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Additive manufacturing in orthopaedics: From 4D-imaging to smart bioactive implants

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Abstract: Recent improvements in the fields of additive manufacturing and medical imaging have introduced generative-fabricated, customized models, implants and instruments to a wide range of medical applications. Through meta-analysis, this paper gives an overview of current and future applications of 3D or 4D printing technologies in medicine, while evaluating their benefits, restrictions and future scope. It is paid special attention to the field of orthopaedics. Current, main areas of interest include patient-specific implants and instruments, smart bioactive implants, tissue engineering, sensory equipped implants, 4D imaging techniques as well as process chain optimization and standardisation. In order to understand the medical additive manufacturing process and its possible applications, the chronological steps of 3D model generation, simulation and manufacturing are explained and a framework for classification is outlined. Results indicate, that rapid prototyping benefits patient-specific treatments of complex conditions in orthopaedics, improves surgery planning and risk assessment, while minimizing long-term complications through individualisation and monitoring. However, as technologies are evolving rapidly, procedures are lacking in standardisation as well as interdisciplinary routine and need highly skilled personnel. Moreover, limitations in object size, structural strength as well as the time- and cost intense process, limit its feasibility for some medical applications. Data science, 4D imaging methods, connected smart implants and biomaterial printing are expected to play a major role for the technology's future expansion.

Keywords: Additive Manufacturing, 3D printing, implants, orthopaedics, 4D printing, 4D MRI, 4D CT, smart implants, medical devices, process chain standardisation, biomaterial printing, tissue engineering, DICOM

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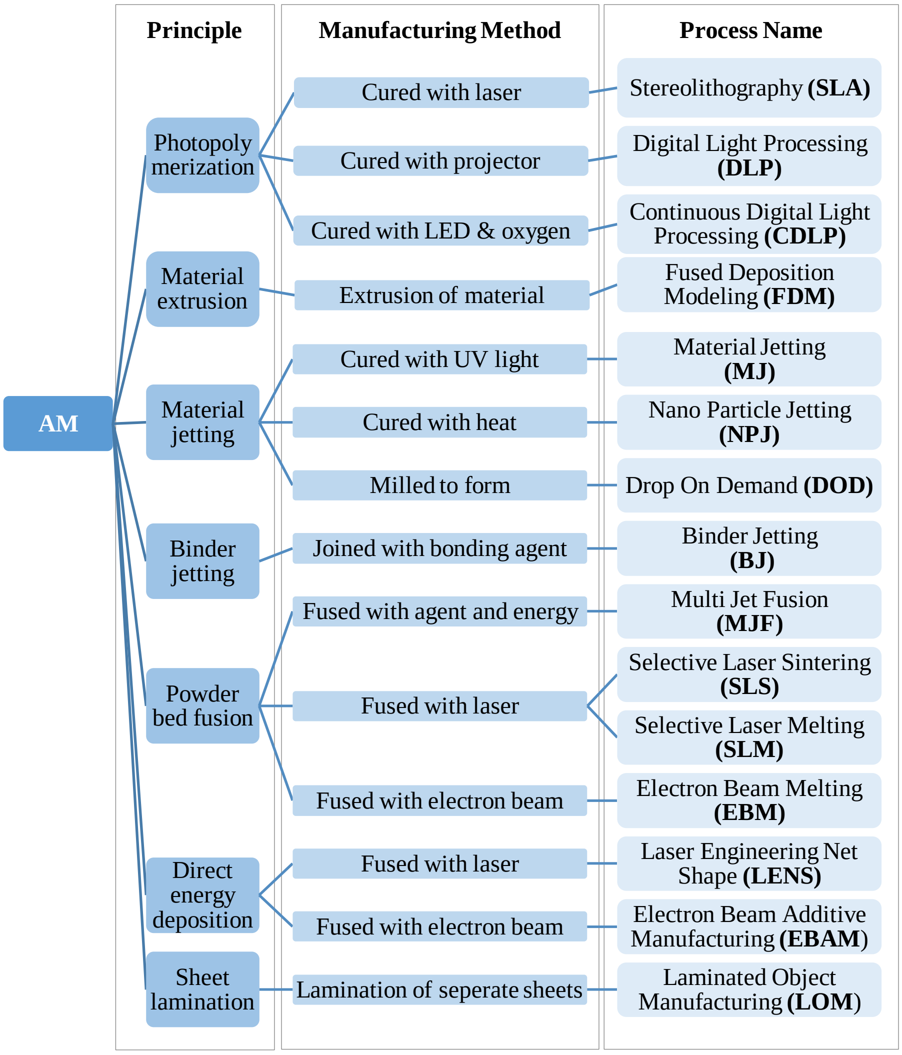
1 Introduction

