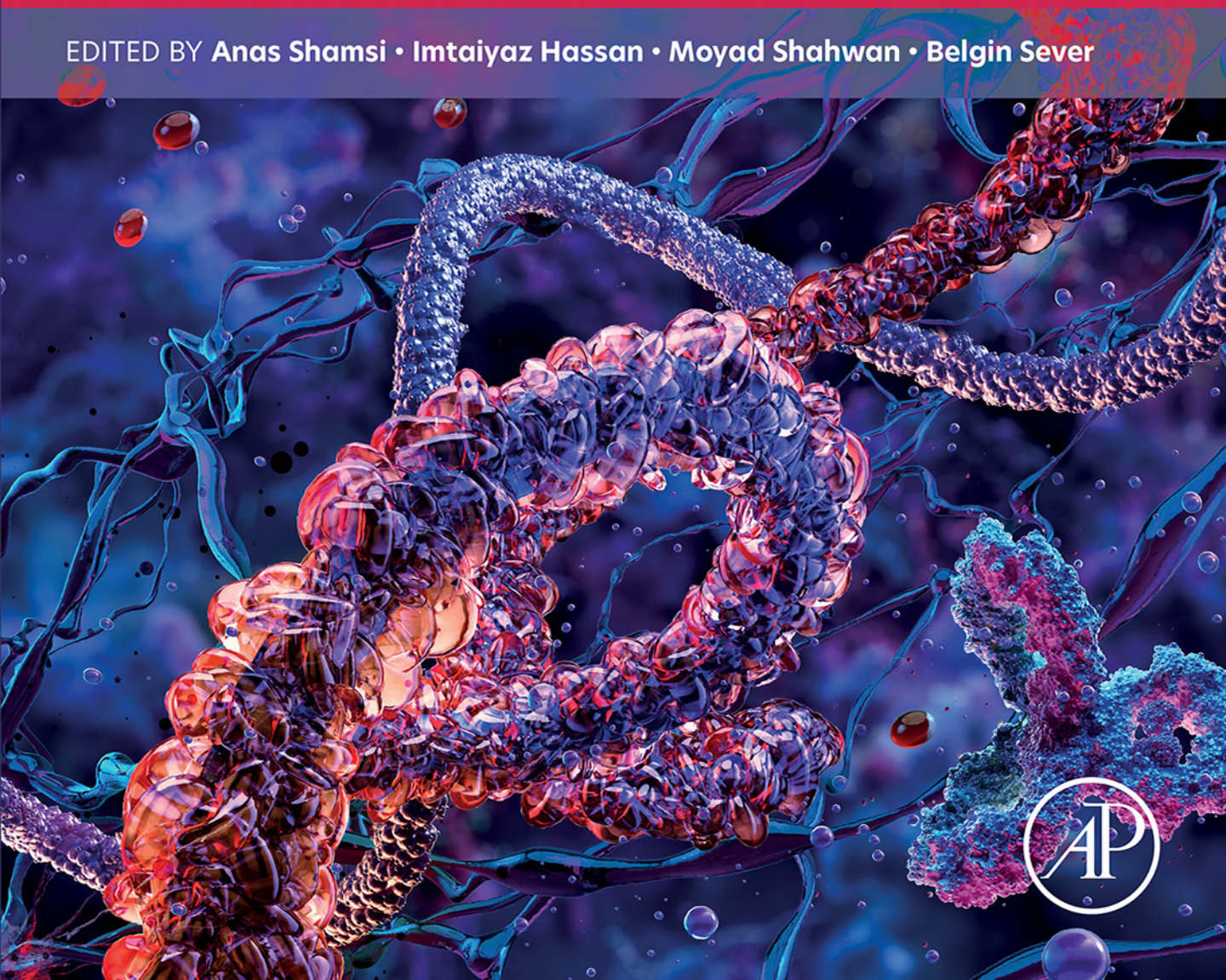
Advances in Structural Biology

Applications in Protein Structure, Function, and Disease

EDITED BY **Anas Shamsi** • **Imtaiyaz Hassan** • **Moyad Shahwan** • **Belgin Sever**



Advances in Structural Biology

This page intentionally left blank

Advances in Structural Biology

Applications in Protein Structure, Function, and Disease

Edited by

ANAS SHAMSI
Centre of Medical and Bio-allied Health Sciences Research, Ajman University, Ajman, United Arab Emirates

