

Mechanical Engineering

# Medical Applications of Additive Manufacturing – Application-Oriented Classification for Case Design and Documentation

---

Jukka Tuomi



# Medical Applications of Additive Manufacturing – Application-Oriented Classification for Case Design and Documentation

**Jukka Tuomi**

A doctoral dissertation completed for the degree of Doctor of Science (Technology) to be defended, with the permission of the Aalto University School of Engineering, at a public examination held at the lecture hall Jeti (A208d), A Grid, Otakaari 5, Espoo on 20 September 2018 at 12.

**Aalto University  
School of Engineering  
Mechanical Engineering  
Production Engineering**

**Supervising professor**

Professor Jouni Partanen, Aalto University, Finland

**Thesis advisor**

Professor Antti Mäkitie, University of Helsinki, Finland

**Preliminary examiners**

Professor Paulo Bartolo, University of Manchester, UK

Professor Alain Bernard, Ecole Centrale de Nantes, France

**Opponent**

Professor Igor Drstvenšek, University in Maribor, Slovenia

Aalto University publication series

**DOCTORAL DISSERTATIONS** 172/2018

© 2018 Jukka Tuomi

ISBN 978-952-60-8172-4 (printed)

ISBN 978-952-60-8173-1 (pdf)

ISSN 1799-4934 (printed)

ISSN 1799-4942 (pdf)

<http://urn.fi/URN:ISBN:978-952-60-8173-1>

Unigrafia Oy

Helsinki 2018

Finland



**Author**

Jukka Tuomi

**Name of the doctoral dissertation**

Medical Applications of Additive Manufacturing – Application-Oriented Classification for Case Design and Documentation

**Publisher** School of Engineering

**Unit** Mechanical Engineering

**Series** Aalto University publication series DOCTORAL DISSERTATIONS 172/2018

**Field of research** Production Engineering

**Manuscript submitted** 5 January 2018

**Date of the defence** 20 September 2018

**Permission to publish granted (date)** 15 May 2018

**Language** English

**Monograph**

**Article dissertation**

**Essay dissertation**

**Abstract**

Rapid development has recently occurred in Additive Manufacturing (AM) technologies, some of which are called 3D Printing. One of driving force behind the development of AM is variation in both industrial and medical applications. Certain applications occur in clinical practice, with others under research or in a developmental phase. The application of these new technologies in medical settings has raised concerns among specialists regarding quality control of the manufacturing process, case documentation and patient safety.

This thesis presents a novel classification system for medical applications of AM; the system is based on both own research cases and patient cases presented in the literature. Combining application classes and procedural phases of clinical patient cases into one representation was an objective of this work. The solution concerned the development of a medical application of additive manufacturing (MAAM) matrix case presentation.

One research goal involved developing a model to support patient-case design, documentation, and learning. According to cognitive psychologists, knowledge is clustered into packets that enable knowledge to be organised, stored and contextually placed. Matrix-based representation aims to help stakeholders understand MAAM cases as packets.

The presented concept uses matrix cells to store actual case data. Such data presentation technology has potential to serve as the basis for further developments related to feature-based product modelling and expert system technologies in medical applications of AM.

This thesis presents a MAAM matrix system with potential application as a qualified standard platform for medical-case design and documentation. The MAAM matrix system supports learning and is an established operational platform for computerised systems.

This thesis demonstrates the validation of the MAAM matrix system in an orbital wall implant clinical case. The second validation case was a research case studying the effects of both applied AM system technology and finishing technology to part cytotoxicity. Both cases involved storing materials and methods data in MAAM matrix cells.

**Keywords** additive manufacturing, 3D printing, medical application, classification, patient case

**ISBN (printed)** 978-952-60-8172-4

**ISBN (pdf)** 978-952-60-8173-1

**ISSN (printed)** 1799-4934

**ISSN (pdf)** 1799-4942

**Location of publisher** Helsinki

**Location of printing** Helsinki **Year** 2018

**Pages** 101

**urn** <http://urn.fi/URN:ISBN:978-952-60-8173-1>



**Tekijä**

Jukka Tuomi

**Väitöskirjan nimi**

Materiaalia lisäävän valmistuksen lääketieteelliset sovellukset – sovellusorientoitunut luokittelujärjestelmä potilastapausten suunnitteluun ja dokumentointiin

**Julkaisija** Insinööritieteiden korkeakoulu**Yksikkö** Konetekniikan laitos**Sarja** Aalto University publication series DOCTORAL DISSERTATIONS 172/2018**Tutkimusala** Tuotantotekniikka**Käsikirjoituksen pvm** 05.01.2018**Väitöspäivä** 20.09.2018**Julkaisuluvan myöntämispäivä** 15.05.2018**Kieli** Englanti **Monografia** **Artikkeliväitöskirja** **Esseeväitöskirja****Tiivistelmä**

Materiaalia lisäävän valmistuksen (Additive Manufacturing, AM) menetelmät ovat kehittyneet nopeasti viime vuosina. Joitain näistä teknologioista kutsutaan 3D-tulostukseksi. Menetelmiä sovelletaan teollisuudessa yhä laajemmin ja moninaisia lääketieteen sovelluksia on esitelty. Osa näistä on kliinisessä käytössä, mutta vielä suurempi määrä tutkimus- ja kehitysvaiheessa. Asiantuntijat ovat esittäneet huolensa liittyen valmistusprosessien laadunhallintaan, potilastapausten dokumentointiin ja potilasturvallisuuteen, kun näitä uusia teknologioita sovelletaan lääketieteessä.

Tässä väitöskirjassa esitellään luokittelujärjestelmä lääketieteen AM-sovelluksille. Järjestelmä perustuu omiin ja kirjallisuudessa esitettyihin tapaus tutkimuksiin. Tutkimuksen yksi tavoite oli yhdistää sovellusten luokittelu ja käytännön potilastapausten vaiheittainen etenemä yhdeksi esitysmuodoksi. Ratkaisuksi kehitettiin lääketieteellisten sovellusten matriisimuotoinen esitys. Yhtenä työn tavoitteena oli kehittää ratkaisu, joka tukisi potilastapausten suunnittelua, dokumentointia ja oppimista. Psykologien mukaan tietämys ryhmittyy paketteihin, jotka mahdollistavat tiedon jäsentymisen, tallentamisen ja asettamisen asiayhteyteensä. Matriisiin pohjautuva esitysmuoto on tarkoitettu helpottamaan asianosaisia ymmärtämään lääketieteen sovelluksia tällaisina paketteina. Konseptissa tapauskohtainen tieto esitetään matriisin soluissa. Tällainen tiedon esitystapa on potentiaalisesti perusta tuleville piirremallinnustekniikan ja asiantuntijajärjestelmien sovelluksille lääketieteessä.

Tässä väitöksessä esitetään lääketieteen AM-sovellusmatriisi, joka on mahdollinen perusta hyväksytyille standardille suunnitella ja tallentaa potilastapauksia. Lääketieteen AM-sovellusmatriisi tukee oppimista ja sen toimivuus on osoitettu tietojärjestelmän perustana. Kehitetty lääketieteen AM-matriisi validoitiin kliinisessä silmänpohjaimplanti potilastapauksessa. Toisessa tapaus tutkimuksessa selvitettiin AM-menetelmän ja kappaleen viimeistelyn vaikutuksia kappaleen sytotoksisuuteen. Molemmista tapauksissa materiaali- ja menetelmädata tallennettiin matriisin soluihin.

**Avainsanat** Materiaalia lisäävä valmistus, 3D-tulostus, lääketieteen sovellus, luokittelu, potilastapaus**ISBN (painettu)** 978-952-60-8172-4**ISBN (pdf)** 978-952-60-8173-1**ISSN (painettu)** 1799-4934**ISSN (pdf)** 1799-4942**Julkaisupaikka** Helsinki**Painopaikka** Helsinki**Vuosi** 2018**Sivumäärä** 101**urn** <http://urn.fi/URN:ISBN:978-952-60-8173-1>



# Preface

Aalto University's Department of Mechanical Engineering was the research location of this dissertation. The dissertation was co-financed by Finnish Funding Agency for Technology and Innovation (Tekes, currently Business Finland) and a number of companies, including DeskArtes Oy, EOS Finland Oy, Planmeca Oy, and Vektor Claims Administration.

I am very grateful to my supervisor, Professor Jouni Partanen, and advisor, Professor Antti Mäkitie, for guiding and encouraging me through the process of conducting research. I would like to address special thanks to Professor Mäkitie for providing academic insight regarding research ethics and methods in the field of medical science.

I wish to thank my preliminary examiners Professor Paulo Bartolo and Professor Alain Bernard for their invaluable comments and input on improving this thesis, and Professor Igor Drstvensek for being my opponent.

I wish to express gratitude to my co-authors and colleagues who have participated in this research, to M.Sc. (Tech.) Pekka Paavola for taking photographs, and to Mrs. Grainne Lehtipuu for proof reading and commenting the manuscript.

Finally, I would like to thank my family for helping me to keep a balance between my private and working life.

Hyvinkää, 20 August 2018

Jukka Tuomi



# Contents

Preface	7
Contents	9
List of abbreviations	11
List of publications	13
Author's contribution	15
1. Introduction	17
1.1. Background and research gap	20
1.2. Objectives, scope and research questions	21
1.3. Research methods and dissertation structure	24
2. Materials and methods	27
2.1. Additive manufacturing technology	27
2.2. Medical applications of additive manufacturing	28
2.2.1. Application process phases	28
2.2.2. Classification of medical applications	30
3. Results and discussion	37
3.1. Medical applications of additive manufacturing matrix	37
3.2. Process data presentation	38
3.3. Scientific results and practical implementations	50
4. Conclusions	51
References	55
Publications	63



# List of abbreviations

AI	Artificial Intelligence
AM	Additive Manufacturing
PBF	Powder Bed Fusion
CAE	Computer Aided Engineering
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
DMLS	Direct Metal Laser Sintering
EBM	Electron Beam Melting
FDA	U.S. Department of Health and Human Services, Food and Drug Administration
FE	Finite Element
HU	Hounsfield Unit
KM	Knowledge Management
MAAM	Medical Applications of Additive Manufacturing
STL	StereoLithography or Standard Tessellation Language
3D-CAD	3-Dimensional Computer-Aided Design



# List of publications

This doctoral dissertation comprises a summary and the following publications, which are numerally referred to in the text.

**1.** Mika Salmi, **Jukka Tuomi**, Kaija-Stiina Paloheimo, Roy Björkstrand, Markku Paloheimo, Jari Salo, Risto Kontio, Karri Mesimäki, Antti A. Mäkitie, 2012. Patient-specific reconstruction with 3D modelling and DMLS additive manufacturing. *Rapid Prototyping Journal*, vol. 18 Iss: 3 pp. 209 – 214, doi: 10.1108/13552541211218126.

**2.** **Jukka Tuomi**, Kaija-Stiina Paloheimo, Juho Vehviläinen, Roy Björkstrand, Mika Salmi, Eero Huottilainen, Risto Kontio, Stephen Rouse, Ian Gibson, Antti A. Mäkitie, 2014. A Novel Classification and Online Platform for Planning and Documentation of Medical Applications of Additive Manufacturing. *Surgical Innovation*, March 9, 2014, doi: 10.1177/1553350614524838.s

**3.** **Jukka Tuomi**, Roy Björkstrand, Mikael Pernu, Mika Salmi, Eero Huottilainen, Jan Wolff, Pekka Vallittu, Antti A. Mäkitie, 2017. In vitro cytotoxicity and surface topography evaluation of additive manufacturing titanium implant materials. *Journal of Materials Science: Materials in Medicine*, February 14, 2017, doi: 10.1007/s10856-017-5863-1.

**4.** Mika Salmi, Kaija-Stiina Paloheimo, **Jukka Tuomi**, Jan Wolff, Antti A. Mäkitie, 2013. Accuracy of medical models made by additive manufacturing (rapid manufacturing). *Journal of Cranio-Maxillo-Facial Surgery*, 41:603-609, 2013, doi: 10.1016/j.jcms.2012.11.041.



# Author's contribution

**Publication 1:** Patient-specific reconstruction with 3D modelling and DMLS additive manufacturing

In this study, second author contribution consists of defining a process-phase model for a medical application of an AM patient case study. In the first phase, the author introduced AM technology capabilities to medical specialists; with the specialists, he collaboratively identified an AM patient case study in the second phase. The author designed the work-flow process phases to design and manufacture the titanium implant. As the project leader, he selected collaborating 3D software and AM process and materials specialists, and coordinated the project activities between the specialists and co-authors. The co-authors together analysed and reported the results. Salmi performed the experimental work related to implant 3D modelling and was the manuscript's principal author. Kontio performed the surgery and commented on the manuscript. Kaija-Stiina Paloheimo, Markku Paloheimo and Mesimäki commented on the manuscript. Mäkitie supervised the work and provided comments on the manuscript.

