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Mini-Workshop: The mathematics of growth and remodelling of soft biological tissues

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Abstract. Biology is becoming one of the most attractive fields of application of mathematics. The discoveries that have characterized the biological sciences in the last decades have become the most fertile matter for application of classical mathematical methods, while they offer a natural environment where new theoretical questions arise. Mathematical Biology has born many years ago and has developed along directions that now constitute its traditional background: population dynamics and reaction–diffusion equations. Nowadays Mathematical Biology is differentiating into several branches, essentially depending on the specific spatial scale size under consideration: molecular scale, i.e., DNA transcription, protein folding and cascades, cellular scale, i.e., motility, aggregation and morphogenesis, and macroscale, i.e., tissue mechanics. Currently one of the most attractive scientific topics is the mathematics of growth and remodelling of soft biological tissues. This area, located at the crossroads of biology, mathematics and continuum mechanics, concerns the statement and analysis of the equations that characterize the mechanics, growth and remodelling of systems like arteries, tumors and ligaments, studied at the macroscopic scale. These are open continuous systems that pose new challenging questions, which go beyond the standard mechanics that is traditionally devoted to closed systems. Past initiatives in Oberwolfach have been devoted to the interaction between biology and mathematics in a broad sense. The idea to this minisymposium is to bring together established researchers on this topic with newer entrants to the field and initiate discussion on established and novel approaches towards the mathematics of growth and remodelling of soft biological tissues.

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Elementary mechanics of muscular exercise

Antonio DiCarlo

The mathematical theory of growth and remodelling of living tissues—either soft or hard—is still in its infancy, as unanimously acknowledged and amply testified during the miniworkshop. In these conditions, the lack of a well-founded and widely recognized axiomatic basis is only to be expected, and could even be regarded as a felicitous opportunity for the emergence of brand new ideas. However, this is no excuse for disregarding clean axiomatics nor for being opportunistic and sloppy in basic assumptions. At best, these are symptoms of a nasty infant disease we should fight against. To this end, I chose to discuss a very simple—but not too simple—macroscopic model of muscular exercise. Admittedly, nobody views muscle contraction—as opposed to muscle buildup—as an example of growth or remodelling. However, it is a fact that the very same formalism—which I call *material remodelling*—fitly covers both phenomena (and many others, either in living or non-living materials). At the same time, the utmost simplicity of the muscle model I consider makes the mathematical structure and the physical motivation of the underlying theory readily accessible.

Prelude. Let me invite you to an easy-to-do experiment: go to the gym, pick up a dumbbell, raise your forearm at ninety degrees with your upper arm, and hold on. Whoever has tried knows that an isometric exercise can be strenuous. However, null work is being done: no motion, no power expended. How is it that a tough isometric workout implies no work? What's wrong? In actual fact, zillions of minuscule myosin heads have to move back and forth inside your biceps in order to keep your arm still under load. A decent model of muscular exercise, while eschewing all molecular details, should account for their net results on the gym scale. I consider the simplest macroscopic caricature of the muscular machinery able to mimic actin-myosin sliding and myosin action as independent mechanisms. Avoiding to lump them into a single effective mechanism is of the essence: in fact, the effort demanded by an isometric exercise and the energy apportionment required are simply cancelled in the lumping. Keeping track of the power expended separately by each mechanism, my model encompasses all regimes of muscular activity. In particular, it provides a non-null estimate of the energy required to perform an isometric exercise for a given amount of time.

A two-bar model. A whole skeletal muscle is modelled as a telescoping unit comprised of two straight bars, sliding into one another. Each bar is assumed to be uniformly tensed, and its present tension $T_i(\tau)$ (with τ the present time, and $i = \mathtt{a}, \mathtt{p}$) to depend only on the present stretch $\lambda_i(\tau)$:

$$T_i(\tau) = \widehat{T}_i\big(\lambda_i(\tau)\big),$$

the stretch being defined as the ratio between the *actual* and the *relaxed* length of the bar, both strictly positive:

$$\lambda_i(\tau) := \ell_i(\tau)/\ell_i^*(\tau) > 0\,.$$

Both response functions

$$\widehat{T}_i :]\,0, +\infty\,[\;\to\; \mathbb{R}$$

are assumed to be one-to-one and monotonously increasing, with inverses

$$\widehat{\lambda}_i := \widehat{T}_i^{\,-1}.$$

Be it noted that $\widehat{T}_i\big(1\big) = 0 \;\Leftrightarrow\; \widehat{\lambda}_i\big(0\big) = 1$. Labels $\mathtt{a}, \mathtt{p}$ stand for *active* and *passive*, respectively: while the $\mathtt{a}$-bar is susceptible of remodelling, *i.e.*, its relaxed length may actually evolve in time, $\ell^*_{\mathtt{p}}$ is assumed to be constant: for all time τ,

$$\ell^*_{\mathtt{p}}(\tau) = \ell_0 \quad \Rightarrow \quad \dot{\ell^*_{\mathtt{p}}} = 0$$

(a superposed dot denotes differentiation with respect to time). The overall length of the two-bar unit at time τ is given by

$$L(\tau) = \ell_{\mathtt{a}}(\tau) + \ell_{\mathtt{p}}(\tau) - s(\tau),$$

where $s(\tau)$ measures the present *overlap* between the two bars. The above assumptions are clearly inspired by the way actin and myosin filaments are organized in sarcomeres and myofibrils. A quote from Andrew F. Huxley [1] is to the point:

> Length changes in muscle take place by relative sliding of two overlapping sets of filaments, composed respectively of myosin and actin. Tension is generated in the overlap regions by cross-bridges formed by the heads of myosin molecules, which attach to an adjacent actin filament, exert force and detach. Attachment ends when a molecule of ATP binds to the myosin head.

