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Abstract

Optimizing Drug Regimens for Tuberculosis: An Integrated
Computational/Experimental Approach

Tuberculosis (TB) is an infectious disease that continues to be a major cause of death in large parts of the world. The principal causative agent of TB is *Mycobacterium tuberculosis*, a slow growing, aerobic bacterium. While the current first-line therapy for drug-susceptible TB has been in clinical use for nearly thirty years, the emergence and spread of drug-resistant strains of *M. tuberculosis* has motivated the search for new, more effective combination regimens. Accordingly, there are many experimental studies underway to design and create better individual drugs to treat this contagious and widespread disease. Our interest, however, is in developing mathematical tools and targeted experiments to supplement the animal studies that are currently necessary to identify and test new multi-drug regimens. In this presentation, I'll describe our overall strategy for engineering and optimizing drug therapies, and detail some of the studies we have conducted so far in this program.

Brief CV

Education

1990 – 1992   Postdoctoral Fellow, Department of Biomedical

	Engineering, Johns Hopkins School of Medicine
1990	Ph.D., Chemical Engineering, Northwestern University
1987	M.S., Chemical Engineering, Pennsylvania State University
1984	B.S., Chemical Engineering, University of California-Davis

Professional Experience and Academic Appointments

2010 –	Associate Professor, Department of Chemical and Biological Engineering & School of Biomedical Engineering, Colorado State University, Fort Collins, CO
2006 – 2010	Assistant Professor, School of Biomedical Engineering, Colorado State University, Fort Collins, CO
2001 – 2010	Assistant Professor, Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, CO
1999 – 2001	Senior Staff Engineer, Modeling and Analysis Group, United Technologies Corporation, Syracuse, NY
1992 – 1999	Staff Engineer, Heat Transfer Group, United Technologies Corporation, Syracuse, NY
1990 – 1992	Postdoctoral Fellow, Department of Biomedical Engineering, The Johns Hopkins School of Medicine, Baltimore, MD

Awards and Honors

2013	Fulbright Scholar Award
2010	Best Teacher Award – Colorado State University, Department of Chemical and Biological Engineering
2010	Best Abstract Award – Chemical Mixtures Specialty Section, Society of Toxicology Annual Meeting
2003	Best Abstract Award – Risk Assessment Specialty Section, Society of Toxicology Annual Meeting
2002	NIH Quantitative Research Career Development Award
2001	Outstanding Achievement Award – United Technologies Research Center, United Technologies Corporation

1999	Special Award for Quality – United Technologies Research Center, United Technologies Corporation
1990	Postdoctoral Fellowship – Johns Hopkins Medical Institutions
1988	Shell Doctoral Fellowship – Northwestern University
1987	Walter P. Murphy Fellowship – Northwestern University
1986	First Prize – Alliance of Engineers in Medicine and Biology International Student Paper Competition
1981	US Army ROTC Scholarship – University of California-Davis
1980	Regents Scholarship – University of California

Professional Organizations

Society of Toxicology
American Association of Pharmaceutical Scientists
International Society for the Study of Xenobiotics
American Institute of Chemical Engineers
American Society of Mechanical Engineers

Patents

U.S. patents: 7186290, 6884399, 6833122, 6716406, 6502413
European patents: EP1281431. EP1281429, EP1706193

Selected Publications

Gilbert, K.M., Reisfeld, B., Kreps, M.N., Erickson, S.W., and Blossom, S.J. Trichloroethylene inhibits liver repair mechanisms in mouse model of autoimmune hepatitis. *Toxicol. Sci.*, In preparation.

Zurlinden, T., Mayeno, A.N., Reisfeld, B. Quantifying the Effects of Macromolecular Crowding on Diffusion using Particle-Based Simulations. *PLOS One*, Submitted.

Lyons, M., Reisfeld, B., Yang, R.S.H, and Lenaerts, A. A Physiologically Based Pharmacokinetic Model of Rifampin in Mice. *Antimicrob. Agents Chemother*, 57(4), 2013

Reisfeld, B., Ivy, J.H., Lyons, M., Wright, J., Rogers, J., and Mayeno, A.N. DoseSim: A Tool for Pharmacokinetic/Pharmacodynamic Analysis and Dose Reconstruction. *Bioinformatics*, 29(3), 2013.

Reisfeld B, Mayeno AN. What is computational toxicology? *Methods Mol Biol.* 929, 2012.

Mayeno AN, Reisfeld B. Tools and techniques. *Methods Mol Biol*, 929, 2012.

Reisfeld, B., Metzler, C., Lyons, M., Mayeno, A.N., Brooks, E., DeGroote, M. A Physiologically Based Pharmacokinetic Model for Capreomycin. *Antimicrob. Agents Chemother.* 56(2), 2012.

