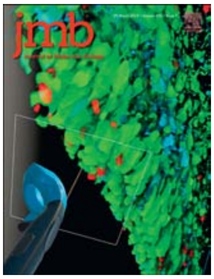
Perspective



Virtual Reality: Beyond Visualization☆

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Abstract

Virtual reality (VR) has recently become an affordable technology. A wide range of options are available to access this unique visualization medium, from simple cardboard inserts for smartphones to truly advanced headsets tracked by external sensors. While it is now possible for any research team to gain access to VR, we can still question what it brings to scientific research. Visualization and the ability to navigate complex three-dimensional data are undoubtedly a gateway to many scientific applications; however, we are convinced that data treatment and numerical simulations, especially those mixing interactions with data, human cognition, and automated algorithms will be the future of VR in scientific research. Moreover, VR might soon merit the same level of attention to imaging data as machine learning currently has. In this short perspective, we discuss approaches that employ VR in scientific research based on some concrete examples.

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Introduction: Virtual Reality for Everyone

Virtual reality (VR) is not a new technology. It has played a role in a number of specialized industrial applications since the 1970s, notably in the automobile and military sectors. However, major recent advances in the technology have made it amenable to new application domains not limited to education, psychiatry, and scientific research. In fact, it is the convergence of three trends that has made this possible. First, desktop computers now have graphics cards sufficiently powerful to meet the real-time rendering requirements necessary for VR. Second, the latest iteration of VR technology has been optimized to ensure visual comfort and ergonomic usage. Finally, widespread consumer availability of VR headsets such as the HTC Vive, Oculus Rift, and Windows Mixed Reality at affordable prices has democratized its usage. VR, at its core, is a technology that uses real-world visual perception within entirely artificial computer-generated environments. Concretely, it is the combination of three effects. (i) A total immersion experience. Users wear an optically hermetic headset designed to block external parasitic light. (ii) Stereoscopic vision. Each eye sees the same scene rendered from a slightly different angle, effectively mimicking how our eyes see the world in three dimensions. (iii) Motion capture. The position of the user's head and controllers are detected with either three or six degrees of freedom allowing precise tracking of movements within rendered scenes.

Through these effects, VR offers a unique visualization context that heightens perception of volumetric details. Compared to visualization on a conventional computer monitor, where users typically view three-dimensional (3D) data as a passive observer, the immersive experience of VR allows users to literally enter inside their data in a manner that feels spatially realistic. For this reason, first-time usage experiences with VR are typically characterized by a surprise or “wow effect” by the user. While applications in entertainment (e.g., video games and film) have largely driven VR technology, its use in the sciences is still being elaborated. So far, VR remains in early adopter laboratories, although emerging platforms will soon bridge gaps in adoption.

The immersive and interactive experience of VR offers a new way to observe data. It is our view that it will play a critical role in spreading scientific knowledge to the non-scientist and serve to attract students to the laboratory. Beyond this, the new opportunities that VR and related technologies confer to the scientist are so transformative that they may permanently change how work in the laboratory is performed and prompt new scientific advances. In the following, we focus our discussion on scientific applications of VR with a focus on its use in the laboratory. We will limit discussions on the advanced technical strategies core to any VR application (e.g., real-time volume rendering, memory management, file management, etc.) to focus rather on applications and uses of VR. Finally, we shall emphasize the integral role VR plays in *human-in-the-loop* (HITL) data analysis.

Data Visualization

Arguably the main advantage of VR for visualizing scientific data is the freedom it grants users to intuitively explore and interact with their environment. Objects can be observed from entirely arbitrary angles and vantage points, just as we observe them in the real world. Interaction using specialized VR controllers available with modern headsets can be performed with millimeter precision. This sense of realism translates to a fluid and natural-feeling experience for the user, in turn allowing otherwise complicated spatial tasks to be performed rapidly, often by orders of magnitude, compared to conventional mouse and monitor configurations. Moreover, the simple act of moving within a VR scene increases the likelihood to detect patterns of interest. VR naturally encourages exploration and curiosity-driven action, which are essential ingredients to promote discoveries.

