Editorial

Mathematics at the eve of a historic transition in biology

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Biology concerns the structure, function, development and evolution of living organisms. It underwent a dramatic transformation from macroscopic to microscopic (i.e., “molecular”) in the 1960s and assumed an omics dimension around the dawn of the millennium. Understanding the rules of life is the major mission of biological sciences in the 21st century. The technological advances in the past few decades have fueled the exponential growth of biological data. For example, the Protein Data Bank (https://www.rcsb.org/pdb/home/home.do) has archived more than one hundred thirty thousand three-dimensional (3D) biomolecular structures and Genbank (https://www.ncbi.nlm.nih.gov/genbank/) has recorded more than 200 million sequences. The accumulation of various biological data in turn has paved the way for biology to undertake another historic transition from being qualitative, phenomenological and descriptive to being quantitative, analytical and predictive. Such a transition provides both unprecedented opportunities and grand challenges for mathematicians.

One of major challenges in biology is the understanding of structure-function relationships in biomolecules, such as proteins, DNA, RNA, and their interacting complexes. Such an understanding is the holy grail of biophysics and has a profound impact to biology, biotechnology, bioengineering and biomedicine. Mathematical apparatuses, including simplicial geometry, differential geometry, differential topology, algebraic topology, geometric topology, knot theory, tiling theory, spectral graph theory and topological graph, are essential for deciphering biomolecular structure-function relationships [1, 2, 3, 4]. In general, geometric modeling is paramount for the conceptualization of biomolecules and their interactions, which is vital to the understanding of intricate biomolecules. Geometric modeling also bridges the gap between biological data and mathematical models involving topology, graph theory and partial differential equations (PDEs) [5, 6] (see Figure 1). Topology dramatically simplifies biological complexity and renders insightful high level abstraction to large biological data [7, 8, 9, 10, 11] (see Figure 2). Graph theory is able to go beyond topological connectivity and incorporates harmonic analysis and optimization

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Figure 1: Geometric modeling of a protein surface in the Eulerian representation, which is crucial for the understanding of the protein structure and interactions, and bridges the gap between biomolecular structure data and mathematical models such as Poisson-Boltzmann equation or Poisson-Nernst-Planck equations. Image credit: Rundong Zhao.
theory to explore biomolecular structure-function relationships.

A striking feature of living organisms is their multiscale nature and tremendous complexity. Subcellular organelles, molecular machines, and dynamics and transport of biomolecules in living organisms, such as membrane transport, signal transduction, transcription and translation, are vital to cellular functions and cannot be simply described by atom-free or molecule-free phenomenological models. However, at the atomic scale, these systems have intractable numbers of degrees of freedom. Multiscale modeling and analysis using quantum mechanics (QM), molecular mechanics (MM), and continuum mechanics (CM) offer an effective reduction in their dimensionality [12, 13, 14]. PDEs (e.g., Schrodinger equation, Poisson-Boltzmann equation, elasticity equation etc.), Newton’s equations of motion, variational analysis, homogenization, differential geometry, persistently stable manifolds, et cetera, underpin multiscale QM/MM/CM modeling of excessively large biological systems [16, 15, 17]. Differential geometry theory of surfaces gives rise to a natural separation between microscopic and macroscopic domains [15, 18]. Conservation law, stochastic analysis and uncertainty quantification can be utilized to reveal how individual biomolecular behavior is related to experimental measurements [19]. A major challenge is how to maintain adequate descriptions of biological properties of interest defined by a given sets of experimental measurements, while dramatically reducing the dimensionality of the underlying biological systems.

It remains poorly understood how various macromolecular complexes interact and give rise to cellular functions and biological pathways, e.g., metabolic, genetic and signal transduction pathways [20]. Differential equations, combinatorics, probability graph, random matrix, statistical models and algebraic geometry are the main workhorses for describing interactive biological networks, such as protein-protein interaction, gene regulation, and enzyme kinetics networks. The systems biology approaches often involve mechanistic models, such as flux balance analysis and chemical kinetics, to reconstruct the dynamical systems from the quantitative properties of their elementary building blocks. Computational biophysics predict reaction flux, rate and equilibrium constants of biological networks.