In recent years, there has been a significant quantitative and qualitative improvement in additive manufacturing techniques. Not only did new methods arise, but the efficiency and accuracy of existing process chains has been improved, leading to an increase in overall process stability and economic feasibility (Huang and Schmid, 2018). In additive manufacturing (AM), physical models are created from digital 3D models, without the need of manufacturing process and tool planning. Thus, it offers great structural design freedom, rapid component realization and unlimited individualization options, beginning with the batch size of 1. However, the additive manufacturing process is limited by restrictions of product sizes, number and characteristics of used materials and specific process parameters (Bauer et al., 2016). Yet, various materials like metals, polymers or biomaterials can be processed therefore enabling the manufacturing of a wide range of complex products. One major target area for AM is the individualized production of implants, like hip or knee endoprostheses with biocompatible materials (Arabin, 2018).

Additive Manufacturing is a manufacturing technique, which creates structural, three dimensional components based on CAD (Computer Aided Design) models by joining together material. There are various attempts of creating an official definition for the term and a consistent classification methodology; however, due to the rapid evolving technology field a standard has yet to be defined (Berger and Schmid, 2017). Common classifications divide the different AM methods into different categories depending on the shapes of the raw materials, the manufacturing principle as well as the product characteristics. A comprehensive classification of the different AM technologies is shown in Figure 1 (Pumpe, 2017). Using powders, solid materials, liquids or sheets in combination with different manufacturing principles, composite, polymer or metal structures can be created. This process differs from traditional manufacturing methods in that it is gradually forming the 3D object by depositing or joining material, without the need of shape cutting chipping technology or tools like moulding forms or assembling machinery (Bauer et al., 2016).

Figure 1 Classification of additive manufacturing technologies according to reference. Technologies are characterized by the manufacturing principle and method, with respect to the form of raw material used. Other common classifications categorize the technologies depending on phase change or product material.



