Emerging Topics in Life Sciences (2020)
https://doi.org/10.1042/ETLS20200010

Perspective

Chromatin as an active polymeric material

Gautam I. Menon[1,2,3,4]

[1]Departments of Physics and Biology, Ashoka University, Plot No. 2, Rajiv Gandhi Education City, National Capital Region, P.O. Rai, Sonepat 131 029, India; [2]Computational Biology and Theoretical Physics Groups, The Institute of Mathematical Sciences, C.I.T. Campus, Taramani, Chennai 600 013, India; [3]Department of Biological Sciences, Tata Institute of Fundamental Research, Homi Bhabha Road, Colaba, Mumbai 400 005, India; [4]Homi Bhabha National Institute, Training School Complex, Anushaktinagar, Mumbai 400 094, India

Correspondence: Gautam I. Menon (gautam.menon@ashoka.edu.in)

The patterns of the large-scale spatial organization of chromatin in interphase human somatic cells are not random. Such patterns include the radial separation of euchromatin and heterochromatin, the territorial organization of individual chromosomes, the non-random locations of chromosome territories and the differential positioning of the two X chromosomes in female cells. These features of large-scale nuclear architecture follow naturally from the hypothesis that ATP-consuming non-equilibrium processes associated with highly transcribed regions of chromosomes are a source of 'active' forces. These forces are in excess of those that arise from Brownian motion. Simulations of model chromosomes that incorporate such activity recapitulate these features. In addition, they reproduce many other aspects of the spatial organization of chromatin at large scales that are known from experiments. Our results, reviewed here, suggest that the distribution of transcriptional activity across chromosomes underlies many aspects of large-scale nuclear architecture that were hitherto believed to be unrelated.

Introduction

The laws of physics underly all natural phenomena. However, the complexity of biological processes and phenomena usually frustrates attempts to find even qualitatively useful physical explanations of biological observations.

Despite this, properties of biological phenomena at scales beyond purely molecular ones are occasionally amenable to physical intuition. One example is that of allometric scaling, the proportionality between metabolic rate Y and body mass M that is represented by the equation $Y \propto M^b$, with $b \approx 3/4$. This relationship, Kleiber's law, holds for body masses between those of mice and blue whales, a range spanning several orders of magnitude [1]. An attractive explanation of Kleiber's law invokes the properties of the dense physical transport networks that carry nutrients, metabolites and waste products across organisms [2]. This organizing principle could not have been guessed by studying the biology of either mice or elephants independently. It involves ideas from disciplines as diverse as physiology, physics, network science and engineering.

There has been much recent progress in the understanding of the mechanobiology of processes ranging in scale from the single cell (cell adhesion and migration) to groups of cells (the organization of tissues and developmental processes such as gastrulation) [3–7]. All current attempts to model these processes invoke 'activity', the term used for the irreversible local consumption of energy that is at least partially converted into the work that cellular processes must constantly perform. The universal currency of energy in living systems is the ATP molecule. Since the cell maintains ATP concentrations away from thermal equilibrium, energy derived from ATP hydrolysis can be used to perform work. An example is the power stroke of a translational molecular motor's step, where the forward motion of the motor and its cargo is resisted by the viscosity of the surrounding medium. The motor must do work to move, using energy supplied by the hydrolysis of ATP. Such non-equilibrium, active forces are not associated with thermal fluctuations. They are, therefore, unlike Brownian forces, from

Received: 19 June 2020
Revised: 31 July 2020
Accepted: 4 August 2020

Version of Record published:
24 August 2020

Emerging Topics in Life Sciences (2020)
https://doi.org/10.1042/ETLS20200010

which work cannot be extracted in a sustained manner. Activity is thus an irreducible part of what separates living matter from dead matter [3–7]. The field of large-scale nuclear architecture is a natural testing ground for ideas concerning the importance of activity [8].

Chromatin remodelling, transcription and DNA repair are energy-consuming processes that use ATP hydrolysis. This leads to the localised, irreversible consumption of energy at the molecular scale [8–11]. Once a cell enters interphase, its chromosomes must readjust their locations in a cell-type-specific manner, settling into conformations and positions that share many statistical features. These features are largely common across cell types. Such rearrangements must involve physical forces, since they involve the movement of large polymers, many microns in size, across similarly sized regions within the nucleus.

Gene-dense and less compact euchromatin regions have been known for many decades now to be more centrally disposed than gene-poor and more compact heterochromatin [12]. That chromosomes are organized into territories has been known for more than a century. However, chromosome territories are not distributed at random [12–14]. Both gene-density-based as well as chromosome length-based radial positioning schemes have been proposed for individual chromosomes [15–17]. For example, in support of the idea of gene-density-based radial positioning, the gene-rich chromosome 19 tends to be more centrally located in the nucleus than the gene-poor chromosome 18. Also, gene-rich regions within chromosomes are most often found to orient towards the nuclear centre. In female cells, the two X chromosomes (Xi,Xa) are differentially positioned, with the more compact Xi closer to the nuclear envelope than Xa [18,19]. Actively transcribed chromosomes also tend to have rougher and more elliptical territories than less active ones [19–21]. These generic features of the large-scale nuclear architecture are seen across multiple cell types [22]. It is natural to ask whether the effects of activity might be responsible for these remarkable regularities and to specifically explore models that incorporate such activity [8,23].

