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Extracting free energies of interaction from chromosome conformation capture data

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A variety of DNA binding proteins are involved in regulating and shaping the packing of chromatin. They aid the formation of loops in the DNA that function to isolate different structural domains. A recent experimental technique, Hi-C, provides a method for determining the frequency of such looping between all distant parts of the genome. Given that the binding locations of many chromatin associated proteins have also been measured, it is possible to make estimates for their influence on the long-range interactions as measured by Hi-C. However, a challenge in this analysis is the predominance of non-specific contacts that has made making quantitative estimates for the strengths of interactions between chromatin factors difficult. In this talk I will show that transforming the Hi-C contact frequencies into free energies of interaction gives a natural method for separating out the distance dependent non-specific interactions. In particular, using Principal Component Analysis (PCA) on the transformed free energy matrix can identify the dominant modes of interaction within the genome. Some of these modes correspond to systematic biases that can then be subtracted out. I will then show that a pairwise interaction model can be fit to the corrected free energies to determine the couplings between known bound chromatin factors. By correcting for the systematic effects identified by PCA, a consistent set of predictions for the couplings among the various chromatin factors can be made. Many of the known interactions within the network of chromatin factors are found along with several novel predictions. Finally, I will present efforts to predict the local 3D structure of chromatin using the fitted interaction model and the locations of bound factors.