

CURRICULUM VITAE

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Education:

1970 Purdue University, Lafayette, Indiana
B.S. in Physics with Highest Distinction

1979 The Johns Hopkins University School of Medicine, Baltimore, Maryland
M.D. and Ph.D. in Biochemistry and Molecular Biology
(Dan Nathans, Thesis Advisor)

Professional Experience:

7/1979 to 3/1982 Massachusetts Institute of Technology
Department of Biology
Postdoctoral Fellow with Dr. David Botstein

3/1982 to 8/1984 State University of New York at Stony Brook School of Medicine
Department of Microbiology
Assistant Professor

8/1984 to present The Johns Hopkins University School of Medicine
Department of Biological Chemistry
Assistant Professor (8/84 - 11/87)
Associate Professor (11/87-1/93)
Professor (2/93 - present)

8/1990 to 8/1991 University of California, San Francisco, Department of Pharmaceutical
Chemistry.
Sabbatical leave spent in the laboratories of Dr. Ken Dill and Dr. Irwin Kuntz

7/1997 to 7/1998 University of Washington, Seattle, Department of Biochemistry.
Sabbatical leave spent in the laboratory of Dr. David Baker.

Professional Service:

1990 - present	Editorial Board of Current Opinion in Structural Biology
1986 - 2012	Editorial Board of the journal Proteins: Structure, Function, and Genetics
1993 - 2004	Editorial Board of Structure , now Structure, with Folding & Design
1996 - 1998	Editorial Boards of Protein Science and Protein Folding & Design
1989 - 1993	Editorial Board of Archives of Biochemistry and Biophysics
1995-1997	Council Member, The Biophysical Society

PUBLICATIONS

1. Mizioroko, H.M., Shortle, D., and Lane, M.D. (1976) Trapping of a novel coenzyme A containing intermediate of 3-hydroxy-3-methyl-glutaryl CoA synthase. **Biochem. Biophys. Res. Commun.** **69**: 92-98.
2. Shortle, D. and Nathans, D. (1978) Local mutagenesis: A method for generating viral mutants with base substitutions in preselected regions of the viral genome. **Proc. Natl. Acad. Sci. USA** **75**: 2170-2174.
3. Shortle, D. and Nathans, D. (1979) Mutants of simian virus 40 with base substitutions at the origin of viral DNA replication. **Cold Spring Harbor Symp. Quant. Biol.** **43**: 663-668.
4. Shortle, D. and Nathans, D. (1979) Regulatory mutants of simian virus 40: Constructed mutants with base substitutions at the origin of DNA replication. **J. Mol. Biol.** **131**: 801-817.
5. Shortle, D., Pipas, J., Lazarowitz, S., DiMaio, D., and Nathans, D. (1979) Constructed mutants of simian virus 40. In: **Genetic Engineering** (Setlow, J. and Hollaender, A., eds.) Plenum Press, New York, New York, pp. 73-92.
6. Shortle, D., Margolskee, R.F., and Nathans, D. (1979) Mutational analysis of the simian virus 40 replicon: Pseudorevertants of mutants with a defective replication origin. **Proc. Natl. Acad. Sci. USA** **76**, 6128-6131.
7. Shortle, D., Koshland, D., Weinstock, G., and Botstein, D. (1980) Segment-directed mutagenesis: Construction *in vitro* of point mutations limited to a small predetermined region of a circular DNA molecule. **Proc. Natl. Acad. Sci. USA** **77**: 5375-5379.
8. Shortle, D., DiMaio, D. and Nathans, D. (1981) Directed mutagenesis. **Ann. Rev. Genet.** **15**: 265-294.
9. Shortle, D. and Botstein, D. (1981) Single-stranded gaps as localized targets for *in vitro* mutagenesis. In: **Molecular and Cellular Mechanisms of Mutagenesis** (Lemontt, J.F. and Generosa, W.M., eds.) Plenum Press, New York, New York.
10. Shortle, D., Grisafi, P., Benkovic, S.J., and Botstein, D. (1982) Gap misrepair mutagenesis: Efficient site-directed induction of transition, transversion and frameshift mutations *in vitro*. **Proc. Natl. Acad. Sci. USA** **79**: 1588-1592.
11. Shortle, D., Haber, J.E., and Botstein, D. (1982) Lethal disruption of the yeast actin gene by integrative DNA transformation. **Science** **217**: 371-373.
12. Shortle, D. and Botstein, D. (1983) Directed mutagenesis with sodium bisulfite. **Meth. Enzymol.** **100**: 457-468.
13. Shortle, D. (1983) A genetic system for analysis of staphylococcal nuclease. **Gene** **22**: 181-189.
14. Shortle, D., Novick, P. and Botstein, D. (1984) Construction and genetic characterization of temperature-sensitive mutant alleles of the yeast actin gene. **Proc. Natl. Acad. Sci. USA** **81**: 4889-4893.
15. Shortle, D. and Lin, B. (1985) Genetic analysis of staphylococcal nuclease: Identification of three intragenic "global" suppressors of nuclease-minus mutations. **Genetics** **110**: 539-555.

