each  $1 \leq j \leq |V|$ , from a normal distribution of zero mean and unit standard deviation (i.e.,  $\Pr\left[a \leq r_j' \leq b\right] = \int_a^b (1/\sqrt{2\pi}) \, \mathrm{e}^{-x^2/2} \, \mathrm{d}x$  for any  $\emptyset \subset [a,b] \subset \mathbb{R}$ ), and then normalizing the coordinates so that the 2-norm of the resulting vector is 1, i.e., setting  $r_j = \frac{r_j'}{\sqrt{\sum_{i=1}^n (r_i')^2}}$  for  $j=1,2,\ldots,|V|$ .

(b) For each  $v \in V$ , set  $\ell_v = \begin{cases} 1, & \text{if } \overrightarrow{r} \cdot \overrightarrow{\ell_v} \geq 0 \\ -1, & \text{otherwise} \end{cases}$  where "·" denotes the vector inner product.

Let  $\ell_{\rm opt}$  be an optimum node labeling function for SGN-Const with  $\left|F_{\ell_{\rm opt}}\right|$  consistent edges. It can be shown that the above randomized algorithm provides a node labeling function  $\ell_{\rm approx}$  to SGN-Const with  $\left|F_{\ell_{\rm approx}}\right|$  consistent edges such that

$$\mathbb{E}\left[\left|F_{\ell_{\rm approx}}\right|\right] \ge \kappa \left|F_{\ell_{\rm opt}}\right|$$

where  $\kappa = \min \left\{ \min_{0 \leq \theta \leq \pi} \frac{2 \theta / \pi}{1 - \cos \theta}, \min_{0 \leq \theta \leq \pi} \frac{2 - (2 \theta / \pi)}{1 + \cos \theta} \right\}$ . It can be shown using elementary calculus that  $\kappa > 0.87856$ ; thus on an average the approximate solution retains at least 87.85% of the number of consistent edges in an optimal solution. The above randomized approach to compute the mappings  $P_v$  can be made deterministic (i.e., can be "de-randomized") [70], but the derandomization procedure is complicated. Instead, one usually runs the randomized algorithm for computing the  $P_v$ s many times and accepts the best of these solutions; it can be shown that such an approach retains at least  $\kappa$  fraction of the optimal number of consistent edges with very high probability [84].

## REFERENCES

- R. Albert, B. DasGupta, A. Gitter, G. Gürsoy, R. Hegde, P. Pal, G. S. Sivanathan and E. Sontag. A New Computationally Efficient Measure of Topological Redundancy of Biological and Social Networks, Physical Review E, 84 (3), 036117, 2011
- 2. R. Albert and H. Othmer. The topology of the regulatory interactions predicts the expression pattern of the segment polarity genes in *Drosophila melanogaster*, Journal of Theoretical Biology, 223, 1-18, 2003.
- 3. F. Alizadeh. Interior point methods in semidefinite programming with applications to combinatorial optimization, SIAM Journal on Optimization, 5, 13-51, 1995.
- 4. R. Alur, C. Belta, F. Ivanc, V. Kumar, M. Mintz, G.J. Pappas, H. Rubin and J. Schlug. Hybrid modeling and simulation of biomolecular networks, in M. D. Di Benedetto and A. Sangiovanni-Vincentelli (editors), Hybrid Systems: Computation and Control, Lecture notes in computer science, 2034, 19-32, Springer Verlag, 2001.
- R. Alur, T. Henzinger, G. Lafferriere and G. J. Pappas. Discrete abstractions of hybrid systems, Proceedings of the IEEE, 88(7), 971-984, 2000.
- D. Angeli, P. De Leenheer and E. D. Sontag. A small-gain theorem for almost global convergence of monotone systems, Systems and Control Letters, 51, 185-202, 2004.
- D. Angeli, J. E. Ferrell Jr. and E. D. Sontag. Detection of multi-stability, bifurcations, and hysteresis in a large class of biological positive-feedback systems, Proceedings of the National Academy of Sciences USA, 101, 1822-1827, 2004.

