Commentary

Delta.AR: An augmented reality-based visualization platform for 3D genome

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Many visualization tools have been developed for 3D genome data integration using two-dimensional (2D) devices such as PC monitors or smartphones. However, the 2D surface is only suitable for displaying linear data, and it has done little to inform our understanding of the complex interconnections between 3D genome architecture and its various associated -omics data. The breakthrough in immersive display technologies, e.g., virtual reality (VR) and augmented reality (AR), has opened a completely new model for data visualization. Immersive visualization has proved a powerful way to enhance 3D structure-related research, e.g., protein structure and drug design. However, visualization in immersive mode, coupled with the integration of 3D genome and its associated -omics data, is challenging. Only a few attempts have been made for single features, e.g., Juicebox VR, which projects a Hi-C contact matrix into a virtual mountain field, and the WashU Epigenome Browser, which provides a 3D scene for epigenome tracks. A visualization tool for immersive integration of 3D genome architecture with high-dimensional -omics data has not yet been published.

Here we describe Delta.AR (http://deltaar.big.ac.cn), an AR technology-based 3D genome visualization platform for the integration of chromatin physical structure with multiple -omics data. Delta.AR is physically composed of three components, a head-mounted display unit, a portable 2D display device, and a data source (Figure 1A). We chose Microsoft HoloLens, which was the first commercially available self-contained holographic device, as the head-mounted unit. By projecting a hologram into the user's eyes, the HoloLens creates a virtual digital object, e.g., a 3D physical model of a genome, into the user's field of view (Figure 1B). The portable 2D display device, for example a smartphone or PC monitor, is designed to complement the relatively small number of tracks that could possibly be annotated onto the hologram simultaneously. With this portable device, any number of -omics tracks can be displayed in a canonical genome browser, which is synchronized with the 3D hologram in HoloLens in real time (Figure 1C). This feature overcomes the limitation of space otherwise occupied by a 3D object painted with -omics tracks. In the data source, we provide two servers, one for -omics data and one for AR modeling. We mounted an improved Delta database,[1] which was previously developed for 2D visualization and contains almost all epigenetic data from the ENCODE project, the NIH epigenetic roadmap, and the Ensembl data for seven cell types. Investigators can also upload their own customized -omics tracks to Delta.AR. Moreover, as part of the China National Center for Bioinformation (CNCB),[2] we now support 3CDB,[3] and we plan to have all data in CNCB supported by Delta.AR in the near future. Communication among the three components has been defined by a newly developed simple application layer protocol (http://deltaar.big.ac.cn/deltaar/pages/help/help_load.jsp#8) that speeds up data traffic and optimizes the distribution of the computational resource used between HoloLens and servers. When the user launches the Delta.AR app from HoloLens, a session ID is assigned. The user then goes to the Delta.AR website (http://deltaar.big.ac.cn) and inputs the session ID to start a visualization process, which is guided step by step on the website. We have also provided an online video demonstration and step-by-step tutorial.

Delta.AR is a new-generation visualization platform for the 3D genome. First, it offers an immersive visualization experience for physical 3D genome architecture. In the 3D genome context, the task of visualization not only shows the physical architecture per se, but also the spatial distribution of -omics data and their association with the genome structure as additional key elements. The "immersive features" of the AR created by Delta.AR can substantially stimulate our curiosity about the connections between -omics data and 3D genome architecture. Second, the hologram is fully interactive. That is, we can easily add or remove annotations on the hologram by simply using gestures. Delta.AR has adopted the four types of tracks we previously developed to annotate 3D genome.[1] These four types of tracks, namely quantitative, regional, labeling, and connective, represent quantitative genome features, genome domains, gene names, and chromatin interactions, respectively, covering almost all -omics data types. Separation of the physical 3D model (in the hologram) from the genome browser (in the handheld PC) not only solves the issue of limited display space but also takes full advantage of the rich information offered by the canonical genome browser. Moreover, the data shared between HoloLens and the portable device are synchronized in real time, meaning that any modification to one device will be simultaneously updated to the other. Third, Delta.AR provides a virtual environment that facilitates productive discussion and data sharing between collaborating investigators. By maintaining a dynamic map between users and sessions, we have developed a user management system that allows multiple investigators simultaneous access to the same virtual 3D object. The hologram is drawn smoothly because Delta.AR is designed to use AR instead of VR. More importantly, Delta.AR allowing face-to-face communication between colleagues with whiteboard, eye contact, body language, or online searching available during the course of discussion. These features offered Delta.AR with the potential to be a model for next-generation visualization in the era of high-dimensional big data.