What should such a model contain? Chromosomes in cell nuclei are, at a biophysical level, highly confined heteropolymers. These polymers move in a crowded, fluid medium filled with constituents of different sizes and physico-chemical properties. Contacts within and between chromosomes give rise to the characteristic contact matrix structure that Hi-C measurements probe at the population level. This information can also be incorporated into polymer models, enabling them to descsribe chromosome structure more realistically [24–36].

Had it not been for the considerations regarding the activity described above, it would have been natural to model chromosomes as being in thermal equilibrium with the environment surrounding them. Indeed, practically all work so far has made precisely this assumption, without questioning whether it should be valid [24,37–41]. However, models that a priori assume that chromosomes are in thermal equilibrium have not yet been shown to exhibit any of the generic features of large-scale nuclear architecture described above. This has been a long-standing problem. The question then pivots to how to best model active processes in the nucleus, if indeed the source of these commonalities is activity.

Recent biophysical approaches suggest that the effects of the activity are best represented in terms of inhomogeneous, stochastic forces that are larger in regions where ATP consumption is larger and are attenuated in regions where it is smaller [3–6]. For our purposes, we may think of this as a local effective temperature that reflects local levels of activity [8,23,42,43]. If we describe each chromosome as a polymer, with each monomer representing a specific section of DNA sequence, different monomers can thus be thought of as experiencing different effective temperatures. These local temperatures correlate to local active processes across the associated piece of chromatin, the logic being that chromatin remodelling, DNA repair and a host of other energy-consuming processes must be enhanced in regions containing highly transcribed genes [8,44].

We choose to model chromosomes in terms of monomers that are each comprised of 1 Mb units, since this is a scale most relevant to chromosome territory formation. We considered local gene density across 1 Mb regions of each chromosome as one proxy for activity and transcriptome-derived levels of gene expression across those regions as another related proxy. We used experimental contact matrix-derived data averaged over the 1 Mb scale to represent contacts between monomers and incorporated other biophysical parameters, such as the density of chromatin, in our description [23]. We then carried out extensive computer simulations of our model, comparing our results to data wherever possible. The model is described in more detail in refs. [8,23,44].

The model

Our simulations model human cells with 23 pairs of chromosomes (diploid, XX) in terms of equivalently sized polymers placed within an impenetrable spherical shell. Each polymer is made up of spherical monomers that

represent consecutive 1 Mb-scale groups of the DNA sequence contained in the chromosome being modelled. The interaction between neighbouring monomers is the finitely extensible non-linear elastic (FENE) potential. Monomers interact with (non-neighbouring) monomers via a soft-core potential — the polymers are self-repelling but not self-avoiding [45]. A different 'effective' temperature T_i is associated to each monomer, reflecting its local level of activity in interphase.

In the gene density model, the gene content of each 1 Mb region, obtained from GENCODE, [46] is mapped to an active temperature. Monomers containing many genes which fall below a preset cutoff are 'inactive' or 'passive'. They are assigned the physiological temperature $T = T_{ph} \simeq 310\ K$. Monomers with a larger number of associated genes are 'active' and assigned $T_a = 20T_{ph}$. For the gene expression model, we infer activity using transcriptome data obtained from processed RNA-seq output, assigning the most active monomers a temperature of $12T_{ph}$ [47]. We do this for five different cell types. For the 'combined' model, we use the same temperature assignments as for the gene expression model but, in addition, take the top 5% of monomers by gene density as inferred from GENCODE and promote them to have the maximum active temperature. The actual magnitudes of these choices is largely irrelevant. What really matters is that active and passive monomers have different active temperatures.

To model chromosome structure we use Hi-C data on each of the cell types we consider, representing the effects of the strongest contacts in terms of permanent connections between the contacting monomers. We refer to such contacts as 'loops' for this reason. For the GM12878 cell type, we incorporate 27 super-loops only for the inactive chromosome (Xi), taking the associated data from ref. [48]. We employ the widely used LAMMPS code, implementing Brownian dynamics, in our simulations [49].