- 8. D. Angeli and E.D. Sontag. Monotone control systems, IEEE Transactions on Automatic Control, 48, 1684-1698, 2003.
- D. Angeli and E. D. Sontag. Multistability in monotone I/O systems, Systems and Control Letters, 51, 185-202, 2004.
- D. Angeli and E. D. Sontag. An analysis of a circadian model using the smallgain approach to monotone systems, IEEE Conference on Decision and Control, 575-578, 2004.
- 11. F. Barahona. On the computational complexity of Ising spin glass models, Journal of Physics A: Mathematical and General, 15 (10), 3241-3253, 1982.
- E. B. Baum and D. Haussler. What size net gives valid generalization?, Neural Computation, 1, 151-160, 1989.
- 13. C. Belta, P. Finin, L. C. G. J. M. Habets, A. Halasz, M. Imielinksi, V. Kumar and H. Rubin. Understanding the bacterial stringent response using reachability analysis of hybrid systems, in R. Alur and G. Pappas (editors), Hybrid Systems: Computation and Control, Hybrid Systems: Computation and Control, Lecture notes in computer science, 2993, 111-125, Springer Verlag, 2004.
- A. Bemporad, G. Ferrari-Trecate, and M. Morari. Observability and controllability
  of piecewise affine and hybrid systems, IEEE Transactions on Automatic Control,
  45 (10), 1864-1876, 2000.
- A. Bemporad and M. Morari. Control of systems integrating logic, dynamics, and constraints, Automatica, 35, 407-428, 1999.
- D. P. Bertsekas and J.N. Tsitsiklis. Parallel and Distributed Computation, Numerical Method. Prentice Hall, Englewood Cliffs, New Jersey, 1989.
- A. Blum and R. L. Rivest. Training a 3-node neural network is NP-complete, Neural Networks, 5, 117-127, 1992.
- A. Blumer, A. Ehrenfeucht, D. Haussler, and M. Warmuth. Learnability and the Vapnik-Chervonenkis dimension, Journal of the ACM, 36, 929-965, 1989.
- J. W. Bodnar. Programming the drosophila embryo, Journal of Theoretical Biology, 188, 391-445, 1997.
- R. L. Casey, H. L. Jong, and J. L. L. Gouzé. Piecewise-linear models of genetic regulatory networks: Equilibria and their stability, Journal of Mathematical Biology, 52, 27-56, 2006.
- 21. M. Chaves, R. Albert and E. D. Sontag. Robustness and fragility of boolean models for genetic regulatory networks, Journal of Theoretical Biology, 235, 431-449, 2005.
- 22. M. Chaves, E.D. Sontag, and R. Albert. Methods of robustness analysis for boolean models of gene control networks, IEE proceedings of Systems Biology, 153 (4), 154-167, 2006.
- 23. O. Cinquin and J. Demongeot. Positive and negative feedback: striking a balance between necessary antagonists, Journal of Theoretical Biology, 216, 229-241, 2002.
- 24. B.A. Cipra. The Ising Model Is NP-Complete, SIAM News, 33 (6), 2000.
- N. Creignou, S. Khanna and M. Sudan. Complexity classifications of Boolean constraint satisfaction problems, SIGACT News, 32 (4), 24-33, 2001.
- G. Cybenko. Approximation by superposition of a sigmoidal function, Mathematics of Control, Signals, and System, 2, 303-314, 1989.
- 27. B. DasGupta, G. A. Enciso, E. Sontag and Y. Zhang. Algorithmic and complexity results for decompositions of biological networks into monotone subsystems, Biosystems, 90 (1), 161-178, 2007.

