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Sensitivity analysis of sex- and functional muscle group-specific parameters for a three-compartment-controller model of muscle fatigue

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ABSTRACT

The three-compartment-controller with enhanced recovery (3CC-r) model of fatigue has been validated, in multiple stages and by different methods, for sustained (SIC) and intermittent isometric contractions (IIC). It has also been validated using a common methodology for both contraction types simultaneously to derive sex-specific representative model parameters for each functional muscle group, at the expense of reducing the sample size used to estimate each parameter set. In this study, a sensitivity analysis of the model to both variations in experimental measurements and to variations in the parameter values is carried out to estimate the robustness of the parameter sets. Torque decline prediction error is found to increase only slowly with increasing randomness injected into experimental data, with <1 % increases in error for 8–29 % variation in experimental endurance times. The results demonstrate that the obtained parameters from our previous study are reliable and can be used for fatigue prediction in multiple scenarios without significant loss of accuracy. For all sexes and functional muscle groups examined, the fatigue process dominates recovery in the experimental conditions examined. Finer estimates of the model's recovery parameter will likely require changes to the experiment design in future studies.

1. Introduction

Muscle fatigue (MF) is a temporary, exercise-induced reduction of a muscle's force generating capacity (Bigland-Ritchie et al., 1995). It is a complex neuromuscular phenomenon with multiple contributing central and peripheral mechanisms (Vøllestad, 1997), but which typically manifests as any combination of discomfort, muscle pain, a sense of tiredness, and reduced performance (Chaffin, 1999).

Fatigue is a useful metric in the fields of rehabilitation, occupational safety, and ergonomics. While its occurrence can never be entirely avoided, steps may be taken to minimize its extent in occupational settings through careful task analysis and design. The goal, in each case, is to design tasks that never exceed the user's capacity. Since direct measurements of strength are often time-consuming, invasive, and impractical during actual task performance, muscle fatigue models (MFMs) are employed to predict the change in strength through the duration of a task.

Empirical and theoretical models exist for activity types ranging from sustained isometric contractions (SICs) to dynamic contractions. The relatively simple empirical models, fit to experimental data, deal with SICs due to the limited number of task parameters required to define an activity, i.e., target load (TL) (Rohmert, 1960). The two additional parameters required to define intermittent isometric tasks (duty cycle (DC) and cycle time (CT)) necessitate the use of theoretical models to obtain any useful predictions. The three-compartment-controller with enhanced recovery (3CC-r) model (Looft et al., 2018) can predict strength decline during both SICs and IICs, and it has previously been indicated that it could be employed for dynamic contractions as well (Xia and Frey-Law, 2008). Moreover, its model parameters have been calculated at the functional muscle group level for both sexes separately for isometric contractions (Rakshit et al., 2021), but the robustness of the model parameters was not examined.

The 3CC-r model divides the constituent motor units (MU) of a muscle or muscle group into 3 compartments corresponding to 3 states—resting, active, and fatigued, and defines rules (Equations 1–6) for the rates at which they transition from one state to another.

$$\frac{dM_R}{dt} = -C(t) + r(k, TL) \times R \times M_F \tag{1}$$

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$$\frac{dM_A}{dt} = C(t) - F \times M_A \tag{2}$$

$$\frac{dM_F}{dt} = F \times M_A - r(k, TL) \times R \times M_F \tag{3}$$

$$\text{If } M_A < TL \text{ and } M_R > TL - M_A,\ C(t) = L_D \times (TL - M_A) \tag{4}$$

$$\text{If } M_A < TL \text{ and } M_R < TL - M_A,\ C(t) = L_D \times M_R \tag{5}$$

$$\text{If } M_A \geq TL,\ C(t) = L_R \times (TL - M_A) \tag{6}$$

M_R, M_A, and M_F are the fractions of motor units in the muscle that are currently resting, active, and fatigued, respectively. $C(t)$ is a bidirectional activation-deactivation drive. F and R are the fatigue and recovery rate constants, respectively, and r is a recovery multiplier that is a discontinuous function of target load (TL) and a constant k, as defined in Equation (7). The model is relatively insensitive to the muscle force development (L_D) and relaxation (L_R) factors (Xia and Frey-Law, 2008), so a constant value of 10 is chosen for both.

$$r = \begin{cases} k, & if \ \ TL = 0 \\ 1, & if \ \ TL > 0 \end{cases} \tag{7}$$

Only MUs in the active state can generate force. Fatigued MUs are unable to generate any force, and resting MUs may move to the active state if required to achieve the target load. When comparing model predictions to experimental data, it is assumed that all MUs are initially resting ($M_R = 1$) when the participant is fully rested. When they perform an MVC, all MUs move to the active state ($M_A = 1$) for a brief instant before being redistributed among the resting and fatigued compartments. The torque output produced by the participant is then directly related to the number of active MUs, and is calculated as:

$$T = MVC \times M_A \tag{8}$$

where MVC is the maximum voluntary contraction torque measured for that muscle group in an unfatigued state. Experimentally, torque decline at a given time t is the difference between the MVC conducted at the beginning of experiment and one conducted at time t. Since fatigued MUs cannot contribute to torque production, the torque decline is calculated by the model simply as:

$$TD = MVC \times M_F \tag{9}$$

Rashedi and Nussbaum (2015) conducted a sensitivity analysis of the 3CC-r model which, at the time, did not include an augmented rest recovery parameter. They analyzed the variance in endurance time (ET) at 36 combinations of the 3 task parameters, and across a range of model parameters (F, R) corresponding to thrice the standard deviation within the model parameters across all joints. As the outcome variable was chosen to be ET, only general and limited assessments of the model's accuracy could be made. Here, we choose the outcome variable to be the torque decline (TD) prediction error (the weighted root mean square difference between the experimental and the model-predicted normalized TDs at a given experimental ET) which allows us to assess the model's accuracy across different regions of the parameter space.