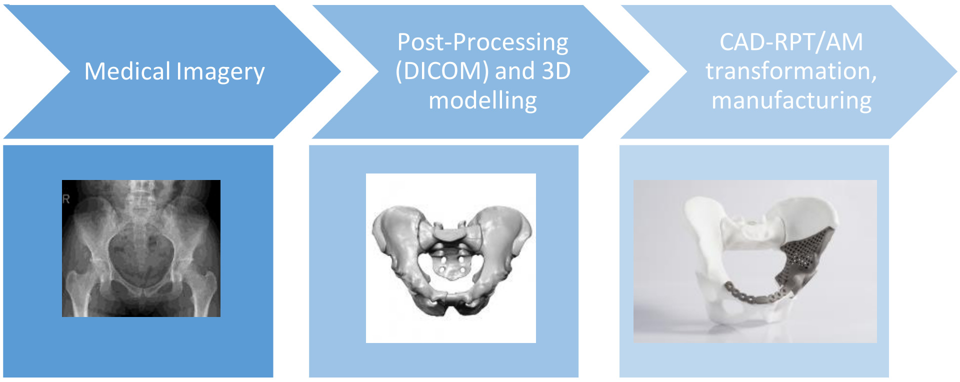
2 Biomedical applications and benefits

In surgical applications, this process can be used to get a better understanding of a patient's complex pathology and anatomy prior to surgery. Custom implants and patient-specific instruments can be created in order to support the physician during the surgery. In biomedical engineering, orthopaedics is a surgical discipline comprising various procedures like joint arthroplasty, ranging from trauma surgery to tumour implants (Greenberg, 2018). Essential for orthopaedic applications is the detailed and accurate analysis of the musculo-skeletal system including exact locating, orientation and circulation information. Herein, AM offers high quality, fast and cost- effective solutions for patient individual procedures like hip arthroplasty or craniomaxillofacial surgeries (Ghai, 2017).
There are several benefits to AM compared to traditional manufacturing process chains in the field of medicine and biotechnology. As already mentioned, traditional tooling, extensive machinery or cost intensive form creating is not needed; therefore, speed and overall efficiency of the process is increased (Bauer et al.,2018). Moreover, the direct CAD-AM process chain allows to convert 3D models into manufacturing parameters precisely and accurately, guaranteeing high quality products. Errors occurring in long manufacturing process, often comprised of different parties, are prevented (Berger and Schmid, 2017). Yet, there are still a view limitations of the manufacturing process in terms of materials used, maximum object size and speed (Ghai, 2017). However, significant improvements have been observed and the number of possible materials, object size and economic efficiency is steadily increasing. For example, it is already possible to use bioactive material, create porous structures or use metal. Especially, the health industry can profit from these developments the individualized products can dramatically optimize treatments, increase long term health benefits for patients and facilitate a surgeon's work (Haleem and Javaid, 2018). The compact and closed process of AM can also easily be adjusted to meet all required standards for biocompatibility and clinical hygiene (Chesner, 2000). In orthopaedics, AM is already used and especially benefits from the limitless structural shaping of the inside of a component, compound materials as well as minimal unpleasant side effects. One major application here is the facilitation of bone ingrowth using complex porous bone implants made of metal. The increased demand of complex implants like spines or knees promotes the development of the AM technologies therefore benefitting both, manufacturing research as well as clinical practice (Haleem and Javaid, 2018).

3 Introduction to the Additive Manufacturing process chain in orthopaedics

In order to guarantee high quality implants and prevent side effects, a thorough and individual analysis of each patient's pathology and anatomy is essential to the successful long term treatment. The whole orthopaedic additive manufacturing process can be divided into three essential steps: Medical Imagery, Post-Processing (DICOM) and the CAD-RPT/AM digital modelling (Eichelberg, 2015). These are illustrated in Figure 2.

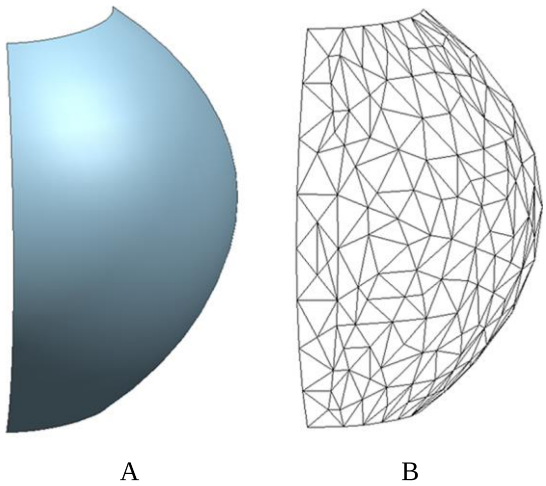
Figure 2 Steps towards generating an additive manufactured biomedical component applied to a pelvis trauma. Source: X-ray and 3D-model from HEAL, university of Utah, 2017; implant from eos.info, 2019.



