BIBLIOGRAPHY

Bibliography

[1] Pedraza, V., Gomez-Capilla, J. A., Escaramis, G., Gomez, C., Torné, P., Rivera, J. M., Gil, A., Araque, P., Olea, N., Estivill, X. and Fárez-Vidal, M. E. Gene expression signatures in breast cancer distinguish phenotype characteristics, histologic subtypes, and tumor invasiveness. *Cancer*, 116(2):486-496, 2010

[2] Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E. and Forman, D. Global cancer statistics. *CA: a cancer journal for clinicians*, 61(2):69-90, 2011.

[3] Sørlie, T., Tibshirani, R., Parker, J., Hastie, T., Marron, J. S., Nobel, A., Deng, S., Johnsen, H., Pesich, R., Geisler, S., and Demeter, J., Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proceedings of the national academy of sciences*, 100(14):8418-8423, 2003.

[4] Chaffer, C. L. and Weinberg, R. A. A perspective on cancer cell metastasis. *Science*, 331(6024):1559-1564, 2011.

[5] Giamas, G., Filipović, A., Jacob, J., Messier, W., Zhang, H., Yang, D., Zhang, W., Shifa, B.A., Photiou, A., Tralau-Stewart, C. and Castellano, L., Green, A. R., Coombes, R. C., Ellis, I. O, Ali, S., Lenz, H. J., and Stebbing, J. Kinome screening for regulators of the estrogen receptor identifies LMTK3 as a new therapeutic target in breast cancer. *Nature medicine*, 17(6):715-719, 2011.

[6] Stebbing, J., Filipovic, A., Lit, L.C., Blighe, K., Grothey, A., Xu, Y., Miki, Y., Chow, L.W., Coombes, R.C., Sasano, H. Shaw, J.A., and Giamas, G. LMTK3 is implicated in endocrine resistance via multiple signaling pathways. *Oncogene*, 32(28):3371-3380, 2013.

[7] Stebbing, J., Filipovic, A., Ellis, I. O., Green, A. R., D'Silva, T. R., Lenz, H. J., Coombes, R.C., Wang, T., Lee, S. C., and Giamas, G., LMTK3 expression in breast cancer: association with tumor phenotype and clinical outcome. *Breast cancer research and treatment*, 132(2):537-544, 2012.

[8] Stebbing, J., Filipovic, A. and Giamas, G., Lemur tyrosine kinase-3 (LMTK3) in cancer and evolution. *Oncotarget*, 2(6):428-429. 2011.

[9] Xu, Y., Zhang, H., Lit, L. C., Grothey, A., Athanasiadou, M., Kiritsi, M., Lombardo, Y., Frampton, A. E., Green, A. R., Ellis, I. O., Ali, S., Lenz, H. J, Thanou, M., Stebbing, J., and Giamas, G. The kinase LMTK3 promotes invasion in breast cancer through GRB2-mediated induction of integrin β1. *Science Signaling*, 7(330):ra58, 2014.

Bibliography

[10] Lucchiari, G., Zhang, H., Nunes, J., Xu, Y., Grothey, A., Stebbing, J. and Giamas, G. Role of phosphorylation in Lmtk3 activation and its contribution in breast cancer progression. *Cancer Research,* 76:85, 2016.

[11] Beltrao, P., Albanese, V., Kenner, L. R., Swaney, D. L., Burlingame, A., Villen, J., Lim, W.A., Fraser, J. S., Frydman, J. and Krogan, N. J. Systematic functional prioritization of protein posttranslational modifications. *Cell*, 150(2):413-425, 2012

[12] Kornev, A. P., Haste, N. M., Taylor, S. S., and Ten Eyck, L. F. Surface comparison of active and inactive protein kinases identifies a conserved activation mechanism. *Proceedings of the national academy of sciences*, 103(47):17783-17788, 2006.

[13] Meharena, H. S., Chang, P., Keshwani, M. M., Oruganty, K., Nene, A.K., Kannan, N., Taylor, S. S., and Kornev, A. P. Deciphering the structural basis of eukaryotic protein kinase regulation. *PLoS biology*, 11(10):e1001680, 2013.

[14] Taylor, S. S., Keshwani, M. M., Steichen, J. M., and Kornev, A. P. Evolution of the eukaryotic protein kinases as dynamic molecular switches. *Philosophical Transactions of the Royal Society B*, 367(1602):2517-2528, 2012.

[15] Johnson, L. N., Noble, M. E. and Owen, D. J. Active and inactive protein kinases: structural basis for regulation. *Cell*, 85(2):149-158, 1996.

[16] IARC (2012).

[17] Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D. and Bray, F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International journal of cancer*, 136(5):E359-E386, 2015.

[18] Gupta, A., Shridhar, K., and Dhillon, P. K. A review of breast cancer awareness among women in India: Cancer literate or awareness deficit? *European journal of cancer*, 51(14):2058-2066, 2015.

[19] National Cancer Registry Programme. National Centre for Disease Informatics and Research. and Indian Council of Medical Research., Three year report of population based cancer registries 2009–2011 national

[20] Bodai, B. I. and Tuso, P. Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. *The Permanente Journal*, 19(2):48-79, 2015.

[21] Palumbo, M.O., Kavan, P., Miller, W., Panasci, L., Assouline, S., Johnson, N., Cohen, V., Patenaude, F., Pollak, M., Jagoe, R. T. and Batist, G. Systemic cancer therapy: achievements and challenges that lie ahead. *Frontiers in pharmacology*, 4:57, 2013.

[22] Horton, J. K., Jagsi, R., Woodward, W. A. and Ho, A. Breast cancer biology: clinical implications for breast radiation therapy. *International Journal of Radiation Oncology* Biology* Physics*, 100(1):23-37, 2018.

[23] Blows, F. M., Driver, K. E., Schmidt, M. K., Broeks, A., Van Leeuwen, F. E., Wesseling, J., Cheang, M. C., Gelmon, K., Nielsen, T. O., Blomqvist, C. and Heikkila, P. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. *PLoS medicine*, 7(5):p.e1000279, 2010.

[24] Haque, R., Ahmed, S. A., Inzhakova, G., Shi, J., Avila, C., Polikoff, J., Bernstein, L., Enger, S.M. and Press, M. F. Impact of breast cancer subtypes and treatment on survival: an analysis spanning two decades. *Cancer Epidemiology and Prevention Biomarkers*, 21:1848-1855, 2012

[25] Perou, C. M. and Børresen-Dale, A. L., Systems biology and genomics of breast cancer. *Cold Spring Harbor perspectives in biology*, 3(2):a003293, 2011.

[26] Bianchini, G., Balko, J. M., Mayer, I. A., Sanders, M. E. and Gianni, L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. *Nature reviews Clinical oncology*, 13(11):674-690, 2016.

[27] Mandusic, V., Dimitrijevic, B., Nikolic-Vukosavljevic, D., Neskovic-Konstantinovic, Z., Kanjer, K. and Hamann, U. Different associations of estrogen receptor β isoforms, ERβ1 and ERβ2, expression levels with tumor size and survival in early-and late-onset breast cancer. *Cancer letters*, 321(1):73-79, 2012.

[28] Hamilton-Burke, W., Coleman, L., Cummings, M., Green, C. A., Holliday, D. L., Horgan, K., Maraqa, L., Peter, M. B., Pollock, S., Shaaban, A. M. and Smith, L. Phosphorylation of estrogen receptor β at serine 105 is associated with good prognosis in breast cancer. *The American journal of pathology*, 177(3):1079-1086, 2010.

[29] Frasor, J., Stossi, F., Danes, J. M., Komm, B., Lyttle, C. R. and Katzenellenbogen, B. S. Selective estrogen receptor modulators: discrimination of agonistic versus antagonistic activities by gene expression profiling in breast cancer cells. *Cancer research*, 64(4):1522-1533, 2004.

[30] Klinge, C. M. Estrogen receptor interaction with estrogen response elements. *Nucleic acids research*, 29(14):2905-2919, 2001.

[31] Lannigan, D. A. Estrogen receptor phosphorylation. *Steroids*, 68(1):1-9, 2003

[32] Murphy, L. C., Seekallu, S. V. and Watson, P. H. Clinical significance of estrogen receptor phosphorylation. *Endocrine-related cancer*, 18(1):R1-R14, 2011.

[33] Ward, R. D. and Weigel, N. L. Steroid receptor phosphorylation: Assigning function to site-specific phosphorylation. *Biofactors*, 35(6):528-53, 2009.

[34] Thomas, R. S., Sarwar, N., Phoenix, F., Coombes, R. C., and Ali, S. Phosphorylation at serines 104 and 106 by Erk1/2 MAPK is important for estrogen receptor-α activity. *Journal of molecular endocrinology*, 40(4):173-84, 2008.

[35] Rogatsky, I., Trowbridge, J. M., and Garabedian, M. J. Potentiation of human estrogen receptor α transcriptional activation through phosphorylation of serines 104 and 106 by the cyclin A-CDK2 complex. *Journal of Biological Chemistry*, 274(32):22296–22302, 1999.

[36] Zwart, W., Griekspoor, A., Berno, V., Lakeman, K., Jalink, K., Mancini, M., Neefjes, J. and Michalides, R. PKA-induced resistance to tamoxifen is associated with an altered orientation of ERα towards co-activator SRC-1. *The EMBO journal*, 26(15):3534–3544, 2007

[37] Anbalagan, M. and Rowan, B. G. Estrogen receptor alpha phosphorylation and its functional impact in human breast cancer. *Molecular and cellular endocrinology*, 418:264-72, 2015.

[38] Osborne, C. K. and Schiff, R. Mechanisms of endocrine resistance in breast cancer. *Annual review of medicine*, 62(1):233-247, 2011.

[39] Ali, S., Buluwela, L., and Coombes, R. C. Antiestrogens and their therapeutic applications in breast cancer and other diseases. *Annual review of medicine*, 62(1):217-232, 2011.

[40] Early Breast Cancer Trialists' Collaborative Group, Tamoxifen for early breast cancer: an overview of the randomised trials. *The Lancet*, 351(9114):1451-1467, 1998.

[41] Coombes, R. C., Kilburn, L. S., Snowdon, C. F., Paridaens, R., Coleman, R. E., Jones, S. E., Jassem, J., Van de Velde, C. J. H., Delozier, T., Alvarez, I., and Del Mastro, L. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment

(Intergroup Exemestane Study): a randomised controlled trial. *The Lancet*, 369(9561):559-570, 2007.

[42] Goss, P. E., Ingle, J. N., Martino, S., Robert, N. J., Muss, H. B., Piccart, M. J., Castiglione, M., Tu, D., Shepherd, L. E., Pritchard, K. I., and Livingston, R. B. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA. 17. *Journal of the National Cancer Institute*, 97(17):1262-1271, 2005.

[43] Dauvois, S., White, R., and Parker, M. G. The antiestrogen ICI 182780 disrupts estrogen receptor nucleocytoplasmic shuttling. *Journal of cell science*, 106(4):1377-1388, 1993.

[44] Dodwell, D. and Vergote, I. A comparison of fulvestrant and the third-generation aromatase inhibitors in the second-line treatment of postmenopausal women with advanced breast cancer. *Cancer treatment reviews*, 31(4):274-282, 2005.

[45] Romond, E. H., Perez, E. A., Bryant, J., Suman, V. J., Geyer Jr, C. E., Davidson, N. E., Tan-Chiu, E., Martino, S., Paik, S., Kaufman, P. A., and Swain, S. M. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New England Journal of Medicine*, 353(16):1673-1684, 2005.

[46] Dent, R., Trudeau, M., Pritchard, K. I., Hanna, W. M., Kahn, H. K., Sawka, C. A., Lickley, L. A., Rawlinson, E., Sun, P., and Narod, S. A. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clinical cancer research*, 13(15):4429-4434, 2007.

[47] Belletti, B., Vaidya, J. S., D'Andrea, S., Entschladen, F., Roncadin, M., Lovat, F., Berton, S., Perin, T., Candiani, E., Reccanello, S., and Veronesi, A. Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. *Clinical Cancer Research*, 14(5):1325-1332, 2008.

[48] Early Breast Cancer Trialists' Collaborative Group, Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *The Lancet*, 365(9472):1687-1717, 2005.

[49] Musgrove, E.A. and Sutherland, R. L. Biological determinants of endocrine resistance in breast cancer. *Nature Reviews Cancer*, 9(9):631-643, 2009.

[50] Encarnacion, C. A., Ciocca, D. R., McGuire, W. L., Clark, G. M., Fuqua, S. A., and Osborne, C. K. Measurement of steroid hormone receptors in breast cancer patients on tamoxifen. *Breast cancer research and treatment*, 26(3):237-246, 1993.

[51] Gutierrez, M. C., Detre, S., Johnston, S., Mohsin, S. K., Shou, J., Allred, D. C., Schiff, R., Osborne, C. K., and Dowsett, M. Molecular changes in tamoxifen-resistant breast cancer: relationship between estrogen receptor, HER-2, and p38 mitogen-activated protein kinase. *Journal of clinical oncology*, 23(11):2469-2476, 2005.

[52] Meng, S., Tripathy, D., Shete, S., Ashfaq, R., Haley, B., Perkins, S., Beitsch, P., Khan, A., Euhus, D., Osborne, C., and Frenkel, E. HER-2 gene amplification can be acquired as breast cancer progresses. *Proceedings of the National Academy of Sciences*, 101(25):9393-9398, 2004.

[53] Murphy, L.C., Niu, Y., Snell, L., and Watson, P. Phospho-serine-118 estrogen receptor-α expression is associated with better disease outcome in women treated with tamoxifen. *Clinical Cancer Research*, 10(17):5902-5906, 2004.

[54] Redmond, A. M., Bane, F. T., Stafford, A. T., McIlroy, M., Dillon, M. F., Crotty, T. B., Hill, A. D., and Young, L. S. Coassociation of estrogen receptor and p160 proteins predicts resistance to endocrine treatment; SRC-1 is an independent predictor of breast cancer recurrence. *Clinical Cancer Research*, 15(6):2098-2106, 2009.

