BIOGRAPHICAL SKETCH

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NAME: **Chapman, Michael S.**

eRA COMMONS USER NAME (credential, e.g., agency login): mschapman

POSITION TITLE: Chair (interim), Biochemistry & Molecular Biology & Jones Professor of Structural Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of London, Kings College, England	B.Sc. / AKC	1982	Cell & Molecular Biol.
University of London, Birkbeck College	M.Sc.	1983	Crystallography
University of California, Los Angeles	Ph.D.	1987	Biochemistry
Purdue University	(Post-Doc)	1988-93	Structural Virology

A. Personal Statement

Michael Chapman is a biophysicist who develops and applies multi-disciplinary approaches to viral-host interactions and enzyme mechanism/dynamics. His research group combines structural techniques: x-ray diffraction, electron microscopy (EM) and NMR with biochemical kinetics, molecular virology and computer modeling to understand the functional workings of large and dynamic complexes. He has had a long-standing interest in methods to optimize structural models using diverse experimental restraints from crystallography, EM and NMR, as well as stereochemical restraints from implicit-solvent electrostatics and hydrogen-bonding. Such multi-disciplinary approaches are used to advance our fundamental understanding of enzyme turnover kinetics, and to understand virus-host interactions central to the development of improved vectors for human gene therapy. He has served in various research / administrative capacities and has mentored 31 graduate students and post-doctoral fellows, many within collaborative and multi-disciplinary projects.

B. Positions and Honors

Employment

1988-93	Post-doctoral Assoc., Dept. of Biological Science, Purdue Univ. (with Michael Rossmann)
1993-98	Asst. Prof., Dept. of Chemistry (Courtesy appts. in Biology & Physics), Florida State Univ.
1998-03	Assoc. Prof., Dept. of Chemistry, Florida State Univ. (Courtesy appt. in College of Med.)
1998-01	Associate Director, Institute of Molecular Biophysics
2000-06	Director, Center of Excellence in Biomolecular Computer Modeling & Simulation
2003-06	Professor, Dept. of Chemistry & Biochemistry, Florida State University
2006-	Jones Prof. Structural Biology, Dept. Biochem. & Mol. Biol., Oregon Health & Science Univ.
2014-	Interim Chair, Dept. Biochem. & Mol. Biol.; Dir. Training, Quant. Biosci. & Biomed. Engin.

Professional Service

1999-	Executive Board SERCAT APS x-ray beam line (1999-06); MBC ALS beam line (2006-).
2001	Conference Chair: Computational Structural Biology–From Simulation to Exper. & Back
2002	Chair, Gordon Research Conference – Diffraction Methods in Structural Biology

Federal Committees

2005-8	*NIH* panel member: Macromolecular Structure & Function C
2000-17	*NIH* Special Panels (21, chair of 7): P41 centers, P01, K99, ZRG1 CB-N MIRA, *etc*..
2004-17	*NIH* panels (7), temp. member: Exp. Virol., Virology, Macromol. Struct./Function B & D.
1999-13	Proposal reviewer: NSF MCB; Dept. Defense; UK Med. Res. Council; Biotech. & Biol. Res. Council, Welcome Trust, French Agence Natl. de Researches; IHFSP.

Recent Honors

2005- Fellow, American Association for the Advancement of Science

C. Contributions to Science

Structural Virology: Picornaviruses and Parvoviruses

Post-doctoral research with Michael Rossmann initially focused on rhinoviruses, and later on canine parvovirus (CPV) with the then surprising finding that a single-stranded DNA virus shared a conserved subunit topology with the RNA viruses studied earlier. My contribution was the crystallography, including new methods for *ab initio* phase determination that by-passed heavy atom derivatives. I developed approaches for analyzing sequence variation within 3D molecular structure, revealing distributions of genetic variation, in several virus families, that suggested competing selective pressures: conservation of cell (receptor) interactions *versus* change to escape recognition by prevailing neutralizing antibodies.

