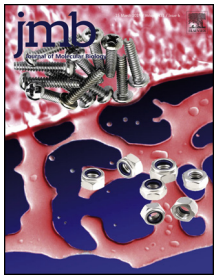

Communicating Genome Architecture: Biovisualization of the Genome, from Data Analysis and Hypothesis Generation to Communication and Learning

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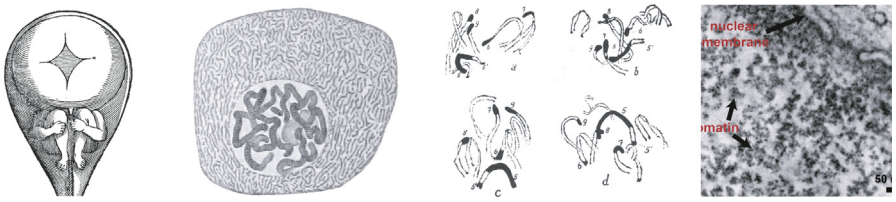
Abstract

Genome discoveries at the core of biology are made by visual description and exploration of the cell, from microscopic sketches and biochemical mapping to computational analysis and spatial modeling. We outline the experimental and visualization techniques that have been developed recently which capture the three-dimensional interactions regulating how genes are expressed. We detail the challenges faced in integration of the data to portray the components and organization and their dynamic landscape. The goal is more than a single data-driven representation as interactive visualization for *de novo* research is paramount to decipher insights on genome organization in space.

Introduction

Visions of the genome have brought deeper knowledge of the biology it encodes. The genome sits at the core of life, not the preformed *homunculus* but rather a collection of molecular possibilities held in genes (Fig. 1a). Organisms thrive by passing on gene combinations and survive by adapting to environment through random changes in the genome. They form strands of DNA which is read in linear sequence. In Bacteria and Archean, this happens fast and continuously, jostled by a crowded cell cytoplasm. Eukaryotes have evolved to wrap these increasingly lengthy polymers within membranes forming the nucleus. This appeared as a dark center of to the cell which revealed more detail with improved lenses and contrast through staining. In 1882, Walther Flemming drew the colored filaments of “chromatin” (later termed chromosomes) he saw condensing within (Fig. 1b), an intermingled square-dance generated reproductive cells (meiosis) or a synced jig for cell division (mitosis), which then aligned and parted, distributing the genome equally into each new cell. Arrayed as a *karyogram*, banded chromosome pairs highlighted commonalities between cells and marked relationships between species, which was a visual confirmation of the biochemistry underlying the mechanisms of inheritability. In 1928, Emil Heitz sketched ghettos of heterochromatin and expanses of euchromatin, which he correlated to gene location and regulation (Fig. 1c) [2]. And in 1952, Rosalind Franklin's skillfully x-rayed molecular shadows provided the visual key to sculpting the spatial arrangement DNA double helix underpinning biochemistry. This code imbues function into proteins automata through complex structure, laid bare through the ribbon diagrams of Jane Richardson in 1981. By 2001, the first complete genome was sequenced, and the simultaneous release of the UCSC browser was an essential utility for browsing across, peering into and aligning to compare this new data. ENCODE's complementary functional mapping was heralded on the September 2012 cover of *Nature* with the



(a) *Homunculus* Hartsoeker, 1695 (b) *Chromatin* Flemming, 1882 (c) *Heterochromatin* Heitz, 1928 (d) ChromEMT Ou et al., 2017

Fig. 1. Historic visions of the genome: (a) *Homunculus*, Hartsoeker, 1695. (b) Nuclear "*Chromatin"* observed by Flemming, 1882. (c) Heterochromatin and euchromatin sketched by Heitz, 1928. (d) ChromEMT imaging of chromatin from the O'Shea lab [1].

novel CIRCOS graph that facilitated non-linear exploration of the interactions noted. That many of these were over large genomic distances set a new frontier to understand the form of the genome in three-dimensions (3D). At each step, investigation of the constituents of the genome has been born of visualization, defined by the width of a lens, pen or pixel. Since then, researchers have expanded the knowledge of these regulatory elements to expose a complex hierarchy of structures and relationships describing the genome as spatial and dynamic. These discoveries have depended on the combination of the different experimental techniques, interdisciplinary collaboration and the power of visualization.

Modeling the Genome

The genome traverses many dimensions and has many facets. It is formed out of an atomic fog into long 2-m polymer packed into a micron-sized cell nucleus visible under a microscope. The biochemistry it encodes rapidly reacts to cell signals and can be used to measure its macromolecular transformations. The immense code it stores is essential for life but is inherently dynamic and error-prone. Its base bonds bend to subatomic forces and its structure to classic Newtonian mechanics, which, though non-trivial and resource intense, can model its behavior. However, until recently, there was a significant gap between the knowledge probed by microscopy and the molecular models built through biochemistry [3]. In the last decade, at least three quantitative techniques have been developed that help determining the structure needed to form a 3D model of the genome.

First, bioimaging encompasses the collection of microcopy techniques for direct and indirect observation of the nucleus [4]. Light microscopy is still used to view cellular features today up to the light diffraction of 200 nm. At the other extreme, electron microscopy (EM) detects the densities of matter to map atomic detail of biomolecules. Filling the mesoscopic void between them, the new field of super-resolution microscopy can use differing of methods to scan the nucleic volume and to site genomic features in 3D using biochemical "oligopaint" tags. Computational microscopy automates what is a classic visualization pipeline for enhancement, identification, classification, filtering and tracking of features [5]. These digital microscopes produce large layered images not only guide theory or validate experiments, but are progressing to resolve the localization of objects to the tens of nm resolution, for example, by the imaging of hetero-/euchromatin by the O'Shea lab, which literally create new 3D models for genome function (Fig. 1d) [1].

