Cranfield University

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THE SELECTION AND APPLICATION OF DESIGN METHODOLOGIES FOR THE DESIGN OF BONE TISSUE SCAFFOLDS

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ABSTRACT

Research motivation: Bone tissue scaffolds offer a way forward in a strategy to change from tissue replacement to tissue regeneration. Bone tissue scaffolds are a combination of a physical construct, with clearly defined three-dimensional spatial properties, and biological cells. The microstructure of this construct is the bridge between the physicochemical properties of the scaffold and the cellular processes responsible for tissue regeneration.

Gap statement: A formal design methodology has yet to be applied for the design of bone tissue scaffolds

Aims and objectives:

The aim of this research thesis is to select and apply design methods to the design of bone tissue scaffolds.

The objectives are:

1. Review the current state of the art in design theory and methodologies for successful applications of design methods
2. Identify which design techniques are currently implemented in bone tissue scaffold design
3. To apply appropriate design methods to the design of bone tissue scaffolds
4. To validate the design outputs via a survey of expert opinion

Methodologies: The following design methodologies were applied; Quality Function Deployment (QFD) and Theory of Inventive Problem Solving (TRIZ), an expanded house of quality, three-dimensional relationship technology chart (3DRTC) and Axiomatic Design (AD).

Results: The multi-tiered literature review for design methodologies, firstly, identified the above design methods and, secondly, found no reason to exclude them for consideration as design methods for bone tissue scaffolds. The second literature review identified extensive computer-image-based-design as the current most advanced design method in the domain for bone tissue scaffolds. No formal design methods were in use.

The first Quality Function Deployment method identified conflicts in the design which were used as inputs into TRIZ to generate potential solutions. The second QFD approach identified an extensive list of design requirements along with target engineering metrics. The three-dimensional relationship technology chart proposed how to organise design requirements into a scaffold design based upon differing scaffold design strategies. In Axiomatic Design, two approaches were followed: the first based upon percolation theory and the second based upon time-dependent behaviour. These models proposed designs at a higher level of abstraction for scaffold designers, rather than the providing the more practical solutions achieved by the QFD and 3DRTC approaches.

Validation: The output of the design methodologies were validated by a survey of expert opinion. The responses indicated that both Axiomatic Design and an expanded house of quality tool offered innovation, and enhancement to, the field of bone tissue scaffold design.

Conclusion: Formal design methodologies such as Axiomatic Design and Quality Function Deployment provide design solutions which offer innovation, and enhancement to, the field of bone tissue scaffold design.

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I owe my deepest gratitude to my friends Diego Lombetti and Lara Berroth for their motivation and support and, to my parents for their patience and belief.

"The Journey is the Reward"

Chinese Proverb

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1 Introduction

This chapter begins with an overview of the current market demand and is developed further by describing where bone tissue scaffolds are situated in relation to current alternatives in tissue engineering and regenerative medicine. The research motivation, problem statement and research goals are presented. The research strategy by which this goal is sought to be achieved and the finally the layout of this research thesis is also described.

1.1 Research Background

This section describes the concept and background for bone tissue scaffolds. The bone tissue scaffold concept was identified at the outset of the research and is the focus on which the thesis undertaken is based upon.

1.1.1 The potential market demand for bone tissue scaffolds

In a report commissioned by Global Industrial Analysts the market share for bone grafts is predicted to reach $2.3 billion by 2017[1]. One of the many bone graft substitutes are bone cements and putties. According to Orthopedic Network News these cements accounted for an estimated $396.5 million in 2010 increasing from $136.3 million in 2000 in the US alone[2]. This is a substantial market share of the overall bone graft market with four manufacturers (Stryker, Zimmer, Depuy and Biomet) supplying 96% of all cements to US hospitals[2].

[1] http://www.strategyr.com/Bone_Grafts_Market_Report.asp?gclid=CNCNnvTllLMCFe_MtAodgCgANg
[2] http://spine.orthopedicnetworknews.com/archives/onn214s7.pdf
Checked 21/10/2012

1.1.2 The bone graft treatment strategy

Bone grafts are used to repair bone defects resulting from injury or disease (Bohner, 2010). These include procedures such as spinal fusions, revision surgeries, healing of non-union fractures and void filling following tumour resections (Clarke et al., 2011). The choice of graft is between allografts or autografts (Laurencin et al., 1999).

Allogenic bone grafts are sourced from deceased donors both human and animal and unlike autografts benefit by providing various shapes and sizes with no need to sacrifice a host harvest site and no donor-site morbidity (Boyce et al., 1999; Greenwald et al., 2001). Despite Allograft distribution being controlled via regional tissue banks, there is both a risk of infectious disease transmission (spongiform encephalopathies (Clarke et al., 2011)) as well as irradiation protocols potentially adversely altering graft biochemical properties (Greenwald et al., 2001).

Allograft bone is also in short supply (Galea et al., 1998). Conversely the *in vivo* performance of autografts sets the benchmark that both allografts and bone graft substitutes seek to emulate (Greenwald et al., 2001). This is due to autograft bone integrating well with the surrounding bone and implants at the site of defects (Kretlow et al., 2009). However the supply of autograft material is limited due to restrictions on harvesting sites from patients, particularly the elderly (Clarke et al., 2011), and the problem of donor site morbidity (Laurencin et al., 1999).

Xenogenic grafts (bone harvested from a different species) like allografts offer a large supply of bone but at risk of bone spongiform encephalopathy (BSE) and immunologic rejection (Kretlow et al., 2009). Therefore biomaterials offer an alternative course of treatment.

1.1.3 Bone graft substitutes

Traditional calcium phosphate cements (CPC) have been used since 1982 (Dorozhkin, 2010; Barrère et al., 2006). Recently, it has been found that the blending of bone marrow with acrylic bone cement has shown promise for bone augmentation in osteoporotic patients (Arens et al., 2011). Effective osteoinduction and osteoconduction are key components in bone regeneration (Greenwald et al., 2001).

A sketch of a Bone Tissue Scaffold concept filed for patent is shown in Figure 1 below to provide a visual example[3] of what may be described as a scaffold.

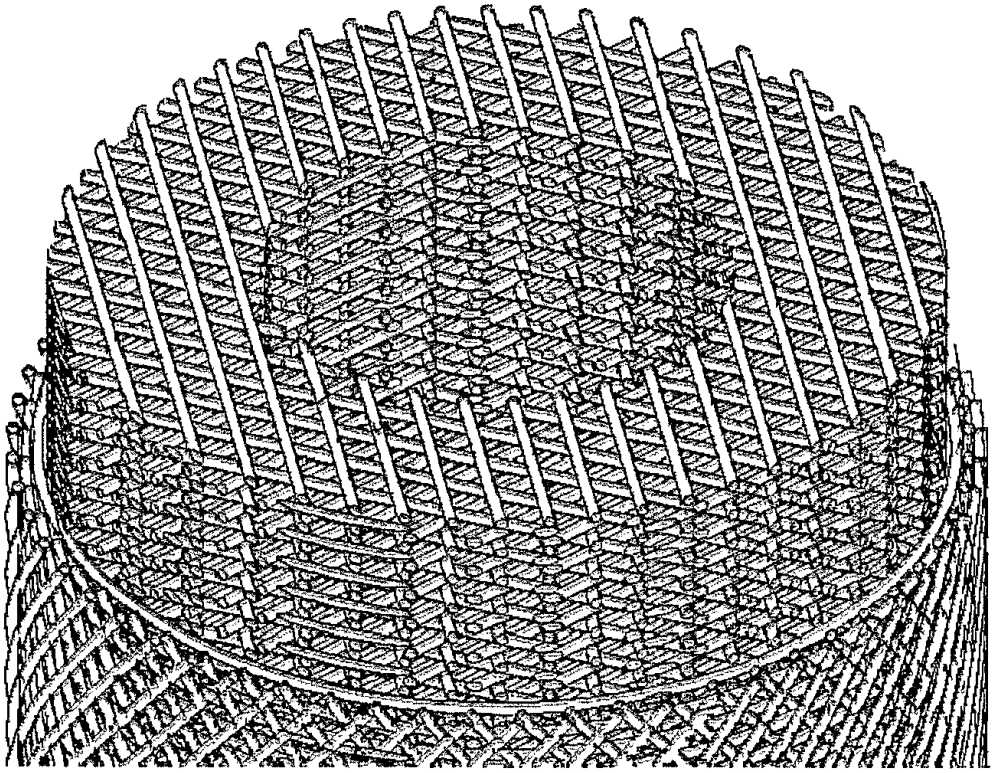


Figure 1. Bone tissue scaffold concept diagram from patent US 20110307073 A1[3]

The purpose of the scaffold in Figure 1 is to provide a specifically designed architecture intended to aid in the regeneration of bone. The mesh like structure is provides a balance between structural integrity and an environment in which bone cells may attach and proliferate into orchestrated tissue regeneration.

[3] http://www.google.com/patents/US20110307073

1.2 Research Motivation

The aim of therapeutic tissue engineering is to restore damaged tissue to its original state and function in order to reduce the demand placed upon transplantation and joint replacements (Mahony and Jones, 2008; Langer and Vacanti, 1993). Key contributors to achieving this aim are artificial constructs termed "scaffolds". The purpose of these scaffolds is to provide an environment that encourages repair of damaged tissue (Chen et al., 2011). However despite the potential that scaffolds offer, they are still far from being implemented in clinical practice (Sanz-Herrera et al., 2010).

To achieve this, optimisation of the architecture of the bone substitute, scaffold is required (Bohner, 2010). The term architecture is used as a catchall term to describe the scale of porosity (10 to 1000 μm) within a tissue scaffold (Hollister, 2005). For the purposes of this thesis the architecture is referred to as the microstructure. It allows for the design considerations beginning at geometric concepts such as shape and size of void spaces, leading to tortuosity and permeability.

The microstructure of a bone tissue scaffold is important as it dictates the local environment for tissue regeneration. The microstructure acts in concert its compositional material to co-ordinated partial mechanical function, a defined internal architecture and ion release. The criteria for an ideal scaffold are well cited (119 citations in Scopus) (Jones and Hench, 2003c).

1.3 Research Question

Based upon the research motivation the following research question can be asked:

"Can a design method be selected and applied to design future bone tissue scaffolds?"

This question will be answered by objective one below.

1.4 Research goals

The aim of this research thesis is to *'select and apply design methods to the design of bone tissue scaffolds'*.

The objectives are:

1. Review the current state of the art in design theory and methodologies for successful applications of design methods (Chapter 2)
2. Identify which design techniques are currently implemented in bone tissue scaffold design (Chapter 3)
3. To apply appropriate design methods to the design of bone tissue scaffolds (Chapters 4-8)
4. To compare the outputs of these design methods (Chapter 9)

1.5 Research strategy

To address the aims and objectives of this thesis five main research phases are proposed in Figure 2. The design outputs are were validated by a survey of expert opinion.

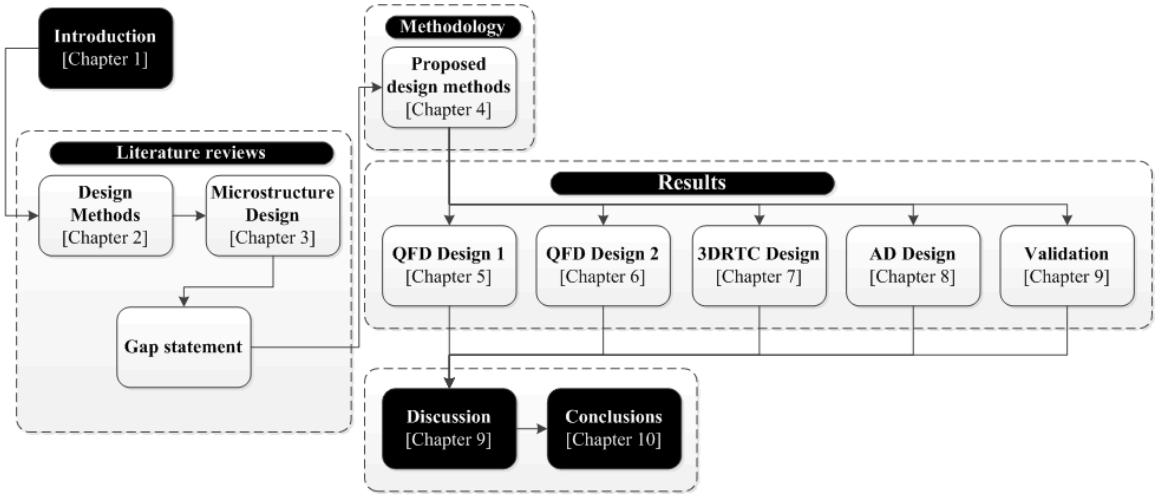


Figure 2. Research strategy for thesis.

1.6 Research contributions

The research contribution of this thesis is to firstly, produce microstructure designs for a bone tissue scaffold that advances the bone tissue scaffold concept. Secondly, increase the awareness of the design methods themselves into the field of tissue engineering so that future researchers are able to implement them for their own scaffold design research.

1.7 Thesis structure

This thesis is divided into eleven chapters as shown in Figure 2.

Chapter 1: This is the introduction to the thesis. An overview of the demand and what is currently known about bone tissue scaffolds is reviewed

Chapter 2: This chapter is an in depth review of current design philosophies, themes and methodologies. Based upon the review and analysis, several design methods are selected to begin to address the problem statement

Chapter 3: This chapter reviews the current design methods used for scaffold design. Based upon these findings the research gap statement is stated

Chapter 4: This chapter contains the detailed description of how the selected design methodologies that were applied for the design of a bone tissue scaffold

Chapters 5 – 8: The design outputs are presented in these chapters. Each chapter presents a single design output

Chapters 9: This chapter describes how the design outputs were validated by a survey of expert opinion

Chapters 10: The discussion interprets the design outputs followed by discussion of the validation before commenting on the future direction of bone tissue scaffolds

Chapter 11: The thesis is concluded with a summary of the research findings and their contributions to knowledge

1.8 Summary

This chapter sets the foundation for the rest of the research thesis. An overview of the current market demand was covered, followed by the motivation for research, a problem statement, the aims and objectives and overall strategy to be implemented for this thesis.

2 Design theories and methodologies

This chapter is the first step towards establishing the research goals of the thesis. An overview of design theory and methodologies are presented from which three were then identified and selected. In order to identify if there were any properties of these particular design methods which would make them unsuitable for the application, a review of the current literature reviews for each of these design methods was performed. A subsequent review of cited examples of product design and development was conducted to determine if any specific caveats were required for individual design methods prior to application. This chapter ends with a critical analysis of the design methodologies.

2.1 Definitions

Design theory: the understanding of design at a conceptual/abstract/academic level

Design methodology: an available pool of methods, which when applied impart the practical act of how to design

2.2 Introduction

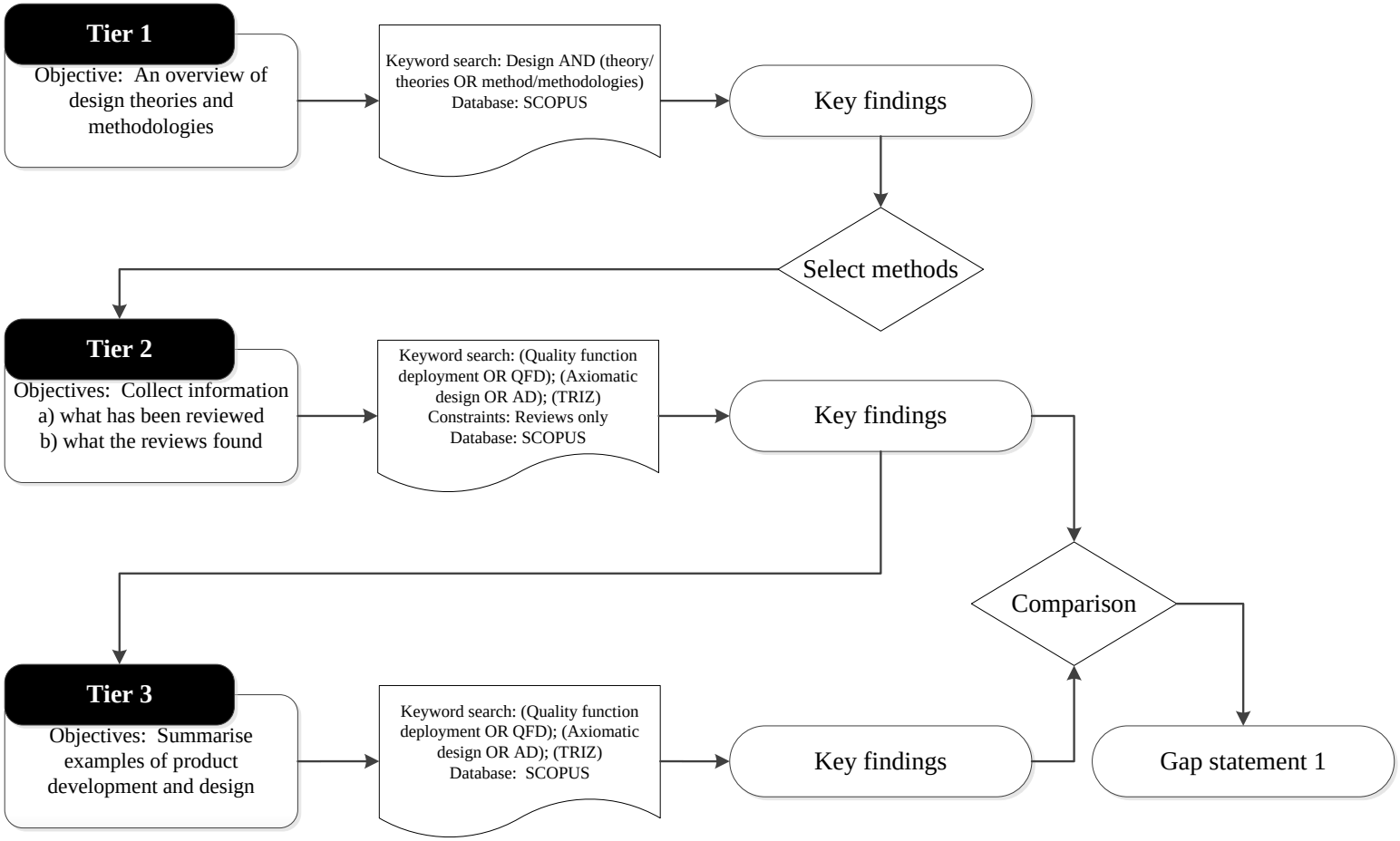


Figure 3. A summary flow diagram showing the multi-tiered structure of the Chapter 2 literature review.

2.3 Research methodological approach

The research methodological approach in this thesis is based upon a multi-tiered literature review (Figure 3). The purpose of which was firstly to establish what had been reviewed previously and secondly to begin to develop the domain knowledge required in the field of design theory and methodology. The following tiers were implemented in order to arrive at the thesis gap statement.

Tier 1: Identify the general literature reviews in the field of design theory and methodology. This was to establish the wider system of interest in terms of general design theories and to see if previous categories of design methods existed. Upon this information, an informed decision could be made for the basis for the outright exclusion of any design methods for the basis of the tier 2 review.

Tier 2: Reduce the system of interest by focusing upon a selection of design methods and identify the current state of the art in literature reviews for each. This was to establish the general capabilities of the design methods and establish the whether or not any should be further excluded.

Tier 3: An analysis of the current state of the art in the application of each of the selected methods. Having selected a number of design methodologies each was analysed in terms of product, service development or design. The intent was to assess the capability of each method in terms of design by investigating the methodological approaches and design focuses. Any prerequisites or caveats for individual design methods were identified.

2.3.1 Methodology for multi-tiered literature reviews

The methodology used to collect the data for the multi-tiered thesis review is stated below. For all three tiers the online scientific search engine 'SCOPUS' was used. The decision was made to tabulate data about the publications where possible for ease of comparison and presentation.

Tier 1: Combinations and variations on the following root words 'design, theory, and method' were used. The search was constrained solely to review publications. The key finding for each review were discussed along with any criteria that substantiated their exclusion. Three design methodologies were selected.

Tier 2: Key word searches for "Quality Function Deployment", "Axiomatic Design", and the abbreviations "AD", "QFD", and "TRIZ" were performed, again with the review constraint applied. The additional search algorithm within SCOPUS that suggested alternative publications was also taken advantage of. This led to suggested examples of hybrid methods which were then also included in the review. Literature reviews for each of the selected methods were analysed and conclusions summarised.

Tier 3: Key word searches for "Axiomatic Design", "Quality Function Deployment", and the abbreviations "AD", "QFD", and "TRIZ" were performed. An initial overview of the publications revealed several types of design method type research. Broadly speaking, two categories existed. The first consisted of research into the methods, proposals for improving or developing the method from a conceptual perspective, and the second category consisted of products or systems that were redesigned, reverse engineered, or systematically analysed via these design methods. Examples of the first category included attempts to integrate fuzzy logic into QFD. However the literature review selected publications only from the second category.

In order to organise the tier 3 findings, the decision was made to categorise the information according to area of interest, inputs and outputs, collection method for the inputs, how the findings were validated and the recommendations for the design methodology.

2.4 Current reviews of design theory and methodology (Tier 1)

Design theory and methodology reviews have previously sought to categorise the various methods behind the cognitive processes involved in creative thinking and innovation.

Finger and Dixon (1989) attempted to categorise design theories and methods into descriptive and prescriptive design processes. Descriptive models are dominated by protocol studies of individual designers such as Ullman and Dietterich (1986; 1987). Prescriptive processes attempt to design for the attributes an object should have rather than how the design process itself should proceed. Examples included Axiomatic Design and Taguchi's quality loss. Quality Function Deployment was omitted in this review.

In a comparison and critique by Fichman & Kemerer 1992[4], object orientated design was compared against conventional design methodologies. They concluded that whilst little empirical evidence supported object oriented design, anecdotal statements from experts and practitioners favoured the former approach. Erbuomwan (1996) agreed with Fisher & Dixon (1989) that AD is a prescriptive model since the design process is based upon the object attributes. In a review by Yazdani and Holmes (1999), Quality Function Deployment is categorised as a process driven design which is able to combine both the customer voice with that of the manufacturing voice to deliver a robust product.

The philosophy of design continually evolves and this was reflected in the recent transition towards hybrid design methodologies.

Sarno et al., (2005) compared both AD and TRIZ and attempted a hybrid methodology that included both and with an attempted validation using a case study. Frey and Dym (2006) reviewed both AD and QFD from a medical treatment-design method perspective and concluded both should be of interest for researchers in engineering design. Tomiyana (2009) reviewed deficiencies amongst current design theories and methodologies included AD, TRIZ and QFD.

[4] http://www.pitt.edu/~ckemerer/CK%20research%20papers/OO%26ConventionalAnalysis_FichmanKemerer92.pdf (Checked 21/10/2012)

According to Tomiyama et al., (2009) in a review of industrial and educational design methodologies, four design categories were presented.

	General	**Individual**
Abstract	*(1) Design theory*	*(3) Math-based methods*
Concrete	*(2a) Methodology to achieve concrete goals* *(2b) Process methodologies*	*(4) Specific design methods*

Table 1. A summary of design theory and methodologies adapted from Tomiyama et al., (2009)

1. *Abstract-general*: The academic breakdown of the intellectual processes that occur in peoples' minds when approaching a design (general design theory/ universal design theory).
2. *Concrete-general*: Design methods focused upon product design and development (design centred engineering – Quality Function Deployment/ TRIZ/ Design for X/ design structure matrix) or design process management (concurrent/sequential engineering)
3. *Abstract individual*: design methods that apply mathematical algorithms and or usually focus on optimization of an aspect of an original design (Axiomatic Design/ Taguchi)
4. *Concrete individual*: Design methods that focus on procedure such as construction of buildings, bridges or jet engines

2.4.1 Tier 1 literature review findings

Based upon the identified categories in Table 1 the decision was made to exclude from this review design theories and methodologies from categories 1 and 4. Category 1 was excluded on the basis that general design theory and universal design theory were primarily an academic interest in the thought processes behind design rather than actual design methods. Category 4 was excluded on the basis that these design methods were too exclusive to a particular design goal or objective.

Of the category 2 design theory and methodologies the design process management methods were excluded. This was done on the basis of their closeness to project management tools for product development rather than concrete design methods. Of the remaining design methods Design for X (DFX) was excluded. DFX incorporates a wide range of contemporary design methods (Huang and Mak, 1997a; Huang and Mak, 1997b; Huang and Mak, 1998; Kuo et al., 2001). DFX was excluded on the basis of the confusion about which DFX tool to select and the lack of clarity perceived by the overlapping nature of these tools. Design Structure Matrix (DSM) consisted of managing complexity and information flow via the matrices. Whilst the DSM appears useful it was excluded due to the extensive overlap with AD, and lack of educational texts that set out the design method.

QFD and TRIZ remained from this category and were both selected. The well characterised nature of these methods with research publications and coupled with the abundance of educational resources justified their selection.

Finally, from the analysis of category 3 the Taguchi Method™ was excluded. It is primarily a parametric design method and has been implemented throughout Japan, US and later Europe (Tomiyama et al., 2009). The Taguchi Method™ has gradually evolved to the extent that parts are included within other design approaches such as QFD and AD. Since the design method focuses upon making a product less sensitive to noise factors, by its nature it suggests that the product must already exist. Since the bone tissue scaffold had to be design first, this method was excluded. AD was selected on the basis of its increasing prominence and based upon designs fulfilling design axioms. It also includes many of the aspects of the Taguchi methods.

