A salient feature of skeletal muscles is their ability to take up an applied slack in a ms time scale. Behind this passive phenomenon is a collective folding of a system of interacting bi-stable elements. These interactions have long range character and therefore the behavior of the system in force and length controlled ensembles is different. As a result, there are two adjacent but distinct critical points. We show that the account of steric incommensuration between myosin and actin filaments places the elementary force producing units of skeletal muscles close to both critical points. Such 'double-criticality' contributes to the system’s ability to perform robustly in the presence of perturbations and suggests that geometric frustration may be functional.

If an isometrically tetanized muscle is suddenly shortened, the force first abruptly decreases but then partially recovers over ~ 1 ms time scale [1–3]. Behind this phenomenon is a passive conformational change in the actin-bound myosin heads, known as the 'power stroke'. Since the power stroke takes place at the time scale which is much faster than the time scale of the active, ATP driven attachment-detachment (~ 100 ms) [4–6], the power-stroke-induced fast force recovery can be modeled as a passive collective folding of a bundle of bi-stable elements [7, 8]. The resultant snap-spring response is resistant to thermal fluctuations because of the dominance of long-range interactions mediated by elastic backbones [9, 10].

If the applied force is fixed, the realistic mean-field theory, viewing the backbone as rigid [11], predicts metastability due to synchronization of the cross-bridges and the existence of a critical point [9]. It has been argued that this critical point is crucial for the functioning of muscle machinery [10]. Critical systems are ubiquitous in biology because of their adaptive advantages [12–16]. Their robustness in the face of random perturbations is due to marginal stability, and skeletal muscles indeed exhibit near zero passive rigidity in physiological (isometric contraction) conditions [2, 17–19].

The presence of long-range interactions [20, 21] leads to a different collective behavior of cross-bridges in force (soft device) and length (hard device) ensembles [9]. In particular, the critical points corresponding to length and force clamp loading conditions do not coincide [22]. Since individual cross-bridge bundles (half-sarcomeres) are embedded in a complex elastic environment, both tension (at fixed displacement) and displacement (at fixed tension) responses are of relevance and to be robust such system should be poised close to both critical points.

In this Letter, we showed that the implied optimality is actualized in the system of muscle cross-bridges due to random inhomogeneity induced by steric incommensuration. The idea that the disregistry between the periodicities of myosin and actin filaments brings the system’s stiffness to zero was pioneered in [23]; the utility of quenched disorder for other aspects of muscle mechanics has been recently discussed in [24].

To explore the reachability of the desired 'double criticality', we reduce the description of the system of interacting cross-bridges to a random field Ising model (RFIM) and compute the equilibrium free energy using the techniques of the theory of glassy systems [25]. We then use the available experimental data on skeletal muscles to justify the claim that geometric frustration is the factor ensuring the targeted response.

Following [2, 11], we associate with each muscle cross-bridge a spin variable \( x \) taking the value 0 in the pre-power-stroke state (unfolded conformation) and -1 in the the post-power-stroke state (folded conformation). Each spin element is placed in series with a linear elastic spring of stiffness \( \kappa_0 \). If we non-dimensionalize lengths by the power-stroke size \( a \) and energy by \( \kappa_0 a^2 \), the dimensionless energy of a cross bridge is: \( (1 + x)v + \frac{1}{2}(y - x)^2 \), where \( y \) is the dimensionless displacement of the myosin filament relative to the actin filament and \( v \) is the dimensionless energetic bias. To represent quenched disorder we assume that \( v \) is different in different cross-bridges [26].

Consider now a parallel connection (bundle) of \( N \) cross-bridges shown schematically in Fig. 1. Individual cross-bridges are attached to a backbone composed of myosin tails. The elasticity of the backbone can be accounted through a hump spring of stiffness \( \kappa_f \) in series with the bundle [27–29]. The system loaded in a hard device is then characterized by the dimensionless energy

\[
E = \sum_{i=1}^{N} [(1 + x_i)v_i + \frac{1}{2}(y - x_i)^2] + \frac{N}{2} \lambda_f (z - y)^2, \tag{1}
\]

where \( z \) is the applied displacement and \( \lambda_f = \kappa_f/(N\kappa_0) \). We assume that parameters \( v_i \) are i.i.d. random variables with probability density \( p(v) \).

