Design and implementation of a bacterial signaling circuit

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Bibliography

1 Adler, J., Chemoreceptors in bacteria. *Science* **166** (3913), 1588 (1969).

2 Adler, J., Chemotaxis in bacteria. *Science* **153** (3737), 708 (1966).

3 Adler, J., A method for measuring chemotaxis and use of the method to determine optimum conditions for chemotaxis by *Escherichia coli*. *J Gen Microbiol* **74** (1), 77 (1973).

4 Adler, J., Hazelbauer, G. L., and Dahl, M. M., Chemotaxis toward sugars in *Escherichia coli*. *J Bacteriol* **115** (3), 824 (1973).

5 Adler, J. et al., Osmotaxis in *Escherichia coli*. *Cold Spring Harb Symp Quant Biol* **53 Pt 1**, 19 (1988).

6 Adler, J. and Shi, W., Galvanotaxis in bacteria. *Cold Spring Harb Symp Quant Biol* **53 Pt 1**, 23 (1988).

7 Ahmed, T., Shimizu, T. S., and Stocker, R., Bacterial chemotaxis in linear and nonlinear steady microfluidic gradients. *Nano Lett* **10** (9), 3379 (2010).

8 Ahmed, T., Shimizu, T. S., and Stocker, R., Microfluidics for bacterial chemotaxis. *Integr Biol (Camb)* **2** (11-12), 604 (2010).

9 Ahmed, T. and Stocker, R., Experimental verification of the behavioral foundation of bacterial transport parameters using microfluidics. *Biophys J* **95** (9), 4481 (2008).

10 Alexander, R. P., Lowenthal, A. C., Harshey, R. M., and Ottemann, K. M., CheV: CheW-like coupling proteins at the core of the chemotaxis signaling network. *Trends Microbiol* **18** (11), 494 (2010).

11 Alexandre, G. and Zhulin, I. B., More than one way to sense chemicals. *J Bacteriol* **183** (16), 4681 (2001).

12 Alon, U., Surette, M. G., Barkai, N., and Leibler, S., Robustness in bacterial chemotaxis. *Nature* **397** (6715), 168 (1999).

13 Amann, E., Ochs, B., and Abel, K. J., Tightly regulated *tac* promoter vectors useful for the expression of unfused and fused proteins in *Escherichia coli*. *Gene* **69** (2), 301 (1988).

14 Amin, D. N. and Hazelbauer, G. L., Chemoreceptors in signalling complexes: shifted conformation and asymmetric coupling. *Mol Microbiol* **78** (5), 1313 (2010).

15 Anand, G. S., Goudreau, P. N., and Stock, A. M., Activation of methylesterase CheB: evidence of a dual role for the regulatory domain. *Biochemistry* **37** (40), 14038 (1998).

[16] Anderson, J. D., Galvanotaxis of slime mold. *J Gen Physiol* **35** (1), 1 (1951).

[17] Aoki, K., Kiyokawa, E., Nakamura, T., and Matsuda, M., Visualization of growth signal transduction cascades in living cells with genetically encoded probes based on Forster resonance energy transfer. *Philos Trans R Soc Lond B Biol Sci* **363** (1500), 2143 (2008).

[18] Asquith, R. S. and Hirst, L., The photochemical degradation of cystine in aqueous solution in the presence of air. *Biochimica et biophysica acta* **184** (2), 345 (1969).

[19] Baker, M. D., Wolanin, P. M., and Stock, J. B., Systems biology of bacterial chemotaxis. *Curr Opin Microbiol* **9** (2), 187 (2006).

[20] Banno, S., Shiomi, D., Homma, M., and Kawagishi, I., Targeting of the chemotaxis methylesterase/deamidase CheB to the polar receptor-kinase cluster in an *Escherichia coli* cell. *Mol Microbiol* **53** (4), 1051 (2004).

[21] Baptist, E. W. and Kredich, N. M., Regulation of L-cystine transport in *Salmonella typhimurium*. *Journal of bacteriology* **131** (1), 111 (1977).

[22] Barkai, N. and Leibler, S., Robustness in simple biochemical networks. *Nature* **387** (6636), 913 (1997).

[23] Barnakov, A. N., Barnakova, L. A., and Hazelbauer, G. L., Allosteric enhancement of adaptational demethylation by a carboxyl-terminal sequence on chemoreceptors. *J Biol Chem* **277** (44), 42151 (2002).

[24] Barnakov, A. N., Barnakova, L. A., and Hazelbauer, G. L., Efficient adaptational demethylation of chemoreceptors requires the same enzyme-docking site as efficient methylation. *Proceedings of the National Academy of Sciences of the United States of America* **96** (19), 10667 (1999).

[25] Berg, H. C., How to track bacteria. *Rev Sci Instrum* **42** (6), 868 (1971).

[26] Berg, H. C., The rotary motor of bacterial flagella. *Annu Rev Biochem* **72**, 19 (2003).

[27] Berg, H. C. and Block, S. M., A miniature flow cell designed for rapid exchange of media under high-power microscope objectives. *J Gen Microbiol* **130** (11), 2915 (1984).

[28] Bespalov, V. A., Zhulin, I. B., and Taylor, B. L., Behavioral responses of *Escherichia coli* to changes in redox potential. *Proc Natl Acad Sci U S A* **93** (19), 10084 (1996).

[29] Bhalla, U. S. and Iyengar, R., Emergent properties of networks of biological signaling pathways. *Science* **283** (5400), 381 (1999).

[30] Bibikov, S. I., Miller, A. C., Gosink, K. K., and Parkinson, J. S., Methylation-independent aerotaxis mediated by the *Escherichia coli* Aer protein. *J Bacteriol* **186** (12), 3730 (2004).

[31] Bibikov, S.I., Biran, R., Rudd, K.E., and Parkinson, J.S., A signal transducer for aerotaxis in *Escherichia coli*. *J Bacteriol* **179** (12), 4075 (1997).

[32] Biemann, H. P. and Koshland, D. E., Jr., Aspartate receptors of *Escherichia coli* and *Salmonella typhimurium* bind ligand with negative and half-of-the-sites cooperativity. *Biochemistry* **33** (3), 629 (1994).

[33] Blat, Y. and Eisenbach, M., Phosphorylation-dependent binding of the chemotaxis signal molecule CheY to its phosphatase, CheZ. *Biochemistry* **33** (4), 902 (1994).

[34] Blattner, F. R. et al., The complete genome sequence of *Escherichia coli* K-12. *Science* **277** (5331), 1453 (1997).

[35] Block, S. M., Segall, J. E., and Berg, H. C., Adaptation kinetics in bacterial chemotaxis. *J Bacteriol* **154** (1), 312 (1983).

[36] Block, S. M., Segall, J. E., and Berg, H. C., Impulse responses in bacterial chemotaxis. *Cell* **31** (1), 215 (1982).

[37] Booth, I. R., The regulation of intracellular pH in bacteria. *Novartis Found Symp* **221**, 19 (1999).

[38] Boucher, Y. and Bapteste, E., Revisiting the concept of lineage in prokaryotes: a phylogenetic perspective. *Bioessays* **31** (5), 526 (2009).

[39] Boukhvalova, M. S., Dahlquist, F. W., and Stewart, R. C., CheW binding interactions with CheA and Tar. Importance for chemotaxis signaling in *Escherichia coli*. *J Biol Chem* **277** (25), 22251 (2002).

[40] Bourret, R. B., Receiver domain structure and function in response regulator proteins. *Curr Opin Microbiol* **13** (2), 142 (2010).

[41] Bray, D., Levin, M. D., and Lipkow, K., The chemotactic behavior of computer-based surrogate bacteria. *Curr Biol* **17** (1), 12 (2007).

[42] Bray, D., Levin, M. D., and Morton-Firth, C. J., Receptor clustering as a cellular mechanism to control sensitivity. *Nature* **393** (6680), 85 (1998).

[43] Briegel, A. et al., Bacterial chemoreceptor arrays are hexagonally packed trimers of receptor dimers networked by rings of kinase and coupling proteins. *Proc Natl Acad Sci U S A* **109** (10), 3766 (2012).

[44] Burkart, M., Toguchi, A., and Harshey, R. M., The chemotaxis system, but not chemotaxis, is essential for swarming motility in *Escherichia coli*. *Proc Natl Acad Sci U S A* **95** (5), 2568 (1998).

[45] Burrows, L. L., *Pseudomonas aeruginosa* twitching motility: type IV pili in action. *Annu Rev Microbiol* **66**, 493 (2012).

[46] Butler, J. D. et al., Amino acid composition and N-terminal sequence of purified cystine binding protein of *Escherichia coli*. *Life Sci* **52** (14), 1209 (1993).

47 Butler, S. M. and Camilli, A., Both chemotaxis and net motility greatly influence the infectivity of *Vibrio cholerae*. *Proc Natl Acad Sci U S A* **101** (14), 5018 (2004).

48 Caetano-Anolles, G. et al., Role of Motility and Chemotaxis in Efficiency of Nodulation by *Rhizobium meliloti*. *Plant Physiol* **86** (4), 1228 (1988).

