SANS spectra of the fractal supernucleosomal chromatin structure models

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Abstract. The eukaryotic genome consists of chromatin—a nucleoprotein complex with hierarchical architecture based on nucleosomes, the organization of higher-order chromatin structures still remains unknown. Available experimental data, including SANS spectra we had obtained for whole nuclei, suggested fractal nature of chromatin. Previously we had built random-walk supernucleosomal models (up to $10^6$ nucleosomes) to interpret our SANS spectra. Here we report a new method to build fractal supernucleosomal structure of a given fractal dimension or two different dimensions. Agreement between calculated and experimental SANS spectra was significantly improved, especially for model with two fractal dimensions—3 and 2.

1. Introduction

The eukaryotic genome is an highly packed nucleoprotein complex—chromatin, that has hierarchical structure based on nucleosomes \cite{1}. The nucleosome was discovered in the mid-1970s \cite{2, 3}, its structure (Fig. 1) was solved at virtually full-atomic resolution 2.8 Å by X-ray diffraction method in 1997 (PDB \cite{4} entry 1AOI) \cite{5}. PDB database \cite{4} contains more than 40 mononucleosome structures (PDB entry 1KX5 \cite{6} has the best resolution of 1.9 Å) and one tetrانucleosome structure (PDB entry 1ZBB \cite{7}, resolution of 9 Å).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig1.png}
\caption{Mononucleosome structure (PDB entry 1KX5). Double-stranded DNA (shown by yellow (for sugar-phosphate backbone) and blue colors) forms ~1.7 turns of superhelix around protein core (shown by red color). Flexible protein tails (residues 1–37 of chains A and E and residues 1–22 of chain H) are shown in backbone representation.}
\end{figure}
30-nm chromatin fiber, observed with electron microscopy [3,8], was proposed to be the next level of DNA compaction. It had been investigated with a number of experimental methods, including SANS [9,10], however, obtained data were controversial and supported different models [1]. Growing evidence suggested irregular organization of 30-nm chromatin fiber based on 10-nm fiber (reviewed in [11]). Thus, structure of chromatin fiber is still an open question.

Recent studies of internal structure of the whole nucleus revealed its fractal nature [12]. New experimental Hi-C technique allowed to capture inter- and intra-chromosomal space interactions at megabase resolution [13]. Contact probability was calculated as a function of DNA strand distance \( a \) and it turned out that the probability was scaled as \( 1/a \) for the range of 0.5–7 Mb. This finding was consistent with fractal globule model [14], that had predicted fractal dimension of 3. Observations of diffusion behavior of fluorescent tracers provided another line of evidence to support fractal organization of chromatin [15]. Authors calculated fractal dimensions of euchromatin (2.6) and heterochromatin (2.2), that were close to estimates of fractal dimension of chromatin (2.3–2.4) made with tree fractal model of the second order [16].

We had investigated native nuclei of chicken erythrocytes [17] and other cells [18] with SANS. Obtained SANS spectra \( I(s) \) had linear regions in double logarithmic scale for sizes from 15 nm to 1.5 \( \mu \)m, that indicated fractal properties of the nuclei [19]. Fractal dimensions of chromatin (calculated as negatives of slopes of linear regions of SANS spectra) were 2.4 for sizes below 420 nm and \( \sim 3 \) for larger sizes. Interestingly, fractal dimension of protein component of the nuclei (in 64% \( D_2O \)) was 2.5 for the whole range of sizes, while fractal dimensions of DNA component (in 40% \( D_2O \)) were 2.2 for sizes below 250 nm and \( \sim 3 \) for larger sizes.

Previously we have reported development of supernucleosomal chromatin structure model to interpret our SANS data [20]. As the first application of the method, SANS spectra were calculated for random-walk chains of \( 10^6 \) nucleosomes. It was shown that calculated and experimental spectra had both common and different features.

In this paper we describe general method to build fractal supernucleosomal structure models of a given fractal dimension (or two different fractal dimensions) and present results of SANS spectra calculations for these structures. New method of structure generation significantly improved agreement between calculated and experimental SANS spectra.

2. Methods

2.1. Nucleosome model

Nucleosome physical model was based on a mononucleosome structure from PDB database [4]. Scattering length density (SLD) parameterization was done at residue level. Scattering lengths in \( H_2O \) \( \{L^H_i\}_{i=1}^{24} \) and in heavy water \( D_2O \) (with full substitution of exchangeable hydrogen atoms by deuterium atoms) \( \{L^D_i\}_{i=1}^{24} \) and volumes \( \{V_i\}_{i=1}^{24} \) for 24 residues (20 amino acids and 4 nucleotides) were taken from [21]. SLDs of \( H_2O \) \( (\rho_H) \) and \( D_2O \) \( (\rho_D) \) were taken from the same source.

