

# Feasibility theory reconciles alternative approaches to neuromuscular control

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We present a conceptual and computational framework to unify today's theories of neuromuscular control called feasibility theory. We begin by describing how the musculoskeletal anatomy of the limb, the need to control individual tendons, and the physics of a motor task uniquely specify the family of all valid muscle activations that accomplish it (its 'feasible activation space'). For our example of static force production with a finger with seven muscles, computational geometry characterizes, in a complete way, the structure of feasible activation spaces as 3-dimensional polytopes embedded in 7-D. The feasible activation space for a given task is the landscape where all neuromuscular learning, control, and performance must occur. This approach unifies current theories of neuromuscular control because the structure of feasible activation spaces can be separately approximated as either low-dimensional basis functions (synergies), high-dimensional joint probability distributions (Bayesian priors), or fitness landscapes (to optimize cost functions).

Neuromechanics | Motor Control | Tendon actuation | ...

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How the nervous system selects specific levels of muscle activations (i.e. a muscle activation pattern) for a given motor task continues to be hotly debated. Some suggest the nervous system either combines low-dimensional synergies (1–7), learns probabilistic representations of valid muscle activation patterns (8–11), or optimizes physiologically-tenable cost functions (12–17). At the core of this problem lies the nature of 'feasible activation spaces,' and the computational challenge of describing and understanding their high-dimensional structure (for an overview, see (18)). A feasible activation space is the family of valid solutions (i.e. muscle activation patterns) available to the nervous system to produce a given motor task. Fig. 1 illustrates the neuromechanical interactions that define the feasible activation space for a particular task.

The most the nervous system can do, therefore, is select a specific muscle activation pattern from within the feasible activation space—as muscle activation patterns outside of this space are, by definition, inappropriate for the task. In fact, the feasible activation space defines the landscape upon which all neuromuscular learning and performance must occur. Understanding neuromuscular control is, therefore, equivalent to understanding how the nervous system finds, explores, inhabits, and exploits the structure of feasible activation spaces (1–6, 22).

But the 'curse of dimensionality' (23–25) makes it computationally challenging to calculate, describe, and understand the nature and structure of high-dimensional feasible activation spaces (4, 12, 19, 20, 26–28)—even for an isolated human fin-

ger or cat leg generating everyday static forces (1, 18, 29, 30). This is due to the computational complexity of algorithms applied upon high dimensional spaces.

Current theories of neuromuscular control are alternative responses to the curse of dimensionality, which at times can be seen as competing, rather than complementary. However, the fundamental neuromechanics of the limb and the physics of the task are the common ground for all theories. Thus, understanding the nature and structure of feasible activation spaces would help compare, contrast and combine these alternative approaches to neuromuscular control.

We now propose a conceptual and computational framework to provide complete characterizations of feasible activation spaces, thereby contextualizing and unifying multiple theories of neuromuscular control. As an example, we leverage prior work (1, 21, 31) to now describe the structure of the feasible activation space for the seven muscles of the index finger when producing static fingertip force. This is the type of fingertip force observed when, for example, pressing hard on a table without finger movement, and is also referred to as an isometric force task. In this case, the feasible activation space is a polytope embedded in 7-dimensional muscle activation space. A polytope is the name given to bounded convex polyhedra in dimensions higher than 3. Our computational approach hinges on the efficient sampling and complete representation of the structure of high-dimensional polytopes. This then characterizes all valid muscle activation patterns. These computational techniques can scale up to ~40 dimensions, which suffices to analyze the neural control of all muscles in a extant vertebrate limb systems. By providing a complete characterization of all muscle activation patterns for a given motor task, we are able

## Significance Statement

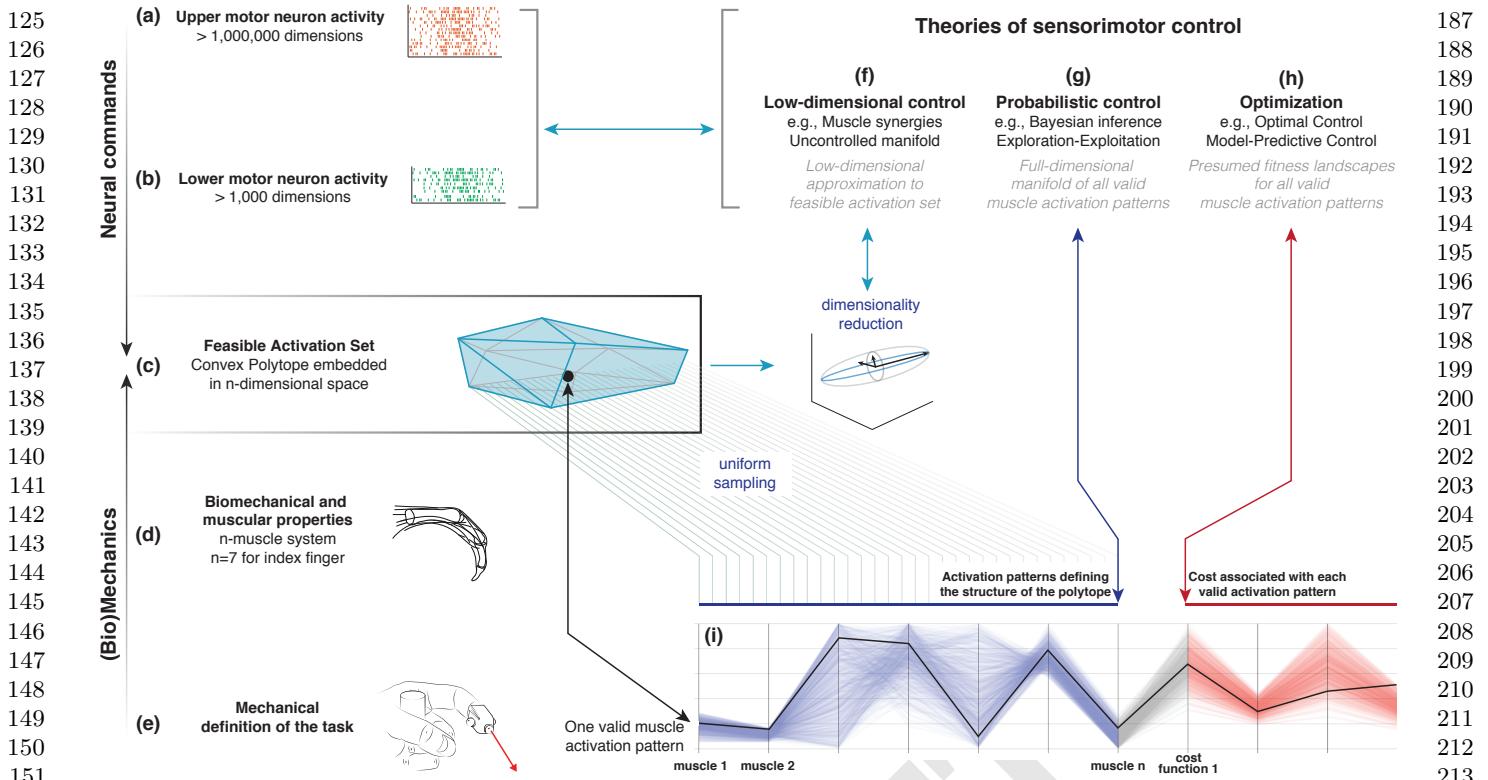
Wings take flight, eyes refract light, and muscles manipulate bones within the interplaying constraints of Newtonian physics. Here we apply the basic tenets of physics to the field of neuromechanical control, to elucidate the neuro-physical-motor landscape upon which evolution and learning operate. With three interweaving hypotheses of motor control in the literature, we fill the gap between the disparate approaches by recontextualizing the problem of force control as a physical constraints problem, thereby lighting the stage of optimal, synergistic, and bayesian control.

Please provide details of author contributions here.

Please declare any conflict of interest here.

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**Fig. 1. Feasible activation spaces guiding sensorimotor control of a task.** The descending motor command for a given task is issued by the primary motor cortex (a), which projects onto alpha-motor neuron pools in the spinal cord (b). The combined drive to all alpha-motor neurons of a muscle can be considered its total muscle activation level (a value between 0 and 1). If we consider that motor commands are sent to multiple independently controlled muscles, then the overall motor command can be conceptualized as a multi-dimensional muscle activation pattern (i.e., a point) in a high-dimensional muscle activation space (12, 19–21) (c). For that muscle activation pattern to be valid, it has to elicit muscle forces (d) capable of satisfying the mechanical requirements of the task—in this case a well directed fingertip force (e). Given the large number of muscles in vertebrates, there is muscle redundancy; there is a large number of valid muscle activation patterns that can produce a given task. We propose that our novel ability to characterize the high-dimensional structure of feasible activation spaces (i) allows us to compare, contrast and reconcile today's three dominant approaches to redundancy in sensorimotor control (f, g, h).