Parameters that best fit a given set of experimental data can readily be obtained through a computationally expensive but relatively straightforward process of optimization (Rakshit et al., 2021). However, it is vital to understand to what extent those parameters can be relied upon to also represent other similar datasets. To that end, in this work we analyze the variation in the prediction error for multiple simulated datasets that we generate using the base dataset. This gives us an estimate of the model's performance for datasets that were not used to develop the parameters. Additionally, we study how far the predictions diverge when the constituent model parameters are perturbed. Plots of the error sensitivity graphically depict the model behavior for mixed-task datasets over various regions of the parameter space and can help identify which parameters may require further tuning, and which may be treated as constants.

2. Methods

The robustness of the model is tested in two key ways: by calculating the sensitivity of the prediction errors (1) to variations in the underlying experimental data, and (2) to variation in model parameters. Each method relies on an error calculation routine that takes as input as a set of experimental data points (task parameters and endurance times) and optimized model parameters (F, R, r) for the corresponding sex × functional muscle group (FMG) combination, and which outputs the weighted root mean square deviation (wRMSD) of the model predicted TD from the experimental TD using the input model parameters. The experimental data used for this work comes from a collection of 172 studies found in literature, the full list of which is detailed in (Rakshit et al., 2021) along with the inclusion and exclusion criteria, and which was itself culled from the meta-analyses of SICs (Frey-Law and Avin, 2010) and IICs (Looft et al., 2018). The combined data is organized in the form of sets of task parameters (TL, DC, CT) and the associated endurance times, along with sex-specific sample sizes. For most studies, the torque decline is simply the difference between 100 % MVC and the target load at the ET, but there are also some studies which detail torque decline at intermediate time points. These are included as well.

2.1. Sensitivity to experimental data variation

Experimental data points are often treated as the "true" values that a model must be able to predict with a certain accuracy. However, experimental data may itself contain variations due to factors such as differences in calibration and varying accuracies of equipment, differences in methodology used to measure MVCs (Vera-Garcia et al., 2010), varying levels of participant effort and techniques to control them, differing physiologies between participants, etc. All of these can contribute to variations in the measured endurance time for the same set of task conditions. Since the measured variable for majority of the studies in the experimental dataset was ET, we chose to introduce variations into ET data (input), and then examine the corresponding changes to the TD prediction error (output). 20 new datasets are generated based on the original dataset. Each of these corresponds to a different maximum ET variation percentage p, ranging from 5 to 100 in increments of 5. p is the maximum percentage variation introduced into each ET data point. For instance, when $p = 15$, an ET of 200 s in the base dataset may be changed to any value between 170 s and 230 s in the generated dataset. The original dataset with maximum 0 % injected ET variation corresponds to $p = 0$. At the other extreme, $p = 100$ corresponds to a dataset in which some of the individual ETs may have been changed by as much as 100 % of their original values (either reduced to 0 s or doubled). The generated i-th ET ($ET_{i_p}^{gen}$) within a dataset corresponding to p% maximum injected variation is expressed as:

$$ET_{i_p}^{gen} = ET_{i_0} \times (1 + 0.01p \times rand(-1, 1)) \tag{10}$$

where $rand(-1, 1)$ is a random whole number between −1 and 1, and ET_{i_0} is the unaltered i-th endurance time.

The task parameters (TL, DC, CT) and the TD corresponding to a given ET are kept intact for every data point in all the generated datasets. Then, the 3CC-r model is used to generate TD predictions for each set of task parameters present in experimental data. The wRMSD between the predicted and the experimental TDs is calculated at the generated experimental ET by the expression:

$$wRMSD_p = \frac{n_s}{\sum n_s} \sqrt{\frac{\sum_i \left(TD_{i_p}^{gen} - TD_{i_p}^{mod} \right)^2}{n_d}} \tag{11}$$

Table 1
Optimized parameter values for the 3CC-r model, segregated by sex and functional muscle group (Rakshit et al., 2021).

Joint	Functional muscle group	Female			Male		
		F	R	r	F	R	r
Ankle	Dorsiflexors	0.00746	0.00081	4.97	0.00725	0.00096	10.36
Elbow	Extensors	0.01874	0.00206	21.22	0.01269	0.00085	30.21
	Flexors	0.00965	0.00197	6.22	0.01302	0.00188	8.99
Hand	First dorsal interosseous	–	–	–	0.01637	0.0036	3.66
	General handgrip	0.01159	0.00217	7.39	0.01238	0.00178	8
Knee	Extensors	0.01407	0.00185	6.32	0.0142	0.00153	10.96

where n_s is the number of participants of sex s contributing to a study, $\sum n_s$ is the total number of participants of sex s counted across all the studies contributing to data for a particular functional muscle group, $TD_{i_p}^{gen}$ is the i-th recorded torque decline in the study corresponding to $ET_{i_p}^{gen}$, $TD_{i_p}^{mod}$ is the model-predicted torque decline corresponding to $ET_{i_p}^{gen}$, and n_d is the number of published data points in the study. Since mean endurance times published for large studies may not be representative of the entire population, the published ET is always weighted by $\frac{n_s}{\sum n_s}$ which assigns a proportionally larger error for larger studies. The random number generator seed is reset for each study so that the results are reproducible. Finally, 21 values of $wRMSD_p$ are obtained for each sex × FMG combination corresponding to $p = 0$–100 % injected error (in increments of 5 %). 0 % error corresponds to the original dataset with unaltered endurance times.

2.2. Sensitivity to parameter variation

To verify that the optimum parameter sets derived correspond to the minimum error and to investigate the change in prediction error with variations in F and R, a sensitivity analysis is set up by first simultaneously varying F and R (23 values of each). F varies between 0.001 and 0.040, while R is varied between 0.0001 and 0.0060. These common limits are chosen to cover 200 % the optimized F and R values (see Table 1) for all sexes and FMGs.