Based upon the above reviews it was decided to focus attention for the Tier 2 review on the three design methods, QFD, AD and TRIZ.

The following sections describe each of the selected design methodologies.

2.4.2 Quality Function Deployment

QFD is a customer-driven quality design methodology that aids in the design of complex products. One of the methodological intents is to provide the customer with an opportunity to influence the product design and deployment. There are a multitude of variations in which this step-by-step process can be implemented such as a series of matrices or by a house of quality approach.

Common across all approaches is the execution of a series of steps that aims to capture the voice of the customer or business, translate them into a list of requirements, incorporate the requirements into product design, identify a manufacturing route and deploy the product into a selected market sector.

The first step is the capture of the voice of the customer via interviews and surveys. A subsequent translation of customer verbatim comments is executed by QFD

practitioners in order to derive statements, each of which indicate a single requirement on which further design can be based upon. Each of these statements is then analysed in order to establish a functional aspect from the perspective of design engineers. These are the properties of the product that will satisfy the requirements identified by the customer requirements. The design step answers a how these product properties can be coordinated with one another into a single master design. Each designed requirement as an engineering target. Finally the process answers how the design can be manufactured and deployed into the market.

The value of applying QFD is that the impact of decisions can be visually tracked along the design and development process. Potential conflicts between requirements, properties at each stage of the design process can also be identified. It is clear to customers and QFD practitioners what factors have been included within the process and what has not. Therefore the design, development and deployment initiatives can be critiqued at every stage. One of the weaknesses of QFD is that it does not innovate new designs but rather coordinate the thoughts of the customer and QFD practitioners. In this sense QFD provides an operational management or strategic thinking element to product design rather than an innovation-driven design methodology.

2.4.3 Theory of Inventive Problem Solving

TRIZ is a problem solving tool whose purpose is rooted in resolving conflicts between requirements and properties in the design and development of a new or existing product. The core of its problem solving methodology is based upon extensive research into patents and how patented changes in technology overcame deficiencies with existing products.

A design conflict is described as when increasing the value of one parameter results in an unfavourable change in another. The identified parameters are entered into the TRIZ matrix where the favoured parameter is compared against the unflavoured change. The

matrix cell in which the two intersect contains numbered TRIZ inventive solutions that may potentially offer a solution to the conflict based upon prior patent research.

The value of TRIZ is the suggestion of innovative principles that may stimulate the TRIZ practitioners' creative thinking in overcoming a design conflict. However TRIZ does not provide inventive principles that are related to bone tissue scaffolds. There an additional step needs to be implemented in the application of TRIZ that translates a specific bone tissue scaffold conflict into a generic TRIZ conflict in order to identify a generic TRIZ solution. This solution then needs to be translated into a bone tissue scaffold specific solution. This process of translating between bone tissue scaffold specific and generic solutions is open to a wide degree of interpretation, the basis of which may be difficult to justify scientifically.

TRIZ can be applied as a standalone methodology or as part of the QFD process. It has been incorporated into the QFD house of quality by the creation of an additional 'room' termed 'the roof'. The structured nature of the house of quality allows the derived properties to be compared in a pairwise comparison in order to identify design conflicts. This QFD-TRIZ combination is intent on overcoming deficiencies in both methodologies (lack of innovation in QFD and unstructured methodology for creating the parameters to compare in TRIZ) whilst incorporating their strengths in order to achieve structured hybrid between customer-driven and innovation-driven design.

2.4.4 Axiomatic Design

AD is a systematic design methodology that approaches design from an alternative perspective than the previously described examples. This design methodology attempts to systematically deconstruct the relationship between the functions the design is intended to serve and how the parameters for the design will satisfy them. The purpose of which is to identify design conflicts termed as 'couplings' using the AD terminology. The purpose of which is to solve these couplings 'uncoupling' in order to create a system of design where individual requirements, functions, parameters and process variables are wholly independent of one another. Only when these conditions have been

achieved is the design ‘ideal’. The deconstruction process between all the variables is unique to AD and its systematic nature is intent on identifying ‘leaf-level’ variables, functions and parameters. These are the factors below which no further deconstruction can take place. Therefore these factors can be considered the key factors on which the design is completely dependent upon. The design is presented in the form of matrices on which practitioners are able to represent which factors are coupled and where.

The weakness of AD is that it does not offer practitioners any innovative solutions to ‘uncouple’ identified couplings. It is left to the AD practitioner to implement innovative solutions from alternative domains of knowledge with no explanation. It is also assumed that whatever solution was selected is correct since very little critique of AD applications takes place.

The strength of AD is the systematic nature of laying out the majority of the factors that are ‘in-play’ in the design of the product. Therefore practitioners are able to identify what has been considered and which factors have not.

2.5 Current state of the art in literature reviews for methods (Tier 2)

The Tier 2 system of interest was defined as recent literature reviews for QFD, AD and TRIZ. The literature reviews for each design method were reviewed to determine whether any of the three design methods had properties which formed the grounds for their exclusion as methods for the design of bone tissue scaffolds.

The following section summarises the findings of the scope of review.

Table 2 below summarises the key findings of the current QFD literature review publications.

	Review findings for Quality Function Deployment	**Reference**
1	1. Historical development and analysis of QFD 2. Attempted inclusion of applications, method development for future reference	(Chan and Wu, 2002)
2	1. QFD found to be a valuable tool in new product development 2. Effectiveness of QFD depends on its integration with the design process	(Rahim and Baksh, 2003)
3	1. QFD allowed linking of customer segments for online management real estate tool agencies 2. Creation of database driven portal	(Hamilton and Selen, 2004)
4	1. QFD allowed engineers to analyse alterations for unacceptable attributes as well as identify dependences 2. QFD found to help reduce the possibility of the omission of dependences	(Chen et al., 2004)
5	1. Under a competition format, where time is a constraint, QFD aided in the design process	(Sanford, 2005)

6	1. QFD found to be a useful tool in making marketing decisions 2. Limitations due to inadequate practitioners and poor definition of customers	(Dikmen et al., 2005)
7	1. New educational curriculum proposed in order to meet customer needs 2. University senate approved new curriculum	(Aytaç and Deniz, 2005)
8	1. Meta-analysis dispels myth that QFD allows "shorter time-to-market" 2. QFD supports product development improvement and information dissemination	(Lager, 2005)
9	1. QFD is useful for the redesign of products or services 2. Limitations in that QFD assumes users will have the necessary resources to overcome constraints	(Omachonu and Barach, 2005)
10	1. Concluded traditional QFD is too subjective 2. Incorporation of fuzzy theory improves quality based calculations	(Chang, 2006)
11	1. Problems identified in QFD are "ambiguity in the voice of the customer", "managing a large house of quality" and "conflicts between customer requirements" 2. Segmentation of customer requirements improves QFD process	(Shahin and Chan, 2006)
12	1. Attempted improvement of QFD 2. Quasi-experiment findings indicate new QFD process reduces time span for development	(Simons and Bouwman, 2006)
13	1. QFD reviewed as an effective tool for management to identify relationships between objectives and performance measures	(Gunduz and Simsek, 2007)

14	1. QFD found to aid in trade-off decisions, enhance teamwork, increase customer satisfaction and shorten time to market 2. Usefulness of QFD linked to accuracy of data collected on initial customer needs	(Mehrjerdi, 2010b)
15	1. QFD delivers product development via quality management and customer need analysis 2. Versatility of method highlighted by different forms of QFD	(Mehrjerdi, 2010a)
16	1. QFD aids management in enhancing profits and enhances product development 2. QFD is relevant to both top and middle management	(Zare Mehrjerdi, 2011)

Table 2. Summary of the conclusions from the literature review publications for quality function deployment.

The reviews for QFD indicate the usefulness in the application towards product development, creation of data bases, the prevention of omission of key technical considerations, decision making and as a management tool. Contrary to the anecdotal belief that QFD reduces the time-to-market, the meta-analysis performed by Lager (2005) found this was not the case. Limitations of QFD are; the user intensive training that is required, the problem of ill-defined starting points and the general assumption that unlimited resources are available to overcome any constraints identified by the process. Finally the ambiguity used in collecting the initial customer information is also a problem with QFD.

Table 3 below summarises the current literature reviews for Axiomatic Design.

	Review findings for Axiomatic Design	**Reference**
1	1. AD found to be usable and produce better product designs 2. Important that an appropriate starting point for design be established prior to application	(Mullens et al., 2005)
2	1. AD seeks to identify optimal design embodiment (crisp point) 2. Designers domain knowledge and product desirability are critical to achieve this	(Ullah, 2005)
3	1. AD applications typically use independence axiom 2. Proposed product designs evaluated by crisp approach	(Kulak et al., 2010)
4	1. AD used to monitor and control time-dependent complexity of manufacturing systems 2. AD able to identify and prioritise in systems described as having high operational complexity	(Matt, 2012)

Table 3. Summary of the conclusions from the review publications for axiomatic design.

The analysis of the literature reviews in Table 3 reveal the benefit of AD in terms of the understanding of complex systems. AD is also beneficial in the optimization of designs. The pre-requisites for AD are seen to be a ‘well-defined’ starting point and significant knowledge of the research domain in which the design occurs.

Table 4 below summarises the TRIZ literature review findings.

	Review findings for TRIZ	**Reference**
1	1. Recognises TRIZ as a valuable tool but has limitations 2. UK companies have not adopted TRIZ as part of their design culture	(Dwyer, 2005)
2	1. TRIZ users requires training and practice 2. Companies should include TRIZ training as part of corporate training programs	(Dew, 2006)
3	1. TRIZ is unable to determine market success of new concept 2. TRIZ limited by focus on technical domain not market forces 3. TRIZ should be combined with alternatives i.e. QFD or AD	(Yezersky, 2007)
4	1. Biomimetics analysis using TRIZ identified limited similarities between technology solutions and biology solutions 2. Technology manipulates energy to solve energy whereas biology uses information and technology	(Vincent et al., 2006)
5	1. TRIZ recommends self-assembly for creation of biological structures in biomimetics 2. Once self-assembly is unsustainable look towards convenient resources such as fields (electromagnetic, gravity)	(Vincent, 2009)
6	1. TRIZ used to link evolutionary concepts in biology, culture and directed evolution 2. Directed evolution translates to business by achieving market and technology leadership	(Mizrachi, 2010)

Table 4. Summary of the conclusions from the review publications for TRIZ.

TRIZ is shown to be widely used but has a number of recognised limitations. Its application is limited by the requirement of education training. This is likely due to the generic nature of the tool and hence leaves users struggling to make the translation of generic problem solutions relevant to the specific problem at hand.

TRIZ is also typically used in combination with QFD, as part of the 'house of quality' tool. This suggests the use of TRIZ in hybrid methods. This in itself is a validation of TRIZ, in that other methods seek to include TRIZ as it benefits the overall design process. The reviews in Table 4 indicate a shift in the use of TRIZ towards an "eco-friendly" TRIZ in response to modern demand for 'green' alternatives and solutions.

Table 5 below summarises the literature reviews for hybrid design methods.

	Methods	**Review findings for hybrid methodologies**	**Reference**
1	TRIZ & AD	Proposal of a hybrid method approach to increase the efficiency and quality of the problem solving process	(Shirwaiker and Okudan, 2008)
2	AD & QFD	Further research required to evaluate proposed model and secondly limitations recognised with QFD	(Carnevalli et al., 2010)

Table 5. Summary of the conclusions from the review publications for the hybrid design method findings.

The purpose of hybrid methods are that limitations in one methodology are overcome by the strengths of another design method. This is already the case with more established methodologies such as QFD, which incorporates TRIZ into the design process. There are attempts at the attempt of a QFD, TRIZ and AD hybrid, proposed by El-Haik (2005).

2.5.1 Tier 2 literature review findings

As a result of the tier 2 literature review no arguments could be raised with regards to the unsuitability of either, QFD, TRIZ or AD for selection in the application for design for this research thesis. The next step was to further review these methods to identify and consider caveats each design method would require for its use as part of the thesis.

2.6 Current state of the art in the application of Quality Function Deployment, Axiomatic Design and TRIZ on product development (Tier 3)

The results of the literature analysis are shown in Table 6, Table 7, Table 8 and Table 11. Information in the following tables is presented in the following categories; area of interest, data collection method, inputs and outputs, validation method and authors recommendations.

Twenty four QFD publications were identified, eighteen AD publications and fourteen TRIZ publications.

	Area of interest	*What were the inputs?*	*How were the inputs collected?*	*What were the outputs?*	*How were the findings validated?*	*Do the authors recommend the method?*	*Reference*
1	Develop a strategic plan for departmental research	Customer requirements of funding agencies	Individual members tasked with tracking a single agency	List of activities for strategic research planning process	Informal approach	Recommended for insular changes to department	(Chen and Bullington, 1993)
2	Retail services	Dynamic, unpredictable Voice of the customer	Survey	Supermarket improvements	Method proposal	Improvements required in algorithm used	(Trappey et al., 1996)
3	Ergonomics, safety shoe users in cold climates	Ergonomic customer needs	Questionnaire/ survey	Thorough analysis of final product characteristics	Case study	Recommended tool for competent ergonomist	(Bergquist and Abeysekera, 1996)
4	Improvement of a health care system	Patients perception on arrival to hospital	Interaction with patients	Suggestions for improved quality in services	Case study	Lack of training limits employees improving services	(Radharamanan and Godoy, 1996)
5	Rapid prototyping of manufactured goods	Customer needs	Hypothetical statements	Technical characteristics	Case study	Recommended for all stages of product development	(Ghahramani and Houshyar, 1996)
6	Designing rule changes for soccer	Market segments, enthusiasts, rules of game	Interviews and discussions with experts from FIFA	Raises aspects for further research	Proposal of trend extrapolating forecasting technique	Further research required to prove benefits of proposed method	(Partovi and Corredoira, 2002)

7	Air transport management	Service requirements and quality technology	Questionnaire/ survey	List of improvements	Case study	Analysis identified factors to satisfy customers	(Wang, 2007)
8	Develop undergraduate supply chain management curriculum	Benchmarking analysis of customer expectations	Structured questionnaire sent to potential employers	Academic programme that met potential employers requirements	Approval of potential employers	Recommended for application to develop academic programmes	(Gonzalez et al., 2008)
9	Service quality management	Banking sector customer needs	Survey of anonymous banks, customers	Bank selection criteria	Case study	Recommended to assess rapid shifts in customer needs	(Andronikidis et al., 2009)
10	Environmental performance of fishing fleets	Stakeholder requirements based on sustainability	Requirements derived from pre-stated attribute set	Fishing fleet reorganisation proposals	Case study	Suggest further work to prove robustness of QFD	(Utne, 2009)
11	Environmental management	Ecological requirements	Data extracted from other reports	Actions that improve quality of life	Case study	Suggests annual use to monitor strategy priorities	(Wolniak and Sędek, 2009)
12	Product development and production in semiconductor industry	Improvements to fixed telecommunicati on network	Contact with anonymous manufacturing company	Improvements to process management and policy development	Case study	Recommended for product and process development	(Chen, 2010)

13	Fruit leather product development	Sensory attributes to various fruit leather products	Consumer survey	Identified optimum product characteristics	Direct application	Customer requirements incorporated into new product	(Vatthanakul et al., 2010)
14	Designing sustainable supply chain	Customer Requirements	Literature review/ Survey	Design requirements	Case study	Proposal of new QFD model	(Büyüközkan and Berkol, 2011)
15	Service quality for an academic library	Readers requirements	Questionnaire/ survey	List of desired improvements (practical suggestions)	Case study	QFD provides improvement in service quality	(Chen and Chou, 2011)
16	Analysis of teaching methods	Employers expectations	Analysis of popular job search websites	Teaching methods	Case study	QFD successful in identifying improvements to teaching courses	(Ictenbas and Eryilmazb, 2011)
17	Lean food supply chain	Lean attributes for lean production	Hypothetical set of lean attribute statements	Lean enablers for canning industry	Case study	Further case studies to validate usefulness	(Zarei et al., 2011)
18	Material selection for vehicular structures	Classes of engineering materials	Statements proposed by authors	Identified trade offs	Case study	QFD recommended for material selection	(Mayyas et al., 2011)
19	Service industry planning process	Member needs and requirements	Survey	Improvements to society services	Case study	Recommended for product improvement or service design	(Cudney et al., 2012)
20	Improving Korean bulgogi for international customers	Taste, juiciness, freshness, flavour, ease of purchase	Customer survey and expert opinion survey	List of preparation and serving improvements	Direct application	Recognises limitations of QFD; future work to improve method	(Park et al., 2012)

21	Build environmentally friendly manufacturing system	Regulations and demands for green implementation	Data extracted from laws and regulations (i.e. Montreal protocol)	Identification of quality assurance and procurement capability	Case study	Presentation of novel strategic model	(Yang et al., 2012)
22	Design of multifunction laparoscopic tool for Surgeons	FRs based upon minimal invasive surgery	Interview with laparoscopic surgeon	Design removes need for multiple tools	Direct application	Suggests the combination of QFD and AD led to improved product quality	(Nelson et al., 2007)
23	Redesign of laparoscopic surgical tool	FRs based upon minimal invasive surgery	AD for systematic decomposition of problem and QFD for mathematically determining design criteria	Tool has improved multi-functionality	Development of prototype tool	Combination of design methods led to development of prototype for further testing	(Miller and Nelson, 2008)
24	Reducing warship cost (BAE systems)	Designing for cost	Structured planning via QFD	Value for money	Conceptual application	Recommends application of QFD for cost reduction	(Harrison, 2004)

Table 6. The selected Quality Function Deployment (QFD) design literature, analysed by area of interest, inputs, outputs and authors recommendations. In total 24 QFD publications were analysed to assess the potential validation of the utilization of this method in this research thesis. Within the 24 QFD applications, it was found that two (22 and 23) contained proposed QFD-AD hybrid methodologies and applications.

	Area of interest	*What were the inputs?*	*How were the inputs collected?*	*What were the outputs?*	*How were the findings validated?*	*Do the authors recommend the method?*	*Reference*
1	Intelligent machine creative design concept	How to establish FRs	Solution neutral statements that are independent of one another	Design parameters	Case study	Authors recommend further work to validate findings	(Suh and Sekimoto, 1990)
2	Design of software systems	FRs are outputs of software	Analysis of software code	Ideal software system	Case study	Establishment of concept design	(Kim et al., 1991)
3	Microcellular polymer processing	Technical problems with manufacture	Analysis and decomposition of problem	Independently controllable functions	Case study	AD used to advance microcellular process technology	(Park et al., 1996)
4	Systematic design of manufacturing systems	Range of FRs to improve furniture manufacturing	Stated by authors	System recommendations and observations	Case study	Method proposes general guidelines for design	(Gu et al., 2001)
5	Design of automotive suspension systems	Kinematic FRs	The authors desired FRs	Theoretical DPs	Case study	Concludes AD can be applied to kinematic designs in general	(Bae et al., 2002)
6	Marine (ship) design problems	Selection of parts requiring modifications	Hypothetical attribute set	Potential solutions based upon redesigns and/ or optimizations	Four example solutions proposed	Further work required for the application of AD to ship design	(Jang et al., 2002)
7	Design of vibratory gyroscope	FR statements	Analysis of current design	Redesign of gyroscope	Theoretical design	Authors intend for attempted manufacture of new design	(Hwang et al., 2003)

8	Cellular manufacturing system design	FRs defined at highest level of system of interest	Statement extracted from literature	Identification of system that can satisfy FR	Theoretical design	Recommends AD; validate findings with future research	(Kulak et al., 2005)
9	Nuclear power plant emergency core cooling system (ECCS)	Redundancy and Independency	Reverse engineering of ECCSs	An evaluation of design process	Alternative designs	AD successfully evaluated design process	(Heo and Lee, 2007)
10	Thermoformed multi-layered plastic containers	FRs derived from existing design process	Stated that inputs based upon interviews	Optimal design proposal deduced	Case study	Provide instant cause analysis, minimize failures and mistakes	(Lee et al., 2007)
11	Design of office cells	FRs based upon office organisational performance	Highest level FR and DP stated based upon experience	Office redesign proposals	Applied in loyalty projects	Future designers to follow method in order to compare redesigns	(Durmusoglu and Kulak, 2008)
12	Design decision making for HVAC systems	Highest level FR and DP based upon HVAC system	Stated by authors	Proposed alternative decoupled designs	Conceptual design	Decoupled design solutions are an improvement over current designs	(Cavique and Gonçalves-Coelho, 2009)
13	Development of nanofluid coolants	FRs based upon area desired area of improvement	Literature review	Suggestions to reduce couplings in design	Conceptual design	Proposed design solutions are an improvement over current technology	(Bang and Heo, 2009)
14	Design of microcellular plastic bumper parts	FRs based upon bumper improvements	FRs stated by authors	Proof of decoupled bumper design	Conceptual design	AD decomposition identified couplings and attempted decoupled redesign	(Lee et al., 2009)

15	Design recovery framework	FR based upon main function of a physical component	Derived via process of context, concept, logic	Potential design improvements at couplings	Case study	Useful tool for designer to assess if current component design is adequate	(Urbanic and El Maraghy, 2009)
16	Design of hospital emergency departments	Patient fast track requirements	Discrete event simulation	Introduction of new index for patient flow	Conceptual model	AD found to be useful in reducing complexity	(Peck and Kim, 2010)
17	Sustainable manufacturing grinding technology	FRs of the machining process	Holistic process model	Metrics for grinding sustainability	Case study	AD useful in clarifying complex process models	(Linke and Dornfeld, 2012)
18	Hydrodynamic flow focusing	FRs derived for consistency, flow and controllability	Design study start point assumed decoupled system	Novel microfluidic method	Experiment-al application	New method met redesigned intent	(Song et al., 2012)

Table 7. The selected Axiomatic Design (AD) literature analysed by area of interest, inputs, outputs and authors recommendations.

	Area of interest	*What were the inputs?*	*How were the inputs collected?*	*What were the outputs?*	*How were the findings validated?*	*Do the authors recommend the method?*	*Reference*
1	Redesign of a motor-scooter wheel	Structural parts	Knowledge management tools	Virtual design and virtual testing	Case study	TRIZ recommended as an alternative to trial and error approach	(Cascini and Rissone, 2004)
2	New service design	Harmful functions	Questionnaire	Problem resolutions	Case study	TRIZ recommended as an innovative tool	(Chai et al., 2005)
3	Design retrofit for a chemical process addressing safety	Generic TRIZ parameters	Literature review of failures relevant to case study	New TRIZ categories for parameters	Case study	Reorganised TRIZ parameters superior to generic parameters	(Kim et al., 2009)
4	Accelerate inventive design in chemical engineering	Chemical processing parameters	Cased-based reasoning to capture and store design knowledge	Identification of and linking of contradictions	Case study	Recommended combined methodology. Further research required in generating TRIZ specific ontologies and tools	(Cortes Robles et al., 2009)
5	Cleaner production by minimizing industrial waste and emissions	Cleaner production strategies	Based upon user experience	Function analysis of processes	Case study	Ease of application of TRIZ, allows the scope of problem solving to expand beyond users	(Fresner et al., 2010)
6	Friction stir welding design	Design conflicts	Text mining of patent database (case analyses)	Suggested conflict resolutions	Case study	TRIZ recognised as useful design tool. Greater domain specific research required for future application	(Hsieh and Chen, 2010)

7	Identifying technology trends (Text mining) for R&D planning	Patents specific to area of interest	Text mining	Evolutionary radar plots of patents according to time periods	Case study	Recognises that "hidden trends" may influence evaluation of technology as TRIZ cannot explain all technology trends	(Wang et al., 2010)
8	Design improvement for a government department	Parameters associated with government bureaucracy	Web resources utilized to collect related documents	New approach to diagnose and improve design	Case study	TRIZ benefits design by minimizing users selective bias associated with brainstorming	(Jiang et al., 2011)
9	Crowd management	Excessive crowding translated to TRIZ specific parameters	Literature review of crowd related incidents	Potential redesigns to stadia	Case study	Provided findings on which to base future studies	(Pin et al., 2011)
10	Innovation in eco-design	Major concerns of customers	Market research of customer concerns	Environmental conscious products	Case study	Integrating design approach to systematic methodologies	(Trappey et al., 2011)
11	Eco-innovation design	New product design information	Case based reasoning, redesign of existing products	Eco-innovation applicable across technological fields	Case study	Recommend as a means of transferring solution from previous problem to new problem	(Yang and Chen, 2011)
12	Eco-product design innovation	Product information	Case based reasoning and simple life cycle assessment	TRIZ evolution pattern data base	Case study	TRIZ recommended as feasible means of identifying new eco-product design	(Yang and Chen, 2012)
13	Eco-innovation design for process engineering	technological eco-innovation	Computer aided model	Creation of new process options	Case study	Further research required to implement transfer from eco-invention to eco-innovation	(Ferrer et al., 2012)

14	TRIZ trade studies for Systems engineering	Identify system conflicts	Trade studies	Trade off metrics	Case study	Useful in the application of trade study since it identifies patterns in prior patents	(Blackburn et al., 2012)

Table 8. The analysis of the selected Theory of Inventive Problem Solving (TRIZ) literature.