12. Chapman, M., Minor, I., Rossmann, M., Diana, G. & Andries, K. (1991). Human rhinovirus 14 complexed with antiviral compound R 61837. ***JMB*** 217:455-63. PMID: 1847215. doi: 10.1016/0022-2836(91)90749-V
13. Tsao, J., Chapman, M. S., Agbandje, M., Keller, W., Smith, K., Wu, H., Luo, M., Smith, T. J., Rossmann, M. G., Compans, R. W. & Parrish, C. (1991). The Three-Dimensional Structure of Canine Parvovirus and its Functional Implications. ***Science*** 251, 1456-1464. PMID: 2006420. DOI: 10.1126/science.2006420
14. Chapman, M. S., Tsao, J. & Rossmann, M. G. (1992). *Ab initio* Phase Determination for Spherical Viruses: Parameter Determination for Spherical Shell Models. ***Acta Crystallogr.*** A48, 301-12. PMID: 1605933. doi: 10.1107/S0108767391013211
21. Chapman, M. S. & Rossmann, M. G. (1993). Comparison of Surface Properties of Picornaviruses: Strategies for hiding the Receptor Site form Immune Surveillance. ***Virology*** 195, 745-765. PMID: 8337843. doi: 10.1006/viro.1993.1425

Structure-function of the Gene Therapy Vector, Adeno-associated Virus (AAV)

As an independent investigator, I turned to AAV, then emerging as a potential gene therapy delivery vector for genetic diseases. AAV was a challenging goal for several structural labs, because its replication depends on co-infection by adenovirus. Our investment in methods for propagation in cell culture yielded milligram quantities and the 1st AAV crystal structure in 2002. AAV-2 opened the door to comparative structural analyses, in our lab and others, of variant AAV serotypes that provided insights into host preferences and immune neutralization. Our work provided a foundation for modulating AAV's cell specificity by inserting randomized peptide display libraries strategically into the structure of AAV-2, and then selecting new cell tropisms. Our most recent structure is of AAV-DJ, a chimeric construct selected for liver tropism and escape from neutralizing human serum, that has been solved by *cryo*-electron microscopy (EM) at 2.8 Å resolution. Differences from the parental serotypes are greatest at two epitopes and would sterically block attachment of neutralizing monoclonal antibody A20, as seen in our EM structure of its complex with AAV-2. This implies that altered cell transduction was a byproduct of changes forced by immune selection.

Cellular attachment and entry are current *foci*. Glycans were previously considered to be the primary receptors for AAV, but our SPR binding analyses with libraries of heparanoids, and our *cryo*-EM structures of complexes with heparin and other analogs, have revealed AAV's adaptability to diverse interactions. This is more typical of low specificity attachment factors than of classical entry receptors. Our studies refuted a widely held belief that glycan-binding triggers conformational changes for viral uncoating. Our most recent breakthrough stemmed from failures to confirm AAV-2's reported co-receptors through physical binding or siRNA inhibition, leading us to screening for cellular genes essential to viral transduction. The most fruitful study came from a collaboration with Jan Carette at Stanford, combining FACS-based selection for cells resistant to AAV transduction with his methods for gene trap screening in a human haploid cell line. This identified a transmembrane protein (AAVR) used by all AAV serotypes to enter all tested cells. Its role has been validated with CRISPR Cas9 knockouts and genetic complementation in cells, and a mouse knock-out. AAVR has many characteristics of a classical viral receptor, including nM binding affinity. Expressed only transiently at the cell surface, AAV takes advantage of AAVR's natural retrograde trafficking, hitching a ride to the perinuclear *trans* Golgi network. This work was recently published in Nature, and presented in the Presidential Symposium at the 2016 conference of the Am. Soc. Gene & Cell Therapy. It overcomes a 20-year impasse, opening the door to the biochemistry and genetics behind AAV's cellular specificity, and is the foundation of structural studies in the Chapman lab that are revealing the molecular interactions between virus and receptor.

