One motor cortex, two different views

TO THE EDITOR—In a recent paper in *Nature Neuroscience*, Todorov[1] referred to our finding that a motor cortical representation of hand trajectory during spiral drawing precedes the hand's movement by an interval that varies with path curvature[2,3]. Although there are several possible explanations for this finding, Todorov, using a simplistic model, argued that because cortical cells share common properties with muscles, this relationship could be due to a combination of inertia, viscosity and stiffness acting on the acceleration, speed and position of the arm, respectively. Although simple, his model is flawed and cannot support this conclusion.

The author models a multijoint arm as a simple cantilever that is converted to single point-mass equation using a Jacobian transformation (web supplement A, http://www.nature.com/neuro/web_specials/). The arm's properties were derived from a simplified version of muscle whose activity is a linear combination of motor cortical activity. This model was used to reinterpret our results[2,3]. In our study, monkeys drew spirals on a vertically oriented computer touchscreen. The center of the spiral was located in front of the monkey, between its shoulders. According to Todorov's model, this location corresponded to the equilibrium point of the arm—the location where the parameters in his model would force the arm to rest. Todorov assumed that cortical activity reflects the inertia, viscosity and stiffness of the arm and showed that his model produces the same variable lags as our cortical population vectors. However, any acceleration representation in the cortical activity would actually decrease lags as a function of curvature, which is exactly opposite to our finding (web supplement B, http://www.nature.com/neuro-/web_specials/).

The increased lag with increasing curvature shown in Todorov's article is due to his positional term. The idea that extrinsic position may be a factor in motor cortical activity is not new[4–6]. However, Todorov's method of equating extrinsic position representation to muscle stiffness is incorrect. This model assumes that muscle viscoelastic properties are independent of muscle activation. Thus, even an inactivated muscle will act as a large spring pulling the arm back to some equilibrium position. In real muscle, the force–length and force–velocity relationships are modulated by muscle activation such that at zero activation, the muscle is essentially a non-force producer. In the real world, the combination of gravity and inactive muscles will force the arm to fall to the side. In Todorov's model, the combined effect of gravity and muscle stiffness on inactive muscles would make the hand float at mid-chest level; muscle activity would be required to force the arm down below chest level. This, of course, is unrealistic. Viscoelastic models like the ones used by Todorov are only valid for perturbation studies where both posture and neural activity are assumed to be constant. Using such equations to solve for time-varying muscle activations violates the basic assumptions of perturbation models. Simple dynamic models can be useful to explain arm mechanics. However, when the models are not consistent with basic physiology, exclude important phenomena, and violate inherent assumptions, they cannot be compared to empirical data.

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TO THE EDITOR—Here we refute claims by Todorov[1] and Scott[7] that the importance of target direction as an explanatory factor for cortical activity in a regression analysis we performed[5] is an 'artifact' of a square-root transformation of neural discharge rates. Specifically, it was touted by Scott[7] that "squaring [*sic*] the discharge rate of neurons in order to stabilize the variance ... causes a dramatic increase in the percentage of neurons that appear to represent movement direction (from 17% [*sic*] to 43% in Todorov's model)." The data to which Todorov[1] referred concerned the percentages of cells for which a particular variable yielded the highest R^2 when used alone in the regression. We re-analyzed these data using the regression analysis we used previously[5] but without any transformation of the discharge rate. The results of the two analyses were practically identical, the average absolute difference being only 1.9% (http://www.nature.com/neuro/web_specials/). However, there was a statistically significant improvement of the regression fit when the square-root transformation was used. The median R^2 for the square-root transformed data was 0.5811, as compared to 0.544 for the non-transformed data ($P < 0.0001$, Wilcoxon's signed-rank test). This was anticipated, because the square-root transformation is expected to make the distribution of counts more symmetrical. This transformation is routinely used when analyzing counts[8–10], given the commonly highly skewed distribution of such data. Finally, we analyzed the data without any transformation or smoothing. In this case, the agreement with the original analysis was even closer, the average absolute difference being only 0.86%. We conclude that the relationship between neural activity and movement parameters found earlier[5] holds irrespective of the specific transformation and/or smoothing used. Finally, while we dealt above with the issue of square-root transformation because of the more general importance of this transformation for analyzing neuronal spike counts, there are also numerous other points raised by Todorov[1] which we also dispute, including the force direction/magnitude issue, which we cannot critically discuss due to space limitations.