2.6.1 Review findings for Quality Function Deployment

The customer requirements cover a range of organisations and agencies. The inputs show trends for dynamic or unpredictable voice of customer, physical needs or perceptions and expectations. The data collection methods include interviews, surveys and questionnaires, data extraction, literature reviews and hypothetical attribute sets.

The outputs are specific to the application itself and are in the form of a list of design improvements, suggestions for implementation, technical characteristics and design requirements. All are proactive in suggesting an area or areas of improvement. There are none that indicate that any improvement is unnecessary or that any would make the subject under analysis worse.

The most common method for the validation was via case studies. Only three QFD methods resulted in a direct application of the findings. The remaining consisted of formal and one informal proposal. From the case studies, sixteen out of twenty four publications recommend the application of QFD, based upon the output of the design method. The only authors to note limitations of the QFD methodology were Trappey et al., (1996), Radharamanan and Godoy (1996) and Park et al., (2012). The limitations were primarily based upon the user intensive training requirements in order to adequately implement QFD.

Partovi and Corredoira (2002), Utne (2009) and Zarai et al., (2011) all state the need for further research in order to validate the findings from the QFD methodology. Büyüközkan and Berkol (2011) and Nelson et al., (2007) propose a new design model based upon their findings.

The tier 3 review of QFD applications concurs with the findings of the tier 2 QFD literature reviews. QFD was not ruled out for product design and development but has stated limitations. One of these is the extensive user training required for application of QFD by businesses.

2.6.2 Review findings for Axiomatic Design

Inputs for AD are all nearly functional requirements and or design requirements. These are the building blocks of the design methodology and are the foundation on which design decomposition begins. The inputs were collected by investigation of an existing problem, hypothetical statements, literature statements and then subsequently derived based upon the author's interpretation. The outputs were all aspects of design that could enable a 'better' design of the system under analysis. Validation of designs consisted of case studies, or theoretical or conceptual designs.

In nearly all applications the authors recommend AD as a design method. Only Jang et al., (2002), Suh & Sekimoto (1990) state the requirement for further research. Since the majority of the research is at the conceptual stage rather than actual manufacture the true power of the design method to manufacture a viable redesigned product is still speculative.

The tier 3 findings concur with the Tier 2 reviews that AD is a useful design method for reducing the complexity of complex systems. AD is shown to be a tool that is able to propose redesigns and establish conceptual models as a basis for further research. However it is yet to validate these proposals, redesigns and concepts with a physical working prototype. This suggests why despite the method receiving positive comments it is yet to be applied widespread across industry.

When investigating the applications from both the literature and worked examples it is the authors opinion that many if not all of the applications of axiomatic design utilize research that was obtained empirically by alternative means, then retrospectively entered into axiomatic design mapping framework in an attempt to present findings that look as if axiomatic design provided the solution or indeed could provide that solution.

There is also a second point of contention. If the above is not true then the alternative is that users of axiomatic design theory do so from the perspective of a state of 'perfect knowledge'. It is only once this state of mind is achieved that users can seemingly state arbitrarily the 'correct Functional Requirements' statements and immediately map across to the design parameters, of which no there is no methodology for arriving at. Explanations frequently refer towards 'intuition' and 'expertise'. Neither of which are helpful in establishing the repeatability requirement of a robust design methodology. Instead readers are left to speculate amongst themselves as to why alternative parameters were not selected or indeed if they were considered at all.

2.6.3 Review findings for TRIZ

The data collection techniques for TRIZ include both verbal and non-verbal forms of communication. Verbal forms in the form of questionnaires, surveys and interviews, and non-verbal forms such as analysis of online literature, text mining, case based reasoning etc.

The TRIZ inputs reflect a desire for improved performance of an existing design whilst the outputs consist of potential solutions, improvements and redesigns. All the findings were validated by case studies with TRIZ being recommended by all authors.

The recognition of TRIZ limitations is based upon the 'difficulty' in translating specific problems into a generic problem, identifying the generic solution, then translating this back towards a problem specific solution. This problem is identified by Cortes Robles et al, (2009) when applying TRIZ to chemical processing parameters.

Despite the limitations due to its generic nature, the biggest endorsement for TRIZ is the growing number of publications associated with a rebranding into an "eco-friendly" application method. This is reflected by both the Tier 3 and Tier 2 reviews. Green 'issues' are very much a current political topic and these eco-TRIZ methods therefore validate TRIZ as a method that designers see continued relevance for in the future.

2.6.4 Comparison between design methods

QFD, AD and TRIZ methodologies have been applied to a wide range of research fields. In each case the justification for the application of the chosen methodology resulted in positive feedback and further recommendations.

QFD is the design method of choice when having a design process that begins with a customer. This is likely due to the extensive tools available within QFD that attempt to integrate the customer's needs into product design. AD also attempts this process but the Tier 3 review does not highlight any ideal examples. However this may also be due to the fact that QFD has been available as a design method for longer than AD.

Both AD and TRIZ show clear preference for non-verbal collection data methods. This is due to their methodology based upon the design improvement perhaps rather than a completely new design. Therefore there is less of a requirement to speak directly to the customer in order to identify the customer's needs. As opposed to QFD which is a method that is based upon delivering a product that suits the customer's needs rather than resolving a particular problem within the design of the product itself.

Optimization and understanding of a complex system is where anecdotally AD is preferred, due to its systematic decomposition of the design problem itself. A thorough process in which design is deconstructed in great detail in order to systematically analyse which components are linked to others.

The difference between the application of TRIZ with QFD and AD is that its application is based upon the desire for innovation of design in order to resolve an identified conflict in the system of interest. In order to do this the TRIZ method is based upon a set of stages that firstly, identify the problem in the user's design, secondly, attempts to translate this design to a generic TRIZ design problem, thirdly, applies the generic TRIZ design solution and finally, this generic solution has to be translated back into the relevant field of its initial application.

The increased number of theoretical designs and conceptual designs for AD over QFD may indicate the 'prescriptive' aspect of AD. AD poses new questions and redesigns whereas QFD attempts to generate a deliverable product.

Finally it may also be the case that many companies do not disclose the full extent of their applications of design methods into the academic research field. Companies are focused on maintaining a competitive advantage, therefore disclosing a successful tool to rivals may not be advisable. Hence there are relatively few cases to cite considering the length of time since the inception of these design methods.

Unfortunately there is a distinct lack of examples of failures of these methods. For the purposes of this thesis it would have been of interest to identify unsuccessful applications and identify at what point along each method the design process was halted and why.

2.7 Conclusion

There are no grounds on which to make the argument that QFD, TRIZ or AD should be excluded for use as design methods for the bone tissue scaffold concept. The lack of examples of these design methods in the field of medical research in general shows a potential gap in for the application of these design methods.

Therefore, based upon the analysis of the state of the art in design methods the following methods, quality function deployment, TRIZ and Axiomatic Design have been selected to be applied to design future bone tissue scaffolds.

2.8 Summary

This chapter consisted of a multi-tiered literature review of the current state of the art in design theories and methodologies. Based upon this review, design methods were selected and their applications with product development and design reviewed. Quality Function Deployment, Axiomatic Design and TRIZ were selected as the design methodologies that would be included in the research strategy to meet the goals of this thesis.

3 Current Scaffold Design Methodologies

The previous chapter established design methodologies that had not previously been applied to the research field of tissue engineering. The next logical step is to ask:

"If traditional design theories and methodologies are not being applied in the design of bone tissue scaffolds, then what design methodologies are being applied?"

This chapter begins by asking this question and attempts to answer it by reviewing the current state of the art in bone tissue scaffold design. The intent is to identify or derive the design methodologies currently being applied by scaffold designers and tissue engineers.

3.1 Research methodology approach

The scope of this review was to identify the design methodologies being used for design and development of bone tissue scaffolds. The following method was followed:

3.1.1 Search strategy

An electronic search of the SCOPUS database was conducted. The following key words were used as search parameters: scaffold AND design AND bone, in the "title, abstract and keywords" search category. The search was limited to articles published between 2009 and November 2012. The eligibility of the articles was based upon screening first by title then by abstract. In order to derive the design methodology used by the authors, articles were analysed for the following information; the goal of research, design process, fabrication technique, materials used and metrology. Further additional, non-automated searches were performed by examining the reference lists of the selected publications for additional eligible publications.

3.2 Literature review

The following table presents the state of the art in scaffold design methodologies. The data is presented using the flowing column headings; research goal, design process, fabrication technique, materials and metrology.

	Research goal	Design process	Fabrication Technique	Materials used	Metrology	Reference
1	To characterise the permeability of the scaffold microstructure	Custom Interactive Data Language™	Solid Free-Form Fabrication (SFF) – 3D printer	Wax	Computational and experimental permeability	(Dias et al., 2012)
2	To design a scaffold that overcomes the conflict between high stiffness and high porosity	Computer-aided design	Selective laser melting (SLM)	Titanium	Stiffness, porosity	(Xiao et al., 2012)
3	The design and metrology of functionally graded scaffolds	-	Rapid prototyping (RP)	Polycaprolactone and β-tricalcium phosphate	Pore size, porosity, mean surface roughness, water uptake, Young's modulus, cell attachment/proliferation	(Kim and Kim, 2012)
4	Design and metrology of a fabricated scaffolds	-	Lab oriented process, e.g. mixing of polymers then post processing	Polyurethane 1,4-butanediisocyanate	Cell proliferation – stem cell procollagen; tensile modulus	(Liu et al., 2012)
5	Assess the optimal stratified scaffold combination by three fabrication techniques	-	Sponge replica method, freeze-drying, electrospinning	45S5 Bioglass®	Bioactivity, compressive strength, surface contact angle, wettability	(Liverani et al., 2012)
6	Design and metrology of fabricated scaffolds	Computer-aided design	Selective laser sintering (SLS)	Polycaprolactone, PCL and (β-TCP)	Young's modulus, microporosity	(Lohfeld et al., 2012)
7	The fabrication and degradation of organic-inorganic hybrid systems	-	Sol-gel process, foaming casting method	Poly (vinyl alcohol) and 30% bioactive glass	Compression testing, degradation kinetics	(Liverani et al., 2012)

8	Characterisation of a manufactured scaffold	-	Lab oriented process	Polycaprolactone (PCL)	Elastic moduli, creep tests, cell behaviour	(Mattioli-Belmonte et al., 2012)
9	Design of core-shell scaffolds for *in situ* protein loading and delivery	-	Co-axial deposition	Alginate/ α-tricalcium phosphate (Alg/α-TCP)	Compositional change, mechanical stiffness	(Perez and Kim, 2012)
10	The effect 3D architecture has on *in vivo* degradation	Image-based design	Indirect solid free-form fabrication (SFF)	Poly(L-lactic acid) (PLLA)	Strut thickness, surface are, porosity, degradation rate (mass loss), compressive moduli	(Saito et al., 2012)
11	The design of a bi-modal scaffold for bone tissue engineering (bTE)	(optimized lab oriented process)	Supercritical CO_2 (scCO2) foaming and porogen leaching techniques	Poly (ε-caprolactone) (PCL)	Biocompatibility, cell adhesion, colonization and proliferation; porosity;	(Salerno et al., 2012)
12	Characterisation of manufactured scaffold	3D design software	3D printing	β-tricalcium phosphate (β-TCP)	Apparent porosity; water absorption, bulk density, compressive strength, cytotoxicity	(Santos et al., 2012)
13	Novel scaffold design	-	Random packing of prefabricated MP or MF	Aggregated alginate microparticles (MP)/ microfiber s (MF)	Swelling profile, pore size and distribution, porosity, compressive strength, cytotoxicity	(Valente et al., 2012)
14	The design of a biphasic scaffold	Fused deposition modelling (FDM)	In house electrospun device	Polycaprolactone (PCL)	*In vitro* cell culture study; *in vivo* cell study	(Vaquette et al., 2012)
15	Fabrication and metrology of PLLA/CPC composite scaffolds	Computer-aided design model (CAD)	Rapid prototyping (RP)	Poly (L-lactic acid) PLLA / calcium phosphate cement	Compressive strength	(Xu et al., 2012)

16	Investigate the relationship between scaffold architecture and bone formation		Biomimetic co-precipitation , freeze-drying	Collagen-hydroxyapatite	Porosity, pore size, compressive modulus	(Yu et al., 2012)
17	Evaluation of 3D printing process for scaffold fabrication	3D design software, Solidworks®	3D printing	high performance composite material	Scaffold dimensional accuracy; porosity; mechanical stiffness	(Castilho et al., 2011)
18	Optimization of scaffold cell seeding	Design of experiment (DOE) statistical method	Gel-casting technique	Foamed titanium, 3D fiber-deposited titanium	Cell seeding efficiency (CSE), cell-specific viability (CSV), cell spatial distribution (CSD)	(Chen et al., 2011)
19	Manufacture and characterisation of novel combinatorial test scaffolds	Combinatorial test sample – Quadrant communication	Micro-robotic deposition (μRD) (SFF method)	Calcium phosphate (CaP)	Interconnection measurements	(Hoelzle et al., 2011)
20	To provide a design basis for biomechanical compatibility	Finite element method	Computer simulation	β-TCP	Porosity, elastic modulus	(Lin et al., 2011)
21	Multiscale modelling approach for scaffold design	Representative volume element (RVE)	Finite element modelling (FEM)	Hydroxyapatite (Hap) in collagen matrix	Simulated uniaxial compression modelling	(Chan et al., 2010)
22	New paradigm for the design of scaffolds	Multiscale osteointegration	Micro-robotic deposition (μRD) (SFF)	Calcium phosphate (CaP)	Microporosity, histological bone growth studies	(Lan Levengood et al., 2010b)
23	Complex multi-objective optimization approach		Mathematical model	Silicon particles embedded in polymer matrix	Stiffness , shear modulus	(Ranganathan et al., 2010)

24	Design and characterise novel materials for fabrication of scaffolds		Melt processed – gas foamed	Polycaprolactone (PCL) – thermoplastic zein (TZ) blend	Tensile tests, dynamic mechanical analysis, hydrophilicity, degradation tests	(Salerno et al., 2010)
25	Multiscale approach to scaffold design for macroscopic and microscopic domains	Representative volume element (RVE)	Finite element modelling (FEM)	Polycaprolactone (PCL)	Apparent stiffness, microporosity, rate of bone tissue formation, Strain energy density distribution	(Sanz-Herrera et al., 2010)
26	Develop a new process for the manufacture of bioactive 3D scaffolds	-	Supercritical phase-inversion	Bioglass® polymeric blend of starch and poly(l-lactic acid) composite	Stiffness, bioactivity,	(Duarte et al., 2009)
27	Novel fabrication technique capable of meeting the precise scaffold architecture	Novel production technique	Microfabrication, soft lithography	Polydimethylsiloxane (PDMS)	Surface topography, pore geometry, porosity	(Mata et al., 2009)
28	The design and fabrication of a scaffold	Surface modification (biomimetic coating)	Micro-stereolithography	Poly(propylene fumerate) (PPF)	Pore size, histological studies	(Lan et al., 2009)

Table 9. The research goals, design methods, fabrication techniques, material choices and metrology for the current state of the art in bone tissue scaffold engineering. The blanks indicate no formal design methodology.

3.3 Review findings for bone tissue scaffold design

The current state of the art in design methodologies for bone tissue scaffolds was reviewed in Table 9. The blanks in column three indicate no stated formal design method for a design method for the scaffold design process.

The research goals indicate a performance requirement; "to fabricate/characterise/design/assess a scaffold on its capability to do *x*'.

Seventeen out of the twenty eight papers reviewed then mention a design process. Fourteen of those are based upon computer modelling. The remaining three are lab based preparations. Eleven do not state a formal design method. Eighteen of the scaffold designs use a form of rapid prototyping or solid free form fabrication process. Six are human based fabrication methods such as sol-gel casting. The remaining four are finite-element models.

A wide range of materials that include polymers and metals are used. These materials are selected on the basis that they are bioactive (stimulate a desired biological response) or inert (non-toxic). None of the materials used were cytotoxic.

The metrics under test were either the stimulation of a biological effect, the characterisation of the scaffold itself or both.

From this analysis the deducted general design methodology is presented in Figure 4.

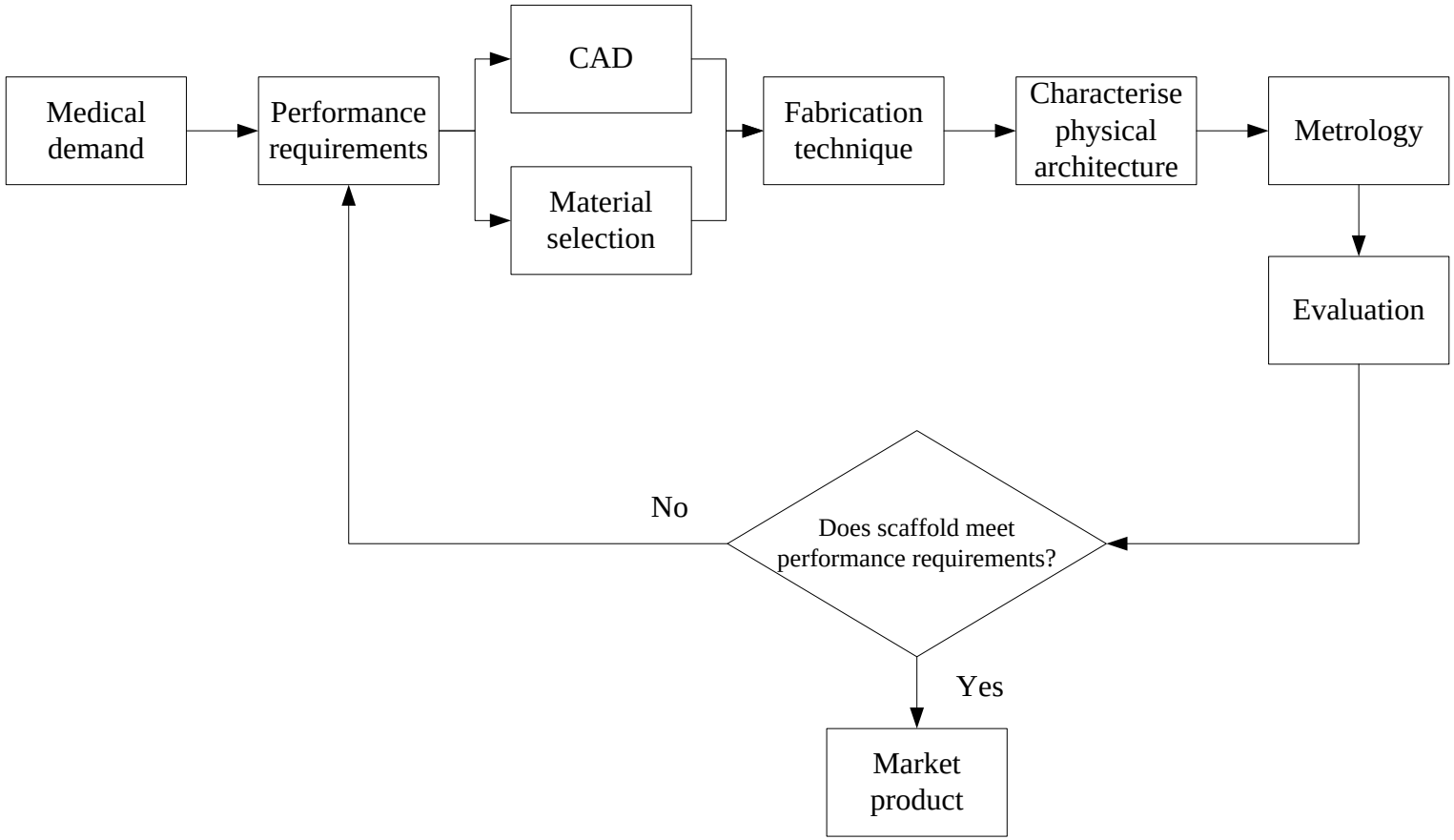


Figure 4. The general derived design methodology used for current bone tissue scaffold design based upon the research publications in Table 9.

It was found that the fabrication technique and the choice of material dictate the design of scaffolds. Hence the characterisation analysis is post fabrication in order to identify what microstructure has actually been fabricated. In the majority of cases the integration between a computer-aided design and subsequent rapid prototyping or solid free-form fabrication technique means that scaffold designs are constrained by limitations in the fabrication technique. Speculation as to this is that by designing for the fabrication process, process conditions, process accuracy, consistency and repeatability can all be controlled (Leong et al., 2003).

Therefore currently, in any scaffold design method, considerable weighting is given to 'what can physically be manufactured with the available techniques' rather than 'what should the design look like regardless of whether the technique exists to manufacture it'. The reasoning behind the application of scaffold design by SFF methods are economic viability (Peltola et al., 2008) and the fabrication of highly reproducible architectures (Hutmacher and Cool, 2007; Hutmacher et al., 2004).

Bone regeneration relies upon a wide variety of biological imperatives e.g. neovascularisation and osteogenesis, which have a narrow range of variability and in some cases very specific requirements that are fundamental for ensuring tissue repair. The dilemma is that by designing a scaffold structure constrained by the process variables of its fabrication technique, the result is a scaffold microstructure geometry which forces the biological imperatives to adapt to an environment that no longer provides the optimum conditions for bone regeneration.

In terms of design this is a back to front approach, where the process dictates design rather than the function of the scaffold dictating the design priorities. Therefore currently scaffold design processes work backwards from fabrication to scaffold microstructure.

3.4 Concluding remarks

Based upon the literature review the following was concluded:

1. Current bone tissue scaffold design methodologies focus upon how a particular fabrication technique is thought to be able to deliver a specific biological imperative
2. The thought process or method explanation for arriving at scaffold design is never stated
3. There is a lack of statements as to how and what design decisions were made, merely that they were made
4. The current state of the art for bone tissue scaffold design methods rests heavily upon the introduction and application of novel fabrication techniques

3.5 Research thesis gap statement

"*A formal design methodology has yet to be applied for the design of bone tissue scaffolds"*

The analysis of both the design theory and methodologies literature and the bone tissue scaffold design literature reveals a disconnect between the two research fields. The absence of a 'traditional' design methodology that has successfully been applied for a wide range of research fields has yet to be applied to the design of microstructure for a bone tissue scaffold.

Therefore it is proposed that in order to further the current bone tissue scaffold concept the following design methods identified in Chapter 2 (Quality Function Deployment, TRIZ and Axiomatic Design) are to be applied for the design of a bone tissue scaffold.

The subsequent outputs of each design method can firstly be analysed based upon the individual technique and secondly, validated via a survey of expert opinion.

3.6 Summary

This chapter reviewed the current state of the art for design in bone tissue scaffolds. This review identified that current design methods are not related to design methods identified in Chapter 2. A frequently followed route is to utilize multiple medical images, convert them into three-dimensional CAD models and then manufacture them via a solid free-form fabrication (SFF) method.

Having identified the absence of traditional design methods it was decided to apply these design methods in an attempt to generate findings that would be a contribution to knowledge.

4 Methodologies

This chapter outlines the five different design methodologies utilized in the design of microstructure for a bone tissue scaffold. The methodologies were followed in the consecutive manner as presented. Three Quality Function Deployment (QFD) based design methods were applied and two Axiomatic Design (AD) models. Of the three QFD methods, the first consisted of a house of quality-TRIZ method, the second, an expanded house of quality application and the third, a three-dimensional relationship technology chart (3DRTC). The outputs of each method were considered, analysed and then selectively entered as the input for the subsequent method.

4.1 Introduction

The outline of the methodological process was as follows. A first design from the utilization of QFD and TRIZ, a second design based upon the expansion of the house of quality (HoQ) aspect of the first method, a 3DRTC as a proposal to better organise parameters within design and finally the AD method. The exception to this is the 3DRTC, which was a tangential adjunct in the pursuit of combining parameters of design within design strategies in general rather than a natural progression that led to AD.

- 4.2: Quality Function Deployment 1 (House of quality + TRIZ)
- 4.3: Quality Function Deployment 2 (Expanded house of quality)
- 4.4: Quality Function Deployment 3 (Three-dimensional relationship technology chart)
- 4.5a: Percolation based Axiomatic Design Model
- 4.5b: Time-dependent Axiomatic Design Model

The reasoning behind each methodology was that whilst the findings of the previous were of interest and made a contribution to advancing the bone tissue scaffold concept they still did not deliver the 'ideal' bone tissue scaffold design. Therefore the application of each methodology was intended to uncover information that could lead to the 'ideal' bone tissue scaffold design.

4.2 Quality Function Deployment and TRIZ

The flowing section outlines the methodology used in the first attempt at the derivation and identification of design conflicts in a bone-tissue scaffold.

4.2.1 Definition of terms

Customer Attributes (CAs) are defined as the "customer's subjective description of the performance desires of the product and its functions" (Terninko, 1997).

Critical-to-Satisfaction (CTS) are the necessary design features, interpreted by the designer, i.e. they are the initial descriptive CA's in the language of the designer. They are the first step in materialising the intent of the customer. There is no requirement for 1-to-1 mapping of CAs to CTS. One CA can be broken into multiple CTSs if deemed necessary. The CTSs form an itemised list of the means by which the customers' intent can be realised (El-Haik, 2005).

