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Computational Hypothesis Testing for Neuromuscular Systems

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Abstract— **Here, we promote the perspective that a computational model can be a rigorous crystallization of a hypothesis for the mechanisms generating observed data. We provide an example of using this approach to discriminate among hypotheses despite uncertainty in parameter values. Humans have been shown to produce non-uniform patterns of force fluctuation when they exert force in different directions with the index finger. We computationally formulated two hypotheses for this observation based on different cost functions of muscle effort, and then stochastically explored the space of unknown parameters to convergence to generate probability distributions of predictions from each hypothesis. The observed data were not within the probability distribution for Hypothesis 1: the sum of muscle forces is minimized, but were within the corresponding distribution for Hypothesis 2: the sum of squared muscle forces is minimized. Therefore, this approach provides rigorous evidence that Hypothesis 2 can not be rejected in favor of Hypothesis 1. The advantages and pitfalls of this computational approach to hypothesis testing are discussed.**

I. INTRODUCTION

Computational modeling has become an important tool to understand neuromuscular systems. Computational models are often used to support an interpretation of experimental findings, but are much less often used as rigorous implementations of hypotheses that could be supported or rejected based on comparison with experimental data. Consequently, computational modeling has not reached its full potential because there is perhaps too much emphasis on finding a model that "fits" the data and not enough emphasis on rejecting models that are inconsistent with experimental observations [1].

Computational hypotheses for neuromuscular function are not routinely rejected because it is always possible that poor agreement with data is simply due to a particular choice of some parameter. Many parameters in biological systems are extremely difficult or impossible to measure, which is particularly true in human neuromuscular systems in which invasiveness must be minimized. However, it may often be possible to estimate reasonable bounds for unknown parameters.

In this paper, we describe a procedure for formulating hypotheses into computational models, and then numerically searching across unknown parameter values to determine if that hypothesis could feasibly predict the data under *any* choice of parameter values. The approach provides a means of confidently rejecting hypotheses that are inconsistent with data, which increases the scientific utility of computational models for studying neuromuscular systems.

II. PROCEDURE

Monte Carlo methods are a well known means to assess the robustness of numerical simulations [2]. The Monte Carlo approach adapted to hypothesis testing involves a chain of steps beginning with some measured experimental data (Figure 1). The experiment produces some data, from which a test statistic is calculated. Computer models, which may have many unknown parameters, are coded for the observed test statistic. All unknown parameters are varied stochastically through their feasible range, and the simulated test statistic is calculated for each generated parameter set. Upon convergence of this stochastic process, it is possible to determine if the model could have *ever* generated the measured value of the test statistic under any possible parameter set. Models that are not consistent with the data can then be confidently rejected as infeasible [1].

We now provide a step by step example of using this approach.

A. Perform experiment

Previous studies have demonstrated that there is significant information about the nervous system controls multiple muscles in the structure of force fluctuations during isometric tasks [3], [4]. One study in particular showed that the pattern of multidirectional force fluctuation varied depending on the direction that the subject was exerting force with their index finger [4]. When the index finger exerted force in some directions, the force tended to fluctuate along the direction of the task (task-directed fluctuations), whereas forces fluctuated more randomly in other task directions (non-task-directed fluctuations) (Figure 2). Force fluctuations were task-directed when the task direction aligned with the direction of muscle action for *some* muscles, consistent with those muscles being the primary muscles used for those tasks. We showed that non-task-directed fluctuations were consistent with the coactivation of multiple muscles with distinct lines of action [4].

What is puzzling about these data, however, is that task-directed fluctuations did not appear around the task direction of flexion, for which the flexors digitorum profundus and superficialis have their lines of action. This observation led us to speculate that the pattern of multidirectional force fluctuation may be indicating something about the "cost function" (i.e., the computational representation of the cost-benefit compromise in terms of unavoidable metabolic, wear, accuracy, speed, etc. consequences of motor actions) used by

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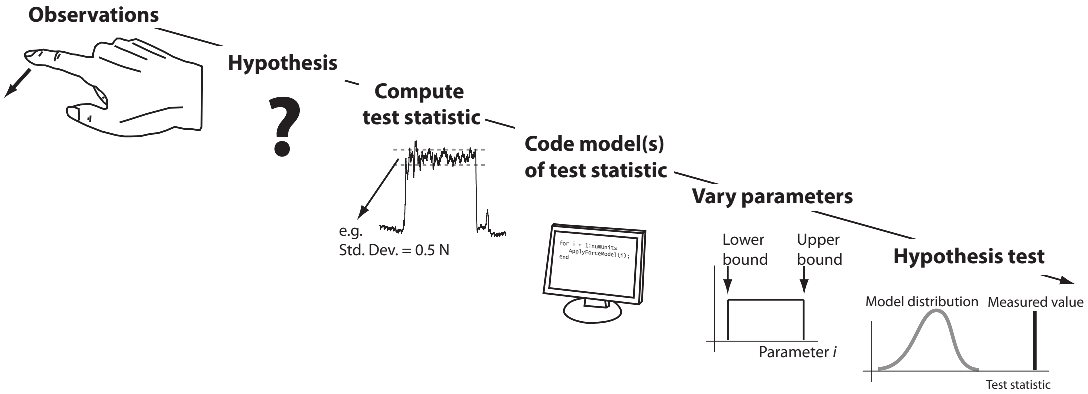

