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# Faces of Contemporary CryoEM Information and Modeling

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Computational modeling of cryoEM data is rooted in—but also has emancipated itself from—both experimental microscopy and theoretical chemistry and has become an important field in its own right. The reconstruction of 3D cryoEM maps and their interpretation are part of the Integrative Structural Biology workflow, which aims to combine different experimental techniques with computational modeling to build structural models of macromolecular complexes.[1] As purely computational approaches, the modeling and simulation of cryoEM data are independent of the experimental constraints of biological specimen preparation, instrumentation, and physical location, and they can be performed with relatively inexpensive hardware from any location with Internet access. The methods facilitate the solving and functional interpretation of biological structures at the tertiary and quaternary level. Therefore, the application is predominantly utilitarian and motivated by structural biology, without necessarily referring to classical theoretical chemistry approaches such as quantum and statistical mechanics, combinatorial chemistry, or kinetics.

Avoiding the hardship of experimental data collection, computer modeling and simulation were once relegated to the bottom of the scientific food chain. But through the allure of virtual immersion, modeling and information technology have become dominant in many scientific fields of cultural importance, and in fact, they have now changed our way of looking at the world.[2] Examples of the disruptive and even dominant power wielded by modeling include the prediction of the paths of destructive storms,[3] computer simulations of volcanic ash clouds (that forced a shut down of 100,000 airline flights in 2010, although authorities had little idea of the real situation),[4] SARS-CoV-2 pandemic infection forecasts,[5] or simulating the air flow of human cough droplets to inform social distancing.[6] For better or worse, major political and public health decision authority is now given over to models and simulations.

In the cryoEM field, the importance of the biological specimen and the quality of the recorded images are still controlled by experimental scientists, but as in many other areas of science, the practical values of computational technology are increasingly driving the progress. For example, the 2014 resolution revolution that was enabled by new direct detection device camera technology and digital image stabilization that eliminated specimen drift culminated in the 2017 Nobel prize shared by our contributor Joachim Frank[7,8] for his fundamental work in single particle cryoEM.

Several other contributions in this issue provide perspectives on the value of contemporary cryoEM modeling ranging from the potential impact of cryoEM in structure prediction approaches by Abriata and Dal Peraro,[9] to assessing the impact of computational modeling at the atomic level by Fraser, Lindorff-Larsen, and Bonomi,[10] and how cryoEM stands to impact cellular-scale structural-omics type studies by McCafferty and colleagues.[11] A review by Sengupta and coauthors[12] covers advances in sample preparation and molecular modeling, whereas one by Ivanov and colleagues[13] discusses recent advances and applications of flexible-fitting approaches for data refinement. Cossio discusses the need for and challenges related to cross-validation for developed models.[14] Sanbonmatsu and colleagues, as well as Kellogg and Cianfrocco, present thoughtful contributions on potential cryoEM-modeling workflow pitfalls and best practices.[15,16]

Methodological advances in integrative modeling cover a wide range of aspects and related experimental approaches. Wriggers and colleagues present a template-based deconvolution and denoising approach that corrects for missing wedge artifacts in tomograms of cytoskeletal filaments.[17] Tama and co-workers present an in-depth look at pixel-size parameters for improving cryoEM maps.[18] Winn and Joseph and colleagues demonstrate a novel method for calculating differences between a cryoEM map and a fitted model that uses amplitude matching in resolution shells, as well as show its utility in highlighting conformational and compositional differences.[19] Cole and colleagues develop ImageDataExtractor, which identifies and extracts microscopy images from the scientific literature, presenting them for use in data-driven materials discovery-type approaches.[20] Kihara and co-workers develop new software, MAINMASTseg, to improve map segmentation and results for cryoEM data sets with multiple chains.[21] He and colleagues establish a cylindrical F1 score similarity metric for alpha-helices in cryoEM maps that provides a classifier for database validation studies as well as a criterion to assess the local quality of maps and their associated atomic models.[22]

Several groups present new tools to improve the end-to-end cryoEM working procedures. Shen and co-workers present a fully automated toolkit, SPREAD, for 3D reconstruction that uses a network-based image clustering algorithm.[23] Marabini and colleagues present a major update to their framework Scipion that improves model building and provenance of the

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complete workflow.[24] Schenk and co-workers present CryoFLARE, an open-source platform for integrating various processing algorithms and development of automated workflows.[25]

Molecular dynamics flexible fitting remains a popular approach for fitting atomic resolution models into density maps, as also reviewed by Ivanov and colleagues.[13] A number of groups present extensions and improvements to the method. Lindert and Leelananda demonstrate how integrating NMR chemical shifts into cryoEM density restraints improves refinement results.[26] Singharoy and co-workers present a new method that integrates neural network potentials together with quantum mechanical/molecular mechanics methods to improve on fitting small molecules into cryoEM maps.[27] A related method presented by Costa and colleagues, MDeNM-EMfit, extends molecular dynamics with excited normal modes in a way that directs sampling toward conformations that have high correlations with the density maps.[28]

Finally, several groups contributed applications to interesting biological systems. Magistrato and colleagues show how MD together with cryoEM provides never before seen insight into splicing modulators.[29] Ravelli and co-workers show how processing algorithm improvements improved size limits for cryoEM using hen egg white lysozyme.[30] Llorca and colleagues present their strategy for modeling the medium-density RUVBL2-binding domain, as well as subsequent simulations to explore biological hypotheses about its interactions with RNA polymerase II.[31] Worrall and co-workers provide a historical perspective of cryoEM studies of the type III secretion system needle complex as well as describe their own workflow that enabled the successful determination of the whole complex.[32]

Overall, the diversity and complexity of the 26 contributions we solicited demonstrate the engrossing nature of cryoEM modeling and information.[33] They also showcase the intriguing ways that cryoEM developers have matured in recent years from shop-class theorists and technicians to influential directors of this new digital frontier.

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### Notes

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