Architecture of human interphase chromosome determines the spatiotemporal dynamics of chromatin loci

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By incorporating the information of human chromosome inferred from Hi-C experiments into a heteropolymer model of chromatin chain, we generate a conformational ensemble to investigate its spatiotemporal dynamics. The heterogeneous loci interactions result in hierarchical organization of chromatin chain, which obeys compact space-filling (SF) statistics at intermediate length scale. Remarkably, the higher order architecture of the chromatin, characterized by the single universal Flory exponent ($\nu = 1/3$) for condensed homopolymers, provides quantitative account of the dynamical properties of the chromosome. The local chromosome structures, exemplified by topologically associated domains ($\sim 0.1 - 1$ Mb), display dynamics with fast relaxation time ($\lesssim 50$ sec), whereas the long-range spatial reorganization of the entire chromatin ($\gtrsim O(10^2)$ Mb) occurs on a much longer time scale ($\gtrsim$ hour), suggestive of glass-like behavior. This key finding provides the dynamic basis of cell-to-cell variability. Active forces, modeled using stronger isotropic white noises, accelerate the relaxation dynamics of chromatin domain described by the low frequency modes. Surprisingly, they do not significantly change the local scale dynamics from those under passive condition. By linking the spatiotemporal dynamics of chromosome with its organization, our study highlights the importance of physical constraints in chromosome architecture on the sluggish dynamics.

The organization of chromosomes, comprised of a long DNA/chromatin chains, depends on the length scale. On $\lesssim 10$ nm scale, dsDNA wraps around histone octamers to form nucleosomes, whose assembly constitutes the chromatin fiber. Evidence that the fiber is further compacted into higher-order structures, such as topologically associated domains (TADs) and chromatin compartments, come from the interaction patterns inferred from Hi-C data (1–3).

The three dimensional (3D) structures of chromatin vary with the developmental stage (4) and cell types, which has resulted in the appreciation that chromatin structure is important in its regulatory role. For long range transcriptional regulation (5–7), two distal genomic loci have to be in proximity. Hi-C maps of chromatin, measuring mean contact frequencies between cross-linked DNA segments from an ensemble of millions of fixed cells, suggest their hierarchical organization. Chromosomes at $\sim 5$ Mb resolution are partitioned into alternating A and B type compartments that are enriched with active and inactive loci, respectively (1). At a higher resolution the data reveals the formation of TADs, the submegabase sized functional building blocks of interphase chromosome (2). While the chromatin chain within TADs is highly dynamic (8), the boundaries between the TADs are well insulated across different cell types. Genome-wide Hi-C maps at even higher resolutions of $\sim O(10)$ Kb indicate at least 6 subcompartment types, characterized by distinctive histone markers and chromatin loops (3). In addition, fluorescence images give glimpses of real-time chromatin dynamics \textit{in vivo} (9–12), allowing us to decipher the link between structure, dynamics, and function (13–15).

Advances towards the mechanistic underpinnings of chromatin compaction are also being made using theory and computations. Based on the knowledge of the convergent orientation of the CTCF-binding motifs, the loop extrusion polymer model (16, 17) was proposed to explain the formation of TADs and predict the contact maps of edited genomes upon deletion of CTCF-binding sites (16, 17). While homopolymer models with geometrical constraints (1, 18–22) capture the physical basis of chromosome organization, one can utilize the information from Hi-C and fluorescence \textit{in situ} hybridization to sharpen the model (23–26).

To explore the spatiotemporal dynamics of a chromosome, we modified a recently developed heteropolymer model, – Minimal Chromatin Model (MiChrom) – whose parameters were trained to reproduce the Hi-C data of Chr10 (chromosome 10) from human B-lymphoblastoid cell (27). The ensemble of chromosome structures generated from the MiChrom reproduced the experimental Hi-C maps of all other autosomes (27). The resulting chromosome structures were characterized with the paucity of entanglements, phase separation of A/B compartments, and enrichment of open chromatin chain at the periphery of chromosome territories (27). Furthermore,

**Significance Statement**

Chromosomes are giant chain molecules made of hundreds of megabase-long DNA intercalated with proteins. Structure and dynamics of interphase chromatin in space and time hold the key to understanding the cell type-dependent gene regulation. In this study, we establish that the crumpled and space-filling organization of chromatin fiber in the chromosome territory, characterized by a single universal exponent used to describe polymer sizes, is sufficient to explain the complex spatiotemporal hierarchy in chromatin dynamics as well as the subdiffusive motion of the chromatin loci. While seemingly a daunting problem at a first glance, our study shows that relatively simple principles, rooted in polymer physics, can be used to grasp the essence of dynamical properties of the interphase chromatin.