Second, quantitative techniques based on biochemistry can isolate and measure the constituents of the genome [6]. Traditional measurement by visual assessment of electrophoresis gels is now complemented with high-throughput sequencing. For example, Chromatin Conformation Capture (3C) "freezes" a population of cells and binds together closely positioned fragments of chromatin that can then be sequenced [7]. The 3C-like Hi-C method captures "reads" at all genomic coordinates, which can be plotted as a matrix of contacts, with higher read count indicating areas of increased interactions. As a population of cell states, careful normalization is required before analysis; however, cell synchronization and new single-cell techniques can give a more reliable picture [8]. In such matrices, a careful color selection highlights features and avoids perceptual bias. Pattern detection by visual inspection can identify interactions: clustering close to the diagonal depict looping at short genomic range; longer range points of contact are indicative of compartmentalization. The largest clusters correspond to chromosomes (Fig. 3a), which occupy specific territories, but additional distinct domains are also observed often with overlapping inner subdomains. Eigen decomposition of the matrix indicates high-order compartmentation that broadly corresponds to the previously observed hetero-/euchromatin domains (Fig. 3b). The hierarchy of self-interacting or topologically associating domains (Fig. 3c: TADs; CIDs in bacteria) delimited in the matrix has been shown to be functionally determinant [9] and to be conserved between cell types and species [10]. Further computational analysis of the

data can reconstruct ensembles of possible spatial conformations of the chromatin [11]. The resulting XYZ coordinate data requires approximated scaling and can be visualized using 3D molecular viewers.

Third, molecular modeling using polymer physics and molecular dynamics can simulate intracellular environments and chromatin structures from theoretical principals and experimentally determined properties [12]. Three physical scales can be modeled [13]. At the subatomic scale, quantum mechanics can model dozens to 100 s of atoms over a few picoseconds. Atomic molecular structures of 10^3–10^6 atoms can be modeled with molecular mechanics calculations in Cartesian space iterating through stochastic events acting upon polymers from 100 s over ns to a few μs. These can describe surface features and properties such as binding sties. However, such precise computation is resource intense and so, where chromatin acts as whole fibers at higher scales, coarse-grain particles can represent the millions of atoms from dozens of μs to ms, while retaining relevant and informative insight. Starting from initial formalized or random configurations that over time reaching a steady state, models adopt globule conformations stored as either atomic structural arrangements or XYZ coordinates.

As separate approaches, these can be used to validate one another using visualization. For example, the task of interactively fitting possible conformations of chromatin to match observed EM density maps, as used in reconstruction of the nuclear pore [14]. Quantitative detection of spatial repression for regulation of the second X chromosome in mammalian females has be confirmed by super-resolution microscopy [15]. The model fractal globule is organized as accessible structure reflecting actual contact probability of the genome during interphase [16]. However, these approaches can also complement each other to build a more integrated holistic informed model (Fig. 2) termed the 4D Nucleome [18]. Indeed, two new initiatives, launched in United States [17] and Europe [19], aim at integrating these different approaches to overcome technical limitations providing new insights, circumventing limitations of technology and bridging the resolution gap [20]. Other initiatives work to provide solutions for specific issues, for example, the Allen Cell Institute for predictive cell modeling (http://www.alleninstitute.org) [21], the Human Cell Atlas for comprehensive profiling (https://www.humancellatlas.org) [22], the Multiscale Genomics VRE for quantitative collaboration (http://multiscalegenomics.eu) and the West-life VRE for structural modeling (http://west-life.eu). This integrated approach is already proving fruitful with theoretical models that advance new functional models of the genome [23].

Integrating data

However, there remain a number of challenges in the integration of the data from these approaches, as

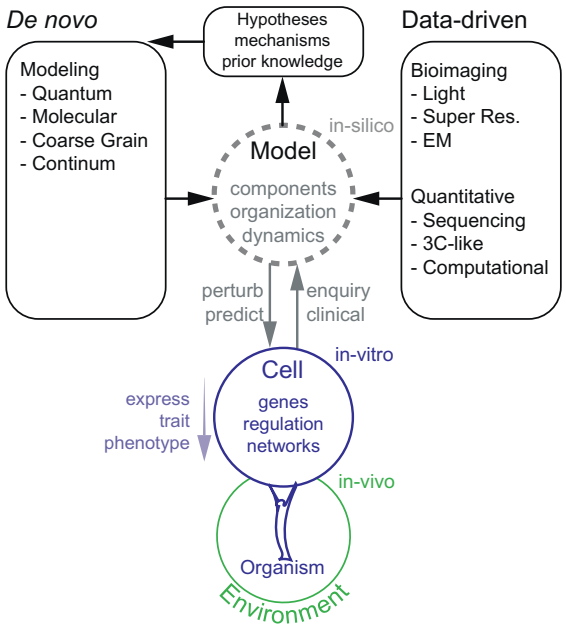


Fig. 2. An Integrated genome model: flowchart for integrating data to models the genome. Adapted from Ref. [17].

discussed in detail in previous reviews [24,25]. While there is increasing overlap of techniques, their resulting data may be very distinct. Their multiscale, resolution and range are difficult to reconcile: heterochromatin is captured distinctly by nucleosome density and as A/B compartmentation; EM density maps of chromatin lack the detail of molecular dynamics simulations; assays may capture non-interacting but proximal strands, among other limitations. They display a variety of coexistent physical and biochemical changes, from the cell cycle to local DNA methylation, interrogating genomes that exists in multiple states. These components and stages are also time dependent, and their structure and properties vary in time frame and duration: the nuclear membrane decomposes and reconstitutes, and chromatin looping unpacks and condenses. On top of these, the data are imbued with uncertainty, which may make integration, alignment, replication or reproducibility more complicated: cell degradation during imaging, reconciling population and single cell data [26], randomization of model seeding and intrinsic structural variability [27].

Once gathered, ease of data accessibility and connectivity cannot be assumed [28]. DNA sequences and epigenomic data can be fetched as needed from BGRA-compliant servers [29]. Standards have advanced for the common microscopy formats and molecular models within shared international archives: OME images on the IDR [30], 3DEM maps in the EMDB [31] and protein-like mmCIF structures in the PDB Archive [32]. Interaction data can be opened in browsers like WashU [33] and coarse-grain models in

Chimera, and while the data size could be handled by existing infrastructure, the added dimensionality and layering of 3D data is not currently served and there are no dedicated formats or repositories for this 3D data. Moreover, current mainstream genome browsers display compact, stacked tracks based on a linear, sequential, per-chromosome coordinate system and are currently unable to display such multi-dimensional non-linear data. Novel formats such as the compressed mm-TF format [34] and, in particular, the multiscale mmCIF-IHM dictionary [35] are addressing these issues and can be viewed with the upcoming ChimeraX [36]. Moreover these formats lack spatial data structures and the viewers generally lack level-of-detail (LOD) interaction key to coherent navigation of multi-resolution scenes.

