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Tasks and Visual Abstractions for 3D Chromatin Representation

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Abstract

The spatial organization of chromatin fiber directly influences its function. However, the high visual complexity of chromatin spatial models makes the understanding of the structure extremely challenging. Therefore, genomic researchers still primarily rely on indirect analysis of chromatin through 2D views, missing the advantages that 3D visualization can offer. In this paper, we first analyze the task space of genomic research and identify biological domain tasks that can benefit from dedicated spatial representations. We organize these tasks into four categories: tasks related to structural features, additional meta-data, structural relationships, and comparative tasks. We analyze these tasks in terms of their complexity, co-dependence, and potential benefits of 3D-based solutions. Secondly, we present four newly designed visual representations of chromatin 3D structure, focused on enhancing the understanding of structural features and solving relationships tasks. These include the hierarchical nature of spatial chromatin sub-units, their visual abstractions, spatial interactions, and a cumulative representation of chromatin dynamic behavior. We also include feedback from four domain researchers and discuss future steps necessary to make spatial representations valid and valuable part of genomic research.

1. Introduction

Genomics research has historically focused on determining the linear nucleotide sequence of DNA but it has been shown that the DNA's three-dimensional (3D) structure is an essential factor for its function [SCF10]. Nevertheless, only in the past decade have the improvements in experimental techniques enabled the reconstruction of plausible spatial folding of chromatin fiber (consisting of DNA and proteins) into chromosomes with sufficient accuracy.

Despite these advances, the actual spatial models are rarely used in genomic research, with researchers relying mostly on 1D or 2D representations. The reasons for this are two-fold. Firstly, the output of reconstruction algorithms often resembles a tangled skein of yarn. This makes it difficult to visually inspect such models, due to the complexity and occlusions that occur with standard 3D visualization methods. At the same time, scarcely any dedicated visualization techniques have been developed. Mostly, the researchers are using basic techniques developed for molecular visualization, such as molecular surfaces or simple sphere or tube-based models. The field of molecular visualization also employs multiple techniques that address issues related to visual complexity and occlusion (e.g., abstracted representations for protein secondary structures). Unfortunately, these are not directly transferable to genomic data.

The second reason why the 3D representations of genomic data have not been thoroughly explored stems from the nature of the data. The spatial reconstructions are based on statistical models. They can significantly differ from the actual spatial arrangements, so the scientists are more prone to rely on representations of the source data (e.g., 2D interaction matrices from which the models are reconstructed). Here, we can draw a parallel with molecular representations, where historically, the 3D models were also based on folding algorithms combined with experimental measurements, yet they were an essential ingredient for research progress. Furthermore, previous validation of chromatin models via experimental data [BSL*11] or simulated models [TSB*15] suggests that the existing statistical models are already of sufficient quality.

Combined, these issues form a vicious circle. The genomic scientists have little incentive to use 3D representation due to their limitations, while the visualization community has minimal incentive to develop better representations, as there is still little demand. However, evidence from related domains [Rob99, KKF*17] shows there is much to be gained from dedicated spatial representations. Although bioinformaticians can derive insights from 1D and 2D representations, they are inherently abstract and do not convey spatial information as intuitively as a 3D model. Spatial models enable observation of features like the density of genetic landmarks, which are not directly visible in 2D representations. In our experience, the best solutions often come from the interplay between spatial and abstract views.

In this paper, we focus on 3D representations, as those are the most underdeveloped in the area of genomic visualization. We analyzed the typical genomic research tasks and questioned how they could benefit from spatial representations. We have categorized these tasks into four groups based on the aspects of the data they examine: structural features, additional meta-data, structural relationships, and comparative tasks. We then analyzed them regarding their complexity, co-dependence, and current support in available

tools. We found that to address comparison and metadata-oriented tasks, we first need to improve support for tasks related to structural features and relationships. Therefore, we designed four types of visual abstractions that can be interactively combined and target these tasks. We validated the usefulness of our newly designed representations on two genomic datasets. The outcomes were consulted with four senior domain researchers. In summary, this paper makes the following contributions:

- We introduce a taxonomy of domain tasks related to the analysis of spatial genomic data.
- We analyze the available tools and literature with respect to the identified domain tasks and discuss the gaps and open challenges in the visualization of the 3D chromatin structure.
- We address some of the unsupported tasks with novel visualization techniques, focusing on structural relationship tasks, which form a natural pre-condition for addressing more complex tasks.

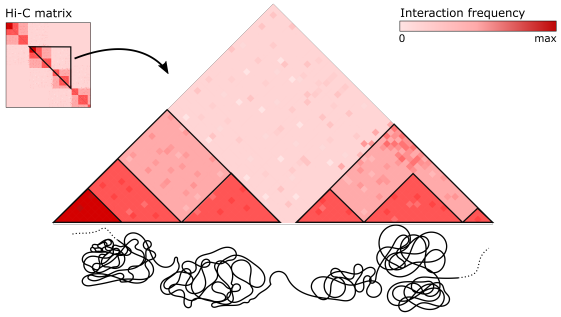

Figure 1: *Illustration of Hi-C matrix portion in triangular form (top) and the implied chromatin spatial organization (bottom). Higher interaction frequency indicates stronger spatial proximity. The hierarchical arrangement of TADs (nested triangles in the matrix) corresponds to spatial clusters with many self-interactions.*

2. Background

The packaging of DNA inside the cell nucleus involves multiple levels of organization. In this paper, we focus on the conformation of the highest levels, where the DNA wrapped around histone proteins forms chromatin fiber, which is further compacted into chromosomes. The concrete 3D conformation of the chromatin fiber is currently estimated through experimental methods that split the DNA sequence into fragments and measure their interaction frequencies. Current high-throughput methods, such as Hi-C [LAVBW*09], enable researchers to infer interaction across the entire chromatin sequence. The disadvantage of this approach is that the size of the DNA sequence fragments limits the resolution. The length of a single fragment, often called a *bin*, can range from thousands to millions of nucleotide bases. The result of the Hi-C method is a 2D *interaction frequency matrix* indicating interaction levels between pairs of bins. Often, only the upper triangle of the matrix is analyzed due to its symmetry (see Figure 1).

The resulting Hi-C matrices inform about the hierarchical organization of chromatin [RG15], which can be seen in the Hi-C matrix as various identifiable, often hierarchically nested patterns. A checkerboard-like pattern signifies active and inactive sections of chromatin [LAVBW*09, FH15] (A/B compartments), point peaks indicate loops in the chromatin conformation, and triangles around the matrix diagonal denote regions with high self-interaction, called Topologically Associated Domains (TADs) [DSY*12]. The hierarchical nesting of TADs [WR16] is shown in Figure 1.