The wRMSD between the modeled (using a specific pair of F, R values) and the expected TDs (from the base dataset, with 0 % injected variation) is calculated as:

$$wRMSD_0(F,\ R) = \frac{n_s}{\sum n_s}\sqrt{\frac{\sum_i \left(TD_{i_0}^{exp} - TD_{i_0}^{mod}(F,\ R)\right)^2}{n_d}} \tag{12}$$

where $TD_{i_0}^{exp}$ is the i-th experimental TD with 0 % injected error, $TD_{i_0}^{mod}(F, R)$ is the modeled TD for specific (F, R) pair at a time corresponding to the unmodified i-th experimental ET.

A generic parameter sensitivity is defined as the change in the weighted RMS deviation (between the modeled and expected TD) in Eq. (12) due to an infinitesimal change in a generic model parameter X, and calculated as:

$$\phi_X = \frac{\partial wRMSD_0}{\partial X} \tag{13}$$

The normalized generic parameter sensitivity is the ratio of the *fractional* change in the weighted RMS deviation in Eq. (12) due to an infinitesimal *fractional* change in the generic parameter X, and is therefore given by:

$$\overline{\phi}_X = \frac{\partial wRMSD_0}{\partial X} \times \frac{X}{wRMSD_0} \tag{14}$$

Had an analytical expression been available for wRMSD as a function of the parameter X, the normalized generic parameter sensitivity $\overline{\phi}_X$ could also have been expressed analytically. However, TD predictions using the 3CC-r model are neither analytical nor continuous and therefore need to be obtained by numerically solving the governing equations using a pair of (F, R) values at each time step between 0 and the specified ET. The normalized generic parameter sensitivity $\overline{\phi}_X$ must therefore be expressed in finite difference form as:

$$\overline{\phi}_X = \frac{wRMSD_{0_{q+1}} - wRMSD_{0_q}}{X_{q+1} - X_q} \times \frac{X_{q+1} + X_q}{wRMSD_{0_{q+1}} + wRMSD_{0_q}} \tag{15}$$

The fatigue and recovery parameter sensitivities are therefore similarly expressed, in finite difference form, as:

$$\overline{\phi}_F(F,\ R) = \frac{wRMSD_{0_{m+1}}(R) - wRMSD_{0_m}(R)}{F_{m+1} - F_m} \times \frac{F_{m+1} + F_m}{wRMSD_{0_{m+1}}(R) + wRMSD_{0_m}(R)} \tag{16}$$

$$\overline{\phi}_R(F,\ R) = \frac{wRMSD_{0_{n+1}}(F) - wRMSD_{0_n}(F)}{R_{n+1} - R_n} \times \frac{R_{n+1} + R_n}{wRMSD_{0_{n+1}}(F) + wRMSD_{0_n}(F)} \tag{17}$$

where m indexes over the range of F values, and n indexes over the range of R values, $wRMSD_{0_m}(R)$ is the weighted RMS deviation corresponding to the m-th F value and a given R value, and $wRMSD_{0_n}(F)$ is the weighted RMS deviation corresponding to the n-th R value and a given F value. Fig. 1 shows a typical plot of RMS prediction error over a range of F and R values. $wRMSD_{0_{m+1}}$, $wRMSD_{0_m}$, (dark blue) F_{m+1}, F_m (orange), $wRMSD_{0_{n+1}}$, $wRMSD_{0_n}$ (light blue), and R_{n+1}, R_n (red) are marked.

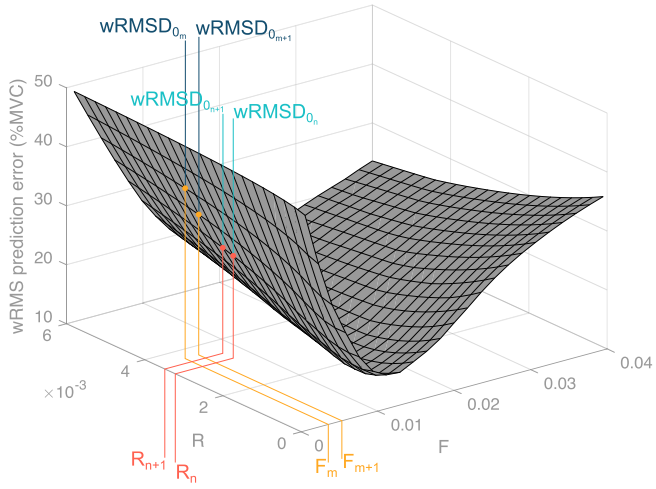

Fig. 1. Weighted RMS deviation in model prediction as a function of F and R for a typical sample. $wRMSD_0$ is calculated separately for each combination of F, R to form a 3D surface. F and R sensitivities are calculated with a finite difference approach using adjacent points on the surface and the corresponding F and R values.

Since minor changes in F and/or R can result in extending or shortening the ET for an IIC task by up to one full cycle, localized peaks sometimes show up in the corresponding $wRMSD_0$ surfaces. These peaks