51. Xie, Q., Bu, W., Bhatia, S., Hare, J., Somasundaram, T., Azzi, A., and Chapman, M.S. 2002. The atomic structure of adeno-associated virus (AAV-2), a vector for human gene therapy. ***Proc Natl Acad Sci USA*** 99: 10405-10410. PMCID: PMC124927; doi: 10.1073/pnas.162250899.
95. McCraw, D., J. O'Donnell, K.A. Taylor, S.M. Stagg & M.S. Chapman (2012). *Structure of adeno-associated virus-2 in complex with neutralizing monoclonal antibody A20.* **Virology** 431: 40-49. PMCID: PMC3383000; doi: 10.1016/j.virol.2012.05.004
109. Pillay, S[1]., Meyer, N.L.[1], Puschnik, A., Davulcu, O., Diep, J., Ishikawa, Y., Jae, L., Wosen, J., Nagamine, C., Chapman, M.S.[2], and Carette, J.E.[2] (2016). *An essential receptor for adeno-associated virus infection*. **Nature** 530, 108-112. [1]Co-1[st] / [2]corresp. auth. PMCID: PMC4962915; doi:10.1038/nature16465.
112. Xie, Q., Noble, A.J., Sousa, D.R., Meyer, N.L., Davulcu, O., Zhang, F., Linhardt, R.J., Stagg, S.M., Chapman, M.S. (2017). *The 2.8 Å Electron Microscopy Structure of Adeno-Associated Virus-DJ Bound by a Heparanoid Pentasaccharide*. **Mol. Ther. Methods Clin. Dev.** 4, *in press. doi:10.1016/j.omtm.2017.02.004.*

Enzyme Structure & Mechanism

Graduate training with David Eisenberg centered on determination of the structure of higher plant RuBisCO, the enzyme responsible for photosynthetic carbon fixation. As an independent investigator, my group has worked with several enzymes, but arginine kinase (AK) has figured prominently. AK, like its homolog creatine kinase, buffers ATP levels in many cells. The structure of a transition state analog (TSA) complex at 1.2 Å resolution showed the reaction components precisely aligned, begging two questions: (1) was alignment a significant part of the catalytic effect? (2) how was precise substrate alignment achieved with substantial protein conformational changes upon substrate-binding? Trying to dissect the contributions to catalysis, my students worked with Jeff Evanseck on Quantum Mechanical (QM) calculations that we hoped to compare to experimental data. Pre-requisite high level *ab initio* calculations led to a more fundamental discovery. We observed a stereoelectronic destabilization of the scissile bond as electron density moved from a neighboring oxygen lone pair into an anti-bonding orbital. We saw this in phosphoarginine, ATP, and a series of organic phosphates whose experimental free energies of hydrolysis were correlated with this stereoelectronic effect. It provides an improvement on text book rationalizations of “high energy” bonds, now accounting for differences between phosphoesters and phosphoguanidines. In recent years, we have shown that the interaction (and potentially catalytic effect) can be modulated by solvent and polar side chains in an active site. A structural survey of kinases from many families showed high incidence of active site configurations that could modulate stereoelctronics, indicating selective value, even though it is unlikely to be the major catalytic driving force.

6. Chapman, M. S., Suh, S. W., Curmi, P. M. G., Cascio, D., Smith, W. W. & Eisenberg, D. S. (1988). *Tertiary Structure of Plant RuBisCO: Domains and their Contacts*. ***Science*** 241, 71-74. PMID: 3133767.
38. Zhou, G., Somasundaram, T., Blanc, E., Parthsarathy, G., Ellington, W. R. & Chapman, M. S. (1998). *Transition state structure of arginine kinase: Implications for catalysis of bimolecular reactions*. **Proc. Natl. Acad. Sci., USA** 95, 8449-54. PMCID: PMC21096
78. Ruben, E.A., M.S. Chapman, and J.D. Evanseck, *Anomeric effect in “high energy” phosphate bonds – selective destabilization of the scissile bond and modulation of the exothermicity of hydrolysis.* **J Am Chem Soc**, 130: 3349-58 (2008). PMID: 18302368; doi: 10.1021/ja073652x
106. Summerton, J.C., Martin, G.M., Evanseck, J.D. and Chapman, M.S. (2014). *Common Hydrogen Bond Interactions in Diverse Phosphoryl Transfer Active Sites*. **PLoS-One**, 9: e108310. PMCID: PMC4169622; doi: 10.1371/journal.pone.0108310

