

References

1. S.R. Accordino, J.A. Rodriguez Fris, G.A. Appignanesi, A. Fernández, A unifying motif of intermolecular cooperativity in protein associations. *Eur. Phys. J. E* **35**(7), 1–7 (2012)
2. H. Adams, K.D.M. Harris, G.A. Hembury, C.A. Hunter, D. Livingstone, J.F. McCabe, How strong is a π -facial hydrogen bond? *Chem. Commun.* 2531–2532 (1996)
3. N. Agmon, Tetrahedral displacement: the molecular mechanism behind the Debye relaxation in water. *J. Phys. Chem.* **100**(1), 1072–1080 (1996)
4. C.J. Allègre, G. Manhès, C. Göpel, The age of the earth. *Geochimica et Cosmochimica Acta* **59**(8), 1445–1456 (1995)
5. M.P. Allen, D.J. Tildesley, *Computer Simulation of Liquids* (Oxford Science Publications, Clarendon Press, Oxford, 1989)
6. I. Anapolitanos, *On van der Waals forces*. Ph.D. thesis, University of Toronto, 2011
7. D.E. Anderson, J.H. Hurley, H. Nicholson, W.A. Baase, B.W. Matthews, Hydrophobic core repacking and aromatic-aromatic interaction in the thermostable mutant of T4 lysozyme Ser 117 \rightarrow . *Protein Sci.* **2**(8), 1285–1290 (1993)
8. D.E. Anderson, W.J. Becktel, F.W. Dahlquist, pH-induced denaturation of proteins: a single salt bridge contributes 3–5 kcal/mol to the free energy of folding of T4 lysozyme. *Biochemistry* **29**(9), 2403–2408 (1990)
9. A. Andreeva, D. Howorth, J.-M. Chandonia, S.E. Brenner, T.J.P. Hubbard, C. Chothia, A.G. Murzin, Data growth and its impact on the SCOP database: new developments. *Nucl. Acids Res.* **36**, D419–425 (2008)
10. J. Applequist, J.R. Carl, K.-K. Fung, Atom dipole interaction model for molecular polarizability. Application to polyatomic molecules and determination of atom polarizabilities. *J. Am. Chem. Soc.* **94**(9), 2952–2960 (1972)
11. D.H. Ardell, G. Sella, No accident: genetic codes freeze in error-correcting patterns of the standard genetic code. *Philos. Trans. R. Soc. Lond. Ser. B: Biol. Sci.* **357**(1427), 1625 (2002)
12. I.T. Arkin, H. Xu, M.O. Jensen, E. Arbely, E.R. Bennett, K.J. Bowers, E. Chow, R.O. Dror, M.P. Eastwood, R. Flitman-Tene, B.A. Gregersen, J.L. Klepeis, I. Kolossvary, Y. Shan, D.E. Shaw, Mechanism of Na^+/H^+ antiporting. *Science* **317**(5839), 799–803 (2007)
13. M.R. Arkin, J.A. Wells, Small-molecule inhibitors of protein-protein interactions: progressing towards the dream. *Nat. Rev.-Drug Discov.* **3**(4), 301–317 (2004)
14. J. Arnórsdóttir, A.R. Sigtryggsdóttir, S.H. Thorbjarnardóttir, M.M. Kristjánsson, Effect of proline substitutions on stability and kinetic properties of a cold adapted subtilase. *J. Biochem.* **145**(3), 325–329 (2009)
15. P.J. Artymiuk, C.C.F. Blake, Refinement of human lysozyme at 1.5 Å resolution analysis of non-bonded and hydrogen-bond interactions. *J. Mol. Biol.* **152**(4), 737–762 (1981)
16. K. Asai, S. Hayamizu, K. Handa, Prediction of protein secondary structure by the hidden Markov model. *Comput. Appl. Biosci.* **9**(2), 141–146 (1993)
17. F. Avbelj, J. Moult, Role of electrostatic screening in determining protein main chain conformational preferences. *Biochemistry* **34**(3), 755–764 (1995)

18. F. Avbelj, Amino acid conformational preferences and solvation of polar backbone atoms in peptides and proteins. *J. Mol. Biol.* **300**(5), 1335–1359 (2000)
19. F. Avbelj, R.L. Baldwin, Role of backbone solvation in determining thermodynamic β propensities of the amino acids. *Proc. Natl. Acad. Sci. USA* **99**(3), 1309–1313 (2002)
20. F. Avbelj, S.G. Grdadolnik, J. Grdadolnik, R.L. Baldwin, Intrinsic backbone preferences are fully present in blocked amino acids. *Proc. Natl. Acad. Sci. USA* **103**(5), 1272–1277 (2006)
21. F. Avbelj, P. Luo, R.L. Baldwin, Energetics of the interaction between water and the helical peptide group and its role in determining helix propensities. *Proc. Natl. Acad. Sci. USA* **97**, 10786–10791 (2000)
22. J.C. Avise, B.W. Bowen, T. Lamb, A.B. Meylan, E. Bermingham, Mitochondrial DNA evolution at a turtle's pace: evidence for low genetic variability and reduced microevolutionary rate in the Testudines. *Mol. Biol. Evol.* **9**(3), 457–473 (1992)
23. R. Azriel, E. Gazit, Analysis of the minimal amyloid-forming fragment of the islet amyloid polypeptide. An experimental support for the key role of the phenylalanine residue in amyloid formation. *J. Biol. Chem.* **276**(36), 34156–34161 (2001)
24. C. Azuara, E. Lindahl, P. Koehl, H. Orland, M. Delarue, PDB_Hydro: incorporating dipolar solvents with variable density in the Poisson-Boltzmann treatment of macromolecule electrostatics. *Nucleic Acids Res.* **34**(Web Server issue), W38 (2006)
25. C. Azuara, H. Orland, M. Bon, P. Koehl, M. Delarue, Incorporating dipolar solvents with variable density in Poisson-Boltzmann electrostatics. *Biophys. J.* **95**(12), 5587–5605 (2008)
26. M. Bachmayr, Adaptive low-rank wavelet methods and applications to two-electron Schrödinger equations. Ph.D. thesis, Universitätsbibliothek, 2012
27. M. Bachmayr, W. Dahmen, Adaptive near-optimal rank tensor approximation for high-dimensional operator equations. *Found. Comput. Math.* 1–60 (2013)
28. R.P. Bahadur, P. Chakrabarti, F. Rodier, J. Janin, Dissecting subunit interfaces in homodimeric proteins. *Proteins: Struct. Funct. Genet.* **53**, 708–719 (2003)
29. R.P. Bahadur, P. Chakrabarti, F. Rodier, J. Janin, A dissection of specific and non-specific protein-protein interfaces. *J. Mol. Biol.* **336**, 943–955 (2004)
30. Y. Bai, S.W. Englander, Hydrogen bond strength and β -sheet propensities: the role of a side chain blocking effect. *Proteins-Struct. Funct. Genet.* **18**(3), 262–266 (1994)
31. Y. Bai, J.S. Milne, L. Mayne, S.W. Englander, Primary structure effects on peptide group hydrogen exchange. *Proteins-Struct. Funct. Genet.* **17**, 75–86 (1993)
32. E.N. Baker, R.E. Hubbard, Hydrogen bonding in globular proteins. *Prog. Biophys. Mol. Biol.* **44**, 97–179 (1984)
33. N.A. Baker, Improving implicit solvent simulations: a poisson-centric view. *Curr. Opin. Struct. Biol.* **15**(2), 137–143 (2005)
34. R.L. Baldwin, In search of the energetic role of peptide hydrogen bonds. *J. Biol. Chem.* **278**(20), 17581–17588 (2003)
35. R.L. Baldwin, Energetics of protein folding. *J. Mol. Biol.* **371**(2), 283–301 (2007)
36. R.L. Baldwin, Protein folding: making a network of hydrophobic clusters. *Science* **295**, 1657–1658 (2002)
37. Y.-E.A. Ban, H. Edelsbrunner, J. Rudolph, Interface surfaces for protein-protein complexes, in *Proceedings of the 8th Annual International Conference on Research in Computational Molecular Biology (RECOMB)* (2004), pp. 205–212
38. A.L. Barabasi, *Linked: The New Science of Networks* (Perseus, New York, 2002)
39. J.P. Bardhan, M.G. Knepley, Communication: modeling charge-sign asymmetric solvation free energies with nonlinear boundary conditions. *J. Chem. Phys.* **141**(13), 131103 (2014)
40. K. Bartik, C. Redfield, C.M. Dobson, Measurement of the individual pK_a values of acidic residues of hen and turkey lysozymes by two-dimensional ^1H NMR. *Biophys. J.* **66**, 1180–1184 (1994)
41. A.P. Bartók, M.J. Gillan, F.R. Manby, G. Csányi, Machine-learning approach for one-and two-body corrections to density functional theory: applications to molecular and condensed water. *Phys. Rev. B* **88**(5), 054104 (2013)
42. M.V. Basilevsky, D.F. Parsons, An advanced continuum medium model for treating solvation effects: nonlocal electrostatics with a cavity. *J. Chem. Phys.* **105**(9), 3734–3746 (1996)
43. V. Basilevsky, G.N. Chuev, Nonlocal solvation theories, in *Continuum Solvation Models in Chemical Physics: From Theory to Applications*, ed. by B. Mennucci, R. Cammi (Wiley, New York, 2008)
44. G.K. Batchelor, *An Introduction to Fluid Dynamics* (Cambridge University Press, Cambridge, 2000)
45. P.A. Bates, P. Dokurno, P.S. Freemont, M.J.E. Sternberg, Conformational analysis of the first observed non-proline cis-peptide bond occurring within the complementarity determining region (CDR) of an antibody. *J. Mol. Biol.* **284**(3), 549–555 (1998)

46. E.R. Batista, S.S. Xantheas, H. Jonsson, Multipole moments of water molecules in clusters and ice Ih from first principles calculations. *J. Chem. Phys.* **111**(13), 6011–6015 (1999)
47. E. Bellacchio, K.L. McFarlane, A. Rompel, J.H. Robblee, R.M. Cinco, V.K. Yachandra, Counting the number of disulfides and thiol groups in proteins and a novel approach for determining the local pK_a for cysteine groups in proteins in vivo. *J. Synchrotron Radiat.* **8**(3), 1056–1058 (2001)
48. A.Y. Ben-Naim, *Hydrophobic Interactions* (Springer, Berlin, 1980)
49. R. Berisio, V.S. Lamzin, F. Sica, K.S. Wilson, A. Zagari, L. Mazzarella, Protein titration in the crystal state. *J. Mol. Biol.* **292**, 845–854 (1999)
50. D. Berleant, M. White, E. Pierce, E. Tudoreanu, A. Boeszoermyeni, Y. Shtridelman, J.C. Macosko, The genetic code—more than just a table. *Cell Biochem. Biophys.* **55**(2), 107–116 (2009)
51. T. Beuming, Y. Che, R. Abel, B. Kim, V. Shanmugasundaram, W. Sherman, Thermodynamic analysis of water molecules at the surface of proteins and applications to binding site prediction and characterization. *Proteins: Struct. Funct. Bioinform.* **80**(3), 871–883 (2012)
52. C.C. Bigelow, On the average hydrophobicity of proteins and the relation between it and protein structure. *J. Theor. Biol.* **16**(2), 187–211 (1967)
53. C. Biot, E. Buisine, M. Rooman, Free-energy calculations of protein-ligand cation- π and amino- π interactions: from vacuum to proteinlike environments. *J. Am. Chem. Soc.* **125**(46), 13988–13994 (2003)
54. M. Bittelli, M. Flury, K. Roth, Use of dielectric spectroscopy to estimate ice content in frozen porous media. *Water Resour. Res.* **40**, W04212 (2004)
55. A.A. Bogan, K.S. Thorn, Anatomy of hot spots in protein interfaces. *J. Mol. Biol.* **280**, 1–9 (1998)
56. A. Bondi, van der Waals volumes and radii. *J. Phys. Chem.* **68**(3), 441–451 (1964)
57. P.A. Bopp, A.A. Kornyshev, G. Sutmann, Static nonlocal dielectric function of liquid water. *Phys. Rev. Lett.* **76**, 1280–1283 (1996)
58. D. Borwein, J.M. Borwein, K.F. Taylor, Convergence of lattice sums and Madelung’s constant. *J. Math. Phys.* **26**(11), 2999–3009 (1985)
59. C. Branden, J. Tooze, *Introduction to Protein Structure*, 2nd edn. (Garland Pub., New York, 1991)
60. S.C. Brenner, L.R. Scott, *The Mathematical Theory of Finite Element Methods*, 3rd edn. (Springer, Berlin, 2008)
61. E. Breslow, V. Mombouyran, R. Deeb, C. Zheng, J.P. Rose, B.C. Wang, R.H. Haschemeyer, Structural basis of neurophysin hormone specificity: geometry, polarity, and polarizability in aromatic ring interactions. *Protein Sci.* **8**(4), 820–831 (1999)
62. D.J. Brooks, J.R. Fresco, A.M. Lesk, M. Singh, Evolution of amino acid frequencies in proteins over deep time: inferred order of introduction of amino acids into the genetic code. *Mol. Biol. Evol.* **19**, 1645–1655 (2002)
63. William Fuller Brown, Jr. Dielectrics, in *Handbuch der Physik*, vol. 14 (Springer, Berlin, 1956), pp. 1–154
64. R.G. Bryant, The dynamics of water-protein interactions. *Annu. Rev. Biophys. Biomol. Struct.* **25**, 29–53 (1996)
65. M. Bryliński, L. Konieczny, I. Roterman, Ligation site in proteins recognized in silico. *Bioinformatics* **1**(4), 127–129 (2006)
66. M. Bryliński, K. Prymula, W. Jurkowski, M. Kočańczyk, E. Stawowczyk, L. Konieczny, I. Roterman, Prediction of functional sites based on the fuzzy oil drop model. *PLoS Comput. Biol.* **3**(5), e94 (2007)
67. A.D. Buckingham, P.W. Fowler, Do electrostatic interactions predict structures of van der Waals molecules? *J. Chem. Phys.* **79**(12), 6426–6428 (1983)
68. A.D. Buckingham, P.W. Fowler, A model for the geometries of van der Waals complexes. *Can. J. Chem.* **63**, 2018–2025 (1985)
69. S.K. Burley, G.A. Petsko, Amino-aromatic interactions in proteins. *FEBS Lett.* **203**(2), 139–143 (1986)
70. S.K. Burley, G.A. Petsko, Electrostatic interactions in aromatic oligopeptides contribute to protein stability. *Trends Biotechnol.* **7**(12), 354–359 (1989)
71. A. Buzzell, Action of urea on tobacco mosaic virus II. The bonds between protein subunits. *Biophys. J.* **2**(2P1), 223–233 (1962)
72. Christopher Byströff, Vesteinn Thorsson, David Baker, HMMSTR: a hidden Markov model for local sequence-structure correlations in proteins. *J. Mol. Biol.* **301**(1), 173–190 (2000)
73. O.M. Cabarcos, C.J. Weinheimer, J.M. Lisy, Competitive solvation of K^+ by benzene and water: cation- π interactions and π -hydrogen bonds. *J. Chem. Phys.* **108**(13), 5151–5154 (1998)
74. D.R. Caffrey, S. Somaroo, J.D. Hughes, J. Mintseris, E.S. Huang, Are protein-protein interfaces more conserved in sequence than the rest of the protein surface? *Protein Sci.* **13**(1), 190–202 (2004)
75. J.W. Caldwell, P.A. Kollman, Cation- π interactions: nonadditive effects are critical in their accurate representation. *J. Am. Chem. Soc.* **117**(14), 4177–4178 (1995)