TRIZ is a method of systemic creativity (Altshuller, 1999). Its most useful contribution is to resolve technical contradictions. This is when two parameters conflict, i.e. where 'improving' one parameter 'worsens' another.

4.2.2 Detailed methodology

The purpose of the methodology used was, firstly, to validate the literature 'voice of the customer' (VOC) and secondly, to identify the potential design structure conflicts, where compromises in design occur due to conflicting technical specifications.

An adapted version of El-Haik's (2005) two house of quality approach was followed. El-Haik's QFD methodology can be summarised as follows:

Step 1: Collect CAs either from the VOC via direct customer engagement (interviews, focus groups, surveys and observations) or market research (questionnaires, media and trade journals).

Obtain Customer Importance (CI) ratings via customer activities such as surveys or clinics using a 1 (not important) to 5 (extremely important).

Step 2: Derive the CTSs to respond to the CAs. Determine the CTS relative importance ratings

Step 3: HoQ 1; Input the CAs, the customer importance values, and CTSs into first HoQ.

Complete the relationship matrix of interactions between CA's to CTSs

Step 4.1: CTS correlation via Roof of the House of Quality

Step 4.2: Resolve couplings via conceptual methods such as TRIZ

Step 5: House of Quality 2;

Input CTSs and determine Functional Requirements that contribute to meeting the CTSs

Step 6: Investigate if there is a current system that meets customer expectations and if not begin creative design process

In this paper El-Haik's QFD methodology was adapted in the following ways:

No design team was formed, the method was followed and applied by a single researcher.

No physical customer existed hence the voice of the customer was replaced via observations and statements extracted from a literature review of bone tissue scaffolds in order to obtain both the CAs and CTSs.

Both CA and CTS statements rather than just CAs, were validated via an email survey of identifiable experts in the field of tissue engineering. The 1-5 scale was replaced with a 1-9 scale in order to achieve a greater number graduations in opinion.

Some features of the traditional HoQ such as competitive benchmarks and targets and limits were not utilized. Competitive benchmarks were ignored since there was no physical market competitor. Targets and limits were unstated as to prevent any design bias interference prior to the TRIZ analysis.

The second HoQ stage was omitted since, El-Haik (2005), intended this to begin a method of using QFD as an input to AD – an approach not followed here

This leads to the methodology for the section as shown in Figure 5.

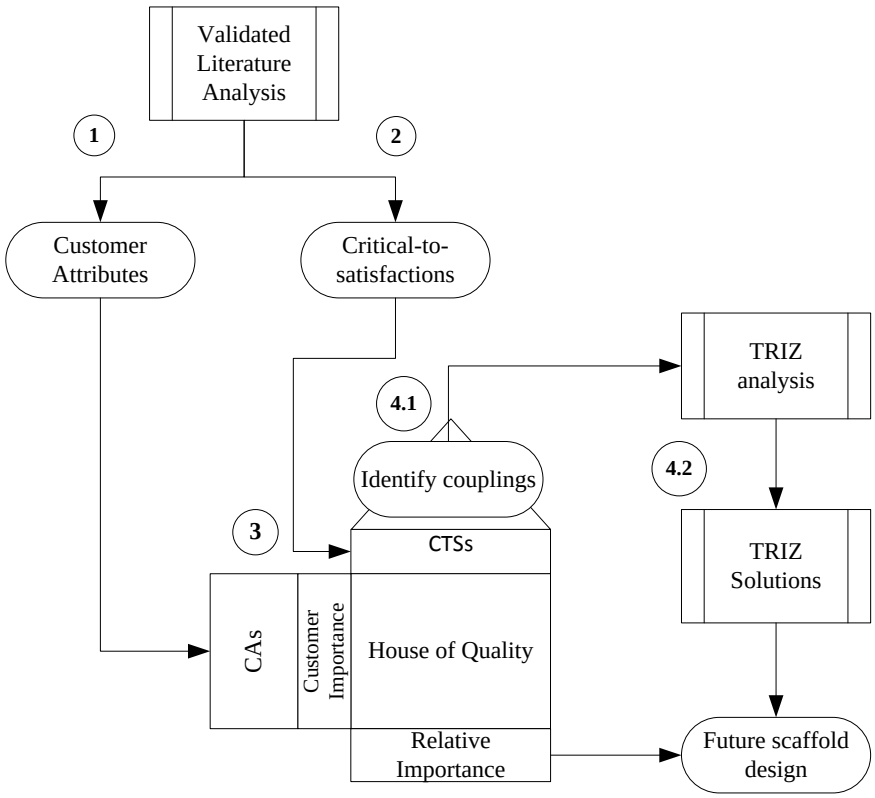


Figure 5. Proposed methodology for deriving and solving design conflicts in bone tissue scaffolds

A general TRIZ methodology used for removing conflicts in a system can be described as below (Terninko, 1997; Rantanen and Domb, 2002; Terninko et al., 1998):

1. Identify the problem contradiction
2. Translate the problem to the closest TRIZ generic problem
3. Identify the TRIZ generic solution from the contradiction matrix
4. Translate the solution to a specific solution for the user

Figure 6 shows the information flow for TRIZ compared to a trial and error approach.

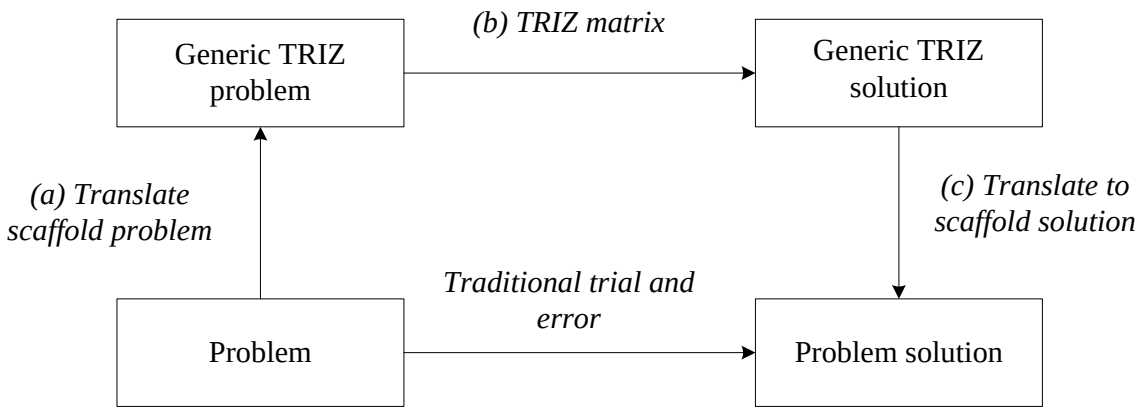


Figure 6. Flow diagram to show TRIZ route compared against trial and error route

In this thesis, TRIZ was combined with QFD and the methodology was adapted as follows:

1. Pairwise comparison of CTSs to identify technical contradictions (couplings) from the roof of the House of Quality (HoQ)
2. Translation of the identified coupled CTSs into the most relevant engineering contradiction characteristics

Since the application of TRIZ is in a new field, the methodology of how the introduction of new physical and biological characteristics were translated to the generic TRIZ characteristics is discussed in greater detail in step 4.

The steps of the approach are given in Figure 5. The detailed methodology following these steps, is given in the sections below. The four steps to apply QFD-TRIZ were: Identifying and validating the CAs; identifying and validating the CTSs, construction of the HoQ; speculate upon future scaffold design concepts by applying TRIZ.

4.2.2.1 Step 1: Identifying and validating the Customer Attributes

The process of scaffold design began with obtaining the Customer Attributes (CA). This was conducted by reviewing the literature for statements about what an ideal implant needs to do in order to successfully regenerate tissue. The seminal paper in this research domain is that by Jones et al., (2003).

In the method of this thesis these statements were taken as the VOC, and hence were taken as an initial set of CAs. This attribute set was validated with experts in the field.

The methodology to do this was as follows. A set of 10 experts was derived, based on their published citations of the seminal paper. Each was contacted via email. The experts were asked three questions (a) whether they agreed with the CAs, (b) whether they wished to suggest further CAs (c) if they could numerically rank the CAs. 5 responses were received. The ranked values on a nine-point scale (one, extremely unimportant to nine, extremely important) were taken as the CI rating in this QFD approach. The CI values were averaged and entered into the first HoQ (see Figure 12). No expert suggested further CAs.

4.2.2.2 Step 2: Identifying and validating the Critical-to-Satisfactions

The validated CAs were further refined in order to apply specifically to the design of a bone tissue scaffold.

The methodology to derive these CTSs was as follows. The work by the original authors that followed the seminal paper was established. The journal papers which cited the seminal and subsequent papers were obtained. The end of this survey was July 2012.

The papers were analysed to see if there were any re-occurring statements which had the characteristics of CTSs, i.e. statements that without these characteristics a bone tissue scaffold design would fail. The details of these CTSs and the papers which included them are given in appendix A.

These statements were again validated via a survey in which 10 experts were asked to indicate the level of importance using the same nine point scale. The survey also again offered the opportunity for experts to input extra statements or amend any if deemed necessary. Again five responses were received from the same experts. No expert suggested further CTSs

The validated statements from Step 1 and 2 were inputted in HoQ 1 (Figure 12).

4.2.2.3 Step 3: Assessing the scaffold concept (House of Quality 1)

A relationship matrix was used to identify the interaction between individual CTSs and CAs. The relationship between the CTSs and CAs was derived based on whether a CTS could cause a CA. For example acting as a template for three-dimensional bone growth might cause the 'ability' to maintain blood supply. For example this is shown in Figure 12 as a strong interaction (●).

The method for populating the matrix was as follows. In order to represent a cause-and-effect relationship between every CA and CTS, symbols denoting the strength of the interaction (●, ○, or Δ) were placed in the appropriate cells. The symbols correspond to a numerical strength of 9, 3, or 1. The strength of the relationship was dependent upon information extracted from the journal papers reviewed for the CTSs. Based upon the description and the frequency of mention of the interactions from the cited papers, a decision was made as to the strength of the relationship.

Based on the relationship matrix the next step was to determine the absolute importance of each CTS. This was calculated for each CTS by multiplying the interaction strengths (either 9 ,3 or 1) between the CTS and each individual CA by the customer importance (as obtained from the survey) and summing the values for the column. Hence for example the absolute importance for 'acting as a template for 3D bone growth is 180. The relative importance is then the figure given as a percentage of the total importance. This provides an indication of the level of priority in terms of scaffold design.

A Direction of Improvement (DOI) was applied to each CTS as a visual aid to help in target setting. CTSs were classified as smaller-the-better, larger-the-better or nominal-the-best. The method for selecting a DOI for each CTS was based upon how researchers of the cited journal papers best advised improving a particular characteristic.

4.2.2.4 Step 4: Generating scaffold design concepts using TRIZ (House of Quality 1)

In this section of the method the couplings were identified and the TRIZ parameters were applied.

4.2.2.4.1 Step 4.1: Identifying the couplings

The roof of HoQ 1 (Figure 12) was used to perform a pair-wise comparison of the CTSs in order to identify potential couplings. A coupling is when variation in one CTS has an effect on one or more CTSs. Couplings can be a synergistic (positive) or contradictory (negative).

Couplings were identified from two domains of knowledge. Firstly, from the literature on bone tissue scaffolds and secondly, from the literature on the mechanical properties of brittle porous materials. The couplings and their supporting references are given in Table 16 (Chapter 5).

The prior review of the publications cited from the seminal paper were analysed in order to locate descriptions and comments from the authors as to how individual CTSs were compromised or affected by other parameters.

Based upon these qualitative statements the roof of the HoQ 1 was populated with symbols to indicate, firstly, if a coupling existed and secondly, the type of coupling.

4.2.2.4.2 Step 4.2 Resolving the couplings

Having identified the couplings another technique was needed to attempt to resolve or 'uncouple' them. The Theory of Inventive Solutions (TRIZ) was applied.

TRIZ is the intersection of 'Altshuller's 39 parameters' with the '40 Inventive principles'. Altshuller's 39 Parameters are statements of features that are common variables which influence product design. These parameters were entered into the contradiction matrix. The 40 inventive principles are a list of design solutions that historically have been found to be of interest relating to certain contradictions/couplings.

In order to apply TRIZ to the scaffold design concept an assumption had to be made that Altshuller's 39 Parameters are capable of describing the inputted CTSs.

Altshuller's parameters that best described the CTS of interest were selected (Table 17 – Chapter 5). This was done by attempting to associate a CTS with the closest matching parameter based upon similarities in the generic feature description.

The following method was used to input the CTSs into the contradiction matrix Table 18 (Chapter 5).

First a numbered coupling that was identified from the roof of the HoQ (Figure 12) was selected. Then of the two CTSs, one was selected as the feature that should be improved and the other that therefore would worsen. The contradiction matrix (Table 18) was consulted with the rows corresponding to the improving feature and the column corresponding to the worsening feature. The cell of the contradiction matrix in which the two intersect contained the numbers of the recommended principles. Finally these numbers were consulted against the list of the 40 principles and used to create a shortlist of potential ideas to solve the coupling.

4.3 Reapplication of Quality Function Deployment

This QFD method is different from the QFD method present in 4.2. For the purposes of this application the TRIZ method has been excluded. The intent of this was to focus upon expanding the HOQ step, in an attempt to generate greater resolution of the scaffold design problem by generating specific design requirements (DRs). Conflict resolution was not the priority at this level of design.

The methodology used for deriving DRs and their prioritisation for a bone-tissue scaffold is given below.

4.3.1 Definition of terms

House of Quality (HoQ): A tool within QFD that is widely used as the first step in the development of a new product. An input-output based strategy that establishes a list of 'What the customer wants' and transitions towards a list of design considerations of 'How these will be met'.

Customer Requirements (CRs): List of needs that the customer requires the product to satisfy. These form the initial customer 'What' statements.

Customer Importance (CIs): The level of importance attributed by the customer to each individual CR. In this case a nine point scale was applied (1, extremely unimportant to 9, extremely important).

Design Requirements (DRs): These are the design 'How' statements. CRs are separated into several DRs, depending on how the designer deems necessary to satisfy the initial attribute.

Relationship matrix: An indication of how the DRs affect the satisfaction of each CR. The strength of the relationship is indicated by correlation intensity (strong, medium, weak or none).

Absolute Importance (AI): An indication of how each DR corresponds to one another when allocating resources for the future design/fabrication phases.

Engineering target values (TGT): A set of target values that will later allow the designers to assess a level of technical benchmarking for the bone-tissue design concept.

Couplings: The 'roof' of the HoQ is a pairwise comparison of the DRs. The purpose is to indicate whether there is, firstly, a relationship, secondly, whether the DR upholds or is in conflict with another DR and finally, the intensity of the interaction. This allows the designer a starting point when deciding on trade-off decisions between conflicting design 'hows'.

4.3.2 Method overview

The purpose of the methodology was to take the bone tissue scaffold concept and develop it further at the initial planning and design stage. In order to do this the methodology uses a HoQ. The methodology outlined by Franceschini (2000) was followed.

The HoQ methodology consisted of 7 steps, see Figure 7.

The following section outlines the method and describes deviations from the referenced methodology.

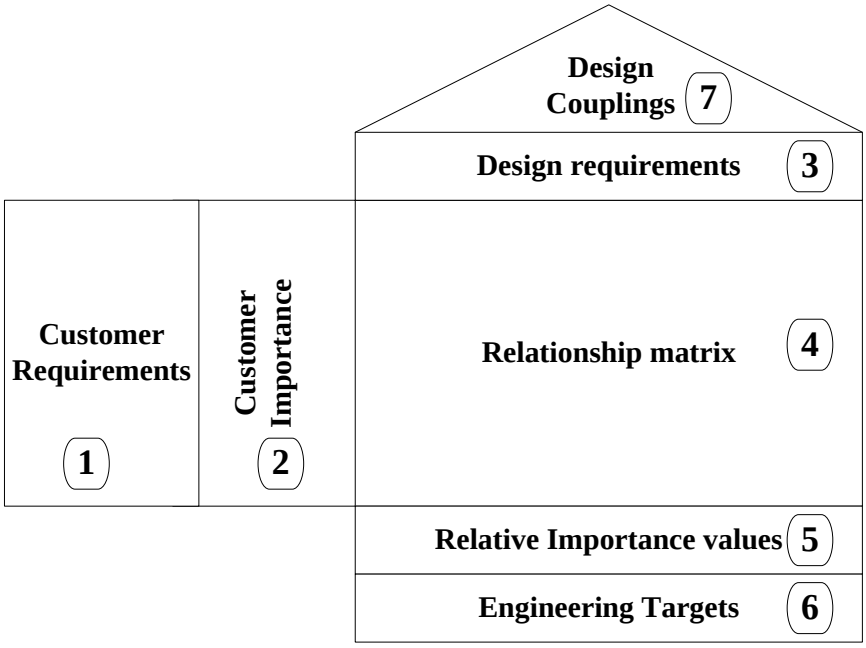


Figure 7. Components that make up the House of Quality. The numbered parts refer to a step in the methodology.

4.3.3 Constructing the House of Quality

4.3.3.1 Step 1 & 2: Obtaining the Customer Requirements and assigning importance ratings

The endpoint from the previous HoQ (Chapter 5) was a list of validated Critical-to-Satisfactions (CTSs) statements and corresponding Customer Importance (CI) ratings. They are listed in Table 10 below and were selected as the starting point for this HoQ in the form of CRs.

The method of collecting these attribute statements from the literature the subsequent survey validating them and the CI ratings is found here section 4.2.2.1 and 4.2.2.2.

#	**Customer Requirement statement**	**Customer Importance**
CR_1	Act as template for three dimensional bone growth	9
CR_2	Resorbs at the same rate as bone is repaired	7
CR_3	Is biocompatible (non-toxic)	9
CR_4	Composed of a bioactive material (class A/B)	8
CR_5	Surface properties promote cell adhesion	9
CR_6	Exhibit mechanical properties that match host bone	6
CR_7	Transmit fluid stress across itself	7
CR_8	Transmit compressive stress	8
CR_9	Have a fabrication process that allows scaffold to fit a differing range of geometries	8
CR_{10}	Be sterilizable and meet regulatory standards	9

Table 10. The Customer Requirement statements and importance ratings on which the House of Quality was based.

4.3.3.2 Step 3: Establishing the Design Requirements

Based upon citations from the seminal papers containing the CRs (see appendix A), publications in the field of bone tissue scaffolds were surveyed for quantitative engineering characteristics that were applicable as potential design requirements (DRs).

This information was disseminated and from which a list of DRs were constructed (Chapter 6). These DRs were based upon empirical research data exploring certain aspects of bone-tissue scaffold design.

The sources of information were collected from several domains of research covering, bone biology, scaffold fabrication, computer simulation, computation fluid dynamics and material science (Chapter 6). This was to extract as much information from multiple disciplines that all relate to a particular attribute that make up scaffold design in its entirety, and provide a foundation on which scaffold design could be explored.

The sources of all information gathered to establish DRs are shown in Table 21 to Table 48 (Chapter 6). These tables form the basis of determining both the technical engineering targets and design couplings.

4.3.3.3 Step 4: Populating the Relationship Matrix

Each DR was compared against CR. Every comparison, was based upon a question of whether the individual DR had any impact on satisfying the CR.

A level of correlation intensity was applied based upon the judgement of descriptions and statements extracted from the review literature publications. Each correlation intensity symbol has an assigned numerical value, strong (9), medium (3), weak (1) or non-existent (0).

4.3.3.4 Step 5: Calculating the Absolute Importance values

For each DR column the assigned numerical value representing the strength of the relationship was multiplied by the corresponding CI value, then summed to provide an Absolute Importance (AI) rating.

4.3.3.5 Step 6: Determining Engineering Targets

The engineering targets were extracted from a wide range of publications. These were identified by a reviewing the results of publications involved in the fabrication and modelling of scaffolds. These were quantitative statements where possible. Multiple targets were included for particular DRs where researchers identified different results.

4.3.3.6 Step 7: Identifying design couplings (interactions)

Research publications that were derived from the original seminal papers were analysed in order to identify descriptions or statements from authors that suggested a relationship between individual DRs.

If the relationship was gathered from only a single source then a ‘weak’ correlation intensity was applied. If the authors findings were based from empirical research then ‘strong’ correlation intensity was applied.

4.4 Three-dimensional Relationship Technology Chart

4.4.1 Introduction

One of the outputs from the second house of quality application in Chapter 6 was a list of design requirements with attached importance values. These values are assumed to be for a generic 'one size fits all' bone tissue scaffold. This is because the customer requirements cover the generic requirements extracted from the literature on bone tissue scaffolds. The next problem was to identify which design requirements are necessary under certain constraints or for a particular design focus.

The next step was to identify a design methodology with the capability of combining different technologies according to both the initial customer demanded qualities and for a set of different design intents. In short, from a common list of technologies, which one should be selected when faced with different design scenarios. The purpose of which is to present to the customer a set of different design options based upon their initial demanded requirements under for a specific set of conditions.

However the review of the current design methods in Chapter 2 uncovered no such example. In Akao's (1988) text book "Quality Function Deployment" a single case study was presented that centred upon a company having a similar problem of choice. The following section briefly describes the case study in which the attempted future design methodology was applied. It is presented, unusually, here in the methodology, rather than the literature review, because it forms the key methodological statement in the literature.

This tool was presented for a case study by Taikisha Ltd., in the application of water technology to design and build air conditioning equipment (Akao, 1988). A summary of the case study is shown in Table 11.

What were the inputs?	*Input collection method*	*What were the outputs?*	*How were the findings validated?*	*Do the authors recommend the method?*	*Reference*
1) Customer demanded quality 2) Corresponding technology 3) Rooms	Not stated	Identification of most appropriate technology choice for each room	Case study	Recommended since it allows designers to explain design decisions to customers	(Akao, 1988)

Table 11. Three-dimensional relationship technology chart literature.

The application of this method in Taikisha Ltd., case study centred around the design problem of integrating different air conditioning technologies into different rooms based upon a wide range of demanded qualities. Examples of thirty-seven listed demanded qualities are "can provide proper humidity, can reduce CO and CO_2, easy to maintain and fits the building design." Examples of the rooms are "hallway system, dining room system and general office system." The twelve technologies are all different air conditioning and climate control systems. The three-dimensional relationship technology chart was used to fit the related technology into design, therefore the most suitable air conditioning technology for each clean room could be identified.

Therefore the decision to select and apply this methodology was based upon the reasoning that it would aid in the decision making when having to select design requirements (identified by the QFD, house of quality tools) for the design of a bone tissue scaffold for different scenarios.

Since little literature is available on this method several assumptions had to be made:

1. Clean rooms and the manufacturing processes within them would be replaced with hypothesised scaffold design strategies
2. Demanded quality statements could be substituted by customer requirement statements
3. Corresponding technologies could be substituted by scaffold design requirements
4. The standard point scores for evaluation used in the case study can be applied without changes for this application

4.4.2 Redefinition of terms for a bone tissue scaffold three-dimensional technology relationship chart

Three-dimensional Relationship Technology Chart: A matrix consisting of three components. Firstly, the customer demanded quality, secondly, design strategies for different scenarios and finally, the design requirements as previously identified (house of quality-Chapter 6).

Customer demanded quality: These are the needs of the customer

Design strategies: Hypothetical statements that are created by the designer to provide a theoretical application of the product in order to create a degree of context for the design problem

Design requirements: A parameter that can be measured or controlled, that when modified, impact upon the satisfaction of meeting the customer demanded quality.

4.4.3 Constructing the Three-dimensional relationship technology chart

The methodology for the three-dimensional technology chart is described by Akao (1988). The following section describes the steps used to create the three-dimensional relationship technology chart and any deviations described.

4.4.3.1 Step 1: Collecting the customer demanded quality

Traditionally this is the customer verbatim. However in this application, the customer demanded quality consists of attribute statements extracted from the literature and are listed in Table 15. The placement of these statements is shown in Figure 8 (vertical axis).

4.4.3.2 Step 2: Creating the design strategies

Design strategies were introduced on the basis that presentation of choice by the addition of differing contexts would add value to the bone tissue scaffold concept. These are a list of hypothetical statements that focus on a particular deliverable for the microstructure and thereby constrain the design requirements.

The design strategies are a statement of a specific function that the microstructure design needed to achieve and how this is to be achieved at the highest level of design. The method for constructing the design strategies was based upon the following:

1. What needed to be achieved by the design
2. For what purpose this was required
3. How this was to be achieved

Each strategy is constrained to a particular design focus with the deliberate intention of limiting ambiguity.

4.4.3.3 Step 3: Selecting the design requirements

The design requirements found from Chapter 6 were reviewed. The following criteria was applied to exclude certain design requirements:

1. Biological design requirements were excluded on the basis that since they formed part of the design intent, they could no longer be considered as part of the microstructure design solution
2. Material characteristics such as stiffness were excluded since they would be used to characterise various engineering metrics of the final product
3. The manufacturing requirements and regulatory approval were removed since they were too far 'downstream' in terms of overall product development for this stage of design

The decision was made not to include additional design requirements at this stage.

4.4.3.4 Step 4: Scoring criteria

The same scoring system was used as Akao's (1988) case study. Table 12 presents the 0-5 scale used to evaluate the intensity of the relationship between the customer demanded qualities and design strategies, and separately, the customer demanded qualities and design requirements.