IMTAIYAZ HASSAN
Center for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi, India

MOYAD SHAHWAN
College of Pharmacy and Health Sciences, Ajman University, Ajman, United Arab Emirates

BELGIN SEVER
Department of Pharmaceutical Chemistry, Anadolu University, Eskişehir, Türkiye

ACADEMIC PRESS
An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States

For accessibility purposes, images in electronic versions of this book are accompanied by alt text descriptions independently provided by Elsevier, generated with the aid of AI. For more information, see https://www.elsevier.com/about/accessibility or Radarweg 29, 1043 NX Amsterdam, Netherlands.

Books and Journals published by Elsevier comply with applicable product safety requirements. For any product safety concerns or queries, please contact our authorised representative, Elsevier B.V., at productsafety@elsevier.com.

Publisher's note: Elsevier takes a neutral position with respect to territorial disputes or jurisdictional claims in its published content, including in maps and institutional affiliations.

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-443-44988-8

For Information on all Academic Press publications
visit our website at https://www.elsevier.com/books-and-journals

Publisher: Megan Ball
Acquisitions Editor: Michelle Fisher
Editorial Project Manager: Harshita Bathla
Production Project Manager: Vijayaraj Purushothaman
Cover Designer: Mark Rogers

Printed in England by CPI Group (UK) Ltd
Croydon CRo 4YY
United Kingdom

Typeset by MPS Limited, Chennai, India

Contents

List of contributors *xv*
About the editors *xxi*
Acknowledgments *xxiii*

Section I Foundations: computational and conceptual

1. Unraveling protein function with structural biology approaches **3**

Sana Qausain, Mohd Basheeruddin, Ashish Anjankar, Md. Khurshid A. Khan, Faez Iqbal Khan, Archana Dhok, Mohammad Affan Kareem and Netri Upadhyay

1.1 Introduction 3
1.2 Protein structure as a dynamic hierarchy 5
1.3 Experimental approaches in structural biology 6
1.4 Computational and integrative approaches 10
1.5 Structural insights into protein function 13
1.6 Emerging paradigms and limitations of structure-function relationships 16
1.7 Translational applications of structural biology 20
1.8 Recent advances and future perspectives in structural biology 22
1.9 Conclusion 24
References 26

2. Bioinformatics tools for protein modeling in neurodegenerative diseases **31**

Shubhi Singh, Rudrani Rath, Sushma Jeyaraj, Aysha Afreen Rafeek and Priya Swaminathan

2.1 Introduction 31
2.2 Protein modelling approaches: foundations and methodologies 32
2.3 Computational tools for protein modelling 37
2.4 Tool selection criteria for neurodegenerative disease research 41
2.5 Case studies: protein modelling in specific neurodegenerative diseases 41
2.6 Molecular docking and dynamics 44
2.7 Protein structure refinement 49
2.8 Challenges and limitations 52
2.9 Future perspectives and emerging technologies 53
2.10 Conclusion 54
References 55

3. Bioinformatics tools for protein modeling in cancer **59**
Alpana Srishti Rai, Seneha Santoshi and Shazia Rashid

3.1 Introduction 59
3.2 The evolving landscape of protein structure prediction 60
3.3 Bioinformatics tools for protein modeling 67
3.4 Key applications in cancer biology and therapeutics 78
3.5 Current challenges and methodological limitations 80
3.6 Future research outlook 81
3.7 Conclusion 82
References 82

4. Unraveling protein folding and structural dynamics **85**
Faiza Iram, Ayesha Aiman, Luqman Ahmad Khan and Asimul Islam

4.1 Introduction 85
4.2 Protein folding problem 87
4.3 Thermodynamics and kinetics of protein folding 88
4.4 The energy landscape of protein folding 90
4.5 Protein dynamics: motion and function 93
4.6 Experimental and computational approaches to study protein folding and dynamics 93
4.7 Protein misfolding, aggregation, and disease 100
4.8 Conclusion and future perspectives 100
References 101

Section II Methodologies: experimental and integrative techniques

5. Cryo-electron microscopy in membrane protein structural biology **113**
Tofayel Ahmed, Antara Saha and Debalaya Mukherjee

