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Extended reality for biomedicine

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Abstract

Extended reality (XR) refers to an umbrella of methods that allows users to be immersed in a three-dimensional (3D) or a 4D (spatial + temporal) virtual environment to different extents, including virtual reality (VR), augmented reality (AR), and mixed reality (MR). While VR allows a user to be fully immersed in a virtual environment, AR and MR overlay virtual objects over the real physical world. The immersion and interaction of XR provide unparalleled opportunities to extend our world beyond conventional lifestyles. While XR has extensive applications in fields such as entertainment and education, its numerous applications in biomedicine create transformative opportunities in both fundamental research and healthcare. This Primer outlines XR technology from instrumentation to software computation methods, delineating the biomedical applications that have been advanced by state-of-the-art techniques. We further describe the technical advances overcoming current limitations in XR and its applications, providing an entry point for professionals and trainees to thrive in this emerging field.

Introduction

With the advent of unparalleled computational power and numerous wearable devices, immersive technology has been developed to extend the real world by creating an interactive three-dimensional (3D) or 4D (spatial + temporal) digital reality. Recent technical progress has resulted in the rise of extended reality (XR), which encompasses virtual reality (VR), augmented reality (AR), and mixed reality (MR). The fundamental concept of these methods is generally to integrate physical reality and virtual environments to different extents, creating an immersive and interactive interface through wearable sensors and hand controllers. Recent advances in applying XR to biomedical fields have been demonstrated in fundamental research, medical training, and preprocedural planning [1–6].

VR is the first widely used method to create a purely digital environment that is either highly similar to or completely different from the real world [7] (Figure 1a). Users can experience the virtual world in different manners, such as a head-mounted display (HMD) or cave automatic virtual environment (CAVE) [8]. Along with hand controllers and haptic gloves **[G]**, VR HMDs allow users to experience immersive interactions in the virtual environment with better portability [9]. In contrast, CAVE provides a larger field of view (FOV) **[G]** and more enhanced immersion of the full-body at the cost of portability [10]. VR prototypes from the late 1950s and 1960s led to the boom of VR in the 1990s when many commercial products were launched. However, these products were criticized due to their deficiency in mature display technology, 3D rendering, and motion detection. Beginning in 2012, the Oculus Rift project, along with other novel VR HMDs, stirred up the second wave of VR technology, drawing attention to a broader audience for the revival of the technique and unlocking more application scenarios for biomedical research and data visualization [6,11], procedural planning [12,13], medical education and clinical training [14–16], as well as digital therapeutics and rehabilitation [17,18].

Both AR and MR combine the real world and virtual environment, providing a partial immersive experience. However, the differentiation between AR and MR is still being debated[19,20]. The interactivity of MR is sometimes considered as a dimension to differentiate it from AR [21,22]. For instance, assuming a virtual donut behind a real apple, AR simply overlays the entire donut on top of the real environment (Figure 1b), while MR will display the donut as partially occluded by the real apple [20] (Figure 1c). However, MR and AR are used interchangeably in most cases [20,23,24]. To avoid confusion, we consider MR to be synonymous with AR in this Primer, defining both as a system that combines the real environment and virtual content, providing a real-time interactive 3D environment [25], and we propose the use of XR as a broad term for both VR and AR. In addition to conventional displays such as monitors, advanced AR HMDs are also being deployed to show the virtual environment integrated with reality [26,27]. As a technical cornerstone in AR, tracking and registration of virtual objects with elements in the real world serves as the key to bridging virtual context and reality [28]. While AR is still nascent in comparison with VR, the inherent capability to combine the virtual and real worlds in AR allows for the transformative development in medical training and intraprocedural navigation [27,29–31].

Immersion and interaction are considered to be innate qualities of XR [32–36], serving as essential features of XR applications in biomedicine. These two capabilities enable us to interpret intricate biomedical data such as multiplexed imaging and multi-omics results in different ways compared to other conventional methods. Specifically, immersion within a stereoscopic environment provides users with a straightforward way to investigate high-fidelity models with 3D depth perception, rather than showcase the dataset on the conventional panel displays [37]. On the other hand, interaction enables user-directed visualization and manipulation through advanced techniques such as hand controllers, motion tracking and haptic feedback, which are different from the pre-defined operations of conventional animations. In this context, immersion and interaction facilitate the applications of XR in biomedicine, creating transformative opportunities for users to explore the data in fundamental research and clinical investigations with maximal efficiency and minimal risk [30,38].

We propose this Primer to provide an overview of intuitive XR approaches and applications. First, we address the working principle of XR by introducing the essential hardware components and software platforms in an XR system. Next, we outline the fundamental approaches to associate biomedical raw data with virtual environment and introduce the mainstream interaction strategies between reality and virtuality. Furthermore, we present the representative implementation of XR methods in biomedical research and healthcare. The general standards for data security, reproducibility, compatibility and deposition within the XR community are also outlined. Lastly, we explore current challenges and optimizations of XR techniques in biomedicine, and envision the development and applications of biomedical XR in the future.

Experimentation

In this section, we discuss the working principle of XR systems in the context of biomedical applications by introducing the hardware components and the advances in software platforms.

Hardware components of XR

To enable immersion and interaction in XR, fundamental hardware components including display, optical lenses, sensors, and computation processors are required (Figure 2a–b). Generally, the display and lenses contribute more to the immersive experience, while sensors are critical to the input and output interface for interactive operations. Computational processors, which include central processing units (CPU) and graphical processing units (GPU), provide the power necessary to generate the virtual experience.

Display and optical lenses—Immersion quality is significantly dependent on the visual display [39]. Optical lenses along with the display contribute to the visualization quality and portability in HMDs, determining the FOV and angular resolution **[G]** for the immersive experience [40,41]. The lenses are placed between the display and the user's eyes to converge light coming from the screen onto the retina, forming a clearer image (Figure 2c–e). Different lens designs include Fresnel [42] and pancake lenses [43] for VR HMDs, and the birdbath combiner, off-axis reflective combiner and waveguide for AR HMDs [44]. While VR HMDs and CAVE both allow for immersive experiences, they differ in technical parameters such as resolution and FOV, leading to distinct biomedical applications. For example, CAVE, which is composed of 3–6 side displays on walls, ceiling, and floor [45], is able to create an immersive feeling for the full-body and provides a unique opportunity for *in vivo* study of unrestrained animals [46]. In contrast, portable HMDs generate a full stereoscopic and immersive experience through binocular disparity **[G]** [37], enabling cost-effective solutions for digital therapeutics [8,47], medical education and training [15,35].

Conventional monitors and HMDs are two dominant display devices in AR applications [48]. Monitor-based AR employs conventional displays such as panel monitors and smartphones to present the real environment with overlaid virtual objects [49]. AR HMDs allow users to directly observe the real environment through an optical combiner **[G]** and use micro-displays to project virtual objects to a user's eyes [50]. In some cases, monitor-based AR is less cumbersome to surgeons as it does not require an additional HMD to be worn throughout an operation [51].

Sensors—Sensors are fundamental to input and output stimuli for enhanced immersion and interaction in XR systems [52]. In medical XR applications such as clinical training and patient rehabilitation, the orientation (yaw, pitch, roll) and position of surgical instruments or a patient's limbs are measured and used as the input. To achieve this, an electromagnetic sensor known as the inertial measurement unit (IMU) **[G]** [53] can be embedded in hand-held instruments and HMDs thanks to its small size and weight [39,54]. However, the metal objects in the operating room may cause artifacts such as distortion errors on electromagnetic sensors like IMUs [55]; optical sensors such as cameras are commonly used instead [56,57]. On the other hand, haptic sensors are able to mimic force feedback, significantly improving authenticity and accuracy when trainees practice medical skills in XR and surgeons perform AR-based robotic-assisted operations [58,59]. In addition, physiological signal sensors for electrodermal, electroencephalographic (EEG) and electrocardiographic (ECG) activity also hold great promise for the characterization of stress levels and different emotional states of users in XR medical applications [60–62].