- B. DasGupta and G. Schnitger. The Power of Approximating: A Comparison of Activation Functions, in C. L. Giles. S. J. Hanson and J. D. Cowan (editors), Advances in Neural Information Processing Systems, 5, Morgan Kaufmann Publishers, 615-622, 1993.
- B. DasGupta and G. Schnitger. Analog versus Discrete Neural Networks, Neural Computation, 8 (4), 805-818, 1996.
- B. DasGupta, H. T. Siegelmann and E. Sontag. On the Intractability of Loading Neural Networks, in V. P. Roychowdhury, K. Y. Siu and A. Orlitsky (editors), Theoretical Advances in Neural Computation and Learning, Kluwer Academic Publishers, 357-389, 1994.
- B. DasGupta, H. T. Siegelmann and E. Sontag. On the Complexity of Training Neural Networks with Continuous Activation Functions, IEEE Transactions on Neural Networks, 6 (6), 1490-1504, 1995.
- 32. B. DasGupta and E. D. Sontag. A polynomial-time algorithm for checking equivalence under certain semiring congruences motivated by the state-space isomorphism problem for hybrid systems, Theoretical Computer Science, 262, 161-189, 2001.
- D. L. DeAngelis, W. M. Post and C. C. Travis. Positive Feedback in Natural Systems, Springer-Verlag, New York, 1986.
- 34. H. de Jong. Modeling and simulation of genetic regulatory systems: A literature review, Journal of Computational Biology, 9 (1), 67-103, 2002.
- 35. P. De Leenheer, D. Angeli and E.D. Sontag. On predator-prey systems and small-gain theorems, Journal of Mathematical Biosciences and Engineering, 2, 25-42, 2005.
- 36. C. De Simone, M. Diehl, M. Junger, P. Mutzel, G. Reinelt and G. Rinaldi. Exact ground states of Ising spin glasses: New experimental results with a branch and cut algorithm, Journal of Statistical Physics, 80, 487-496, 1995.
- 37. R. Edwards, H. T. Siegelmann, K. Aziza and L. Glass. Symbolic dynamics and computation in model gene networks, Chaos, 11 (1), 160-169, 2001.
- 38. G. Enciso and E. Sontag. Global attractivity, I/O monotone small-gain theorems, and biological delay systems, Discrete and Continuous Dynamical Systems, 14, 549-578, 2006.
- T. Gedeon and E. D. Sontag. Oscillation in multi-stable monotone system with slowly varying positive feedback, Journal of Differential Equations, 239, 273-295, 2007
- R. Ghosh and C. J. Tomlin. Symbolic reachable set computation of piecewise affine hybrid automata and its application to biological modeling: Delta-notch protein signaling, IEE proceedings on Systems Biology, 1, 170-183, 2004.
- R. Ghosh and C. J. Tomlin. Lateral inhibition through Delta-notch signaling: A piecewise affine hybrid model, in M. D. D. Benedetto and A. Sangiovanni-Vincentelli (editors), Hybrid Systems: Computation and Control, LNCS 2034, 232-246, Springer Verlag, 2001.
- A. Ghysen and R. Thomas. The formation of sense organs in drosophila: A logical approach, BioEssays, 25, 802-807, 2003.
- 43. L. Glass and S. A. Kauffman. The logical analysis of continuous, non-linear biochemical control networks, Journal of Theoretical Biology, 39 (1), 103-129, 1073.
- 44. M. Goemans and D. Williamson. Improved approximation algorithms for maximum cut and satisfiability problems using semidefinite programming, Journal of the ACM, 42 (6), 1115-1145, 1995.