Gilbert, K.M., Nelson, A.R., Cooney, C.A., Reisfeld, B., and Blossom, S.J. Epigenetic alterations may regulate temporary reversal of CD4+ T cell activation caused by trichloroethylene exposure. *Toxicol. Sci.*, 127(1):169-78, 2012.

Mayeno A.N., Robinson J., Reisfeld B. Rapid estimation of activation enthalpies for cytochrome-P450-mediated hydroxylations. *J Comput Chem.* 32(4):639-57, 2011.

Mayeno, A.N., Robinson, J., Yang, R.S.H., Reisfeld, B. Predicting Activation Enthalpies of Cytochrome-P450-mediated Hydrogen Abstractions: Comparison of Semi-Empirical PM3, SAM1, AM1, with a Density Functional Theory Method. *J. Chem. Inf. Mod.* , 49(7), 1692–1703, 2009.

Lyons, M., Yang, R.S.H., Mayeno, A.N., Reisfeld, B. Computational Toxicology of Chloroform: Reverse Dosimetry using Bayesian Inference, Markov Chain Monte Carlo Simulation, and Human Biomonitoring Data *Environ. Health Persp.*, 116 (8), 1040-6, 2008.

Brown, C., Reisfeld, B., and Mayeno, A. Cytochromes P450: A Structure-Based Summary of Biotransformations Using Representative Substrates. *Drug. Metab. Rev.* 40(1), 2008.

Yang, R.S. H., Mayeno, A., Liao, K.H., Reardon, K.F., and Reisfeld, B. A Biologically-Based Computer Modeling Approach to Handle Chemical Mixture Toxicology. *Pest Manag. Sci.*

Yang, R.S. H., Mayeno, A., Liao, K.H., Reardon, K.F., and Reisfeld, B. Integration of PBPK and Reaction Network Modeling: Predictive Xenobiotic Metabolomics. *ALTEX*.

Mayeno, A., Yang, R.S.H, Reisfeld, B. Biochemical Reaction Network Modeling: Predicting Metabolism of Organic Chemical Mixtures. *Env. Sci. Tech.* 39 (14), 5363-71, 2005.

Yang, R.S.H, El-Masri, H., Thomas, R.S., Dobrev, I.D., Dennison, J.E., Bae, D., Campain, J.A., Liao, K.H., Reisfeld B., Andersen M.E., Mumtaz, M. Chemical Mixture Toxicology: From Descriptive to Mechanistic, and Going on to *In Silico* Toxicology. *Env. Tox. Pharm.* 18 (2), 65-81, 2004.

Reisfeld, B., Yang, R.S.H. A Reaction Network Model for CYP2E1-Mediated Metabolism of Toxicant Mixtures. *Env. Tox. Pharm.* 18 (2), 173-179, 2004.

Reisfeld, B., Mayeno, A., Yang, R.S.H. Predictive Metabolomics: The Use Of Biochemical Reaction Network Modeling for the Analysis of Toxicant Metabolism. *Drug Met. Rev.* 36, Suppl. 1, 2004.

Reisfeld B, Reardon K, Yang R A reaction network model for CYP2E1-mediated metabolism of toxicants. *Toxicol. Sci.* 72 (1): 175 Suppl. S, Mar 2003.

Liao, K.H., Dobrev, I., Dennison, J.E., Andersen, M. E., Reisfeld, B., Reardon, K.F., Campain, J.A., Wei, W., Klein, M.T., Quann, R.J., Yang, R.S.H. Application of computer modeling to simple or complex mixtures. *Environ. Health Perspect.* 110, 957-963, 2002.

Reisfeld, B., Kalyanasundaram, S., Leong, K. A mathematical model of polymeric controlled drug release and transport in the brain. *J. Cont. Rel.* 3:36,1995.

Reisfeld, B., Blackband, S., Grossman, S., Calhoun, V., Eller, S., Leong, K. The use of NMR Imaging to track controlled drug release in the brain. *Mag. Res. Imag.* 11:24, 1993.

Books
Reisfeld, B. and Mayeno, A.N. (Editors) Computational Toxicology I, Methods in Molecular Biology Series, Springer-Humana Press, New York, NY, 2013.
Reisfeld, B. and Mayeno, A.N. (Editors) Computational Toxicology II, Methods in Molecular Biology Series, Springer-Humana Press, New York, NY, 2013.

Book Chapters
Reisfeld, B. and Ivy, A. "Mathematical Models" in Trichloroethylene, Springer Press, New York, NY, In preparation.

Reisfeld, B. and Mayeno, A.N. "What is Computational Toxicology?" in Computational Toxicology I, Methods in Molecular Biology Series, Springer-Humana Press, New York, NY, 2013.