49 Cardozo, M. J., Massazza, D. A., Parkinson, J. S., and Studdert, C. A., Disruption of chemoreceptor signalling arrays by high levels of CheW, the receptor-kinase coupling protein. *Mol Microbiol* **75** (5), 1171 (2010).

50 Celani, A. and Vergassola, M., Bacterial strategies for chemotaxis response. *Proc Natl Acad Sci U S A* **107** (4), 1391 (2010).

51 Chau, A. H. et al., Designing synthetic regulatory networks capable of self-organizing cell polarization. *Cell* **151** (2), 320 (2012).

52 Cheng, S. Y. et al., A hydrogel-based microfluidic device for the studies of directed cell migration. *Lab Chip* **7** (6), 763 (2007).

53 Chock, P. B., Rhee, S. G., and Stadtman, E. R., Interconvertible enzyme cascades in cellular regulation. *Annu Rev Biochem* **49**, 813 (1980).

54 Christian, F. et al., Small molecule AKAP-protein kinase A (PKA) interaction disruptors that activate PKA interfere with compartmentalized cAMP signaling in cardiac myocytes. *J Biol Chem* **286** (11), 9079 (2011).

55 Clark, D. A. and Grant, L. C., The bacterial chemotactic response reflects a compromise between transient and steady-state behavior. *Proc Natl Acad Sci U S A* **102** (26), 9150 (2005).

56 Clausznitzer, D. et al., Chemotactic response and adaptation dynamics in *Escherichia coli*. *PLoS Comput Biol* **6** (5), e1000784 (2010).

57 Cohan, F. M., What are bacterial species? *Annu Rev Microbiol* **56**, 457 (2002).

58 Cohen-Saidon, C. et al., Dynamics and variability of ERK2 response to EGF in individual living cells. *Mol Cell* **36** (5), 885 (2009).

59 Corazziari, E. S., Intestinal mucus barrier in normal and inflamed colon. *J Pediatr Gastroenterol Nutr* **48 Suppl 2**, S54 (2009).

60 Corfield, A. P. et al., Mucins and mucosal protection in the gastrointestinal tract: new prospects for mucins in the pathology of gastrointestinal disease. *Gut* **47** (4), 589 (2000).

61 Danino, T. et al., In Vivo Gene Expression Dynamics of Tumor-Targeted Bacteria. *ACS Synth Biol* **1** (10), 465 (2012).

62 Datsenko, K. A. and Wanner, B. L., One-step inactivation of chromosomal genes in *Escherichia coli* K-12 using PCR products. *Proc Natl Acad Sci U S A* **97** (12), 6640 (2000).

63 de Gennes, P. G., Chemotaxis: the role of internal delays. *Eur Biophys J* **33** (8), 691 (2004).

64 de Hemptinne, A., Marrannes, R., and Vanheel, B., Influence of organic acids on intracellular pH. *Am J Physiol* **245** (3), C178 (1983).

65 de Pina, K. et al., Purification and characterization of the periplasmic nickel-binding protein NikA of *Escherichia coli* K12. *Eur J Biochem* **227** (3), 857 (1995).

66 DeFranco, A. L., Parkinson, J. S., and Koshland, D. E., Jr., Functional homology of chemotaxis genes in *Escherichia coli* and *Salmonella typhimurium*. *J Bacteriol* **139** (1), 107 (1979).

67 Delong, E. F., Frankel, R. B., and Bazylinski, D. A., Multiple evolutionary origins of magnetotaxis in bacteria. *Science* **259** (5096), 803 (1993).

68 Diehn, B., Phototaxis and sensory transduction in *Euglena*. *Science* **181** (4104), 1009 (1973).

69 Djordjevic, S. et al., Structural basis for methylesterase CheB regulation by a phosphorylation-activated domain. *Proc Natl Acad Sci U S A* **95** (4), 1381 (1998).

70 Doran, J. W. and Linn, D. M., Bacteriological quality of runoff water from pastureland. *Appl Environ Microbiol* **37** (5), 985 (1979).

71 Drews, G., Contributions of Theodor Wilhelm Engelmann on phototaxis, chemotaxis, and photosynthesis. *Photosynth Res* **83** (1), 25 (2005).

72 Duke, T. A. and Bray, D., Heightened sensitivity of a lattice of membrane receptors. *Proc Natl Acad Sci U S A* **96** (18), 10104 (1999).

73 Ehrenberg, L., Harmsringdahl, M., Fedorcsak, I., and Granath, F., Kinetics of the Copper-Catalyzed and Iron-Catalyzed Oxidation of Cysteine by Dioxygen. *Acta Chem Scand* **43** (2), 177 (1989).

74 Eisenbach, M., Sperm chemotaxis. *Rev Reprod* **4** (1), 56 (1999).

75 Eisenbach, M. and Adler, J., Bacterial cell envelopes with functional flagella. *J Biol Chem* **256** (16), 8807 (1981).

76 Endres, R. G. et al., Variable sizes of *Escherichia coli* chemoreceptor signaling teams. *Mol Syst Biol* **4**, 211 (2008).

77 Englert, D. L., Adase, C. A., Jayaraman, A., and Manson, M. D., Repellent taxis in response to nickel ion requires neither Ni2+ transport nor the periplasmic NikA binding protein. *J Bacteriol* **192** (10), 2633 (2010).

78 Erbse, A. H. and Falke, J. J., The core signaling proteins of bacterial chemotaxis assemble to form an ultrastable complex. *Biochemistry* **48** (29), 6975 (2009).

79 Escobar-Paramo, P. et al., Decreasing the effects of horizontal gene transfer on bacterial phylogeny: the *Escherichia coli* case study. *Mol Phylogenet Evol* **30** (1), 243 (2004).

[80] Falke, J. J., Cooperativity between bacterial chemotaxis receptors. *Proc Natl Acad Sci U S A* **99** (10), 6530 (2002).

[81] Fechner, G. T., *Elements of Psychophysics*. (Holt, Rinehart and Winston, New York, 1966).

[82] Feng, X., Baumgartner, J. W., and Hazelbauer, G. L., High- and low-abundance chemoreceptors in *Escherichia coli*: differential activities associated with closely related cytoplasmic domains. *Journal of bacteriology* **179** (21), 6714 (1997).

[83] Feng, X., Lilly, A. A., and Hazelbauer, G. L., Enhanced function conferred on low-abundance chemoreceptor Trg by a methyltransferase-docking site. *Journal of bacteriology* **181** (10), 3164 (1999).

[84] Frank, V., Koler, M., Furst, S., and Vaknin, A., The physical and functional thermal sensitivity of bacterial chemoreceptors. *J Mol Biol* **411** (3), 554 (2011).

[85] Friedman, N., Cai, L., and Xie, X. S., Linking stochastic dynamics to population distribution: an analytical framework of gene expression. *Phys Rev Lett* **97** (16), 168302 (2006).

[86] Frye, J. et al., Identification of new flagellar genes of Salmonella enterica serovar Typhimurium. *J Bacteriol* **188** (6), 2233 (2006).

[87] Gao, R., Mack, T. R., and Stock, A. M., Bacterial response regulators: versatile regulatory strategies from common domains. *Trends Biochem Sci* **32** (5), 225 (2007).

[88] Gao, R. and Stock, A. M., Molecular strategies for phosphorylation-mediated regulation of response regulator activity. *Curr Opin Microbiol* **13** (2), 160 (2010).

[89] Garcia-Quintanilla, M. and Casadesus, J., Virulence plasmid interchange between strains ATCC 14028, LT2, and SL1344 of *Salmonella enterica* serovar Typhimurium. *Plasmid* **65** (2), 169 (2011).

[90] Gegner, J. A., Graham, D. R., Roth, A. F., and Dahlquist, F. W., Assembly of an MCP receptor, CheW, and kinase CheA complex in the bacterial chemotaxis signal transduction pathway. *Cell* **70** (6), 975 (1992).

[91] Goentoro, L. and Kirschner, M. W., Evidence that fold-change, and not absolute level, of beta-catenin dictates Wnt signaling. *Mol Cell* **36** (5), 872 (2009).

[92] Goentoro, L., Shoval, O., Kirschner, M. W., and Alon, U., The incoherent feedforward loop can provide fold-change detection in gene regulation. *Mol Cell* **36** (5), 894 (2009).

93 Gosink, K. K., Buron-Barral, M. C., and Parkinson, J. S., Signaling interactions between the aerotaxis transducer Aer and heterologous chemoreceptors in *Escherichia coli*. *J Bacteriol* **188** (10), 3487 (2006).

94 Greenfield, D. et al., Self-organization of the *Escherichia coli* chemotaxis network imaged with super-resolution light microscopy. *PLoS Biol* **7** (6), e1000137 (2009).

95 Guttman, D. S. and Dykhuizen, D. E., Clonal divergence in *Escherichia coli* as a result of recombination, not mutation. *Science* **266** (5189), 1380 (1994).

96 Guzman, L. M., Belin, D., Carson, M. J., and Beckwith, J., Tight regulation, modulation, and high-level expression by vectors containing the arabinose PBAD promoter. *J Bacteriol* **177** (14), 4121 (1995).

