



On the Trail of Genomic Pioneers



Meet Dr. Mark Biggin
Genomics Division
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1) Would you tell us a bit about your research interests?

The broad goal of my research is to learn how to read the cis regulatory information in animal genome sequences, which contain much of the genetic information specifying animal form.

2) You are involved in The Berkeley Drosophila Transcription Network Project (BDTNP). Can you tell us a bit about this project?

Our goal is to gain a more rigorous understanding of animal transcription networks. The BDTNP has developed methods to produce and quantitatively analyze data for transcription factors' in vitro and in vivo DNA binding specificities, the expression patterns of factors and their target genes, and the accessibility of DNA in chromatin. Studying all of these components of the network together is, we believe, an essential step towards our eventual goal of deriving predictive computational models of animal transcription system wide.

3) A great deal of your work focuses on Drosophila. How does Drosophila help in understanding of animal gene regulatory networks ?

Drosophila melanogaster is a great model organism for the study of transcriptional control in animals because it allows both genetic and biochemical analyses. The pioneering work of geneticists discovered the

set of 40 or so transcription factors that we now study. However, early on it became clear that it was difficult to relate the results of simple in vitro biochemical DNA binding analyses of transcription factors with the results of genetic experiments. This is unlike the case in bacteria, which have relatively simple networks. Animal networks are too complex to be analyzed by genetics and *in vitro* biochemistry alone. That is why in 1990 we began to use *in vivo* biochemistry, employing a cross linking assay that can determine how molecules behave in cells rather than in the test tube. This assay crosslinks endogenous transcription factors to DNA in intact embryos, then uses immunoprecipitation to identify which DNAs each protein binds in vivo. Initial experiments relied on sampling binding to just a few tens of genomic regions. The completion of the euchromatic DNA sequence of *Drosophila*, however, allowed larger scale analysis of binding throughout the genome, which allowed us to confirm and extend our first results.

4) Having worked in this space for a while, what are the genomic technologies and approaches which are promising in this area?

Pioneering ways to look at the dynamics of transcription factor behavior in living cells is an exciting area, as is the development of various single molecular methods to study molecular interactions in cells.

5) Your laboratory collaborates with people coming from different background. Could you tell us about it?

My laboratory collaborates with people with



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different backgrounds, including bioinformaticists, statisticians, systems engineers, molecular geneticists, engineers, and image analysis experts. Working with people with advanced math skills has proven critical to analyzing the large quantitative data sets we have produced.

6) Where do you see your research leading in future?

We are working towards a general theory to model how transcription factors are targeted to DNA in vivo and how they subsequently function to produce intricate patterns of gene transcription. It is a general model at this stage, but we do have an intellectual framework. We need to extend our data sets to include quantitative perturbation data. We want to be able to predict protein-protein interactions computationally using our current datasets and ultimately model how gene expression patterns are generated.

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