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REPLY TO MORAN AND SCHWARTZ—Assuming that M1 cells control the activation of muscle groups, I have previously derived an equation[1] relating the M1 population vector (PV) to hand kinematics and kinetics. In addition to force and acceleration terms, this equation includes velocity and positional terms needed to compensate for muscle visco-elasticity. The interplay among these terms offers a simple explanation to several puzzling phenomena[1] including the curvature-dependent time-lag between PV direction and tangential velocity[2,3]. The strength of the model is that multiple phenomena are explained simultaneously, using the most basic properties of the musculoskeletal apparatus and thus avoiding the danger of curve fitting.

Moran and Schwartz claim that the fit to their data[2,3] is somehow an artifact of the approximation I used, and that the results will change if additional details are considered. It is not explained how a first-oreer approximation could produce such

artifacts. The absence of gravity and activation-dependent stiffness in my model are discussed at length, without any explanation as to why adding them should change the results. Unlike hand acceleration, which is time-varying, the gravitational force is roughly constant for small variations in limb configuration. Therefore, its effect is absorbed in the baseline (defined as postural activity in the center of the workspace). The constant stiffness approximation is reasonable once a certain activation level is reached[11]. It is true that setting stiffness to zero abolishes the time lag–curvature effect; however, that point is irrelevant—whether or not muscle stiffness is constant, it certainly exists and there is no justification for setting it to zero. To compensate for muscle stiffness, M1 cells have to exhibit well-documented positional gradients—which, in combination with the acceleration term, produce the negative time lag–curvature relationship[1].

Moran and Schwartz have only shown that my model is approximate—which is very different from being "flawed." Still, is it possible that the results are an artifact of the approximation, for reasons that these authors did not identify? To assess the sensitivity to previously unmodeled details, I repeated the analysis using a state-of-the-art muscle model[12] (http://www.nature.com/neuro/web_specials/). Muscle force was expressed as a complex function of muscle length, velocity and stimulation frequency; this function depends on 19 experimentally derived parameters and incorporates numerous results from muscle physiology[12]. For a wide range of parameters, the predicted relationship between PV time lag and path curvature was quantitatively similar to the original result[1] as well as to the experimental data[2,3]. Thus, when Moran and Schwartz wrote that my model "is not consistent with basic physiology, excludes important phenomena, and violates inherent assumptions," their concerns were misplaced.

REPLY TO GEORGOPOULOS AND ASHE—In their letter, Georgopoulos and Ashe address the issue of whether data preprocessing affects M1 cell classification. Their results do not refute my main point[1], which is that previous classification procedures[5,13] can be seriously biased—with or without data preprocessing. Here I focus on the procedure[5] for classifying cells as direction- (D), position- (P), velocity- (V) or acceleration-related (A) according to the largest R^2.

By definition, the bias of a statistical estimator is the expected difference between the correct and estimated values of a given parameter. The identical percentages found by Georgopoulos and Ashe with and without data preprocessing only prove that, for this particular dataset, the bias is equal in both cases. The value of this bias cannot be inferred from their results (or anything else computed on real data), because the correct answer is unknown. In the absence of analytical insight, the only way to identify the bias of an estimator is to apply it to synthetic datasets where the correct answer is known. When applied to synthetic data[1] with no separate directional component, the above classification procedure finds D 43%, V 39%, P 16%, A 2% on smoothed square-root-transformed spike trains, and D 26%, V 56%, P 16%, A 2% on raw binned spike trains (different from continuous mean firing rates which were labelled MFR previously[1]). The effects of the data transformation (8% on average) are to be expected in general, and could exist in other datasets. With or without the transformation, the above percentages are very far from the correct answer: D 0%, V 49%, P 46%, A 5%—that is, the classification procedure itself is biased. Thus the burden of proof lies on Georgopoulos and Ashe. Unless they identify the exact conditions under which their procedure is unbiased, and ascertain by independent means that these conditions hold for the M1 population, their results remain hard to interpret.