**Publication 2:** A Novel Classification and Online Platform for Planning and Documentation of Medical Applications of Additive Manufacturing

In this study, first author contribution consists of defining the classification and process phases for medical applications of AM. The author investigated the process and classification matrix model for a medical AM case description. The results were interpreted together by the co-authors. The first author was the principal author. Paloheimo, Vehviläinen, Björkstrand, Salmi, Huotilainen, Kontio, Rouse and Gibson commented on the manuscript. Mäkitie supervised the work and commented on the manuscript.

**Publication 3:** In vitro cytotoxicity and surface topography evaluation of additive manufacturing titanium implant materials

In this study, the research plan design was executed by the first author. Experimental work was carried out in collaboration with the co-authors. The first author verified both AM technologies and materials, and test item post-processing methods. The results were interpreted together by the co-authors. The first author was the principal author, who wrote the first draft of the manuscript's full version, and further edited it collaboratively with the co-authors. Pernu performed SEM imaging of the test items and provided comments on the manuscript. Björkstrand, Salmi, Huotilainen, Wolff and

Vallittu provided their comments on the manuscript. Mäkitie supervised the work and provided comments on the manuscript.

**Publication 4:** Accuracy of medical models made by additive manufacturing (rapid manufacturing)

In this study, the third author defined the research question and conducted the research plan as principal investigator. He led the research group and coordinated the experimental design with internal and external collaborators. He presented the concept of attaching measuring balls to 3D skull models and of obtaining measurements using a coordinate measuring machine. Mika Salmi was the principal author and performed the experimental work. Paloheimo, Tuomi, Wolff and Mäkitie co-authored the manuscript.

**Publications 1-4:** Jukka Tuomi was principal investigator of the research programs in which publications 1-4 were published.

# 1. Introduction

Additive Manufacturing, AM, also known as 3D printing, is the general term for technologies that create physical objects by successive addition of material. The ISO 52900 terminology standard (ISO/ASTM 52900:2015) defines AM as the process of joining materials to make objects from 3D model data, usually layer upon layer, as opposed to subtractive manufacturing technologies. The AM process involves shaping material into objects by an additive shaping process. The two other principles are formative shaping and subtractive shaping.

Subtractive shaping processes produce the desired shape by selective removal of material; for example, drilling, milling, and turning. Formative shaping achieves the desired shape by directing pressure onto raw material; for example, forging, bending, casting, and injection moulding.

A specific feature of AM technology involves acquiring the desired shape in a fully automated process that does not require any specific tools or instruments. The realisation of complicated 3D geometries in a rapid and automated manufacturing process has increased the popularity of AM, such as in many fields of science, industry and culture. (Wohlers 2017).

In 1987, the first commercial AM process and equipment was introduced. The US company 3D Systems presented photo-curing based stereolithography equipment SLA-1. The equipment was based on Charles Hull's patent *Apparatus for Production of Three-Dimensional Objects by Stereolithography* (Hull 1986). According to the industrial standard (ISO/ASTM 52900:2015), this technology belongs to the vat photopolymerization technology group. During the 1980s, several other researchers and companies studied various possibilities of manufacturing objects with photo-curing. Among those were Andre, Mehaute and Witte (1984); in 1984, they filed a patent application *Apparatus for Fabricating a Model of an Industrial Part*. Charles Hull, 3D Systems was the first person who successfully invented the photo-curing process and reached commercial success, and is consequently often considered the founder of 3D Printing. Soon after the introduction of SLA-1 equipment followed the introduction of also other AM principles. The patent for powder bed fusion technology was published in 1989 (Deckard 1989). Material extrusion technology is based on the patent *Apparatus and method for creating three-dimensional objects* filed in 1992 (Crump 1989).

The ISO standard (ISO/ASTM 52900:2015) defines seven different subgroups for AM. This classification uses manufacturing process principle features; the process categories are as follows:

*Vat Photopolymerization*; liquid photopolymer in a vat is selectively cured by light-initiated polymerization.

*Powder Bed Fusion*; selectively focused energy on a cross-section of powder binds the powder together.

*Binder Jetting*; a liquid-bonding agent is deposited according to the cross-section with inkjet print head technology.

*Material Jetting*; object material is passed through print head ink channels.

*Material Extrusion*; solid material is melted and extruded selectively.

*Directed Energy Deposition*; focused thermal energy is used to fuse materials by melting them as they are deposited.

*Sheet Lamination*; sheets are cut and laminated to form an object.

Initially in AM technology, most parts were manufactured for industrial prototyping and conceptual design studies. In 2003, Levy, Schindel and Kruth (Levy et al. 2003) presented application-oriented classification for AM as follows:

*Concept modelling*; 1–10 parts manufactured with 3D Printing (3DP) technology.

*Rapid Prototyping and Rapid Tooling*; 10–1000 parts manufactured with Selective Laser Sintering (SLS), Stereolithography (SLA) and Fused Deposition Modelling (FDM) technologies.

*Rapid Manufacturing*; more than 1000 parts manufactured with Selective Laser Melting (SLM) and 3DP technologies.

Later realised was that manufacturing lot size did not fully define practical applications of AM or applied technology. Wohlers (2006) classified applications as 1) 3D printing for design and modelling, 2) fit and function prototypes, 3) rapid manufacturing, and 4) tooling. Later Wohlers (2017) named nine different application groups, classifying industrial AM applications as 1) visual aids, 2) presentation models, 3) prototypes for fit and assembly, 4) patterns for prototype tooling, 5) patterns for metal casting, 6) tooling components, 7) functional parts, 8) education/research, and 9) other.

According to Wohlers (2017), medical and dental applications represent 11% of the revenues of the total value of served industries.

Wohlers (2017) lists various AM technology applications, in which parts are used as secondary tooling components. Medical settings similarly apply AM technologies. Eppley (2002) used AM parts for dental replication. Singare et al. (2005) (2009) used AM parts to manufacture silicone rubber moulds for investment casting pattern making, with the goal of manufacturing titanium chin implants and custom titanium prosthesis.

AM processes manufacture physical parts from numerical definition automatically, layer-by-layer vice, without similar constraints as conventional manufacturing processes (Kruth 1991). Numerical definition usually refers to a 3-dimensional computer-aided design, 3D-CAD, system or other software tool for geometry processing. AM suits the manufacture of complex physical objects of organic shapes. The manufacturing data's origin can be patient-oriented imaging data, thus enabling customised medical solutions.

When applying AM in the medical field, powder bed fusion, material extrusion, binder jetting, vat photopolymerization, and material jetting are the most suitable processes for plastics and composite materials. When manufacturing metal parts for medical applications, powder bed fusion is the most relevant technology (Gibson et al. 2009).

AM technology enables complex design features and is a cost-effective way of manufacturing complex physical parts. These technological features are utilised in various industrial products and processes. Presented are a wide selection of new design studies of conventional products. Figure 1 demonstrates AM's ability to create lightweight fashion design study.



**Figure 1.** AM aluminium part (Manufacturer: FIT AG, Germany)

## 1.1 Background and research gap

This dissertation classifies medical applications of additive manufacturing, AM, based on a journal publication literature review and case studies implemented within four different academic research projects funded by Tekes, the Finnish Funding Agency for Innovation. The research projects were Bioman I (2005), Bioman II (2007-2010), MedAMan (2010-2012), and BioScaf (2010-2013). Development of the matrix representation of medical applications of additive manufacturing involved combining classifications of applications and use-case process phases.

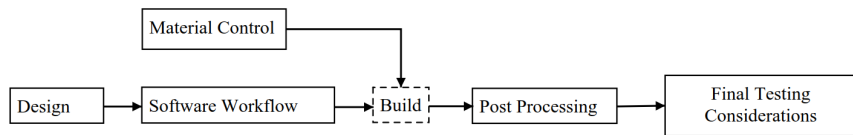
In 1990, Mankovich et al. (1990) presented a concept to display patient anatomy using stereolithography technology to display patient anatomy. Stereolithography equipment was used to produce a model of cranial bony anatomy from CT image data. In 1997, Berry et al. (1997) applied powder bed fusion technology to medical models used in surgical planning, the design of customised implants, and training. Above-mentioned articles show that soon after presenting the AM technologies, applications in medical field were presented. Bibb et al. (2009) reported a set of maxillofacial surgery case studies, involving the application of powder bed fusion technology in manufacturing stainless steel custom-fitting surgical guides. Poukens et al. (2008), Rouse (2009), and Probst et al. (2010) have reported clinical examples of the manufacture of customised implants with AM technology. Yan et al. (2003) presented several concepts of biomanufacturing, using freeform culture media AM. These applications include both biologically compatible parts and parts used in manufacturing these components, aiming to replace tissues such as bone and cartilage.

A wide variety of AM medical applications exists. Practitioners are concerned with how to manage safety and regulatory issues related to applied technologies and procedures. According to Siblani (2017), AM technology enables the process of moving things closer to the end user, often taking the manufacture of medical objects out of actual manufacturing facilities. According to Siblani (2017), this shift to more local manufacturing raises serious safety and regulatory issues, along with questions such as *Do all 3D printers really offer the same level of quality as a laboratory or manufacturer?*.

Requirements for materials used in the manufacture of medical devices are specified in several regulatory requirements and directives. One such regulation is the Medical Device Regulation 2017/745 for Medical Devices (EU 2017). Based on industrial practice, Freudenstein (2017) has expressed concerns related to biocompatibility of plastic materials. Medical device manufacturers tend to rely on plastic materials certified as biocompatible. Such certification implies the material in question performs similarly to the batch tested for certification. However, materials producers optimise their production to develop operational efficiency, potentially both changing a material's specifications and leading to a situation whereby each production batch does

not fulfil the requirements. Consequently, Freudenstein (2017) proposes committing to change management and notification procedures regarding the processing of materials.

The U.S. Department of Health and Human Services Food and Drug Administration (FDA) has published a draft guidance, ‘Technical Considerations for Additive Manufactured Devices’ (FDA 2017). This draft documents several technical considerations specific to medical devices using AM. The overall medical AM process covers steps from design process, software workflow phase, material control, build process, post-processing and testing (see Figure 2). Chahine et al. (2008) have described a macro-level workflow related to the medical-device manufacturing process. The FDA document highlights several process phase-oriented technical considerations requiring attention as part of fulfilling a device’s quality system requirements.



**Figure 2.** Flow chart of the additive manufacturing process (FDA 2017)

When designing 3D modelling and AM processes for medical devices, several parameters and features for consideration exist (FDA 2017). Examples of such parameters are instantaneous power of the energy delivery system, build or beam speed, build bath, total energy density, and focal point or nozzle diameter of an AM process and equipment. Final medical device performance and material properties are affected by the post-processing steps of AM. The FDA (2017) recommends documenting all post-processing steps; included is a discussion of post-processing effects on the materials used and the final device.

## 1.2 Objectives, scope and research questions

The medical application of AM is a highly multidisciplinary field, involving the combination of expertise from mechanical engineering, computer science, and medicine. Human organs have complex geometries; medical surgeons operate with, for example, medical imaging, preoperative models, special tools and instruments, and custom-made implants. Abbaszadeh et al. (2004) have listed resources and expertise needed in the custom-made hip implant application of AM, along with medical imaging, design and manufacturing, tooling, biomaterials, IT-technology, and bioengineering.

Since the 1980s, studies have involved expert system technology and artificial intelligence in conjunction with feature modelling technology. Several researchers developed concepts and technologies to enrich product geometry data with product feature attributes. When extending product model

information content became expert system based reasoning operations possible. A typical application area has been process planning for mechanical engineering factory operations (Mäntylä et al. 1987), (Shah et al. 1988), (Laakko et al. 1990). Central to such systems is both knowledge base and process plan representation. Recent application of feature-based models allow quicker analysis of complex geometries in Computer Aided Engineering (CAE) systems (Kulkarni et al. 2016).