- 45. P. Goldberg and M. Jerrum. Bounding the Vapnik-Chervonenkis dimension of concept classes parameterized by real numbers, Machine Learning, 18, 131-148, 1995.
- M. Goldmann and J. Hastad. On the power of small-depth threshold circuits, Computational Complexity, 1 (2), 113-129, 1991.
- G. H. Golub and C. F. Van Loan. Matrix computations, 3<sup>rd</sup> edition, Johns Hopkins University Press, 1996.
- 48. M. Grötschel, L. Lovász and A. Schrijver. Geometric Algorithms and Combinatorial Optimization, Springer-Verlag, New York, 1988.
- P. Gupta, R. Janardan, M. Smid and B. DasGupta. The rectangle enclosure and point-dominance problems revisited, International Journal of Computational Geometry and Applications, 7 (5), 437-455, 1997.
- V. V. Gursky, J. Reinitz and A. M. Samsonov. How gap genes make their domains: An analytical study based on data driven approximations, Chaos, 11, 132-141, 2001.
- 51. J. Håstad and S. Venkatesh. On the advantage over a random assignment, Random Structures & Algorithms, 25 (2), 117-149, 2004.
- A. Hajnal, W. Maass, P. Pudlak, M. Szegedy and G. Turan. Threshold circuits of bounded depth, Journal of Computer and System Sciences, 46, 129-154, 1993.
- D. Haussler. Decision theoretic generalizations of the PAC model for neural nets and other learning applications, Information and Computation, 100, 78-150, 1992.
- 54. M. Hirsch. Systems of differential equations that are competitive or cooperative II: Convergence almost everywhere, SIAM Journal of Mathematical Analysis, 16, 423-439, 1985.
- M. Hirsch. Differential equations and convergence almost everywhere in strongly monotone flows, Contemporary Mathematics, 17, 267-285, 1983.
- J. E. Hopcroft, R. Motwani and J. D. Ullman. Introduction to Automata Theory, Languages, and Computation, Addison Wesley; 3 edition, 2006.
- 57. F. Hüffner, N. Betzler and R. Niedermeier. Optimal edge deletions for signed graph balancing, 6<sup>th</sup> Workhop on Experimental Algorithms, LNCS 4525, 297-310, Springer-Verlag, 2007.
- S. Istrail. Statistical Mechanics, Three-Dimensionality and NP-Completeness: I. Universality of Intractability of the Partition Functions of the Ising Model Across Non-Planar Lattices, Thirty-Second Annual ACM Symposium on Theory of Computing, 87-96, 2000.
- M. Karpinski and A. Macintyre. Polynomial Bounds for VC Dimension of Sigmoidal and General Pfaffian Neural Networks, Journal of Computer and Systems Science, 54, 169-176, 1997.
- S. Kauffman, C. Peterson, B. Samuelsson, and C. Troein. Random boolean network models and the yeast transcriptional network, Proceedings of the National Academy of Sciences USA, 100, 14796-14799, 2003.
- 61. A. N. Kolmogorov. On the representation of continuous functions of several variables by superposition of continuous functions of one variable and addition, Doklady Akademii Nauk (proceedings of the Russian Academy of Sciences), 114, 953-956, 1957.
- 62. K. M. Kyoda, M. Morohashi, S. Onami and H. Kitano. A gene network inference method from continuous-value gene expression data of wild-type and mutants, Genome Informatics, 11, 196-204, 2000.

- J. Lewis, J.M. Slack and L. Wolpert. Thresholds in development, Journal of Theoretical Biology, 65, 579n590, 1977.
- 64. G. Marnellos, G. A. Deblandre, E. Mjolsness, and C. Kintner. Delta-notch lateral inhibitory patterning in the emergence of ciliated cells in Xenopus: Experimental observations and a gene network model, Pacific Symposium on Biocomputing, 326-337, 2000.
- 65. W. Maass. Perspectives of current research about the complexity of learning in neural nets, in Theoretical Advances in Neural Computation and Learning, V. P. Roychowdhury, K. Y. Siu, and A. Orlitsky (editors), Kluwer Acedemic Publishers, 295-336, 1994.
- 66. W. Maass. Bounds for the computational power and learning complexity of analog neural nets, SIAM Journal of Computing, 26 (3), 708-732, 1997.
- 67. W. Maass, G. Schnitger, and E. D. Sontag. On the computational power of sigmoid versus boolean threshold circuits, proceedings of the 32<sup>nd</sup> annual IEEE symposium on Foundations of Computer Science, 767-776, 1991.
- W. Maass and E. D. Sontag. Analog neural nets with gaussian or other common noise distributions cannot recognize arbitrary regular languages, Neural Computation, 11 (3), 771-782, 1999.
- 69. A. Maayan, R. Iyengar and E.D. Sontag. Intracellular Regulatory Networks are close to Monotone Systems, IET Systems Biology, 2, 103-112, 2008.
- S. Mahajan and H. Ramesh. Derandomizing semidefinite programming based approximation algorithms, SIAM Journal of Computing, 28 (5), 1641-1663, 1999.
- 71. H. Meinhardt. Space-dependent cell determination under the control of morphogen gradient, Journal of Theoretical Biology, 74, 307ŋ321, 1978.
- L. Mendoza, D. Thieffry, and E. R. Alvarez-Buylla. Genetic control of flower morphogenesis in arabidopsis thaliana: a logical analysis, Bioinformatics, 15, 593-606, 1999
- 73. M. Minsky and S. Papert. Perceptrons, The MIT Press, 1988.
- J. Monod and F. Jacob. General conclusions: telenomic mechanisms in cellular metabolism, growth, and differentiation, Cold Spring Harbor Symposium on Quantitative Biology, 26, 389-401, 1961.
- Y. Nesterov and A. Nemirovskii. Self-Concordant Functions and Polynomial Time Methods in Convex Programming, Central Economic and Mathematical Institute, USSR Academy of Science, 1989.
- 76. Y. Nesterov and A. Nemirovskii. Interior Point Polynomial Methods in Convex Programming, Society of Industrial and Applied Mathematics, Philadelphia, 1994.
- 77. I. Parberry. A Primer on the Complexity Theory of Neural Networks, in Formal Techniques in Artificial Intelligence: A Sourcebook, R. B. Banerji (editor), Elsevier Science Publishers B. V. (North-Holland), 217-268, 1990.
- 78. E. Plathe, T. Mestl and S.W. Omholt. Feedback loops, stability and multistationarity in dynamical systems, Journal of Biological Systems, 3, 409n413, 1995.
- C. V. Rao, D. M. Wolf and A. P. Arkin. Control, exploitation and tolerance of intracellular noise, Nature, 420, 231-237, 2002.
- 80. J. H. Reif. On threshold circuits and polynomial computation, SIAM Journal on Computing, 21 (5), 896-908, 1992.
- J. Reinitz and D. H. Sharp. Mechanism of eve stripe formation, Mechanisms of Development, 49 (1-2), 133-158, 1995.