We calculate $S_i(R) = 4\pi R^2\ P_i(R)$, where $P_i(R)\ dR$ is proportional to the probability of finding a monomer of chromosome i at a radial vector R from the origin. For a uniform distribution, $S_i(R) = 4\pi R^2$ so any deviation from that simple result must indicate a preference for a special radial location over another. We compute the averaged three-dimensional shapes of chromosome territories, both in three dimensions as well as their shapes projected into two dimensions. We calculate the volume asphericity and prolateness of chromosome territories as well as the ellipticity and regularity of the two-dimensional projections of these territories. Since our simulations provide us a series of snapshots, in steady-state, of the configurations of all our simulated chromosomes, all large-scale structural features can be calculated from these. In addition, with a suitable mapping of time-scales, we can address questions of the dynamics of changes in chromosome configuration and positioning.

Results

Our simulations recover the territorial organization of chromosomes, as shown in Figure 1A. (These results are reported for the combined model discussed above. Our results for the other related models are similar.) The radial variation of the averaged effective temperature is shown in Figure 1B. It mirrors the variation of gene density between the centre of the simulated nucleus and its periphery, as shown in Figure 1C, representing the spatial separation of outer heterochromatin and inner euchromatin regions. A central consequence of our model is that gene expression should correlate to a larger strength of activity, and that the distribution of both these quantities should be attenuated towards the boundaries of the nucleus. The simulation results of Figure 1B,C illustrate this.

As was the case for Kleiber's law, this is emergent behaviour, in this case, attributable to the combination of differential activity and confinement. In practice, this is further complicated by the fact that chromosomes have different lengths and different extents of compaction as a consequence of chromosome-dependent contact structure. All these features are included in our model.

Chromosome-specific distribution functions $S(R)$ are obtained experimentally using confocal slices of FISH images from an ensemble of fixed nuclei. Our computed $S(R)$ for the gene-poor chromosome 18 and the gene-rich chromosome 19 in the GM12878 cell type are compared, in Figure 1D, with experimental results from ref. [50]. (These chromosomes have comparable lengths but differ in gene density by a factor of about 4.) The $S(R)$ for chromosomes 18 and 19 exhibit well-separated peaks. For comparison, the $R2$ rise of $S(R)$ towards the nuclear envelope, expected if the distribution of chromosomes were random, is shown in magenta, specified as 'Random' in the legend of the subfigure. Comparisons with experimentally derived distribution functions for chromosomes 12 and 20, chosen because they have comparable gene densities but different lengths, also yield consistent results. Figure 1E, displays 2d FISH data for chromosome regularity and ellipticity, from ref. [51], compared with predictions from our simulations. The simulations and experimental data track each other, with