76. C. Caleman, J.S. Hub, P.J. van Maaren, D. van der Spoel, Atomistic simulation of ion solvation in water explains surface preference of halides. *Proc. Natl. Acad. Sci.* **108**(17), 6838–6842 (2011)
77. H.A. Carlson, J.A. McCammon, Accommodating protein flexibility in computational drug design. *Mol. Pharmacol.* **57**(2), 213–218 (2000)
78. F.J. Carver, C.A. Hunter, D.J. Livingstone, J.F. McCabe, E.M. Seward, Substituent effects on edge-to-face aromatic interactions. *Chem.-A. Eur. J.* **8**(13), 2847–2859 (2002)
79. A. Cauerhff, F.A. Goldbaum, B.C. Braden, Structural mechanism for affinity maturation of an anti-lysozyme antibody. *Proc. Natl. Acad. Sci. USA* **101**(10), 3539–3544 (2004)
80. P. Chakrabarti, R. Bhattacharyya, Geometry of nonbonded interactions involving planar groups in proteins. *Prog. Biophys. Mol. Biol.* **95**(1–3), 83–137 (2007)
81. P. Chakrabarti, J. Janin, Dissecting protein-protein recognition sites. *Proteins: Struct. Funct. Genet.* **47**, 334–343 (2002)
82. J. Chalupsky, J. Vondrasek, V. Spirko, Quasiplanarity of the peptide bond. *J. Phys. Chem. A* **112**(4), 693–699 (2008)
83. D. Chandler, Interfaces and the driving force of hydrophobic assembly. *Nature* **437**(7059), 640–647 (2005)
84. J. Chen, X. Zhang, A. Fernández, Molecular basis for specificity in the druggable kinome: sequence-based analysis. *Bioinformatics* **23**(5), 563–572 (2007)
85. D.A. Cherepanov, Force oscillations and dielectric overscreening of interfacial water. *Phys. Rev. Lett.* **93**, 266104 (2004)
86. H. Choi, H. Kang, H. Park, New angle-dependent potential energy function for backbonebackbone hydrogen bond in proteinprotein interactions. *J. Comput. Chem.* **31**(5), 897–903 (2010)
87. L.T. Chong, Y. Duan, L. Wang, I. Massova, P.A. Kollman, Molecular dynamics and free-energy calculations applied to affinity maturation in antibody 48G7. *Proc. Natl. Acad. Sci.* **96**(25), 14330–14335 (1999)
88. T.C. Choy, Van der Waals interaction of the hydrogen molecule: an exact implicit energy density functional. *Phys. Rev. A* **62**, 012506 (2000)
89. J.E. Chrencik, J. Orans, L.B. Moore, Y. Xue, L. Peng, J.L. Collins, G.B. Wisely, M.H. Lambert, S.A. Kliewer, M.R. Redinbo, Structural disorder in the complex of human pregnane X receptor and the macrolide antibiotic rifampicin. *Mol. Endocrinol.* **19**(5), 1125–1134 (2005)
90. G.N. Chuev, M.V. Basilevsky, Molecular models of solvation in polar liquids. *Rus. Chem. Rev.* **72**, 735–757 (2003)
91. T. Clackson, J.A. Wells, A hot spot of binding energy in a hormone-receptor interface. *Science* **267**, 383–386 (1995)
92. A.J. Cohen, P. Mori-Sánchez, W. Yang, Insights into current limitations of density functional theory. *Science* **321**(5890), 792–794 (2008)
93. M. Cohen, D. Reichmann, H. Neuvirth, G. Schreiber, Similar chemistry, but different bond preferences in inter versus intra-protein interactions. *Proteins: Struct. Funct. Bioinform.* **72**(2), 741–753 (2008)
94. M.S. Cohen, C. Zhang, K.M. Shokat, J. Taunton, Structural bioinformatics-based design of selective, irreversible kinase inhibitors. *Science* **308**(5726), 1318–1321 (2005)
95. P. Cohen, Protein kinases—the major drug targets of the twenty-first century? *Nat. Rev.-Drug Discov.* **1**(4), 309–315 (2002)
96. C. Colovos, T.O. Yeates, Verification of protein structures: patterns of nonbonded atomic interactions. *Protein Sci.* **2**(9), 1511–1519 (1993)
97. B.A. Colson, T. Bekyarova, D.P. Fitzsimons, T.C. Irving, R.L. Moss, Radial displacement of myosin cross-bridges in mouse myocardium due to ablation of myosin binding protein-C. *J. Mol. Biol.* **367**(1), 36–41 (2007)
98. P.R. Connelly, R.A. Aldape, F.J. Bruzzese, S.P. Chambers, M.J. Fitzgibbon, M.A. Fleming, S. Itoh, D.J. Livingston, M.A. Navia, J.A. Thomson et al., Enthalpy of hydrogen bond formation in a protein-ligand binding reaction. *Proc. Natl. Acad. Sci. USA* **91**(5), 1964–1968 (1994)
99. S. Costantini, G. Colonna, A.M. Facchiano, ESBRI: a web server for evaluating salt bridges in proteins. *Bioinformation* **3**(3), 137 (2008)
100. F.-X. Coudert, R. Vuilleumier, A. Boutin, Dipole moment, hydrogen bonding and IR spectrum of confined water. *ChemPhysChem* **7**(12), 2464–2467 (2006)
101. C.J. Cramer, *Essentials of Computational Chemistry*, 2nd edn. (Wiley, New York, 2004)
102. E. Thomas, *Creighton, Proteins: Structures and Molecular Properties* (W. H. Freeman, New York, 1993)
103. P.B. Crowley, A. Golovin, Cation- π interactions in protein-protein interfaces. *Proteins: Struct. Funct. Bioinform.* **59**, 231–239 (2005)
104. L.E. Cybulski, M. Martín, M.C. Mansilla, A. Fernández, D. De Mendoza, Membrane thickness cue for cold sensing in a bacterium. *Curr. Biol.* **20**(17), 1539–1544 (2010)

105. B.I. Dahiyat, D. Benjamin Gordon, S.L. Mayo, Automated design of the surface positions of protein helices. *Protein Sci.* **6**(6), 1333–1337 (1997)
106. M. Davies, C. Toseland, D. Moss, D. Flower, Benchmarking pK_a prediction. *BMC Biochem.* **7**(1), 18 (2006)
107. A. De Simone, G.G. Dodson, C.S. Verma, A. Zagari, F. Fraternali, Prion and water: tight and dynamical hydration sites have a key role in structural stability. *Proc. Natl. Acad. Sci. USA* **102**, 7535–7540 (2005)
108. A. De Simone, R. Spadaccini, P.A. Temussi, F. Fraternali, Toward the understanding of MNEI sweetness from hydration map surfaces. *Biophys. J.* **90**(9), 3052–3061 (2006)
109. A. De Simone, A. Zagari, P. Derreumaux, Structural and hydration properties of the partially unfolded states of the prion protein. *Biophys. J.* **93**(4), 1284–1292 (2007)
110. P. Debye, *Polar Molecules* (Dover, New York, 1945)
111. W.L. DeLano, M.H. Ultsch, A.M. de Vos, J.A. Wells, Convergent solutions to binding at a protein-protein interface. *Science* **287**, 1279–1283 (2000)
112. O. Demerdash, E.-H. Yap, T. Head-Gordon, Advanced potential energy surfaces for condensed phase simulation. *Annu. Rev. Phys. Chem.* **65**, 149–174 (2014)
113. O.N.A. Demerdash, J.C. Mitchell, Using physical potentials and learned models to distinguish native binding interfaces from de novo designed interfaces that do not bind. *Proteins: Struct. Funct. Bioinform.* **81**(11), 1919–1930 (2013)
114. G.D. Demetri, Structural reengineering of imatinib to decrease cardiac risk in cancer therapy. *J. Clin. Investig.* **117**(12), 3650–3653 (2007)
115. A.H. DePace, A. Santoso, P. Hillner, J.S. Weissman, A critical role for amino-terminal glutamine/asparagine repeats in the formation and propagation of a yeast prion. *Cell* **93**(7), 1241–1252 (1998)
116. C. Deremble, R. Lavery, Macromolecular recognition. *Curr. Opin. Struct. Biol.* **15**(2), 171–175 (2005)
117. F. Despa, R.S. Berry, The origin of long range attraction between hydrophobes in water. *Biophys. J.* **92**, 373–378 (2007)
118. F. Despa, A. Fernández, R.S. Berry, Dielectric modulation of biological water. *Phys. Rev. Lett.* **93**, 269901 (2004)
119. M. Di Giulio, On the origin of the genetic code. *J. Theor. Biol.* **187**(4), 573–581 (1997)
120. C.M. Dobson, Protein folding and misfolding. *Nature* **426**, 884–890 (2003)
121. M. Dobson, M. Luskin, Iterative solution of the quasicontinuum equilibrium equations with continuation. *J. Sci. Comput.* **37**(1), 19–41 (2008)
122. J.E. Donald, D.W. Kulp, W.F. DeGrado, Salt bridges: geometrically specific, designable interactions. *Proteins: Struct. Funct. Bioinform.* **79**(3), 898–915 (2011)
123. D.A. Dougherty, Cation- π interactions in chemistry and biology: a new view of benzene, Phe, Tyr, and Trp. *Science* **271**(5246), 163–168 (1996)
124. J. Doyle, Beyond the spherical cow. *Nature* **411**, 151–152 (2001)
125. Y. Duan, C. Wu, S. Chowdhury, M.C. Lee, G. Xiong, W. Zhang, R. Yang, P. Cieplak, R. Luo, T. Lee et al., A point-charge force field for molecular mechanics simulations of proteins based on condensed-phase quantum mechanical calculations. *J. Comput. Chem.* **24**(16), 1999–2012 (2003)
126. J.J. Duistermaat, *Fourier Integral Operators* (Springer, Berlin, 1996)
127. J. Dunbar, H.P. Yennawar, S. Banerjee, J. Luo, G.K. Farber, The effect of denaturants on protein structure. *Protein Sci.* **6**, 1727–1733 (1997)
128. W.E.W. Ren, E. Vanden-Eijnden, A general strategy for designing seamless multiscale methods. *JCP* **1**(1), 1–1 (2010)
129. S.R. Eddy, Profile hidden Markov models. *Bioinformatics* **14**(9), 755–763 (1998)
130. D. Eisenberg, R.M. Weiss, T.C. Terwilliger, The hydrophobic moment detects periodicity in protein hydrophobicity. *Proc. Natl. Acad. Sci. USA* **81**(1), 140–144 (1984)
131. A. Elgsaeter, B.T. Stokke, A. Mikkelsen, D. Branton, The molecular basis of erythrocyte shape. *Science* **234**, 1217–1223 (1986)
132. J.L. Ericksen, *Introduction to the Thermodynamics of Solids* (Springer, Berlin, 1998)
133. L. Esposito, A. De Simone, A. Zagari, L. Vitagliano, Unveiling the omega/psi correlation in high resolution protein structures. *Acta Crystallogr. Sect. A* **61**(a1), C482 (2005)
134. L. Esposito, A. De Simone, A. Zagari, L. Vitagliano, Correlation between ω and ψ dihedral angles in protein structures. *J. Mol. Biol.* **347**(3), 483–487 (2005)
135. E. Eyal, S. Gerzon, V. Potapov, M. Edelman, V. Sobolev, The limit of accuracy of protein modeling: influence of crystal packing on protein structure. *J. Mol. Biol.* **351**(2), 431–442 (2005)
136. D.H. Fagan, D. Yee, Crosstalk between IGF1R and estrogen receptor signaling in breast cancer. *J. Mammary Gland Biol. Neoplasia* **13**(4), 423–429 (2008)