In the post-omics era, the availability of high-throughput sequencing strategies have resulted in genomics, proteomics and metabolomics. Omics aims at the integrative studies of whole set of biomolecular information that translates into the structure, function, and evolution of living organisms. One major challenge is how to predict phenomics from genomics aided by ChIA-PET and/or trait information. Another challenge is the understanding of genome evolution due to gene-gene and gene-environment interactions. Statistical methods, such as longitudinal study, causal analysis, statistical inference, fuzzy logic, boosting and regression, play a vital role in analyzing omic data sets. Machine learning is another powerful tool for revealing the genotype to phenotype mapping [21]. Mathematical, statistical, and machine learning approaches are essential for the understanding and prediction of genetic data, such as gene sequencing, expression, regulation, evolution, mutation and biological pathways so as to result in therapeutic benefit to patients [22].

Structural bioinformatics concerns the modeling, analysis and prediction of biomolecular structural properties, including protein folds, protein pKa, mutation induced free energy changes, binding affinities of protein-protein and protein-nucleic acid interactions, and the 3D structures of RNA and RNA-protein complexes [11]. Mathematical techniques using geometry, topology and graph theory have a competitive edge in structural bioinformatics [23, 24]. For example, persistent homology strikes a balance between biological detail and topological simplification to achieve appropriate abstractions to massive 3D structural data [25].

The importance of biotechnologies for 3D structure determination and for nucleotide sequencing to biological sciences cannot be over emphasized. High-throughput sequencing methods based on chemical synthesis, fluorescent labeling, capillary electrophoresis, and general automation have fundamentally changed molecular biology, evolutionary biology metagenomics, medicine, forensics and anthropology. Macromolecular X-ray crystallography, nuclear magnetic resonance (NMR), cryo-electron microscopy (cryo-EM), electron paramagnetic resonance (EPR), multiangle light scattering, confocal laser-scanning microscopy, scanning capacitance microscopy, small angle scattering, ultra-fast laser spectroscopy, et cetera, determine 3D structures of macromolecules. Mathe-
matics, such as harmonic analysis, approximation theory, Tikhonov-regularization, inverse scattering theory, et cetera, plays an important role in advancing biotechnologies. For example, cryo-EM is one of the most promising techniques for the structure determination of excessively large biomolecules and relies on mathematical algorithms for image analysis and structure reconstruction [20]. Additionally, the accuracy of electrophoresis based sequencing can be improved through mathematical modeling of microfluidic and nanofluidic devices.

The development of accurate, efficient and robust computational algorithms, methods and schemes is a prerequisite for the implementation of mathematical approaches to biological modeling, analysis and prediction. The importance of numerical methods in solving PDEs is gradually appreciated by the biological community [21, 22, 23]. Computational geometry is an important aspect in structural biology and biophysics [6]. Computational topology analyzes the intriguing topology of complex biomolecules, such as topological invariants of proteins and knot invariants of nucleosomes and chromosomes [30]. The development of efficient graph theory algorithms is crucial for the description of biomolecular binding [31]. Advanced statistic methods underpin various bioinformatic predictions, including 3D protein folds from sequence information. Deep learning algorithms promise the discovery of geometry-function relationships and topology-function relationships from massive biological data.

