Tom Chou

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Education

1989–1995 ..... **Ph.D. Physics**, Harvard University

1989–1991 ..... **M.A. Physics**, Harvard University

1985–1989 ..... **S.B. Physical Chemistry**, Massachusetts Institute of Technology

Employment

Jul 2009 – ..... **Professor**, Depts. of Biomathematics & Mathematics, UCLA

Jul 2006 – Jun 2009 ..... **Associate Professor**, Dept. of Mathematics, UCLA

Jul 2005 – Jun 2009 ..... **Associate Professor**, Dept. of Biomathematics, UCLA

Jul 2000 – Jun 2005 ..... **Assistant Professor**, Dept. of Biomathematics, UCLA

Jul 1998 – Jun 2000 ..... **Lecturer**, Dept. of Mathematics, Stanford

Oct 1996 – Jun 1998 ..... **Research Fellow**, DAMTP, University of Cambridge

Aug 1995 – Aug 1996 ..... **Research Assistant**, Dept. of Physics, Cornell University

Other Appointments and Professional Honors

Jan 2017 – ..... **Director**, NIGMS T32 Systems and Integrative Biology Training Grant

Sep 2013 – ..... **Fellow of the American Physical Society**, American Physical Society

Oct 2013 – ..... **Participating Faculty**, Bioinformatics IDP

Jul 2013 – Jan 2017 ..... **Co-Director**, NIGMS Systems and Integrated Biology Training Grant

Oct 2012 – ..... **Affiliate Faculty**, Dept. of Bioengineering

Sep 2012 – Sep 2015 ..... **Scientific Advisory Committee**, Mathematical Biosciences Institute, OSU

Mar 2010 – Nov 2011 ..... **Defense Science Study Group**, Institute of Defense Analyses

2009 – 2011 ..... **Vice-Chair**, Computational and Systems Biology Interdepartmental Program

Oct 2004 – ..... **Participating Faculty**, Physiology IDP

May 1989 – Aug 1989 ..... **Resident Researcher**, DuPont Central Research & Development

Grants and Awards

04/01/2019 – 03/31/2023: ..... "Tracking clonal dynamics during hematopoiesis: mechanistic insight via modeling and data analysis"
NIH R01HL146552, 11$^{\text{th}}$ precentile, recommended for funding (PI: T. Chou)

07/15/2018 – 07/14/2021: ..... "Pathophysiology of the stressed brain: Insights from mathematical models of glucocorticoid hormones affecting timing and memory"
Army Research Office W911NF-18-1-0345 (PI: D'Orsogna)

07/01/2018 – 06/30/2023: ..... "Systems and Integrative Biology Training Grant"
NIH NIGMS T32GM008185 (PI: T. Chou)

08/01/2018 – 07/31/2021: ..... "Collaborative Research: Understanding generation, maintenance, and dynamics of immune diversity via clone-count models"
NSF DMS-1814364 (PI: T. Chou)

International Congress of Chinese Mathematicians ICCM 2012-2017 distinguished paper award: *A Path-Integral Approach to Bayesian Inference for Inverse Problems Using the Semiclassical Approximation*

06/01/2018 – 05/31/2019: ..... "Using quality-of-life scores to guide prostate RT"
Breast Cancer Research Foundation (PI: Chou)

05/19/2017 – 05/21/2017: ..... "Workshop on Applied Mathematics in Germinating Oncology Solutions"
Breast Cancer Research Foundation/JKTG Foundation (PI: T. Chou)

10/01/2015 – 09/30/2018: ..... "Quantification and mathematical modeling of viral entry assays"
NSF DMS-1516675 (PI: T. Chou)

09/01/2014 – 08/31/2017 ..... "Warfighter neuroendocrinology: quantifying stress and modeling PTSD"
Army Research Office (co-PI: T. Chou)

09/06/2014 – 08/31/2016: ..... "Mouse and Mathematical Models for HIV-1 suppression through HSPC"
NIH-NHLBI R56HL126544 (co-PI: T. Chou)

09/15/2013 – 12/31/2015 ..... "Brain Activity Maps of Novelty Detection"
NSF Behavioral and Cognitive Sciences, (PI: J. W. Young)

11/20/2013 – 10/31/2015: ..... "Hematopoietic stem/progenitor cell reservoirs"
NIH-NIAID R01AI110297 (PI: I. Chen)

09/15/2010 – 08/31/2014 ..... "Mathematical Imaging and Modeling of Cortical Spreading Depression and Wound Healing,"
Army Research Office (PI: T. Chou)

10/01/2010 – 09/30/2014 ..... "Hierarchical kinetic models for self-propelled organisms,"
NSF DMS-1021818 (PI: T. Chou)

06/01/2010 – 05/31/2012 ..... "Quantifying differential CD4/CCR5 usage in HIV1/SIV strains"
NIH-NIAIDS R21AI092218 (PI: B. Lee)

09/15/2010 – 02/28/2012 ..... "Mathematics for microscopy and cell biology,"
NSF DMS-1032131 (PI: T. Chou)

06/01/2010 – 07/31/2011 ..... "Models for corneal mechanics and tonometer calibration"
Oppenheimer Foundation Center for Prevention of Eye Disease, UCLA (PI: Chou)

09/15/2009 ..... "Drug metabolite excretion kinetics"
Innocentive Challenge co-winner

09/01/2004 – 08/31/2010 ..... "Stochastic inverse problems in biophysics"
NSF CAREER Award, DMS-0349195 (PI: T. Chou)

02/01/2004 – 11/30/2009 ..... "Multiscale studies of HIV infection and treatment"
NIH Career Development Award, K25 AI058672 (PI: T. Chou)

08/01/2001 – 07/31/2005 ..... "Models of one-dimensional transport"
NSF DMS-0206733 (PI: T. Chou)

09/01/2001 – 08/31/2002 ..... "Statistical mechanics RecA-mediated recombination"
UCLA Frontiers in Research Grant (PI: T. Chou)

09/01/1998 – 08/31/2000 ..... "Mathematical Sciences Postdoctoral Fellowship"
NSF DMS-9804370 (PI: T. Chou)

Patents

1. Benhur Lee, Chikere kelechi, and Tom Chou, A novel, rapid, and highly sensitive cell-based system for the detection and characterization of HIV, International Application Number: PCT/US2013/032178, International Publication Date: Sep 26, 2013.

Mentoring

Postdoctoral Researchers

8. Dr. Renaud Dessalles (2017–present):
   Ph.D., Applied Mathematics, INRIA, Paris, 2017.

7. Dr. Yao-Li Chuang (2014–present):
   Ph.D., Mathematics, Duke University 2006.

6. Dr. Bijan Berenji (2012–2013):
   Ph.D., Physics, Stanford University 2011.
   Lecturer, CalState-Los Angeles

5. Dr. Yanxiang Zhao (2012):
   Ph.D., Mathematics, Penn. State Univ., 2011.
   Assistant Professor, Dept. of Mathematics, Georgetown.