97 Hader, D. P., Lebert, M., and Richter, P., Gravitaxis and graviperception in Euglena gracilis. *Adv Space Res* **21** (8-9), 1277 (1998).

98 Hart, Y., Mayo, A. E., Shoval, O., and Alon, U., Comparing apples and oranges: fold-change detection of multiple simultaneous inputs. *PLoS One* **8** (3), e57455 (2013).

99 Hartwell, L. H., Hopfield, J. J., Leibler, S., and Murray, A. W., From molecular to modular cell biology. *Nature* **402** (6761 Suppl), C47 (1999).

100 Hayashi, T. et al., Complete genome sequence of enterohemorrhagic *Escherichia coli* O157:H7 and genomic comparison with a laboratory strain K-12. *DNA Res* **8** (1), 11 (2001).

101 Hazelbauer, G. L., Bacterial chemotaxis: the early years of molecular studies. *Annu Rev Microbiol* **66**, 285 (2012).

102 Hazelbauer, G. L., Falke, J. J., and Parkinson, J. S., Bacterial chemoreceptors: high-performance signaling in networked arrays. *Trends Biochem Sci* **33** (1), 9 (2008).

103 Hedblom, M. L. and Adler, J., Chemotactic response of *Escherichia coli* to chemically synthesized amino acids. *J Bacteriol* **155** (3), 1463 (1983).

104 Hobman, J. L., Penn, C. W., and Pallen, M. J., Laboratory strains of *Escherichia coli*: model citizens or deceitful delinquents growing old disgracefully? *Mol Microbiol* **64** (4), 881 (2007).

105 Hong, C. B., Fontana, D. R., and Poff, K. L., Thermotaxis of *Dictyostelium discoideum* amoebae and its possible role in pseudoplasmodial thermotaxis. *Proc Natl Acad Sci U S A* **80** (18), 5646 (1983).

106 Hood, M. A. and Ness, G. E., Survival of *Vibrio cholerae* and *Escherichia coli* in estuarine waters and sediments. *Appl Environ Microbiol* **43** (3), 578 (1982).

107 Ibarra, R. U., Edwards, J. S., and Palsson, B. O., *Escherichia coli* K-12 undergoes adaptive evolution to achieve in silico predicted optimal growth. *Nature* **420** (6912), 186 (2002).

[108] Inoue, M., Kishimoto, A., Takai, Y., and Nishizuka, Y., Studies on a cyclic nucleotide-independent protein kinase and its proenzyme in mammalian tissues. II. Proenzyme and its activation by calcium-dependent protease from rat brain. *J Biol Chem* **252** (21), 7610 (1977).

[109] Insall, R. and Andrew, N., Chemotaxis in *Dictyostelium*: how to walk straight using parallel pathways. *Curr Opin Microbiol* **10** (6), 578 (2007).

[110] Ishii, S., Ksoll, W. B., Hicks, R. E., and Sadowsky, M. J., Presence and growth of naturalized *Escherichia coli* in temperate soils from Lake Superior watersheds. *Appl Environ Microbiol* **72** (1), 612 (2006).

[111] Ishii, T., Itoh, K., Sato, H., and Bannai, S., Oxidative stress-inducible proteins in macrophages. *Free Radic Res* **31** (4), 351 (1999).

[112] Jarvik, T., Smillie, C., Groisman, E. A., and Ochman, H., Short-term signatures of evolutionary change in the *Salmonella enterica* serovar typhimurium 14028 genome. *J Bacteriol* **192** (2), 560 (2010).

[113] Jiang, L., Ouyang, Q., and Tu, Y., A mechanism for precision-sensing via a gradient-sensing pathway: a model of *Escherichia coli* thermotaxis. *Biophys J* **97** (1), 74 (2009).

[114] Jiang, L., Ouyang, Q., and Tu, Y., Quantitative modeling of *Escherichia coli* chemotactic motion in environments varying in space and time. *PLoS Comput Biol* **6** (4), e1000735 (2010).

[115] Kalinin, Y. V., Jiang, L., Tu, Y., and Wu, M., Logarithmic sensing in *Escherichia coli* bacterial chemotaxis. *Biophys J* **96** (6), 2439 (2009).

[116] Karatan, E., Saulmon, M. M., Bunn, M. W., and Ordal, G. W., Phosphorylation of the response regulator CheV is required for adaptation to attractants during *Bacillus subtilis* chemotaxis. *J Biol Chem* **276** (47), 43618 (2001).

[117] Karsten, V. et al., Chemotaxis activation of peritoneal murine macrophages induced by the transplantation of free and encapsulated pancreatic rat islets. *Cell Transplant* **9** (1), 39 (2000).

[118] Kelln, R. A. and Lintott, L. G., Construction of plasmid-free derivatives of *Salmonella typhimurium* LT2 using temperature-sensitive mutants of pKZ1 for displacement of the resident plasmid, pSLT. *Mol Gen Genet* **222** (2-3), 438 (1990).

[119] Kentner, D., Thiem, S., Hildenbeutel, M., and Sourjik, V., Determinants of chemoreceptor cluster formation in *Escherichia coli*. *Mol Microbiol* **61** (2), 407 (2006).

[120] Keymer, J. E. et al., Chemosensing in *Escherichia coli*: two regimes of two-state receptors. *Proc Natl Acad Sci U S A* **103** (6), 1786 (2006).

121 Khan, S., Macnab, R. M., DeFranco, A. L., and Koshland, D. E., Jr., Inversion of a behavioral response in bacterial chemotaxis: explanation at the molecular level. *Proc Natl Acad Sci U S A* **75** (9), 4150 (1978).

122 Khan, S., Spudich, J. L., McCray, J. A., and Trentham, D. R., Chemotactic signal integration in bacteria. *Proc Natl Acad Sci U S A* **92** (21), 9757 (1995).

123 Kihara, M., Homma, M., Kutsukake, K., and Macnab, R. M., Flagellar switch of *Salmonella typhimurium*: gene sequences and deduced protein sequences. *J Bacteriol* **171** (6), 3247 (1989).

124 Kihara, M. and Macnab, R. M., Cytoplasmic pH mediates pH taxis and weak-acid repellent taxis of bacteria. *Journal of bacteriology* **145** (3), 1209 (1981).

125 Kim, Y. S. and Ho, S. B., Intestinal goblet cells and mucins in health and disease: recent insights and progress. *Curr Gastroenterol Rep* **12** (5), 319 (2010).

126 Kirschner, M. and Gerhart, J., Evolvability. *Proc Natl Acad Sci U S A* **95** (15), 8420 (1998).

127 Kollmann, M. et al., Design principles of a bacterial signalling network. *Nature* **438** (7067), 504 (2005).

128 Kollmann, M. and Sourjik, V., In silico biology: from simulation to understanding. *Curr Biol* **17** (4), R132 (2007).

129 Kondoh, H., Ball, C. B., and Adler, J., Identification of a methyl-accepting chemotaxis protein for the ribose and galactose chemoreceptors of Escherichia coli. *Proc Natl Acad Sci U S A* **76** (1), 260 (1979).

130 Kosek, M., Bern, C., and Guerrant, R. L., The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ* **81** (3), 197 (2003).

131 Krikos, A. et al., Chimeric chemosensory transducers of Escherichia coli. *Proc Natl Acad Sci U S A* **82** (5), 1326 (1985).

132 Lan, G., Schulmeister, S., Sourjik, V., and Tu, Y., Adapt locally and act globally: strategy to maintain high chemoreceptor sensitivity in complex environments. *Mol Syst Biol* **7**, 475 (2011).

133 Lane, M. C. et al., Uropathogenic *Escherichia coli* strains generally lack functional Trg and Tap chemoreceptors found in the majority of *E. coli* strains strictly residing in the gut. *J Bacteriol* **188** (15), 5618 (2006).

134 Larremore, D. B., Shew, W. L., Ott, E., and Restrepo, J. G., Effects of network topology, transmission delays, and refractoriness on the response of coupled excitable systems to a stochastic stimulus. *Chaos* **21** (2), 025117 (2011).

135 Laughlin, S., A simple coding procedure enhances a neuron's information capacity. *Z Naturforsch C* **36** (9-10), 910 (1981).

136 Lawrence, J. G. and Ochman, H., Molecular archaeology of the *Escherichia coli* genome. *Proc Natl Acad Sci U S A* **95** (16), 9413 (1998).

137 Lazova, M. D. et al., Response rescaling in bacterial chemotaxis. *Proc Natl Acad Sci U S A* **108** (33), 13870 (2011).

138 Lazova, M. D., Butler, M. T., Shimizu, T. S., and Harshey, R. M., *Salmonella* chemoreceptors McpB and McpC mediate a repellent response to *L*-cystine: a potential mechanism to avoid oxidative conditions. *Mol Microbiol* **84** (4), 697 (2012).

139 Lecointre, G., Rachdi, L., Darlu, P., and Denamur, E., *Escherichia coli* molecular phylogeny using the incongruence length difference test. *Mol Biol Evol* **15** (12), 1685 (1998).

140 Lertsethtakarn, P., Ottemann, K. M., and Hendrixson, D. R., Motility and chemotaxis in *Campylobacter* and *Helicobacter*. *Annu Rev Microbiol* **65**, 389 (2011).

