Article:
Lorimer, George H., Horovitz, Amnon and McLeish, Tom (2018) Allostery and molecular machines. Philosophical Transactions of the Royal Society B: Biological Sciences. 20170173. ISSN: 1471-2970

https://doi.org/10.1098/rstb.2017.0173

PHILOSOPHICAL TRANSACTIONS B

rstb.royalsocietypublishing.org

Introduction

Cite this article: Lorimer GH, Horovitz A, McLeish T. 2018 Allostery and molecular machines. *Phil. Trans. R. Soc. B* **373**: 20170173. http://dx.doi.org/10.1098/rstb.2017.0173

Accepted: 14 March 2018

One contribution of 17 to a discussion meeting issue 'Allostery and molecular machines'.

Subject Areas:
biochemistry, biophysics, structural biology, computational biology

Author for correspondence:
George H. Lorimer
e-mail: glorimer@umd.edu

Allostery and molecular machines

George H. Lorimer[1], Amnon Horovitz[2] and Tom McLeish[3]

[1]Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 27042, USA
[2]Department of Structural Biology, Weizmann Institute of Science, Rehovot 7610001, Israel
[3]Department of Physics, University of York, Heslington, York YO10 5DD, UK

GHL, 0000-0003-2805-8792; AH, 0000-0001-7952-6790

1. Introduction

Machines undergo repeated energy (fuel)-driven cycling between various functional and structural states. Such cycling involves motions of the machine parts, which take place in a highly coordinated manner in time and space. This description applies not only to man-made machines but also to the molecular machines that mediate many of the key processes in all forms of life [1]. Examples include protein synthesis by the ribosome, DNA unwinding by helicases during replication, protein degradation by the proteasome and protein folding by chaperones. The coordinated movements of most biomolecular machines are achieved by allosteric regulation of ATP binding and hydrolysis. Consequently, a molecular level understanding of how the essential machines of life work requires invoking and further developing allosteric theory. Hence, the motivation for the Royal Society Discussion Meeting entitled 'Allostery and molecular machines' that took place in June 2017. The meeting brought together scientists interested in allostery, in general, with others who are studying specific biomolecular machines of interest. The meeting led to many interesting discussions and resulted in this special issue of the *Philosophical Transactions B*.

In 1965, Monod, Wyman & Changeux published a seminal paper [2] that described a so-called 'concerted model' (referred to here and generally as the MWC model) for cooperative ligand binding by oligomeric proteins. This issue contains a paper by one of the co-authors of this landmark paper in which the MWC model is explained in brief and its application to the nicotinic acetylcholine receptor is then described [3]. The MWC model remains important but its elegance has come at the price of several restrictive assumptions. One key assumption is that cooperativity is due to a shift in equilibrium between different quaternary states of the protein. It is well documented, however, that cooperativity can also occur (i) owing to tertiary conformational changes, (ii) in monomeric proteins and (iii) in the absence of a mean structural change. A simple 'allosteron' model according to which cooperativity arises owing to changes in fluctuations, in the absence of a mean structural change, is described in this issue by McLeish *et al.* [4]. This seems to capture the essentials of the 'fluctuation-route' to allosteric signalling (originally due to Cooper & Dryden [5]) at the same highly coarse-grained level as the MWC model invokes for structural change.

A second restrictive assumption of the MWC model is that symmetry is conserved. A consequence of this assumption is that the MWC model is unable to account for negative cooperativity, in contrast with the sequential model of Koshland, Némethy & Filmer (referred to as the KNF model) [6]. In cases of positive cooperativity in ligand binding, it has been difficult to distinguish between the MWC and KNF models because sigmoidal plots (which are diagnostic for positive cooperativity) are insensitive to ligation intermediates. Given that many machines are ring-shaped oligomers (helicases, chaperonins, etc.), Gruber & Horovitz [7] show in this issue that native mass spectrometry can be used to distinguish between the MWC, KNF and probabilistic (i.e. subunit conformational changes can occur in any order around the ring) models for such assemblies.