Protein Dynamics

Structures of substrate-bound and –free arginine kinase revealed a wide repertoire of conformational changes from loop closures to domain rotations. In spite of its 42 kDa size, AK yields exceptional NMR data, providing dynamics information that complements the crystallographic structures. In collaboration with Jack Skalicky and Rafael Brűschweiler, we examined the intrinsic dynamics with relaxation dispersion (RDA) and residual dipolar coupling analyses (RDC), starting with the substrate-free form. We were struck by the correspondence to the catalytic turnover rate of a loop closure and a domain rotation. Comparing the temperature dependence of the NMR exchange constants and catalytic turnover, we found indistinguishable activation barriers. This implies that the concerted millisecond motions were limiting turnover rate. Continuing interests have included the extent to which large slow motions are correlated to (and perhaps built from) faster lower-barrier modes of flexibility, and the extent to which substrate-associated changes arise from selection among conformers

sampled in the intrinsic motions. The same quasi-rigid clustering of atoms can be used to explain much of the crystallographically-observed anisotropic thermal displacement of atoms, and the equilibrium solution structure observable from NMR RDCs. This suggests correlation between the small pico- and nano-second oscillations reflected in crystallographic B-factors, and slower / larger conformational rearrangements. The hinges implied from these rigid group approximations are consistent with the locations of NMR-measurable relaxation exchange, likely because there is intrinsic flexing in the milli- to micro-second regime at these hinge points. Recently, we have found that, surprisingly, the dynamics of the transition state analog complex are more widespread and somewhat faster than without bound substrates. This leads to current efforts to characterize the dynamics in reacting enzyme, and to determine which motions might be limiting at each step on the reaction path. We also continue to develop new computational analyses that support more exacting comparisons of the disparate data types, differing in time- and length-scales. Thus, we are using AK as a model system to address fundamental questions of how proteins move in executing their functions, a topic that is little understood.

92. Davulcu, O., Skalicky, J. J. & Chapman, M. S. (2011). *Rate-Limiting Domain and Loop Motions in Arginine Kinase*. **Biochemistry** 50: 4011-4018. PMID: 21425868; PMCID: PMC3091953; doi: 10.1021/bi101664u
107. Chapman, B.K., Davulcu, O., Skalicky, J., Brűschweiler, R. & Chapman, M. (2015). *Parsimony in Protein Conformational Change*, **Structure**, 23: 1190-98. PMCID: PMC4497923; doi:10.1016/j.str.2015.05.011
113. Peng,Y., Hansen, A.L., Bruschweiler-Li, L., Davulcu, O., Skalicky, J.J., Chapman, M.S. and Brüschweiler, R.P. (2017). *The Michaelis Complex of Arginine Kinase Samples the Transition State at a Frequency that Matches the Catalytic Rate*. **J. Am. Chem. Soc.**, 139: 4846-4853; doi:10.1021/jacs.7b00236 PMID: 28287709.
115. Davulcu O, Peng Y, Brüschweiler R, Skalicky JJ, Chapman MS. *Elevated μs-ms timescale backbone dynamics in the transition state analog form of arginine kinase*. (2017) **J. Struct. Biol**., in press. doi:https://doi.org/10.1016/j.jsb.2017.05.002. NIHMS877940.

Hybrid Methods for Structural Analysis

Our experimental projects led us to develop computational methods for structural analysis based on diverse and sparse data sets. Our goal is broadly applicable algorithms that afford the community new insights from emerging biophysical technology. As hybrid x-ray/EM approaches were introduced, we developed algorithms to optimize the agreement of an atomic model with an experimental cryo-EM map. Our approach rigorously accounts for resolution and overlap in atomic density, and was used to refine ribosome, virus and acto-myosin structures, and recently the SUR1/Kir6.2 potassium channel in the Shyng lab.. It was adopted in the DIREX/DEN program of Schröder, Levitt & Brűnger, but, with molecular dynamics (MD) optimization, crude approximations are the norm, which our recent code vectorization makes unnecessary. Of great concern, publ. #100 (below) revealed overfitting in MD-refinements of *cryo*-EM structure below 4 or 5Å resolution. Our priority became a reduced-parameter flexible modeling that avoided over-fitting sparse datasets and maintained stereochemistry (publ. #107, above). Through comparison to NMR relaxation dispersion data, we are evaluating experimentally how well such parameterizations capture real conformational changes. We are also developing the means to include more diverse data types, having previously worked with solid-state NMR data, and now with solution state NMR residual dipolar couplings. Thus, current objectives are: (1) methods that integrate disparate data types into unified atomic models of conformational change and dynamics; and (2) realistic parsimonious model parameterizations yielding robust well-conditioned refinements with the sparse datasets available.

