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ARGV: 3D genome structure exploration using augmented reality

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Abstract

Over the past two decades, scientists have increasingly realized the importance of the three-dimensional (3D) genome organization in regulating cellular activity. Hi-C and related experiments yield 2D contact matrices that can be used to infer 3D models of chromosome structure. Visualizing and analyzing genomes in 3D space remains challenging. Here, we present ARGV, an augmented reality 3D Genome Viewer. ARGV contains more than 350 pre-computed and annotated genome structures inferred from Hi-C and imaging data. It offers interactive and collaborative visualization of genomes in 3D space, using standard mobile phones or tablets. A user study comparing ARGV to existing tools demonstrates its benefits.

Keywords: 3D genome browser, 3D genome organization, Augmented reality AR, Virtual reality VR, Mobile app

Background

The dynamic three-dimensional (3D) organization of chromosomes within a cell's nucleus plays a major role in regulating gene expression and cellular differentiation, and can be seen as the ultimate layer of epigenetic information [1, 2]. Alterations of 3D genome structure have been linked to various types of cancer [3–5], while germline mutations can cause birth defects [3, 6]. Significant progress has been made recently in experimentally assessing the 3D organization of genomes. For example, sequencing-based approaches such as Hi-C [7], GAM [8], micro-C [9], and imaging approaches including multiplexed fluorescent in-situ hybridization [10] enable studying the 3D genome organization inside nuclei. Among them, Hi-C and its derivatives [9, 12, 13] are currently the most widely used approach. They produce a matrix, known as a contact map, with rows and columns corresponding to fixed-size bins along the genome, and entries representing the contact frequency of two genomic fragments in 3D space. This matrix is commonly visualized as a 2D heatmap to hint at the spatial organization of the genome. The analysis of 2D contact maps enabled the discovery of hierarchical organizational principles involving the formation of loops, topologically associating domains, and A/B compartments [7, 11, 12]. Yet these 1D and 2D representations fail to provide

complete insights into genome organization, which can only be obtained from full 3D representations.

There is a rich literature on inferring 3D genome models from HiC-like data [14]. At a high-level, these approaches typically aim to infer piece-wise linear 3D models of chromosomes that best fit the contacts captured in a HiC data set. Notions of fit include likelihood-based [15–17] and least-squared models [18–21], while a variety of optimization and sampling algorithms have been proposed [15, 21–24]. While HiC data captures both intra- and inter-chromosomal contacts, the latter are often weak and non-specific, and 3D genome models typically consist of a series of 3D models of individual chromosomes (or portions thereof). Despite significant caveats, including the fact that Hi-C data averages interaction frequencies over large populations of potentially heterogeneous cells and over autosome pairs, the 3D models inferred have been shown to yield valuable insights into the organization of genomes within the nucleus [7, 16, 18].

Insights from 3D genome models are best gained through visualization. Although several 3D genome visualization tools have been proposed in recent years [14, 25–27], none has yet been widely adopted by the research community. Each approach has its own advantages and challenges which are still being discussed [28–31]. Therefore, the modelling, visualization, storage, and sharing of 3D genome structures are key challenges that remain to be fully addressed [31].

After exploring the potential of new visualization technologies, we believe that augmented reality (AR) offers promising functionalities for 3D genome data visualization and manipulation. AR is a technology that allows computer-generated content to be visually and interactively overlaid onto the physical world. Unlike fully immersive experiences such as virtual reality (VR), this technology does not rely on dedicated hardware (i.e., a mobile phone or tablet is sufficient), which makes the technology more accessible to any user and easier to deploy in various environments (e.g., personal usage, lab, classroom) with minimal investment (e.g., time, cost). Furthermore, the navigation is often more intuitive as it does not require to develop specific techniques to manipulate the data as it is the case in virtual environments. As a result, AR blends more naturally into regular working spaces and there is a growing number of innovative applications of this technology in the commercial, industrial, or educational sectors. For example, agencies in automotive industry adopt it to let customers interactively customize cars, and real estate agents use it for property tours and furniture staging [32, 33]. Yet, its most significant impact might be on the educational sector, where such applications are being developed for the scientific community such as medical training [34]. Augmented reality usage surged by 143% in the last 3 years, reaching 1.07 billion users, with a projected 62% growth in the next 2 years to reach 1.73 billion users [35]. With the rapid technological advances in both AR hardware and software, we anticipate professionals in many fields will embrace AR in the near future.