However, the greatest impediment to integration is the lack of common metadata by which data can be matched and meshed to be FAIR [37]. The data types that result from the three approaches are very distinct—images of loci, arrays of interactions and coordinates—but they do share some common relating to the subjects, properties or experimental assumptions, for example, organism, cell-cycle phase, area of interest, and so on. Unfortunately, there is in general a lack of consistent metadata, which can identify the experimental source and processing [38]. The ontology appropriate for the data must rely on standards for, for example, component description, but we also suggest others through analysis of required grammar and idioms that follow in the discussion of appropriate visualization methods.

Genome Architecture

While these challenges are being addressed, a consensus is emerging through the integrative projects describing the structure, organization and dynamics of the genome. The genome is found with higher-order organization components that document the range and complexity to be visualized. The experiments detailed above give a perspective on these core higher-order components that form the genome at the chromatin scale, progressively filling this gap in knowledge between cell and DNA (Fig. 3). A number of reviews of current genomic models propose starting points to 4D Nucleome research [18,39]. Recent observations made from the O'Shea lab using innovative labeled EM tomography (ChromEMT) have helped clarify key features and have led to a better understanding at intermediate scales [1,23]. To encapsulate this and relate it to visualization techniques, the genome model is conceptualized here as architectural components whose organization and states form a dynamic and interactive landscape.

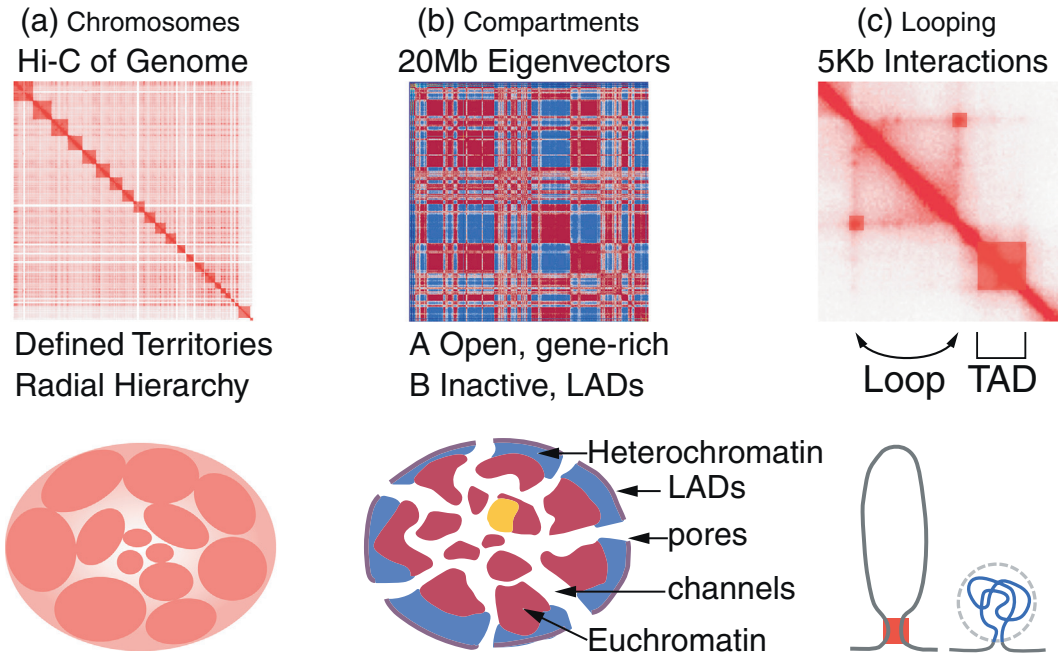


Fig. 3. Quantitative determination of genome architecture. (a) Hi-C identifies chromosome territories within the nucleus organized radially, with smaller more conserved chromosomes at the center. (b) A/B compartmentation reveals chromatin activity. Gene-rich areas of euchromatin form a landscape of activity accessed from nuclear pores along intra-chromosomal channels. Inactive, tightly packed heterochromatin and LADs are found at the periphery of the nucleus. (c) Looping can be identified with in matrices by interaction of non-proximal regions of the genome, with forming more closed TADs, which regulate gene expression.

The genome is enveloped by the nuclear membrane, a protective lipid that has evolved to maintain and moderate the frenetic activity within. It controls access from the cell cytoplasm through nuclear pores and its inner surface contributes to the regulatory and spatial order of the nucleus. The nucleoplasm is densely packed with soluble macromolecules of a range of sizes from small protein machinery, through small bodies like *speckles*, to ribosome production complexes, which are assembled in the large globular nucleolus. Lengthy fibrous polymers of chromatin of few tens of nanometers account for a substantial part of nuclear volume.

In 3D/*in vivo* cell conditions, the genome organization exhibits high-order organization by its constituent chromosomes. Compartmentation exists in both the classic condensed forms and as chromosome territories when uncondensed during interphase with smaller chromosomes housing evolutionary conserved genes more central to the nucleus. Biomolecules permeate from the pores through lower density inter-chromosomal channels between chromosome territories, which may facilitate interchromsomal regulation, or coalesce by phase separation to form the larger bodies [40]. Compact heterochromatin lines the inner membrane as laminar-associated domains (LADs) around more accessible euchromatin and is structured by nuclear bodies like the nucleolus and speckles [41]. Within these, architectural proteins like CTCF help cohesin to pull the chromatin into loops that bundle into the TADs and sub-TADs described above.

The spatial organization of the genome is, above all, dynamic in nature. The membrane breaks down and reforms during mitosis, cell stress or differentiation, and increases porosity during interphase to enable transport. Through crowding, the nucleoplasm regulates diffusion and interaction rates and thereby metabolism. Rates of loop formation are key to the speed of chromatin condensation, compartment formation and thereby epigenetic expression. And of course, at the smallest scale there is the frenetic transcribing of molecules, which may also be governed by quantum dynamic changes.

