The nucleus of a eukaryotic cell is a nonequilibrium system where chromatin is subjected to active processes that continuously rearrange it over the cell’s life cycle. Tracking the motion of chromosomal loci provides information about the organization of the genome and the physical processes shaping that organization. Optical experiments report that loci move with subdiffusive dynamics and that there is spatially coherent motion of the chromatin. We recently showed that it is possible to predict the 3D architecture of genomes through a physical model for chromosomes that accounts for the biochemical interactions mediated by proteins and regulated by epigenetic markers through a transferable energy landscape. Here, we study the temporal dynamics generated by this quasi-equilibrium energy landscape assuming Langevin dynamics at an effective temperature. Using molecular dynamics simulations of two interacting human chromosomes, we show that the very same interactions that account for genome architecture naturally reproduce the spatial coherence, viscoelasticity, and the subdiffusive behavior of the motion in interphase chromosomes as observed in numerous experiments. The agreement between theory and experiments suggests that even if active processes are involved, an effective quasi-equilibrium landscape model can largely mimic their dynamical effects.

Significance

Several active processes operate on eukaryotic genomes, dictating their three-dimensional arrangement and dynamical properties. The combination of structural organization and dynamics is essential to the proper functioning of the cell. We show that an effective energy landscape model for chromatin provides a unifying description of both the structural and dynamical aspects of the genome, recapitulating many of its features. Using this quasi-equilibrium energy landscape model, we demonstrate that the physical interactions accounting for genome architecture also lead to the nontrivial dynamical behavior of genomes previously described in multiple experimental observations.
also exist, however, strong intrachromosomal contacts in the absence of CTCF or cohesin as well as strong interchromosomal contacts (referred to as “links”) associated with the presence of superenhancers and bound transcription factors (15). Another key feature of chromatin architecture, in our view, is the tendency of chromatin to exhibit liquid crystalline order, a tendency that becomes dominant in the metaphase chromosome (12, 16, 17). In addition to these features chromatin turns out to be compartmentalized (13).

A model for chromatin folding [the minimal chromatin model or MiChroM (12)] that incorporates all of these features argues that compartmentalization arises from microphase separation of chromatin segments having different biochemical properties. Quantifying the correlations between compartmentalization and epigenetic markings leads to a predictive energy landscape with transferable interactions. The interactions between locally encoded types of chromatin turn out to be sufficient to predict the specific patterns of compartmentalization in genomes (18).

Together with the compartmentalization of chromosomes coming from contact interactions, MiChroM also regards the local structure of the chromatin polymer and the CTFC-mediated looping interactions as coming from direct interactions in space that ultimately are mediated by proteins, about whose identity and activity the model remains however agnostic. The quasi-equilibrium effective landscape theory for genome structural organization (19) provided by MiChroM generates 3D chromosomal structural ensembles, whose contact maps agree in detail with those found by ligation assays (Hi-C). The ensembles also are consistent with the results from fluorescence in situ hybridization (FISH) studies that mark locations in 3D space (18).

In MiChroM the genome architecture (in interphase) is encoded in the one-dimensional sequence of epigenetic markings and loops much as 3D protein structures are determined by their 1D sequence of amino acids and by the position of disulfide bonds (Fig. 14). In contrast to the situation for proteins, however, the sequence code provided by the epigenetic marks is not fixed but is dynamically rewritten during cell differentiation, modulating both the 3D structure and gene expression in different cell types. Under the regulation of the epigenetic markings, proteins act to generate the quasi-equilibrium energy landscape shaping the genomic conformational ensemble. In this ensemble, some contacts are transient and short-lived, like the ones leading to compartmentalization, while others, like those related to CTFC for example, are strong and long lasting. In the latter case, experimental data indicate lifetimes that span from minutes to tens of hours (20).

