Anomalous diffusion in crumpled (fractal) globules and the dynamics of diffusion-limited reactions in the chromatin.

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The question of how the chromatin matter is packed within the nuclei of eukaryotic cells have been one of the long-standing mysteries of molecular biology. In recent years, a new evidence of the Hi-C maps of the human chromosomes [1] has emerged, and the analysis of this data has allowed to get a new insight into the three-dimensional architecture of a genome. The data analysis shows [1, 2] that these results are not compatible with the architecture of the standard equilibrium globule, however they are in good agreement with the hypothetical crumpled globule conformation conjectured in [3], which is a non-entangled fractal object of dimension 3 reminiscent of space-filling curves (e.g., Peano and Moore curves). These crumpled globule state is supposed to be metastable and relax slowly to the entangled equilibrium globule state, but the typical time of entanglement for realistic models of chromosomes is supposed to be or order hundreds of years [2].

In this work, we address the study the self-diffusion of monomers in this fractal globule state. To do that, we employ the conventional Rouse-like scaling model and obtain the universal scaling dependence describing the mean monomer (subchain) displacement over time in a system with fractal dimension D_f: $\langle(\Delta x)^2\rangle^{1/2} \sim t^{1/(2+Df)}$, applying this expression for the case of $D_f = 3$ one gets $\langle(\Delta x)^2\rangle^{1/2} \sim t^{1/5}$ for the monomer displacement in a crumpled globule. Moreover, we use this scaling relation to obtain the mean time for two DNA subchains separated by genomic distance N to meet each other in space for the first time. It reads $\langle t_{MPT}\rangle \sim N^{(2+Df)/Df} \sim N^{5/3}$. We argue that this result describes, in particular, the typical time needed to form enhancer-promoter complexes in the transcription regulation process. Moreover, we emphasize that this typical time is fast compared two the typical Rouse time for the polymer coil, and exceptionally fast compared to the typical first passage time in the equilibrium globule state. In our opinion, this is an additional argument showing the effectiveness of the crumpled globule packing of chromatin.

We check the correctness of our theoretical results by performing extended computer simulations of the dynamics of globular polymer chains with different starting conformations. For that end, we use the

DPD (dissipative particle dynamic) method for the monomer dynamics, and we conduct the simulations with the use of the Lomonosov supercomputer at MSU, for start conformations. We present the corresponding simulation results, which are in good agreement with the predictions of the scaling theory.

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1. Lieberman-Aiden E, van Berkum NL, Williams L, Imakaev M, Ragoczy T, Telling A, Amit I, Lajoie BR, Sabo PJ, Dorschner MO, Sandstrom R, Bernstein B, Bender MA, Groudine M, Gnirke A, Stamatoyannopoulos J, Mirny LA, Lander ES, Dekker J. (2009) Comprehensive mapping of long-range interactions reveals folding principles of the human genome, *Science*, **326**:289-293.

2. L.A. Mirny (2011) The fractal globule as a model of chromatin architecture in the cell, *Chromosome Res.*, **19**: 37–51.

3. A. Yu. Grosberg, S. K. Nechaev and E. I. Shakhnovich (1988) The role of topological constraints in the kinetics of collapse of macromolecules, *J. Phys. France*, **49**: 2095-2100.