[55] Miller, T. W., Balko, J. M., and Arteaga, C. L. Phosphatidylinositol 3-kinase and antiestrogen resistance in breast cancer. *Journal of clinical oncology*, 29(33):4452-4461, 2011.

[56] Creighton, C. J., Hilger, A. M., Murthy, S., Rae, J. M., Chinnaiyan, A. M. and El-Ashry, D. Activation of mitogen-activated protein kinase in estrogen receptor α–positive breast cancer cells in vitro induces an in vivo molecular phenotype of estrogen receptor α–negative human breast tumors. *Cancer research*, 66(7):3903-391, 2006.

[57] Blume-Jensen, P., and Hunter, T. Oncogenic kinase signalling. *Nature*, 411(6835):355-365, 2001.

[58] Hunter, T. Signaling - 2000 and beyond. *Cell*, 100(1):113-127, 2000.

[59] Manning, G., Whyte, D. B., Martinez, R., Hunter, T., and Sudarsanam, S. The protein kinase complement of the human genome. *Science*, 298(5600):1912-1934, 2002.

[60] Hunter, T. Protein Kinase Classification. *Methods in Enzymology*, 200:3-37, 1991.

[61] Ardito, F., Giuliani, M., Perrone, D., Troiano, G. and Lo Muzio, L. The crucial role of protein phosphorylation in cell signaling and its use as targeted therapy. *International journal of molecular medicine*, 40(2):271-280, 2017.

[62] Ciardiello, F., De Vita, F., Orditura, M. and Tortora, G. The role of EGFR inhibitors in nonsmall cell lung cancer. *Current opinion in oncology*, 16(2):130-135, 2004.

[63] Buchdunger, E., O'Reilley, T., and Wood, J. Pharmacology of imatinib (STI571). *European Journal of Cancer*, 38:S28-S36, 2002.

[64] Knighton, D. R., Zheng, J. H., Ten Eyck, L. F., Ashford, V. A., Xuong, N. H., Taylor, S. S., and Sowadski, J. M. Crystal structure of the catalytic subunit of cyclic adenosine monophosphate-dependent protein kinase. *Science*, 253(5018):407-414, 1991.

[65] Herberg, F. W., Doyle, M. L., Cox, S., and Taylor, S. S. Dissection of the Nucleotide and Metal− Phosphate Binding Sites in cAMP-Dependent Protein Kinase. *Biochemistry*, 38(19):6352–6360, 1999.

[66] Johnson, D. A., Akamine, P., Radzio-Andzelm, E., and Taylor, S. S., 2001. Dynamics of cAMP-dependent protein kinase. *Chemical reviews*, 101(8):2243–2270

[67] Kornev, A. P. and Taylor, S. S. Defining the conserved internal architecture of a protein kinase. Biochimica et Biophysica Acta (BBA)-*Proteins and Proteomics*, 1804(3):440-444, 2010.

[68] Madhusudan, Pearl, A., Xuong, N. H., Taylor S. S. Crystal structure of a transition state mimic of the catalytic subunit of cAMP-dependent protein kinase. *Nature Structural and Molecular Biology*, 9(4):273–277, 2002.

[69] Adams, J. A. Activation loop phosphorylation and catalysis in protein kinases: is there functional evidence for the autoinhibitor model? *Biochemistry*, 42(3):601–607, 2003.

[70] Johnson, L.N. and Lewis, R.J. Structural basis for control by phosphorylation. *Chemical reviews*, 101(8):2209–2242, 2001.

[71] Nolen, B., Taylor, S., and Ghosh, G. Regulation of protein kinases: controlling activity through activation segment conformation. *Molecular cell*, 15(5):661-675, 2004.

[72] Huse, M. and Kuriyan, J. The conformational plasticity of protein kinases. *Cell*, 109(3):275-282, 2002.

[73] Lochhead, P. A. Protein kinase activation loop autophosphorylation in cis: overcoming a Catch-22 situation. *Science Signaling*, 2(54):pe4-pe4, 2009.

[74] Hantschel, O. and Superti-Furga, G. Regulation of the c-Abl and Bcr–Abl tyrosine kinases. *Nature reviews Molecular cell biology*, 5(1):33–44, 2004.

[75] Markus Seeliger, M. A., Ranjitkar, P., Kasap, C., Shan, Y., Shaw, D. E., Shah, N. P., Kuriyan, J., and Maly, D. J. Equally potent inhibition of c-Src and Abl by compounds that recognize inactive kinase conformations. *Cancer research*, 69(6):2384-2392, 2009.

[76] Wang, H. and Brautigan D. L. A novel transmembrane Ser/Thr kinase complexes with protein phosphatase-1 and inhibitor-2. *The Journal of biological chemistry*, 277(51):49605-49612, 2002.

[77] Schlessinger, J., Mohammadi, M., Margolis, B., and Ullrich, A. Role of Sh2-Containing Proteins in Cellular Signaling by Receptor Tyrosine Kinases. *Cold Spring Harbor Symposia on Quantitative Biology*, 57:67-74:1992.

[78] Bar-Sagi, D., Rotin, D., Batzer, A., Mandiyan, V. and Schlessinger, J. SH3 domains direct cellular localization of signaling molecules. *Cell*, 74(1):83-91, 1993.

[79] Xu, Y Investigation of the Function of LMTK3 in Breast Cancer Invasion and Transcriptional Regulation. Ph. D thesis Department of Surgery and Cancer, Imperial College London Hammersmith Hospital, 2014

[80] Gsponer, J. and Babu, M. M. The rules of disorder or why disorder rules. *Progress in biophysics and molecular biology*, 99(2-3):94-103, 2009.

[81] Anbarasu, K. and Jayanthi, S., Structural modeling and molecular dynamics studies on the human LMTK3 domain and the mechanism of ATP binding. *Molecular BioSystems*, 10(5):1139-1145, 2014.

[82] Allam, L., Lakhlili, W., Tarhda, Z., Akachar, J., and Ghrifi, F. Three-dimensional Structure Prediction of the Human LMTK3 Catalytic Domain in DYG-in Conformation. *Journal of Biomolecular Research & Therapeutics*, 6:151, 2017.

[83] Tyner, J. W., Walters, D. K., Willis, S. G., Luttropp, M., Oost, J., Loriaux, M., Erickson, H., Corbin, A. S., O'Hare, T., Heinrich, M.C. and Deininger, M. W. RNAi screening of the tyrosine kinome identifies therapeutic targets in acute myeloid leukemia. *Blood*, 111(4): 2238-2245, 2008.

[84] Naik, S., Dothager, R. S., Marasa, J., Lewis, C. L., and Piwnica-Worms, D. Vascular endothelial growth factor receptor-1 is synthetic lethal to aberrant β-catenin activation in colon cancer. *Clinical cancer research*, 15(24):7529-7537, 2009.

[85] Wakatsuki, T., LaBonte, M. J., Bohanes, P. O., Zhang, W., Yang, D., Azuma, M., Barzi, A., Ning, Y., Loupakis, F., Saadat, S., and Volz, N. Prognostic role of lemur tyrosine

kinase-3 germline polymorphisms in adjuvant gastric cancer in Japan and the United States. *Molecular cancer therapeutics*, 12(10): 2261-2272, 2013.

[86] Li, Z., Wu, J., Ji, M., Shi, L., Xu, B., Jiang, J., and Wu, C. Prognostic role of lemur tyrosine kinase 3 in postoperative gastric cancer. *Molecular and clinical oncology*, 2(5):756-760, 2014.

[87] Shi, H., Li, Q., Ji, M., Wu, J., Li, Z., Zheng, X., Xu, B., Chen, L., Li, X., Lu, C., and Tan, Y. Lemur tyrosine kinase-3 is a significant prognostic marker for patients with colorectal cancer. *International journal of clinical and experimental pathology*, 7(3):1101–1107, 2014.

[88] Shi, H., Wu, J., Ji, M., Zhou, Q., Li, Z., Zheng, X., Xu, B., Deng, H., and Zhao., W. Serum lemur tyrosine kinase 3 expression in colorectal cancer patients predicts cancer progression and prognosis. *Medical oncology*, 30: 754, 2013.

[89] Lu, L., Yuan, X., Zhang, Q., Zhang, H., and Shen, B. LMTK3 knockdown retards cell growth and invasion and promotes apoptosis in thyroid cancer. *Molecular medicine reports*, 15(4):2015-2022, 2017.

[90] Hammond, M.E.H., Hayes, D.F., Dowsett, M., Allred, D.C., Hagerty, K.L., Badve, S., Fitzgibbons, P.L., Francis, G., Goldstein, N.S., Hayes, M. and Hicks, D.G., Lester, S., Love, R., Mangu, P. B., McShane, L. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of and progesterone receptors in breast cancer. *Journal of Clinical Oncology*, 28(16):2784–2795, 2010.

[91] Jordan, V. C. and O'Malley, B. W. Selective estrogen-receptor modulators and antihormonal resistance in breast cancer. *Journal of clinical oncology*, 25(36):5815-5824, 2007.

[92] Beniashvili, D. S. An overview of the world literature on spontaneous tumors in nonhuman primates. *Journal of medical primatology*, 18(6):423-437, 1989.

[93] McClure, H. M. Tumors in nonhuman primates: Observations during a six-year period in the Yerkes Primate center colony. *American journal of physical anthropology*, 38(2):425-429, 1973.

[94] Puente, X. S., Velasco, G., Gutiérrez-Fernández, A., Bertranpetit, J., King, M. C., and López-Otín, C. Comparative analysis of cancer genes in the human and chimpanzee genomes. *BMC genomics*, 7(1):15, 2006.

[95] Seibold, H. R. Neoplasms and Proliferative Lesions in 1065 Nonhuman Primate Necropsies. *Laboratory animal science*, 23:533-539, 1973.

[96] Waters, D. J., Sakr, W. A., Hayden, D. W., Lang, C. M., McKinney, L., Murphy, G. P., Radinsky, R., Ramoner, R., Richardson, R. C., and Tindall, D. J. Workgroup 4: spontaneous prostate carcinoma in dogs and nonhuman primates. *The Prostate*, 36(1):64-67, 1998.

[97] Belguise, K. and Sonenshein, G. E. PKCθ promotes c-Rel–driven mammary tumorigenesis in mice and humans by repressing estrogen receptor α synthesis. *The Journal of clinical investigation*, 117(12):4009-4021, 2007.

[98] Johnson, A. B. and O'Malley, B. W. ERasing breast cancer resistance through the kinome. *Nature medicine*, 17(6):660-661, 2011.

[99] Roy, A., Kucukural, A., and Zhang, Y. I-TASSER: a unified platform for automated protein structure and function prediction. *Nature protocols*, 5(4):725-738, 2010.

[100] Gong, J., Wang, D., Sun, L., Zborowska, E., Willson, J. K., and Brattain, M. G. Role of alpha 5 beta 1 integrin in determining malignant properties of colon carcinoma cells. *Cell growth & Differentiation*, 8(1):83–90, 1997.

[101] Maschler, S., Wirl, G., Spring, H., v Bredow, D., Sordat, I., Beug, H., and Reichmann, E. Tumor cell invasiveness correlates with changes in integrin expression and localization. *Oncogene*, 24(12):2032–2041, 2005.

[102] dos Santos, P. B., Zanetti, J. S., Ribeiro-Silva, A., and Beltrão, E. I. Beta 1 integrin predicts survival in breast cancer: a clinicopathological and immunohistochemical study. *Diagnostic pathology*, 7(1):104, 2012.

[103] Yao, E. S., Zhang, H., Chen, Y. Y., Lee, B., Chew, K., Moore, D., and Park, C. Increased β1 integrin is associated with decreased survival in invasive breast cancer. *Cancer Research*, 67(2):659–664, 2007.

[104] Zhang, Z., Vuori, K., Reed, J. C., and Ruoslahti, E. The alpha 5 beta 1 integrin supports survival of cells on fibronectin and up-regulates Bcl-2 expression. *Proceedings of the National Academy of Sciences*, 92(13):6161–6165, 1995.

[105] Daly, R. J., Binder, M. D., and Sutherland, R. L. Overexpression of the Grb2 gene in human breast cancer cell lines. *Oncogene*, 9(9):2723–2727, 1994.

[106] Lowenstein, E. J., Daly, R. J., Batzer, A. G., Li, W., Margolis, B., Lammers, R., Ullrich, A., Skolnik, E.Y., Bar-Sagi, D., and Schlessinger, J. The SH2 and SH3 domain containing protein GRB2 links receptor tyrosine kinases to ras signaling. *Cell*, 70(3):431–442, 1992.

[107] Rozakis-Adcock, M., McGlade, J., Mbamalu, G., Pelicci, G., Daly, R., Li, W., Batzer, A., Thomas, S., Brugge, J., Pelicci, P.G., and Schlessinger, J. Association of the Shc and Grb2/Sem5 SH2-containing proteins is implicated in activation of the Ras pathway by tyrosine kinases. *Nature*, 360(6405):689–692, 1992.

[108] Tortora, G., Damiano, V., Bianco, C., Baldassarre, G., Bianco, A. R., Lanfrancone, L., Pelicci, P. G., and Ciardiello, F. The RIα subunit of protein kinase A (PKA) binds to Grb2 and allows PKA interaction with the activated EGF-receptor. *Oncogene*, 14(8):923-928, 1997.

[109] Xu, Y., Zhang, H., and Giamas, G. Targeting lemurs against cancer metastasis. *Oncotarget*, 5(14):5192, 2014.

[110] Thornton, K. H., Mueller, W. T., McConnell, P., Zhu, G., Saltiel, A. R., and Thanabal, V. Nuclear magnetic resonance solution structure of the growth factor receptor-bound protein 2 Src homology 2 domain. *Biochemistry*, 35(36):11852–11864, 1996.

[111] Moroco, J. A., Craigo, J. K., Iacob, R. E., Wales, T. E., Engen, J.R., and Smithgall, T. E., 2014. Differential sensitivity of Src-family kinases to activation by SH3 domain displacement. *PLoS One*, 9(8), p.e105629.

