BIOGRAPHICAL SKETCH

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NAME: Anat Kreimer

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

POSITION TITLE: Assistant Professor at the Department of Biochemistry and Molecular Biology in Robert Wood Johnson Medical School (RWJMS) at Rutgers University and Resident Faculty Member in the Center of Advanced Biotechnology and Medicine (CABM) with a secondary faculty appointment in the Department of Pediatrics at RWJMS.

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
Tel Aviv University, Israel	B.Sc.	07/2005	Mathematics and Computer Science
Tel Aviv University, Israel	M.Sc.	08/2008	Applied Mathematics with thesis in Bioinformatics
Columbia University, NY, NY	Ph.D.	10/2014	Biomedical Informatics
UC Berkeley & UCSF	Postdoctoral Fellow	08/2020	Computational Functional Genomics

A. Personal Statement

The goal of my research is to provide a working model that consists of the key regulatory components (transcription factors, chromatin modifying enzymes and cis-acting DNA elements) that drive the response of mammalian cells to stimulation, and the interactions between them. This work will also open the way for understanding how the activity of these components is modulated by natural variation in humans, thus providing new hypotheses about the functional implications of risk loci, and the specific mechanisms that are impaired in disease.

During my postdoctoral appointment, I have been investigating the determinants of gene regulation and their implications on phenotype and specifically human disease by supplementing observational epigenetic data with functional assays - Massively Parallel Reporter Assays (MPRAs). I was selected to serve as the assessor of the Critical Assessment of Genome Interpretation CAGI4- eQTL causal SNPs challenge. For this community challenge, I focused on comparing and developing methods for prediction of regulatory regions and the effect of small variants on their regulatory potential in MPRAs. I extended this work to understand the robustness of regulatory potential across different cell types. The results from this work highlighted which features are reflective of the cellular context and which are intrinsic to DNA sequence, by exploring the extent of transfer knowledge between cell types. Applying the methods I developed to predict functional variants in regulatory elements that are associated with disease, achieved top performance in the CAGI5 challenge. My recent efforts were focused on leading a project to comprehensively map and investigate the function of gene regulatory elements associated with early neural differentiation and understand their role in neural disease, which involves co-developing methods for processing and statistical modeling of MPRA data.

In my lab, we will aim to develop innovative computational methods for predicting transcriptional regulation determinants by incorporating various genomic datasets and highlighting condition specific regulatory processes. In conjunction with experimental validation and collaboration with clinicians, we will leverage such techniques to understand which regulatory elements play a role in specific conditions, cells and tissues; how they interact to achieve transcriptional regulation; and what are the mechanisms by which genetic variation in these non-coding regions drives disease in humans.

Ongoing and recently completed projects that I would like to highlight include:

NIH/ NIMH 4R00MH117393
PI: Kreimer/ Yosef
07/01/2018-06/30/2023
Early Epigenetic Footprint of Nervous System Diseases

NIH/ NIMH 1R01MH129372
PI: Yang/ Kreimer
04/01/2022-03/31/2027
Functional mapping of noncoding regulatory variants in human neuronal Subtypes

NJGCA FY23 Autism Grant #CAUT23BSP004
PI: Kreimer
07/01/2022-06/30/2024
Decoding autism regulatory variants using computational genomics in human iPSC-derived neurons

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020-present: Assistant Professor at the Department of Biochemistry and Molecular Biology in Robert Wood Johnson Medical School (RWJMS) at Rutgers University and Resident Faculty Member in the Center of Advanced Biotechnology and Medicine (CABM) with a secondary faculty appointment in the Department of Pediatrics at RWJMS.

2014-2020: Postdoctoral appointment, UC Berkeley and UCSF

2009-2014: Pre-doctoral appointment, Columbia University.

2012: internship eScience Research Group, Microsoft Research Los Angeles CA.

University level teaching experience

2011-2012: Teaching Assistant, Columbia University Department of Computer Science, New York, USA

2006 – 2007: Teaching Assistant, TAU School of Mathematical Sciences, Tel-Aviv, Israel.

Honors

2022-2027: NIH R01 as Co-PI.

2018-2023: NIH K99/R00 Pathway to Independence Award.

2009-2014: Pre-doctoral appointment - including full tuition scholarship, stipend and full medical insurance from the Department of Biomedical Informatics, Columbia University.

2005-2008: Full tuition Master’s degree research scholarship and stipend from the School of Computer Science, Tel-Aviv University.