Computational processors—The computational power of processors significantly impacts the immersive and interactive experience through key factors such as frame rate **[G]**. Current deployments of processors lead to three types of HMD including smartphone-based, tethered and standalone (Table 1) [63–66]. Among these, tethered HMDs, which are connected to external computers provide powerful rendering and computation at the cost of mobility and safety concerns in XR-assisted surgeries [67 39], while standalone HMDs allow for greater freedom of movement but with limited computational power [68]. No matter the type of XR system, recent progress has demonstrated that a latency rate of more than 15–20 ms between head movement and the corresponding virtual scene update in XR leads to vergence-accommodation conflict (VAC) **[G]** and motion sickness [69]. Therefore, processing power that establishes a high frame rate (> 90 frames per second) is required to reduce latency and provide a successful immersive experience [70,71].

Software advances and platforms

XR development engines—There are multiple popular software platforms to create virtual environments for XR, such as Unity 3D, Unreal Engine 5, CryEngine, Blender and Amazon Lumberyard, among others. Unity 3D and Unreal Engine are widely used platforms that enable novices to create XR solutions. Unity is a game engine, with scripting based on C#, that has extensive resources for VR and AR software development. Unreal Engine 5, the latest iteration of the tool, allows developers to create projects for conventional rendering or XR with C++ code. Users can create 3D models from sketches, or purchase models directly from the Unity Asset Store or Unreal Engine Marketplace.

Biomedical XR platforms—In addition to these commercial XR engines numerous biomedical-related XR platforms and software have also been developed to promote broad applications. For instance, representative platforms such as ChimeraX [11], ConfocalVR [72] and vLUME [6], are established for interactive visualization and analysis of biomedical images. Medical education and clinical training can be performed through HumanSim, AnatomyX, SimSurgery [73] and hapTEL [74], among others. In parallel, the Food and Drug Administration (FDA) has cleared some platforms, such as PrecisionOS, VisAR, Knee+, and RelieVRx, for preprocedural planning, intraprocedural navigation, and digital therapeutics. Some representative platforms are listed in Table 2.

Results

Due to XR's capability for immersion and interaction, continuing efforts have been made over the past decades to create virtual models via computer graphics-based simulation (commonly used in entertainment) or to transform real experimental datasets into a virtual environment. We focus on the latter in this Primer, involving the conversion of biomedical results into virtual objects. Using these virtual objects in XR strengthens clinical investigations and fundamental research by leveraging computational power and interactive analysis of real-world data such as multidimensional imaging and macromolecular structures [11]. Data volumes can be visualized using various conversion pipelines and graphics rendering which are enhanced by the immersive aspect of XR. The interactive aspect of XR allows for greater manipulative capabilities and analysis than conventional viewing on a monitor [75]. In this section, we discuss the different methods of biomedical data visualization and interactions in XR applications.

Biomedical data visualization

Rather than viewing virtual data on a single 2D screen, XR can enable 3D visualization in an immersive environment, allowing for more effective qualitative insights into biomedical datasets. The use of this technology has great potential in the medical field, as conventional analysis of clinical images is restricted to viewing 2D slices or a 3D reconstruction on a flat monitor [76]. Conversion of this data into a model within XR can permit full visibility of patient data. Image segmentation can be used as an initial step when generating a model based on user-specified boundaries. In addition to its usefulness in medicine, XR can be used for the visualization of biomolecular structures and sequences. The greater observability is an appealing aspect to researchers in the field of biology, as relationships and links within the data can be better discerned [77]. Conversion of both imaging and biomolecular data to XR models are discussed further below.

Multidimensional imaging data—3D XR models based on imaging data can be useful to physicians in both preprocedural planning and intraprocedural operation. A model can be visualized using a VR system so that planning can take place in a completely immersive environment, such as with the platform PrecisionOS. In addition, overlaying a model onto a real patient using AR can provide guidance to surgeons in minimally invasive procedures [78]. To display a 3D model in the virtual environment, collected images are stored as data volumes, followed by visualization through three rendering methods: point cloud rendering, surface rendering, or volume rendering. A point cloud is a set of points in space representing information about an object [79]. Point cloud-based data can be acquired through segmentation of any imaging modality, or through post-processing of images acquired from pointillism-based modalities, notably single-molecule localization microscopy [80]. Individual fluorescent molecules are localized in this modality, and therefore each molecule can be represented as a point with coordinates. Point cloud data containing the coordinates is stored and imported to VR platforms such as vLUME, for subsequent rendering into the virtual scene [2,6]. Surface rendering is used for datasets containing gross structures, such as bone and vessels highlighted by contrast computed tomography (CT) [81]. Surface rendering is a technique that involves displaying a 3D surface model in the virtual environment. The data that is used to create this surface can be the original volume or an extracted volume based on image segmentation, with the latter able to be accomplished in an imaging processing platform such as 3D Slicer or Amira [82]. When using the original volume, surfaces can be extracted using algorithms such as marching cubes [83]. In this method, a threshold value must be predefined by the user in order to generate a surface [84,85]. The overall structures can be visualized from the data once their surfaces are constructed; however, depth and underlying detail are lost. To retain as much detail from the original dataset as possible, volume rendering generates a 3D model based on the entire imaging volume, including all its voxels [83,86,87]. This technique bypasses any image pre-processing or annotation and is thus suitable for cases in which segmentation or labeling is difficult, such as when the surrounding objects are small or poorly defined, causing spurious surfaces or erroneous surface holes to generate. The depth and visual detail of the underlying tissue morphology is an advantage of volume rendering as it is rendered based on pixel data.

Image segmentation methods—To convert biomedical images to an editable 3D model in XR, image segmentation, which is regarded as a pixel-wise classification problem, can be used as an important preprocessing step to divide a digital image into contiguous parts [88]. Segmentation strategies are constantly being developed, evolving from conventional methods (e.g., threshold-based post-processing [89], statistical learning-based bundling [90], watershed methods [91], and k-means clustering [92]) to more advanced algorithms (e.g., graph cuts [93], sparsity-based methods [94], active contouring [95], and Markov random fields [96]). Manual segmentation is generally considered to be the gold standard, but it has low efficiency and is time-consuming due to large data processing needs, and so its use for generating XR models is limited. Manual segmentation also has the potential for low reproducibility due to both intra-rater and inter-rater variability. Integration of deep learning methods in segmentation has achieved remarkably improved performance on biomedical images [97,98]. Based on the nature of input data, deep learning can be categorized into supervised learning, semi-supervised learning, unsupervised learning and deep reinforcement learning [88,99]. More detailed information can be referred to the Supplementary Information or elsewhere [88,99–102].

Biomolecular Data—3D biomolecular structures (e.g., protein surfaces, and atomic structures) and sequencing data (e.g., DNA sequences, and scRNA-seq) can also be converted to models for visualization within XR. Current XR applications for studying molecular structures and sequences expand upon conventional 2D platforms for visualization

[77] [103]. Input file types depend on the biomolecule of interest, and conversion pipelines to generate a model vary with each platform. 3D data about protein structures can be found on popular repositories such as the Protein Data Bank (PDB) and eF-site, while sequencing data can be found on UniProt and NCBI [11,103,104]. In the academic platform BioVR, PDB data is imported and converted into 3D mesh objects, while mRNA sequences are loaded and viewed alongside those objects [77]. VR is intuitively used in this case to allow for a more explorative view of different data types simultaneously, enhancing the analysis of sequence-structure relationships [77]. AR has also been used to visualize PDB data in learning environments, as the real world remains visible to provide social contexts and promote collaboration [103].