[112] Keaton, M. A. Review of" The Cell Cycle: Principles of Control" by David O. Morgan. *Cell division*, 2(1):1-2, 2007.

[113] Olsen, J. V. and Mann, M. Status of large-scale analysis of post-translational modifications by mass spectrometry. *Molecular and cellular proteomics*, 12(12):3444–3452, 2013

[114] Ban, D., Funk, M., Gulich, R., Egger, D., Sabo, T. M., Walter, K. F., Fenwick, R.B., Giller, K., Pichierri, F., de Groot, B. L. and Lange, O. F., Grubmuller, H., Salvatella, X., Wolf, M., Loidl, A., Kree, R., Becker, S., Lakomek N. A., Lee, D., and Lunkenheimer, P., Christian Griesinger, C. Kinetics of conformational sampling in ubiquitin. *Angewandte Chemie International Edition*, 50(48):11437–11440, 2011.

[115] Waldrop, M. M. The big guns. *Nature*, 505(7485):604-606, 2014.

Bibliography

[116] Childers, M. and Daggett, V. Validating Molecular Dynamics Simulations Against Experimental Observables in Light of Underlying Conformational Ensembles. *The Journal of Physical Chemistry B*, 2018. DOI: 10.1021/acs.jpcb.8b02144

[117] Vitkup, D., Ringe, D., Petsko, G. A., and Karplus, M. Solvent mobility and the protein'glass' transition. *Nature Structural and Molecular Biology*, 7(1):34-38, 2000.

[118] Hagen, S. J., Hofrichter, J., and Eaton, W. A. Protein reaction kinetics in a room-temperature glass. *Science*, 269(5226):959-962, 1995.

[119] Karplus, M. and McCammon, J. A. Molecular dynamics simulations of biomolecules. *Nature Structural and Molecular Biology*, 9(9):646-652, 2002.

[120] Phillips, J. C., Braun, R., Wang, W., Gumbart, J., Tajkhorshid, E., Villa, E., Chipot, C., Skeel, R. D., Kale, L., and Schulten, K. Scalable molecular dynamics with NAMD. *Journal of computational chemistry*, 26(16):1781-1802, 2005.

[121] Pronk, S., Páll, S., Schulz, R., Larsson, P., Bjelkmar, P., Apostolov, R., Shirts, M. R., Smith, J. C., Kasson, P. M., Van Der Spoel, D., and Hess, B. GROMACS 4.5: a high-throughput and highly parallel open source molecular simulation toolkit. *Bioinformatics*, 29(7): 845-85, 2013.

[122] Case, D. A., Darden, T. A., Cheatham, T. E., Simmerling, C. L., Wang, J., Duke, R. E., Luo, R., Walker, R. C., Zhang, W., Merz, K. M., Roberts, B., Hayik, S., Roitberg, A., Seabra, G., Swails, J., Gots, A. W., Kolossváry, I., Wong, K. F., Paesani, F., Vanicek, J., Wolf, R. M., Liu, J., Wu, X., Brozell, S. R., Steinbrecher, T., Gohlke, H., Cai, Q., Ye, X., Wang, J., Hsieh, M. J., Cui, G., Roe, D. R., Mathews, D. H., Seetin, M. G., Salomon-Ferrer, R., Sagui, C., Babin, V., Luchko, T., Gusarov, S., Kovalenko, A., Kollman, P. A. (2011). AMBER 12; University of California, San Francisco.

[123] Dror, R. O., Dirks, R. M., Grossman, J. P., Xu, H., and Shaw, D. E. Biomolecular simulation: a computational microscope for molecular biology. *Annual review of biophysics*, 41: 429-452, 2012.

[124] Sunada, S., Go, N., and Koehl, P. Calculation of nuclear magnetic resonance order parameters in proteins by normal mode analysis. *The Journal of chemical physics*, 104(12):4768-4774, 1996.

[125] Tolman, J. R., Al-Hashimi, H. M., Kay, L. E., and Prestegard, J. H. Structural and dynamic analysis of residual dipolar coupling data for proteins. Journal of the American Chemical Society, 123(7):1416-1424, 2001.

[126] Maragakis, P., Lindorff-Larsen, K., Eastwood, M. P., Dror, R. O., Klepeis, J. L., Arkin, I. T., Jensen, M. O., Xu, H., Trbovic, N., Friesner, R. A., and Palmer, A. G. Microsecond molecular dynamics simulation shows effect of slow loop dynamics on backbone amide order parameters of proteins. *The Journal of Physical Chemistry B*, 112(19):6155-6158, 2008.

[127] Best, R. B. and Vendruscolo, M. Determination of protein structures consistent with NMR order parameters. *Journal of the American Chemical Society*, 126(26): 8090-8091, 2004.

[128] Lipari, G., Szabo, A., and Levy, R. M. Protein dynamics and NMR relaxation: comparison of simulations with experiment. *Nature*, 300(5888):197–198, 1982.

[129] da Silva, R. A., Degrève, L., and Caliri, A. LMProt: an efficient algorithm for Monte Carlo sampling of protein conformational space. *Biophysical journal*, 87(3):1567-1577, 2004.

[130] Lu, H. and Schulten, K. Steered molecular dynamics simulations of force-induced protein domain unfolding. *Proteins: Structure, Function, and Bioinformatics*, 35(4):453-63, 1999.

[131] van der Kamp, M. W. and Mulholland, A. J. Combined quantum mechanics/molecular mechanics (QM/MM) methods in computational enzymology. *Biochemistry*, 52(16):2708-2728, 2013.

[132] Chen, N., Zhou, J., Li, J., Xu, J., and Wu, R. Concerted cyclization of lanosterol C-ring and D-ring under human oxidosqualene cyclase catalysis: an ab initio QM/MM MD study. *Journal of chemical theory and computation*, 10(3):1109−1120, 2014.

[133] Nielsen, S. O., Lopez, C. F., Srinivas, G., and Klein, M. L. Coarse grain models and the computer simulation of soft materials. Journal of Physics: *Condensed Matter*, 16(15):R481–R512, 2004.

[134] Elcock, A. H. Molecular Simulations of Diffusion and Association in Multimacromolecular Systems. *Methods in Enzymology*, 383:166-198, 2004.

[135] Ermak, D. L. and McCammon, J. A. Brownian dynamics with hydrodynamic interactions. *The Journal of chemical physics*, 69(4):1352-1360, 1978.

[136] Go, N., Noguti, T., and Nishikawa, T. Dynamics of a small globular protein in terms of low-frequency vibrational modes. *Proceedings of the National Academy of Sciences*, 80(12):3696-3700, 1983.

Bibliography

[137] Brooks, B. and Karplus, M. Harmonic dynamics of proteins: normal modes and fluctuations in bovine pancreatic trypsin inhibitor. *Proceedings of the National Academy of Sciences*, 80(21):6571-6575, 1983.

[138] Hosen, M. J., Zubaer, A., Thapa, S., Khadka, B., De Paepe, A., and Vanakker, O. M. Molecular docking simulations provide insights in the substrate binding sites and possible substrates of the ABCC6 transporter. *PLoS One*, 9(7):e102779, 2014.

[139] McQuarrie, D. A. Statistical Mechanics, Harper & Row, New York, 1976

[140] Chandler, D. Introduction to Modern Statistical Mechanics, page 288, Oxford University Press, 1987.

[141] Wilde, R. E. and Singh, S. Statistical mechanics: Fundamentals and modern applications. Vol. 76, pages 761, Wiley-Interscience, New York, 1997.

[142] Alder, B. J. and Wainwright, T. E. J. Phase Transition for a Hard Sphere System. *Journal of Chemical Physics*, 27:1208-1209, 1957

[143] Alder, B. J. and Wainwright, T. E. Studies in molecular dynamics. I. General method. *The Journal of Chemical Physics*, 31(2):459-466, 1959.

[144] Rahman, A. Correlations in the motion of atoms in liquid argon. *Physical Review*, 136(2A):A405, 1964.

[145] Stillinger, F. H. and Rahman, A. Improved simulation of liquid water by molecular dynamics. *The Journal of Chemical Physics*, 60(4):1545-1557,1974

[146] McCammon, J. A., Gelin, B. R., and Karplus, M. Dynamics of folded proteins. *Nature*, 267(5612):585, 1977.

[147] Leitner, D. M., Gruebele, M., and Havenith M. Solvation dynamics of biomolecules: Modeling and terahertz experiments. *Human Frontier Science Program Journal*, 2(6):314–323, 2008.

[148] Schneider, M., Fu, X., and Keating, A. E. X-ray vs. NMR structures as templates for computational protein design. *Proteins: Structure, Function, and Bioinformatics*, 77(1): 97–110, 2009.

[149] Van Gunsteren, W. F. and Berendsen, H. J. C. A leap-frog algorithm for stochastic dynamics. *Molecular Simulation*, 1(3): 173-185, 1988.

[150] Case, D. A., Cheatham, T. E., Darden, T., Gohlke, H., Luo, R., Merz, K. M., Onufriev, A., Simmerling, C., Wang, B., and Woods, R. J. The Amber biomolecular simulation programs. *Journal of computational chemistry*, 26(16):1668-1688, 2005.

[151] Tolman, J. R., Al-Hashimi, H. M., Kay, L. E., and Prestegard, J. H. Structural and dynamic analysis of residual dipolar coupling data for proteins. *Journal of the American Chemical Society*, 123(7):1416-1424, 2001

[152] Sunada, S., Go, N., and Koehl, P. Calculation of nuclear magnetic resonance order parameters in proteins by normal mode analysis. *The Journal of chemical physics*, 104(12):4768-4775, 1996.

[153] Maragakis, P., Lindorff-Larsen, K., Eastwood, M. P., Dror, R. O., Klepeis, J. L., Arkin, I.T., Jensen, M.O., Xu, H., Trbovic, N., Friesner, R. A., and Palmer, A. G. Microsecond molecular dynamics simulation shows effect of slow loop dynamics on backbone amide order parameters of proteins. *The Journal of Physical Chemistry B*, 112(19):6155-6158, 2008.

[154] Duan, Y., Wu, C., Chowdhury, S., Lee, M. C., Xiong, G., Zhang, W., Yang, R., Cieplak, P., Luo, R., Lee, T., and Caldwell, J. A point-charge force field for molecular mechanics simulations of proteins based on condensed-phase quantum mechanical calculations. *Journal of computational chemistry*, 24(16):1999-2012, 2003.

[155] Cornell, W. D., Cieplak, P., Bayly, C. I., Gould, I.R., Merz, K.M., Ferguson, D. M., Spellmeyer, D. C., Fox, T., Caldwell, J. W., and Kollman, P. A. A second generation force field for the simulation of proteins, nucleic acids, and organic molecules. *Journal of the American Chemical Society*, 117(19):5179-5197, 1995.

[156] Kollman, P. A. Advances and continuing challenges in achieving realistic and predictive simulations of the properties of organic and biological molecules. *Accounts of Chemical Research*, 29(10):461-469, 1996.

[157] Foloppe, N. and MacKerell, Jr, A. D. All-atom empirical force field for nucleic acids: I. Parameter optimization based on small molecule and condensed phase macromolecular target data. *Journal of computational chemistry*, 21(2):86–104, 2000.

[158] Kaminski, G. A. and Friesner, R. A. Tirado-Rives, J., and Jorgensen, W. L. Evaluation and reparametrization of the OPLS-AA force field for proteins via comparison with

accurate quantum chemical calculations on peptides. *The Journal of Physical Chemistry B*, 105(28):6474–6487, 2001.

[159] Oostenbrink, C., Villa, A., Mark, A. E., and Van Gunsteren, W. F. A biomolecular force field based on the free enthalpy of hydration and solvation: the GROMOS force-field parameter sets 53A5 and 53A6. *Journal of computational chemistry*, 25(13):1656-1676, 2004.

[160] Schuler, L. D., Daura, X., and Van Gunsteren, W. F. An improved GROMOS96 force field for aliphatic hydrocarbons in the condensed phase. *Journal of Computational Chemistry*, 22(11):1205–1218, 2001.

[161] Wang, J., Wolf, R. M., Caldwell, J. W., Kollman, P. A., and Case, D. A. Development and testing of a general amber force field. *Journal of computational chemistry*, 25(9):157-1174, 2004.

[162] Jakunowski, H. Molecular Mechanics and Dynamics. Biochemistry Online: An Approach Based on Chemical Logic. 2016

[163] Makov, G. and Payne, M. C. Periodic boundary conditions in ab initio calculations. *Physical Review B*, 51(7):4014, 1995.

[164] Fincham, D. Optimisation of the Ewald sum for large systems. *Molecular Simulation*, 13(1):1-9, 1994

[165] Ryckaert, J. P., Ciccotti, G., and Berendsen, H. J. Numerical integration of the cartesian equations of motion of a system with constraints: molecular dynamics of n-alkanes. *Journal of Computational Physics*, 23(3): 327-341, 1977.

[166] Berendsen, H. J., Postma, J. V., van Gunsteren, W. F., DiNola, A. R. H. J., and Haak, J. R. Molecular dynamics with coupling to an external bath. *The Journal of chemical physics*, 81(8): 3684-3690, 1984.

[167] Jorgensen, W. L., Chandrasekhar, J., Madura, J. D., Impey, R. W., and Klein, M. L. Comparison of simple potential functions for simulating liquid water. *The Journal of chemical physics*, 79(2):926-935, 1983.

[168] Mahoney, M. W. and Jorgensen, W. L. A five-site model for liquid water and the reproduction of the density anomaly by rigid, nonpolarizable potential functions. *The Journal of Chemical Physics*, 112(20):8910-8922, 2000.

Bibliography

[169] Berendsen, H. J. C., Grigera, J, R., and Straatsma, T. P. The missing term in effective pair potentials. *The Journal of Physical Chemistry*, 91: 6269-6271,1987

[170] Jorgensen, W. L. and Jenson, C. Temperature dependence of TIP3P, SPC, and TIP4P water from NPT Monte Carlo simulations: Seeking temperatures of maximum density. *Journal of Computational Chemistry*, 19(10):1179-1186, 1998.