Weight of a pair distance between two atoms of residues of types \( i \) and \( j \) (used to calculate SANS spectra) was defined as product of contrast values of the residues, concentration (volume fraction) of \( D_2O \) in solvent \( W_D \) and probability of H/D exchange \( P_{H/D} \) were taken into account in this evaluation. First, SLD of solvent was calculated as

\[
\rho_S(W_D) = p_H + W_D(\rho_D - \rho_H).
\]

Next, SLD of a residue of type \( i \) was equal to

\[
\rho_i(W_D, P_{H/D}) = \frac{1}{V_i}[L^H_i + W_DP_{H/D}(L^D_i - L^H_i)]
\]

and its contrast was defined as \( \Delta_i(W_D, P_{H/D}) = \rho_i - \rho_S \). Finally, weight of a pair distance was calculated as

\[
w_{ij}(W_D, P_{H/D}) = \Delta_i \Delta_j \tag{1}
\]
2.2. Structure generation

One of the methods to generate fractal is self-similarity transformation [22]. Let us consider a generation of a fractal of topological dimension $T = 1$. At the beginning fractal initiator (fractal of the 0th order) is straight interval of length $L$. At the first step, the initiator is replaced by generator that is broken line of $n$ intervals of length $L/f$, thus producing fractal of the 1st order. Each interval of the generator is replaced by the whole generator at the next steps (Fig. 2). Fractal of the 2nd order consists of $n^2$ intervals of length $(L/f)^2$. For an ideal fractal obtained with this procedure (that consists of infinite number of self-similar subsets) fractal dimension $d$ is defined as similarity dimension

$$d_s = \frac{\ln n}{\ln f}.$$  (2)

If generator is randomly changed (but $n$ and $f$ are kept constant) at each step of generation, than a stochastic fractal will be built (Fig. 2). Its structure is locally irregular, however, statistical characteristics of ideal and stochastic fractals are similar, especially for large structures.

Figure 2. First three orders of generation of a fractal of topological dimension $T = 1$ (curve) by self-similarity transformation in space which Euclidean dimension is $E = 2$ (plane). Left panel shows growth of classic triadic Koch curve with $n = 4$ intervals of length reduced by a factor of $f = 3$, thus its fractal dimension is $d = \ln 4/\ln 3 \approx 1.2618 > T$. Right panel shows growth of stochastic fractal structure formed by random generators equal (in terms of $n$ and $f$) to the generator of the Koch curve.

Self-similarity transformation in 3D space (Euclidean dimension $E = 3$) was used to generate fractal model of supernucleosomal chromatin structure of topological dimension $T = 1$. Initiator was straight interval of length $L$ formed by two points that were the first and the last points of the final structure. Generator was broken line of $n$ randomly oriented intervals of length $(L/f)^k$, where $k$—order of generation. Generation was started from the initiator (fractal of order $k = 0$) and was stopped at order $k = K$. Thus, final fractal structure consisted of $N = n^K$ points that were connected with intervals of length $\ell = (L/f)^K$. 


N nucleosome structures were placed (in random orientation) to Cartesian coordinates of N
points of fractal structure thus forming complete supernucleosomal chromatin structure model.
To take into account finite size of the nucleosome structure self-intersections were not allowed
during fractal structure generation: in case newly generated points were closer to previously
generated points than effective size of the nucleosome structure \(r_{\text{max}}\), they were deleted and
generation step was performed again using another random generator. In rare cases existing
points left no space for new points and generation algorithm continued to the next step after
definite number of unsuccessful tries (technically, generation algorithm was recursive tree-walk
and there was no method to delete points once they were recorded into the structure). To
eliminate self-intersections simple Monte Carlo dynamics was applied to the generated fractal
structure. Since \(r_{\text{max}} \ll \ell\) this procedure had a slight impact on overall geometry of the structure.