Interaction techniques

Interactions between the user and virtual environment play key roles to help maintain immersion as well as allowing for the manipulation of virtual objects. Efficient manipulative capabilities within XR enable inherent biomedical applications such as image analysis, medical training, and preprocedural planning, differing from the simple interaction based on flat graphics displays [40]. As a vital feature of XR, interaction methodology recognizes user input from multiple channels such as movements and gestures, along with generating real-time sensory output with visual, auditory, haptic, and olfactory information. In addition to direct manipulation through voice, physical devices (for example, hand controllers, gamepad, joystick, and touch screen), and head movement tracking accomplished by IMUs, other advanced interaction methods in XR have been widely used to improve the interaction and immersion quality in XR and they are summarized as follows.

Motion tracking and gesture recognition—Motion tracking is vital to the immersive experience in XR and lies at the core of AR technology, especially in image-guided surgical navigation [56]. This technology aims to locate the real-time position of the human body or instrument in real-world coordinates via various sensors that may take optical, ultrasonic, and inertial measurements [105]. Methods of tracking include inside-out tracking (Figure 3a), where sensors are mounted on the HMD itself, and outside-in tracking, where sensors are placed in stationary locations in the environment (Figure 3b) [64,106]. In the latter strategy, the sensors track and position a set of markers that are placed on the target. Outside-in tracking generally allows for the high precision and reliability required in medical applications, compared to inside-out tracking [107]. However, the peripheral equipment restricts the free movement of surgeons and physicians. The additional calibration between the AR device and intraprocedural navigation systems also limits progress [108]. Combining both tracking methods is an emerging solution to improve the accuracy and reduce the safety risks in XR biomedical applications [109]. In addition to general motion tracking, XR can employ gestures **[G]** for the sake of input and output with higher efficiency [110]. Since gestures are so frequently used in the real world to communicate and perform tasks, recognition of gestures is an easier input modality for XR systems. This is applicable for the navigation and control of the manipulator in robot-assisted surgery [111], non-contact control of clinical software in operating rooms to avoid contamination [111,112], and the monitoring and guidance of patient movement in XR rehabilitation [113].

Haptic feedback—In medical education, clinical skill training, and preprocedural planning, an ideal haptic interaction would significantly enhance the authenticity and immersion when users explore the virtual environment, providing intuitive feedback for users when manipulating virtual objects similar to the real world [114]. A successful haptic feedback interaction includes collision detection in the virtual environment and force feedback delivery in the real world through smart gloves and teleoperation controllers [36,115,116] (Figure 3c). As haptic feedback sensation is important in conventional surgery, it can enhance the performance of XR-assisted pre-procedural planning, such as for craniomaxillofacial reconstruction [117], and teleoperated robot-assisted minimally invasive surgeries [59].

Applications

XR enables numerous activities including user-defined visualization and analysis due to the unparalleled interaction and immersion established between the user and virtual environment. In recent decades, XR has been increasingly employed in a broad range of biomedical science and clinical investigations[6,75,118–123], following the rapid advances in hardware and software platforms. Among these integrated platforms, multiple XR strategies have been cleared or approved by the FDA for planning of surgical procedures. VR allows the surgeon to take a patient's CT scan and create a 3D reconstruction, thereby permitting the focusing and definition of anatomic regions of interest, such as with the PrecisionOS platform [124]. AR also has been approved to assist surgeons during spinal procedures, such as with VisAR. In this approach, surgeons virtually annotate a patient's imaging data and is then converted into an immersive hologram mapped to the patient's body [125]. Another AR approach, Knee+, has been approved for knee replacement surgery in which the surgeon can judge the alignment of instruments with the knee joint in 3D space [126]. In addition to these clinical applications, the controlled simulation of a visual environment in XR also enables researchers in the field of biology to study animal activity, behavior and molecular expression, along with promoting 3D anatomy medical training and patient education of specific pathologies [127]. Moreover, XR is increasingly being studied for its use in digital therapeutics and rehabilitation [128–132], as the immersive virtual setting can serve as a distraction technique. In this section, we have listed representative XR applications in data visualization and analysis, in vivo biological study, preprocedural planning and intraprocedural navigation, as well as digital therapeutics and rehabilitation.

VR as a visualization and analysis tool

XR is an emerging platform for 3D or 4D visualization and interactive analyses of microscopic and radiological images and genomic data. The immersion and interaction of XR foster the advent of multiple tools including ChimeraX [11], ConfocalVR [72], ProteinVR [133], vLUME [6], TeraVR [72], and VR-LSFM [118]. For instance, ChimeraX enables interactive visualization and analysis of multi-channel molecular images in a large data volume [11]. In parallel, a VR-based visualization platform, vLUME, has been developed to render large 3D single-molecule localization microscopy datasets for enhanced interactivity and immersion [6] (Figure 4a), bridging the gap between high-fidelity exploration and volumetric datasets. These models enable users to navigate inside intricate architectures, localize distributions, and interact with tremendous numbers of data points in a straightforward way from the molecular to cellular to tissue level. The EchoPixel True 3D Virtual Reality Solution system integrated into a diagnostic grade digital imaging and communications in medicine (DICOM) workstation was one of the first 3D displays to be cleared by the FDA. True 3D permits volumetric visualization and depth perception of anatomic structures from various imaging modalities, including echocardiography, CT, and magnetic resonance imaging (MRI). This stereoscopic visualization tool allows for virtual examination of anatomic structures such as mitral valve annulus size and mitral valve prolapse distance in the clinical setting with low intra-rater and inter-rater variability [134 135].

Experimental environment for *in vivo* study

Besides the straightforward applications in data visualization and analysis, recent progress also demonstrates that the modulated VR landscape has been used to generate great immersion for animal models. This has allowed the creation of controlled environments to study the response of animals to visual stimuli, which is especially promising for the study of neural activity and cognitive behaviors [5,46,136–138]. For example, neural development and plasticity have been investigated in honeybees under the control of visual cues in the VR environment, providing a new insight of *Egr1* gene upregulation in brain sections [136]. Similarly, visual stimuli in VR have been used to study the neural activity and cognitive behavior in the dorsal encephalon of zebrafish [137]. Another report in mice demonstrates the contribution of VR to the investigation of dopamine signals driven by dynamic stimulus, proving the feasibility of immersive VR in broad biomedical applications ranging from invertebrates to vertebrates to mammals [5] (Figure 4b).

Procedural planning and navigation

XR's capability for interaction provides a unique opportunity to manipulate 3D and 4D clinical models, instead of viewing conventional coronal, axial, and sagittal planes, holding great potential for procedural planning and navigation. This ability can allow physicians to uncover details in an intricate environment, such as obscured blood vessels behind tumor [29,139]. HMD-based systems have demonstrated their usage in the field of neurosurgery including craniotomy, lumbar biopsy, ventriculoperitoneal shunt, and endoscopy [29], enabling surgeons to focus on the operation at hand rather than switching back and forth between the surgical field and a monitor [140]. XR is also a platform for more effective communication between surgeons and patients, providing a straightforward method for the sake of training and education in a low stake setting [141]. Collectively, the advent of XR is an emerging way to address the issues of patient safety, surgical complexity, and the challenges associated with medical training in the operating room.

