Supplement to "Chaos in three physical systems, Section 3: Ergodic pumping"

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Abstract

This supplement comments on various complications that will have to be taken into account in a genuine application of ergodic pumping to myosin, and lists some other potential biomolecular applications.

1 Complications in myosin

The references that I found most helpful for experimental facts about myosin structure and function (as opposed to the many others on proposed mechanisms with which ergodic pumping shall have to compete!) are [Ho, F+, GH, MC+]. Here is a list of some of the facts which should be taken into account in a serious application of ergodic pumping to myosin.

1. The P is not really free in the initial state (though it is claimed to tumble), being bound electrostatically and by hydrogen bonds to various parts of the binding pocket and an Mg; so first it has to be dug out of a potential well. This might be compensated for later on by increased association of water.

2. Binding of myosin to actin progressively strengthens during the early stages of the power stroke and one can speculate that this source of free energy is used to unbind the P, e.g. by pulling on the hydrogen bond from the glycine of the switch II linker; one could treat this by adding a second slow degree of freedom to represent the extent of actin binding.

3. It is almost sure that the ADP also participates in the power stroke, because there is evidence for an additional movement of the lever arm between P release and ADP release; this is also logical because the ADP gains a lot of entropy by leaving the ATP binding pocket (the ADP concentration in the cellular fluid is only 0.02mM, i.e. 80MÅ^3 per molecule), so it can contribute even more free energy than P, and could do ergodic

pumping too. My guess is that part of the work done by the P is to unbind the ADP by pushing apart the sides of the binding pocket, and then the ADP does the bulk of the external work by pushing the pocket fully open.

4. It may be that the Mg, whose presence is said to be essential for the ATP hydrolysis, might also play an ergodic pumping role, for example in getting the ADP unbound (but note that ATP and ADP spend most of their time with an Mg bound to them); there is also 0.4 of a proton released during the power stroke [MHG] (presumably fractional because the P exchanges between its HPO_4^{2-} and $H_2PO_4^-$ forms).

5. The free energy decrease of about $8T$ on binding a new molecule of ATP once the P and ADP have left is presumably important for releasing the myosin from the actin; this would probably not be an ergodic pumping step as there is no evidence that external work is done, but it could still be a closely balanced exchange of free energy from actin binding to ATP binding.

6. The P and ADP have rotational degrees of freedom and the ADP some flexural ones too, which also gain entropy on escaping from the ATP binding pocket. This additional entropy (particularly likely to be large for ADP) can also be turned to work by ergodic pumping.

7. Damping of the pocket opening is probably due much more to water around the whole lever arm than just the P and ADP bouncing inside, so the motion of the lever would be much slower than in the model example.

8. There is not really an external potential against which a single myosin molecule works; rather it is the whole muscle that works against an external force and the force is distributed in some dynamic way among the individual molecules; in particular, elastic compliance of the actin and myosin need incorporating (note that this is likely to be entropic in nature too).

9. I have neglected the effects of external pressure: there is a nett volume change associated with the power stroke and I should really use Gibbs free energy, appropriate to changes at constant pressure instead of constant volume.

10. A puzzle is that the hydrolysis of ATP in myosin is claimed [Ko] to lead to an entropy increase of about $24T$ (compensated for by a $22T$ increase in energy), but its location is unclear: one suggestion referred to in [Ko] is destructuring of water around the actin binding site, but maybe it could just be the increase in freedom of the P and Mg and the liberated 0.4 of a proton. Alternatively, David MacKay suggests that it could be an irrelevant transfer of free energy between two parts of the myosin under strain, one principally an entropic spring and the other an energetic spring, as a result of a slight shift in equilibrium.

11. It is unrealistic to expect the trap for P to expand to 800,000Å^3; 800Å^3 would be more reasonable (e.g. the space between the switch 2 helix, loop 2 and the α-helix containing SH1). The remaining $7T$ of free energy decrease could be used, however, if on expansion of the trap some positive charges are revealed in the walls (indeed, there are two positive charges in the SH1 α-helix, in contrast to the large number of negative charges on the other two parts and in the cleft). Because P is negatively charged, the density of P (or really its two states with charges $Z = -1$ and -2) in equilibrium with 2mM concentration far away is enhanced near a positive charge by a Boltzmann factor of $e^{-\beta ZeV(q)}$, where V is the appropriate effective potential (modified from a straight Coulomb potential by polarisation of water, screening by ions, and a short range repulsion) and e the unit of charge. It is possible that, integrated over the trap when it is open enough for the P to leave, this yields a factor of 1000, thus matching one P in the trap to 2mM concentration far away, and so achieving release of the P without any free energy change (indeed, I believe similar considerations are vital for the functioning of proton motors, for example, where the final step is that a proton must be released from being bound to an acidic residue into a low concentration).

12. The concentrations of P, ADP and pH have measured effects on muscle force and velocity [CP] (see also [BLBT] for some additional results). The observed decrease in force as [P] is increased or pH decreased is totally consistent with the ergodic pumping mechanism, as increase in product concentrations would decrease the entropy increase available. The observed increase in force with ADP concentration is puzzling, though can probably be rationalised along the lines of [CP].

2 Other potential applications

I also propose that ergodic pumping is a significant aspect of the mechanism of some other molecular motors like kinesin and F_1 ATP-ase, which have similar ATP binding pockets to myosin, though their power strokes appear to be associated with ATP binding rather than release of P and ADP, so the ergodic pumping is probably just to unbind the products of hydrolysis and empty the pocket. Ergodic pumping is probably also relevant to dynein and DNA-helicases, which are other ATP-powered motors. It could even be relevant to the molecular switches called G-proteins, which have an analogous GTP-binding pocket to myosin, though instead of doing work these catalyse generation of chemical signals. I suspect it could also play a role in some ion pumps (e.g. the 3Na/2K ATP-ase, the sarcoplasmic Ca ATP-ase and the H/K exchanger in the stomach wall, with the transported ions and a P as drivers of the conformation changes). More generally, phosphorylation is a widespread mechanism for altering the conformation of enzymes and thus regulating their activity, and one may ask whether some of the conformation changes are achieved by ergodic pumping of the P which is transferred from ATP and then released. On the same theme, ATP is hydrolysed to ADP in the binding pocket of actin shortly after its polymerisation, causing a conformation change which presumably locks the actin molecules together more strongly, and I wonder whether the conformation change is being performed by ergodic pumping of the released P. It might also be relevant to proton motors like the F_0 of ATP-synthase and bacterial flagellar motors (with the proton as driver, or Na ions for some flagellar motors).

Just as for myosin, there is a large literature on all of these other biomolecules, about both experiments and models, which I have not attempted to cite here.

References

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