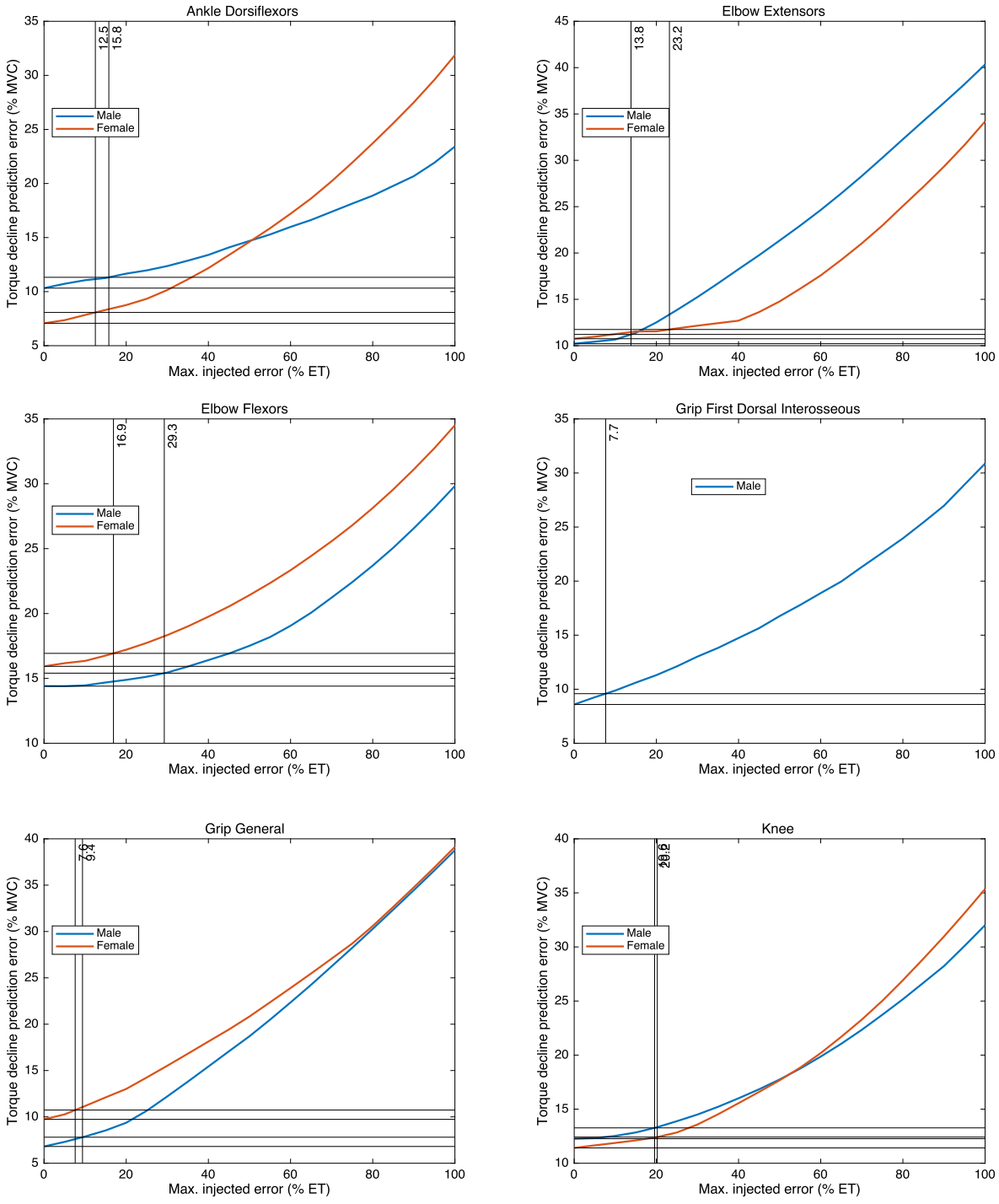

Fig. 2. Root mean square prediction error as a function of maximum percentage injected error in experimental ET data. The plot for the first dorsal interosseous in females is excluded due to insufficient sample size. The horizontal intercepts mark the minimum prediction error and the MID (1% more than the minimum error) for each sex, and the vertical intercepts mark the maximum percentage of injected error corresponding to the MID.

propagate to the $\overline{\phi}_F$ and $\overline{\phi}_R$ surfaces, resulting in what appear to be small discontinuities when plotted on a coarse parameter grid. To more clearly reveal the overall trend of sensitivity, the resulting values are finally smoothed out to eliminate local peaks by nearest-neighbor averaging, where each sensitivity value is replaced by the arithmetic mean of itself and its 8 surrounding values on the grid.

Only sensitivity to the F and R parameters are studied here, while using constant values of the augmented recovery parameter r detailed in Table 1. For error sensitivity to r the reader is referred to (Looft et al., 2018).

3. Results

3.1. Experimental data errors

The variation in wRMSD with increasing injected TD error is depicted in Fig. 2 (See Table 1 for optimized parameter values used) for all possible sex × FMG combinations. The plot for first dorsal interosseous (female) is omitted due to insufficient studies contributing to the underlying experimental data. Prediction errors increase steadily with increasing injected error for all groups.

