BIOGRAPHICAL SKETCH.

NAME: Marks, Debora S

eRA COMMONS USER NAME (credential, e.g., agency login): DMARKS10

POSITION TITLE: Associate Professor, Department of Systems Biology, Harvard Medical School.

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	DATE	FIELD OF STUDY
University of Bristol	2ndMBChB	06/1980	Medicine
University of Manchester, Manchester, UK	BSc Hons	06/1993	Mathematics
University of Manchester, Manchester, UK		08/1994-06/1998	Drug design, computational biology
University of Manchester, Manchester, UK		07/1998-12/1999	Research Assistant Bioinformatics
Harvard Medical School, Cell Biology Dept.		01/2000-09/2000	Bioinformatics Fellow
Bauer Center for Genomics Research, Harvard		09/2000-06/2001	Bioinformatics Fellow
Harvard Medical School, Fontana Lab		06/2005-03/2008	Predoctoral Fellow
Humboldt University, Berlin, Germany	PhD	07/2010	Mathematical Biology
Harvard Medical School, Systems Biology Dept.		06/2012-09/2014	Instructor, Computational Biology
Harvard Medical School, Systems Biology Dept.		09/2014-2017	Assistant Professor
Harvard Medical School, Systems Biology Dept.		2018-present	Associate Professor
The Broad Institute of Harvard and MIT		2016-present	Associate Member

1. Personal Statement

I am a mathematician and computational biologist with a track record of developing novel algorithms, statistical methods and machine learning to successfully address unsolved biological problems. I am driven by a passion to understand, predict and design biomolecular systems in a way that impacts biomedical applications and synthetic biology at many scales.

My lab has focused specifically on developing new methods in probabilistic modeling that exploit the huge and increasing corpus of natural and synthetic sequence diversity. My lab continues to build on our early success of predicting 3D structures from sequences alone using undirected graphical models of covariation; Over the past five years we have developed methods that accelerate structural biology with applications to cryoEM, crystallography, protein design and computed 3D structures of thousands of proteins with unknown folds, complexes and RNA

interactions as well as flexible, dynamic and even disordered protein ensembles. To address our newest challenges in protein design we have adapted and developed deep neural methods particularly those that have been so successful in other areas such as in natural language processing. We are applying and testing these in tightknit collaborations with experimental groups (i) designing focused libraries of high affinity, specific nanobodies, antibodies that bypass the need for expensive rounds of selection or labor intensive specificity assays and (ii) design and prediction of proteins that induce membranes compartmentalization and potentially biostasis in human cells

A second goal of my lab has is to transform our ability to predict the consequences of genetic variation to predict the effect of mutations for disease and drug response. We are now expanding our focus here to address the challenge of unexplained microbial resistance to antibiotics. After the success of discovering he effect of combinations of mutations on protein function and disease phenotypes, we were encouraged to develop these methodologies to scale genome-wide in bacterial sequences. Our initial work on resistance in N. gonorrhea, recently published, showed the promise of these approaches to identify genetic dependencies.

My lab in Systems Biology at Harvard Medical School and my affiliation with the Broad puts me in a perfect position to engage in deep collaborations with diverse experimentalists and theorists across the campuses; nine of my twelve current students and postdocs work together with another lab.

B. Positions and Honors

1982-1984	Clinical Research Officer, Wyeth Pharmaceuticals
1984-1990	Clinical Research Officer, Merck, Sharp and Dohme
2012-2014	Instructor, Systems Biology, Harvard Medical School
2014-2017	Assistant Professor, Systems Biology, Harvard Medical School
2018-present	Associate Professor, Systems Biology, Harvard Medical School
2017-present	Associate Member, The Broad Institute, MIT and Harvard.

2016 ICSB Overton Award for outstanding accomplishment in the early to mid stage of career with significant contribution to the field of computational biolog

2018 CZI Ben Barres Early Career Acceleration Award

C. 15 selected papers

1. Schubert B, Maddamsetti R, Nyman J, Farhat MR, Marks DS. Genome-wide discovery of epistatic loci affecting antibiotic resistance in Neisseria gonorrhoeae using evolutionary couplings. Nat Microbiol. 2018 Dec 3. doi: 10.1038/s41564-018-0309-1. [Epub ahead of print] PubMed PMID: 30510172.
2. Riesselman AJ, Ingraham JB, Marks DS. Deep generative models of genetic variation capture the effects of mutations. Nat Methods. 2018 Oct;15(10):816-822. doi: 10.1038/s41592-018-0138-4. Epub 2018 Sep 24. PubMed PMID: 30250057.
3. Ingraham, J. & Marks, D.. (2017). Variational Inference for Sparse and Undirected Models. Proceedings of the 34th International Conference on Machine Learning, in PMLR; 70:1607-1616
4. Hopf TA, Ingraham JB, Poelwijk FJ, Scharfe CPI, Springer M, Sander C, et al. Mutation effects predicted from sequence co-variation. Nat Biotech. 2017;. doi: 10.1038/nbt.3769
5. Toth-Petroczy A, Palmedo P, Ingraham J, Hopf TA, Berger B, Sander C, Marks DS**.** (2016) Structured States of Disordered Proteins from Genomic Sequences. Cell. 2016 Sep 22;167(1):158-70. PMCID: PMC5451116.
6. Weinreb C, Riesselman AJ, Ingraham JB, Gross T, Sander C, Marks DS. (2016) 3D RNA and Functional Interactions from Evolutionary Couplings. Cell. 165:4. PMID: 27087444. PMCID: 5024353.
7. Schmiedel JM, Klemm SL, Zheng Y, Sahay A, Blüthgen N*, Marks DS*, van Oudenaarden A*. Gene expression. MicroRNA control of protein expression noise.
8. Hopf T. A., Colwell L. J., Sheridan R., Rost B., Sander C., Marks D. S. (2012). Three-dimensional structures of membrane proteins from genomic sequencing. Cell, 149(7): 1607-1621. PMCID: PMC3641781.
9. Arvey A., Larsson E., Sander C., Leslie C. S. *, Marks D. S. *. (2010). Target mRNA abundance dilutes microRNA and siRNA activity. Molecular Systems Biology 6, 363. PMCID: PMC2872614.
10. Larsson E., Sander C., Marks D. (2010). mRNA turnover rate limits siRNA and microRNA efficacy. Molecular Systems Biology, 6:433. PMCID: PMC3010119.