The generation of a VR scene comes at a high computational cost. A different scene has to be rendered for each eye (i.e., stereoscopy) at a refresh rate exceeding 60 Hz (often 90 Hz is recommended) for smooth navigation. The sheer size and richness of scientific data make this requirement particularly difficult to meet on some computing platforms. The most general approach for ameliorating rendering speed is by reducing rendered image quality, although graphics card manufacturers such as NVIDIA propose VR-specific features such as single-pass stereo rendering, headset lens-matched pixel resolution, and multiple graphics card configurations to improve rendering performance. Efforts to unify all VR technology under a single framework such as OpenVR and SteamVR have simplified development; however, upcoming features such as foveated rendering, environment mapping, and inside-out tracking imply a prolonged technological turnover that will present challenges to the widespread adoption of VR for both the developer and consumer.

The visualization of volumetric imaging data (i.e., image stacks) presents some particularly difficult challenges. The first of these is the design of a 3D look-up table or *transfer function* for efficient data visualization. The transfer function assigns optical properties such as color and transparency to each voxel of the visualized scene. It defines the physical rule of light propagation in the sample. Moreover, it ensures optimal information representation in the visualization of the 3D image. This can mean allowing structures inside a cell to be seen from the outside while revealing the barriers between domains with different properties. An example of such a challenge is shown in a complex microscopy image of the mouse neocortex (Fig. 1(a)) [1]. Note the level of detail revealed in the corresponding VR rendering.

VR data visualization is not limited to image stacks; it can be applied to deconvolved or post-treated images. Single-molecule localization microscopy, a key methodology for exploring nanometric cellular function, generates spot localizations (i.e., point clouds) in two-dimensional and more recently 3D from raw imaging data [2]. In general, 3D point clouds are difficult to spatially assess, and VR can be instrumental in this task [3]. An example is shown in Fig. 1(b). Immersive visualization can also be facilitating complicated segmentation tasks of microscopic structures within image stacks. Figure 2(a) shows a segmented portion of neurons in the mouse olfactory bulb imaged using confocal microscopy. Here, surfaces have been pre-annotated by the user and the transfer function has been optimized to ensure their visibility. Combined with stereoscopy, a simple glance reveals both geometric and some topologic features of this local network.

Beyond imaging data, VR can be used to visualize many forms of scientific data. Scientific laboratories generate large amounts of high-dimensional data on a daily basis, and immersive environments can be exploited to more efficiently extract information from them. In Fig. 2(d), we show an example of a user visualizing and interacting with a macromolecule in VR. Similarly, we show 3D yeast chromosome geometry based on statistical properties of Hi-C maps (Fig. 1(c)) [4]. In both of these examples, immersive visualization provides an enhanced geometric understanding. Proximity of data points in complex data sets can be immediately assessed, and complex correlations in structures that may escape automated analysis can be directly seen.

