simulations for each time instant t , the sensitivity of each
119 parameter P_k regarding the metric $\epsilon_{res}(t, \mathbf{P})$ can be estimated numerically using the four-
120 points central difference approximation:

$$\begin{aligned} \frac{\partial \epsilon_{res}(t, \mathbf{P})}{\partial P_k} &\approx -\frac{1}{12q_k} (8\epsilon_{res}(t, P_k^* - q_k) - 8\epsilon_{res}(t, P_k^* + q_k) \\ &\quad + \epsilon_{res}(t, P_k^* + 2q_k) - \epsilon_{res}(t, P_k^* - 2q_k)) \end{aligned} \quad (3)$$

121

Figure 2: Representation of the computation of $\partial \epsilon_{res}(t, \mathbf{P}) / \partial P_k$. At the left-hand side it is represented the evolution of the metric value $\epsilon_{res}(t, \mathbf{P})$ in function of the time t and the parameter value P_k . At the right-hand side, the sensitivity of $\epsilon_{res}(t, \mathbf{P})$ regarding variations on the P_k around a given value P_k^* is approximated by a four-point numerical derivative. The variation coefficient is $2q_k$.

122 As Eq. 3 is formulated for a given instant t , a set of sensitivities is obtained when
 123 considering all time instants from t_{start} to t_{end} of the simulation. From these values, a global
 124 sensitivity index is defined for the k -th parameter as follows:

$$S_k = \max \left(\frac{\partial \epsilon_{res}(t, \mathbf{P})}{\partial P_k} \right) - \min \left(\frac{\partial \epsilon_{res}(t, \mathbf{P})}{\partial P_k} \right), \quad \forall t \in [t_{start}; t_{end}] \quad (4)$$

125 In order to determine the set of FGPs having the greatest sensitivity, a Pareto heuristic
 126 (also known as the 80/20 rule) can be used. This heuristic, which is used in decision
 127 making, suggests that 20% of parameters produce 80% of the effects. In our case, these
 128 effects correspond to the cumulative sum of sensitivity factors. These FGPs are those that
 129 are going to be adjusted for reducing the dynamic inconsistencies of the computation, as
 130 explained in the next section.

131 2.3. Response surface regression and model optimization

132 The set of FGPs identified as significant after screening are those chosen for optimization.
 133 The cumulative sum of squared reserve actuators was chosen as the cost function to be
 134 minimized:

$$\begin{aligned}
& \text{Given } \mathbf{P} = [P_1, P_2, \dots, P_d] \\
& \text{minimize } C_{res}(\mathbf{P}) = \sum_{t=t_{start}}^{t_{end}} \epsilon_{res}(t, \mathbf{P}) \\
& \text{with } t = t + t_{step}
\end{aligned} \tag{5}$$

135 where t_{step} is the time frame of the experimental data.

136 The response surface methodology was used to perform this optimization. This method-
137 ology consists in generating an empirical mathematical model that relates some design vari-
138 ables with a response variable. A hypersurface is fitted to the response variable on a region
139 of interest by a systematic variation of the design variables. In our case, the design variables
140 (or factors) correspond to the model FGPs $\mathbf{P} = [P_1, P_2, \dots, P_d]$ and the response variable to
141 the dynamic residuals C_{res} . This surface is used to find the design variable values (FGPs)
142 that minimize the response variable (dynamic residuals). The definition of the response
143 surface and the optimization process are summarized in Algorithm 2 and explained below.

Algorithm 2 Parameter adjustment via response surface regression

Require: Musculoskeletal model, kinematic data,

Require: external forces, set of influencing FGPs

Ensure: Set of optimal FGP values

- 1: $d =$ get the number of influencing FGPs (from §2.2)
 - 2: Create the design matrix
 - 3: **for** $run = 1 : m$ **do**
 - 4: Modify the P_k value $\forall k \in [1 : d]$ according to the experiment design
 - 5: Estimate muscle forces for time $t = t_{start} : t_{end}$
 - 6: Get joint reserve values for time $t = t_{start} : t_{end}$
 - 7: **for** ($t = t_{start}; t < t_{end}; t = t + t_{step}$) **do**
 - 8: Compute the metric value $\epsilon_{res}(t, \mathbf{P})$ (Eq. 2)
 - 9: **end for**
 - 10: Compute the sum of the squares of reserves: $\mathbf{y}[run] = C_{res}(\mathbf{P})$ (Eq. 2.3)
 - 11: Compute the surface response coefficient vector $\hat{\mathbf{b}}$ (Eq. 9)
 - 12: Find $\mathbf{x}_{min} = [x_0, \dots, x_d]$ that minimizes $y(x_0, \dots, x_d)$
 - 13: Evaluate the predicted results by means of the SCB(\hat{y}) (Eqs. 13 and 14)
 - 14: Validate the predicted results
 - 15: **end for**
-

