Area: Statistical Mechanics and Computational Biology

Miniprojects with Mario Nicodemi & Sach Mukherjee

Project description

- **TITLE: The interaction network of Cis-Regulatory Modules in gene regulation**

Mammalian genes are switched on and off with extraordinary spatial and temporal precision by a remarkably complex set of regulatory mechanisms. In recent work, we have shown, using an ensemble of around 10^6 single-cell measurements, that a key aspect of such regulation - namely, control via DNA sequences called cis-regulatory modules (CRMs) - is far more complex than was previously thought (Vance et al. 2009). In particular, we have uncovered evidence of fascinating, hitherto undiscovered higher-order interactions between CRMs. Understanding the molecular mechanism underlying the dynamical spontaneous organisation of these elements for functional purposes is one of the big challenges in current biology. We are using Statistical Mechanics models to envisage the fundamental principles which produce interactions and gene regulation.

Current model falls short of a true description of the system. Computational simulations of DNA polymers can, in principle, reveal much of what is currently unknown about these systems, and fill the gaps in our knowledge of these CRM-mediated gene regulatory mechanisms. Indeed, in recent work we have exploited precisely these methods to reveal the physical basis of loci interactions on X chromosomes, by investigating the scenario where a molecular bridge is responsible for their colocalization (Scialdone et al. 2008).

The aim of this project is to use advanced computation to develop a similar Stat.Mech. model of CRM-mediated gene regulation. A successful project will help shed light on the precise mechanisms underpinning our striking empirical findings and contribute to understanding the physical basis of a key genomic control system. This mini-project is perfectly suited to become a full PhD research project, but the student will need a solid background in math and computation.

Further readings: K. Vance et al. submitted 2009. A. Scialdone and M. Nicodemi, "Mechanics and dynamics of X-chromosome pairing at X inactivation", **PLoS Comp. Bio.** *5*, e10002444 (2008). M. Nicodemi, B. Panning, A. Prisco, "A thermodynamic switch for chromosome colocalization", **Genetics** *179*, 717 (2008).