To gain more insight into why the R^2 classification procedure fails, I analyzed the family of synthetic responses misclassified as directional (http://www.nature.com/neuro/web_specials/). These responses do not look directional: the temporal fluctuations of the underlying position, velocity and acceleration terms do not cancel out. The artificially created 'directional' region of parameter space is centered at the point where the correct classification boundaries meet. Therfore responses are misclassified as directional just because they do not fit well in the other categories. It would be interesting to re-analyze the data of Georgopoulos and Ashe for that possibility. Do responses labeled as directional vary only with movement direction and contain no systematic temporal fluctuations (which is how a truly directional cell should behave), or do they fluctuate over time in ways that do not happen to fit in any of the alternative categories? The latter type of response is more properly labeled 'unknown' rather than 'directional.'

Finally, this debate obscures a more fundamental problem[1,14] with M1 cell classification, a problem that remains even if unbiased procedures are developed. The different components of the cell response are not fixed, but instead increase monotonically with the magnitude of the corresponding kinematic and kinetic terms. Thus a cell classified in one task as 'velocity-related' could become 'position-related' in another task if the movement is slow enough, 'acceleration-related' if the movement is fast enough, and 'load-related' if a large enough external load is imposed (http://www.nature.com/neuro/web_specials/). Given this sensitivity to task parameters, classifying M1 cells according to the largest component of their response should perhaps be avoided altogether.

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REPLY—The article by Todorov[1] and associated letters illustrate clear opinion differences regarding the function of motor cortex during goal-directed arm movements. This controversy is partially generated by the different experimental protocols used to examine motor cortex function in non-human primates. The first, introduced by Evarts, examines single-joint movements and relates neural activity to muscle-based or joint-based variables[15]. The second, introduced by Georgopoulos, examines whole-arm movements and relates neural activity to hand-based variables[16]. Practitioners of the former find correlates of muscle-based or joint-based variables; practitioners of the latter find correlates of hand-based variables.

T. S. Kuhn captures the present situation: "proponents of competing paradigms practice their trades in different worlds ... the two groups of scientists see different things when they look from the same point in the same direction."[17] With regard to motor cortex function, neural correlates of hand direction are seen as evidence by one group that hand direction is an important and potentially dominant signal, whereas the other group views this observation as an obvious by-product of neural activity that controls muscles to move the limb.

These differences of opinion are important for understanding not only the function of motor cortex, but also the function of other cortical and subcortical regions of the CNS, such as the spinal cord. At the extremes, the spinal cord could be viewed as the central location where all decisions on the details of motor selection are generated from a simple descending command specifying the global goal of the task. Alter-

Daniel Moran and Andrew Schwartz - Web Supplement A

The author models a multijoint arm as a simple cantilever which is converted to single point-mass equation using a Jacobian transformation. Thus:

$$\sum F_m + F_e = m\ddot{x} \qquad 1$$

where $\boldsymbol{F_m}$ represents individual muscle forces and $\boldsymbol{F_e}$ represents any external forces applied to hand (*e.g.*, manipulandum), $\boldsymbol{m}$ represents the inertia of the arm and $\ddot{x}$ represents hand acceleration. The arm's combined muscle properties were derived from a simplified version of muscle activity defined as:

$$f(a,l,\dot{l}) = a - k(l_0 - l) - \lfloor b\dot{l} \rfloor \qquad 2$$

where $\boldsymbol{f, a, l, l_0}$ represent a single muscle's force, activation, length, and rest length, respectively. Summing Equation 2 over all muscles, and substituting into Equation 1 yields:

$$\sum au + F_e = m\ddot{x} + b\dot{x} + kx \qquad 3$$

where the viscous (***b***) and elastic (***k***) terms are due combined muscle properties. The left term in Equation 3 represents muscle activation (multiplied by the muscle's preferred direction) which the author equates with M1 activity (*i.e.*, a motor cortical cell is an upper motor neuron). Therefore, the first term of Equation 3 represents a motor cortical population vector which, when there are no external forces, is a linear combination of acceleration, velocity and position of the hand.