4. Dr. Filippo Posta (2008–2010):
   Ph.D., Mathematics, New Jersey Inst. of Tech. 2008.
   Assistant Professor, Grand Canyon University

3. Dr. Melissa Gibbons (2008–2010):
   Ph.D., Mechanical Engineering, UCLA 2008.
   Research Associate, L3 Communications, San Diego, CA

2. Dr. Buddhapriya Chakrabarti (2007–2008):
   Ph.D., Physics, Indian Institute of Science, Bangalore 2004.
   Senior Lecturer, Dept. of Physics, University of Sheffield

1. Dr. Pak-Wing Fok (2006–2009):
   Ph.D., Mathematics, MIT 2006.
   Associate Professor, Dept. of Mathematics, University of Delaware

Students

11. Bhaven Mistry (2017–present) — Ph.D. Candidate, UCLA Biomathematics

10. Stephanie Lewkiewicz (2013–2018) — Ph.D. Candidate, UCLA Mathematics

9. Song Xu (2014–2018) — Ph.D., UCLA Biomathematics
   Postdoc, Dept. of Medicine, Stanford University

8. Lae Un Kim (2013–2017) — Ph.D., UCLA Biomathematics
   Postdoc/Instructor, Dept. of Applied Mathematics, Northwestern University

7. Joshua Chang (2009–2012) — Ph.D., UCLA Biomathematics
   Postdoc, National Institutes of Health

6. Ben Hertz-Shargel (2007–2010) — Ph.D., UCLA Mathematics
   Vice President, ThinkEco, Inc.

5. Sarah A. Nowak (2005–2009) — Ph.D., UCLA Biomathematics
   Professor, Pardee RAND Graduate School

4. Robert Rovetti (2004–2008) — Ph.D., UCLA Biomathematics
   Associate Professor, Dept. of Mathematics, Loyola Marymount University

3. John Marshall (2004–2008) — Ph.D., UCLA Biomathematics
   Assistant Professor, School of Public Health, UC Berkeley

2. Kevin D. Klapstein (2000-2004) — Ph.D., UCLA Biomathematics
   Assistant Professor, Tuoro University

1. Gregory W. Lakatos (1999-2000) MS, Stanford Mechanical Engineering
   Zymeworks, Vancouver, BC

Recent Invited Talks

- *Lineage tracking in hematopoiesis: the role of self-renewal and generational aging in clonal extinction and resurrection* , Mathematisches Forschungsinstitut Oberwolfach, Germany, September 24, 2018
- *Inference and Uncertainty Quantification in high-dimensional stochastic systems*, IBS Symposium, Seoul, Korea, July 31, 2018
- *Dynamics of stress disorders and Novelty Detection*, Fields Institute, Toronto, September 8, 2017
- *Hematopoietic stem cell self-renewal and clonal aging determine clone size fluctuations of granulocyte populations in rhesus macaque*, Math-bio seminar, Univ. of Pennsylvania, March 27, 2017
- *Path Integration and Regularization in Uncertainty Quantification: Reconstruction of Bond Energies and Mobility in Dynamic Force Spectroscopy*, Sanya TSIMF Program: Mathematics Biophysics and Molecular Biosciences, Dec 22, 2016, Sanya, China
- *A kinetic theory of age-structured populations*, Statistical Physics Seminar, IPST, University of Maryland, Sept. 13, 2016
- *Path integral-based Bayesian inference of bond energy and mobility* , Spatially Distributed Stochastic Dynamical Systems in Biology, Isaac Newton Institute, Cambridge, June 22, 2016
- *Lineage-tracking of stem cell differentiation: a neutral model of hematopoiesis in rhesus macaque*, Invited Talk, APS March Meeting, Baltimore, MD, March 14, 2016
- *Inference in Biophysics*, Institute for Pure and Applied Mathematics, UCLA, Uncertainty Quantification, Jan. 19, 2016
- *Winter School: Modeling, Simulation and Analysis of Biology and Physiology*, National Center for Theoretical Sciences, National Taiwan University, Taipei, Taiwan, Dec. 18-30, 2015
- *Subcellular Biophysics and Cellular Proliferation*, Special course, Universidad Autonoma de al Cuidad de Mexico, Mexico, Nov. 11-13, 2015
- *Methods for modeling aging, differentiation and fixation in stochastic populations*, Kavli Institute for Theoretical Physics, UCSB, Santa Barbara, CA, Sept. 24, 2015
- *First passage times in discrete stochastic self-assembly*, Invited Speaker, Santa Fe Institute, Santa Fe, NM, Sept. 19, 2015
- *A kinetic theory for age-structured particles*, Invited speaker, Chinese Academy of Sciences, Beijing, Aug. 8, 2015
- *Fixation times in differentiation and evolution on a network*, Invited speaker, Institute of natural Sciences, Shanghai Jiaotong University, Shanghai, Aug. 5, 2015
- *First passage times in discrete stochastic self-assembly*, Mathematics Seminar, National University of Singapore, Aug. 3, 2015
- *A kinetic theory for age-structured particles*, Invited speaker: Hot Topics Workshop, IMA, Univ. Minnesota, July 23, 2015
- *Fixation times in differentiation and evolution in the presence of bottlenecks and oases*, SIAM Dynamical Systems, Snowbird, Utah, May 20, 2015
- *Discreteness and first passage times in nucleation*, University of Arizona, Mathematics Colloquium, Mar. 27, 2015
- *Stochastic nucleation and self assembly in cell biology*, Plenary Speaker, Gordon Research Conference, Ventura, CA, Jan. 14, 2013

Service

Organizing Committee, SIAM Conference on the Life Sciences, Minneapolis, 2018

"Computational Psychiatry" Minisymposium organizer, SIAM Dynamical Systems 2017, Snowbird, Utah (May 21–25, 2017)

UCLA David Geffen School of Medicine Biomedical Informatics Task Force (Oct 2013 – Feb 2014)

Associate Editor, Multiscale Modeling and Simulation (Jan 2013 –)

Editorial Board: Computers in Medicine and Biology, (Feb 2011 – 2013)

Associate Editor, Mathematical Medicine and Biology (Jul 2010 –)

Organizer: Inst. for Pure and Applied Math Workshop: Translating data, models, and concepts in cancer biology to clinical practice (Feb 2014)

Elected Member at Large: Division of Biological Physics, American Physical Society (2009–2012)

Invited Participant: 25^{th} Workshop on Mathematical Problems in Industry, University of Delaware (Jun 15–19, 2009)

Invited Participant: Workshop in Microfluidics: Electrokinetic and Interfacial Phenomena, Institute for Mathematics and its Applications (Dec 7-11, 2009)

Faculty Mentor: Research in Industrial Projects, Inst Pure and Applied Math/Aerospace Corporation (Jun 23 – Aug 22, 2008)

Co-Organizer: SIAM Annual Meeting Minisymposium on Mathematical Modeling and Simulation of Biological Membranes (Jul 7 – 11, 2008)

Co-Organizer: SIAM Annual Meeting Minisymposium on Intracellular Transport (Jul 2 – 16, 2010)

Organizer and longterm participant: Inst. for Pure and Applied Math: Cells & Materials (Mar 2006 – Jun 2006)

Organizer: Keck Seminar Series in Computational Biology (Sep 2000 – Jun 2007)

Core Participant: Inst. for Pure and Applied Math: Nanoscience (Sep 2003 – Jan 2004)

Invited speaker: Workshop on the Role of Theory in Biological Physics, National Science Foundation (May 2003)

UCLA Committee on Diversity and Equal Opportunity (Sep 2008 – 2010)

Chair, UCLA Committee on Diversity and Equal Opportunity (Jan 2010 – Jul 2010)

UCLA Student Conduct Committee (Sep 2005 – Aug 2008)

Chair, Faculty Search Committee, Biomathematics (2006–2008)

National Academies of Science 4th Frontiers in Science Invited Participant, Tokyo, Japan, Oct 2004

Study Section/Panel Service: NSF, NIH, UC Discovery Grants, Petroleum Research Fund, (2000 – present)

Member: American Physical Society, Biophysical Society, Society for Industrial and Applied Mathematics

Teaching Experience

UCLA: Computer Science M184/M186A: Introduction to Cybernetics, Biomodeling & Biomedical Computing

UCLA: Computational and Systems Biology 187: Thesis Research & Research Communication in Computational & Systems Biology

UCLA: Biomath 201: Deterministic Models in Biology

UCLA: Biomath 202: Fourier Methods in Biology

UCLA: Biomath 209: Mechanisms and Modeling of Bioanalytical Assays

UCLA: Biomath/Physics 243: Condensed Matter Physics of the Cell

Stanford: Math 115: Ordinary Differential Equations

Stanford: Math 220C: Asymptotic Methods for PDEs

Peer-reviewed Publications

106. Mingtao Xia and Tom Chou, *Unifying PDE models of adder, sizer, and timer cell division mechanisms*, Submitted: SIAM Journal on Applied Mathematics, (2018).

105. Tom Chou, *Fixation and order of mutation in a stochastic parallel-path two-hit model*, Submitted to: Journal of Theoretical Biology, (2018).

104. Farid Manuchehrfar, Wei Tian, Tom Chou, and Jie Liang, *Stochastic Evolution of Coagulation-Fragmentation processes using the Accurate Chemical Master Equation approach*, Submitted: Communications in Information and Systems, (2018).