If instead of variables \( x_i \) we use variables \( s_i = 2x_i + 1 = \pm 1 \) and adiabatically eliminate \( y \), assuming that \( \partial E/\partial y = 0 \), the energy (1) takes the form,

\[
E = -J/(2N) \sum_{i,j} s_i s_j - \sum_i h_i s_i + c,
\]
where \( J = 1/4(1 + \lambda_f) \), \( c \) is a \( z \) dependent constant, and the coefficients \( h_i \) are linear in \( v_i \) [30]. Therefore (1) is an extension of the mean-field RFIM and the corresponding equilibrium problem can be solved explicitly [31, 32].

Using the self-averaging property of the free energy in the thermodynamic limit, we write

\[
\mathcal{F}(\beta, z) = -\lim_{N \to \infty} (N\beta)^{-1} < \log \mathcal{Z}(\beta, z; \{v\}) >_v,
\]

where the averaging \(< \cdot >_v\) is over the disorder, \( \beta = \kappa_0 a^2/(k_B T) \), and

\[
\mathcal{Z} = \int dy \sum_{x \in \{0, -1\}^N} \exp(-\beta E(x, y, z; \{v\})).
\]

The mean field nature of the model allows one to rewrite (2) in the form

\[
\mathcal{Z} = \int dy \exp(-\beta N[\lambda_f(z-y)^2 - \frac{1}{N} \sum_{i=1}^{N} \log \mathcal{Z}])),
\]

where \( \mathcal{Z} = e^{-\frac{\beta}{2}(y+1)^2} + e^{-\beta(y^2/2 + v_0)} \) is the partition function of a single Huxley-Simmons element [2, 11]. In the thermodynamic limit, we can use the law of large numbers and apply the saddle-point approximation to obtain

\[
\mathcal{F}(\beta, z) = \mathcal{F}(y_0, \beta, z) = \beta \frac{N}{2}(z-y)^2 - < \log \mathcal{Z} >_v \text{ and } y_0(\beta, z) \text{ is the minimum of } \mathcal{F}.
\]

More explicitly,

\[
\mathcal{F}(\beta, z) = \frac{\lambda_f}{2}(z - y_0)^2 + \frac{1}{4}(y_0 + 1)^2 + \frac{1}{2} \left( \frac{y_0^2}{2} + v_0 \right) - \frac{1}{\beta} \int dv p(v) \log \left[ 2 \cosh \left( \frac{\beta}{4}(1 + 2y_0 - 2v) \right) \right],
\]

where \( y_0 \) solves the self-consistency equation,

\[
y_0 = \frac{2\lambda_f z - 1}{2(\lambda_f + 1)} + \int dv \frac{p(v)}{2(\lambda_f + 1)} \tanh \left( \frac{\beta}{4}(1 - 2v + 2y_0) \right).
\]

The tension-elongation relation is then \( t = \partial \mathcal{F} / \partial z = \lambda_f(z - y_0) \). If we assume that the disorder is Gaussian \( p(v) = (2\pi\sigma^2)^{-1/2} \exp\left(-\frac{(v-v_0)^2}{2\sigma^2}\right) \), the behavior of the system will be fully defined by the temperature \( 1/\beta \), the variance of disorder \( \sigma^2 \) and the parameter \( \lambda_f \), characterizing the degree of cooperativity. The phase/regime diagram at a given \( \lambda_f \) is shown in Fig. 2. The section \( \sigma = 0 \) was studied in [22] and at \( \sigma > 0 \) the system responds as if it were subjected to higher effective temperature [33, 34].

The behavior of the Helmholtz free energy and the tension-elongation relation in the three 'phases' I, II and III is shown in Fig. 3. In phase I the cooperativity is absent and the cross-bridges fluctuate independently. In phase III the discontinuity in the tension-elongation relation corresponds to a synchronous switch between two pure states. In the intermediate phase II the tension-elongation relation exhibits negative stiffness in the regimes where the system fluctuates between pure states.