The interaction frequency data imply the underlying three-dimensional configuration of the genome because frequently interacting DNA fragments are assumed to be spatially close to allow for high levels of interaction, as illustrated in Figure 1. Therefore, computational approaches, such as probabilistic algorithms and polymer simulations can be used to infer the chromatin's 3D structure [OHC19], taking the Hi-C interaction matrix as an input and mapping each bin to a specific spatial location.

3. Task Analysis

To better understand the needs of genomic scientists and the potential benefits of 3D chromatin representations, we investigate the domain tasks related to the analysis of chromatin. Domain tasks can be interpreted as objectives that a user has when dealing with biological topics (for example, analyzing the differences between the 3D structure of an altered and reference genome). These tasks differ from low-level tasks, which represent the operations for interacting with the data (e.g., selection, navigation, or highlighting). Furthermore, they are independent from abstract representations, which define the visualizations used to complete domain tasks. We first compiled a preliminary set of tasks with four domain scientists based on their experience in the field. As their specific expertise does not fully cover the intended domain, we further expanded the set with tasks we extracted from related literature. The complete list was validated again with the help of domain scientists. We then arranged the collected tasks into a domain task taxonomy.

3.1. Literature Review

As an entry point to literature analysis, we used Google Scholar to collect surveys related to genomics visualization based on their titles and abstracts, yielding five surveys discussed below.

Goodstadt and Marti-Renom [GMR17] analyzed important challenges of visualizing three-dimensional genomics data, including challenges caused by properties inherent in the genome, such as its multiscale or time-dependent nature. Regarding user tasks, they only mention general low-level tasks and their problems, such as navigation, selection, comparison, classification, or annotation, without delving into the tasks themselves. In their following work, Goodstadt and Marti-Renom [GMR19] further expand on the low-level challenges of visualizing genomic data and provide a short overview of existing tools.

Nusrat et al. [NHG19] created a comprehensive review of genomics visualization from a research outlook. They introduce three distinct taxonomies. The data taxonomy is based on represented genomic features. The visualization taxonomy looks at the type of view, layout, abstraction level, encoding, and more. The task taxonomy adapts and further expands the low-level task taxonomy by Bremer et al. [BM13], organizing tasks into categories such as lookup, locate, browse, explore, or compare.

Yardimci and Noble [YN17] surveyed five popular genomic visualization tools. They reviewed these tools based on their functionality and available non-spatial visualization types. They emphasized tools' abilities to display large-scale and local interactions.

Simmons and Vaquerizas [SV19] reviewed common visualization approaches, such as heatmaps or linear tracks. They analyzed the advantages and disadvantages of these approaches and the common tasks they can address. To help the analysis of the approaches, they list several domain tasks for general genomics data that can be used for evaluation but do not discuss them in detail.

In summary, most surveys focused on low-level tasks or abstract representations, while domain tasks are only sporadically mentioned. This is understandable, as these tasks are essential for identifying the basic features a visualization tool should support. Furthermore, as Nusrat et al. [NHG19] note, domain tasks can be represented as a sequence of low-level tasks. While this is true, a good understanding of the domain tasks describing the overall goals of researchers is necessary to identify the gaps in available visualizations and missing low-level task and abstract representation requirements. Therefore, we used a snowball technique, where papers commonly cited within our initial survey pool were also inspected, and we extracted additional domain tasks from these papers. We also examined papers that cited the initially identified survey papers to cover recent research.

3.2. Task Taxonomy

We present a taxonomy of the extracted domain tasks, which categorizes the research intents of domain experts analyzing spatial genomic data. As indicated earlier, we decided to limit ourselves to tasks directly related to 3D chromatin structure due to the lack of research in this area. We divided the tasks into four categories to group similar tasks together. However, the increased complexity of domain tasks also means several tasks could be assigned to multiple categories. For each category, we discuss the available solutions and potential benefits of novel spatial representations.

Structural-features tasks directly analyze the 3D structure of the chromatin strand, such as occurrence of loops [RHD*14] and TADs [WR16]. Based on our research, we found the following tasks within this category:

- **S1** Identify and classify known chromatin features, such as TADs or loops
- **S2** Find new and presently unknown distinct structural features, such as reoccurring spatial arrangement patterns
- **S3** Explore the shape of individual structural chromatin sub-units (e.g., a specific TAD)
- **S4** Identify outliers within a pool of similar structural patterns

Structural features are nowadays commonly examined using Hi-C matrices. Here, researchers look for patterns, such as point peaks to identify loops, or dark rectangles to identify TADs. A 3D model simplifies this process since loops are depicted directly as loops in the 3D, and TADs appear as coherent clusters. Furthermore, the 3D structure often shows structural features that are otherwise barely visible in the Hi-C matrix. This can help discover new yet undescribed patterns and features [DMRM13]. Nevertheless, in a standard 3D visualization of a detailed chromatin model, structural features can be challenging to spot for untrained eyes or can be hidden by occlusion. Some existing tools support structural tasks with pattern recognition or clustering algorithms detecting the regions of interest. However, dedicated visualization techniques highlighting different structural features relevant to chromatin fiber do not exist, although they could significantly improve their recognition.

Metadata-oriented tasks use additional data that can be mapped onto the genome to provide extra context. This data can be calculated directly from the properties of the structure (e.g., density) or can be provided as an annotation for the underlying genomic sequence. For instance, Stevens et al. [SLB*17] study how gene expression relates to the 3D chromatin structure. We identified the following tasks within this category:

- **M1** Show discrete metadata, e.g., positions of known disease genes or categorization to active and inactive compartments
- **M2** Show continuous metadata, such as density, accessibility, interactivity, or genomic expression
- **M3** Extract additional descriptors for genomic data (e.g., gene expression variability) across the genome or its sub-regions
- **M4** Show the correlation between two or multiple sets of different metadata (e.g., connecting a gene and its activation region)

In traditional 2D browsers, metadata are usually displayed as one or multiple tracks (bar charts, line charts, and other types of 1D plots) below the genome sequence or Hi-C matrix. This creates a physical distance between the metadata values and the genome structure, hindering analysis. In 3D, the metadata values can be shown directly on the 3D model, resulting in a more natural analysis. Unfortunately, most tools can only map a single meta-dataset on the color channel of the model. Some tools allow discrete point annotations, such as gene locations, to be displayed as additional markers. However, other visual variables, such as size, texture, or shape, could be used to display multiple meta-datasets at once. Additionally, complex glyphs inspired by the ones used in 1D genome tracks could be mapped to smaller regions of the model.