Cognitive psychologists believe knowledge is clustered into packets in human reasoning, language, perception and memory. These packets are considered to have both factual and procedural contents, explaining the performance of mental activities. The packets enable knowledge to be organised, stored and placed in context. Once the mind finds the relevant packet, all attributes and relationships become readily accessible (Sanford 1985). 3D CAD modelling is key to applying AM in any field. 3D CAD modelling represents any part's characteristics in a micro view. A macro view is provided by features and attribute data. In a product's feature model, combined micro and macro characteristics can answer questions related to part features, such as weight, feature constraints and surface quality. Designers can converse with a feature modelling system, because the system knows general characteristics of features that are relevant to the application. The above-mentioned packets do not exist for novel situations; consequently, feature-based models must be limited within well-bounded domains defined by limited generic features (Shah & Mäntylä 1995). Laroche et al. (2016) have proposed a knowledge-based system called the *Digital Factory Assistant*. The system is designed for use by production line workers, but can also be applied to the product design phase.

Moura et al. (2010) have applied expert system technology to support the selection of biopolymers for medical applications. Application of expert system technology can support the selection of biopolymers for medical applications (Moura et al 2010). Defining the system as a computational tool allows solving complex decision-making problems requiring human intelligence and biomedical expertise. The system asks questions and clarifications and guides the user through the decision-making process, offering help on the way. The example chosen is the application area regarding the creation of an ideal scaffold or implant. In such a biomanufacturing case, many mechanical and biological requirements need consideration; according to the authors, a knowledge-based system could serve as an automated expert on the matter.

Classifying medical applications of AM and defining data models for describing patient cases was the general aim of this dissertation. The ultimate goal was to both integrate application process phases with mentioned classification and present case-based evidence regarding application-oriented classification system functionality as applications' planning and documentation tool.

The specific themes and related aims of this dissertation are as follows:

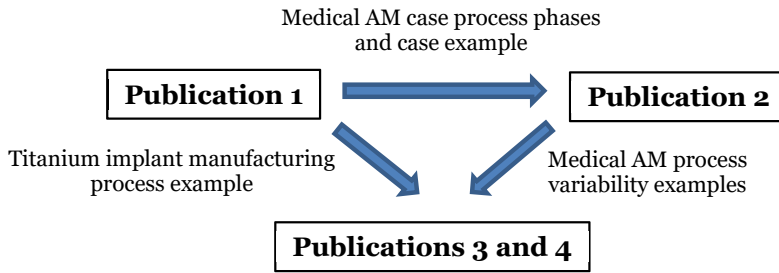
- Understanding the original purposes of medical applications of AM in defining characteristics of the applications.
- Presenting logical sequences of data processing and manufacturing phases of medical applications of AM.
- Presenting an application-oriented framework that integrates the classification system and generic sequencing of medical applications of the AM process model.
- Studying AM-specific process features in medical applications and demonstrating the variability of AM process planning and realisation in the medical device approval process.

Table 1 presents themes with links to each specific contribution regarding this dissertation and other publications.

**Table 1.** Dissertation themes, specific contributions, and links to publications

Themes	Specific contribution	Link to publication
Characteristics of medical applications of AM	Classification system with practical case examples	Publication 2
Logical sequencing of process phases	Process phase descriptions with practical case examples	Publication 1, Publication 2
Integrated classification system	Extended classification system and matrix presentation for medical applications of AM	Publication 2
Variability of AM process planning	Variability proved with biocompatibility testing and AM process accuracy testing	Publication 3, Publication 4

The characterisation of medical applications of AM in this dissertation is based on both case studies performed at Aalto University and a literature review. Publication 1 involves the analysis of a clinical case study, with descriptions of the main process phases from medical imaging to actual clinical operation. DMLS process was applied in the clinical case study described in publication 1. Publication 2 concerns the classification system, with descriptions of characteristics of AM medical applications. Documentation relates to process phases from clinical need to ready-to-use AM medical devices. The publication includes descriptions of the matrix framework for medical applications of AM, with relevant content in each cell. A clinical case study presented in publication 1 is used as an example case study in publication 2. Publication 3 compares the titanium implant manufacturing process results: AM methods are Direct Metal Laser Sintering (DMLS) and Electron Beam Melting (EBM). Publication 4 evaluates the effect of 3D model data accuracy and AM process selection from the point of view of the resulting geometrical accuracy. Publication 4 is linked to publications 1 and 3. Figure 3 describes connecting links between publications.



**Figure 3.** Links between publications

Two main research questions of this dissertation are as follows:

**Research question 1**

What is a relevant model to describe and store application-oriented case data of medical applications of additive manufacturing?

**Research question 2**

What are the best methods to manage variations of applied technologies and process parameters?

This research question was divided into two sub-questions.

In science literature, what are the presented product modelling technologies to support application-oriented data?

How can these technologies be applied when describing AM case data in medical applications?

**1.3 Research methods and dissertation structure**

This dissertation applies mixed research methods. Classification is used to characterise medical applications of AM. Process phases of medical AM clinical cases are mainly analysed using constructive research methods, that is, a research study producing an innovative solution to a real-world problem (Kasanen et al. 1993). The presented matrix-model classification is based on constructive research and a literature review. The variability of technology options and related matrix-cell data content in publications 3 and 4 are studied as constructive research cases.

The first chapter of this dissertation introduces the topic and discusses both the background of the research and the research gap. The following chapters describe the empirical evidence and new scientific data.

The second chapter describes both materials and methods used in this dissertation and the use of AM as a tool in medical applications. Subsequently presented is the process chain from medical imaging to AM part finishing, and identified application classes. The chapter ends with case examples and presentation of scientific methodologies.

The third chapter introduces a matrix model for medical applications of additive manufacturing, involving case-based evidence regarding matrix-model applicability and relevance. Evidence is based on clinical case studies and a variability study of AM processes and manufacturing process parameters.

The fourth chapter of this dissertation presents both conclusions and future research topics emerging from this study. Also discussed are practitioners' concerns related to patient safety issues. The chapter ends with a presentation of practical and theoretical implications of the dissertation results.



## 2. Materials and methods

### 2.1 Additive manufacturing technology

Since the late 1980s, industrial settings have applied AM. Physical parts can be manufactured from numerical definitions automatically, layer-by-layer; the process does not have similar constraints as conventional manufacturing processes (Kruth 1991). When building a part using an AM process, directional dependence exists between the material properties of that part and the technology of the AM process and materials. Therefore, material properties in a 3D printed part depend on chosen technology, materials, and process parameters.

Reduced manufacturability constraints and relatively low manufacturing costs results in AM being well suited to the manufacture of complex, organic-shaped physical objects. Furthermore, essential in medical settings, parts can be easily manufactured using an individual person's imaging data, thus making it possible to create customised solutions (Gibson et al. 2009).

This dissertation covers all AM processes described in industrial terminology standard ISO (ISO/ASTM 52900:2015). The most popular manufacturing processes for plastic and composite parts are powder bed fusion, material extrusion, binder jetting, vat photopolymerization, and material jetting. Powder bed fusion is the most popular process for metals (Gibson et al. 2009). In publication 1, powder bed fusion technology is used both as a preoperative model manufacturing technology and a metal AM technology for the titanium implant manufacturing process. The presented clinical case matrix model in publication 2 does not limit the type of AM technology applied. Publication 3 describes the application of two different powder bed fusion technologies in manufacturing titanium implant material samples. Similarly realised was the post-processing procedure for the samples. Publication 4 evaluated the accuracy of material jetting (brand name PolyJet), powder bed fusion (brand name Laser sintering) and binder jetting (brand name 3D Printing) processes as medical-model manufacturing technologies.

## 2.2 Medical applications of additive manufacturing

AM is widely used in clinical settings, with the number of applications increasing rapidly. Currently in medical treatment planning and training purposes, commonly practiced is the application of AM preoperative models (McDonald et al. 2001). Such models are also used for implant planning (Labadie et al. 2008) and manufacturing special tools and instruments (Bibb et al. 2009). Extremely complicated physical objects can be manufactured in the AM process with these technologies, which are fully automated, thus making them highly applicable in the medical setting. In some cases, saving time in the labour intensive medical device manufacturing phase has been an essential reason to apply AM (Ng et al. 2002). Figure 4 illustrates a case example involving the manufacture of a fracture reduction forceps concept instrument using AM equipment. The process was developed and tested concerning the design and manufacture of the novel surgical instrument, fulfilling the theoretical requirements of a certain specific facial trauma case.



**Figure 4.** The additive manufactured medical instrument (Kontio et al. 2012) (Photo: M.Sc. (Tech.) Pekka Paavola)

Medical applications of AM require collaboration across disciplines. This multidisciplinary field draws resources from fields including radiography, computer science, engineering design, and surgery, thus highlighting the need for collaborative platforms and data management tools of AM medical applications. Well-structured, conceptual tools positively impact the community by enhancing knowledge transfer, research and clinical case documentation practice, and patient safety.

### 2.2.1 Application process phases

Regardless of the application, all medical applications of AM cases essentially fall into five sequential engineering process phases. During workflow, these five engineering tasks logically lie between medical examination and clinical application or implementation.

### *Medical Imaging and 3-Dimensional Digitising*

Medical imaging and digitising is the first phase in the process. To create medical models, several different technologies exist. These technologies include magnetic resonance imaging and ultrasound; however, computed tomography is most commonly used in medical applications of additive manufacturing (Bibb & Winder 2010). Strongly impacting the quality of the medical model used in the following process phases is medical imaging and 3D digitising, as the first phase of the process. This phase results in row data (DICOM images) used in the next process phases. Huotilainen et al. (2013) suggest multidisciplinary collaboration in this phase between various surgical specialities, radiology, and AM engineers to optimise process quality, imaging parameters, and radiation dose.

### *Three-Dimensional Modelling*

This process phase involves the reconstruction of anatomical multi-slice 2D images and their conversion into 3D format. Input data are typically in DICOM format; output format for the next phase is typically an STL file. This phase includes data adjustments, such as removing unnecessary tissue based on radiodensity threshold in Hounsfield scale or imaging artefacts. The methodology used is the so-called grey-scale value method, which describes the variation of density intensity (Kalender 2005), (Sun et al. 2005). For example, designing implants or tools requires 3D geometry operations; for this, the 3D CAD system is often used. This process phase may include Fineti Element (FE) analysis and usage of special software for topology optimisation (Cabibihan 2011), (Abdulsalam et al. 2017).

### *Additive Manufacturing*

This phase involves the manufacture of physical parts designed in the previous phase. AM parts must meet specified material properties and manufacturing accuracy. These requirements depend on aimed medical application and usage of the parts (Robieny et al. 2007). The AM method and material must be chosen according to these specifications in an application-oriented approach. For a medical application, several classified AM process and materials options are typically available. These processes may vary according to the end accuracy point of view, surface finish, or material properties. Thus, achieving an optimal result requires expertise (Bibb & Winder 2010). Publication 3 presents two different kinds of AM processes that result in classified titanium implants.

### *Finishing*

Manufactured AM parts typically require a finishing phase. The finishing phase covers different surface treatments, such as washing, coating, polishing, or sterilisation. Inert implants and objects invading the body must be sterilised prior to their clinical use. Occasionally, the accuracy of an AM process does not meet the clinical case requirements (Winder & Bibbs 2005). Such cases might apply finishing by machining, grinding, or polishing. Publication 3 compared the AM titanium implant materials as processed and surface finished states.

### *Clinical Application*

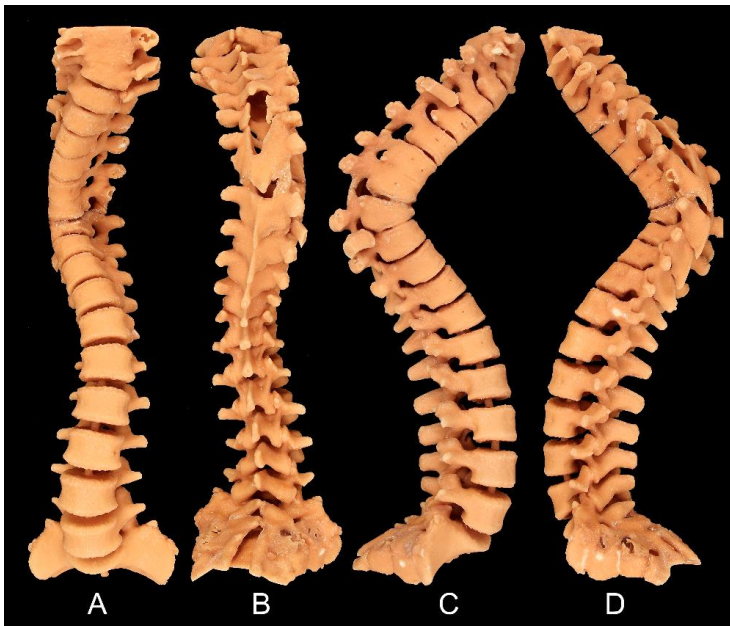
The final goal of the process is clinical application; it describes the purpose of the manufactured AM parts. Applications range from pre- and postoperative models for treatment planning and monitoring, to surgical tools, implants, and laboratory-grown tissues. A case may include one or several of these processes during the medical procedure.

