

Graham T. Holt

POSTDOCTORAL ASSOCIATE · COMPUTER SCIENCE

Duke University, Durham, NC 27705

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Education

Duke University

Durham, NC, USA

PHD COMPUTATIONAL BIOLOGY & BIOINFORMATICS

2016 - 2022

- Thesis: *Ensemble-based Computational Protein Design: Novel Algorithms and Applications to Energy Landscape Approximation, Antibiotic Resistance, and Antibody Design*
- Advisor: Dr. Bruce R. Donald
- GPA: 3.9/4.0

Dartmouth College

Hanover, NH, USA

BA BIOMEDICAL ENGINEERING WITH HONORS

2010 - 2014

- Honors thesis: *Examination of the Bioengineering of Polarized Microstructures*
- Research advisor: Dr. Henry N. Higgs
- Minor in Computer Science
- GPA: 3.7/4.0
- Cum laude

Professional Experience

- 2022- **Postdoctoral Associate**, Dept. of Computer Science, Duke University
- 2016-2020 **James B. Duke Fellow**, Duke University
- 2019 **Head Graduate Teaching Assistant**, Dept. of Computer Science, Duke University
- 2018 **Graduate Teaching Assistant**, Dept. of Computer Science, Duke University
- 2014-2016 **Research Technician**, Howard Hughes Medical Institute, Janelia Campus
- 2010-2014 **Undergraduate Researcher**, Dept. of Biochemistry, Geisel School of Medicine
- 2012 **Science Undergraduate Laboratory Intern**, U.S. Dept. of Energy, Lawrence Berkeley National Laboratory

Research Experience

Duke University - Department of Computer Science

Durham, NC, USA

SUPERVISORS: DR. BRUCE DONALD

2022 - present

- Postdoctoral Associate
- Developing distribution-based representations of protein structure and applying these representations to ML protein structure prediction and structure generation.

Duke University - Program in Computational Biology & Bioinformatics

Durham, NC, USA

ADVISOR: DR. BRUCE DONALD

2016 - 2022

- Dissertation: "Ensemble-based Computational Protein Design: Novel Algorithms and Applications to Energy Landscape Approximation, Antibiotic Resistance, and Antibody Design"
- Developed provable algorithms to compute the partition function and energy landscape of a protein conformation ensemble.
- Applied algorithms to design protein therapeutics and investigate the structural biology of peptide binding, antibiotic resistance, and antibody:antigen interactions.

Howard Hughes Medical Institute, Janelia Campus - GENIE Project / Schreiter Lab

Ashburn, VA, USA

SUPERVISORS: DR. DOUGLAS KIM AND DR. ERIC SCHREITER

2014-2016

- Performed mutagenesis and high-throughput screening of genetically encoded calcium indicator (GECI) variants.
- Improved activity of CaMPARI, a novel calcium-dependent green to red photoconvertible fluorescent protein.

Geisel School of Medicine - Dept. of Biochemistry

Hanover, NH, USA

ADVISORS: DR. HENRY N. HIGGS

2010-2014

- Honors Thesis: "Examination of the Bioengineering of Polarized Microstructures"
- Characterized the localization and behavior of a mammalian cytoskeleton regulatory protein, FMNL3.
- Performed alanine scanning of putative binding sites and fluorescence microscopy.

Lawrence Berkeley National Laboratory - Division of Biological Systems and Engineering

Berkeley, CA, USA

SUPERVISORS: DR. PRISCILLA COOPER, DR. KELLY TREGO

2012

- Science Undergraduate Laboratory Intern
- Evaluated putative transcription factors of XPG, a double-stranded break DNA repair protein.
- Inhibited TFs in cultured human cells and evaluated the levels of XPG via qRT-PCR and Western blotting.

Publications

PUBLISHED

Wang, S., Reeve, S. M., Holt, G. T., Ojewole, A. A., Frenkel, M. S., Gainza, P., *et al.* Chiral evasion and stereospecific antifolate resistance in *Staphylococcus aureus*. *PLOS Computational Biology* **18** (ed Slusky, J.) e1009855. ISSN: 1553-7358 (Feb. 2022).

Lowegard, A. U., Frenkel, M. S., Holt, G. T., Jou, J. D., Ojewole, A. A. & Donald, B. R. Novel, provable algorithms for efficient ensemble-based computational protein design and their application to the redesign of the c-Raf-RBD:KRas protein-protein interface. *PLOS Computational Biology* **16** (ed Dunbrack, R. L.) e1007447. ISSN: 1553-7358 (June 2020).

Jou, J. D., Holt, G. T., Lowegard, A. U. & Donald, B. R. Minimization-Aware Recursive K*: A Novel, Provable Algorithm that Accelerates Ensemble-Based Protein Design and Provably Approximates the Energy Landscape. *Journal of Computational Biology* **27**. PMID: 31855059, 550–564 (2020).

Holt, G. T., Jou, J. D., Gill, N. P., Lowegard, A. U., Martin, J. W., Madden, D. R., *et al.* Computational analysis of energy landscapes reveals dynamic features that contribute to binding of inhibitors to CFTR-associated ligand. *The Journal of Physical Chemistry B* **123**, 10441–10455 (2019).