137. M. Fandrich, M.A. Fletcher, C.M. Dobson, Amyloid fibrils from muscle myoglobin. *Nature* **410**(6825), 165–166 (2001)
138. E. Fatuzzo, W.J. Merz, *Ferroelectricity* (North-Holland, Amsterdam, 1967)
139. E. Fermi, *Thermodynamics* (Dover, New York, 1956)
140. A. Fernández, S. Bazán, J. Chen, Taming the induced folding of drug-targeted kinases. *Trends Pharmacol. Sci.* **30**(2), 66–71 (2009)
141. A. Fernández, A. Sanguino, Z. Peng, E. Ozturk, J. Chen, A. Crespo, S. Wulf, A. Shavrin, C. Qin, J. Ma et al., An anticancer C-Kit kinase inhibitor is reengineered to make it more active and less cardiotoxic. *J. Clin. Investig.* **117**(12), 4044 (2007)
142. A. Fernández, Conformation-dependent environments in folding proteins. *J. Chem. Phys.* **114**, 2489–2502 (2001)
143. A. Fernández, Cooperative walks in a cubic lattice: protein folding as a many-body problem. *J. Chem. Phys.* **115**, 7293–7297 (2001)
144. A. Fernández, Intramolecular modulation of electric fields in folding proteins. *Phys. Lett. A* **299**, 217–220 (2002)
145. A. Fernández, Buffering the entropic cost of hydrophobic collapse in folding proteins. *J. Chem. Phys.* **121**, 11501–11502 (2004)
146. A. Fernández, Keeping dry and crossing membranes. *Nat. Biotechnol.* **22**, 1081–1084 (2004)
147. A. Fernández, Direct nanoscale dehydration of hydrogen bonds. *J. Phys. D: Appl. Phys.* **38**, 2928–2932 (2005)
148. A. Fernández, Incomplete protein packing as a selectivity filter in drug design. *Structure* **13**, 1829–1836 (2005)
149. A. Fernández, What factor drives the fibrillogenic association of beta-sheets? *FEBS Lett.* **579**, 6635–6640 (2005)
150. A. Fernández, Nanoscale thermodynamics of biological interfacial tension. *Proc. R. Soc. A* **299**, 1–10 (2010)
151. A. Fernández, *Transformative Concepts for Drug Design* (Springer, Berlin, 2010)
152. A. Fernández, Episturctural tension promotes protein associations. *Phys. Rev. Lett.* **108**(18), 188102 (2012)
153. A. Fernández, The principle of minimal episturctural distortion of the water matrix and its steering role in protein folding. *JChemPhys* **139**(8), 085101 (2013)
154. A. Fernández, Communication: chemical functionality of interfacial water enveloping nanoscale structural defects in proteins. *JChemPhys* **140**(22), 221102 (2014)
155. A. Fernández, Water promotes the sealing of nanoscale packing defects in folding proteins. *J. Phys.: Condens. Matter* **26**(20), 202101 (2014)
156. A. Fernández, Packing defects functionalize soluble proteins. *FEBS Lett.* **589**(9), 967–973 (2015)
157. A. Fernández, Quantum theory of interfacial tension quantitatively predicts spontaneous charging of nonpolar aqueous interfaces. *Phys. Lett. A* (2015)
158. A. Fernández, Acidbase chemistry of frustrated water at protein interfaces. *FEBS Lett.* **590**(2), 215–223 (2016)
159. A. Fernández, *Physics at the Biomolecular Interface* (Springer, Berlin, 2016)
160. A. Fernández, R.S. Berry, Extent of hydrogen-bond protection in folded proteins: a constraint on packing architectures. *Biophys. J.* **83**(5), 2475–2481 (2002)
161. A. Fernández, R.S. Berry, Proteins with H-bond packing defects are highly interactive with lipid bilayers: implications for amyloidogenesis. *Proc. Natl. Acad. Sci. USA* **100**, 2391–2396 (2003)
162. A. Fernández, R.S. Berry, Molecular dimension explored in evolution to promote proteomic complexity. *Proc. Natl. Acad. Sci. USA* **101**, 13460–13465 (2004)
163. A. Fernández, R.S. Berry, Golden rule for buttressing vulnerable soluble proteins. *J. Proteome Res.* **9**(5), 2643–2648 (2010)
164. A. Fernández, M. Boland, Solvent environment conducive to protein aggregation. *FEBS Lett.* **529**, 298–303 (2002)
165. A. Fernández, J. Chen, A. Crespo, Solvent-exposed backbone loosens the hydration shell of soluble folded proteins. *J. Chem. Phys.* **126**(24), 245103 (2007)
166. A. Fernández, A. Crespo, S. Maddipati, L.R. Scott, Bottom-up engineering of peptide cell translocators based on environmentally modulated quadrupole switches. *ACS Nano* **2**, 61–68 (2008)
167. A. Fernández, J. Kardos, L.R. Scott, Y. Goto, R.S. Berry, Structural defects and the diagnosis of amyloidogenic propensity. *Proc. Natl. Acad. Sci. USA* **100**(11), 6446–6451 (2003)
168. A. Fernández, S. Maddipati, A priori inference of cross reactivity for drug-targeted kinases. *J. Med. Chem.* **49**(11), 3092–3100 (2006)

169. A. Fernández, K. Rogale Plazonic, L.R. Scott, H.A. Scheraga, Inhibitor design by wrapping packing defects in HIV-1 proteins. *Proc. Natl. Acad. Sci. USA* **101**, 11640–11645 (2004)
170. A. Fernández, A. Sanguino, Z. Peng, A. Crespo, E. Ozturk, X. Zhang, S. Wang, W. Bornmann, G. Lopez-Berestein, Rational drug redesign to overcome drug resistance in cancer therapy: imatinib moving target. *Cancer Res.* **67**(9), 4028–4033 (2007)
171. A. Fernández, A. Sanguino, Z. Peng, E. Ozturk, J. Chen, A. Crespo, S. Wulf, A. Shavrin, C. Qin, J. Ma, J. Trent, Y. Lin, H.-D. Han, L.S. Mangala, J.A. Bankson, J. Gelovani, A. Samarel, W. Bornmann, A.K. Sood, G. Lopez-Berestein, An anticancer C-Kit kinase inhibitor is reengineered to make it more active and less cardiotoxic. *J. Clin. Investig.* **117**(12), 4044–4054 (2007)
172. A. Fernández, H.A. Scheraga, Insufficiently dehydrated hydrogen bonds as determinants of protein interactions. *Proc. Natl. Acad. Sci. USA* **100**(1), 113–118 (2003)
173. A. Fernández, L.R. Scott, Adherence of packing defects in soluble proteins. *Phys. Rev. Lett.* **91**(4), 18102 (2003)
174. A. Fernández, L.R. Scott, Dehydron: a structurally encoded signal for protein interaction. *Biophys. J.* **85**, 1914–1928 (2003)
175. A. Fernández, L.R. Scott, Under-wrapped soluble proteins as signals triggering membrane morphology. *J. Chem. Phys.* **119**(13), 6911–6915 (2003)
176. A. Fernández, L.R. Scott, Modulating drug impact by wrapping target proteins. *Expert Opin. Drug Discov.* **2**, 249–259 (2007)
177. A. Fernández, L.R. Scott, Drug leads for interactive protein targets with unknown structure. *Drug Discov. Today* **21**, 531–535 (2016)
178. A. Fernández, L.R. Scott, Three-body interactions in drug design: reconciling “counterintuitive” decisions in lead optimization. *Nat. Biotechnol.* submitted, 1–4 (2016)
179. A. Fernández, L.R. Scott, R.S. Berry, The nonconserved wrapping of conserved protein folds reveals a trend towards increasing connectivity in proteomic networks. *Proc. Natl. Acad. Sci. USA* **101**(9), 2823–2827 (2004)
180. A. Fernández, L.R. Scott, R.S. Berry, Packing defects as selectivity switches for drug-based protein inhibitors. *Proc. Natl. Acad. Sci. USA* **103**, 323–328 (2006)
181. A. Fernández, L.R. Scott, H.A. Scheraga, Amino-acid residues at protein-protein interfaces: why is propensity so different from relative abundance? *J. Phys. Chem. B* **107**(36), 9929–9932 (2003)
182. A. Fernández, T.R. Sosnick, A. Colubri, Dynamics of hydrogen bond desolvation in protein folding. *J. Mol. Biol.* **321**(4), 659–675 (2002)
183. J.C. Ferreon, V.J. Hilser, The effect of the polyproline II (PPII) conformation on the denatured state entropy. *Protein Sci.* **12**(3), 447–457 (2003)
184. R.D. Finn, J. Tate, J. Mistry, P.C. Coghill, S.J. Sammut, H.-R. Hotz, G. Ceric, K. Forslund, S.R. Eddy, E.L. Sonnhammer, A. Bateman, The Pfam protein families database. *Nucl. Acids Res.* **36**, D281–288 (2008)
185. J.E. Fitzgerald, A.K. Jha, T.R. Sosnick, K.F. Freed, Polypeptide motions are dominated by peptide group oscillations resulting from dihedral angle correlations between nearest neighbors. *Biochemistry* **46**(3), 669–682 (2007)
186. A.F. Fliri, W.T. Loging, P.F. Thadeio, R.A. Volkman, Biological spectra analysis: linking biological activity profiles to molecular structure. *Proc. Natl. Acad. Sci. USA* **102**(2), 261–266 (2005)
187. B. Folch, M. Rooman, Y. Dehouck, Thermostability of salt bridges versus hydrophobic interactions in proteins probed by statistical potentials. *J. Chem. Inf. Model.* **48**(1), 119–127 (2008)
188. L.R. Forrest, B. Honig, An assessment of the accuracy of methods for predicting hydrogen positions in protein structures. *Proteins: Struct. Funct. Bioinform.* **62**(2), 296–309 (2005)
189. W.R. Forsyth, J.M. Antosiewicz, A.D. Robertson, Empirical relationships between protein structure and carboxyl pK_a values in proteins. *Proteins-Struct. Funct. Genet.* **48**(2), 388–403 (2002)
190. R. Franklin, R.G. Gosling, Evidence for 2-chain helix in crystalline structure of sodium deoxyribonucleate. *Nature* **172**, 156–157 (1953)
191. F. Franks, *Water: a Matrix for Life* (Royal Society of Chemistry, Cambridge, 2000)
192. J.S. Franzen, R.E. Stephens, The effect of a dipolar solvent system on interamide hydrogen bonds. *Biochemistry* **2**(6), 1321–1327 (1963)
193. C.M. Fraser, A. Fernández, L.R. Scott, Dehydron analysis: quantifying the effect of hydrophobic groups on the strength and stability of hydrogen bonds, in *Advances in Computational Biology* ed. by H.R. Arabnia (Springer, New York, 2010)
194. C.M. Fraser, A. Fernández, L.R. Scott, Wrappa: a screening tool for candidate dehydron identification. Research Report UC/CS TR-2011-5, Department of Computer Science, University, Chicago, 2011

195. E. Freire, The propagation of binding interactions to remote sites in proteins: analysis of the binding of the monoclonal antibody D1.3 to lysozyme. *Proc. Natl. Acad. Sci. USA* **96**, 10118–10122 (1999)
196. R.H. French, Origins and applications of London dispersion forces and Hamaker constants in ceramics. *J. Am. Ceram. Soc.* **83**(9), 2117–46 (2000)
197. V. Fridkin, S. Ducharme, *The Ferroelectricity at the Nanoscale* (Springer, Berlin, 2013)
198. E. Fry, R. Acharya, D. Stuart, Methods used in the structure determination of foot-and-mouth disease virus. *Acta Crystall. A* **49**, 45–55 (1993)
199. R.L. Fulton, The nonlinear dielectric behavior of water: comparisons of various approaches to the nonlinear dielectric increment. *J. Chem. Phys.* **130**, 204503 (2009)
200. J.P. Gallivan, D.A. Dougherty, Cation- π interactions in structural biology. *Proc. Natl. Acad. Sci. USA* **96**(17), 9459–9464 (1999)
201. J. Gao, D.A. Bosco, E.T. Powers, J.W. Kelly, Localized thermodynamic coupling between hydrogen bonding and microenvironment polarity substantially stabilizes proteins. *Nat. Struct. Mol. Biol.* **16**(7), 684–690 (2009)
202. A.E. García, K.Y. Sanbonmatsu, α -helical stabilization by side chain shielding of backbone hydrogen bonds. *Proc. Natl. Acad. Sci. USA* **99**(5), 2782–2787 (2002)
203. R.E. Georgescu, E.G. Alexov, M.R. Gunner, Combining conformational flexibility and continuum electrostatics for calculating pK_{as} in proteins. *Biophys. J.* **83**(4), 1731–1748 (2002)
204. A.K. Ghosh, S. Gemma, *Structure-based Design of Drugs and Other Bioactive Molecules: Tools and Strategies* (Wiley, New York, 2014)
205. R. Giles, *Mathematical Foundations of Thermodynamics* (Macmillan, New York, 1964)
206. D. Gilis, S. Massar, N.J. Cerf, M. Rooman, Optimality of the genetic code with respect to protein stability and amino-acid frequencies. *Genome Biol.* **2**(11), 49–1 (2001)
207. I. Gitlin, J.D. Carbeck, G.M. Whitesides, Why are proteins charged? networks of charge-charge interactions in proteins measured by charge ladders and capillary electrophoresis. *Angew. Chem. Int. Edition* **45**(19), 3022–3060 (2006)
208. F. Glaser, D.M. Steinberg, I.A. Vakser, N. Ben-Tal, Residue frequencies and pairing preferences at protein-protein interfaces. *Proteins: Struct. Funct. Genet.* **43**, 89–102 (2001)
209. G.A. Grant, C.W. Luetje, R. Summers, X.L. Xu, Differential roles for disulfide bonds in the structural integrity and biological activity of κ -bungarotoxin, a neuronal nicotinic acetylcholine receptor antagonist. *Biochemistry* **37**(35), 12166–12171 (1998)
210. J.K. Gregory, D.C. Clary, K. Liu, M.G. Brown, R.J. Saykally, The water dipole moment in water clusters. *Science* **275**(5301), 814–817 (1997)
211. A.V. Grinberg, R. Bernhardt, Effect of replacing a conserved proline residue on the function and stability of bovine adrenodoxin. *Protein Eng.* **11**(11), 1057–1064 (1998)
212. V. Nick, Grishin, Fold change in evolution of protein structures. *J. Struct. Biol.* **134**(2–3), 167–185 (2001)
213. J.A. Gruenke, R.T. Armstrong, W.W. Newcomb, J.C. Brown, J.M. White, New insights into the spring-loaded conformational change of influenza virus hemagglutinin. *J. Virol.* **76**(9), 4456–4466 (2002)
214. J.I. Guijarro, M. Sunde, J.A. Jones, I.D. Campbell, C.M. Dobson, Amyloid fibril formation by an SH3 domain. *Proc. Natl. Acad. Sci. USA* **95**(8), 4224–4228 (1998)
215. S. Günther, J. Von Eichborn, P. May, R. Preissner, JAIL: a structure-based interface library for macromolecules. *Nucleic Acids Res.* **37**(suppl 1), D338–D341 (2009)
216. I. Halperin, H. Wolfson, R. Nussinov, Protein-protein interactions; coupling of structurally conserved residues and of hot spots across interfaces. implications for docking. *Structure* **12**, 1027–1038 (2004)
217. D. Hamelberg, J.A. McCammon, Fast peptidyl cis-trans isomerization within the flexible Gly-rich flaps of HIV-1 protease. *J. Am. Chem. Soc.* **127**(40), 13778–13779 (2005)
218. Y. Harpaz, M. Gerstein, C. Chothia, Volume changes on protein folding. *Structure* **2**, 641–649 (1994)
219. M.J. Hartshorn, C.W. Murray, A. Cleasby, M. Frederickson, I.J. Tickle, H. Jhoti, Fragment-based lead discovery using X-ray crystallography. *J. Med. Chem.* **48**(2), 403–413 (2005)
220. J.B. Hasted, *Aqueous Dielectrics* (Chapman and Hall, London, 1974)
221. B. Hayes, The invention of the genetic code. *Am. Sci.* **86**(1), 8–14 (1998)
222. J.P. Helfrich, Dynamic laser light scattering technology for the molecular weight and hydrodynamic radius characterization of proteins. *Pharm. Lab.* **1**, 34–40 (1998)
223. Z.S. Hendsch, B. Tidor, Do salt bridges stabilize proteins? A continuum electrostatic analysis. *Protein Sci.: Publ. Protein Soc.* **3**(2), 211 (1994)
224. D.H. Herce, L. Perera, T.A. Darden, C. Sagui, Surface solvation for an ion in a water cluster. *J. Chem. Phys.* **122**(2), 024513 (2005)
225. M. Heuberger, T. Drobek, N.D. Spencer, Interaction forces and morphology of a protein-resistant poly(ethylene glycol) layer. *Biophys. J.* **88**(1), 495–504 (2005)