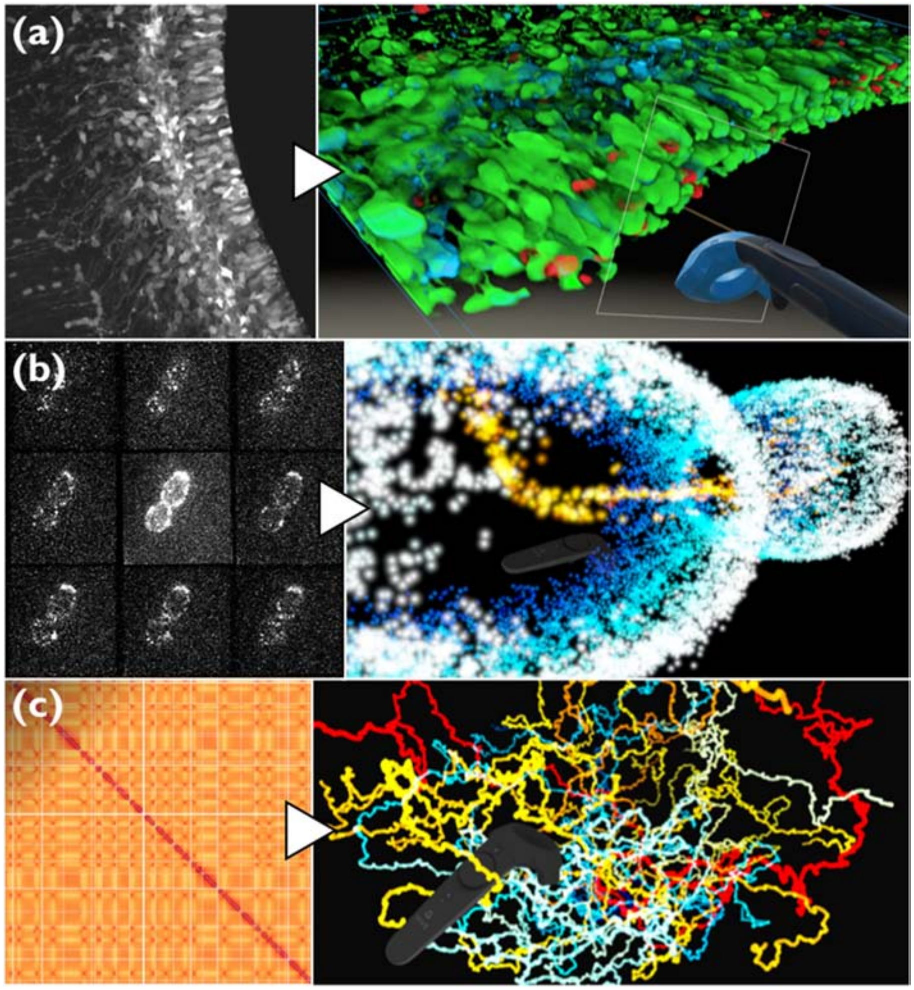

Fig. 1. Visualizing data in VR. (A) Example of visual representations of scientific data using VR. On the left, a maximum intensity projection of an image stack of neurons imaged by spinning disk confocal microscopy [1]. On the right, a capture of the same data set in VR. There is a significant increase in volumetric cues and information in the VR mode (see supplementary material); 3D geometry is accessible, boundaries can be enhanced, and complex geometrical relation between neurons is clearly observed. (B) Single-molecule point cloud originating from multifocus microscopy [13]. On the left, the raw image acquisition. On the right, the VR representation. In blue-white, the wall of a *Saccharomyces cerevisiae* yeast; in red-yellow a filament of alpha tubulin passing between the dividing mother and daughter cells. (C) A volumetric representation of the simulated positions of 16 *S. cerevisiae* yeast chromosomes (distinguished by color) based on the statistical properties in a Hi-C map, an example of which is shown on the left [4]. All VR screen captures were generated with the DIVA software platform.

Besides visualization, data navigation is a second major challenge. Figures 1 and 2 display screen captures of images rendered in the VR headset. The supplementary video reveals how easily data are moved, rotated, and scaled by the user. Visualizing data on a two-dimensional screen is now a relatively standardized task, and consensus exists for navigation (e.g., using a mouse-wheel to zoom, dragging with the mouse button clicked to rotate). This is not the case for VR, and significant work is required to establish standard modes of interaction. The use of VR controllers is critical in this regard. It provides a means to perform basic tasks such as grabbing, scaling, and rotation, although data-specific challenges still exist (e.g., changing display parameters of the transfer function). Consensus will emerge as the number of users increases and the technologies introduced in VR controllers continues to mature [5,6]. The INRIA Naviscope project [7], for example, addresses a number of challenges related to data navigation.

As the use of VR technologies will increase for scientific research, automating some procedures for visualization and navigation will become appealing and, in some cases, necessary. Naturally, this shall be determined based on user testimonials and case studies. Several publications have already investigated the reaction of users using VR in specific tasks [8–12]. These studies serve the purpose of surveying user preferences and will enable developers to address their