	Design Strategy	**Design Requirement**
Score	*The requirement for this quality is…*	*The corresponding design requirement is…*
5	Strong	Excellent
4	↕	↕
3	Average	Average
2	↕	↕
1	Unnecessary	Inferior
0	Negative	Bad

Table 12. Scorings used for the Three-dimensional relationship techonology chart.

The scoring between demanded quality and design strategy was based upon how relevant each demanded quality was to a particular design strategy.

The scoring criteria between the demanded qualities and design requirements were based upon the intensity of relationship between the two.

4.4.3.5 Step 5: Constructing the technology chart

Figure 8 shows the basic construction of a three-dimensional relationship technology chart. The demanded qualities, design requirements and design strategies formed the x, y and z plane struts, interspaced by the three matrices.

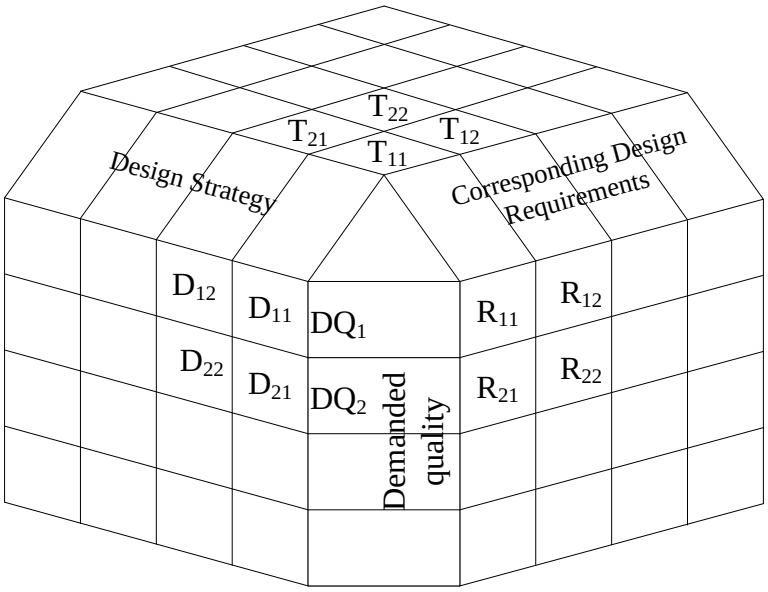


Figure 8. Construction of a three-dimensional relationship technology chart for a bone tissue scaffold, where DQ = demanded quality, D = design Strategy, R = design requirements and T = total score. Adapted from Akao (1988).

The matrices were populated using the scores in Table 12. In order to find the overall degree of effectiveness, individual design requirements had for each design strategy the following calculation was used:

$$T_{21} = D_{11} \cdot R_{11} + D_{21} \cdot R_{21}$$

For example if $D_{11} = 5$, $D_{21} = 1$, $R_{11} = 5$ and $R_{21} = 3$

$$T_{11} = 5 \times 5 + 1 \times 3$$

$$T_{11} = 28$$

4.5 Axiomatic Design methodology overview

This section of the methodology describes two different models of bone tissue scaffold design constructed using axiomatic design. The first model investigates the application of percolation theory to design a bone tissue scaffold. The second model takes the concept further by using time as the metric on which to design a bone tissue scaffold.

4.5.1 Definitions

Axiomatic Design (AD): A systematic approach for establishing the design entity structural hierarchy via the decomposition of Functional Requirements (FRs) and identifying coupling vulnerabilities (Suh, 2001).

Customer attributes (CAs): The needs of the customer

Functional requirements (FRs): The required properties of that the scaffold needs to fulfil. The question for each FR in its simplest form is described as 'what do you want?'

Design parameters (DPs): Propositions as to 'how' the property requirements can be fulfilled in terms of a physical structure in a way that can be quantified and designed for

Mapping: The intellectual thought process behind the movement of "what" to "how" is termed as mapping. For each FR an attempt is made to map to an appropriate DP

Decomposition: The result of the interplay (zig-zagging) between "what needs to be achieved" and "how that need can be achieved"

Matrix: The design matrices are used to compare individual FRs against respective DPs. Based upon these matrices it is possible to identify which FRs and DPs are coupled and which are not.

Couplings: An incremental change in one variable (FR) has an impact on another (DP). In an ideal scenario, one variable only influences one other. If a single variable influences multiple variables then decoupling is attempted.

This is an attempt to uncouple a variable from another by introducing additional, or by removal of, parameters (FRs or DPs), in an attempt to improve the overall design.

Endpoints of AD: The decomposition continues until:

1. There is not enough domain knowledge to break the FRs or DPs down any further in which case proceed to 2
2. There is not enough out of domain knowledge for the detailed design of physical structure.
3. A physical design hierarchy exists that extends over several levels, and potentially domains, which can be used as a basis for fabrication

4.5.2 Axiomatic Design model 1 methodology

This methodology describes the proposal of a bone tissue scaffold design based upon percolation theory. In previous design solutions the lack of a defined microstructure in terms of particle arrangements and organisation was noted. Therefore percolation theory was selected on the basis of its use to describe fluid flow through randomly packed media. Percolation theory was best choice due to its research into parameters and factors that influence the transportation of micro-organisms, such as bacteria, and fluid, through porous media such as soil and rocks. An overview of the methodological process is shown below in Figure 9.

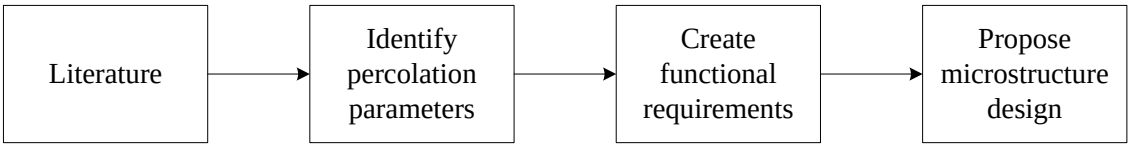


Figure 9. Flow diagram of the methodology used to design a bone tissue scaffold based upon percolation theory.

4.5.2.1 Design literature

Analysis of research papers that related the transportation of bacteria through porous media via percolation theory was the foundation on which this process occurred (Dias et al., 2012; Pooyan et al., 2012; Li et al., 1996; Tommasini et al., 2008; Haugen et al., 2004; Ochoa et al., 2009; Marshall and Ratner, 2005; Innocentini et al., 2010; Ghassemi and Pak, 2011).

4.5.2.2 Identification of percolation theory parameters

These research papers were analysed for percolation parameters that could be extracted and had the potential to be applied for the design of a bone tissue scaffold. Parameters specifically associated with lattice arrangements were identified. An appreciation of how percolation interacts with its porous surrounding as well as the reaction kinetics for gaseous and nutrient transport for bacteria was also developed (see appendix B for further details).

4.5.2.3 Constructing functional requirements

This was done by on a functional basis in order to minimize confusion, as recommended in the literature (Hirtz et al., 2002; Shiba et al., 1993). Intangible terms, auxiliary verbs and abstract words were all avoided. The FRs were constructed according to the function definition template of verb + noun + qualifier.

4.5.2.4 Microstructure design

The traditional Axiomatic Design decomposition methodology was applied as described by Suh (2001) in order to generate percolation-theory-based microstructural design. The design was presented in the form of matrices. This section describes how the matrices were formed and how they are to be interpreted.

At each hierarchical level of design, matrices were used to analyse the relationship between each FR and each DP. Once the DPs had been prescribed to an FR (in some cases more than a single DP was used) an 'x' indicated a coupling whereas a '0' indicated no relationship.

$$\begin{Bmatrix} FR_1 \\ FR_2 \end{Bmatrix} = \begin{bmatrix} X & 0 \\ 0 & X \end{bmatrix} \begin{Bmatrix} DP_1 \\ DP_2 \end{Bmatrix} \quad (1)$$

$$\begin{Bmatrix} FR_1 \\ FR_2 \end{Bmatrix} = \begin{bmatrix} X & X \\ 0 & 0 \end{bmatrix} \begin{Bmatrix} DP_1 \\ DP_2 \end{Bmatrix} \quad (2)$$

$$\begin{Bmatrix} FR_1 \\ FR_2 \end{Bmatrix} = \begin{bmatrix} 0 & 0 \\ X & X \end{bmatrix} \begin{Bmatrix} DP_1 \\ DP_2 \end{Bmatrix} \quad (3)$$

As examples from matrix 1, FR_1 is only coupled to DP_1 and FR_2 is coupled to only DP_2. This is interpreted as any variation in FR_1 will only impact DP_1. In matrix 2, FR_1 is coupled to both DP_1 and DP_2. This means altering FR_1 will impact both DPs, whereas variation in FR_2 has no impact upon DP_1 or DP_2. Matrix 3 is simply the reverse of the situation described by example 2.

4.5.3 Axiomatic Design 2 – Time dependent design approach

The previous designs did not specifically target time as a metric on which to base the design of a bone tissue scaffold. Previously, the action in which the FRs are required to perform have an assumed time factor that is not stated. It is unclear from these FRs at which point or period in time that the action being asked to deliver is optimal. Some FRs may benefit from an immediate action, from a delayed onset of action or a constant period of application. In order to clarify this design challenge FRs should be organised in a sequential order of preferential action.

Therefore in order to combine scaffold design with knowledge about time dependent fluid properties in porous media deviations from the standard AD approach were implemented. These are detailed in the section below.

Deviations from the traditional axiomatic design approach

Firstly the identification of both the FRs and DPs were based upon the findings of the QFD analysis (Table 20 – Chapter 6). This is in contrast to the reviewed AD applications in Chapter 2, where a combination of knowledge, expertise and intuition were used as the foundation on arriving at the statements.

Secondly the FR statements were generated with consideration to time as a factor. A design decision was made that since bone regeneration is a time dependent process then it would make sense to introduce time as a variable in this design methodology. The QFD analysis revealed design requirements (DRs) whose desired effect is time-dependent. Aspects of percolation theory are time-dependent.

Assumptions were constructed on the basis of making the design challenge tractable. The methodology for constructing the assumptions was to begin from an operational perspective that revolves around three points; preparation, application and the end of application. Therefore for the purposes of AD the decision was made to select three 'time instances'.

The first (t = 0) described the microstructure solely as a porous material. The second instance (t = 0.5) described the microstructure whilst undergoing the cell seeding process and the final instance (t = 1) described the influence the microstructure has on guiding the bone tissue in-growth.

Finally, to aid in the mapping process, the FR and DPs were initially created based upon the expanded HoQ in Chapter 6. From this list of DRs, FRs were created and DPs selected or excluded. Then on the basis of comparing a designated DP with a FR statement the most relevant DP was selected. The associations were based upon the couplings identified in Table 21 to Table 48 (Chapter 6).

4.5.3.1 *Methodology for the creation of functional requirements and design parameters*

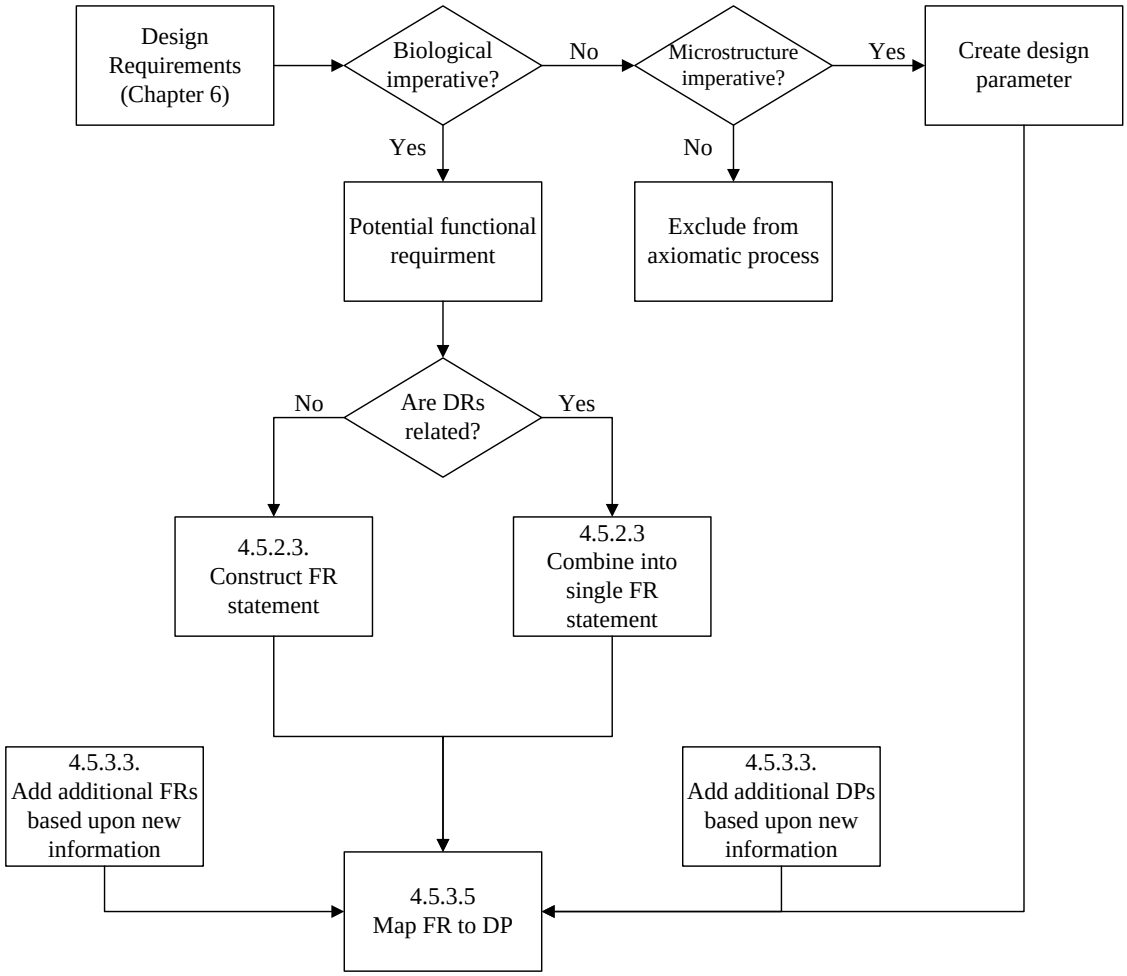


Figure 10. A flow diagram of the process for the creation of functional requirements and design parameters for the axiomatic design process

The DRs as produced by the expanded house of quality in Table 20 were reviewed. Each DR could either be an FR or a DP. In order to distinguish between the two, the following constraint was applied. FRs had to be related to a biological imperative where as a DP had to related to the microstructure of the scaffold (Figure 10).

Having made the initial separation, the DRs which were in contention to be FRs were analysed again with a time criterion. This design decision enabled one or more DRs to

be combined if necessary into a single FR if they were deemed to be part of a similar biological process (in order to minimize the complexity of the design task).

DRs were segregated to a particular 'time instances' based upon the demand for the effect of a particular requirement to occur in at the designated time.

The next step was to translate the selected DRs into FRs (Table 15). This was executed in the methodology previously described in 4.5.2.3.

4.5.3.2 Methodology for additions and exclusions

As shown in Figure 9, extra consideration was given to the possibility of adding additional FRs or DPs. Additional FRs and DPs were included if there were new parameters from fluid flow that suggested that the previous QFD processes had not included. This decision was based upon time dependent properties of fluid flow in porous media.

4.5.3.3 Methodology for design hierarchy assumptions

For each operational point the environment was defined chronologically by constructing FRs using the method in 4.5.3. Based upon the question of how these FRs could be accomplished the DPs were selected from the list of DRs generated by methodology in 4.3.3.2 and assigned accordingly.

4.5.3.4 Methodology for the design matrices (M_1, M_2 and M_3)

Having decided to use time as a factor, the division of which into three time instances, meant attempting to design three different scaffolds. Each design was desired as a descriptive model of what could happen at that time instance. Each model was used to derive the functional requirements and design parameters. The stated FRs for each time instance were compared against the pool of design requirements in Table 51 in 8.1. DPs were then selected that best delivered the property required by the FR. DPs could be used more than once.

4.5.3.5 Constructing the transitory matrices (M_4 & M_5)

Two additional scaffold designs were proposed. These were termed here as 'transitory' matrices. The purpose of these matrices was to determine which FRs from a previous time instance to the one currently being designed may affect the present time instance. Therefore these matrices may provide additional couplings from a previous time instance.

4.5.3.6 Overview time dependent complexity design

In summary the design based upon time dependent complexity consists of five different scaffold designs. One for each time instance, and two for the time transition instances.

4.6 Validation Methodology

The Quality Function Deployment validation is described in Chapter 4 and 5. This chapter describes the validation of the outputs of the different design methodologies applied in this research thesis. The validation step was performed via an email expert opinion survey of mostly UK-based University tissue engineering groups. Figure 11 presents the validation approach for the results obtained in Chapters 5-8, followed by the results and their discussion.

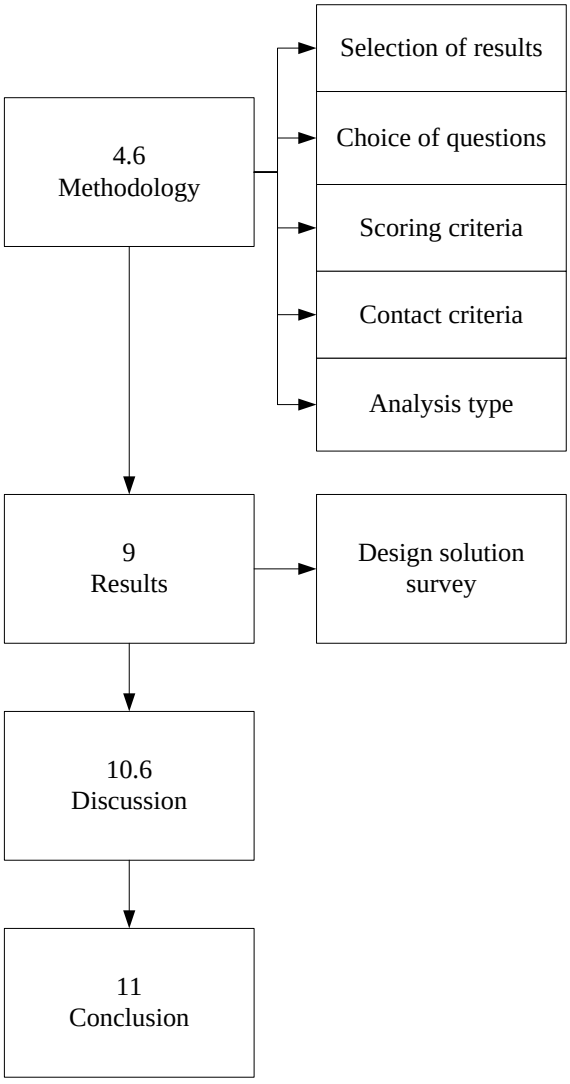


Figure 11. Validation organisation structure. The numbers refer to the chapters in which the relevant information can be found.

4.6.1 Selection of results

The first stage was to send the results without any attached discussion to the participants of the study. It was decided to select an edited 'master' figure from each of the results chapters. Only a single figure per design method was used, due to a self-imposed restriction on the length of the survey questionnaire. The exception to this rule was the Chapter 8 Axiomatic Design results. For this single results chapter the time-dependent design solution was presented in two parts due to the complex nature of the results obtained. The axiomatic percolation model was not included in the survey.

These figures were consolidated into a single word document consisting of the following parts:

1. Quality Function Deployment TRIZ solution
2. Expanded house of quality solution
3. Three-dimensional relationship technology chart solution
4. Axiomatic Design functional requirement time solution
5. Axiomatic Design functional requirement, design parameters and time solution

4.6.2 Choice of questions

The purpose of the validation was to collect opinion on the design solutions themselves and not the design methods used to achieve the results.

For each figure the following set of questions were asked:

1. The design solution could lead to innovation (new or improved product capabilities) in bone tissue scaffold design
2. The content of the design solution enhances current bone tissue scaffold design
3. The solution needs significant improvements
4. I am keen to apply the solution or aspects of it in my future work
5. The solution is….

The questions were all stated from a positive perspective therefore the option to strongly disagree was integrated into the scoring system.

4.6.3 Scoring

A five point scale (Table 13) was selected for the contributors to rate their response to each question. A five point scale was selected on the basis of its popularity in evaluation questionnaires and that it required minimal time for the respondent to complete. Therefore, it was hoped that this would increase the likelihood of people completing the survey due to its simplicity.

Scoring	Statement
5	Strongly agree
4	Agree
3	Neither agree nor disagree (neutral)
2	Disagree
1	Strongly disagree

Table 13. Five point scale used for the validation questionnaire survey

4.6.4 Contact criteria

The next stage was identifying whom to contact for this survey. A decision was taken to base the contact group on the mailing list for the UK Society for Biomaterials. The reason for using this Society as the foundation for this validation stage and its suitability were due to the Societies own description of itself:

"The United Kingdom Society for Biomaterials (UKSB) was set up to serve the diverse, interdisciplinary biomaterials research community. This was in response to the findings of a joint working party of the Institute of Materials and the Institute of Physics & Engineering in Medicine. The UKSB is the democratic Society for the whole biomaterials community[5]*."*

The mailing list was scanned for email addresses. Since it was likely that many 'likeminded' biomaterial and tissue engineering experts would be contained upon this

[5] http://www.uksb.org.uk/about_us.html

list, the research profiles for each were investigated using google.co.uk as the search engine. Based upon this list, researchers in the field of tissue engineering were contacted along with the experts used in the previous validation survey in Chapter 5. Based upon this initial search, further experts were identified and subsequently contacted. All correspondence was performed via email, with the survey sent as an attached word document. In total, twenty four experts were contacted.

The details for the UK Society for Biomaterials were available from the following online address:

http://www.uksb.org.uk/ (access date: 22/01/2013)

4.6.5 Analysis type

Radar charts were selected as the method of presentation for the results. These charts were selected on the basis of their formality to QFD practitioners.

4.7 Summary

This chapter summarises how the selected design methodologies identified in Chapters 2 and 3 were applied in order to implement the research strategy. Two different variations on the house of quality tool were applied, one three-dimensional relationship technology chart and two Axiomatic Design models. The first based incorporated percolation theory and the second, a time-dependent model split over three time instances. The outputs of each design method formed the inputs of the next, with the exception of the three-dimensional relationship technology chart. The inputs of the Axiomatic Design method were selected from the second house of quality attempt. These designs (with the exception of the percolation model) were then incorporated into a survey to be validated by experts in the field of tissue engineering.

5 Results: Quality Function Deployment and TRIZ

This chapter presents the results of the first attempt at the application of Quality Function Deployment in the design of microstructure for a bone tissue scaffold. This process is centred upon the house of quality tool. The process begins with establishing the needs of the customer, by using the literature as the source of the attribute statements. Once these statements were validated via an emailed survey, the house of quality allowed for the co-ordination of information for the application of TRIZ to resolve design problems identified in the roof of the house of quality. The results are presented in the sequence of the steps outlined in the method.

The starting point for the literature Voice of the Customer (VOC) was to use the criteria by which living tissue is defined (Jones et al., 2006). These statements are shown below in Table 14. Therefore the first part of the results was to obtain a set of validated VOC statements in order to form the foundation of the design process.

5.1 Step 1: The validated Voice of the Customer

In order to use the agreed literature criteria of living tissue these statements were validated as described in the method. The response from the regarded experts is presented in Table 14. The averaged nine-point scale customer importance (CI) scores indicate two extremely important attributes (maintain blood supply and self-repair) and one important attribute (modify in response to environmental factors).

Number	Customer Attributes	Averaged CI score
1	Ability to maintain a blood supply	9
2	Ability to self-repair	9
3	Ability to modify in response to environmental factors	6

Table 14. The average Customer Importance scores from the survey for the literature Customer Attributes.

5.2 Step 2: The literature derived CTSs

The critical-to-satisfaction statements (CTSs) were also extracted from the literature. These statements are the current criteria that an ideal bone tissue scaffold should fulfil. These were also validated by the email survey as described in the method. The averaged nine-point CI scores for the CTS statements are shown in Table 15.

The averaged CI scores indicate firstly that all the CTSs are at the very least important and secondly since no expert suggested additional statements the VOC step was halted here.