Enhanced electrophysiology visualization and interaction—Currently, visualization in the electrophysiology laboratory relies on fluoroscopy, echocardiography, and electroanatomic mapping systems, constituting a wealth of 3D information however presented on 2D monitors. An AR approach named ĒLVIS (Enhanced Electrophysiology Visualization and Interaction System) — which employs a HMD with custom rendering software — was developed for electroanatomic mapping display during real-time transcatheter ablation procedures in which cardiac electrical signals are induced and abnormal electrical foci that cause arrhythmias ablated [142] (Figure 4c). ĒLVIS permits patient-specific visualization of 3D cardiac geometry with real-time catheter locations and voltage maps, as well as direct, hands-free control of the display by the interventional electrophysiologist's gesture, gaze, or voice [143]. The system can integrate preprocedural data obtained by CT or MRI. ĒLVIS leads to a 33% improvement in mean navigation accuracy over standard visualization tools [144]. Importantly, whereas ĒLVIS is controlled by a single person at any given time, the system can be shared by up to five users and controller privileges passed on to others.

AR-assisted cardiac invasive procedures—Another AR strategy named RealView Holographic Display was developed, applicable to complex cardiac invasive procedures such as transcatheter atrial septal defect closure, without the need for any human-mounted device or goggles [145] (Figure 4d). At present, fluoroscopy images during invasive angiograms are displayed on 2D screens, thus requiring multiple images to be obtained using different angles to have a better understanding of the spatial distribution and dimensionality of the underlying structure of interest. Using 3D rotational angiography and 3D transesophageal echocardiography, RealView permits real-time 3D digital hologram visualization with the ability to mark, crop, zoom, magnify, rotate and slice images [145]. XR guidance would have great value in transcatheter aortic valve replacement, as it is a complex interventional procedure involving careful completion of multiple steps. VR or AR can be used to simulate and plan this procedure, allowing for identification of an optimal landing zone for the replacement aortic valve [127].

Digital therapeutics and rehabilitation

Mental health care providers have been using VR-based exposure therapy for more than a decade as part of treatment plans for patients with various psychiatric disorders, such as post-traumatic stress disorder [128]. Exposing patients to triggers via a VR platform enables the mental health care provider to provide a safe and controlled environment for progressive desensitization [146]. Furthermore, by offering an interactive environment with control over stimuli, VR is effective in many phobias [147,148]. VR also has applicability in neurological disorders, particularly in stroke rehabilitation, by making neurological rehabilitation therapeutics more widely accessible and affordable to patients [149], leading to improved physical function, activity levels, as well as cognitive function [150]. The FDA-cleared platform Luminopia One provides unique digital therapies for amblyopia. RelieVRx is approved with Emergency Use Authorization by FDA to help release chronic lower back pain. In addition, VR has been shown to help post-stroke patients in recovery by exploiting active movement. However, this same technique is difficult to apply in patients with a low level of motor control. The impact of an EEG-based brain-computer interface (BCI) VR intervention was assessed on a male chronic stroke patient [151,152] (Figure 4e) using clinical scales, motor imagery capability assessment, functional MRI data, and EEG data. The patient setup involved a first-person BCI game developed in Unity wherein a user boat rowing task consisted of mental imagery and audio feedback. All three modes of the evaluation showed that the patient gained an increase in motor functioning and activity in associated brain regions through the BCI-VR system.

Reproducibility and data deposition

As is usual for emerging technologies, standards for XR solutions remain to be defined [153]. With advances in XR hardware and software platforms, reproducibility remains an unmet need for the design, implementation and assessment of XR systems and applications [154]. Technical standards hold great potential to regulate the development of XR hardware and software. Additionally, human factors contribute considerably to the reliability and applicability of XR development and applications [30,155]. While independent raters are always required to conduct rating surveys and assess new XR platforms and biomedical approaches [118,156], both intra-rater and inter-rater reliability should be considered for further analysis in consistency, accuracy, and reproducibility. In parallel, specific committees and advisory groups have been formed to develop systematic approaches and standards for XR solutions to ensure reproducibility, making the technique transparent, accessible, and interoperable to everyone [157,158].

XR standards

The main organizations pursuing guidelines and standards for XR are IEEE [158], the Khronos Group, the Video Electronics Standards Association, the Moving Picture Experts Group, and the Society for Information Display, with the first two providing published standards. The Virtual Reality Industry Forum has also pursued setting VR guidelines, addressing the idea that the XR industry needs standards in production, compression, storage, delivery, and security. In addition, Meta released a Best Practices Guidelines, outlining soft standards in sections such as general user experience, vision, locomotion, user input, audio, user orientation and positional tracking, avatars, and rendering.

The IEEE VR/AR Working Group has initiated twelve standards termed P2048 to cover various areas of work, ranging from device taxonomy to immersive user interface, stream formats to file types, person identity to environment safety, map for virtual objects to in-vehicle AR, and quality metrics to content ratings [158]. Until now, device manufacturers, technology developers, service providers, government agencies, and end users have been encouraged to contribute to the development of standards for the rapid rise of XR.

Data deposition

While many academic libraries have expertise in the storage, preservation, display, and exchange of conventional 2D objects such as images and videos for scientific research, standards and practices for managing XR contents are currently lacking. To keep up with emerging trends, research needs, application development, and to curate all types of information, it is imperative that libraries and other institutes create digital collections of 3D data in XR [159]. Various repository workflows and infrastructures have been proposed for metadata collection, access and reuse the raw files, and 3D model generation procedures [160–166]. However, standard repository solutions for the management of 3D datasets and online access to reuse original 3D data remain to be defined [159]. While standardized XR data repositories are currently missing, a notable exception is the project sponsored by the Institute of Museum and Library Services, proposing to address this issue. We envision that the establishment of a standard XR data repository will promote data reproducibility, repeatability, and collaborative development of XR applications.

Data security

While it is critical to keep technology visible for inspection and auditing, regulation and policies to address user privacy, data security and ethical concerns of XR need to be defined [167,168]. With the rapid growth of XR, common cyber-security threats to computers, servers and mobile devices still exist in this emerging territory [169]. New policy to protect user identity and data fidelity from attacks is fundamental in both standalone and client-server XR systems [169]. For this reason, authorized access to input and output devices such as cameras and GPS is required for XR implementations in biomedicine, assuring high-fidelity virtual contents displayed in front of users with minimal impact on the interaction, immersion, and network communication [170–172]. In addition to protecting developers' intellectual property, addressing privacy, security, and ethical concerns of patients in clinical settings also needs to be considered [173]. For clinical practices, international standards such as DICOM and picture archiving and communication system (PACS) [174] are also able to be used for data management and exchange in support of security and privacy. The extension of current protocols holds the promise to bridge the gap in biomedical XR.

Limitations and optimizations

XR solutions are not always preferable over conventional methods, and their utility can sometimes be contradictory in clinical investigations [14]. A recent systematic review concludes moderate evidence of accuracy improvement using augmented reality surgical navigation (ARSN) as compared to freehand surgery [175], while others reported ARSN outperformed conventional methods in screw placement in the thoracic[176] and spine fixation surgery[177]. Similarly in another orthopedic surgery investigation, the results demonstrate that no notable differences among trainees were observed between the VR platform and the physical simulation [178]. In this context, XR for surgical procedures must demonstrate convincing improvement in procedural accuracy, with reduced complications and mortality rates before entering routine clinical practice. In medical education and training, some similar results have also been reported that VR-based training has the same effectiveness with traditional approaches [179–182]. A neuroanatomy training test also reports no statistical difference between the VR-based training group and the physical model training group [183]. Another report also points out the immersive VR platform potentially distracts learners from contents in comparison to those who used simulation on desktop computers [184]. Collectively, the instructional effectiveness of immersive virtual environments in medical education and training needs to be further investigated. Causes of the issues are multifaceted, ranging from hardware to software to XR reproducibility. We have summarized some representative limitations leading to the restricted use of XR in biomedicine as follows.