### **2.2.2 Classification of medical applications**

This dissertation develops the application of a solution-oriented classification system for medical applications of AM. For each category presented, identification of common requirements for AM technologies is possible.

#### *Medical Models for Pre- and Postoperative Planning, Education, and Training*

In clinical use, manufacturing models for preoperative planning or surgical simulation is possible using AM (McDonald et al. 2001). Typical applications also relate to communication with technicians, educating students, and counselling patients and families regarding complicated surgical procedures. The application type determines the validity of the different kinds of quality requirements, including material characteristics, haptic response, or anatomical accuracy. Figure 5 illustrates the preoperative model used for scoliosis treatment planning.



**Figure 5.** Preoperative model picture of an AM part; A and B sagittal plane directions and B and C frontal plane directions (Photo: M.Sc. (Tech.) Pekka Paavola)

### *Medical Aids, Orthoses, Splints, and Prostheses*

Enhanced healing from trauma or anomaly can incorporate AM technologies by the anatomic personalisation of medical devices. This involves the manufactured part being typically external to the body or non-invasive. For example, external AM support for a patient-specific external ankle-support device (Björkstrand et al. 2010), (Lindahl et al. 2014), (Figure 6). Another example is treatment of dental malocclusion by manufacturing appliances, or tools for the appliances' manufacturing process (Joffe 2003), (Salmi et al. 2012 & 2013), (Miller & Derakhshan 2002).



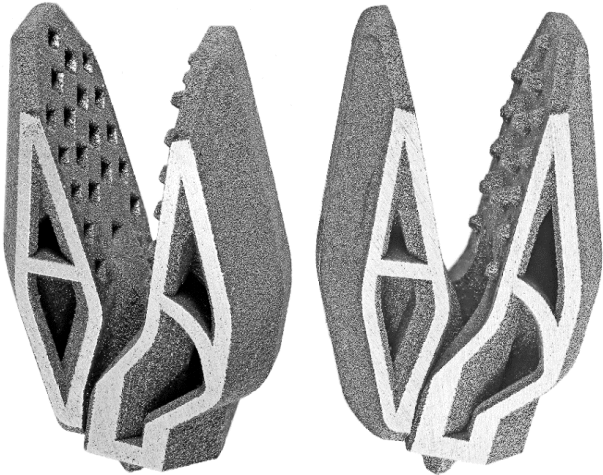
**Figure 6.** Patient-specific ankle-support device, in which white AM parts are custom made according to measured ankle movements. (Photo: M.Sc. (Tech.) Pekka Paavola)

### *Tools, Instruments, and Parts for Medical Devices*

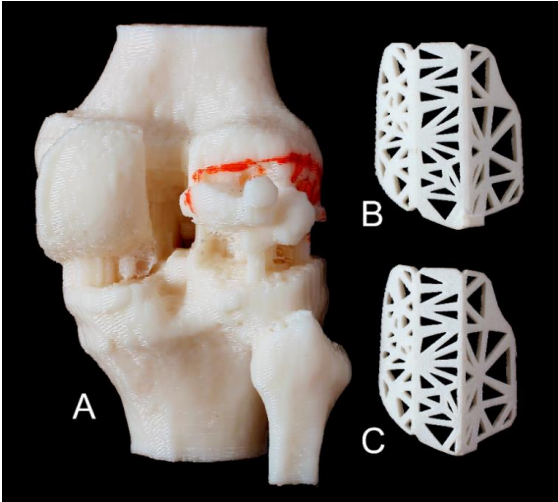
Additive manufacturing may be used to manufacture tools, instruments, and hardware for medical applications, and to improve or secure medical or surgical procedures. Poukens, Haex and Riediger (2003) have reported applications concerning the use of custom-made surgical guides in cranio-maxillofacial surgery. AM parts can also be applied as non-invasive positioning guides, such

as an auricular template for craniofacial implant positioning (Ciocca et al. 2009). This class of devices are typically in contact with body fluids, mucous membranes, or tissues for a limited time; thus they may be invasive but non-implantable.

One feature of AM technology is freedom of design, allowing practitioners to innovate new enhanced designs for standard instruments (Kontio et al. 2012). Figure 7 illustrates a surgical instrument component manufactured with micro laser sintering AM technology. Figure 8 portrays a postoperative model (Figure 8A) for fresh cadaveric osteochondral allograft surgery and a pair of custom sawing guides (Figures 8B and 8C) used to saw and fit the allograft (Paatela et al. 2012).



**Figure 7.** Example of AM surgical instrument component (Photo: M.Sc. (Tech.) Pekka Paavola)



**Figure 8.** Preoperative model of lateral femoral condyle and pair of surgical saw guides (Photo: M.Sc. (Tech.) Pekka Paavola)

### *Inert Implants*

Inert implants are typically custom-made patient-oriented devices intended for long-term use. Surgical operations often use AM implants based on medical imaging and 3D modelling. Janssens and Poukens (2007) have presented a cranial plate for direct implantation, digitally designed and manufactured by AM technologies. Alternatively, patient-oriented implants can be manufactured indirectly, by using an AM part as a model or pattern in the manufacturing process (Sekou et al. 2009). Sometimes, AM devices may be standard implants but manufactured because of biological, implant micro and macro structural reasons, or both. Murr et al. (2012) have studied Electron Beam Melting AM technology as orthopaedic implant manufacturing technology. Publication 1 presents a typical procedure involving the manufacture of a preoperative model of a defect and implant with AM technology. Applying AM technology allows the realisation of complicated light-weight implant structures (Figure 9). Topology optimisation of orthopaedic implant structures potentially minimises stress shielding and bone-loss problems (Abdulsalam et al. 2017).



**Figure 9.** Light-weight implant mesh structure (Photo: M.Sc. (Tech.) Pekka Paavola)

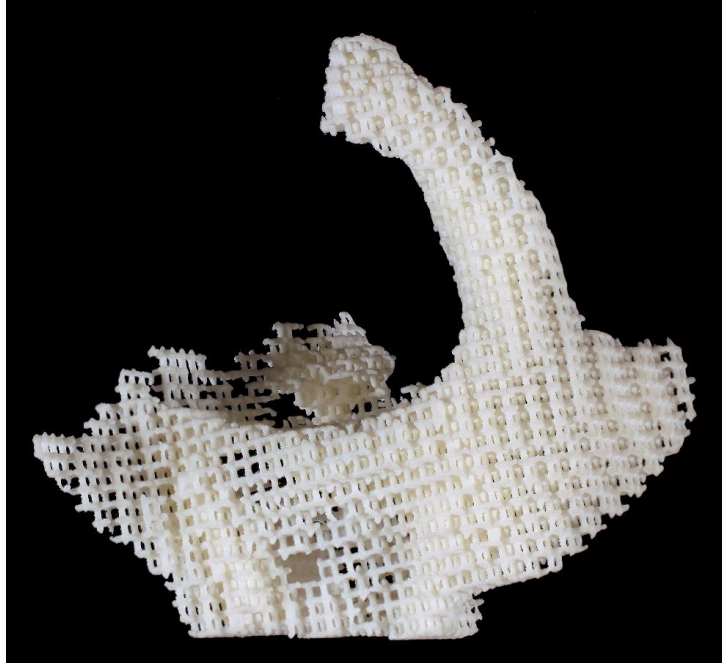
### *Biomanufacturing*

AM scaffolds can be used as skeletons for cell cultures, to act as support or protection from external physical forces and to provide an optimal medium for 3D cell cultures (Yan et al. 2003). These applications include both biologically compatible parts and parts to use when manufacturing these components. The AM structures are designed to be active whether they are resorbable or non-resorbable; used materials for scaffolds may be natural or synthetic, organic or inorganic, or in any combination. The ultimate goal is to replace tissues such as bone, cartilage, or liver. Currently, corresponding research is increasing rapidly; however, also presented are over-exaggerated estimations regarding time scales for clinical applications (Babylak et al. 2012), (Gibbs et al. 2014), (Tan et al. 2012).

The fields of tissue engineering and regenerative medicine overlap with biomanufacturing. In this field, researchers aim to create structurally and functionally equivalent tissue constructs by combining cells, biomaterials and signalling factors (Langer & Vacanti 1993). AM-customised scaffolds may be constructed and seeded, for example, to support bone growth (Smith et al. 2007) or to increase the amount of calcification in a scaffold (Schantz et al. 2003).

Conventional scaffold manufacturing technologies include solvent casting, freeze-drying, phase separation, gas foaming, melt moulding and particle-leaching. The main limitations and drawbacks of these technologies are related to poor control over the porosity, pore size, spatial distribution and interconnectivity. Some of the above-mentioned techniques require using toxic solvents to prevent manufacturing parts from containing living cells and biological molecules. Biomanufacturing was introduced to address the limitations of conventional manufacturing technologies. The benefits of these technologies include precise control of the scaffold porosity, architecture, shape and pore interconnectivity (Bartolo et al. 2011), (Melchels et al. 2012).

The two main approaches currently used in biomanufacturing are scaffold-based and cell-laden based so-called scaffold-less approaches. In the scaffold-based approach, a porous, biocompatible or biodegradable 3D scaffold is seeded with donor cells and treated *in vitro* in a dynamic culture system, called a bioreactor. In cell-laden based biomanufacturing, living cells are seeded to a construct with the materials like hydrogels in an integrated process. Melchels et al. (2012) have evaluated characteristics of AM techniques for tissue engineering, and reported that the typical biomaterials require process parameters not conducive to direct inclusion or co-deposition of cells. Thus, the most promising approach in tissue engineering seems to involve scaffold-based technologies (Domingos et al. 2009).



**Figure 10.** Example of AM scaffold structure study (Photo: M.Sc. (Tech.) Pekka Paavola)

Table 2 shows the positioning of some research studies based on applied AM technology and medical application class.

**Table 2.** Examples of research studies positioned according to applied AM technology and medical application class.

	Pre- and postoperative models	Medical aids	Tools and instruments	Inert implants	Biomanufacturing
Vat Photo-polymerization	(Mankovich et al. 1990) (Poukens et al. 2003)	(Salmi et al. 2013)	(Sarment et al. 2003) (Poukens et al. 2003)		(Levy et al. 1997)
Powder Bed Fusion	(Berry et al. 1997) (Salmi et al. 2012)	(Lindahl et al. 2014) (Björkstrand et al. 2010)	(Bibb et al. 2009)	(Salmi et al. 2012) (Poukens et al. 2008) (Stübinger et al. 2013)	(Williams et al. 2005)
Binder Jetting	(Mäkitie et al. 2016) (Salmi et al. 2013)				(Kim et al. 1998) (Lam et al 2002)
Material Jetting	(Salmi et al. 2013)				(Cui & Boland 2009)
Material Extrusion	(Akmal et al. 2018) (Salmi 2016)		(Kondor et al. 2013)		(Domingos et al. 2009)
Directed Energy Deposition				(Bandyopadhyay et al. 2009) (Murr et al. 2012)	
Sheet Lamination	(Olszewski et al. 2014)				(Masuda et al. 2008)

# 3. Results and discussion

## 3.1 Medical applications of additive manufacturing matrix


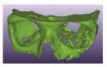

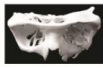
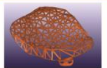



Matrix representation of medical applications of additive manufacturing, MAAM, consists of process phases on the horizontal axis and application classes on the vertical axis. Using such a matrix framework with relevant content in each cell allows planning and documenting of clinical case applications. Logical sequences of case data processing and manufacturing phases are presented in columns and classification-oriented AM applications are listed in rows. Table 3 describes the MAAM matrix skeleton.

**Table 3.** Medical applications of AM case matrix

	Medical Imaging and 3D Digitising	3D Modelling	Additive Manufacturing	Finishing	Clinical Application
Pre- and Post-operative Models					
Medical Aids					
Tools and Instruments					
Inert Implants					
Biomanufacturing					

Table 4 is an example of patient-case documentation using the matrix. This case shows the role of process phases and MAAM application classes in a surgical reconstruction of the orbit. The case study applies two MAAM classes. First, a preoperative model was produced and used to help the design and production of the orbital implant. Medical imaging data were used for preoperative model manufacturing; the same data were used for implant design in process flow.

