## BIOGRAPHICAL SKETCH

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NAME: Russ B. Altman

eRA COMMONS USER NAME (credential, e.g., agency login): ALTMAN.RUSS

POSITION TITLE: Professor of Bioengineering, Genetics, & Medicine and, by courtesy, of Computer Science

EDUCATION/TRAINING

| INSTITUTION AND LOCATION | DEGREE | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Harvard College | A.B. | 06/1983 | Biochemistry & Molecular Biology |
| Stanford University Medical School | Ph.D. | 06/1989 | Medical Information Sciences |
| Stanford University Medical School | M.D. | 06/1990 | Medicine |

### A. Personal Statement

I am a Professor of Bioengineering, Genetics, Medicine and (by courtesy) Computer Science. My area of professional expertise is bioinformatics, the creation of methods to analyze molecular data of importance to problems in medicine and health. My specific application area of interest is drug action, including molecular analysis of protein structure and dynamics, datamining for discovery of unexpected drug actions, functional genomics (particularly pharmacogenomics) to understand drug action and the impact of human variation on drug response. We build the PharmGKB resource (http://www.pharmgkb.org/) of curated information about how human genetic variation impacts drug-response phenotypes. We develop and use a broad array of machine learning algorithms for natural language processing, clustering, classification and deep learning. I am also Co-PI of an FDA Center of Excellence. This project focuses on systems pharmacology methods to improve our understanding of drug action and opportunities for new therapeutic strategies.

### B. Positions and Honors

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE**

1982 Undergraduate Research Assistant. Supervisor: Prof. William N. Lipscomb, Nobel Laureate, Harvard Department of Chemistry
1982-1983 Undergraduate Research Assistant. Supervisor: Prof. Stephen C. Harrison, Harvard Department of Biochemistry and Molecular Biology
1984-1988 Graduate Research Assistant to Bruce G. Buchanan, Stanford Dept. of Computer Science
1989-1992 Post-Doctoral fellow (part time). Prof. Oleg Jardetzky, Stanford Magnetic Resonance Laboratory
1990-1992 Intern and Resident, Stanford University Medical Center
1992-1999 Assistant Professor of Medicine (& Computer Science, by courtesy), Stanford University
1993-1997 Member, Executive Steering Committee, San Diego Supercomputer Center
1994-1995 Organizing Committee, 2nd & 3rd Intl. Conf. on Intelligent Systems for Molecular Biology
1996- Organizing Committee, Pacific Symposium on Biocomputing
1996 Founding Board of Directors, International Society for Computational Biology (ISCB)
1997 Molecular Science Thrust Leader, National Partnership for Advanced Computer Infrastructure
1999-2004 Associate Professor of Medicine (& Computer Science, by courtesy) tenure, Stanford University
2000- Director, Biomedical Informatics Program, Stanford University
2000-2002 President, International Society for Computational Biology
2004- Professor of Genetics, Bioengineering, & Medicine (& Comp. Sci., by courtesy) Stanford University
2007-2009 Chair, Department of Bioengineering, Stanford University
2009-2012 Guidant Chair of Bioengineering, Stanford University
2012 President-Elect, American Society for Clinical Pharmacology and Therapeutics
2013-2014 President, American Society for Clinical Pharmacology and Therapeutics

2013-2014 Chair, Science Board to the Food and Drug Administration

## HONORS AND AWARDS

1983 Phi Beta Kappa, Harvard College Chapter
1983 Summa Cum Laude, Harvard College
1983 NIH Medical Scientist Training Program pre-doctoral fellowship at Stanford
1987 Departmental Ph.D. oral exams passed "with high distinction"
1991 Howard Hughes Fellowship for Physicians
1993 Charles E. Culpeper Scholarship in Medical Science
1996 National Science Foundation CAREER Award
1997 U.S. Presidential Early Career Award for Scientists and Engineers (NIH)
1998 Western Society for Clinical Investigation, Annual Young Investigator Award
1998 Fellow, American College of Medical Informatics
1999 Fellow, American College of Physicians
2000 Stanford Graduate Teaching Award
2005 General Internal Medicine, Honorable Mention for Clinical Teaching
2009 Fellow, American Institute of Medical and Biological Engineering
2009 Member, Institute of Medicine of the National Academies
2010 Fellow, International Society for Computational Biology
2014 Stanford Medical School Mentorship Award
2014 Fellow, American Association for the Advancement of Science