L.L., G. S., B. T., and C.H. designed and performed research, analyzed data, and wrote the paper. The authors declare no conflict of interest.

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the multistability of free energy landscape for individual chromosomal models (28) rationalizes the cell-to-cell variability observed in single-cell Hi-C data (7, 29, 30).

The primary aim of this study is to elucidate the physical principles underlying the chromatin dynamics, which has received much less attention. To this end, we imposed the chain non-crossing constraint on the chromosome structures generated from MiChroM, and carried out Brownian dynamics simulations. Our study shows that the basic features of the chromatin dynamics observed in experiments is quantitatively determined by the crumpled, hierarchical, and territorial organization of interphase chromosomes. By incorporating active forces onto active loci, we also address the extent to which the activity contributes to the dynamic properties of the interphase chromatin.

Results and Discussions

Heteropolymer model for chromosome. In MiChroM (27), each monomer represents 50 Kb of DNA segment. As a consequence, the model describes chromosome organization on large length scales, a feature that is crucial for dynamics. Based on the correlation between the distinct patterns of interchromosomal contacts and epigenetic information, MiChroM assigns one of six types of subcompartments (B3, B2, B1, NA, A1, and A2) to each CG monomer (3). In the Hi-C map, candidate binding sites for CTCF (16) or lamin A (12) show much higher contact frequencies than their local background. As a result, the interactions between monomers are accounted for by the potential of a homopolymer, monomer type dependent interactions, attractions between loop sites, and genomic distance-dependent condensation energies (See Supporting Information (SI)). We confine the chromatin to a sphere with a volume fraction of 10%.

To sample the chromatin conformations at equilibrium, we performed Langevin simulations at low friction (31) (see SI Text). The resulting conformational ensemble of Chr10 captures the “checkerboard” pattern of the Hi-C contact map (3) (Fig. 1A), and reproduces the characteristic scaling of contact probability $P(s) \sim s^{-1}$ over the intermediate range of genomic distance $1 < s < 10$ Mb (Fig. S1B). The distribution of Alexander polynomial, $|\Delta(t = -1)|$ (32) (Fig. S1D), characterizing chain entanglement, has the highest mode at zero, indicating that the majority of chromosome conformations are free of knots. The radial distributions of monomers belonging to the different type of subcompartment (27, 33) reveal that in contrast to the condensed and transcriptionally inactive loci, which are buried in the chromosome interior, open and active loci are enriched near the surface, presumably improving the accessibility to transcription factors (Figs. S1E, S1F).

There is substantial heterogeneity in the structures. We use the distance-based root-mean-square deviation (DRMS, $D$),

$$D_{\alpha,\beta} = \sqrt{\frac{2}{N(N-1)} \sum_{i>j} (r_{i,j}^{\alpha} - r_{i,j}^{\beta})^2},$$

[1]

to quantify the similarity between two conformations and partition them into multiple clusters. In this method, two chromosome structures, say $\alpha$ and $\beta$, that are within a cutoff value ($D_{\alpha,\beta} < D_c$) are considered similar and grouped together. We carried out hierarchical clustering by repeating this procedure by varying the value of $D_c$ to produce a dendrogram (Fig. 1B); the ensemble is decomposed into many clusters (see Fig. S2). At $D_c(=4.5a \approx (D))$, distinction between the structures belonging to different clusters is visually clear (Fig. 1B), suggesting the cell-to-cell variability seen in the recent single-cell Hi-C data (7, 29, 30). The partitioning of the conformations into distinct clusters is a first indication that the folded landscape of chromosome is rugged. Consequently, we expect that the underlying dynamics should exhibit glass-like behavior (22).