Emerging Topics in Life Sciences (2020)
https://doi.org/10.1042/ETLS20200010

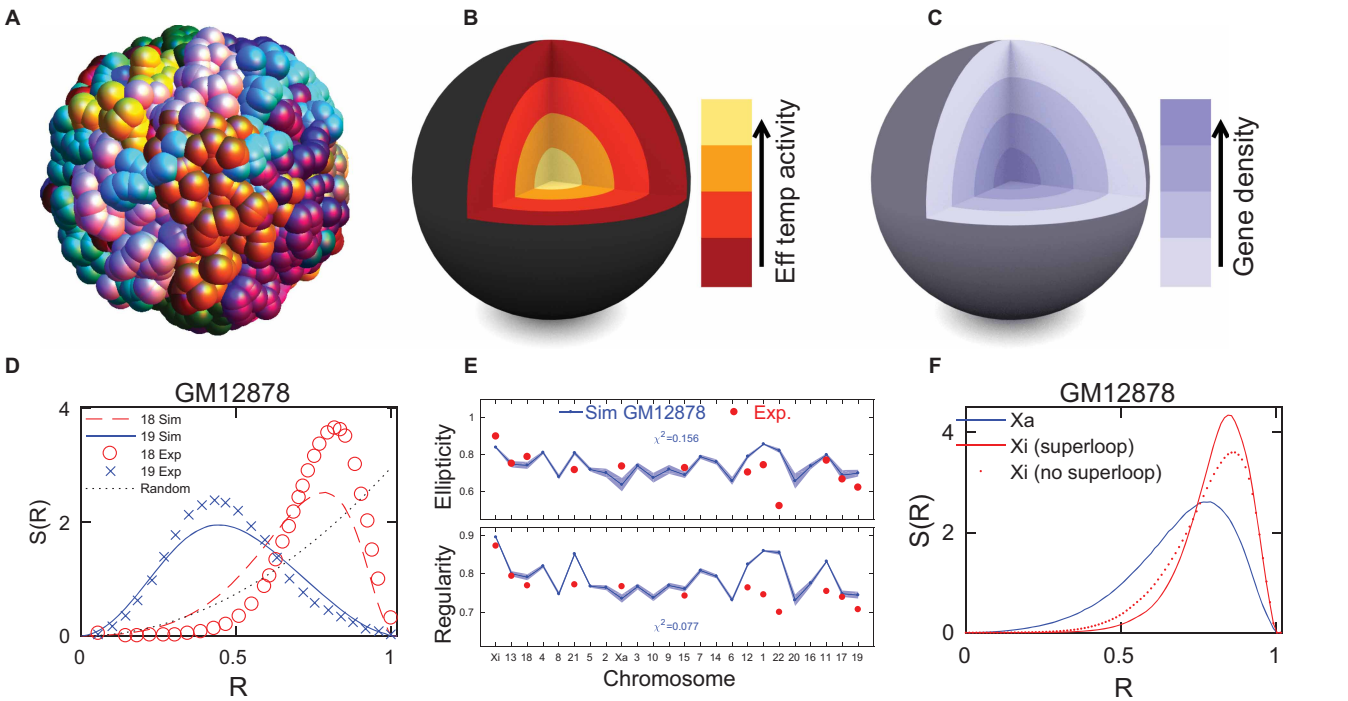

Figure 1. A summary of model results, modified from figures originally presented in Ref. [23] and reproduced with permission.
(**A**) Snapshot of simulation configurations of 23 pairs of model chromosomes within a spherical nucleus. Each bead represents a 1 Mb section of genome associated with a specific chromosome. (**B**) A cutaway sphere representation of average effective temperatures within the simulated nucleus, in a model representing the GM12878 cell type. (**C**) A cutaway sphere representation of the average gene density within the simulated nucleus, in a model for the GM12878 cell type. This illustrates the excess in gene density seen towards the centre of the nucleus in comparison with the gene density in the nuclear periphery. (**D**) Distribution of monomer density $S(R)$, reflecting the local density of DNA, for chromosomes 18 and 19 (red (dashed) and blue (smooth) lines, respectively) in our model for the GM12878 cell type. Experimental data obtained from ref. [50] for this cell type is plotted together with the simulation predictions, (red ovals: Chr 18, blue crosses: Chr 19). If chromosomes are distributed randomly across the nucleus, $S(R)$ $R2$ is expected, as shown in the magenta (dotted) line. (**E**) Ellipticity and regularity for each chromosome as predicted by the model and obtained from simulations representing the GM12878 (blue) and IMR90(green) cell types. These are compared with experimental data (red ovals) from 2d FISH experiments ref. [51] for a cell type closely related to the IMR90 cell type. Ellipticity values of 1 represent a perfect elliptical chromosome and regularity values of 1 refer to a perfectly regular chromosome, without roughness. The x-axis is in order of increasing gene density. (**F**) Monomer density distribution $S(R)$ vs. R, for the Xi and Xa chromosome for the GM12878 cell type. The inactive X chromosome, Xi, is shown in red (solid or dotted line) and the active X chromosome, Xa, is shown with a blue dashed line. (Loops on the Xi in the GM12878 cell type can include (red solid line) or exclude (red dotted line) 'superloops' as seen in recent experiments ref. [48,52].).

the simulations finding the same dip, and subsequent rise, of both ellipticity and regularity around chromosome 22.

The X chromosomes in female cells within interphase have consistently been found to be differentially positioned. The inactive X chromosome Xi is usually found towards the periphery of the nucleus [19]. This contrasts to the more central disposition of the active X chromosome Xa. Our model recovers this remarkable feature, as shown in Figure 1F. Incorporation of the recently discovered super-loop structure of Xi alters the distribution slightly, but does not affect the relative positioning of these chromosomes.

These results, together with many others, were first presented in refs. [8,23], where they are described in more detail.

Conclusions

We began by noting that large-scale nuclear architecture in higher eukaryotes exhibited many striking regularities. These regularities are apparent at scales that are much larger than molecular scales but still smaller than

the size of the cell. This scale does not fit comfortably into what we think of as either conventionally biological or physical regimes.

To describe biological phenomena at this intermediate scale, it is important to use cell-type-specific biological input. However, it is just as important to transform this input so it can be incorporated into physics-based methodologies appropriate to that scale. (The choice of a scale of description is a choice we usually make automatically. For example, we avoid discussions of quarks when discussing B-DNA and speaking of carbon atoms makes no sense when discussing Kleiber's law.) Our choice of biophysical model was also dictated by the need to render our calculations tractable while remaining sensitive to the details of the underlying biological system. Our biophysical model for large-scale nuclear architecture thus treads the delicate line between being respectful of the biological complexity on the one hand and retaining the simplicity that is the most useful aspect of a physical description on the other.

We stressed the importance of non-equilibrium effects, arising from local transcriptional activity, for a biophysical description, proposing that the magnitude of active processes should increase as local transcription levels increased. Levels of transcription were translated into an effective temperature seen by each monomer in our polymer model of chromosomes.