144 In the response surface methodology, a typically employed model is a second-order hy-
145 persurface $y(x_0, \dots, x_d) \in \mathbb{R}^d$:

$$y(x_0, \dots, x_d) = \sum_{k=0}^d \sum_{j=k}^d x_k x_j b_{kj} \quad (6)$$

146 where d corresponds to the number of FGPs chosen for the experiment after screening, b_{kj}
147 are the surface coefficients, $x_0 = 1$ and x_k is the normalized value of the parameter P_k (with
148 $k = 1 : d$).

149 The number of terms in Eq. 6 is defined by both the order of the surface (2 in our case)
150 and the dimension d of the space, and it is $n = C(d + 2, 2) = (d + 2)! / (2!d!)$. Hence, in
151 order to determine the n coefficients that define the surface, it is necessary to run at least n
152 experiments.

153 According to DoE methodology, more than n experiments are usually executed. For
154 the execution of these experiments, the values of the design variables (factor levels) are

155 systematically moved around an initial value. These initial values, which are assumed to be
 156 near to a locally optimal solution, define the central point of the experiment. The variation
 157 of the values of these parameters around the central point is defined by the design type.

158 For fitting a second-order model, a central composite design (CCD) type is a popular
 159 choice. This type of design defines the same number of levels for the different factors. For
 160 each factor, five levels are considered. Factor levels are normalized in such a way that their
 161 inputs were coded as $+1$, $+1/\sqrt{d}$, 0 , $-1/\sqrt{d}$ and -1 . A CCD can be constructed using a full or
 162 a fractional factorial design. Choosing a full or a fractional factorial design type depends on
 163 the number of factors to consider. This choice defines the number of experiments to perform
 164 and the fidelity (or the uncertainty) of the empirical model regarding the represented process
 165 (see [7] for more details). For a full factorial design, which is recommended when $d \leq 4$, the
 166 number of required runs is $m = 2^d + 2d + 1$. For $d > 4$, a half factorial design can be used
 167 (number of runs: $m = 2^{(d-1)} + 2d + 1$).

168 According to the design type and the number of factors, the design matrix can be ob-
 169 tained. This matrix provides a program for the m experiments by defining the normalized
 170 values of the x_k factors (with $k = 1 : d$) for each run. This matrix can be obtained, for
 171 example, using the Matlab (Mathworks Inc.) function *ccd*. From the execution of the
 172 m experiments, a set of m values of the response variable are obtained:

$$\begin{bmatrix} y_1 \\ \vdots \\ y_m \end{bmatrix} = \begin{bmatrix} 1 & x_{11} & \dots & x_{1n} \\ \vdots & \vdots & \ddots & \vdots \\ 1 & x_{m1} & \dots & x_{mn} \end{bmatrix} \begin{bmatrix} b_0 \\ \vdots \\ b_n \end{bmatrix} \quad (7)$$

173 In matrix form, Eq. 7 becomes:

$$\mathbf{y} = \mathbf{Xb} \quad (8)$$

174 where \mathbf{y} is the response vector ($m \times 1$), the matrix \mathbf{X} ($m \times n$) is called matrix of independent
175 variables and it is obtained from the design matrix and the vector \mathbf{b} ($n \times 1$) contains the
176 coefficients b_{kj} of the response surface. As \mathbf{X} is in general a non-square matrix ($m > n$), one
177 can compute an equivalent vector $\hat{\mathbf{b}}$ that best estimate of the surface response coefficients
178 using the pseudo-inverse method as follows:

$$\hat{\mathbf{b}} = (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{X}^T \mathbf{y} \quad (9)$$

179 From the calculated surface, a local minimum $y_{min} = C_{res}^{pre}$ can be predicted, which is
180 to search for a set of normalized parameter values $\mathbf{x}_{min} = [x_0, \dots, x_d]$ that minimizes the
181 response value $y(x_0, \dots, x_d)$. This is a nonlinear optimization that can be soled by using, for
182 example, the generalized reduced gradient method [21].

183 In order to asses the quality (or inaccuracy) of the fit of the surface regarding the ex-
184 perimental values can be assessed by means of the root mean square (RMS) of the residues
185 (Eq. 10). These residues are calculated as the difference between the experimental results
186 (\mathbf{y}) and the corresponding points on the response surface ($\mathbf{X}\hat{\mathbf{b}}$) :

$$E = \text{RMS}(\mathbf{y} - \mathbf{X}\hat{\mathbf{b}}) \quad (10)$$

187 The E value can also be used to calculate the statistical confidence boundary (SCB) (or
188 error bar) of a predicted value \hat{y} . This is based on classical uncertainty propagation method
189 as explained as follows (for more details refer to [6]).