16. Botstein, D. and Shortle, D. (1985) Strategies and applications of *in vitro* mutagenesis. **Science** **229**: 1193-1201.
17. Shortle, D. (1985) Guanidine hydrochloride denaturation studies of mutant forms of staphylococcal nuclease. **J. Cell. Biochem.** **30**: 281-289.
18. Serpersu, E.H., Shortle, D., and Mildvan, A.S. (1986) Kinetic and magnetic resonance studies of effects of genetic substitution of a calcium-liganding amino acid in staphylococcal nuclease. **Biochemistry** **25**: 68-77.
19. Shortle, D. (1986) Stability mutants of staphylococcal nuclease: A correlation between nuclease activity in an agar gel assay and stability to guanidine hydrochloride denaturation. In **Protein Engineering: Applications to Science, Medicine, and Industry** (M. Inouye and R. Sarma, eds.) Academic Press, New York, New York. pp. 233-241.
20. Shortle, D. and Meeker, A.K. (1986) Mutant forms of staphylococcal nuclease with altered patterns of guanidine hydrochloride and urea denaturation. **Proteins: Structure, Function, Genetics** **1**: 81-89.
21. Serpersu, E.H., Shortle, D., and Mildvan, A.S. (1987) Kinetic and magnetic resonance studies of active site mutants of staphylococcal nuclease: Factors contributing to catalysis. **Biochemistry** **26**: 1289-1300.
22. Shortle, D. (1987) Genetic strategies for analyzing proteins. In **Protein Engineering** (D.L. Oxender and C.F. Fox, eds.), Alan R. Liss, Inc. New York, New York, pp. 103-108.
23. Shortle, D. (1987) Equilibrium and kinetic intermediates in protein folding: An alternative explanation. in **Protein Structure, Folding, and Design** **2**, (D. Oxender, ed.), Alan R. Liss, Inc., New York, pp. 353-361.
24. Kuliopulos, A., Shortle, D., and Talalay, P. (1987) Isolation and sequencing of the gene encoding Δ^5 -3-ketosteroid isomerase of *Pseudomonas testosteroni*: Overexpression of the protein. **Proc. Natl. Acad. Sci. USA** **84**: 8893-8897.
25. Shortle, D., Meeker, A.K., and Freire, E. (1988) Stability mutants of staphylococcal nuclease: Large compensating enthalpy-entropy changes for the reversible denaturation reaction. **Biochemistry** **27**: 4761-4768.
26. Loll, P.J., Meeker, A.K., Shortle, D., Pease, M., and Lattman, E.E. (1988) Crystallization and preliminary X-ray analysis of a quadruple mutant of staphylococcal nuclease. **J. Biol. Chem.** **263**: 18190-18192.
27. Kuliopulos, A., Mildvan, A.S., Shortle, D., and Talalay, P. (1989) Kinetic and ultraviolet spectroscopic studies of active-site mutants of Δ^5 -3-ketosteroid isomerase. **Biochemistry** **28**: 149-159.
28. Shortle, D., Meeker, A.K., and Gerring, S.L. (1989) Effects of denaturants at low concentrations on the reversible denaturation of staphylococcal nuclease. **Arch. Biochem. Biophys.** **272**: 103-113.
29. Shortle, D. and Meeker, A.K. (1989) Residual structure in large fragments of staphylococcal nuclease: Effects of amino acid substitutions. **Biochemistry** **28**: 936-944.
30. Shortle, D. (1989) Probing the determinants of protein folding and stability with amino acid substitutions (A Minireview). **J. Biol. Chem.** **264**: 5315-5318.
31. Shortle, D., Stites, W.E., and Meeker, A.M. (1990) Contributions of the large hydrophobic amino acids to the stability of staphylococcal nuclease. **Biochemistry** **29**: 8033-8041.
32. Dunn, T.M. and Shortle, D. (1990) Null alleles of *SAC7* suppress temperature-sensitive actin mutations in *Saccharomyces cerevisiae*. **Mol. Cell. Biol.** **10**: 2308-2314.
33. Sonddek, J.E. and Shortle, D. (1990) Accommodation of single amino acid insertions by the native state of staphylococcal nuclease. **Proteins: Structure, Function, Genetics** **7**: 299-305.

