Gene Structure Heterogeneity and Loop Extrusion Drive Transcriptional Noise in Human Cells

Transcriptional noise, or heterogeneity, provides phenotypic variation within a cell population, but the molecular basis for this phenomenon is unclear. In this study we use computer simulations based on biophysical principles of genome organisation to simultaneously predict 3D structure and transcriptional output of human chromatin genome-wide. Exploration of this dataset shows that genes can adopt different 3D structures, while influential nodes within a locus control structural diversity and are linked to gene function. Furthermore, structural snapshots from within simulations show that transcription strongly correlates with the formation of protein-mediated microphase separated clusters of promoters and enhancers, and concomitantly transcriptional noise is determined by gene structure heterogeneity and loop extrusion.

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Nick is a group leader at the MRC Human Genetics Unit and is Director of Graduate Research for the Institute of Genetics and Molecular Medicine. He started his career as a PhD student in the biochemistry department at Edinburgh University, before doing a postdoc with Wendy Bickmore. Nick started his lab in the Edinburgh Cancer Research Centre in 2006 with a fellowship from the Wellcome Trust and moved to the Human Genetics Unit in 2012, after obtaining an MRC Senior Fellowship.

Over the last five years his group has focused on two complementary areas of chromatin biology. Firstly, they have collaborated with the Marenduzzo group in physics to develop predictive polymer models of large-scale chromatin structures, i.e. at the level of a gene. These mechanistic models explore parameter space, predict structure, and generate hypotheses, which together provide a framework and order for laboratory-based experiments. Using lab-based experimentation the Gilbert group tested their original models and observed that experimental data did not match the simulations. This suggested there were important additional aspects of chromatin folding that were not incorporated, and created speculation that chromatin fibre flexibility was too rigidly defined, giving rise to a new highly predictive heteromorphic polymer (HiP-HoP) model. Using this approach, they predicted Pax6 gene structures and showed they exhibited significant structural heterogeneity. Furthermore, the HiP-HoP model provides a frame-word to add features to the simulations including additional levels of chromatin folding, further epigenetics marks that describe chromatin fibre properties and, importantly, an ability to incorporate other features such as RNA density. This need has been triggered by the second main area of research where Gilbert has asked what are the molecular mechanisms responsible for regulating chromatin fibre structure. In recent studies he showed that faulty condensin recruitment to chromatin after replication stress leads to aberrant chromosome folding, visible as cytological lesion on chromosomes. But he also showed that nuclear RNA (evidence suggests it is derived from spliced out introns) interacts with proteins in the nucleus to form a concentration dependent nuclear gel. Counter-intuitively he showed that this gel has the ability to decompact chromatin, which simulations indicate is because the gel counteracts the natural tendency of chromatin to collapse in on itself. This is a new idea that will refocus our understanding of how chromatin compaction is regulated and will be further explored in this talk.

Sponsored by the Center for Physical Genomics and Engineering, the Cancer and Physical Sciences Program at the Robert H. Lurie Comprehensive Cancer Center, and NIH Grants T32GM142604 and U54CA268084

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