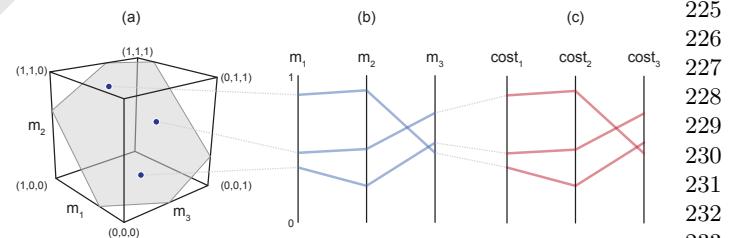
to compare, contrast, combine—and reconcile—today's three dominant approaches to neuromuscular control.

## Results

The goal of this work is to use different perspectives to describe the high-dimensional structure of these feasible activation spaces; we then show how these spaces allow us to unify today's theories of neuromuscular control. We used our realistic index finger model to calculate the feasible activation space for the task of producing static fingertip force in the distal direction (see Fig. 1). The model represents each muscle's contribution to fingertip force as a directed force vector at the fingertip; there are 7 of these force vectors at the index fingertip. As described briefly in the Methods, Hit-and-Run is a method in polytope sampling that we use to sample from the infinite number of muscle activations within the feasible activation space. In effect, given a fingertip task force and the maximum linear fingertip forces each muscle creates, we can collect the muscle activations required to produce that task. As we can now collect thousands of muscle activation patterns for any isometric force task, we examined how the feasible activation spaces (and their representations) change with increasing task intensity in the distal direction (Fig. 1e).

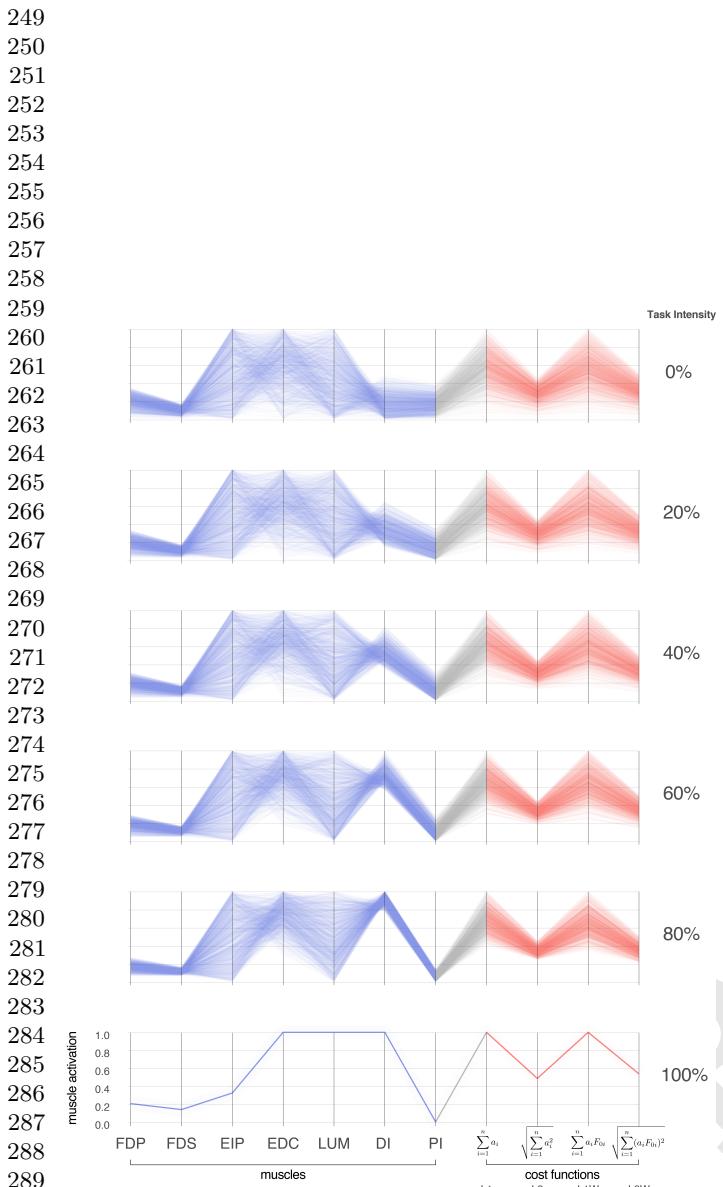
We collected points for multiple task intensities between 0% (i.e., pure co-contraction without output force) and 100%

of maximal static force.



**Fig. 2. Characterizing the high-dimensional structure of a feasible activation space via parallel coordinates.** Consider three points (i.e., muscle activation patterns in Supplemental Fig. ??e) from the feasible activation space (a). The activation level for each muscle (i.e., the coordinates of each point) are sewn across three vertical parallel axes (b). As is common when evaluating multiple valid coordination patterns, each point can be assigned a cost as per an assumed cost function. The associated cost for each muscle activation pattern can also be shown as an additional dimension. We show three representative cost functions (c). Activation levels are bound between 0 and 1, and costs are normalized to their respective observed ranges.

**Parallel coordinate visualization naturally reveals the structure of the feasible activation space.** We used Hit-and-Run to sample from feasible activation spaces for 6 task intensities, labeled as task intensities  $\alpha$  of 0.0, 0.2, 0.4, 0.6, 0.8 and 1.0. For each task intensity, we ran 100,000 Hit-and-Run iterations and



**Fig. 3. Activation patterns of the seven muscles of the index finger across six magnitudes of a fingertip force** The connectivity across parallel coordinates shows how muscle activation patterns are related in multiple ways to produce a fingertip force vector between 0 (a) to 100% (f) of maximal magnitude. At these extremes we have, respectively, the coordination patterns that produce pure co-contraction and the one unique solution for maximal output. In between, we see the how the structure of the feasible activation spaces changes as redundancy is lost. In blue are the activation values, and in red are normalized costs for four cost functions common in the literature. *FDP*: flexor digitorum profundus, *FDS*: flexor digitorum superficialis, *EIP*: extensor indicis proprius, *EDC*: extensor digitorum communis, *LUM*: lumbrical, *DI*: dorsal interosseous, *PI*: palmar interosseous.

down-sampled to every 100<sup>th</sup> point to produce 1,000 points that are (in our experiments) uncorrelated and uniformly distributed in  $P$ . Recall that approaching 100% of maximal force shrinks  $P$  to a single, unique solution (? ).

Parallel coordinate visualization effectively reveals correlations that exist among the 1,000 valid muscle activation patterns for each magnitude of desired fingertip force, and activation pattern cost, Fig. 2 and Fig. 3.

An interactive parallel coordinate visualization plot can be accessed at <https://briancohn.github.io/space-parcoords/>. This interactive interface for parallel coordinate visualization allows us to explore subsets of the valid muscle activation patterns.

For example, restricting the range of muscle activation of one or more muscles shows us the necessary activation levels of the remaining muscles. This can be used to, say, simulate a 40% reduction in possible activation to some muscles (e.g., due to a peripheral neuropathy) in the extrinsic extensor muscles of the index finger innervated by the radial nerve (EIP and EDC) (32).

Figures in the Supplemental Material show how, for 80% of task intensity (i.e., 80% of maximal force output), only 29% (i.e.,  $\frac{290}{1,000}$ ) of all possible solutions survive when capping the maximal excitation of EIP and EDC at 60%. Thus, any neural or muscle dysfunction that compromises the ability of the extensor muscles will limit the choices the nervous system has to produce this force—even at sub-maximal levels. These results further challenge the notion of muscle redundancy as discussed in detail in (18, 33).

Moreover, this same case of task intensity of 80% and maximal excitation of EIP  $\leq$  60% reveals important and counterintuitive consequences in the control of musculature. For example, the range of feasible activation level for some muscles do not change too much (FDP, FDS, and LUM), but does change for others (DI and PI). Most interestingly, the range of costs across valid solutions remains broad.

Similarly, we can describe any subset of muscle activation patterns associated with specific ranges for a given cost function. Figures in the Supplemental Material also show how can characterize all muscle activation patterns associated with the lowest 10% of L2 weighted costs. The coordination patterns that meet this strict criterion are quite different from one another (note the broad ranges and criss-cross patterns).