THE ROYAL SOCIETY PUBLISHING

Being able to distinguish between the MWC, KNF and probabilistic models is important because the efficiency of machines is path-dependent. In other words, it is important to characterize not only the relatively stable allosteric states (e.g. the T and R states in the MWC model) but also the pathways by which they interconvert. This naturally invokes a finer scale of structure and dynamics. Given that allostery is 'action at a distance', a key question in the field has concerned the mechanisms by which remote sites in a protein communicate with each other. Insights into this issue can be obtained by characterizing allosteric intermediates and identifying communication routes (if such exist) in the protein structures. Stock & Hamm [8] describe time-resolved infrared spectroscopy experiments and non-equilibrium molecular dynamics simulations that actually indicate the absence of well-defined communication pathways in the structure of the small monomeric protein PDZ2, thereby suggesting that allosteric transitions may resemble downhill folding. By contrast, allosteric wiring is found to exist in the chaperonin GroEL as reported by Thirumalai & Hyeon [9], who use a structural perturbation computational method. Ozkan and co-workers describe a related metric termed 'dynamic flexibility index' that provides a measure for how much an amino acid is affected by perturbations elsewhere in the protein and apply it for the case of thioredoxin [10]. These approaches show that when finer-grained understandings of allostery are explored, the physical components of MWC-like structural change and allosteron fluctuation both tend to be present.

Computational approaches for studying allosteric mechanisms are also described by other papers in this issue. Sengupta & Strodel [11] show that Markov state models can be used to characterize allosteric intermediates. Bahar and co-workers show that insights into the allosteric mechanism of LeuT transporters can be gained via anisotropic network models [12]. They also highlight the role oligomerization can play in facilitating allosteric transitions. The latter topic is also discussed by Wodak and co-workers, who focus in their paper on how homo-dimerization can give rise to allosteric behaviour [13].

Several papers in this issue describe studies aimed at understanding the molecular mechanisms of specific biomolecular machines such as the double-ring chaperonin GroEL, which displays positive intra-ring and negative inter-ring cooperativity with respect to ATP binding. Lorimer *et al.* [14] describe a molecular mechanism for the inter-ring negative allostery, which affects the relative populations of GroEL in complex with one or two co-chaperonin GroES molecules. Noshiro & Ando [15] use high-speed atomic force microscopy to measure these relative populations and determine whether they are affected by the presence of substrate proteins. Thirumalai & Hyeon [9] show how allostery in GroEL impacts its folding function, and Willison [16] reviews aspects of the mechanism of action of CCT/TRiC, the eukaryotic homologue of GroEL. Members of the Hsp70 family of molecular chaperones also undergo ATP-driven allosteric transitions, as reviewed by Mayer [17]. Tafoya & Bustamante [18] compare several other ATP-driven systems such as kinesin, the φ29 DNA packaging motor and the ClpXP degradation machinery. They show how ATP binding, hydrolysis and exchange differ between these machines in a manner tailored for their respective functions.

Cooperativity in biological systems is manifested not only in binding but also in folding reactions. Moreover, binding and folding reactions can take place in a coupled fashion. Itzhaki and co-workers [19] discuss cooperativity in the folding of repeat proteins, and Hilser and co-workers [20] show that signal propagation between domains is maximized when one or more of them are disordered. They also discuss the concept of 'energetic frustration' used in the field of protein folding with regard to allostery. One of the important conclusions of the meeting was, in fact, that a better understanding of allostery can be achieved by borrowing ideas and using methods in the area of protein folding.

The meeting itself, and this issue of the *Transactions*, indicate a current resurgence of interest in the vital information-transmitting process of allostery in molecular biology. Jacques Monod termed allostery the 'second secret of life' [21]. Prescient as always, the import of this deep remark is only now becoming clear. Biological matter must be able to metabolize, transport and reproduce—but all of these depend on the transmission and processing of information. At the molecular level, allostery provides the biological equivalent of circuit components, or logic gates, on which complex signalling networks can build. As this meeting demonstrated, the thermal, randomizing environment of living cells might have been thought to offer insuperable challenges to faithful information transfer. But the subtle processes that the contributors to this issue explore testify once more to the power of evolution to discover ways of bringing the necessity of order from the chance of randomness.

The meeting gave a strong impression that this subject area is moving very fast. New experimental spectroscopies and microscopies, new computational and theoretical techniques, and new biomolecular examples of allostery are emerging continually. The editors hope that this community will meet again after a few years and find their field once more transformed.

Data accessibility. This article has no additional data.
Competing interests. We declare we have no competing interests.
Funding. We received no funding for this work.