Fractal dimension of the final structure could be estimated by Eq. (2) or obtained from
expected dependence of mean radius of gyration \(r_g\) on number of points \(N_g\)
\[
\langle r_g \rangle \propto [N_g]^{1/d_g},
\]
where
\[
r_g = \left[ \frac{1}{N_g} \sum_{i=1}^{N_g} (x_i - \langle x \rangle)^2 + (y_i - \langle y \rangle)^2 + (z_i - \langle z \rangle)^2 \right]^{1/2},
\]
\(\{x_i, y_i, z_i\}\)—Cartesian coordinates of \(N_g\) points of a continuous subset of the fractal structure.
If dependence \(\langle r_g(N_g) \rangle\) was linear in double logarithmic coordinates, fractal dimension \(d_g\) could
be calculated as an inverse of slope of linear fit in accordance with Eq. (3). Despite generated
fractal structures were not the ideal fractals, preliminary calculations shown good agreement
between two estimates of fractal dimension made with Eqs. (2) and (3).

2.3. SANS spectra calculations
The method was described in full details in our previous work [20]. In brief, Cartesian coordinates
of a fractal supernucleosomal structure and the physical nucleosome model were used to perform
Monte Carlo simulation of unweighted histogram of distance distribution function (DDF). Each
element of this histogram contained distance value and types of two residues, atoms of which
were used to calculate the distance. The histogram was weighted by 0 and 1 to calculate simple
geometrical DDF of DNA or protein parts of the whole structure. To obtain SANS spectra
the histogram was weighted by products of contrast values of residues that formed particular
distance (Eq. (1)), and Fourier-transformed into spectra.

3. Results and Discussion
3.1. Mononucleosome structure properties
Geometrical and SANS properties of 33 mononucleosome structures from PDB database [4] were
analyzed in our previous work [20]. It was shown that all these structures were highly similar,
an average nucleosome consisted of 12.1 thousand atoms, 146-bp double-stranded DNA formed
superhelix with diameter of 84.0 Å and pitch of 25.8 Å.
Solvent match points (SMPs) of DNA and protein components of the average nucleosome structure varied in wide range of heavy water concentrations (SMP of protein was 0.308–0.391) depending on probability of H/D exchange \(P_{H/D}\). For nucleosomal DNA \(P_{H/D} \approx 1\) [23], while protein core had complex pattern of H/D exchange rate [24]. It was shown, that value of \(P_{H/D}\)
had significant impact on SANS spectra only for \(W_D\) values close to SMPs [20]. Thus for all
further calculations \(P_{H/D}\) was set to 1.
Among analyzed mononucleosome structures nucleosome 1KX5 [6] was selected for further
calculations because this structure was solved at the best resolution of 1.9 Å and its properties
were close to that of the average nucleosome.
Nucleosome 1KX5 had flexible protein tails (Fig. 1), that were located outside of core particle and poorly ordered—their particular conformation might have been affected by the crystal packing. DDF calculations shown that these tails increased maximal size of the nucleosome from 124.0 to 174.2 Å, while differences in corresponding SANS spectra were negligible [20]. Thus flexible protein tails were removed from the nucleosome structure and this model with effective size $r_{\text{max}} = 120$ Å was used to build supernucleosomal chromatin structure.

3.2. SANS spectra of fractal supernucleosomal chromatin structure models

Fractal supernucleosomal chromatin structures of $\sim 10^5$ nucleosomes were generated for several values of $n$ up to $n_{\text{max}} = 10$. Value of $n = 2$ was found to be the most efficient in terms of computational time. Series of structures of $2^{20} \approx 10^6$ nucleosomes were generated for $n = 2$ and different values of internucleosomal distance $\ell$ and fractal dimension $d_s$.

“Soft” self-intersections (distance between $i$-th and $j$-th nucleosomes $r_{ij} \approx r_{\text{max}}$) turned out to be relatively frequent and were observed for several percent of total number of nucleosomes. “Hard” self-intersections ($r_{ij} \ll r_{\text{max}}$) were very rare (a few cases per the whole structure). Increase of internucleosomal distance $\ell$ decreased number of self-intersections, especially that of soft type. All self-intersections of both types were completely eliminated by simple Monte Carlo dynamics, having slight impact on overall geometry.

Dependence of radius of gyration $\langle r_g \rangle$ on size $N_g$ of a continuous subset was calculated for the fractal structures. As expected, in all cases it had linear region in double logarithmic scale and fractal dimension $d_g$ was evaluated by Eq. (3).

SANS spectra were calculated for all generated supernucleosomal structures with protocol, described in our previous work [20]. Key points of the protocol were summarized in the Methods.