5.1 Introduction 113
5.2 Transient receptor potential channels 116
5.3 Potassium (K^+) channels 118
5.4 Gamma-aminobutyric acid type A receptors, 5-HT3A, and glycine receptors 122
5.5 Ion channel complexes from a native source 124
5.6 G-protein coupled receptors 125
5.7 Bacterial secretion systems 128
5.8 NADH:ubiquinone oxidoreductase (complex I) 130
5.9 ATP synthase 132
5.10 Conclusion 134

Acknowledgements 135
Conflict of interests 135
References 135

6. Computational and artificial intelligence methodologies for big data analytics in structural biology 145

Mohammad Kalim Ahmad Khan, Umme Aiman and Salman Akhtar

6.1 Introduction 145
6.2 Sources and types of biological big data 149
6.3 Characteristics of biological big data 156
6.4 Computational methodologies for big data analytics 159
6.5 Applications in structural biology and bioinformatics 163
6.6 Case studies 174
6.7 Future directions and emerging trends in integrative drug discovery 179
6.8 Future directions 182
6.9 Conclusion 185
Acknowledgments 185
References 185

7. Big data enabled discovery in bioinformatics and structural biology 193

Jaoud Ansari, Shabana Khatoon, MD Kaif, Gourav Choudhir, Naseem Gaur and Asimul Islam

List of abbreviations 193
7.1 Introduction 194
7.2 Types of big data in structural biology and bioinformatics 195
7.3 Challenges in big data analytics 199
7.4 Analytical techniques and tools for structural biology big data 203
7.5 Machine learning and artificial intelligence 211
7.6 Applications of big data analytics 216
7.7 Conclusions 218
References 218

8. AI and machine learning in structural biology 229

Sanjay Kumar

8.1 Introduction 229
8.2 Fundamentals of artificial intelligence in structural biology 231
8.3 How artificial intelligence works 235
8.4 How to create an artificial intelligence model? 237
8.5 Landmark breakthroughs 238

8.6 Artificial intelligence applications in structural biology 244
8.7 Challenges and limitations 247
8.8 Future directions 248
8.9 Conclusion 248
References 249

9. Integrating structural and omics data for drug discovery 253
Neha and Khushi Raza

List of abbreviations 253
9.1 Introduction 253
9.2 Structural biology technologies and their applications 259
9.3 Omics technologies: comprehensive molecular profiling through integrated data layers 261
9.4 Computational frameworks for data integration 265
9.5 Network-guided target selection and iterative lead optimization 268
9.6 Personalized medicine and precision drug discovery: from population-level therapeutics to patient-specific treatment 271
9.7 Technical challenges and limitations 273
9.8 Conclusion and future directions 275
Acknowledgment 276
Conflict of interest 276
Compliance with ethical standards 276
References 276

Section III Applications

10. Applications of structural biology in drug discovery 287
Saira Hamid, Sarah Siddiquah, Hanzla Shaz and Imtaiyaz Hassan

10.1 Introduction 287
10.2 Fundamental techniques of structural biology used in drug discovery 288
10.3 Role of structural biology across drug design 294
10.4 Understanding drug-target interactions 298
10.5 Structural biology in studying drug resistance 301
10.6 Applications in biologics and macromolecular drugs 303
10.7 Integration with computational and AI-based approaches 305
10.8 Case studies in structure-guided drug discovery 307
10.9 Challenges and limitations 310
10.10 Future perspectives 311
AI disclosure 311
References 311

11. Structural biology approaches in vaccine development **319**

Aaliya Taiyab and Imtaiyaz Hassan

11.1 Introduction 319
11.2 Structural biology tools used in vaccine development 322
11.3 Structural biology in identifying vaccine targets 326
11.4 Structure-based antigen design/reverse vaccinology 2.0 328
11.5 Epitope-focused vaccine design 330
11.6 Nanoparticle-based vaccines designed using structural biology 332
11.7 Computational integration in structural vaccine design 334
11.8 Challenges and future perspectives 336
11.9 Conclusions 338
References 338