- E. Remy, B. Mosse, C. Chaouiya and D. Thieffry. A description of dynamical graphs associated to elementary regulatory circuits, Bioinformatics, 19 (Suppl. 2), ii172ηii178, 2003.
- D. E. Rumelhart and J. L. McClelland. Parallel Distributed Processing: Explorations in the Microstructure of Cognition, The MIT Press, 1986.
- 84. L. Sánchez and D. Thieffry. A logical analysis of the drosophila gap-gene system, Journal of Theoretical Biology, 211, 115-141, 2001.
- 85. H. T. Siegelmann. Neural Networks and Analog Computation: Beyond the Turing Limit, Birkhäuser publishers, 1998.
- H. T. Siegelmann and E. D. Sontag. Analog computation, neural networks, and circuits, Theoretical Computer Science, 131, 331-360, 1994.
- H. T. Siegelmann and E. D. Sontag. On the Computational Power of Neural Nets, Journal of Computer and System Sciences, 50, 132-150, 1995.
- 88. H. L. Smith. Systems of ordinary differential equations which generate an order-preserving flow: A survey of results, SIAM Reviews, 30, 87-111, 1988.
- 89. H. L. Smith. Monotone Dynamical Systems, Providence, R.I., AMS 1995.
- E. H. Snoussi. Necessary conditions for multistationarity and stable periodicity, Journal of Biological Systems, 6, 3η9, 1998.
- E. D. Sontag. Nonlinear regulation: The piecewise linear approach, IEEE Transaction on Automatic Control, 26 (2), 346-358, 1981.
- E. D. Sontag. Remarks on piecewise-linear algebra, Pacific Journal of Mathematics, 98, 183-201, 1982.
- E. D. Sontag. Molecular systems biology and control, European Journal of Control, 11, 396-435, 2005.
- E. D. Sontag. Some new directions in control theory inspired by systems biology, Systems Biology, 1, 9-18, 2004.
- 95. R. Thomas. Boolean formalization of genetic control circuits, Journal of Theoretical Biology, 42, 563-585, 1973.
- 96. R. Thomas. Logical analysis of systems comprising feedback loops, Journal of Theoretical Biology, 73, 631 $\eta$ 656, 1978.
- P. Vaidya. A new algorithm for minimizing convex functions over convex sets, Mathematical Programming, 73 (3), 291-341, 1996.
- V. N. Vapnik and A. Chervonenkis, Theory of Pattern Recognition (in Russian), Moscow, Nauka, 1974.
- 99. V. V. Vazirani. Approximation Algorithms, Springer-Verlag, Berlin, 2001.
- 100. G. von Dassow, E. Meir, E. M. Munro and G. M. Odell. The segment polarity network is a robust developmental module, Nature, 406, 188-192, 2000.
- S. M. Welch, J. L. Roe and Z. Dong. A genetic neural network model of flowering time control in arabidopsis thaliana, Agronomy Journal, 95, 71-81, 2003.
- 102. C. H. Yuh, H. Bolouri, J. M. Bower, and E. H Davidson. A logical model of cisregulatory control in a eukaryotic system, in Computational Modeling of Genetic and Biochemical Networks, J. M. Bower and H. Bolouri (editors), 73-100, The MIT Press, 2001.