As was noticed in the Introduction, fractal dimension $d_I$ of the structure could be calculated from SANS spectrum assuming that

$$I \propto s^{d_I}, \tag{4}$$

i.e. the SANS spectrum had linear region in double logarithmic scale. We observed this behavior for all calculated SANS spectra of fractal supernucleosomal chromatin structure models and evaluated fractal dimension $d_I$ by Eq. (4), in addition to known values of $d_s$ and $d_g$.

Difference between continuous and infinite ideal fractals and our discrete and finite fractal structures led to dependence of fractal dimension of generated supernucleosomal structure on characteristic lengths $r_{\text{max}}$ and $\ell$. Value of $\ell = 300$ Å was found to provide good agreement of three estimates of fractal dimension $d$ (Fig. 3).

Figure 3. Correlation plot of three estimates of fractal dimension of generated supernucleosomal chromatin structures of $2^{20}$ nucleosomes ($n = 2$, $\ell = 300$ Å): $d_s$, $d_g$ and $d_I$, calculated by Eqs. (2), (3) and (4), respectively. Symbols ◦, □ and ○ denote plots of $d_g$ vs. $d_s$, $d_I$ vs. $d_s$ and $d_I$ vs. $d_g$, respectively. Solid lines represent linear fits (without the intercept term, $y = \beta x$) of these correlations. Slopes (with error and coefficient of determination) were $0.987 \pm 0.004$ ($R^2 = 0.987$), $1.007 \pm 0.005$ ($R^2 = 0.984$) and $1.021 \pm 0.002$ ($R^2 = 0.997$), respectively. Dashed line with slope of 1.000 is shown for comparison.
We had to note that there was a difference between $d_s$ (known by generation) and $d_g$ and $d_I$ (both based on the structure) at larger values ($d_s > 2.7$) (Fig. 3). Correlation between $d_g$ and $d_I$ at that region was significantly more robust than that between both of them and $d_s$, indicating some limitations of the generation method.

Fractal supernucleosomal structure of $2^{20}$ nucleosomes with fractal dimension $d_s = 2.4$ is shown on Fig. 4a. Initiator length was $L = 9.70 \times 10^4 \text{ Å}$, while radius of gyration of the obtained structure was $R_g = 4.98 \times 10^4 \text{ Å}$. 3D structure was irregular, with several clearly distinguished “focuses” of different sizes that were similar to the whole structure, illustrating scale invariance of the fractals.

As mentioned above, dependence of radius of gyration $\langle r_g(N_g) \rangle$ was calculated for the fractal structure and its plot in double logarithmic scale is shown on Fig. 4b. It had very short region ($N_g < 10$) with “slope” above 0.5 driven by effective repulsion of the nucleosomes. Then dependence $\langle r_g(N_g) \rangle$ was linear with slope of 0.42 that corresponded to $d_g = 2.38$ that was close to expected value $d_s = 2.4$.

SANS spectra of the structure were calculated for different values of volume fraction $W_D$ of heavy water in solvent (shown on Fig. 4c) and had two distinct regions: supernucleosomal region ($s < 0.02 \text{ Å}^{-1}$) and nucleosomal region. There was no dependence of SANS spectra on $W_D$ value in supernucleosomal region. In contrast, in nucleosomal region protein ($W_D = 0.65$) and DNA ($W_D = 0.40$) parts of the structure had different SANS spectra with clearly seen patterns. Both observations were expected for supernucleosomal fractal structure as for discrete non-ideal fractal.

Nucleosomal part of the SANS spectra was resulted from locally-regular nucleosome packing (on a scale of several nucleosomes) that was a consequence of the generation algorithm. Observed SANS spectra patterns were more abundant in features in comparison with that of SANS spectra of random-walk structures [20]. These patterns are of particular interest in context of possible organization of 30-nm chromatin fibers. We have investigated a number of locally-regular supernucleosomal chromatin structures and are preparing data for publication.

Supernucleosomal part of the SANS spectra was linear in double logarithmic scale for $s < 0.01 \text{ Å}^{-1}$ with slope of $-2.45$, that corresponded to fractal dimension $d_I = 2.45$, while $d_s = 2.4$ and $d_g = 2.38$, thus there was a good agreement between different estimates of fractal dimension. Similar behavior was shown for supernucleosomal structures generated for several $d_s$ values in range [2, 3] (Fig. 3).

We had observed fractal dimensions $d_I$ in range from 2.2 to $\sim3$ in experimental SANS spectra for the whole nuclei [17]. Data obtained with other experimental methods also supported different estimates of fractal dimension of chromatin in the same range, from 2.2 (diffusion studies [15]) to 3 (Hi-C technique [13]). This motivated us to generate supernucleosomal structure with two different $d_s$ values.