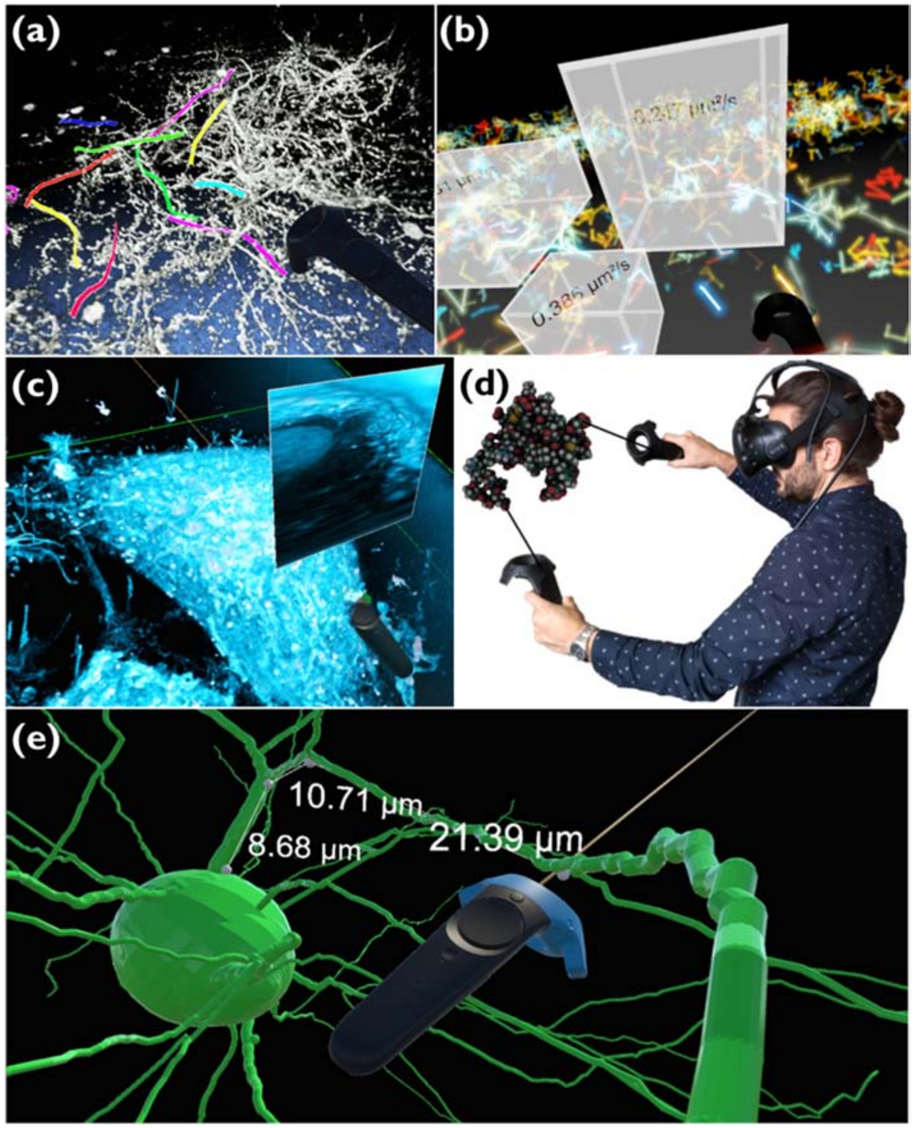

Fig. 2. Data treatment in VR: an HITL approach. (A) Use of VR in an HITL segmentation task. Raw confocal images of fluorescent mouse olfactory bulb neurons with a reduced signal-to-noise ratio. VR allows for easy determination of axon position and direction permitting a rapid segmentation with the VR controller. (B) Bayesian inference of local diffusivity of tracer fluorescent beads in the nucleus of a U2OS cell using VR. A video demonstration can be seen in http://goo.gl/dnNueu. The user identifies a local ROI in 3D, uses the VR controller to define the limits of the ROI, and triggers a program (based on the InferenceMAP software [14]) that computes the diffusion using a Bayesian inference approach. The results are then overlaid. (C) Projection tool aligned to the VR controller used to map the inside of a plated HeLa cell in a serial block-face scanning electron microscopy image stack [34]. (D) UnityMol VR [17]. This software allows the user to visualize and interact with large molecules in VR. (E) Precise measurement of axon segments using the VR controller in a segmented mouse neuron database. All VR screen captures were generated with the DIVA software platform.

requirements. This is particularly vital for user-centric technologies such as VR, where development based on the needs of domain experts can be a conduit for transmitting knowledge to novices. In our experience, we have observed consistent trends in user behavior when trying our VR applications. For example, it is not uncommon to witness users standing up, moving the data vertically, moving around the data in order to explore its spatial extents before manipulating it. Automated protocols to encourage initial data exploration can aid in this regard.

Data Treatment and Numerical Simulations

The visual intuition provided by VR extends further than facilitating spatial understanding of complex volumetric data. In our view, it provides an excellent canvas for data treatment and interaction. It is its place at the frontier of human cognition, data visualization, and direct treatment that VR could have its greatest impact. Through some examples, we discuss some major topics where we predict VR to have an immediate impact.