We showcase the utility of Delta.AR with a canonical β-globin locus, which has a complex structure and developmental gene activation pattern. The human β-globin locus contains a family of genes regulated by the distal locus control region (LCR) consisting of five DNase I hypersensitive sites (HSs). The region we chose for modeling was larger (Chr11: 4,500,000–6,500,000) than the 5′HS5-3′HS1 region, essentially because the local structure might have been influenced by external sequences. We modeled the physical 3D structure of this region and visualized it in Delta.AR. A loop between 3′HS1 and 5′HS5, located at each of two poles in the structure, can be easily seen (Figure 1B). Because the physical 3D model was a consensus average from a structure ensemble, we speculated that the loop may indicate a higher than expected frequency of transitory interactions and that it may, in turn, be functional in the regulation of globin genes. Within the 3′HS1 and 5′HS5 loop, the LCR did, indeed, closely attach to the globin genes in the physical 3D model with no special loop identified between any particular HSs and globin genes. If the LCR contact can sufficiently express globin genes, we would expect to see the active expression of all globin genes in the cells. However, RNA-sequencing data indicated that only HBE, HBG1, and HBG2 genes

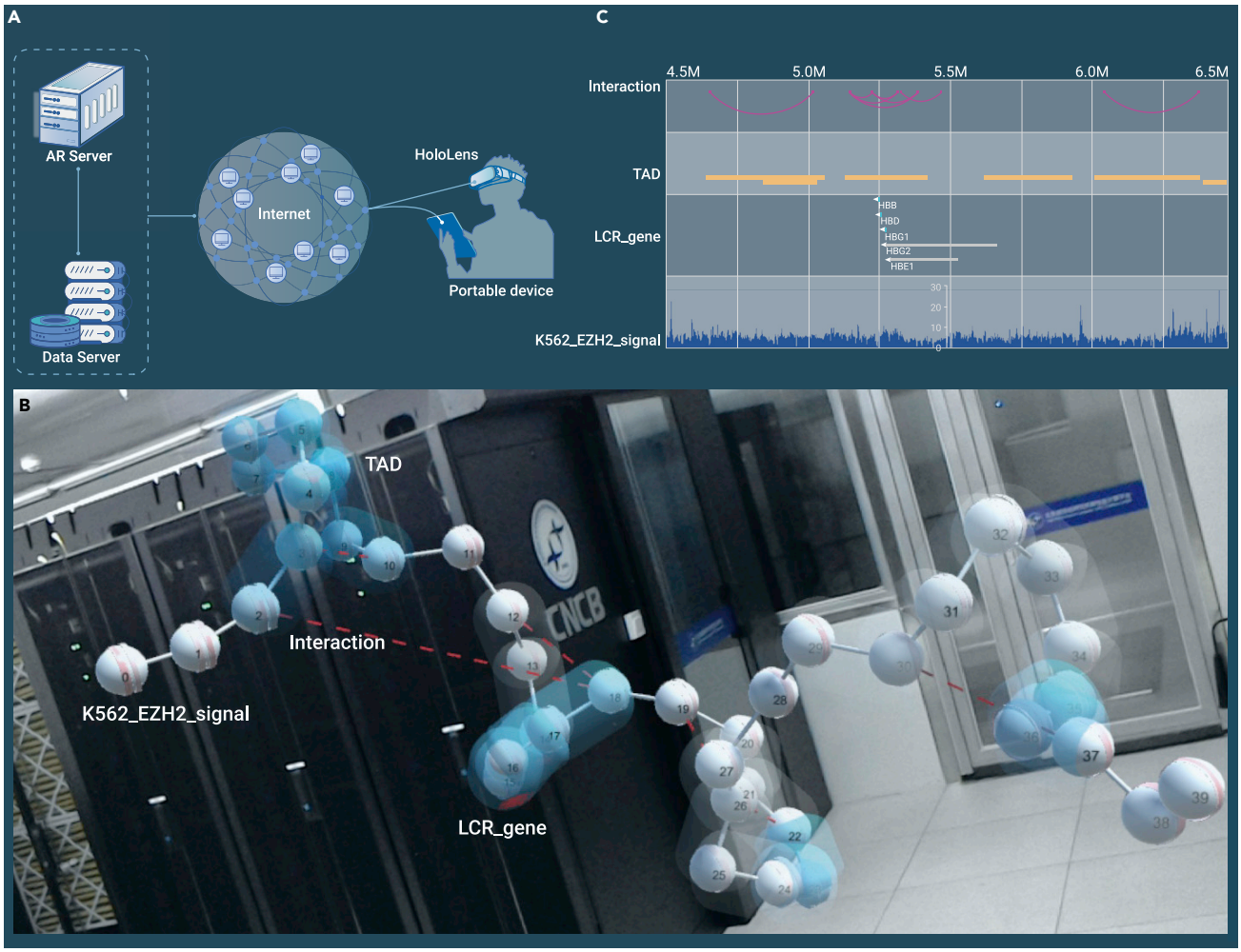

Figure 1. Design and screenshot of Delta.AR (A) System design of Delta.AR. The three components of Delta.AR, HoloLens, portable device, and data source, are interconnected through the Internet. The data source consists of the AR server and the data server, and these are provided by the China National Center for Bioinformation (CNCB) through http://deltaar.big.ac.cn. (B) Example of the visual field from HoloLens, showing a 3D model with annotated tracks for the human β-globin locus Chr11: 4,500,000–6,500,000 in K562 cells. The human β-globin locus contains a family of genes regulated by the distal locus control region (LCR), consisting of five DNase I hypersensitive sites (HSs). The region we chose for modeling was larger than the 5′HS5-3′HS1 region, essentially because the local structure might have been influenced by external sequences. The tracks, including chromatin interactions, gene names, TAD (topologically associating domain), and chromatin immunoprecipitation sequencing signal of EZH2, are represented as dashed lines, labels, shadows, and stripes, respectively. (C) Associated genome browser view.

were actively expressed and enriched for the active promoter marks DHS and H3K4me3. In the promoter regions of HBD and HBB genes, which were not actively expressed, the DNase-sequencing data showed a moderate peak, but no obvious peaks of H3K4me3 that could be spotted. Thus, this visualization pattern implies that three features, namely contacts from LCR, an accessible promoter, and an active histone mark, may be necessary to activate expression of globin genes. It is known that transcriptionally active globin genes are positioned closely to the LCR HSs. However, it was also reported that the transcription activity of globin genes per se does not maintain this chromatin loop structure.[4] On the other hand, once the loop between 5′HS5 and 3′HS1 was disrupted by CCCTC-binding factor (CTCF) knockdown in K562 cells, the transcription of globin genes was also substantially reduced.[5] While this result suggests that the three features noted above would not be sufficient for the correct expression of globin genes, it also suggests that the transient loops between 5′HS5 and 3′HS1 are still critical in this regulatory network. This example demonstrates the utility of visualizing the 3D physical models alongside various genomic data using Delta.AR.

With the rapid growth in sizes and dimensions of "multi-omics" datasets of human cells and model systems, Delta.AR will facilitate the translation of -omics signals into molecular mechanisms, leading to increased knowledge and clinical advances.

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DECLARATION OF INTERESTS

The authors declare no competing interests.