These relationships among all valid 7-dimensional muscle activations patterns reveal important aspects of the structure of the feasible activation space, and its associated cost landscapes. We see one muscle can affect other muscles in different ways: while limiting PI to 20% of maximal activation eliminates 30.1% of the valid solutions, limiting DI to 20% eliminates 42.8% of them. Similarly we can distinguish between changes in the extreme values of muscle activation from changes in the number of valid solutions. Consider the range of activation for DI and PI at task intensity of 80% which lies between 0 and 0.52 and 0.39, respectively. Limiting DI to 20% pulls PI's maximum down by nearly 0.20, and the converse has nearly the same effect. However, in both cases, the median activation among surviving solutions changes no more than 0.06. This emphasizes that understanding feasible activation spaces requires and understanding of its internal density and not just its bounds. The density of **between-muscle** connec-

373 tivity is seen directly by the density of the lines connecting  
374 the different muscles and cost functions. The **within-muscle**  
375 density can be computed by binning points at each activation  
376 level value.

377     Lastly, those same connecting lines in the parallel coordinate  
 378 visualization allow us to characterize the interrelatedness  
 379 of valid solutions in 7-dimensional space. For example, the  
 380 lines connecting FDP and FDS are mostly parallel, indicating  
 381 a strong positive correlation. In fact, looking at these lines  
 382 allows one to directly see and understand the Pearson product-  
 383 moment correlation coefficients of 0.99, -0.50, and -0.06 in the  
 384 adjacent muscle pairs FDP—FDS, LUM—DI, and EIP—EDC,  
 385 respectively. The interactive parallel coordinate visualization  
 386 also allows for any pairwise comparison by simply dragging  
 387 and reordering the vertical axes—and hovering over individual  
 388 data rows highlight an individual valid activation pattern atop  
 389 all others.

**391 Low-dimensional approximations to the feasible activation**  
**392 space.** We applied PCA (Principal Component Analysis) to

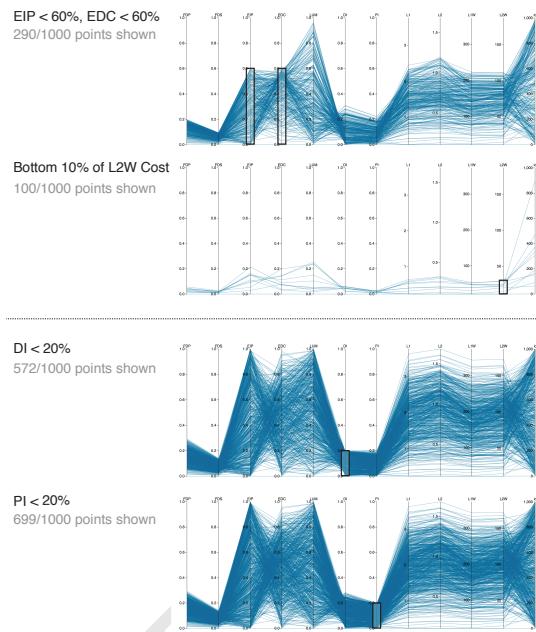
**Space.** We applied PCA (Principal Component Analysis) to the valid muscle activation patterns sampled uniformly at random from the feasible activation space. We show results for 10 levels of task intensity. However, we did this in an iterative fashion to replicate the fact that experimental studies can only collect a finite amount of data from each subjects. Thus, from the total pool of 10,000 sub-sampled points sampled by Hit-and-Run (i.e., accepting every 100th point from 100,000 total samples to remove potential autocorrelation among points); sample sizes of 10, 100, and 1,000 points (i.e., simulated ‘experimental’ sample sizes) were replicated 100 times each. We applied PCA to each set of sampled points.

The variance explained by PC1 and PC2 (and its boxplot distribution) for all iterations are shown to change with task intensity for all sample sizes (Fig. 5). Explaining about 13-15% of the variance, PC3 is exactly equal to the remaining variance not explained by the first two components—this is a result of the feasible activation space being a 3-dimensional polytope  $P$  by construction (i.e., recall that 4 task constraints applied to 7 muscles produce a 3-dimensional polytope embedded in the 7-dimensional muscle activation space).

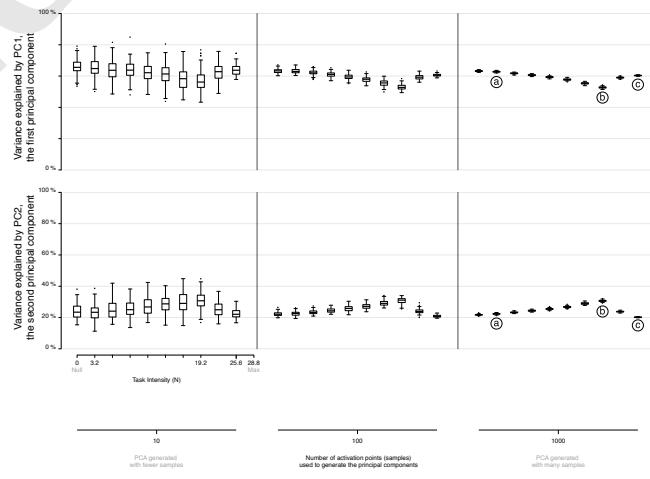
The boxplots in Fig. 5 quantify how different amounts of data change the estimates of variance explained by PC1 and PC2 with task intensity (c.f. labels a vs. b vs. c). We see this dispersion is small in the center and right columns. Note that the ratio of variance explained between PC1 and PC2 between 50 to 80% of task intensity is indicative of changes in the aspect ratio of the feasible activation space—which we see changes with task intensity.

Importantly, using experimentally realistic samples sizes of 10 repetitions per subject (leftmost column) not only does not capture this change, but its standard deviation is large enough to blur the statistically significant differences that are known to appear with larger (but experimentally unrealistic) sample sizes. The impact of impoverishing the number of samples fed to PCA reminds us that inadequate amounts of data obfuscate the underlying changes in the structure of the data analyzed (Fig. 5).

There were also important changes in the loadings of the PC1 and PC2 vectors. While the ratio of variance explained between PC1 and PC2 gives a sense of the aspect ratio of the feasible activation space, the loadings of PC1 and PC2 speak to its orientation. Fig. 6 shows how the loadings of



**Fig. 4. Supplemental Figure: Posthoc constraints on a task intensity of 80%**  
 Here we show four unique examples of constraints applied to the points collected from the feasible activation space. With this, we can rapidly predict how index finger control must change in the event of weakness in specific muscles. We also can see how many points remain once the constraints are added—signaling how the structure of the feasible force space is affected.



**Fig. 5. Approximating the structure of feasible activation spaces via principal components analysis (PCA) is sensitive to both the number of points used and the intensity of the task.** Rows show the variance explained by the first (top) and second (bottom) principal components with increasing data points (left to right). It is not possible to generalize the variance explained across tasks intensities, and large numbers of points (i.e., > 100) are needed to confidently estimate the real changes in variance explained as a function of task intensity (cf. points labeled a, b, c).

497 the PC1 and PC2 vectors change across labels a, b, and c  
498 (Fig. 5) corresponding to 11, 66 and 88% of task intensity,  
499 respectively. What these loadings indicate are the direction in  
500 7-dimensional space, which changes dramatically.

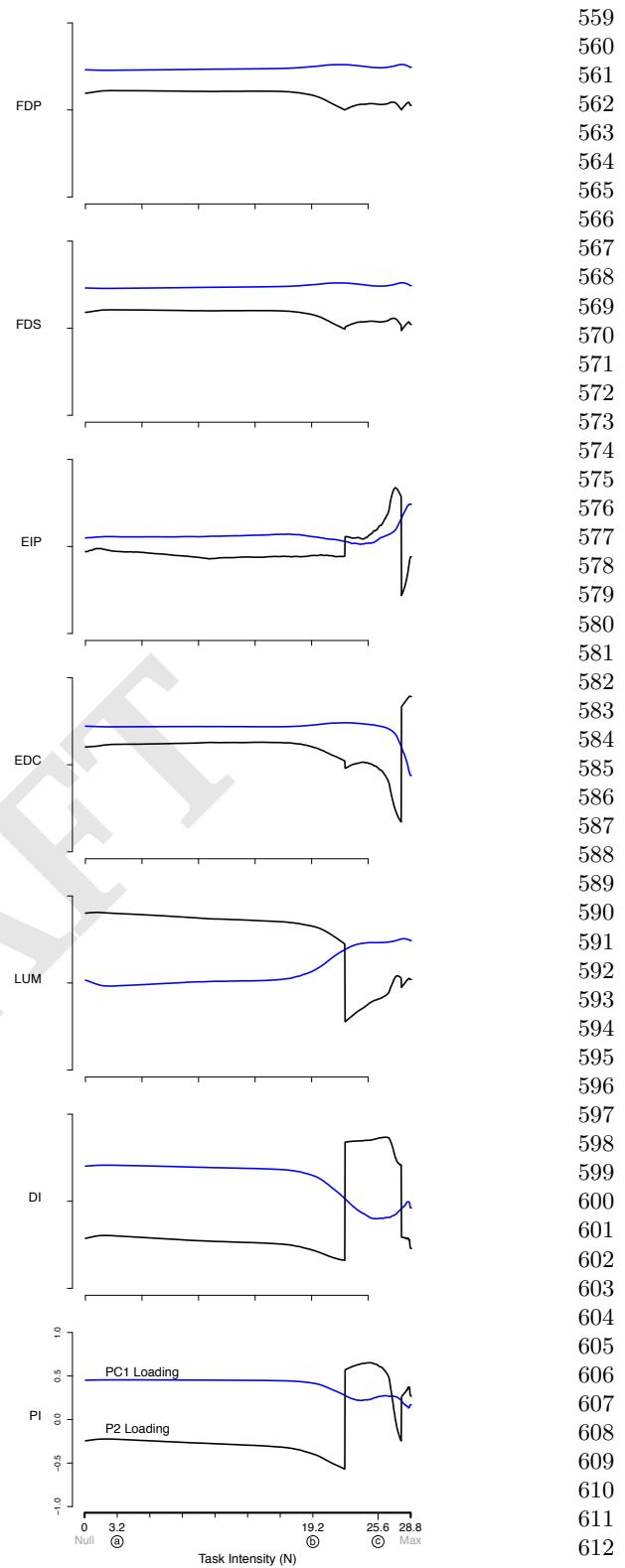
501 These changes we see in (i) the lower and upper bounds of  
502 activations, and in (ii) the relative variance explained and (iii)  
503 loadings for PC1 and PC2, demonstrate that the size, shape  
504 and orientation of the feasible activation space changes with  
505 task intensity. Moreover, these changes represent the best-case  
506 scenario given the absence of experimental noise, within- and  
507 across-subject variability, and measurement error.