**C. Contribution to Science**

I have 331 papers on PubMED (as of 6/21/2017) at NCBI. Five key areas of contribution over the last decade include:

1. I have served as the original PI, now Co-PI, of the **Pharmacogenomics Knowledgebase** (PharmGKB, http://www.pharmgkb.org/) Resource. This is a premier human-curated knowledge base of how human genetic variation impacts drug response phenotypes. It gets 25,000-35,000 unique IP hits each month, publishes review articles on drug pathways and genes of significance to pharmacogenomics (and thus precision medicine), and is the basis for several clinical implementation research efforts, including the Clinical Pharmacogenetic Implementation Consortium guidelines (CPIC). We also have made primary contributions to PGx discovery. We have written more than 110 papers as part of the PharmGKB project, available at http://www.ncbi.nlm.nih.gov/sites/myncbi/russ.altman.1/collections/47836341/public/
   a. Province MA, Altman RB, Klein TE. Interpreting the CYP2D6 results from the International Tamoxifen Pharmacogenetics Consortium. Clin Pharmacol Ther. 2014 Aug;96(2):144-6. PMID: 25056393; PMCID: PMC4147833.
   b. Johnson JA, …, Altman RB; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clin Pharmacol Ther. 2011 Oct;90(4):625-9. Epub 2011 Sep 7. Review. PMID: 21900891; PMCID: PMC3187550.
   c. Daneshjou R, …, Altman RB. Pathway analysis of genome-wide data improves warfarin dose prediction. BMC Genomics. 2013;14 Suppl 3:S11. doi: 10.1186/1471-2164-14-S3-S11. Epub 2013 May 28. PMID: 23819817; PMCID: PMC3829086.
   d. Perera MA, …, Altman RB, …, Johnson JA. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. Lancet. 2013 Aug 31;382(9894):790-6. PMID: 23755828; PMCID: PMC3759580.

2. My group has created the **FEATURE suite of programs** for understanding the molecular mechanism of proteins, particularly with respect to drug binding, druggability and drug design. WebFEATURE is a publicly available interface for analyzing protein structures for functional sites (http://feature.stanford.edu/webfeature/). The PocketFEATURE program uses pocket similarity between proteins to predict whether ligands for one pocket will bind a similar pocket (https://simtk.org/home/pocketfeature). The DrugFEATURE program analyzes a protein pocket and determines the likelihood that it will specifically bind a small molecule drug (https://simtk.org/home/drugfeature). The FragFEATURE program analyzes a protein pocket and

determines small molecule fragments that are likely to bind in different sections within the pocket (https://simtk.org/home/frag-feature). We have more than thirty papers as part of this effort available at: http://www.ncbi.nlm.nih.gov/sites/myncbi/russ.altman.1/collections/47836347/public/

a. Liu T, Altman RB. Using multiple microenvironments to find similar ligand-binding sites: application to kinase inhibitor binding. PLoS Comput Biol. 2011 Dec;7(12):e1002326. PMID: 22219723; PMCID: PMC3248393.
b. Liu T, Altman RB. Identifying druggable targets by protein microenvironments matching: application to transcription factors. CPT Pharmacometrics Syst Pharmacol. 2014 Jan 22;3:e93. PMID: 24452614; PMCID: PMC3910014.
c. Liu T, Altman RB. Relating Essential Proteins to Drug Side-Effects Using Canonical Component Analysis: A Structure-Based Approach. J Chem Inf Model. 2015 Jul 27;55(7):1483-94. doi: 10.1021/acs.jcim.5b00030. PMID: 26121262; PMCID: PMC4875781.
d. Liu T, Oprea T, Ursu O, Hasselgren C, Altman RB. Estimation of Maximum Recommended Therapeutic Dose Using Predicted Promiscuity and Potency. Clin Transl Sci. 2016 Dec;9(6):311-320. doi: 10.1111/cts.12422. PMID: 27736015; PMCID: PMC5161261.