References

1. Alberts B. 1998 The cell as a collection of protein machines: preparing the next generation of molecular biologists. *Cell* **92**, 291–294. (doi:10.1016/S0092-8674(00)80922-8)
2. Monod J, Wyman J, Changeux J-P. 1965 On the nature of allosteric transitions: a plausible model. *J. Mol. Biol.* **12**, 88–118. (doi:10.1016/S0022-2836(65)80285-6)
3. Changeux J-P. 2018 The nicotinic acetylcholine receptor: a typical 'allosteric machine'. *Phil. Trans. R. Soc. B* **373**, 20170174. (doi:10.1098/rstb.2017.0174)
4. McLeish T, Schaefer C, von der Heydt AC. 2018 The 'allosteron' model for entropic allostery of self-assembly. *Phil. Trans. R. Soc. B* **373**, 20170186. (doi:10.1098/rstb.2017.0186)
5. Cooper A, Dryden DT. 1984 Allostery without conformational change. A plausible model. *Eur. Biophys. J.* **11**, 103–109.
6. Koshland Jr DE, Némethy G, Filmer D. 1966 Comparison of experimental binding data and theoretical models in proteins containing subunits. *Biochemistry* **5**, 365–385. (doi:10.1021/bi00865a047)

7. Gruber R, Horovitz A. 2018 Unpicking allosteric mechanisms of homo-oligomeric proteins by determining their successive ligand binding constants. *Phil. Trans. R. Soc. B* **373**, 20170176. (doi:10.1098/rstb.2017.0176)
8. Stock G, Hamm P. 2018 A non-equilibrium approach to allosteric communication. *Phil. Trans. R. Soc. B* **373**, 20170187. (doi:10.1098/rstb.2017.0187)
9. Thirumalai D, Hyeon C. 2018 Signalling networks and dynamics of allosteric transitions in bacterial chaperonin GroEL: implications for iterative annealing of misfolded proteins. *Phil. Trans. R. Soc. B* **373**, 20170182. (doi:10.1098/rstb.2017.0182)
10. Modi T, Huihui J, Ghosh K, Ozkan SB. 2018 Ancient thioredoxins evolved to modern-day stability–function requirement by altering native state ensemble. *Phil. Trans. R. Soc. B* **373**, 20170184. (doi:10.1098/rstb.2017.0184)
11. Sengupta U, Strodel B. 2018 Markov models for the elucidation of allosteric regulation. *Phil. Trans. R. Soc. B* **373**, 20170178. (doi:10.1098/rstb.2017.0178)
12. Ponzoni L, Zhang S, Cheng MH, Bahar I. 2018 Shared dynamics of LeuT superfamily members and allosteric differentiation by structural irregularities and multimerization. *Phil. Trans. R. Soc. B* **373**, 20170177. (doi:10.1098/rstb.2017.0177)
13. Garton M, MacKinnon SS, Malevanets A, Wodak SJ. 2018 Interplay of self-association and conformational flexibility in regulating protein function. *Phil. Trans. R. Soc. B* **373**, 20170190. (doi:10.1098/rstb.2017.0190)
14. Lorimer GH, Fei X, Ye X. 2018 The GroEL chaperonin: a protein machine with pistons driven by ATP binding and hydrolysis. *Phil. Trans. R. Soc. B* **373**, 20170179. (doi:10.1098/rstb.2017.0179)
15. Noshiro D, Ando T. 2018 Substrate protein dependence of GroEL–GroES interaction cycle revealed by high-speed atomic force microscopy imaging. *Phil. Trans. R. Soc. B* **373**, 20170180. (doi:10.1098/rstb.2017.0180)
16. Willison KR. 2018 The substrate specificity of eukaryotic cytosolic chaperonin CCT. *Phil. Trans. R. Soc. B* **373**, 20170192. (doi:10.1098/rstb.2017.0192)
17. Mayer MP. 2018 Intra-molecular pathways of allosteric control in Hsp70s. *Phil. Trans. R. Soc. B* **373**, 20170183. (doi:10.1098/rstb.2017.0183)
18. Tafoya S, Bustamante C. 2018 Molecular switch-like regulation in motor proteins. *Phil. Trans. R. Soc. B* **373**, 20170181. (doi:10.1098/rstb.2017.0181)
19. Perez-Riba A, Synakewicz M, Itzhaki LS. 2018 Folding cooperativity and allosteric function in the tandem-repeat protein class. *Phil. Trans. R. Soc. B* **373**, 20170188. (doi:10.1098/rstb.2017.0188)
20. White JT, Li J, Grasso E, Wrabl JO, Hilser VJ. 2018 Ensemble allosteric model: energetic frustration within the intrinsically disordered glucocorticoid receptor. *Phil. Trans. R. Soc. B* **373**, 20170175. (doi:10.1098/rstb.2017.0175)
21. Monod J. 1977 *Chance and necessity: essay on the natural philosophy of modern biology*. London, UK: Penguin Books.