141 Letunic, I., Doerks, T., and Bork, P., SMART 7: recent updates to the protein domain annotation resource. *Nucleic Acids Res* **40** (Database issue), D302 (2012).

142 Levring, T. B. et al., Activated human CD4 T cells express transporters for both cysteine and cystine. *Sci Rep* **2**, 266 (2012).

143 Li, J., Li, G., and Weis, R. M., The serine chemoreceptor from *Escherichia coli* is methylated through an inter-dimer process. *Biochemistry* **36** (39), 11851 (1997).

144 Li, M. and Hazelbauer, G. L., The carboxyl-terminal linker is important for chemoreceptor function. *Mol Microbiol* **60** (2), 469 (2006).

145 Linden, S. K., Florin, T. H., and McGuckin, M. A., Mucin dynamics in intestinal bacterial infection. *PLoS One* **3** (12), e3952 (2008).

146 Liu, J. D. and Parkinson, J. S., Role of CheW protein in coupling membrane receptors to the intracellular signaling system of bacterial chemotaxis. *Proc Natl Acad Sci U S A* **86** (22), 8703 (1989).

147 Liu, J. et al., Molecular architecture of chemoreceptor arrays revealed by cryoelectron tomography of *Escherichia coli* minicells. *Proc Natl Acad Sci U S A* **109** (23), E1481 (2012).

148 Lovdok, L. et al., Role of translational coupling in robustness of bacterial chemotaxis pathway. *PLoS Biol* **7** (8), e1000171 (2009).

149 Lowenthal, A. C. et al., A fixed-time diffusion analysis method determines that the three *cheV* genes of *Helicobacter pylori* differentially affect motility. *Microbiology* **155** (Pt 4), 1181 (2009).

150 Luo, C. et al., Genome sequencing of environmental *Escherichia coli* expands understanding of the ecology and speciation of the model bacterial species. *Proc Natl Acad Sci U S A* **108** (17), 7200 (2011).

151 Lux, R. et al., Coupling the phosphotransferase system and the methyl-accepting chemotaxis protein-dependent chemotaxis signaling pathways of *Escherichia coli*. *Proc Natl Acad Sci U S A* **92** (25), 11583 (1995).

152 Macnab, R. M., How bacteria assemble flagella. *Annu Rev Microbiol* **57**, 77 (2003).

153 Maddock, J. R. and Shapiro, L., Polar location of the chemoreceptor complex in the *Escherichia coli* cell. *Science* **259** (5102), 1717 (1993).

154 Manson, M. D., Blank, V., Brade, G., and Higgins, C. F., Peptide chemotaxis in *E. coli* involves the Tap signal transducer and the dipeptide permease. *Nature* **321** (6067), 253 (1986).

155 Manson, M. D., Boos, W., Bassford, P. J., Jr., and Rasmussen, B. A., Dependence of maltose transport and chemotaxis on the amount of maltose-binding protein. *J Biol Chem* **260** (17), 9727 (1985).

156 Mao, H., Cremer, P. S., and Manson, M. D., A sensitive, versatile microfluidic assay for bacterial chemotaxis. *Proc Natl Acad Sci U S A* **100** (9), 5449 (2003).

157 Marcos, Fu, H. C., Powers, T. R., and Stocker, R., Bacterial rheotaxis. *Proc Natl Acad Sci U S A* **109** (13), 4780 (2012).

158 Masson, J. B. et al., Noninvasive inference of the molecular chemotactic response using bacterial trajectories. *Proc Natl Acad Sci U S A* **109** (5), 1802 (2012).

159 Mazel, D., Dychinco, B., Webb, V. A., and Davies, J., Antibiotic resistance in the ECOR collection: integrons and identification of a novel *aad* gene. *Antimicrob Agents Chemother* **44** (6), 1568 (2000).

160 McClelland, M. et al., Complete genome sequence of *Salmonella enterica* serovar Typhimurium LT2. *Nature* **413** (6858), 852 (2001).

161 McEvoy, M. M., Bren, A., Eisenbach, M., and Dahlquist, F. W., Identification of the binding interfaces on CheY for two of its targets, the phosphatase CheZ and the flagellar switch protein *fliM*. *J Mol Biol* **289** (5), 1423 (1999).

162 McGhie, E. J. et al., *Salmonella* takes control: effector-driven manipulation of the host. *Curr Opin Microbiol* **12** (1), 117 (2009).

163 Meir, Y. et al., Precision and kinetics of adaptation in bacterial chemotaxis. *Biophys J* **99** (9), 2766 (2010).

164 Meister, M., Lowe, G., and Berg, H. C., The proton flux through the bacterial flagellar motor. *Cell* **49** (5), 643 (1987).

165 Mello, B. A. and Tu, Y., An allosteric model for heterogeneous receptor complexes: Understanding bacterial chemotaxis responses to multiple stimuli. *Proc Natl Acad Sci U S A* **102** (48), 17354 (2005).

166 Mello, B. A. and Tu, Y., Effects of adaptation in maintaining high sensitivity over a wide range of backgrounds for *Escherichia coli* chemotaxis. *Biophys J* **92** (7), 2329 (2007).

167 Mello, B. A. and Tu, Y., Perfect and near-perfect adaptation in a model of bacterial chemotaxis. *Biophys J* **84** (5), 2943 (2003).

168 Mello, B. A. and Tu, Y., Quantitative modeling of sensitivity in bacterial chemotaxis: the role of coupling among different chemoreceptor species. *Proc Natl Acad Sci U S A* **100** (14), 8223 (2003).

169 Melton, T. et al., Chemotaxis of *Salmonella typhimurium* to amino acids and some sugars. *Journal of bacteriology* **133** (2), 708 (1978).

170 Mesibov, R. and Adler, J., Chemotaxis toward amino acids in *Escherichia coli*. *J Bacteriol* **112** (1), 315 (1972).

171 Mesibov, R., Ordal, G. W., and Adler, J., The range of attractant concentrations for bacterial chemotaxis and the threshold and size of response over this range. Weber law and related phenomena. *J Gen Physiol* **62** (2), 203 (1973).

172 Miki, K. and Clapham, D. E., Rheotaxis guides Mammalian sperm. *Curr Biol* **23** (6), 443 (2013).

173 Milkman, R., Electrophoretic variation in *Escherichia coli* from natural sources. *Science* **182** (4116), 1024 (1973).

174 Milkman, R. and Crawford, I. P., Clustered third-base substitutions among wild strains of *Escherichia coli*. *Science* **221** (4608), 378 (1983).

175 Miller, L. D., Russell, M. H., and Alexandre, G., Diversity in bacterial chemotactic responses and niche adaptation. *Adv Appl Microbiol* **66**, 53 (2009).

176 Monod, J., Wyman, J., and Changeux, J. P., On the Nature of Allosteric Transitions: A Plausible Model. *J Mol Biol* **12**, 88 (1965).

177 Mori, I., Genetics of chemotaxis and thermotaxis in the nematode *Caenorhabditis elegans*. *Annu Rev Genet* **33**, 399 (1999).

178 Morrison, D. K. and Davis, R. J., Regulation of MAP kinase signaling modules by scaffold proteins in mammals. *Annu Rev Cell Dev Biol* **19**, 91 (2003).

179 Moszer, I., The complete genome of *Bacillus subtilis*: from sequence annotation to data management and analysis. *FEBS Lett* **430** (1-2), 28 (1998).

180 Mowbray, S. L. and Koshland, D. E., Jr., Additive and independent responses in a single receptor: aspartate and maltose stimuli on the tar protein. *Cell* **50** (2), 171 (1987).

181 Nakamura, T. and Matsuda, M., In vivo imaging of signal transduction cascades with probes based on Forster Resonance Energy Transfer (FRET). *Curr Protoc Cell Biol* **Chapter 14**, Unit 14 10 (2009).

182 Nelson, K. and Selander, R. K., Evolutionary genetics of the proline permease gene (putP) and the control region of the proline utilization operon in populations of *Salmonella* and *Escherichia coli*. *J Bacteriol* **174** (21), 6886 (1992).

183 Nelson, K., Wang, F. S., Boyd, E. F., and Selander, R. K., Size and sequence polymorphism in the isocitrate dehydrogenase kinase/phosphatase gene (*aceK*) and flanking regions in *Salmonella enterica* and *Escherichia coli*. *Genetics* **147** (4), 1509 (1997).

184 Nelson, K., Whittam, T. S., and Selander, R. K., Nucleotide polymorphism and evolution in the glyceraldehyde-3-phosphate dehydrogenase gene (*gapA*) in natural populations of *Salmonella* and *Escherichia coli*. *Proc Natl Acad Sci U S A* **88** (15), 6667 (1991).

185 Neumann, S., Grosse, K., and Sourjik, V., Chemotactic signaling via carbohydrate phosphotransferase systems in *Escherichia coli*. *Proc Natl Acad Sci U S A* **109** (30), 12159 (2012).

186 Neumann, S., Hansen, C. H., Wingreen, N. S., and Sourjik, V., Differences in signalling by directly and indirectly binding ligands in bacterial chemotaxis. *EMBO J* **29** (20), 3484 (2010).