103. Yao-Li Chuang, Tom Chou, and Maria R. D'Orsogna, *A network model of immigration: how social linking and cultural adjustment lead to segregation or integration*, In Press: Networks and Heterogeneous Media, (2018).

102. Song Xu and Tom Chou, *Immigration-induced phase transition in a regulated multispecies birth-death process*, Journal of Physics A: Mathematical and Theoretical, **51**, 425602, (2018).

101. Renaud Dessalles, Maria R. D'Orsogna, and Tom Chou, *Exact steady-state distributions of multispecies birth-death-immigration processes: effects of mutations and carrying capacity on diversity*, Journal of Statistical Physics, **173**, 182–221, (2018).

100. Shyr-Shea Chang and Tom Chou, *A Model for Bipolar Disorder based on Learned Expectation*, In Press: Computational Psychiatry, (2018).

99. Stephanie Lewkiewicz, Yao-Li Chuang, and Tom Chou, *Aging dynamics of naive T-cell diversity: a model predicting lifetime decay of the T-cell pool*, Submitted to: Bulletin of Mathematical Biology, (2018).

98. Bhaven Mistry, Maria R. D'Orsogna, and Tom Chou, *Stochastic effects of multiplicity of infection on virus quantification and infectivity assays*, Biophysical Journal, **114**(11), (2018).

97. Song Xu, S. Kim, I. S. Y. Chen, and Tom Chou, *Modeling large fluctuations of thousands of clones during hematopoiesis: the role of stem cell self-renewal and bursty progenitor dynamics in rhesus macaque*, PLoS Computational Biology, **14**, e1006489, (2018).

96. Yao-Li Chuang, Tom Chou, M. R. D'Orsogna, *Age-structured social interactions enhance radicalization and extremism*, Journal of Mathematical Sociology, **42**, 128–151, (2018).

95. J. C. Chang, Y. Liu, and Tom Chou, *High-resolution reconstruction of cellular traction-force distributions: the role of physical constraints and compressed optimization*, Biophysical Journal, **113**, 2530–2539, (2017).

94. J. De Anda, E. Y. Lee, C. K. Lee, R. Bennett, X. Ji, Mark C. Harrison, S. Soltani, M. C. Harrison, A. E. Baker, Y. Luo, Tom Chou, G. A. O'Toole, A. M. Armani, R. Golestanian, G. C. L. Wong, *High-speed 4D computational microscopy of flagellum-driven surface motility in Pseudomonas aeruginosa*, Nano Letters, **11**, 9340–9351, (2017).

93. Lae Un Kim, Maria D'Orsogna, and Tom Chou, *Perturbing the hypothalamic-pituitary-adrenal stress response system: mathematical modeling to improve diagnosis of post-traumatic and related stress disorders*, Computational Psychiatry, **2**, 28–49, (2017).

92. Sam C. P. Norris, Tom Chou, and Andrea M. Kasko *Diffusion of photoabsorbing degradation byproducts in photodegradable polymer networks*, Macromolecular Theory and Simulation, **26**, 1700007, (2017).

91. G. Suryawanshi, Song Xu, Yiming Xie, Tom Chou, Namshin Kim, Irvin S.Y. Chen, Sanggu Kim, *Bidirectional Retroviral Integration Site PCR Methodology and Quantitative Data Analysis Workflow*, Journal of Visualized Experiments, **124**, e55812, (2017).

90. Yao-Li Chuang, M. R. D'Orsogna, and Tom Chou, *A bistable belief model for radicalization and conflict*, Quarterly of Applied Mathematics, **LXXV**, 19–37, (2016).

89. Bhaven Mistry, M. D'Orsogna, N. Webb, B. Lee, and Tom Chou, *Quantifying sensitivity of HIV-1 viral entry to receptor and coreceptor expression through kinetic models*, Journal of Physical Chemistry B, **120**, 6189–6199, (2016).

88. Tom Chou and C. D. Greenman, *A hierarchical kinetic theory of birth, death, and fission in age-structured interacting populations*, Journal of Statistical Physics, **164**, 49–76, (2016).

87. Lae Un Kim, M. D'Orsogna, and Tom Chou, *Onset, timing, and exposure therapy of stress disorders: mechanistic insight from a mathematical model of oscillating neuroendocrine dynamics*, BMC Biology Direct, **11**, 13, (2016).

86. Yao-Li Chuang, Tom Chou, and M. R. D'Orsogna, *Swarming in viscous fluids: three-dimensional patterns in swimmer- and force-induced flows*, Physical Review E, **93**, 043112, (2016).

85. Chris D. Greenman and Tom Chou, *A kinetic theory of age-structured stochastic birth-death processes*, Physical Review E, **93**, 012112, (2016).

84. Joshua C. Chang, Pak-Wing Fok, and Tom Chou, *Bayesian Uncertainty Quantification for Bond Energies and Mobilities Using Path Integral Analysis*, Biophysical Journal, **109**, 966–974, (2015).

83. S. Goyal, S. Kim, I. Chen, and Tom Chou, *Mechanisms of blood homeostasis: lineage tracking and a neutral model of cell populations in rhesus macaques*, BMC Biology, **13**, 85, (2015).

82. Maria R. D'Orsogna, Qi Lei, and Tom Chou, *First assembly times and equilibration in stochastic coagulation-fragmentation*, Journal of Chemical Physics, **143**, 014112, (2015).

81. Tom Chou and Yu Wang, *First passage times in differentiation and evolution in the presence of bottlenecks, deserts, and oases*, Journal of Theoretical Biology, **372**, 65–73, (2015).

80. Pak-Wing Fok, Qunhui Han, and Tom Chou, *Reconstruction of the Broadwell process from exit time distributions*, The IMA Journal of Applied Mathematics, **80**, 1–23, (2015).

79. N. Amini, S. Nowroozizadeh, N. Cirineo, S. Henry, T. Chang, Tom Chou, A. L. Coleman, J. Caprioli, and K. Nouri-Mahdavi, *Influence of The disc-fovea angle on limits of RNFL variability and glaucoma discrimination*, Investigative Ophthalmology & Visual Science, **55**, 7332–7342, (2014).

78. K. Chikere, N. E. Webb, Tom Chou, K. Borm, J. Sterjovski, P. R. Gorry and B. Lee, *Distinct HIV-1 entry phenotypes are associated with transmission, subtype specificity, and resistance to broadly neutralizing antibodies*, Retrovirology, **11**, 48, (2014).

77. S. Nowroozizadeh, N. Cirineo, N. Amini, S. Knipping, T. Chang, Tom Chou, J. Caprioli, and K. Nouri-Mahdavi, *Influence of correction of ocular magnification on performance of spectral-domain retinal nerve fiber layer measurements*, Investigative Ophthalmology & Visual Science, **55**, 3439–3446, (2014).

76. Joshua C. Chang, Van M. Savage, and Tom Chou, *A path integral approach to Bayesian inference for inverse problems using the semiclassical approach*, Journal of Statistical Physics, **157**, 582–602, (2014).

75. Bijan Berenji, Tom Chou, and M. R. D'Orsogna, *Recidivism and rehabilitation of criminal offenders: a carrot and stick evolutionary game*, PLoS One, **9**, e85531, (2014).

74. Tom Chou and M. R. D'Orsogna, *First Passage Problems in Biology*, in First-Passage Phenomena and Their Applications, eds. R. Metzler, G. Oshanin and S. Redner (World Scientific, 2014), pp. 306–345.

73. Joshua C. Chang and Tom Chou, *Iterative graph cuts for image segmentation with a nonlinear statistical shape prior*, Journal of Mathematical Imaging and Vision, **49**, 87–97, (2014).

72. Hamid Hosseini, Nariman Nassiri, Parham Azarbod, JoAnn Giaconi, Tom Chou, Joseph Caprioli, Kouros Nouri-Mahdavi, *Measurement of the optic disc vertical tilt angle with spectral-domain optical coherence tomography and influencing Factors*, American Journal of Ophthalmology, **156**, 737–744, (2013).