Structural-relationships tasks analyze how different parts of the genome affect each other and how these relationships change and evolve. For example, Weinreb et al. [WR16] studied hierarchical organization of TADs, while Nagano et al. [NLV*17] and Naumova et al. [NIF*13] used a temporal sequence of 3D models to analyze changes in chromosome organization at different stages of the cell cycle. We extracted the following list of related tasks:

- **R1** Analyze mutual relationships between multiple structural features, or structural features and metadata (e.g., interactions between TADs or the effect of spatial conformation on activity)
- **R2** Analyze the dynamic changes of the structure and values of the corresponding metadata during biological processes, such as folding and unfolding, or at different cell phases
- **R3** Analyze relationships between multiple levels of the genome hierarchy (e.g., presence of TADs within an active compartment vs an inactive compartment or analyzing a dataset of a genome at different base pair resolutions)
- **R4** Analyze a region of interest in detail within the context of the entire dataset (e.g., one chromosome in the context of the entire cell nucleus)

Tasks in this category are quite diverse. Thus, there is no single unifying solution to help solve all these tasks simultaneously. Moreover, they often operate with more complex, less common datasets, and the limited data availability hinders the development of visualization tools. Some tools offer focus + context view or multiple separate views showing the same region at different scales, which allows rudimentary analysis of the hierarchy. However, these tasks could also be solved by using abstraction, simplifying parts of the genome, and allowing multiple scales to be seen in a single view. Similarly, dynamic changes can currently be visualized at a rudimentary level by animation. However, important events can be easily missed in such cases. Therefore, algorithms that automatically detect points of interest or temporal abstractions, such as streamlines that show the change in a single frame, could be used.

Comparison tasks are concerned with finding the differences between two (1:1 comparison) or more (N:N or N:M) of the same objects. These objects can range from entire genomes to individual structural features and associated metadata. The compared data can differ by biological origin (e.g., human vs mouse genome) and experimental modality, posing challenges with data alignment and resolution. For example, Nagano et al. [NLS*13] analysed cell-to-cell variability in chromosome structure. Later, they also compared results from different experimental procedures [NVS*15]. There are many possible variations of the comparative tasks. Here, we present several exemplary cases:

- **C1** Compare two datasets of the same or different genome (e.g., reference genome vs diseased one, human vs mouse)
- **C2** Analyze variability across multiple datasets of the same genome (e.g., repeated experiments on the same data, multiple reconstruction models of the same experimental data)
- **C3** Find differences between multiple datasets (e.g., one cell at multiple evolution states)
- **C4** Compare models from different modalities (e.g., models based on Hi-C data and outputs of electron microscopy) or data of different resolutions

These tasks are vital to researchers as they can, for example, allow them to see how chromosomal rearrangement events, such as deletion or duplication, affect the structural integrity of the entire genome [SLM18]. In 2D tools, a typical solution is to create a difference matrix of two Hi-C matrices. This approach works well for large differences but is only effective when comparing two samples of the same genome and is susceptible to noise. Most tools also enable comparison by simply stacking two views next to each other, but this type of comparison is very demanding for large datasets. This problem is further amplified for 3D views because of occlusion. It is possible to use an animation that transitions from one object to another, but this comparison becomes hard for longer DNA sequences as researchers experience change blindness outside of the area they are focusing on. Despite these problems, differences in structural features, such as their position or orientation, could be interpreted more intuitively in dedicated spatial representations.

As we previously noted, the categorization is not fully discreet, and many tasks span multiple categories. There is also a level of co-dependence between all task categories. For example, metadata-oriented tasks often require the context of structural features, particularly in terms of 3D views, where the metadata is typically mapped onto the structural representation. Structural-relationships tasks are also naturally dependent on structural-features tasks since we first need a representation of structural features to be able to address their relationships. Furthermore, many of the relationship-oriented tasks study the interplay between structural features and metadata. Therefore, they rely on methods for metadata-oriented tasks. At the same time, there is a feedback loop between the tasks. For example, both metadata and structural relationships might play an important role in the classification task (**S1**). Finally, comparative tasks add an additional layer of complexity by introducing multiple datasets. While the solution of these tasks often requires specific techniques for the visualization of differences, they also inherently build on the other three task categories. For example, we first need to represent the hierarchical organization of a single chromatin conformation before we can proceed with a comparison of multiple ones.

4. Related Work

Using our task taxonomy, we first evaluate the current 3D chromatin visualization tools to see if there is any disparity between the researchers' needs and the functionality provided by available solutions. Then we present related work from visualization research that could serve as inspiration for addressing the identified gaps.

4.1. Task-based Analysis of Existing Tools

Here, we focused on the fulfillment of the tasks with the support of the 3D view and therefore excluded some well-established genomic tools such as Juicebox [DRS*16], UCSC Genome Browser [KSF*02], HiGlass [KAL*18], or Gosling [LWLG21] as they do not support 3D representations.

One of the first tools focused specifically on 3D spatial exploration of chromatin was Genome3D [AMTZ10]. The tool allows visualizing in separate views models at four distinct resolution levels corresponding to the genomes' multiscale hierarchy. Thus, it supports basic tasks related to hierarchical relationships (**R3**). It also supports annotations (**M1**, **M2**), which can be either mapped to the models via color channel or appear as extra objects. GMOL [NWO*16] built upon Genome3D by increasing the resolution levels from 4 to 6 but did not support annotations.

3DGB [BMB*15] is a database tool that allows complex querying with a supplemental 3D view. Subsequently, the 3D view supports only a simplistic tube model, which allows for highlighting transcription binding sites as colored regions (**M1**).

3Disease Browser [LLLL16] was developed to visualize chromosomal rearrangement (CR) events altering genomic structure. The tool focuses on standard 1D and 2D genome visualization with a sequence track, a Hi-C matrix, and annotation tracks. However, it also contains a simple 3D view depicting the close neighborhood model of CRs. It can show the event location and uses a color channel to overlay various annotations on the model (**M1**, **M2**).