The first step of this procedure is the accurate medical imagery. Therefore, data from Magnetic resonance imaging (MRI), computed tomography (CT), X-rays and 3D scans is gathered and consolidated. The high resolution data of modern devices allows the creation of an exact digital model of the actual physical system. This first step in the process chain is critical to the overall outcome, since the accuracy of the 3D model highly depends on the used capturing techniques (Nandikurli, 2017).
The transformation of the imaging data to useful three dimensional data for a digital prototype requires special image post processing, following the standard of DICOM (Digital Imaging in Communications in Medicine) for data exchange and storage. The generated 3D CAD models offers and visualizes exact information about joint alignment and fractures. Not only can the acquired data be rendered for better understanding of the anatomy, but it can also be used for simulations in order to examine possible multi body interactions or reactions to environmental circumstances (Haleem and Javaid, 2018). Simulation techniques, widely used in mechanical engineering, like Finite Element Analysis (FEM), Multi-Body Systems (MBS) or Computational Fluid Dynamics (CFD) can be adapted to biomedical problems. Using these techniques, implant shapes, orientations and forces can be optimized and negative side effects prevented in order to offer the best results for patients (Hawlitzky et al.,2017).
There are various data formats used when it comes to CAD modelling as every CAD program often offers its own data storage format. When considering generative manufacturing it is necessary to transfer the information into the standard STL (stereolithography) format (Zimmermann et al., 2016). This format saves three dimensional objects by triangulation. A STL file describes a raw, triangulated surface by the unit normal and vertices of the triangular planes using a 3D Cartesian coordinate system (Barreiro et al., 2014). Therefore, it differs from the CAD model as it is only an approximation of the exact three dimensional shape (Navangul et al., 2013). This is illustrated in Figure 3. Using the STL file implants,

anatomic models or surgery tools can be generated using the additive manufacturing method of choice (Zheng, 2018). In some cases, there is a need of post-processing after the generation procedure depending on target accuracy, strength and surface characteristics of the component. Common, post-processing treatments include: surface polishing, part dividing, removal of supporting structures and heat treatments (bland, 2018). In order to control and increase the quality of biomedical products, methods of quality assurance are applied. However, there is no uniform standard procedure methodology or guideline for the additive manufacturing process of health critical medical objects and procedures are evolving rapidly with technology (American Society for Testing and Materials, 2017).

Figure 3 The exact three dimensional shape of a CAD model (A) and its approximation using triangulation of the surface in the STL format (B), according to Navangul et al., 2013, p.2.



4 Adding one dimension: 4D imaging and generating technology

Recently, there has been an introduction of upcoming technologies in the field of medical imagery like 4D computed tomography (4D-CT) or 4D Magnetic Resonance Imaging (4D-MRI). These technologies add time as another dimension to the three dimensional scanning processes (Kwong, 2015). The image recording is performed with respect to time therefore adding new data to the acquired models, while not changing the basic procedure described in the last paragraph. Results from 4D scans provide important information for the calculation of the motional behaviour of bones, tissues and other body parts. These can be used to optimize and predict the interactions of implants or specific environmental conditions more precisely. Thus, it is essentially helpful for endoprostheses, surgery tools and devices. Referring to Figure 2, new 4D scans can strongly improve stage one of the process chain and ease as well as improve the modelling in stage two. They provide fast results and have been shown to be more accurate than traditional methods, incorporating even minor non-conformities. Another great benefit is the possibility to observe the natural motion of body parts therefore making it easier to mimic and simulate the motion in the digital model. Thus,