71. M. R. D'Orsogna, Bingyu Zhao, Bijan Berenji, and Tom Chou, *Combinatoric analysis of heterogeneous stochastic self-assembly*, Journal of Chemical Physics, **139**, 121918, (2013).

70. K. Chikere, N. E. Webb, Tom Chou, P. R. Gorry, and B. Lee, *Affinofile profiling: How efficiency of CD4/CCR5 usage impacts the biological and pathogenic phenotype of HIV*, *Virology*, **435**, 81–91, (2013).

69. Pak-Wing Fok and Tom Chou, *Reconstruction of the Bellman-Harris branching process from extinction probabilities and number distributions*, Journal of Statistical Physics, **152**, 769–786, (2013).

68. Romain Yvenic, M. R. D'Orsogna, and Tom Chou, *First passage times in stochastic self-assembly*, Journal of Chemical Physics, **137**, 244107, (2012).

67. Tom Chou and M. Siegel, *Mechanics of retinal detachment*, Physical Biology, **9**, 046001, (2012).

66. J. Chang, K. C. Brennan, and Tom Chou, *Tracking monotonically advancing boundaries in biomedical images*, IEEE Transactions on Medical Imaging, **31**, 1008–1020, (2012).

65. Tom Chou, K. Mallick, and R. K. P. Zia, *Non-equilibrium statistical mechanics: Fundamental issues, a paradigmatic model, and applications to biological transport*, Reports on Progress in Physics, **74**, 116601, (2011).

64. M. D'Orsogna, G. Lakatos, and Tom Chou, *Stochastic self-assembly of incommensurate clusters*, Journal of Chemical Physics, **136**, 084110, (2011).

63. Tom Chou and M. D'Orsogna, *Coarsening and accelerated equilibration in mass-conserving heterogeneous nucleation*, Physical Review E, **84**, 011608, (2010).

62. Melissa Gibbons, Tom Chou, Maria D'Orsogna, *Diffusion-dependent mechanisms of receptor engagement and viral entry*, Journal of Physical Chemistry B, **114**, 15403–15412, (2010).

61. Benjamin H. Shargel, Maria D'Orsogna, and Tom Chou, *Interarrival times in a zero-range process with injection and decay*, Journal of Physics A, **43**, 305003, (2010).

60. Pak-Wing Fok and Tom Chou, *Reconstructing bond potentials from multiple rupture time distributions*, Proceedings of the Royal Society A, **466**, 3479–3499, (2010).

59. Filippo Posta and Tom Chou, *A mathematical model of intercellular signaling during epithelial wound healing*, Journal of Theoretical Biology, **266**, 70–78, (2010).

58. Sarah A. Nowak and Tom Chou, *Models of dynamic extraction of lipid tethers from cell membranes*, Physical Biology, **7**, 026002, (2010).

57. Sarah A. Nowak, B. Chakrabarti, Ajay Gopinathan, and Tom Chou, *Frequency-dependent chemotactic target selection*, Physical Biology, **7**, 026003, (2010).

56. Benjamin H. Shargel and Tom Chou, *Fluctuation theorems for entropy production and heat dissipation in periodically driven Markov chains*, Journal of Statistical Physics, **137**, 165–188, (2009).

55. Tom Chou, *Enhancement of charged macromolecule capture by nanopores in a salt gradient*, Journal of Chemical Physics **131**, 034703, (2009).

54. K. G. Lassen, M. A. Lobritz, J. R. Bailey, S. Johnston, S. Nguyen, B. Lee Tom Chou, R. F. Siliciano, M. Markowitz, and E. J. Arts, Elite suppressor-derived HIV-1 envelope glycoproteins exhibit reduced entry efficiency and kinetics, PLoS Pathogens, **5**, e1000377, (2009).

53. Filippo Posta, Maria D'Orsogna and Tom Chou, *Enhancement of cargo processivity by cooperating molecular motors*, Physical Chemistry and Chemical Physics, **11**, 4851–4869, (2009).

52. Maria D'Orsogna and Tom Chou, *Optimal transport and apparent drug resistance in viral infections*, PLoS One, **4**, e8165, (2009).

51. Pak-Wing Fok and Tom Chou, *Accelerated search of DNA repair enzymes through charge-transport mediated kinetics*, Biophysical Journal, **96**, 3949–3958, (2009).

50. Sarah A. Nowak and Tom Chou, *Mechanisms of receptor/coreceptor-mediated entry of enveloped viruses*, Biophysical Journal, **96**, 2624–2636, (2009).

49. S. H. Johnston, M. A. Lobritz, S. Nguyen, K. Lassen, S. Delair, F. Posta, Y. J. Bryson, E. J. Arts, Tom Chou, and Benhur Lee, *A quantitative affinity-profiling system that reveals distinct CD4/CCR5 usage patterns amongst HIV-1 and SIV strains*, (cover article) Journal of Virology, **83**, 11016–11026, (2009).

48. Pak-Wing Fok and Tom Chou, *Interface growth driven by surface kinetics and convection*, SIAM Appl. Math., **70**, 24–39, (2009).

47. Sarah A. Nowak and Tom Chou, *Membrane lipid segregation in endocytosis*, Physical Review E, **78**, 021908, (2008).

46. Pak-Wing Fok, Chin-Lin Guo, and Tom Chou, *Guanine radical-mediated adsorption of DNA repair enzymes*, Journal of Chemical Physics, **129**, 235101, (2008).

45. Ken S. Kim, Tom Chou, and Joseph Rudnick, *Degenerate ground-state lattices of membrane inclusions*, Physical Review E, **78**, 011401, (2008).

44. Amit Lakhanpal and Tom Chou, *Brownian ratchets driven by asymmetric nucleation of hydrolysis waves*, Physical Review Letters, **99**, 248302, (2007).

43. Sarah A. Nowak, Pak-Wing Fok, and Tom Chou, *Free Boundaries in Asymmetric Exclusion Processes*, Physical Review E, **76**, 031135, (2007).

42. Tom Chou, *The stochastic entry of enveloped viruses: Fusion vs. endocytosis*, Biophysical Journal, **93**, 1116–1123, (2007).

41. Tom Chou, *Peeling and Sliding in Nucleosome Repositioning*, Physical Review Letters, **99**, 058105, (2007).

40. Tom Chou and M. R. D'Orsogna, *Multistage adsorption of diffusing macromolecules and viruses*, Journal of Chemical Physics, **127**, 105101, (2007).

39. M. R. D'Orsogna, Tom Chou, and Tibor Antal, *Exact steady-states for translocation ratchets driven by random sequential adsorption*, Journal of Physics A, **40**, 5575–5584, (2007).

38. Tom Chou, *Band gaps and the Kelvin-Helmholtz instability*, Physical Review E, **75**, 016315, (2007).

37. Greg Lakatos, John D. O'Brien, Tom Chou, *Hydrodynamic solutions of 1D exclusion processes with spatially varying hopping rates*, Journal of Physics A, **39**, 2253–2264, (2006).

36. Greg Lakatos, Tom Chou, Birger Bergersen, and Gren N. Patey, *First passage times of driven DNA hairpin unzipping*, Physical Biology, **2**, 166–174, (2005).

35. Maria R. D'Orsogna and Tom Chou, *Queueing and Cooperativity in Ligand-Receptor Binding*, Physical Review Letters, **95**, 170603, (2005).

34. Greg Lakatos, Tom Chou, and Anatoly Kolomeisky, *Steady-state properties of a totally asymmetric exclusion process with periodic structure*, Physical Review E, **71**, 011103, (2005).

33. Maria R. D'Orsogna and Tom Chou, *Interparticle gap distributions on one-dimensional lattices*, Journal of Physics A, **38**, 531–542, (2005).

32. Sally M. Blower and Tom Chou, *Modelling the emergence of the "Hot Zones": tuberculosis and the amplification dynamics of drug resistance*, Nature Medicine, **10**, 1111–1116, (2004).

31. Tom Chou, *External fields, dipolar coupling, and lubrication in water-wire proton transport*, Biophysical Journal, **86**, 2827–2836, (2004).