[171] Karplus, M. and McCammon, J. A. Molecular dynamics simulations of biomolecules. *Nature Structural Biology*, 9(9):646-652, 2002.

[172] Moraitakis, G., Purkiss, A. G., and Goodfellow, J. M. Simulated dynamics and biological macromolecules. *Reports on Progress in Physics*, 66(3):383-406, 2003

[173] Roux, B. and Simonson, T. Implicit solvent models. *Biophysical chemistry*, 78(1-2):1-20, 1999.

[174] Cheatham, T. I., Miller, J. L., Fox, T., Darden, T. A. and Kollman, P. A. Molecular dynamics simulations on solvated biomolecular systems: the particle mesh Ewald method leads to stable trajectories of DNA, RNA, and proteins. *Journal of the American Chemical Society*, 117(14):4193-4194, 1995.

[175] Standard, J.M., Energy minimization methods. *Chemistry*, Volume 380, 2015.

[176] Jaidhan, B. J., Rao, P. S., and Apparao, A. Energy Minimization and Conformation Analysis of Molecules using Steepest Descent Method. *International Journal of Computer Science and Information Technologies*, 5(3):3525-3528, 2014.

[177] A Conjugate Gradient Method for Unconstrained Optimization Problems. *International Journal of Mathematics and Mathematical Sciences*, 2009:1-4. 2009.

[178] Kabsch, W. and Sander, C. Dictionary of protein secondary structure: pattern recognition of hydrogen-bonded and geometrical features. *Biopolymers*, 22(12):2577-2637, 1983.

[179] Humphrey, W., Dalke, A. and Schulten, K. VMD: visual molecular dynamics. *Journal of molecular graphics*, 14(1):33-38, 1996.

[180] Pettersen, E. F., Goddard, T. D., Huang, C. C., Couch, G. S., Greenblatt, D. M., Meng, E. C., and Ferrin, T. E. UCSF Chimera—a visualization system for exploratory research and analysis. *Journal of computational chemistry*, 25(13):605-1612, 2004.

[181] Kirkwood, J. G. Statistical mechanics of fluid mixtures. *The Journal of Chemical Physics*, 3(5):300-313, 1935.

[182] Leach, A. and Kier, L.B., Molecular modeling: principles and applications. *Journal of Medicinal Chemistry*, 40(18):2969, 1997.

[183] Torrie, G. M., and Valleau, J. P, Nonphysical sampling distributions in Monte Carlo free energy estimation: Umbrella sampling. *Journal of Computational Physics*, 23:187-199, 1977.

[184] Kumar, S., Rosenberg, J. M., Bouzida, D., Swendsen, R. H. and Kollman, P. A. The weighted histogram analysis method for free-energy calculations on biomolecules. I. The method. *Journal of computational chemistry*, 13(8):1011-1021, 1992.

[185] Souaille, M. and Roux, B. Extension to the weighted histogram analysis method: combining umbrella sampling with free energy calculations. *Computer physics communications*, 135(1):40-57, 2001.

[186] Kollman, P. A., Massova, I., Reyes, C., Kuhn, B., Huo, S., Chong, L., and Donini, O. Calculating structures and free energies of complex molecules: combining molecular mechanics and continuum models. *Accounts of chemical research*, 33(12): 889-897, 2000.

[187] Hou, T., Wang, J., Li, Y., and Wang, W. Assessing the performance of the MM/PBSA and MM/GBSA methods. 1. The accuracy of binding free energy calculations based on molecular dynamics simulations. *Journal of chemical information and modeling*, 51(1):69-82, 2010.

[188] Wang, J., Hou, T. and Xu, X. Recent advances in free energy calculations with a combination of molecular mechanics and continuum models. *Current Computer-Aided Drug Design*, 2(3):287-306, 2006.

[189] Sato, R., Harada, R. and Shigeta, Y. The binding structure and affinity of photodamaged duplex DNA with members of the photolyase/cryptochrome family: A computational study. *Biophysics and physicobiology*, 15:18-27, 2018.

[190] Metz, A., Pfleger, C., Kopitz, H., Pfeiffer-Marek, S., Baringhaus, K. H., and Gohlke, H. Hot spots and transient pockets: predicting the determinants of small-molecule binding to a protein–protein interface. *Journal of chemical information and modeling*, 52(1):120−133, 2011.

[191] Gohlke, H., Kiel, C., and Case, D. A. Insights into protein–protein binding by binding free energy calculation and free energy decomposition for the Ras–Raf and Ras–RalGDS complexes. *Journal of molecular biology*, 330(4):891−913, 2003.

[192] Miller III, B. R., McGee Jr, T. D., Swails, J. M., Homeyer, N., Gohlke, H., and Roitberg, A. E. MMPBSA. py: an efficient program for end-state free energy calculations. *Journal of chemical theory and computation*, 8(9):3314-3321, 2012.

[193] Ahmad, R., Brandsdal, B. O., Michaud-Soret, I., and Willassen, N. P. Ferric uptake regulator protein: Binding free energy calculations and per-residue free energy decomposition. *Proteins: Structure, Function, and Bioinformatics*, 75(2):373–386, 2009.

[194] Chen, J., Zhang, S., Liu, X., and Zhang, Q. Insights into drug resistance of mutations D30N and I50V to HIV-1 protease inhibitor TMC-114: free energy calculation and molecular dynamic simulation. *Journal of molecular modeling*, 16(3): 459–468, 2010.

[195] Khosa, S., Frieg, B., Mulnaes, D., Kleinschrodt, D., Hoeppner, A., Gohlke, H., and Smits, S. H. Structural basis of lantibiotic recognition by the nisin resistance protein from Streptococcus agalactiae. *Scientific reports*, 6(1):18679–18692, 2016.

[196] Cele, F. N., Ramesh, M., and Soliman, M. E. Per-residue energy decomposition pharmacophore model to enhance virtual screening in drug discovery: a study for identification of reverse transcriptase inhibitors as potential anti-HIV agents. *Drug design*, development and therapy, 10:1365–1377, 2016

[197] Massova, I. and Kollman, P. A. Combined molecular mechanical and continuum solvent approach (MM-PBSA/GBSA) to predict ligand binding. *Perspectives in drug discovery and design*, 18(1):113-135, 2000.

[198] Massova, I. and Kollman, P. A. Computational alanine scanning to probe protein− protein interactions: a novel approach to evaluate binding free energies. *Journal of the American Chemical Society*, 121(36):8133-8143, 1999.

[199] Jain, A. N. Scoring functions for protein-ligand docking. *Current Protein and Peptide Science*, 7(5):407-420, 2006.

[200] Leach, A. R. and Kuntz, I. D. Conformational analysis of flexible ligands in macromolecular receptor sites. *Journal of Computational Chemistry*, 13(6):730–748, 1992.

[201] Ewing, T. J., Makino, S., Skillman, A. G., and Kuntz, I. D. DOCK 4.0: search strategies for automated molecular docking of flexible molecule databases. *Journal of computer-aided molecular design*, 15(5):411–428, 2001.

[202] Shoichet, B. K., Stroud, R. M., Santi, D. V., Kuntz, I. D., and Perry, K. M. Structure-based discovery of inhibitors of thymidylate synthase. *Science*, 259(5100):1445–1450, 1993.

[203] Miller, M. D., Kearsley, S. K., Underwood, D. J., and Sheridan, R. P. FLOG: a system to select 'quasi-flexible' ligands complementary to a receptor of known three-dimensional structure. *Journal of computer-aided molecular design*, 8(2):153–174, 1994.

[204] Bron, C. and Kerbosch, J. Algorithm 457: finding all cliques of an undirected graph. *Communications of the ACM*, 16(9):575–576, 1973.

[205] Koshland, D. E. Correlation of structure and function in enzyme action. *Science*, 142(3599):1533-1541, 1963.

[206] Hammes, G. G. Multiple conformational changes in enzyme catalysis. *Biochemistry*, 41(26):8221–8228, 2002.

[207] Morris, G. M., Goodsell, D. S., Halliday, R. S., Huey, R., Hart, W. E., Belew, R. K., and Olson, A. J. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. *Journal of computational chemistry*, 19(14):1639-1662, 1998.

[208] Rarey, M., Kramer, B., Lengauer, T., and Klebe, G. A fast flexible docking method using an incremental construction algorithm. *Journal of molecular biology*, 261(3):470–489, 1996.

[209] Morris, G. M., Goodsell, D. S., Halliday, R. S., Huey, R., Hart, W.E., Belew, R. K., and Olson, A. J. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. *Journal of computational chemistry*, 19(14):1639-1662, 1998.

[210] Trott, O., Olson, A. J. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of computational chemistry*, 31(2):455-461, 2009

[211] Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S. and Olson, A. J. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of computational chemistry*, 30(16):2785-2791, 2009.

[212] Morris, G. M., Goodsell, D. S., Pique, M. E., Lindstrom, W. L., Huey, R., Forli, S., Hart, W. E., Halliday, S., Belew, R., and Olson, A. J. AutoDock Version 4.2: Automated Docking of Flexible Ligands to Flexible Receptors. 1-66, 2012

[213] Cohen, F. E., and Prusiner, S. B. Pathologic conformations of prion proteins. *Annual Review of Biochemistry*, 67(1):793–819, 1998.

[214] Selkoe, D. J. The cell biology of β-amyloid precursor protein and presenilin in Alzheimer's disease. *Trends in cell biology*, 8(11):447-453, 1998.

[215] Loregian, A., Marsden, H. S., and Palu, G. Protein–protein interactions as targets for antiviral chemotherapy. *Reviews in medical virology*, 12(4):239–262, 2002.

[216] Conte, L. L., Chothia, C., and Janin, J. The atomic structure of protein-protein recognition sites1. *Journal of molecular biology*, 285(5):2177-2198, 1999.

[217] Arkin, M. R. and Wells, J. A. Small-molecule inhibitors of protein–protein interactions: progressing towards the dream. *Nature reviews Drug discovery*, 3(4):301-317, 2004.

[218] Wells, J. A. and McClendon, C. L. Reaching for high-hanging fruit in drug discovery at protein–protein interfaces. *Nature*, 450(7172):1001-1009, 2007.

[219] Janin, J. Protein–protein recognition. *Progress in Biophysics & Molecular Biology*, 64 (2–3):145-166, 1995.

[220] Jones, S. and Thornton, J. M. Principles of protein-protein interactions. *Proceedings of the National Academy of Sciences*, 93(1):13–20, 1996.

[221] Janin, J. and Chothia, C. The structure of protein–protein recognition sites. *Journal of Biological Chemistry*, 265(27):16027–16030, 1990.

[222] Keskin, O., Gursoy, A., Ma, B., and Nussinov, R. Principles of protein− protein interactions: What are the preferred ways for proteins to interact? *Chemical reviews*, 108(4):1225-1244, 2008.

[223] Archakov, A. I., Govorun, V. M., Dubanov, A. V., Ivanov, Y. D., Veselovsky, A. V., Lewi, P., and Janssen, P. Protein-protein interactions as a target for drugs in proteomics. *Proteomics*, 3(4):380–391, 2003.

[224] Camacho, C. J., Gatchell, D. W., Kimura, S. R., and Vajda, S. Scoring docked conformations generated by rigid-body protein-protein docking. *Proteins: Structure, Function, and Bioinformatics*, 40(3):525–537, 2000.

[225] Goldman, B. B. and Wipke, W. T. QSD quadratic shape descriptors. 2. Molecular docking using quadratic shape descriptors (QSDock). *Proteins: Structure, Function, and Bioinformatics*, 38(1):79-94, 2000.

[226] Gardiner, E. J., Willett, P., and Artymiuk, P. J. Protein docking using a genetic algorithm. *Proteins: Structure, Function, and Bioinformatics*, 44(1):44-56, 2001.

[227] Chen, R. and Weng, Z. Docking unbound proteins using shape complementarity, desolvation, and electrostatics. *Proteins: Structure, Function, and Bioinformatics*, 47(3):281–294, 2002.

[228] Gray, J. J., Moughon, S., Wang, C., Schueler-Furman, O., Kuhlman, B., Rohl, C. A., and Baker, D. Protein–protein docking with simultaneous optimization of rigid-body displacement and side-chain conformations. *Journal of molecular biology*, 331(1):281–299, 2003.

[229] Duhovny, D., Nussinov, R., and Wolfson, H. J. Efficient unbound docking of rigid molecules. *In International workshop on algorithms in bioinformatics*, Springer, Berlin, Heidelberg, 185-200, 2002.

[230] Kozakov, D., Hall, D. R., Xia, B., Porter, K. A., Padhorny, D., Yueh, C., Beglov, D., and Vajda, S. The ClusPro web server for protein–protein docking. *Nature protocols*, 12(2):255–278, 2017.

[231] Chen, R., Mintseris, J., Janin, J., and Weng, Z. A protein–protein docking benchmark. *Proteins: Structure, Function, and Bioinformatics*, 52(1):88–91, 2003.

[232] Connolly, M. L. Shape complementarity at the hemoglobin α1β1 subunit interface. *Biopolymers*, 25(7):1229–1247, 1986.

[233] Jiang, F. and Kim, S. H. "Soft docking": matching of molecular surface cubes. *Journal of molecular biology*, 219(1):79–102, 1991.

[234] Walls, P. H. and Sternberg, M. J. New algorithm to model protein-protein recognition based on surface complementarity: Applications to antibody-antigen docking. *Journal of molecular biology*, 228(1):227–297, 1992.

[235] Inbar, Y., Schneidman-Duhovny, D., Halperin, I., Oron, A., Nussinov, R., and Wolfson, H. J. Approaching the CAPRI challenge with an efficient geometry-based docking. *Proteins: Structure, Function, and Bioinformatics*, 60(2):217-223, 2005

[236] Kuntz, I. D., Blaney, J. M., Oatley, S. J., Langridge, R., and Ferrin, T. E. A geometric approach to macromolecule-ligand interactions. *Journal of molecular biology*, 161(2): 269-288, 1982

[237] Hu, Z., Ma, B., Wolfson, H., and Nussinov, R. Conservation of polar residues as hot spots at protein interfaces. *Proteins: Structure, Function, and Bioinformatics*, 39(4):331-342, 2000.