2007: Google Global Community Scholarship for the Grace Hopper Celebration of Women in Computing.

C. Contributions to Science

1. Community modeling of bacterial metabolic interactions

The composition of bacterial communities is a major factor in human health. The microorganisms that live inside and on humans are estimated to outnumber human somatic and germ cells by a factor of ten. The genomes of these microbial symbionts provide functions that humans did not evolve on their own. Considering its medical and ecological implications, successful modeling of bacterial communities is thus likely to have broad consequences.

During my Master degree I have developed several network based computational methods for characterizing the modularity of metabolic networks across the bacterial tree of life (Kreimer et al. PNAS 2008), linking an organism with its biochemical habitat and studying the interactions of microbes with other species thriving in similar habitats (Freilich & Kreimer et al. Genome Biology 2009, PLOS Comp Bio 2010; NAR 2010). This ability to produce a genomic driven environmental model lays down a computational foundation for the study of a variety of aspects of the communal metabolic life.

a. The large scale organization of the bacterial ecological-interaction network. Shiri Freilich, **Anat Kreimer**, Isacc Meilijson, Uri Gophna, Roded Sharan & Eytan Ruppin. *Nucleic Acids Research* 2010. doi:10.1093/nar/gkq118
b. Decoupling Environment-Dependant and Independent Genetic Robustness across Bacterial Species**.** Shiri Freilich*, **Anat Kreimer***, Elhanan Borenstein, Uri Gophna, Roded Sharan, and Eytan Ruppin (*Equal contribution). *PLOS Computational biology* 2010, Volume: 6, Issue: 2.
c. Metabolic-network driven analysis of bacterial ecological strategies**.** Shiri Freilich*, **Anat Kreimer***, Elhanan Borenstein , Nir Yosef, Uri Gophna, Roded Sharan, and Eytan Ruppin(*Equal contribution). *Genome Biology* 2009, 10(6):R61.
d. The Evolution of Modularity in Bacterial Metabolic Networks. **Anat Kreimer***, Elhanan Borenstein*, Uri Gophna and Eytan Ruppin (*Equal contribution). *Proceedings of the National Academy of Sciences* 2008, Volume: 105, No. 19, Pages: 6976–6981.

2. Developing web interfaces for calculating bacterial metabolic interactions

During my Master degree and as part of our effort to model bacterial metabolic interactions, we developed two web interfaces for the use of the research community. The first one, NetCmpt can be utilized for calculating the metabolic competition between bacterial species (Kreimer et al. Bioinformatics 2012). The second one NetCooperate can be used for inferring host-microbe and microbe-microbe cooperation (BMC Bioinformatics 2015).

a. NetCooperate: a network-based tool for inferring host-microbe and microbe-microbe cooperation. Roie Levy, Rogan Carr, **Anat Kreimer**, Shiri Freilich and Elhanan Borenstein. *BMC Bioinformatics*, 2015, 16:164. doi:10.1186/s12859-015-0588-y
b. NetCmpt: a network-based tool for calculating the metabolic competition between bacterial species. **Anat Kreimer***, Adi Doron-Faigenboim*, Elhanan Borenstein and Shiri Freilich (*Equal contribution). *Bioinformatics*, 2012. 28 (16):2195 2197.doi:10.1093/bioinformatics/bts323

3. Analysis of trans eSNPs infers regulatory network architecture

eSNPs are genetic variants associated with transcript expression levels. The characteristics of such variants highlight their importance and present a unique opportunity for studying gene regulation. eSNPs affect most genes and their cell type specificity can shed light on different processes that are activated in each cell. They can identify functional variants by connecting SNPs that are implicated in disease to a molecular mechanism. Examining eSNPs that are associated with distal genes can provide insights regarding the inference of regulatory networks but also presents challenges due to the high statistical burden of multiple testing. Such association studies allow: simultaneous investigation

of many gene expression phenotypes without assuming any prior knowledge and identification of unknown regulators of gene expression while uncovering directionality.