12. Structural biology in antiviral drug design **343**

Sana Tanweer, Sanchit Varma and Malika Adam Abeeda

12.1 Introduction 343
12.2 Fundamentals of structural biology in drug design 344
12.3 Viral entry and immune response 345
12.4 Immune evasion by viruses 347
12.5 Antiviral drugs and their classification 348
12.6 Antiviral drug development and target identification 348
12.7 Antiviral drug targets 348
12.8 Target identification and selection 353
12.9 In silico techniques for synthesis of candidate drugs 354
12.10 Computer aided structure based drug design 355
12.11 Structural mapping methods 359
12.12 X-ray crystallography 359
12.13 Nuclear magnetic resonance Spectroscopy 361
12.14 Cryo-electron microscopy 364
12.15 Drugs developed by structure-based drug design 366
12.16 Structure-based drug design for antivirals against HIV 366
12.17 Structure-based drug design for antivirals against hepatitis B 366
12.18 Structure-based drug design for antivirals against influenza 368
12.19 Structure-based drug design for SARS-CoV-2 antivirals 368
12.20 Advantages of structural-based drug design 369
12.21 Disadvantages of structural-based drug design 369
12.22 Challenges and limitations 370
12.23 Prospects for the future and global health readiness 371

12.24 Conclusion 371
References 372

13. Structural bioinformatics in personalized medicine 381
Sarika Bano, Aaliya Javed, Anas Shamsi and Asimul Islam

13.1 Introduction 381
13.2 Personalized medicine and structural medicine: introduction 382
13.3 Significance of structural bioinformatics and PM 383
13.4 Bioinformatics steps in genomic data processing for PM 384
13.5 Application of structural bioinformatics in PM and vaccine development 386
13.6 Genomic analysis in PM 387
13.7 Challenges in incorporating structural bioinformatics into PM design 388
13.8 Advantages and disadvantages of PM 389
13.9 Advancement in methods for PM development 390
13.10 Future perspective 391
13.11 Conclusion 392
References 392

14. Structural biology in understanding bacterial resistance 397
Deepali Gupta, Mukesh Kumar, Dominic Skaria Mathew, Ishaan Bhardwaj, Shivani Dixit and Punit Kaur

14.1 Introduction 397
14.2 Molecular mechanism underlying antimicrobial resistance 398
14.3 Structure biology approaches to study antimicrobial resistance 400
14.4 Structural basis of major antimicrobial resistance mechanism 400
14.5 Advanced structural and computational approaches for understanding antimicrobial resistance 413
14.6 Future perspectives 416
14.7 Conclusion 416
AI disclosure 417
References 417

15. Structural biology approaches in neurodegeneration and aging 423
Minhal Abidi, Sana Iram, Jamal-E -Fatima, Hamda Khan, Shaheda Perween, Safia Habib and Moinuddin

15.1 Introduction: aging and neurodegeneration–a structural view 423
15.2 Molecular pathways of protein misfolding and aggregation during aging of the brain 426

15.3 Mitochondrial dysfunction and oxidative stress structural biology 431
15.4 Cell and structural mechanisms of synaptic degeneration 436
15.5 Role of posttranslational modifications in structural alterations 441
15.6 Interplay of proteostasis, autophagy, and neuroinflammation 446
15.7 Computational approaches and integrative structural biology 449
15.8 Translational implications: structural insights to therapeutic development 452
15.9 Novel horizons: structural biomarkers and interventions to aging 455
15.10 Conclusions and perspectives 457
References 458

16. Structural biology of protein misfolding and aggregation: from disease to therapeutic innovations 471

Neha Kausar Ansari and Aabgeena Naeem

16.1 Introduction 471
16.2 Structural determinants of protein misfolding and aggregation 472
16.3 Mechanism of misfolding and aggregation 475
16.4 Molecular and cellular consequences 481
16.5 Structural themes for protein aggregation diseases 487
16.6 Disease-specific structural themes 489
16.7 Therapeutic and structural modulation strategies 494
16.8 Conclusions 497
Acknowledgments 497
Conflict of interest 498
References 498

17. Integrated structural approaches in immunotherapy 513

Hamda Khan, Minhal Abidi, Safia Habib, Arbab Husain, Afreen Khanam, Rizwan Ahmad, Mohd Mustafa and Moinuddin