Existing tools designed for exploring 3D genome structures consist of standalone [36–38] and web applications [25–27, 39–41]. Unavoidably, the browsing experience is limited by the representation of 3D structures as 2D projections on a screen and the manipulation of the data through a keyboard and a mouse. Immersive technologies present an opportunity to address this challenge. With the ever-increasing accessibility of personal electronic devices, AR technologies are ready to be used for scientific

visualization [42, 43]. Delta.AR [44] is the only AR application for 3D chromatin visualization, but works only at low resolution or small scale. It requires users to wear a commercial headset and synchronize information with a computer to control the visualization. Besides, it only offers a limited number of 3D genome models. These represent obstacles to the adoption of this tool by the research community. As a large number of 3D genome data sets are produced each year, there are several 3D genome data hubs for sharing raw and processed 3D genome data sets [45–47]. Many of these provide 2D contact map viewers and local structural annotations. In contrast, few provide genome-wide 3D models [48]. Hence 3D genomics researchers are spending most of their time studying 2D contact maps rather than truly 3D models.

Here we introduce the Augmented Reality Genome Viewer (ARGV). ARGV enables the visualization and manipulation of annotated chromosome structures in an immersive environment using common personal mobile devices. ARGV allows users to overlay multiple annotation tracks onto a 3D chromosome model. Powered by augmented reality, users can easily navigate to any portion of the chromosome. In addition, ARGV is equipped with a database currently containing 343 whole-genome, high-resolution 3D models and annotations inferred from Hi-C and other omics data, as well as several imaging-based structures. We also report the results of a survey to assess the benefits and adoption of this technology by bioinformatics trainees. Overall, we believe ARGV can boost 3D genomics education and ease 3D genome visualization, storage, and sharing within the scientific community.

Results

Overview of ARGV

ARGV is an augmented reality 3D genome visualization tool, which enables one or multiple users to view and interact with a predicted chromosome structure through a tablet or cell phone, as if it existed in their real-world working environment (Fig. 1). Figure 2 and Video Additional file 1 illustrate the overall architecture and main functions of ARGV. The AR mode of ARGV is accessible on most mobile devices (i.e., Android, iOS). Users can also execute ARGV in non-AR mode from computers and mobile devices. Irrespective of the mode, ARGV provides users with access to hundreds of 3D genome models at high resolution (see "Methods")—the largest array of pre-computed structures available among all 3D genome browsers. All of these models are complemented with spatial annotations (i.e., TAD, and A/B compartment),

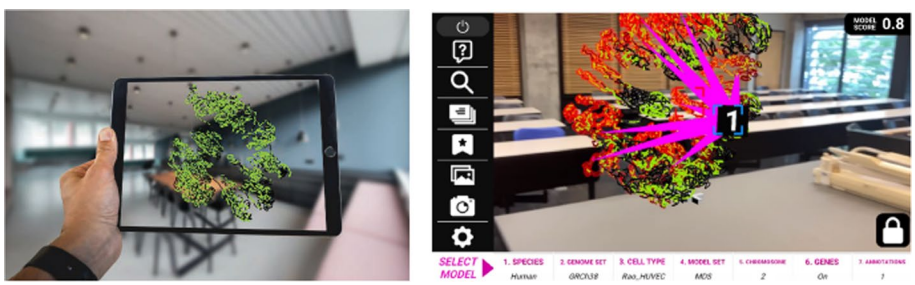

Fig. 1 An example of using ARGV to visualize a 3D chromatin and annotations in augmented reality