A direct form of interaction is the selection of 3D regions of interest (ROIs) for exportation and performing analysis. As an example, 3D single-molecule imaging has emerged as a powerful approach to probe complex biological processes at the nanometric scale in native cellular environments. Identifying 3D patterns (static or dynamic) indicative of biological activity is not a simple task, nor is it easily automated. Figure 2(b) illustrates an example where the user defines ROIs using the VR controller, upon which an inference program is executed to estimate the local value of diffusivity of all single molecules moving in that volume [14]. Similarly, being immersed in data provides valuable intuition of data with complex geometries. In Fig. 2(c) we show an example of a user effectively mapping the inside of a mammalian cell by using the VR controller to perform a planar projection in a high-resolution electron microscopy data set. In being able to arbitrary position the projection plane with the VR controller, this function allows structures of interest to be easily revealed to the user. Finally, and similarly to the previous example, the user can directly create 3D annotations to data and perform simple measurements that are difficult and taxing to perform outside of the VR context. We show an example in Fig. 2(e), where dendrites of a segmented neuron are interactively and precisely measured. These annotations can be exported and fed to other programs to characterize the geometrical properties of the tagged structures. Notably, all these examples demonstrate that we can transform, in a matter of seconds, intuition and perception into quantitative results.

Another possibility is to couple human interaction with simulation to understand the processes driving the dynamics of living systems. A direct example is that of molecular simulations. The high-dimensional energy landscapes associated with biomolecule folding problems entail a significant combinatorial complexity of solutions. Optimized molecular dynamics software packages show continuous improvements, but the task remains computationally intensive, especially for large molecules [15,16]. Introducing visual intuition and external knowledge can massively improve performance. In Ref. [10], the authors created a software platform where interactive simulations enable multiple users to simultaneously manipulate molecules and observe their dynamics, computed from physical equations in the cloud, in VR. Here, VR is the vehicle that provides the geometric intuition, where the user can pull, push, and introduce or release molecules and observe the resultant physical effects of the interactions. Note that the authors added an innovative "multi-user presence" in VR as a component of their software. Researchers can learn and interact in virtual environments together while they manipulate the molecules. Similarly, UnityMol is a software package that brings VR and human interaction to molecule editing and prototyping, a photograph of which is shown in Fig. 2(d) [17].

Finally, we address the concept of HITL data treatment and the integral role that VR plays. HITL means that the user and the machine (i.e., learning algorithm) work simultaneously to achieve a specific data treatment task [18–21]. It is our view that such mixed approaches will be instrumental in the context of explainable artificial intelligence, where human intuition and reasoning are used to justify predictions in artificial intelligence systems. Motivation for HITL approaches derives from two often-encountered scenarios present in scientific research. In the first, data are complex to acquire, non-standardized, and limited in number (e.g., images of neural connectomes, organism atlases, etc.). Developing fully automated algorithms or leveraging machine learning in these situations is challenging. The time required to develop efficient algorithms can exceed the time for semi-manual analysis in its own right. Furthermore, generalization is not ensured due to complexities in data acquisition protocols and the limited number of examples to train on. Relating physical interactions to learning algorithms in VR may greatly reduce the time to treat data, improve the efficiency in performing tasks, and reveal possible strategies to automate treatment. For example, in Ref. [22], the authors developed a manual interface to trace neurons from 3D image stacks. VR allows for easy vision of neurons in 3D, even within noisy confocal microscopy data sets. In this context, the user traces neurons by simply moving the VR controller within the data as if it were a real object. Eventually, human intervention can be used to simply define initial "starting points" in the segmentation task, after which an algorithm will perform the optimization. Human intervention can also be intermittent in the training of a learning algorithm, similar to the workflow described in software such as ilastik and others [23,24]: VR would be used for fast data tagging in 3D, and afterward, the algorithm locally learns rules to classify data.

HITL is equally applicable in cases of massive, complex, and standardized data. A direct example is the collaborative efforts to trace neurons from EM serial imaging [25–28]. As mentioned prior, VR human interaction will most likely be used to accelerate data tagging. Interacting and learning is possible on small portions of data loaded in the VR environment, which can then be propagated to the remainder of the data set. Several challenges will still have to be resolved, namely, loading and visualizing image files that are significantly larger than the graphics card live memory. Approaches such as MaMuT [29] and hierarchical file encoding [30,31] offer a promising path, although it will be challenging to ensure efficiency and robustness of results across multiple users performing tagging, testing, and visual verification.