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Research Interests and Plans

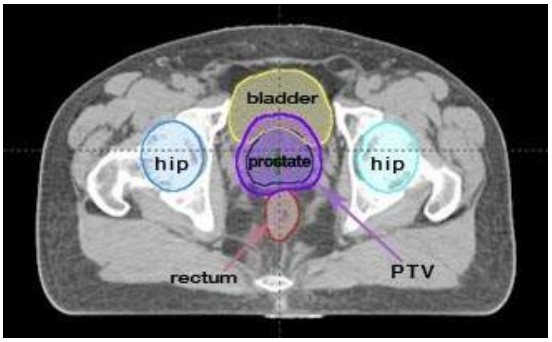
Tom Chou, August 2018

My current research focuses on quantitatively understanding biological and physiological processes from two perspectives. First, I collaborate with experimentalists and clinicians and combine mathematical modeling, data analysis, and inference to seek answers to basic questions in cell biology and physiology. In doing so, deeper mathematical questions arise, motivating a large part of my research effort. For example, I am currently developing multiplicative noise stochastic models and investigating high-dimensional functional inverse problem techniques to better "validate" models and improve subsequent mathematical analysis of complex biological systems. The approach that I believe will be most fruitful for making lasting scientific impact include emphasis on fundamentals of applied mathematics and physical understanding, rigorous use of ideas from statistical physics, data science, and stochastic processes to understand inference and data analysis, and a very interdisciplinary outlook.

In the basic sciences, high-dimensional stochastic processes, speciation, and evolution are areas where statistical ideas and inference can be further exploited. Specific applied areas in which data science can be harnessed to make an impact include pathway analysis, cellular and stem cell biology, and biomedical assays and diagnosis (including the use of imaging). Below are a few examples of current projects and biological directions that my group and I are exploring that employ data analysis and the development of basic supporting theory.

Quantitative Biology and Medicine - Three specific research efforts that encompass physical and mathematical modeling in physiology and medicine are outlined below:

• ***Using quality-of-life scores to guide prostate RT dosing -*** I have recently initiated a funded project to explore learning ideas to optimize radiation dosing for prostate cancer based solely on quality-of-life survey outcomes. Almost 200,000 men are diagnosed with prostate cancer in the U.S. each year, and about half of these men will receive radiation therapy with curative intent. Patients who undergo radiation therapy (RT) for prostate cancer (PC) suffer toxicity from radiation damage to the bladder and rectum. This toxicity diminishes quality of life for PC patients. Quantifying the doses of radiation to the bladder and rectal regions that cause this damage is essential for knowing how to better design radiation treatment to minimize toxicity and patient suffering. Surprisingly, the relationship between how much radiation is delivered to surrounding organs and structures (such as the bladder and rectum) and the probability and severity of toxicity (urinary and bowel) is not well-understood.



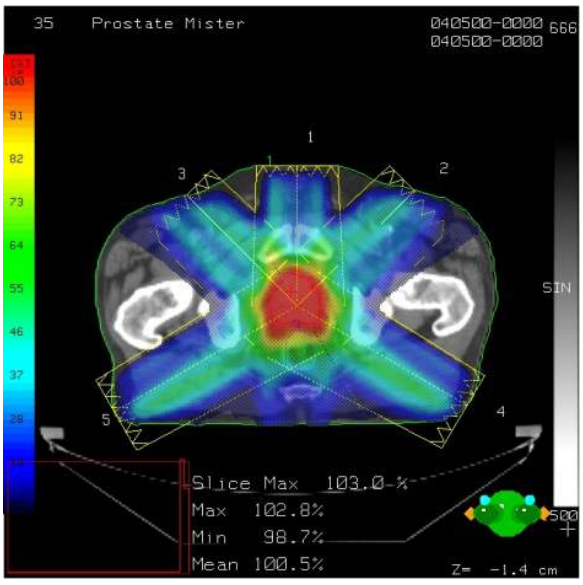


Figure 1: Above: A CT image of patient anatomy. Right: The corresponding RT dose applied to treat prostate cancer. Approximately 400 patients were treated at the the University of North Carolina School of Medicine, Chapel Hill. CT images and dosing patterns will be registered to determine the radiation intensity delivered to all relevant tissues.

However, a two-part, 14-question quality-of-life survey has been given to over 400 patients treated at University of North Carolina School of Medicine, Chapel Hill (see Appendix). Patients filled out the survey before, during, and after RT. Seven questions each for urinary and bowel function and pain were posed, with respondents scoring each on a 1-5 scale. These same patients answered questionnaires before starting radiation treatment, and weekly during treatment. Patients scored their urinary function according to attributes such as frequency, night time urination, urgency, leakage, bladder spasms, and

ease of flow. For bowel movements, patients scored features such as diarrhea, blood in stool, urgency, and leakage. Age, race, prostate cancer stage and other diagnostic details were also recorded for each patient. In this proposal, data from detailed quality-of-life surveys will be correlated with RT dosing to help guide future dosing protocols.

The project employs a number of steps including processing and segmenting computed tomography (CT) images to understand tissue boundaries using both standard image analysis methods and machine learning. Radiation doses applied in each identifiable tissue region will be computed to define a spatially resolved dose volume histogram (DVH).

Next a correlative study between questionnaire answers and radiation doses has to be performed. In addition to the global DVH, we will explore using the tissue-specific DVHs and stratify the patients according to their scores from the 14 quality-of-life questions. We will explore and develop machine and deep learning approaches to correlate features of images and RT dosing to quality-of-life survey data.

Finally, we will attempt to construct a new, spatially dependent or tissue-specific "energy" or objective function that penalizes radiation in the areas that correlate with diminished urinary function, control, quality of life, and survival. The new objective function will be incorporated as an additional constraint into the beam shaping algorithm. The new radiation dosing profiles will be optimized with the additional constraint imposed by outcome of quality of life.

• ***Clonal analysis of stem cell dynamics -*** I have been trying to understand a number of observations in differentiation and development, particularly those involving hematopoiesis, pancreatic development, and T cell diversity during aging and after bone marrow transplant. For example, in hematopoiesis, the goal is to understand how hematopoietic stem cell (HSC) differentiation is regulated and how the dynamics of intermediate progenitors correlate with final peripheral blood type. In a recent experiment, HSCs were extracted from rhesus macaques and infected with a lentiviral vector. After myeloablation and autologous transplantation of the infected HSCs, blood samples from four animals were periodically drawn and sequenced for over 13 years. In collaboration with Irvin Chen (UCLA, MIMG), I have been analysing deep sequences of sampled peripheral blood cells. As shown in Fig. 2, labeled stem cells give rise to peripheral blood cells that carry the identical viral integration site, possibly allowing one to infer correlations between lineages and cell types.

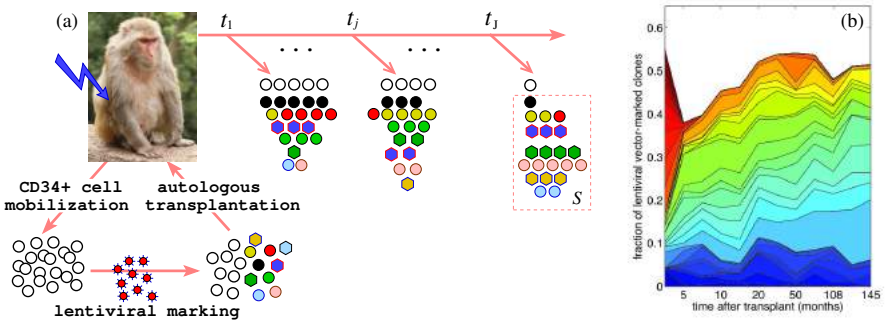
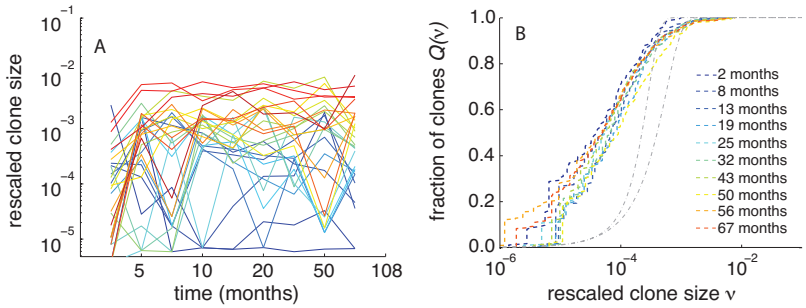


Figure 2: Setup of our clonal analysis study. (A) CD34+ cells are harvested from rhesus macaques and infected with lentivirus. The animals are then myeloablated before the infected HSCs, each with a unique viral integration site, are autologously transplanted back into the animal. Progeny of each labeled stem cell (each lineage) are tracked by periodic sampling for 12 years and sequenced. (B) Clonal populations as a function of sample time.