508 **Changes in the probabilistic structure of the feasible activation  
509 space with increasing task intensity, or how muscle re-  
510 dundancy is lost.** The maximal static fingertip force vector in  
511 a given direction is produced by a single and unique combina-  
512 tion of muscle activations. In contrast, any sub-maximal mag-  
513 nitude of that same vector is produced by an infinite number  
514 of solutions (12, 18, 19, 34). Our analysis of feasible activation  
515 spaces at different task intensities allows us to characterize how  
516 this redundancy changes and is lost. The histogram heatmaps  
517 in Fig. 7 illustrate the changes and shrinking of within-muscle  
518 density of valid activation levels for sub-maximal forces, con-  
519 verging to a single solution for maximal force output. These  
520 surface plots show how the normalized histograms (of 1,000  
521 valid activation levels for each muscle) change at each of 100  
522 levels of task intensity between 0 and 1. Following a muscle's  
523 column from bottom to top shows the activation histograms  
524 for each magnitude of distal force and ending, naturally, with  
525 a spike about the unique value at maximal force production.

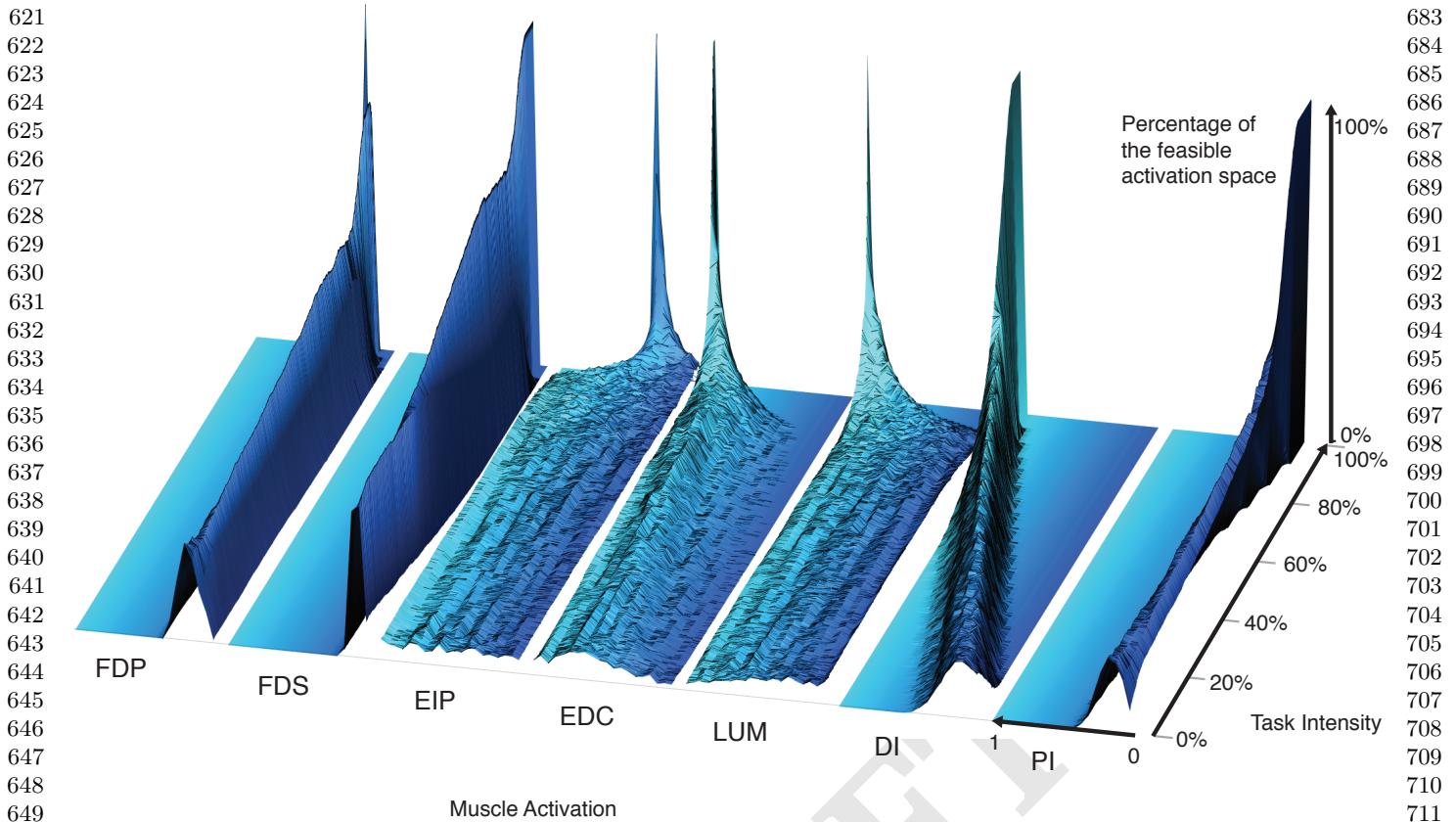
526 The flat areas in each surface plot (e.g. clearly visible  
527 for DI) represent muscle activation levels that are not valid  
528 for that task intensity. That is, there exist no valid muscle  
529 activation patterns that contain that muscle at that level, and  
530 thus no points are found there.

531 These plots show the nature and rate of convergence to the  
532 unique solution for maximal force output across muscles. We  
533 find that the histograms of activation levels for each muscle  
534 need not be symmetric, nor have the same shape (skewness  
535 and kurtosis) as the magnitude of the output force increases.  
536 For some muscles the convergence accelerates after 60% or  
537 80% of task intensity (as in LUM and EIP), while others  
538 converge monotonically along the entire progression (e.g. DI  
539 and PI). The peaks (i.e. modes) of each histogram at each  
540 task intensity represents the slice of the polytope that has  
541 the largest relative volume along that muscle dimension (i.e.,  
542 greatest frequency of that level of muscle activation across all  
543 valid solutions). Importantly, for most muscles (FDP, FDS,  
544 EIP, EDC, and LUM), the mode is not necessarily located at  
545 the same relative level of activation needed for maximal force  
546 output. That is, the histogram at high levels of force is not  
547 simply a shifted version of the histogram at low levels of force.  
548 The histograms for DI are the exception, whose modes seems  
549 to scale linearly with task intensity.

550 These histograms, in conjunction with the results in the  
551 parallel coordinate visualization, also demonstrate that the  
552 structure of feasible activation spaces cannot be inferred from  
553 their bounding boxes alone (i.e., upper and lower activation  
554 bounds for each muscle). An immediate example is how,  
555 for most task intensities, both EIP and LUM have similar  
556 lower and upper bounds near 0 and 1, respectively—yet their  
557 distributions are thoroughly distinct.