Daniel Moran and Andrew Schwartz - Web Supplement B

The effect of acceleration on lag in Todorov's formulation can be demonstrated by eliminating the position term (*i.e.*, setting the stiffness coefficient to zero) in his lag equation (Figure 4 caption). Figure 1 shows that increasing acceleration actually decreases lag in drawing tasks. Thus, acceleration has exactly the opposite effect of that needed to explain our observations. Therefore, the increased lags with increasing curvature shown in Figure 4 of Todorov's article are due solely to his positional term. This contrary effect of acceleration is due to the inverse speed-curvature relation characteristic of drawing movements (*i.e.*, $^2/_3$ power law). When drawing the outside of a spiral, acceleration is low and velocity is high; thus, the phase of a weighted signal of velocity and acceleration would lie closer to the velocity signal than the acceleration signal. When the hand is on the inside of the spiral, the opposite is true and a mixed signal would be closer to the acceleration signal in phase. However, because the angular velocity of the movement increases with higher curvature, the time lag actually decreases. This is shown graphically in Figure 2 where a mixed signal of 50% velocity and 50% acceleration is compared temporally to velocity during a spiral drawing task adhering to the $^2/_3$ power law.

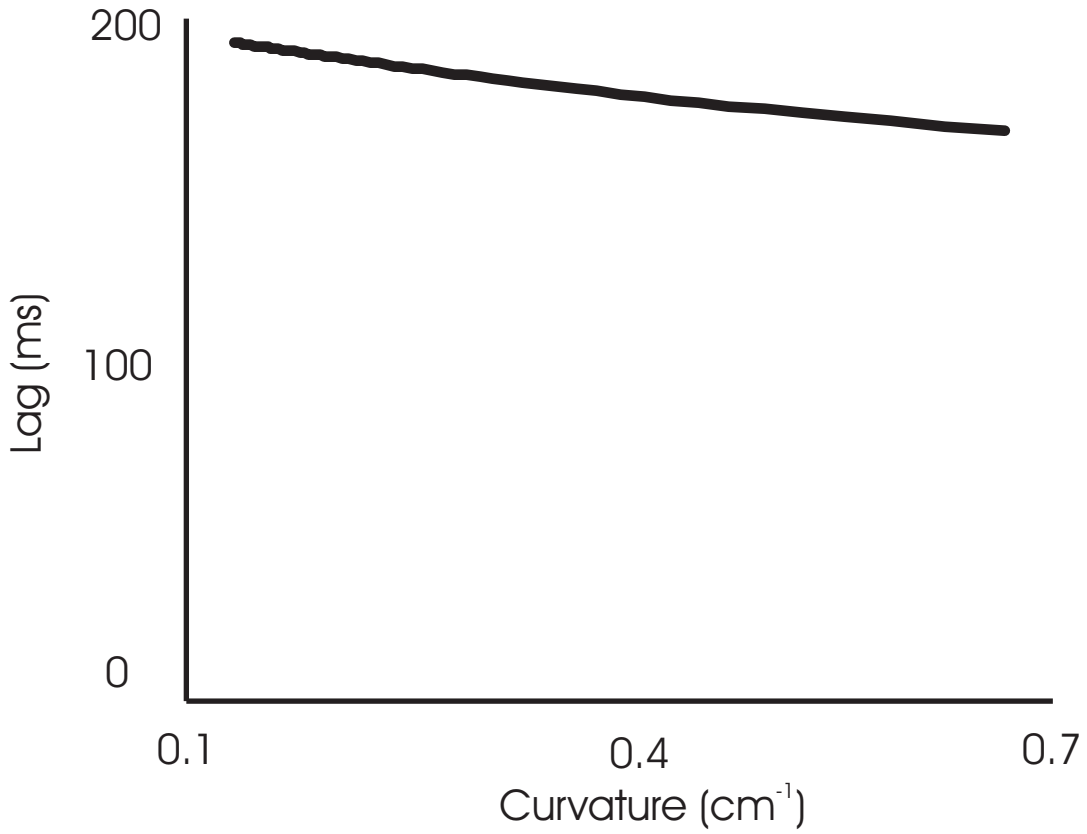

Figure 1: Effects of acceleration on M1 population vector lags as a function of curvature. Even though acceleration increases under higher curvature, the time lag of a PV sensitive to both acceleration and velocity decreases. Based on equation in Figure 4 caption of Todorov's paper without the stiffness term.