An interesting concept that is bound to drive the development of data treatment procedures in VR is that of “gamification” or “serious games.” Recently, numerous initiatives have used video games as inspiration (e.g., point scoring, competition, rules) to facilitate scientific discovery for specialists and non-specialists alike. VR seems an ideal setting for such approaches [32]. The design of visually appealing environments, efficient human–data interaction procedures, and various game-like features will motivate the non-specialist. It will also ensure the continuous motivation of the specialist for complex tasks that may otherwise be tedious. The examples of protein folding and EM neuron tracing are relevant [33].

Another important feature of treating data in VR is the transfer of expert knowledge to the uninitiated. Immersive environments engage the user to interact with the data. Active interaction promotes better learning than passive observation. The possibility of following the actions of experts performing tasks while being inside data can be transformative in training and education. Mutual interaction in the environment can also drastically reduce learning curves [10].

Conclusion

We are in a period where the impacts of VR technologies on scientific research are starting to be understood and realized. All signs indicate that VR will have a major and sustained impact on the way research is done. Naturally, visualization will provide intuitive visual comprehension of volumetric data and promote rapid knowledge transmission and training in the laboratory. It is data treatment, however, that will most likely dominate future uses of VR in scientific research. Bridging of knowledge gaps between experts and newcomers, the facilitation of segmentation tasks, and the streamlining of studies of system dynamics are just a few applications that demonstrate how VR is positioned to accelerate scientific discovery. Even still, we emphasize that two main challenges lie ahead. The first centers on arriving to a consensus on how to properly interact with data in VR. The second will focus on numerical and hardware challenges, as real-time stereoscopic data visualization remains a demanding task. Simultaneously performing analysis and simulations in the same context will require skillfully designed software and optimized hardware configurations.

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§M. Dahan and J-B. Masson are senior authors.

Abbreviations used:
VR, virtual reality; 3D, three-dimensional; ROIs, regions of interest; HITL, human-in-the-loop.

References

[1] J.-B. Brault, C. Khou, J. Basset, L. Coquand, V. Fraisier, M.-P. Frenkiel, B. Goud, J.-C. Manuguerra, N. Pardigon, A.D. Baffet, Comparative analysis between flaviviruses reveals specific neural stem cell tropism for zika virus in the mouse developing neocortex, EBioMedicine 10 (2016) 71–76, https://doi.org/10.1016/0003-4916(63)90068-X.

[2] B. Hajj, M.E. Beheiry, I. Izeddin, X. Darzacq, M. Dahan, Accessing the third dimension in localization-based super-resolution microscopy, Phys. Chem. Chem. Phys. 16 (31) (2014) 16340–16348, https://doi.org/10.1039/C4CP01380H.

[3] M.E. Beheiry, M. Dahan, Visp: representing single-particle localizations in three dimensions, Nat. Methods 10 (8) (2013) 689–690, https://doi.org/10.1038/nmeth.2566.

[4] S.A. Schalbetter, A. Goloborodko, G. Fudenberg, J.-M. Belton, C. Miles, M. Yu, J. Dekker, L. Mirny, J. Baxter, Smc complexes differentially compact mitotic chromosomes according to genomic context, Nat. Cell Biol. 19 (2017) 1071–1080, https://doi.org/10.1038/ncb3594.