Here, we revisit the results of several experimental observations regarding chromatin dynamics in the light of the quasi-equilibrium landscape theory for genome structural organization outlined above. The simulations of the energy landscape of chromosomes, in addition to recapitulating their structural ensembles, turn out to reproduce also the main dynamical observations: anomalous diffusion, viscoelasticity, and spatially coherent dynamics.

Subdiffusivity and Viscoelasticity

The transport of individual biomolecules is usually modeled as occurring through Brownian diffusion. Ordinary diffusion of a single particle leads to ergodic, self-similar trajectories in which the mean-square displacement shows linear scaling with the time $r$ over which the displacement is observed ($<(r(t + \tau) - r(t))^2$) $\sim \tau$). Multiple experiments on chromatin dynamics, however, report significant deviations from the simple one-particle diffusive behavior. In mammalian cells, Bronstein et al. (2) found that the motion of telomeres is initially subdiffusive with mean-square displacement scaling as $r^\alpha$ with the rather small exponent $\alpha = 0.3$ for much of the observed time course. Only in the long time limit do the displacements begin to transition into a regime describable as normal diffusion. In bacterial cells, the trajectories in the experiments from Weber et al. (9) gave an $\alpha$ exponent of about 0.4. Depleting the ATP of the cell slows down active processes and significantly reduces the diffusion constant but apparently leaves unchanged the subdiffusive scaling, suggesting that ATP-dependent enzymatic activity somehow contributes to molecular agitation but is not the origin of the subdiffusive nature of the displacements (1).

The connectivity of the chromosomal polymer chain reduces the amount of space explored by the monomers composing the biopolymer and could therefore be one of the causes of the subdiffusive behavior. Several models of polymer dynamics do indeed give rise to subdiffusive behavior. de Gennes’s reptation model of chains confined in tubes predicts very slow diffusion with a scaling exponent $\alpha = 0.25$, while freely connected chain diffusion in the Rouse model leads to $\alpha = 0.5$, and when the hydrodynamic streaming is accounted for by Zimm’s model yields an exponent $\alpha = 0.67$.

The anomalous diffusion of genomic loci has also been variously ascribed to the viscoelastic nature of medium surrounding the chromosomes, the transient binding/unbinding of proteins, and to obstructed diffusion. Likely, all of these factors may operate in the nucleus of eukaryotic cell. Phenomenological descriptions to account for such effects include fractional Brownian motion, continuous time random walks, and obstructed diffusion models (2, 6, 7). These phenomenological models can describe the motions of...
individual tracked particles but cannot describe the spatial structure or coherence of the motions. The high-dimensional energy landscape encoded in the MiChroM contains elements of all these qualitative phenomena. The MiChroM landscape, by being polymeric, includes chain connectivity, but also encodes the structural effects of transient binding of proteins and the obstructed diffusion of loci due to steric interactions of one part of the chain with other parts. Transient binding of proteins determines the number and the strength of the protein-mediated cross-links, which affect the diffusion of individual loci. Bronstein et al. (21) found that depleting protein lamin A leads to much faster diffusion. While Lamin A is not explicitly accounted for in the MiChroM landscape, the intensity of cross-linking present in MiChroM is determined by the thermodynamical interpretation of the in situ structural data provided by Hi-C and therefore to some extent may include also the effect of this specific protein.

In this paper we focus on simulating the dynamics of chromosomes 17 and 18 of human lymphoblastoid cells. These simulations employ dynamics generated by a Langevin equation for the chain moving on the MiChroM energy landscape. No large steps, as might arise from far from equilibrium motors, are allowed in the algorithm. Such steps could give rise to active flows (22).

As already observed in ref. 12, the intrachromosomal contact maps obtained by these simulations closely reproduce the maps obtained from the DNA–DNA ligation assays (14), indicating that the structural ensemble of the chromosomes is reasonably well reproduced (Fig. 1B). The 3D structural ensemble exhibits phase separation of chromatin structural types that extends to both chromosomes, creating regions of space occupied by one single chromatin type but coming from both chromosomes (Fig. 1C). We also found that, despite there being extensive spatial contacts between the chromosomes, distinct chromosomes themselves do not become topologically entangled with one another; instead, the landscape leads to the formation of nonoverlapping chromosome territories (Fig. 1C).