We then performed simulations of these confined polymers, with properties chosen to reflect generic biophysical aspects of chromosomes. The monomers in our simulation represented 1 Mb sections of chromosomes, although we could have defined our model at the smaller scales of 0.1 or even 0.01 Mb without a problem. Inhomogeneous activity across the length of the chromosome provides a 'fingerprint' for each chromosome. This fingerprint at least partially encodes the statistics of its positioning. If we did not account for inhomogeneous activity we would have obtained unstructured distributions for the chromosome gene density and none of the results we highlighted as evidence for non-random organization of chromatin at large scales would have been obtained.

A central prediction of our work, one that distinguishes it from other approaches to large-scale nuclear architecture, is that there should be a gradient of ATP consumption, and thus a gradient of active forces, between the cell nucleus and its periphery. Since ATP is a small, labile molecule with a large diffusion constant, a priori it might have been expected to be uniformly distributed across the nucleus. Any gradient in ATP consumption can thus only come from the fact that ATP turnover occurs inhomogeneously between nuclear centre and periphery. It would be interesting to see if this simple prediction could be checked in experiments.

Some lines of our ongoing work include the following: following DNA damage through chemotherapy agents such as cisplatin, chromatin decondenses, chromosome mobility increases and chromosome positions change [53]. However, at longer times, as DNA damage repair proceeds, chromosomes recover the distributions that existed prior to the damage event [54]. This bolsters the idea that transcription programs are connected to positioning and that changes in these programs have predictable consequences for changes in positioning. These are aspects that our model is well-equipped to explore and our preliminary results are consistent with what is observed in experiments. The nuclear lamina, a complex network of lamins and lamin-associated proteins, lines the nuclear envelope. It couples to lamin-associated domains on chromosomes in regions that are typically associated with repressive compartments [55]. These specific interactions of chromosomes with the nuclear envelope conjoins the 'bulk' effects that our model describes with cell-type-specific 'surface' effects governed by this binding. Our preliminary results suggest that incorporating interactions with the nuclear envelope helps to favour specific patterns of chromosome organization over others.

Phase separation has emerged as an fascinating paradigm for how cells and nuclei might create localized reaction compartments within them that need not be membrane-bound [56]. These compartments can be enriched in specific biochemical components. This then allows reactions within them to take place far more efficiently than in the well-mixed case [57,58]. It has been suggested that DNA loops originating in different chromosomes might colocalize in such compartments, leading to the co-expression of sets of genes associated with specific genetic programs [59]. Activity-based chromosome positioning, as described here, should underly the preference of specific chromosomes to be spatially proximate, enhancing the probability of such interactions. Variations in the activity-induced positioning of chromosomes are known to be specific to cell type; in our calculations, these variations can be subtle but are nonetheless present. These ideas might thus add a layer of additional information to the phase-separation paradigm in the context of nuclear organization.

We conclude by reproducing verbatim the concluding lines of ref. [23], since we have not found a way to phrase them better: 'If such biophysical approaches have any truth to them, they indicate that a small set of initial model assumptions, argued for on general grounds, must yield consistent explanations and descriptions

Emerging Topics in Life Sciences (2020)
https://doi.org/10.1042/ETLS20200010

for all data, not just those the model abstracts in its construction. The advantage of simple models is that they enable us to concentrate on underlying principles that are often obscured by the complexity of real data, including intrinsic heterogeneities across cell populations, varied experimental and analysis procedures and the lack of sufficient statistics in some cases. Prior models for nuclear architecture in mammalian cells fail to reproduce many general attributes of nuclear architecture known from the experiment. These properties — certainly their important trends — are emergent in our calculations, since they were not directly encoded in our model specification. This suggests that our methodologies provide hitherto unavailable biophysical insights into the determinants of large-scale nuclear architecture in metazoans.'

Summary

- Several common features of large-scale nuclear architecture have been known for a while but have lacked explanation
- A model for large-scale nuclear architecture that incorporates non-equilibrium activity is described
- Inhomogeneous activity and looping patterns underlie celltype-specific features of such architecture
- Simulations of the model recapitulate many known features of nuclear architecture and predict new ones.

Competing Interests
The author declares that there are no competing interests associated with this manuscript.

Funding
The author declares that there are no sources of funding to be acknowledged.

Acknowledgements
The work reviewed here was done in collaboration with Ankit Agrawal, Nirmalendu Ganai and Surajit Sengupta. We acknowledge the use of the Annapurna cluster at IMSc.

Abbreviations
FENE, finitely-extensible non-linear elastic.