Visualizing the Genome

Visualization is a mature field that has evolved from elaborate artwork into a precise, evidence-based science of visual communication. The writings of Tufte [42] lead the drive for clear, concise graphic presentation of the data, a ratio of data to ink or pixel. Research by Ware [43] and many others have detailed human perception as a fast and intuitive tool for image comprehension and have provided guidance on avoiding perceptual biases that can affect our reading of the data conveyed. Specific concerns related to 3D images are as follows: 3D can hinder analysis as there is a loss of planar reference and object occlusion; depth and perspective distort the image; and for large varied data sets, the amount and spread of data taxes the users visual memory [44]. Overall, as demonstrated in the stimulating presentations of Rosling *et al.* [45], visual delight encourages a critical reading, highlighting the readers own prejudices to ensure communication is "factful." These goals of legibility, clarity and engagement are extolled in the field of molecular graphics which, haltered to developments in computer graphics, has depended on efficient imaging to enable effective research and accessible education of discoveries with important social implications. In response to the above visualization caveats and the unlimited expressivity of the computer graphics medium, principles have been described that together with the broader goals can address the specific challenges for genomic visualization [46,47].

The base visualization of the genome is the linear track of DNA sequence that demarcate local arrangements genes and, when stacked against tracks of other species or assays, reveals patterns of inheritance and regulatory mechanisms. Two-dimensional track browsers share a visual notation of colors and glyphs, and common interaction tasks to filter and analyze, which have been key to genome research. A number of designs use innovative notation by depicting the data in 3D to augment the user experience: zoomable karyograms [48], haptic Circos diagrams [49] or as 3D big-data landscapes [50]. However, integration into 2D browsers of 3D data such as long-range interactions loses clarity and fails to convey the message as matrices, commonly used as 2D representations of 3D genomes, are expansive and break legibility. These can now also visualized as the arcs or even as links across the center of Circos plots [51] but have also been explored in abstractions, for example, as neighborhoods of a Hilbert curve [52]. While 2D images aid communication especially in print, they rely on idiosyncratic, specialized workspaces and still reside in the "Flatland" of the 2D genomic visualization [53].

The many dimensions from integrating imaging, assays and simulations may impede facile analysis, but these experiments characterize a novel, complex and dynamic architecture from which emerges biological function and form. To aid examination beyond mere file management, a number of authors have variously formulated an underlying process for construction of coherent visualizations [44], the initial step being to perform data and user abstraction to determine effective encoding [54] and efficient interaction [55]. A taxonomy of genomic tasks can be derived by correlating visualization expertise [56], cell microscopy [57], biological pathways [58], structural modeling [59,60], the 4D Nucleome initiatives [17,19] and genomics in clinical domains [61] (Table 1). In the next sections, we assess existing biovisualization and

Table 1. Genomic visualization task taxonomy: examples of tasks are derived from citations (adapted from Ref. [58] Table 2)

Category	Example task
Grammar	
(G1) Characterize	Stratify surface features and structural motifs.
(G2) Accentuate	Overlay known disease-related genes.
Structure	
(S1) Assemblies	Generate stochastic solubles around modeled chromatin.
(S2) States	Map interactions through scales to chart repression.
Variation	
(V1) Score	Highlight regions and outliers up-regulation networks.
(V2) Animate	Simulate chromatin reconfiguration by cell type.
Manipulation	
(M1) Orient	Situate exocentric viewpoint to observe LAD interactions.
(M2) Supplement	Dial through cell states to find repressive signatures.
Analysis	
(A1) Compare	Align chromatin conformation to EM density maps.
(A2) Classify	Perturb and filter model to trace disease pathways.
Curation	
(C1) Augment	Explore collaboratively as immersive haptic model.
(C2) Document	Track and explain treatment decision in patient records.

(*1) Research method. (*2) Visualization approach.

specific molecular graphic techniques [83,84] required for these tasks and indicate bottlenecks between data input and the user experience requiring novel solutions. For exploratory visualization, the data need encoding with the following: *representative grammar* for heterogeneous and novel components, *coherent structure* to convey the massive and complex organization and *descriptive variation* capturing the dynamics and uncertainty in the model (Fig. 4). In this form, it can enable explanatory analysis through the following: *interactive manipulation* of views coordinated across scale and state, *adaptive analysis* to facilitate interrogation of the diversity and *collaborative curation* for rapid interdisciplinary sharing of results (Fig. 5).

Representative grammar

As described above the genome is heterogeneous, polyvalent and largely dynamic. However, a photoreal graphical language is often employed to represent the genome as an "organism in miniature," a still-life of colorful, shiny objects in a fluid, with a well-lit setting. Lying deep within the cytoplasm, the atomic forms and actions of molecules can be more precisely studied in abstract and without cinematic license as described in a number of specific guidelines for molecular visualization [46]. Lipid membranes, small proteins and DNA components can be rendered as particle clouds, ball-and-stick diagrams or functionally descriptive "cartoons" [95]. Adopting the visual grammar of proteins is logical for close inspection, but the crowded cytoplasm obligates greater clarity, for example, by the use of distinct colored molecular glyphs (Fig. 4a) [85]. Water and other "solubles" are molecular at this scale and should be modeled without macroscopic aqueous phenomena (caustics, refraction, distortion, crepuscular rays) and assigned transparency to reveal larger bodies [62]. The immense nucleoplasmic arena is dominated by larger complexes and polymers that could be conveyed as molecular surfaces and volumes, a process that may able to be derived through an imaging pipeline [96]. To distinguish between levels of interrogation of such multiscale high-order components, these can be treated as more than mere tubules to express relevant granularity as explored DNA by shifting LOD [86] (Fig. 4b) and dynamic color mapping [97] or resolving areas of inspection [98]. Further figurative styling of components can also provide a spatial framework that can be overlaid with data attributes, for example, gene locations, component density, and so on. The model becomes a canvas onto which other data can be displayed, thus gaining a new perspective on it, for example, using chromatin strands to graph colocation of linearly distant genes (Fig. 4c). Overall, while there is a lack of "primitives" to describe genome components, it may prove useful to make automated preselection of grammar (e.g., the centroid from an ensemble) to aid initial assessment by the researcher.