187 Neurath, H. and Walsh, K. A., Role of proteolytic enzymes in biological regulation (a review). *Proc Natl Acad Sci U S A* **73** (11), 3825 (1976).

188 O'Toole, R. et al., The chemotactic response of *Vibrio anguillarum* to fish intestinal mucus is mediated by a combination of multiple mucus components. *J Bacteriol* **181** (14), 4308 (1999).

189 Ochman, H. and Selander, R. K., Standard reference strains of *Escherichia coli* from natural populations. *J Bacteriol* **157** (2), 690 (1984).

190 Ochman, H. and Wilson, A. C., Evolution in bacteria: evidence for a universal substitution rate in cellular genomes. *J Mol Evol* **26** (1-2), 74 (1987).

191 Ohtsu, I. et al., The *L*-cysteine/*L*-cystine shuttle system provides reducing equivalents to the periplasm in *Escherichia coli*. *The Journal of biological chemistry* **285** (23), 17479 (2010).

192 Oleksiuk, O. et al., Thermal robustness of signaling in bacterial chemotaxis. *Cell* **145** (2), 312 (2011).

193 Olszewski, J., Haehnel, M., Taguchi, M., and Liao, J. C., Zebrafish larvae exhibit rheotaxis and can escape a continuous suction source using their lateral line. *PLoS One* **7** (5), e36661 (2012).

194 Parkinson, J. S., Ames, P., and Studdert, C. A., Collaborative signaling by bacterial chemoreceptors. *Curr Opin Microbiol* **8** (2), 116 (2005).

195 Parkinson, J. S. and Houts, S. E., Isolation and behavior of Escherichia coli deletion mutants lacking chemotaxis functions. *J Bacteriol* **151** (1), 106 (1982).

196 Pineda-Molina, E. et al., Evidence for chemoreceptors with bimodular ligand-binding regions harboring two signal-binding sites. *Proc Natl Acad Sci U S A* **109** (46), 18926 (2012).

197 Pittman, M. S., Goodwin, M., and Kelly, D. J., Chemotaxis in the human gastric pathogen *Helicobacter pylori*: different roles for CheW and the three CheV paralogues, and evidence for CheV2 phosphorylation. *Microbiology* **147** (Pt 9), 2493 (2001).

198 Poelwijk, F. J., de Vos, M. G., and Tans, S. J., Tradeoffs and optimality in the evolution of gene regulation. *Cell* **146** (3), 462 (2011).

199 Prinz, H., Hill coefficients, dose-response curves and allosteric mechanisms. *J Chem Biol* **3** (1), 37 (2010).

200 Rafelski, S. M. and Marshall, W. F., Building the cell: design principles of cellular architecture. *Nat Rev Mol Cell Biol* **9** (8), 593 (2008).

201 Rao, C. V., Kirby, J. R., and Arkin, A. P., Design and diversity in bacterial chemotaxis: a comparative study in *Escherichia coli* and *Bacillus subtilis*. *PLoS Biol* **2** (2), E49 (2004).

202 Rebbapragada, A. et al., The Aer protein and the serine chemoreceptor Tsr independently sense intracellular energy levels and transduce oxygen, redox, and energy signals for *Escherichia coli* behavior. *Proc Natl Acad Sci U S A* **94** (20), 10541 (1997).

203 Rieke, F. and Rudd, M. E., The challenges natural images pose for visual adaptation. *Neuron* **64** (5), 605 (2009).

204 Rosario, M. M., Fredrick, K. L., Ordal, G. W., and Helmann, J. D., Chemotaxis in *Bacillus subtilis* requires either of two functionally redundant CheW homologs. *J Bacteriol* **176** (9), 2736 (1994).

205 Rosner, J. L. and Storz, G., Regulation of bacterial responses to oxidative stress. *Curr Top Cell Regul* **35**, 163 (1997).

206 Russo, A. F. and Koshland, D. E., Jr., Identification of the tip-encoded receptor in bacterial sensing. *J Bacteriol* **165** (1), 276 (1986).

207 Sabariegos, R. et al., Fluorescence resonance energy transfer-based assay for characterization of hepatitis C virus NS3-4A protease activity in live cells. *Antimicrob Agents Chemother* **53** (2), 728 (2009).

208 Salis, H. M., The ribosome binding site calculator. *Methods Enzymol* **498**, 19.

209 Salis, H. M., Mirsky, E. A., and Voigt, C. A., Automated design of synthetic ribosome binding sites to control protein expression. *Nat Biotechnol* **27** (10), 946 (2009).

210 Salman, H. and Libchaber, A., A concentration-dependent switch in the bacterial response to temperature. *Nat Cell Biol* **9** (9), 1098 (2007).

211 Sanders, D. A., Mendez, B., and Koshland, D. E., Jr., Role of the CheW protein in bacterial chemotaxis: overexpression is equivalent to absence. *J Bacteriol* **171** (11), 6271 (1989).

212 Sano, G. et al., Flagella facilitate escape of *Salmonella* from oncotic macrophages. *Journal of bacteriology* **189** (22), 8224 (2007).

213 Schmidt, J. et al., The Pseudomonas aeruginosa chemotaxis methyltransferase CheR1 impacts on bacterial surface sampling. *PLoS One* **6** (3), e18184 (2011).

214 Schnitzer, M. J., Block, S. M., Berg, H. C., and Purcell, E. M., Strategies for chemotaxis. *Symp Soc Gen Microbiol* **46**, 15 (1990).

215 Schulmeister, S., Grosse, K., and Sourjik, V., Effects of receptor modification and temperature on dynamics of sensory complexes in *Escherichia coli* chemotaxis. *BMC Microbiol* **11**, 222 (2011).

216 Schulmeister, S. et al., Protein exchange dynamics at chemoreceptor clusters in Escherichia coli. *Proc Natl Acad Sci U S A* **105** (17), 6403 (2008).

217 Schultz, J., Milpetz, F., Bork, P., and Ponting, C. P., SMART, a simple modular architecture research tool: identification of signaling domains. *Proc Natl Acad Sci U S A* **95** (11), 5857 (1998).

218 Segall, J. E., Block, S. M., and Berg, H. C., Temporal comparisons in bacterial chemotaxis. *Proc Natl Acad Sci U S A* **83** (23), 8987 (1986).

219 Selander, R. K. et al., Methods of multilocus enzyme electrophoresis for bacterial population genetics and systematics. *Appl Environ Microbiol* **51** (5), 873 (1986).

220 Selander, R. K. and Levin, B. R., Genetic diversity and structure in *Escherichia coli* populations. *Science* **210** (4469), 545 (1980).

221 Seymour, J. R., Simo, R., Ahmed, T., and Stocker, R., Chemoattraction to dimethylsulfoniopropionate throughout the marine microbial food web. *Science* **329** (5989), 342 (2010).

222 Shimizu, T. S., Aksenov, S. V., and Bray, D., A spatially extended stochastic model of the bacterial chemotaxis signalling pathway. *J Mol Biol* **329** (2), 291 (2003).

223 Shimizu, T. S. and Bray, D., Modelling the bacterial chemotaxis receptor complex. *Novartis Found Symp* **247**, 162 (2002).

224 Shimizu, T. S., Delalez, N., Pichler, K., and Berg, H. C., Monitoring bacterial chemotaxis by using bioluminescence resonance energy transfer: absence of feedback from the flagellar motors. *Proc Natl Acad Sci U S A* **103** (7), 2093 (2006).

225 Shimizu, T. S. et al., Molecular model of a lattice of signalling proteins involved in bacterial chemotaxis. *Nat Cell Biol* **2** (11), 792 (2000).

226 Shimizu, T. S., Tu, Y., and Berg, H. C., A modular gradient-sensing network for chemotaxis in *Escherichia coli* revealed by responses to time-varying stimuli. *Mol Syst Biol* **6**, 382 (2010).

227 Shinohara, K. and Kilpatrick, M., The stability of cystine in acid solution. *Journal of Biological Chemistry* **105**, 241 (1934).

228 Shiomi, D., Okumura, H., Homma, M., and Kawagishi, I., The aspartate chemoreceptor Tar is effectively methylated by binding to the methyltransferase mainly through hydrophobic interaction. *Mol Microbiol* **36** (1), 132 (2000).

229 Shiomi, D., Zhulin, I. B., Homma, M., and Kawagishi, I., Dual recognition of the bacterial chemoreceptor by chemotaxis-specific domains of the CheR methyltransferase. *J Biol Chem* **277** (44), 42325 (2002).

230 Shoval, O., Alon, U., and Sontag, E., Symmetry invariance for adapting biological systems. *SIAM J Appl Dyn Syst* **In Press** (2011).

231 Shoval, O. et al., Fold-change detection and scalar symmetry of sensory input fields. *Proc Natl Acad Sci U S A* **107** (36), 15995 (2010).

232 Si, G., Wu, T., Ouyang, Q., and Tu, Y., Pathway-based mean-field model for Escherichia coli chemotaxis. *Phys Rev Lett* **109** (4), 048101 (2012).