226. J. Higo, M. Nakasako, Hydration structure of human lysozyme investigated by molecular dynamics simulation and cryogenic X-ray crystal structure analyses: on the correlation between crystal water sites, solvent density, and solvent dipole. *J. Comput. Chem.* **23**(14), 1323–1336 (2002)
227. A. Hildebrandt, R. Blossey, S. Rjasanow, O. Kohlbacher, H.-P. Lenhof, Novel formulation of nonlocal electrostatics. *Phys. Rev. Lett.* **93**(10), 108104 (2004)
228. A. Hildebrandt, R. Blossey, S. Rjasanow, O. Kohlbacher, H.P. Lenhof, Electrostatic potentials of proteins in water: a structured continuum approach. *Bioinformatics* **23**(2), e99 (2007)
229. M.K. Hill, M. Shehu-Xhilaga, S.M. Crowe, J. Mak, Proline residues within spacer peptide p1 are important for human immunodeficiency virus type 1 infectivity, protein processing, and genomic RNA dimer stability. *J. Virol.* **76**, 11245–11253 (2002)
230. N.E. Hill, W.E. Vaughan, A.H. Price, M. Davies (eds.), *Dielectric Properties and Molecular Behaviour* (van Nostrand, London, 1969)
231. S. Hirohashi, Y. Kanai, Cell adhesion system and human cancer morphogenesis. *Cancer Sci.* **94**(7), 575–581 (2003)
232. U. Hobohm, M. Scharf, R. Schneider, C. Sander, Selection of representative protein data sets. *Protein Sci.* **1**(3), 409–417 (1992)
233. B. Honig, A.S. Yang, Free energy balance in protein folding. *Adv. Protein Chem.* **46**, 27–58 (1995)
234. A.L. Hopkins, J.S. Mason, J.P. Overington, Can we rationally design promiscuous drugs? *Curr. Opin. Struct. Biol.* **16**(1), 127–136 (2006)
235. M. Hoshino, H. Katou, Y. Hagihara, K. Hasegawa, H. Naiki, Y. Goto, Mapping the core of the beta(2)-microglobulin amyloid fibril by H/D exchange. *Nat. Struct. Biol.* **19**, 332–336 (2002)
236. T. Hou, P. Koumoutsakos, Special section on multiscale modeling in materials and life sciences. *SIAM J. Multiscale Model. Simul.* **4**(1), 213–214 (2005)
237. S. Hövöller, T. Zhou, T. Ohlson, Conformations of amino acids in proteins. *Acta Crystallogr. Sect. D* **58**(5), 768–776 (2002)
238. Z. Hu, B. Ma, H. Wolfson, R. Nussinov, Conservation of polar residues as hot spots at protein interfaces. *Proteins: Struct. Funct. Genet.* **39**, 331–342 (2000)
239. M.A. Huntley, G.B. Golding, Simple sequences are rare in the Protein data bank. *Proteins: Struct. Funct. Bioinform.* **48**(1), 134–140 (2002)
240. B.M.P. Huyghues-Despointes, T.M. Klingler, R.L. Baldwin, Measuring the strength of side-chain hydrogen bonds in peptide helices: the Gln-Asp (i, i + 4) interaction. *Biochemistry* **34**, 13267–13271 (2002). doi:[10.1021/bi00041a001](https://doi.org/10.1021/bi00041a001)
241. L.M. Iakoucheva, K.A. Dunker, Order, disorder, and flexibility: prediction from protein sequence. *Structure* **11**, 1316–1317 (2003)
242. W. Im, D. Beglov, B. Roux, Continuum solvation model: electrostatic forces from numerical solutions to the Poisson-Boltzmann equation. *Comput. Phys. Commun.* **111**, 59–75 (1998)
243. R. Improta, L. Vitagliano, L. Esposito, Peptide bond distortions from planarity: new insights from quantum mechanical calculations and peptide/protein crystal structures. *PLoS ONE* **6**(9), e24533, 09 (2011)
244. J. Israelachvili, *Intermolecular and Surface Forces*, 2nd edn. (Academic Press, London, 1991)
245. A. Jabs, M.S. Weiss, R. Hilgenfeld, Non-proline cis peptide bonds in proteins. *J. Mol. Biol.* **286**(1), 291–304 (1999)
246. C. Jarzynski, Nonequilibrium equality for free energy differences. *Phys. Rev. Lett.* **78**(14), 2690 (1997)
247. M. Jaskolski, M. Gilski, Z. Dauter, A. Wlodawer, Stereochemical restraints revisited: how accurate are refinement targets and how much should protein structures be allowed to deviate from them? *Acta Crystallogr. Sect. D* **63**(5), 611–620 (2007)
248. E.T. Jaynes, R. Smoluchowski, Ferroelectricity. *Phys. Today* **6**, 17 (1953)
249. G.A. Jeffrey, *An Introduction to Hydrogen Bonds* (Oxford Science Publications, Clarendon Press, Oxford, 1997)
250. G.A. Jeffrey, Hydrogen-bonding: an update. *Crystallogr. Rev.* **9**, 135–176 (2003). doi:[10.1080/08893110310001621754](https://doi.org/10.1080/08893110310001621754)
251. J.H. Jensen, H. Li, A.D. Robertson, P.A. Molina, Prediction and rationalization of protein pK_a values using QM and QM/MM methods. *J. Phys. Chem. A* **109**(30), 6634–6643 (2005)
252. A.K. Jha, K.F. Freed, Solvation effect on conformations of 1, 2: dimethoxyethane: charge-dependent nonlinear response in implicit solvent models. *J. Chem. Phys.* **128**, 034501 (2008)
253. C.G. Ji, J.Z.H. Zhang, Quantifying the stabilizing energy of the intraprotein hydrogen bond due to local mutation. *J. Phys. Chem. B* **115**(42), 12230–12233 (2011)
254. S. Ji, The linguistics of DNA: words, sentences, grammar, phonetics, and semantics. *Ann. N. Y. Acad. Sci.* **870**, 411–417 (1999)

255. L. Jiang, L. Lai, CH··· O hydrogen bonds at protein-protein interfaces. *J. Biol. Chem.* **277**(40), 37732 (2002)
256. R.O. Jones, Density functional theory: its origins, rise to prominence, and future. *Rev. Mod. Phys.* **87**(3), 897 (2015)
257. S. Jones, J.M. Thornton, Principles of protein-protein interactions. *Proc. Natl. Acad. Sci. USA* **93**, 13–20 (1996)
258. S. Jones, J.M. Thornton, Analysis of protein-protein interaction sites using surface patches. *J. Mol. Biol.* **272**, 121–132 (1997)
259. S. Jones, J.M. Thornton, Prediction of protein-protein interaction sites using patch analysis. *J. Mol. Biol.* **272**, 133–143 (1997)
260. F. Jourdan, S. Lazzaroni, B.L. Méndez, P.L. Cantore, M. de Julio, P. Amodeo, N.S. Iacobellis, A. Evidente, A. Motta, A left-handed α -helix containing both L- and D-amino acids: the solution structure of the antimicrobial lipopeptide tolaasin. *Proteins: Struct. Funct. Bioinform.* **52**(4), 534–543 (2003)
261. U. Kaatzke, R. Behrends, R. Pottel, Hydrogen network fluctuations and dielectric spectrometry of liquids. *J. Non-Cryst. Solids* **305**(1), 19–28 (2002)
262. R. Kaufmann, U. Junker, M. Schilli-Westermann, C. Klötzer, J. Scheele, K. Junker, Meizothrombin, an intermediate of prothrombin cleavage potentially activates renal carcinoma cells by interaction with par-type thrombin receptors. *Oncol. Rep.* **10**, 493–496 (2003)
263. W. Kauzmann, Some factors in the interpretation of protein denaturation, in *Advances in Protein Chemistry*, vol. 14 (Academic Press, New York, 1959), pp. 1–63
264. J. Kemmink, T.E. Creighton, The physical properties of local interactions of tyrosine residues in peptides and unfolded proteins. *J. Mol. Biol.* **245**(3), 251–260 (1995)
265. F.N. Keutsch, J.D. Cruzan, R.J. Saykally, The water trimer. *Chem. Rev.* **103**(7), 2533–2578 (2003)
266. A.I. Khinchin, *Mathematical Foundations of Statistical Mechanics* (Dover, New York, 1949)
267. J. Kim, J. Mao, M.R. Gunner, Are acidic and basic groups in buried proteins predicted to be ionized? *J. Mol. Biol.* **348**(5), 1283–1298 (2005)
268. S.S. Kim, T.J. Smith, M.S. Chapman, M.C. Rossmann, D.C. Pevear, F.J. Dutko, P.J. Felock, G.D. Diana, M.A. McKinlay, Crystal structure of human rhinovirus serotype 1A (HRV1A). *J. Mol. Biol.* **210**, 91–111 (1989)
269. S. Kim, S.J. Karrila, *Microhydrodynamics: Principles and Selected Applications* (Dover Publications, New York, 2005)
270. C. King, E.N. Garza, R. Mazor, J.L. Linehan, I. Pastan, M. Pepper, D. Baker, Removing T-cell epitopes with computational protein design. *Proc. Natl. Acad. Sci. USA* **111**(23), 8577–8582 (2014)
271. W. Klopper, J.G.C.M. van Duijneveldt-van, F.B. de Rijdt van Duijneveldt, Computational determination of equilibrium geometry and dissociation energy of the water dimer. *Phys. Chem. Chem. Phys.* **2**, 2227–2234 (2000)
272. I.M. Klotz, Solvent water and protein behavior: view through a retroscope. *Protein Sci.* **2**(11), 1992–1999 (1993)
273. I.M. Klotz, J.S. Franzen, Hydrogen bonds between model peptide groups in solution. *J. Am. Chem. Soc.* **84**(18), 3461–3466 (1962)
274. Z.A. Knight, K.M. Shokat, Features of selective kinase inhibitors. *Chem. Biol.* **12**(6), 621–637 (2005)
275. O. Koch, M. Bocola, G. Klebe, Cooperative effects in hydrogen-bonding of protein: a systematic analysis of crystal data using scbbase. *Proteins: Struct. Funct. Bioinform.* **61**(2), 310–317 (2005)
276. P. Koehl, H. Orland, M. Delarue, Computing ion solvation free energies using the dipolar Poisson model. *J. Phys. Chem. B* **113**(17), 5694–5697 (2009)
277. P.A. Kollman, L.C. Allen, The theory of the hydrogen bond. *Chem. Rev.* **72**(3), 283–303 (1972)
278. J. Kongsted, P. Söderhjelm, U. Ryde, How accurate are continuum solvation models for drug-like molecules? *J. Comput.-Aided Mol. Design* **23**(7), 395–409 (2009)
279. J. Korlach, P. Schwille, W.W. Webb, G.W. Feigenson, Characterization of lipid bilayer phases by confocal microscopy and fluorescence correlation spectroscopy. *Proc. Natl. Acad. Sci. USA* **96**, 8461–8466 (1999)
280. A.A. Kornyshev, A. Nitzan, Effect of overscreening on the localization of hydrated electrons. *Zeitschrift für Physikalische Chemie* **215**(6), 701–715 (2001)
281. A.A. Kornyshev, G. Sutmann, Nonlocal dielectric saturation in liquid water. *Phys. Rev. Lett.* **79**, 3435–3438 (1997)
282. V. Korobov, A. Yelkhovsky, Ionization potential of the helium atom. *Phys. Rev. Lett.* **87**(19), 193003 (2001)
283. T. Kortemme, A.V. Morozov, D. Baker, An orientation-dependent hydrogen bonding potential improves prediction of specificity and structure for proteins and protein-protein complexes. *J. Mol. Biol.* **326**, 1239–1259 (2003)