558  
559 **Fig. 6. PCA loadings change dramatically as task intensity increases** For each  
560 of 1,000 task intensities, we collected 1,000 points from the feasible activation space,  
561 and computed three principal components. Note that the signs of the loadings depend  
562 on the numerics of the PCA algorithm, and are subject to arbitrary flips in sign—  
563 thus for clarity we plot them such that FDP's loadings in PC1 are positive at all  
564 task intensities. Synergies at representative task intensities a, b, c in Fig. 5 differ.  
565 This reflects changes in the geometric structure of the feasible activation space as  
566 redundancy is lost.



**Fig. 7. The within-muscle probabilistic structure of feasible muscle patterns across 1,000 levels of fingertip task intensity.** The changes in the breadth and height for each muscle reveal muscle-specific consequences of task intensity on their probability distributions. The cross-section of each density plot is the 50-bin histogram of activation for each muscle, at that task intensity. Height represents the percentage of solutions for that task. The axis going into the page indicates increasing fingertip task intensity up to 100% of maximal. Color is used to provide perspective.

## Discussion

**Summary.** Feasibility theory, as a conceptual and computational approach, is a means to pierce the curse of dimensionality to establish a physics-based ground truth for neuromuscular control. This practical approach can now characterize—in a complete way—the set of all valid ways to activate multiple muscles to produce a given task. Feasible activation spaces are, in fact, *the* neuromechanical landscapes upon which all neuromuscular learning, control, and performance must occur. Therefore, we provide an integrative and unifying perspective that demonstrates how today’s dominant theories of neuromuscular control are alternative approximations to feasible activation spaces from optimization, geometric, and probabilistic perspectives.

**The value of a cost function.** Optimization is the oldest computational approach to finding valid muscle activation patterns that produce limb function (e.g., (12)). While optimization is a reasonable hypotheses to explore neuromuscular control (15), some criticize it as mathematical abstraction that anthropomorphizes neurons with the ability to choose, evaluate and follow cost functions in high-dimensions (35, 36). There is an intimate relationship between optimization and feasible activation spaces (37). Optimization is analogous to finding a best solution in the dark—guided by repeated evaluations of a cost-function. Computing the feasible activation space is

then a means to ‘turn on the lights’ to see all possible valid solutions independently of cost (18). Our complete sampling of high-dimensional feasible activation spaces (38, 39) allows us to compare and contrast *families* of solutions instead of *individual* optimal solutions for a particular cost function. Fig. 3 demonstrates a complete description of families of valid coordination patterns and their relationship to alternative costs. Importantly, similar valid muscle activation patterns can have dissimilar costs, and vice versa.

Because these explorations can be done for alternative cost functions, they can provide quantitative overall descriptions of high-dimensional ‘cost landscapes.’ By not having to insist on (or settle for) individual optimal—or near-optimal—solutions, we now have the same ability the nervous system has to explore, compare and contrast multiple valid ways to coordinate muscles. Importantly, the relationships among valid muscle activation patterns emerge naturally from the physical properties of the limb and definition of the task. This cost-agnostic approach allows us to re-evaluate our assumptions about what the nervous system cares—and does not care—about. Lastly, this cost-agnostic approach also provides a powerful tool for inverse optimization, i.e., uncovering latent cost functions from data (40). Our comparison across cost functions using parallel coordinates is already a form of inverse optimization.

**Structure, correlation, and synergies.** The physical properties of the limb and definition of the task also define a low-

745 dimensional structure of the feasible activation space (18).  
746 Therefore, it is expected that experimental recordings of muscle  
747 activations during limb function will exhibit a dimensionality  
748 that is smaller than the number of muscles (1, 7). Thus,  
749 applying PCA to the points sampled from the feasible activation  
750 space also finds that few PCs can explain the variance in  
751 the data.

752 This application of PCA at increasing task intensities (i.e.,  
753 as muscle redundancy is lost) allows us to demonstrate—for  
754 the first time to our knowledge—several important features  
755 and limitations of dimensionality reduction. For example, we  
756 see that the aspect ratio (Fig. 5) and orientation (Fig. 6) of the  
757 feasible activation spaces change as their size shrinks (Fig. 7).  
758 Thus, such *descriptive* synergies extracted from limited exper-  
759 imental observations likely do not generalize well across task  
760 intensities. It is important to distinguish *descriptive* synergies  
761 (the dominant approach in the literature to extract synergies  
762 from experimental data using dimensionality reduction tech-  
763 niques such as PCA) from *prescriptive* synergies (those known  
764 to be implemented by the controller) (18).

765 This also has important consequences to motor control and  
766 learning. Producing force vectors at the endpoint of a finger  
767 or limb with accurate magnitude and direction are critical  
768 for versatile manipulation and locomotion (41–43). If a given  
769 synergy can produce such accurate force vectors only for a  
770 given task intensity (and thus inaccurate ones at other in-  
771 tensities), then the attractiveness of synergies to simplify the  
772 neuromuscular control of the limb is reduced. To compensate,  
773 the nervous system would need to learn, recall and implement  
774 specific synergies for each force level. In prior experimental  
775 work, we have shown that the nervous system produces accu-  
776 rate fingertip forces of different magnitudes by, instead, likely  
777 scaling a remembered muscle activation pattern to produce  
778 forces of different magnitudes, together with a full-dimensional,  
779 real-time error correction neural controller (44). Note that  
780 interpreting this experimental result still as a synergy-based  
781 approach would defeat the purpose of synergies as a means to  
782 simplify the control by reducing its dimensionality.

783 Our results also show how experiments with realistically  
784 moderate numbers of participants and test trials likely do  
785 not contain sufficient data to produce robust estimates of de-  
786 scriptive synergies across task intensities. As per the curse  
787 of dimensionality, sampling uniformly at random from high-  
788 dimensional spaces is exponentially difficult. Thus, even for  
789 this anatomically complete 7-muscle finger model, PCA de-  
790 pends strongly on the number of independent observations,  
791 such as uncorrelated trials from one subject or different sub-  
792 jects. Figure 5 shows that 100 to 1,000 such ideal data points  
793 from a simulated ‘test subject’ are needed to produce accurate  
794 estimates of changes in PC1 and PC2 with task intensity (c.f.  
795 labels a vs. b vs. c). Future studies should explore how many  
796 experimental data points are sufficient from a given subject  
797 when recording from only a subset of the many (20+) muscles  
798 of human limbs in the presence of experimental noise, inherent  
799 stochasticity of EMG, and within- and between-subject vari-  
800 ability. Some studies have begun to ask subjects to explore  
802 different ways to perform a given task (45) (i.e., estimate  
803 the structure of the feasible activation space), but in practice  
804 such studies cannot likely collect sufficient data uniformly  
805 at random to obtain accurate estimates of the descriptive  
806 synergies (1). While our results suggest caution when inter-

807 preting synergies obtained experimentally, we underscore that  
808 dimensionality-reduction is a useful approach to capture global  
809 geometric properties of feasible activation spaces.

810 **Toward probabilistic neuromuscular control.** Our results are  
811 particularly empowering for the emerging field of probabilistic  
812 neuromuscular control (8?–10). Suppose that the nervous  
813 system uses some form of probabilistic or Bayesian learning  
814 and control strategy. Such approach requires two enabling—  
815 and biologically feasible—elements: *trial-and-error iterative*  
816 *exploration*, and *memory-based exploitation* of the probability  
817 density functions used to approximate the feasible activation  
818 spaces (8). The parallel coordinate plots and histograms  
819 in Fig. 2 and 7 provide, to our knowledge, the first com-  
820 plete (38, 39) characterization of such multi-dimensional joint  
821 probability density functions for a realistic tendon-driven sys-  
822 tem performing a well-defined task.

823 These techniques and results now empower the study of  
824 fundamental aspects of probabilistic control. For example, an  
825 organism can only execute so many trial-and-error iterations  
826 during learning, likely too few to completely and exhaustively  
827 sample the high-dimensional feasible space of interest. This  
828 makes it much more likely that, by virtue of being more  
829 easily found, an organism will find and preferentially exploit  
830 the strong modes (i.e., narrow and high peaks in Figs. 3, 4,  
831 and 7) of the multi-dimensional probability density functions  
832 than any other region of feasible activation spaces. Thus,  
833 first, the maximal ranges of feasible activations described by  
834 the bounding box (29, 30) may have little practical bearing  
835 on how those tasks are learned and executed. And second,  
836 those same strong modes would represent strong attractors  
837 to create and reinforce motor habits. Habitual control has  
838 been proposed based on experimental and empirical data as an  
839 alternative to a strict optimization approach to neuromuscular  
840 control (35). Our work now provides the computational means  
841 to link habitual to probabilistic control. This allows us to  
842 generate testable hypotheses of how these motor habits are  
843 defined by the structure of the feasible activation space, how  
844 they are learned by the organism, and how difficult or easy it  
845 is to break out of them.