233 Simms, S. A., Keane, M. G., and Stock, J., Multiple forms of the CheB methylesterase in bacterial chemosensing. *J Biol Chem* **260** (18), 10161 (1985).

234 Slivka, P. F. and Falke, J. J., Isolated bacterial chemosensory array possesses quasi- and ultrastable components: functional links between array stability, cooperativity, and order. *Biochemistry* **51** (51), 10218 (2012).

235 Slonczewski, J. L., Macnab, R. M., Alger, J. R., and Castle, A. M., Effects of pH and repellent tactic stimuli on protein methylation levels in *Escherichia coli*. *J Bacteriol* **152** (1), 384 (1982).

236 Smith, J. M., Smith, N. H., O'Rourke, M., and Spratt, B. G., How clonal are bacteria? *Proc Natl Acad Sci U S A* **90** (10), 4384 (1993).

[237] Sourjik, V., Receptor clustering and signal processing in *E. coli* chemotaxis. *Trends Microbiol* **12** (12), 569 (2004).

[238] Sourjik, V. and Armitage, J. P., Spatial organization in bacterial chemotaxis. *EMBO J* **29** (16), 2724 (2010).

[239] Sourjik, V. and Berg, H. C., Binding of the *Escherichia coli* response regulator CheY to its target measured in vivo by fluorescence resonance energy transfer. *Proc Natl Acad Sci U S A* **99** (20), 12669 (2002).

[240] Sourjik, V. and Berg, H. C., Functional interactions between receptors in bacterial chemotaxis. *Nature* **428** (6981), 437 (2004).

[241] Sourjik, V. and Berg, H. C., Receptor sensitivity in bacterial chemotaxis. *Proc Natl Acad Sci U S A* **99** (1), 123 (2002).

[242] Sourjik, V., Vaknin, A., Shimizu, T. S., and Berg, H. C., In vivo measurement by FRET of pathway activity in bacterial chemotaxis. *Methods Enzymol* **423**, 365 (2007).

[243] Sourjik, V. and Wingreen, N. S., Responding to chemical gradients: bacterial chemotaxis. *Curr Opin Cell Biol* **24** (2), 262 (2012).

[244] Soyer, O. S., The promise of evolutionary systems biology: lessons from bacterial chemotaxis. *Sci Signal* **3** (128), pe23 (2010).

[245] Steuer, R., Waldherr, S., Sourjik, V., and Kollmann, M., Robust signal processing in living cells. *PLoS Comput Biol* **7** (11), e1002218 (2011).

[246] Stevens, R., Stevems, L., and Price, N.C., The stabilities of various thiol compounds used in protein purifications. *Biochemical Education* **11**, 70 (1983).

[247] Stevens, S. S., Neural events and the psychophysical law. *Science* **170** (3962), 1043 (1970).

[248] Stock, J., Sensitivity, cooperativity and gain in chemotaxis signal transduction. *Trends Microbiol* **7** (1), 1 (1999).

[249] Stock, J. B., Maderis, A. M., and Koshland, D. E., Jr., Bacterial chemotaxis in the absence of receptor carboxylmethylation. *Cell* **27** (1 Pt 2), 37 (1981).

[250] Stock, J., Kersulis, G., and Koshland, D. E., Jr., Neither methylating nor demethylating enzymes are required for bacterial chemotaxis. *Cell* **42** (2), 683 (1985).

[251] Stocker, R., Reverse and flick: Hybrid locomotion in bacteria. *Proc Natl Acad Sci U S A* **108** (7), 2635 (2011).

[252] Stocker, R. et al., Rapid chemotactic response enables marine bacteria to exploit ephemeral microscale nutrient patches. *Proc Natl Acad Sci U S A* **105** (11), 4209 (2008).

[253] Swidsinski, A. et al., Comparative study of the intestinal mucus barrier in normal and inflamed colon. *Gut* **56** (3), 343 (2007).

254 Szurmant, H. and Ordal, G. W., Diversity in chemotaxis mechanisms among the bacteria and archaea. *Microbiol Mol Biol Rev* **68** (2), 301 (2004).

255 Taylor, B. L., Zhulin, I. B., and Johnson, M. S., Aerotaxis and other energy-sensing behavior in bacteria. *Annu Rev Microbiol* **53**, 103 (1999).

256 Tenaillon, O., Skurnik, D., Picard, B., and Denamur, E., The population genetics of commensal *Escherichia coli*. *Nat Rev Microbiol* **8** (3), 207 (2010).

257 Tomb, J. F. et al., The complete genome sequence of the gastric pathogen *Helicobacter pylori*. *Nature* **388** (6642), 539 (1997).

258 Trevors, J. T. and Basaraba, J., Toxicity of benzoquinone and hydroquinone in short-term bacterial bioassays. *Bull Environ Contam Toxicol* **25** (4), 672 (1980).

259 Tso, W. W. and Adler, J., Negative chemotaxis in *Escherichia coli*. *J Bacteriol* **118** (2), 560 (1974).

260 Tu, Y., Shimizu, T. S., and Berg, H. C., Modeling the chemotactic response of Escherichia coli to time-varying stimuli. *Proc Natl Acad Sci U S A* **105** (39), 14855 (2008).

261 Turner, L., Ryu, W. S., and Berg, H. C., Real-time imaging of fluorescent flagellar filaments. *J Bacteriol* **182** (10), 2793 (2000).

262 Ulrich, L. E. and Zhulin, I. B., The MiST2 database: a comprehensive genomics resource on microbial signal transduction. *Nucleic Acids Res* **38** (Database issue), D401 (2010).

263 Vaknin, A. and Berg, H. C., Osmotic stress mechanically perturbs chemoreceptors in *Escherichia coli*. *Proc Natl Acad Sci U S A* **103** (3), 592 (2006).

264 Vaknin, A. and Berg, H. C., Physical responses of bacterial chemoreceptors. *J Mol Biol* **366** (5), 1416 (2007).

265 Vladimirov, N. and Sourjik, V., Chemotaxis: how bacteria use memory. *Biol Chem* **390** (11), 1097 (2009).

266 Wadhams, G. H. and Armitage, J. P., Making sense of it all: bacterial chemotaxis. *Nat Rev Mol Cell Biol* **5** (12), 1024 (2004).

267 Wang, Q. et al., Uncovering a large set of genes that affect surface motility in *Salmonella enterica* serovar Typhimurium. *J Bacteriol* **188** (22), 7981 (2006).

268 Wang, Q. et al., Sensing wetness: a new role for the bacterial flagellum. *Embo J* **24** (11), 2034 (2005).

269 Ward, S., Chemotaxis by the nematode *Caenorhabditis elegans*: identification of attractants and analysis of the response by use of mutants. *Proc Natl Acad Sci U S A* **70** (3), 817 (1973).

[270] Watts, K. J., Ma, Q., Johnson, M. S., and Taylor, B. L., Interactions between the PAS and HAMP domains of the *Escherichia coli* aerotaxis receptor Aer. *J Bacteriol* **186** (21), 7440 (2004).

[271] Weerasuriya, S., Schneider, B. M., and Manson, M. D., Chimeric chemoreceptors in *Escherichia coli*: signaling properties of Tar-Tap and Tap-Tar hybrids. *Journal of bacteriology* **180** (4), 914 (1998).

[272] Whitesides, G. M. et al., Soft lithography in biology and biochemistry. *Annu Rev Biomed Eng* **3**, 335 (2001).

[273] Whitman, W. B., Coleman, D. C., and Wiebe, W. J., Prokaryotes: the unseen majority. *Proc Natl Acad Sci U S A* **95** (12), 6578 (1998).

[274] Winfield, M. D. and Groisman, E. A., Role of nonhost environments in the lifestyles of *Salmonella* and *Escherichia coli*. *Appl Environ Microbiol* **69** (7), 3687 (2003).

[275] Wirth, T. et al., Sex and virulence in *Escherichia coli*: an evolutionary perspective. *Mol Microbiol* **60** (5), 1136 (2006).

[276] Wolfe, A. J. and Berg, H. C., Migration of bacteria in semisolid agar. *Proc Natl Acad Sci U S A* **86** (18), 6973 (1989).

[277] Wouters, F. S. and Bastiaens, P. I., Imaging protein-protein interactions by fluorescence resonance energy transfer (FRET) microscopy. *Curr Protoc Cell Biol* **Chapter 17**, Unit 17 1 (2001).

[278] Wright, S., Walia, B., Parkinson, J. S., and Khan, S., Differential activation of *Escherichia coli* chemoreceptors by blue-light stimuli. *J Bacteriol* **188** (11), 3962 (2006).

[279] Wu, K. et al., Attractant binding induces distinct structural changes to the polar and lateral signaling clusters in *Bacillus subtilis* chemotaxis. *J Biol Chem* **286** (4), 2587 (2011).

[280] Wu, Y., Zhang, X., Yu, J., and Ouyang, Q., Identification of a topological characteristic responsible for the biological robustness of regulatory networks. *PLoS Comput Biol* **5** (7), e1000442 (2009).

[281] Wuichet, K. and Zhulin, I. B., Origins and diversification of a complex signal transduction system in prokaryotes. *Sci Signal* **3** (128), ra50 (2010).