TADbit [SBG*17] is a Python library for working with chromatin data, providing functionality such as preprocessing, automatic TAD detection, comparison of different Hi-C matrices, reconstruction of 3D model from Hi-C, or numerical analysis of the 3D model. A web-based application called TADkit is available.

However, it mainly focuses on 2D visualizations, providing only a simple 3D tube model and bounding sphere outlining identified TADs (**S1**). It also offers a color channel for annotations (**M1**, **M2**).

HiC-3DViewer [DWZG17] is a web-based tool focused primarily on the 3D view, but it also contains interactively linked 1D and 2D views. In addition to mapping various annotation tracks to the color channel (**M1**, **M2**), HiC-3DViewer also enables loading multiple chromosomes at once and displays the inter- and intra-chromosomal interactions as connection lines (**R1**).

Delta [TLL*18] is a tool that mainly focuses on calculating and displaying structural patterns in the data. It automatically finds common structural features, such as TADs or loops, from the Hi-C matrix. The 3D view contains a simple ball-and-stick model that displays the detected TADs as transparent regions on the model (**S1**). The model can also display inter-chromosomal interactions via connection lines (**R1**) and gene location as text (**M1**).

GenomeFlow [TOWC19] is primarily focused on modeling the 3D genome structure. The tool visualizes the reconstruction of the 3D model in real-time and is capable of automatically detecting the positions of loops and TADs (**S1**). Additionally, the color channel can be used to overlay gene locations (**M1**).

CSynth [TTM*21] is a tool similar to GenomeFlow in its ability to model the 3D structure from Hi-C data. Similarly, annotation data is overlaid using color and text (**M1**, **M2**). However, as opposed to previous tools, CSynths' primary focus is comparison of different datasets achieved by smooth interpolation between two models (**C1**). In addition to interpolation, the comparison can also be shown as a movement history trace in a single frame.

WashU Epigenome Browser [LPH*22] is a genome browser that combines 1D, 2D, 3D, and imaging data. The tool provides advanced functionality for 1D and 2D data but lacks 3D options. The 3D view can show multiple chromosomes simultaneously and allows for complex filtering and annotation by coloring or using text and glyphs to highlight point data (**M1**, **M2**). While any number of point data can be visible at once, continuous or sequence annotations can be seen only one at a time. Additionally, the tool allows users to load a sequence of models at once and animate them (**R2**).

Nucleome Browser [ZZW*22] integrates many possible modalities of data, providing linked 1D, 2D, 3D, and image views. Unfortunately, the rudimentary 3D view can only show multiple chromosomes simultaneously and overlay annotations as color (**M1**, **M2**).

ARGV [DZZ*24] is an augmented reality mobile application primarily focused on interaction with the data. It uses simple tube models to represent the data. Uniquely, it allows two different metadata to be visible at once by using the color channel and transparent tubes to highlight regions (**M1**).

Molina et al. [MKI*24] use virtual reality for interactive exploration of a ball and stick model. Most importantly, the tool presents a focus+context technique (**R4**) where regions outside of focus are shrunk. The tool can also map metadata to the color channel (**M1**).

This review of the tools further highlights the limitations of spatial representations in the existing software tools. At their most basic level, **structural-features** tasks require only a simple 3D model to be completable. Besides this, only two of the reviewed tools [TLL*18, TOWC19] offer techniques specifically dedicated to these tasks. Only **S1** is commonly supported, while **S2**-**S4** lack dedicated views. Similarly, many tools support simple **metadata-oriented** tasks with basic annotations. However, most tools can only overlay a single annotation track on the color channel at a time. This makes it difficult to assess the relationships between different metadata since the user has to alternate between different mappings to view them. As a result, while **M1**, **M2** are commonly addressed, they are limited in their implementations, and **M3**, **M4** are not supported at all. **Structural-relationships** tasks are challenging to achieve with current 3D visualization tools. One tool [LPH*22] animates dynamic changes, two tools incorporate rudimentary visualizations of structural interactions [DWZG17, TLL*18], and two different tools can show multiple levels of hierarchy at once [AMTZ10, NWO*16]. In total, **R1**-**R4** have few implementations, most of which are quite simple and do not allow the completion of more complex tasks due to occlusions and high visual complexity. Lastly, for **comparison tasks**, only one tool was designed with comparative tasks in mind [TTM*21], supporting **C1**, and no dedicated visualizations exist for **C2**-**C4**.

4.2. Visualization of Biological Structures

Only a few existing works in genomic visualization focus on spatial representations. Miao et al. [MDLI*18] studied the multiscale representation of DNA nanostructures from atomistic scale up to the DNA double helix arrangement. Klein et al. [KMA*19] proposed an algorithm for the illustrative rendering of a bacterial genome, and Halladjian et al. [HMK*19, HKM*21] studied the visualization of spatial genome organization from atomistic to chromosomal level. However, they used only standard representations, limiting them to the most basic structural feature tasks.

In terms of more complex tasks, we can find inspiration in other areas of molecular visualization, surveyed by Kozlíková et al. [KKF*17]. They classify the techniques into categories that can be linked to our task taxonomy, such as general representations (structural tasks) and techniques for visualization of molecular dynamic and interactions (structural relationships). Here, the vast majority of works incorporate some form of spatial view, often taking advantage of well-established ribbon diagram abstractions for protein secondary structures limiting their applicability to other data types. Illustrative techniques [TCM06, vDZLBI11] and surface simplifications [CG07, PJR*14] are also used. Several dedicated views have been proposed for the analysis of molecular interactions and comparisons. For example, VIA-MD [SLK*18] uses a density field to reveal interaction hotspots in molecular dynamics simulation, Furmanová et al. [FBG*18] proposed several techniques for studying the contact zones between interacting proteins, and Schatz et al. [SKB*19] introduced a mapping of molecular surface to a sombrero shape to ease the comparison of binding sites.