**3.** We have helped demonstrate **how whole human genomes can be annotated**, and the issues of genome annotation in the context of next generation sequencing. This leadership has been through highly collaborative papers showing the first clinical analysis of a whole human genome, the analysis of a family quartet of genomes, an analysis of a series of genomes with an analysis of accuracy, and papers on the appropriate interpretation and triage of variations discovered in genome sequencing applications, both for pharmacogenomics and more broadly. We have 14 papers as part of this effort available at: http://www.ncbi.nlm.nih.gov/sites/myncbi/russ.altman.1/collections/47836351/public/

a. Ashley EA, …, Altman RB. Clinical assessment incorporating a personal genome. Lancet. 2010 May 1;375(9725):1525-35. PMID: 20435227; PMCID: PMC2937184.
b. Dewey FE, …, Altman RB, …, Quertermous T. Clinical interpretation and implications of whole-genome sequencing. JAMA. 2014 Mar 12;311(10):1035-45. PMID: 24618965; PMCID: PMC4119063.
c. MacArthur DG, …, Altman RB, …, Gunter C. Guidelines for investigating causality of sequence variants in human disease. Nature. 2014 Apr 24;508(7497):469-76. PMID: 24759409; PMCID: PMC4180223.
d. McDonagh EM, Whirl-Carrillo M, Altman RB, Klein TE. Enabling the curation of your pharmacogenetic study. Clin Pharmacol Ther. 2015 Feb;97(2):116-9. PMID: 25670512; PMCID: PMC4352230.

**4.** Our group has engaged in a program of **translational bioinformatics** to show how systems pharmacology approaches can be used to understand the relationship of molecular mechanism to adverse events. We have shown that we can link data mining of the FDA adverse events database and electronic medical records to extract and validate novel and unexpected drug interactions. We have used crowdsourcing to prioritize adverse events based on their severity. We have created algorithms for linking molecular networks to drugs and diseases in order to generate and understand pathways of drug response, and how drug interactions may result from intersections of underlying molecular mechanisms of individual drug responses. We have more than 25 papers as part of this effort, available at: http://www.ncbi.nlm.nih.gov/sites/myncbi/russ.altman.1/collections/47836366/public/

a. White RW, …, Altman RB, Horvitz E. Web-scale pharmacovigilance: listening to signals from the crowd. J Am Med Inform Assoc. 2013 May 1;20(3):404-8. PMID: 23467469; PMCID: PMC3628066.
b. Tatonetti NP, …, Altman RB. Detecting drug interactions from adverse-event reports: interaction between paroxetine and pravastatin increases blood glucose levels. Clin Pharmacol Ther. 2011 Jul;90(1):133-42. PMID: 21613990; PMCID: PMC3216673.
c. Gottlieb A, …, Altman RB. Ranking adverse drug reactions with crowdsourcing. J Med Internet Res. 2015 Mar 23;17(3):e80. PMID: 25800813; PMCID: PMC4387295.
d. Gottlieb A, Altman RB. Integrating systems biology sources illuminates drug action. Clin Pharmacol Ther. 2014 Jun;95(6):663-9. PMID: 24577151; PMCID: PMC4029855.

**5.** We have contributed to **RNA structure and function modeling**. We created models of the ribosome structure (before the crystal structures were available) based on a knowledgebase (RiboWEB, https://simtk.org/home/ribosomalkb) of multimodal experimental assays (such as crosslinking, RNA footprinting and others), and were able to anticipate some of the large scale motions of the ribosome. More recently we created publicly available software for analyzing RNA protection experiments (the SAFA

software, available at https://simtk.org/home/safa. We also created knowledge-based potentials for predicting RNA structure from sequence and predicted secondary structure (Nucleic Acid Simulation Tool, https://simtk.org/home/nast). We have nearly twenty papers on this topic, available at: http://www.ncbi.nlm.nih.gov/sites/myncbi/russ.altman.1/collections/47836350/public/

a. Gabashvili IS, …, Altman RB. Ribosomal dynamics inferred from variations in experimental measurements. RNA. 2003 Nov;9(11):1301-7. PMID: 14561879; PMCID: PMC1287051.
b. Whirl-Carrillo M, …, Altman RB. Mining biochemical information: lessons taught by the ribosome. RNA. 2002 Mar;8(3):279-89. PMID: 12003488; PMCID: PMC1370250.
c. Laederach A, …, Altman RB. Semiautomated and rapid quantification of nucleic acid footprinting and structure mapping experiments. Nat Protoc. 2008;3(9):1395-401. PMID: 18772866; PMCID: PMC2652576.
d. Jonikas MA, Radmer RJ, Laederach A, Das R, Pearlman S, Herschlag D, Altman RB. Coarse-grained modeling of large RNA molecules with knowledge-based potentials and structural filters. RNA. 2009 Feb;15(2):189-99. PMID: 19144906; PMCID: PMC2648710.

