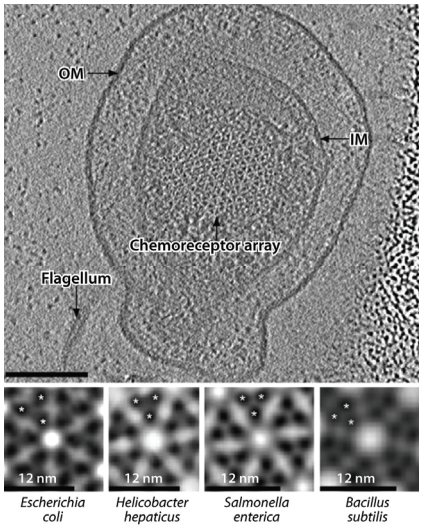
Annual Review of Biophysics, 2017. Ken A. Dill and Xiaowei Zhuang (eds). Annual Reviews, 4139 El Camino Way, P.O. Box 10139, Palo Alto, California 94303-0139, USA. Vol. 46. vii + 561 pages. Price: US$ 107.

This volume effectively summarizes the diversity in the rapidly expanding area of biophysics. As is to be expected, cryo-electron microscopy and electron cryo-tomography (ECT) find a large representation both in the use of the methodology as well as in applications to understand macromolecular processes. The volume has articles to entice the traditionalist as well – an example would be an article on geometric principles for designing symmetric self-assembling protein nanomaterials. Several articles in this volume describe the prominent role of ribonucleic acid (RNA). This is, in a sense, a reflection of the understanding gained in the recent past on the role of riboswitches, structured and non-structured RNA, insights into the theory and modelling of RNA structures and as a corollary – advances in the assessment of 3D RNA structure prediction.

Technological improvements drive experimental biology. In just the way that macromolecular crystallography influenced research programmes since the 1990s – primarily by technological advancements (synchrotron radiation, high-sensitivity detectors and improved computational resources), cryo-electron microscopy now leads the pack as the technique of choice for structural biology. The first review by Brigel and Jensen describes the progress and potential of ECT in the study of bacterial chemoreceptors. ECT, that has been demonstrated to provide three-dimensional images of intact cells at near macromolecular (ca 4 nm) resolution, has witnessed a marked resurgence in the recent past. Improvements in detectors, phase plates and more stable stages contribute to higher resolution images. Structural biology clearly appears to now make the transition from *in vitro* to *in situ*.

Biological nanomaterials are sought after for diverse applications. In this context, the article by Todd Yeates would be of interest to both a nanomaterials designer as well as a mathematically inclined researcher. In an approach to define fundamental principles on which self-assembling protein nanomaterials can be designed, finite supramolecular assemblies were examined. These were seen to obey one of the possible point-group symmetries in three dimensions. These symmetries, in turn, lead to architectures that generally resemble cages or shells similar to any of the five platonic solids, viz. tetrahedron, cube, octahedron, icosahedron and dodecahedron. The prospective utilities are diverse ranging from encapsulation and delivery of molecular cargo to the display of specific binding motifs or epitopes. Yeates then describes strategies for making proteins self-assemble. Some of these are clearly challenging from a protein engineering standpoint. For example, in the case where a simple protein oligomer serves as a starting point for design, elaborate computational approaches are necessary to introduce an interface between multiple copies of that oligomer type. These oligomeric components then need to be assembled with specific geometric arrangements. As point groups cover the symmetries typically exhibited by natural oligomeric proteins, all architectures that can be realized by combining two separate point group symmetries can be tabulated. Employing these possibilities in the design of protein nanomaterials still remains unexplored in the case of two- or three-dimensional designs. The reason this is a challenging research proposition is put across thus – standard tables of crystallographic space groups list points and axes (the so-called Wycoff positions) where local symmetry is obeyed within a space group. Oligomers, therefore, cannot 'sit' on an axis whose rotational symmetry exceeds the symmetry of the oligomer. Mathematically allowed combinations can also lead to steric collision. These complexities, however, also offer advantages. Unusually shaped proteins can be exploited with different symmetry combinations to produce topologically complex materials.