References

1 Kleiber, M. (1947) Body size and metabolic rate. *Physiol. Rev.* **27**, 511–541 https://doi.org/10.1152/physrev.1947.27.4.511
2 West, G.B., Brown, J.H. and Enquist, B.J. (1997) A general model for the origin of allometric scaling laws in biology. *Science* **276**, 122–126 https://doi.org/10.1126/science.276.5309.122
3 Menon, G.I. (2010). Active matter. In *Rheology of Complex Fluids*, Springer, New York, NY, pp. 193–218
4 Prost, J., Jülicher, F. and Joanny, J.-F. (2015) Active gel physics. *Nat. Phys.* **11**, 111 https://doi.org/10.1038/nphys3224
5 Marchetti, M.C., Joanny, J., Ramaswamy, S., Liverpool, T., Prost, J., Rao, M. et al. (2013) Hydrodynamics of soft active matter. *Rev. Mod. Phys.* **85**, 1143 https://doi.org/10.1103/RevModPhys.85.1143
6 Needleman, D. and Dogic, Z. (2017) Active matter at the interface between materials science and cell biology. *Nat. Rev. Mater.* **2**, 17048 https://doi.org/10.1038/natrevmats.2017.48
7 Gross, P., Kumar, K.V. and Grill, S.W. (2017) How active mechanics and regulatory biochemistry com- bine to form patterns in development. *Ann. Rev. Biophys.* **46**, 337–356 https://doi.org/10.1146/annurev-biophys-070816-033602
8 Ganai, N., Sengupta, S. and Menon, G.I. (2014) Chromosome positioning from activity-based segregation. *Nucleic Acids Res.* **42**, 4145–4159 https://doi.org/10.1093/nar/gkt1417
9 Weber, S.C., Spakowitz, A.J. and Theriot, J.A. (2012) Nonthermal ATP-dependent fluctuations contribute to the in vivo motion of chromosomal loci. *Proc. Natl. Acad. Sci. U.S.A.* **109**, 7338–7343 https://doi.org/10.1073/pnas.1119505109
10 Zidovska, A., Weitz, D.A. and Mitchison, T.J. (2013) Micron-scale coherence in interphase chromatin dynamics. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 15555–15560 https://doi.org/10.1073/pnas.1220313110