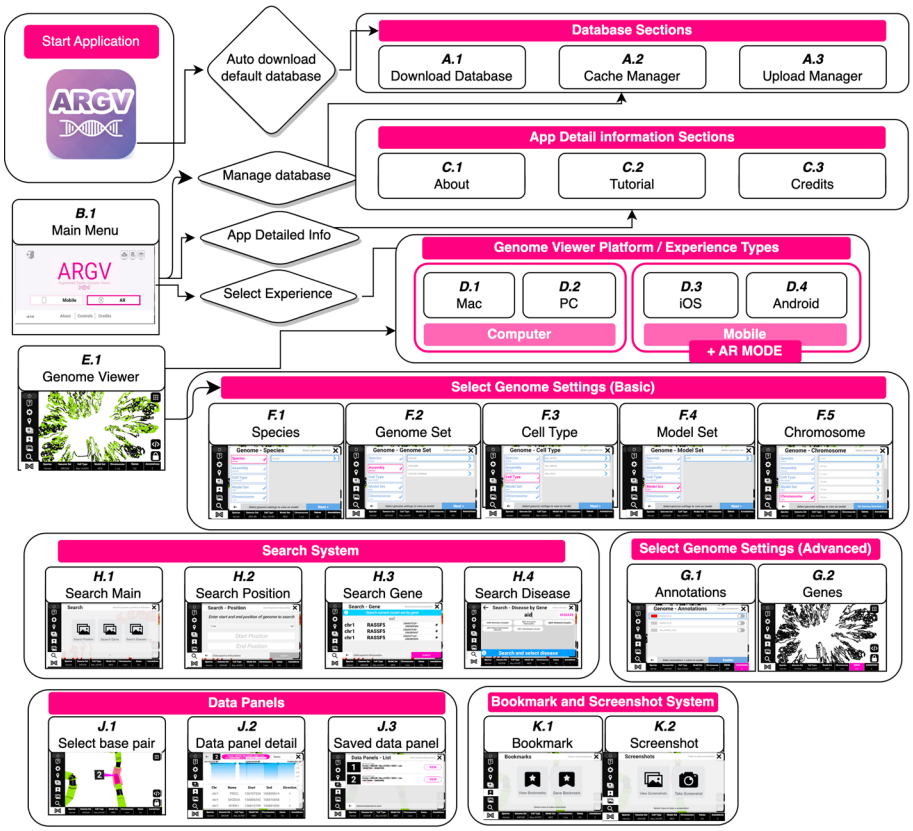

Fig. 2 Overview of the architecture and functions of ARGV

and multiple linear sequence annotation tracks can be displayed, including gene annotations, various ENCODE [47] data sets, as well as disease-to-gene connections. Custom models and annotations can also be provided by the user. ARGV allows users to load and visualize these models and annotations on the fly, perform queries, and export and share the 3D genome visualization (Fig. 2E–J).

ARGV is a 3D genome study environment

Exploring a 3D chromosome structure in augmented reality

In ARGV, both 3D chromosome structures and annotations are objects in augmented reality. To enter the AR mode, ARGV requires users to initialize the environment for placing a 3D chromosome structure. The model can be scaled to fit on a small area of a desk or an entire room. Once initialized, users can see a 3D chromosome appear in real space through their mobile devices (Fig. 1 and Video Additional file 1). Similar to other AR applications, users only need to move their devices around to investigate different portions of the model. An important improvement of ARGV over other AR based 3D genome viewers [44] is that it does not require dedicated or multiple equipment. For example, users can interact with ARGV to select different regions or load different annotations directly from their mobile devices. In addition, users can access an information panel for a region of interest on the mobile device in use (Fig. 2J).

This panel enables accessing data relevant to specific annotation tracks of the selected region as graphs or tables.

Manipulating 3D genomes and annotations

During the installation of our application, ARGV automatically downloads several 3D genome models and annotations to make the tool ready to be explored; other models can be loaded on demand. Upon launching the genome browser, users can select the desired genome, cell type, 3D model, and chromosome to visualize (Fig. 2F). Users can also enable structural and regular 1D annotations (e.g. genes) with each type of annotations uniquely highlighted in its corresponding color in the 3D model.

Rendering BED-format annotations

As ARGV renders annotation in BED format, it allows users to load and visualize a wide array of annotations, such as those from ENCODE [47]. Each BED region is represented as a polygonal tube. Multiple BED tracks can be visualized jointly using the different colors and transparency levels.

Searching regions of interest

Querying a portion of a genome is a fundamental function in any genome browser. ARGV supports queries by genomic coordinates or by gene name (Fig. 3), highlighting the selected region/gene and popping up a panel with relevant information. It also supports searching by phenotype (Fig. 4), where ARGV highlights all genes associated with the phenotype, based on the Comparative Toxicogenomics database [49].