284. G.V. Kozhukh, Y. Hagihara, T. Kawakami, K. Hasegawa, H. Naiki, Y. Goto, Investigation of a peptide responsible for amyloid fibril formation of β_2 -microglobulin by achromobacter protease I. *J. Biol. Chem.* **277**(2), 1310–1315 (2002)
285. L.M. Krauss, *Fear of Physics* (Basic Books, New York, 1994)
286. S. Krishnaswamy, M.G. Rossmann, Structural refinement and analysis of mengo virus. *J. Mol. Biol.* **211**, 803–844 (1990)
287. J. Kroon, J.A. Kanters, J.G.C.M. van Duijneveldt-van De, F.B. van Rijdt, J.A. Vliegthart Duijneveldt, O-H · · O hydrogen bonds in molecular crystals a statistical and quantum-chemical analysis. *J. Mol. Struct.* **24**, 109–129 (1975)
288. M.F. Kropman, H.J. Bakker, Dynamics of water molecules in aqueous solvation shells. *Science* **291**(5511), 2118–2120 (2001)
289. S. Kumar, R. Nussinov, Salt bridge stability in monomeric proteins. *J. Mol. Biol.* **293**(5), 1241–1255 (1999)
290. S. Kumar, R. Nussinov, Relationship between ion pair geometries and electrostatic strengths in proteins. *Biophys. J.* **83**(3), 1595–1612 (2002)
291. W. Kunz, *Specific Ion Effects* (World Scientific Pub Co Inc., Singapore, 2010)
292. J. Kyte, R.F. Doolittle, A simple method for displaying the hydropathic character of a protein. *J. Mol. Biol.* **157**, 105–132 (1982)
293. L.D. Landau, E.M. Lifshitz, *Fluid mechanics, in Course of Theoretical Physics*, vol. 6 (Buterworth-Heineman, Oxford, 1987)
294. I. Langmuir, The arrangement of electrons in atoms and molecules. *J. Am. Chem. Soc.* **41**(6), 868–934 (1919)
295. P.I. Lario, A. Vrieling, Atomic resolution density maps reveal secondary structure dependent differences in electronic distribution. *J. Am. Chem. Soc.* **125**, 12787–12794 (2003). doi:[10.1021/ja0289954](https://doi.org/10.1021/ja0289954)
296. R.A. Laskowski, M.W. MacArthur, D.S. Moss, J.M. Thornton, Procheck: a program to check the stereochemical quality of protein structures. *J. Appl. Crystallogr.* **26**(2), 283–291 (1993)
297. W.M. Latimer, W.H. Rodebush, Polarity and ionization from the standpoint of the Lewis theory of valence. *J. Am. Chem. Soc.* **42**, 1419–1433 (1920). doi:[10.1021/ja01452a015](https://doi.org/10.1021/ja01452a015)
298. C. Laurence, M. Berthelot, Observations on the strength of hydrogen bonding. *Perspect. Drug Discov. Design* **18**, 3960 (2000)
299. E. Lax, *The mold in Dr. The Story of the Penicillin Miracle* ((Macmillan, Florey's Coat, 2004)
300. A. Leaver-Fay, Y. Liu, J. Snoeyink, X. Wang, Faster placement of hydrogens in protein structures by dynamic programming. *J. Exp. Algorithmics* **12**, 2.5:1–2.5:16 (2008)
301. D.N. LeBard, D.V. Matyushov, Ferroelectric hydration shells around proteins: electrostatics of the protein-water interface. *J. Phys. Chem. B* **114**(28), 9246–9258 (2010)
302. B. Lee, F.M. Richards, The interpretation of protein structures: estimation of static accessibility. *J. Mol. Biol.* **55**, 379–400 (1971)
303. E.C. Lee, B.H. Hong, J.Y. Lee, J.C. Kim, D. Kim, Y. Kim, P. Tarakeshwar, K.S. Kim, Substituent effects on the edge-to-face aromatic interactions. *J. Am. Chem. Soc.* **127**(12), 4530–4537 (2005)
304. J. Lehmann, Physico-chemical constraints connected with the coding properties of the genetic system. *J. Theor. Biol.* **202**(2), 129–144 (2000)
305. S. Leikin, A.A. Kornyshev, Theory of hydration forces. Nonlocal electrostatic interaction of neutral surfaces. *J. Chem. Phys.* **92**(6), 6890–6898 (1990)
306. P.A. Leland, K.E. Staniszewski, C. Park, B.R. Kelemen, R.T. Raines, The ribonucleolytic activity of angiogenin. *Biochemistry* **41**(4), 1343–1350 (2002)
307. M. Levitt, A simplified representation of protein conformations for rapid simulation of protein folding. *J. Mol. Biol.* **104**, 59–107 (1976)
308. M. Levitt, M.F. Perutz, Aromatic rings act as hydrogen bond acceptors. *J. Mol. Biol.* **201**, 751–754 (1988)
309. Y. Levy, J.N. Onuchic, Water and proteins: a love-hate relationship. *Proc. Natl. Acad. Sci. USA* **101**(10), 3325–3326 (2004)
310. G.N. Lewis, The atom and the molecule. *J. Am. Chem. Soc.* **38**(4), 762–785 (1916)
311. H. Li, A.D. Robertson, J.H. Jensen, Very fast empirical prediction and rationalization of protein pK_a values. *Proteins-Struct. Funct. Bioinform.* **61**(4), 704–721 (2005)
312. Y. Li, H. Li, F. Yang, S.J. Smith-Gill, R.A. Mariuzza, X-ray snapshots of the maturation of an antibody response to a protein antigen. *Nat. Struct. Mol. Biol.* **10**, 482–488 (2003). doi:[10.1038/nsb930](https://doi.org/10.1038/nsb930)
313. L. Limozin, E. Sackmann, Polymorphism of cross-linked actin networks in giant vesicles. *Phys. Rev. Lett.* **89**(16), 168103 (2002)

314. M. Lisal, J. Kolafa, I. Nezbeda, An examination of the five-site potential (TIP5P) for water. *J. Chem. Phys.* **117**, 8892–8897 (2002)
315. S.J. Littler, S.J. Hubbard, Conservation of orientation and sequence in protein domain-domain interactions. *J. Mol. Biol.* **345**(5), 1265–1279 (2005)
316. B.A. Liu, K. Jablonowski, M. Raina, M. Arcé, T. Pawson, P.D. Nash, The human and mouse complement of SH2 domain proteins - establishing the boundaries of phosphotyrosine signaling. *Mol. Cell* **22**(6), 851–868 (2006)
317. J. Liu, L.R. Scott, A. Fernández, Interactions of aligned nearest neighbor protein side chains. *J. Bioinform. Comput. Biol.* **7** (2006) (submitted)
318. J.-L. Liu, B. Eisenberg, Poisson-fermi model of single ion activities in aqueous solutions. *Chem. Phys. Lett.* **637**, 1–6 (2015)
319. K. Liu, M.G. Brown, C. Carter, R.J. Saykally, J.K. Gregory, D.C. Clary, Characterization of a cage form of the water hexamer. *Nature* **381**, 501–503 (1996)
320. L. Lo Conte, C. Chothia, J. Janin, The atomic structure of protein-protein recognition sites. *Mol. Biol.* **285**, 2177–2198 (1999)
321. V.V. Loladze, G.I. Makhatazde, Energetics of charge-charge interactions between residues adjacent in sequence. *Proteins: Struct. Funct. Bioinform.* **79**(12), 3494–3499 (2011)
322. F. London, Zur Theorie und Systematik der Molekularkräfte. *Zeitschrift für Physik A Hadrons and Nuclei* **63**, 245–279 (1930). doi:[10.1007/BF01421741](https://doi.org/10.1007/BF01421741)
323. S.C. Lovell, J.M. Word, J.S. Richardson, D.C. Richardson, The penultimate rotamer library. *Proteins: Struct. Funct. Genet.* **40**, 389–408 (2000)
324. H. Lu, L. Lu, J. Skolnick, MULTIPROSPECTOR: an algorithm for the prediction of protein-protein interactions by multimeric threading. *Proteins: Struct. Funct. Genet.* **49**, 350–364 (2002)
325. P. Luo, R.L. Baldwin, Interaction between water and polar groups of the helix backbone: an important determinant of helix propensities. *Proc. Natl. Acad. Sci. USA* **96**(9), 4930–4935 (1999)
326. B. Ma, T. Elkayam, H. Wolfson, R. Nussinov, Protein-protein interactions: structurally conserved residues distinguish between binding sites and exposed protein surfaces. *Proc. Natl. Acad. Sci. USA* **100**(10), 5772–5777 (2003)
327. J.C. Ma, D.A. Dougherty, The cation- π interaction. *Chem. Rev.* **97**(5), 1303–1324 (1997)
328. M.W. MacArthur, J.M. Thornton, Deviations from planarity of the peptide bond in peptides and proteins. *J. Mol. Biol.* **264**(5), 1180–1195 (1996)
329. J.D. Madura, J.M. Briggs, R.C. Wade, M.E. Davis, B.A. Luty, A. Ilin, J. Antosiewicz, M.K. Gilson, B. Bagheri, L.R. Scott, J.A. McCammon, Electrostatics and diffusion of molecules in solution: simulations with the University of Houston Brownian dynamics program. *Comput. Phys. Commun.* **91**, 57–95 (1995)
330. M.W. Mahoney, W.L. Jorgensen, A five-site model for liquid water and the reproduction of the density anomaly by rigid, nonpolarizable potential functions. *J. Chem. Phys.* **112**, 8910–8922 (2000)
331. M. Maleki, M.M. Aziz, L. Rueda, Analysis of obligate and non-obligate complexes using desolvation energies in domain-domain interactions, in *Proceedings of the Tenth International Workshop on Data Mining in Bioinformatics* (ACM, 2011), p. 2
332. R.J. Mallis, K.N. Brazin, D.B. Fulton, A.H. Andreotti, Structural characterization of a proline-driven conformational switch within the Itk SH2 domain. *Nat. Struct. Biol.* **9**, 900–905 (2002)
333. N. Mandel, G. Mandel, B.L. Trus, J. Rosenberg, G. Carlson, R.E. Dickerson, Tuna cytochrome c at 2.0Å resolution. III. Coordinate optimization and comparison of structures. *J. Biol. Chem.* **252**(13), 4619–4636 (1977)
334. K. Manikandan, S. Ramakumar, The occurrence of C-H...O hydrogen bonds in α -helices and helix termini in globular proteins. *Proteins: Struct. Funct. Bioinform.* **56**(4), 768–781 (2004)
335. R. Mannhold, G.I. Poda, C. Ostermann, I.V. Tetko, Calculation of molecular lipophilicity: state-of-the-art and comparison of log P methods on more than 96,000 compounds. *J. Pharm. Sci.* **98**(3), 861–893 (2009)
336. P.E. Mason, G.W. Neilson, C.E. Dempsey, A.C. Barnes, J.M. Cruickshank, The hydration structure of guanidinium and thiocyanate ions: implications for protein stability in aqueous solution. *Proc. Natl. Acad. Sci. USA* **100**(8), 4557–4561 (2003)
337. C. Matzler, U. Wegmuller, Dielectric properties of freshwater ice at microwave frequencies. *J. Phys. D: Appl. Phys.* **20**(12), 1623–1630 (1987)
338. B. McCoy, T.T. Wu, *The Two-Dimensional Ising Model* (Harvard University Press, Harvard, 1973)
339. I.K. McDonald, J.M. Thornton, Satisfying hydrogen bonding potential in proteins. *J. Mol. Biol.* **238**, 777–793 (1994)

340. L.P. McIntosh, G. Hand, P.E. Johnson, M.D. Joshi, M. Körner, L.A. Plesniak, L. Ziser, W.W. Wakarchuk, S.G. Withers, The pK_a of the general acid/base carboxyl group of a glycosidase cycles during catalysis: a ^{13}C -NMR study of bacillus circulans xylanase. *Biochemistry* **35**(12), 9958–9966 (1996)
341. V.J. McParland, A.P. Kalverda, S.W. Homans, S.E. Radford, Structural properties of an amyloid precursor of beta(2)-microglobulin. *Nat. Struct. Biol.* **9**(5), 326–331 (2002)
342. C. Mead, L. Conway, *Introduction to VLSI Systems* (Addison-Wesley, Reading, 1979)
343. S. Mecozzi, A.P. West, D.A. Dougherty, Cation- π interactions in aromatics of biological and medicinal interest: electrostatic potential surfaces as a useful qualitative guide. *Proc. Natl. Acad. Sci. USA* **93**(20), 10566–10571 (1996)
344. E.L. Mehler, F. Guarnieri, A self-consistent, microenvironment modulated screened Coulomb potential approximation to calculate pH-dependent electrostatic effects in proteins. *Biophys. J.* **77**, 3–22 (1999)
345. I. Mihalek, I. Reš, O. Lichtarge, On itinerant water molecules and detectability of protein-protein interfaces through comparative analysis of homologues. *J. Mol. Biol.* **369**(2), 584–595 (2007)
346. C. Millot, A.J. Stone, Towards an accurate intermolecular potential for water. *Mol. Phys.* **77**(3), 439–462 (1992)
347. D.J. Mitchell, L. Steinman, D.T. Kim, C.G. Fathman, J.B. Rothbard, Polyarginine enters cells more efficiently than other polycationic homopolymers. *J. Pept. Res.* **56**(5), 318–325 (2000)
348. J.B.O. Mitchell, J. Smith, D-amino acid residues in peptides and proteins. *Proteins: Struct. Funct. Genet.* **50**(4), 563–571 (2003)
349. S. Miyazawa, R.L. Jernigan, Estimation of effective interresidue contact energies from protein crystal structures: quasi-chemical approximation. *Macromolecules* **18**(3), 534–552 (1985)
350. D.L. Mobley, A.E. Barber, C.J. Fennell, K.A. Dill, Charge asymmetries in hydration of polar solutes. *J. Phys. Chem. B* **112**(8), 2405–2414 (2008)
351. A. Möglich, F. Krieger, T. Kiefhaber, Molecular basis for the effect of urea and guanidinium chloride on the dynamics of unfolded polypeptide chains. *J. Mol. Biol.* **345**(1), 153–162 (2005)
352. C. Momany, L.C. Kovari, A.J. Prongay, W. Keller, R.K. Gitti, B.M. Lee, A.E. Gorbalenya, L. Tong, J. McClure, L.S. Ehrlich, M.F. Carter, M.G. Rossmann, Crystal structure of dimeric HIV-1 capsid protein. *Nat. Struct. Biol.* **3**, 763–770 (1996)
353. F.A. Momany, R.F. McGuire, A.W. Burgess, H.A. Scheraga, Energy parameters in polypeptides. VII. Geometric parameters, partial atomic charges, nonbonded interactions, hydrogen bond interactions, and intrinsic torsional potentials for the naturally occurring amino acids. *J. Phys. Chem.* **79**(22), 2361–2381 (1975)
354. J. Montes de Oca, A. Rodriguez Fris, G. Appignanesi, A. Fernández, Productive induced metastability in allosteric modulation of kinase function. *FEBS J.* **281**(13), 3079–3091 (2014)
355. A.V. Morozov, T. Kortemme, K. Tsemekhman, D. Baker, Close agreement between the orientation dependence of hydrogen bonds observed in protein structures and quantum mechanical calculations. *Proc. Natl. Acad. Sci. USA* **101**, 6946–6951 (2004)
356. J.A. Morrill, R. MacKinnon, Isolation of a single carboxyl-carboxylate proton binding site in the pore of a cyclic nucleotide-gated channel. *J. Gen. Physiol.* **114**(1), 71–84 (1999)
357. R. Moss, A. Fernández, Inhibition of MyBP-C binding to myosin as a treatment for heart failure (2015)
358. D.W. Mount, *Bioinformatics* (Cold Spring Harbor Laboratory Press, 2001)
359. A.S. Muresan, H. Diamant, K.-Y. Lee, Effect of temperature and composition on the formation of nanoscale compartments in phospholipid membranes. *J. Am. Chem. Soc.* **123**, 6951–6952 (2001)
360. R. Nelson, M.R. Sawaya, M. Balbirnie, A.O. Madsen, C. Riekel, R. Grothe, D. Eisenberg, Structure of the cross- β spine of amyloid-like fibrils. *Nature* **435**, 773–778 (2005). doi:10.1038/nature03680
361. G. Némethy, I.Z. Steinberg, H.A. Scheraga, Influence of water structure and of hydrophobic interactions on the strength of side-chain hydrogen bonds in proteins. *Biopolymers* **1**, 43–69 (1963)
362. A. Neumeister, N. Praschak-Rieder, B. Hesselmann, O. Vitouch, M. Rauh, A. Barocka, J. Tauscher, S. Kasper, Effects of tryptophan depletion in drug-free depressed patients who responded to total sleep deprivation. *Arch. Gen. Psychiatry* **55**(2), 167–172 (1998)
363. A. Nicholls, K.A. Sharp, B. Honig, Protein folding and association: insights from the interfacial and thermodynamic properties of hydrocarbons. *Proteins: Struct. Funct. Genet.* **11**(4), 281–296 (1991)
364. K.T. No, O.Y. Kwon, S.Y. Kim, M.S. Jhon, H.A. Scheraga, A simple functional representation of angular-dependent hydrogen-bonded systems. 1. Amide, carboxylic acid, and amide-carboxylic acid pairs. *J. Phys. Chem.* **99**, 3478–3486 (1995)
365. M.E.M. Noble, J.A. Endicott, L.N. Johnson, Protein kinase inhibitors: insights into drug design from structure. *Science* **303**(5665), 1800–1805 (2004)
366. I.M.A. Nooren, J.M. Thornton, Diversity of protein-protein interactions. *EMBO J.* **22**, 3486–3492 (2003)