By analysing rescaled and sample-normalized lineage abundances (Fig. 3A), we recently discovered that the cumulative distribution reaches steady-state within only a few months after transplantation, as shown in Fig. 3B. In other words, while any particular clone was fluctuating in population, the number of clones that are within a particular abundance quickly reached steady-state in the animals. In order to

Figure 3: (A) Even though the size of each clone varies across an animal's lifetime, the clone size distribution (B) is stationary. We find maximum-likelihood estimates for two model parameters, an effective stem cell differentiation rate, and a parameter that incorporates the terminal differentiation rate, the bone marrow carrying capacity, and the blood sampling size.



gain a preliminary understanding of this difference, we consider the clone abundances by quantifying the sampled cells using the hodograph transform or "density of states." A five-compartment mathematical model is shown in Fig. 4. The pools consist of long-term bone marrow stem cells (I) that can self-renew (II), finite-generation progenitor or transit-amplifying (TA) cells (III), and fully differentiated peripheral blood cells (IV). The statistics of how blood sampling (V) affects the observed clone size distributions were also carefully calculated. We found that the normalized clone size distributions (Fig. 3B) depend

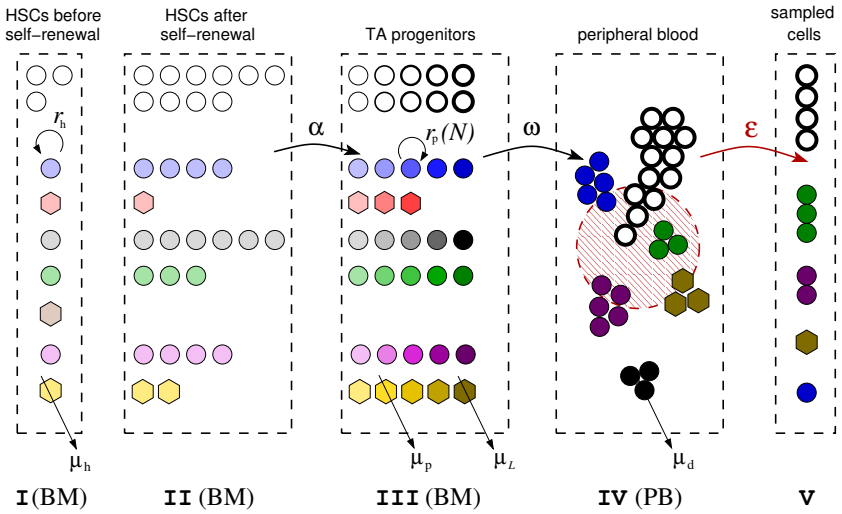


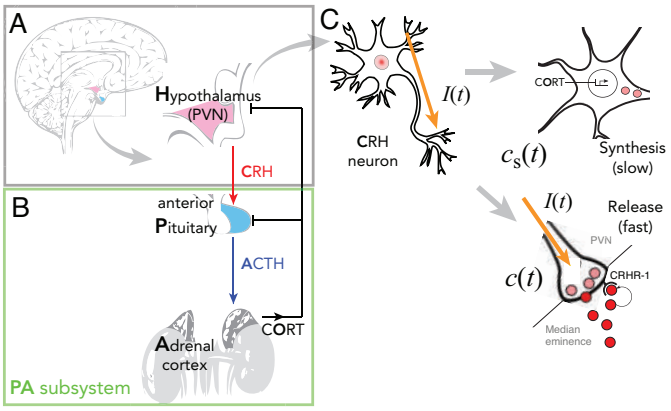
Figure 4: A five-compartment model for hematopoiesis. A distribution of stem cells arising from self-renewal feeds the transit-amplifying progenitor cell population with rate α, which ultimately feeds the fully differentiated peripheral blood population with rate ω. The clonal abundances are modeled throughout these compartments. The effects of sampling a small fraction ε of the peripheral blood of the entire animal is also calculated. BM: Bone marrow, PB: Peripheral Blood.

most strongly on only two combinations of parameters: the first one proportional to the sample size ε and the second one proportional to the initial differentiation rate α. Estimates for α and the total number of active HSCs after transplantation were obtained through maximum-likelihood fitting to data.

Despite the static nature of the clone size distribution, the dynamics of the individual clone populations continued to vary in size over the animals' lifetimes (Fig. 3A). The most likely sources of this variability are lineage aging and/or quiescent HSCs. To analyse individual lineage dynamics, we must revert to the high-dimensional stochastic model based on numbers of cells n_j in each clone j. Through mathematical modeling and computational data analysis of the full clone size dynamics, I plan to investigate the relative roles of stem cell heterogeneity, lineage aging, and intrinsic stochasticity in HSC differentiation in the observed lineage "spectrum."

More generally, different experimental protocols such as viral integration sites, barcoding, and *in situ* Cre expression-mediated labeling have been used in different animals under homeostatic or transplant conditions. Key attributes that are not well understood include the number of active stem cells (estimates varying by two orders of magnitude in mice), stem cell heterogeneity, regulation mechanisms governing stem cell self-renewal, and clonal patterns across cell lineages. A unified understanding of the results inferred from these different but related experiments is currently lacking and can be resolved only through careful mathematical and statistical modeling and analysis.

Figure 5: A schematic of neuroendocrine dynamics of the HPA axis. (A) Stress $I(t)$ induces the hypothalamus to produce corticotropin releasing hormone (CRH), stimulating the pituitary to produce ACTH. (B) ACTH stimulates the adrenal glands to produce oscillating levels of cortisol, which negatively feeds back on the pituitary and the hypothalamus over two different timescales. (C) CRH release is composed of a two-step mechanism involving stored CRH that can be quickly released and slower upregulation of CRH expression.



• ***Understanding neuroendocrine dynamics and therapies*** - I am also keen on understanding the dynamics of neuromodulators and physiological mechanisms of neuroendocrine response to stress. The major glands that control stress response make up the hypothalamic-pituitary-adrenal (HPA) axis depicted in Fig. 5. One of the key functions of the HPA axis is regulation of cortisol production. One

intriguing feature is how cortisol production is dysregulated during the onset of depressive disorder, and in the long term, how hormonal dysregulation influences immune response, metabolic disease, and cancer initiation. Depressive disorders such as PTSD are often associated with dysregulation of cortisol, with patients exhibiting lower time-averaged levels. Counterintuitively, the most promising model of treatment is exposure therapy, in which re-exposure to stress alleviates the hypocortisolism seen in PTSD patients.

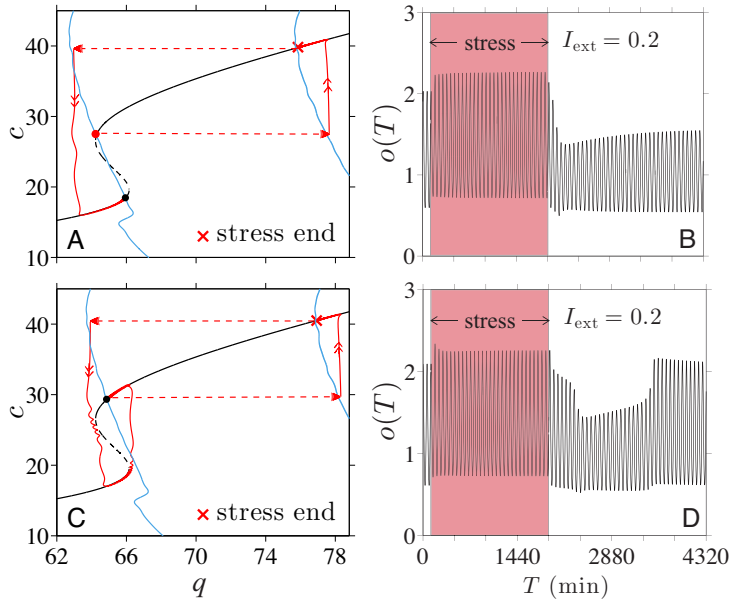


Figure 6: The intersection of nullclines associated with the fast and slow variables define the steady-states (possibly oscillating). Two possible steady-states correspond to normal and diseased stable states. During external stress, the slow nullcline (light blue) shifts towards the right pulling the trajectory with it. Upon switching off of the stress, the slow nullcline returns, but the trajectory may (A) or may not (C) transition to the other stable state. The resulting cortisol levels can permanently (B) or temporarily (D) change levels.