34. Weber, D.J., Serpersu, E.H., Shortle, D., and Mildvan, A.S. (1990) Diverse interactions between the individual mutations in a double mutant at the active site of staphylococcal nuclease. **Biochemistry** **29**: 8632-8642.
35. Stites, W.E., Gittis, A., Shortle, D., and Lattman, E.E. (1991) In a staphylococcal nuclease mutant the side chain of a lysine replacing valine 66 is fully buried in the hydrophobic core **J. Mol. Biol.** **221**: 7-14.
36. Dill, K.A. and Shortle, D. (1991) Denatured states of proteins. **Ann. Rev. Biochem.** **60**: 795-825.
37. Flanagan, J.M., Kataoka, M., Shortle, D., and Engelman, D.M. (1992) Truncated staphylococcal nuclease is compact but disordered. **Proc. Natl. Acad. Sci. USA** **89**: 748-752.
38. Sondek, J.E. and Shortle, D. (1992) Structural and energetic differences between insertions and substitutions in staphylococcal nuclease. **Proteins: Structure, Function, Genetics** **13**: 132-140.
39. Shortle, D., Chan, H.S., and Dill, K.A. (1992) Modelling the effects of mutations on the denatured states of proteins. **Protein Science** **1**: 201-215.
40. Shortle, D. (1992) Mutational studies of protein structures and their stabilities. **Quart. Rev. Biophys.** **25**: 205-250.
41. Sondek, J. and Shortle, D. (1992) A general strategy for random insertion and substitution mutagenesis: Substoichiometric coupling of trinucleotide phosphoramidites. **Proc. Natl. Acad. Sci. USA** **89**: 3581-3585.
42. Green, S.M., Meeker, A.K., and Shortle, D. (1992) Contributions of the polar, uncharged amino acids to the stability of staphylococcal nuclease: Evidence for mutational effects on the free energy of the denatured state. **Biochemistry** **31**: 5717-5728.
43. Shortle, D. (1993). Denatured states of proteins and their roles in folding and stability. **Current Opinion Struct. Biol.** **3**: 66-74.
44. Keefe, L.J., Sondek, J., Shortle, D. and Lattman, E.E. (1993). The alpha aneurism: A structural motif revealed in an insertion mutant of staphylococcal nuclease. **Proc. Natl. Acad. Sci. USA** **90**: 3275-3279.
45. Green, S.M. and Shortle, D. (1993). Patterns of nonadditivity between pairs of stability mutations in staphylococcal nuclease. **Biochemistry** **32**: 10131-10139.
46. Shortle, D. and Abeygunawardana, C. (1993). NMR analysis of the residual structure in the denatured state of an unusual mutant of staphylococcal nuclease. **Structure** **1**: 121-134.
47. Stites, W.E., Meeker, A. K., and Shortle, D. (1994). Evidence for strained interactions between side-chains and the polypeptide backbone. **J. Mol. Biol.** **235**: 27-32.
48. Alexandrescu, A.T., Abeygunawardana, C. and Shortle, D. (1994) Structure and dynamics of a denatured 131-residue fragment of staphylococcal nuclease: A heteronuclear NMR study. **Biochemistry** **33**: 1063-1072.
49. Alexandrescu, A.T. and Shortle, D. (1994) Backbone dynamics of a highly disordered 131-residue fragment of staphylococcal nuclease. **J. Mol. Biol.** **242**: 527-546.
50. Shortle, D. (1994) Assignment of amino acid type in ^1H - ^{15}N correlation spectra by labeling with ^{14}N -amino acids. **J. Magn. Reson. Series B.** **105**: 88-90.
51. Creighton, T.E. and Shortle, D. (1994). Electrophoretic characterization of the denatured states of staphylococcal nuclease. **J. Mol. Biol.** **242**: 670-682.
52. Shortle, D. (1995) Staphylococcal nuclease: A showcase of m-value effects. **Advances in Protein Chem.** **46**: 217-247.
53. Alexandrescu, A.T., Gittis, A.G., Abeygunawardana, C. and Shortle, D. (1995). NMR structure of a stable "OB-fold" sub-domain isolated from staphylococcal nuclease. **J. Mol. Biol.** **250**, 134-143.
54. Wang, Y., Alexandrescu, A.T. and Shortle, D. (1995) Initial studies of the equilibrium folding pathway of staphylococcal nuclease. **Phil. Trans. R. Soc. Lond. B.** **348**, 27-34.