Subdiffusive dynamics of chromatin loci. We calculated the ensemble- and time-averaged mean square displacement (MSD) for chromatin loci using, $\text{MSD}_B(t) = \langle (\hat{\mathbf{r}}(t) - \hat{\mathbf{r}}(0)) \cdot (\hat{\mathbf{r}}(t) - \hat{\mathbf{r}}(0)) \rangle$ = $\frac{1}{T^2} \int_0^T dt \langle (\hat{\mathbf{r}}(t) - \hat{\mathbf{r}}(0)) \cdot (\hat{\mathbf{r}}(t) - \hat{\mathbf{r}}(0)) \rangle$. The ensemble averaged MSD is obtained using $\text{MSD}(t) = \sum_B\text{MSD}_B(t)/N$. As shown in Fig. 2A, the diffusion of chromatin loci is characterized by three different time regimes. At short times ($t < 10^{-7} \tau_{BD}$), the loci diffuse freely with $MSD \sim t$. At the intermediate times, corresponding to the Brownian time $t \sim \tau_{BD} \sim a^2/D$, each locus starts to feel the neighboring monomers along the chain. For $t > 10^3 \tau_{BD}$, a subdiffusive behavior of $MSD \sim t^{\beta}$ with $\beta \approx 0.4$ is observed. This exponent is in line with the reported values of $\beta = 0.38 \pm 0.44$ (34) and $\beta = 0.4 \pm 0.7$ (12) in live human cells, and is also in reasonable agreement with the diffusion exponent $\beta = 0.32 \pm 0.03$ measured for the whole genome of ATP-depleted HeLa cells (9).

The exponent $\beta = 0.4$ can be rationalized using the following argument. The spatial distance ($R$) between two loci separated by the genomic distance, $s$, satisfies $R(s) \sim s^{\nu}$, where $\nu$, the Flory exponent (20, 35), is $\nu = 1/2$ for ideal chain obeying Gaussian statistics, and $\nu = 1/3$ for space-filling (SF) chain. Notice that the MSD of an expanded locus of any length $s$ scales with time as $t^{\beta} \sim D(s) \times s \times D_o \times t/s$, where the scaling relationship of the diffusion constant of freely draining chain $D(s) \sim D_o/s$ is used. The use of the relation of $MSD \sim R^2(s) \sim s^{2\nu}$ allows us to relate $s$ with $t$ as $s \sim t^{\nu/2\nu}$. It follows that $MSD \sim t^{\beta} \sim t^{1-\beta/2\nu}$, giving $\beta = 2\nu/(2\nu + 1)$.
The SF organization of chromosome implies \( \nu = 1/3 \), and hence \( \beta = 0.4 \), which explains our BD simulation result at \( t/\tau_{BD} \gg 1 \). A similar argument was used to explain the time-dependence of \( \text{MSD}(t) \) found in an entirely different model (36).

Meanwhile, it has recently been shown using high-throughput chromatin motion tracking in living yeast that \( \text{MSD} \sim t^{0.5} \) for all chromosomes (10). The yeast chromosomes obey Gaussian statistics, \( R(s) \sim s^{1/2} \) and \( P(s) \sim s^{3/2} \), indicative of \( \nu = 1/2 \). Evidently, from Eq 2, \( \text{MSD} \sim t^{1/2} \) (10).

Therefore, Eq 2 suggests that the diffusivity of loci is closely linked to the global architecture of chromatin (34, 37).

**Euchromatin versus heterochromatin dynamics.** According to a recent single nucleosome imaging experiment (34), diffusion of the heterochromatin-rich loci in the nuclear periphery is slower than the euchromatin-rich loci in the interior. The time-averaged MSD (\( \text{MSD}_t \)) exhibits substantial dispersion among different loci (Fig. 2A, inset). Depending on the sub-compartment types, loci move with different diffusivity (see Fig. 2B). The \( \Lambda \)-type loci, which are less condensed and close to the chromosome surfaces, diffuse faster than the loci of type B2 and B3. Similarly, transcriptionally active loci move slightly faster compared with inactive ones. Although the diffusivity is greater for the active loci, they still have the same \( \beta = 0.4 \), which suggests that the chain architecture is the key determinant of the diffusion exponent. Below we will show that even if active forces are incorporated into the dynamics, the value of \( \beta \) is unchanged.