My PhD research focused on such distal eSNPs to map regulatory interactions between different loci and expose the architecture of the regulatory network defined by such interactions. I developed novel computational approaches and applied them to genetics-genomics data in human. Going beyond pairwise interactions to define network motifs, including regulatory modules (Kreimer et al., NAR 2012) and bi-fan structures (Kreimer et al. PLOS Genetics 2014), showing them to be prevalent in real data and exposing distinct attributes of such arrangements. Projection of eSNP associations onto a protein-protein interaction network exposed topological properties of eSNPs and their targets and highlighted different modes of distal regulation (Kreimer et al. Genome Biology 2013). Overall, this work offers insights concerning the topological structure of human regulatory networks and the role genetics plays in shaping them.

a. Co-regulated transcripts associated to cooperating eSNPs define bi-fan motifs in human gene networks. **Anat Kreimer** and Itsik Pe'er. PLOS Genetics 2014. doi:10.1371/journal.pgen.1004587
b. Variants in exons and in transcription factors affect gene expression in trans. **Anat Kreimer** and Itsik Pe'er. *Genome Biology* 2013, 14:R71. doi:10.1186/gb-2013-14-7-r71
c. Inference of modules associated to eQTLs. **Anat Kreimer**, Oren Litvin, Ke Hao, Cliona Molony, Dana Pe'er and Itsik Pe'er . Nucleic Acids Research 2012. doi: 10.1093/nar/gks269

4. Elucidating the determinants of gene regulation

In many human diseases, associated genetic changes tend to occur within noncoding regions, whose effect might be related to transcriptional control. A central goal in human genetics is to understand the function of such noncoding regions. Pivotal questions in this field include: identification of functional regions and the transcription factors that bind them, associating those regions to their target genes and elucidating the effect genetic variants in those region have on phenotype and specifically in human disease. For my postdoctoral appointment, I aim to tackle these questions in a multi-disciplinary approach, combing both computational and experimental biology. To this end, I served as the assessor of the Critical Assessment of Genome Interpretation CAGI4- eQTL causal SNPs challenge. For this community challenge, I focused on comparing and developing methods for prediction of regulatory regions and the effect of small variants on their regulatory potential in MPRAs (Kreimer et al. Human Mutation 2017). I extended this work to understand the robustness of regulatory potential across different cell types. The results from this work highlighted which features are reflective of the cellular context and which are intrinsic to DNA sequence, by exploring the extent of transfer knowledge between cell types. Applying the methods I developed to predict functional variants in regulatory elements that are associated with disease, achieved top performance in the CAGI5 challenge (Kreimer et al. Human Mutation 2019). Additionally, I contributed to a project for characterizing the effect of antibiotic treatment on gene expression. My recent efforts were focused on leading projects to comprehensively map and investigate the function of gene regulatory elements associated with early neural differentiation and understand their role in neural disease (Kreimer et al. Nature Communications 2022; Inoue & Kreimer et al. Cell Stem Cell 2019; best poster award - 2018 ENCODE meeting), which involves co-developing methods for statistical modeling of MPRA data (Genome Biology 2019). Current work from my lab include the characterization of the role of non-coding disease associated variants in different neuronal cell types (International Journal of Molecular Sciences 2023).

a. Predicting gene expression in massively parallel reporter assays: a comparative study. **Anat Kreimer**, Haoyang Zeng, Matthew D Edwards, Yuchun Guo, Kevin Tian, Sunyoung Shin, Rene Welch, Michael Wainberg, Rahul Mohan, Nicholas A Sinnott-Armstrong, Yue Li, Gökcen Eraslan, Talal Bin AMIN, Jonathan Goke, Nikola S Mueller, Manolis Kellis, Anshul Kundaje, Michael A Beer, Sunduz Keles, David K Gifford, Nir Yosef. *Human Mutation* 2017. Doi:10.1002/humu.23197
b. Meta-analysis of massively parallel reporter assays enables prediction of regulatory function across cell types. **Anat Kreimer**, Zhongxia Yan, Nadav Ahituv, Nir Yosef. Human Mutation

2019. doi: doi.org/10.1002/humu.23820

c. Identification and Massively Parallel Characterization of Regulatory Elements Driving Neural Induction. Fumitaka Inoue & **Anat Kreimer**, Tal Ashuach, Nadav Ahituv, Nir Yosef. Cell Stem Cell 2019. doi:https://doi.org/10.1016/j.stem.2019.09.010

d. Massively parallel reporter perturbation assays uncover temporal regulatory architecture during neural differentiation. **Anat Kreimer**, Fumitaka Inoue, Tal Ashuach, Alex Khodaverdian, Chengyu Deng, Nir Yosef, Nadav Ahituv. *Nature Communications* (2022). https://doi.org/10.1038/s41467-022-28659-0

Link to publications

http://www.ncbi.nlm.nih.gov/pubmed/?term=Anat+kreimer