[282] Yamamoto, K. and Imae, Y., Cloning and characterization of the *Salmonella typhimurium*-specific chemoreceptor Tcp for taxis to citrate and from phenol. *Proc Natl Acad Sci U S A* **90** (1), 217 (1993).

[283] Yamamoto, Y. et al., NEXAFS studies on the structure of perfluoroalkyl carbonic acid Langmuir Blodgett films. *J Synchrotron Radiat* **6** (Pt 3), 796 (1999).

[284] Yang, Y. and Sourjik, V., Opposite responses by different chemoreceptors set a tunable preference point in *Escherichia coli* pH taxis. *Mol Microbiol* (2012).

[285] Yaryura, P. M. et al., Assessment of the role of chemotaxis and biofilm formation as requirements for colonization of roots and seeds of soybean plants by *Bacillus amyloliquefaciens* BNM339. *Curr Microbiol* **56** (6), 625 (2008).

[286] Yi, T. M., Huang, Y., Simon, M. I., and Doyle, J., Robust perfect adaptation in bacterial chemotaxis through integral feedback control. *Proc Natl Acad Sci U S A* **97** (9), 4649 (2000).

[287] Yuan, J. and Berg, H. C., Characterization of the adaptation module of the signaling network in bacterial chemotaxis by measurement of step responses. *Biophys J* **103** (6), L31 (2012).

[288] Yuan, J. and Berg, H. C., Resurrection of the flagellar rotary motor near zero load. *Proc Natl Acad Sci U S A* **105** (4), 1182 (2008).

[289] Yuan, J., Branch, R. W., Hosu, B. G., and Berg, H. C., Adaptation at the output of the chemotaxis signalling pathway. *Nature* **484** (7393), 233 (2012).

[290] Zeke, A., Lukacs, M., Lim, W. A., and Remenyi, A., Scaffolds: interaction platforms for cellular signalling circuits. *Trends Cell Biol* **19** (8), 364 (2009).

[291] Zhou, Q., Ames, P., and Parkinson, J. S., Biphasic control logic of HAMP domain signalling in the *Escherichia coli* serine chemoreceptor. *Mol Microbiol* **80** (3), 596 (2011).

Summary

The chemotaxis signaling circuit that enables enteric bacteria to sense and respond to chemicals and physical changes in their environment is one of the best characterized signaling networks in biology. The detailed molecular knowledge about this system has enabled quantitative experimental and theoretical studies that have explained the characteristics of chemotaxis response, such as precise adaptation and high signal amplification. Many of the properties of the chemotactic signaling in bacteria are also observed in the more complex sensory systems of multicellular organisms. Thus, insights from studies of the bacterial chemotaxis system could facilitate the understanding of fundamental properties of sensory systems in biology.

In this thesis, the chemotactic signaling of enteric bacteria was investigated from a functional point of view. Quantitative experiments measuring the chemotactic signaling response of *Escherichia coli* and *Salmonella typhimurium* were used to characterize the properties of the receptor response and adaptation at the systems level. Behavioral strategies were predicted from the transfer functions of the signaling response and confirmed experimentally. The roles of previously uncharacterized chemotaxis proteins were explored using physiological measurements and quantitative imaging.

Physiological studies of sensory responses have highlighted that the threshold of response to a stimulus is proportional to the magnitude of the original stimulus: a property, known as Weber's law. However, Weber's law addresses only the instantaneous response to small step stimuli. In Chapter 2, we provide the first demonstration that an adaptive sensory system rescales the entire dynamics of its response to time-varying inputs. We show for the chemotaxis response of *E. coli* to α-methylaspartate (MeAsp) that the entire shape of the output depends only on the fold changes in the input and not on its absolute levels, a property recently described as fold-change detection (FCD). We used fluorescence resonance energy transfer (FRET) to probe this rescaling of the signaling response in *E. coli*, and we found two ranges of background concentrations, in which

FCD holds, i.e. "FCD regimes". The amplitude of the response differed between the two regimes; however, the adaptation timescale was invariant. We identified three sufficient conditions for FCD in bacterial chemotaxis. FCD was also observed for the distributions of *E. coli* swimming in spatial gradients of MeAsp created in microfluidic platforms.

Input-output relationships of the chemotaxis response have been thoroughly characterized in the model strain *E. coli* K12. FRET-based studies showed high receptor sensitivity and cooperativity and explored the properties of the adaptation system, using time-varying stimuli. However, even within the species *E. coli*, there is a great variety in the chemotactic performance between different strains, as we showed in Appendix B. In Chapter 3 we performed a detailed comparison of the physiological response of *E. coli* K12 and the closely related species *S. typhimurium* LT2 that share homologous chemotactic networks. We revealed that adaptation to MeAsp in *S. typhimurium* is three-fold faster and the apparent cooperativity of the receptor response is three-fold lower than that of *E. coli*. Moreover, the response-rescaling properties differed between the two species: in contrast to *E. coli*, *S. typhimurium* showed a single FCD regime. Using the obtained parameters for the chemotactic signaling transfer functions of both species, we explained the differences in the sensitivity modulation of the response.

In Chapter 4 we study two chemoreceptors of *S. typhimurium*, McpB and McpC, with hitherto unknown functions. The radial migration in soft-agar plates suggested that these receptors sense the amino acid cysteine and its oxidized dimeric form cystine as chemoattractants. However, our FRET measurements of the chemotactic kinase response showed that cells expressing only McpB / C chemoreceptors respond only to the oxidized form, and the response was unexpectedly in the repellent direction. Furthermore, we showed that the reduced form, cysteine, is an attractant sensed by Tsr and Tar. We showed that the adaptation to both cystine and cysteine is methylation dependent, and the adaptation to cystine is incomplete, *i.e.* imperfect adaptation. We discuss that cystine-cysteine interconversion and imperfect adaptation to cystine could explain the attractant-like responses to both components in the soft-agar assays. We explore the dose-response dependence of the opposite responses to

cystine / cysteine redox pair in Appendix A. We observed linear scaling of the magnitude of the response to cystine with the logarithm of cystine concentration. Unexpectedly, we detected McpB / C independent responses to cystine in *S. typhimurium* LT2, which might represent a redox response. In Chapter 6, we present our preliminary results on testing the responses of *S. typhimurium* to redox gradients.

Another chemotaxis protein with previously uncharacterized function in *S. typhimurium* is CheV: a hybrid protein consisting of a scaffolding domain and a phosphorylatable receiver domain. CheV plays a role in receptor-kinase scaffolding and adaptation to chemoeffectors in some bacterial species. The distinctive phenotype of knocking out *cheV* in *S. typhimurium* strains incapable of methylation-dependent adaptation suggested that CheV has a function in *S. typhimurium*'s chemotactic response. Our FRET measurements presented in Chapter 5 revealed methylation-independent partial adaptation to MeAsp, which is CheV-dependent. To understand the mechanistic origin of this partial adaptation, we performed quantitative image analysis of receptor clusters and showed that the number of detectable clusters decreases in *cheV* knockout cells. In particular there are less clusters that are not localized at the poles, *i.e.* lateral clusters, in the *cheV* knockout cells. We speculate that a phosphorylation-dependent feedback on the receptor cluster stability might explain the role of CheV in *S. typhimurium.*

We explored another phosphorylation-dependent feedback mechanism: the negative feedback loop introduced by phosphorylation of the methylesterase CheB in *E. coli* chemotaxis in Appendix C. Using FRET, we characterized the adaptation kinetics of genetically modified cells with disrupted CheB phosphorylation site. We showed that the strong nonlinearity in the transfer function characterizing the rate of change of methylation as a function of the kinase activity could be a consequence of the phosphorylation feedback on CheB activity.

In summary, we have studied the input-output relationships of the chemotaxis response in *E. coli* and *S. typhimurium* using *in vivo* experiments. We have demonstrated the fold-change detection strategy in both species at both the signaling and behavioral levels. We have shown differences in the chemotactic performance of bacteria with homologous chemotaxis

networks, and explained the observed differences in terms of the underlying control physiology. We have used the existing experimental tools to probe the functions of uncharacterized chemotaxis components. Future functional studies of signaling responses could further advance our understanding how biological systems are designed.

Samenvatting

(Translated in Dutch by Johannes Keegstra)

Het chemotaxis netwerk is het systeem welke bacterien in staat stelt fysische en chemische veranderingen omgeving waar te nemen en op deze te reageren. Het is een van de best gekarakteriseerde signaalnetwerken in de biologie. De gedetailleerde kennis van dit systeem op moleculair niveau heeft kwantitatief onderzoek mogelijk gemaakt, zowel theoretisch als experimenteel. Dit onderzoek heeft geleid tot een uitgebreide karakterisatie van het chemotaxis systeem, waaronder het effect van volledige aanpassing en de hoge signaalvesterking. Veel van de eigenschappen van het chemotaxis systeem in bacterien spelen ook een rol bij complexere sensorische systemen bij meercellige organismen. Zo kan inzichten uit studies van de bacteriele chemotaxis het begrip van fundamentele eigenschappen van sensorische systemen binnen de biologie vergemakkelijken.