In conclusion we have to deal with 4 DOFs overall, the evolution of the muscle during an exercise being parameterized by the *extended motion*

$$\tau \;\mapsto\; \big(\ell_{\mathtt{a}}(\tau), \ell_{\mathtt{p}}(\tau), s(\tau), \ell^*_{\mathtt{a}}(\tau)\big). \tag{1}$$

The governing equations are obtained following the uniform procedure set forth in [2]. The equations corresponding to the first three DOFs in (1) are standard, while the fourth is not.

Power and balance. The total power expended is assumed to be given by the sum

$$\Big(R^{\mathtt{o}}\dot{\ell^*_{\mathtt{a}}} + F\dot{L}\Big) + \Big(R^{\mathtt{i}}\dot{\ell^*_{\mathtt{a}}} + C\dot{s} - T_{\mathtt{a}}\dot{\ell}_{\mathtt{a}} - T_{\mathtt{p}}\dot{\ell}_{\mathtt{p}}\Big), \tag{2}$$

where parentheses group the *outer* and the *inner* contribution, in this order. In (2) F is the (standard) force applied to the muscle ends by the tendons; $R^{\mathtt{o}}$ and $R^{\mathtt{i}}$ are the outer and inner *remodelling forces*, $R^{\mathtt{o}}$ representing the essential interaction with the chemical degrees of freedom, which are left out—but not ignored!—by the model; C is the (standard) force exchanged between the two bars, which—as established by the assumptions in (2)—are connected in series.

The principle of virtual power yields the 4 balance equations:

$$T_{\mathtt{a}} = T_{\mathtt{p}} = C = F, \tag{3}$$

$$R^{\mathtt{o}} + R^{\mathtt{i}} = 0\,. \tag{4}$$

Energetics. The free energy is assumed to be the sum of the elastic energies of the two bars—the energy apportion from biochemical sources being accounted for by the outer remodelling force R^{o}:

$$\Psi(\tau) = \widehat{\Psi}_{\mathsf{a}}\big(\lambda_{\mathsf{a}}(\tau)\big) + \widehat{\Psi}_{\mathsf{p}}\big(\lambda_{\mathsf{p}}(\tau)\big).$$

A *dissipation principle* [2, 3] is enforced, requiring that the power dissipated—defined as the difference between the power expended along a motion and the time derivative of the free energy—should be non-negative:

$$-\Big(R^{\mathsf{i}}\dot{\ell}^{*}_{\mathsf{a}} + C\dot{s} - T_{\mathsf{a}}\dot{\ell}_{\mathsf{a}} - T_{\mathsf{p}}\dot{\ell}_{\mathsf{p}}\Big) - \dot{\Psi} \geq 0. \tag{5}$$

A distinguished set of constitutive assumptions satisfying identically inequality (5) is the following (a prime denotes differentiation):

$$\widehat{T}_i = \widehat{\Psi}_i' \,, \tag{6}$$

$$C = -(1/\mathsf{M})\dot{s} \quad (\text{with } \mathsf{M}>0)\,, \tag{7}$$

$$R^{\mathsf{i}} = \lambda_{\mathsf{a}}\widehat{T}_{\mathsf{a}}(\lambda_{\mathsf{a}}) - \mathsf{D}\,\dot{\ell}^{*}_{\mathsf{a}} \quad (\text{with } \mathsf{D}>0)\,. \tag{8}$$

Note that the additive structure of the right side of (8) is a necessary consequence of the dissipation principle postulated. In particular, the energetic term $\lambda_{\mathsf{a}}\widehat{T}_{\mathsf{a}}(\lambda_{\mathsf{a}}) = \lambda_{\mathsf{a}}\widehat{\Psi}'_{\mathsf{a}}(\lambda_{\mathsf{a}})$ is the pertinent *Eshelby coupling* between hyperelasticity and remodelling of the a-bar.

Evolution equations. Substitution of eqs. (6–8) into (3) and (4) yields the equations determining the time rates of the overlap s and of the relaxed length of the a-bar ℓ^{*}_{a}:

$$\dot{s} = -\mathsf{M}F,$$
$$\mathsf{D}\,\dot{\ell}^{*}_{\mathsf{a}} = \widehat{\lambda}_{\mathsf{a}}(F)F + R^{\mathsf{o}},$$

plus the rate-independent balances $\widehat{T}_{\mathsf{a}}(\lambda_{\mathsf{a}}) = \widehat{T}_{\mathsf{p}}(\lambda_{\mathsf{p}}) = F$.

Biochemical power expended. It is readily seen that in an *isometric* ($\dot{L} = 0$) and *isotonic* ($\dot{F} = 0$) exercise the outer power coincides with the power expended by the outer remodelling force and is non-null (unless $F = 0$):

$$R^{\mathsf{o}}\dot{\ell}^{*}_{\mathsf{a}} = \Big(1 + \mathsf{DM}\,/(\widehat{\lambda}_{\mathsf{a}}(F))^2\Big)\mathsf{M}F^2.$$

Note that $\widehat{\lambda}_{\mathsf{a}}(F) = 1 + \mathcal{O}(F)$. Hence, $R^{\mathsf{o}}\dot{\ell}^{*}_{\mathsf{a}} = (1 + \mathsf{DM})\mathsf{M}F^2 + \mathsf{DM}^2\,\mathcal{O}(F^4)$. Consider, however, that there is no reason why the mobility M and the resistance (or inverse mobility) D should not depend on F.

References

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