# SCIENCE AT THE EDGE

2018 SEMINAR SERIES

**Quantitative Biology Graduate Program | Gene Expression in Development and Disease**


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## "Sibling Rivalry in Transcription Factor Families"


Most human transcription factors (TFs) belong to large families of proteins that share a common DNA-binding domain and have similar DNA-binding preferences. However, members of the same family (i.e. paralogous TFs) generally perform different regulatory functions by interacting with distinct sets of genomic targets in the cell. The competition for DNA binding between paralogous TFs is largely ignored in genomics studies, and the molecular mechanisms by which these proteins achieve this functional specificity in the cell are poorly understood. Differential genomic targeting by paralogous TFs is generally assumed to be due to interactions with protein cofactors or the chromatin environment. Contrary to these assumptions, we find that paralogous TFs have different intrinsic preferences for DNA, not captured by current motif models. Our finding was possible due to a unique combination of carefully designed high-throughput TF-DNA binding assays and rigorous computation modeling, integrated into a unified framework we call iMADS (Integrated Modeling and Analysis of Differential Specificity). We used iMADS to quantify, model, and analyze specificity differences between human paralogous TFs from four structural families. We show that these differences in intrinsic specificity partly explain differential genomic binding and functional specificity of paralogous TFs. In addition, we are developing high-throughput in vitro competition assays to understand the interplay between related TFs. Our findings have important implications for the interpretation of non-coding genetic variants that fall within TF binding sites, as the effects of these variants will depend on the DNA-binding affinities


References:


Shen N, Zhao J, Schipper J, Zhang Y, Bepler T, Leehr D, Bradley J, Horton J, Lapp H, Gordan R (2017) Intrinsic specificity differences between transcription factor paralogs partly explain their differential in vivo binding. Preprint in bioRxiv: https://doi.org/10.1101/208561


## FRIDAY, JANUARY 19, 2018

## 11:30 AM, ROOM 1400 BPS

*Refreshments at 11:15*

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