Number	Critical-to-satisfactions	Averaged CI score
1	Act as template for three dimensional bone growth	**9**
2	Resorbs at the same rate as bone is repaired	**7**
3	Is biocompatible (non-toxic)	**9**
4	Composed of a bioactive material (class A/B)	**8**
5	Surface properties promote cell adhesion	**9**
6	Exhibit mechanical properties that match host bone	**6**
7	Transmit fluid stress across itself	**7**
8	Transmit compressive stress	**8**
9	Have a fabrication process that allows scaffold to fit a differing range of geometries	**8**
10	Be sterilizable and meet regulatory standards	**9**

Table 15. The averaged importance scores from the survey for the literature critical-to-satisfaction statements

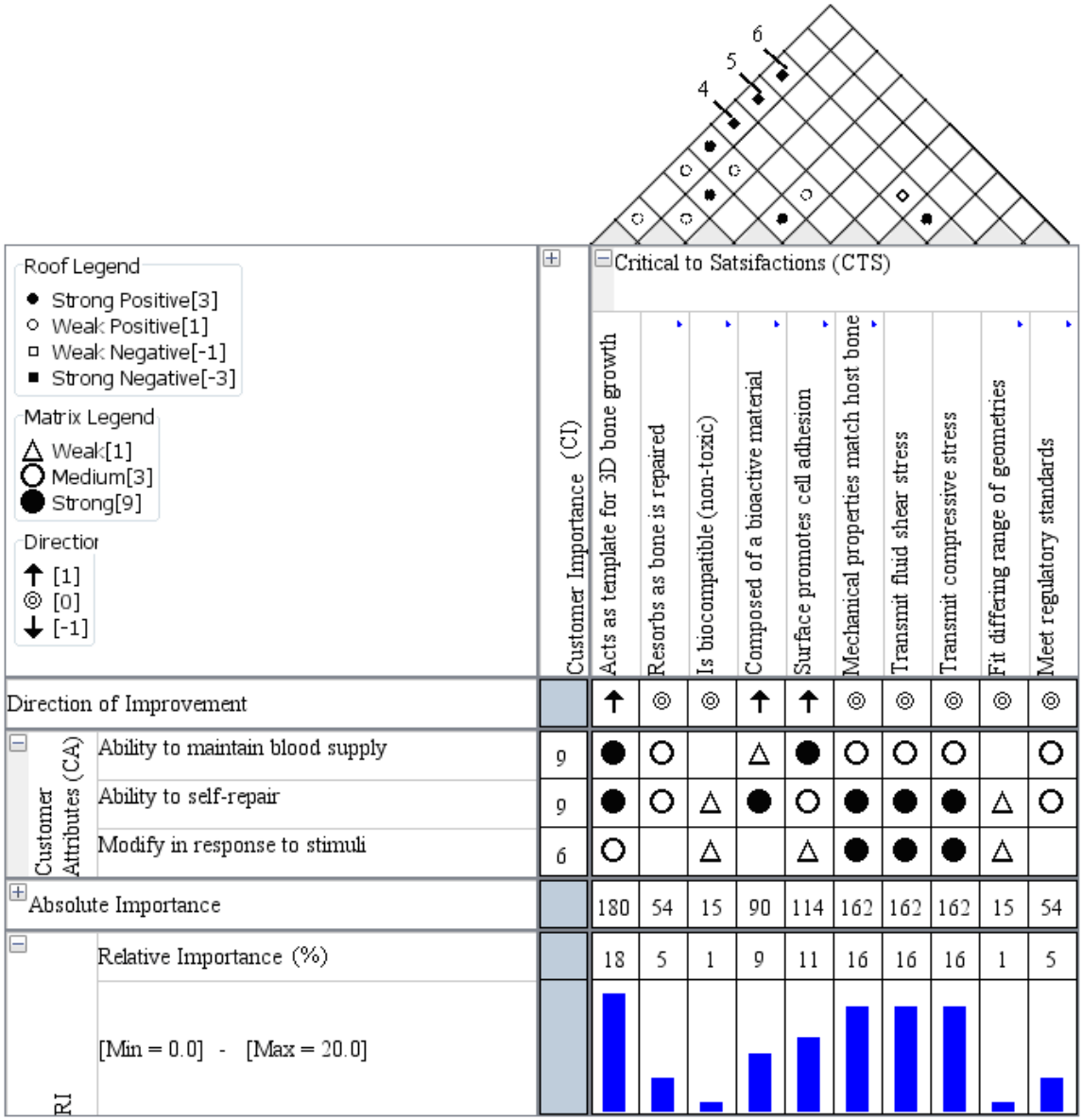
Having generated two sets of validated attribute sets the house of quality tool allowed the flow of information to be co-ordinated through a single focal point. This is presented in Figure 12 where the link between attributes of living tissue and the attributes of an ideal scaffold are analysed. The house of quality tool establishes a visual representation of the relationship between the two hierarchical sets of attribute statements and potential interactions.

5.3 Step 3: House of Quality 1

In Figure 12 the CAs are listed vertically on the *y*-axis and the CTSs listed horizontally along the *x*-axis. The central populated relationship matrix shows the interactions between the weighted CA CI scores against the CTSs. The percentage relative importance (RI) scores are listed along the foot of the house of quality and correspond to the CTS in the same column. A bar chart acts as a visual aid for ease of discussion should the results be presented either back to the customer or to design teams further along the production chain. The second matrix is the roof of the house of quality at the centre top of the figure. In this matrix each CTS is compared against itself in order to determine the antagonist, synergistic or absence of interaction. These interactions are numbered 1-13 bottom left to top right for each slanted row. The information on which these numbered couplings were based upon are referenced to in Table 16.

The CTSs with the four highest RIs are the scaffolds ability to act as a template, mechanical properties match host bone, transmission of fluid stress and transmission of compressive stress. The following RI values are stated on order of the CTSs presented above, 18, 16, 16, and 16. These values are percentages and contribute to approximately two thirds of the overall design intent.

Each CTS has a designated direction of improvement. The CTSs, acting as a template, composed of bioactive material and surface properties that promote cell adhesion are all assigned to “more-is-better” (up arrow). The other CTSs are designated as “target –is-best” (circle).



		Acts as template for 3D bone growth	Resorbs as bone is repaired	Is biocompatible (non-toxic)	Composed of a bioactive material	Surface promotes cell adhesion	Mechanical properties match host bone	Transmit fluid shear stress	Transmit compressive stress	Fit differing range of geometries	Meet regulatory standards
Direction of Improvement		↑	◎	◎	↑	↑	◎	◎	◎	◎	◎
Ability to maintain blood supply	9	●	○		△	●	○	○	○		○
Ability to self-repair	9	●	○	△	●	○	●	●	●	△	○
Modify in response to stimuli	6	○		△		△	●	●	●	△	
Absolute Importance		180	54	15	90	114	162	162	162	15	54
Relative Importance (%)		18	5	1	9	11	16	16	16	1	5

Figure 12. House of Quality 1, Customer Attributes to Critical-to-Satisfaction mapping. The feedback from the survey is shown in the CI column. The relationship matrix shows strong interactions for four CTSs, reflected by the Relative Importance scores. The roof shows that the scaffolds ability to act as a template is the most coupled characteristic. The literature relevant to identify the "couplings" in the roof is shown in Table 16. The numbered couplings are discussed in Table 19.

5.3.1 Step 4.1: Identifying the couplings

Table 16 presents the literature used to support the identification of the couplings shown previously in the 'roof' of Figure 12.

Coupling	Pairwise comparison		Sources
	CTS_A	CTS_B	
1	Template for 3D bone growth	Resorbs as bone is repaired	(Jones et al., 2006b)
2	Template for 3D bone growth	Composed of Bioactive material	(Sepulveda et al., 2002a; Sepulveda et al., 2002c)
3	Template for 3D bone growth	Surface properties support cell adhesion	(Blecha et al., 2010; Chang et al., 2000; Goshima et al., 1991; Jones et al., 2007; Silva et al., 2006; Powers et al., 1997)
4	Template for 3D bone growth	Mechanical properties match host bone	(Chang et al., 2000; Jones and Hench, 2003a; Habraken et al., 2007; Hollister et al., 2002; Milan et al., 2010; Kumbar et al., 2011)
5	Template for 3D bone growth	Transmit Fluid shear stress	(Blecha et al., 2010; Olivares et al., 2009; Boschetti et al., 2006; McAllister and Frangos, 1999; Knothe Tate, 2003; Gemmiti and Guldberg, 2009; Chen et al., 2010; Amirkhani et al., 2012)(
6	Template for 3D bone growth	Transmit compressive stress	(Baas et al., 2009; Blaker et al., 2005; Milan et al., 2009; Gutierrez and Crumpler, 2008)
7	Resorbs as bone is repaired	Biocompatible (non-toxic)	(Lai et al., 2002; Lai et al., 2005)
8	Resorbs as bone is repaired	Composed of Bioactive material	(Hench et al., 1999; Xynos et al., 2001; Sepulveda et al., 2002b; Yao et al., 2007)
9	Resorbs as bone is repaired	Surface properties support cell adhesion	(Xynos et al., 2001)
10	Composed of Bioactive material	Surface properties promote cell adhesion	(Sepulveda et al., 2002a; Jones et al., 2007; Hench et al., 1999; Gough et al., 2004; Jones et al., 2006; Ohura et al., 1991; Verrier et al., 2004; Chen et al., 2008)

11	Composed of Bioactive material	Mechanical properties match host bone	(Habraken et al., 2007; Kumbar et al., 2011)
12	Mechanical properties match host bone	Transmit compressive stress	(Milan et al., 2010)
13	Transmit Fluid shear stress	Transmit compressive stress	(Milan et al., 2009; Claes and Heigele, 1999; Prendergast et al., 1997; Hillsley and Frangos, 1994)

Table 16. Literature relevant to the pairwise comparison of CTSs in the 'roof' of the House of Quality in Figure 12. The numbered couplings are in order of how they appear in the HoQ.

5.3.2 Step 4.2: Resolving the couplings

As shown in the 'roof' of Figure 12 (labelled 4, 5 and 6), the strongest contradictive couplings based upon the weight of the literature resources are between the scaffold's ability to act as a template, and (1) mechanical properties that match host bone, (2) transmission of fluid stress and (3) transmission of compressive stress. These three couplings form the focus of the TRIZ analysis.

TRIZ uses generic solutions to generic problems. Therefore an assumption was made that the specific contractions between CTSs for a bone tissue scaffold could be translated into generic TRIZ problems.

Table 17 is the translation of the coupled CTSs into generic TRIZ parameters. The generic definition of the parameter is stated alongside a justification statement for why that particular parameter applies to the CTS attribute.

Critical-to-Satisfaction	**Altshuller's Parameter**	**Parameter Description** (Rantanen and Domb, 2002)
Template for 3D bone growth	*36. Complexity of Device*	*Number and diversity of elements and element interrelationships within a system. The difficulty of mastering the system is a measure of its complexity*
Mechanical properties match host bone	*14. Strength*	*Extent to which the object is able to resist changing in response to force*
Transmit fluid stress	*11. Stress or Pressure*	*Force per unit area* *Tension*
Transmit compressive stress	*10. Force*	*Force measures the interaction between systems. In TRIZ, force is any interaction that is intended to change an object's condition*

Table 17. Translation of desired CTSs to Altsuller's Parameters. These parameters are then entered into the contradiction matrix in order to deliver potential design solutions.

Table 18 shows an abridged contradiction matrix that comprises only the previously identified parameters from Table 17. For the sake of clarity the unused parameters are included with the columns and rows remaining blank.

The matrix shows that for two instances three inventive principles apply, for one instance two apply.

Altshuller's 39 Parameters		**Parameters that become worse**					
		1-9	**10. Force**	**11. Stress**	**12-13**	**14. Strength**	**15-39**
Parameters that improve	**1-35**	…	…	…	…	…	…
		…	…	…	…	…	…
	36. Device complexity	…	26, 16	19, 1, 35	…	2, 13, 28	…
	37-39	…	…	…	…	…	…

Table 18. Abridged TRIZ Contradiction Matrix used to identify the relevant 40 Inventive Principles. The inputted parameters are based upon Table 17 translations. Improving parameters in the vertical axis, parameters that become worse in the horizontal axis.

Table 19 presents a summary of the couplings, the TRIZ parameters and the applicable inventive principles.

Coupling	Statement of coupling or conflict	Relationship		TRIZ Parameter	Applicable TRIZ Principles
4	Preferred increase in the template porosity for desired bone cell penetration and bone in- growth but results in a compromise to Stiffness	↑	Template for 3D bone growth	36. Device complex	2. Separation 13. The other way around 28. Mechanical interaction substitution
		↓	Mechanical properties match host bone	14. Strength	
5	Desired increase in template porosity by random pore anisotropy but leads to creation of zones of random fluid shear stresses	↑	Template for 3D bone growth	36. Device complexity	19. Periodic action 1. Segmentation 35. Parameter changes
		↓	Transmit fluid stress	11. Stress	
6	Desired increase in template porosity leads to increased potential for microcracking when under compression	↑	Template for 3D bone growth	36. Device complexity	26. Copying 16. Partial or excessive actions
		↓	Transmit compressive stress	10. Force	

Table 19. Potential inventive design solutions for uncoupling the CTSs.

5.4 Summary

This chapter describes the first Quality Function Deployment design. This consisted of the house of quality tool and TRIZ. The voice of the customer consisted of attribute statements extracted from the literature, and validated against the opinions of experts. The house of quality delivered a list of percentage importance scores for Critical-to-Satisfaction statements as well as an indication of likely design problems via the roof. The end of this design attempt was the attempted resolution of these problems via the application of TRIZ.

6 Results: Quality Function Deployment second design

This chapter presents the second application of the Quality Function Deployment tool, known as the house of quality (HoQ). This design began with the previous HoQ outputs as the starting inputs. The validated Critical-to-Satisfaction statements in Chapter 5 were re-entered into this house of quality as the starting customer requirements. This was done in order to generate a greater level of design detail by expanding the house of quality. No TRIZ analysis was performed in this application, rather the intent was to focus upon the generation of design requirements (DRs), target engineering values, and recognising design conflicts for the purposes of design.

The results are presented in the order of methodology. For presentation the house of quality has been split into several parts.

The results presented in this chapter begin at Step 3 of the method presented in section 4.3.3.2 since Steps 1 and 2 were based upon results from Table 14 and Table 15. Steps 3-5 of the method all refer to Figure 13.

6.1 Step 3: Establishing the Design Requirements

The DRs are presented horizontally in the house of quality as shown in Figure 13. In Table 20 the DRs are listed alongside the category of research from which they were obtained. The first category are those design requirements extracted from 'porosity theory'. The second are requirements that dictate the bioresorption of the material (i.e. its degradation kinetics). The third group list the biological requirements necessary for bone regeneration. The forth are the common measurable material science properties of porous materials. The fifth group are the key mechano-transduction requirements that result from the intersection between fluid flow through the scaffold and the internal geometry of the microstructure. The final category dictates the generic requirements for scaling up the process so that it can be validated and mass produced for commercialization.

6.2 Step 4: Relationship Matrix

Figure 13 presents the customer requirements, the DRs and the populated relationship matrix. Starting from the left of the Figure, the CRs are listed vertically with the DRs listed horizontally along the top.

The corresponding correlation intensity ratings are located in the centre of the Figure, with the output absolute importance ratings for each DR along the bottom. The bars act as a visual aid so the importance ratings can been more readily identified by the reader.

The relationship matrix shows a clear indication of strong relationships between DRs corresponding to characteristics of 'pores' and the CRs. This is indicated by the cluster of strong interactions on the left hand side of the relationship matrix. The notable exception to this is the strong interactions for fluid flow mediated wall shear stress with the CRs. These interactions are supported by the corresponding AI scores.

6.3 Step 5: Calculating the Absolute Importance values

The CI scores are listed adjacent to the corresponding CR statements, with the numerical weighting applying horizontally across all the DRs. The combined interaction between the weighted CR and correlation intensity within the relationship matrix results in the AI ratings.

The top five DRs in order of significance (AI scores bracketed) are; Fluid flow mediated wall shear stress (399), pore body diameter (390), strut thickness (390), Textural porosity (384) and pore throat diameter (346).

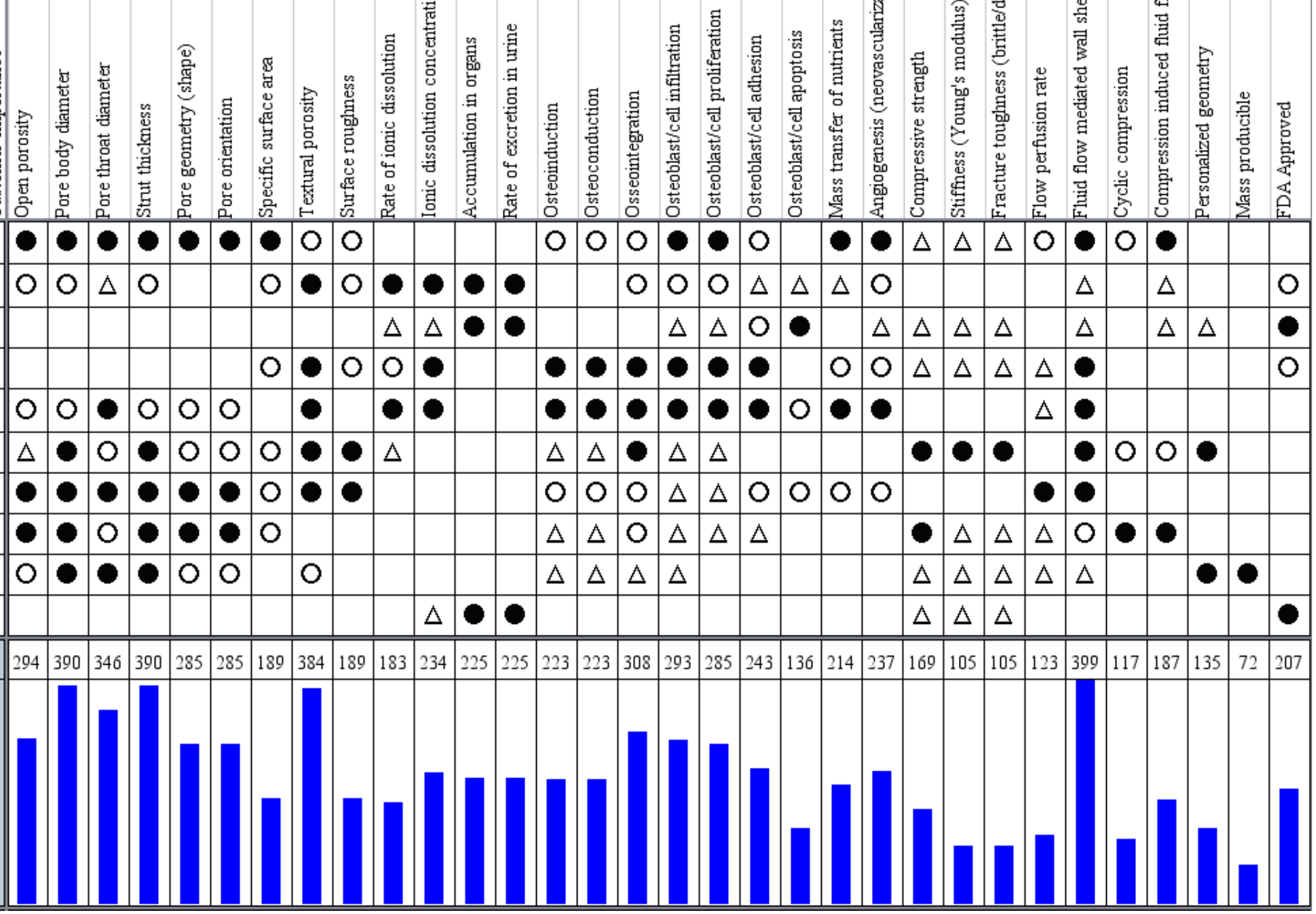
Customer Requirements (CRs)	Customer Importance	Design Requirements (DRs): Open porosity	Pore body diameter	Pore throat diameter	Strut thickness	Pore geometry (shape)	Pore orientation	Specific surface area	Textural porosity	Surface roughness	Rate of ionic dissolution	Ionic dissolution concentration	Accumulation in organs	Rate of excretion in urine	Osteoinduction	Osteoconduction	Osseointegration	Osteoblast/cell infiltration	Osteoblast/cell proliferation	Osteoblast/cell adhesion	Osteoblast/cell apoptosis	Mass transfer of nutrients	Angiogenesis (neovascularization)	Compressive strength	Stiffness (Young's modulus)	Fracture toughness (brittle/ductile)	Flow perfusion rate	Fluid flow mediated wall shear stress	Cyclic compression	Compression induced fluid flow	Personalized geometry	Mass producible	FDA Approved
Act as a template for 3D bone growth	9	●	●	●	●	●	●	●	○	○					○	○	○	●	●	○		●	●	△	△	△	○	●	○	●			
Resorb as bone is regenerated	7	○	○	△	○			○	●	○	●	●	●	●			○	○	○	△	△	△	○				△		△			○
Is biocompatible (non-toxic)	9										△	△	●	●				△	△	○	●		△	△	△	△		△		△	△		●
Is composed of bioactive material	8							○	●	○	○	●			●	●	●	●	●	●		○	○	△	△	△	△	●					○
Surface properties promote cell adhesion	9	○	○	●	○	○	○		●		●	●			●	●	●	●	●	●	○	●	●				△	●					
Mechanical properties match host bone	6	△	●	○	●	○	○	○	●	●	△				△	△	●	△	△					●	●	●		●	○	○	●		
Transmit fluid shear stress	7	●	●	●	●	●	●	○	●	●					○	○	○	△	△	○	○	○	○				●	●					
Transmit compressive stress	8	●	●	○	●	●	●	○							△	△	○	△	△	△				●	△	△	△	○	●	●			
Fabrication of differening geometries	8	○	●	●	●	○	○		○						△	△	△	△						△	△	△	△	△			●	●	
Sterilizable/meet FDA requirements	9											△	●	●										△	△	△							●
Absolute Importance		294	390	346	390	285	285	189	384	189	183	234	225	225	223	223	308	293	285	243	136	214	237	169	105	105	123	399	117	187	135	72	207
[Min = 0.0] - [Max = 400.0]																																	

Figure 13. House of quality. Relationship Matrix from which the Absolute Importance rating for each Design Requirement was calculated. The size of the bar indicating the importance of each Requirement. Pore body diameter, pore throat diameter, strut thickness, textural porosity and Fluid flow mediated wall shear stress are the most important DRs.

6.4 Step 6: Determining Engineering Targets

Table 20 summarises the engineering target values for each design requirement where applicable. The applicable referenced sources are stated alongside the identified target values.

The biological processes that dictate ossification/ osteogenesis are reduced to simple yes/no choices. These indicate whether or not a requirement is desired or not. For example, Osteoinduction is a desired requirement as a result of the scaffold microstructure, however apoptosis is not.

Category		Design Requirement (DR)	Target Value	Reference
1	Porosity theory	Open porosity	59/ 65/ 77/ 89 %	(Boschetti et al., 2006)
			86/88 %	(Jones et al., 2006a)
			67.5/68.9 %	(Melchels et al., 2010)
		Pore body diameter	< 10 µm	(Lan Levengood et al., 2010a)
			2 – 20 µm	(Papenburg et al., 2009)
			100 µm	(Blaker et al., 2005)
			>300 µm	(Blecha et al., 2010)
			50/100/150 µm	(Boschetti et al., 2006)
			300 µm	(Chang et al., 2000)
			500 µm	(Jones et al., 2006a)
			255/290 µm	(Melchels et al., 2010)
		Pore throat size	10 -50 µm	(Blaker et al., 2005)
			50 µm	(Chang et al., 2000)
			100 µm	(Jones et al., 2006a)
		Strut thickness	394/646 µm	(Lan Levengood et al., 2010a)
			0.6 – 1.0 mm	(Sudarmadji et al., 2011)
		Pore geometry (shape)	Cube / hexagonal prism	(Amirkhani et al., 2012)
			Tubular	(Blaker et al., 2005)
			Spherical	(Boschetti et al., 2006)
			Cylindrical	(Chang et al., 2000)
		Pore orientation	Cubic/hexagonal stacking	(Amirkhani et al., 2012)
			Cubic stacking	(Boschetti et al., 2006)
			Gyroid/Salt-leached	(Melchels et al., 2010)
		Specific surface area	126 – 164 m^2/g	(Sepulveda et al.,

				2002b)
			107.4 – 122.7 m^2/g	(Jones et al., 2006a)
		Surface roughness	10 – 100 nm	(Chung et al., 2003)
		Textural porosity	10 – 20 nm	(Jones et al., 2006a)
			2 – 50 nm	(Sepulveda et al., 2002b)
2	**Bioresorption theory**	Rate of ion dissolution	Positive gene-expression profile on osteoblasts	(Xynos et al., 2001)
		Ion dissolution concentration	Positive gene-expression profile on osteoblasts	(Christodoulou et al., 2006)
			pH; ion release lowers pH	(Gough et al., 2004)
		Accumulation in major organs	Negligible Parts Per Million in major organs	(Lai et al., 2002)
		Rate of excretion in urine	1.8 mg/day (rabbits); 24 to 28 weeks	(Lai et al., 2002)
3	**Ossification/ osteogenesis**	Osteoinduction	Yes	
		Osteoconduction	300 µm pores optimal	(Chang et al., 2000)
		Osseointegration	Yes	
		Osteoblast infiltration	10 µm/min	(Isaksson et al., 2008)
		Osteoblast proliferation	Proliferation rate: 20 hours (doubling time)	(Isaksson et al., 2008)
		Osteoblast/cell adhesion	Surface roughness 10-100 nm	(Chung et al., 2007)
		Osteoblast apoptosis	35 cells/mm	(Isaksson et al., 2008)

			Undiluted dissolution products	(Gough et al., 2004)
		Mass transfer of nutrients	Cellular/substrate parameters	(Chung et al., 2007)
		Neovascularization / angiogenesis	33 µm/h (rate of vessel growth); 100 µm (O_2 diffusion distance)	(Checa and Prendergast, 2010)
			>300 µm	(Karageorgiou and Kaplan, 2005)
			>400 µm	(Feng et al., 2011)
4	**Characteristics of porous materials**	Compressive strength	0.1 - 0.15 MPa pre immersion 0.05 – 0.1 MPa after 6 days immersion	(Chen et al., 2008)
			86 ± 5 MPa (Composite – PDLLA)	(Blaker et al., 2005)
			7 – 14 MPa	(Chang et al., 2000)
			1.3 MPa	(Gemmiti and Guldberg, 2009)
			0.34 – 2.26 MPa	(Jones et al., 2006a)
		Stiffness (young's modulus)	5MPa	(Gemmiti and Guldberg, 2009)
		Fracture toughness	-	-
5	**Mechano-transduction**	Flow perfusion rate	0.1 ml/min	(Baas et al., 2009)
			0.5 ml/min	(Boschetti et al., 2006; Cioffi et al., 2006)
			20 µm/s	(Chung et al., 2007)
			0.08 – 0.89 ml/min (Glucose); 0.51 – 1.23 ml/min (Oxygen)	(Provin et al., 2008)

		Fluid flow mediated wall shear stress	2 – 5 MPa	(Boschetti et al., 2006)
			2.45/ 2.90/ 3.48 MPa	(Cioffi et al., 2006)
			0.1 MPa; Continuous	(Gemmiti and Guldberg, 2009)
			0.2 – 1.0 MPa	(Chung et al., 2007)
			1.7 – 2.0 MPa	(Sakai et al., 1999)
			1.5 – 12 dyn/cm^2	(Williams et al., 2002)
			6 dyn/cm^2 ;Nitric Oxide release rate of 9.8 $nmol.h^{-1}.mg\ protein^{-1}$	(Johnson et al., 1996)
			148 dyn/cm^3	(Smalt et al., 1997)
		Cyclic compression	0.1 MPa	(Checa and Prendergast, 2010)
			500 – 5000 microstrain	(Smalt et al., 1997)
		Cyclic compression induced fluid flow	1.5%, 1Hz, 1 hour daily / static	(Baas et al., 2009)
6	**Fabrication processing**	Personalized external geometry	Computer-Aided Design	(Saito et al., 2012; Amirkhani et al., 2012; Sudarmadji et al., 2011)
		Mass producible	RP/SFF fabrication technologies	(Saito et al., 2012; Amirkhani et al., 2012; Sudarmadji et al., 2011)
		FDA approved	Yes	

Table 20. The engineering target values for each design requirement with supporting references.