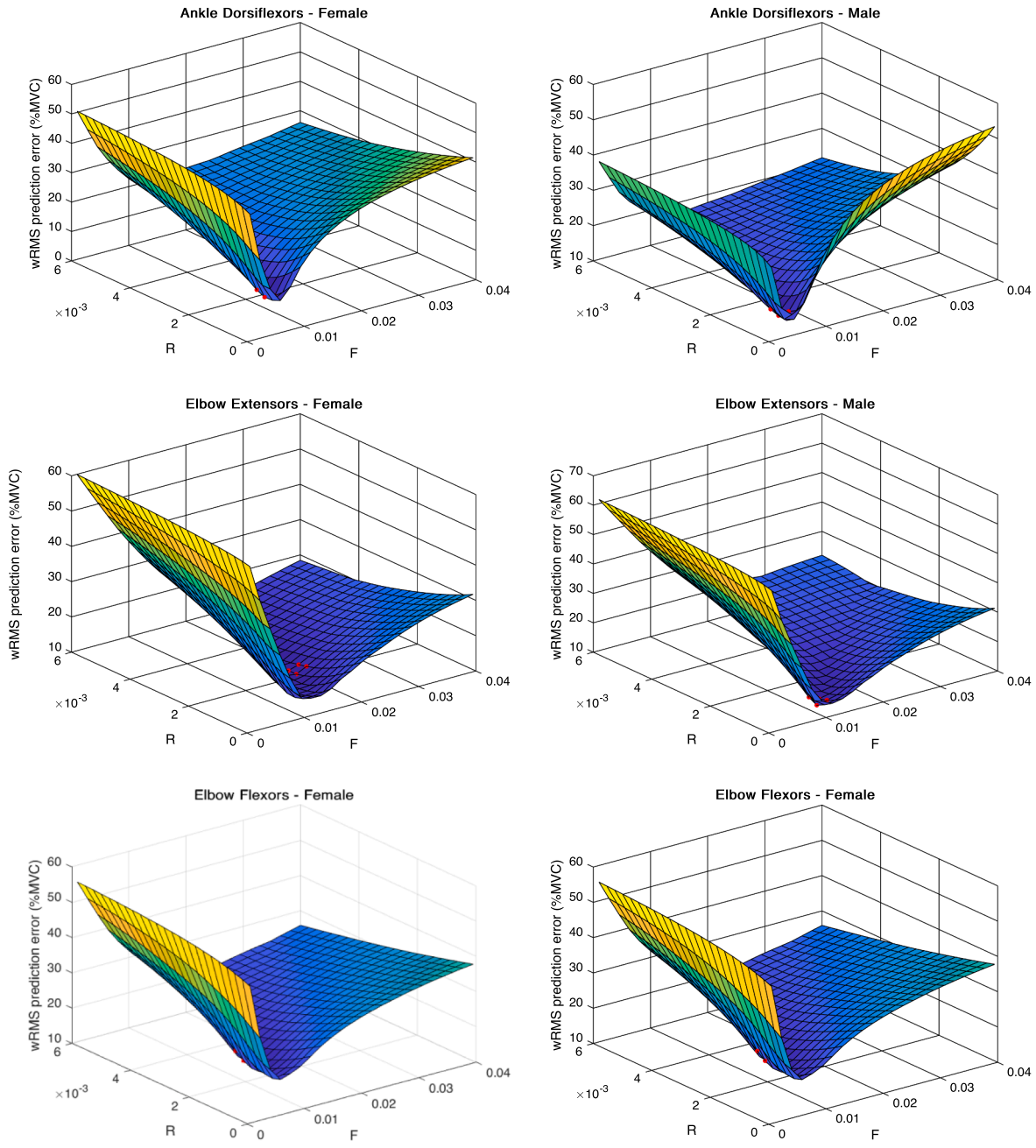

Fig. 3. Weighted RMS prediction error as a function of F and R for all evaluated functional muscle groups for female (left) and male (right) participants. The plot for the first dorsal interosseous depicts $wRMSD^0$ for male participants only. The 4 nodes marked in red in each plot are those surrounding the point of minimum error (optimized F, R values).

3.2. Parameter variation

The $wRMSD_0$ for each sex × FMG combination plotted against a grid of F and R is depicted in Fig. 3. The combination excluded in Fig. 1 is also excluded here for the same reason. Normalized fatigue and recovery parameter sensitivities, derived from the $wRMSD_0$ plots for the same combinations, are depicted in Fig. 4 (female) and Fig. 5 (male), respectively.

4. Discussion

As expected, RMS prediction errors are observed to increase with increasing fractions of maximum injected TD error into the experimental data. However, there is only a marginal increase in $wRMSD^p$ (<1%) compared to the base dataset for up to 7.6 % injected error in the case of female general handgrip and up to 29.3 % injected error for male elbow flexors (Table 2). The range of injected error that gives rise to a minimally important difference (MID) of < 1 % $wRMSD_p$ is between ~ 8 % and ~ 29 % for the other sex × FMG combinations, indicating that there will be negligible change in model predictions for a reasonable variation in measured endurance times. For fractions higher than 40 %, $wRMSD_p$ increases are disproportionately higher and too large to yield valuable estimates of fatigue. Thus, the model using optimized parameters is capable of accommodating reasonable (up to 8 %) ET deviations across