55. Shortle, D. (1995) Protein Fold Prediction, (a News & Views Review), **Nature Struct. Biol.** **2**, 91-93.
56. Shortle, D. and Sondek, J. (1995). The emerging role of insertions and deletions in protein engineering. **Current Opin. Biotechn.** **6**, 387-393.
57. Wang, Y. and Shortle, D. (1995). The equilibrium folding pathway of staphylococcal nuclease: Identification of the most stable chain-chain interactions by NMR and CD spectroscopy. **Biochemistry** **34**, 15895-15905.
58. Shortle, D. (1996). The denatured state (the other half of the folding equation) and its role in protein stability. **FASEB Journal** **10**: 27-34.
59. Shortle, D., Wang, Yi, Gillespie, J., and Wrabl, J.O. (1996) Protein folding for realists: A timeless phenomenon (An Invited Review). **Protein Science** **5**: 991-1000.
60. Shortle, D. (1996) Structural analysis of non-native states of proteins by NMR methods. **Current Opinion Struct. Biology**, **6**: 24-30..
61. Meeker, A.K., Garcia-Moreno, B, and Shortle, D. (1996) Contributions of the ionizable amino acid residues to the stability of staphylococcal nuclease. **Biochemistry** **35**, 6443-6449.
62. Wang, Y. and Shortle, D. (1996). A dynamic bundle of four adjacent hydrophobic segments in the denatured state of staphylococcal nuclease. **Protein Science** **5**: 1898-1906
63. Wrabl, J. O. and Shortle, D. (1996). Perturbations of the denatured state ensemble: Modeling their effects on protein stability and folding kinetics. **Protein Science** **5**: 2343-2352.
64. Zhang, O., Forman-Kay, J.D., Shortle, D. & Kay, L.E. (1996) Triple-resonance NOESY-based experiments with improved spectral resolution: Applications to structural characterization of unfolded, partially folded, and folded proteins. **J. Biomol. NMR** **9**: 181-200.
65. Gillespie, J.R. & Shortle, D. (1997) Characterization of long range structure in the denatured state of staphylococcal nuclease. I. Paramagnetic relaxation enhancement by nitroxide spin labels. **J. Mol. Biol.** **268**: 158-169.
66. Gillespie, J.R. & Shortle, D. (1997) Characterization of long range structure in the denatured state of staphylococcal nuclease. II. Distance restraints from paramagnetic relaxation and calculation of an ensemble of structures **J.Mol. Biol.** **268**: 170-184.
67. Zhang, O., Kay, L.E., Shortle, D., and Forman-Kay, J.D. (1997) Comprehensive NOE characterization of a partially folded large fragment of staphylococcal nuclease, D131D, using NMR methods with improved resolution. **J. Mol. Biol.** **272**, 9-20.
68. Shortle, D. (1997) Folding proteins by pattern recognition. **Curr Biol.** **7**: R151-R154.
69. Mori, S., van Zijl, P.C.M., and Shortle, D. (1997) Measurement of water-amide proton exchange rates in the denatured state of staphylococcal nuclease by a magnetization transfer technique. **Proteins: Struct. Funct. Genet.** **28**: 325-332.
70. Zhang, O., Kay, L.E., Shortle, D., and Forman-Kay, J.D. (1997) Comprehensive NOE characterization of a partially folded large fragment of staphylococcal nuclease, Δ 131 Δ , using NMR methods with improved resolution. **J. Mol. Biol.** **272**: 9-20.
71. Wang, Y. and Shortle, D. (1997). Residual helical and turn structure in the denatured state of staphylococcal nuclease: analysis of peptide fragments. **Folding & Design** **2**:93-100.
72. Shortle, D., Simons, K.T. and Baker, D. Clustering of low energy conformations near the native structures of small proteins. (1998) **Proc. Natl. Acad. Sci. USA** **95**: 11158-11162.
73. Sinclair, J.F. and Shortle, D. (1999) Analysis of long range interactions in a model denatured state of staphylococcal nuclease based on correlated changes in backbone dynamics. **Protein Science**, **8**: 991-1000.
74. Shortle, D. (1999) Protein folding as seen from water's perspective. (News & Views) **Nature Structural Biology**, **6**: 202 - 205.