5. Design of New Visual Abstractions

As a reaction to the identified gaps in the available 3D chromatin representations, we designed four novel representations to address a subset of the unexplored tasks. In this paper, we primarily focus on **structural-features** and **structural-relationships** tasks. We see

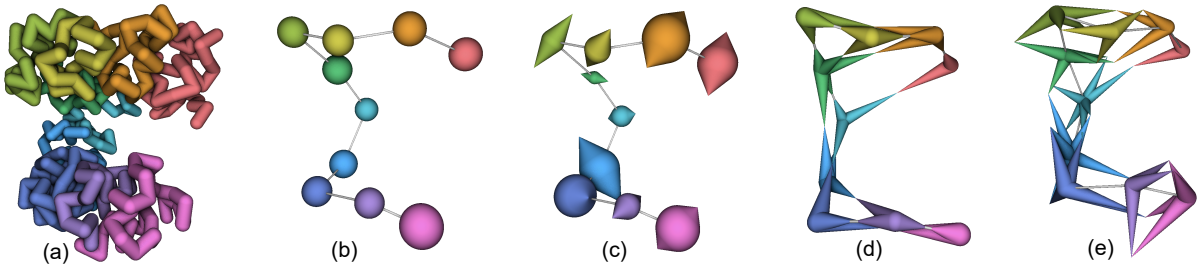

Figure 2: *Examples of abstraction techniques: (a) original tubular chromosome model colored according to identified sub-regions; (b) spherical abstraction; (c) cone abstraction; interaction abstraction with (d) simple contact mode, and (e) detailed contacts. The last two examples highlight the interaction between red and turquoise regions that are far apart in a linear sequence.*

addressing these tasks as a necessary pre-condition for other tasks, since metadata-oriented tasks in 3D view typically require underlying structure and comparative tasks form a natural extension of all other tasks. First, we introduce abstraction techniques for the representation of spatial sub-units of chromatin fiber (**S1**) to combat the effects of occlusions which are a common issue in traditional representations. Second, we extend the abstraction techniques to show sub-unit interactions (**R1**). Then, we present a technique for chromatin temporal dynamics (**R2**). Lastly, we introduce a technique for studying the hierarchical organization of spatial features (**R3**). We also discuss how these techniques can be combined to support additional tasks, such as focus+context exploration (**R4**).

5.1. Structure Abstractions

Spatial chromatin models can be visually very complex, making analysis difficult due to occlusions (Figure 2a). One possible solution is to remove sections of the chromatin sequence or use cutting planes as was previously done in molecular visualization [LMMS*16, KKK*18]. However, this removes the affected elements completely, leading to a loss of necessary context (**R4**). To preserve this context, we propose two abstraction techniques that divide the chromatin structure into cohesive spatial regions (e.g., TADs) and represent all or a subset of these regions with simple shapes that keep the key properties of the original regions. The underlying linear sequence can be indicated by a tube connecting the abstract models.

The first technique represents each selected chromatin region as a sphere located at the average position of all bins forming the abstracted region (Figure 2b). Initially, we mapped the sphere size to the number of bins the region contained. However, this representation was inverse to intuitive interpretation: spatially small regions with densely packed fiber (i.e., with a high number of bins) were represented by large spheres, while spatially large regions with loose fiber were represented by small spheres. Therefore, we changed the radius mapping proportionally to the distance between the region center and its furthest bin. To manage possible occlusions, users can adjust the size's scale factor.

Unfortunately, the spherical representation offers limited information about the underlying structure. The second technique replaces spheres with cones, adding two parameters (cone orientation and length) for mapping additional properties on the abstraction. We use the direction of the model's first principal component as the cone orientation and the lengths of the first and second components as the cone length and base radius, thus providing better information about the shape of the underlying region (Figure 2c).

In our prototypical implementation, the chromatin regions are detected automatically based on spatial hierarchical clustering (emulating TAD detection). However, the regions can also be manually assigned, since the technique was designed to be flexible enough to arbitrarily extend to other types of structural elements (**S1**), such as independent chromosomes. Besides directly encoding the structural elements, the reduction of occlusion allows for easy evaluation of their mutual positions and orientations (**R1**).

5.2. Spatial Interactions—Stars

A key studied structural relationship is the interaction between structural features (**R1**), especially areas that are far apart on the DNA sequence or on different chromosomes but close in space. Existing tools are achieving this task by searching for proximal areas in detailed 3D models. Some tools highlight the interactions by line connections. In both cases, occlusions complicate the tasks. Therefore, we have designed a dedicated technique for this task.

The input of the technique is a selected region (e.g., one TAD) along with data representing the surrounding regions. Next, we use the abstract spherical representation from the previous section as the base model for the selected region. Subsequently, we take all bins in the selected region and compare them to all bins in the surrounding regions. When the distance of two bins is smaller than the user-defined threshold, a contact is detected, and we attach a cone pointing to that region to the base spherical representation.

Users can choose one of two modes for adding cones. In simple contact mode, only one cone pointing to the center of the other region is shown (Figure 2d), providing an overview of the interacting structural units. Alternatively, in detailed mode, multiple cones are added, each pointing directly to the location of the individual contacts. Thus, the cones indicate the number of contacts and their positions (Figure 2e), resulting in the star-shaped 3D glyphs. To avoid many cones pointing to the same contact area (since usually many neighboring bins fulfill the contact condition), we filter the contact points in the same neighborhood. First, we sort the detected contact points by the contact distance. Then, we traverse the list start-

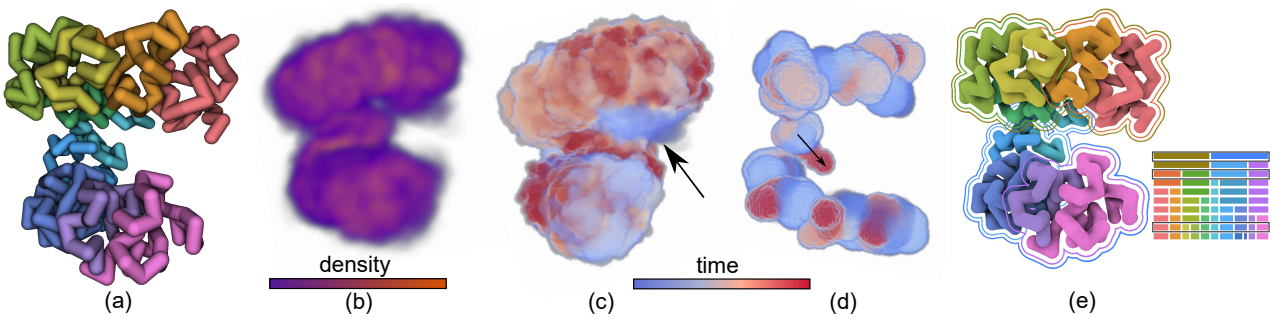

Figure 3: *Temporal aggregation and hierarchical outlines: (a) tubular chromosome model; (b) temporal density—transparent purple areas are occupied less often than opaque red ones; (c) movement trend—showing that part of the structure moved from the blue area (beginning) to the red areas (space occupied at the end of dynamics), opening a gap in the middle of the structure, marked by an arrow; (d) combination of the technique with abstract sphere representation showing dynamic paths of individual structural regions (e.g., a diagonal downward motion in the middle area); (e) hierarchy visualization shows three levels of the hierarchy selected in the simplified 2D view on the right.*

ing from the closest contact (as those are the most important) and remove all other contacts in the list that are within a given radius of the processed contact. The radius is a user-adjustable parameter, although it should be set with data resolution in mind.