367. I.M.A. Nooren, J.M. Thornton, Structural characterisation and functional significance of transient protein-protein interactions. *J. Mol. Biol.* **325**(5), 991–1018 (2003)
368. M. Novotny, G.J. Kleywegt, A survey of left-handed helices in protein structures. *J. Mol. Biol.* **347**(2), 231–241 (2005)
369. Y. Nozaki, C. Tanford, The solubility of amino acids and two glycine peptides in aqueous ethanol and dioxane solutions. *J. Biol. Chem.* **246**(7), 2211–2217 (1971)
370. Y. Ofren, B. Rost, Analysing six types of protein-protein interfaces. *J. Mol. Biol.* **335**, 377–387 (2003)
371. D.O. Omecinsky, K.E. Holub, M.E. Adams, M.D. Reily, Three-dimensional structure analysis of μ -agatoxins: further evidence for common motifs among neurotoxins with diverse ion channel specificities. *Biochemistry* **35**(9), 2836–2844 (1996)
372. T. Ooi, Thermodynamics of protein folding: effects of hydration and electrostatic interactions. *Adv. Biophys.* **30**, 105–154 (1994)
373. T. Orlova, L.R. Scott, The role of solvation in hydrogen bond geometry in protein helices. Research Report UC/CS TR-2016-? Department of Computer Science, University Chicago, 2016
374. D.R. Owen, *A First Course in the Mathematical Foundations of Thermodynamics* (Springer, Berlin, 1984)
375. C.N. Pace, G.R. Grimsley, J.M. Scholtz, Protein ionizable groups: pK values and their contribution to protein stability and solubility. *J. Biol. Chem.* **284**(20), 13285–13289 (2009)
376. C.N. Pace, S. Treviño, E. Prabhakaran, J.M. Scholtz, Protein structure, stability and solubility in water and other solvents. *Philos. Trans. R. Soc. B: Biol. Sci.* **359**(1448), 1225–1235 (2004)
377. D. Pahlke, D. Leitner, U. Wiedemann, D. Labudde, COPS-cis/trans peptide bond conformation prediction of amino acids on the basis of secondary structure information. *Bioinformatics* **21**(5), 685–686 (2005)
378. S.K. Pal, J. Peon, A.H. Zewail, Biological water at the protein surface: dynamical solvation probed directly with femtosecond resolution. *Proc. Natl. Acad. Sci. USA* **99**(4), 1763–1768 (2002)
379. P. Paricaud, M. Předota, A.A. Chialvo, P.T. Cummings, From dimer to condensed phases at extreme conditions: accurate predictions of the properties of water by a Gaussian charge polarizable model. *JChemPhys* **122**, 244511 (2005)
380. W. Pauli, The connection between spin and statistics. *Phys. Rev.* **58**(8), 716–722 (1940)
381. W. Pauli, *Thermodynamics and the Kinetic Theory of Gases* (Dover, New York, 2000)
382. L. Pauling, *Nature of the Chemical Bond*, 3rd edn. (Cornell University Press, Ithaca, 1960)
383. L. Pauling, *General Chemistry* (Dover, New York, 1970)
384. L. Pauling, R.B. Corey, H.R. Branson, The structure of proteins: two hydrogen-bonded helical configurations of the polypeptide chain. *Proc. Natl. Acad. Sci. USA* **37**(4), 205–211 (1951)
385. L. Pauling, E.B. Wilson, *Introduction to Quantum Mechanics with Applications to Chemistry* (Dover, New York, 1985)
386. J. Pavlicek, S.L. Coon, S. Ganguly, J.L. Weller, S.A. Hassan, D.L. Sackett, D.C. Klein, Evidence that proline focuses movement of the floppy loop of Arylalkylamine N-Acetyltransferase (EC 2.3.1.87). *J. Biol. Chem.* **283**(21), 14552–14558 (2008)
387. M.Y. Pavlov, R.E. Watts, Z. Tan, V.W. Cornish, M. Ehrenberg, A.C. Forster, Slow peptide bond formation by proline and other n-alkylamino acids in translation. *Proc. Natl. Acad. Sci.* **106**(1), 50–54 (2009)
388. G. Pei, T.M. Laue, A. Aulabaugh, D.M. Fowlkes, B.R. Lentz, Structural comparisons of meizothrombin and its precursor prothrombin in the presence or absence of procoagulant membranes. *Biochemistry* **31**, 6990–6996 (1992)
389. J.K. Percus, *Kinetic Theory and Statistical Mechanics* (University Courant Institute of Mathematical Sciences, New York, 1970)
390. S. Persson, J.A. Killian, G. Lindblom, Molecular ordering of interfacially localized tryptophan analogs in ester- and ether-lipid bilayers studied by ^2H -NMR. *Biophys. J.* **75**(3), 1365–1371 (1998)
391. M.F. Perutz, The role of aromatic rings as hydrogen-bond acceptors in molecular recognition. *Philos. Trans. R. Soc. A* **345**(1674), 105–112 (1993)
392. D. Petrey, B. Honig, Free energy determinants of tertiary structure and the evaluation of protein models. *Protein Sci.* **9**(11), 2181–2191 (2000)
393. G.A. Petsko, D. Ringe, *Protein Structure and Function* (New Science Press, London, 2004)
394. M. Petukhov, D. Cregut, C.M. Soares, L. Serrano, Local water bridges and protein conformational stability. *Protein Sci.* **8**, 1982–1989 (1999)
395. A. Pierucci-Lagha, R. Feinn, V. Modesto-Lowe, R. Swift, M. Nellissery, J. Covault, H.R. Kranzler, Effects of rapid tryptophan depletion on mood and urge to drink in patients with co-morbid major depression and alcohol dependence. *Psychopharmacology* **171**(3), 340–348 (2004)

396. N. Pietrosevoli, A. Crespo, A. Fernández, Dehydration propensity of order-disorder intermediate regions in soluble proteins. *J. Proteome Res.* **6**(9), 3519–3526 (2007)
397. G.C. Pimentel, A.L. McClellan, Hydrogen bonding. *Annu. Rev. Phys. Chem.* **22**(1), 347–385 (1971)
398. M. Planck, *Treatise on Thermodynamics* (Dover, New York, 2008)
399. L.A. Plesniak, G.P. Connelly, L.P. McIntosh, W.W. Wakarchuk, Characterization of a buried neutral histidine residue in *Bacillus circulans* xylanase: NMR assignments, pH titration, and hydrogen exchange. *Protein Sci.* **5**(11), 2319–2328 (1996)
400. E.V. Pletneva, A.T. Laederach, D.B. Fulton, N.M. Kostic, The role of cation- π interactions in biomolecular association. Design of peptides favoring interactions between cationic and aromatic amino acid side chains. *J. Am. Chem. Soc.* **123**(26), 6232–6245 (2001)
401. J.W. Ponder, F.M. Richards, Tertiary templates for proteins: use of packing criteria in the enumeration of allowed sequences for different structural classes. *J. Mol. Biol.* **193**, 775–791 (1987)
402. P.K. Ponnuswamy, M. Prabhakaran, P. Manavalan, Hydrophobic packing and spatial arrangement of amino acid residues in globular proteins. *Biochim. Biophys. Acta (BBA) - Protein. Structure* **623**(2), 301–316 (1980)
403. P. Popelier, *Atoms in Molecules* (Prentice-Hall, Harlow, 2000)
404. C.J. Preston, *Gibbs States on Countable Sets* (Cambridge University Press, Cambridge, 2008)
405. M.J. Previs, S. Beck Previs, J. Gulick, J. Robbins, D.M. Warshaw, Molecular mechanics of cardiac myosin-binding protein C in native thick filaments. *Science* **337**(6099), 1215–1218 (2012)
406. S.B. Prusiner, Prions. *Proc. Natl. Acad. Sci. USA* **95**(23), 13363–13383 (1998)
407. J. Qian, N.M. Luscombe, M. Gerstein, Protein family and fold occurrence in genomes: power-law behaviour and evolutionary model. *J. Mol. Biol.* **313**(4), 673–681 (2001)
408. S. Radaev, P. Sun, Recognition of immunoglobulins by $Fc\gamma$ receptors. *Mol. Immunol.* **38**(14), 1073–1083 (2002)
409. D. Rajamani, S. Thiel, S. Vajda, C.J. Camacho, Anchor residues in protein-protein interactions. *Proc. Natl. Acad. Sci. USA* **101**, 11287–11292 (2004)
410. C. Ramakrishnan, Ramachandran and his map. *Resonance* 48–56 (2001)
411. C. Ramakrishnan, G.N. Ramachandran, Stereochemical criteria for polypeptide and protein chain conformations. II Allowed conformations for a pair of peptide units. *Biophys. J.* **5**, 909–933 (1965)
412. R. Ramesh, *Thin Film Ferroelectric Materials and Devices* (Kluwer Academic Publishers, Boston, 1997)
413. J.J. Ramsden, Review of optical methods to probe protein adsorption at solid-liquid interfaces. *J. Stat. Phys.* **73**, 853–877 (1993)
414. J.B. Rauch, L.R. Scott, The electrostatics of periodic crystals. to appear (2017)
415. S.W. Rick, R.E. Cachau, The nonplanarity of the peptide group: molecular dynamics simulations with a polarizable two-state model for the peptide bond. *J. Chem. Phys.* **112**(11), 5230–5241 (2000)
416. R. Riek, G. Wider, M. Billeter, S. Hornemann, R. Glockshuber, K. Wuthrich, Prion protein NMR structure and familial human spongiform encephalopathies. *Proc. Natl. Acad. Sci. USA* **95**(20), 11667–11672 (1998)
417. D. Ringe, What makes a binding site a binding site? *Curr. Opin. Struct. Biol.* **5**, 825–829 (1995)
418. G.G. Roberts (ed.), *Langmuir-Blodgett Films* (Plenum Press, New York, 1990)
419. D. Robinson, T. Bertrand, J.-C. Carry, F. Halley, A. Karlsson, M. Mathieu, H. Minoux, M.-A. Perrin, B. Robert, L. Schio, W. Sherman, Differential water thermodynamics determine PI3K-Beta/Delta selectivity for solvent-exposed ligand modifications. *J. Chem. Inf. Modeling* 0(0):null, 0. PMID: 27144736
420. D.D. Robinson, W. Sherman, R. Farid, Understanding kinase selectivity through energetic analysis of binding site waters. *ChemMedChem* **5**(4), 618–627 (2010)
421. C. Rodriguez-Aguayo, P. Vivas-Mejia, J.M. Benito, A. Fernandez, F.-X. Claret, A. Chavez-Reyes, A.K. Sood, G. Lopez-Berestein, JNK-1 inhibition leads to antitumor activity in ovarian cancer. *Cancer Res.* **70**(8 Supplement), 5468–5468 (2010)
422. J. Römer, T.H. Bugge, L.R. Lund, M.J. Flick, J.L. Degen, K. Danò, Impaired wound healing in mice with a disrupted plasminogen gene. *Nat. Med.* **2**(3), 287–292 (1996)
423. M. Rooman, J. Liévin, E. Buisine, R. Wintjens, Cation- π /H-bond stair motifs at protein-DNA interfaces. *J. Mol. Biol.* **319**, 6776 (2002)
424. P.C. Rosas, Y. Liu, M. Abdalla, C. Thomas, D. Kidwell, R. Kumar, K. Baker, B. Patel, C. Warrens, R. Solaro et al., Phosphorylated cardiac myosin binding protein-c enhances lusitropy. *J. Am. Coll. Cardiol.* **12**(63), A871 (2014)
425. B. Roux, T. Simonson, Implicit solvent models. *Biophys. Chem.* **78**(1), 1–20 (1999)
426. D. Ruell, *Thermodynamic Formalism: The Mathematical Structures of Classical Equilibrium Statistical Mechanics* (Addison-Wesley, Reading, 1978)
427. D. Ruell, *Statistical Mechanics: Rigorous Results* (Addison-Wesley, Reading, 1989)