Since phase III is characterized by the non-uniqueness of \( y_0 \) solving Eq. 5, the boundary between phases II and III, the curve \( p - q \) in Fig. 2, is defined by the condition that the three roots of Eq. 5 collapse into one. In such points \( \partial^2 \mathcal{F}(\beta, z, y)/\partial y^2 = 0 \) or

\[
\lambda_f + 1 - \frac{\beta}{4} \int dv p(v) \sech^2 \left( \frac{\beta}{4}(1 - 2v + 2y_0) \right) = 0,
\]

where \( y_0 \) has to satisfy the self-consistent relation Eq. 5.
In the limiting case $\sigma \to 0$ the point $p$ is given by the condition $\beta = 4(\lambda f + 1)$. Around this point the $p - q$ curve is described by the low-disorder approximation $\beta_c = 4(\lambda f + 1)$ where $\beta_c = (\beta - 2 + \sigma^2/2)^{-1/2}$ is the effective inverse temperature [30]. In another limiting case $\beta \to \infty$, point $q$ can be found from the equation $\sigma = 1/\sqrt{2\pi(\lambda f + 1)}$ and around this point the $p - q$ curve is given by the small temperature approximation $\sigma_e = 1/\sqrt{2\pi(\lambda f + 1)}$, where $\sigma_e^2 = (\sigma^2 + 2\beta^{-2}) - 2\beta^{-2}$ is the variance of the effective disorder [30].

The boundary $p - q$ corresponds to the second order phase transition: the order parameter $\phi = N^{-1}\sum_{i=1}^N(s_i)_\beta$, where $<s>_\beta$ is the thermal average, is double-valued in phase III and single-valued in phase II. To distinguish between different microscopic configurations, we also compute the Edwards-Anderson parameter $q_{EA} = N^{-1}\sum_{i=1}^N(\langle s_i \rangle)_\beta$. Fig. 4 shows that $q_{EA}$ is different from zero in the 'paramagnetic' phase II close to the $p - q$ boundary, which indicates weakly glassy behavior [31, 32].

To find the boundary between phases I and II (curve $r - s$ in Fig. 2) we need to solve the equation $\partial^2 F/\partial z^2 = 0$ or $\partial y_0/\partial z = 1$, where again $y_0$ is a solution of Eq. 5. When $\sigma = 0$ we obtain $\beta = 4$ which defines the location of point $s$ in Fig. 2, see also [9, 28]. The low disorder approximation gives $\beta_c = 4$. In another limiting case $\beta \to \infty$ the location of the point $r$ in Fig. 2 is given by $\sigma = \sqrt{1/2\pi}$. In the low temperature approximation we obtain $\sigma_e = \sqrt{1/2\pi}$.

Note that the boundary $r - s$ can be also interpreted as a line of second order phase transitions, but now in the soft device (force clamp) ensemble. In this case the presence of a series spring is irrelevant and we can assume that $\lambda f \to 0$, $z \to \infty$, but $\lambda f z \to t$, where tension $t$ is the new control parameter. The relevant potential is,

$$G = \sum_{i=1}^N \left[ 1 + x_i v_i + \frac{1}{2} (y - x_i)^2 \right] - ty. \quad (7)$$

Following the approach used in the case of hard device, we obtain the expression for the Gibbs free energy

$$G(\beta, t) = -ty_0 + \frac{1}{4}(y_0 + 1)^2 + \frac{1}{2} \left( \frac{y_0^2}{2} + v_0 \right) - \frac{1}{\beta} \int dv p(v) \log \left[ 2 \cosh \left( \frac{\beta}{4} (1 + 2y_0 - 2v) \right) \right] \quad (8)$$

where now $y_0$ solves the equation

$$t = y_0 + \frac{1}{2} - \frac{1}{2} \int dv p(v) \tanh \left( \frac{\beta}{4} (1 - 2v + 2y_0) \right). \quad (9)$$

The tension elongation relation is then a solution of $y = -\partial G/\partial t$.

In Fig. 5 we show that the soft device tension-elongation relation in phase II is monotone but discontinuous. On the boundary $r - s$ in Fig. 2 the system exhibits zero stiffness in stall conditions, which means that it corresponds to the set of critical points in the soft device ensemble. This line, targeted numerically in [23], represents regimes that can be expected to deliver the optimal trade-off between robustness and flexibility [35, 36].