Fig. 1. Monte Carlo approach to model evaluation and hypothesis testing. An experiment is performed that produces some data, from which a test statistic is calculated. A computer model is coded that generates an output comparable to the statistics of the experimental data (or target test statistic). All parameters are varied stochastically within their feasible range, and a distribution of possible test statistics are generated for that model. One can then determine whether there exist sets of parameter values for the model that can replicate the distribution of the experimental data. If possible predictions of the model cannot replicate the experimental data, the hypothesis encoded in the model is likely untrue and a new hypothesis needs to be developed and encoded. Adapted from [1].

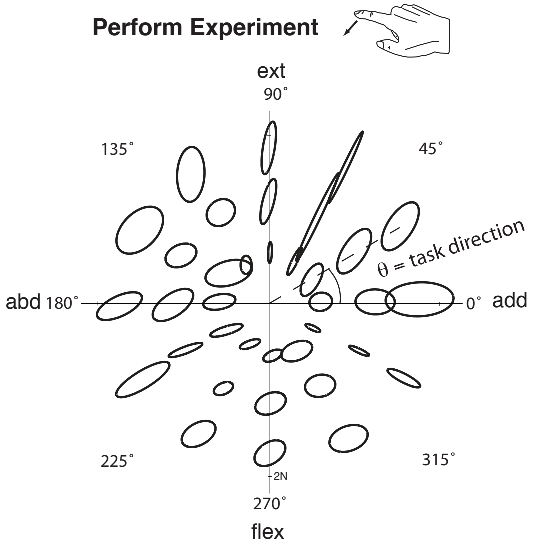

Fig. 2. Ellipses showing the magnitude and shape of the covariance of force for many tasks in the flexion/ extension-abduction/adduction force plane. Adapted from [4].

the brain to activate redundant muscles. Different cost functions naturally favor different muscle coordination patterns.

B. Formulate Hypotheses

These simple force-production tasks are underconstrained, thus the central nervous system (CNS) has flexibility in the choice of coordination pattern (i.e., the contribution of each muscle) for a particular output force. Researchers have repeatedly hypothesized that the CNS selects a particular coordination pattern by minimizing some cost function (see [5] for a review).

We first consider the question of whether our multidirectional force fluctuation measurements could potentially disambiguate different cost functions. A simple abstraction of the lines of action for the 7 muscles controlling the index finger is helpful for this purpose (Figure 3). Muscle 1 is an representation of the two extensor muscles, extensor indicis (EI) and extensor digitorum communis (EDC). Muscle 2 is a representation of the first dorsal interosseous (FDI) and lumbrical (LUM) muscles. Muscle 3 is a representation of the flexors, flexors digitorum superficialis (FDS) and profundus (FDP). Muscle 4 is a representation of the first palmar interosseous (FPI). We consider 2 cost functions for m muscles, where F is a desired fingertip force, A is a matrix encoding the mechanical action of all muscles, f is a vector of muscle forces:

$$\text{Hypothesis 1} : \min \sum_{i=1}^{m} f_i \text{ subject to } Af = F \text{ and } f_i \geq 0 \tag{1}$$

$$\text{Hypothesis 2} : \min \sum_{i=1}^{m} f_i^2 \text{ subject to } Af = F \text{ and } f_i \geq 0 \tag{2}$$

For muscles 1, 2, and 3, tasks in the direction of the muscle action are best accomplished, independent of cost function choice, by using each muscle alone, because all of these muscles do not have another muscle within 90° *on both sides* (Figure 3). In contrast, muscle 3 has muscles on each side within 90°. For tasks in the flexion direction, Hypothesis 1 would predict activation of muscle 3 alone, but Hypothesis 2 would predict load sharing among muscles with very different lines of action. Therefore, we predict that Hypothesis 1 would generate task-directed ellipses in the flexion direction, and would therefore be inconsistent with the observed data. Hypothesis 2 would generate non-task-directed ellipses for tasks in the flexion direction, and therefore would serve as plausible alternative.

