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# HUXLEY-SIMMONS MODEL REVISITED

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**SUMMARY**

Muscle contraction is a largely mechanical process taking place at the sub-cellular level. While being an intrinsically active system the contractile apparatus also displays some intriguing passive mechanical properties including negative stiffness and a fundamental nonequivalence of isometric and isotonic loading protocols. We reveal the origin of this unusual behavior by analyzing a conceptual model which represents a delicate generalization of the Huxley-Simmons model. Our analytically explicit study sheds light on the crucial role of long-range interactions in this system. The model can be easily adapted to a wide class of biological phenomena involving cooperative switching mediated by effective backbones, from muscle power-stroke to gating, binding and folding.

**Key words:** *Muscle, Statistical mechanics, Metamaterials, Protein unfolding, Hair cells*

## 1 INTRODUCTION

In distributed biological systems collective effects are usually revealed through synchronized conformational changes that can be broadly interpreted as folding-unfolding transitions. A prototypical example of such transition can be found in muscle sarcomeres which are the elementary contractile units of skeletal muscles. A schematic representation of a sarcomere, shown in Fig. 1, contains actin (thin) and myosin (thick) filaments cross-linked by myosin cross-bridges.

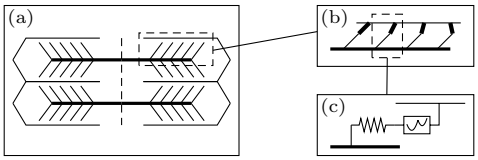


FIGURE 1: Schematic structure of the three layers of organization inside a sarcomere : (a) global architecture with domineering parallel links ; (b) structure of an elementary contractile unit shown in more detail in Fig. 2 ; (c) individual attached cross-bridge represented by a bistable element in series with a shear spring.

Active behavior of skeletal muscles is associated with time scales of about 30 ms which allow for the metabolic fuel (ATP) to be delivered to the cross-bridges. At shorter times ($\sim$1 ms) muscles exhibit a nontrivial *passive* response : if a tetanized muscle is suddenly extended, it comes loose, and if it is shortened, it tightens up with apparently no involvement of ATP. This behavior was first revealed in the study of Huxley and Simmons [1] who attributed the observed quick force recovery (relaxation) to the conformational change (power-stroke) taking place in myosin cross-bridges that are bound to actin filaments. The authors proposed a chemo-mechanical model of a sarcomere where the pre- and post-power-stroke conformations of the myosin heads are represented as discrete chemical states (spin model) and considered only isometric loading (hard device). While the Huxley-Simmons model serves as a paradigm for many other similar models in biophysics involving elastically interacting switching units [2, 3], it was not systematically studied in isotonic conditions and, in particular, it has not been confronted with the retarded muscle response observed in the load clamp protocols (soft device setting) [4].

To clarify the origin of this retardation, we systematically compare in this communication the mechanical response of the Huxley-Simmons model in soft and hard device ensembles. We show that already at zero temperature the behavior of the mechanical system in both protocols is different and we argue that this difference is due to the long-range interactions that are present only in the soft device setting [5]. At finite temperature the response in a hard device is characterized by uncorrelated fluctuations of individual cross-bridges and leads to negative stiffness as in the original Huxley-Simmons model. In a soft device the response is collective manifesting itself through synchronized oscillations of all attached cross-bridges. We prove that in this case the equilibrium stiffness is necessarily positive.

## 2 THE HUXLEY AND SIMMONS MODEL

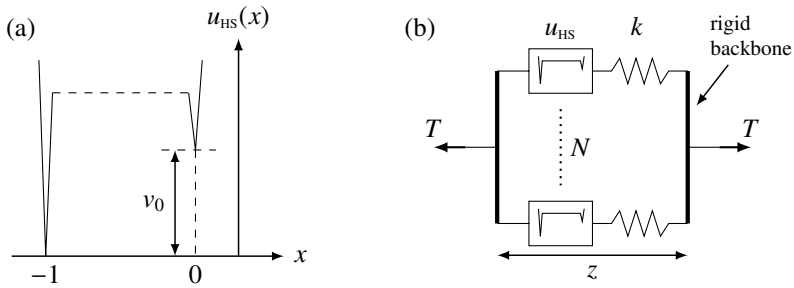


FIGURE 2: A reformulation of the Huxley-Simmons model as a parallel bundle of bistable cross-bridges. (a) Energy landscape of an individual crosslinker ; (b) $N$ crosslinkers loaded in a soft device.

