

Muscular Contraction and the Calcium Pump

As was shown by Huxley (1953), Huxley & Niedergerke (1954) and Huxley & Hanson (1954), the contraction of skeletal muscles is due to the sliding motion of myosin filaments along actin filaments. The interaction between the filaments is created by cross bridges (Fig. 1) extending from the myosin. According to the theory by Huxley (1969), the heads of the filaments first attach to the actin and then undergo a conformational change whereby the angle of attachment is changed. This then causes a movement of the myosin along the actin. The energy for this process is derived from the hydrolysis of ATP to ADP and inorganic phosphate Pi. ATP binds to the myosin head and hydrolysis takes place. The calcium ions are stored in the sarcoplasmic reticulum, an organelle made for that purpose. When the nerve releases sodium and potassium ions, the surface of the reticulum depolarizes and the calcium ions are released into the sarcoplasm around the muscle fibers (Fig. 2). The calcium then binds to the actin, after which the myosin head also binds to the actin. The ADP and the Pi then detach from the myosin head, which uses the energy for the conformational change to shorten the muscle fibre. When the muscle relaxes, Ca²⁺-ATPase pumps the calcium ion back to the reticulum, the myosin head detaches from the actin, and ATP binds to the myosin head. (Fig. 3)

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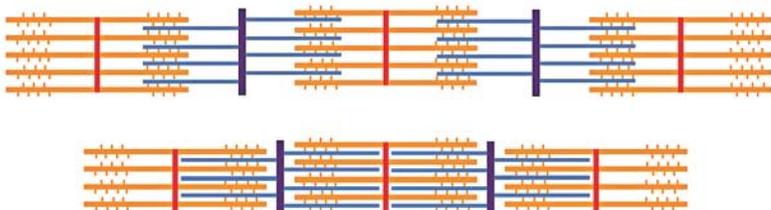


Fig. 1: The top figure illustrates a relaxed muscle fibre and the bottom one a contracted muscle. The orange lines are myosin and the blue lines are actin.

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Fig. 2: After two calcium ions (brown) attach to the actin, the myosin head also attaches to the actin molecule.

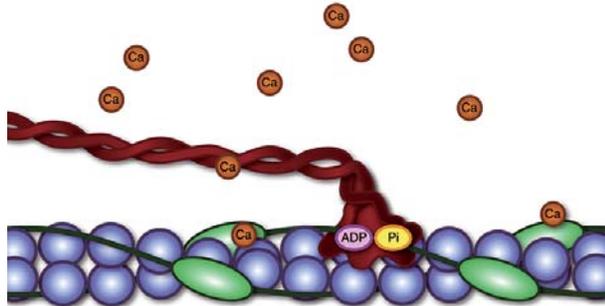
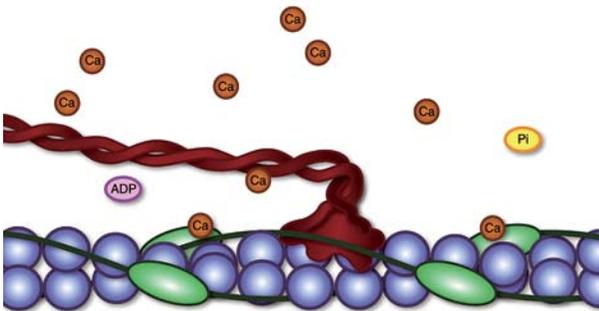


Fig. 3: After ADP (purple) and Pi (yellow) detach, the myosin head changes conformation and moves the actin relative to the myosin.



The calcium pump, the Ca^{2+} -ATPase (a protein), plays an important role in the whole process, and we will mainly focus on the description of this pump using non-equilibrium thermodynamics. It is common to describe how this works by using a diagram of the enzyme cycle, i.e. a so-called Post-Albers diagram, see Fig. 6. The protein has two configurations, E_1 and E_2 . In the first state in the left top corner, the protein is in the E_1 configuration and nothing is bound to it. In the first step, two calcium ions are bound inside the protein. In the second step, ATP is bound to the protein and splits into ADP, which goes back into the sarcoplasm, and organic phosphate, Pi, which binds to the protein. In the third step, the Pi changes location in the protein and the energy is used to modify the E_1 configuration into an E_2 configuration. In the fourth step in the cycle, the high energy of E_2 allows calcium ions to go into the reticulum. In the fifth

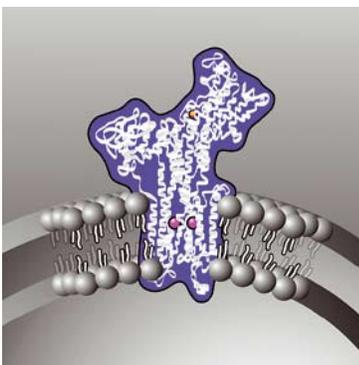


Fig. 4: The Ca-ATPase with 2 bound Ca ions in the lower part and 1 ATP molecule in the upper part.