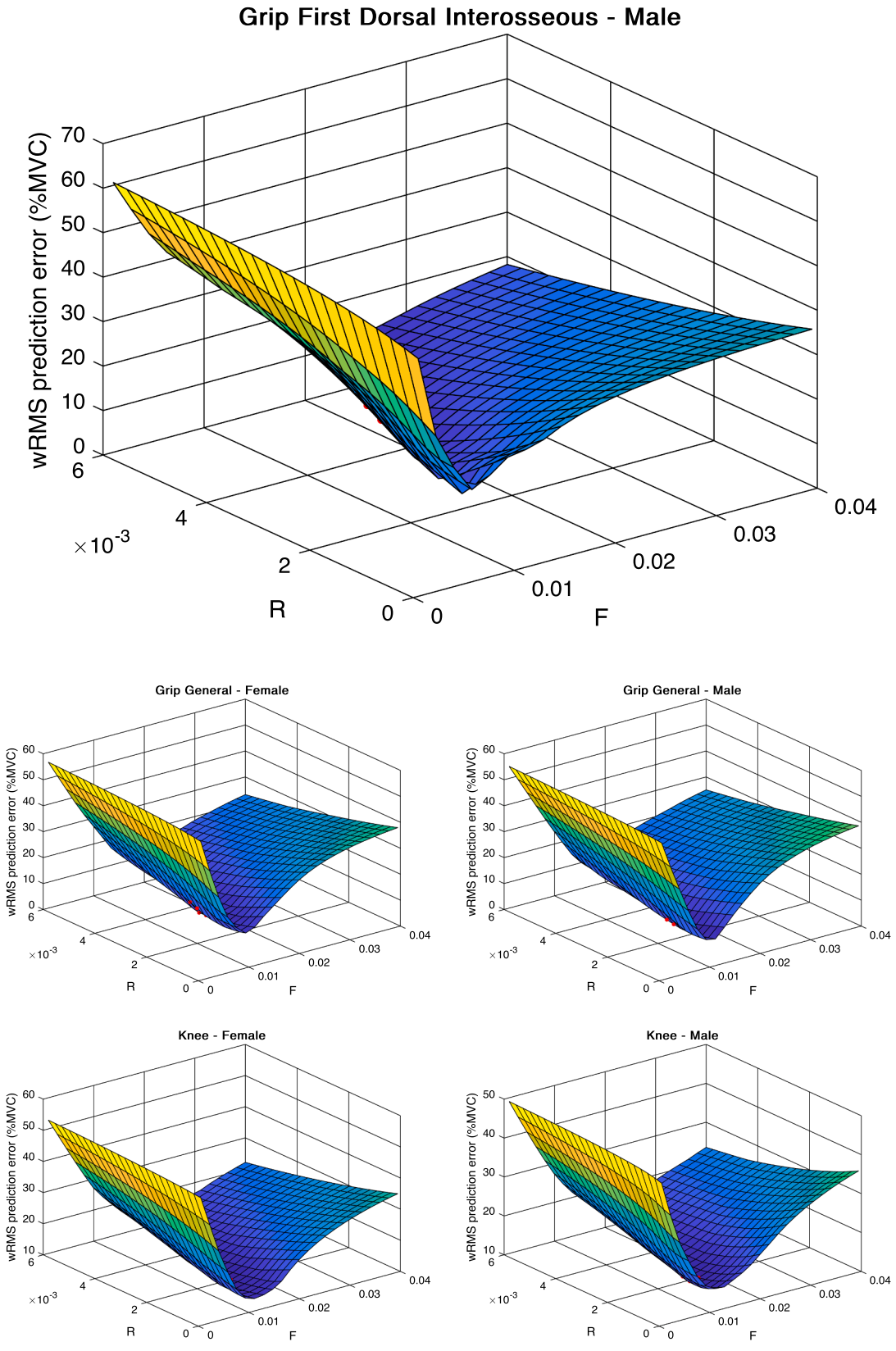

Fig. 3. (*continued*).

all sexes and FMGs with a negligible performance penalty. In practice, the model should be able to predict TD for a given time to within 1 % of the base error value for each FMG. For higher fractions of maximum injected error, the prediction errors are observed to increase, as is the sensitivity of the errors. The increased sensitivity is explained by the fact that since a higher fraction of each ET is being replaced by a random time value, the model predictions for each experimental condition (which do not change) are compared to the experimental TDs at

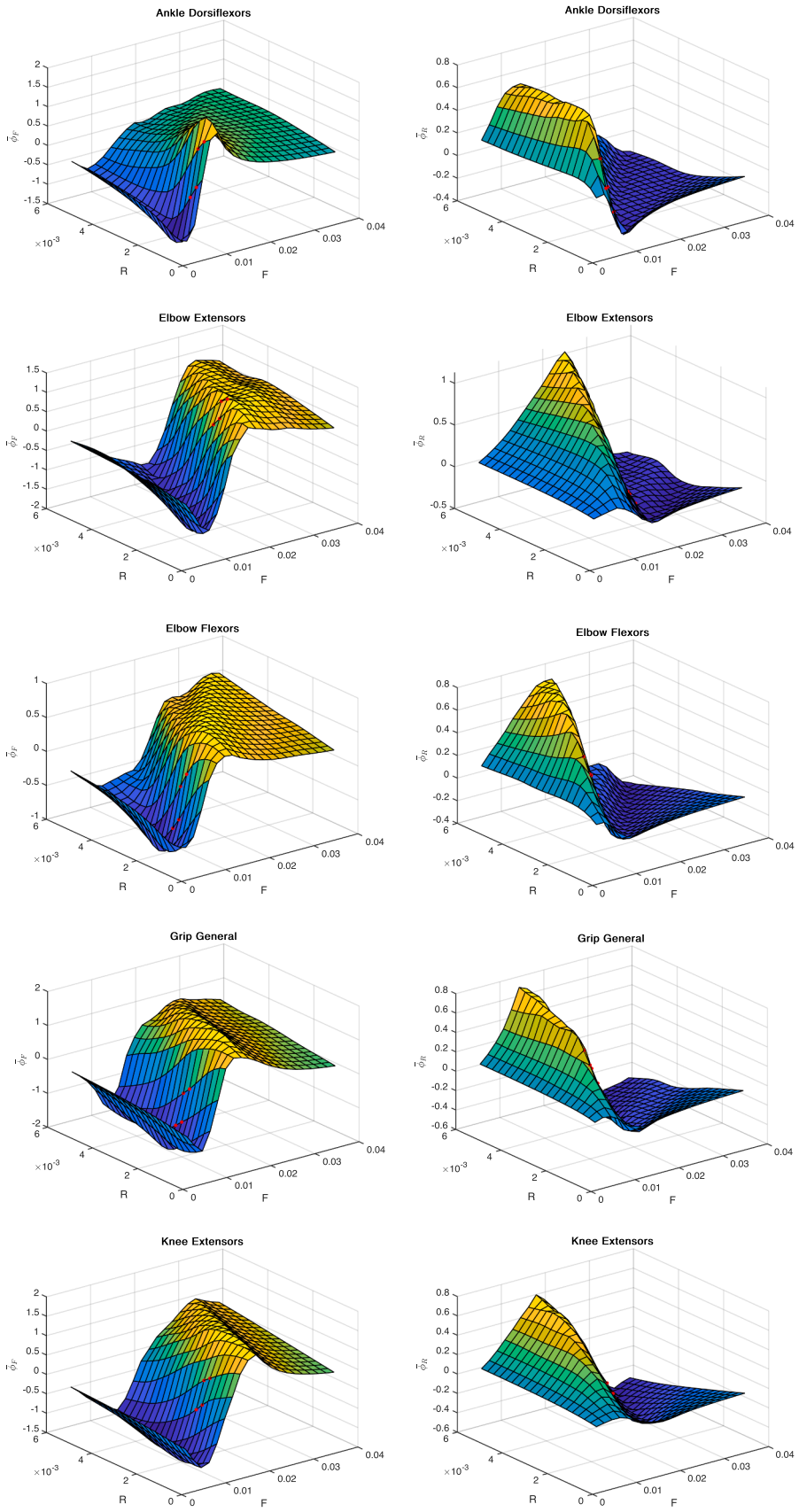

Fig. 4. Sensitivity plots for all evaluated functional muscle groups for female participants. On the left are F sensitivity plots, and on the right are R sensitivity plots. The 4 nodes marked in red in each plot are those surrounding the point of minimum error (optimized F, R values).