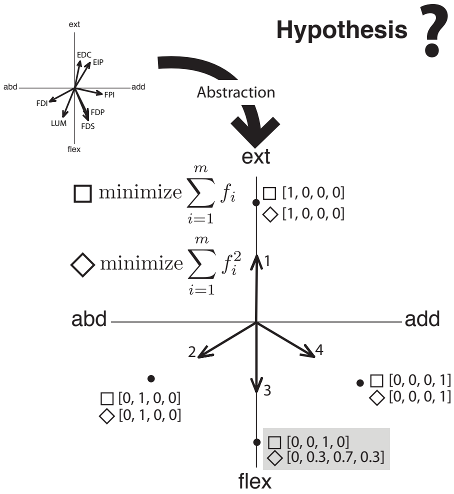

Fig. 3. An abstraction of the lines of action for the 7 index finger muscles allows an insight that minimizing $\sum f_i$ would activate the flexor by itself for tasks in flexion, whereas optimizing $\sum f_i^2$ would lead to load sharing with muscles 2 and 4. The best balance of muscles is shown in brackets next to each desired force output.

C. Compute Test Statistic

To compare these hypotheses numerically against the experimental data, it is necessary to have a rigorous and tenable test statistic (a.k.a goodness-of-fit metric). In the case of multidirectional patterns of force fluctuation, we decided to use a test statistic which was the fraction of total variance in the direction of the task itself, and then examine this test statistic as a function of the task direction. We call this test statistic the *task-directed variance fraction*, and denote it by the symbol η. If the average output force is $\bar{F}$, and $\hat{\bar{F}}$ represents a unit vector in the direction of $\bar{F}$, η can be calculated from:

$$\eta = \frac{\hat{\bar{F}}^T \mathrm{cov}[F] \hat{\bar{F}}}{\mathrm{Trace}(\mathrm{cov}[F])} \tag{3}$$

η will be close to 1 when the force covariance ellipse is narrow and elongated along the direction of the task, and will be small when the ellipse is non-task-directed (Figure 4). A polar plot in which each point represents a trial, with direction indicating the task direction, magnitude indicating the value of η for that trial, shows the consistency of the η statistics across subjects (Figure 4). When this data is averaged across subjects (black curve in (Figure 4)), it is clear that task direction near flexion (270°) corresponded to relatively low values of η. We will now examine the parametric sensitivity of Hypothesis 1 and 2 to determine if the observed η-function rules out either of these hypotheses.

D. Code Model(s) of Test Statistic

We used an action matrix A, which maps from muscle force to fingertip force, from the literature [6]. For each task around a circle in the adduction/abduction-extension/flexion plane, we identified coordination patterns of muscle forces satisfying each hypothesis separately. The coordination pattern, $f^{\star}$, was then used to predict the endpoint force mean and covariance according to the equation:

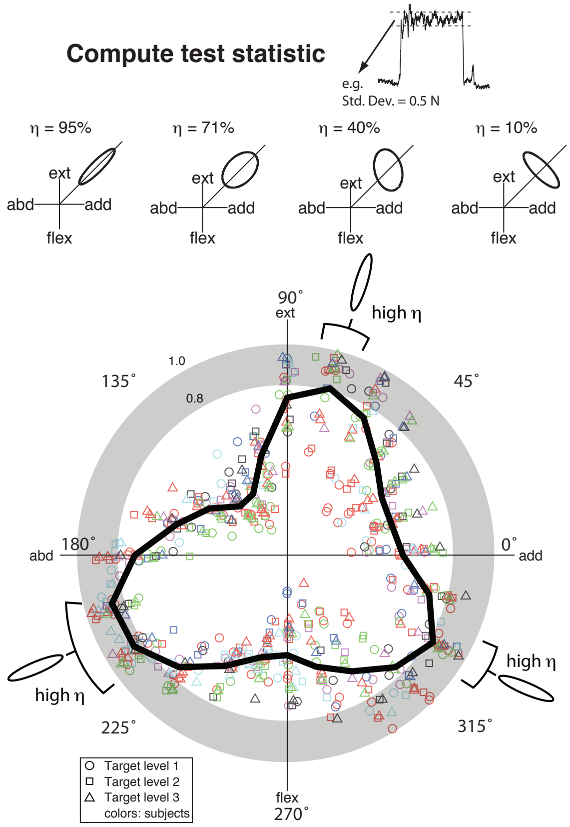

Fig. 4. The test statistic η quantifies the fraction of variance total variance in the direction of the task. Examples of the η value for four covariance ellipses are shown at the top, where the diagonal line represents the direction of the task. Adapted from [4].

$$\bar{F} = A\bar{f}^{\star} \tag{4}$$

$$\mathrm{cov}[F] = A\mathrm{cov}[f^{\star}]A^T \tag{5}$$

η could then be predicted for each simulated task using Equation 3.