**Correlated loci motion in space and time.** For complex systems like genomes or chromosomes, various correlation functions can be used to quantify the dynamic properties of the system in space and time.

**Correlation in time.** We first calculated the correlation function of displacement of the \( i^{th} \) and \( j^{th} \) loci divided by waiting time \( \Delta t \), which defines the mean velocity correlation function (11, 38),

\[
C_{V,(i,j)}^{\Delta t}(t) = \frac{\langle \Delta \vec{r}_i(t + \tau; \Delta t) \cdot \Delta \vec{r}_j(t; \Delta t) \rangle}{\langle \Delta t \rangle^2},
\]

where \( \Delta \vec{r}_i(t; \Delta t) = \vec{r}_i(t + \Delta t) - \vec{r}_i(t) \) and \( \langle \cdot \rangle_0 \equiv 1/T_s \int_0^{T_s} dt \langle \cdot \rangle \), with \( T_s \) being the total simulation time, denotes an average over \( t_0 \). Regardless of \( \Delta t \), the auto-correlation function \( C_{V,(m,m)}^{\Delta t}(t) \) calculated for the midpoint monomer \( (m = N/2) \) displays a negative correlation peak \( (C_{V,(m,m)}^{\Delta t}(t) < 0) \) at \( t = \Delta t \) (Fig. 3a), followed by a slow relaxation to \( C_{V,(m,m)}^{\Delta t}(t) \approx 0 \) for increasing lag time \( \Delta t = 200, 500, 2000, 3000 \tau_{BD} \) from the top to bottom. (D) Scaling relation of Fourier modes \( X_k \) with \( k < X_k^2 \sim k^{-\alpha} \), for large \( k \) and \( \alpha = 1.7 \) for large \( k \).

Based on the interpretation of fractional Langevin motion, one could posit that the dynamic behavior of chromatin locus captured in \( C_{V,(m,m)}^{\Delta t}(t) \) is caused by viscoelasticity of the effective medium (40). However, even the ideal Rouse chain in free space \( \beta = 0.5 \) displays a similar curve \( C_{V,(m,m)}^{\Delta t}(t) \) (Fig. 3B). For the Rouse chain in free space, the negative correlation peak, which arises from restoring forces acting on the monomer, is solely due to the chain connectivity with the neighboring monomer along the chain. As Fig. 3B shows that the difference between \( C_{V,(m,m)}^{\Delta t}(t) \) with \( \beta = 0.4 \) for the chromatin model and with \( \beta = 0.5 \) for the Rouse chain is subtle, and not easy to discern.

The behavior of our chromatin model can be distinguished from the Rouse chain by calculating the Fourier modes, \( X_k(t) = N^{-1/2} \sum_{n=1}^{N} \cos(kn\pi/N)\vec{r}_n(t) \). While \( (X_k)^2 \sim k^{-2} \) is anticipated for the free Rouse chain (41), we find \( (X_k)^2 \sim k^{-1.7} \) for large \( k \) values (\( N/k \leq 100 \). See Fig. 3D). The Fourier modes for chromatin are expected to scale \( (X_k)^2 \sim k^{-1.5} \).
Thus, the exponent of 1.7 is explained again by the SF statistics with $\nu = 1/3$.

Cross-correlations of mean velocity between the midpoint ($i = N/2$) and other loci ($j \neq N/2$) show how the correlation of our chromatin model changes with time (Fig. 3C). In contrast to the viscoelastic Rouse polymer model (39), the mean velocity cross-correlation reveals non-uniform and diminishing correlation pattern, which suggests that the chromosome structure is maintained through heterogeneous loci interactions defying complete equilibration, an indication of glassy dynamics.