Coherent structure

Neither a fibrous hairball nor the conceit of a hierarchy by "Powers of Ten" [99] adequately describes the overlapping functional landscapes and transitions of state of the genome. Complex networks can be difficult to tame and comprehend, but recent concepts of visualization help stratify connections for comparison, for example, as Hive plots [100]. The genome can be arranged into coincident layered models (Fig. 4d). For example, the wwPDB initiative's Integrative Hybrid model format (mmCIF-IHM) is viewable in the prototype ChimeraX, but the functional scales can only be toggled manually [101]. Representation of large collections of molecules has been demonstrated by animations of small volumes of cytoplasm using generative software like MegaMol [102] or CellView [103], but time for assembly is prohibitive for rapid, interactive exploration. Recently, faster techniques have been demonstrated to automate fast assembly of crowded models such as the

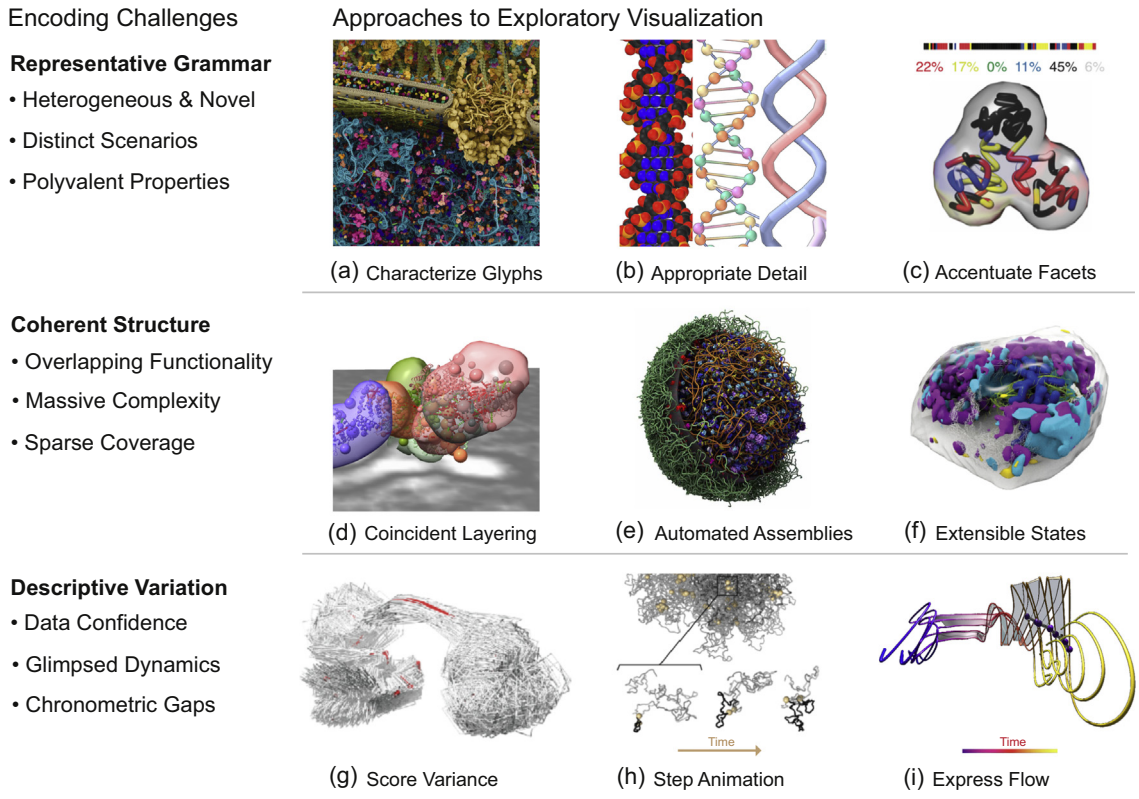


Fig. 4. Genome visualization—exploratory encoding, challenges and approaches: Representative grammar: (a) explanatory cellular landscape in the style of Goodsell *et al.* [85], (b) DNA shown with shifting levels of detail [86], (c) Chromatin fiber overlaid with chromatin typologies [11]. Coherent structure: (d) layering in integrative IHM hybrid multiscale/state models [35], (e) automated generation of crowded cell [87] and (f) segmentation and predictive assembly in Allen Cell Explorer [82]. Descriptive variation: (g) Hi-C-derived ensemble of possible TAD conformations revealing common structure, (h) stepped illustrations to explain chromatin dynamics [17] and (i) flowlines making molecular dynamics explicit [88].

interior of a bacteria using CellPack (Fig. 4e) [87]. The scene is organized into membrane bounded compartments; each volume is voxelized and populated with a pre-calculated mix of soluble molecules; then fibrous structures are generated though the nucleoplasm by random walk. Further accuracy could be introduced by incorporating density and segmentation data of sub-nuclear bodies (e.g., from Ref. [1]) to inform the compartmentation of the scene (Fig. 4f). More significantly, chromatin structure is not random and the overall path should be based on the model algorithms and/or experimental data. The varied compartmentation of chromatin, often shown simply as diagrammatic 2D boundaries, will also require more detailed assemblies, from the density patchwork and wooly borders of chromatin, hetero-/euchromatin or TADs. Other genomic bodies appear formed from phase-separated components and are still little understood, which gives the opportunity for novel computational visualizations to provide biological insights.

Descriptive variation

Variation in the data is an important factor to represent for assessment of quality, aptness, or relevance of the modeling (e.g., data confidence, possible conformations, etc.). For example, Cell Atlas provides a reliability score for every annotated location and protein on a four-tiered scale: “validated,” “supported,” “approved” and “uncertain” [104]. Depicting such variation is important for characterizing and conveying the dynamic nature of the genome and presenting the physical ensembles modeled from quantitative data reminds the user of properties and limitations of the data shown (Fig. 4g) [105]. Movement can be shown in a number of ways: simple stop motion correctly shows time-lapsed video as captured by microscopy over hours [106], or sparse positional data sets of quantitative experiments (Fig. 4h); full animation may be more appropriate if trajectory data are captured; volumetric flow lines can convey electrostatics, density and eddies (Fig. 4i) [88].