Rational drug design is an imperative life science problem that ultimately tests out our understanding of biological systems. Designing efficient drugs for curing diseases is one of the most challenging tasks in biological sciences. It involves a complex procedure, including disease identification, target hypothesis (i.e., the activation or inhibition of drug targets), screening of potential drugs that can effectively bind to the target while having low affinity to off-targets, optimization of the structures of selected drug candidates, in vitro and in vivo preclinical tests, clinical trials to examine bioavailability and therapeutic potential, and the optimization of a drug’s efficacy, toxicity, and pharmacokinetic properties. Mathematics plays a crucial role in hot-spot prediction, drug pose analysis, binding affinity prediction, structure optimization, toxicity analysis and pharmacokinetic simulation [32]. For example, the integration of machine learning with multiscale weighted colored graphs and multicomponent persistent homology provided the best free energy ranking for Set 1 (Stage 2) in D3R Grand Challenge 2, a worldwide competition in computer aided drug design (http://users.math.msu.edu/users/wei/D3RFreeEnergy.pdf). It is expected that most new drugs in the next decade will be initiated by artificial intelligence.

References

[1] K. L. Xia and G. W. Wei. A review of geometric, topological and graph theory apparatuses for the modeling and analysis of biomolecular data. arXiv:1612.01735 [q-bio.BM], pages 1 – 76, 2016.

[2] R. Twarock and N. Jonoska. Blueprints for dodecahedral DNA cages. Journal of Physics A: Mathematical and Theoretical, 41:304043 –304057, 2008.

[3] N. Jonoska and G. McColm. Complexity classes for self-assembling flexible tiles. Theoretical Computer Science, 410:332–346, 2009.

[4] R. Brasher, R. G. Scharein, and M. Vazquez. New biologically motivated knot table. Biochemical Society Transactions, 41:606–611, 2013.

[5] Z. Y. Yu, M. Holst, Y. Cheng, and J. A. McCammon. Feature-preserving adaptive mesh generation for molecular shape modeling and simulation. Journal of Molecular Graphics and Modeling, 26:1370–1380, 2008.

[6] Beibei Liu, Bao Wang, Rundong Zhao, Yiyong Tong, and Guo Wei Wei. ESES: software for Eulerian solvent excluded surface. Journal of Computational Chemistry, 38:446–466, 2017.

[7] A. Zomorodian and G. Carlsson. Computing persistent homology. Discrete Comput. Geom., 33:249–274, 2005.

[8] D. W. Sumners. Knot theory and DNA. In Proceedings of Symposia in Applied Mathematics, volume 45, pages 39–72, 1992.

[9] Y. Yao, J. Sun, X. H. Huang, G. R. Bowman, G. Singh, M. Lesnick, L. J. Guibas, V. S. Pande, and G. Carlsson. Topological methods for exploring low-density states in biomolecular folding pathways. The Journal of Chemical Physics, 130:144115, 2009.
[10] I. K. Darcy and M. Vazquez. Determining the topology of stable protein-DNA complexes. *Biochemical Society Transactions*, 41:601–605, 2013.

[11] C. Heitsch and S. Poznanovic. Combinatorial insights into rna secondary structure, in N. Jonoska and M. Saito, editors. *Discrete and Topological Models in Molecular Biology*, Chapter 7:145–166, 2014.

[12] B. S. Eisenberg, Yun Kyong Hyon, and Chun Liu. Energy variational analysis of ions in water and channels: Field theory for complex models of ionic fluids. *Journal of Chemical Physics*, 133:104104, 2010.

[13] Duan Chen. A new Poisson–Nernst–Planck model with ion–water interactions for charge transport in ion channels. *Bulletin of Mathematical Biology*, 78(8):1703–1726, 2016.

[14] K. Baker, D. Chen, and Wei Cai. Investigating the Selectivity of KcsA Channel by an Image Charge Solvation Method (ICSM) in Molecular Dynamics Simulations. *Communications in Computational Physics*, 19:927–943, 2016.

[15] G. W. Wei. Differential geometry based multiscale models. *Bulletin of Mathematical Biology*, 72:1562 – 1622, 2010.

[16] Y. C. Zhou, M. J. Holst, and J. A. McCammon. A nonlinear elasticity model of macromolecular conformational change induced by electrostatic forces. *Journal of Mathematical Analysis and Applications*, 340:135–164, 2008.