**Correlation in space.** Recently, study of displacement correlation spectroscopy (DCS) using fluorescence, employed to study the dynamics of a single nucleus, revealed that a coherent motion of the µm-sized chromosome territories could persist for µs to tens of seconds (9). In order to provide structural insights into these findings, we studied the spatial correlation of the chromosome structure. The spatial correlation between chromatin loci from our simulations can be evaluated using

$$C_s(r) = \left\langle \sum_{i,j>\gamma} [\Delta r_i(t; \Delta t) \cdot \Delta r_j(t; \Delta t)] \delta(r_{i,j} - r) \right\rangle_t \tag{4}$$

$$C_s^2(r) \propto \frac{\delta(r_{i,j} - r)}{\sum_{i,j>\gamma} \delta(r_{i,j} - r)} \tag{4}$$

$C_s^2(r)$ quantifies the displacement correlations between loci separated by the distance $r$ over the time interval $\Delta t$. $C_s^2(r)$ decays more slowly with increasing $\Delta t$. The correlation length calculated using $l_c = \int_0^\infty [C_s^2(r)/C_s^2(0)] dr$ shows how $l_c$ increases with $\Delta t$ (Fig. 4B). To paint an image of displacement correlation over the structure, we project displacements of the monomers near the equator of the confining sphere (−$a \leq z \leq a$) onto the $xy$ plane, and visualize the dynamically correlated loci moving parallel to each other by using similar colors (see Fig. 4C). If $\Delta t < 1000 \tau_{BD}$, the spatial correlation of loci dynamics is short-ranged and the displacement vectors appear to be random. But, with a longer waiting time ($\Delta t > 500 \tau_{BD}$), we observe multiple groups of coherently moving loci that form substantially large domains ($\sim 5a \approx 0.75 \mu$m).

**Scale-dependent chromatin relaxation time.** We explored the dynamical stability of chromosome structure at varying length scales. We calculated the time-evolution of the averaged mean square deviation of the distances between two loci with respect to the initial value (see Fig. 5A) and the caption for the definition of $\delta(t)$. Within our simulation time ($\tau_{max} = 4 \times 10^4 \tau_{BD}$), the largest value $\delta_{max} (= 4.0 \pm 0.3 a)$ is smaller than the value, $\delta_c = 4.5 a$, chosen to define different conformational clusters in Fig 1B. An extrapolation of $\delta(t)$ to $\delta(\tau) = \delta_c$ gives an estimate of $\tau_c \approx 10^5 \tau_{BD} \approx 1.4$ hours, which is a long-time scale considering that most cells of adult mammals spend about 20 hours in the interphase (42).

From the definition of $\delta(t)$, it follows that $\lim_{t \to 0}\delta(t) = \delta_0$. Here, $\delta_0$ is finite, and $\langle \cdots \rangle$ is an ensemble average, meaningful only if equilibrium is reached. We estimate $\delta_0$ assuming that the long time limit of the mean deviation of the distance between two loci is approximately the mean end-to-end distance between the loci. Thus, $\lim_{t \to \infty}(r_{ij}(t) - r_{ij}(0)^2) \sim R_{ij}^2$ where $R_{ij}$ is the mean end-to-end distance between $i^{th}$ and $j^{th}$ loci. For $|i - j| \gg 1$, we expect that $R_{ij}^2 \sim \sum_{i}^{a^2}|i - j|^{2\nu}$. Consequently, $\delta_0$ can be calculated using $\delta_0^2 = \frac{2}{N(N-1)} \sum_{i=1}^{N} (N-s) R_{ij}^2(s) = \frac{2}{N(N-1)} \sum_{i=1}^{N} (N-s) s^{2\nu}$. For $N = 2712$, and with $\nu = 1/3$ we estimate $\delta_0 \approx 9.4 a$, which is greater than the value ($\delta_{max} \approx 4.0 a$) reached at the longest times in the simulations (Fig. 5A). An upper bound for $\delta_0$ is $16.4 a$ (see SI). These considerations suggest that the chromosome dynamics is far from equilibrium on the time scale of a single cell cycle.