55. Gao, H., Sengupta, J., Valle, M., Korostelev, A., Eswar, N., Stagg, S., VanRoey, P., Agrawal, R., Harvey, S., Sali, A., Chapman, M., & Frank, J. *Study of the Structural Dynamics of the E. coli 70S Ribosome Using Real Space Refinement.* **Cell**, 2003. 113: 789-801. PMID: 12809609. doi: 10.1016/S0092-8674(03)00427-6
58. Bertram, R., Asbury, T., Fabiola, F., Quine, J., Cross, T. & Chapman, M. (2003). *Atomic Refinement with Correlated Solid-State NMR Restraints*. **J. Mag. Res.**, 2003. 163: 300-9. PMID: 12914845.
65. Fabiola, F. and Chapman, M.S. (2005) *Fitting of High Resolution Structures into Electron Microscopy Reconstruction Images*, **Structure**, 13: 389-400. PMID: 15766540. doi: 10.1016/j.str.2005.01.007
100. Chapman, M.S., A. Trzynka, and B.K. Chapman (2013), *Atomic Modeling of cryo-Electron Microscopy Reconstructions - Joint refinement of Model and Imaging Parameters*. **J. Struct. Biol.** 182:10-21. PMCID: PMC3662558; doi:10.1016/j.jsb.2013.01.003

Complete publication list:
http://www.ncbi.nlm.nih.gov/sites/myncbi/michael.chapman.1/bibliography/41153213/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1R35 GM122564-01 Chapman (PI) — 8/1/17–7/31/22
NIH NIGMS – MIRA Outstanding Investigator Award
Adeno-Associated Virus Gene Therapy Vectors: Molecular Interactions on Cell Entry.
The goals are: (1) to identify and characterize structurally the interactions of AAV on cell entry; and (2) to characterize the protein dynamics as arginine kinase steps along its reaction path.
Role: PI

Hearst Fdn., Chapman (Director) — 12/1/14 – 11/30/17
Quantitative Bioscience & Biomedical Engineering Scholars Program.
This supports interdisciplinary training through graduate fellowships and u-grad internships.
Role: PD

Completed Research Projects (last 3 years)

Pilot Project, Chapman (PI) — 7/1/13 – 6/30/15
OHSU OCSSB
Visualizing specificity in the targeting of AAV gene therapy vectors.
The goal was to establish that electron microscopy could be used in analysis of structure activity relationships.
Role: PI

ETIC training grant, Chapman (Director) — 7/1/14 – 6/30/16
Oregon Engineering & Technology Industry Council
Quantitative Bioscience & Biomedical Engineering.
This was the fore-runner of the training program that became OTC 16098-0002, above, when the State funding agency was re-organized and awards were re-competed.
Role: PD

1R01 GM77643-08 Chapman (PI) — 2/1/07 – 5/31/17
NIH NIGMS
Functional Dynamics during Induced-fit Turnover.
The goal is NMR and crystallographic characterization of protein dynamics during the turnover cycle of an induced-fit two-substrate enzyme.
Role: PI

State of Oregon Employment Dept.: Oregon Talent Council 16098-0002 Chapman (PI) — 04/01/16 – 06/30/17
Industry-relevant Training and Research Experiences for Biomedical Engineering and Data Science Students.
The goal is to facilitate the entrance of engineering, physics, math & comp. sci. students into biomedical and data science R&D careers. The PI leads a partnership between a medical school and a research university, developing curricula, and providing on-/off-site internships.

1R01 GM66875-13 Chapman (PI) — 2/1/03–8/31/17
NIH NIGMS
Structure-Function of AAV - a Viral Gene Therapy Vector.
The goal is structural characterization of viral-host interactions through crystallography, biophysical techniques & molecular virology to understand cell entry & antibody recognition.
Role: PI