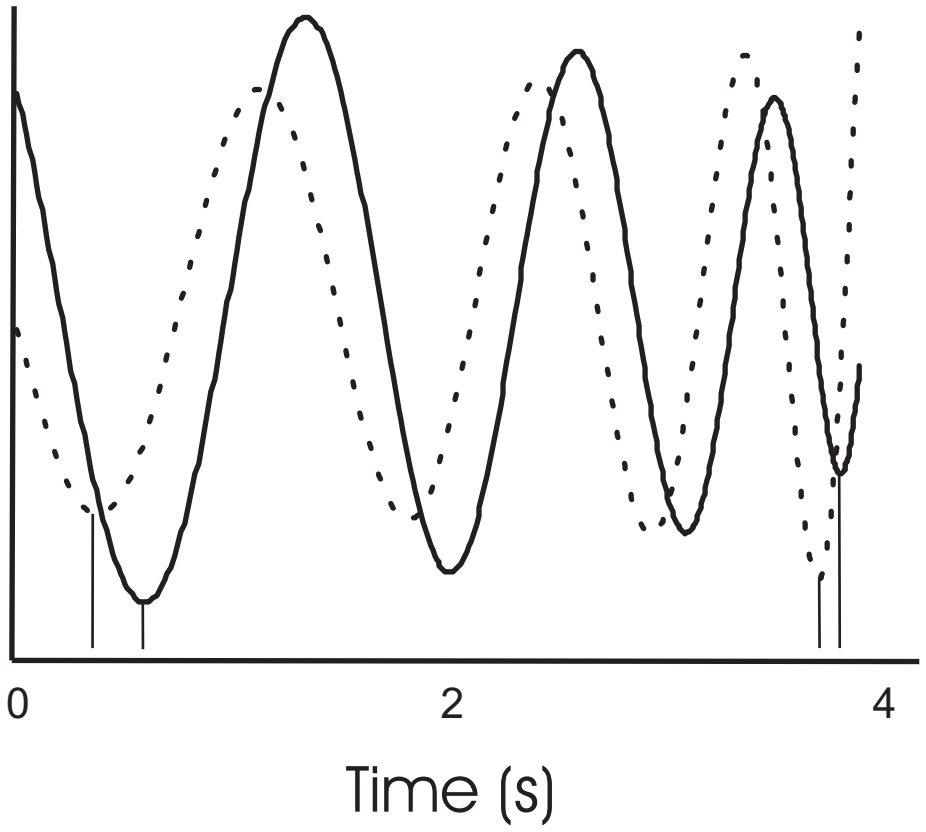

Figure 2: Temporal comparison of a simulated motor cortical cell and hand velocity during an outside->in spiral drawing task. The cell's activity (dotted line) is modulated by 50% velocity and 50% acceleration information. The second line (solid) represents the hand velocity signal (the component aligned with the cell's preferred direction). As the task progresses from the outside of the spiral inward toward higher curvatures, the cortical activity behaves more like the acceleration signal; however, since the angular velocity is also increasing, the time lag between cortical activity and velocity (thin lines) actually decreases.

Supplementary information for Apostolos P. Georgopoulos and James Ashe
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Table 1. Percentages of cells for which the noted variable yielded the highest R^2.