190 In order to calculate the SCB value at a given point, it is required to start calculating
191 the covariance matrix of $\hat{\mathbf{b}}$ by the following expression:

$$\text{cov}(\hat{\mathbf{b}}) = (\mathbf{X}^T \mathbf{X})^{-1} E^2 \quad (11)$$

192 The deviation of the response surface at a given point \hat{y} can be evaluated by calculating the
 193 mean square error (MSE):

$$\text{MSE}(\hat{y}) = \mathbf{J} \text{cov}(\hat{\mathbf{b}}) \mathbf{J}^T \quad (12)$$

194 where \mathbf{J} is the Jacobian of the function $y = f(x_0, \dots, x_d)$ (Eq. 6) with respect to the b_{kj}
 195 coefficients. In other words, \mathbf{J} is the vector of the partial derivatives $\frac{\partial y}{\partial b_{kj}}$. Using equation
 196 12, the SCB of the surface at a given point \hat{y} can be calculated:

$$\text{SCB}(\hat{y}) = \hat{y} \pm k_n \sqrt{\text{MSE}(\hat{y})} \quad (13)$$

197 where k_n is calculated using a normal law distribution for a given two-sided confidence level.

198 Even if the response variable C_{res} is based on a squared value (Eqs. 2.3 and 2), the lower
 199 bound of the SBC of a given predicted value \hat{y} could be negative. In this case, the SBC
 200 value must be corrected using a folded normal distribution, as follows:

$$\text{SCB}(\hat{y}) = 0 + k_r \sqrt{\text{MSE}(\hat{y})} \quad (14)$$

201 where k_r is calculated using the folded normal distribution for a given one-sided confidence
 202 level.

203 *2.4. Case study: adjustment of a sheep forelimb model*

204 In order to illustrate the proposed approach, a sheep forelimb musculoskeletal model
 205 was used. The musculoskeletal model was composed by 4 segments and 16 hill-type muscle-
 206 tendon units (see Figure 3). The external geometry of the bones was obtained by 3D optical
 207 scanning. The extensor and flexor groups of the digital joints were treated each one as
 208 a whole unit as no degree of freedom at these joints were considered. Elbow and carpal
 209 joints were modeled as hinge joints and shoulder joint as a ball-and-socket joint. Inertial
 210 parameters were estimated using a CAD software. A geometrical model of the segments was

211 created by considering all soft tissue (see Figure 4). The model and the gait trial data used
212 in this case study are available at <https://simtk.org/projects/sheepforelimb>. The
213 considerations made for carrying out this study were:

- 214 • Bones were considered as rigid bodies,
- 215 • Segments' inertial properties were considered time-independent,
- 216 • Biological joints were modelled as frictionless joints,
- 217 • The initial values of the FGPs were considered near to a locally optimal solution.

Figure 3: Musculoskeletal model of sheep forelimb used as case study. The musculoskeletal model was composed by 4 segments and 16 hill-type muscle-tendon units (represented as red lines) Anconaeus (ACN), Biceps brachii (BCB), Brachialis (BRC), Caput mediale tricipitis brachii (MET), Caput laterale tricipitis brachii (LAT), Caput longum tricipitis brachii (LOT), Coracobrachialis (CCB), Deltoideus (DET), Extensor group (EXT), Flexor group (FLE), Infraspinatus (ISP), Subscapularis (SUB), Supraspinatus (SUP), Tensor fasciae antebranchii (TFA), Teres major (TMA), Teres minor (TMI).

Figure 4: Computation of the inertial parameters (inertia matrix, mass and center of gravity) of the model's segments using a CAD software. For each segment, soft tissues were considered.

218 The open source tool OpenSim [10, 33] was used to perform MFP of the gait cycle. For
219 these computations, the static optimization algorithm was used. The algorithms proposed in
220 this paper were implemented in Jython and the computations were automatically performed
221 through the OpenSim API on a standard laptop (64-bit i7 processor @ 2.7GHz, 16 GB RAM,
222 running Microsoft Windows 7). For the screening process, four FGPs per muscle (those
223 assumed to be specific to each actuator) were considered, namely maximal isometric force,
224 optimal fiber length, tendon slack length and pennation angle. For the numerical derivative
225 computations, a variation coefficient of $2q_k = 0.1P_k^*$, $\forall k$ was chosen. This is a commonly
226 used value in biomechanics [35, 14]. According to Algorithm 1, that implies running $16 \times 4 \times 4$
227 computations to calculate each sensitivity index. Muscle forces were computed before and

228 after FGPs adjustment. Reserve actuator values were compared with the net joint torques
229 for each time instant from the results of the two computations.