846 Thus, motor learning likely needs to proceed from adopting  
847 easily-found solutions independently of their cost, to using  
848 some low dimensional approximation to the gradient of the cost  
849 landscape, to then transitioning to less likely but potentially  
850 less costly subregions of the solutions space. This integrative  
851 perspective leads us to propose a hybrid approach to motor  
852 learning and execution where the practical limits on trial-and-  
853 error iterations are coupled with the low-dimensional structure  
854 of the solution space to enable some form of heuristic local  
855 optimization to create sub-optimal motor habits. Importantly,  
856 the organism performs strict optimization or synergy control at  
857 its peril. Take, for example, the case of a 2-dimensional feasible  
858 activation space embedded in 3-D, Fig. ??e. Taking a step from  
859 any one valid point to another valid point on the plane runs the  
860 risk of ‘falling off’ the solution space and failing at the task—a  
861 risk that is exponentially exacerbated in higher-dimensions.  
862 Thus, improvements in the neighborhood of a good solution  
863 necessarily risk task failure and potential injury. These are all  
864 arguments in support of the evolutionary and developmentally  
865 useful strategy to use good-enough control based on habit or  
866 sensorimotor memory rather than optimization (35, 46). This  
867 may explain why mass practice and coaches are so critical to

869	achieve elite athletic performance (47).	931
870		932
871	<b>Clinical implications.</b> This line of thinking has consequences 872 to neurorehabilitation. Neurological conditions disrupt feasible 873 activation spaces, be it by affecting anatomy of the limb, 874 muscle strength and independence with which muscles can be 875 controlled. Functional recovery following the disruption, if 876 not destruction, of the landscape of valid muscle activation 877 patterns requires re-learning existent, or building new, proba- 878 bility density functions. This occurs just when older adults 879 suffer from reduced perceptuo-motor learning rates (48).	933
880	A probabilistic landscape for neuromuscular function begins 881 to explain why neurorehabilitation in aging adults is so difficult 882 (e.g., (49)) and why motor learning in children takes thousands 883 of repetitions (50)—while also generating new rehabilitation 884 strategies, and testable hypotheses around them, that leverage 885 knowledge of the nature and structure of feasible activation 886 spaces.	934
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931	where $H$ is the matrix of linear constraints defined by the muscu- loskeletal anatomy of the limb (29), $\mathbf{a}$ is the input vector of $n$ muscle activations, $\mathbf{f} \in \mathbb{R}^m$ is the $m$ -dimensional limb output ‘wrench’ (i.e., the forces and torques the finger can produce at the endpoint).	979
932	The output wrench, $m$ , is at most 6-dimensional (i.e., 3 forces 933 and 3 torques) depending on the number of kinematic degrees of 934 freedom of the limb, and usually $m < n$ because limbs have more 935 muscles than kinematic degrees of freedom (18). Muscles can only 936 pull, so elements of $\mathbf{a}$ cannot be negative, and are capped at 1 (i.e., 937 100% of maximal muscle activation).	980
938	What are the muscle coordination patterns that produce a given 939 task? As explained in (18), the task of producing a static fingertip 940 force vector is defined by specifying the desired values for the 941 elements of the endpoint forces and torques of $\mathbf{w}$ . Each such 942 constraint equation defines a hyperplane of dimension $n-1$ , and their 943 combination defines the task completely. The <i>feasible activation</i> 944 space of the task, if it is well posed (37), is defined by the points $\mathbf{a}$ 945 that lie within the $n$ -cube and at the intersection of all constraint 946 hyperplanes.	981
947	Geometrically speaking, the feasible activation space is a $(n-m)$ - 948 dimensional convex polytope $P$ embedded in $\mathbb{R}^n$ that contains all $n$ - 949 dimensional muscle coordination patterns (i.e., points $\mathbf{a}$ ) that satisfy 950 all constraints, and therefore can produce the task. Increasing 951 task specificity by adding more constraints naturally decreases 952 the dimensionality and changes the size and shape of the feasible 953 activation space (20, 30, 51).	982
954	<b>The Hit-and-Run algorithm uniformly samples from feasible activa- 955 tion spaces</b> Calculating the geometric properties of convex poly- 956 topes in high dimensions is computationally challenging. Taking 957 the generalized concept of an $n$ -dimensional volume as an example 958 of a geometric property of interest, the exact volume computations 959 for $n$ -dimensional polytopes is known to be tractable only in a poly- 960 nomial amount of time (i.e., $\#P$ -hard) (52). Currently available 961 volume algorithms can only handle polytopes embedded in small 962 dimensions like 10 or slightly more (53). Studying vertebrate limbs 963 in general, however, can require including several dozen muscles, 964 such as our studies of a 17-muscle human arm and a 31-muscle cat 965 hindlimb model (29); and other limb models have over 40 muscles 966 such as (1, 54–56).	983
967	Similar difficulties arise when computing other geometric proper- 968 ties such as the shape and aspect ratio of $P$ in high dimensions. We 969 and others have described polytopes $P$ by their bounding box (i.e., 970 the range of values in every dimension) (30, 33), but that singularly 971 overestimates the shape and volume of the feasible activation space 972 as discussed in (29). Take Fig. ??e as an example, where the bound- 973 ing box of the 2-dimensional polygon has a volume—even though a 974 plane has zero volume—, and can be almost as large as the positive 975 unit cube itself. Similar problems arise in the interpretation of the 976 inscribed and circumscribed ball (57).	984
977	We applied the Hit-and-Run method to sample points from the 978 feasible activation space—a method that is evaluated and justified in 979 (18?). This complete probabilistic method describes the structure 980 of feasible activation spaces $P$ with a set of uniformly-at-random 981 muscle activation patterns that produce the same wrench. This 982 enables us to derive descriptive statistics, histograms, and point 983 densities of the set of valid muscle activation patterns $\mathbf{a}$ uniformly 984 sampled from the polytope. To do so, we use the Hit-and-Run 985 method. We have presented a detailed explanation of the theory 986 (In Chapter 9 of (18)), and have justified the utility of this method 987 on tendon-driven models of the index finger (? ).	985
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993 where

$$\mathbf{a} = \begin{pmatrix} a_{FDP} \\ a_{FDS} \\ a_{EIP} \\ a_{EDC} \\ a_{LUM} \\ a_{DI} \\ a_{PI} \end{pmatrix} \quad [5]$$

1000 In Cartesian coordinates, the 4-D output wrench corresponds to  
1001 the anatomical directions shown in Fig. 1e.

$$\mathbf{w} = \begin{pmatrix} f_x \\ f_y \\ f_z \\ \tau_x \end{pmatrix} = \begin{pmatrix} f_{radial} \\ f_{distal} \\ f_{palmar} \\ \tau_{radial} \end{pmatrix} \quad [6]$$

1007 The biomechanical model  $H$  includes three serial links articulated  
1008 by four kinematic degrees of freedom (ad-abduction, flexion-  
1009 extension at the metacarpophalangeal joint, and flexion-extension at  
1010 the proximal and distal interphalangeal joints). The action of each  
1011 of the seven muscles (FDP: *flexor digitorum profundus*, FDS: *flexor*  
1012 *digitorum superficialis*, EIP: *extensor indicis proprius*, EDC: *exten-*  
1013 *sor digitorum communis*, LUM: *lumbrical*, DI: *dorsal interosseous*,  
1014 and PI: *palmar interosseous*) on each joint to produce torque is  
1015 given by the moment arm matrix  $R \in \mathbb{R}^{4 \times 7}$ . Lastly,  $J \in \mathbb{R}^{4 \times 4}$   
1016 and  $F_0 \in \mathbb{R}^{7 \times 7}$  are the Jacobian of the fingertip with 4 kinematic  
1017 degrees of freedom, and the diagonal matrix containing the maximal  
1018 strengths of the seven muscles, respectively (18, 44). The finger  
1019 posture was defined to be 0° ad-abduction and 45° flexion at the  
1020 metacarpophalangeal joint, and 45° and 10° flexion, respectively,  
1021 at the proximal and distal interphalangeal joints.

1022 **Feasible activation space for a static fingertip force task** Our goal  
1023 is to find the family of all feasible muscle activation patterns that  
1024 can produce a given task. In particular, the task we explored is  
1025 producing various magnitudes of a submaximal static force in the  
1026 distal direction  $f_{distal}$  — in the absence of any  $\tau_{radial}$ , shown in  
1027 Fig. 1f. Therefore the feasible activation space is a polytope  $P$  in  
1028 7-dimensional activation space that meets the following four linear  
1029 constraints in  $\mathbf{a}$  (18, 21, 44)

$$f_{radial} = 0 \quad [7]$$

$$f_{distal} = \text{desired magnitude as \% of maximal} \quad [8]$$

$$f_{palmar} = 0 \quad [9]$$

$$\tau_{palmar} = 0 \quad [10]$$

1032 These four constraints on the static output of the finger yield a 3-  
1033 dimensional (i.e.,  $7 - 4 = 3$ ) polytope  $P$  embedded in 7-dimensional  
1034 activation space. For details on how to create such models, apply  
1035 task constraints and find such polytopes via vertex enumeration  
1036 methods, see (18).