[17] Weihua Geng and Shan Zhao. A two-component matched interface and boundary (mib) regularization for charge singularity in implicit solvation. *Journal of Computational Physics*, 351:25–39, 2017.

[18] Z. Chen, Shan Zhao, J. Chun, D. G. Thomas, N. A. Baker, P. B. Bates, and G. W. Wei. Variational approach for nonpolar solvation analysis. *Journal of Chemical Physics*, 137(084101), 2012.

[19] Huan Lei, Xiu Yang, Bin Zheng, Guang Lin, and Nathan A Baker. Constructing surrogate models of complex systems with enhanced sparsity: quantifying the influence of conformational uncertainty in biomolecular solvation. *Multiscale Modeling & Simulation*, 13(4):1327–1353, 2015.

[20] Natalia L Komarova, Xiufen Zou, Qing Nie, and Lee Bardwell. A theoretical framework for specificity in cell signaling. *Molecular Systems Biology*, 1(1), 2005.

[21] Michael A Newton, Christina M Kendziorski, Craig S Richmond, Frederick R. Blattner, and Kam-Wah Tsui. On differential variability of expression ratios: improving statistical inference about gene expression changes from microarray data. *Journal of computational biology*, 8(1):37–52, 2001.

[22] Kaixian Yu, Qing-Xiang Amy Sang, Pei-Yau Lung, Winston Tan, Ty Lively, Cedric Sheffield, Mayassa J Bou-Dargham, Jun S Liu, and Jinfeng Zhang. Personalized chemotherapy selection for breast cancer using gene expression profiles. *Scientific Reports*, 7, 2017.

[23] O. N. A. Demerdash, M. D. Daily, and J. C. Mitchell. Structure-based predictive models for allosteric hot spots. *PLOS Computational Biology*, 5:e1000531, 2009.

[24] Z. X. Cang and G. W. Wei. Analysis and prediction of protein folding energy changes upon mutation by element specific persistent homology. *Bioinformatics*, pages bt6:460, https://doi.org/10.1093/bioinformatics/btx460, 2017.

[25] Z. X. Cang and G. W. Wei. TopologyNet: Topology based deep convolutional and multi-task neural networks for biomolecular property predictions. *Plos Computational Biology*, 13(7):e1005690, https://doi.org/10.1371/journal.pcbi.1005690, 2017.

[26] Amit Singer and Yoel Shkolnisky. Three-dimensional structure determination from common lines in cryo-EM by eigenvectors and semidefinite programming. *SIAM Journal on Imaging Sciences*, 4(2):543–572, 2011.

[27] Shan Zhao. Pseudo-time-coupled nonlinear models for biomolecular surface representation and solvation analysis. *International Journal for Numerical Methods in Biomedical Engineering*, 27:1964–1981, 2012.
[28] W. H. Geng and R. Krasny. A treecode-accelerated boundary integral Poisson-Boltzmann solver for continuum electrostatics of solvated biomolecules. *J. Comput. Phys.*, 247:62–87, 2013.

[29] D. Xie, Y. Jiang, and L. R. Scott. Efficient algorithms for solving a nonlocal dielectric model for protein in ionic solvent. *SIAM Journal on Scientific Computing*, 38:B1267–1284, 2013.

[30] T. Schlick and W. K. Olson. Trefoil knotting revealed by molecular dynamics simulations of supercoiled DNA. *Science*, 257(5073):1110–1115, 1992.

[31] D. D. Nguyen, Tian Xiao, M. L. Wang, and G. W. Wei. Rigidity strengthening: A mechanism for protein-ligand binding. *Journal of Chemical Information and Modeling*, 57:1715–1721, 2017.

[32] Bao Wang, Zhixiong Zhao, Duc D Nguyen, and G. W. Wei. Feature functional theory - binding predictor (FFT-BP) for the blind prediction of binding free energy. *Theoretical Chemistry Accounts*, 136:55, 2017.