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A Review on the 3D Printing of Functional Structures for Medical Phantoms and Regenerated Tissue and Organ Applications

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A B S T R A C T

Medical models, or "phantoms," have been widely used for medical training and for doctor-patient interactions. They are increasingly used for surgical planning, medical computational models, algorithm verification and validation, and medical devices development. Such new applications demand high-fidelity, patient-specific, tissue-mimicking medical phantoms that can not only closely emulate the geometric structures of human organs, but also possess the properties and functions of the organ structure. With the rapid advancement of three-dimensional (3D) printing and 3D bioprinting technologies, many researchers have explored the use of these additive manufacturing techniques to fabricate functional medical phantoms for various applications. This paper reviews the applications of these 3D printing and 3D bioprinting technologies for the fabrication of functional medical phantoms and bio-structures. This review specifically discusses the state of the art along with new developments and trends in 3D printed functional medical phantoms (i.e., tissue-mimicking medical phantoms, radiologically relevant medical phantoms, and physiological medical phantoms) and 3D bio-printed structures (i.e., hybrid scaffolding materials, convertible scaffolds, and integrated sensors) for regenerated tissues and organs.

1. Introduction

Since its invention in the 1980s, techniques in three-dimensional (3D) printing, which is more formally referred to as additive manufacturing (AM), have been developed, matured, and applied in various applications by a large number of researchers and industrial companies worldwide. In its early years, 3D printing was primarily a rapid prototyping technique; today, it is revolutionizing manufacturing and many other industries with new processes, materials, and applications. In addition to plastic prototypes, complex engine components, houses, food, and even human organs can now be 3D printed. The 3D printing industry is experiencing rapid growth: Worldwide revenues of the industry grew by 17.4% in 2016 and are worth over $6 billion [1].

One major market for 3D printing is the medical field. For this important application area, 3D printing has provided effective solutions and shown great potential for personalized medicine and care. Current widely practiced medical uses of 3D printing include custom-made dentures, hearing aid shells, surgical and medical models, orthotic and prosthetic components, and artificial hip and knee implants [2–7]. One unique use of 3D printing technology is for the fabrication of "phantoms," or mock-ups of body parts, to allow doctors or surgeons to visualize body parts when preparing, planning, or optimizing complex medical operations or procedures [5,6]. Such phantoms can also be effective tools for surgical training and patient education purposes.

Since the early 2000s, 3D bioprinting technology has been developed and investigated by a number of research groups and biotech companies [8]. 3D bioprinting involves depositing layers of living cells onto gel media to build up 3D bio-functional structures. The

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ultimate goal is to use the 3D printing technology for tissue engineering (TE) applications in order to build organs and body parts [9,10].

With the rapid advancement of 3D printing and 3D bioprinting technologies, a huge body of research and practical applications exists for these technologies. This paper reviews the applications of 3D printing and 3D bioprinting technologies, with a focus on fabrication of functional materials and structures for medical applications. This review specifically discusses the state of the art and trends for 3D-printed functional structures and bio-structures for medical phantoms and for regenerated tissue and organ applications.

2. 3D printing-enabled medical phantoms and structures

2.1. Need for physical medical phantoms

Medical imaging technologies have advanced dramatically in the past decade. With the evolution of imaging techniques such as multi-detector computed tomography (MD-CT) and magnetic resonance imaging (MRI), radiological diagnosis has become less invasive and more informative [11,12]. High-resolution 3D image data can be acquired in a short time. Image processing plays an increasingly important role in presenting human organs and structures with high fidelity and providing indispensable support in the diagnosis and treatment of many diseases and medical conditions [13–16]. Today's image-guided surgeries illustrate how radiologists have been integrated into therapeutic teams together with other surgical specialists. 3D visualization, multi-planar reformation, and image navigation help radiology to be pivotal in many clinical disciplines [17]. However, there is an unmet need to render digital imaging and communications in medicine (DICOM) images. Digital models are limited by the use of flat screens for the visualization of 3D imaging data. In addition to surgical planning applications, tangible medical phantoms are very useful for medical computational models validation, as well as for medical training and patient education. Therefore, there is a great need for high-fidelity physical medical phantoms for clinical practice and educational purposes.