Note that we have operated under an implicit assumption that in the thermodynamic limit $\kappa f \to \infty$, while $\lambda f$ remains finite. This assumption is based on the picture of myosin filament as a parallel arrangement of $N$
myosin tails, all contributing to the lump stiffness of the backbone. A more realistic assumption may be that the effective stiffness of the backbone $\kappa_f$ depends only weakly on the number of attached cross-bridges $N$ and in this case we have a different scaling $\lambda_f \sim N^{-1}$. Then the phase diagram, presented in Fig. 6, shows the size effect and suggests that scaling may be narrowly linked to a particular number of attached cross-bridges.

To apply our results to a realistic muscle system, we use the data for *Rana temporaria* at $T = 277.15K$ [22]. From structural analysis we obtain the value $a \sim 10$ nm [37–39]. Measurements of the fiber stiffness in rigor mortis, where all the 294 cross-bridges per half-sarcomere were attached, produced the estimate $\kappa_0 = 2.7 \pm 0.9$ pN/nm [17, 18]. The number of attached cross-bridges in physiological conditions is $N = 106 \pm 11$ and experimental measurements at different $N$ converge on the value $\kappa_f = 154 \pm 8$ pNm$^{-1}$ for the lump filaments stiffness [5, 40, 41]. This gives $\lambda_f = 0.54 \pm 0.2$. Given $\kappa_0$ and $a$ we are able to estimate the non-dimensional inverse temperature $\beta = 71 \pm 26$. In our simulations we used $\lambda_f = 0.35$ and $\beta = 52$, consistent with the value $\kappa_0 = 3.3$ pN/nm recommended in [17].

Knowing that for $y > v_0 - 1/2$ the minimum of the energy of a single cross-bridge is in the pre-power-stroke and that the amount of shortening per half-sarcomere needed to bring tension to zero from its isometric value is $\sim 4$ nm [2, 23], we conclude that $v_0 \sim 24.3pN/\kappa_0a$. It was experimentally shown [42] that at least 60% of the cross-bridges are axially displaced within half of the spacing between actin monomers, which corresponds to $\sim 2.76$ nm shift from the nearest actin binding site, see also [23]. Using Chebyshev’s inequality [43], we can then obtain a bound on the standard deviation of the disorder $\sigma \sim 3.5$nm/$a$ [30].

Based on these data we find that, rather remarkably, the system appears to be operating in a narrow domain of stability of phase II, close to both critical lines $p - q$ and $r - s$, see the point marked by a triangle in Fig. 2. The gap between these boundaries corresponds to $\sim 1$ nm difference in the cross-bridge attachment positions which is rather small given that the size of a single actin monomer is about 5.5 nm. The mechanical responses in the adjacent critical regimes $A$ and $B$ are illustrated in Fig. 7. In the associated critical points, marked by small circles, the interactions between distant portions of the system become anomalously strong, but if in the hard device ensemble we imply coherent fluctuations of tension (infinite rigidity), in the soft device we expect system size correlations of strain (zero rigidity). Note also that critical slowing down makes the kinetic response to perturbations in these points microscopically slow which may explain the detectability of active fluctuations in stall conditions [7, 44, 45].

Our study suggests that evolution may have used geometrical frustration to tune muscle machinery to perform near the conditions where both the Helmholtz and the Gibbs free energies are singular. Such design is highly functional when elementary force producing units affect each other performance and are therefore loaded in a mixed, soft-hard device. Access to the whole spectrum of rigidities from zero (adaptability) to infinite (control), would then be the factor ensuring the robust response.

In conclusion, we established new links between muscle physiology and the theory of spin glasses and revealed a tight relation between steric incommensuration and the optimal mechanical performance of force generating machinery. While we neglected many important features of actual muscles, we drew attention to the beneficial role of geometrical frustration for the functioning of this biological system. Similar disorder-mediated tuning towards criticality can be expected in other systems with long range interactions, including, for instance, focal adhesions and hair cells [46, 47].

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![Figure 7. The response of the system in the critical regimes A and B shown in Fig. 2: (a) and (b) are the Helmholtz free energy and the tension-elongation curve in the hard device ensemble; (c) and (d) are the Gibbs free energy and the associated tension-elongation curve in the soft device ensemble. Critical points are marked by the small circles.](image-url)