5.3. Temporal Aggregation

Analysis of temporal chromatin changes (**R2**) is essential since chromatin architecture and its functions change over time [NIF*13, NLV*17]. Currently, dynamic changes can be studied via animations, but those are problematic for long sequences. One solution is the automatic detection of key timeframes [BTM*19], but no metrics for chromatin currently exist for this detection. A different approach aggregates the timeseries into a single image [SLK*18], encoding essential properties.

Inspired by the latter approach, we introduce a technique encoding the temporal changes of the chromatin conformation within a single image. First, we divide the bounding volume of the chromatin structure into a three-dimensional grid [RBT14]. Then, by iterating through the temporal sequence, the grid cells are updated based on a property selected for the final cumulative image, using one of flowing two properties. The *temporal density* captures how many times each grid cell was occupied by the chromatin model (Figure 3b). The *movement trend* reflects its directional behavior across time by recording the index of the last timestep of the sequence when the cell was occupied (Figure 3c).

The cell occupancy is, by default, computed based on the standard tubular representation of the structure. However, the temporal aggregation technique can also be combined with the previously described abstraction techniques. In such cases, the volumes are calculated from the abstracted spheres instead, showing the motion of individual regions separately (Figure 3d). Additionally, the user can adjust the thickness or size of the chromatin representations from which the properties are calculated—larger sizes lead to more cells being affected by the chromatin representations and, thus, to visually denser volumes. The grid is then rendered using traditional volumetric rendering methods [EHK*04], with property values interpreted as volume density. To color the volumes, the user can adjust the transparency and toggle between a region color and colormaps that are sampled based on the property value.

This representation can support analysis of the chromatin behavior over time (**R2**). The temporal density shows the overall stability of the model since stable regions become dense areas in the volume. Conversely, volatile regions that are subject to a lot of movement become lighter, less dense areas. The movement trend volume can show the overall conformation change of chromatin, e.g., how different regions open or close as the structure moves.

5.4. Hierarchical Outlines

Studying the underlying natural hierarchy of chromatin (**R3**), introduced in Section 2, is essential for understanding the relationships between these levels. For example, scientists study the placement of gene loops within A/B compartments [DTC*17]. Unfortunately, existing spatial representations are incapable of showing these hierarchies within a single image. Yet, such views are imperative to keep the context of the entire hierarchy visible at once.

To communicate the underlying relationships to the user, we take inspiration from nested Matryoshka dolls. We interpret each level of the structural hierarchy as a group of spatial clusters, each with a unique color. We used an approach similar to TreeColors [TdJ14], mapping hue to position along the linear DNA sequence while adjusting chroma and luminance at different hierarchy levels. While this produces similar colors for neighbors in the hierarchy, it can produce indistinguishable colors at lower levels. To address this, we track cluster color similarity and slightly perturb overly similar colors [LFC*20], preserving hierarchy while enhancing distinguishability. Users can override this with highly distinguishable palettes from ColorBrewer [HB03] and iWantHue [Jac16], which, however do not reflect hierarchy. Alternatively they can assign cluster colors manually. The clusters at the lowest level of the hierarchy are, by default, visualized using the standard chromatin tubular model, ensuring that they are shown in full detail. Subsequently, higher levels are represented only with an outline (see Figure 3e). Originally, we used nested transparent surfaces instead of outlines, but this design was visually cluttered. The user can control which hierarchy lev-

els are visible using a 2D hierarchy representation that shows the splitting of linear sequence. Although an arbitrary amount of hierarchy levels can be displayed, the visual complexity of the view increases with each added level. Thus, no more than four levels are recommended. Fortunately, four levels sufficiently cover the most common hierarchy (chromosomes, compartments, and TADs).

We emulate TAD detection by hierarchically splitting the linear sequence based on spatial proximity. However, since not all regions of chromatin form hierarchical features, we also support the definition of 'unclassified' regions, representing areas with loose chromatin fiber. We also allow manual hierarchy mapping based on additional data (e.g., other biologically relevant regions). In this way, our solution supports the exploration of relationships such as mutual orientation, shape, and size of the interaction zones at different levels of the structural organization simultaneously (**R3**).

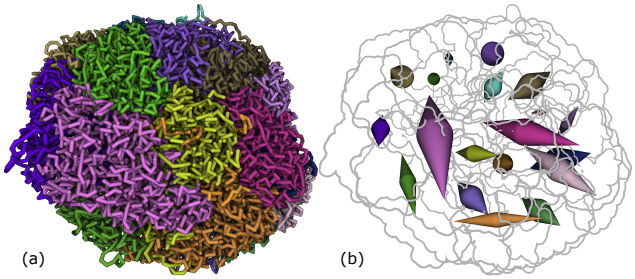

Figure 4: *Arrangement of 20 chromosomes inside the cell nucleus. The traditional view (a) suffers from occlusions. Abstract cone representation (b) reveals chromosomes located on the nuclear periphery as well as those reaching the deep interior of the cell nucleus.*

5.5. Combinations and Interactions

Each of our visualization techniques addresses specific issues and tasks related to the analysis of 3D chromatin structure. However, we designed these techniques with their interactive combination and connection to other views in mind. For example, the abstraction techniques can be combined with traditional tubular models, so some parts of the chromatin structure can be explored in detail, while other parts are simplified to preserve the context (e.g., position, size, orientation, or interactions shown with star representation) of neighboring elements (**R4**). We also experimented with hybrid representations, such as abstract representations combined with the outline (Figure 5d). This approach highlights the exact boundaries of each abstracted unit, thus providing more information while minimizing occlusion. The users can interactively choose what level of the structural hierarchy should be depicted for each part of the dataset. Thus, they can control the level of detail by setting appropriate granularity.

Our representations can be animated to show temporal sequence. This can reveal changes not visible in aggregated views or the animation of standard representations. For example, the animation of cone abstractions shows the change in principal shape and orientation of the underlying data often hidden by occlusions in fully detailed representation. The abstract animations could also illustrate changes in structural hierarchy, such as the split of one structural feature into smaller subunits.