The scale-dependent relaxation dynamics of the chromatin domain is quantified using the time evolution of intermediate scattering function $F_k(t)$ (43, 44) calculated at different length scales ($\sim 2\pi/k$) (Fig. 5B).

$$F_k(t) = \left\langle \left\langle \frac{1}{N} \sum_{m=0}^{N} e^{i\vec{k} \cdot \vec{r}_m(t + \tau_0)} \sum_{\eta} e^{-i\vec{k} \cdot \vec{r}_m(\tau_0)} \right\rangle_\eta \right\rangle_{\tau_0} \tag{5}$$

where $\langle \langle \cdots \rangle_\eta \rangle_{\tau_0}$ is an average over $\tau_0$ and over the direction of vectors $\vec{k}$ with magnitude $k (\equiv |\vec{k}|)$. $F_k(t)$ shows that the
chromatin chains are locally fluid-like (2π/k ≲ a), which is reminiscent of the recent analysis on the structural deformation of TADs (8), but their spatial organizations on intermediate to global scales (2π/k ≫ a) are characterized by slow relaxation dynamics. This scale-dependent relaxation time is reminiscent of a similar finding in random heteropolymers (45).

\[
\tau_{\text{rel}} = \int_0^\infty \langle |F_b(t)|^2/F_b(0)|^2 \rangle dt
\]

is estimated using \(\tau_{\text{rel}} = \int_0^\infty \langle |F_b(t)|^2/F_b(0)|^2 \rangle dt\), which can in turn be related to the number of segments comprising the subdomain as \(\tau_{\text{rel}} \sim 2\pi/k \sim s^{1/3}\). Since the chromosome domain loses memory of the initial conformation by spatial diffusion, the relaxation time \(\tau\) is expected to obey \(\tau \sim \xi^2/D_{\text{eff}} \sim (s^{1/3})^2/(D_0/s) \sim s^{2/3}\). The relaxation times estimated from our chromosome model indeed scales with the domain size as \(\tau \sim s^{2/3}\) (cyan symbols and solid line in Fig. 6C).

**Effects of active forces on chromosome dynamics.** Thus far, the findings from our simulations are based on using only passive forces in dictating chromatin dynamics. It could be argued that such a model neglects the most critical component of living systems. Live cells abound in a plethora of activities such as replication, transcription, and error-correcting dynamics. While these processes produce local directionality, when mapped onto the phenomenological description, the effects of vectorial forces on the surrounding environment at time scale longer than the correlation time of active noises can be assumed isotropic. We study how an increased noise strength \((\langle \dot{R}_b(t) \cdot \dot{R}_b(t') \rangle = 6D_0\delta(t-t') \rightarrow 12D_0\delta(t-t'))\) (46, 47) on the A1 and A2 monomers occupying 40% of loci population for Chr10, which are classified as the active loci based on the epigenetic information (3), affects the dynamical properties of entire chromosome.

In the presence of active forces, while the diffusion exponent (\(\beta\) in MSD~\(s^\beta\)) is unaltered, the average MSD of A1 loci exhibits \(\sim 70\%\) increase relative to the passive case (Fig. 6A). The disproportionate increase in the mobility of A and B type monomers promotes the phase segregation of the two monomer types (Fig. 6B, and see SI Movies 1 and 2). The active forces push A-type monomers towards the surface of the chromosome, and B-type monomers are pulled towards the center to offset this effect.

In terms of Fourier modes, the active forces mainly influence the chain relaxation described by the low frequency modes. For the high frequency modes or at local length scales (\(k \gtrsim 2\pi/a\)), the intermediate scattering function is practically indistinguishable between active and passive cases (Fig. S3). The chromatin domains in the presence of active forces, on average, relax faster when the domain size is greater than the sub-Mb. A comparison of the relaxation times in Fig. 6C under passive and active conditions highlight this difference.

Similarly, the effect of active forces on the correlation length \(\langle \delta(t)\delta(t+\tau) \rangle\) is evident only at large waiting time \((\Delta t)\). We find that \(\langle \delta(t)\delta(t+\tau) \rangle\) increases with \(\Delta t\) under the passive condition, whereas a decrease of \(\langle \delta(t)\delta(t+\tau) \rangle\) is observed for large \(\Delta t\) under active force (Fig. 6D). There is no distinction between the effects of passive and active forces on \(\langle \delta(t)\delta(t+\tau) \rangle\) for small \(\Delta t\); however, they deviate from each other for \(\Delta t\gtrsim 10^3\mu\text{sec} \sim 50\text{ sec}\) (Fig. 6D). It is noteworthy that a similar dependence of correlation length with \(\Delta t\) has been discussed in DCS measurement on genomewide dynamics of live cell (9). Compared to thermal noise, active noise randomizes the global structure of chromatin chain more efficiently, which shortens the correlation length at sufficiently large lag time.