17.1 Immunotherapy 513
17.2 Mechanism of cancer immunotherapy 514
17.3 Immune checkpoint inhibitors 515
17.4 Monoclonal antibodies and cancer therapy 518
17.5 Chimeric antigen receptor T cell in cancer therapy 520
17.6 Viro immunotherapy in cancer therapy 522
17.7 Cytokines and immune modulators in cancer therapy 523
17.8 Cancer Immunotherapy targeting glycation 524
17.9 Glycosylation and cancer immunotherapy 526
17.10 Conclusion 527
References 527

Section IV Translational biology

18. Structural and systems biology in cancer therapy **535**

Mohd Basheeruddin, Sana Qausain, Ashish Anjankar, Faez Iqbal Khan, Samarth Shukla, Shazia Jamal, Neesar Ahmed, Vaibhav Anjankar, Zahoor Ahmad Parray and Netri Upadhyay

18.1 Introduction 535
18.2 Foundations of structural biology in cancer research 542
18.3 Omics integration 550
18.4 Computational modeling and dynamic simulations 558
18.5 Convergence of structural and systems biology 560
18.6 Structural systems pharmacology 562
18.7 Illustrative examples 565
18.8 Applications in cancer therapy 567
18.9 Future direction and potential role of artificial intelligence 573
18.10 Conclusion 574
References 575

19. Protein structural biology in precision medicine and clinical translation **583**

Maryam Khan, Minal Richi and Sara Othman

List of abbreviations 583
19.1 Introduction 583
19.2 Structural basis of protein dysfunction in disease 589
19.3 Protein structure-guided drug discovery 592
19.4 Translational and clinical applications 595
19.5 Conclusion and future direction 602
Contributions 603
Conflict of Interest 603
References 603

20. Future trends in structural biology **613**

Saleha Anwar, Sumaiya Khan, Sahar Afzal Khan, Khuzin Dinislam, Suhel Parvez and Anas Shamsi

20.1 Introduction 613
20.2 Advancements in hybrid and integrative structural biology 615
20.3 Mass spectrometry 624
20.4 Structural biology as a foundation for translational research 627
20.5 Structure-guided therapeutics and drug discovery 631
20.6 New paradigms in fragment-based and allosteric drug discovery 635

20.7 Structural biology in vaccine and antiviral design 637
20.8 Structural systems biology and network modeling 637
20.9 Conclusions 640
Acknowledgement 641
References 641

Index *651*

CHAPTER 6

Computational and artificial intelligence methodologies for big data analytics in structural biology

Mohammad Kalim Ahmad Khan, Umme Aiman, and Salman Akhtar
Department of Bioengineering, Integral University, Lucknow, Uttar Pradesh, India

6.1 Introduction

The explosive growth of high-throughput biological technologies has deeply impacted the life sciences world, making it a data-intensive field. Modern platforms such as next-generation sequencing (NGS), cryo-electron microscopy (cryo-EM), high-resolution mass spectrometry (MS), and large-scale interactomes have been capable of generating enormous genomic, transcriptomic, proteomic, structural, and imaging datasets at extremely high speeds and scales (Park et al., 2021). As a result, there have been major analytical and computational challenges, primarily in the domain of structural biology and bioinformatics, where comprehending the functional, structural, and evolutionary impact of these data requires the use of advanced computational methods. The biological data have several core features, such as their massive scale, high throughput, natural heterogeneity, a high degree of uncertainty, and the need for biological significance. These features call for the creation of strong analytical frameworks that can connect different types of data, reduce noise, guarantee reproducibility, and yield biologically meaningful results (Auslander et al., 2021).

Biomedical major repositories are a good example of exponential data growth due to multimodality and strong dependence on biological context. Protein sequences, three-dimensional structures, and multiomics profiles ought to be processed using computational strategies that handle the noise and enable reproducible inference. The enormous growth of protein sequences illustrated in Figs. 6.1, 6.2, and 6.3 demonstrates that current sequencing technologies consistently outperform traditional computational pipelines.

Conventional computer-based methods or heuristic computational approaches have had a hard time trying to address these challenges at scale. To address this gap, machine learning (ML), deep learning (DL), and advanced statistical modeling frameworks have gradually become the main tools and emerged as central pillars of modern structural biology. DL has brought about a significant change in structural biology (Cui et al.,

Advances in Structural Biology
DOI: https://doi.org/10.1016/B978-0-443-44988-8.00012-5