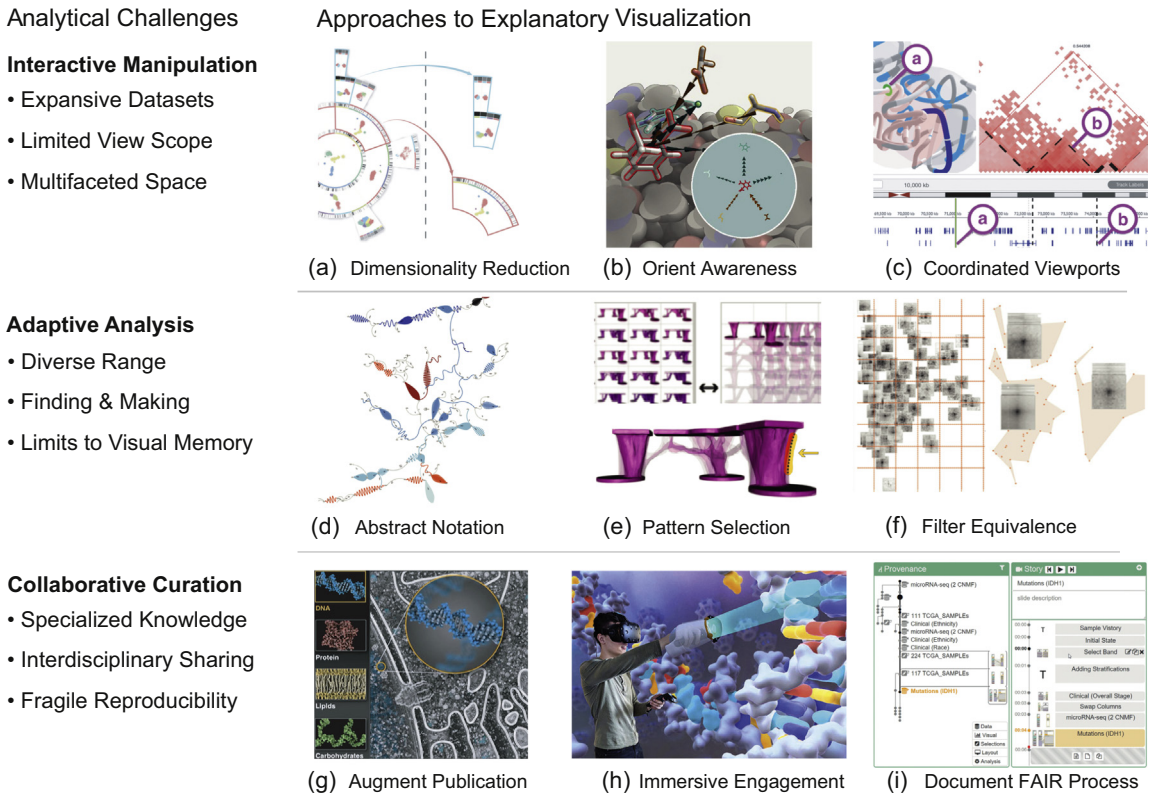


Fig. 5. Genome visualization—explanatory analysis, challenges and approaches. Interactive manipulation: (a) moderated navigation by dimensionality reduction in cyteGuide [89], (b) situational awareness orienting using spatial axial radar [90] and (c) coordinated views with three-way data connectivity between sequence tracks, Hi-C matrices and 3D models in TADkit [80]. Adaptive analysis: (d) abstract genome notation in ABySS-Explorer [91], (e) filtering computer-assisted clustering of 3D models with Dream Lens [92] and (f) computer filtering equivalence of Hi-C data in HiPiler [108] and HiGlass [74]. Collaborative curation: (g) engaging interactive figures by Gaël McGill for "E.O. Wilson's Life on Earth" [93], (h) immersive educational game "Guardians of the Genome" by AXS Studio (htttps://guardiansofthegenome.com) and (i) documentation of visualization process for improved FAIR metadata and reproducibility [94].

These observed processes occur at a vast range of speeds and time frames: picoseconds of transcription, mechanically limited or enzymatically accelerated over nanoseconds, and causing interactions through pathways, which range from microseconds to hours. Investigation of appropriate indication of the rates within the genome is essential as a full formed genome model will require controls of scene playback and more importantly indication of the chronometric gaps still present when different genomic data sets are combined (Fig. 6).

Interactive manipulation

Interaction with correctly encoded genomic model presents further challenges of coherent navigation within a multifaceted space and the limits on scope of the data in view [107]. In 2D, this can be addressed by zoomed call-outs/scalable insets [108], layouts of multiple figures (e.g., [1,17]) and dimensionality reduction, for example, cyteGuide (Fig. 5a) [89], in addition to visual clues, such as overviews, scale bars and object limits, that help orient the user. Both 3D non-domain apps [109] and genomic software (see Existing Tools) bring fast and fluid interaction of spatially structured scenes [110], optimized and rendered on-the-fly in GPU born of the CAD and games industries [110,111]. As in 2D maps, grids and markers [112] create common frames of reference and automatically decluttered at higher scales by aggregation [113]. A number of 3D-specific constructs can reduce the loss of reference when navigating these complex scenes: task-appropriate viewpoint and controls can be pre-selected by calculating the information of each voxel [114], and axial radars (Fig. 5b) [90] and "birds-eye"/"flower garden" give a 360° situational awareness and orient using avatar landmarks [112]. Other techniques reserve user interaction and interface selection for objective-focused intuitive spatial inspection and interaction: navigation can be steered [115] or condensed as gimbals (e.g., ViewCube [116]) or cell state dials [82],

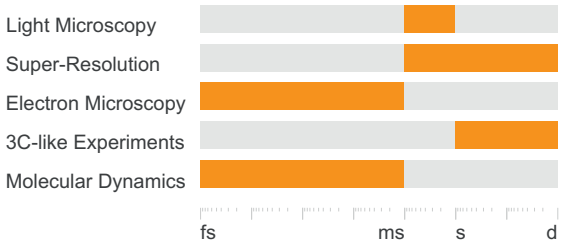


Fig. 6. Gaps in time frames of genomic data. Overview of time frames captured by different experimental techniques, indicating chronological gaps in current knowledge, on a logarithmic scale from femtoseconds (fs), through millisecond (ms) to seconds (s) and days (d).

and layers can be dynamically loaded, instead of picked, by moving through a scenes or LODs [117]. Even with these aids, as mentioned previously, 3D can distort the data and so hinder visual tasks when compared to a well-considered 2D layout. Multiple views of 3D data can help by providing distinct slices to confirm and coordinate navigation of synchronized data sets, for example, metabolic pathways [118], structural motifs [119] or genetic features [80] (Fig. 5c). They can also provide intuitive filtering by direct selection of data features or removing unchanged or irrelevant data [92]. The potential augmentation of the user's interactions is also being explored via AR, VR and CAVEs with haptic controllers [120], for example, with cutting planes for inspection of VR models.