To gain insight into the mechanism of exposure therapy, we are developing a five-variable dynamical systems model of the HPA axis that captures hourly cortisol oscillations and defines normal and diseased states as two stable equilibria. The key feature of our model is that it separates fast negative feedback mechanisms from slow ones. This is a reasonable assumption since the negative feedback on the pituitary is activated by receptor-mediated signaling while the negative feedback on the hypothalamus results from a slower down-regulation of CRH synthesis. The separation of timescales allows the five-dimensional model to be projected onto two dimensions described by a fast and a slow dimensionless variable ("q" and "c" respectively). We have recently discovered that the slow dynamics allow for stress-input-mediated *transitions* between stable states (see Fig. 6), providing a clue into a possible mechanism of exposure therapy. This model will also allow us to more easily investigate the effects and mechanisms of psychoactive drugs and to provide guidelines for treatments.

The paradigm of fast-slow timescale separation is borrowed from theories in mathematical neuroscience and can be used in many other unexplored physiological systems of clinical relevance. Another medical controversy is the choice of clinical protocols to control ovulation for *e.g.*, *in vitro* fertilization (IVF). The ovulation process is controlled by the hypothalamus-pituitary-gonadal (HPG) axis and involves specific timing of a spiked release of luteinizing hormone (LH). The control of this release is critical for harvesting follicles, and different mechanistically *contradictory* hormone treatment protocols have been promoted. To gain mechanistic insight and help resolve this uncertainty, we plan to systematically parse and analyse clinical data, carefully develop physiological models, and apply control theory to this clinical problem.

High-dimensional theories of aging, transport, and inverse problems - In our study of hematopoiesis and cell aging, new theoretical approaches that can efficiently treat stochastic populations of age-structured birth-death processes have been needed. In addition to being challenging physics and applied mathematics problems, developing new theoretical tools will be valuable for the quantitative and computational analysis of future bioscience studies. Below are three theoretical projects that are complementary to the more biological/physiological projects in my lab. A mathematical theme of high-dimensional stochastic processes and analysis is common across all of these efforts.

• ***Functional Bayesian inference and inverse problems*** - Another important theoretical tool I am developing (with J. Chang, NIH) is a Bayesian description of inverse problems. Here, we incorporate data directly into an "action" and apply path integral techniques for uncertainty quantification. We have recently used this method to simultaneously reconstruct spatially dependent macromolecular bond free energies and diffusivities from trajectories obtained from dynamic force spectroscopy (DFS) (see Fig. 7). In DFS, one wishes to infer the potential energy profile of a molecular bond that is being pulled apart by a prescribed pulling protocol. These bond energies are important for understanding macromolecular structure and function and for drug design. Many approaches including analysis of rupture force distributions and work theorems have been applied to this problem; however, none of these approaches are able to simultaneously reconstruct the bond potential *and* the mobility along the bond coordinate.

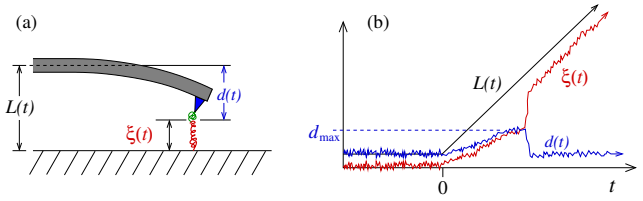


Figure 7: Schematic of a dynamic force spectroscopy experiment. A device pulls on a macromolecular bond while the device displacement $d(t)$ is measured.

To address this problem, we used Tikhonov regularization in the form of Bayesian priors for both the bond potential and bond coordinate diffusivity. The aggregated trajectory data are incorporated into a path-integral, and maximum-likelihood potentials and diffusivities are computed. Moreover, using

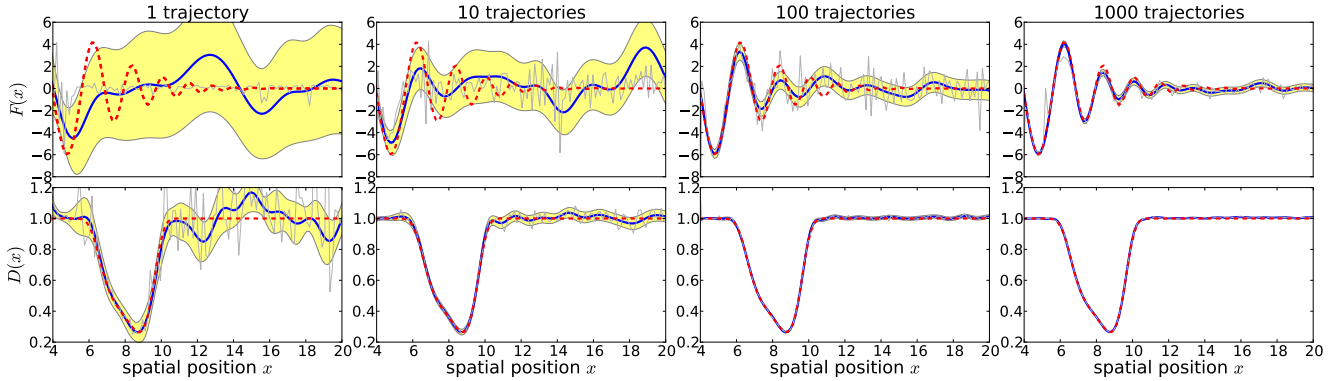


Figure 8: Simultaneous reconstruction (from simulated data) of a complex bond potential (top) and spatially varying diffusivity (bottom). Ground truth functions are shown by red-dashed curves, while the optimal reconstructions are given by the solid blue curves. Reconstruction of the bond force $F(x) = -\nabla U(x)$ fails if diffusivity is held constant. Simultaneous reconstruction improves dramatically with proper regularization and the number of trajectories sampled. The bond potential can be accurately reconstructed only if the bond diffusivity is unconstrained and simultaneously recovered from data. The yellow bands represent 95% confidence regions.

empirical Bayes theory, we derived optimal values for the regularization parameters, providing uncertainty quantification for our results. Our approach was tested by first performing simulations of a driven random walk and then sampling trajectories in order to recover the driving bond potentials. Fig. 8 shows that our approach is able to simultaneously recover complex multi-minimum potentials and bond coordinate diffusivities. Ultimately, we plan to incorporate data analysis and develop Web-based tools for DFS.

On some mesoscopic length or timescale, the target functions describing the potential of mean force and the diffusivity of the bond coordinate are smooth functions. For other applications where nonsmooth parameter functions are expected, we are exploring how ℓ_1 type regularization terms can be used. Promising preliminary results have been obtained when an ℓ_1 regularization is used to reconstruct the positions of compact cellular focal adhesions from image tracking of substrate displacements. We hope to adapt

these and related approaches and apply them to kinetic and branching models in order to reconstruct waiting time distributions and differentiation fate probabilities from data.

• ***Stochastic evolution and transport on a network*** - Most models of stem cell differentiation and cellular and organismic evolution require treatment of multiple genetic, epigenetic, and phenotypic species or "states." While the above approach allows for regulation, age-structure, and age-dependent birth and death, it is difficult to generalize to more than one or two species. In order to treat evolution across many states and retain the nonexponential waiting times between birth, death, and mutation events, we have generalized the single-component branching process to evolution on a network (Fig. 9).

