Expressing geometry

Twenty years ago, many biologists believed in a simple story — that DNA-encoded genetic information controls the development of living organisms, as well as their adaptive responses to the changing environment. Genes determine the proteins that make up the functioning tissues of any cell as well as the signalling molecules; complex gene regulatory networks involving myriad positive and negative feedbacks exert the adaptive control.

Increasingly, this is an outdated story, as the regulation of cell growth and function turns out to rely on a vast range of other mechanisms. During cell division, for example, daughter cells inherit not only the genome, but also the cell type, function and pattern of activity. The burgeoning field of epigenetics studies exactly this — heritable changes in gene expression. The controls come not from the genetic sequence, but from a variety of chemical modifications of DNA and the histone proteins within the chromosomes in which the genome is packed. In all of this, physics plays an important role.

After all, chromatin — the material of the chromosomes — is an extremely large, complex polymer. Its physical behaviour as a polymer links up tightly with a variety of mechanisms of biological control. As Ruggero Cortini and colleagues note in a forthcoming review in *Reviews of Modern Physics* (preprint at http://arxiv.org/abs/1509.04145; 2015), physics may offer useful concepts for elucidating the associated non-genetic mechanisms that evolution uses for exquisite functional control.

Chromatin is a linear chain made of elements called nucleosomes. Each of these units is comprised of a section of helical DNA wrapped around a basic histone core, this being attached to a DNA linker, which serves to connect one nucleosome to the next. The chain carries a net negative charge, which influences its tendency to fold, as do a variety of functional motifs — so-called epigenetic markers — that dress the basic chromatin structure and influence the interactions between different sections of it. Epigenetic markers are, mainly, covalent modifications of either the wrapping DNA or of the core histones. The important point: these modifications persist through cell division and are inherited from one cell to its descendants.

The key challenge of epigenetics is to understand in detail how these epigenetic

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markers influence regulation. As always in biology, the story is complex, with features varying from one species to the next. However, in higher organisms at least, there is a general theme. The way chromatin is packed in the cell nucleus during normal times — that is, not during the phase of cell division — is characterized by a distinct mixture of regions of different density. Denser regions, called heterochromatin, tend to be located near the nuclear periphery and the genes within are largely inactive. In contrast, active genes tend to gather near the nuclear centre, where chromatin — in a more disperse euchromatin phase — is more accessible.

The density difference is all important, as high density effectively excludes genes from being accessed for regulatory control, whereas lower density makes them accessible. Hence, the physics of polymer folding seems to be central to the functional differences between cell types. Biologists refer to the process of chromatin collapse into dense heterochromatin regions as gene silencing, and it's the patterning of epigenetic markers that determines how and when it happens.

As Cortini *et al.* point out, the bulk of epigenetic marks take place on the histones of the chromatin. Crudely speaking, a fairly small number of distinct patterns of markings determine how the polymer folds. Experimental chromatin data from fruit flies, for example, indicates that chromatin structure comes in essentially five distinct 'colours' or qualitative patterns of epigenetic markings. Some colours correspond to non-compact euchromatin, with active, transcribing genes, and others to dense heterochromatin and genetic repression.

On a general level, physicists have made good progress in relating the basic existence of these dense and non-dense areas to the folding physics of such polymers. Indeed, one model of polymer folding views the chromosome as a roughly fractal structure, and neatly produces several generic features of real chromatin structures — the existence of compact and non-compact regions, the general lack of knots in folded chromatin, and a broad power-law dependence of contact probability (the probability of binding) with increasing linear distance along the genomic chain.

More detailed agreement between models and actual data is also becoming possible. For example, using a block copolymer model, a recent study (D. Jost *et al.*, *Nucl. Acids Res.* **42,** 9553–9561; 2014) started by assigning one of the chromatin colours (from fruit flies) to each subregion of the genome, matching these to the pattern of histone marks in that region. They then postulated plausible interaction potentials between elements of the same or different colours, and computed — by folding the polymer computationally — a contact map of the pairwise interactions between genomic segments. Biologists can now measure such data — the pairwise contacts in various organisms and cell types. The computations, with particular parameters, reproduced the experimental results.

In effect, we're learning something about how biology uses geometry for control. One interesting further point coming from physics-based modelling is that evolution appears to have tuned the chromatin polymer near a structural bifurcation point, presumably because this allows more delicate control. During development, for example, even very small signals may be sufficient to knock the system into a different state, initiating an irreversible sequence of further changes.

There is much more to be learned, in particular about the mechanisms that initiate changes in epigenetic markings and then spread them over the chromosome. Moreover, biology seems to have a broad spectrum of topological techniques. For example, DNA is a natural coil, but that coil can coil around itself on a larger scale — and this also seems to influence the affinity of the underlying DNA sequence to specific transcription factors. We're only beginning to see how evolution has exploited three-dimensional space. No doubt it has discovered some tricks that we, as yet, cannot comprehend. ❐

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