In het onderzoek beschreven in dit proefschrift werd het chemotaxis systeem van bacterien onderzocht vanuit het perspectief van functionaliteit. Metingen aan de chemotaxis respons van *Escherichia coli* en *Salmonella typhimurium* werden gebruikt om de eigenschappen van de receptorrespons en -aanpassing te karakteriseren op het niveau van de informatieverwerking. Uit de overdrachtsfuncties van de signaal-verwerking werden strategieen van de bacterien voorspeld en met behulp van experimenten werden deze voorspellingen bevestigd. De functie van eerder ongekarakteriseerde eiwitten van het chemotaxis systeem werden onderzocht met behulp van fysiologische metingen en kwantitatieve beeldverwerking.

Fysiologische studies van zintuiglijke reacties geven aan dat de drempelwaarde van de reactie op een stimulus evenredig is met de grootte van de oorspronkelijke stimulus, wat bekend staat als de wet van Weber. Echter, de wet van Weber beschrijft de respons van een systeem op stimuli met een kleine stapgrootte op een bepaald tijdstip. In Hoofdstuk 2 tonen wij voor het eerst aan dat een adaptief zintuiglijk systeem voor het gehele

tijdsinterval van zijn reactie het ingangssignaal herschaalt. We laten zien dat de chemotaxis respons van *E. coli* op *α-methylaspartate* (MeAsp) dat het uitgangssignaal gelijk is voor veelvouden van hetzelfde ingangssignaal en dus niet afhankelijk is van het absolute niveau, een eigenschap welke recent beschreven is als detectie veelvoudverandering (Fold-change detection - FCD). We gebruikten een fysische techniek gebaseerd op energieoverdracht door resonantie van verschillende fluorescerende deeltjes (Fluorescence resonance energy transfer - FRET) om de herschaling van het ingangssignaal in *E. coli* te bestuderen, en we hebben twee reeksen van achtergrondconcentraties gevonden voor waar FCD geldt, zogenaamde "*FCD regimes*". De amplitude van de respons verschilde tussen de twee regimes, maar de tijdschaal van de aanpassing was hetzelfde. We identificeerden drie voldoende voorwaarden voor FCD in bacteriële chemotaxis. FCD werd ook waargenomen voor de verdelingen van zwemmende *E. coli* in de ruimtelijke gradiënten van MeAsp welke tot stand kwamen in vloeistofcellen op micrometerschaal.

Ingang-uitgangs relaties van de chemotaxis respons zijn grondig gekarakteriseerd in de modelstam *E. coli* K12. Onderzoek met FRET toonde een hoge gevoeligheid van, alsmede een hoge cooperativiteit tussen, de receptoren. Ook de eigenschappen van het aanpassingssysteem werden onderzocht, met behulp van de tijd varierende stimuli. Echter, zelfs binnen de soort *E. coli* is er een grote variatie in de chemotactische prestaties van verschillende stammen, zoals is te zien in Appendix B. In Hoofdstuk 3 maken we een gedetailleerde vergelijking van de fysiologische respons van *E. coli* K12 en de nauw verwante species *S. typhimurium* LT2, welke homologe chemotactische netwerken bezitten. Het bleek dat de aanpassing aan MeAsp in *S. typhimurium* driemaal sneller is en de gemeten cooperativiteit van de receptor respons driemaal lager dan die van *E. coli*. Bovendien is de respons herschaling verschillend tussen de twee soorten: in tegenstelling tot *E. coli*, toonde *S. typhimurium* een FCD regime. Met behulp van de verkregen parameters voor de signaaloverdrachtsfuncties van beide soorten konden we de verschillen in de modulatie van de gevoeligheid van de reactie verklaren.

In Hoofdstuk 4 bestuderen we twee chemoreceptors van *S. typhimurium*, McpB en McpC, met tot nu toe onbekende functies. Radiale

migratie in halfzachte agar platen gesuggereert dat deze receptoren reageren op het aminozuur cysteine en zijn geoxideerde dimeer cystine als stoffen met een aantrekkende functie. Onze FRET metingen van de chemotactische kinase reactie toonden echter aan dat cellen met alleen McpB / C chemoreceptors slechts reageren op de geoxideerde vorm, en de respons was onverwacht in de afstotende richting. Verder toonden we aan dat de gereduceerde vorm, cysteine, als een aantrekkende stof wordt waargenomen door Tsr en Tar. We toonden aan dat de aanpassing aan zowel cystine en cysteine methylatie afhankelijk is, en dat de aanpassing aan cystine onvolledig is, dat wil zeggen dat de adaptatie het signaal niet terugbrengt naar het niveau voor de stimulus. We bespreken dat cystine-cysteine omzetting en de onvolledige aanpassing aan cystine de aantrekkend-achtige reacties aan beide componenten in de halfzachte agar assays kunnen uitleggen. De dosis-respons afhankelijkheid van de tegenovergestelde reacties op het cystine / cysteine redoxsysteem wordt besproken in Appendix A. We observeerden lineaire schaling van de omvang van de respons op cystine met de logaritme van cystine concentratie. Onverwacht, we ontdekten enkele McpB / C onafhankelijke reacties op cystine in *S. typhimurium* LT2, welke een redox respons zou kunnen representeren. In Hoofdstuk 6 presenteren wij onze voorlopige resultaten over het testen van de reacties van *S. typhimurium* aan redox gradienten.

Een ander chemotaxis eiwit zonder eerder gekenmerkte functie *S. typhimurium* is CheV: een hybride eiwit dat bestaat uit een structuurdomein en een fosforyleerbare ontvangdomein. CheV speelt een rol in receptor-kinase structuur en aanpassing aan chemo-effectoren in sommige bacteriesoorten. Het kenmerkende fenotype van cellen zonder het *cheV* gen in stammen van *S. typhimurium* welke niet in staat waren tot methylatie suggereert dat CheV een andere functie heeft binnen het chemotaxis netwerk van *S. typhimurium*'s. Onze FRET metingen gepresenteerd in Hoofdstuk 5 toonden gedeeltelijke aanpassing aan MeAsp onafhankelijk van methylatie en afhankelijk van CheV. Voor een mechanistisch begrip van deze gedeeltelijke aanpassing voerden we een kwantitatieve beeldanalyse van de receptorclusters uit, en daarmee toonden we aan dat het aantal detecteerbare clusters afneemt bij cellen

waarin het *cheV* gen is verwijderd. Er is met name minder laterale clusters, dwz clusters die niet gelokaliseerd bij de polen van de bacterie, in de cellen zonder het *cheV* gen. We speculeren dat een fosforylatie-afhankelijke terugkoppeling op de stabiliteit van de receptorclusters de rol van CheV bij S. *typhimurium* zou kunnen verklaren.

We verkenden een andere fosforylatie-afhankelijke terugkoppelingsmechanisme: de negatieve terugkoppeling geïntroduceerd door fosforylering van de methylesterase CheB in *E. coli* chemotaxis, hetgeen is beschreven in Appendix C. Met behulp van FRET hebben we de adaptatiekinetica van cellen met genetisch gemodificeerde CheB fosforylatieposities onderzocht. We hebben laten zien dat de sterke niet-lineariteit in de overdrachtsfunctie die de methylatiesnelheid als een functie van de kinase activiteit een gevolg zou kunnen zijn van de fosforylatie terugkoppeling van CheB activiteit.

Samengevat hebben we de overdrachtsfunctie van het chemotaxis systeem in *E. coli* en *S. typhimurium* met *in vivo* experimenten onderzocht. We hebben de FCD eigenschap aangetoond in zowel soorten op zowel de signalering en gedragsniveau. We hebben verschillen aangetoond in de functionaliteit van chemotaxis netwerken in homologe bacteriën, en legde de waargenomen verschillen in de onderliggende fysiologie. We hebben bestaande experimentele technieken gebruikt om de functies van niet eerder gekenmerkte chemotaxis componenten in kaart te brengen. Toekomstige studies van signaalverwerking in functioneel perspectief kunnen leiden tot een beter begrip van de vraag hoe biologische systemen zijn ontworpen.

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Curriculum Vitae

Milena D. Lazova was born on October 29, 1984 in Sofia, Bulgaria. She obtained her secondary education at Sofia High School of Mathematics in 2003. In the same year she started her undergraduate studies in Molecular Biology at Sofia University. In August 2007 she moved to The Netherlands to start a Master's program in Molecular and Cellular Biology in Leiden University. Under the supervision of Dr. B. Ewa Snaar-Jagalska from Leiden Institute of Biology and Prof. Dr. Thomas Schmidt from Leiden Institute of Physics, she used single-molecule microscopy to study the G protein mobility in chemotactic social amoeba *Dictyostelium discoideum*. After graduating with honors, in May 2009 she joined FOM Institute AMOLF as the first PhD student in the group of Dr. Tom Shimizu. During the summer of 2012 she worked as a visiting student in the group of Prof. Dr. Roman Stocker at the Massachusetts Institute of Technology. Her research on chemotactic signaling and behavior of bacteria is presented in this thesis. Upon receipt of her PhD, Milena will investigate the control of bacterial replication cycle as a postdoctoral researcher with Prof. Dr. Alan Grossman at the Massachusetts Institute of Technology.