75. Shortle, D. (1999) Structure prediction: the state of the art. **Current Biology** 9: R205 - 209.
76. Wrabl, J.O. and Shortle, D. (1999) A model of the changes in denatured structure underlying m-value effects in staphylococcal nuclease. **Nature: Structural Biology** 6: 876-883.
77. Wrabl, J.O., Shortle, D. and Woolf, T.B. (2000) Correlation between changes in nuclear magnetic resonance order parameters and conformational entropy: molecular dynamics simulations of native and denatured staphylococcal nuclease. **Proteins: Struct. Funct. Genet.** 38: 123-133.
78. Shortle, D. (2000) Prediction of protein structure (a primer). **Current Biol.** 10: R49-R51.
79. Shortle, D. and Ackerman, M. S. (2001) Persistence of native-like topology in a denatured protein in 8 M urea. **Science** 293: 487-489.
80. Shortle, D. (2002) Composites of Local Structural Propensities: Evidence for Local Encoding of Long Range Structure. **Protein Science** 11: 18-26.
81. Ackerman, M. S. and Shortle, D. (2002) Molecular Alignment of Denatured States of Staphylococcal Nuclease with Strained Polyacrylamide Gels and Alkyl-PEG Bicelles. **Biochemistry** 41: 3089-3095.
82. Ackerman, M. S. and Shortle, D. (2002) Robustness of the long-range structure in denatured staphylococcal nuclease to changes in sequence. **Biochemistry** 41: 13791-13797.
83. Shortle, D. (2002) The Expanded Denatured State: An Ensemble of Conformations Trapped in a Locally Encoded Topological Space. **Adv. Protein Chem.** 62: 1-23.
84. Ohnishi, S. and Shortle, D. (2003) Observation of residual dipolar couplings in short peptides. **Proteins:** 50: 546-51
85. Choy, W.-Y., Shortle, D. and Kay, L.E. (2003) Side chain dynamics in unfolded protein states: A 2H spin relaxation study of D131D. **J. Amer. Chem. Soc.**, 125:1748-1758.
86. Fang, Q. and (2003) Prediction of Protein Structure by Emphasizing Local Side-Chain / Backbone Interactions in Ensembles of Turn Fragments **Proteins:** 53: 486-490.
87. Shortle, D. (2003) Propensities, probabilities, and the Boltzmann hypothesis. **Protein Science** 12: 1298-1302.
88. Ohnishi S. and Shortle, D. (2003) Effect of denaturants and substitutions of hydrophobic residues on backbone dynamics of denatured staphylococcal nuclease. **Protein Science** 12: 1530-1537.
89. Ohnishi, S., Lee, A.L., Edgell, M.H. and Shortle, D. (2004) Direct demonstration of structural similarity between native and denatured eglin C. **Biochemistry** 43: 4064-4070.
90. Fang Q. and Shortle, D. (2005) A consistent set of statistical potentials for quantifying local side-chain and backbone interactions. **Proteins** 60: 90-96.
91. Fang, Q. and Shortle, D. (2005) Enhanced sampling near the native conformation using statistical potentials for local side-chain and backbone interactions. **Proteins.** 60: 97-102.
92. Fang, Q and Shortle, D.(2006) Protein refolding *in silico* with atom-based statistical potentials and conformational search using a simple genetic algorithm **J. Mol. Biol.** 359:1456-1467.
93. Gebel, E. Ruan, K.; Tolman, J.R and Shortle, D. (2006) Multiple alignment tensors from a denatured protein. **J. Am. Chem. Soc.**, 128: 9310-9311.
94. Ohnishi S, Kamikubo H, Onitsuka M, Kataoka M, and Shortle D. (2006) Conformational

- preference of polyglycine in solution for elongated structures. **J Am Chem Soc.** 128:16338-16344.
95. Gebel, E. and Shortle, D(2007) Characterization of denatured proteins using residual dipolar couplings. **Methods in Molecular Biology**, 350: 39-48.
96. Shortle D. (2008) The Denatured States of Proteins: How Random Are They? In Unfolded Proteins, Trevor Creamer, editor. Nova Science Publishers, Inc., New York.
97. Shortle D. (2009) One sequence plus one mutation equals two folds. **Proc Natl Acad Sci USA** 106: 21011-21012
98. Shortle D (2010) Protein structure prediction with statistical potentials and genetic algorithms. **Abstract** submitted as part of the **CASP9** structure prediction competition.
99. Shortle D. (2012) Protein structure prediction using epicycles of Monte Carlo sampling. **Abstract** submitted as part of the **CASP10** structure prediction competition.

Inventions, Patents, Copyrights

Patent Title: Mutagenesis with Trinucleotides Date: 9/29/93