Precomputed 3D models and annotations

ARGV currently includes 343 whole-genome 3D structures inferred from Hi-C data of various human cell types, as well as 10 imaging-based structures for specific

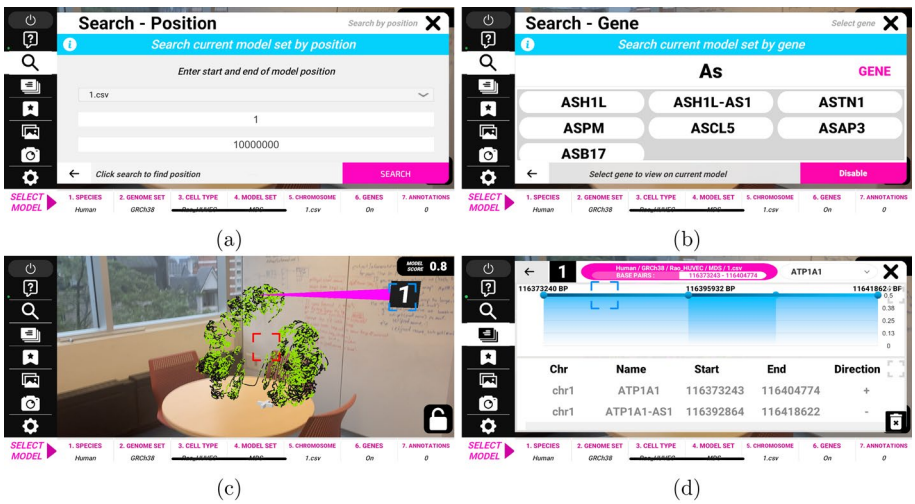

Fig. 3 Querying a region of interest in ARGV. **a** Searching a chromosomal region with start and end position. **b** Searching a chromosomal region with a gene name. **c** Highlighting and labelling selected region on the 3D chromatin. **d** Investigating a selected region from the information panel