Immersion and portability

Immersion is crucial to the performance of biomedical XR applications, especially for medical training, digital therapeutics, and patient rehabilitation. The first challenge of immersion in XR is the tradeoff between FOV and HMD weight, that is, both VR and

AR suffer from a weight requirement in tandem with computational capabilities when attempting to advance the FOV. Advanced technologies such as metasurface eyepiece [185] and Pancharatnam-Berry phase lenses [186] hold the potential to balance the FOV and HMD weight. Secondly, an FOV of greater than 100° is prone to chromatic aberration, leading to visual and motion artifacts[187 188]. To address this issue, a transparent screen using three-layered diffuser-holographic optical elements is proposed to minimize chromatic aberration [189]. Faster response times with sub-millisecond latency by utilizing a low viscosity liquid crystal also holds the potential to mitigate motion artifacts and overcome the tradeoff between FOV and resolution [187].

Limited computation capability

Clinical applications via XR systems require powerful computation capabilities to enable detailed rendering and precise image registration for accurate diagnosis, preprocedural planning and intraprocedural navigation. While untethered XR hardware is preferred to ensure portability, and safety, the limited computational capability on devices prevents the implementation of XR. Meanwhile, increasing FOV, resolution, and frame rate in XR leads to an exponential growth in rendering computation, thus decreasing immersive performance. In addition to the hardware upgrades, cloud computing and advanced algorithms such as the foveated rendering **[G]** coupled with eye tracking could significantly lower the threshold for hardware requirements [89,190,191].

XR standards

Current limitations of XR in biomedicine are partially attributed to the reproducibility in XR development and implementation. Well-accepted standards covering hardware, software, service, management, testing, and immersive experience assessment are indispensable to promoting the development of the XR ecosystem. The hardware and software developed under unified standards and guidelines will have better generality, scalability, and compatibility. The integrative platform also holds the potential to allow novice users from different fields to participate and enrich more application scenarios.

Outlook

With the advent of XR technology, the integration of XR with conventional biomedical study and clinical practice draws attention to a wide audience interested in this transformative opportunity. Current trends have already shown its popularity in multiple areas including biomedical data visualization and analysis [6,11], medical training and education [14,15], surgical procedures [140,141], digital therapeutics [128,149], rehabilitation [151,152] and remote medical practice [192–194]. Emerging platforms are attempting to address unmet challenges in fundamental research and clinical investigations as discussed in previous sections. As opposed to conventional methods, XR adds another dimension to allow for user-directed operations in an immersive and interactive context. This capability enables users to delve deeper into intricate structure and function, from molecular to tissue level and under physiological and pathophysiological conditions. The high level of immersion also allows researchers to create controlled environments for visual stimuli in animal studies. In clinical settings, XR can allow for greater depth in education, training, and planning due to its immersive and interactive environment, simulating environments for users to have realistic practice for high-risk procedures such as surgery. The benefits of XR further permit digital therapeutics for anxiety and pain management as the immersive interaction distracts users. While numerous examples have been reported, the full potential of XR in biomedicine is still under investigation. The absence of a flagship application of VR or AR in either fundamental research or clinical investigation is still a bottleneck. More powerful and influential biomedical applications using XR remain to be defined, yet there is ongoing technical development.

Distributed virtual environment

The long-term development of XR is inseparable from a full ecosystem of devices, services, and content, as well as a viable and profitable economy. With the popularization of the internet, the distributed XR systems will be connected under a coordinated network structure, standards, protocols, and databases, creating a virtual environment that is spatiotemporally coupled and allows for collaborative interaction and remote medical practices. In addition, user-friendly platforms will emerge under the functional ecosystem for less experienced users to create their own XR demos, and the increasing number of active users will further facilitate the development of XR, thereby creating a virtuous circle.

Mobile XR

Interactive programs continue to increase in the era of the internet, and this computing-intensive and delay-sensitive application limits the immersion of standalone XR with independent computation and tethered XR. The large latency could significantly affect the accuracy and security in the XR-assisted surgical operations [195,196]. Substantial opportunities for XR adoption will be untethered via 5G and mobile edge computing [197–201], which deploys servers at the network edges to provide cloud computing and capabilities to mobile users with reduced latency [197,198]. XR applications using these new technologies will provide excellent transmission efficiency and an immersive experience with reduced motion sickness. The convergence of XR with advanced computing and communication technology will reduce the security concerns in healthcare and synergize more opportunities for the realization of XR-based biomedical applications [202].

Multi-sensory engagement

The real physical world is a multi-sensory environment, while virtual environments only provide degraded sensations due to under-developed audiovisual stimulation and haptic feedback [203–205]. Aside from wearable gloves, more efforts have been made towards wireless devices applied on the skin to provide coordinated vibrotactile feedback for XR applications such as virtual prosthetics [206,207]. There is also ongoing development of olfactory and gustatory sensory renderings [203,208–210], holding the potential to further enhance the immersive experience. Multi-sensory engagement not only enhances the immersion in the virtual environment, but also holds the promise to advance sustainable decisions, green choices, and prosocial behavior [211]. While technical development is still in process, the integration of multi-sensory engagement with BCIs is one of the most promising and exciting directions in the future.

Our aim with this Primer is to emphasize the theoretical potential of XR by delineating its technical advances and biomedical applications. While multiple issues of XR practice remain to be addressed, this novel strategy has shed light on its potential in numerous biomedical fields. With increasing interdisciplinary collaborations, the contribution of XR to biomedicine will be characterized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

Haptic Gloves

A type of wearable device that functions to provide realistic sensation and manipulation of virtual objects through hand motion tracking, force feedback and tactile feedback

Field of View

The visual field as one eye is stationary. In general, the monocular FOV of a human eye is about 160° × 130° (horizontal × vertical), and the combined binocular FOV is about 200° × 130°, with an overlapped region of 120° horizontally

Binocular Disparity

The slight difference between left and right retinal images of the same object due to the location difference of the left and right eyes

Angular Resolution

The ratio between the number of horizontal pixels and horizontal FOV

Optical Combiner

The component of the augmented reality display that delivers images produced by the display engine to the user's eye while also transmitting environmental light

Frame Rate

The number of consecutive images that are displayed and delivered to the user every second

Vergence-accommodation Conflict

A visual phenomenon that occurs when the brain receives mismatching cues between vergence and accommodation of the eye

Inertial Measurement Unit

An electronic device containing a gyroscope, an accelerometer and a magnetometer used to measure the specific force, angular rate and orientation of the body

Gestures

The posture or movement of the user's upper limbs, including fingers, hands and arms, containing significant interactive intentions as the input for extended reality

Foveated Rendering

A rendering method designed to improve graphics performance by maintaining high visual detail near the fovea, while decreasing quality towards the eye's periphery