2.2. Fabrication of medical phantoms

Physical medical phantoms have traditionally been produced by means of conventional manufacturing processes such as casting and molding. Such fabrication processes involve time-consuming and often expensive tooling preparation steps. In addition, it is not economical to fabricate individual, patient-specific medical phantoms due to the high tooling cost. Therefore, most of these phantoms are mass-produced, population-averaged, idealized models for general planning and educational purposes.

2.2.1. Tissue-mimicking medical phantoms

In medical imaging, phantoms are commonly used for developing and characterizing imaging systems or algorithms, as they provide imaging specimens with known geometric and material compositions. Tissue-mimicking medical phantoms can imitate the properties of biological tissue, and can therefore provide a more clinically realistic imaging environment [18]. In the past, casting or injecting molding processes have been used to fabricate tissue-mimicking medical phantoms. Applications of such phantoms can be found in the development and validation of medical imaging modalities such as ultrasound [19,20], MRI [21–24], computed tomography (CT) [25], and others [26]. With the increasing needs of biomedical research, other applications of tissue-mimicking medical phantoms, such as simulation of the electromagnetic properties of tissues [27], mechanical properties mimicking [28], and focused ultrasound ablation [29], have also been demonstrated. In those applications, phantoms were fabricated as population-averaged, idealized models, and the individual differences among patients were overlooked.

2.2.2. 3D printing of medical phantoms

3D printing technologies overcome the drawback of traditional manufacturing processes and are an effective tool for rapidly producing patient-specific, high-fidelity, medical phantoms at low cost, as the need for tooling is eliminated. 3D-printed medical models and phantoms fabricated from CT, MRI, or echocardiography data provide the advantage of tactile feedback, direct manipulation, and comprehensive understanding of a patient's anatomy and underlying pathologies. In many cases, 3D-printed medical phantoms can assist and facilitate surgeries and shorten the cycle times of medical procedures [30–33]. For example, an orthopedic surgery trainee used CT scan images to create printable copies of a patient's bones. He then had them printed and used these custom models to plan the patient's surgery [34]. 3D models have also been used for surgical planning by neurosurgeons [4,6]. Such 3D-printed neuroanatomical models can provide physical representations of some of the most complicated structures in the human body. These detailed high-fidelity phantoms can help neurosurgeons discover and visualize the intricate, sometimes obscured relationships between cranial nerves, vessels, cerebral structures, and skull architecture that are difficult to interpret based solely on two dimensional (2D) radiographic images [35]. This can reduce errors and avoid potentially devastating consequences in surgery.

2.3. Recent progress and future trends in functional medical phantoms

2.3.1. 3D printing of tissue-mimicking medical phantoms

Recent advances in computer-aided design (CAD), medical imaging, and 3D printing technologies have provided a rapid and cost-efficient method of generating patient-specific, tissue-mimicking medical phantoms from computational models that are reconstructed from the CT or MRI results of individuals [36]. Those patient-specific phantoms have unparalleled advantages in many biomedical applications, such as computational model validation, medical device testing, surgery planning, medical education, and doctor-patient interaction. Biglino et al. [37] demonstrated the fabrication of compliant arterial phantoms with PolyJet™ technology by Stratasys Ltd. (Eden Prairie, MN), an AM technique that deposits a liquid photopolymer layer by layer through orifice jetting and then solidifies it by UV exposure. A rubber-like material named TangoPlus was used in this study for its mechanical properties, which are close to those of real tissue. Cloonan et al. [36] conducted a comparative study on the use of common tissue-mimicking materials and 3D printing materials, including TangoPlus, for abdominal aortic aneurysm phantoms. Their results suggested that TangoPlus was a suitable material for modeling arteries in terms of dispensability, and that its uniaxial tensile properties outperformed those of poly(dimethylsiloxane) (PDMS) SYLGARD elastomers, which are commonly used in the investment casting process.

2.3.2. Radiologically relevant medical phantoms

3D printing technologies have been used to fabricate radiology-realistic phantoms that have regions with different attenuations [38]. In this study, the multi-material PolyJet™ printing technique from Stratasys Ltd. was used to construct liver and brain phantoms with realistic pathologies, anatomic structures, and heterogeneous backgrounds. The liver and head CT images of patients were segmented into tissue, vessels, liver lesions, white and gray matter, and cerebrospinal fluid. Printing materials that had different CT numbers were assigned to these objects after test scans. Finally, 3D-printed