**D. Research Support**

**Active**

**R01 LM05652** (PI: Altman) Role: PI 07/01/94-06/30/19 NIH/NLM
*Text mining for high-fidelity curation and discovery of gene-drug-phenotype relationships* The main goal is to apply methods and develop methods for annotating biological structures so that active sites, binding sites and interaction sites in biological structures can be automatically identified and annotated.

**R24 GM061374** (Co-PI: Altman) 04/01/00 – 07/31/19 NIH/NIGMS
*PharmGKB: pharmacogenomic knowledge for precision medicine*
The Stanford Pharmacogenomics Knowledge Base (PharmGKB, http://www.pharmgkb.org/), an integrated data resource to support the NIGMS Pharmacogenetic Research Network and Database Initiative focuses on how genetic variation contributes to variation in the response to drugs, and will produce data from a wide range of sources, therefore interlinking genomic, molecular, cellular and clinical information about gene systems important for modulating.

**UCSF / FDA** (PI: Giacomini, Kathleen) Role: PI 04/15/2014 – 08/31/2018 Subcontract.
*UCSF-Stanford Center of Excellence in Regulatory Science and Innovation.*
Goal: Stanford will engage in research collaborations with UCSF and FDA scientists to pursue projects in the area of regulatory science, with a focus on informatics.

**HHSF223201510108C** (PI: Altman) FDA 10/01/15- 9/30/18
*Improving the Efficiency and Rigor of Pharmacovigilance at FDA*
The overall goal of this project is to use natural language processing (NLP) and machine learning to triage reports to FAERS in order to identify high-value reports.

**NIH / NCATS** 01/01/18 – 12/28/18
*Stanford Effort for Biomedical Data Translator*
The Biomedical Data Translator (BDT) will deliver capabilities for hypothesis generation by combining rich data with powerful inferential reasoning.

**R01 GM102365** NIH/NIGMS (PI: Altman) 09/01/2012 – 03/31/2022
*Combining systems biology and structural biology to find new therapeutics*
Goal: To combine systems biology approaches with structure-based approaches to find new purposes for existing drugs, and to better predict off-target effects of drugs.

**COMPLETED**

**U54** (Co-PI: Altman) NIH/Northwestern University (Subcontract) 07/01/2016 – 06/30/2021
*African American Cardiovascular Pharmacogenetics CONsorTium (ACCOuNT): Discovery and Translation*
The PharmGKB team will manage the data for this project by providing data coordination, curation, harmonization, standardization and dissemination support for each consortium.

**U54-HL117798** (PI: Altman) NIH/University of Pennsylvania / Subcontract 08/01/2012-05/31/2017
*Personalization of Therapeutic Efficacy and Risk.*
The goal is to build an integrated network of genes, drugs and phenotypes that will be an important asset in integrating information from multiple integrated efforts to understand the individual response to NSAIDs.

**IC2014-1387** (PI: Altman) Pfizer 12/17/2015-12/16/2017
*Strategic Effort in Precision Immunology –I-GPS*
The vision for this collaboration is to create analytic methods for understanding drug response at the molecular level and quantitatively based on retrospective and prospective data analysis.

**Genentech, Inc.** (PI: Altman) 02/01/2016-03/01/2017
*Identifying new drug targets and assessing drug efficacy and safety with systems pharmacology*
This project will have three parts: (1) side effect prediction of Genentech small molecules administered as a single agent; (2) side effect prediction and data-driven dose selection of Genentech small molecules administered in combination; (3) identification of genetic signatures of drug response and new indications for Genentech drugs.
Role: PI

**P50 MH094267** (PI: Altman) NIH/University of Chicago / Subcontract 09/22/11 – 10/31/16
*Conte Center for Computational Systems Genomics of Neuropsychiatric Phenotypes*
The goal is to consolidate in a single modeling framework a number of disparate approaches for analysis of complex neuropsychiatric disorders.

**U10 HL105198** (Co-PI: Altman) NIH/University of Maryland, Baltimore / Subcontract 8/30/2011 – 8/31/2016
*Pharmacogenomics of Anti-platelet Intervention-2 (PAPI-2) Study*
The overall goal of the TPP is to operationalize the work of the PGRN Clinical Pharmacogenomics Implementation Committee (CPIC) by translating widely accepted actionable pharmacogenetic discoveries into real-world clinical practice.