[238] Wolfson, H. J. and Rigoutsos, I. Geometric hashing: An overview. *IEEE computational science and engineering*, 4(4):10-21, 1997.

[239] Stockman, G. Object recognition and localization via pose clustering. *Computer vision, graphics, and image processing*, 40(3):361–387, 1987.

[240] Sandak, B., Wolfson, H. J., and Nussinov, R. Flexible docking allowing induced fit in proteins: insights from an open to closed conformational isomers. *Proteins: Structure, Function, and Bioinformatics*, 32(2):159-174, 1998.

[241] Schneidman-Duhovny, D., Inbar, Y., Nussinov, R., and Wolfson, H. J. PatchDock and SymmDock: servers for rigid and symmetric docking. *Nucleic acids research*, 33:W363–W367, 2005.

[242] Zhang, C., Vasmatzis, G., Cornette, J. L., and DeLisi, C. Determination of atomic desolvation energies from the structures of crystallized proteins1. *Journal of molecular biology*, 267(3):707–726, 1997.

[243] Comeau, S. R., Gatchell, D. W., Vajda, S., and Camacho, C. J. ClusPro: a fully automated algorithm for protein-protein docking. *Nucleic Acids Research*, 32:W96–99, 2004

[244] Comeau, S. R., Gatchell, D. W., Vajda, S., and Camacho, C. J. ClusPro: an automated docking and discrimination method for the prediction of protein complexes. *Bioinformatics*, 20(1):45–50.

[245] Comeau, S. R., Kozakov, D., Brenke, R., Shen, Y., Beglov, D., and Vajda, S. ClusPro: performance in CAPRI rounds 6–11 and the new server. *Proteins: Structure, Function, and Bioinformatics*, 69(4):781–785, 2007.

[246] Kozakov, D., Hall, D. R., Beglov, D., Brenke, R., Comeau, S. R., Shen, Y., Li, K., Zheng, J., Vakili, P., Paschalidis, I. C., and Vajda, S. Achieving reliability and high accuracy in automated protein docking: ClusPro, PIPER, SDU, and stability analysis in CAPRI rounds 13–19. *Proteins: Structure, Function, and Bioinformatics*, 78(15):3124–3130, 2010.

[247] Kozakov, D., Beglov, D., Bohnuud, T., Mottarella, S. E., Xia, B., Hall, D. R., and Vajda, S. How good is automated protein docking? *Proteins: Structure, Function, and Bioinformatics*, 81(12):2159–2166, 2013.

[248] Kozakov, D., Hall, D.R., Xia, B., Porter, K.A., Padhorny, D., Yueh, C., Beglov, D. and Vajda, S. The ClusPro web server for protein–protein docking. *Nature protocols*, 12(2):255-278, 2017.

[249] Kozakov, D., Brenke, R., Comeau, S.R. and Vajda, S., 2006. PIPER: an FFT-based protein docking program with pairwise potentials. *Proteins: Structure, Function, and Bioinformatics*, 65(2):392–406.

[250] Laskowski, R. A., Jablonska, J., Pravda, L., Vařeková, R. S. and Thornton, J. M. PDBsum: Structural summaries of PDB entries. *Protein Science*, 27(1):129-134, 2018.

[251] Greene, L. H., Lewis, T. E., Addou, S., Cuff, A., Dallman, T., Dibley, M., Redfern, O., Pearl, F., Nambudiry, R., Reid, A., and Sillitoe, I. The CATH domain structure database: new protocols and classification levels give a more comprehensive resource for exploring evolution. *Nucleic acids research*, 35:D291-D297, 2006.

[252] Laskowski, R. A. PDBsum new things. *Nucleic Acids Research*, 37:D355–D359, 2009,

[253] Hutchinson, E. G. and Thornton, J. M. HERA—a program to draw schematic diagrams of protein secondary structures. *Proteins: Structure, Function, and Bioinformatics*, 8(3):203–212, 1990.

[254] Laskowski, R. A. and Swindells, M. B. LigPlot+: multiple ligand–protein interaction diagrams for drug discovery. *Journal of Chemical Information and Modeling*, 51 (10): 2778-2786, 2011

[255] Clackson, T., and Wells, J. A. A hot spot of binding energy in a hormone-receptor interface. *Science*, 267(5196):383-386, 1995.

[256] Thorn, K. S. and Bogan, A. A. ASEdb: a database of alanine mutations and their effects on the free energy of binding in protein interactions. *Bioinformatics*. 17(3):284-5, 2001.

[257] Moreira, I. S., Fernandes, P. A., and Ramos, M. J. Hot spots—A review of the protein–protein interface determinant amino-acid residues. *Proteins: Structure, Function, and Bioinformatics*, 68(4):803-812, 2007.

[258] Keskin, O., Ma, B., and Nussinov, R. Hot regions in protein–protein interactions: the organization and contribution of structurally conserved hot spot residues. *Journal of molecular biology*, 345(5):1281-1294, 2005.

[259] Caffrey, D. R., Somaroo, S., Hughes, J. D., Mintseris, J., and Huang, E. S. Are protein–protein interfaces more conserved in sequence than the rest of the protein surface? *Protein Science*, 13(1):190-202, 2004.

[260] Lockless, S. W. and Ranganathan, R. Evolutionarily conserved pathways of energetic connectivity in protein families. *Science*, 286, 295-299, 1999.

[261] Schreiber, G. and Fersht, A. R. Energetics of protein-protein interactions: Analysis of the Barnase-Barstar interface by single mutations and double mutant cycles. *Journal of molecular biology*, 248(2):478-486, 1995.

[262] Moreira, I. S., Fernandes, P. A., and Ramos, M. J. Hot spots - a review of the protein–protein interface determinant amino-acid residues. *Proteins: Structure, Function, and Bioinformatics*, 68:803-812, 2007.

[263] Bogan, A. A. and Thorn, K. S. Anatomy of hot spots in protein interfaces1. *Journal of molecular biology*, 280(1):1-9, 1998.

[264] González-Ruiz, D. and Gohlke, H. Targeting protein-protein interactions with small molecules: challenges and perspectives for omputational binding epitope detection and ligand finding. *Current medicinal chemistry*, 13(22):2607-2625, 2006.

[265] Darnell, S. J., LeGault, L. and Mitchell, J. C. KFC Server: interactive forecasting of protein interaction hot spots. *Nucleic acids research*, 36:W265-W269, 2008.

[266] Deng, L., Zhang, Q.C., Chen, Z., Meng, Y., Guan, J., and Zhou, S. PredHS: a web server for predicting protein–protein interaction hot spots by using structural neighborhood properties. *Nucleic acids research*, *42*(1):W290-W295, 2014.

[267] Kim, D.E., Chivian, D., and Baker, D. Protein structure prediction and analysis using the Robetta server. *Nucleic acids research*, 32:W526-W531, 2004.

[268] Kortemme, T., Kim, D. E., and Baker, D. Computational alanine scanning of protein-protein interfaces. *Science Signaling*., 2004(219):pl2-pl2, 2004.

[269] Kruger, D. M. and Gohlke, H. DrugScorePPI webserver: fast and accurate in silico alanine scanning for scoring protein–protein interactions. *Nucleic acids research*, 38:W480-W486, 2010.

[270] Shoichet, B. K. Virtual screening of chemical libraries. *Nature*, 432(7019): 862-865, 2004.

[271] Kitchen, D. B., Decornez, H., Furr, J. R., and Bajorath, J. Docking and scoring in virtual screening for drug discovery: methods and applications. *Nature reviews Drug discovery*, 3(11): 935-948, 2004.

[272] Bissantz, C., Folkers, G., and Rognan, D. Protein-based virtual screening of chemical databases. 1. Evaluation of different docking/scoring combinations. *Journal of medicinal chemistry*, 43(25):4759-4767, 2000.

[273] Willett, P., Barnard, J. M., and Downs, G. M. Chemical similarity searching. *Journal of chemical information and computer sciences*, 38(6):983-996, 1998.

[274] Bender, A. and Glen, R. C. A discussion of measures of enrichment in virtual screening: comparing the information content of descriptors with increasing levels of sophistication. *Journal of chemical information and modeling*, 45(5):1369-1375, 2005.

[275] Irwin, J. J., Shoichet, B. K., Mysinger, M. M., Huang, N., Colizzi, F., Wassam, P., and Cao, Y. Automated docking screens: a feasibility study. *Journal of medicinal chemistry*, 52(18):5712-5720, 2009.

[276] Irwin, J. J., Sterling, T., Mysinger, M. M., Bolstad, E. S., and Coleman, R. G. ZINC: a free tool to discover chemistry for biology. *Journal of chemical information and modeling*, 52(7):1757-1768, 2012.

[277] Coleman, R. G. and Sharp, K. A. Protein pockets: inventory, shape, and comparison. *Journal of chemical information and modeling*, 50(4):589-603, 2010.

[278] Wermuth, C. G., Ganellin, C. R., Lindberg, P., and Mitscher, L. A. Glossary of terms used in medicinal chemistry (IUPAC Recommendations 1998). *Pure and applied Chemistry*, 70(5):1129-1143, 1998.

[279] Sastry, G. M., Adzhigirey, M., Day, T., Annabhimoju, R., and Sherman, W. Protein and ligand preparation: parameters, protocols, and influence on virtual screening enrichments. *Journal of computer-aided molecular design*, 27(3):221-234, 2013.

[280] Banks, J. L., Beard, H. S., Cao, Y., Cho, A. E., Damm, W., Farid, R., Felts, A. K., Halgren, T. A., Mainz, D. T., Maple, J. R., and Murphy, R. Integrated modeling program, applied chemical theory (IMPACT). *Journal of computational chemistry*, 26(16):1752-1780, 2005.

[281] Greenwood, J. R., Calkins, D., Sullivan, A. P., and Shelley, J. C. Towards the comprehensive, rapid, and accurate prediction of the favorable tautomeric states of drug-like molecules in aqueous solution. *Journal of computer-aided molecular design*. 24(6-7):591-604, 2010.

[282] Eldridge, M. D., Murray, C. W., Auton, T. R., Paolini, G. V., and Mee, R. P. Empirical scoring functions: I. The development of a fast empirical scoring function to estimate the binding affinity of ligands in receptor complexes. *Journal of computer-aided molecular design*, 11(5):425-445,1997.

[283] Salam, N. K., Nuti, R., and Sherman, W. Novel method for generating structure-based pharmacophores using energetic analysis. *Journal of chemical information and modeling*, 49(10):2356-2368, 2009.

[284] Albrand, G. and Terret, C. Early breast cancer in the elderly: assessment and management considerations. *Drug Aging*; 25(1):35-45, 2002.

[285] Labrie, F., Labrie, C., Bélanger, A., Simard, J., Gauthier, S., Luu-The, V., Mérand, Y., Giguere, V., Candas, B., Luo, S., and Martel, C. EM-652 (SCH 57068), a third generation SERM acting as pure antiestrogen in the mammary gland and endometrium. *The Journal of steroid biochemistry and molecular biology*, 69(1-6):51-84, 1999.

[286] Ali, S. and Coombes, C. Endocrine-responsive breast cancer and strategies for combating resistance. *Nature Reviews Cancer*, 2(2):101-112, 2002.

[287] Wu, R. C., Qin, J., Yi, P., Wong, J., Tsai, S. Y., Tsai, M. J., and O'Malley, B. W. Selective phosphorylations of the SRC-3/AIB1 coactivator integrate genomic reponses to multiple cellular signaling pathways. *Molecular cell*, 15(6):937-949, 2004.

[288] Jiang, J., Sarwar, N., Peston, D., Kulinskaya, E., Shousha, S., Coombes, R. C., and Ali, S. Phosphorylation of estrogen receptor-α at Ser167 is indicative of longer disease-free and overall survival in breast cancer patients. *Clinical Cancer Research*, 13(19):5769-5776, 2007.

[289] Giamas, G., Castellano, L., Feng, Q., Knippschild, U., Jacob, J., Thomas, R.S., Coombes, R.C., Smith, C.L., Jiao, L.R., and Stebbing, J. CK1δ modulates the transcriptional activity of ERα via AIB1 in an estrogen-dependent manner and regulates ERα–AIB1 interactions. *Nucleic acids research*, 37(9):3110-3123, 2009.

[290] Giamas, G., Stebbing, J., Vorgias, C. E., and Knippschild, U. Protein kinas as target for cancer treatment. *Pharmacogenomics*, 8:1005-1016, 2007

Bibliography

[291] Hanks, S.K. and Hunter, T. Protein kinases 6. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification. *The FASEB journal*, 9(8):576-596, 1995.

[292] Manning, B. D. and Cantley, L. C. Hitting the target: emerging technologies in the search for kinase substrates. *Science Signaling*, 2002(162):49pe, 2002.

[293] Inoue, T., Kon, T., Ohkura, R., Yamakawa, H., Ohara, O., Yokota, J., and Sutoh, K. BREK/LMTK2 is a myosin VI-binding protein involved in endosomal membrane trafficking. *Genes to Cells*, 13(5):483-495, 2008.

[294] Robinson, D. R., Wu, Y. M., and Lin, S. F. The protein tyrosine kinase family of the human genome. *Oncogene*, 19(49):5548-5557, 2000.

[295] Tomomura, M., Morita, N., Yoshikawa, F., Konishi, A., Akiyama, H., Furuichi, T., and Kamiguchi, H. Structural and functional analysis of the apoptosis-associated tyrosine kinase (AATYK) family. *Neuroscience*, 148(2):510-521, 2007.

[296] Boutet, E., Lieberherr, D., Tognolli, M., Schneider, M., and Bairoch, A. UniProtKB/Swiss-Prot. *Methods in Molecular Biology*, 406:89-112, 2007.