**Table 4.** Surgical case documentation example in MAAM matrix

	Medical Imaging and 3D Digitizing	3D Modeling	Additive Manufacturing	Finishing	Clinical Application
Pre- and Postoperative Models					
Medical Aids					
Tools & Instruments					
Inert Implants					
Biomanufacturing					

### 3.2 Process data presentation

Presented as an example is a patient clinical case, with the related MAAM matrix process data. In the MAAM matrix, each process step containing information is shown in the matrix as a picture. The picture visually depicts a result or work content in each cell. Overall, the matrix view describes the top level of a medical case, and each cell contains process phase oriented data. Arrows in a matrix describe the process phase sequence.

This case involved a 67-year-old male patient, who had been in a severe accident 20 years earlier. Previous surgical reconstructive treatment had resulted in increased orbital volume and disturbing displacement of the prosthetic eyeball. The repair was performed by reducing orbital volume with a suitable orbital wall implant. Earlier research showed that an increase in orbital volume is related to eye displacement in depth direction (Ahn et al. 2008). The surgery’s goal was to achieve an anatomically correct shape of the orbital wall and appearance of the eye symmetry. 3D-CAD modelling and AM were central in treatment planning and manufacturing of medical models and the implant.

The first process step involved medical imaging with X-ray computed tomography (CT). The used medical imaging equipment was Philips Brilliance CT 16-slice, with imaging slice thickness of 1,25 mm. Creation of a 3D model from the facial bone orbital area structure used the patient’s CT images. Tomography images contain information about bones and soft tissue. Thus, geometry information not needed in the medical 3D modelling must be removed by the so-called grey-scale value method, which describes the variation of density intensity (Kalender 2005). In this case, creation of the medical 3D model of the skull from tomography images used Osirix 2.7.5 software. This software is based on creating voxels between medical imaging slices. Voxel is a

3D equivalent of pixel. Segmentation of bone and higher density structures used 500 Hounsfield Units' value. The 3D model was then cleaned from artefacts caused by dental fillings and other sources of interference. The processed 3D model was used in the later process phases as a 3D data representation of the patient's orbital bone structure. The resulting 3D model was in STL file format.

In the 3D modelling phase, the model was cut to smaller volumes to separate the orbital areas from both eyes. Working with smaller models made medical 3D modelling easier, because modelling software works much faster with smaller models. 3D model reconstruction can be unreliable due to partial volume effects during imaging and the thin walls of skull cavities (Lamecker et al. 2007). In the above-mentioned case, the surgeon determined anatomically meaningful patches or regions of the orbital wall. In such methodology, corresponding points can be determined on the computerised model to produce a statistical model based on principal component analysis (Kamer et al. 2006).

Creation of the orbital implant's geometry involved mirroring the shape of the facial structure from the opposite side and repositioning it to the actual side. This surface was combined to the surface created from the edges of the fractured orbital. Surface modelling used Rhinoceros 2.0 modelling software (McNeel Europe, Spain). The surface was transferred to the volumetric net macro structure by using 3Data Expert (DeskArtes Oy, Finland) software. 0.4 mm net thickness and 3 mm hole size, which are close to those of commercial standard bendable orbital reconstruction plates. A net structure allows tissues and cells to grow through to surrounding tissues, and reduces a patient's sensitivity to hot and cold temperatures.

The next phase applied the Powder Bed Fusion (PBF) AM process with fine polyamide 2200 powder to manufacture a preoperative physical model. This model was used to interactively design and develop implant geometry co-operatively between the technical and surgical staff. The surgeons marked the implant design instructions on the physical model and drawings, later transferring these to the implant's 3D model. Subsequently, the manufacture of a verification model with PBF process called Direct Metal Laser Sintering (DMLS) from stainless steel was then matched to the preoperative orbital model. PBF processes use lasers for sintering metal powder layer by layer. The process has three steps: first, a fresh layer of powder is spread on the building platform with a sweeper; second, the laser sinters the powder at desired places. Finally, the building platform descends by one layer thickness, and then continues the manufacturing cycle from the first step.

The final surgery version of the titanium implant 3D model was based on this verification. Manufacture of the reconstructive surgery version of the implant used DMLS technology from titanium Ti64 ELI material, which fulfils the mechanical and chemical requirements of ASTM F 136 standard for surgical implant applications. Ti64 ELI is the pre-alloyed version of Ti6AlV4 ELI (extra-

low interstitial) and has particularly low levels of impurities. The manufacturing system was EOSINT M270 Ti (EOS GmbH, Germany), with a used layer thickness of 30  $\mu\text{m}$ . Several AM systems are available for titanium implant manufacturing. The choice of the DMLS system in this case relates to its tested capability to manufacture high-accuracy titanium components. Figure 11 is a photo of the implant structure.











**Figure 11.** AM titanium implant structure (Photo: M.Sc. (Tech.) Pekka Paavola)

Polishing and sterilisation finished the implant surface; simultaneously, laboratory results confirming compliance with ASTM F 136 requirements were obtained from a test piece. The test pieces were manufactured in the same production run as the actual implant. According to ISO standard, production run means that all parts are produced in one build cycle or sequential series of build cycles using the same feedstock batch and process conditions (ISO/ASTM 52900:2015).

The surgical procedure used a conventional infraorbital approach; the procedure involved placing the patient-specific custom-made orbital reconstruction implant onto the inferior orbital wall and fixing it to the bone with two screws. This kind of surgery normally lasts approximately 45 minutes, that is, when the reconstruction plate is detailed by hand during the operation. In this case study, the surgery lasted about 30 minutes.

Table 4 describes a surgical orbit reconstruction case. Presented as examples are three process steps and related cell-data content, including parameters and attributes. Table 5 shows example cells.

**Table 5.** Surgical case documentation example in MAAM matrix

	Medical Imaging and 3D Digitizing	3D Modeling	Additive Manufacturing	Finishing	Clinical Application
Pre- and Postoperative Models					
Medical Aids					
Tools & Instruments					
Inert Implants					
Biomanufacturing					

## Preoperative models

### Medical imaging and 3D digitising

Medical imaging: X-ray computed tomography (CT)

Medical imaging machine: Philips Brilliance CT 16-slice

Slice thickness: 1,25 mm

Description: Tomography images contain information about skin, bones, and soft tissue; part of this information is not useful and can be removed by the so-called grey-scale value method, which describes the variation of density intensity.

### Additive manufacturing

Additive manufacturing technology: Powder bed fusion (SLS)

Additive manufacturing supplier: Alphaform

Type of material: Polyamide white

Additive manufacturing commercial material: PA 2200

Additive manufacturing description: Additive manufacturing was used to create a preoperative model of the orbital area, using SLS fine polyamide 2200.

## Inert implants

### Additive manufacturing

Additive manufacturing technology: Powder bed fusion (DMLS)

Additive manufacturing supplier: EOS Finland

Type of material: Titanium alloy

Additive manufacturing commercial material: EOS Titanium Ti64 Eli

Layer thickness: 0,03 mm

Additive manufacturing description: The manufacture from stainless steel of some implant prototypes were used for verification with the preoperative

model. The final orbital reconstruction implant was additive manufactured by direct metal laser sintering (DMLS) technology, with a layer thickness of 0,03 mm.

Publication 3 evaluated two different AM processes as a method of manufacturing custom titanium implants. Custom titanium implants are typically applied in class inert implants. Such parts are commonly manufactured using two different AM technologies: direct metal laser sintering (DMLS) and electron beam melting (EBM) (Ciocca et al. 2011) (Sidambe 2014). These technologies belong to the powder bed fusion AM technology group. After the actual AM process, finishing such implants can involve drilling, milling, and polishing to finalise an implant for clinical use. The purpose of the case study was to characterise the surface structure and assess the *in vitro* cytotoxicity of titanium alloys processed using DMLS and EBM technologies. Two surface finish forms were tested: as built and polished. 'As built' refers to the ISO standard terminology (ISO/ASTM 52900:2015), referring to the state of parts made by an additive process before any post-processing. Additionally, 'as built' refers to the removal from a build platform and the removal of support, unprocessed feedstock, or both. In Publication 3 'as processed' refers to the term 'as built'.

Managing large bony defects uses autologous bone grafts combined with metallic, and more recently, with polymer and composite reconstruction plates. A major drawback of using titanium plates is the need to manually customise such plates during surgery; that is, to fit the defect site, the plates must be bent and cut. Bending the plate may predispose the plate to fatigue fractures. Recently, AM technologies have been applied to pre-fabricate patient specific, and hence customised, reconstruction plates. AM reconstruction plates do not require any intraoperative bending, thereby offering a good passive fit to the defect site, better fatigue resistance and subsequently, shorter operation time (Poukens et al. 2008) (Ciocca et al. 2011).

AM-processed material surfaces often result in a relatively rough surface finish compared to conventionally manufactured medical constructs (Sidambe 2014). Following the AM process, the implant surface of some applications, for instance artificial joints, require manual treatment, such as polishing. Furthermore, the elimination of surface flaws requires surface finishing, which may predispose to fatigue failures. Sidambe (2014) reported the effect of implant macrostructures and surface finishing on the overall clinical performance of AM implants.

Large groups of patients have been treated using customised metal implants, manufactured either using direct metal laser sintering (DMLS) or electron beam melting (EBM) (Poukens et al. 2008), (Salmi et al. 2012). EBM technology utilises a high-power electron beam that generates energy to melt powder, layer by layer. DMLS technology uses lasers to sinter the metal powder, layer by layer

(Bibb et al. 2009), (Rouse 2009). Currently, titanium and cobalt-chrome alloys are the most commonly used metals in medical AM.

Stübinger et al. (2013) have studied osteointegration between milled, grit blasted, etched and DMLS titanium implants, and reported no differences in grade of osseointegration. Reports on EBM-made titanium alloys concern their biocompatibility (Haslauer et al. 2010); however, no information exists regarding differences between the biocompatibility of DMLS- and EBM-processed titanium alloys as built and surface finished. The finishing process for eliminating surface flaws can also hypothetically influence the components' biocompatibility. Thus, using cytotoxicity tests to determine the biocompatibility of two different titanium alloys that were processed and finished in two ways was the objective of this case study.

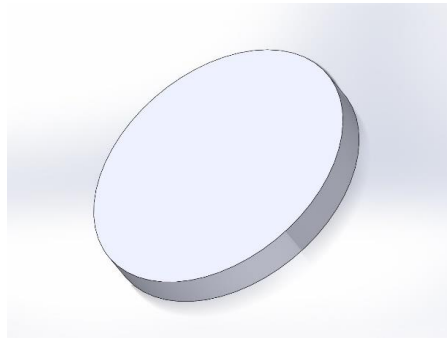
This case study involved manufacturing disc-shaped TiAL6V4 ELI alloy specimens using an EBM device (Arcam AB, Mölndal, Sweden, service provider FIT AG, Lupburg, Germany). Manufacturing the DMLS disc specimens used Ti64 ELI alloy (Electro Optical Systems GmbH, Krailling, Germany). The acquired discs were compared to a control, that was forged stock titanium alloy mandible plate (TICP, Synthes GmbH, Zuchwil, Switzerland), commonly used in maxillofacial surgery.

Finishing the disc samples comprised two phases. First, in the preliminary grinding phase, grinding the discs used silicon-carbide abrasive paper with a FEPA grit size of P320 to P4000 (ISO 6344-1:1998). Application of a 3 µm diamond suspension and a polishing cloth achieved the final grinding. Lastly, purification of all discs involved ultrasonic cleaning (ethanol) for three minutes. Subsequently, implementing scanning electron microscopy (SEM) allowed examining the surfaces of the EBM and DMLS discs. Surface topography of the specimens was analysed by measuring Ra values with the Innovatest TR-200 (Maastricht, The Netherlands) measuring equipment. The EBM as built specimens were beyond the measuring range of the Innovatest TR-200 equipment; consequently, the Taylor Hobson Form Talysurf Inductive 120 (Leicester, UK) equipment was used for these specimens.