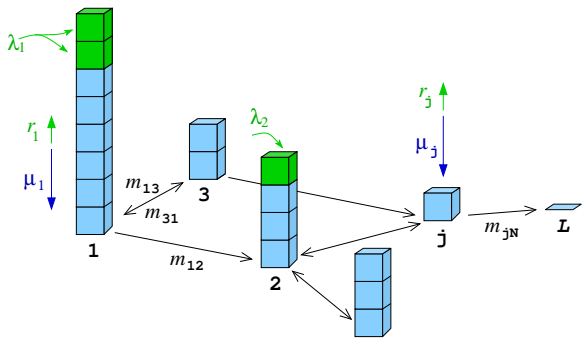


Figure 9: Evolution on a network. Each node represents a distinguishable state, while the population at each node represents the number of cells or organisms in that state. Multiple types of transitions (different types of mutations, immigration, replication, differentiation, death) can be incorporated. The weights of transitions from state i are defined by a vector $\mathbf{a}^{(i)}$ of probabilities (not to be confused with age in the previous example). Single particle injection events (immigration) into state i, occurring with waiting time distribution $h_i(\tau)$, are also easily treated in our approach.

This approach involves an integral evolution equation for the high-dimensional generating function associated with $P(n_1, n_2, \ldots, n_N; t)$, the joint probability of n_1 cells in state 1, n_2 cells in state 2, and so on. Upon assigning $\mathbf{z} \equiv (z_1, z_2, \ldots, z_L, z_{L+1})$, the $L+1$ dimensional generating function is defined as

$$F_k(\mathbf{z}; t) = \sum_{n_1=0}^{\infty} \cdots \sum_{n_{L+1}=0}^{\infty} P_k(\mathbf{n}; t) z_1^{n_1} \cdots z_{L+1}^{n_{L+1}}, \tag{1}$$

where $P_k(\mathbf{n}; t)$ denotes the probability that at time t the system is in state $\mathbf{n}$, given that it started with one cell in state k at time $t = 0$. The kernel in this integral equation is a function $g_k(\tau)$ describing the waiting time distribution for a cell of type k to undergo any type of transition.

Using this more statistical approach, we are able to describe all types of cell divisions (self-renewal, asymmetric/symmetric differentiation, death, and somatic mutations) connecting an arbitrary number of states through a vector of coupled integral equations. This framework is amenable to numerical computation and statistical quantities such as fixation times, and mutational fluxes can be straightforwardly estimated. After further development, I will apply this approach in the study of other cellular evolutionary pathways, including differentiation and cancer progression. The main shortcoming of the multispecies branching process lies in the recursive nature of the derivation, which precludes population interactions such as growth regulation. However, one method to incorporate interactions is to self-consistently solve the integral equations for $F_k(\mathbf{z}; t)$, assuming that the waiting time distributions $g_k(\tau; n(t))$ are functions of, for example, the total *expected* population $\langle n(t) \rangle = \sum_{i=1}^{L+1} [\partial F / \partial z_i]_{z_i=1}$.

• ***Stochastic and kinetic theories of cell aging and population dynamics*** - Since the typical approach for describing stochastic populations using master equations implicitly assumes exponentially distributed times between birth, death, mutation, and differentiation events, master equations cannot resolve age structure or be used to analyse processes that depend on *e.g.*, the cell cycle.

In collaboration with Dr. C. Greenman (Univ. of East Anglia, UK), I have applied ideas from gas kinetic theory to derive a new theoretical framework describing stochastic age-structured populations. We first consider an age-dependent simple birth-death process as shown in Fig. 10A. By introducing $\rho_n(a_1, a_2, \ldots, a_n; t) \mathrm{d}a_1 \mathrm{d}a_2 \ldots \mathrm{d}a_n$, the probability density that there exist n individuals, one with age in $(a_1, a_1 + \mathrm{d}a_1]$, another with age in $(a_2, a_2 + \mathrm{d}a_2]$, and so on, we derived a corresponding "Liouville" equation

$$\frac{\partial \rho_n(\mathbf{a}_n; t)}{\partial t} + \sum_{j=1}^{n} \frac{\partial \rho_n(\mathbf{a}_n; t)}{\partial a_j} = -\sum_{i=1}^{n} \gamma_n(a_i) \rho_n(\mathbf{a}_n; t) + (n+1) \int_0^{\infty} \mu_{n+1}(y) \rho_{n+1}(\mathbf{a}_n, y; t) \mathrm{d}y, \tag{2}$$

where $\mathbf{a}_n \equiv (a_1, a_2, \ldots, a_n)$, and $\beta_n(a)$ and $\mu_n(a)$ ($\gamma_n \equiv \beta_n + \mu_n$) are age-dependent individual birth and death rates. An associated boundary condition connects ρ_n with ρ_{n+1}. Thus, the smooth evolution of $\rho_n(\mathbf{a}_n)$ on each "n-manifold" is punctuated by jumps to the $n+1$ and $n-1$ manifolds through age-dependent birth and death, respectively. This kinetic equation can be formally solved using a multidimensional method of characteristics. Furthermore, equations for the reduced distributions $\rho_n^{(k)}(\mathbf{a}_k; t) = \int_0^\infty \prod_{j=k+1}^{n} \mathrm{d}a_j \rho_n(\mathbf{a}_n; t)$ depend on $\rho_n^{(k+1)}$ and form a hierarchy of equations. Closure methods used to approximate BBGKY hierarchies can be employed, and systematic corrections to deterministic mean-field models of age-structured populations can be found. However, in this system, the population statistics are very sensitive to initial conditions and closure methods relying on factorisation of higher order densities are not expected to be accurate. Nonetheless, we can systematically derive corrections to classical population models by perturbing across three different properties: large system size (low stochasticity), weak regulatory interactions, and/or exponentially distributed age structure.

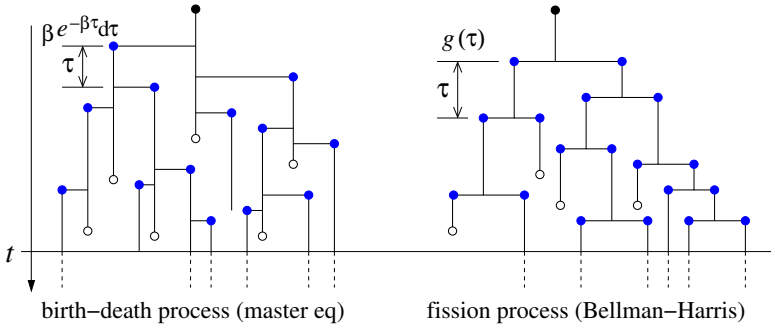


Figure 10: (A) A birth-death process with a general waiting time distribution $g(\tau)$. For example, for an age-dependent birth process with birth rate $\beta(\tau)$, $g(\tau) = \beta(\tau) \exp\left[-\int_0^\tau \beta(\tau')\mathrm{d}\tau'\right]$. (B) A birth, fission, death process. Here, fission leads to twins of identical age, which must be counted separately from those of single particles.

In problems involving cell division, especially symmetric stem cell self-renewal, the birth-death process described above requires another subtle modification as shown in Fig. 10B. In symmetric divisions, the parent cell renews itself upon division, simultaneously creating two zero-age daughters. In these scenarios, the dimensionality of the problems is doubled and the appropriate probability density function takes the form $\rho_{m,n}(\mathbf{a}_m, \mathbf{a}'_n; t)$, which describes the probability that there are m single cells with ages in the intervals $(a_i, a_i + \mathrm{d}a_i]$ and n twins with ages in $(a'_i, a'_i + \mathrm{d}a'_i]$. Transitions from the twin population to the singlet population occur when, for example, one twin dies. Likewise, when an individual cell divides symmetrically, it removes one element of the singlet population and generates a twin. We have derived the full kinetic equation analogous to Eq. 2 and have found a number of tractable analytic or semi-analytic solutions to both age-structured birth-death and age-structured self-renewal problems. Results from this research will provide an improved, computationally efficient mathematical framework for future modeling and analysis of stem cell population dynamics.