The quasi-equilibrium Langevin simulations lead to a scaling exponent of 0.29 for the mean-square displacement of the telomeres in 3D space (Fig. 2). This exponent value is consistent with the experimental results reported by Bronstein et al. (2) for other human cells (osteosarcoma cell line U2OS) (Fig. 2). The velocity autocorrelation functions \( C_{v}(t) = \langle v(t + r) \cdot v(t) \rangle \) with \( v(t) = 1/\delta (r(t + r) - r(t)) \) obtained from the simulations reveal a negative correlation at characteristic relaxation time scales (23). We see the chromosome behaves as if it were viscoelastic (Fig. 3A). Identical viscoelastic behavior was observed in vivo by Lucas et al. (3) in mammalian cells. The simulated velocity autocorrelation functions measured for different time lags, when rescaled by the corresponding time lag \( \delta \), all collapse to a universal curve, indicating self-similarity of motion. The experimental data also collapse in the same universal fashion (3).

MiChroM contains no explicit viscoelastic medium or dynamical memory kernel; instead, the memory and elasticity come from the chains and their interactions. At the bead level the motion does actually start out as a simple diffusion, as dictated by the Langevin equation, but the motion then becomes slower because of the interactions between loci encoded in MiChroM. In making comparisons of the simulations with experiments, the unit of length in our simulation was previously calibrated using FISH (18). The unit of time was chosen to reproduce the free passive diffusive properties of loci (i.e., the beads of the model) in pure water treated hydrodynamically at room temperature (SI Appendix). As we shall see, hydrodynamic diffusion is slowed but in discussing the comparisons between theory and experiments below no further adjustable quantity is needed to fit the experimental data. The viscoelasticity manifested by the chromosomal loci displacements together with the specific subdiffusive dynamics of individual locus motion apparently emerge directly from the same physical mechanisms that lead to the spatial organization of the genome.

The trajectories of different loci in vivo are known to be highly heterogeneous. The square displacements of different loci at the 1-s time interval are scattered over a range of values spanning one (2, 3) or even two orders (9) of magnitude. The MiChroM simulations also display heterogeneity, with displacements at the same time ranging over almost one order of magnitude, thus somewhat smaller than the experimentally observed scatter (Fig. 2B). The far from equilibrium activity of motor proteins, which cannot be accounted for by the quasi-equilibrium energy landscape of MiChroM, is a possible explanation for the higher heterogeneity of the trajectories observed experimentally. Additional cross-linking that does not show up in the Hi-C data might also contribute to this heterogeneity, as well as significantly affect the diffusive properties of chromosomal loci (21).
To uncover the origin of the dynamics and correlated motions in the chain we calculated the relaxation times for the Rouse modes of the chromosome chains. For a simply connected chain without excluded volume or hydrodynamic interactions the Rouse picture leads to overdamped vibrational modes. These modes correspond to the vibrations of the polymeric chain and are labeled by their inverse wavelength. For harmonic chains the modes are independent of each other and uncorrelated. Their individual correlation functions are expected to decay as simple exponentials; for each mode of wavelength $p$ we expect \( \langle X_p(t) X_p(0) \rangle = X_p^2 \exp(-t/\tau_p) \) and \( X_p^2 \sim p^{-2} \). The dynamics of real chains, however, deviates from predictions of the Rouse model, which only treats the interactions along the chain. There are contributions from excluded volume effects, intramolecular bond correlations, chain stiffness, confinement, and tertiary interactions. Our simulations reveal, contrary to the predictions of the free-chain Rouse theory, that the correlation functions of the Rouse modes of the simulated chromosomes are individually best fit by stretched exponential functions \( \langle X_p(t) X_p(0) \rangle \sim A_p e^{-t/\tau_p^{\beta_p}} \) with exponents $\beta_p$ varying between 0.4 and 1, and typically increasing with the mode number (Fig. 2C, Inset). This complex decay of even a single mode reveals there is a nontrivial hierarchy of relaxation time scales (24) (Fig. 2C and D). The scaling of relaxation times with the mode number is also more complex than predicted for the free chain. The effective relaxation times of the vibrational modes in the simulations, which can be quantified through a time integral over the relaxation function as \( \tau_{\text{eff}} = \int_0^\infty e^{-t/\tau_p^{\beta_p}} dt = \tau_p/\beta_p \Gamma(\beta_p^{-1}) \), deviate from those of the idealized Rouse dynamics that predicts the universal scaling \( \tau_{\text{eff}} \sim p^{-2} \). In MiChroM, the observed scaling of the effective relaxation times with the mode number is \( \tau_{\text{eff}} \sim p^{-0.5} \) for the long-wavelength modes (\( P = 1–15 \)) but do follow approximately Rouse behavior having \( \tau_{\text{eff}} \sim p^{-1.7} \) for the shorter-wavelength modes (\( P = 15–100 \)).