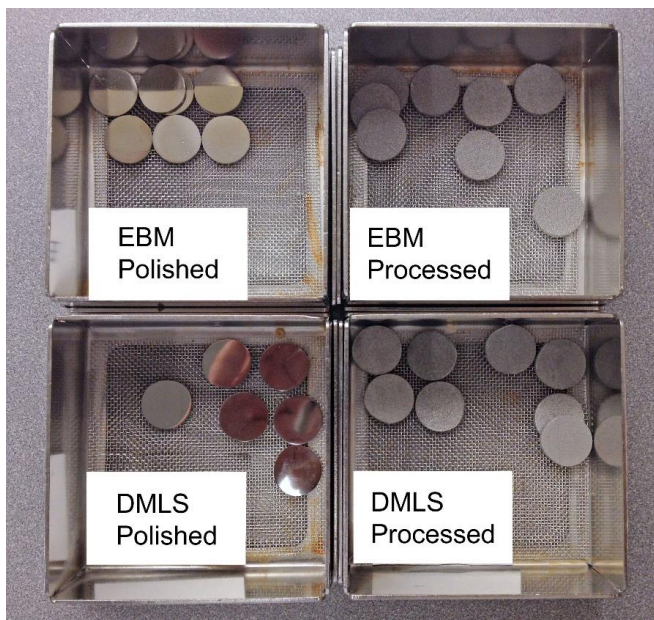
Surface roughness (Ra) was higher for EBM manufactured (Ra 29.94) than DMLS manufactured (Ra 7.867) discs. Polishing lowered the surface roughness (EBM Ra 0.085 and DMLS Ra 0.028). The manufacture of EBM and DMLS discs used different titanium particle sizes, thus resulting in different surface topographies. Polished EBM and DMLS have homogeneous microstructures with some small defect or flaw areas.

Before the actual cytotoxicity test procedure discs and the control construct were sterilised using a dedicated autoclave according to the ISO (ISO 17664:2004) specifications. AM test specimens numbered 30 (EBM as built n = 8, EBM polished n = 8, DMLS as built n = 8, DMLS polished n = 6). Additionally

used were control material specimens. The test specimen nominal dimensions were diameter  $d = 17 \text{ mm}$  and thickness  $2 \text{ mm}$ , representing a surface area of  $560 \text{ mm}^2$ . Figure 12 illustrates a 3D CAD model of a specimen disc structure; Figure 13 shows AM test specimens.



**Figure 12.** AM titanium implant 3D CAD model (Picture: B.Sc. (Tech.) Roy Björkstrand)



**Figure 13.** AM titanium test samples (Picture: Assoc. Prof. Jan Wolff)

Performance of the test procedure in this case study complied with the recommendations of the ISO standards (ISO 10993-1:2009), (ISO 10993-5:2009), (ISO 10993-12:2008). The positive control used was Positive Bioreaction. The Positive Bioreaction test material contains an organo-tin compound; upon release in cell culture tests, this compound causes cell damage. Used as a negative control was high-density polyethylene. High-density polyethylene is considered non-toxic and non-hazardous. Used as a blank control was cell culture medium.

Calculation of the reduction of viability caused by the test item compared to the blank used the following equation:

Viability % =  $100 \times OD_{570e}/OD_{570b}$  where,

$OD_{570e}$  = mean value of the measured optical density of the 100% extracts of the test item,

$OD_{570b}$  = mean value of the measured optical density of the blanks.

According to the ISO standard 10993 when cell viability is reduced to <70% of the blank, the test item is considered to have cytotoxic potential.

Set as 100% was the viability of the blank control, that is, cells cultured with only normal medium. The viability of cells treated with the test item extract, that is, 100% without dilution, was then compared with the viability of the blank. Of the same test specimen, a 50% extract means one volume of test item extract plus one volume of normal culture medium.

This case study revealed all the tested items as non-cytotoxic. Consequently, AM parts as built and surface finished according to described manufacturing practice are safe in clinical use regarding cytotoxicity. Publication 3 presents in detail the cytotoxicity test procedure. The cell viability results of the tested items were as follows:

Ti64 ELI EOS DMLS as built: 89.67%

Ti64 ELI EOS DMLS polished: 77.40%

TiAL6V4 ELI EBM as built: 80.74%

TiAL6V4 ELI EBM polished: 82.65%

Synthes lock mandible plate: 83.30%

Tables 6–9 describe the tested inert implant material manufacturing procedures. Testing concerned the finishing procedures of two different AM technologies and two implant materials, resulting in four combinations and related matrix description with cell data content variations.

**Table 6.** *In vitro* cytotoxicity test case matrix (DMLS, as processed)



	Medical Imaging and 3D Digitising	3D Modelling	Additive Manufacturing	Finishing	Clinical Application
Pre- and Post-operative Models					
Medical Aids					
Tools and Instruments					
Inert Implants					Cytotoxicity test, ISO 10993
Biomanufacturing					

Table 6 relevant cell data content is as follows:

### **Inert implants**

#### 3D Modelling

File format: STL

Disc plate nominal diameter: 17 mm

Disc plate nominal thickness: 2 mm

#### Additive manufacturing

Additive manufacturing technology: Powder bed fusion (DMLS)

Additive manufacturing supplier: EOS Finland

Type of material: Ti64 ELI

Test item surface roughness (Ra): 7,867

#### Clinical application

Cytotoxicity test: ISO 10993

Test result: Non-cytotoxic

**Table 7.** *In vitro* cytotoxicity test case matrix (DMLS, polished)




	Medical Imaging and 3D Digitising	3D Modelling	Additive Manufacturing	Finishing	Clinical Application
Pre- and Post-operative Models					
Medical Aids					
Tools and Instruments					
Inert Implants					Cytotoxicity test, ISO 10993
Biomanufacturing					

Table 7 relevant cell data content is as follows:

## Inert implants

### 3D Modelling

File format: STL

Disc plate nominal diameter: 17 mm

Disc plate nominal thickness: 2 mm

### Additive manufacturing

Additive manufacturing technology: Powder bed fusion (DMLS)

Additive manufacturing supplier: EOS Finland

Type of material: Ti64 ELI

Test item surface roughness (Ra): 7,867

### Finishing

Grinding (FEPA, ISO 6344): P320 – P4000

Final grinding: 3 µm diamond suspension

Test item surface roughness (Ra): 0,028

Purification: Ultrasonic cleaning (ethanol) for three minutes

### Clinical application

Cytotoxicity test: ISO 10993

Test result: Non-cytotoxic

Table 8. *In vitro* cytotoxicity test case matrix (EBM, as processed)



	Medical Imaging and 3D Digitising	3D Modelling	Additive Manufacturing	Finishing	Clinical Application
Pre- and Post-operative Models					
Medical Aids					
Tools and Instruments					
Inert Implants					Cytotoxicity test, ISO 10993
Biomanufacturing					

Table 8 relevant cell data content is as follows:

## Inert implants

### 3D Modelling

File format: STL

Disc plate nominal diameter: 17 mm

Disc plate nominal thickness: 2 mm

### Additive manufacturing

Additive manufacturing technology: Powder bed fusion (EBM)  
 Additive manufacturing supplier: Arcam AB, Mölndal, Sweden  
 Type of material: TiAL6V4 ELI  
 Test item surface roughness (Ra): 29.94

**Clinical application**

Cytotoxicity test: ISO 10993  
 Test result: Non-cytotoxic

**Table 9.** *In vitro* cytotoxicity test case matrix (EBM, polished)




	Medical Imaging and 3D Digitising	3D Modelling	Additive Manufacturing	Finishing	Clinical Application
Pre- and Post-operative Models					
Medical Aids					
Tools and Instruments					
Inert Implants					Cytotoxicity test, ISO 10993
Biomanufacturing					

Table 9 relevant cell data content is as follows:

**Inert implants**

**3D Modelling**

File format: STL  
 Disc plate nominal diameter: 17 mm  
 Disc plate nominal thickness: 2 mm

**Additive manufacturing**

Additive manufacturing technology: Powder bed fusion (EBM)  
 Additive manufacturing supplier: Arcam AB, Mölndal, Sweden  
 Type of material: TiAL6V4 ELI  
 Test item surface roughness (Ra): 29.94

**Finishing**

Grinding (FEPA, ISO 6344): P320 – P4000  
 Final grinding: 3 µm diamond suspension  
 Test item surface roughness (Ra): 0,085  
 Purification: Ultrasonic cleaning (ethanol) for three minutes

## Clinical application




Cytotoxicity test: ISO 10993

Test result: Non-cytotoxic

Process phases such as EBM or DMLS manufacturing, polishing, and sterilisation affect the implant macro-, micro-, and nanostructure. Forged stock titanium-alloy mandible reconstruction plates are commonly used in maxillofacial surgery. The research question associated with this case study was whether EBM and DMLS custom implants would be safe for clinical use, from the point of view of cytotoxicity. In the cytotoxicity test, the reference material was a mass-produced implant. All the test pieces produced and tested in the present study seemed non-cytotoxic; consequently, they are safe for clinical use.

Publication 4 studied geometrical accuracy of medical models. The two variable process phases in the studied manufacturing process were accuracy of 3D model data and AM process. Created for the experiments were three versions of the 3D model (STL format) with different levels of accuracy: 'original', 'moderate' and 'worse'. The AM methods used were material jetting (PolyJet), Powder Bed Fusion (SLS) and Binder Jetting (3DP). The skull model DICOM data used in this study and segmentation procedure using 500 Hounsfield Unit (HU) value with OsiriX 2.7.5 software were fixed for all test trials. Also fixed was the coordinate measuring procedure to measure geometrical accuracy of the final parts. Table 10 presents relevant MAAM matrix cells, in which cells *3D modelling* and *Additive Manufacturing* include variants. In this research case, five different matrix representations would describe the main parameters of materials and methods content data. If all the theoretical combinations were tested, the number of MAAM matrixes would be higher.

**Table 10.** Example MAAM matrix describing medical models accuracy study

	Medical Imaging and 3D Digitising	3D Modelling	Additive Manufacturing	Finishing	Clinical Application
Pre- and Post-operative Models	Dicom				
Medical Aids					
Tools and Instruments					
Inert Implants					
Biomanufacturing					

Many medical studies in clinical scenarios regarding diagnosis, treatment and predicting outcome concern Artificial Intelligence (AI) and Knowledge Management (KM). Ramesh et al. (2004) conclude that AI techniques can

potentially be applied in almost every field of medicine. Dawes and Sampson (2003) have studied KM in clinical practice, and conclude the wide variation in information-seeking behaviour implies a need for further categorisation of information need and information sources. This dissertation presents methodologies for an application-oriented classification of MAAM cases. The aim of the data presentation model is to create building blocks for the development, documentation and learning systems of future medical AM technology applications. Subsequently, the applications would be applicable in clinics, institutions, or company level systems. Future research requires big-data type information, and thus is highly dependent on success to gather an extended classified clinical case data bank. The development of data gathering systems and resource allocations for such activities is challenging, however.

### **3.3 Scientific results and practical implementations**

The two main research questions in this dissertation were 1) to describe a relevant model for MAAM case data structure and 2) to present a model for the management of data variations and process parameters. Answering the first research question involved constructing a MAAM matrix model that combines the presented application-oriented classification system and process model for MAAM. Answering the second research question required implementing clinical and research cases based on the matrix presentation. The process phase principle of the MAAM matrix concept is presented in publication 1 and the extended MAAM matrix is presented in publication 2. Publications 3 and 4 present the variation in options in clinical cases related to matrix cell data content. Presentation of such cell data content has been described in paragraph 3.2.

To enable the collaboration of specialists in this context, Vehviläinen (2011) implemented the MAAM matrix concept as a web software tool. The online platform development included building a viable general-purpose web server and using a content management system to create a dynamic website. The purpose of the system was to demonstrate various possibilities in developing MAAM matrix-based web tools for documentation, collaboration, and viewing clinical cases.

## 4. Conclusions

Within industrial part manufacturing, AM technology is the youngest manufacturing technology group. Subtractive manufacturing, for example, milling, grinding, and turning, is the oldest part fabrication technology group. Formative processes involve casting, bending and similar technologies. AM is considered a game-changing technology in many fields of industry and society (Fawcett & Waller 2014). The first AM technology innovations aimed at manufacturing prototype and concept parts for product development purposes; examples of the first AM technology innovations include vat photopolymerization, that is, stereolithography, and extrusion, that is, fused deposition modelling, FDM. The introduction of five other technology groups soon followed: powder bed fusion, lamination, directed energy deposition, binder jetting, and material jetting. As technology platforms developed, they became application-field diverse. High-end, qualified plastic and metal materials enabled the direct manufacture of qualified components for safety critical industrial and medical applications.