To introduce crossover point (in terms of $d_s$) in our supernucleosomal chromatin structure model, we modified original algorithm of structure generation described in the Methods. Generation started with fixed number of segments $n = 2$ and length ratio $f = f_1$ that provided fractal dimension $d_{s1}$. At definite order of generation $k = k_c$ length ratio was changed to $f = f_2$ that corresponded to $d_{s2}$.

Supernucleosomal structure model of $2^{20}$ nucleosomes with $\ell = 300 \text{ Å}$, $n = 2$, $k_c = 14$ and fractal dimensions $d_{s1} = 3$ and $d_{s2} = 2$ is shown on Fig. 4d. It was similar to fractal structure with fractal dimension $d_s = 2.4$, but was more compact—radius of gyration was $R_g = 3.19 \times 10^4 \text{ Å}$. Detailed analysis of dependence $\langle r_g(N_g) \rangle$ (Fig. 4e) revealed biphasic organization of the structure with crossover point 584 nucleosomes (2933 Å), while crossover point known by generation was 256 nucleosomes (1097 Å). This difference was slightly more than one order of fractal generation and may reflect transition from one dimension to another.
Two supernucleosomal chromatin structure models of $2^{20}$ nucleosomes, $\ell = 300$ Å. Fractal dimensions were (a–c) $d_s = 2.4$ and (d–f) $d_s = \{2, 3\}$. (a, d) 3D structures: each nucleosome is a sphere with diameter of $r_{\text{max}}$, color is smoothly varying from blue (beginning of the chain) to red, cubes with edge of $2 \times 10^4$ Å are shown for comparison. (b, e) Dependence $\langle r_g(N_g) \rangle$: symbols • denote observed values, solid lines represent values predicted with $d_s$, dotted lines show linear fits, dashed lines for $d_g = \{1, 2, 3\}$ are shown for comparison. (b) Linear fit $y = \alpha + \beta x$: slope of $0.420 \pm 0.001$ ($R^2 = 0.999$) that corresponds to $d_g = 2.38$ shown on Fig. 3. (e) Crossover point (indicated by ↑) was 256 nucleosomes (1697 Å) by generation. Two linear fits $y = \alpha + x/d_s$ provided another crossover point (indicated by ↓)—584 nucleosomes (2933 Å), in both cases $R^2 = 0.999$. (c, f) SANS spectra: solid lines show spectra for specified $W_D$ values, dotted lines represent linear fits, additional x-axis shows sizes in real space (in Å). (c) Linear fit $y = \alpha + \beta x$: slope $-2.450 \pm 0.002$ ($R^2 = 0.999$) that corresponds to $d_I = 2.45$ shown on Fig. 3. (f) Linear fits $y = \alpha - 2x$ ($R^2 = 0.998$) and $y = \alpha - 3x$ ($R^2 = 0.991$).
SANS spectra of the structure with crossover (Fig. 4f) were similar to that of supernucleosomal structure with fractal dimension \(d_s = 2.4\) and consisted of the supernucleosomal \((s < 0.01 \text{ Å}^{-1})\) part with \(I \propto s^{-d_I}\) and the nucleosomal part with characteristic pattern of locally-regular structure. Two different values of fractal dimension \(d_I \approx d_s\) were observed, however, crossover point was less pronounced in comparison to \(\langle r_g(N_g)\rangle\) plot and may be found in a range of \(5\text{–}7 \times 10^3\ \text{Å}\).

Supernucleosomal part of calculated SANS spectra of fractal supernucleosomal chromatin structure models were in a good agreement with that we had observed experimentally for cell nuclei, especially spectra of the structure with two different values of fractal dimension—3 and 2 (for smaller sizes). Interestingly, diffusion studies had explored the nuclei at characteristic lengths up to 100 nm, and the obtained data supported low fractal dimension of 2.2–2.6 [15], while data acquired with Hi-C technique (resolution \(\sim 5 \times 10^3\) nucleosomes) had been described by fractal globule model that predicted fractal dimension of 3 [13]. Thus, single chromatin structure model with crossover point fitted the data obtained with three different experimental methods.

In conclusion, analysis of available data suggested that supernucleosomal structures presented here are appropriate models of chromatin structure and are capable of reproducing its biphasic behavior. Future work is required to investigate dependence of observable parameters (radius of gyration, contact map captured with Hi-C technique, etc.) on fractal dimensions and crossover point of the supernucleosomal structure model.

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