Similarly, the amplitudes of the Rouse modes of the simulated chains also deviate from the free-chain prediction. Once again, the deviations from the Rouse theory are seen in longer-wavelength modes (Fig. 2D).

Overall, the analysis of the correlations reveals two distinct regimes. While the short-wavelength modes are reasonably well approximated by the free chain, the behavior of the first 10–20 modes, which are long in wavelength, deviates quite significantly from the free-chain model. In the next paragraph, in analyzing the motions of chromatin in simulations, we provide evidence suggesting that these deviations from the Rouse picture originate from the coherent motion of dynamically associated domains.

**Spatial Coherence, Compartmentalization, and Microphase Separation**

Zidovska et al. were able to map the projected motion of chromatin simultaneously across the whole nucleus of human cells to generate a 2D vector field of chromatin displacements (4). The analysis of the resulting projected displacement field shows that the motion of chromatin is coherent across large regions for several seconds. The modes of coherent extend over the micrometer scale and cross the boundaries of chromosome territories. When ATP is depleted the coherent motion is eliminated, indicating that such coherence results from protein activity.

Fig. 4 shows the 3D displacement fields predicted by MiChroM. The map shows the existence of coherent motion, in a way that parallels the experimental maps, noting however that in the simulations the data do not need to be projected into two dimensions as was done in experiments. The velocity fields \( \langle v(r, t) \rangle = 1/\delta \int_0^\infty \delta \langle r(t) - r(t+\delta) \rangle / \delta \) obtained for different time lags $\delta$ are shown for comparison in Fig. 4A. As in the experiments, it is evident that coherence grows for longer time lags. Fig. 3B shows the velocity correlation $C_{v}(\delta) = \langle v(r(t), \delta) \cdot v(r(t), \delta) \rangle$ as a function of the spatial displacement $\Delta r$ and for different time lags $\delta$.

The boundaries between the regions of coherent motions seen in simulations are not the same as the boundaries between the chromosomal territories that are occupied by chromosomes 17 and 18. One easily verifies this observation by inspecting the matrix of the velocity correlations \( C_{v}(i,j) = \langle v(r(t), i) \cdot v(r(t), j) \rangle \) between loci $i$ and $j$ (Fig. 4B) and comparing it to the structural map. In the matrix of velocity correlations one can observe once again that coherence grows for longer time lags, as the domains of coherent motion encompass larger chromosomal regions for larger time lags $\delta$.