1037 For the index finger model used in this paper, the published  
1038 maximal feasible force in the distal direction is 28.81 Newtons. We  
1039 defined the normalized desired distal task intensity as a value ranging  
1040 between 0 and 1, i.e., each submaximal force can be produced by  
1041 any of the points contained in its corresponding feasible activation  
1042 space. For the production of a maximal force, the feasible activation  
1043 space shrinks to a single point (12, 19, 37, 44).

#### 1044 Analysis of feasible activation spaces.

1045 **Parallel coordinates visualization shows the location of all points**  
1046 **across all dimensions** Parallel coordinates are a common graphical  
1047 approach to visualize interactions among high-dimensional data  
1048 (59, 60). To demonstrate this visualization method, consider the  
1049 results of the simple 3-dimensional example shown in Fig. 2. We  
1050 begin by drawing  $n$  parallel vertical lines for each of the dimensions  
1051  $n$  (i.e., 3 muscles). With the axis limits of each line set between 0  
1052 and 1, each point (Fig. 2a) is then represented by connecting their  
1053 coordinates by  $n - 1$  lines as shown in Fig. 2b.

1054 **Neural and metabolic cost functions** As mentioned in the Introduction,  
1055 the field of neuromuscular control has a long historical tradition of using optimization to find muscle activation patterns

1055 that minimize effort, which requires the (often contentious) definition  
1056 of cost functions (12, 13, 16, 19). Therefore, we used four representative  
1057 cost functions to calculate the relative fitness of each of the muscle activation  
1058 patterns sampled—in effect also calculating the fitness landscape across all possible solutions. The cost functions are defined at the level of neural effort ( $L_1$ , and  $L_2$  norms);  
1059 and at the level of metabolic cost, thought to be approximated by neural drive weighted by the strength of each muscle ( $L_1^w$  and  $L_2^w$  norms) (13, 16).

1060 To visualize the costs associated with each valid muscle coordination  
1061 pattern, we simply added four vertical lines at the far right of the parallel coordinates plot, one for each cost function, Fig. 2c. The variables  $a_i$  and  $F_{0i}$  represent the activation of the  $i^{th}$  muscle  
1062 in a given muscle activation pattern, and the maximal strength of each muscle (13, 16). Maximal muscle strengths are approximated by multiplying each muscle's physiological cross-sectional area,  
1063 in  $\text{cm}^2$ , by the maximal active muscle stress of mammalian muscle,  
1064 35  $\text{N}/\text{cm}^2$  (61). These four cost functions are but four examples as the literature contains many others as any investigator is in fact  
1065 free to chose any cost function deemed relevant to their study.

1066 **Histograms of the activation level of each muscle across all valid solutions** Muscle-by-muscle histograms are another straightforward  
1067 way to visualize the many points sampled from the convex polytope.  
1068 Histograms are particularly helpful because they are approximations  
1069 to probability density functions. They visualize the relative number  
1070 of solutions (i.e., density of solutions) that required a particular  
1071 level of activation from a particular muscle within its range of [0, 1].  
1072 In addition, the upper and lower bounds of the histograms show,  
1073 in fact, the size of the side of the bounding box of the polytope in  
1074 every dimension (i.e., for independently controlled muscle).

1075 **Dimensionality reduction** Investigators have repeatedly reported  
1076 that electromyographical signals (i.e., experimental estimates of  
1077 muscle activation patterns) tend to exhibit strong correlations with  
1078 one another. In these experimental descriptions of dimensionality  
1079 reduction of neuromuscular control, only few independent functions—  
1080 sometimes called synergies—suffice to explain the majority of the  
1081 variability in the observed muscle activation patterns (1–4, 6, 7, 62).  
1082 Principal components analysis (PCA) is a widely used technique  
1083 to extract these few independent basis functions (correlation vectors  
1084 called principal components, PCs) from high-dimensional data (63).  
1085 In this case, PCs are often called the experimental representations  
1086 of synergies of neural origin (1).

1087 Therefore, we also applied PCA to points (i.e., muscle coordination  
1088 patterns) sampled from the feasible activation space at each force level.  
1089 This provides the PCs that describe the correlations among valid muscle activation  
1090 patterns for a given task. For example, the feasible activation space  $P$  in Fig. ??e is a 2-dimensional  
1091 polygon embedded in 3-dimensional activation space. Thus, applying  
1092 PCA to points sampled from the polygon will extract 2 synergies  
1093 (i.e., 3-dimensional correlation vectors PC1 and PC2) that wholly  
1094 explain the feasible activation space. By extension, in the case of  
1095 fingertip force production in Fig. 1, the feasible activation space is  
1096 a 3-dimensional polytope embedded of the 7-dimensional activation  
1097 space. And PCA should extract, by construction, as many synergies  
1098 as there are dimensions in the feasible activation space. For static  
1099 force production with the index fingertip (i.e., 7 muscles and 4  
1100 constraints), we know that 3 principal components should describe  
1101 100% of the variance in points sampled from the feasible activation  
1102 space (i.e., 7-dimensional correlation vectors PC1, PC2, and PC3).

1103 Applying PCA to our data allows us to test whether and how  
1104 its results change when applied to feasible activation spaces for  
1105 different magnitudes of fingertip force. We applied PCA to feasible  
1106 activation spaces for fingertip task intensities ranging from 0 to 90%  
1107 of maximal. We compare both the variance explained by each PC  
1108 and their vector direction (i.e., the ‘loadings’ or correlations among  
1109 muscle (64)) as the force level increases. Lastly, we tested whether  
1110 our PCA results are sensitive to the number of points sampled  
1111 from each feasible activation space. This is important because  
1112 experimental studies test 10 or so subjects in practice, which may  
1113 be too few when sampling from high-dimensional spaces.

