The role of protein dynamics in allosteric effects—introduction

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Certainly no subject or field is making more progress on so many fronts at the present moment, than biology, and if we were to name the most powerful assumption of all, which leads one on and on in an attempt to understand life, it is that all things are made of atoms, and that everything that living things do can be understood in terms of the jiggings and wiggings of atoms.

Richard Feynman

(*Feynman Lectures on Physics*, vol. 1, Ch. 3. 1963; <http://www.feynmanlectures.caltech.edu/>)

Control at the molecular level is an essential feature of cellular function, and a key mechanism of this control is ‘allosteric’ regulation, a concept introduced some 50 years ago by Monod, Changeux, Jacob and Wyman (see (Changeux 2012, 2013; Changeux and Edelstein 2005)) and which is as important now as it was then. The central idea of allosteric regulation is that interaction of a ligand at one site on a protein can change the functional (binding or catalytic) properties at another site without direct spatial proximity of the two sites. While the initial ‘MWC’ model for allosteric effects focussed on oligomeric proteins existing in two conformational states (Monod et al. 1965), subsequent work has led to a number of extensions to the concept. First, it is clear that monomeric proteins can show functionally important allosteric effects—

for example, the regulatory proteins CheY and NtrC (Cui and Karplus 2008; McDonald et al. 2012; Villali et al. 2014; Volkman et al. 2001). The transmission of the effects of distal mutations is analogous in many ways to the transmission of the effects of ligand binding, and is of course seen in many monomeric proteins (e.g., Clarkson et al. 2006; Lee and Goodey 2011), while it has been studied in particular detail in dihydrofolate reductase (Boehr et al. 2013; Wong et al. 2005). Secondly, such effects are clearly not restricted to small molecule ligands—allosteric effects involving the binding of other macromolecules or covalent modification (such as phosphorylation) are of fundamental importance in the regulation of signal transduction and of metabolism. Thirdly, the concept of population shifts between pre-existing states, the basis of the MWC model, has been discussed more broadly within the ‘energy landscape’ or ‘ensemble’ formalism (Frauenfelder et al. 1991; Hilser et al. 2012; Itoh and Sasai 2010; Motlagh et al. 2014) and has also come to the fore thanks to the recent development of NMR methods for detecting and characterising conformational states present in low populations (Baldwin and Kay 2009; Manley and Loria 2012; Mittermaier and Kay 2006; Sekhar and Kay 2013).

The prevailing view of allostery still tends to focus on structure. Yet, since allostery is fundamentally thermodynamic in nature, involving changes in enthalpy and/or entropy, communication across the protein could be mediated not only by changes in the mean conformation but also by changes in the dynamic fluctuations about the mean conformation (Cooper and Dryden 1984; Tsai et al. 2008). Thirty years ago, Cooper and Dryden (1984) noted that in principle even in the absence of a ligand-induced change in the *time-averaged* conformation, changes in protein dynamics leading to changes in the *distribution* around the average structure could produce allosteric communication between distinct binding sites. They showed that free energies of a few kcal/mol can be derived

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from only a slight stiffening of a few of the many global dynamic modes of motion available to a protein. With the increasing understanding of the importance of dynamics in enzyme catalysis (see the recent virtual special issue of *Accounts of Chemical Research* on ‘Protein Motions in Catalysis’; Bhabha et al. 2015; Callender and Dyer 2015; Hanoian et al. 2015; Klinman 2015; Kohen 2015; Palmer 2015) and in protein function in general, the importance of dynamics as a contributory mechanism in allosteric effects is now recognised (Jardetzky 1996; Kern and Zuiderweg 2003; Tsai et al. 2008).

In the last few years, there have been a number of reports describing clear roles for protein dynamics in allosteric effects, both in the transitions between states and in making substantial contributions to the thermodynamics of the allosteric effect itself (Jiao et al. 2012; Kern and Zuiderweg 2003; Law et al. 2014; Manley and Loria 2012; McElroy et al. 2002; Palazzi et al. 2013; Popovych et al. 2006; Rivalta et al. 2012; Shi and Kay 2014; Stevens et al. 2001). (It is of course difficult to demonstrate the existence of allosteric effects produced *solely* by changes in dynamics, since the failure to observe a structural change does not mean that it does not occur; Nussinov and Tsai 2014.)

Bearing in mind the 50th anniversary of the Monod, Wyman and Changeux paper and the 30th anniversary of the Cooper and Dryden paper, we felt that it would be timely and interesting to review the current concepts on ‘The Role of Protein Dynamics in Allosteric Effects’ in a dedicated issue of *Biophysical Reviews*.

This issue includes reviews of specific examples where there is clear evidence for the importance of dynamics in allosteric effects. There are discussions of monomeric proteins such as the PBX1 homeodomain (Mittermaier 2015) and CheY (Lee 2015), the dimeric catabolite activator protein (CAP; (Townsend 2015; Tzeng 2015), the tetrameric protein kinase A (Ping 2015) and a number of multi-domain proteins (Lee 2015; Motlagh 2015; Peng 2015; Whitney 2015) and finally the large pentameric acetylcholine receptor channel (Changeux 2014). Many of these examples show the importance of global low-frequency protein fluctuations in allosteric effects, and a successful theoretical approach to these by normal mode analysis is discussed by Townsend et al. (Townsend 2015). Several articles discuss the use of NMR spectroscopy to study the dynamic effects of interest, and Mittermaier and Farber (Mittermaier 2015) describe the use of relaxation dispersion NMR in detail; other new physical methods of considerable potential value in this area are neutron spin echo spectroscopy (Callaway 2015) and terahertz spectroscopy (Niessen 2015).

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