[5] F. Argelaguet, C. Andujar, A survey of 3D object selection techniques for virtual environments, Comput. Graph. 37 (3) (2017) 121–136, https://doi.org/10.1016/j.cag.2012.12.003.
[6] D.F. Keefe, T. Isenberg, Reimagining the scientific visualization interaction paradigm, IEEE Comput. 46 (5) (2013) 51–57, https://doi.org/10.1109/MC.2013.178.
[7] https://project.inria.fr/naviscope.
[8] N. Padmanaban, R. Konrad, T. Stramer, E.A. Cooper, G. Wetzstein, Optimizing virtual reality for all users through gaze-contingent and adaptive focus displays, Proc. Natl. Acad. Sci. 114 (9) (2014) 2183–2188, https://doi.org/10.1073/pnas.1617251114.
[9] D. Duncan, R. Garner, I. Zrantchev, T. Ard, B. Newman, A. Saslow, E. Wanserski, A.W. Toga, Using virtual reality to improve performance and user experience in manual correction of MRI segmentation errors by non-experts, J. Digit. Imaging (2018) 1–8, https://doi.org/10.1007/s10278-018-0108-5.
[10] M. O'Connor, H.M. Deeks, E. Dawn, O. Metatla, A. Roudaut, M. Sutton, L.M. Thomas, B.R. Glowacki, R. Sage, P. Tew, M. Wonnacott, P. Bates, A.J. Mulholland, D.R. Glowacki, Sampling molecular conformations and dynamics in a multiuser virtual reality framework, Sci. Adv. 4 (2018) 1–9, https://doi.org/10.1126/sciadv.aat2731.
[11] P.M. Maloca, J.E.R. de Carvalho, T. Heeren, P.W. Hasler, F. Mushtaq, M. Mon-Williams, H.P. Scholl, K. Balaskas, C. Egan, A. Tufail, L. Witthauer, P.C. Cattin, High-performance virtual reality volume rendering of original optical coherence tomography point-cloud data enhanced with real-time ray casting, Transl. Vis. Sci. Technol. 7 (4) (2018) 1–11, https://doi.org/10.1167/tvst.7.4.2.
[12] R.P. Theart, B. Loos, T.R. Niesler, Virtual reality assisted microscopy data visualization and colocalization analysis, BMC Bioinformatics 18 (2016) 1–16, https://doi.org/10.1186/s12859-016-1446-2.
[13] B. Hajj, J. Wisniewski, M.E. Beheiry, J. Chen, A. Revyakin, C. Wu, M. Dahan, Whole-cell, multicolor superresolution imaging using volumetric multifocus microscopy, Proc. Natl. Acad. Sci. 111 (49) (2014) 17480–17485, https://doi.org/10.1073/pnas.1412396111.
[14] M.E. Beheiry, M. Dahan, J.-B. Masson, Inferencemap: mapping of single-molecule dynamics with Bayesian inference, Nat. Methods 12 (7) (2015) 594–595, https://doi.org/10.1038/nmeth.3441.
[15] R. Salomon-Ferrer, D.A. Case, R.C. Walker, An overview of the amber biomolecular simulation package, Wiley Interdiscip. Rev.: Comput. Mol. Sci. 3 (2) (2012) 198–210, https://doi.org/10.1002/wcms.1121.
[16] S. Doutreligne, T. Cragnolini, S. Pasquali, P. Derreumaux, M. Baaden, Unitymol: Interactive scientific visualization for integrative biology, 2014 IEEE 4th Symposium on Large Data Analysis and Visualization (LDAV) 2014, pp. 109–110, https://doi.org/10.1109/LDAV.2014.7013213.
[17] X. Martinez, S. Doutreligne, J. Rodrigues, P. Ghossoub, M. Trellet, G. Amdur, D.C. Kostin, P.K. Ghatty, P. Derreumaux, A.M. Bonvin, P. Bourdot, N. Férey, M. Levitt, M. Baaden, Open framework to explore and manipulate molecular structures and trajectories in VR, 2019 (submitted for publication).
[18] D. Xin, L. Ma, J. Liu, S. Macke, S. Song, A.G. Parameswaran, Accelerating human-in-the-loop machine learning: Challenges and opportunities (2018) arXiv abs/1804.05892.
[19] S. Ren, K. He, R.B. Girshick, J. Sun, Faster R-CNN: towards real-time object detection with region proposal networks (2015) arXiv abs/1506.01497.
[20] M. Gillies, R. Fiebrink, A. Tanaka, J. Garcia, F. Bevilacqua, A. Heloir, F. Nunnari, W. Mackay, S. Amershi, B. Lee, N. d'Alessandro, Jo Human-centred machine learning, Proceedings of the CHI Conference Extended Abstracts on Human Factors in Computing Systems, 2016.