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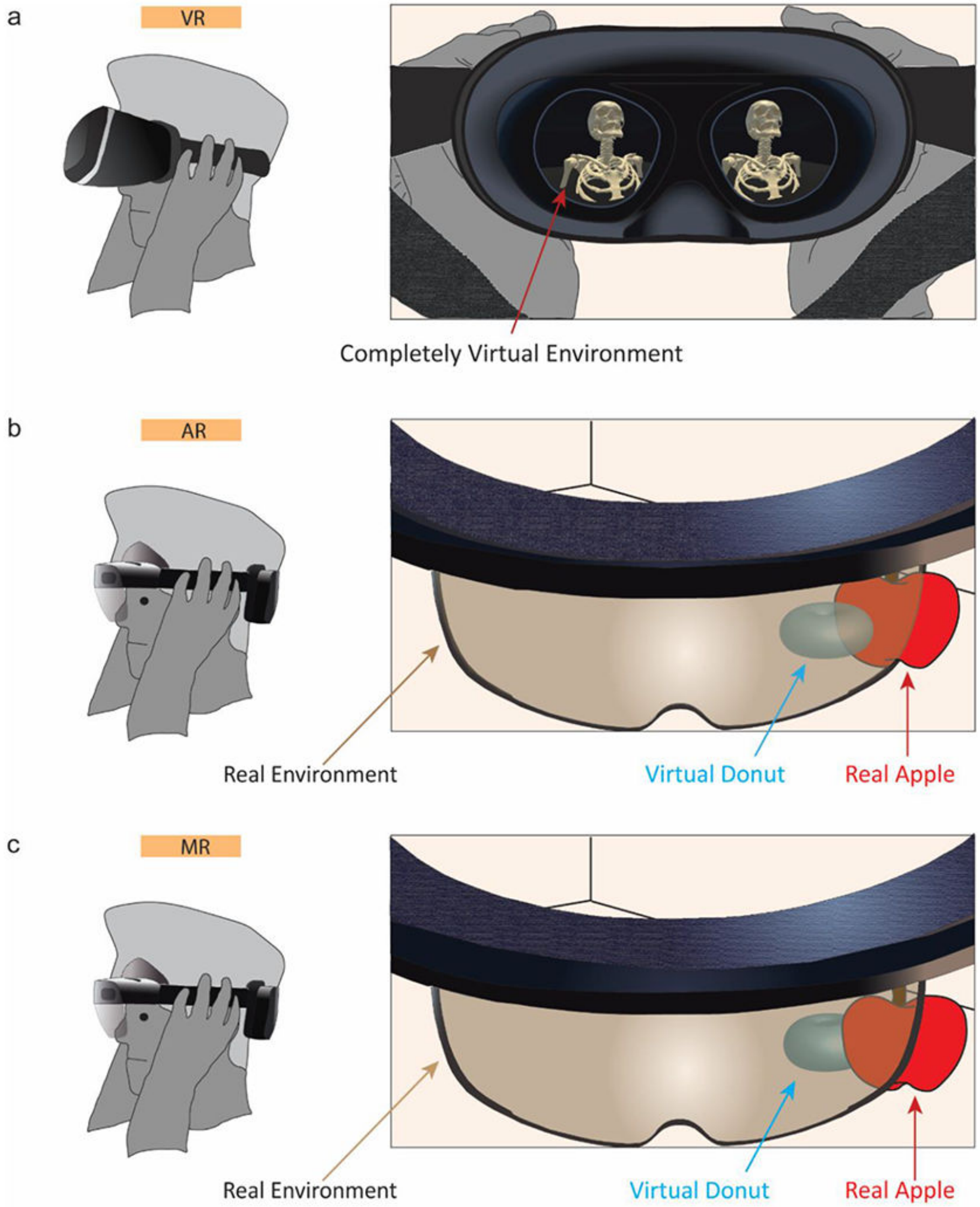

Figure 1. Schematic of virtual reality (VR), augmented reality (AR) and mixed reality (MR).

a| The point-of-view for a VR head-mounted display (HMD) allows a user to be fully immersed in a virtual environment. **b|** AR overlays the virtual donut on top of the real apple regardless of the relative position between two objects. **c|** MR allows to display the virtual donut partially occluded by the real apple based on the depth information and relative position.

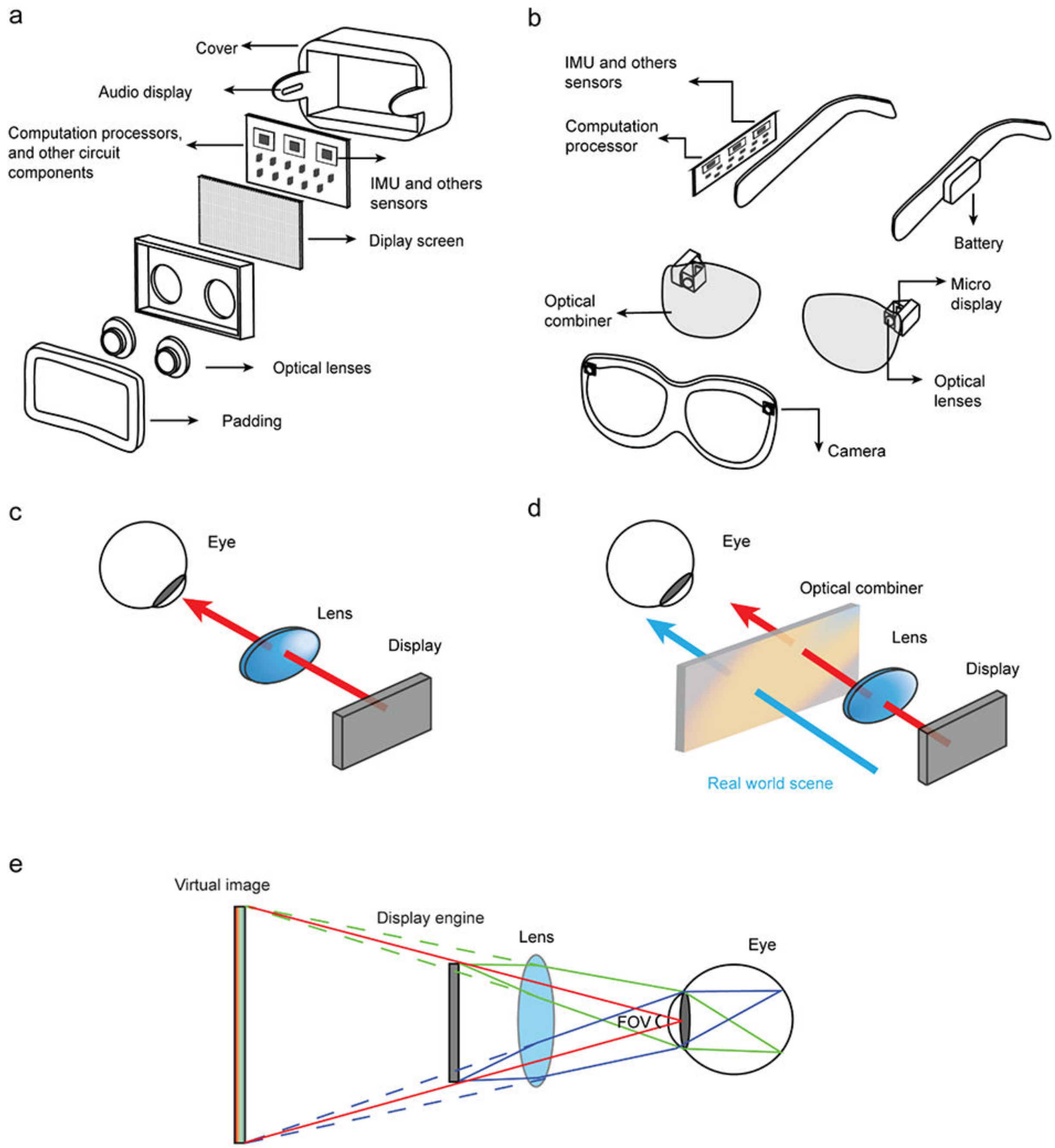

Figure 2. Instrumentation and optical structure of virtual reality (VR) and augmented reality (AR) head-mounted displays (HMDs).

a| Main hardware components of VR HMDs. **b|** Main hardware components of AR HMDs. **c|** The display in a VR HMD projects virtual objects to eyes through optical lenses. **d|** The optical combiner in an AR HMD merges the real-world scene with virtual objects projected by lenses and the display. **e|** Field of view (FOV) is defined as the visual field as one eye is relatively stationary, and the edge of a well-designed FOV should be equal to the display screen border.