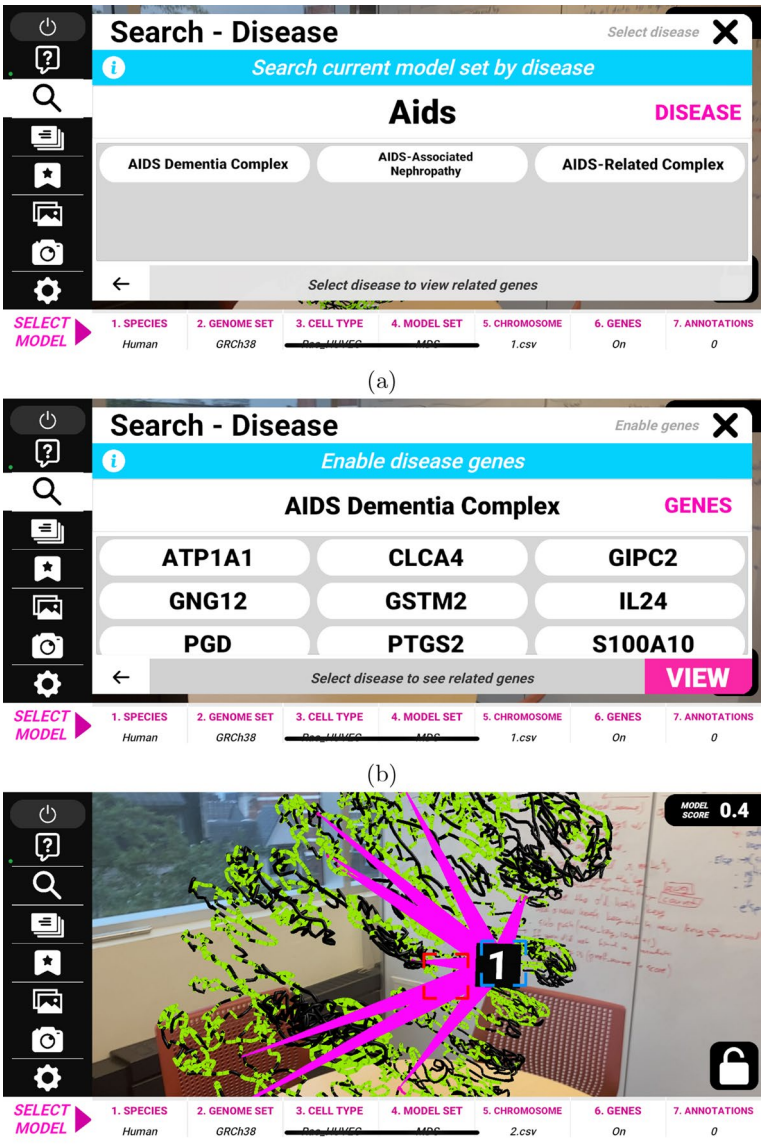

Fig. 4 Selecting disease-associated genes in ARGV . **a**, **b** Searching genes with a disease name in a auto-complete form in ARGV. **c** Highlighting and labelling disease associated genes on the 3D chromatin

chromosome fragments. Hi-C-based models are accompanied by TAD and A/B compartment annotations. All models and annotations can be visualized and also downloaded for offline analysis.

ARGV *facilitates 3D genomics data interpretation*

We conducted a user study to evaluate the impact of ARGV as a teaching support tool for 3D genomics research and education. We asked students enrolled at McGill University to complete 3D genomics related tasks with both AR and non-AR modes of ARGV, as well as with HiGlass [50], a popular 2D visualization tool for Hi-C contact maps. Due to a lack of essential equipment, we did not include other AR or VR-based genome

browsers in this user study. Eleven students participated in this anonymous survey. Among them, one student was only able to execute the desktop version of ARGV in non-AR mode. Following the completion of the tasks, users answered a questionnaire. The first part aimed to study the usefulness of AR in exploring 3D structures. We asked students to load a model and epigenetic signals, search for specific genes, identify disease associated loci, and load A/B compartments and TADs. We then asked them to study how genes distributed among A/B compartments and to identify proteins enriched at domain boundaries by loading various ChIP-Seq signals. In the second part, we aimed at studying the advantages of analyzing genome structures with a 3D model over with a contact map. We asked participants to compare chromatin structures of two cell lines in terms of 2D Hi-C matrices and 3D models.

The survey results indicates that ARGV provides a better user experience in 3D genome visualization and helps students to better learn 3D genome (Fig. 5). Among the 10 participants who were able to execute the mobile application, 70% preferred ARGV 's AR mode over its non-AR mode or HiGlass's 2D contact map visualization approach, and 80% thought that our AR mode helps better understand 3D genomes. Among all 11 participants, overall, 89.1% of participants think ARGV outperforms the contact map based visualization tool in locating loci and exploring spatial relations among selected loci. In addition, 81.8% of participants think using ARGV helps understand the importance of 3D genomics structures. Accordingly, 80–90% of participants indicated that functions that help them complete the required tasks, including querying and annotation visualization, were useful. In contrast, only half of the students think the AR mode and the 3D genome

Fig. 5 A summary of questionnaire responses in our survey study

database are useful. We believe this is due to the fact that those two functions were not necessary for completing all required tasks.

ARGV completes existing tools

We compared ARGV against four 3D genome viewers—the Nucleome Browser [26], the WashU Epigenome Browser [27], CSynth [41], and DeltaAR [44]—in terms of visualization method, functionality, and access to existing annotations (Table 1). Among these browsers, only ARGV and DeltaAR support visualization in AR mode. ARGV offers AR mode from most mobile devices, whereas DeltaAR requires synchronizing a computer with a Microsoft HoloLens to perform the visualization. In contrast, the WashU Epigenome Browser and CSynth support 3D genome visualization in VR mode from dedicated equipment. The Nucleome Browser only offers 3D genome visualization in a 2D web browser. An important feature of a genome browser is the query function. While ARGV, the WashU Epigenome Browser, Csynth, and DeltaAR all support querying and highlighting the 3D genome structures by various methods, the Nucleome Browser only supports querying through the 1D genome browser. Both Nucleome Browser, and WashU Epigenome Browser substantially integrate the UCSC Genome Browser into their applications, thus they provide the most diverse 1D annotation tracks. ARGV provides fewer 1D annotation tracks but allows users to load annotation tracks from UCSC Genome Browser or ENCODE data portal. Besides, only ARGV provides genotype-phenotype associations. More importantly, among all tools, only ARGV provides the