simulations using multi-body system CAD analysis can be adapted leading to more realistic results (Kwong, 2015). Schooled orthopaedists are able to observe, track and analyse the recorded scan videos. Additionally, the scans can benefit the operation planning as well as the risk assessment, since they allow for better analysis of cardiovascular diseases and side effects by recording the blood flow in areas of interest (Haleem, 2018).
However, since the 4D scanning methods are not widely used yet, it needs a high amount of specific knowledge to adapt and apply the principles properly. Moreover, the transformation of the videos into 3D CAD models or simulations in stage two are more complicated than in the traditional procedure. Due to this procedural and knowledge related complications as well as necessary technical equipment, 4D scanning is yet a relatively cost intensive process (Markl, 2012).
Parallel to the development of four-dimensional medical scanning, there has been an emerging trend of 4D printing technologies. These additive manufacturing technologies allow the use of smart bioactive materials, which can adapt and change over time. Like traditional additive manufacturing methods, they use 3D printing technologies to generate objects from 3D- CAD models, while adding the new dimension of time through smart materials (Kuang et al., 2018). These materials change their shape or structural characteristics based on surrounding factors like humidity, temperature or pressure over time. There is a great need for these opportunities, especially when it comes to applications like bone implants or stents, which can grow with the human body or allow ingrowth. Moreover, the creation of composite material comprised of different raw and bioactive materials can have positive effects on the stiffness, durability, flexibility and loading capacity of printed objects (Maniruzzaman, 2018).
Nevertheless, due to the early developmental stages of the 4D manufacturing technique, there are a few limitations which need to be considered regarding overall process outcome and economic feasibility. Yet, the accuracy of these processes still needs to be improved in order to prevent discomfort in the patient. Additionally, the long-term effects of smart materials used in the human body as well as general material characteristics still need further research (André, 2017).

5 Additive manufacturing applications in orthopaedics

Generative technologies with their benefits and process steps described previously, offer a great solution for various orthopaedic problems. The innovative power of additive manufacturing in orthopaedics can especially be helpful in the areas collected in Table 1. This comprehensive list is based on an extensive literature review and includes common and future applications. Applications mainly fall into three categories: Surgery planning and clinical practice, patient specific solutions and functional aspects and other benefits. The first group includes all applications concerned with surgery planning, pre-surgery anatomical modelling, surgical templates, tools and patient specific instruments. The second area is comprised of patient specific implant design, tissues engineering and the functional improvement of implants. Other applications focus on educational and economic purposes (Narra et al., 2019).

Table 1 Applications of additive manufacturing technologies in orthopaedics. Listed areas and specific purposes are the result of extensive meta-analysis. Application fields can essentially be divided into three main topics: Surgery planning and clinical practice, patient-specific implant solutions and functional aspects as well as secondary purposes.

Surgery planning and clinical practice

Area	Description	References
Anatomical models	• Models of patient's pathology and anatomy using 3D or 4D scans • 3D CAD model can be generated from imagery data using DICOM standards • Digital model can be used for simulation, implant planning, additive manufacturing and surgery planning • Facilitates the operator's understanding and visualization of the patient specific problem	Um, 2016; Vaish and Vaish, 2018; Pietrabissa et al., 2016
Patient-specific instruments and traditional tooling remake	• Using the generated 3D anatomy models, individualized instruments for the surgery can be designed and printed • Used for easy replication of surgeries including drills and saw guides • Ease difficult procedures like osteotomy or knee implants • Improves bone resection accuracy and bone tumour surgeries • Optimization of traditional tooling using 3D printing methods for finer, more accurate, stronger and more versatile tools • Recent innovations allow for antimicrobial tools • Generation of microscale tooling for endoscopy	Pattinson, 2017; Scott, 2017; Souzaki et al., 2015
Surgical templates	• Individualized, patient-specific guides used for tumours surgeries, total joint arthroplasty and correction of deformations • Increases the quality of the surgery by facilitating accuracy and precision of adapted cutting templates • Support for difficult procedures like spinal or pelvic tumours	Salmi et al., 2012; Souzaki et al., 2015; Yap et al., 2017
Patient-specific surgery Risk	• Accurate analysis of individual predispositions and cardiovascular diseases or risk factors by using accurate 3D or 4D scanning methods • Imaging and virtual as well as printed anatomic models can help examining and minimizing patient-specific risks • Visualization and explanation of risk in front of the patient	Choi and Kim, 2015; Salmi et al., 2012; Yap et al., 2017; Wong et al., 2015

