More Can Mean Less,

Or- Simplifying sometimes requires ideas to be more complicated

Michael A Geeves,

School of Biosciences, University of Kent, Canterbury, UK

m.a.geeves@kent.ac.uk

In 1984 I was lucky enough to gain one of the first Royal Society University Fellowships which had been established because, at this time, there were very few academic jobs available in the UK university system. This allowed me to work on longer-term problems, and by 1993, I was reaching the end of 10 years of the Fellowship at the University of Bristol. As outlined by Bill Lehman, I had worked over the period of my Fellowship to establish a 2- or 3-step process by which myosin docked onto actin. The ideas were originally set out in 1984[1], but collecting the evidence to fully support the idea went on long after the publication of the paper[2]. Prior to this work, there were two contrasting views on the actin myosin ATPase – the Lymn-Taylor model[3] and the Eisenberg view[4] and all three models were used and debated throughout the 1980's.

Our 1984 model had implications for the calcium regulation of the actin myosin interaction and a new project on this regulation was initiated by a PhD student, Dave Halsall. Dave established a way of modelling the cooperative binding of S1 to actin by assuming that tropomyosin only blocked the A to R -state isomerisation (see the first scheme in Lehman's commentary), which was controlled by equilibrium constant K_2 [5]. This model explained how larger values of K_2 (determined by the nucleotide; ADP, ADP + Pi or ATP present in the myosin binding pocket) resulted in a more effective displacement of tropomyosin from the blocking position by myosin. The elements were then all in place to solve the whole problem in 1987. However, the ideas and approach were not universally welcomed. Others were promoting different ideas [6]; the model was quite complex, not easily understood, and the implications of a two-step binding of myosin binding to actin was not widely appreciated.

When Danny McKillop joined the group as a PhD student, he improved the methods used to measure myosin binding to actin and the precision with which the model could be defined. His work revealed anomalies in the data; specifically, that the equilibrium binding constants derived from equilibrium binding and kinetic binding measurements could not be made to agree. The better the measurements became, the clearer the anomalies. Danny pointed out that allowing for three states of the actin

filament would resolve the problem, but I was reluctant to entertain this idea. I had spent 10-years trying to convince the muscle community about the two or three state docking of myosin to actin and 5-years arguing that the docking model together with a two-state model of the thin filament could account for the cooperativity in myosin binding to thin filament. Adding one more state felt like a step too far, and the general rule for any modelling is that you don't add a new state unless all other possibilities have been eliminated.

Bill Lehman refers to me generously as "a simplifier par excellence". This did not feel like my reputation at the time. The Lymn & Taylor actomyosin ATPase model had 4-states, and the Eisenberg model 6-states. The Geeves, Goody Gutfreund model had 12-states, and this seemed complex - or even too complex for many observers. Ralph Yount, when summarizing a late 1980's Gordon conference commented that the early USA had only 13 states but eventually needed 50 states to unify the whole country. Now myosin ATPase models appeared to be heading towards a similar number of states! The idea of introducing yet more states into the models was not attractive. Luckily Danny McKillop persisted with the idea and eventually we sat down to work through the model in detail. What happened then is what happens when a model comes together, lots of contradictory evidence suddenly all makes sense and everything seems to fit: one of the rare *eureka moments* that makes scientific discovery so special.

When introduced, the names *Blocked-Closed-Open* caused some confusion as to the precise meaning. The *Blocked-state* was already well established. The opposite of *Blocked* was *Open* and already in common use. We needed a name for the third state that was not quite so "turned off" as *Blocked*. For inspiration we turned to Napoleon, who it is claimed referred to the British as "a nation of shopkeepers" (and indeed our recently replaced Prime Minister at that time, Mrs Thatcher, was famously the daughter of a small town grocer). Small shops will normally have a sign on the door which can be flipped to read either *OPEN* or *CLOSED*. *Closed* does not necessarily mean the shop is no longer open for business rather the shopkeeper may have just popped next door. At the end of the day the metal shutters are drawn down and padlocked; the entrance to the shop is now firmly *Blocked*. Hence our use of the terms *Blocked/Closed/Open* These terms were later modified to be Blocked/Calcium-induced /Myosin-induced (B/C/M) based on the three positions observed for tropomyosin on the surface of actin in structural studies.

The model was quite slow be taken up, as can be seen in the citation record, except by a few like Sam Lehrer who was very quick to see the implications of what we had proposed and became a great advocate of the model, a great collaborator and friend. The ideas in the model did gradually take hold because it had such great power to explain many different contradictory experimental details from both purified proteins and work in contracting muscle fibres. But it was not until the publication

of negatively stained images of Tm in three distinct positions on actin by Vibert, Craig & Lehman [7] that the model really took off.

We all live in the hope that we are doing work of significance (or impact in the current bean-counters jargon) that will be recognised as such by our peers. To have written a paper that was useful in 1993, and which continues to inform our thinking about how muscle regulation works is a humbling realisation of how good work gets established. The paper would not have been considered for inclusion in the UK Research Assessment Exercise. This is the UK assessment of each university's research standing that takes place every 5-7 years and required all academic staff to submit 4 published papers. Work published in a society journal with moderate Impact Factor like Biophysical Journal would have been considered far too risky to submit in such an exercise. This underlines how difficult it is to evaluate the real impact of scientific research. I would contend that every "important" piece of published work is built on dozens of smaller building blocks and without which the headline work would struggle to exist. We do science a disservice if we *only* recognise and celebrate the headline grabbing research. Biophysical Journal is a great scientific journal with continuous high standards and excellent refereeing. I am proud that this paper was publish in Biophysical Journal and grateful for the platform that this gave for this work.

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