BIOGRAPHICAL SKETCH

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NAME: Dolatshahi, Sepideh

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POSITION TITLE: Assistant Professor of Biomedical Engineering

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Tehran, Tehran, Iran	B.Sc.	07/2007	Electrical Engineering
University of Massachusetts, Amherst, MA	M.Sc.	09/2009	Electrical Engineering
Georgia Institute of Technology, Atlanta, GA	M.Sc.	08/2013	Bioengineering
Georgia Institute of Technology, Atlanta, GA	Ph.D.	08/2015	Electrical Engineering
Massachusetts Institute of Technology (MIT), Cambridge, MA	Postdoctoral	2016-2019	Systems Biology
Ragon Institute of MGH, MIT and Harvard, Cambridge, MA	Postdoctoral	2018-2019	Systems Immunology

A. Personal Statement

I am a tenure-track Assistant Professor of Biomedical Engineering at the University of Virginia (UVA), a core member of UVA Cancer Center, and a member of the Carter Immunology Center. I started my independent research laboratory in January 2020. My laboratory currently comprises of four PhD students, one postdoctoral fellow, three undergraduate students, and one MD researcher. As descried below, my experiences to date have prepared me to lead research projects that combine engineering design, quantitative experimental measurements, and computational analysis to solve imminent problems at the intersection of systems biology, immunology, glycobiology and cancer.

I received my Ph.D. in 2015 under the supervision of Professor Eberhard Voit at Georgia Institute of Technology, where I developed computational methods for the task of identification of metabolic pathway systems based on time series data measurements. In my research efforts during my master's studies and prior to developing a passion to biology, I pursued systems approaches toward information-theoretic identification and compensation of nonlinear devices with applications in wireless telecommunication systems.

In 2016 I started my postdoctoral research in the Department of Biological Engineering at MIT, working with Professor Douglas Lauffenburger, where I developed systems biology– machine learning and kinetic modeling– approaches to investigate innate immune cell-dependent regulation and dysregulation to ultimately improve cancer immunotherapies. Furthermore, co-mentored by Professor Ron Weiss at the Synthetic biology center at MIT, I led the systems biology team in a highly collaborative systems-synthetic biology project toward precise control of the post-translational modifications of monoclonal antibodies by mammalian producer cell lines. In 2018, co-mentored by professors Lauffenburger and Galit Alter, as a postdoctoral fellow at the Ragon Institute of MGH, MIT and Harvard, I developed data-driven approaches to study systems serology of vaccine and mother-to-child antibody transfer.

The primary goal of my independent research program is to create and utilize new systems biology approaches to understand the fundamental mechanisms of immune regulation and dysregulation, with an ultimate objective of identifying strategies to improve immunotherapies and vaccines. By building computational models and

machine-learning strategies that integrate experimental data across various molecular and cellular scales, my laboratory seeks to: **(1)** ascertain how biophysical properties of the immune factors (defined as their subclass and post-translational modifications) determine their function, **(2)** uncover mechanisms responsible for dysregulation of these properties in pregnancy and cancer, and **(3)** use this knowledge to guide biomarkers for early disease diagnosis, patient stratification and optimized vaccines and immunotherapies.

Ongoing or recently completed projects that I would like to highlight include:
Cancer Systems Biology Cross Consortium award (University of Virginia Center for Systems Analysis of Stress-adapted Cancer Organelles, **NCI U54 CA274499**)
Sepideh Dolatshahi (PIs), Kathryn Miller-Jensen (co-I, Yale University) 01/01/24 – 12/31/2024
Golgi stress and aberrant glycosylation in hypoxic conditions: regulation and immune interactions

Jeffress Trust Award in Health Equity Research
Sepideh Dolatshahi (PI), Donald Dudley and Becca Krukowski (co-Is) 06/30/2023 – 06/29/2026
Uncovering Immune Inflammatory Axes of Racial Disparities Linked with Gestational Weight Gain in Pregnant Women

UVA Cancer Center Lung Translational Research Team pilot award
Sepideh Dolatshahi (PI), Michael Brown (co-PI), Timothy Bullock (co-PI) 04/01/2024 – 03/31/2025
Systems immunology approaches to characterize the immune interactions linked with survival and response to immune check point inhibitors in human NSCLC

Selected Citations:

1. Wessel RE, Dolatshahi S Quantitative mechanistic model reveals key determinants of placental IgG transfer and informs prenatal immunization strategies. **PLoS Comput Biol.** 2023 19(11): e1011109. https://doi.org/10.1371/journal.pcbi.1011109 PubMed PMID: 37934786; PubMed Central PMCID: PMC10656024
2. Wessel RE, Ageeb N, Joseph M Obeid, Mauldin I, Goundry KA, Hossain M, Lehman C, Gentzler RD, Wages NA, Slingluff CL, Bullock TNJ, Dolatshahi S*†, Brown MG†. Spatial analysis reveals combinative role for natural killer and CD8 T cells in antitumor immunity despite profound MHC class I loss in non-small cell lung cancer. ***bioRxiv***. 2024 doi: https://doi.org/10.1101/2024.02.20.581048, † shared senior authorship, * corresponding author
3. Dolatshahi S, Butler AL, Pou C, Henckel E, Bernhardsson AK, Gustafsson A, Bohlin K, Shin SA, Lauffenburger DA, Brodin P, Alter G. Selective transfer of maternal antibodies in preterm and fullterm children. ***Sci Rep.*** 2022 Sep 2;12(1):14937. doi: 10.1038/s41598-022-18973-4. PubMed PMID: 36056073; PubMed Central PMCID: PMC9440225.
4. Dolatshahi S, Butler AL, Siedner MJ, Ngonzi J, Edlow AG, Adong J, Jennewein MF, Atyeo C, Bassett IV, Roberts DJ, Lauffenburger DA, Alter G, Bebell LM. Altered maternal antibody profiles in women with HIV drive changes in transplacental antibody transfer. ***Clin Infect Dis.*** 2022 Mar 4;. doi: 10.1093/cid/ciac156. PubMed PMID: 35245365.

B. Positions, Scientific Appointments, and Honors
Positions and Employment

05/2020 -	Faculty Member, Carter Immunology Center, University of Virginia
04/2020 -	Faculty Member, Cancer Center, University of Virginia
01/2020 -	Tenure-Track Assistant Professor of Biomedical Engineering, University of Virginia
2018-2019	Research Fellow, Ragon Institute of MGH, MIT and Harvard, Cambridge, MA
2016-2019	Postdoctoral Research Associate, Massachusetts Institute of Technology, Cambridge, MA
2015-2016	Postdoctoral Fellow, University of Pennsylvania, Department of Genetics, School of Medicine, Cambridge, MA
2009-2015	Graduate Student Research Assistant, Biomedical Engineering, Georgia Institute of Technology
2007-2009	Graduate Student Research Assistant, Electrical and Computer Engineering, University of Massachusetts, Amherst, MA

Other Experience and Professional Membership

2023	NSF division of Molecular and Cellular Biosciences (MCB) advisory panelist
2023	Member of the reviewing committee and session chair, BMES 2023
2023	Session Chair, Southeastern Immunology Symposium, Nashville, TN
2021-	Associate Editor, IET Systems Biology journal
2022	Session Chair, American Association of Immunologists (AAI) Meeting- Big Data: The Key to Unlocking Immune Mediated Mechanisms of Tumor Progression and Therapy Response
2021	NSF Reviewer
2019-2020	Platform Session Chair and Member of Reviewing Committee, BMES Annual Meeting (Track: Translational Applications of Omics Modeling and Analysis)
2020-	Member, American Society for Reproductive Immunology (ASRI)
2015-	Scientific Review Service; Biophys J, PLoS Comp Biol, PLoS ONE, Math. Biosc. etc
2008-	Member, Biomedical Engineering Society (BMES)

Honors

2023	Inclusive Professor of the Year in the Classroom, student-selected, awarded by the Biomedical Engineering Society
2023	American Association of Immunologists (AAI) Chambers-Thermo Fisher Scientific award
2021	Jeffress Trust Award in Interdisciplinary Research
2013	Computational Cell Biology summer course scholarship award from Cold Spring Harbor Laboratory
2010	School of Information Theory scholarship award, University of Southern California, Los Angeles, CA

C. Contributions to Science

C1. Using systems immunology to understand mother-child antibody transfer

Systems serology attempts to quantify the entire humoral response via functional and biophysical assays. In this subset of publications, we set out to define the rules that govern transfer of antibody functionality across placenta from mother to child. We examined paired maternal and cord blood of a cohort of mothers and children for their antigen-specific immune profiles including: (a) antibody subclasses, (b) glycan profiles and the incurred antibody dependent phagocytosis by neutrophils and monocytes, (c) cytotoxicity and secretion of cytokines and chemokines by natural killer (NK) cells, and (d) complement deposition. Using data-driven computational methods such as Partial Least Squares Discriminant Analysis (PLSDA) or Regression (PLSR), we defined the top contributors to the immune profile differences between moms and infants and those that might contribute to function and infant immunity. In addition to studying antibody transfer in health, we have studied how this process was perturbed in cohorts of mothers living with HIV as well as in preterm birth. Our recent efforts are focused on developing kinetic dynamic model spanning the full duration of gestation toward the most effective mathematical models with predictive power. We continue to characterize maternal immune remodeling during pregnancy, placental development and how these are perturbed in various disease contexts and can be boosted by engineering vaccines that maximize protective antibodies transferred to the newborn.