The realisation of physical parts in an AM process is relatively easy. The starting point simply needs digital representation of a part. Digitalised subtractive processes require a process planning phase, which needs a relatively high level of manufacturing technology expertise. Process planning involves choosing cutting tools, along with machining parameters and part fixture planning (Shah & Mäntylä 1995). Applying formative processes normally requires moulds and similar aids. Prior to actual part production, therefore, these moulds and aids must be manufactured, creating additional cost and extra manufacturing logistics. Required for AM is merely a part's 3D model, that is, an STL-file, and AM equipment parameter settings. Thus, AM is clearly easier to apply than conventional manufacturing technologies. Another feature exists that makes AM suitable for medical applications: the capability to realise complicated mechanical structures. Biomechanical structures are complex freeform compositions. Dependent on applied AM technology, such highly complicated structures can be manufactured in an automated processes.

Five application classes for medical applications exist in additive manufacturing. Soon after the first AM technology innovations were presented, Mankovich et al. (1990) reported on the concept of applying stereolithography AM technology to manufacturing preoperative models of patient anatomy.

Materials and AM process development were needed to apply AM in inert implants, special tools and instruments, and medical aids and orthoses use cases. Within these four groups, clinical applications and combinations are diverse; however, the fifth application group, biomanufacturing, relates mainly to research and development phases, with clinical applications being scarce.

The process from medical imaging to clinical applications is divided into five main process steps. The first step is medical imaging and 3D digitising, which highly impact the applicability of imaging data within later steps of MAAM. Imaging process parameters and data handling procedures affect part accuracy and quality issues in later steps of the process (Huotilainen et al. 2013), (Salmi et al. 2013). Medical imaging typically results in patient-specific sliced data in Digital Imaging and Communications in Medicine (DICOM) format. These data are basis for medical 3D modelling, which involves processing imaging data to 3D representation, with further processing according to clinical application requirements. For AM, typical input is an STL file, which defines the geometry of the parts to be manufactured. Finishing and post-processing finalise features and properties of AM parts to be finally implemented in clinical application.

A clear need exists for knowledge management tools to support design and documentation of medical applications of additive manufacturing clinical cases. Both practitioners and authorities, such as FDA, have expressed concerns related to AM applications in medicine (FDA 2017). Many of those concerns relate to safety and quality issues associated with AM manufacturing processes and related work flows. MAAM clinical case design is a typical multidisciplinary task requiring collaboration between various surgical specialities, radiology, and engineering. To support designing MAAM cases, often proposed is expert system technology (Moura et al. 2010). However, cognitive psychologists claim knowledge is clustered in packets, considered to have factual and procedural context, to help us organise, store and place knowledge in a specific context.

Research question 1 of this dissertation was: *What is a relevant model to describe and store application-oriented case data of medical applications of additive manufacturing?* Medical applications of additive manufacturing (MAAM) matrix links the above-mentioned clinical application classes and process phases to a data representation. MAAM matrix is applied both as a clinical case design and documentation tool, consisting of active matrix cells with relevant data content, including parameters and attributes. One or several matrixes describe a case study, and actual data content can be designed according to the initial knowledge modelling purpose. Process phase modelling for pre- and postoperative modelling obviously varies from the modelling of biomanufacturing applications, which may include, for example, *in vitro* bioreactor process phases.

Research question 2 of this dissertation was: *What are the best methods to manage variations of applied technologies and process parameters?* This

dissertation studied feature-based product modelling technologies and applied them in the AM medical application field. Based on these technologies and within the limitations of this dissertation, the issues presented are: MAAM classification, process phases, and matrix system as a tool for clinical documentation system. Additionally presented are practical case studies. Accordingly, this dissertation did not present a complete expert- or reasoning system to support clinical practitioners' work; this is something to focus on in future research. The huge potential for such a matrix tool as presented, however, aims at being a core database structure in this context.

Many multidisciplinary specialist groups are currently developing MAAM applications. Simultaneously, regulatory documents and process requirements for MAAM applications are prepared by authorities responsible for patient safety and clinical regulatory issues. For such authorities, current change is challenging, because they are accustomed to identifying material subtractive and material formative manufacturing processes as methods to manufacture medical devices. Subtractive methods have been developed over tens of thousands of years, and material formative methods over thousands of years. The first additive manufacturing processes were presented in the late 1980s. In a highly dynamic medical application field; consequently, preparation of instructions and regulations for AM clinical cases has happened within a short timeframe. Authorities have already recognised the need to control, for example, process and material parameters when applying AM in medical settings. Systematic approaches and detailed instructions are under preparation. Accordingly, this dissertation provides a schematic construction block to generate tools for future safe medical applications of AM.



# References

- Abbaszadeh, F. et al. (2004). Novel Methodology in design of custom-made hip prosthesis. *Innovative Developments in Design and Manufacturing*. Bártolo et al. (eds.), Taylor & Francis Group, London, pp. 3–12., ISBN 978-0-415-87307-9.
- Abdulsalam, et al. (2017). Topology Optimization to reduce the stress shielding effect for orthopedic applications. *Procedia CIRP* 65 ( 2017 ) 202 – 206, 10.1016/j.procir.2017.04.032.
- Ahn, H.B., et al. (2008). Prediction of enophthalmos by computer based volume measurement of orbital fractures in a Korean population. *Ophthalmic Plastic & Reconstructive Surgery*, 2008, vol. 24 No. 1, pp. 36-9.
- Akmal J.S., et al. (2018). Implementation of Industrial Additive Manufacturing: Intelligent Implants and Drug Delivery Systems. *J. Funct. Biomater.* 2018, 9(3), 41.
- Andre, J.C., Mehaute, A.L., Witte O.D. (1984). Device for producing a model of an industrial part. French patent FR2567668, 1986.
- Badylak, S.F. et al. (2012). Engineered whole organs and complex tissues. *Lancet*, 2012;379:943-952.
- Bandyopadhyay, A. et al. (2009). Application of laser engineered net shaping (LENS) to manufacture porous and functionally graded structures for load bearing implants. *J Mater Sci Mater Med* 2009;20:S29–34.
- Bártolo, P.J. et al. (2011). Biofabrication Strategies for Tissue Engineering. *Advances on Modeling in Tissue Engineering*, Springer, 10.1007/978-94-007-1254-6.s.
- Berry, E. et al. (1997). Preliminary experience with medical applications of rapid prototyping by selective laser sintering. *Medical Engineering and Physics*, 1997 Jan;19(1):90-6.
- Bibb, R. et al. (2009). Rapid manufacture of custom-fitting surgical guides. *Rapid Prototyping J.* 2009;15:346-354.
- Bibb, R., Winder, J. A. (2010). Review of the issues surrounding three-dimensional computed tomography for medical modeling using rapid prototyping techniques. *Radiography*. 2010;16:78-83.

- Björkstrand, R. et al. (2010). 3D-Digitalization of ankle movement and 3D-CAD-method for patient specific external ankle support development and Rapid Manufacturing. *Innovative Developments in Design and Manufacturing. Advanced Research in Virtual and Rapid Prototyping*, pp. 199-204. Taylor & Francis Group, London, 2010.
- Cabibihan, J.J. (2011). Patient-specific prosthetic fingers by remote collaboration — a case study. *PLoS One*. 2011;6(5):e19508. doi:10.1371/journal.pone.0019508.
- Chahine, C. et al. (2008). The design and production of Ti-6Al-4V ELI customized dental implants. *JOM Journal of the Minerals, Metals & Materials Society*, Vol. 60 No. 11, pp. 50-5.
- Ciocca, L. et al. (2009). CAD-CAM construction of an auricular template for craniofacial implant positioning: a novel approach to diagnosis. *Eur J Radiol*. 2009;71:253-256.
- Ciocca, L. et al. (2011). Direct metal laser sintering (DMLS) of a customized titanium mesh for prosthetically guided bone regeneration of atrophic maxillary arches. *Med Biol Eng Comput*. 2011;49:1347-52.
- Crump, S. (1989). U.S. Patent 5121329 A, 1992, Apparatus and method for creating three-dimensional objects.
- Cui, X., Boland, T. (2009). Human microvasculature fabrication using thermal inkjet printing technology, *Biomaterials*, 30, 6221-6227.
- Dawes, A.N., Sampson, C. (2016). Knowledge management in clinical practice: a systematic review of information seeking behavior in physicians. *International Journal of Medical Informatics*, [https://doi.org/10.1016/S1386-5056\(03\)00023-6](https://doi.org/10.1016/S1386-5056(03)00023-6), 2003.
- Domingos, M. et al. (2009) Polycaprolactone scaffolds fabricated via bioextrusion for tissue engineering applications. *Int. J. Biomater*. 2009, 239643.
- Deckard, C. (1989). US Patent 4863538 A, 1989, Method and apparatus for producing parts by selective sintering.
- Eppley, B.L. (2002). Craniofacial reconstruction with computer-generated HTR patient-matched implants: use in primary bony tumor excision. *Journal of Craniofacial Surgery*, vol. 13 No. 5, pp. 650-7.
- EU (2017). EU Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices. Available at: [www.eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN](http://www.eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN).
- Fawcett, S.E., Waller, M.A. (2014). Supply Chain Game Changers—Mega, Nano, and Virtual Trends—And Forces That Impede Supply Chain Design (i.e., Building a Winning Team). *Journal of Business Logistics*, 2014, 35(3): 157-164.

- FDA (2017). U.S. Department of Health and Human Services Food and Drug Administration (FDA), Technical Considerations for Additive Manufactured Devices, Draft Guidance for Industry and Food and Drug Administration Staff, 2017. Available at: [www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM499809.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM499809.pdf)
- Freudenstein, M. (2017). The “medical grade” polymer dilemma. *The magazine for Europe’s plastic processors*, June/July 2017, vol. 19, Issue 03, pp. 8-9.
- Gibbs, D.M.R. et al. (2014). Hope versus hype: what can additive manufacturing realistically offer trauma and orthopaedic surgery? *Regenerative Medicine*, Vol. 9, no. 4, 2014.
- Gibson, I., Rosen, D.W., Stucker, B. (2009). *Additive Manufacturing Technologies: Rapid Prototyping to Direct Digital Manufacturing*. New York, NY: Springer; 2009.
- Haslauer, C.M, et al. (2010). In vitro biocompatibility of titanium alloy discs made using direct metal fabrication. *Med Eng Phys*. 2010;32(6):645–52.
- Hull, C. (1986). U.S. Patent 4,575,330, 1986, Apparatus for Production of Three-Dimensional Objects by Stereolithography.
- Huutilainen, E. et al. (2013). Imaging requirements for medical applications of additive manufacturing. *Acta Radiologica*, 2013, doi:10.1177/0284185113494198, 2013.
- International Organization for Standardization. ISO 17664:2004 Sterilization of medical devices – Information to be provided by the manufacturer for the processing of resterilizable medical devices.
- International Organization for Standardization. ISO 10993 - 1 (Fourth edition 2009-10-15): Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.
- International Organization for Standardization. ISO 10993 - 5 (Third edition 2009-06-01): Biological evaluation of medical devices – Part 5: Test for in vitro cytotoxicity.
- International Organization for Standardization. ISO 10993 - 12 (Third edition 2007-11-15; Corrected version 2008-02-15): Biological evaluation of medical devices – Part 12: Sample preparation and reference materials.
- International Organization for Standardization. ISO/ASTM 52900:2015: Additive manufacturing – General principles – Part 1: Terminology.
- International Organization for Standardization, ISO 6344-1:1998: Grain size distribution test.