Finally, our representations are designed with future linking with standard 1D and 2D representations in mind. This would mean that the user could select regions of the Hi-C map to be highlighted in the 3D view or use the map or other metadata to define the hierarchies and hybrid representations. The implementation is prepared for this, by supporting custom hierarchy definition.

6. Implementation

Our implementation is split into two parts. The rendering is implemented in a WebGPU-based graphics library, that can be connected to other frameworks. The library uses implicit representations of spatial data and raycasting to render the objects. This library is used by a prototypical client-only web application written in the Svelte framework. The application defines the proposed representations as independent reusable components. The repository with our implementation is available at `http:www.muni.cz/go/6f6942`.

7. Exemplary Use Cases

To evaluate the proposed representations, we prepared several use case scenarios, which were then discussed with four senior domain researchers. In this section, we describe three of these use cases, compare them to contemporary techniques, and summarize the collected expert feedback. The use cases were demonstrated on two datasets. Dataset 1 contains a static model of the entire mouse genome (20 chromosomes) in the cell nucleus [SLB*17]. Dataset 2 contains a simulation of structural changes during cell reprogramming from B cells into pluripotent stem cells (PCS) [DSSF*20]. For each dataset, we also have interaction matrices that represent distances between individual bins and thus mimic the Hi-C data. We have also prepared additional figures showing these use cases that can be seen in the Supplementary material.

Whole Genome Arrangement First, we explore the whole mouse genome dataset. The arrangement of the chromosomes within the cell nucleus is known to affect their activity and function (e.g., gene-rich chromosomes are found predominantly towards the interior of the cell nucleus, while the periphery contains gene-poor chromosomes). However, when the full dataset is displayed with standard representation (Figure 4a), the size, shape, and positioning of the individual chromosomes (shown with different colors) are difficult to infer due to occlusion. To rectify this, we employ abstracted cone representation (Figure 4b). Here, each chromosome is represented by a single cone. To provide better spatial context, the outlines of each chromosome are preserved. This gives us an immediate overview of the chromosome arrangement (**S3**). We can see which chromosomes are located closer to the nuclear periphery, and which of them are located in the interior. We can also identify chromosomes that span from the periphery to the interior (**R1**).

Chromosome 3 Organization Next, we took a closer look at chromosome 3 from Dataset 1. When looking at the standard 3D representation, we clearly see the chromosome is divided into three high-level TADs, but no other interesting observations can be made

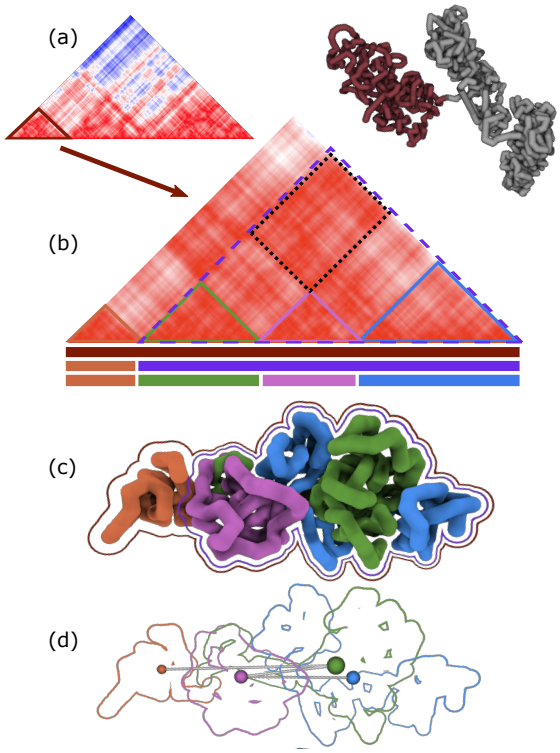

Figure 5: *Spatial organization of the whole chromosome 3 (a). The distance map of the red part of chromosome 3 (b) shows the green TAD is positioned between the orange and pink one in the linear sequence. The dashed black rectangle indicates many interactions between green and blue TADs. The 3D arrangement (c) shows that the green TAD is nested in the blue TAD, but obscures the linear arrangement of the sequence. Abstract representation (d) provides an overview of spatial and linear arrangement at the same time.*

at first glance (Figure 5a). However, in the interaction matrix of the chromosome, we see further lower-scale patterns that we would like to explore (**R3**). Therefore, we focus our exploration on the first of the three high-level TADs. In the matrix, 4 smaller TADs can be seen (Figure 5b). These are detected by our spatial clustering algorithm and the 3D representation is colored to reflect them (Figure 5c). We also detect one intermediate-level TAD that groups together three of the four TADs (purple outline, dashed triangle in matrix). This catches our attention as this intermediate TAD is not so apparent in the matrix. Upon closer inspection, we see a possible cause. In linear sequence, the green TAD is positioned between the orange and pink TADs, and the sequence ends with the blue TAD. This is not immediately clear in the 3D view, in which, at a glance, it seems that the orange TAD is followed by the pink and then the blue and green TADs. Without closer analysis, such situations can lead to wrong conclusions. However, we can clearly see what is happening when we switch to abstracted sphere representation (Figure 5d) which forms a bridge between the spatial arrangement and linear sequence. Moreover, when we use this representation in combination with outlines, we preserve other interesting spatial relationships, such as the fact that the green TAD is nested in the blue one. The interaction matrix shows a lot of interaction between these two TADs (black dashed rectangle), but the spatial arrangement of the interaction zone cannot be easily interpreted from the matrix alone. This case highlights the importance of the interplay between multiple views and the need for abstraction.