- Wessel RE, Dolatshahi S (2023) Quantitative mechanistic model reveals key determinants of placental IgG transfer and informs prenatal immunization strategies. ***PLoS Comput Biol.*** 2023 19(11): e1011109. https://doi.org/10.1371/journal.pcbi.1011109 PubMed PMID: 37934786; PubMed Central PMCID: PMC10656024
- Dolatshahi S, Butler AL, Pou C. *et al.* Selective transfer of maternal antibodies in preterm and fullterm children. ***Sci. Rep.*** 12, 14937 (2022). https://doi.org/10.1038/s41598-022-18973-4
- Dolatshahi S, Butler AL, Siedner MJ, Ngonzi J, Edlow AG, Adong J, Jennewein MF, Atyeo C, Bassett IV, Roberts DJ, Lauffenburger DA, Alter G*, Bebell LM*. Altered maternal antibody profiles in women with HIV drive changes in transplacental antibody transfer. ***Clin Infect Dis***. 2022 Mar 4:ciac156. doi: 10.1093/cid/ciac156. *co-corresponding author. PMID: 35245365.
- Jennewein MF, Goldfarb I, Dolatshahi S, Cosgrove C, Noelette FJ, Krykbaeva M, Das J, Sarkar A, Gorman MJ, Fischinger S, Boudreau CM, Brown J, Cooperrider JH, Aneja J, Suscovich TJ, Graham BS, Lauer GM, Goetghebuer T, Marchant A, Lauffenburger D, Kim AY, Riley LE, Alter G. Fc Glycan-Mediated Regulation of Placental Antibody Transfer. ***Cell***. 2019 Jun 27;178(1):202-215.e14. PMID: 31204102; PMCID: PMC6741440.

C2. Systems and synthetic biology of antibody (immune factor) glycosylation

Human proteome is vastly more complex than human genome partly due to the diversity facilitated by post-translational modifications (PTMs) of proteins. Glycosylation is a key PTM for protein and monoclonal antibody (mAb) therapeutics. Chemical addition of sugars to proteins in endoplasmic reticulum (ER) and Golgi plays a key role in modulating their structural and interaction capabilities. These modifications affect mAb stability, solubility, immunogenicity, and effector functions such as antibody-mediated cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-mediated cellular phagocytosis (ADCP). There is a critical need, therefore, to identify and acquire the ability to control the key regulators of glycosylation profiles in mAb therapeutics. Toward this goal, we have been pursuing two parallel efforts: **(1)** probed the time-course dynamics of transcriptomics, metabolomics, metal ions, and antibody throughout a 12-day fed-batch culture of antibody-producing Chinese Hamster Ovary (CHO) cells. By using a combination of supervised and unsupervised machine learning approaches (including time-course gene- and metabolic-set enrichment analysis, cross-correlation, clustering and principal component analysis), we identified regulatory bottlenecks to be at the metabolic level, namely the nucleotide sugar donor biosynthesis and transport. **(2)** We used advanced synthetic biology tools to engineer Chinese hamster ovary cells with synthetic genetic circuits to tune N-glycosylation of a stably expressed IgG. Simultaneous and independent control of antibody galactosylation and fucosylation was achieved by genomically integrating circuits expressing two key glycosyltransferase genes, α-1,6-fucosyltransferase (FUT8) and β-1,4-galactosyltransferase (β4GALT1) under orthogonal constitutive or small molecule inducible promoters. Effector function studies confirmed that glycosylation profile changes affected antibody binding to a cell surface receptor. Integrating data from diverse datasets into a single multi-compartment kinetic model, we were able to capture nonlinear relationships between diverse glycosylation mechanisms (e.g. galactosylation and fucosylation) and discover new metabolic regulatory mechanisms.

- Sumit M, Dolatshahi S, Chu AA, Cote K, Scarcelli JJ, Marshall JK, Cornell RJ, Weiss R, Lauffenburger DA, Mulukutla BC, Figueroa B Jr. Dissecting N-Glycosylation Dynamics in Chinese Hamster Ovary Cells Fed-batch Cultures using Time Course Omics Analyses. ***iScience***. 2019 Feb 22;12:102-120. doi: 10.1016/j.isci.2019.01.006. Epub 2019 Jan 7. PubMed PMID: 30682623; PubMed Central PMCID: PMC6352710.
- Chang MM, Gaidukov L, Jung G, Tseng WA, Scarcelli JJ, Cornell R, Marshall JK, Lyles JL, Sakorafas P, Chu AA, Cote K, Tzvetkova B, Dolatshahi S, Sumit M, Mulukutla BC, Lauffenburger DA, Figueroa B Jr, Summers NM, Lu TK, Weiss R. Small-molecule control of antibody N-glycosylation in engineered mammalian cells. ***Nat Chem Biol***. 2019 Jul;15(7):730-736. doi: 10.1038/s41589-019-0288-4. Epub 2019 May 20. PubMed PMID: 31110306.
- Grace PS†, Dolatshahi S†, Lu LL, Cain A, Palmieri F, Petrone L, Fortune SM, Ottenhoff THM, Lauffenburger DA, Goletti D, Joosten SA, Alter G. Antibody Subclass and Glycosylation Shift Following Effective TB Treatment. ***Front Immunol***. 2021;12:679973. doi: 10.3389/fimmu.2021.679973. eCollection 2021. † co-first authors. PubMed PMID: 34290702; PubMed Central PMCID: PMC8287567.