Variable	Motor cortex (N = 290)	
	Original analysis (from Table 1 in ref. 3)	New analysis
	Square-root transformed	Non-transformed
Target direction	46.55	42.76
Velocity	39.66	40.00
Position	7.24	8.97
Acceleration	6.55	8.27

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Response to Moran and Schwartz

Figure Legend:

Muscle force is $F(M,L,V) = (\text{af fl fv} + \text{f}_{\text{PE1}} + \text{af f}_{\text{PE2}})\, F_{\max}$, where muscle length L, velocity V, and stimulation frequency M are in dimensionless units[12], $F_{\max}$ is maximum potentiated force in endpoint space. The functions $\text{af}(M,L)$, $\text{fl}(L)$, $\text{fv}(L,V)$, $\text{f}_{\text{PE1}}(L)$, $\text{f}_{\text{PE2}}(L)$ with all 19 parameters defining them are described elsewhere[12]. The simpler form of the activation-frequency function $\text{af}(M,L)$ was used. All parameters were set to the average values for slow-twitch and fast-twitch muscles[12]. The plot in A) shows the surface $F(M,L,V)$ for M set to 1 (cyan), 0.5 (magenta), and 1.5 (yellow). Note that stiffness and damping (the partial derivatives with respect to Length and Velocity) are both determined by M and cannot be controlled independently.

The hand was modeled as a m = 1 kg point mass in 2-dimensional endpoint space, pulled by N muscles with uniformly distributed (unit) force directions $\mathbf{u}_{1\ldots N}$. With the new muscle model, stiffness and damping could no longer be set explicitly— instead they depended on the cocontraction level. Also, the PV could no longer be computed independent of tuning— so a concrete tuning function (cosine) was used. Given hand kinematics (1.5cm–7.5cm spiral traced in 2.5 seconds according to the 2/3 power law[2,3]), the PV at each point in time was computed in 5 steps:

1) Net force was $\mathbf{f} = m\ddot{\mathbf{x}}$.

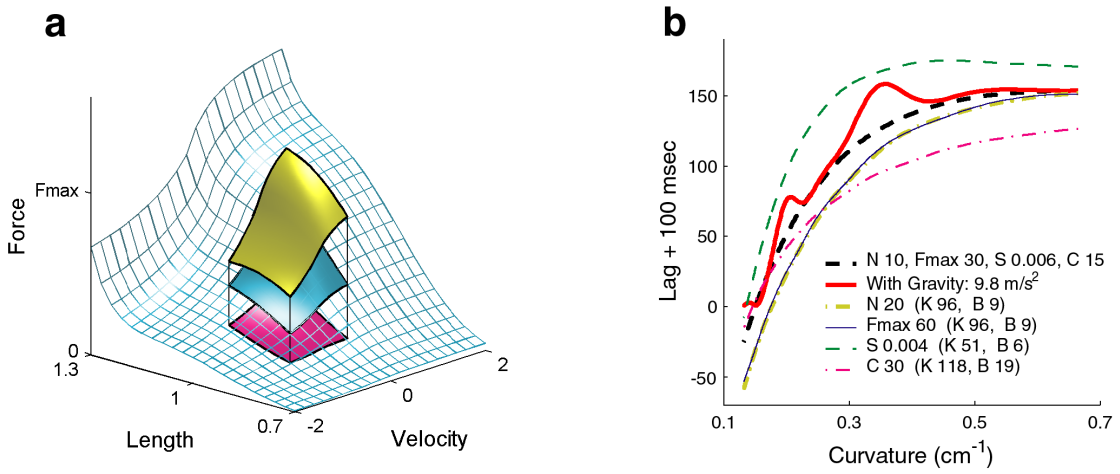
2) Lengths L_i and velocities V_i were[1] $L_i = r_i - S\mathbf{x}^T\mathbf{u}_i$ and $V_i = -S\dot{\mathbf{x}}^T\mathbf{u}_i$. The scaling constant $S = 0.006$ mapped a 100cm range of motion in $\mathbf{x}$ to a 0.7–1.3 physiological range of normalized lengths L, and $r_{1\ldots N}$ defined the muscle lengths at the center $\mathbf{x} = \mathbf{0}$ of the workspace.

3) The individual force contribution F_i of each muscle was determined from the cosine tuning function $F_i = \frac{2}{N}\lfloor C + \mathbf{f}^T\mathbf{u}_i \rfloor$.

4) Stimulation frequencies M_i were found by solving $F_i = F(M_i, L_i, V_i)$.

5) The population vector $\sum (M_i - \overline{M}_i)\mathbf{u}_i$ was formed, with baselines $\overline{M}_i$ corresponding to maintained posture.