	• Using adapted implants and tools, the risk of surgery as well as future negative side effects can be minimized • Minimal invasive techniques using micro tooling helps decreasing surgery risks and patient stress	
Osteochondral and chondral defects	• Importance of these traumatic injuries or chronic defects can be quantified and isolated cartilage defects improved	Boonen et al., 2012; Klennert et al., 2017; Pacione, 2016; Wu et al., 2018
Patient-specific component solutions and functional aspects		
Customized implants	• Patient-specific implants can be designed from 3D or 4D scans using CAD technology and printed with little to no design and manufacturing limitations • Customized implants are shown to significantly increase the comfort, functionality and long-time outcome for treated patient compared with traditional standard implants • In contrast to traditional manufactured implants, implants generated with additive manufacturing can have complex and porous inner structures. This is for example used to facilitate bone ingrowth • Better fitting implants decrease surgery risks	Han et al., 2017; Negi et al., 2014; Trace et al., 2016; Zein et al., 2002
Smart material implants	• Implants manufactured with 4D methods, including smart materials enable implants modifications with time depending on surrounding pressure, temperature and humidity. This allows components to grow with the human body and is used for stents or bone implants. • Better fitting implants decrease surgery risks • Bone tissue engineering and the use of biomaterials like cells and biochemical factors allow the precise imitation of natural structures and processes. • Difficult components like bioscaffolds can be produced with AM technologies	An et al., 2015; Bader, 2016; Derakhshanfar, 2018; Kotz, 2018;
Weight reduction and optimization of implants	• Through efficient outer and inner design of AM manufactured implants material mass and therefore weight can be decreased. Hollow inner structures allow significant material saving while guaranteeing functional strength. • Use of different raw materials can reduce weight additionally compared to traditional implants	Bader, 2016; Haleem and Javaid, 2019; Süß et al., 2018; Yan et al., 2019

	• Comfort and mobility in patients is increased due to light implants	
Monitoring implants	• Connected sensors for monitoring and analysing purposes can be introduced to optimize treatment, monitor implant wear and anticipate future complications in early stages. • Data from sensors can be used to further develop implant structures and AM technologies • Implant surrounding health metrics of the patient can also be monitored • AM technologies make it easier to implement sensor and actor components into implants	Huang et al., 2018; Parkash et al., 2019; Phedy et al., 2018
Secondary aspects		
Educational purposes	• Additive manufactured models can be used in education to visualize difficult anatomic and pathophysiological situations. This can benefit university level medical as well as patient education. Blount disease, Perthe's diease, physical bars or coalitions are some areas of interest. • Prior surgery models help the understanding of patient-specific predispositions and visualize the operation for physicians, patients and their families • Patient satisfaction is increased due to higher trust, safety and transparency • Surgeons can practice and prepare different surgery scenarios using model	Haleem and Javaid, 2018;
Economic considerations	• Increased time efficiency through rapid prototyping which makes complex, time consuming manufacturing stages obsolete. No need for casting mould. • Patient-specific implants and instruments can be economically feasible from batch sizes beginning from one, since AM technologies are easily adaptable. • Customized, high quality products with high accuracy can be purchased at lower cost, therefore benefitting patient and hospital • Less follow up operations or complications save cost, time and stress for patients	Bouten et al., 2018; Huang et al., 2018; Narra et al., 2019; Prakash et al., 2018