The boundaries of the coherent regions appear to change stochastically through thermal fluctuations; at times a particularly weak interface can be created, allowing reconfiguration. In simulations, according to our model, these weaker interfaces are defined by the three kinds of interactions present in the Hamiltonian, i.e., chain connectivity, soft-core repulsive interactions, and the “stickiness” that models the effect of protein-mediated
crosslinking. The MiChroM explains the formation of spatial chromosomal compartments through a process of microphase separation of chromatin sharing similar epigenetic marking patterns. Segments of similarly marked chromatin are brought together by their differential stickiness, modeling the effect of protein-mediated contact interactions. These contact interactions generate an energy landscape in which chromatin of the same kind segregates into liquid droplets that retain some identity dynamically.

By averaging the matrix of the velocity correlations between genomic loci over the ensemble of structures, $\langle v(r_j(t),\delta)\cdot v(r_i(t),\delta)\rangle$, we smooth out the noise to analyze the qualitative elements of the dynamics generated by MiChroM (Fig. 4C).

The dominant features of the matrices of the ensemble-averaged pairwise velocity correlations $c_{ij}(\delta)$ differ at the various time lags $\delta$, which represent the degree of temporal coarse-graining over which the velocity field is calculated. For short intervals of time separation, $\delta$, only the correlations due to chain connectivity can be easily seen, strictly manifested along the diagonal of the matrix. Loci that sit close along the chain tend to move coherently. For correlations at longer time intervals, one sees, arising somewhat further away from the diagonal, additional domains of coherence that apparently are related to the motion of dynamically associated domains. These DADs, much as do their structural counterparts topologically associated domains (TADs), often align with the A/B chromatin-type annotation. Off the diagonal, the velocity correlation map does exhibit weaker correlations due to phase separation; this indicates that domains belonging to the same chromatin type often segregate in the same liquid droplet and therefore show, on average, more coherence than otherwise. Lastly, on the very longest time scales one uncovers dynamical correlations associated with chromosomal territories (SI Appendix, Fig. S6).

Each of the two chromosomes contains roughly 10–20 DADs, suggesting that the coherence of the motion of DADs is indeed responsible for the significant deviations found in the first 10–20 long-wavelength vibrational modes between the simulated chromosomes and the continuum theoretical predictions.

A similar analysis can also be carried out using the matrices of the velocity correlations between genomic loci with a time delay $\Delta t$, $c_{ij}(\delta,\Delta t) = \langle v(r_j(t),\delta)\cdot v(r_i(t+\Delta t),\delta)\rangle$; in these matrices (SI Appendix, Fig. S7) we see a more detailed version of the negative correlation dip seen in the one-dimensional velocity autocorrelation plot. The positive correlations, on and off the diagonal, quickly decay with increasing $\Delta t$. Successively, chain connectivity generates a negative velocity correlation between neighbors, which then spreads to the DADs along the diagonal.

Due to the unavailability of assays combining correlation spectroscopy with knowledge of the genomic identity of the tracked loci, these predictions concerning the relation between dynamics and structure coming from the MiChroM energy landscape about the origin of the coherence remain to be tested in the laboratory.

**Conclusion**

It is not immediately obvious whether the same energy landscape that describes the structural ensemble would also be adequate to describe the dynamics. Nevertheless, if the step sizes of the motions induced by the nonequilibrium engines are smaller than the characteristic length scales of the forces, it has been shown that an active motorized system can still be described as a quasi-equilibrium system with a renormalized temperature and diffusion coefficient as has been discussed in the context of cytoskeleton models (22). If instead the step sizes are larger than the range of the forces, vectorial flows can develop which would be missing from a Langevin simulation using a quasi-equilibrium landscape description of the system. In this article we have analyzed the motion of the human chromosomes predicted by a quasi-equilibrium landscape that fits accurately the known structural data. Remarkably, the quasi-equilibrium landscape description turns out to be compatible with numerous dynamical observations of the chromosomes in vivo. The very same interactions that account for 3D organization of the genome in interphase seem to reproduce naturally several nontrivial features of the genome’s four-dimensional dynamics, namely, the spatial coherence of mobile regions, the diffusive nature of the trajectories of individual loci, and the apparent viscoelastic nature of chromatin itself.

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