For nominal parameters $N = 10$, $F_{\max} = 30\,\mathrm{N}$, cocontraction was adjusted to $C = 15$ so that empirical stiffness K = 76 N/m and damping B = 9 Ns/m (found via perturbation experiments in the model) were close to the previously[1] used values of K = 50 N/m and B = 10 Ns/m. Results for 6 different parameter sets are shown, each averaged over 10 simulation runs with random $r_{1\ldots N}$ in the interval 0.9–1.1. The legend shows which parameter was varied from its nominal value (with resulting stiffness and damping). For all parameter settings, the timelag-curvature function closely resembled the original result[1] as well as the experimental data[2,3]. When gravity compensation was added to $\mathbf{f}$, the function fluctuated near the nominal curve. Similar fluctuations are present in experimental data[2,3], although the latter could be due to noise.

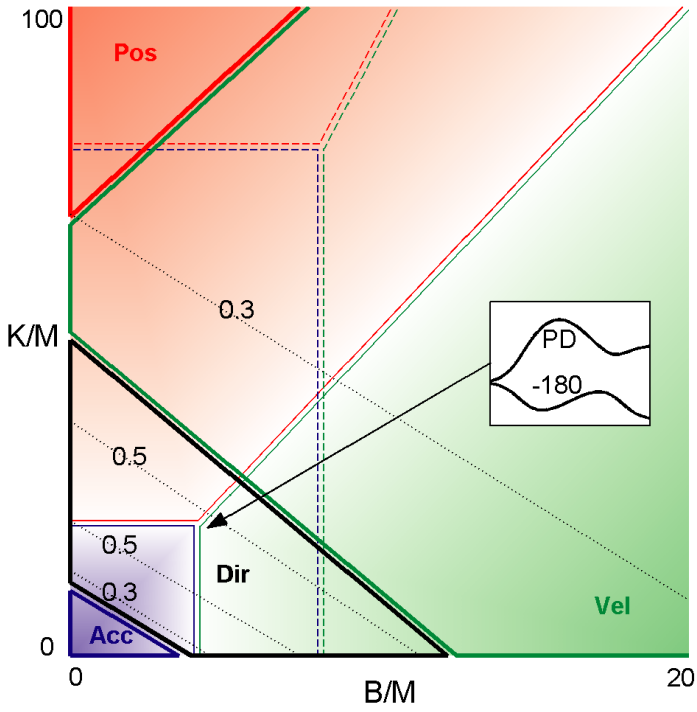


Response to Georgopoulos and Ashe:

Figure legend:

The plot visualizes the parameter space of synthetic response profiles. As before[1], synthetic mean firing rates at time t and angle q away from the preferred direction are $\mathrm{mfr}(t,q) = C + M\ddot{x}(t)\cos(q) + 2B\lfloor \dot{x}(t)\cos(q)\rfloor + Kx(t)\cos(q)$, where C, M, B, K are sampled uniformly from 0–34, 0–4, 0–40, 0–200. Both the correct classification (the term with maximal absolute contribution) and the R^2 procedure applied to mfr are scale and translation invariant— so a two parameter plot $(B/M, K/M)$ can be obtained by subtracting C and dividing by M. The classification regions in the figure are computed through extensive simulations. Thin lines correspond to correct classification; thick lines - R^2 procedure applied to mfr; dotted lines - probability contours of classifying a cell as directional, R^2 procedure applied to raw binned spike trains; dashed lines - correct classification, two times faster movement. Line colors: red - position; green - velocity; blue - acceleration; black - direction. Color intensity corresponds to the 'confidence' of the correct classification, defined as the difference between the maximum and next

largest contribution. Spike train classification generally depends on all four parameters C, M, B, K, and is probabilistic because the same cell can be classified differently if a new set of Poisson spike trains are sampled. So the deterministic classification regions become probability distributions (dotted lines show the p = 0.5 and p = 0.3 contours of the probability of misclassifying cells as directional). When the same reaching movement is executed two times faster, hand displacement remains unchanged, velocity doubles, and acceleration quadruples - so the correct classification regions (dashed lines) change. The inset shows the response in the center of the region misclassified as directional. Note that this response does not look directional— it just does not fit in any of the alternative categories.



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