We represent the Huxley-Simmons model in a non-orthodox way as a cluster of $N$ bistable units connecting two rigid backbones, see Fig. 2. Each cross-bridge is described by a sharply welled bistable potential so that the configurational spin variable $x$ can take only two values $x = 0$ and $x = -1$. With the unfolded (pre-power-stroke) state we associate the energy level $v_0$ while the folded (post-power-stroke) configuration is considered as a zero energy state. Each bi-stable element is connected to its own series spring with stiffness $k = 1$. We can write the dimensionless energy of the system (per cross-bridge) in the form

$$v(\boldsymbol{x}; z) = \frac{1}{N}\sum_{i=1}^{N}\left[(1+x_i)\,v_0 + \frac{1}{2}(z-x_i)^2\right]. \tag{1}$$

In the hard device case each cross-bridge is exposed to the same total elongation $z$ and thus the individual units are independent. In the soft device case, where the control parameter is the total tension $T$, the energy per cross-bridge is

$$w(\boldsymbol{x}, z; t) = v(\boldsymbol{x}, z) - tz = \frac{1}{N}\sum_{i=1}^{N}\left[(1+x_i)\,v_0 + \frac{1}{2}(z-x_i)^2 - tz\right], \tag{2}$$

where $t = T/N$ is the force per cross-bridge. Now there is a mean field interaction among individual cross-bridges.

## 3 RESULTS

*Athermal model.* Since each of the internal degrees of freedom $x_i$, for $1 \le i \le N$, can take two discrete values, an equilibrium state is characterized by the distribution of the $N$ cross-bridges between these two configurations. Due to the permutational invariance, each equilibrium state is fully characterized by a discrete parameter $p$ representing the fraction of cross-bridges in the post-power-stroke configuration ($x_i = -1$). At a given value of $p$, the energies (per crosslinker) of the marginal states are equal to

$$\hat{v}(p; z) = p\frac{1}{2}\,(z+1)^2 + (1-p)\big(\frac{1}{2}z^2 + v_0\big), \tag{3}$$

$$\hat{w}(p; t) = -\frac{1}{2}t^2 + pt + \frac{1}{2}p(1-p) + (1-p)v_0, \tag{4}$$

in hard and soft device, respectively. The corresponding tension-elongation curves $t = z+p$ are shown for both ensembles by the gray lines in Fig. 3(a). Since we have $\frac{\partial^2 \hat{v}}{\partial p^2} = 0$ and $\frac{\partial^2 \hat{w}}{\partial p^2} < 0$, the global minimum of the energy always corresponds to one of the pure states, $p = 0$ or $p = 1$ with a sharp transition occurring at $z = 0$ in a hard device and $t = 1$ in a soft device, see bold lines in Fig. 3(a). Hence, while the tension-elongation relation corresponding to the global minimum is characterized by a plateau with zero stiffness in a soft device, the hard device transition shows extreme negative stiffness. This difference which persists in the continuum limit is the signature of the fundamental non-equivalence between the two protocols.

Notice also that the energy (3) is the combination of two limiting configurations, the first fully in pre-power-stroke ($p = 0$) and the other fully in post-power-stroke ($p = 1$). The absence of a *mixing* energy is a sign that the two coexisting populations of cross-bridges do not interact. In a soft device, the nontrivial coupling term $p(1-p)$ describes the energy of mixing, see (4). The presence of this term is a signature of a mean-field interaction among individual crosslinkers. This interaction has a simple physical meaning : if one element changes configuration, its contribution to the common tension changes and the other elements must adjust to maintain the force balance. As a result, the

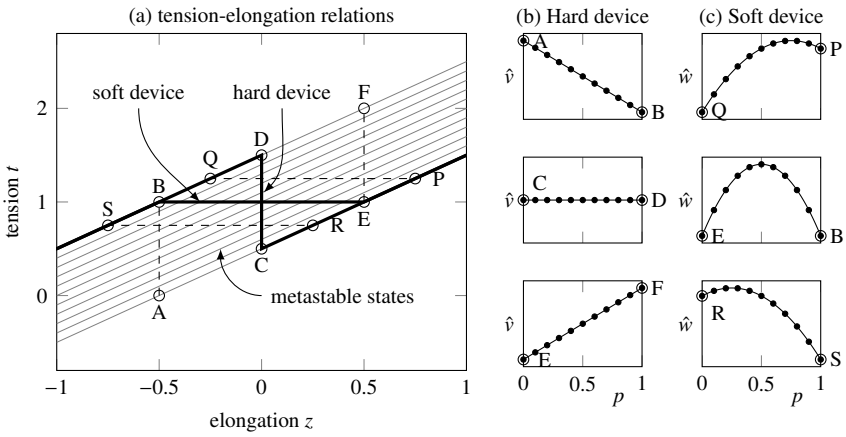


FIGURE 3: Huxley-Simmons model at zero temperature and $N = 10$. (a) Gray lines : tension-elongation relations corresponding to $p = 0, 0.1, \ldots, 1$ ; Bold lines : the global minimum of the energy ; (b,c) Internal energy landscape corresponding to various paths shown by dashed lines in (a).

energies of the mixed states are higher than the energies of the homogenous states and the transition from one pure configuration to the other requires crossing a macroscopic energy barrier. In a hard device this barrier is absent, see Fig. 3 (b) and (c). To summarize, the difference between the hard and the soft device behaviors manifests itself already in the purely mechanical case.