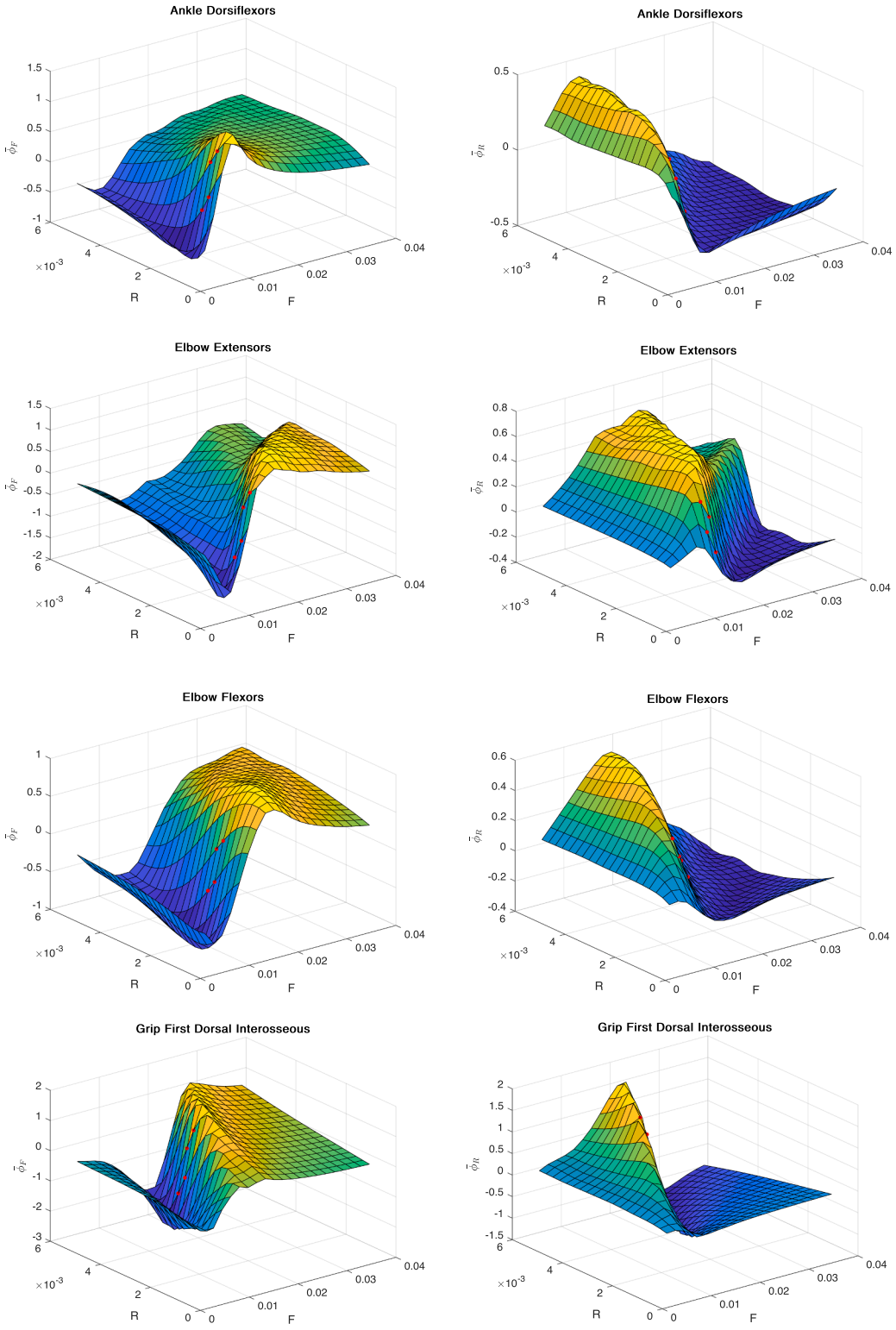

Fig. 5. Sensitivity plots for all evaluated functional muscle groups for male participants. On the left are F sensitivity plots, and on the right are R sensitivity plots. The 4 nodes marked in red in each plot are those nearest to the point of minimum error (optimized F, R values).

increasingly different time points.

In each of the F and R sensitivity plots, it is observed that the range of $\overline{\phi}_F$ is always 2–3 times greater than the maximum $\overline{\phi}_R$ within the specified (F, R) range, corroborating prior findings of the dominance of the fatigue compared to the recovery process (Rashedi and Nussbaum, 2015) where the sensitivity *of* ET was studied. A thorough investigation of the R parameter will therefore require a dataset whose experiments allow for greater recovery. It must be noted that the model, like the physiological system it represents, tends to conserve and recover strength by boosting recovery when excessively fatigued, so torque decline (or strength) does not vary excessively beyond a certain time despite continued cyclic exertion. This allows for absolute sensitivity of TD to be much lower