- Janssens, M., Poukens, J. (2007). Rapid technologies in medicine: what can, can't be done and why. The International Conference on Competitive Manufacturing; January 31-February 6; Stellenbosch, South Africa; 2007.
- Joffe, L. (2003). Current products and practice in visalign: early experiences. *J. Orthod.* 30, 348–352. 2003, doi:10.1093/ortho/30.4.348.
- Kalender, W.A. (2005). *Computed Tomography: Fundamentals, System Technology, Image Quality, Applications*. 2nd ed., Publicis Corporate Publishing, Erlangen.
- Kamer, L. et al. (2006). Three-dimensional statistical shape analysis – a useful tool for developing a new type of orbital implant, AO Foundation, New Products Brochure 2/06, pp. 20-1.
- Kasanen, E. et al. (1993). The Constructive Approach in Management Accounting Research. *Journal of Management Accounting Research* 5, 1993, pp. 243-264.
- Kim, S.S. et al. (1998). Survival and function of hepatocytes on a novel three-dimensional synthetic biodegradable polymer scaffolds with an intrinsic network of channels, *Annals of Surgery*, 228, 8-13.
- Kondor, S. et al. (2013). On Demand Additive Manufacturing of a Basic Surgical Kit. *Journal of Medical Devices*, 2013, 030916-1.
- Kontio, R. et al. (2012). Designing and additive manufacturing a prototype for a novel instrument for mandible fracture reduction. *Surgery*. 2012;S1:002. doi:10.4172/2161-1076.S1-002.
- Kulkarni, Y.H. et al. (2016). Leveraging feature information for defeaturing sheet metal feature-based CAD part model. *J Computer-Aided Design and Applications*, vol. 13, 2016, 10.1080/16864360.2016.1168238.
- Kruth, J.P. (1991). Material ingress manufacturing by rapid prototyping techniques. *Annals of CIRP* 1991;40:603-614.
- Laakko, T. et al. (1990). Feature Models for Design and Manufacturing. *Proceedings of the Hawaii International Conference on System Sciences (HICSS-23)*, Jan. 1990.
- Labadie, R.F. et al. (2008). Clinical validation of percutaneous cochlear implant surgery: initial report. *Laryngoscope*. 2008;118:1031-1039.
- Lam, C.X. et al. (2002). Scaffold development using 3D printing with a starch-based polymer. *Materials Science and Engineering*, 20, 49-56.
- Lamecker, H. et al. (2007). A method for the three-dimensional statistical shape analysis of the bony orbit, in Freysinger, W., Weber, S. and Caversaccio, M. (Eds), *Computer Aided Surgery Around the Head: 4th International Conference*, Innsbruck, Austria, February 21-24, 2007, pp. 94-7.
- Langer, R., Vacanti J.P. (1993). *Tissue Engineering*. *Science* 1993; 260: 920–6.

- Laroche, F. et al. (2016). Accessing enterprise knowledge: A context-based approach. *CIRP Annals - Manufacturing Technology*, vol 65, 10.1016/j.cirp.2016.04.136.
- Levy, G.N., Schindel, R. & Kruth, J.P. (2003). Rapid Manufacturing and Rapid Tooling with Layer Manufacturing (LM) Technologies, State of The Art and Future Perspectives. *Annals of the CIRP*, 2003, vol. 52, issue 2, pp 605.
- Levy, R.A. et al. (1997). CT-generated porous hydroxyapatite orbital floor prosthesis as a prototype bioimplant. *American Journal of Neuroradiology*, 1997, 18, 1522-1525.
- Lindahl, J. et al. (2014). US patent US2014257286 (A1), 2014. Anatomically customized and mobilizing external support, method for manufacture.
- Mankovich, N.J., Cheeseman A.M., Stoker N.G. (1990). The display of three-dimensional anatomy with stereolithographic models. *Journal of Digital Imaging*, 1990 Aug;3(3):200-3.
- Masuda, S. et al. (2008). Cell sheet engineering for heart tissue repair. *Advanced Drug Delivery Reviews* 60 (2008) 277-285.
- McDonald, J.A. et al. (2001). *Rapid Prototyping Casebook*. London, England, Professional Engineering; 2001.
- Melchels, F.P.W. et al. (2012). Additive manufacturing of tissues and organs. *Progress in Polymer Science*, 37, 1079-1104.
- Miller, J.R., Derakhshan, M. (2002). The Invisalign system: case report of a patient with deep bite, upper incisor flaring, and severe curve of Spee. *Semin Orthod*. 2002;8:43-50.
- Moura, C.S. et al. (2010). Intelligent biopolymer selector system for medical applications. *Innovative Developments in Design and Manufacturing – Bártolo et al. (eds.)*, pp. 81-87. Taylor & Francis Group, London, ISBN 978-0-415-87307-9.
- Murr, L.E. et al. (2012). Next Generation Orthopaedic Implants by Additive Manufacturing Using Electron Beam Melting. *International Journal of Biomaterials*, vol 2012, doi:10.1155/2012/245727.
- Mäkitie A.A. et al. (2016). 3D printing for restoration of the donor face: a new digital technique tested and used in the first facial allotransplantation patient in Finland. *J Plast Reconstr Aesthet Surg*. 2016 Oct 5. pii: S1748-6815(16)30329-1. doi: 10.1016/j.bjps.2016.09.021.
- Mäntylä, M. et al. (1987). A Prototype System for Generative Process Planning of Prismatic Parts. *Modern Production Management Systems*, North-Holland, Amsterdam, 1987. Proc. APMS '87.

- Ng, P. et al. (2002). Prosthetic sockets fabrication using rapid prototyping technology. *Rapid Prototyping J.* 2002;8:53-59.
- Olszewski, R., Szymor P., Kozakiewicz M. (2014). Accuracy of three-dimensional, paper-based models generated using a low-cost, three-dimensional printer. *Journal of Cranio-Maxillofacial Surgery*, vol. 42, 8 (2014): 1847-1852.
- Paatela, T. et al. (2012). Fresh allograft threatment of large osteochondral defect – case report. *Finnish orthopedigs and traumatology*, vol. 35, 2-2012.
- Poukens, J., Haex, J., Riediger, D. (2003) The use of rapid prototyping in the preoperative planning of distraction osteogenesis of the cranio-maxillofacial skeleton. *Computer Aided Surgery*. 2003;8(3):146-54.
- Poukens, J. et al. (2008). A classification of cranial implants based on the degree of difficulty in computer design and manufacture. *Int J Med Robot Comput Assist Surg* 4:46-50, 2008.
- Probst, F.A. et al. (2010). Calvarial reconstruction by customized bioactive implant. *Handchir Mikrochir plast Chir*, vol. 42 No. 6, pp. 369-73.
- Ramesh, A.N. et al. (2004). Artificial intelligence in medicine. *Annals of the Royal College of Surgeons of England*, 2004; 86: 334–338, doi 10.1308/147870804290.
- Robiony, M. et al. (2007). Virtual reality surgical planning for maxillofacial distraction osteogenesis: the role of reverse engineering, rapid prototyping and cooperative work. *J Oral Maxillofac Surg*. 2007;65:1198-1208.
- Rouse, S. (2009). At the speed of light – Additive manufacturing of custom medical implants. *The TCT Magazine*, 2009, vol. 17, no.6, pp. 47-50.
- Salmi, M. et al. (2012). Patient-specific reconstruction with 3D modelling and DMLS additive manufacturing. *Rapid Prototyping Journal*, vol. 18 Iss: 3 pp. 209 – 214, doi: 10.1108/13552541211218126.
- Salmi, M. et al. (2012). Rapid tooling method for soft customized removable oral appliances. *Open Dent J.* 2012;6:85-89.
- Salmi, M. et al. (2013). A digital process for additive manufacturing of occlusal splints: a clinical pilot study. *J. R. Soc. Interface* 2013 10.
- Salmi, M. et al. (2013). Accuracy of medical models made by additive manufacturing (rapid manufacturing). *Journal of Cranio-Maxillo-Facial Surgery*, 41:603-609, 2013, doi: 10.1016/j.jcms.2012.11.041.
- Salmi M. (2016). Possibilities of Preoperative Medical Models Made by 3D Printing or Additive Manufacturing. *Journal of Medical Engineering*, vol. 2016, 6191526.
- Sanford, A. (1985). *Cognition & Cognitive Psychology*, Basic Books, New York.

- Sarment, D. P. et al. (2003). Accuracy of implant placement with a stereolithographic surgical guide. *International Journal of Oral & Maxillofacial Implants*, vol. 18, No. 4, pp. 571-577.
- Schantz, J.T. et al. (2003). Repair of calvarial defects with customised tissue-engineered bone grafts II. Evaluation of cellular efficiency and efficacy in vivo. *Tissue Engineering*, 2003, vol. 9, pp. 127-39 (supplement 1).
- Sekou, S. et al. (2009). Rapid prototyping assisted surgery planning and custom implant design. *Rapid Prototyping J.* 2009;15:19-23.
- Shah, J.J., Mäntylä, M. (1995). *Parametric and Feature-Based CAD/CAM - Concepts, Techniques, Applications*. John Wiley & Sons, Inc. USA, 1995.
- Shah, J.J. et al. (1998). Functional Requirements and Conceptual Design of the Feature-Based Modeling System. *Computer Aided Eng. Journal*, Inst. of Elect. Eng., U.K., Feb.1988.
- Siblani, A. (2017). 3D Printers used to manufacture medical parts should be regulated. *TCT Magazine*, blog April 10, 2017. Available at: <https://www.tctmagazine.com/tctblogs/guest-blogs/3d-printers-used-to-manufacture-medical-parts-should-be-regu/>
- Sidambe, A.T. (2014). Biocompatibility of advanced manufactured titanium implants—a review. *Materials* ISSN 1996-1944. *Materials*. 2014;7:8168–88. doi:10.3390/ma7128168.
- Singare, S. et al. (2005). Customized design and manufacturing of chin implant based on rapid prototyping. *Rapid Prototyping Journal*, 2005, vol. 11 No. 2, pp. 113-18.
- Singare, S. et al. (2009). Rapid prototyping assisted surgery planning and custom implant design. *Rapid Prototyping Journal*, 2009, vol. 15 No. 1, pp. 19-23.
- Smith, M.H., et al. (2007). Computed tomography-based tissue-engineered scaffolds in craniomaxillofacial surgery. *Int. J. Med. Robot. Comput. Assist. Surg.*, vol. 3, pp. 207-16.
- Stübinger, S. et al. (2013). Histological and biomechanical analysis of porous additive manufactured implants made by direct metal laser sintering: A pilot study in sheep. *J Biomed Mater Res Part B* 2013;101B:1154–1163.
- Sun, W. et al. (2005). Bio-CAD modeling and its applications in computer aided tissue engineering. *Computer-Aided Design*, vol. 37 No. 11, pp. 1097-114.
- Tuomi, J. et al. (2014). A Novel classification and online platform for planning and documentation of medical applications of additive manufacturing. *Surgical Innovation*, March 9, 2014, doi: 10.1177/1553350614524838.
- Tuomi, J. et al. (2017). In vitro cytotoxicity and surface topography evaluation of additive manufacturing titanium implant materials. *Journal of Materials*

Science: Materials in Medicine, February 14, 2017, doi: 10.1007/s10856-017-5863-1.

Tan, J.Y. et al. (2012). Esophageal tissue engineering: an in-depth review on scaffold design. *Biotechnol Bioeng.* 2012;109:1-15.

Vehviläinen, J. (2011). Process and Web Application Development of Medical Applications of Additive Manufacturing. Masters theses, Aalto University, 2011.

Williams, J.M. et al. (2005). Bone tissue engineering using polycaprolactone scaffolds fabricated via selective laser sintering. *Biomaterials* 26, 4817-4827.

Winder, R.J., Bibb, R. (2005). Medical rapid prototyping technologies: state of the art and current limitations for application in oral and maxillofacial surgery. *J Oral and Maxillofac Surg.* 2005;63:1006-1015.

Wohlers, T. (2006). Wohlers Report, Wohlers Report, Rapid Prototyping & Tooling State of the Industry Annual Worldwide Progress Report. Wohlers Associates, OakRidge Business Park, 1511 River Oak Drive, Fort Collins, Colorado, USA, 2006, ISBN 0-9754429-2-9. pp. 21-22.

Wohlers, T. (2017). Wohlers Report 2017, 3D Printing and Additive Manufacturing State of the Industry, Annual Worldwide Progress Report. Wohlers Associates, OakRidge Business Park, 1511 River Oak Drive, Fort Collins, Colorado, USA, 2017, ISBN 978-0-9913332-3-3. pp. 22-24.

Yan, Y. et al. (2003). Research and application on biomanufacturing. The First International conference on Advanced Research in Virtual and Rapid Prototyping, October 1-4, 2003, Leiria, Portugal.

Additive Manufacturing, AM, also known as 3D printing, is considered a game-changing technology in many fields of industry and society. Specific feature that makes AM suitable for medical applications is the capability to realise complicated mechanical structures. Both practitioners and authorities have expressed concerns related to AM applications in medicine. Many of those concerns relate to safety and quality issues associated with AM manufacturing processes and related work flows. For stakeholders, current change is challenging, because they are accustomed to identifying material subtractive and material formative manufacturing processes as methods to manufacture medical devices.



ISBN 978-952-60-8172-4 (printed)  
ISBN 978-952-60-8173-1 (pdf)  
ISSN 1799-4934 (printed)  
ISSN 1799-4942 (pdf)

**Aalto University**  
**School of Engineering**  
**Mechanical Engineering**  
[www.aalto.fi](http://www.aalto.fi)

**BUSINESS +  
ECONOMY**

**ART +  
DESIGN +  
ARCHITECTURE**

**SCIENCE +  
TECHNOLOGY**

**CROSSOVER**

**DOCTORAL  
DISSERTATIONS**