Structural Changes Lastly, we explore Dataset 2, consisting of a sequence of 600 frames showing changes in a chromosome 3 region centered around the SOX2 gene during cell reprogramming. We first look at the overview of the dynamics with our temporal aggregation techniques (Figure 3b,c). In the temporal density view, we observe a relatively stable Σ-shape of the structure, although increased 'blurriness' can be observed at both endpoints, suggesting more mobility in these areas. The movement trend view confirms this and shows that these areas were occupied in the early frames of the dynamics, when the two endpoints were much closer together. Subsequently, the endpoints moved apart, opening a gap in the middle. While these representations give us a good overview at first glance, the high-level changes are also apparent from the animation of a standard 3D view. To get a deeper insight into structural relationships, we split the structure into sub-regions and use star glyphs with an interaction threshold of 65 nm between bin centers to study how the intra-chromosomal interactions change during the dynamics (**R1**, **R2**). At the beginning, mostly just interactions between linearly neighboring regions are present. However, between frames 110 and 270 we see that the turquoise region (approximate location of the SOX2 gene) interacts with the beginning of the linear sequence indicated in red (Figure 2d,e). To study this interaction, we use a composite representation with the turquoise region shown as a star glyph with an outline and the rest of the structure shown using a standard tubular representation. We see that the interaction is formed by the part of chromatin fiber that separates from the turquoise region and reaches toward the red region (Figure 6a). However, in the second part of the dynamics, this 'bond' disappears, the turquoise region gains more spherical conformation and moves away (also seen in Figure 3d). Subsequently, the whole structure opens up, widening the gap in the middle (Figure 6b) as we initially observed in the temporal aggregation view.

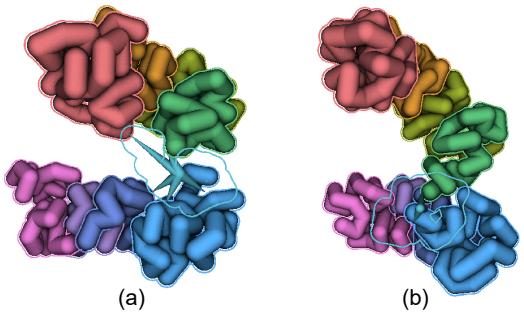

Figure 6: *Changing interactions during cell reprogramming. In the first part of the dynamics (frame 188), we can see the turquoise region (shown with star glyph and outline) extending towards the red region and forming a contact (a). Once the contact disappears the gap in the middle of the structure opens up (b). This figure shows the same dataset as Figure 2 rotated by 180°.*

7.1. Expert Feedback

Overall, the four interviewed experts rated our representations as very beneficial and suggested several further scenarios where they could be useful. When discussing the first scenario (chromosome arrangement in the cell nucleus), one of the experts noted that this view could also be useful for the comparison of chromosome territories between cells from different tissues of the same organism and for the evaluation of changes in healthy and damaged cells (**C1**). However, he also noted that these changes might be too small to be reflected in this abstract representation. Regarding the star glyphs, application to protein-protein interactions was suggested as the problem with occlusion is analogical there. Other experts noted that the view, together with a contextual outline, could also be helpful for the analysis of transchromosomal interactions or to identify areas where translocation can occur when chromosomes are damaged, and the fragmented pieces are re-attached to different chromosomes during the repair process (**R1**). Regarding the temporal aggregations, they were suggested as a good initial overview for comparison of multiple dynamics (in a side-by-side view) (**C3**). However, one expert noted that the movement trend mapping was not intuitive, while the temporal density was understood well.

Overall, the experts claimed that our visual representations give them a better understanding of spatial relationships than the commonly used interaction matrices and standard 3D representations alone. They highlighted the usefulness of the hierarchical outlines for showing biologically relevant units, such as TADs and compartments. At the same time, they noted some limitations and provided suggestions for future improvements. Unsurprisingly, linking with 2D and 1D representations was mentioned, but we already planned this as the next necessary step. It was noted that when there are many structural units, the colors become too similar, which we acknowledge. For the outlines, different styles of lines were suggested for different levels of hierarchy (e.g., different thicknesses or dashed lines), since the change in the color is not that prominent. Finally, the use of other visual abstractions and glyphs was discussed. One expert suggested the use of X-shaped glyphs to indicate chromosomes in the first use case, but it was noted by others that it could be misleading since the chromosomes only take on the X conformation in a certain phase of mitosis. The use of other glyphs and shapes was suggested to mark significant locations, such as transcription starting sites or replication foci.

8. Limitations and Next Steps

The task analysis presented in the first part of this paper reveals many areas where dedicated 3D representations could be highly beneficial. Our newly proposed techniques aim to address some identified gaps but still suffer from some limitations. Here, we discuss them and outline the next steps.

Our implementation is supposed to be only a proof of concept. While all techniques achieve interactive frame rates, the performance of the temporal aggregation technique is highly dependent on the resolution of the grid. In our current implementation, the resolution might not be sufficient for very large datasets such as an entire genome. However, we are confident that more advanced volume rendering techniques [SZD*23] would make this feasible. Further, the use of color to distinguish structural elements is limiting. We have already tried to improve this issue after receiving user feedback, but alternative solutions should be examined.

Besides these limitations, the next natural step is interactive linking between 3D representations and other commonly used 1D and 2D views (e.g., selection and navigation across views). While we argue that 3D representations have many advantages, we acknowledge that many tasks likewise benefit from non-spatial representations. Linking the views could be particularly useful for structural tasks, such as the exploration of new motifs in the data (**S2**) that can be hard to see or understand from Hi-C matrix alone, as well as for validation of the reconstructed structural models (i.e, to check if the motifs from Hi-C matrix translate to 3D model).

Equally important is addressing the metadata-oriented tasks. Besides integration with standard methods such as glyph and text annotations, we would like to explore other options, such as mapping continuous properties on the surface of abstract representations.

These two issues need to be resolved to make 3D representations a useful part of genomic research. Once they are addressed, we plan to focus on comparative tasks, where there are still many open challenges due to the task and data complexity (i.e., size and number of datasets) and diversity of data sources (e.g., alignment and resolution issues). Comparative tasks could be supported by automated methods to detect differences and guide user attention. We would also like to improve the support for the analysis of dynamic data. For example, existing techniques do not directly highlight events such as the formation and splitting of structural features. The animation of some of our abstracted and hierarchical techniques could be used for that, but the analysis of events in dynamic data might be better supported by additional non-spatial representations.

9. Conclusion

In this paper, we take the first steps towards making 3D visual representations an integral part of genomic research. We analyzed the needs of the domain experts with respect to the representation of spatial data and presented four categories of tasks that can benefit from 3D visualizations. We then focused on a subset of these tasks predominantly related to structural relationships and presented four newly proposed dedicated visual representations to address these tasks. A follow-up discussion with the experts revealed that our solutions improved the perception and understanding of the data and could be used in many analytical scenarios. Yet, much work still needs to be done. Our next step includes linking our solution with the existing genomic visualization techniques as well as developing new techniques for the representation of additional metadata. Finally, we would like to address the comparative tasks, which is a task category that is highly demanded by domain scientists but is currently very poorly supported by the existing solutions.

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