11 Chu, F.-Y., Haley, S.C. and Zidovska, A. (2017) On the origin of shape fluctuations of the cell nucleus. *Proc. Natl. Acad. Sci. U.S.A.* **114**, 10338–10343 https://doi.org/10.1073/pnas.1702226114
12 Cremer, T. and Cremer, M. (2010) Chromosome territories. *Cold Spring Harb. Perspect. Biol.* **2**, a003889 https://doi.org/10.1101/cshperspect.a003889
13 Meaburn, K.J. and Misteli, T. (2007) Cell biology: chromosome territories. *Nature* **445**, 379–781 https://doi.org/10.1038/445379a
14 Bickmore, W.A. and van Steensel, B. (2013) Genome architecture: domain organization of interphase chromosomes. *Cell* **152**, 1270–1284 https://doi.org/10.1016/j.cell.2013.02.001
15 Takizawa, T., Meaburn, K.J. and Misteli, T. (2008) The meaning of gene positioning. *Cell* **135**, 9–13 https://doi.org/10.1016/j.cell.2008.09.026
16 Croft, J.A., Bridger, J.M., Boyle, S., Perry, P., Teague, P. and Bickmore, W.A. (1999) Differences in the localization and morphology of chromosomes in the human nucleus. *J. Cell Biol* **145**, 1119–1131 https://doi.org/10.1083/jcb.145.6.1119
17 Boyle, S., Gilchrist, S., Bridger, J.M., Mahy, N.L., Ellis, J.A. and Bickmore, W.A. (2001) The spatial organization of human chromosomes within the nuclei of normal and emerin-mutant cells. *Hum. Mol. Genet.* **10**, 211–219 https://doi.org/10.1093/hmg/10.3.211
18 Dyer, K., Canfield, T. and Gartler, S. (1989) Molecular cytological differentiation of active from inactive X domains in interphase: implications for X chromosome inactivation. *Cytogenet. Genome Res.* **50**, 116–120 https://doi.org/10.1159/000132736
19 Jégu, T., Aeby, E. and Lee, J.T. (2017) The X chromosome in space. *Nat. Rev. Genet.* **18**, 377–389 https://doi.org/10.1038/nrg.2017.17
20 Eils, R., Dietzel, S., Bertin, E., Schröck, E., Speicher, M.R., Ried, T. et al. (1996) Three-dimensional reconstruction of painted human interphase chromosomes: active and inactive X chromosome territories have similar volumes but differ in shape and surface structure. *J. Cell Biol.* **135**, 1427–1440 https://doi.org/10.1083/jcb.135.6.1427
21 Berezney, R., Malyavantham, K.S., Pliss, A., Bhattacharya, S. and Acharya, R. (2005) Spatio-temporal dynamics of genomic organization and function in the mammalian cell nucleus. *Adv. Enzyme Regul.* **45**, 17–26 https://doi.org/10.1016/j.advenzreg.2005.02.013
22 Bickmore, W.A. (2013) The spatial organization of the human genome. *Annu. Rev. Genom. Hum. Gente.* **14**, 67–84 https://doi.org/10.1146/annurev-genom-091212-153515
23 Agrawal, A., Ganai, N., Sengupta, S. and Menon, G.I. (2020) Nonequilibrium biophysical processes influence the large-scale architecture of the cell nucleus. *Biophys. J.* **118**, 2229–2244 https://doi.org/10.1016/j.bpj.2019.11.017
24 Imakaev, M.V., Fudenberg, G. and Mirny, L.A. (2015) Modeling chromosomes: Beyond pretty pictures. *FEBS Lett.* **589**, 3031–3036 https://doi.org/10.1016/j.febslet.2015.09.004
25 Amitai, A. and Holcman, D. (2017) Polymer physics of nuclear organization and function. *Phys. Rep.* **678**, 1–83 https://doi.org/10.1016/j.physrep.2017.02.002
26 Tjong, H., Li, W., Kalhor, R., Dai, C., Hao, S., Gong, K. et al. (2016) Population- based 3D genome structure analysis reveals driving forces in spatial genome organization. *Proc. Natl. Acad. Sci. U.S.A.* **113**, E1663–E1672 https://doi.org/10.1073/pnas.1512577113
27 Odenheimer, J., Kreth, G. and Heermann, D.W. (2005) Dynamic simulation of active/inactive chromatin domains. *J. Biol. Phys.* **31**, 351–363 https://doi.org/10.1007/s10867-005-7286-3
28 Jost, D., Carrivain, P., Cavalli, G. and Vaillant, C. (2014) Modeling epigenome folding: formation and dynamics of topologically associated chromatin domains. *Nucleic Acids Res.* **42**, 9553–9561 https://doi.org/10.1093/nar/gku698
29 Jost, D., Vaillant, C. and Meister, P. (2017) Coupling 1D modifications and 3D nuclear organization: data, models and function. *Curr. Opin. Cell Biol.* **44**, 20–27 https://doi.org/10.1016/j.ceb.2016.12.001
30 Chiariello, A.M., Bianco, S., Piccolo, A., Annunziatella, C., Barbieri, M., Pombo, A. et al. (2015) Polymer models of the organization of chromosomes in the nucleus of cells. *Mod. Phys. Lett. B* **29**, 1530003 https://doi.org/10.1142/S0217984915300033
31 Haddad, N., Jost, D. and Vaillant, C. (2017) Perspectives: using polymer modeling to understand the formation and function of nuclear compartments. *Chromosome Res.* **25**, 35–50 https://doi.org/10.1007/s10577-016-9548-2
32 Ghosh, S.K. and Jost, D. (2018) How epigenome drives chromatin folding and dynamics, insights from efficient coarse-grained models of chromosomes. *PLoS Comput. Biol.* **14**, e1006159 https://doi.org/10.1371/journal.pcbi.1006159
33 Zhang, B. and Wolynes, P.G. (2017) Genomic energy landscapes. *Biophys. J.* **112**, 427–433 https://doi.org/10.1016/j.bpj.2016.08.046
34 Tiana, G., Amitai, A., Pollex, T., Piolot, T., Holcman, D., Heard, E. et al. (2016) Structural fluctuations of the chromatin fiber within topologically associating domains. *Biophys. J.* **110**, 1234–1245 https://doi.org/10.1016/j.bpj.2016.02.003
35 Di Pierro, M., Zhang, B., Aiden, E.L., Wolynes, P.G. and Onuchic, J.N. (2016) Transferable model for chromosome architecture. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 12168–12173 https://doi.org/10.1073/pnas.1613607113
36 Di Pierro, M., Cheng, R.R., Aiden, E.L., Wolynes, P.G. and Onuchic, J.N. (2017) De novo prediction of human chromosome structures: Epigenetic marking patterns encode genome architecture. *Proc. Natl. Acad. Sci. U.S.A.* **114**, 12126–12131 https://doi.org/10.1073/pnas.1714980114
37 Cook, P.R. and Marenduzzo, D. (2009) Entropic organization of interphase chromosomes. *J. Cell Biol.* **186**, 825–834 https://doi.org/10.1083/jcb.200903083
38 Tark-Dame, M., van Driel, R. and Heermann, D.W. (2011) Chromatin folding–from biology to polymer models and back. *J. Cell Sci.* **124**, 839–845 https://doi.org/10.1242/jcs.077628
39 Marti-Renom, M.A. and Mirny, L.A. (2011) Bridging the resolution gap in structural modeling of 3D genome organization. *PLoS Comput. Biol.* **7**, e1002125 https://doi.org/10.1371/journal.pcbi.1002125
40 Heermann, D.W., Jerabek, H., Liu, L. and Li, Y. (2012) A model for the 3D chromatin architecture of pro and eukaryotes. *Methods* **58**, 307–314 https://doi.org/10.1016/j.ymeth.2012.04.010
41 Vasquez, P.A. and Bloom, K. (2014) Polymer models of interphase chromosomes. *Nucleus* **5**, 376–390 https://doi.org/10.4161/nucl.36275
42 Fodor, É., Guo, M., Gov, N., Visco, P., Weitz, D. and van Wijland, F. (2015) Activity-driven fluctuations in living cells. *Europhys. Lett.* **110**, 48005 https://doi.org/10.1209/0295-5075/110/48005
43 Hameed, F.M., Rao, M. and Shivashankar, G. (2012) Dynamics of passive and active particles in the cell nucleus. *PLoS One* **7**, e45843 https://doi.org/10.1371/journal.pone.0045843
44 Agrawal, A., Ganai, N., Sengupta, S. and Menon, G.I. (2017) Chromatin as active matter. *J. Stat. Mech. Theory Exp.* **2017**, 014001 https://doi.org/10.1088/1742-5468/aa5287
45 Stillinger, F.H. (1976) Phase transitions in the Gaussian core system. *J. Chem. Phys.* **65**, 3968–3974 https://doi.org/10.1063/1.432891