Reeve, S. M., Si, D., Krucinska, J., Yan, Y., Viswanathan, K., Wang, S., *et al.* Toward Broad Spectrum Dihydrofolate Reductase Inhibitors Targeting Trimethoprim Resistant Enzymes Identified in Clinical Isolates of Methicillin Resistant *Staphylococcus aureus*. *ACS Infectious Diseases* **5**. PMID: 31565920, 1896–1906 (2019).

Moeyaert, B., Holt, G., Madangopal, R., Perez-Alvarez, A., Fearey, B. C., Trojanowski, N. F., *et al.* Improved methods for marking active neuron populations. *Nature Communications* **9**, 4440 (2018).

Hallen, M. A., Martin, J. W., Ojewole, A., Jou, J. D., Lowegard, A. U., Frenkel, M. S., *et al.* OSPREY 3.0: Open-source protein redesign for you, with powerful new features. *Journal of Computational Chemistry* **39**, 2494–2507 (2018).

de Juan-Sanz, J., Holt, G. T., Schreiter, E. R., de Juan, F., Kim, D. S. & Ryan, T. A. Axonal Endoplasmic Reticulum Ca²⁺ Content Controls Release Probability in CNS Nerve Terminals. *Neuron* **93**, 867–881.e6. ISSN: 0896-6273 (2017).

Dana, H. *et al.* Sensitive red protein calcium indicators for imaging neural activity. *eLife* **5** (ed Häusser, M.) e12727. ISSN: 2050-084X (Mar. 2016).

Henderson, M. J., Baldwin, H. A., Werley, C. A., Boccardo, S., Whitaker, L. R., Yan, X., *et al.* A Low Affinity GCaMP3 Variant (GCaMPer) for Imaging the Endoplasmic Reticulum Calcium Store. *PLOS ONE* **10**, 1–17 (Oct. 2015).

IN REVIEW

Holt, G. T., Gorman, J., Wang, S., Lowegard, A. U., Zhang, B., Liu, T., *et al.* Improved HIV-1 Neutralization Breadth and Potency of V2-Apex Antibodies by *In Silico* Design. *Cell Reports*.

Awards, Fellowships, & Grants

2020 Teaching Assistant Award, Dept. of Computer Science

2019 Poster Award, Dept. of Biochemistry
RECOMB Travel Fellowship, NSF

- 2016 **James B. Duke Fellowship**, Duke University
- 2013 **Junior Research Scholarship**, Dartmouth College
- 2012 **Sophomore Research Scholarship**, Dartmouth College

Presentations

CONTRIBUTED PRESENTATIONS

- Holt, G. T.**, April 2022. *Ensemble-based computational protein design: Algorithms and applications*. Dissertation defense seminar, Program in Computational Biology & Bioinformatics, Duke University, Durham, NC, USA.
- Holt, G. T.**, March 2022. *In silico design of V2-apex antibodies yields improved HIV-1 breadth and potency by improving non-conserved side-chain interactions*. Oral presentation: Joint HIV-1 Meeting (Passive), Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA (Remote).
- Holt, G. T.**, October 2021. *Ensemble-based computational protein design: Algorithms and applications*. Oral presentation: Departmental seminar for Program in Computational Biology & Bioinformatics, Duke University, Durham, NC, USA
- Holt, G. T.**, Jou, J. D., Lowegard, A. U., Donald, B.R. May 2019. *Minimization-Aware Recursive K*: A novel, provable algorithm that accelerates ensemble-based protein design and provably approximates the energy landscape*. Contributed talk: Research in Computational Molecular Biology (RECOMB), Washington, DC, USA.
- Holt, G. T.**, October 2019. *Using ensemble-based computational protein design to propose mechanisms of binding and resistance*. Oral presentation: Departmental retreat for Dept. of Biochemistry, Duke University, Wrightsville Beach, NC, USA
- Holt, G. T.**, Jou, J. D., Lowegard, A. U., Donald, B.R. October 2018. *Minimization-Aware Recursive K* (MARK*) enables approximation and visualization of energy landscapes*. Poster: Departmental retreat for Program in Computational Biology & Bioinformatics, Duke University, Wrightsville Beach, NC, USA.
- Holt, G. T.** 2012. *Transcriptional Regulation of XPG in the DNA Damage Response*. Poster: LBNL Science Undergraduate Laboratory Intern Program, Berkeley, CA, USA.

Teaching Experience

- Fall 2019 **Discrete Mathematics for Computer Science (COSC230)**, Head Teaching Assistant
- Fall 2018 **Discrete Mathematics for Computer Science (COSC230)**, Teaching Assistant

Mentoring

- 2020-2022 **Hong Niu**, Research Technician, Duke University

Professional Development

PROFESSIONAL MEMBERSHIPS

Tau Beta Pi Engineering Honors Society

TECHNICAL SKILLS

Python
scikit-learn
Java
MATLAB
Scheme
L^AT_EX
Unix
Version control (Git)

Algorithm development
Protein biochemistry
Automated liquid-handling
Fluorescence microscopy
Tissue culture
PCR
SDS-PAGE