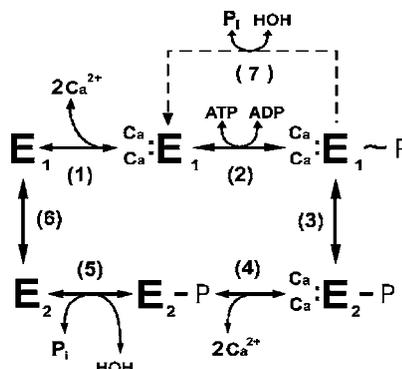


Fig. 5: The enzyme cycle.

step, Pi unbinds. In the sixth step, the configuration changes back to E_1 . Depending on the thermodynamic forces involved, all these steps may be in a forward or backward direction. The process just described is completely coupled in the sense that each ATP molecule that reacts leads to the transfer of two calcium ions into the reticulum. An alternative process, indicated by step 7 in the diagram, occurs after the second step when inorganic phosphate leaves the protein, while the energy is dissipated as heat. Calcium ions can leave the reticulum when we add a leak pathway to the membrane. This path is parallel to the transport through the protein and is not indicated in the diagram in Fig. 6. Both return pathways results in an *uncoupled* overall process.

The description that follows from this diagram is not satisfactory for one reason in particular. It describes the processes in terms of pure reaction kinetics. Temperature differences and heat flows are not described. As shown by de Meis and others (1997, 2001), temperature plays an important role (e.g. in thermogenesis), and this description is therefore not thermodynamically satisfactory.

Classical non-equilibrium thermodynamics (de Groot and Mazur 1984, Kjelstrup and others 2006, Kjelstrup and Bedeaux 2008) gives linear relations between the Gibbs energy differences involved and the temperature difference with the reaction rate of ATP, calcium ion flux and heat flux. The linear nature of this description is not satisfactory.

A new methodology called mesoscopic non-equilibrium thermodynamics has been developed in recent years to address this problem. In 2005, Kjelstrup, Rubi and Bedeaux gave the first description of a calcium pump, which is nonlinear and contains the temperature as a variable. A short overview of the results is given here, indicating further work in progress.

In equilibrium, the reaction, Gibbs energy for the ATP conversion, DG^i , is zero and the chemical potential and temperature outside the membrane, m_{Ca}^i and T^i , are equal to those in the reticulum, m_{Ca}^o and T^o . Outside equilibrium, this is not the case, and a reaction rate, calcium ion flux and a total heat flux develop as a result. Both fluxes are positive when they are into the reticulum. Using mesoscopic non-equilibrium thermodynamics, we were able to show that

$$\begin{aligned}
 r &= -D_{rr}[1 - \exp(\frac{DG^i}{RT^i})] - D_{rd}[\frac{m^o}{RT^o} - \frac{m^i}{RT^i}] - D_{rq}[1 - \frac{T^i}{T^o}] \\
 J_{Ca}^o &= -D_{dr}[1 - \exp(\frac{DG^i}{RT^i})] - D_{dd}[\frac{m^o}{RT^o} - \frac{m^i}{RT^i}] - D_{dq}[1 - \frac{T^i}{T^o}] \\
 J_q &= -D_{qr}[1 - \exp(\frac{DG^i}{RT^i})] - D_{qd}[\frac{m^o}{RT^o} - \frac{m^i}{RT^i}] - D_{qq}[1 - \frac{T^i}{T^o}]
 \end{aligned}$$

In the paper, expressions were given for the elements of the D conductivity matrix in terms of the parameters used in the mesoscopic context. For now, one only needs to know that the matrix is not symmetric. The important tasks currently being worked on are to:

- i) Rewrite the equations using the measurable heat flux \mathcal{J}_q' rather than the total heat flux \mathcal{J}_q and to obtain the D' conductivity matrix using available experimental results. Convert these conductivities into those in the D matrix using the necessary enthalpies.
- ii) Obtain some of these enthalpies from a first law analysis of the experiments.
- iii) Obtain additional enthalpies from a quantum mechanical analysis of the calcium ions in the protein in the E_1 and the E_2 conformations.
- iv) Obtain the conductivities in the mesoscopic description.

Once this is done, phenomena such as, for instance, thermogenesis may be described. Depending on the success of the analysis in the description of various details, the model can be further developed.

In this manner, we hope to learn much about this important and highly efficient element of biological systems. Such knowledge may be useful to develop other efficient chemical processes at the nano level. A better understanding of the Ca^{2+} -ATPase molecule could, for instance, give us new insight into obesity, a growing problem in many affluent countries.

References

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