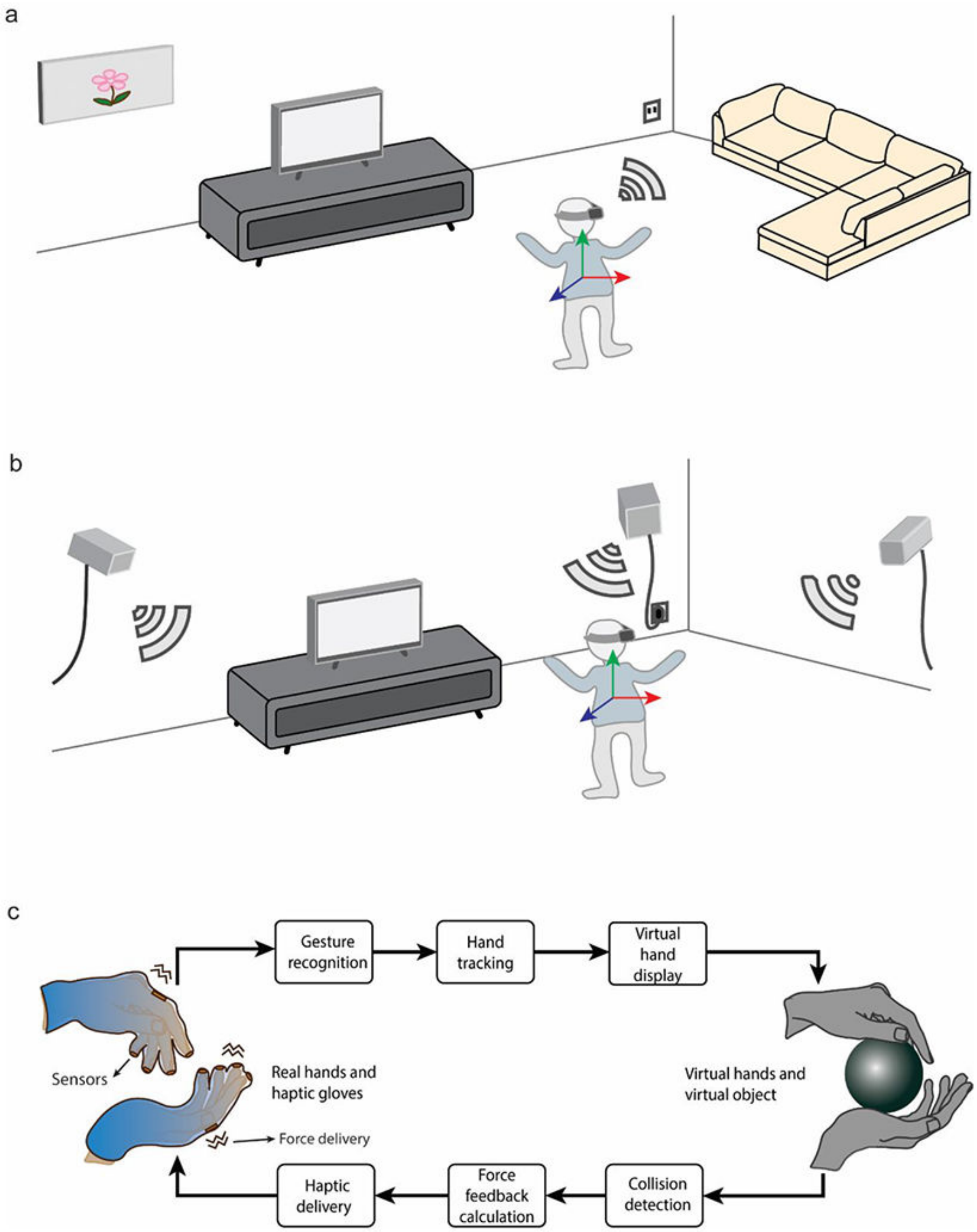

Figure 3. Tracking and haptic feedback in extended reality (XR) applications.

a| Inside-out tracking. The sensors such as cameras are mounted on the head-mounted display (HMD) to detect the changes in surroundings with or without markers. **b|** Outside-in tracking. The sensors are mounted in the stationary location and the markers to be tracked are placed on the target such as HMDs. **c|** Haptic feedback. Hand gestures are recognized and tracked by sensors for virtual hands display. The collision between virtual hands and virtual objects are detected for the force feedback calculation. The calculated force feedback is delivered through the sensors on the haptic gloves.