428. S. Samsonov, J. Teyra, M.T. Pisabarro, A molecular dynamics approach to study the importance of solvent in protein interactions. *Proteins: Struct. Funct. Bioinform.* **73**(2), 515–525 (2008)
429. R. Samudrala, M. Levitt, Decoys RUs: a database of incorrect conformations to improve protein structure prediction. *Protein Sci.* **9**(07), 1399–1401 (2000)
430. L. Sandberg, R. Casemyr, O. Edholm, Calculated hydration free energies of small organic molecules using a nonlinear dielectric continuum model. *J. Phys. Chem. B* **106**(32), 7889–7897 (2002)
431. L. Sandberg, O. Edholm, Nonlinear response effects in continuum models of the hydration of ions. *J. Chem. Phys.* **116**, 2936–2944 (2002)
432. R.T. Sanderson, Electronegativity and bond energy. *J. Am. Chem. Soc.* **105**, 2259–2261 (1983)
433. J.L.R. Santos, R. Aparicio, I. Joeques, J.L. Silva, J.A.C. Bispo, C.F.S. Bonafe, Different urea stoichiometries between the dissociation and denaturation of tobacco mosaic virus as probed by hydrostatic pressure. *Biophys. Chem.* **134**(3), 214–224 (2008)
434. B. Santra, J. Klimeš, D. Alfè, A. Tkatchenko, B. Slater, A. Michaelides, R. Car, M. Scheffler, Hydrogen bonds and van der Waals forces in ice at ambient and high pressures. *Phys. Rev. Lett.* **107**(18), 185701 (2011)
435. C.F. Sanz-Navarro, R. Grima, A. García, E.A. Bea, A. Soba, J.M. Cela, P. Ordejón, An efficient implementation of a QM-MM method in SIESTA. *Theor. Chem. Acc.* **128**(4–6), 825–833 (2011)
436. V. Sasisekharan, Stereochemical criteria for polypeptide and protein structures, in *Collagen* (Wiley, New York, 1962), pp. 39–78
437. A.J. Saunders, G.B. Young, G.J. Pielak, Polarity of disulfide bonds. *Protein Sci.* **2**(7), 1183–1184 (1993)
438. L. Sawyer, M.N.G. James, Carboxyl-carboxylate interactions in proteins. *Nature* **295**, 79–80 (1982). doi:10.1038/295079a0
439. J.A. Schellman, Fifty years of solvent denaturation. *Biophys. Chem.* **96**(2–3), 91–101 (2002)
440. J.M. Scholtz, D. Barrick, E.J. York, J.M. Stewart, R.L. Baldwin, Urea unfolding of peptide helices as a model for interpreting protein unfolding. *Proc. Natl. Acad. Sci. USA* **92**(1), 185–189 (1995)
441. I. Schomburg, A. Chang, C. Ebeling, M. Gremse, C. Heldt, G. Huhn, D. Schomburg, BRENDA, the enzyme database: updates and major new developments. *Nucl. Acids Res.* **32**(database issue), D431–433 (2004)
442. E. Schrodinger, *Statistical Thermodynamics* (Dover, New York, 1989)
443. L. Schwartz, *Théorie des Distributions* (Hermann, Paris, 1966)
444. L.R. Scott, T.W. Clark, B. Bagheri, *Scientific Parallel Computing* (Princeton University Press, Princeton, 2005)
445. L.R. Scott, Nonstandard dielectric response. Research Report UC/CS TR-2010-06, Department of Computer Science, University Chicago, 2010
446. L.R. Scott, The impact of wrapping on sidechain-mainchain hydrogen bonds. Research Report UC/CS TR-2017-3, Department of Computer Science, University Chicago, 2017
447. L.R. Scott, M. Boland, K. Rogale, A. Fernández, Continuum equations for dielectric response to macromolecular assemblies at the nano scale. *J. Phys. A: Math. Gen.* **37**, 9791–9803 (2004)
448. L.R. Scott, Y. Jiang, X. Dexuan, Comparison of a nonlocal dielectric model with a discontinuous model. Research Report UC/CS TR-2015-06, Department of Computer Science, University Chicago, 2015
449. L.R. Scott, T. Orlova, M. Golubitsky, Parameterizations of hydrogen bond quality. Research Report UC/CS to appear, Department of Computer Science, University Chicago, 2017
450. L.R. Scott, A. Fernández Stigliano, A disruptive dipole-dipole alignment promotes a stable molecular association. Research Report UC/CS TR-2013-10, Department of Computer Science, University Chicago, 2013
451. R. Scott, Finite element convergence for singular data. *Numer. Math.* **21**, 317–327 (1973)
452. R. Scott, Optimal L^∞ estimates for the finite element method on irregular meshes. *Math. Comput.* **30**, 681–697 (1976)
453. J. Seelig, A. Seelig, Lipid conformation in model membranes and biological membranes. *Q. Rev. Biophys.* **13**(1), 19–61 (1980)
454. Z. Shi, C.A. Olson, N.R. Kallenbach, Cation- π interaction in model α -helical peptides. *J. Am. Chem. Soc.* **124**(13), 3284–3291 (2002)
455. Z. Shi, K. Chen, Z. Liu, T.R. Sosnick, N.R. Kallenbach, PII structure in the model peptides for unfolded proteins - studies on ubiquitin fragments and several alanine-rich peptides containing QQQ, SSS, FFF, and VVV. *Proteins - Struct. Funct. Bioinform.* **63**(2), 312–321 (2006)
456. K. Shimomura, T. Fukushima, T. Danno, K. Matsumoto, M. Miyoshi, Y. Kowa, Inhibition of intestinal absorption of phenylalanine by phenylalaninol. *J. Biochem.* **78**(2), 269–275 (1975)
457. H. Shull, G.G. Hall, Atomic units. *Nature* **184**, 1559–1560 (1959). doi:10.1038/1841559a0

458. M.B. Sierra, S.R. Accordino, J.A. Rodriguez-Fris, M.A. Morini, G.A. Appignanesi, A. Fernández, Stigliano, Protein packing defects “heat up” interfacial water. *Eur. Phys. J. E* **36**(6), 1–8 (2013)
459. A. Singer, Z. Schuss, R.S. Eisenberg, Attenuation of the electric potential and field in disordered systems. *J. Stat. Phys.* **119**(5–6), 1397–1418 (2005)
460. U.C. Singh, P.A. Kollman, A water dimer potential based on ab initio calculations using Morokuma component analyses. *J. Chem. Phys.* **83**(8), 4033–4040 (1985)
461. N. Sinha, S. Mohan, C.A. Lipschultz, S.J. Smith-Gill, Differences in electrostatic properties at antibody-antigen binding sites: implications for specificity and cross-reactivity. *Biophys. J.* **83**(6), 2946–2968 (2002)
462. O. Sipahioglu, S.A. Barringer, I. Taub, A.P.P. Yang, Characterization and modeling of dielectric properties of turkey meat. *J. Food Sci.* **68**(2), 521–527 (2003)
463. G.R. Smith, M.J. Sternberg, Prediction of protein-protein interactions by docking methods. *Curr. Opin. Struct. Biol.* **12**, 28–35 (2002)
464. J.D. Smith, C.D. Cappa, K.R. Wilson, B.M. Messer, R.C. Cohen, R.J. Saykally, Energetics of hydrogen bond network rearrangements in liquid water. *Science* **306**, 851–853 (2004)
465. P. Sondermann, R. Huber, V. Oosthuizen, U. Jacob, The 3.2-Å crystal structure of the human IgG1 Fc fragment-Fc γ RIII complex. *Nature* **406**, 267–273 (2000)
466. A.K. Soper, K. Weckström, Ion solvation and water structure in potassium halide aqueous solutions. *Biophys. Chem.* **124**(3), 180–191 (2006)
467. B.J. Stapley, T.P. Creamer, A survey of left-handed polyproline II helices. *Protein Sci.* **8**, 587–595 (1999)
468. T. Steiner, Competition of hydrogen-bond acceptors for the strong carboxyl donor. *Acta Crystallogr. Sect. B* **57**(1), 103–106 (2001)
469. T. Steiner, G. Koellner, Hydrogen bonds with π -acceptors in proteins: frequencies and role in stabilizing local 3D structures. *J. Mol. Biol.* **305**(3), 535–557 (2001)
470. D.F. Stickle, L.G. Presta, K.A. Dill, G.D. Rose, Hydrogen bonding in globular proteins. *J. Mol. Biol.* **226**(4), 1143–1159 (1992)
471. A. Fernández Stigliano, *Biomolecular Interfaces: Interactions, Functions and Drug Design* (Springer, Berlin, 2015)
472. A.J. Stone, Distributed multipole analysis, or how to describe a molecular charge distribution. *Chem. Phys. Lett.* **83**(2), 233–239 (1981)
473. A.J. Stone, *The Theory of Intermolecular Forces* (Oxford University Press, USA, 1997)
474. A.J. Stone, M. Alderton, Distributed multipole analysis: methods and applications. *Mol. Phys.* **56**(5), 1047–1064 (1985)
475. K. Subramanian, S. Lakshmi, K. Rajagopalan, G. Koellner, T. Steiner, Cooperative hydrogen bond cycles involving O-H $\cdots\pi$ and C-H \cdots O hydrogen bonds as found in a hydrated dialkyne. *J. Mol. Struct.* **384**(2–3), 121–126 (1996)
476. P.A. Suci, G.G. Geesey, Comparison of adsorption behavior of two mytilus edulis foot proteins on three surfaces. *Coll. Surf. B Biointerfaces* **22**, 159–168 (2001)
477. S. Sudarsanam, S. Srinivasan, Sequence-dependent conformational sampling using a database of ϕ_{i+1} and ψ_i angles for predicting polypeptide backbone conformations. *Protein Eng.* **10**(10), 1155–1162 (1997)
478. M. Sundd, N. Iverson, B. Ibarra-Molero, J.M. Sanchez-Ruiz, A.D. Robertson, Electrostatic interactions in ubiquitin: stabilization of carboxylates by lysine amino groups. *Biochemistry*, 7586–7596 (2002)
479. A. Szabo, N.S. Ostlund (eds.), *Modern Quantum Chemistry* (Dover, New York, 1996)
480. I. Szalai, S. Nagy, S. Dietrich, Nonlinear dielectric effect of dipolar fluids. *J. Chem. Phys.* **131**, 154905 (2009)
481. C. Tanford, *Hydrophobic Effect* (Wiley, New York, 1973)
482. C. Tanford, J. Reynolds, *Nature’s Robots, a History of Proteins* (Oxford University Press, Oxford, 2001)
483. R. Taylor, O. Kennard, Hydrogen-bond geometry in organic crystals. *Acc. Chem. Res.* **17**(9), 320–326 (1984)
484. C.J. Thompson *Mathematical Statistical Mechanics* (Macmillan, New York, 1972)
485. C.J. Thompson, *Classical Equilibrium Statistical Mechanics* (Oxford University Press, Oxford, 1988)
486. R.L. Thurlkill, G.R. Grimsley, J.M. Scholtz, C.N. Pace, Hydrogen bonding markedly reduces the pK of buried carboxyl groups in proteins. *J. Mol. Biol.* **362**(3), 594–604 (2006)
487. R.L. Thurlkill, G.R. Grimsley, J.M. Scholtz, C.N. Pace, pK_a values of the ionizable groups of proteins. *Protein Sci.* **15**(5), 1214–1218 (2006)
488. I.J. Tickle, Experimental determination of optimal root-mean-square deviations of macromolecular bond lengths and angles from their restrained ideal values. *Acta Crystallogr. Sect. D* **63**(12), 1274–1281 (2007)
489. C.E. Tognon, P.H.B. Sorensen, Targeting the insulin-like growth factor 1 receptor (IGF1R) signaling pathway for cancer therapy. *Expert Opin. Ther. Targets* **16**(1), 33–48 (2012)