The past few years in biophysics research has arguably been influenced by the ascent of RNA biology. Nitzan *et al.* provide an overview of bacterial small RNAs in regulatory networks. The authors describe the global characteristics of the sRNA-target networks in bacteria analysed using graph-theoretic approaches. This provides insights on the local integration of sRNAs in mixed regulatory circuits with feed-forward and feed-back loops and circuits involving an sRNA with another regulator, both derived from the same transcript. This analysis furthers our understanding regarding bacterial phenotypes, and on the mechanisms that help bacteria rapidly adapt to new environmental conditions and respond to different stresses. The review also spells out the challenges in this area – both in the methodology to determine sRNA interactions as well as determining if the sRNA is a repressor or an activator. The two other RNA-centric articles in this volume are on the long-range interactions in riboswitch control of gene expression (Jones and Ferré-D'Amaré) and on the assessment of 3D structure prediction (Miao and Westhof). RNA structure is often dominated by two-dimensional structures governed, primarily, by Watson–Crick (WC) base pairs. Miao and Westhof, on the other hand, focus on non-WC base pairs and RNA modules. They describe the challenges in the detection of RNA 3D modules from sequence data alone. The section on RNA 3D structure prediction in this article would be of interest to bioinformaticians both from the perspective of evaluating crystal structures as well as molecular models built using information from diverse experimental methods and theroretical inputs.



Architecture of native chemoreceptor arrays as seen by electron cryotomography (ECT). An example of a tomograph of a *Salmonella enteric* minicell is shown alongside those in other bacteria. These tomographic images provide a model of receptor density wherein high resolution crystal structures can be fitted to obtain mechanistic insights that were hitherto unclear.

The collection of articles in the broad areas of theoretical and computational biophysics in this volume reveals the sound theoretical underpinnings of research in this area as well as scope for methodology development. The article on rate-constants and mechanisms of protein–ligand binding by Pang and Zhou, for example, provides an overview of microscopic formulation of the kinetic problem and its reduction to simple rate equations. They proceed thereafter to describe aspects of binding mechanisms and physical factors that control binding rate constants and mechanisms. Other related topics that find elegant descriptions in this volume include a review on binding free energies (Mobley and Gilson). Molecular simulations often provide the route for binding free energy calculations leading to estimates of affinities for biomolecular complexes. This is an important research component in early-stage drug discovery.

The research on structural characterization of large multi-component macromolecular complexes is also adequately represented in this volume. These include a review on the progress in human and tetrahymena telomerase structure (Chan *et al.*), structural insights into the eukaryotic transcription machinery (Nogales *et al.*) and on the CRISPR-Cas9 structures and mechanisms (Jiang and Doudna). The review by Jiang and Doudna provides a succinct summary of research in this area that is a staple of general and specialized subject journals as well as the popular press, on occasion. Biochemical and structural studies on the CRISPR-Cas9 systems have provided a robust framework for enzyme engineering involving RNA specificity changes, thereby reducing off-target activity. This methodology of gene editing is touted as a viable platform for therapeutic intervention in genetic diseases. The article is thus likely to be of interest to both a specialized researcher as well as a lay reader trying to understand the challenges and potential of this methodology.

Two thought-provoking reviews on protein evolution are likely to be of interest to structural biologists and biochemists. The first, entitled 'Biophysical models of protein evolution: understanding the patterns of evolutionary sequence divergence' by Echave and Wilke questions the logic behind correlating rates of protein evolution with functional importance. In this school of thought, slowly evolving proteins (or even sites within proteins) are assumed to be subject to stronger evolutionary pressure and thus functionally more important. The article evaluates this idea with an alternate rationale – slowly evolving proteins do so slowly as they are selected against toxic misfolding and non-specific interactions. The rate of evolution is thus linked to their abundance. While this could be less distracting than the discourse on evolution and Darwin's theory in popular media, it is likely to perturb researchers in protein engineering to examine biophysical models of evolution that combine population genetics models of evolution with the fitness landscape. The other review by Hochberg and Thornton is entitled 'Reconstructing ancient proteins to understand the causes of structure and function'. An argument put forth here is that if one were to dissect the historical trajectory of functional or structural changes in proteins, one is more likely to conclude that features of structure and mechanism are more due to historical constraints and chance than functional optimization. A conclusion, quoted verbatim is this – Complex aspects of proteins, normally thought to be functionally important, are often the result of evolutionary tinkering with subtle degradation of ancestral forms. Now, that is a biophysical lesson that a practitioner of green chemistry (enzymology-based chemical synthesis) cannot afford to ignore.

Put together, the choice of articles in this volume suggests that substantial ground needs to be covered to be able to understand biological machines or macromolecular complexes from fundamental principles. Biophysics covers the entire scale of modern-day biology with vital inputs to translational research. Indeed, reviews in this volume are relevant for early-stage drug discovery (protein–ligand interactions), macromolecular engineering and gene therapy (a potential application of the CRISPR-Cas9 module).

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