6.5 Step 7: Identifying design couplings

The following Tables, Table 21 to Table 48 present the design couplings and the supporting references that on which Figure 14 is based upon. There is no correlation between the AI ratings for individual DRs and the number of couplings identified. The strength of the coupling is indicated by whether multiple sources confirm that a coupling exists; (--) strong negative (-) weak negative, (+) weak positive and (++) strong positive.

Strut thickness	--	(Jones et al., 2006b; Jones and Hench, 2003a; Mccoy et al., 2012)
Specific surface area	-	(Melchels et al., 2010)
Rate of ionic dissolution	+	(Jones et al., 2006b)
Osteoconduction	+	(Chang et al., 2000)
Osseointegration	+	(Lan Levengood et al., 2010a)
Osteoblast/cell proliferation	++	(Papenburg et al., 2009; Melchels et al., 2011)
Osteoblast/cell adhesion	+	(Papenburg et al., 2009)
Angiogenesis	++	(Karageorgiou and Kaplan, 2005; Feng et al., 2011)
Fluid flow mediated WSS	++	(Blecha et al., 2010; Boschetti et al., 2006)

Table 21. Pore body diameter couplings

Strut thickness	--	(Jones et al., 2006b; Jones and Hench, 2003a)
Osteoconduction	+	(Chang et al., 2000)
Osteoblast/cell infiltration	++	(Silva et al., 2006; Melchels et al., 2010)

Table 22. Pore throat diameter couplings

Rate of ionic dissolution	-	(Jones et al., 2006b)
Compressive strength	++	(Saito et al., 2012; Jones and Hench, 2003a; Jones et al., 2006a; Jones et al., 2004b)
Stiffness (Young's modulus)	+	(Sudarmadji et al., 2011)
Pore throat diameter	--	(Jones et al., 2006b; Jones and Hench, 2003a)
Pore body diameter	--	(Jones et al., 2006b; Jones and Hench, 2003a; Mccoy et al., 2012)

Table 23. Strut thickness couplings

Compressive strength	+	(Chang et al., 2000)
Cyclic compression	+	(Amirkhani et al., 2012)

Table 24. Pore geometry couplings

Compressive strength	++	(Chang et al., 2000; Blaker et al., 2005)
Cyclic compression	+	(Amirkhani et al., 2012)

Table 25. Pore orientation couplings

Textural porosity	+	(Karageorgiou and Kaplan, 2005)
Rate of ionic dissolution	++	(Lai et al., 2002; Lai et al., 2005; Sepulveda et al., 2002b; Karageorgiou and Kaplan, 2005)
Stiffness (Young's modulus)	+	(Kapfer et al., 2011)
Pore body diameter	-	(Melchels et al., 2010)

Table 26. Specific surface area couplings

Specific surface area	+	(Karageorgiou and Kaplan, 2005)
Rate of ionic dissolution	+	(Sepulveda et al., 2002b)

Table 27. Textural porosity

Osseointegration	+	(Karageorgiou and Kaplan, 2005)
Osteoblast/cell proliferation	++	(Chen et al., 2008; Chung et al., 2003)
Osteoblast/cell adhesion	++	(Chen et al., 2008; Chung et al., 2003)

Table 28. Surface roughness couplings

Ionic dissolution concentration	+	(Lai et al., 2002; Lai et al., 2005)
Textural porosity	+	(Sepulveda et al., 2002b)
Specific surface area	++	(Lai et al., 2002; Lai et al., 2005; Sepulveda et al., 2002b; Karageorgiou and Kaplan, 2005)
Strut thickness	-	(Jones et al., 2006b)
Pore body diameter	+	(Jones et al., 2006b)

Table 29. Rate of ionic dissolution couplings

Accumulation in organs	+	(Lai et al., 2002; Lai et al., 2005)
Osteoinduction	+	(Xynos et al., 2001)
Osseointegration	+	(Ohura et al., 1991)
Osteoblast/cell proliferation	++	(Gough et al., 2004; Verrier et al., 2004; Chen et al., 2008; Christodoulou et al., 2006)
Osteoblast/cell adhesion	++	(Gough et al., 2004; Verrier et al., 2004)
Osteoblast/cell apoptosis	++	(Xynos et al., 2001; Gough et al., 2004)
Rate of ionic dissolution	+	(Lai et al., 2002; Lai et al., 2005)

Table 30. Ionic dissolution concentration couplings

Rate of excretion on urine	++	(Lai et al., 2002; Lai et al., 2005)
Ionic dissolution concentration	+	(Lai et al., 2002; Lai et al., 2005)

Table 31. Accumulation in major organs couplings

Accumulation in major organs	++	(Lai et al., 2002; Lai et al., 2005)

Table 32. Rate of excretion in urine coupling

Ionic dissolution concentration	+	(Xynos et al., 2001)
Fluid flow mediated wall shear stress	++	(McAllister and Frangos, 1999; Hillsley and Frangos, 1994; Sakai et al., 1999; Mccoy et al., 2012; Sakai et al., 1998; Hidalgo-Bastida et al., 2012; Ban et al., 2011; Meinel et al., 2004)
Cyclic compression	-	(Baas et al., 2009)
Compression induced fluid flow	++	(Prendergast et al., 1997; Hillsley and Frangos, 1994; Johnson et al., 1996)

Table 33. Osteoinduction couplings

Pore throat diameter	+	(Chang et al., 2000)
Pore body diameter	+	(Chang et al., 2000)

Table 34. Osteoconduction couplings

Surface roughness	+	(Karageorgiou and Kaplan, 2005)
Ionic dissolution concentration	+	(Ohura et al., 1991)
Pore body diameter	+	(Lan Levengood et al., 2010a)

Table 35. Osseointegration couplings

Flow perfusion rate	+	(Chung et al., 2007)
Pore throat diameter	++	(Silva et al., 2006; Melchels et al., 2010)

Table 36. Osteoblast/cell infiltration couplings

Osteoblast/ cell adhesion	+	(Powers et al., 1997)
Mass transfer of nutrients	++	(Hidalgo-Bastida et al., 2012)
Angiogenesis	+	(Checa and Prendergast, 2010)
Compressive strength	+	(Chen et al., 2008)
Fluid flow mediated wall shear stress	++	(Melchels et al., 2011; Meinel et al., 2004)
Ionic dissolution concentration	++	(Gough et al., 2004; Verrier et al., 2004; Chen et al., 2008; Christodoulou et al., 2006)
Surface roughness	++	(Chen et al., 2008; Chung et al., 2003)
Pore body diameter	++	(Papenburg et al., 2009; Melchels et al., 2011)

Table 37. Osteoblast/cell proliferation couplings

Fluid flow induced wall shear stress	+	(Melchels et al., 2011)
Osteoblast/ cell proliferation	+	(Powers et al., 1997)
Ionic dissolution concentration	++	(Gough et al., 2004; Verrier et al., 2004)
Surface roughness	++	(Chen et al., 2008; Chung et al., 2003)
Pore body diameter	+	(Papenburg et al., 2009)

Table 38. Osteoblast/cell adhesion couplings

Ionic dissolution concentration	++	(Xynos et al., 2001; Gough et al., 2004)

Table 39. Osteoblast/cell apoptosis coupling

Flow perfusion rate	++	(Chung et al., 2007; Provin et al., 2008; Hidalgo-Bastida et al., 2012; Cartmell et al., 2003)
Osteoblast/cell proliferation	++	(Hidalgo-Bastida et al., 2012)

Table 40. Mass transfer of nutrients couplings

Pore body size	++	(Karageorgiou and Kaplan, 2005; Feng et al., 2011)
Cyclic compression	+	(Checa and Prendergast, 2010)
Osteoblast/cell proliferation	+	(Checa and Prendergast, 2010)

Table 41. Angiogenesis couplings

Cyclic compression	-	(Pui et al., 2012)
Osteoblast/ cell proliferation	+	(Chen et al., 2008)
Pore orientation	++	(Chang et al., 2000; Blaker et al., 2005)
Pore geometry	+	(Chang et al., 2000)
Strut thickness	++	(Saito et al., 2012; Jones and Hench, 2003a; Jones et al., 2006a; Jones et al., 2004b)

Table 42. Compressive strength couplings

Specific surface area	+	(Kapfer et al., 2011)
Strut thickness	+	(Sudarmadji et al., 2011)

Table 43. Stiffness couplings

Fluid flow mediated wall shear stress	++	(Boschetti et al., 2006; Chung et al., 2007; Cioffi et al., 2006; Mccoy et al., 2012; Hidalgo-Bastida et al., 2012; Cartmell et al., 2003)
Mass transfer of nutrients	++	(Chung et al., 2007; Provin et al., 2008; Hidalgo-Bastida et al., 2012; Cartmell et al., 2003)
Osteoblast/ cell infiltration	+	(Chung et al., 2007)

Table 44. Flow perfusion rate couplings

Cyclic compression	+	(Smalt et al., 1997; Sakai et al., 1998)
Personalized geometry	+	(Gutierrez and Crumpler, 2008)
Flow perfusion rate	++	(Boschetti et al., 2006; Chung et al., 2007; Cioffi et al., 2006; Mccoy et al., 2012; Hidalgo-Bastida et al., 2012; Cartmell et al., 2003)
Osteoblast/ cell proliferation	++	(Melchels et al., 2011; Meinel et al., 2004)
Osteoblast/ cell adhesion	+	(Melchels et al., 2011)
Osteoinduction	++	(Hillsley and Frangos, 1994; Sakai et al., 1999; Mccoy et al., 2012; Sakai et al., 1998; Hidalgo-Bastida et al., 2012; Ban et al., 2011; Meinel et al., 2004)
Pore body diameter	++	(Blecha et al., 2010; Boschetti et al., 2006)

Table 45. Fluid flow mediated wall shear stress couplings

Compression induced fluid flow	++	(Claes and Heigele, 1999; Prendergast et al., 1997; Hillsley and Frangos, 1994; Johnson et al., 1996)
Fluid flow mediated wall shear stress	+	(Smalt et al., 1997; Sakai et al., 1998)
Compressive strength	-	(Pui et al., 2012)
Angiogenesis	+	(Checa and Prendergast, 2010)
Osteoinduction	+	(Baas et al., 2009)
Pore orientation	+	(Amirkhani et al., 2012)
Pore geometry (shape)	+	(Amirkhani et al., 2012)

Table 46. Cyclic compression couplings

Cyclic compression	++	(Claes and Heigele, 1999; Prendergast et al., 1997; Hillsley and Frangos, 1994; Johnson et al., 1996)
Osteoinduction	++	(Prendergast et al., 1997; Hillsley and Frangos, 1994; Johnson et al., 1996)

Table 47. Compression induced fluid flow couplings

Fluid flow mediated wall shear stress	+	(Gutierrez and Crumpler, 2008)

Table 48. Personalized geometry coupling

Figure 14 below represents the roof of the HoQ. The individual design requirements identified by the pairwise comparisons in the above Tables 21-48 were used to construct the roof. The number of positive couplings outnumbers the number of negative couplings.

Figure 15 presents the house of qualities from both Chapter 5 and 6. The co-ordinated flow of information is linked from the first to the second HoQ. The output of the first house of quality are the CTSs which are then the customer requirements (CRs) for the second HoQ. On comparison the expanded HoQ shows the interactions both in the relationship matrix and the roof at a lower design hierarchy level.

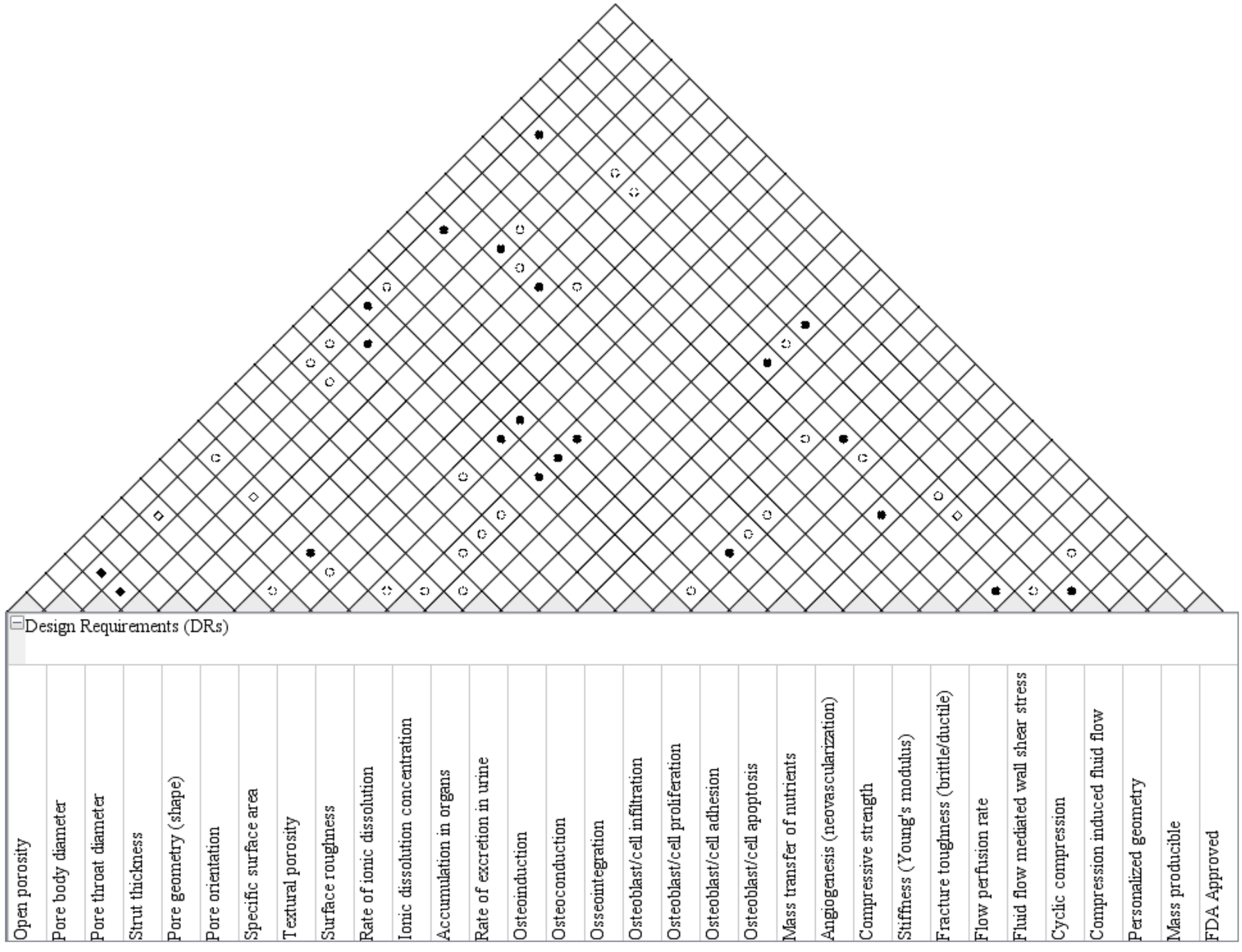


Figure 14. The roof of the House of Quality displaying the Couplings between Design Requirements. Couplings: (●) Strong positive, (○) weak positive, (□) weak negative, (■) Strong negative.

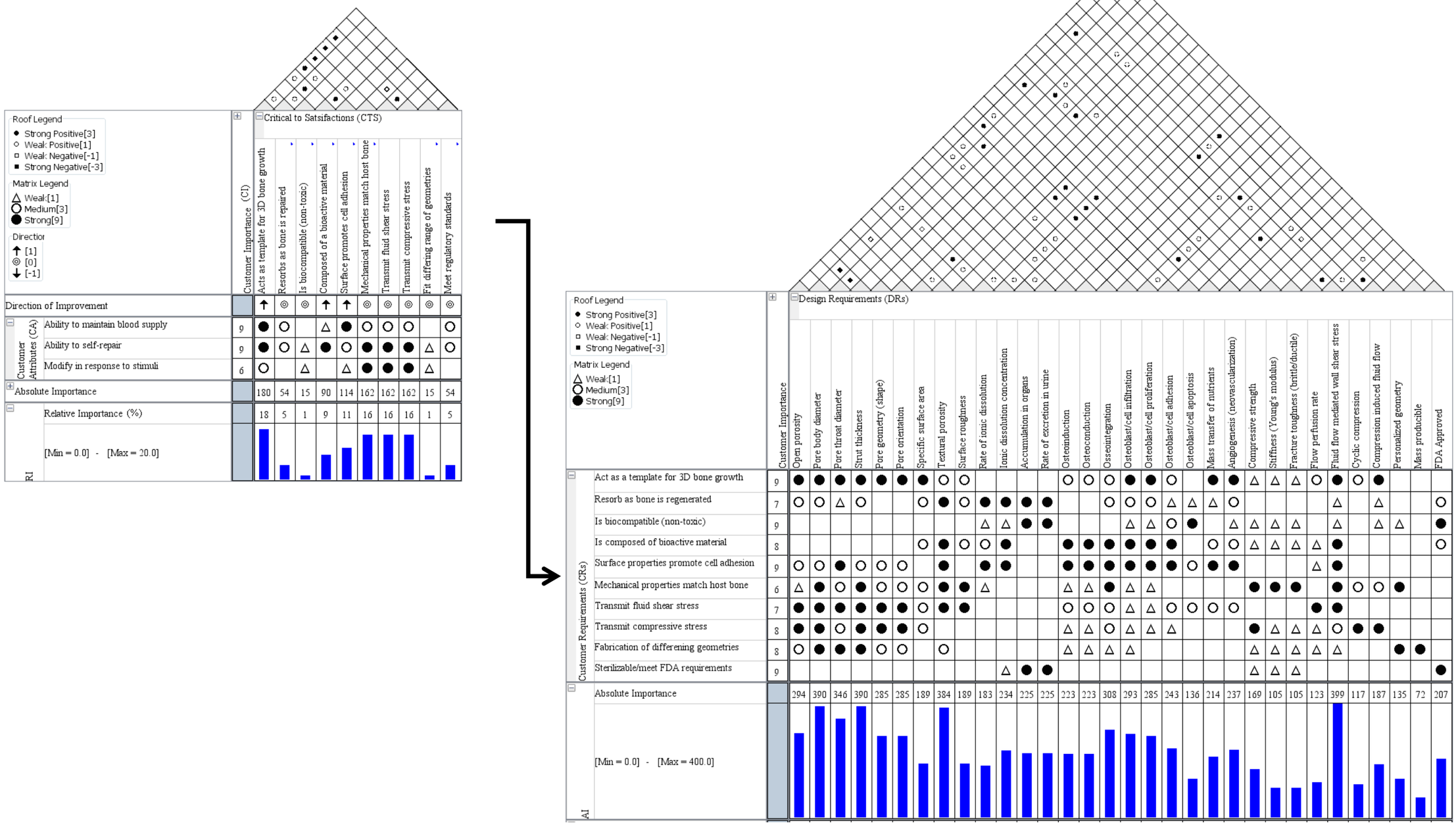


Figure 15. Summary diagram showing the house of quality from Chapter 5 links to the expanded house of quality in Chapter 6.

6.6 Summary

This chapter presented the second house of quality application. This house of quality was an expanded version of the one applied in Chapter 5. The starting point was shifted towards beginning with the Chapter 5 critical-to-satisfaction attributes as the customer requirements rather than using the criteria for living tissue as previously shown. The justification for this shift in starting point was to generate a house of quality that presented greater technical details in terms of conflict identification and engineering targets for the purposes of achieving a superior scaffold microstructure design attempt.

7 Results: Three-dimensional relationship technology chart

This chapter presents the application of the three-dimensional relationship technology chart in order to further the bone tissue scaffold concept. This design tool was applied to aid in the decision making process behind selecting design requirements for design different design strategies. This allows the designer to present the customer with different design options. The inputs for this design tool combined the validated critical-to-satisfaction statements from Table 15.

7.1 Step 1: Collecting the customer demanded quality

See section 5.2, Table 15.

7.2 Step 2: Creating the design strategies

The following design strategies were created:

1. The up-regulation of the genes in order to stimulate the osteogenic processes via manipulation of fluid flow
2. Effective distribution of nutrients in order to maintain cell population viability via perfusion parameters (convective transport supersedes diffusion limitations)
3. Guided cell proliferation in order to stimulate bone regeneration via optimized cell sites
4. Uniform cell distributions in order to maximise cell infiltration (to prevent necrotic cores) via optimized cell channels

These design strategies offer four potential routes of design for which a scaffold designer may pursue. This further refines the scaffold design problem into manageable segments of information.

7.3 Step 3: Selecting the design requirements

Table 49 lists design requirements that were included and excluded for the three-dimensional relationship technology chart. These design requirements were extracted from the expanded house of quality in Chapter 6.

	Included design requirements	**Excluded design requirements**
1	Open porosity	Accumulation in organs
2	Pore body diameter	Rate of excretion in urine
3	Pore throat diameter	Osteoinduction
4	Strut thickness	Osteoconduction
5	Pore geometry (shape)	Osseointegration
6	Pore orientation	Osteoblast infiltration
7	Specific surface area	Osteoblast proliferation
8	Textural porosity	Osteoblast adhesion
9	Surface roughness	Osteoblast apoptosis
10	Rate of ionic dissolution	Mass transfer of nutrients
11	Ionic dissolution concentration	Angiogenesis
12	Flow perfusion rate	Compressive strength
13	Fluid flow wall shear stress	Stiffness
14	-	Fracture toughness
15	-	Cyclic compression
16	-	Compression induced fluid flow
17	-	Personalized geometry
18	-	Mass producible
19	-	FDA approved

Table 49. The pool of design requirements from which thirteen were selected for inclusion in the three-dimensional relationship technology chart.

7.4 Steps 4 & 5: Three-dimensional relationship technology chart

Figure 16 presents the culmination of all the methodological steps into the three-dimensional relationship technology chart. As described in Figure 7 of the method, the x-axis presents the design requirements obtained from the expanded house of quality from Chapter 6. The y-axis lists the ten critical-to-satisfaction attribute statements also obtained from Chapter 6. The z-axis are the design strategies from section 7.2 created by the method in section 4.4.3.2. The numbers in both the left and right matrix are based upon a five-point scale (1 minimum and 5 the maximum). The centre top matrix is read by intersecting a design strategy with a design requirement. For each design strategy the individual design requirements are scored. In each design strategy the most effective design requirement is the cell that contains the largest value.

The values in the matrix are ordinal data, the scoring of which indicates which design requirement is most effective to a particular design strategy. The highest scoring cells are most effective compared to a lower scoring cell. For example for an up-regulation design strategy ‘strut thickness’ (119) is more effective than ‘rate of ionic dissolution’ (65). Therefore the design of strut thickness should take priority over rate of ionic dissolution for scaffold designers.