[21] D. Acuna, H. Ling, A. Kar, S. Fidler, Efficient interactive annotation of segmentation datasets with polygon-RNN++, Proc. IEEE Conf. Comput. Vis. Pattern Recognit. (2018) 859–868.
[22] W. Usher, P. Klacansky, F. Federer, P.-T. Bremer, A. Knoll, J. Yarch, A. Angelucci, V. Pascucci, A virtual reality visualization tool for neuron tracing, IEEE Trans. Vis. Comput. Graph. 24 (1) (2018) 994–1003, https://doi.org/10.1109/TVCG.2017.2744079.
[23] C. Sommer, C. Straehle, U. Köthe, F.A. Hamprecht, Ilastik: interactive learning and segmentation toolkit, 2011 IEEE International Symposium on Biomedical Imaging: From Nano to Macro 2011, pp. 230–233, https://doi.org/10.1109/ISBI.2011.5872394.
[24] I. Arganda-Carreras, V. Kaynig, C. Rueden, K.W. Eliceiri, J. Schindelin, A. Cardona, H.S. Seung, Trainable weka segmentation: a machine learning tool for microscopy pixel classification, Bioinformatics 33 (15) (2017) 2424–2426, https://doi.org/10.1093/bioinformatics/btx180.
[25] A.A. Wanner, C. Genoud, T. Masudi, L. Siksou, R.W. Friedrich, Dense EM-based reconstruction of the interglomerular projectome in the zebrafish olfactory bulb, Nat. Neurosci. 19 (2016) 816–825, https://doi.org/10.1038/nn.4290.
[26] M. Januszewski, J. Kornfeld, P.H. Li, A. Pope, T. Blakely, L. Lindsey, J. Maitin-Shepard, M. Tyka, W. Denk, V. Jain, High-precision automated reconstruction of neurons with flood-filling networks, Nat. Methods 15 (8) (2018) 605–610, https://doi.org/10.1038/s41592-018-0049-4.
[27] M. Joesch, D. Mankus, M. Yamagata, A. Shahbazi, R. Schalek, A. Suissa-Peleg, M. Meister, J.W. Lichtman, W.J. Scheirer, J.R. Sanes, Reconstruction of genetically identified neurons imaged by serial-section electron microscopy, eLife 5 (2016), e15015https://doi.org/10.7554/eLife.15015.
[28] J. Funke, F.D. Tschopp, W. Grisaitis, A. Sheridan, C. Singh, S. Saalfeld, S.C. Turaga, Large scale image segmentation with structured loss based deep learning for connectome reconstruction, IEEE Trans. Pattern Anal. Mach. Intell. (2018) https://doi.org/10.1109/TPAMI.2018.2835450.
[29] C. Wolff, J.-Y. Tinevez, T. Pietzsch, E. Stamataki, B. Harich, L. Guignard, S. Preibisch, S. Shorte, P.J. Keller, P. Tomancak, A. Pavlopoulos, Multi-view light-sheet imaging and tracking with the MaMuT software reveals the cell lineage of a direct developing arthropod limb, eLife 7 (2018), e34410https://doi.org/10.7554/eLife.34410.
[30] C. Crassin, F. Neyret, S. Lefebvre, E. Eisemann, Gigavoxels: Ray-guided streaming for efficient and detailed voxel rendering, Proceedings of the 2009 Symposium on Interactive 3D Graphics and Games 2009, pp. 15–22, https://doi.org/10.1145/1507149.1507152.
[31] J. Beyer, M. Hadwiger, H. Pfister, State-the-art in GPU-based large-scale volume visualization, Comput. Graphics Forum 34 (8) (2015) 13–37, https://doi.org/10.1111/cgf.12605.
[32] J. Vera, G. Santos, Can gamification contribute to computer modeling-driven biomedical research? Front. Physiol. 9 (2018), 908https://doi.org/10.3389/fphys.2018.00908.
[33] C.B. Eiben, J.B. Siegel, J.B. Bale, S. Cooper, F. Khatib, B.W. Shen, F. Players, B.L. Stoddard, Z. Popovic, D. Baker, Increased Diels-Alderase activity through backbone remodeling guided by Foldit players, Nat. Biotechnol. 30 (2) (2012) 190–192, https://doi.org/10.1038/nbt.2109.
[34] D. Boassa, J. Lee, G. Enciso, C. Chander, T. Lou, S. Pairawan, M. Guo, F. Wan, M. Ellisman, C. Sütterlin, M. Tan, *Chlamydia trachomatis*, human hela, The Cell Image Library.