6 Discussion

Highly versatile and evolving additive manufacturing technologies have great impact on medical procedures and solutions, when it comes to patient-specific treatments, innovative bioactive implants and long-term treatment optimization. Their benefits begin to exceed, the ones observed with traditional manufactured medical devices, in most areas, making them a primary option for physicians, hospitals and patients (Narra et al., 2019). The AM technologies can be especially valuable in the field of orthopaedics, where they significantly improve patient comfort and surgery procedures (Huang et al., 2018). Individualized implants and instruments can be produced time and cost efficiently, beginning from batch sizes of one, making a customized solution for every patient possible. The great flexibility and small number of design restrictions for additive manufactured components makes the creation of complex inner and outer material structures possible. These can strongly improve weight, functionality and strength of the medical products (Yan et al., 2019). Clinical practice and AM technologies are interacting and steadily exchanges, therefore facilitating scanning and AM technology research activities. Consequently, there have been various new developments in the field of medical related additive manufacturing like smart implants with time depending deformations, biomaterial printing or microscale applications. Anatomic and pathophysiological models can also benefit physicians and help their understanding of the patient’s state as well as support their surgery planning. Likewise, these models can also be used for university level medical education, helping students to better visualize difficult diseases and defects. The great palette of raw materials as well as post-processing steps make it possible to adapt AM technologies to uphold hygiene standards for clinical practice (André, 2017). However, the fast changing field is yet not fully developed and still rapidly evolving. As scanning and printing technologies change quickly, it is needs a great amount of specific knowledge as well as time to keep adapting to new introductions. This process can also come at financially high costs.

7 Restrictions and future scope

Yet, the financial cost of the first introduction of additive manufacturing technologies to the clinical practice is high. The process chain includes steps which need extensive software as well as hardware. Not only does it require the purchase of these components, but it also requires a great amount of specific process related knowledge, thus making it necessary to employ highly educated personnel. Maintenance and raw material costs are generally moderate, but wages and special materials can increase this level significantly (Haleem and Javaid, 2018).

The AM process is not only cost intense, but also time consuming. The generation of customized implants and instruments is time consuming as it requires complex steps like scanning, modelling, transferring and manufacturing. Thus, it takes more time than the simple introduction of standard implants and instruments. However, compared with individualized components, created with traditional manufacturing methods, time and cost saving are immense (Schniederjans, 2017). Processing time and size of AM technologies are still limited. Printing processes can take up to 24h and have restriction for the outer dimensions of the fabricated objects (Wooden et al., 2019).

Moreover, due to its rapid development the process of medical additive manufacturing is still not uniformly standardized making it hard to control the procedure and assure quality (Low et al., 2018). Protocols and monitoring steps vary greatly depending on 3D printing provider, used CAD software, medical field and hospital. The implementation of 4D scans with a time component into CAD models is difficult and can further complicate this standardisation process (Aquino et al., 2018).

As the field is highly interdisciplinary, smooth interdisciplinary work and communication are required to prevent process errors and increase treatment success (Yan et al., 2019).
Lastly, only few long-term studies have been conducted yet and some mechanical and chemical strength requirements exclude additive manufactured components from actual usage. Still, models can be used for visualization.

Future scenarios include the increasing use of active materials, biomaterials and smart connected medical devices, which are equipped with sensors. These will be able to adapt to the natural in vivo environment, grow with time and monitor implant wears as well as patient health metrics. Therefore, making it possible to detect and anticipate future complications in early stages and optimize the overall implant design further (Phedy et al., 2018).
Additionally, optimization in current AM technologies will provide more cost- and time-effective solutions as well as functional strength improvements, therefore making the use more widely feasible. Herein, the increased number of microscale devices plays an important role (Huang et al., 2018)
Ongoing developments in data science and computing will increase the quality of captured data, monitoring measures and model simulation, therefore improving the overall AM process chain. These improvements lead to a higher amount of process standardisation and long-term treatment success. Pattern recognition can be used to identify small nonconformities prior surgery or suspect values in monitored in vivo metrics. Latter development makes it possible to detect and anticipate complications in early stages and prevent additional surgeries. Moreover, the condition monitoring of implants can increase the patients psychological well-being by creating a feeling of safety and trust.
Overall smoothening of interdisciplinary teamwork and communication will improve time-saving and quality of manufactured components. Additionally, errors in the transitional stages in between the necessary steps of the medical AM process chain can be prevented.
By improving the accuracy and precision of the first step of this process chain, the medical imaging the outcome can be further improved. Therefore, 4D scans like 4D MRI or CT with a time dimension will play an increased role.
As the transition of data-heavy video material is complex when it comes to the creation of an adequate CAD model, it is necessary to examine new transformation- and simulation protocols.

Conflict of interest

None.

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