[297] Shen, H., Zhu, Y., Wu, Y. J., Qiu, H. R. and Shu, Y. Q. Genomic alterations in lung adenocarcinomas detected by multicolor fluorescence in situ hybridization and comparative genomic hybridization. *Cancer genetics and cytogenetics*, 181(2):100-107, 2008.

[298] Hindie, V., Stroba, A., Zhang, H., Lopez-Garcia, L. A., Idrissova, L., Zeuzem, S., Hirschberg, D., Schaeffer, F., Jørgensen, T. J., Engel, M., and Alzari, P. M. Structure and allosteric effects of low-molecular-weight activators on the protein kinase PDK1. *Nature chemical biology*, 5(10):758-764, 2009.

[299] Choucair, K. A., Guérard, K. P., Ejdelman, J., Chevalier, S., Yoshimoto, M., Scarlata, E., Fazli, L., Sircar, K., Squire, J. A., Brimo, F., and Cunha, I. W. The 16p13. 3 (PDPK1) genomic gain in prostate cancer: a potential role in disease progression. Translational oncology, 5(6):453-460, 2012.

[300] Wiederstein, M. and Sippl, M. J. ProSA-web: interactive web service for the recognition of errors in three-dimensional structures of proteins. *Nucleic acids research*, 35:W407-W410, 2007.

[301] Bowie, J. U., Luthy, R., and Eisenberg, D. A method to identify protein sequences that fold into a known three-dimensional structure. *Science*, 253(5016):164-170, 1991.

[302] Lüthy, R., Bowie, J. U., and Eisenberg, D. Assessment of protein models with three-dimensional profiles. *Nature*, 356(6364):83-85, 1992.

[303] Lovell, S. C., Davis, I. W., Arendall III, W. B., De Bakker, P. I., Word, J. M., Prisant, M. G., Richardson, J. S., and Richardson, D. C. Structure validation by Cα geometry: ϕ, ψ and Cβ deviation. *Proteins: Structure, Function, and Bioinformatics*, 50(3):437-450, 2003.

[304] Sievers, F. and Higgins, D. G. Clustal Omega for making accurate alignments of many protein sequences. *Protein Science*, 27(1):135-145, 2018.

[305] Kaus, J. W., Pierce, L. T., Walker, R. C., and McCammon, J. A. Improving the efficiency of free energy calculations in the amber molecular dynamics package. *Journal of chemical theory and computation*, 9(9):4131-4139, 2013.

[306] Hornak, V., Abel, R., Okur, A., Strockbine, B., Roitberg, A., and Simmerling, C. Comparison of multiple Amber force fields and development of improved protein backbone parameters. *Proteins: Structure, Function, and Bioinformatics*, 65(3):712-725, 2006.

[307] Tsodikov, O. V., Record Jr, M. T., and Sergeev, Y. V. Novel computer program for fast exact calculation of accessible and molecular surface areas and average surface curvature. *Journal of computational chemistry*, 23(6):600-609, 2002.

[308] Chakraborty, C. and Agrawal, A. Computational analysis of C - reactive protein for assessmentof Molecular Dynamics and Interaction Properties. *Cell Biochemistry and Biophysics*, 67:645–656, 2013.

[309] Roseman, M. A. Hydrophilicity of polar amino acid side-chains is markedly reduced by flanking peptide bonds. *Journal of molecular biology*, 200(3):513-522, 1988.

[310] Callebaut, I., Labesse, G., Durand, P., Poupon, A., Canard, L., Chomilier, J., Henrissat, B., and Mornon, J. P. Deciphering protein sequence information through hydrophobic cluster analysis (HCA): current status and perspectives. *Cellular and Molecular Life Sciences CMLS*, 53(8):621-645, 1997.

[311] Sharp, K.A. and Honig, B. Electrostatic interactions in macromolecules: theory and applications. *Annual review of biophysics and biophysical chemistry*, 19(1):301-332, 1990.

[312] Huang, B. and Schroeder, M. LIGSITE csc: predicting ligand binding sites using the Connolly surface and degree of conservation. *BMC structural biology*, 6(1):19, 2006.

[313] Dyson, H. J., Wright, P. E., and Scheraga, H. A. The role of hydrophobic interactions in initiation and propagation of protein folding. *Proceedings of the National Academy of Sciences*, 103(35):13057-13061, 2006.

[314] Spolar, R. S., Ha, J. H., and Record, M. T. Hydrophobic effect in protein folding and other noncovalent processes involving proteins. *Proceedings of the National Academy of Sciences*, 86(21):8382-8385, 1989.

[315] Munson, M., Balasubramanian, S., Fleming, K. G., Nagi, A. D., O'Brien, R., Sturtevant, J. M., and Regan, L. What makes a protein a protein? Hydrophobic core designs that specify stability and structural properties. *Protein Science*, 5(8):1584-1593, 1996.

[316] Dill, K. A., Bromberg, S., Yue, K., Chan, H. S., Ftebig, K. M., Yee, D. P., and Thomas, P. D. Principles of protein folding—a perspective from simple exact models. *Protein science*, 4(4): pp.561-602, 1995.

[317] Giovambattista, N., Lopez, C. F., Rossky, P. J., and Debenedetti, P. G. Hydrophobicity of protein surfaces: Separating geometry from chemistry. *Proceedings of the National Academy of Sciences*, 105(7):2274-2279, 2008.

[318] Honig, B. and Nicholls, A. Classical electrostatics in biology and chemistry. *Science*, 268:1144-1149, 1995.

[319] Warshel, A. and Aqvist, J. Electrostatic energy and macromolecular function. *Annual review of biophysics and biophysical chemistry*, 20(1):267-298, 1991.

[320] Bashford, D. Macroscopic electrostatic models for protonation states in proteins. *Frontiers in Bioscience*, 9(1-3): 1082-1099, 2004.

[321] Chikalov, I., Yao, P., Moshkov, M., and Latombe J. C. Learning probabilistic models of hydrogen bond stability from molecular dynamics simulation trajectories. *BMC Bioinformatics*, 12(1): S1-S34, 2011.

[322] Laurie, A. T. and Jackson, R. M. Q-SiteFinder: an energy-based method for the prediction of protein–ligand binding sites. *Bioinformatics*, 21(9):1908-1916, 2005.

[323] Colditz, G. A. Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. *Journal of the National Cancer Institute*, 90(11):814-823, 1998.

[324] Hankinson, S. E., Colditz, G. A., and Willett, W. C. Towards an integrated model for breast cancer etiology: the lifelong interplay of genes, lifestyle, and hormones. *Breast Cancer Research*, 6(5):213-218, 2004.

[325] Utsumi, T., Kobayashi, N., and Hanada, H. Recent perspectives of endocrine therapy for breast cancer. *Breast Cancer*, 14(2):194-199, 2007.

[326] McDonnell, D. P. and Norris, J. D. Connections and regulation of the human estrogen receptor. *Science*, 296(5573):1642-1644, 2002.

[327] Guo, S. and Sonenshein, G. E. Forkhead box transcription factor FOXO3a regulates estrogen receptor alpha expression and is repressed by the Her-2/neu/phosphatidylinositol 3-kinase/Akt signaling pathway. *Molecular and cellular biology*, 24(19):8681-8690, 2004.

[328] Sarwar, N., Kim, J. S., Jiang, J., Peston, D., Sinnett, H. D., Madden, P., Gee, J. M., Nicholson, R. I., Lykkesfeldt, A. E., Shousha, S., and Coombes, R. C. Phosphorylation of ERα at serine 118 in primary breast cancer and in tamoxifen-resistant tumours is indicative of a complex role for ERα phosphorylation in breast cancer progression. *Endocrine-related cancer*, 13(3):851-861, 2006.

[329] Khan, S. H., Ahmad, F., Ahmad, N., Flynn, D. C., and Kumar, R. Protein-protein interactions: principles, techniques, and their potential role in new drug development. *Journal of Biomolecular Structure and Dynamics*, 28(6):929-938, 2011.

[330] Andrusier, N., Nussinov, R., and Wolfson, H. J. FireDock: fast interaction refinement in molecular docking. *Proteins: Structure, Function, and Bioinformatics*, 69(1):139-159, 2007

[331] Verbeek, B. S., Adriaansen-slot, S. S., Rijksen, G., and Vroom, T.M. Grb2 overexpression in nuclei and cytoplasm of human breast cells: a histochemical and biochemical study of normal and neoplastic mammary tissue specimens. The Journal of Pathology: *A Journal of the Pathological Society of Great Britain and Ireland*, 183(2):195-203, 1997.

[332] Blazer, L. L. and Neubig, R. R. Small molecule protein–protein interaction inhibitors as CNS therapeutic agents: current progress and future hurdles. *Neuropsychopharmacology*, 34(1):126–141, 2009.

[333] Gurung, A. B., Bhattacharjee, A., Ali, M. A., Al-Hemaid, F., and Lee, J. Binding of small molecules at interface of protein–protein complex–A newer approach to rational drug design. *Saudi journal of biological sciences*, 24(2):379-388, 2017.

[334] Kuenemann, M. A., Sperandio, O., Labbé, C. M., Lagorce, D., Miteva, M. A., and Villoutreix, B. O. In silico design of low molecular weight protein–protein interaction inhibitors: overall concept and recent advances. *Progress in biophysics and molecular biology*, 119(1):20-32, 2015.

[335] Panwar, D., Rawal, L., and Ali, S. Molecular docking uncovers TSPY binds more efficiently with eEF1A2 compared to eEF1A1. *Journal of Biomolecular Structure and Dynamics*, 33(7):1412-1423, 2015.

[336] Rognan, D. Rational design of protein–protein interaction inhibitors. *MedChemComm*, 6(1):51-60, 2015.

[337] Xu, J., Xu, J., and Chen, H. Interpreting the structural mechanism of action for MT7 and human muscarinic acetylcholine receptor 1 complex by modeling protein–protein interaction. *Journal of Biomolecular Structure and Dynamics*, 30(1):30-44, 2012.

[338] Jin, L., Wang, W., and Fang, G. Targeting protein-protein interaction by small molecules. *Annual review of pharmacology and toxicology*, 54(1):435-456, 2014.

[339] Zinzalla, G. and Thurston, D. E. Targeting protein–protein interactions for therapeutic intervention: a challenge for the future. *Future medicinal chemistry*, 1(1):65-93, 2009.

[340] Cheung, L. S. L., Kanwar, M., Ostermeier, M., and Konstantopoulos, K. A hot-spot motif characterizes the interface between a designed ankyrin-repeat protein and its target ligand. *Biophysical journal*, 102(3):407-416, 2012.

[341] Thornton, J. M. The Hans Neurath Award lecture of The Protein Society: proteins—a testament to physics, chemistry, and evolution. *Protein Science*, 10(1):3-11, 2001.

[342] Cunningham, B. C. and Wells, J. A. High-resolution epitope mapping of hGH-receptor interactions by alanine-scanning mutagenesis. Science, 244(4908):1081-1085, 1989.

[343] Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N., and Bourne, P. E. The protein data bank. *Nucleic acids research*, 28(1):235-242, 2000.

[344] Rose, P. W., Prlic, A., Altunkaya, A., Bi, C., Bradley, A. R., Christie, C. H., Di Costanzo, L., Duarte, J. M., Dutta, S., Feng, Z., Green, R. K., Goodshell, D. S., Hudson, B., Kalro, T., Valasatava, Y., Voigt, M., Westbrook, J. D., Woo, J., Yang, H., Young, J. Y., Zardecki, C., Berman, H. M., Burley, S. K. The RCSB protein data bank: integrative view of protein, gene and 3D structural information. *Nucleic acids research*, 45(D1):D271-D281, 2017.

[345] Arkin, M. R., Randal, M., DeLano, W. L., Hyde, J., Luong, T. N., Oslob, J.D., Raphael, D. R., Taylor, L., Wang, J., McDowell, R. S., and Wells, J. A. Binding of small molecules to an adaptive protein–protein interface. *Proceedings of the National Academy of Sciences*, 100(4):1603-1608, 2003.

[346] Castro, G., Boswell, C. A., and Northrup, S. H. Dynamics of protein-protein docking: cytochrome c and cytochrome c peroxidase revisited. *Journal of Biomolecular Structure and Dynamics*, 16(2):413-424, 1998.

[347] Eyrisch, S. and Helms, V. Transient pockets on protein surfaces involved in protein−protein interaction. *Journal of medicinal chemistry*, 50(15):3457-3464, 2007.

[348] Eyrisch, S. and Helms, V. What induces pocket openings on protein surface patches involved in protein–protein interactions? *Journal of computer-aided molecular design*, 23(2):73–86, 2009.

[349] Eyrisch, S., Medina-Franco, J. L. and Helms, V. Transient pockets on XIAP-BIR2: toward the characterization of putative binding sites of small-molecule XIAP inhibitors. *Journal of molecular modeling*, 18(5):2031–2042, 2012.

[350] Saranya, N., Saravanan, K. M., Michael, G. M., and Selvaraj, S. Analysis of secondary structural and physicochemical changes in protein–protein complexes. *Journal of Biomolecular Structure and Dynamics* 34(3):508-516, 2016

[351] Rapp, C., Kalyanaraman, C., Schiffmiller, A., Schoenbrun, E. L. and Jacobson, M. P. A molecular mechanics approach to modeling protein–ligand interactions: relative binding affinities in congeneric series. *Journal of chemical information and modeling*, 51(9):2082-2089, 2011.

[352] Källberg, M., Wang, H., Wang, S., Peng, J., Wang, Z., Lu, H. and Xu, J. Template-based protein structure modeling using the RaptorX web server. Nature protocols, 7(8):1511-1522, 2012.

[353] Peng, J. and Xu, J. RaptorX: exploiting structure information for protein alignment by statistical inference. *Proteins: Structure, Function, and Bioinformatics*, 79(S10):161-171, 2011.

[354] Ma, J., Wang, S., Zhao, F. and Xu, J. Protein threading using context-specific alignment potential. *Bioinformatics*, 29(13):257-265, 2013.

[355] Lensink, M.F. and Wodak, S.J., Docking and scoring protein interactions: CAPRI 2009. *Proteins: Structure, Function, and Bioinformatics*, 78(15):3073–3084, 2010.