E. Vary Parameters

We considered the unknown parameters of the model defined by Equations (4-5) to be the constant of proportionality between average muscle force and the standard deviation of muscle force. For each muscle i, the standard deviation of muscle force σ_i is given by $\sigma_i = k_i \bar{f}_i$. Since we are assuming no correlation among the forces exerted by different muscles, this relation completely defines the covariance matrix of muscle force $\mathrm{cov}[f]$. We varied the coefficients k_i across a 5-fold range from 0.01 to 0.05, consistent with the literature [7], [8].

F. Hypothesis Test

Our Monte Carlo analysis revealed that, despite an exhaustive search of combinations of force fluctuation standard de-

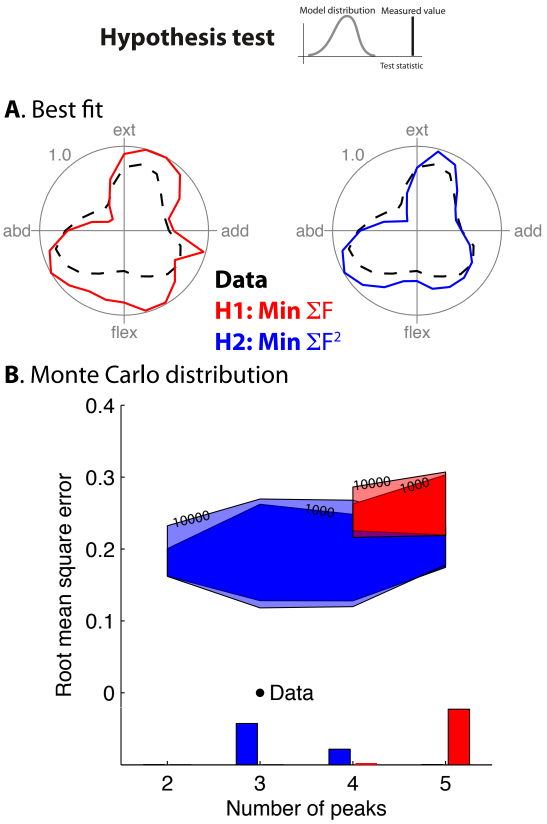

Fig. 5. Results of varying force fluctuation standard deviation coefficients. A. The closest simulated η- function to the data for Hypothesis 1 (H1) and Hypothesis 2 (H2). Notice that Hypothesis 1 produces an η- function with four peaks, while Hypothesis 2 can produce a 3 peak η-function that is very close to the data. B. Across all combinations of force fluctuation standard deviation coefficients, only Hypothesis 2 can produce η- functions with 3 peaks, whereas Hypothesis 1 always produced η functions with 4 and 5 peaks. The shaded regions show the convex hulls for the number of peaks versus the RMS error across all parameter combination examined (for both 1000 and 10000 Monte Carlo iterations). The bar graph on the x-axis shows the marginal distribution of the number of peaks.

viation coefficients, minimization of the sum of muscle force (Hypothesis 1) could not ever reproduce the experimentally-observed η-function. In contrast, minimization of the sum of squared muscle forces (Hypothesis 2) remained a viable hypothesis. Not only did Hypothesis 1 generate larger deviations from the experimental data across the Monte Carlo search, but Hypothesis 1 always generated η-functions with 4 or more peaks, which was inconsistent with the experimental η-function which had 3 peaks.

III. DISCUSSION

Here we have shown that experimental measurements of human motor noise are incompatible with a cost function that minimizes the simple sum of muscle forces. This hypothesis testing framework has the advantage that models are treated as computational implementations of specific hypotheses, which allows hypotheses to be numerically tested against experimental data.

A pitfall of the Monte Carlo approach is that parameter ranges must be carefully chosen to reflect the experimenters *a priori* beliefs about the potential range of parameters. In this study, we chose to vary the force fluctuation standard deviation coefficients within a range that was plausible given previous studies. It is possible that a larger range could revel different results, and thus the results of Monte Carlo simulations must always be evaluated in the context of the range over which particular parameters were varied. While the computational cost grows exponentially with the number of variables to explore, these methods are amenable to parallelized implementations, and there are extensions such as Markov chains that remain tractable even for complex biomechanical models [9].

Relating to the hypotheses tested in this example, cost functions for multi-muscle coordination have traditionally been studied by comparing predictions of different cost functions against EMG data (typically intramuscular). Our results indicate that the cost functions could be studied much more non-invasively by exploring the patterns of force fluctuations that are emitted by the body during natural force production. However, since the dependence of muscle force fluctuations on average muscle force is not known exactly for all muscles, this study also highlights the importance of Monte Carlo simulations to check that the desired hypotheses can be distinguished from the non-invasive data.

IV. ACKNOWLEDGEMENTS

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