Adaptive analysis

The identification of patterns within genomic data relies in part on visual inspection, yet the multidisciplinary data sets vary in their descriptions, resolutions or experimental approaches. They also cover a vast range of species, cell types, component scales and time series, taxing perceptual acuity and precision in comparison and classification. Two-dimensional genomics have been assisted by honing the data for comparison using abstract notation (Fig. 5d) [91] and by computer-assisted clustering (Fig. 5e) [121,122]. Pattern finding within 3D models by side-by-side or overlaid comparison is a common idiom of standard molecular viewers, but the expansive spatial data sets of the genome can overwhelm visual memory and their dispersed arrangement can induce change blindness [123]. Other idioms can help, for example, transparent stacking and view-switching (jump-cuts) can aid and highlight salient features [124]. Automated extraction and clustering of data small multiples can also help determine patterns of 3D data (Fig. 5f). This could be applied to unlabeled genomic components to assess their statistical distribution and functional relevance, as demonstrated in the Allen Cell Explorer, which uses segmentation to create predictive 3D models [82]. Knowledge can be fed back into shared models, which can provide focus for study, both in an expert and non-expert context through online repositories. The integration of such methodologies creates a system enabling "clinical queries" on an *in silico* model through a "computational" genome microscope, which could predict and diagnose [125]. As complete integrated genome models are assembled, automation of this 3D scouting and trail blazing must be explored by incorporation of web development technologies for automated UX testing to help ensure streamlined and reproducible observations.

Collaborative curation

Stewardship of integrated models and publication of findings are specialist, laborious tasks that output what are still primarily static 2D arrays of images [96]. Collation and processing can be assisted by graphical tools, such as BioRender.io and MAGI [126]. Extensions to professional-grade rendering packages have made production of molecular 3D stills and animation significantly faster and accessible to non-domain and non-expert users on both sides of science and illustration [63], in particular: Molecular Maya [62], Molecular Flipbook [63], ePMV [64] and BioBlender [65]. Intriguingly, these tools have begun to straddle between scientific and illustrative modeling as they can use code developed for research to correctly figure and animate the scenes (Fig. 5g). For publications, various means are being explored to embed 3D [93] and even animated visuals [127] within documentation bringing it from the supplementary section to the fore. Publishers are also looking to embed interactive illustrations [128] and 3D online (https://www.elsevier.com/authors/author-services/data-visualization) through apps like Juicebox.js [129] and NGL [130]. Furthermore, visualization formats such as Vega-Lite [131] aim to capture idiomatic intent, and formats, following the legacy of VRML, are being developed for AR, which could do the same for integrated 3D models. HCI and Visualization advances such as haptic interfaces and augmented environments are already being used to aid collaboration [132] and outreach [133] in genomics (Fig. 5h). Such exchanges will rely on maintaining FAIR metadata, and RICH visualization tools [25] can assist the fractured realm of genomic data by providing not only analytics but also increased fluidity in the process of metadata management and annotation (Fig. 5i): for example, 3D BioNotes, part of the West-Life initiative [134]; Autodesk Life Sciences' Bio/Nano suite [135]; and the Satori ontology-guided data exploration tool [136]. The process of visualization is itself also important to document as, by becoming a virtual microscope, the assembly of data, processing, consultation and adjudication are scientific method and form protocols, which permit reproducibility [137]. Saving session states and data collections is found in most tools, but a more detailed recording of the choices made in encoding and interacting with the data is not.

Capturing this visualization process and retelling the intricate histories of discovery that result from it remain a significant challenge, which is incompletely addressed in current genomic tools [94].

Existing Tools

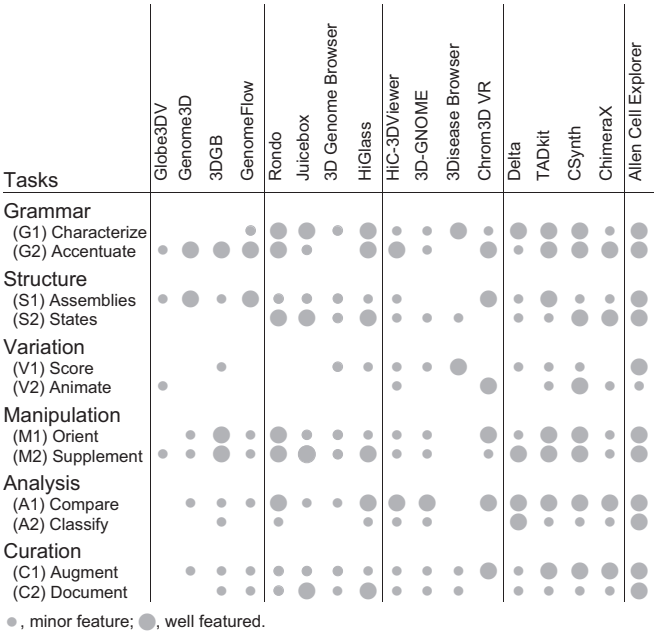
A number of tools create integrated visualization of genomic data [138,139]. Lower-order components at the DNA and nucleosome atomic scales are extensively catered for in conventional protein modeling platforms. Apart from Chimera, there are many quality viewers for PDB-like data, which leverage web browser WebGL rendering most notably the following: NGL leads with embeddable viewing [130] iCN3D implements a task focused approach [60,140]; Aquaria has innovative track to model annotation [141]; Autodesk Molecular Viewer is feature rich with easy sharing and VR [142]; and Nucleus-scale models on the users browser may be feasible if compressed data and focused LOD rendering are used to avoid slow loading and lags in interactivity. There are a number of molecular modeling tools designed to handle large molecular data sets, for example, MegaMol [102], CellView [103], VMD [143] and the commercial Amira suite [144]. At the other end of the scale, a number of tools integrate imaging, network and "multiomics" data sets (i.e., epigenetic, transcriptomic and proteomic networks, disease pathways, phylogeny, comparative genomics, etc.) to enable study across scales, states and time frames: Virtual Metabolic Human using Recon3D [145] and the Allen Cell Explorer hosts a library of 3D cell imaging the complete range of states throughout the cell-cycle [82]. However, while they are all powerful at processing data, none as yet address the concerns of genomic data and the demands of visualizing the genome.