11. Khan A. A., Betel D., Miller M. L., Sander C., Leslie C. S. *, Marks D. S. * (2009). Transfection of small RNAs globally perturbs gene regulation by endogenous microRNAs. Nature biotechnology, 27(6): 549-555. PMCID: PMC2782465.
12. Chen P. Y., Manninga H., Slanchev K., Chien M., Russo J. J., Ju J., Sheridan R., John B., Marks D. S., Gaidatzis D., Sander C., Zavolan M., Tuschl T. (2005). The developmental miRNA profiles of zebrafish as determined by small RNA cloning. Genes & development,19, 1288-1293. PMCID: PMC1142552.
13. Pfeffer. S., Zavolan M., Grasser F. A., Chien M., Russo J. J., Ju J., John B., Enright A. J., Marks D., Sander C., Tuschl T.(2004). Identification of virus-encoded microRNAs. Science, 304(5671):734-6.
14. John B., Enright A.J., Aravin A., Tuschl T., Sander C., Marks DS. (2004). Human MicroRNA targets. PLoS Biol 2, e363. PMCID: PMC521178.
15. Enright A.J., John B., Gaul U., Tuschl T., Sander C., Marks D. S. (2003). MicroRNA targets in Drosophila. Genome Biol 5(1), R1. PMCID: PMC395733.

Fuller Lists of Published Work

Google Scholar
https://scholar.google.com/citations?user=qFmoeNkAAAAJ&hl=en

MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/46469257/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

DARPA W911NF1920017 (Silver and Marks CoPIs)
12/1/2018-5/31/2020
DARPA Design and Engineering of Biostasis Proteins
Cellular stasis. We are designing intrinsically disordered proteins inspired by polyextremophile eukaryotes to reversibly and non-specifically pause biological activity in human cells. This technology has far-reaching therapeutic and commercial applications
Role: Co- PI

CZI Chan Zuckerberg Initiative 2018-191853 12/1/2018-11/30/2023.
Neurodegeneration Challenge Network Ben Barres Early Career Acceleration Award

Computational discovery tools for large-scale structure determination of macromolecules, of conformational changes and for quantitative prediction of effects human genetic variants in neurodegenerative disease
Role: PI

NIH R01GM120574 (G. Montelione) 09/01/2017-06/30/2021
Membrane Protein Structure Using Evolutionary Couplings and Sparse NMR Data
This collaboration aims to develop the EC-NMR method for (i) higher success rates for membrane proteins structure determination than either ECs or NMR alone can achieve. In particular, this aims to develop methods for structure determination of large membrane proteins that have been mostly inaccessible to NMR studies previously and (ii) Use ECs with NMR to identify allosteric states of proteins with sparse NMR data.
Role: Co-Investigator

IARPA 2660011824505 (P. Silver) 06/04/2018-12/03/2021
Rapid Tests for Signatures of Genetic Engineering in Biological Samples
We will address how to detect potentially hazardous DNA sequences that have been engineered or are signatures of pandemics.
Role: Co-Investigator

Deans Innovation Grant (Kruse, Rudner, Marks) 09/01/2018-08/31/2020
Nutrient Sensing and Spore Germination
We seek to define the germination signal transduction pathway in molecular terms, taking an integrative approach combining genetic, biochemical, structural, and computational methods. A complete molecular dissection of germination will facilitate the development of treatments that inhibit germination or inappropriately induce it, leaving cells vulnerable to standard antibacterial therapies.
Role: Co-PI

Completed Research Support

NIH R01GM106303 (Sander, C.) 05/03/2013 – 09/30/2017
Accelerated determination of 3D structures of large proteins and protein complexes and functional interpretation
The project aims to broadly apply and improve our recently published computational technology for the prediction of 3D protein structures, including large complexes, from sequence information; and, for the functional interpretation of evolutionary constraints in both known and previously unknown structures. We will also predict functional hotspots, ligand-binding sites over and above those that can be detected by conservation of single residues alone. The new technology exploits the power of evolutionary information made accessible because of two advances: (1) the enormous increase in protein sequence information based on advances in DNA sequencing technology and (2) our recent algorithm for extracting evolutionary constraints based on the maximum entropy principle.
Role: Co-Investigator

NIHP50GM107618 (Sorger, P) 07/01/2014-05/31/2017
Systems Pharmacology Center Grant
One FTA, postdoctoral researcher
The computational biologists, physician-scientists and pharmacologists in the Laboratory of Systems Pharmacology will apply a combined measure-model approach to understanding the mechanisms of action of therapeutic drugs in multiple disease areas. They will develop and apply new tools to (i) investigate the factors that determine the therapeutic index of drugs at a single cell level and in tissues (ii) apply knowledge of cellular networks to develop a rational approach to combination therapy (iii) identify and qualify new drug targets for significant unmet medical needs. Success with our approach will advance personalized medicine and reduce the frequency of late-stage failure in drug discovery, thereby reducing the cost of new medicines.
Role: Co-Investigator