230 3. Results

231 3.1. Initial simulation

232 When computing muscle forces with the initial set of FGP values, a cumulative sum of
233 squared reserve actuators of $C_{res}^{ini} = 21.385e-3$ (BW m)² was obtained. This value was nor-
234 malized according to the body weight (BW) of the specimen. Figure 5 shows the behaviour
235 of these reserves during the whole computation at the shoulder, elbow and wrist regarding
236 the net torque of each joint. At the shoulder, the peak reserve actuator was 9% of the peak
237 joint torque. At the elbow, the peak reserve actuator was 51% of the peak joint torque.
238 And at the wrist, the peak reserve actuator was 100% of the peak joint torque. Following
239 modelling good practices [17], these values must be less than 10%, which indicates that the
240 model must be adjusted.

(a) Shoulder

(b) Elbow

(c) Wrist

Figure 5: Evolution of the joint net torque (continuous line) for the three joints during the simulation in comparison with the reserve actuators required to run the simulation with the initial model (dashed line) and with the adjusted model (dotted line): (a) for the shoulder joint, (b) for the elbow joint, (c) for the wrist joint.

241 3.2. Parameter screening

242 For screening purposes, a total of 256 MFP were executed, which took approximately 40
243 minutes. These results are summarized in Figure 6 by means of a Pareto chart. This chart
244 represents the sensitivity factors sorted by magnitude. The curve over the bars represents
245 the percentage of the cumulative sum of sensitivity factors. By means of this chart, the most
246 influencing model parameters can be identified. We chose a set of 9 FGPs, that corresponds

247 to 14% of the whole set. This set generates 97% of the sum of the sensitivity factors. As it
 248 can be noticed, among the whole set of muscle-tendon units of the model, three have a high
 249 influence on the dynamic consistency of the simulation: the extensor group of the digital
 250 joints (EXT), the biceps brachii (BCB) and the brachialis (BRC). Among the four FGPs
 251 considered, muscle pennation angles had less influence.

252 3.3. Surface regression

253 A response surface was calculated in the neighborhood of the initial values of these FGPs.
 254 The computation of this response surface required simulating 275 ($2^{(9-1)+2 \times 9+1}$) gait trials,
 255 which took approximately 48 minutes. The obtained surface coefficients are presented in
 256 Table 1. The convexity of a second-order surface depends on the sign of the second-order
 257 coefficients. As it can be seen, all the second order coefficients are positive, which indicates
 258 that the obtained surface is convex.

Figure 6: Pareto chart of the sensitivity analysis. FGPs are represented in the horizontal axis sorted its own sensitivity index (vertical left-hand axis). The curve over the bars represents the percentage of the cumulative sum of sensitivity factors (vertical right-hand axis).

Table 1: Set of 55 b_{kj} coefficients of the response surface calculated from the results of the experiments by least-squares fitting.

k	b_{0k}	b_{1k}	b_{2k}	b_{3k}	b_{4k}	b_{5k}	b_{6k}	b_{7k}	b_{8k}	b_{9k}
0	5.24									
1	-7.72	3.72								
2	-6.85	9.48	3.72							
3	-11.01	7.56	6.64	2.70						
4	-7.48	4.95	4.35	8.16	2.90					
5	-6.32	4.16	3.66	6.85	4.29	2.48				
6	-2.81	1.90	1.66	1.32	2.09	1.75	1.53			
7	-0.67	0.47	0.41	0.83	-0.58	-0.49	0.21	1.36		
8	-0.67	0.50	0.44	-0.74	0.59	0.49	-0.14	0.06	1.36	
9	-0.37	0.01	0.01	0.36	0.23	0.19	0.09	0.03	0.03	1.38

259 *3.4. Validation of the results*

260 The obtained surface predicted an optimal design solution at $C_{res}^{pre} = 0$ (BW m)² with
261 a statistical confidence boundary of $0 \leq \text{SCB}(C_{res}^{pre}) < 4.763\text{e-}3$ (BW m)². The confidence
262 boundary was calculated considering a folded normal distribution (Eq. 14) and it is depicted
263 in Figure 7.

Figure 7: Folded normal distribution used to calculate the corrected statistical confidence boundary of the predicted value C_{res}^{pre} for a confidence level of 95%.