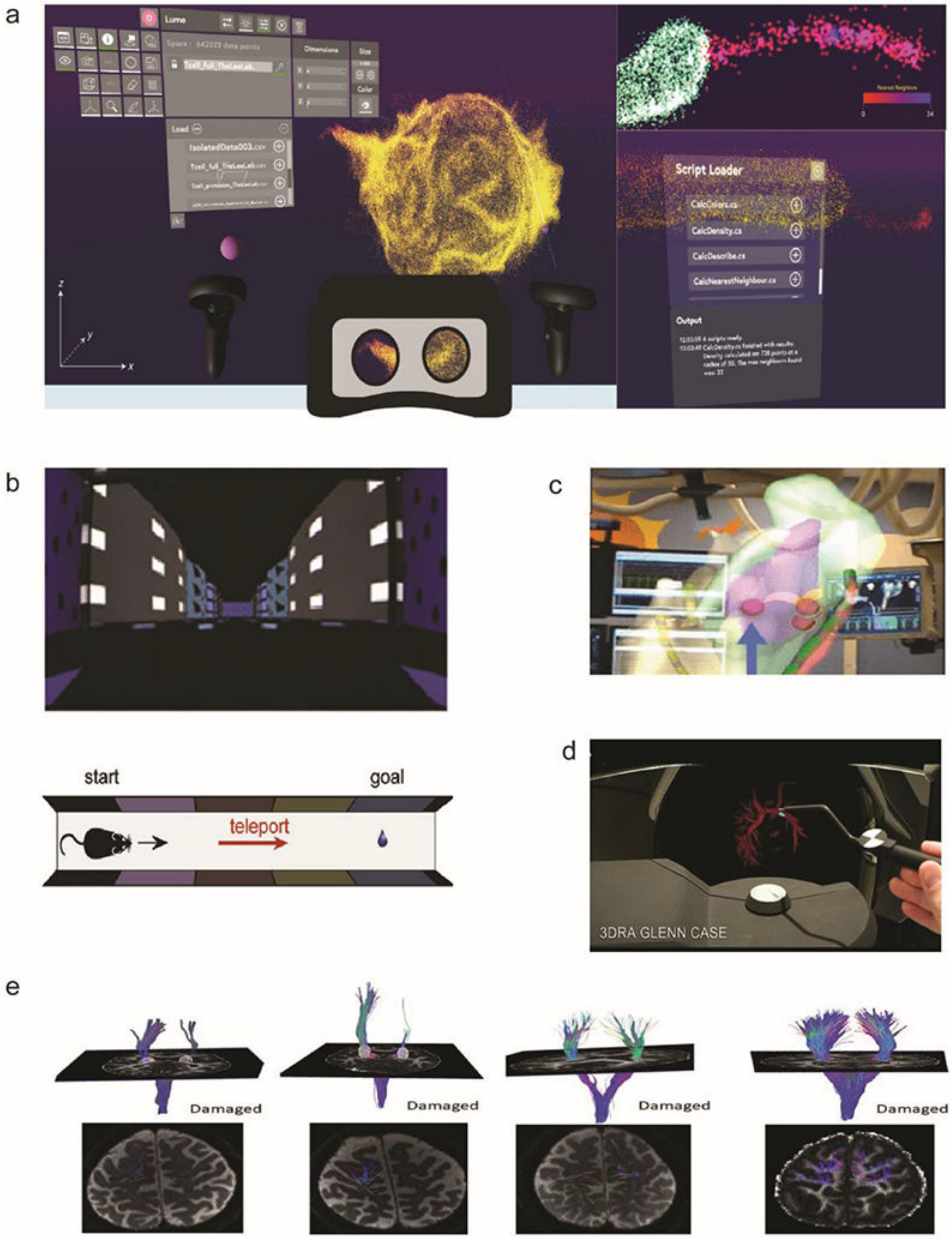

Figure 4. Biomedical applications of extended reality (XR).

a| vLUME facilitates the 3D virtual reality (VR) visualization of millions of molecules, demonstrated by the super-resolved membrane of the T cell [6]. Uses can easily select and isolate complex biological features at the nanoscale. **b|** The head-fixed mouse placed on a cylindrical styrofoam treadmill is surrounded in a VR environment [5]. Dynamic virtual scenes are created to provide the mouse with the illusion of movement for the investigation of the dopamine circuit activity at various stages. **c|** The ĒLVIS pipeline allows users to navigate through the real-time diagnostic mapping information on the electroanatomic system [142]. **d|** Live 3D holograms are created from live transesophageal echocardiography or rotational angiography for the user-directed interaction and manipulation [145]. **e|** A VR and brain-computer-interface-based training platform induces movement illusion for severe stroke patients, providing patient-driven action observation in head-mounted VR [152].

Table 1:

Representative XR HMDs.

Product name	XR	HMD type	Optical lenses	Visible FOV in degrees (horizontal / vertical / diagonal)	Tracking type
Meta Quest 2	VR	Standalone	Fresnel	97 / 93 / NA	Inside-out
Oculus Rift S	VR	Tethered	Fresnel	88 / 88 / NA	Inside-out
Samsung Odyssey	VR	Tethered	Fresnel	101 / 105 / NA	Inside-out
Sony PlayStation VR	VR	Tethered	Aspherical	96 / 111 / NA	Outside-in
Valve Index	VR	Tethered	Fresnel	108 / 104 / NA	Outside-in
HTC Vive Pro 2	VR	Tethered	Fresnel	116 / 96 / 113	Outside-in
HP Reverb G2	VR	Tethered	Fresnel	98 / 90 / 107	Inside-out
Google Daydream View	VR	Smartphone	Fresnel	NA / NA / 90	NA
Magic Leap 1	AR	Standalone	Waveguide	40 / 30 / 50	Inside-out
Magic Leap 2	AR	Tethered	Waveguide	44 / 53 / 70	Inside-out
Microsoft HoloLens 2	AR	Standalone	Waveguide	43 / 39 / 52	Inside-out
Snap Spectacles	AR	Standalone	Waveguide	NA / NA / 26.3	Inside-out
Nreal Light	AR	Smartphone	Birdbath	NA / NA / 52	Inside-out

Abbreviations: XR, extended reality; VR, virtual reality; AR, augmented reality; NA, not applicable.

Table 2:

XR platforms for biomedical applications.

Application	Software	XR	Function
Data visualization and analysis	TeraVR/Vaa3D [212]	VR	Enable big data reconstruction and visualization
	vLume [6]	VR	Enable analysis of single-molecule localization microscopy datasets
	BioVR [77]	VR	Enable protein analysis
	Harvis [213]	VR	Provide simulation of computational fluid dynamics
	Scenery [214]	VR	Provide rendering framework for multi-dimensional images
	VRNetzer [215]	VR	Enable exploration of genome-scale molecular network
	singleCellVR [216]	VR	Enable single-cell data visualization
	ProteinVR [133]	VR	Provide web-based molecular visualization
	Genuage [2]	VR	Enable analysis of point cloud data
	ConfocalVR [72]	VR	Enable interactive visualization of multi-channel molecular images
	*EchoPixel True3D	AR	Provide a holographic digital model of anatomic structures
	ChimeraX [11]	VR	Enable big data visualization and analysis
Medical education and training	AnatomyX	AR	Enable trainees to learn biomedical knowledge and explore surgical solutions
	RASimsAs	VR	Enable injection skills practice and provide surgeons with operation scenarios
	SimSurgery [73]	VR	Provide simulation for invasive surgery training
	hapTEL [74]	VR	Enable dental procedures skills training
	HumanSim	VR	Enable students to experience rapid sedation and intubation techniques
Preprocedural planning and intraprocedural navigation	3D Slicer	VR	Enable image analysis, preprocedural planning, and surgical guidance
	*PrecisionOS	VR	Provide 3D reconstruction for surgical panning and training
	*OpenSight	AR	Generate and register models with patients for surgical procedures
	*VisAR	AR	Provide guidance for intraprocedural stereotactic spinal surgeries
	*xvision Spine	AR	Display 3D model of patient’s spinal anatomy and superimpose virtual trajectory on the model
	*Clarifeye	AR	Create real-time 3D model with automatic spine segmentation for surgical procedures
	NeuroPlanner [217]	VR	Enable stereotactic trajectory establishment, simulating the insertion of microelectrode, and postoperative analysis
	NeuroTouch [218]	VR	Simulate craniotomy-based neurosurgical procedures with haptic feedback
	*NextAR	AR	Display 3D orthopedic model for knee arthroplasty procedures, with the extension to shoulder, spine, and hip procedures
	*IntraOpVSP	AR	Displays 3D holograms of patient’s anatomy with the actual scale in surgery
	*Knee+	AR	Assist the surgical procedure for the implant positioning during total knee arthroplasty operations

Application	Software	XR	Function
	SyncAR & StealthStation S8	AR	Deliver virtual models and navigation to microscope oculars during surgical procedure
Digital therapeutics and rehabilitation	XRHealth	VR	Provide pain management, stroke rehabilitation solutions, cognitive training for executive functions and memory span
	Immersive Rehab	VR	Provide digital therapeutics for neuro rehabilitation
	*Luminopia One	VR	Provide digital therapeutics for amblyopia
	Social Engagement	VR	Provide digital therapeutics for serious mental illness and behavioral health
	**RelieVRx	VR	Assist to relieve chronic lower back pain
	Amelia	VR	Provide therapy on fears, stress, addiction, anxiety, and depression
	Happinss	VR	Provide stress management
	Balloon Blast	VR	Provide upper extremity rehabilitation and assessment of active shoulder range
	REAL y-Series	VR	Provide physical and cognitive rehabilitation

Abbreviations: XR, extended reality; VR, virtual reality; AR, augmented reality; FDA, US Food and Drug Administration.

*represents FDA-cleared

**represents FDA emergency use authorized