Between the atomistic and cellular scales, there are dedicated software for integrating sequence and 3D data (Tables 2 and 3). Globe3DV [66] is of particular interest as it foreshadows the move toward an integrative model by arranging 1D sequences, 2D reads and 3D models, all within a single virtual space. Genome3D [67], 3DGB [68] and Gmol [146] navigate discrete scales of detail as precomputed layered spatial models, with 3DGB and GenomeFlow [69], the successor to Gmol, adding the ability to align 2D track data to the 3D. However, Globe3DV and 3DGB the 3D setting for non-3D data, and the extra navigational perceptual overhead to manipulate data may overwhelm comprehension and, in Genome3D and Gmol/GenomeFlow GSS format, have restrictive hierarchies, which may not reflect current (and future) models of genome organization. Hi-C data browsers, on the other hand, supply tools to inform 3D knowledge of the genome in 2D: Rondo CIRCOS-style graphs [70] and Juicebox matrices [71] align Hi-C interactions with epigenomic tracks; several dedicated tools provide databases for exploring interactions, for example, "3D Genome Browser" [72] and 3Div [73]; and HiGlass facilitates interactive comparison of matrices [74]. Other tools integrate modeling and visualization of 3D from Hi-C: HiC-3Dviewer displays matrix and 3D side-by-side [75]; 3Dgnome provides an analytical suite that can output 3D [76]; and 3Disease Browser integrates disease-associated data for comparison [77], Also of note, a number of prototypes propose how such 3D data may be explored in VR [78,120,139]. Finally, three further examples expand on this by taking

Table 2. Genome visualization tools

Data type	Tool	Website/repository	Ref.
3D rendering	Molecular Maya	clarafi.com/tools/mmaya	[62]
	Molecular Flipbook	molecularflipbook.org	[63]
	ePMV	epmv.scripps.edu	[64]
	BioBlender	bioblender.org	[65]
3D viewers	Globe3DV	none available	[66]
	Genome3D	genome3d.org	[67]
	3DGB	3dgb.cs.mcgill.ca	[68]
	GenomeFlow	github.com/jianlin-cheng/GenomeFlow	[69]
Hi-C viewers	Rondo	rondo.ws	[70]
	Juicebox	aidenlab.org/juicebox	[71]
	3D Genome Browser	promoter.bx.psu.edu/hi-c	[72]
	3Div	kobic.kr/3div	[73]
	HiGlass	higlass.io	[74]
Hi-C ➔ 3D	HiC-3DViewer	bioinfo.au.tsinghua.edu.cn/member/nadhir/HiC3DViewer	[75]
	3D-GNOME	3dgnome.cent.uw.edu.pl	[76]
	3Disease	3dgb.cbi.pku.edu.cn/disease	[77]
	Chrom3D VR	github.com/NoobsDeSroobs/VRVizualizer	[78]
Hi-C & 3D	Delta	delta.big.ac.cn	[79]
	TADkit	3dgenomes.github.io/TADkit	[80]
	CSynth	csynth.org	[81]
	ChimeraX	rbvi.ucsf.edu/chimerax	[36]
Microscopy	Allen Cell Explorer	allencell.org	[82]

Table 3. Comparison of Genome Visualization Tools



distinct routes to an integrative model. Delta presents a suite of tools for bringing together data [79]. Csynth generates interactive 3D, which can be overlaid with external sources [81]. TADkit, used in the Multiscale Genomics VRE, is able to interconnect and display all three types of data within a single exploratory interface [80].

Concluding Perspectives

Since Hooke's Micrographia and Jenner's pro-vaccination pamphleteering in 1888, the visual image has played a key role, not only in construct and explore biology but also to disseminate convincingly the important learnings. The power invested in biovisualization to shape understanding is not merely representative. Likewise, the image can distort the data it represents and therefore requires careful study. In particular, the move toward a 3D comprehension of the components and mechanisms of the genome creates the need for 3D representation. The data tasks need to be clearly defined to assess whether to use abstract or spatial models of the genome. These tasks can be assembled into a common tool, a "virtual" or modeling microscope. The collation of live data sets into a unified parametric visualization can be used as a simulacrum of a genome for either hypothesis testing or exploratory perturbation by setting parameters for specific genotypes, epigenetic states, arrangements or conformations. This is already being practiced in laboratories as they explore disjointed and quite often poorly annotated data in disparate, self-assembled software pipelines.

With the gap in 3D genome resolution [3] closing, it brings discernment of a functional cartography, although the new tools reveal new gaps in our knowledge. As we leave the genomic Flatland exploration of new unexplored realms, phase separation, quantum mechanics and computational-microscopic resolution will sharpen our focus and expand research frontiers. Defining new conceptual visualization of this is a non-trivial, iterative process that requires the support not only of browsers but also of analytical engines for classification assisted by machine learning, predictive models and discussion in mixed reality. Biovisualization is vital to this journey, to chart, to test and to tell of the discoveries. Principles of genome visualization can be distilled from the inheritance Eduard Tufte: reducing visual clutter, increasing the data to voxel ratio and 3D where 3D is concerned. The model genome must aim to become an extended experimental environment that facilitates research bringing together the data for intuitive exploration. The model will not only be used by differing classes of user for differing tasks but also be essential for new contexts, especially clinical, and this will require new forms of tools [147]. Also, through biovisualization, the genome can be shared with the public by initiatives such as the immersive dome of the Cell Observatory at the Garvan Institute, the VR installation Chromos, by Andy Lomas for Max Cooper's musical collaboration with the Babraham Institute [148] and the exhibition of Csynth as part of the Royal Academy Summer Exhibition [149].

As Emil Heitz was sketching genome function, architect Le Corbusier was defining fresh, functional design for novel human activity, inspired by technological innovations. Today, there exists a new spirit in research, discovering how biological form follows function. We must rely even more on biovisualization to move toward an new genome architecture.

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EM, electron microscopy; LOD, level of detail; LADs, laminar-associated domains.

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