[356] Lensink, M. F. and Wodak, S. J. Docking, scoring, and affinity prediction in CAPRI. *Proteins: Structure, Function, and Bioinformatics*, 81(12):2082-2095, 2013.

[357] Padhorny, D., Kazennov, A., Zerbe, B. S., Porter, K. A., Xia, B., Mottarella, S. E., Kholodov, Y., Ritchie, D.W., Vajda, S., and Kozakov, D. Protein–protein docking by fast generalized Fourier transforms on 5D rotational manifolds. *Proceedings of the National Academy of Sciences*, 113(30):4286-4293, 2016.

[358] Roe, D. R. and Cheatham III, T. E. PTRAJ and CPPTRAJ: software for processing and analysis of molecular dynamics trajectory data. *Journal of chemical theory and computation*, 9(7):3084-3095, 2013.

[359] Corbi-Verge, C., Marinelli, F., Zafra-Ruano, A., Ruiz-Sanz, J., Luque, I., and Faraldo-Gomez, J. D. Two-state dynamics of the SH3–SH2 tandem of Abl kinase and the allosteric role of the N-cap. *Proceedings of the National Academy of* Sciences, 2013, 110(36):3372-3380.

[360] Boggon, T. J. and Eck, M. J. Structure and regulation of Src family kinases. *Oncogene*, 23(48):7918-7927, 2004,

[361] Sarma, H. and Mattaparthi, V. S. K. Unveiling the Transient Protein-Protein Interactions that Regulate the Activity of Human Lemur Tyrosine Kinase-3 (LMTK3) Domain by Cyclin Dependent Kinase 5 (CDK5) in Breast Cancer: An in silico Study. *Current Proteomics*, 15(1):62-70, 2018.

[362] Taylor, S. S., Knighton, D. R., Zheng, J., Sowadski, J. M., Gibbs, C. S., and Zoller, M. J. A template for the protein kinase family. *Trends in biochemical sciences*, 18(3):84-89, 1993.

[363] Baker, E. N. and Hubbard, R. E. Hydrogen bonding in globular proteins. *Progress in biophysics and molecular biology*, 44(2):97-179, 1984.

[364] Jeffrey, G.A. and Jeffrey, G.A., An introduction to hydrogen bonding, Vol. 12, page 228, New York: Oxford university press, 1997.

[365] Lu, Q., Ren, J., Song, J., and Li, J. Co-Occurring Atomic Contacts for the Characterization of Protein Binding Hot Spots. *PloS one*, 10(12):e0144486, 2015.

[366] Cho, K. I., Kim, D., and Lee, D. A feature-based approach to modeling protein–protein interaction hot spots. *Nucleic acids research*, 37(8):2672–2687, 2009.

[367] Xu, Z., Qi, X., Zhang, X., and Yu, L. Preoperative serum LMTK3 as a novel biomarker in non-small cell lung cancer. *Tumor Biology*, 35(5):5007-5011, 2014.

[368] Kornev, A. P. and Taylor, S. S. Dynamics-driven allostery in protein kinases. *Trends in biochemical sciences*, 40(11):628–647, 2015.

[369] Hanks, S. K. and Quinn, A. M. Protein kinase catalytic domain sequence database: Identification of conserved features of primary structure and classification of family members. *Methods in Enzymology*, 200:38–62, 1991.

[370] Scheeff, E. D. and Bourne, P. E. Structural evolution of the protein kinase-like superfamily. *PLoS Computational Biology*, 1(5):e49, 2005.

[371] Ahn, J. S., Radhakrishnan, M. L., Mapelli, M., Choi, S., Tidor, B., Cuny, G. D., Musacchio, A., Yeh, L. A., and Kosik, K. S. Defining Cdk5 ligand chemical space with small molecule inhibitors of tau phosphorylation. *Chemistry & biology*, 12(7):811-823, 2005.

[372] Chou, K. C. and Chen, N. Y. The biological functions of low-frequency vibrations (phonons). *Biophysical Chemistry volume*, 22(3):219-235, 1985.

[373] Chou, K. C., Chen, N. Y., and Forsen, S. The biological functions of low-frequency phonons. 2. Cooperative effects. *Chemica Scripta*, 18(3):126-132, 1981.

[374] Chou, K. C. and Mao, B. Collective motion in DNA and its role in drug intercalation. Biopolymers: *Original Research on Biomolecules*, 27(11):1795-1815, 1988.

[375] Chou, K. C., Maggiora, G. M., and Mao, B. Quasi-continuum models of twist-like and accordion-like low-frequency motions in DNA. *Biophysical Journal*, 56(2):295-305, 1989.

[376] Martel, P. Biophysical aspects of neutron scattering from vibrational modes of proteins. *Progress in biophysics and molecular biology*, 57(3):129-179, 1992.

[377] Chou, K. C. Low-frequency collective motion in biomacromolecules and its biological functions. *Biophysical chemistry*, 30(1):3-48, 1988.

[378] Wang, J. F., Gong, K., Wei, D. Q., Li, Y. X., and Chou, K. C. Molecular dynamics studies on the interactions of PTP1B with inhibitors: from the first phosphate-binding site to the second one. *Protein Engineering, Design & Selection*, 22(6):349-355, 2009.

[379] Chou, K. C. Low-frequency resonance and cooperativity of hemoglobin. *Trends in Biochemical Sciences*, 14(6):212-213, 1989.

[380] Chou, K. C., Zhang, C. T., and Maggiora, G. M. Solitary wave dynamics as a mechanism for explaining the internal motion during microtubule growth. *Biopolymers: Original Research on Biomolecule*s, 34(1):143-153, 1994.

[381] Chou, K. C. An unprecedented revolution in medicinal chemistry driven by the progress of biological science. *Current topics in medicinal chemistry*, 17(21):2337-2358. 2017.

[382] Gordon, G. A. Designed electromagnetic pulsed therapy: clinical applications. *Journal of Cellular physiology*, 212(3):579-582, 2007.

[383] Gordon, G. A. Extrinsic electromagnetic fields, low frequency (phonon) vibrations, and control of cell function: a non-linear resonance system. *Journal of Biomedical Science and Engineering*, 1(03):152-156, 2008.

[384] Madkan, A., Blank, M., Elson, E., Chou, K.C., Geddis, M.S. and Goodman, R. Steps to the clinic with ELF EMF. *Natural Science*, 1(03):157-165, 2009.

[385] Chou, K. C. Structural bioinformatics and its impact to biomedical science. *Current medicinal chemistry*, 11(16):2105-2134, 2004.

[386] Chou, K. C., Watenpaugh, K. D., and Heinrikson, R. L. A model of the complex between cyclin-dependent kinase 5 and the activation domain of neuronal Cdk5 activator. *Biochemical and biophysical research communications*, 259(2):420-428, 1999.

[387] Zhang, J., Luan, C. H., Chou, K. C., and Johnson, G. V. Identification of the N-terminal functional domains of Cdk5 by molecular truncation and computer modeling. *Proteins: Structure, Function, and Bioinformatics*, 48(3):447-453, 2002.

[388] Chou, K. C., Wei, D. Q., and Zhong, W. Z. Binding mechanism of coronavirus main proteinase with ligands and its implication to drug design against SARS. *Biochemical and biophysical research communications*, 308(1):148-151, 2003.

[389] Huang, R. B., Du, Q. S., Wang, C. H., and Chou, K. C. An in-depth analysis of the biological functional studies based on the NMR M2 channel structure of influenza A virus. *Biochemical and biophysical research communications*, 377(4):1243-1247, 2008.

[390] Wang, S. Q., Du, Q. S., and Chou, K. C. Study of drug resistance of chicken influenza A virus (H5N1) from homology-modeled 3D structures of neuraminidases. *Biochemical and biophysical research communications*, 354(3):634-640, 2007.

[391] Chou, K. C. Molecular therapeutic target for type-2 diabetes. *Journal of proteome research*, 3(6):1284-1288, 2004.

[392] Li, X. B., Wang, S. Q., Xu, W. R., Wang, R. L., and Chou, K.C. Novel inhibitor design for hemagglutinin against H1N1 influenza virus by core hopping method. *PloS one*, 6(11):e28111, 2011.

[393] Wang, J. F. and Chou, K. C. Insights from modeling the 3D structure of New Delhi metallo-β-lactamse and its binding interactions with antibiotic drugs. *PLoS One*, 6(4):e18414, 2011.

[394] Wang, J. F. and Chou, K. C. Insights into the mutation-induced HHH syndrome from modeling human mitochondrial ornithine transporter-1. *PLoS One*, 7(1):e31048, 2012.

[395] Pielak, R. M., Schnell, J. R., and Chou, J. J. Mechanism of drug inhibition and drug resistance of influenza A M2 channel. *Proceedings of the National Academy of Sciences*, 106(18):7379-7384, 2009.

[396] Bakail, M. and Ochsenbein, F. Targeting protein–protein interactions, a wide open field for drug design. *Comptes Rendus Chimie*, 19(1-2):19-27, 2016.

[397] Li, H., Xiao, H., Lin, L., Jou, D., Kumari, V., Lin, J., and Li, C. Drug design targeting protein–protein interactions (PPIs) using multiple ligand simultaneous docking (MLSD) and drug repositioning: discovery of Raloxifene and Bazedoxifene as novel inhibitors of IL-6/GP130 interface. *Journal of medicinal chemistry*, 57(3):632−641, 2014.

[398] Schnell, J. R. and Chou, J. J. Structure and mechanism of the M2 proton channel of influenza A virus. *Nature*, 451(7178):591-595, 2008.

[399] Du, Q., Wang, S., Wei, D., Sirois, S., and Chou, K. C. Molecular modeling and chemical modification for finding peptide inhibitor against severe acute respiratory syndrome coronavirus main proteinase. *Analytical Biochemistry*, 337(2):262-270, 2005.

[400] Du, Q. S., Huang, R. B., Wang, C. H., Li, X. M., and Chou, K. C. Energetic analysis of the two controversial drug binding sites of the M2 proton channel in influenza A virus. *Journal of Theoretical Biology*, 259(1):159-164, 2009.

[401] Du, Q. S., Huang, R. B., Wang, S. Q., and Chou, K. C. Designing inhibitors of M2 proton channel against H1N1 swine influenza virus. *PloS one*, 5(2):e9388, 2010.

[402] Wang, S. Q., Du, Q. S., Huang, R. B., Zhang, D. W., and Chou, K. C. Insights from investigating the interaction of oseltamivir (Tamiflu) with neuraminidase of the 2009

H1N1 swine flu virus. *Biochemical and Biophysical Research Communications*, 386(3):432-436, 2009.

[403] Cai, L., Wang, Y., Wang, J. F., and Chou, K. C. Identification of proteins interacting with human SP110 during the process of viral infections. *Medicinal chemistry*, 7(2):121-126, 2011.

[404] Ma, Y., Wang, S. Q., Xu, W. R., Wang, R. L., and Chou, K. C. Design novel dual agonists for treating type-2 diabetes by targeting peroxisome proliferator-activated receptors with core hopping approach. *PLoS One*, 7(6):e38546, 2012.

[405] Chou, K. C. and Shen, H. B. Recent advances in developing web-servers for predicting protein attributes. *Natural Science*, 1(02):63-92, 2009.

[406] Jia, J., Liu, Z., Xiao, X., Liu, B., and Chou, K. C. Identification of protein-protein binding sites by incorporating the physicochemical properties and stationary wavelet transforms into pseudo amino acid composition. *Journal of Biomolecular Structure and Dynamics*, 34(9):1946-1961, 2016.

[407] Jia, J., Liu, Z., Xiao, X., Liu, B., and Chou, K. C. iSuc-PseOpt: identifying lysine succinylation sites in proteins by incorporating sequence-coupling effects into pseudo components and optimizing imbalanced training dataset. *Analytical biochemistry*, 497:48-56, 2016.

[408] Jia, J., Liu, Z., Xiao, X., Liu, B., and Chou, K. C. iCar-PseCp: identify carbonylation sites in proteins by Monte Carlo sampling and incorporating sequence coupled effects into general PseAAC. *Oncotarget*, 7(23):34558-34570, 2016.

[409] Jia, J., Zhang, L., Liu, Z., Xiao, X., and Chou, K. C. pSumo-CD: predicting sumoylation sites in proteins with covariance discriminant algorithm by incorporating sequence-coupled effects into general PseAAC. *Bioinformatics*, 32(20):3133-3141, 2016.

[410] Qiu, W.R., Sun, B.Q., Xiao, X., Xu, Z.C. and Chou, K.C. iPTM-mLys: identifying multiple lysine PTM sites and their different types. *Bioinformatics*, 32(20):3116-3123, 2016.

[411] Qiu, W. R., Xiao, X., Xu, Z. C. and Chou, K. C. iPhos-PseEn: identifying phosphorylation sites in proteins by fusing different pseudo components into an ensemble classifier. *Oncotarget*, 7(32):51270-51283, 2016.

[412] Zhang, C. J., Tang, H., Li, W. C., Lin, H., Chen, W., and Chou, K. C. iOri-Human: identify human origin of replication by incorporating dinucleotide physicochemical properties into pseudo nucleotide composition. *Oncotarget*, 7(43):69783-69793, 2016.

[413] Cheng, X., Zhao, S.G., Xiao, X. and Chou, K.C. iATC-mISF: a multi-label classifier for predicting the classes of anatomical therapeutic chemicals. *Bioinformatics*, 33(3):341-346, 2016.

[414] Cheng, X., Zhao, S. G., Xiao, X., and Chou, K. C. iATC-mHyb: a hybrid multi-label classifier for predicting the classification of anatomical therapeutic chemicals. *Oncotarget*, 8(35):58494, 2017.

[415] Feng, P., Ding, H., Yang, H., Chen, W., Lin, H., and Chou, K. C. iRNA-PseColl: identifying the occurrence sites of different RNA modifications by incorporating collective effects of nucleotides into PseKNC. *Molecular Therapy-Nucleic Acids*, 7:155-163, 2017.