Table 1 Comparison of features of ARGV to other applications

Feature/application	ARGV	WashU Epigenome Browser	Nucleome Browser	CSynth	DeltaAR
PLATFORM MODES					
AR Mode (Augmented reality)	✓	X	X	X	✓
VR Mode (Virtual reality)	✓	✓	X	✓	X
Mobile device compatible	✓	X	X	X	X
SEARCH FUNCTIONALITY					
Search by position	✓	✓	X	✓	✓
Search by gene	✓	✓	X	✓	✓
Search by phenotype	✓	X	X	X	X
MODEL FEATURES					
TAD annotation	✓	X	X	X	X
Gene highlight	✓	✓	✓	✓	✓
3D genome database	353	11,045	20+	5	15
Epigenomics annotations	✓	✓	✓	✓	✓
OTHER FEATURES					
Share	✓	✓	✓	X	✓
Bookmark	✓	X	X	X	X

Comparing different features between ARGV with existing genome browsers and 3D genome visualization tools. The checkmark and the "X" icons indicate a feature is supported and not supported by a tool respectively. ARGV is the only application that supports AR mode on a mobile device, and the only application that supports query and annotation of phenotype-related loci. Both ARGV and WashU Epigenome Browser provide access to a large collection of 3D genomes, with most of WashU Epigenome Browser's models being low resolution and coming from single Hi-C experiments, and ARGV 's models representing a more diverse group of high resolution models

annotations of spatial features. Key features of a 3D genome browser are the number and diversity of 3D models included. Nucleome Browser, CSynth, and DeltaAR only provides tens of genome structures. In contrast, ARGV provides more than 300 diverse high-resolution models inferred from bulk Hi-C and imaging experiments. WashU Genome Browser provides 30 times more structures than ARGV, but its models are less diverse and at much lower resolutions, as most of them are derived from single-cell Hi-C experiments. Finally, as 3D genome studies often involve collaboration among researchers from different labs, all four genome browsers support data sharing and collaboration to some extent.

Discussion

ARGV is the first AR-enabled mobile application that was specifically developed for visualizing high-resolution whole chromosome level 3D conformations. It combines the advantages of the AR environment and a mobile application, allowing easy adoption without the need for specialized equipment.

Although ARGV provides a number of advantages over other 3D genome browsers, several directions for improvements are being considered. First, ARGV 's visual field is limited to the screen of a mobile device, sometimes preventing users from fully embracing the AR environment. Having observed how recently introduced commercial products such as Meta's Quest Pro and Apple's Vision Pro significantly enhance AR user experience, we plan to expand the capabilities of ARGV to seamlessly integrate with these platforms. It is relatively easy for us to update the build to include new devices as we developed ARGV fully within the Unity framework. We anticipate this extension to allow professional users (i.e., museums, exhibitors, schools, etc.) to fully embrace 3D genome conformation in an AR environment without borders. Second, ARGV currently provides direct access to a limited set of annotation tracks. In contrast, existing tools, such as WashU Epigenome Browser and Nucleome Browser, provide annotating tracks from a 1D genome browser. We plan to update our 1D annotation tracks by including a 1D genome browser similar to the UCSC genome browser in future releases. Third, although multiple tools exist for 3D genome visualization, the modelling of 3D genome conformation remains far from perfect. Different tools or parameter settings could produce very different reconstructions. As we aim at inferring hundreds of 3D genomes, we used a modified version of a simple and efficient multidimensional scaling approach—SuperRec [21]. We also inferred several models with other tools [51]. As we continue to expand the scope of our database by incorporating new samples, we are concurrently exploring alternative tools to modelling existing 3D genomes in our database. Fourth, we note that only 50% of participants felt that the AR mode was useful for the completion of the assigned tasks, while ~70% of participants indicated that this mode improved the visualization and understanding of 3D genome organization. This difference is attributed to the nature of tasks assigned to the users, which could easily be carried out in the non-VR mode of ARGV. However, we expect that several types of analyses may be significantly easier to before in AR mode than non-AR mode. These include the identification of multi-way contacts (e.g. one promoter with multiple enhancers) and the analysis of other types of complex substructures.