*Thermal equilibrium.* At finite temperature the equilibrium behavior is found by computing statistical sum. One can show, that in thermodynamic limit the free energies in hard and soft device can be written as [4]

$$f(p; z, \beta) = \hat{v}(p, z) - s(p)/\beta, \tag{5}$$

$$g(p; t, \beta) = \hat{w}(p, t) - s(p)/\beta \tag{6}$$

where $\hat{v}$ and $\hat{w}$ are given by (3) and (4), respectively, and $\beta$ is the inverse temperature. The term $-s(p) = [p\log(p) + (1-p)\log(1-p)]$ is a convex function of $p$ describing ideal mixing. Since $\hat{v}$ is convex in $p$ the free energy $f$ always has a single minimum representing a disordered temporal microstructure of pre- and post-power-stroke cross-bridges. In a soft device, the function $w$ is concave in $p$ and it favors homogenous states. Therefore the system in a soft device can undergo an order-disorder phase transition. One can show that the critical temperature is $\beta_c = 4$. At higher temperatures ($\beta < 4$) the entropic term dominates and the system is characterized by incoherent fluctuations (see B in Fig. 4 (a)) like in a hard device. Instead, at lower temperatures ($\beta > 4$) the mechanical energy dominates and the power-stroke is completely synchronized so that all cross-bridges are either in the pre-power-stroke state ($p \approx 0$) or in the post-power-stroke state ($p \approx 1$), see A and C in Fig. 4.

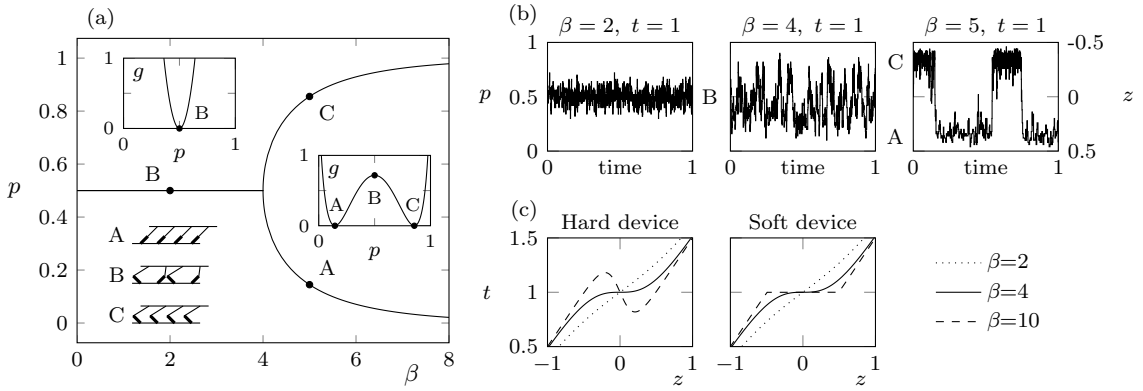


FIGURE 4: Huxley-Simmons model at finite temperatures. (a) Bifurcation diagram showing the location of the minima of $g$ as function of $\beta$. The inserts show typical energy landscape below and above the critical point. A, B, C, internal configuration corresponding to the critical points of the free energy. (b) Stochastic trajectories of $p$ for $t = 1$ at $\beta = 2,\ 4$ and 5. (c) Stress-strain relations in hard and soft devices for $\beta = 2$, 4 and 5.

This phase transition has a significant impact on kinetics, see Fig. 4 (b). At low temperatures, the system shows fast collective hoping (*temporal microstructure*) between the two long-living ordered configurations which can be regarded as quasi-stationary states. At large temperatures the phase trajectory remains localized around the disordered state. In thermal equilibrium, the tension-elongation relations can be written in the form $t = z + \langle p \rangle$ where the average $\langle p \rangle$ is the minimizer of the free energy (in the thermodynamic limit). One can show that in a hard device the stiffness $\frac{\partial t}{\partial z}$ is always positive if $\beta < 4$ and becomes negative in a finite interval of $z$ if $\beta > 4$ while the stiffness in a soft device is always positive, see Fig. 4(c). Hence we recover the ensemble non-equivalence which was already present at zero temperature.

## 4 CONCLUSION

We have shown that the Huxley-Simmons models exhibits different mechanical responses in hard and soft device loading protocols. The reason is that long-range interactions in the soft device create strong mechanical feedback forcing cross-bridges to perform in a synchronized manner. As the collective conformational change requires crossing a high energy barrier, the system may remain trapped in a quasi-stationary state which is a possible explanation of the retarded response of skeletal muscles observed in a force clamp protocol.

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