Mayeno, A.N. and Reisfeld, B. "Tools and techniques" in Computational Toxicology I, Methods in Molecular Biology Series, Springer-Humana Press, New York, NY, 2013.

Yang, R.S.H., Mayeno, A.N., Lyons, M.A., and Reisfeld, B. "The Application of Physiologically Based Pharmacokinetics, Bayesian Population PBPK Modeling, and Biochemical Reaction Network Modeling to Chemical Mixture Toxicology" in Principles and Practice of Mixtures Toxicology, Wiley-VCH Verlag GmbH & Co., 2010.

Reisfeld, B., Mayeno, A., Lyons, M. Yang, R.S.H. "Physiologically-Based Pharmacokinetic/Pharmacodynamic Modeling" in Computational

Toxicology : Risk Assessment for Pharmaceutical and Environmental Chemicals, John Wiley & Sons, Hoboken, N.J., 2007.

Yang, R. S. H., Andersen, M. E., Dennison, J. E., Ou, Y.C., Liao, K. H., and Reisfeld, B. "Physiologically Based Pharmacokinetic and Pharmacodynamic Modeling" in Mouse Models of Cancer, Wiley Inc., New York, NY, 2004.

Recent Presentations and Posters
Ivy, J., Reisfeld, B. Platform Presentation: A Novel Design of Experiments Approach to Assess Biomarker Usage with Experiments Involving PBPK Models, Society of Toxicology Annual Meeting, San Antonio, Texas, March 10–14, 2013.

Zurlinden, T.J., Reisfeld, B. Reconstructing Population Exposure using Biomarker Data: A Case Study Using Chlorpyrifos, Society of Toxicology Annual Meeting, San Antonio, Texas, March 10–14, 2013.

Reisfeld, B., Ivy, J., Lyons, M., and Mayeno, A.N. Platform Presentation: DoseSim: Continuing Development and Applications of a Computational Framework for Characterizing Biomarkers of Organophosphorus Insecticide Mixture Exposure, Society of Toxicology Annual Meeting, San Francisco, California, March 11–15, 2012.

Reisfeld, B., Ivy, J., Lyons, M., and Mayeno, A.N. A Computational Framework for Characterizing Biomarkers of Organophosphorus Insecticide Mixture Exposure, Society of Toxicology Annual Meeting, Washington, DC, March 6-10, 2011

Carpenter,E., Mayeno, A.N., and Reisfeld, B., A Novel Computer-Assisted Method of Predicting Partition Coefficients, Society of Toxicology Annual Meeting, Washington, DC, March 6-10, 2011

Zurlinden, T., Mayeno, A.N., and Reisfeld, B., Anomolous Enzyme-Mediated Reaction Kinetics Resulting from Macromolecular Crowding. Meeting of the American Chemical Society, August 28-Sept 1, 2011

Ivy, J., Lyons, M., Mayeno, A.N., and Reisfeld, B. A Computational Framework for Characterizing Biomarkers of Organophosphorus Insecticide Mixture Exposure, Meeting of the American Chemical Society, August 28-Sept 1, 2011

Mayeno, A.N., Robinson, J., and Reisfeld, B. Rapid Estimation of Activation Enthalpies for Cytochrome-P450-Mediated Hydroxylations, Meeting of the American Chemical Society, Denver CO, August 2011

Mayeno, A., Robinson, J., and Reisfeld, B. Predicting Activation Enthalpies of Cytochrome- P450-Mediated Hydrogen Abstractions: Comparison of Semi-

Empirical PM3, SAM1, and AM1 with a Density Functional Theory Method, Society of Toxicology Annual Meeting, Salt Lake City, UT, March 8-11, 2010.

Ivy, J., Lyons, M., Mayeno, A.N., and Reisfeld, B. Development and Demonstration of a Computational Framework for Forward and Reverse Dosimetry of Organophosphorus Insecticide Mixtures, Society of Toxicology Annual Meeting, Salt Lake City, UT, March 8- 11, 2010.

Meek, E., Reisfeld, B., Chambers, J. Cholinesterase Inhibition and Urinary Metabolite Levels from Repeated Exposures to a Mixture of Two Organophosphorus Insecticides in Rats, Society of Toxicology Annual Meeting, Salt Lake City, UT, March 8-11, 2010.

Recent Review Panels
National Institutes of Environmental Health Sciences, Career Development Award review panel National Institutes of Health Interdisciplinary Molecular Sciences and Training (IMST) Integrated Review Group (IRG) U.S. Army Corps of Engineers Engineer Research and Development Center grant review panel U.S. Environmental Protection Agency: Bioinformatics/Computational Toxicology Center grant

U.S. Environmental Protection Agency: Science to Achieve Results (STAR) grant review panel