46 Harrow, J., Frankish, A., Gonzalez, J.M., Tapanari, E., Diekhans, M., Kokocinski, F. et al. (2012) GENCODE: the reference human genome annotation for The ENCODE project. *Genome Res.* **22**, 1760–1774 https://doi.org/10.1101/gr.135350.111

47 Dunham, I., Birney, E., Lajoie, B.R., Sanyal, A., Dong, X., Greven, M. et al. (2012) An integrated encyclopedia of DNA elements in the human genome. *Nature* **489**, 57–74 https://doi.org/10.1038/nature11247

48 Rao, S.S., Huntley, M.H., Durand, N.C., Stamenova, E.K., Bochkov, I.D. and Robinson, J.T. (2014) A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping. *Cell* **159**, 1665–1680 https://doi.org/10.1016/j.cell.2014.11.021

49 Plimpton, S., Crozier, P. and Thompson, A. (2007) LAMMPS-large-scale atomic/molecular massively parallel simulator. *Sandia National Laboratories* **18**, 43 [https://lammps.sandia.gov/]

50 Kreth, G., Finsterle, J., Von Hase, J., Cremer, M. and Cremer, C. (2004) Radial arrangement of chromosome territories in human cell nuclei: a computer model approach based on gene density indicates a probabilistic global positioning code. *Biophys. J.* **86**, 2803–2812 https://doi.org/10.1016/S0006-3495(04)74333-7

51 Sehgal, N., Fritz, A.J., Morris, K., Torres, I., Chen, Z., Xu, J. et al. (2014) Gene density and chromosome territory shape. *Chromosoma* **123**, 499–513 https://doi.org/10.1007/s00412-014-0480-y

52 Darrow, E.M., Huntley, M.H., Dudchenko, O., Stamenova, E.K., Durand, N.C., Sun, Z. et al. (2016) Deletion of DXZ4 on the human inactive X chromosome alters higher-order genome architecture. *Proc. Natl. Acad. Sci. U.S.A.* **113**, E4504–E4512 https://doi.org/10.1073/pnas.1609643113

53 Hauer, M.H. and Gasser, S.M. (2017) Chromatin and nucleosome dynamics in DNA damage and repair. *Genes Dev.* **31**, 2204–2221 https://doi.org/10.1101/gad.307702.117

54 Mehta, I.S., Kulashreshtha, M., Chakraborty, S., Kolthur-Seetharam, U. and Rao, B.J. (2013) Chromosome terri- tories reposition during DNA damage-repair response. *Genome Biol.* **14**, R135 https://doi.org/10.1186/gb-2013-14-12-r135

55 Reddy, K.L., Zullo, J., Bertolino, E. and Singh, H. (2008) Transcriptional repression mediated by repositioning of genes to the nuclear lamina. *Nature* **452**, 243–247 https://doi.org/10.1038/nature06727

56 Peng, A. and Weber, S.C. et al. (2019) Evidence for and against liquid–liquid phase separation in the nucleus. *Non-Coding RNA* **5**, 50 https://doi.org/10.3390/ncrna5040050

57 Strom, A.R. and Brangwynne, C.P. (2019) The liquid nucleome-phase transitions in the nucleus at a glance. *J. Cell Sci.* **132** https://doi.org/10.1242/jcs.235093

58 Berry, J., Brangwynne, C.P. and Haataja, M. (2018) Physical principles of intracellular organization via active and passive phase transitions. *Rep. Prog. Phys.* **81**, 046601 https://doi.org/10.1088/1361-6633/aaa61e

59 Mir, M., Bickmore, W., Furlong, E.E.M. and Narlikar, G. (2019) Chromatin topology, condensates and gene regulation: shifting paradigms or just a phase? *Development* **146**, dev182766 https://doi.org/10.1242/dev.182766