A couple of features such as screenshots and bookmarks were also less elicited by the participants to the survey. In this case, it is probably because these functions are less essential to the AR user experience. Yet, we believe that recurring users could have a better appreciation of them since they aim to avoid repetitive or convoluted actions. Finally, we are investigating approaches that can visually capture uncertainties in the construction of 3D genome structures, e.g. by superimposing multiple candidate structures from an ensemble of solutions, or using dynamic rather than static structures. Likewise, the visualization of structural ensembles is also helpful for analyzing the conformational landscape and folding dynamics of 3D structures. Even though, the representation of these ensembles is still open to debate, even more in the context of an AR tool, we acknowledge its importance toward a broad adoption of our technology.

Conclusions

Here we present ARGV, a mobile application for 3D genome visualization in augmented reality. ARGV augments a user's surrounding with an annotated 3D model of a chromosome, enabling intuitive exploration of genome conformation via simple manipulation of a mobile device. Our user survey confirms the benefits of this approach over 2D visualization approaches. ARGV is supported by a database server providing access to the most comprehensive repository of high resolution whole-genome structures available to date. We believe ARGV has the potential to help advance 3D genomics research and education.

Methods

Application design and implementation

ARGV is a 3D genome browser that allows users to visualize 3D chromosome structures and annotations in augmented reality through personal mobile devices. It consists of (i) a back-end database and (ii) a visualization interface. Figure 2 provides an overview of the application architecture and functions. We implemented all functions using the Unity SDK (2020.1.0a11), ARKit (4.1) and ARCore (4.1). Users can also use ARGV as a non-VR visualization tool. We deployed the database on a PHP web server (Ubuntu 18.04, PHP 8). Briefly, we used PHP scripts to respond to requests from our application. Our back-end scripts can retrieve data from files on disk, and send models and annotations to end users. To facilitate data retrieval, we also created a JSON file to store relational information of models and annotations. Following previous work [21, 25, 52], we store 3D models of chromosomes as a sequence of Cartesian coordinates, and render its 3D structure in AR as a combination of lines, polygons, and spheres. We represent annotated regions as colored polygons superimposed onto the 3D chromosome structure. To speed up data loading, we split annotations and structures into multiple files according to chromosome names. The visualization interface offers nine groups of functions, and each group allows users to perform a set of sub-functions within the same pop-up window.

The size of our current database is 349MB, downloading and saving all data to local disk is unnecessary. In our implementation, we allow users to download and manage selected models and annotations before visualization. In addition, we allow users to load private models and annotation tracks into ARGV from their local drive. On standard mobile devices, our current implementation should support 3D models with up to ten thousand 3D coordinates.

Hi-C data analysis and 3D genome modelling

Data preprocessing

We downloaded 343 published human Hi-C datasets from the GEO database and uniformly processed them with distiller [53]. We mapped reads against hg38 and discarded reads with a mapping quality below 10. We produced Hi-C contact maps at fixed bin resolutions of 1kb, 5kb, 50kb and stored processed contact maps in multi-resolution cooler format (.mcool). Last, we removed systematic biases using the iterative correction algorithm provided in Cooler [54, 55]. Due to budget and technical limitations, most of these collected Hi-C data contains several hundred millions of read pairs and these contact maps are not ready for 3D genome modelling. Most existing 3D modeling tools suffer from one or both of the following drawbacks: (1) difficulty to use low or moderate coverage Hi-C data; (2) impractical running times for chromosome-scale, high-resolution inference. Hence, we started with enhancing Hi-C contact maps with HIFI [56], to get the maximum likelihood estimation of the normalized Hi-C contact maps before genome modeling. These enhanced Hi-C contact maps are dense and robust estimations of the contact probabilities of spatial interactions between genomic fragments regardless of the experimental sequencing coverage.

TADs and A/B compartments annotation

We annotate TADs with TopDom [57] and A/B compartments with FAN-C [58] using recommend parameters and provided them as tracks in ARGV.