490. T. Tokushima, Y. Harada, O. Takahashi, Y. Senba, H. Ohashi, L.G.M. Pettersson, A. Nilsson, S. Shin, High resolution X-ray emission spectroscopy of liquid water: the observation of two structural motifs. *Chem. Phys. Lett.* **460**(4–6), 387–400 (2008)
491. J. Tomasi, B. Mennucci, R. Cammi, Quantum mechanical continuum solvation models. *Chem. Rev.* **105**(8), 2999–3094 (2005)
492. C. Truesdell, S. Bharatha, *The Concepts and Logic of Classical Thermodynamics as a Theory of Heat Engines* (Rigorously Constructed Upon the Foundation Laid by S. Carnot and F. Reech (Springer, Berlin, 1977)
493. C.-J. Tsai, S.L. Lin, H.J. Wolfson, R. Nussinov, Studies of protein-protein interfaces: a statistical analysis of the hydrophobic effect. *Protein Sci.* **6**, 53–64 (1997)
494. J. Tsai, R. Taylor, C. Chothia, M. Gerstein, The packing density in proteins: standard radii and volumes. *J. Mol. Biol.* **290**, 253–266 (1999)
495. G.E. Uhlenbeck, L.S. Ornstein, On the theory of the Brownian motion. *Phys. Rev.* **36**(5), 823–841 (1930)
496. H. Umeda, M. Takeuchi, K. Suyama, Two new elastin cross-links having pyridine skeleton. *J. Biol. Chem.* **276**(16), 12579–12587 (2001)
497. A. Unzue, M. Xu, J. Dong, L. Wiedmer, D. Spiliotopoulos, A. Caffisch, C. Nevado, *Fragment-based design of selective nanomolar ligands of the CREBBP bromodomain* *J. Med. Chem.* (2015)
498. D.W. Urry, The gramicidin a transmembrane channel: a proposed π (L, D) helix. *Proc. Natl. Acad. Sci. USA* **68**(3), 672–676 (1971)
499. J.D. Van der Waals, *Over de Continuïteit van den Gas-en Vloeïstoestand*, vol. 1 (Sijthoff, 1873)
500. P.T. Van Duijnen, M. Swart, Molecular and atomic polarizabilities: thole's model revisited. *J. Phys. Chem. A* **102**(14), 2399–2407 (1998)
501. E. Vanden-Eijnden, J. Weare, Rare event simulation of small noise diffusions. *Commun. Pure Appl. Math.* **65**(12), 1770–1803 (2012)
502. M. Vieth, R.E. Higgs, D.H. Robertson, M. Shapiro, E.A. Gragg, H. Hemmerle, Kinomics-structural biology and chemogenomics of kinase inhibitors and targets. *Biochim. Biophys. Acta* **1697**, 243–257 (2004)
503. J.A. Vila, D.R. Ripoll, M.E. Villegas, Y.N. Vorobjev, H.A. Scheraga, Role of hydrophobicity and solvent-mediated charge-charge interactions in stabilizing alpha-helices. *Biophys. J.* **75**, 2637–2646 (1998)
504. D. Vitkup, E. Melamud, J. Moul, C. Sander, Completeness in structural genomics. *Nat. Struct. Mol. Biol.* **8**, 559–566 (2001). doi:[10.1038/88640](https://doi.org/10.1038/88640)
505. D. Voet, J.G. Voet, *Biochemistry* (Wiley, New York, 1990)
506. C. Vogel, C. Berzuini, M. Bashton, J. Gough, S.A. Teichmann, Supra-domains: evolutionary units larger than single protein domains. *J. Mol. Biol.* **336**(3), 809–823 (2004)
507. J. Von Eichborn, S. Günther, R. Preissner, Structural features and evolution of protein-protein interactions. *Genome Inf.* **22**, 1–10 (2010)
508. W.L. Wang, Y. Deng Yujie, B. Kim, L. Pierce, G. Krilov, D. Lupyan, S. Robinson, M.K. Dahlgren, J. Greenwood et al., Accurate and reliable prediction of relative ligand binding potency in prospective drug discovery by way of a modern free-energy calculation protocol and force field. *J. Am. Chem. Soc.* **137**(7), 2695–2703 (2015)
509. X. Wang, M. Bogdanov, W. Dowhan, Topology of polytopic membrane protein subdomains is dictated by membrane phospholipid composition. *EMBO J.* **21**(21), 5673–5681 (2002)
510. A. Warshel, A. Papazyan, Electrostatic effects in macromolecules: fundamental concepts and practical modeling. *Curr. Opin. Struct. Biol.* **8**, 211–217 (1998)
511. A. Warshel, Electrostatic origin of the catalytic power of enzymes and the role of preorganized active sites. *J. Biol. Chem.* **273**, 27035–27038 (1998)
512. J.D. Watson, F.H.C. Crick, Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. *Nature* **171**, 737–738 (1953)
513. G.J. Wedemayer, P.A. Patten, L.H. Wang, P.G. Schultz, R.C. Stevens, Structural insights into the evolution of an antibody combining site. *Science* **276**(5319), 1665–1669 (1997)
514. S. Weggler, V. Rutka, A. Hildebrandt, A new numerical method for nonlocal electrostatics in biomolecular simulation. *J. Comput. Phys.* **229**(11), 4059–4074 (2010)
515. A.K.H. Weiss, T.S. Hofer, B.R. Randolph, B.M. Rode, Guanidinium in aqueous solution studied by quantum mechanical charge field-molecular dynamics (QMCF-MD). *Phys. Chem. Chem. Phys.* **14**(19), 7012–7027 (2012)
516. Ph Wernet, D. Nordlund, U. Bergmann, M. Cavalleri, M. Odelius, H. Ogasawara, L.Å. Näslund, T.K. Hirsch, L. Ojamäe, P. Glatzel, L.G.M. Pettersson, A. Nilsson, The structure of the first coordination shell in liquid water. *Science* **304**(5673), 995–999 (2004)

517. M. Wilkins, A.R. Stokes, H.R. Wilson, Molecular structure of deoxyribose nucleic acids. *Nature* **171**, 738–740 (1953)
518. R.W. Williams, A. Chang, D. Juretic, S. Loughran, Secondary structure predictions and medium range interactions. *Biochim. Biophys. Acta (BBA) - Protein Struct. Mol. Enzymol.* **916**(2), 200–204 (1987)
519. R. Wintjens, J. Liévin, M. Rooman, E. Buisine, Contribution of cation- π interactions to the stability of protein-DNA complexes. *J. Mol. Biol.* **302**, 394–410 (2000)
520. S.T. Wlodek, T.W. Clark, L.R. Scott, J.A. McCammon, Molecular dynamics of acetylcholinesterase dimer complexed with tacrine. *J. Am. Chem. Soc.* **119**, 9513–9522 (1997)
521. S.T. Wlodek, T. Shen, J.A. McCammon, Electrostatic steering of substrate to acetylcholinesterase: analysis of field fluctuations. *Biopolymers* **53**(3), 265–271 (2000)
522. G. Wohlfahrt, Analysis of pH-dependent elements in proteins: geometry and properties of pairs of hydrogen-bonded carboxylic acid side-chains. *Proteins: Struct. Funct. Bioinform.* **58**, 396–406 (2005)
523. Y.I. Wolf, S.E. Brenner, P.A. Bash, E.V. Koonin, Distribution of protein folds in the three superkingdoms of life. *Genome Res.* **9**(1), 17–26 (1999)
524. Y.I. Wolf, N.V. Grishin, E.V. Koonin, Estimating the number of protein folds and families from complete genome data. *J. Mol. Biol.* **299**(4), 897–905 (2000)
525. R. Wolfenden, L. Andersson, P.M. Cullis, C.C.B. Southgate, Affinities of amino acid side chains for solvent water. *Biochemistry* **20**(4), 849–855 (1981)
526. J. Wong, Coevolution theory of the genetic code at age thirty. *BioEssays* **27**(4), 416–425 (2005)
527. J.M. Word, S.C. Lovell, J.S. Richardson, D.C. Richardson, Asparagine and glutamine: using hydrogen atom contacts in the choice of side-chain amide orientation. *J. Mol. Biol.* **285**(4), 1735–1747 (1999)
528. C.K. Wu, B. Hu, J.P. Rose, Z.-J. Liu, T.L. Nguyen, C. Zheng, E. Breslow, B.-C. Wang, Structures of an unliganded neuropeptide and its vasopressin complex: implications for binding and allosteric mechanisms. *Protein Sci.* **10**(9), 1869–1880 (2001)
529. S. Wuchty, Scale-free behavior in protein domain networks. *Mol. Biol. Evolut.* **18**(9), 1694–1702 (2001)
530. D. Xie, Y. Jiang, A nonlocal modified Poisson-Boltzmann equation and finite element solver for computing electrostatics of biomolecules. *J. Comput. Phys.* **322**, 1–20 (2016)
531. D. Xie, Y. Jiang, P. Brune, L.R. Scott, A fast solver for a nonlocal dielectric continuum model. *SISC* **34**(2), B107–B126 (2012)
532. D. Xie, Y. Jiang, L.R. Scott, Efficient algorithms for solving a nonlocal dielectric model for protein in ionic solvent. *SISC* **35**(6), B1267B1284 (2014)
533. D. Xie, J.-L. Liu, B. Eisenberg, Nonlocal poisson-fermi model for ionic solvent. *Phys. Rev. E* **94**, 012114 (2016)
534. D. Xie, J.-L. Liu, B. Eisenberg, L.R. Scott, A nonlocal Poisson-Fermi model for ionic solvent. [arXiv:1603.05597](https://arxiv.org/abs/1603.05597) [physics.chem-ph], 2016
535. X. Dong, C.-J. Tsai, R. Nussinov, Hydrogen bonds and salt bridges across protein-protein interfaces. *Protein Eng.* **10**(9), 999–1012 (1997)
536. M. Xu, A. Unzue, J. Dong, D. Spiliotopoulos, C. Nevado, A. Caflich, *Discovery of CREBBP bromodomain inhibitors by high-throughput docking and hit optimization guided by molecular dynamics* (J. Med. Chem, 2015)
537. B. Xue, R.L. Dunbrack, R.W. Williams, A.K. Dunker, V.N. Uversky, PONDR-FIT: a meta-predictor of intrinsically disordered amino acids. *Biochim. Biophys. Acta (BBA)-Proteins. Proteomics* **1804**(4), 996–1010 (2010)
538. W.-M. Yau, W.C. Wimley, K. Gawrisch, S.H. White, The preference of tryptophan for membrane interfaces. *Biochemistry* **37**, 14713–14718 (1998)
539. W. Yu, S.K. Lakkaraju, E.P. Raman, L. Fang, A.D. MacKerell Jr., Pharmacophore modeling using site-identification by ligand competitive saturation (SILCS) with multiple probe molecules. *J. Chem. Inf. Model.* **55**(2), 407–420 (2015)
540. H. Yuki, Y. Tanaka, M. Hata, H. Ishikawa, S. Neya, T. Hoshino, Implementation of π - π interactions in molecular dynamics simulation. *J. Comput. Chem.* **28**(6), 1091–1099 (2007)
541. R. Zahn, A. Liu, T. Luhrs, R. Riek, C. von Schroetter, F. Lopez Garcia, M. Billeter, L. Calzolari, G. Wider, K. Wüthrich, NMR solution structure of the human prion protein. *Proc. Natl. Acad. Sci. USA* **97**(1), 145–150 (2000)
542. D.T. Zallen, Despite franklin’s work, wilkins earned his nobel. *Nature* **425**(6953), 15–15 (2003)
543. A. Zarrine-Afsar, A. Mittermaier, L.E. Kay, A.R. Davidson, Protein stabilization by specific binding of guanidinium to a functional arginine-binding surface on an SH3 domain. *Protein Sci.* **15**, 162–170 (2006)
544. Z. Zeng, H. Shi, W. Yun, Z. Hong, *Survey of natural language processing techniques in bioinformatics* (Comput. Math, Methods Med, 2015)

-
545. Q. Zhai, M.B. Landesman, H. Robinson, W.I. Sundquist, C.P. Hill, Identification and structural characterization of the ALIX-binding late domains of simian immunodeficiency virus SIVmac239 and SIVagmTan-1. *J. Virol.* **85**(1), 632–637 (2011)
546. H.-X. Zhao, X.-J. Kong, H. Li, Y.-C. Jin, L.-S. Long, X.C. Zeng, R.-B. Huang, L.-S. Zheng, Transition from one-dimensional water to ferroelectric ice within a supramolecular architecture. *Proc. Natl. Acad. Sci.* **108**(9), 3481–3486 (2011)
547. W. Zhong, J.P. Gallivan, Y. Zhang, L. Li, H.A. Lester, D.A. Dougherty, From ab initio quantum mechanics to molecular neurobiology: a cation- π binding site in the nicotinic receptor. *Proc. Natl. Acad. Sci. USA* **95**(21), 12088–12093 (1998)
548. R. Zhou, X. Huang, C.J. Margulis, B.J. Berne, Hydrophobic collapse in multidomain protein folding. *Science* **305**(5690), 1605–1609 (2004)
549. Z.H. Zhou, M.L. Baker, W. Jiang, M. Dougherty, J. Jakana, G. Dong, G. Lu, W. Chiu, Electron cryo-microscopy and bioinformatics suggest protein fold models for rice dwarf virus. *Nat. Struct. Biol.* **8**, 868–873 (2001)
550. Z.H. Zhou, W. Chiu, K. Haskell, H. Spears, J. Jakana, F.J. Rixon, L.R. Scott, Parallel refinement of herpesvirus B-capsid structure. *Biophys. J.* **73**, 576–588 (1997)
551. Z.H. Zhou, M. Dougherty, J. Jakana, J. He, F.J. Rixon, W. Chiu, Seeing the herpesvirus capsid at 8.5 Å. *Science* **288**, 877–880 (2000)
552. Z.H. Zhou, S.J. Macnab, J. Jakana, L.R. Scott, W. Chiu, F.J. Rixon, Identification of the sites of interaction between the scaffold and outer shell in herpes simplex virus-1 capsids by difference electron imaging. *Proc. Natl. Acad. Sci. USA* **95**, 2778–2783 (1998)
553. M. Zorko, Ü. Langel, Cell-penetrating peptides: mechanism and kinetics of cargo delivery. *Adv. Drug Deliv. Rev.* **57**(4), 529–545 (2005)

Index

Symbols

pK_a , 78

A

acceptor, 86

action, 255

alanine scanning, 111

alternate locations, 61

altloc, 61

atomic mass unit (amu), 253

B

B-factors, 231

blocking, 116

Boltzmann distribution, 250

bonds, 31

buried, 125

C

C-terminal end, 48

C-terminus, 48

calorie, 252

carbonaceous groups, 50

catalysis, 181

catalyze, 181

cation- π interaction, 108, 111

chains, 62

cis, 48

codons, 132

comma free code, 132

crystal contacts, 180

D

Da, 253

dalton, 253

data mining, 16

decoy structures, 111

dehydron, 13, 22

denature, 55

dielectric, 213

dihedral, 71

dihedral angle, 71

dipole, 35

disulfide bonds, 53

disulfide bridges, 53

domain, 68

donor, 86

dynamic viscosity, 260

E

electronegativity scale, 119

entanglement, 44

epidiorthotic force, 13

F

ferro-electric, 149

fine structure constant, 256

fold, 68

free energy, 250

frequency, 59

G

gauche+, 73

gauche-, 73

glycosylation, 54

H

hetatoms, 62

hot spots, 111

hydrodynamic radius, 139

hydrogen bond, 12, 33, 48

hydrophobic effect, 21, 23, 50

hydrophobic force, 21

I

icode, 61

insertion code, 61

K

kcal/mole, 252
kinematic viscosity, 260

L

lipid, 137
lipophilicity, 101
log odds ratio, 75
loop, 67

M

molecular clock, 258
mutant, 87

N

N-terminal end, 48
N-terminus, 48
nonpolar groups, 50
nonredundant PDB (NRPDB), 62

O

obligate interactions, 103
octet rule, 8
odds ratio, 75

P

partition function, 250
PDB, 14
percentage divergence, 258
phospholipid bilayer, 137
phosphorylation, 54
polarity-synonymous mutations, 134
polarization, 214
post-translational modification, 54
primary structure, 66
protein complex, 68

Q

quaternary structure, 68

R

Ramachandran plot, 73

reading frame, 132
relative frequency, 105
relative propensity, 105
resonance, 206

S

salt bridge, 32, 53
scale free network, 81
secondary structure, 66
self energy, 226
shielding, 116
solvent exclusion surface, 103
solvent-accessible surface, 103
sphere-accessible surface, 103
Stokes radius, 139
substrate, 181
svedberg, 253
synonymous mutations, 134

T

temperature factors, 231
tertiary structure, 68
torsion, 71
trans form of the peptide bond, 48
trans: rotamers, 73

U

under-wrapped hydrogen bonds (UWHB), 23

V

van der Waals radius, 42
viscosity, 260

W

wrapping, 13
wrapping of hydrogen bonds, 50

Y

yotta, 252