**Conclusions**

Our study highlights the importance of chromosome architecture in determining the subdiffusive behavior and dynamic correlations between distinct loci. Most notably, we have shown that structure alone explains many of the dynamical features observed in living cells (9). In other words, chromosome organization dictates its dynamics. Remarkably, several static and dynamic properties of the model, including \(R(s) \sim s^{\nu}, P(s) \sim s^{-2\nu}, X_s^2 \sim k^{-(1+2\nu)}, \text{MSD} \sim s^{2\nu/(2\nu-1)},\) and \(\tau \sim s^{2\nu+1},\) are fully explained by the SF organization characterized by the single universal Flory exponent \(\tau = 1/3,\) offering a unified perspective on both the structure and dynamics of chromosomes.

The relaxation time \(\tau\) of the chromatin domain spans several orders of magnitude depending on its size \(s\), satisfying the scaling relation \(\tau \sim s^{5/3}\) (Fig. 6C). To be more concrete, while local chromatin domains of size \(s \lesssim 1\mu\text{Mb},\) which include TADs and subcompartments, continuously reorganize on the time scale of \(t < 10^7\text{sec} \sim 50\text{ seconds},\) it takes more than hours to a day for an entire chromosome chain \((\geq 100\ \mu\text{Mb})\) to lose memory of its initial conformation. This timescale associated is expected to grow even further at higher volume fractions (22). It is likely that under in vivo conditions, with 46 chromosomes segregated into chromosome territories, the time scale for relaxation can be considerable.

The effects of active forces on chromatin dynamics (9, 48) deserve further discussion. While active forces enhance chain fluctuations and structural reorganization, the effect on chromatin domain manifests itself only on length scales greater than \(5.5\ \mu\text{m}\) and, on a time scale greater than 50 sec (Fig. 6D). This is closely related to the active cytoskeletal
network using microrheology measurements (49), where the effect of myosin activity is observable only at low frequencies in the power spectrum of the response function. Of course, the active forces in live cell nuclei is not a scalar, and it remains a challenge to model their vectorial nature in the form of force dipole or vector force in the context of chromatin dynamics (46). Vector activities would render loci with super-diffusive motion (MSD, \( \sim t^\beta \) with \( 1 < \beta < 2 \)) dominant, and could in principle elicit a qualitative change in the dynamical scaling relations. However, the dynamic scalings discussed in this study (e.g., MSD, \( \sim t^\delta \)) are in good agreement with those observed in interphase chromatin (9, 12, 34). In terms of power generated in a cell, the passive (thermal) power \( W_p \sim k_B T/\eta_s \) is many orders of magnitude greater than the active power (e.g., molecular motors, \( W_a \sim 20 k_B T/10 \text{ms} \) (42)). At least in the interphase, the gap between the total passive and active power is substantial, because the number of active loci \((N_a)\) is smaller than the number of passive loci \((N_s)\), satisfying the relation \(N_p W_p > N_s W_a\). The robustness of the diffusion exponent indicates that the total contribution of the scalar and vector activities during the interphase is negligible compared to thermal agitation, and does not entirely offset the effects of chromosome architecture on the dynamics. Taken together, our study unequivocally shows that chromosome architecture alone, captured by the single Flory exponent, determines much of the loci dynamics during the interphase.

Materials and Methods
To build the chromosome 10 model of human lymphoblastoid cell, we employed the potential in MiChroM. The coarse graining of vector activities during the interphase is negligible compared to thermal agitation, and does not entirely offset the effects of chromosome architecture on the dynamics. Taken together, our study unequivocally shows that chromosome architecture alone, captured by the single Flory exponent, determines much of the loci dynamics during the interphase.

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