TAD-aware structure modelling

Though ensemble approaches, physical and statistical modelling approaches proposed in recent years are known to outperform multidimensional scaling (MDS) approaches for modelling small regions (i.e. TADs, genes, etc.) at low resolutions, MDS remains the approach of choice for high-resolution, chromosome-scale modelling. Bearing the large size of our database size and the relatively high resolution (50 kb) in mind, we used the consensus-weighted MDS approach superRec [21] for 3D chromatin modelling. The following modifications were made the default arguments: (1) We set $\alpha = 1/3$ in power-law conversion, as suggested in [7, 15]; (2) We disabled the shortest-path distance refinement step as we provided enhanced Hi-C contact maps; (3) we increased the weights assigned to within-TAD contact pairs, as explained below. The structure modelling task can be formulated as minimizing $\mathcal{L}$:

$$\mathcal{L}(d, \hat{d}) = \sum_{ij} w_{ij}(d_{ij} - \hat{d}_{ij})^2$$

$$\hat{d}_{ij} = \frac{1}{f_{ij}^{\alpha}}$$

$$w_{ij} = \begin{cases} \lambda f_{ij}^2, & \text{if (i,j) pair belongs to the same TAD} \\ f_{ij}^2, & \text{otherwise} \end{cases}$$

where f_{ij} is the enhanced interaction frequency, and d_{ij} is the spatial distance between fragments i and j in the 3D model. λ is a hyper-parameter; we chose $\lambda = 5$ after performing a grid-search to find the value that yields the highest correlation between $\hat{d}_{ij}$ and d_{ij}.

Availability and requirements

ARGV and its documentation are available at argv.cs.mcgill.ca. It can be executed on various platforms and devices, provide they are compatible with Unity, or support AR mode using native libraries. Users can use the AR mode from most mobile devices (i.e., Android $\geq$ 8.1 and iOS $\geq$ 11.0). The non-AR mode is accessible from any system that supports Unity. An internet connection is required to fetch new 3D genome structures from our database server (Note: we currently estimate that our infrastructure can sustain a couple of hundreds of simultaneous downloads), but once this is done the system can operate offline. We also release on this website the code and modeling pipeline used to generate the 3D structures.

Survey implementation and participants

We designed a user study to evaluate the effectiveness of ARGV at supporting research and education in 3D genomics. We designed a set of tasks (Additional file 2) that require participants to study 3D genomes by investigating 3D models or 2D contact maps with ARGV and alternative tools. Participants needed to interact extensively with each tool and carefully explore both 3D models and 2D contact maps derived from high-coverage Hi-C data sets for K562 and IMR-90 cell lines [12].

All participants in this study were enrolled at McGill University and had diverse levels of maturity in computational biology. All had used various genomics data visualization tools prior to this study.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12859-024-05882-8.

Additional file 1. A video demo of ARGV. A video demo of our application that illustrates different functions provided in ARGV.

Additional file 2. Questionnaire in our survey study. This is a copy of the questionnaire including detailed tasks that we ask participants to perform in our survey study.

Additional file 3. Table S1. A list of Hi-C samples with accession numbers that we used in this study.

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Author contributions

JW and MB conceived and supervised the project. CD designed and implemented the ARGV application. YZ processed data and created 3D models, with JM supervising this process and giving input. CD and YZ wrote the manuscript. EZ created an initial prototype. All authors read and approved the final manuscript. RSG coordinated the user study and helped conceptualize the user experience for the VR browser. Finally, YC has provided insight for the VR/AR technological side of the project.

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Availability of data and materials

The raw data analyzed during the current study are available in the GEO repository, with accession numbers provided in Additional File 3. All processed data and annotation tracks can be downloaded within our application. The application and full documentation is available at https://argv.cs.mcgill.ca/. Project name: Augmented Reality Genome Viewer (ARGV). Project home page: http://argv.cs.mcgill.ca/. Operating system(s): (Android 7.0 + / iOS 11 + / Windows 10 / MacOS Catalina 10.15+). Programming language: C# / PHP (Server Side). Other requirements: N/A. License: CC BY-NC-ND 4.0 DEED. Any restrictions to use by non-academics: Free to use for educational purposes

Declarations

Ethics approval and consent to participate
All participants were informed about the purpose of the survey and participation was voluntary basis. Answers were anonymous.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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