264 The adjusted FGP values (shown in Table 2) were introduced in the model and the MFP
265 executed again. The obtained sum of reserve actuators was significantly reduced compared
266 to the computation performed using the initial set of FGP values. The new computed value,
267 which is included in the confidence boundary, was of $C_{res}^{cmp} = 0.120\text{e-}3$ (BW m)². Reserve
268 actuator values of the simulation with the adjusted model are presented in Figure 5. After
269 adjustment, peak reserve values reached a maximum of 9%, 11% and 23% of the peak joint
270 torque of the shoulder, elbow and wrist, respectively. The average reduction of the reserve
271 value vs the net joint torque all along the simulation was of 1% for the shoulder, 18% for
272 the elbow and 16% for the wrist.

273 From both the initial model and the adjusted one, we computed the radiohumeral re-
274 action force (Figure 8). The magnitude of this force in both axial and anterior-posterior
275 directions shows differences before and after the FGPs adjustment. These differences are
276 more significant especially during the stance phase.

(a)

(b)

Figure 8: Radiohumeral reaction forces predicted from the sheep forelimb musculoskeletal model before (continuous line) and after FGPs adjustment (dashed line). Force values were normalized according to the body weight (BW) of the specimen. (a) axial force and (b) anterior-posterior force

Table 2: Set of initial and adjusted values of the 9 FGPs selected after screening.

Variable	Unit	Initial values	Adjusted values
Opt. Fiber Len. EXT	m	0.0900	0.1116
TendonLen EXT	m	0.1700	0.1508
Opt. Fiber Len. BRC	m	0.0680	0.0843
Opt. Fiber Len. BCB	m	0.0680	0.0843
Tendon Len BCB	m	0.0910	0.1128
Tendon Len BRC	m	0.0340	0.0421
Max Force BCB	N	488.1200	509.1856
Max Force BRC	N	361.5700	375.1500
Max Force EXT	N	1193.1820	1201.3149

277 4. Discussion and conclusions

278 In response to the multiple challenges in estimating model parameters in musculoskeletal
 279 modelling, this paper proposes a multivariate statistical strategy to adjust FGPs. The
 280 methodology follows a DoE-based approach to generate a response surface, which is used to
 281 determine optimal levels of the FGPs. In contrast to conventional optimization methods,
 282 DoE-based methodologies offer a means to determine the optimal operating conditions of a
 283 process at low computational cost while considering the interdependence of the factors.

284 We found that the use of response surfaces in musculoskeletal dynamics computations
 285 is an effective way to optimally adjust model FGPs, making the model more dynamically
 286 consistent. In agreement with the findings of Modenese *et al.* [26], the results of our com-
 287 putation suggest that the reserve actuators have an impact on the predicted joint reaction
 288 forces. Such an impact reached, in our case study, magnitudes of up to 1.7 BW. As re-
 289 serve actuators are applied directly over the joint (as a pure torque) without a moment
 290 arm, they do not generate reaction forces at the joints. In consequence, if a joint reaction
 291 analysis is performed with high reserve actuator values the calculated reaction forces are
 292 underestimated.

293 Depending on the cost function used to generate the response surface, this methodology
 294 can be used to adjust geometrical, inertial or muscle parameters. The focus of this paper is

295 on the adjustment of FGPs to reduce joint reserve actuators. However, its application for a
296 geometrical or a inertial adjustment is straightforward.

297 It should be stressed out that the proposed method does not ensure the robustness of the
298 model, but it does help in the adjustment of the parameters during the model development
299 process. Furthermore, a model adjustment carried out following this approach is valid for
300 the used experimental data and it may not be for another dataset.

301 This work has several limitations. First, as in the case of most of optimization techniques,
302 the response surface methodology is very sensitive to the initial values of the optimization
303 variables. Thus, the method proposed in this study should be employed using a realistic
304 set of initial FGP values. During the optimization, keeping parameter values in physical
305 levels depends on the chosen variation coefficient. Having small variation levels prevents
306 the optimization process to allocate a non-physical value to a given parameter. Second,
307 the proposed methodology could become impractical when the number of parameters to
308 optimize is significant (greater than 15), hence the importance of the parameter screening
309 before the optimization. Future work is in progress to develop a DoE-based strategy that
310 uses several locomotion trials for the adjustment of the FGPs.

311 This study showed that the use of multivariate statistical strategy seems to be a good
312 alternative to optimally adjust FGPs. This contribution constitutes a step towards a more
313 robust methodology in musculoskeletal modelling, methodology that can be applied both to
314 human and non-human studies.

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320 **Conflict of interest statement**

321 The authors declare no conflict of interest.

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