C3. Computational Biology – Multi-scale modeling of molecular and cellular networks

Emerging technologies to profile complex biological phenomena increasingly drive advances in biomedical sciences. These technologies provide multi-modal snapshots of biological systems at a range of spatial and temporal scales. To weave mechanistic stories based on a multitude of intracellular molecular measurements, inter-cellular, tissue-level and functional data, sophisticated computational methods are required. To this end, we combine multiplex experimental measurements with computational methods to solve problems in the context of cancer, infectious disease and maternal-neonatal immunology among others. A central paradigm of our research is development and testing of integrative computational models including data-driven statistical machine learning, network inference, information theory, and signal processing as well as bottom-up mechanistic kinetic-dynamic modeling.

- Dolatshahi S, Voit EO. Identification of Metabolic Pathway Systems. ***Front Genet***. 2016;7:6. doi: 10.3389/fgene.2016.00006. eCollection 2016. PubMed PMID: 26904095; PubMed Central PMCID: PMC4748741
- Dolatshahi S, Fonseca LL, Voit EO. New insights into the complex regulation of the glycolytic pathway in Lactococcus lactis. II. Inference of the precisely timed control system regulating glycolysis. ***Mol Biosyst***. 2016 Jan;12(1):37-47. doi: 10.1039/c5mb00726g. PubMed PMID: 26609780.
- Dolatshahi S, Fonseca LL, Voit EO. New insights into the complex regulation of the glycolytic pathway in Lactococcus lactis. I. Construction and diagnosis of a comprehensive dynamic model. ***Mol Biosyst***. 2016 Jan;12(1):23-36. doi: 10.1039/c5mb00331h. Epub 2015 Nov 26. PubMed PMID: 26609637.

- Fischinger S, Dolatshahi S, Jennewein MF, Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Michael N, Vasan S, Ackerman ME, Streeck H, Alter G. IgG3 collaborates with IgG1 and IgA to recruit effector function in RV144 vaccinees. ***JCI Insight***. 2020 Nov 5;5(21). doi: 10.1172/jci.insight.140925. PubMed PMID: 33031099; PubMed Central PMCID: PMC7710302.

C4. Handling spatial heterogeneity and noise in computational modeling

My vision is that one day computation and mathematics will be capable of reliably predicting, manipulating and optimizing biological systems for the progress of medicine, drug development, and biotechnology as well as sustainable stewardship of the environment. Developing mathematical models of highly nonlinear biological processes requires experimentally measurements, which are often noisy and limited. This highlights the importance of developing mathematical methodologies that enable the task of information retrieval from noisy data. To this end, we have developed creative algorithms based on the fundamentals of statistical signal processing, information theory and wavelet transformation for the identification of nonlinear systems under various noise regimes.

- Wessel RE, Ageeb N, Joseph M Obeid, Mauldin I, Goundry KA, Hossain M, Lehman C, Gentzler RD, Wages NA, Slingluff CL, Bullock TNJ, Dolatshahi S*†, Brown MG†. Spatial analysis reveals combinative role for natural killer and CD8 T cells in antitumor immunity despite profound MHC class I loss in non-small cell lung cancer. ***bioRxiv***. 2024 doi: https://doi.org/10.1101/2024.02.20.581048, † shared senior authorship, * corresponding author
- Wolfe C, Feng Y, Chen D, Purcell E, Talkington A, Dolatshahi S and Shakeri H. GeoTyper: Automated Pipeline from Raw scRNA-Seq Data to Cell Type Identification. ***2022 Systems and Information Engineering Design Symposium (SIEDS)***, 2022, pp. 223-228, doi: 10.1109/SIEDS55548.2022.9799321.
- Dolatshahi S, Vidakovic B, Voit E. A constrained wavelet smoother for pathway identification tasks in systems biology. ***Computers & Chemical Engineering***. 2014/12; 71:728-733.
- Polak AC, Dolatshahi S, Goeckel DL. Identifying Wireless Users via Transmitter Imperfections. ***IEEE Journal on Selected Areas in Communications***. 2011; 29(7):1469-1479. doi: 10.1109/JSAC.2011.110812.

Complete List of Published Work: https://www.ncbi.nlm.nih.gov/myncbi/1hU3jjjMv6g5y/bibliography/public/