[416] Liu, B., Wang, S., Long, R., and Chou, K. C. iRSpot-EL: identify recombination spots with an ensemble learning approach. *Bioinformatics*, 33(1):35-41, 2016.

[417] Liu, B., Wu, H., and Chou, K. C., Pse-in-One 2.0: an improved package of web servers for generating various modes of pseudo components of DNA, RNA, and protein sequences. *Natural Science*, 9(04):67-91, 2017.

[418] Liu, B., Wu, H., Zhang, D., Wang, X., and Chou, K. C. Pse-Analysis: a python package for DNA/RNA and protein/peptide sequence analysis based on pseudo components and kernel methods. *Oncotarget*, 8(8):13338-13343, 2017.

[419] Liu, B., Yang, F., and Chou, K. C., 2L-piRNA: a two-layer ensemble classifier for identifying piwi-interacting RNAs and their function. *Molecular Therapy-Nucleic Acids*, 7:267-277, 2017.

[420] Liu, L.M., Xu, Y., and Chou, K. C. iPGK-PseAAC: identify lysine phosphoglycerylation sites in proteins by incorporating four different tiers of amino acid pairwise coupling information into the general PseAAC. *Medicinal Chemistry*, 13(6):552-559, 2017.

[421] Qiu, W.R., Jiang, S.Y., Xu, Z.C., Xiao, X., and Chou, K. C. iRNAm5C-PseDNC: identifying RNA 5-methylcytosine sites by incorporating physical-chemical properties into pseudo dinucleotide composition. *Oncotarget*, 8(25):41178-41188, 2017.

[422] Wang, J., Yang, B., Revote, J., Leier, A., Marquez-Lago, T. T., Webb, G., Song, J., Chou, K. C., and Lithgow, T. POSSUM: a bioinformatics toolkit for generating

numerical sequence feature descriptors based on PSSM profiles. *Bioinformatics*, 33(17), pp.2756-2758, 2017.

[423] Xu, Y., Wang, Z., Li, C. and Chou, K. C. iPreny-PseAAC: identify C-terminal cysteine prenylation sites in proteins by incorporating two tiers of sequence couplings into PseAAC. *Medicinal Chemistry*, 13(6):544-551, 2017.

[424] Chen, W., Tang, H., Ye, J., Lin, H., and Chou, K. C. iRNA-PseU: Identifying RNA pseudouridine sites. *Molecular Therapy-Nucleic Acids*, 5:e332, 2016.

[425] Liu, Z., Xiao, X., Yu, D.J., Jia, J., Qiu, W. R., and Chou, K. C. pRNAm-PC: Predicting N6-methyladenosine sites in RNA sequences via physical–chemical properties. *Analytical biochemistry*, 497:60-67, 2016.

[426] Chou, K. C. Impacts of bioinformatics to medicinal chemistry. *Medicinal chemistry*, 11(3):218-234, 2015.

[427] Blom, N., Sicheritz-Pontén, T., Gupta, R., Gammeltoft, S., and Brunak, S. Prediction of post-translational glycosylation and phosphorylation of proteins from the amino acid sequence. *Proteomics*, 4(6):1633-1649, 2004.

[428] Blom, N., Sicheritz-Pontén, T., Gupta, R., Gammeltoft, S., and Brunak, S. Prediction of post-translational glycosylation and phosphorylation of proteins from the amino acid sequence. *Proteomics*, 4(6):1633-1649, 2004.

[429] Charbon, G., Breunig, K.D., Wattiez, R., Vandenhaute, J., and Noël-Georis, I. Key role of Ser562/661 in Snf1-dependent regulation of Cat8p in Saccharomyces cerevisiae and Kluyveromyces lactis. *Molecular and cellular biology*, 24(10):4083–4091, 2004.

[430] Kassenbrock, C. K. and Anderson, S. M. Regulation of ubiquitin protein ligase activity in c-Cbl by phosphorylation-induced conformational change and constitutive activation by tyrosine to glutamate point mutations. *Journal of Biological Chemistry*. 279(27): 28017–28027,

[431] Huang, W. and Erikson, R. L. Constitutive activation of Mek1 by mutation of serine phosphorylation sites. *Proceedings of the National Academy of Sciences*, 91(19):8960–8963, 1994.

[432] Klose, K. E., Weiss, D. S., and Kustu, S. Glutamate at the site of phosphorylation of nitrogen-regulatory protein NTRC mimics aspartyl-phosphate and activates the protein. *Journal of molecular biology*, 232(1):67–78, 1993.

[433] McCabe, T. J., Fulton, D., Roman, L. J., and Sessa, W. C. Enhanced electron flux and reduced calmodulin dissociation may explain "calcium-independent" eNOS activation by phosphorylation. *Journal of Biological Chemistry*, 275(9):6123–6128, 2000.

[434] Lewis-Wambi, J. S. and Jordan, V. C. Treatment of postmenopausal breast cancer with selective estrogen receptor modulators (SERMs). *Breast disease*, 24(1):93-105, 2006.

[435] Leary, A. and Dowsett, M. Combination therapy with aromatase inhibitors: the next era of breast cancer treatment? British journal of cancer, 95(6):661-666, 2006.

[436] Anbarasu, K. and Jayanthi, S. Designing and optimization of novel human LMTK3 inhibitors against breast cancer–a computational approach. *Journal of Receptors and Signal Transduction*, 37(1):51-59, 2017.

[437] Huang, D., Zhou, T., Lafleur, K., Nevado, C., and Caflisch, A. Kinase selectivity potential for inhibitors targeting the ATP binding site: a network analysis. *Bioinformatics*, 26(2):198-204, 2009.

[438] Stamos, J., Sliwkowski, M. X., and Eigenbrot, C. Structure of the epidermal growth factor receptor kinase domain alone and in complex with a 4-anilinoquinazoline inhibitor. *Journal of Biological Chemistry*, 277(48):46265-46272, 2002.

[439] Shrivastava, A. K., Kumar, S., Sahu, P. S., and Mahapatra, R. K. In silico identification and validation of a novel hypothetical protein in Cryptosporidium hominis and virtual screening of inhibitors as therapeutics. *Parasitology research*, 116(5):1533-1544, 2017.

[440] Sodero, A. C. R., Dos Santos, A. C. G., Mello, J. F. E., De Jesus, J. B., De Souza, A. M., Rodrigues, M. I. C., De Simone, S. G., Rodrigues, C. R. and Guedes, H. L. D. M., Oligopeptidase B and B2: comparative modelling and virtual screening as searching tools for new antileishmanial compounds. *Parasitology*, 144(4):536-545, 2017.

[441] Arrigoni, A., Bertini, L., De Gioia, L. and Papaleo, E. Inhibitors of the Cdc34 acidic loop: A computational investigation integrating molecular dynamics, virtual screening and docking approaches. *FEBS open bio*, 4(1):473-484, 2014.

[442] Lipinski, C. A. Lead-and drug-like compounds: the rule-of-five revolution. *Drug Discovery Today: Technologies*, 1(4):337-341, 2004.

[443] Wang, J., Wang, W., Kollman, P. A., and Case, D. A. Automatic atom type and bond type perception in molecular mechanical calculations. *Journal of molecular graphics and modelling*, 25(2):247-260, 2006.

[444] Jakalian, A., Jack, D. B., and Bayly, C. I. Fast, efficient generation of high-quality atomic charges. AM1-BCC model: II. Parameterization and validation. *Journal of computational chemistry*, 23(16):1623-1641, 2002.

[445] Kumar, S., Rosenberg, J. M., Bouzida, D., Swendsen, R. H., and Kollman, P. A. The weighted histogram analysis method for free-energy calculations on biomolecules. I. The method. *Journal of computational chemistry*, 13(8):1011-1021, 1992.

[446] Sun, H., Li, Y., Li, D. and Hou, T., Insight into crizotinib resistance mechanisms caused by three mutations in ALK tyrosine kinase using free energy calculation approaches. *Journal of chemical information and modeling*, 53(9):2376-2389, 2013.

[447] Sun, H., Li, Y., Tian, S., Wang, J. and Hou, T., P-loop conformation governed crizotinib resistance in G2032R-mutated ROS1 tyrosine kinase: clues from free energy landscape. *PLoS computational biology*, 10(7):e1003729, 2014.

[448] Sun, H., Tian, S., Zhou, S., Li, Y., Li, D., Xu, L., Shen, M., Pan, P., and Hou, T. Revealing the favorable dissociation pathway of type II kinase inhibitors via enhanced sampling simulations and two-end-state calculations. *Scientific reports*, 5:8457, 2015.

[449] Noble, M. E., Endicott, J. A., and Johnson, L. N. Protein kinase inhibitors: insights into drug design from structure. *Science*, 303(5665):1800-1805, 2004.

[450] Pargellis, C., Tong, L., Churchill, L., Cirillo, P.F., Gilmore, T., Graham, A.G., Grob, P.M., Hickey, E.R., Moss, N., Pav, S., and Regan, J. Inhibition of p38 MAP kinase by utilizing a novel allosteric binding site. *Nature Structural and Molecular Biology*, 9(4):268–272, 2002.

[451] Kwarcinski, F. E., Brandvold, K. R., Phadke, S., Beleh, O. M., Johnson, T. K., Meagher, J. L., Seeliger, M. A., Stuckey, J. A., and Soellner, M. B. Conformation-selective analogues of dasatinib reveal insight into kinase inhibitor binding and selectivity. *ACS chemical biology*, 11(5):1296-1304, 2016.

[452] Roskoski Jr, R. Classification of small molecule protein kinase inhibitors based upon the structures of their drug-enzyme complexes. *Pharmacological research*, 103:26-48, 2016.

[453] Suebsuwong, C., Pinkas, D.M., Ray, S. S., Bufton, J. C., Dai, B., Bullock, A. N., Degterev, A. and Cuny, G. D. Activation loop targeting strategy for design of receptor-interacting protein kinase 2 (RIPK2) inhibitors. *Bioorganic & medicinal chemistry letters*, 28(4):577-583, 2018.

[454] Park, J. W. and Jo, W. H. Computational design of novel, high-affinity neuraminidase inhibitors for H5N1 avian influenza virus. *European journal of medicinal chemistry*, 45(2):536-541, 2010.

[455] Lipinski, C. A., Lombardo, F., Dominy, B.W., and Feeney P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced drug delivery reviews*, 64:4-17, 2012.

[456] Dar, A. C. and Shokat, K. M. The evolution of protein kinase inhibitors from antagonists to agonists of cellular signaling. *Annual review of biochemistry*, 80(1):769-795, 2011.

[457] Cowan-Jacob, S. W., Jahnke, W., and Knapp, S. Novel approaches for targeting kinases: allosteric inhibition, allosteric activation and pseudokinases. *Future medicinal chemistry*, 6(5):541-561, 2014.

[458] Fang, Z., Grütter, C., and Rauh, D. Strategies for the selective regulation of kinases with allosteric modulators: exploiting exclusive structural features. *ACS chemical biology*, 8(1):58-70, 2012.

[459] Kalyaanamoorthy, S. and Chen, Y. P. P. Energy based pharmacophore mapping of HDAC inhibitors against class I HDAC enzymes. *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics*, 1834(1):317-328, 2013.

[460] Katari, S.K., Natarajan, P., Swargam, S., Kanipakam, H., Pasala, C. and Umamaheswari, A. Inhibitor design against JNK1 through e-pharmacophore modeling docking and molecular dynamics simulations. Journal of Receptors and Signal Transduction, 36(6):558-571, 2016.

[461] Loving, K., Salam, N. K., and Sherman, W. Energetic analysis of fragment docking and application to structure-based pharmacophore hypothesis generation. *Journal of computer-aided molecular design*, 23(8):541-554, 2009.

[462] Salam, N. K., Nuti, R., and Sherman, W. Novel method for generating structure-based pharmacophores using energetic analysis. *Journal of chemical information and modeling*, 49(10):2356-2368, 2009.

[463] Malik, R., Choudhary, B. S., Srivastava, S., Mehta, P., and Sharma, M. Identification of novel acetylcholinesterase inhibitors through e-pharmacophore-based virtual screening and molecular dynamics simulations. *Journal of Biomolecular Structure and Dynamics*, 35(15):3268-3284, 2017.

[464] Friesner, R. A., Murphy, R. B., Repasky, M. P., Frye, L. L., Greenwood, J. R., Halgren, T. A., Sanschagrin, P. C., and Mainz, D. T. Extra precision glide: Docking and scoring incorporating a model of hydrophobic enclosure for protein− ligand complexes. *Journal of medicinal chemistry*, 49(21):6177-6196, 2006.

[465] Case, D. A., Babin, V., Berryman, J. T., Betz, R. M., Cai, Q., Cerutti, D. S., Cheatham, T. E., Darden, T. A., Duke, R. E., Gohlke, H., Goetz, A. W., Gusarov, S., Homeyer, N., Janowski, P., Kaus, J., Kolossvary, I., Kovalenko, A., Lee, T. S., LeGrand, S., Luchko, T., Luo, R., Madej, B., Merz, K. M., Paesani, F., Roe, D. R., Roitberg, A., Sagui, C., Salomon-Ferrer, R., Seabra, G., Simmerling, C. L., Smith, W., Swails, J., Walker, R. C., Wang, J., Wolf, R. M., Wu X., and Kollman, P. A. (2014). AMBER 14; University of California, San Francisco.

[466] Jakalian, A., Jack, D. B., and Bayly, C. I. Fast, efficient generation of high-quality atomic charges. AM1-BCC model: II. Parameterization and validation. *Journal of computational chemistry*, 23(16):1623-1641, 2002.

[467] Gavrin, L. K. and Saiah, E. Approaches to discover non-ATP site kinase inhibitors. *MedChemComm*, 4(1):41-51, 2013.

[468] Simard, J. R., Klüter, S., Grütter, C., Getlik, M., Rabiller, M., Rode, H. B., and Rauh, D. A new screening assay for allosteric inhibitors of cSrc. *Nature chemical biology*, 5(6):394-396, 2009.