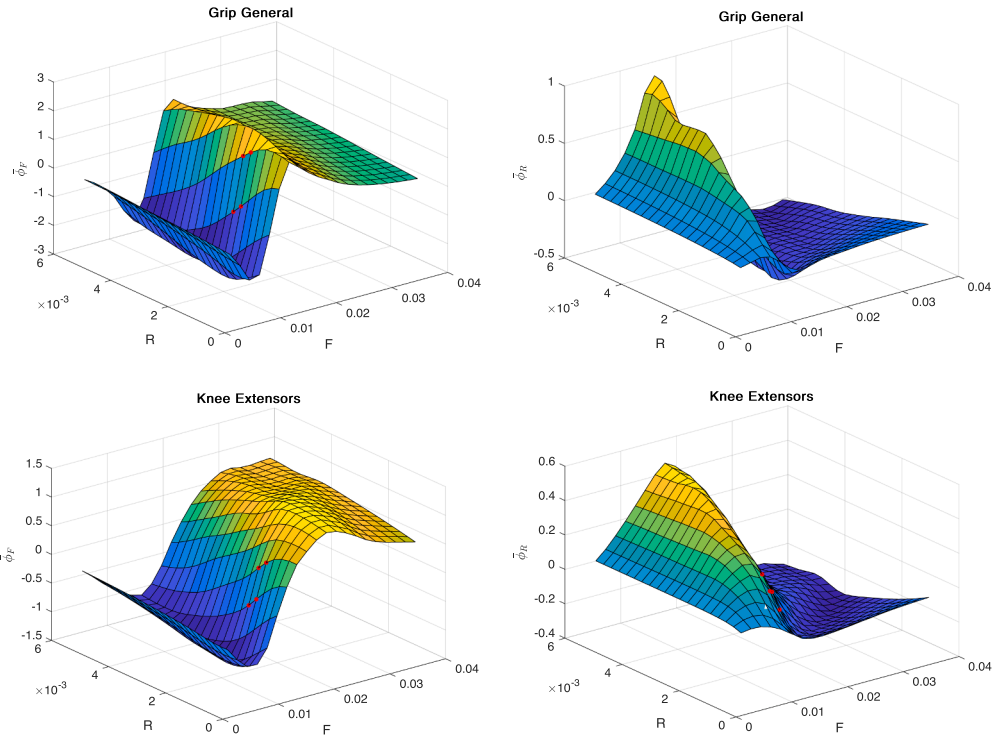

Fig. 5. (*continued*).

Table 2
Maximum ET deviation resulting in MID of 1% in TD prediction errors for different functional muscle groups.

Joint	Functional muscle group	Maximum percentage of ET deviation injected at MID	
		Male	Female
Ankle	Dorsiflexors	15.8	12.5
Elbow	Extensors	13.8	23.2
	Flexors	29.3	16.9
Hand	First dorsal interosseous	7.7	–
	General handgrip	9.4	7.6
Knee	Extensors	20.2	19.6

than absolute sensitivity of ET, and for absolute sensitivity of TD *prediction error* to be lower still as only a small variation in TD will be found for a relatively wide range of ETs given fixed task conditions, but the normalization of the sensitivities in each case makes them comparable.

Both $\overline{\phi}_F$ and $\overline{\phi}_R$ are also observed to flatten out at high F and low R values (which also correspond to shorter ETs), confirming the model's propensity for having low ET sensitivity at those conditions. While this may appear to make it more difficult for the model to be employed in low-demand tasks (with longer endurance times), the minima of the $wRMSD_0$ plots in the low F-low R regions and the existence of extended zones of near-zero sensitivity in all the $\overline{\phi}_F$ and $\overline{\phi}_R$ plots indicate that proper selection of model parameters for these common tasks may be easier in practice than previously thought. It is also observed that the zones of zero sensitivity in both $\overline{\phi}_F$ and $\overline{\phi}_R$ always pass through the region of minimum error in the corresponding $wRMSD_0$ surface, which is a necessary consequence of the grid-search method of finding the optimized model parameters. In the case of the elbow extensors for female participants, the optimized parameters used result in $\overline{\phi}_F \approx 0.95$ (interpolated from the four surrounding nodes) implying that a lower F-value (associated in this case with a lower $\overline{\phi}_F$) is necessary to obtain minimum prediction error, but the current optimized R-value is still suitable.

A number of important limitations remain in this analysis. The inclusion of studies that report strength as an aggregate for its male and female participants may skew the prediction error for both sexes, since the true value for neither group is available, and the average must be assumed to be true for both groups. The preponderance of SIC data (83 % of the total participants performed SICs) and the overrepresentation of male participants, who represented 72 % of the total sample size, also makes the conclusions less reliably applicable to women and IICs. Lastly, since a pseudo-random number generator (PRNG) was used for repeatability and the individual sample sizes for each combination of task conditions were still rather limited, it is possible that the choice of PRNG and of the seed influenced the values of the maximum allowable ET variation for a minimally important difference of 1 %. However, different choices in this regard are not expected to introduce vast changes, and the general conclusions without regard to the exact ranges of allowable variation should still hold.

5. Conclusion

Prior work (Rashedi and Nussbaum, 2015) has indicated that the 3CC-r model's predicted endurance times are more sensitive under "easy" task conditions which are less likely to be a target for MFM application. Despite this heightened sensitivity, the model appears to have fairly stable predictions under mixed task conditions as evidenced by the presence of extended low-sensitivity zones in its sensitivity plots. Additionally, it is also able to retain its predictive accuracy for reasonable deviations in recorded endurance times, making it a good candidate for further development and extension to wider task conditions. Future work should focus on expanding the model's capabilities to include prediction fatigue for low-to-medium velocity dynamic contractions to make it more occupationally relevant.

CRediT authorship contribution statement

Ritwik Rakshit: Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing - original draft. **Shuvrodeb Barman:** Methodology, Writing - review & editing. **Yujiang Xiang:**

Supervision, Funding acquisition, Conceptualization, Writing - review & editing. **James Yang:** Supervision, Methodology, Funding acquisition, Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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