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- Kutch J, Valero-Cuevas F (2012) Challenges and new approaches to proving the existence of muscle synergies of neural origin. *PLoS Computational Biology* 8(5):e1002434.
  - Steele KM, Tresch MC, Perreault EJ (2013) The number and choice of muscles impact the results of muscle synergy analyses. *Frontiers in computational neuroscience* 7.
  - Bizzi E, Cheung VC (2013) The neural origin of muscle synergies. *Frontiers in computational neuroscience* 7.
  - Dingwell JB, John J, Cusumano JP (2010) Do humans optimally exploit redundancy to control step variability in walking? *PLoS computational biology* 6(7):e1000856.
  - Rácz K, Valero-Cuevas FJ (2013) Spatio-temporal analysis reveals active control of both task-relevant and task-irrelevant variables. *Frontiers in computational neuroscience* 7.
  - Steele KM, Tresch MC, Perreault EJ (2015) Consequences of biomechanically constrained tasks in the design and interpretation of synergy analyses. *Journal of neurophysiology* 113(7):2102–2113.
  - Alessandro C, Delis I, Nori F, Panzeri S, Berret B (2013) Muscle synergies in neuroscience and robotics: from input-space to task-space perspectives. *Frontiers in computational neuroscience* 7.
  - Kording KP, Wolpert DM (2004) Bayesian integration in sensorimotor learning. *Nature* 427(6971):244–247.
  - Kording KP (2014) Bayesian statistics: relevant for the brain? *Current Opinion in Neurobiology* 25:130 – 133. Theoretical and computational neuroscience.
  - Berniker M, O'Brien MK, Kording KP, Ahmed AA (2013) An examination of the generalizability of motor costs. *PLoS one* 8(1):e53759.
  - Sanger TD (2011) Distributed control of uncertain systems using superpositions of linear operators. *Neural computation* 23(8):1911–1934.
  - Chao E, An K (1978) Graphical interpretation of the solution to the redundant problem in biomechanics. *Journal of Biomechanical Engineering* 100:159–67.
  - Priulitsky BI (2000) Muscle coordination: the discussion continues. *Motor Control* 4(1):97–116. 0 1087-1640 Journal article.
  - Scott SH (2004) Optimal feedback control and the neural basis of volitional motor control. *Nature Reviews Neuroscience* 5(7):532–546.
  - Todorov E, Jordan MI (2002) Optimal feedback control as a theory of motor coordination. *Nature neuroscience* 5(11):1226–1235.
  - Crowninshield R, Brand R (1981) A physiologically based criterion of muscle force prediction in locomotion. *Journal of Biomechanics* 14(11):793–801.
  - Higginson J, Neptune R, Anderson F (2005) Simulated parallel annealing within a neighborhood for optimization of biomechanical systems. *Journal of biomechanics* 38(9):1938–1942.
  - Valero-Cuevas FJ (2015) *Fundamentals of Neuromechanics*, Biosystems and Biorobotics. (SpringerVerlag London) Vol. 8.
  - Spoor C (1983) Balancing a force on the fingertip of a two-dimensional finger model without intrinsic muscles. *Journal of Biomechanics* 16(7):497–504.
  - Kuo A, Zajac F (1993) Human standing posture: multi-joint movement strategies based on biomechanical constraints. *Progress in Brain Research* 97:349–358.
  - Valero-Cuevas FJ, Zajac FE, Burgar CG (1998) Large index-fingertip forces are produced by subject-independent patterns of muscle excitation. *Journal of Biomechanics* 31:693–703.
  - Gallego JA, Perich MG, Miller LE, Solla SA (2017) Neural manifolds for the control of movement. *Neuron* 94(5):978–984.
  - Bellman R, Osborne H (1958) Dynamic programming and the variation of green's functions. *Journal of Mathematics and Mechanics* pp. 81–85.
  - Bellman RE (2015) *Adaptive control processes: a guided tour*. (Princeton university press).
  - Avis D, Fukuda K (1992) A pivoting algorithm for convex hulls and vertex enumeration of arrangements and polyhedra. *Discrete & Computational Geometry* 8(3):295–313.
  - Valero-Cuevas FJ, Hoffmann H, Kurze MU, Kutch JJ, Theodorou EA (2009) Computational models for neuromuscular function. *IEEE Reviews in Biomedical Engineering* (2) October p. 110n135.
  - Theodorou E, Valero-Cuevas FJ (2010) Optimality in neuromuscular systems in *Engineering in Medicine and Biology Society (EMBC), 2010 Annual International Conference of the IEEE*. (IEEE), pp. 4510–4516.
  - Scholz JP, Schöner G (1999) The uncontrolled manifold concept: identifying control variables for a functional task. *Exp Brain Res* 126:289–306.
  - Valero-Cuevas FJ, Cohn BA, Yingvason HF, Lawrence EL (2015 In Press) Exploring the high-dimensional structure of muscle redundancy via subject-specific and generic musculoskeletal models. *Journal of Biomechanics* doi:10.1016/j.jbiomech.2015.04.026.
  - Sohn MH, McKay JL, Ting LH (2013) Defining feasible bounds on muscle activation in a redundant biomechanical task: practical implications of redundancy. *Journal of biomechanics* 46(7):1363–1368.
  - Venkadesan M, Valero-Cuevas FJ (2008) Neural control of motion-to-force transitions with the fingertip. *J. Neurosci.* 28:1366–1373.
  - Valero-Cuevas FJ, Towles JD, Hertz VR (2000) Quantification of fingertip force reduction in the forefinger following simulated paralysis of extensor and intrinsic muscles. *Journal of biomechanics* 33(12):1601–1609.
  - Kutch JJ, Valero-Cuevas FJ (2011) Muscle redundancy does not imply robustness to muscle dysfunction. *Journal of Biomechanics* 44(7):1264–1270.
  - Valero-Cuevas FJ (2000) Predictive modulation of muscle coordination pattern magnitude scales fingertip force magnitude over the voluntary range. *J. Neurophysiol.* 83:1469–1479.
  - De Rugy A, Loeb GE, Carroll TJ (2012) Muscle coordination is habitual rather than optimal. *The Journal of Neuroscience* 32(21):7384–7391.
  - Loeb G (2012) Optimal is not good enough. *Biological Cybernetics* 106(11-12):757–765.
  - Chvatal V (1983) *Linear programming*. (Macmillan).
  - Smith RL (1984) Efficient monte carlo procedures for generating points uniformly distributed over bounded regions. *Operations Research* 32(6):1296–1308.
  - Lovász L (1999) Hit-and-run mixes fast. *Mathematical Programming* 86(3):443–461.
  - Tsirakos D, Baltzopoulos V, Bartlett R (1997) Inverse optimization: functional and physiological considerations related to the force-sharing problem. *Critical Reviews™ in Biomedical Engineering* 25(4-5).
  - Cole KJ (2006) Age-related directional bias of fingertip force. *Experimental brain research* 175(2):285–291.
  - Valero-Cuevas FJ, Zajac FE, Burgar CG (1998) Large index-fingertip forces are produced by subject-independent patterns of muscle excitation. *Journal of Biomechanics* 31(8):693–704.
  - Donegan JM, Shipman DW, Kram R, Kuo AD (2004) Mechanical and metabolic requirements for active lateral stabilization in human walking. *Journal of biomechanics* 37(6):827–835.
  - Valero-Cuevas FJ (2000) Predictive modulation of muscle coordination pattern magnitude scales fingertip force magnitude over the voluntary range. *J Neurophysiol* 83(3):1469–1479.
  - Berger DJ, d'Avella A (2014) Effective force control by muscle synergies. *Frontiers in computational neuroscience* 8.
  - Fu Q, Santello M (2012) Context-dependent learning interferes with visuomotor transformation for manipulation planning. *Journal of Neuroscience* 32(43):15086–15092.
  - Gladwell M (2008) *Outliers: The story of success*. (Hachette UK).
  - Coats RO, Wilson AD, Snapp-Chidts W, Fath AJ, Bingham GP (2014) The 50s cliff: perceptuo-motor learning rates across the lifespan. *PLoS one* 9(1):e85758.
  - Hardwick RM, Rajan VA, Bastian AJ, Krakauer JW, Celnik PA (2016) Motor learning in stroke: Trained patients are not equal to untrained patients with less impairment. *Neurorehabilitation and Neural Repair* p. 1545968316675432.
  - Adolph KE, et al. (2012) How do you learn to walk? thousands of steps and dozens of falls per day. *Psychological science* 23(11):1387–1394.
  - Inouye JM, Valero-Cuevas FJ (2016) Muscle synergies heavily influence the neural control of arm endpoint stiffness and energy consumption. *PLoS Comput Biol* 12(2):e1004737.
  - Dyer M, Frieze A, Kannan R (1989) A random polynomial time algorithm for approximating the volume of convex bodies. *Proc. of the 21st annual ACM Symposium of Theory of Computing* pp. 375–381.
  - Büeler B, Enge A, Fukuda K (2000) Exact volume computation for polytopes: A practical study. *Polytopes: Combinatorics and Computation* 29:131–154.
  - Arnold EM, Ward SR, Lieber RL, Delp SL (2010) A model of the lower limb for analysis of human movement. *Annals of biomedical engineering* 38(2):269–279.
  - Hammer SR, Seth A, Delp SL (2010) Muscle contributions to propulsion and support during running. *Journal of biomechanics* 43(14):2709–2716.
  - De Sapio V, Earl D, Green R, Saul K (2014) Human factors simulation using demographically tuned biomechanical models in *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*. (SAGE Publications Sage CA: Los Angeles, CA), Vol. 58, pp. 944–948.
  - Inouye JM, Kutch JJ, Valero-Cuevas FJ (2014) Optimizing the topology of tendon-driven fingers: Rationale, predictions and implementation in *The Human Hand as an Inspiration for Robot Hand Development*. (Springer), pp. 247–266.
  - Valero-Cuevas F, Hoffmann H, Kurze M, Kutch J, Theodorou E (2009) Computational models for neuromuscular function. *Biomedical Engineering, IEEE Reviews in* 2:110–135.
  - Bachynskyi M, Oulasvirta A, Palmas G, Weinkauf T (2013) Biomechanical simulation in the analysis of aimed movements in *CHI'13 Extended Abstracts on Human Factors in Computing Systems*. (ACM), pp. 277–282.
  - Krekel PR, et al. (2010) Visual analysis of multi-joint kinematic data in *Computer Graphics Forum*. (Wiley Online Library), Vol. 29, pp. 1123–1132.
  - Zajac FE (1993) Muscle coordination of movement: a perspective. *J Biomech* 26 Suppl 1:109–124.
  - Krishnamoorthy V, Goodman S, Zatsiorsky V, Latash ML (2003) Muscle synergies during shifts of the center of pressure by standing persons: identification of muscle modes. *Biological cybernetics* 89(2):152–161.
  - Clewley RH, Guckenheimer JM, Valero-Cuevas FJ (2008) Estimating effective degrees of freedom in motor systems. *IEEE Trans Biomed Eng* 55:430–442.
  - Valero-Cuevas FJ, Klamroth-Marganska V, Winstein CJ, Riener R (2016) Robot-assisted and conventional therapies produce distinct rehabilitative trends in stroke survivors. *Journal of neuroengineering and rehabilitation* 13(1):92.