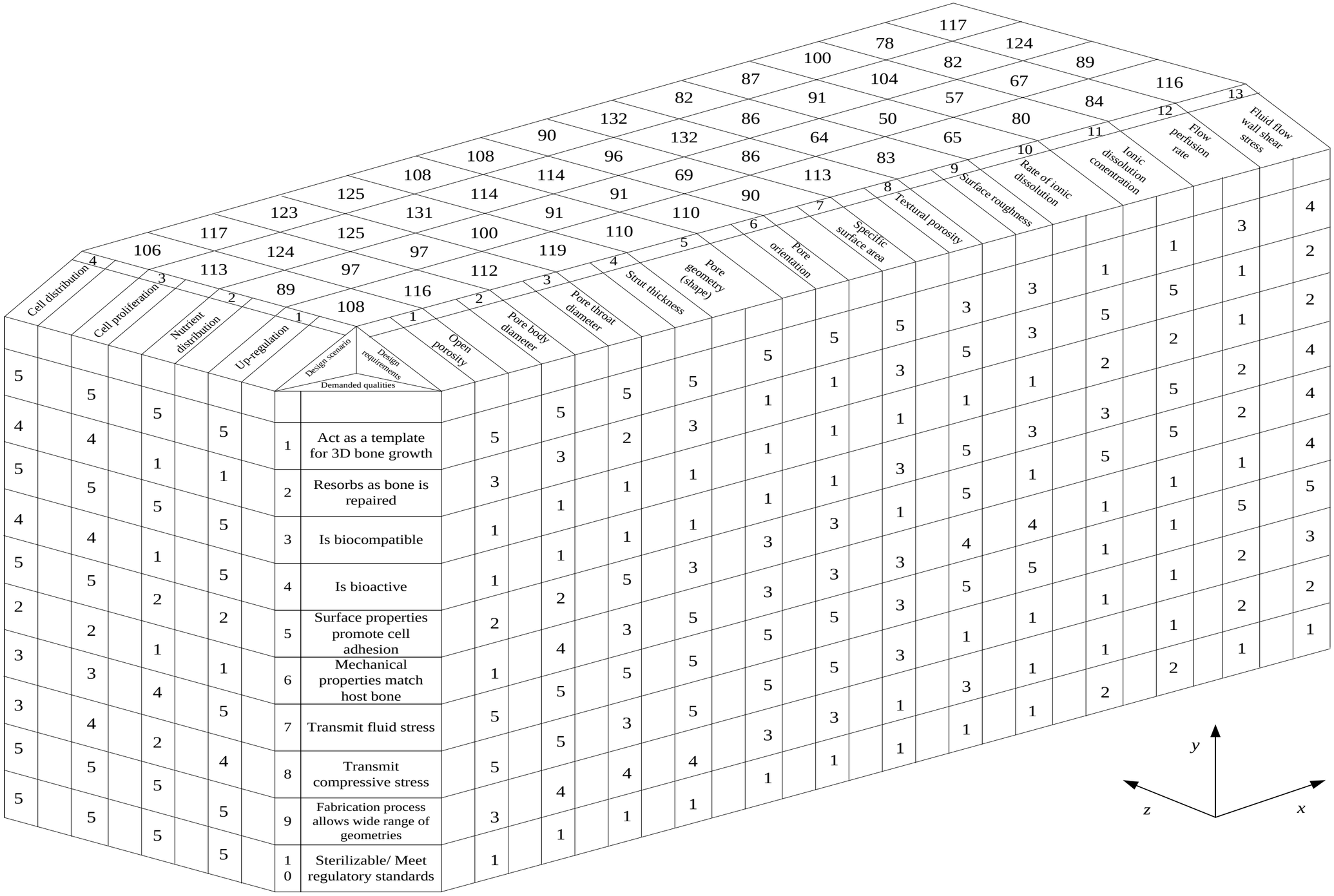


Figure 16. Three-dimensional relationship technology chart.

7.5 Strategic design requirements

Table 50 shows the result of the three-dimensional relationship technology chart. The three most effective design requirements are listed for each design strategy.

	Scaffold design strategy	**Design Requirements**		
		Primary	**Secondary**	**Tertiary**
1	Up-regulation	Strut thickness (119)	Wall shear stress (116)	Pore body diameter (116)
2	Nutrient distribution	Strut thickness (100)	Pore throat diameter (97)	Pore body diameter (97)
3	Cell proliferation	Textural porosity (132)	Strut thickness (131)	Pore throat diameter (125)
4	Cell distribution	Textural porosity (132)	Strut thickness (125)	Pore throat diameter (123)

Table 50. A summary of the most effective design requirements for each design strategy as identified from the three-dimensional relationship technology chart. The bracketed numbers indicate the overall 'effectiveness'.

Regardless of the chosen strategy, strut thickness appears in all four and twice as the primary design requirement. Textural porosity appears twice as the primary design requirement. Pore throat diameter appears in three of the four strategies.

7.6 Summary

This chapter presents the design requirements that are most effective for different hypothetical bone tissue scaffold microstructure design strategies. The three-dimensional relationship technology chart is shown to be a tool that allows the customer to view exactly which design requirements are indicated to be effective based upon different strategic goals.

8 Results: Axiomatic Design

This chapter presents the results of the Axiomatic Design methodologies. These are alternatives to the designs generated by Quality Function Deployment (QFD) methodologies. Contained within this chapter are two descriptive design models. In the first percolation theory is used to derive models for Axiomatic Design (AD). In the second three time instances of AD are considered. Each stage of the design is initiated by a descriptive statement of what is required for the design in the form of Functional Requirements (FRs) and ends with a list of Design Parameters (DPs) which indicate how these FRs should be fulfilled.

8.1 Bone tissue scaffold design model based upon percolation theory

8.1.1 Model of function

In line with percolation theory the design of the bone tissue scaffold microstructure is imagined as a lattice. According to percolation theory if a lattice is open to flow then this can be described as conducting flow. The main parameters extracted from percolation theory are the minimum probability of a network lattice being able to conduct flow across itself, known as the percolation threshold, which is dictated in part by the lattice co-ordination number. The co-ordination number is the number of bonds connected to a single site that are open to conduct flow. In this case of the scaffold, sites are the locations in which it is intended for the cells to reside and proliferate and the bonds describes the internal geometry by which the cells are able to be transported to the sites. Based upon this model the following FRs and DPs are proposed:

FR_1 To provide mechanical strength across the microstructure (zone A)

FR_2 To distribute cells throughout the microstructure (zone B)

FR_3 To provide locations for cells to attach and proliferate (zone C)

8.1.2 Model of microstructure

The model assumes that the microstructure has isotropic properties. It is unlikely that each FR would need the same percolation threshold. It is more likely that each FR has an optimal percolation threshold. If each FR dictates a unique zone within the scaffold microstructure, each with an exclusive percolation threshold then this would satisfy the independence axiom for AD. Therefore the next step of design is to segment the scaffold into three distinct zones (A, B and C), each with an ascribed percolation threshold.

The following design parameters are proposed:

DP_1 Percolation threshold of zone A

DP_2 Percolation threshold of zone B

DP_3 Percolation threshold of zone C

8.1.3 Model of function sub-level

If each of the microstructure zones has a different particle packing design in order to fulfil its function then it follows that each zone would have a different percolation threshold. Since FR_1 is concerned with the provision of mechanical strength the particle packing density should be the greatest of the three FRs. This would be reflected by a compact particle arrangement for DP_1 compared to DP_2 and DP_3. In order to establish a hierarchy within the packing densities of the particles to meet the requirements of each FR, the lattice arrangements and co-ordination numbers of the sites would have to be unique in each zone of the microstructure.

The next step of the axiomatic decomposition process is to generate a lower level of design hierarchy. This increases the detail proposed by the design. The percolation parameters that are required for the next level of design are described by the lattice arrangement and site co-ordination numbers. These are proposed as the parameters by which the percolation threshold prescribed for each individual FR stated in the above design hierarchy level can be achieved. At this design level the following sub-level FRs are proposed:

FR_{11} To control the lattice arrangement (zone A)

FR_{12} To control the co-ordination number (zone A)

FR_{21} To control the lattice arrangement (zone B)

FR_{22} To control the co-ordination number (zone B)

FR_{31} To control the lattice arrangement (zone C)

FR_{32} To control the co-ordination number (zone C)

8.1.4 Model microstructure of sub-level

Therefore in order to fit within the organised constraints of the microstructure zones such that the packing arrangement of particles is different for each three different lattice arrangements are required. Each lattice design is optimized to perform its desired function. In order to accommodate different possible lattice arrangements and site co-ordination numbers the following DPs are proposed:

DP_{11} Face-centred cubic

DP_{12} 12

DP_{21} Body-centred cubic

DP_{22} 8

DP_{31} Diamond

DP_{32} 4

8.1.5 Summary of percolation theory model

The following tree-diagram (Figure 17) presents the proposed microstructure model for a bone tissue scaffold based upon percolation theory. Three levels of design hierarchy are displayed; $FR_0 - DP_0$ is the first level, $FR_{1-3} - DP_{1-3}$ is the second and $FR_{11-32} - DP_{11-32}$ is the third and final sub-level. Each level of the design hierarchy was reached by decomposition of the previous level until no further decomposition was possible.

With each sub-level the design detail becomes more specific with the gradual transition from an abstract concept to actionable design details on which the design can be discussed further.

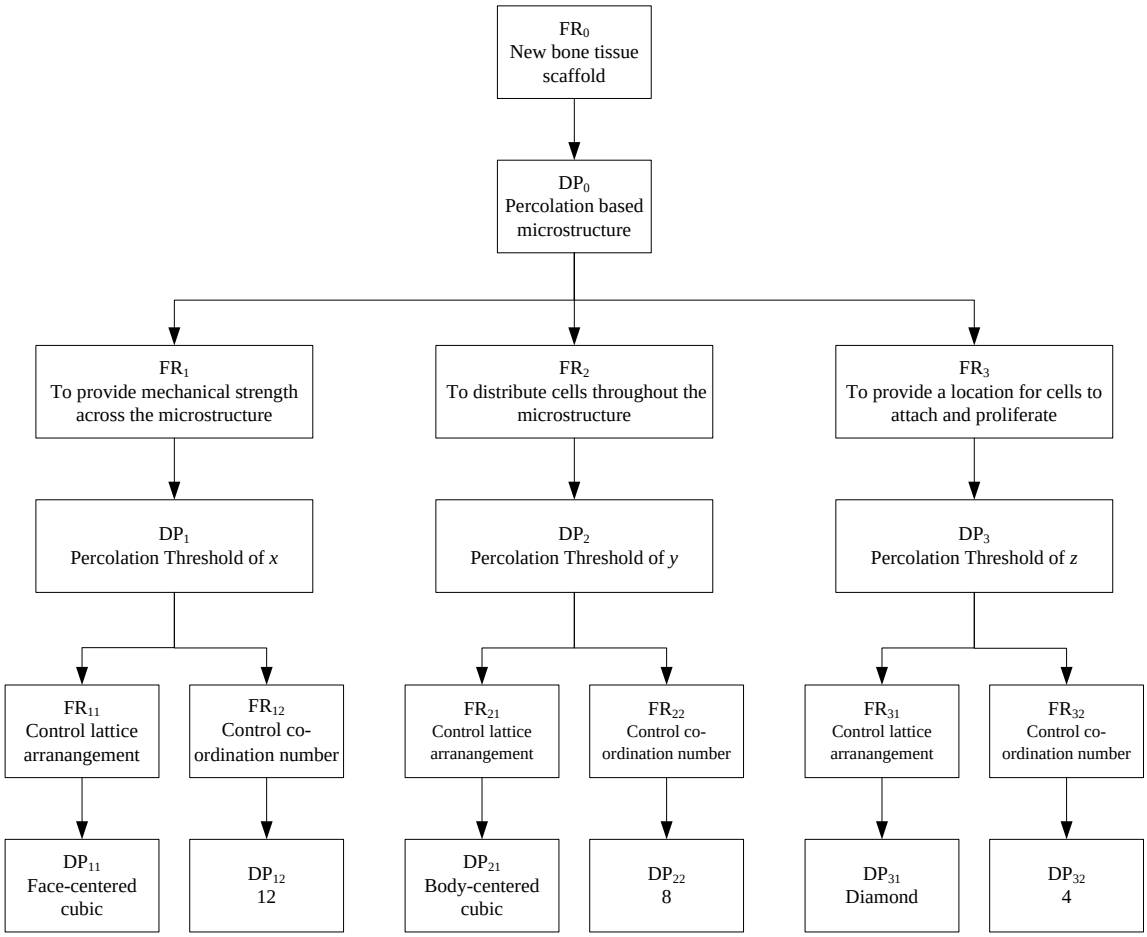


Figure 17. Tree of proposed microstructure model based upon percolation thresholds. FR_1, FR_2 and FR_3 all refer to different property requirements of the scaffold. The design parameters (DPs) are percolation parameters that need to be controlled in order to achieve the desired property requirements.

The design matrix for this model at the furthest point of design decomposition is presented as follows:

$$\begin{Bmatrix} FR_{11} \\ FR_{12} \\ FR_{21} \\ FR_{22} \\ FR_{31} \\ FR_{32} \end{Bmatrix} = \begin{bmatrix} X & 0 & 0 & 0 & 0 & 0 \\ 0 & X & 0 & 0 & 0 & 0 \\ 0 & 0 & X & 0 & 0 & 0 \\ 0 & 0 & 0 & X & 0 & 0 \\ 0 & 0 & 0 & 0 & X & 0 \\ 0 & 0 & 0 & 0 & 0 & X \end{bmatrix} \begin{Bmatrix} DP_{11} \\ DP_{12} \\ DP_{21} \\ DP_{22} \\ DP_{31} \\ DP_{32} \end{Bmatrix}$$

Each FR is coupled to only a single DP indicating the ideal decoupled design according to the independence axiom in AD theory. This is the endpoint for the proposed percolation theory based bone tissue scaffold design concept.

8.2 Bone tissue scaffold design model based upon time dependent complexity

The design requirement (DR) outputs of the expanded HoQ in Chapter 6 were utilized by the AD process. In a deviation from the traditional approach, scaffold design was based upon three time instances in order to account for the variation in requirements for tissue growth with time and to see if this impacts upon different microstructure requirements.

8.2.1 Setting the constraints

The following subsections of the results were those required to make the scaffold design challenge tractable from an AD perspective.

8.2.1.1 New functional requirement

An additional FR statement was included:

'To regulate microstructure permeability to osteoblasts/cells'

It was included on the basis that a review of the t = 0.5 time instance, there was no requirement from the prior QFD analysis that related to the regulation of cells throughout the microstructure. Therefore it was included.

8.2.1.2 New design parameters

Two additional DPs were also included into the AD process:

'*Tortuosity' and 'inlet fluid velocity'*

Although previously unconsidered it was decided that it was an important enough porosity characteristic related to microstructure that it should be included. The degree with which a scaffold is able to retain seeded cells as well as effectively distribute seeded cells was proposed to be dependent on tortuosity in this model.

8.2.1.3 Exclusions

Four of the DRs identified via the QFD analysis were unused. Open porosity, personalized external geometry, mass producible and FDA approval were the four variables that that were not included. The latter three's exclusion was based upon the fact that they were too far outside of the physical domain to be used at this stage. Open porosity was excluded because using percolation theory it was superseded by more appropriate terms to describe porosity.

#	Design Requirement	Functional Requirement statement	Selected as Design Parameter	Designated 'time instance' (0, 0.5 or 1)
1	Open porosity	Excluded		
2	Pore body diameter		Yes	
3	Pore throat size		Yes	
4	Strut thickness		Yes	
5	Pore geometry (shape)		Yes	
6	Pore orientation		Yes	
7	Specific surface area		Yes	
8	Surface roughness		Yes	
9	Textural porosity		Yes	
10	Rate of ion dissolution	To **remove** microstructure from host body (via resorption)		1
11	Ion dissolution concentration			
12	Accumulation in major organs			
13	Rate of excretion in urine			
20	Osteoblast/cell apoptosis			
14	Osteoinduction	To **secure** osteogenesis on internal surfaces sites (location)		0.5
15	Osteoconduction			
19	Osteoblast/cell adhesion			
16	Osseointegration	To **link/join/connect** microstructure bone to host bone (Osseointegration)		1
17	Osteoblast/cell infiltration	To **distribute** osteoblast/cells (infiltration/migration)		0
18	Osteoblast/cell proliferation	To **guide** bone in-growth throughout microstructure		1
21	Mass transfer of nutrients	To **distribute** nutrients throughout the microstructure		0
22	Neovascularization/ Angiogenesis	To **guide** angiogenesis (to provide fully vascularized microstructure)		1

23	Compressive strength	To **support** physical handling with adequate "compressive" strength (withstand)		0
24	Stiffness			
25	Fracture toughness			
26	Flow perfusion rate	To **regulate** nutrient perfusion throughout microstructure		0.5
27	Fluid flow mediated wall shear stress	To **distribute** fluid flow induced wall shear stress throughout internal surfaces		0.5
28	Cyclic compression	To **transfer/distribute** stresses induced by cyclic compressions		0
29	Cyclic compression induced fluid flow			
30	Personalized external geometry	Excluded		
31	Mass producible	Excluded		
32	FDA approved	Excluded		

Table 51. Summary of the Design Requirements and their translation into Functional Requirements or Design Parameters. Several DRs are combined into single FR statements. The DRs that were not included in the AD process are also shown. Alongside each FR statement is the time instance in which its impact is desired.

8.2.2 Assumptions used to construct the design matrices

In order to explore the time-dependency that is associated with a biological system the following assumptions were made:

1. Three time frames exist, t = 0, 0.5 and 1. At t = 0 it is assumed the microstructure is void of cells and fluid. At t = 0.5, the microstructure is immersed with both cells and fluid, with the regeneration processes occurring at a cellular level. At t = 1, the cells viability and proliferation has reached a critical point to form the beginning of what can be described as bone tissue
2. Passive diffusive properties dictate the local environment at t = 0
3. Perfusion becomes the dominant factor in the transport of nutrients and distribution of cells throughout the microstructure at t = 0.5
4. The microstructure has reached a point that segments are vascularised with capillaries t = 1
5. The use of identical DPs was acceptable across different time instances
6. The level of decomposition was kept constant in order to simplify the process (all decomposition stopped at the same hierarchy of design)
7. Combining several closely related DRs into a single FR where necessary to reduce the scale of complexity of the design task
8. The type of material used in the design of microstructure is assumed to have the desired bioactive properties
9. That the transition from each time instance is positive due to the regeneration of bone
10. Assumed that that microstructure does not have a filtering coefficient that results in the accumulation of material on the external surface that prevents the input of material into the microstructure

8.2.3 Top level of design hierarchy

Based upon the introduction of time-dependency to the scaffold design process, and in addition to both the previous attempted percolation theory design and quality function deployment designs (Chapter 6) leads to the new top FR and DP to be described as:

FR_0 Design a model bone tissue scaffold in which FRs are divided by time, dependent on what the desired biological imperatives are in each instance

DP_0 Time-dependent Microstructure

It is intended that for each of the following time instances a specific scaffold is designed to meet the desired needs of that time instance. The designs are descriptive models and in each case the design was performed in isolation from other time instances.

8.2.4 Matrix 1 (M_1): Design model of a bone tissue scaffold at t = 0

8.2.4.1 Model of function

At time M_1 the following conditions are set. It is intended that the immediate form of nutrient transport will be via diffusion. The scaffold has sufficient strength to withstand physical handling during transportation and preparation prior to implantation. The initial microstructure is ready to conduct flow across itself in order to allow cell migration. The scaffold microstructure should be able to distribute external stresses due to imposed cyclic compressions.

These conditions lead to the following statements of FRs at t = 0:

FR_1 To **distribute** nutrients throughout the microstructure

FR_2 To **support** physical handling with adequate "compressive" strength (withstand)

FR_3 To **distribute** osteoblast/cells (infiltration/migration)

FR_4 To **transfer/distribute** stresses induced by cyclic compressions

8.2.4.2 Model of microstructure

The following is an explanation of proposed design parameters that will deliver the FRs 1-4 set out above. Since the initial nutrient transport mechanism is passive (diffusion), the kinetics of nutrient flux will be determined by the diffusive path length in this model. The strength of the microstructure will be determined by the design of the physical struts that comprise the walls of the internal void spaces. These physical struts will be closed to flow. The degree of tortuosity of the internal geometry of the microstructure will influence the distribution of cells. If the degree of tortuosity is too great then the cells may be unable to penetrate into the core of the scaffold creating necrotic cores. If the internal geometry if not tortuous enough cells will be able to penetrate the microstructures core but just as easily migrate back out of the scaffold and into the surrounding fluid. Based upon porosity theory the distribution of stresses throughout the microstructure will be determined by the orientation and shape of the void spaces.

Based upon this description the following statements of design parameters are proposed:

DP_1 Diffusion path length

DP_2 Strut thickness

DP_3 Tortuosity

DP_4 Pore orientation

DP_5 Pore geometry

The design matrix of this level FRs is proposed as (M_1)

$$\begin{Bmatrix} FR_1 \\ FR_2 \\ FR_3 \\ FR_4 \end{Bmatrix} = \begin{bmatrix} X & 0 & 0 & 0 & 0 \\ 0 & X & 0 & 0 & 0 \\ 0 & 0 & X & 0 & 0 \\ 0 & 0 & 0 & X & X \end{bmatrix} \begin{Bmatrix} DP_1 \\ DP_2 \\ DP_3 \\ DP_4 \\ DP_5 \end{Bmatrix}$$

The matrix presents the couplings between the initial FRs and DPs when t = 0. The microstructure is absent of both cells and fluid. Passive diffusive mechanisms are intended to be responsible for both nutrient and cell transport on the immediate immersion of the microstructure *in situ*, either *in vitro* or *in vivo*. According to AD theory since the number of DPs is greater than the number of FRs indicating a redundant design (Suh, 2001).

8.2.5 Matrix 2 (M_2): Design model of bone tissue scaffold at t = 0.5

8.2.5.1 Model of function

This is the second microstructure design model for a time dependent bone tissue scaffold. At this stage in the development life cycle of the microstructure cell seeding and fluid perfusion are intended. The scaffold has begun its transition from an "off the shelf" product and is in 'use' either *in vitro* or *in vivo*. The characterisation of the scaffold is no longer based upon the relationship between critical porosity and strength but between the fluid phase, porosity and strength. The microstructure is now assumed to be a biocomposite; a mix of living cells and scaffold material.

The nutrients are now supplied to the cells throughout the microstructure via fluid perfusion as opposed to the passive processes previously described. The constant perfusion of nutrients throughout the microstructure is crucial to maintaining the life cycle of cells present. The microstructure has to be able to attract and secure cells to its internal surfaces in order to maintain osteogenesis. The cells must be able to permeate throughout the microstructure in support of bone regeneration. The wall shear stress induced by perfusive fluid flow is important requirement for the mechano-transduction of the preferred differentiation of bone forming cells. This leads to the following statements for the FRs at t = 0.5 instance:

FR_5 To **regulate** nutrient perfusion throughout microstructure

FR_6 To **secure** osteogenesis on internal surfaces sites (location)

FR_7 To **regulate** microstructure permeability to osteoblasts/cells

FR_8 To **distribute** fluid flow induced wall shear stress throughout internal surfaces

8.2.5.2 Model of microstructure

The rate of fluid flow used to perfuse the scaffold dominates the distribution of nutrients throughout the microstructure. If an in vitro incubation strategy is being applied then perfusion may also be intermittent or continuous based on the desired operations type. The adhesion of cells onto the internal surfaces of the microstructure is determined both by the size of the pore bodies and the surface roughness. The permeability of the microstructure to the cells migrating throughout is determined by the smallest interconnect diameters, termed pore throat diameters. The inlet fluid velocity is related to the distribution of flow regimes throughout the microstructure. Wall shear stress is the most dominant factor in the creation of the mesengenic environment, responsible for the mechano-transduction mechanisms for osteoblast differentiation into the desired linages. The following DPs are proposed:

DP_6 Flow perfusion rate

DP_7 Surface roughness

DP_8 Pore body diameter

DP_9 Pore throat size

DP_{10} Inlet fluid velocity

The design matrix M_2 is shown as

$$\begin{Bmatrix} FR_5 \\ FR_6 \\ FR_7 \\ FR_8 \end{Bmatrix} = \begin{bmatrix} X & 0 & 0 & 0 & x \\ x & X & x & 0 & x \\ X & 0 & 0 & X & 0 \\ X & 0 & X & 0 & X \end{bmatrix} \begin{Bmatrix} DP_6 \\ DP_7 \\ DP_8 \\ DP_9 \\ DP_{10} \end{Bmatrix}$$

The matrix above (M_2) shows that the addition of fluid serves as a coupling medium between the microstructure and the cells. The fluid serves three functions, firstly to change the dominant nutrient transport mechanism from diffusion to perfusion, secondly to distribute osteoblasts throughout the microstructure and finally to provide the necessary mechano-transduction mechanisms for osteoblast differentiation and proliferation. The small x indicates there is an interaction that, whilst not the most significant, still warrants attention. The independence axiom of AD theory no longer holds true at this stage. This is because of the couplings between FR_5 with DP_{10} and FR_6 with DP_{10}. The addition of the fluid adds couplings to the system as shown by DP_6, flow perfusion.

8.2.6 Matrix 3 (M_3): Design model matrix at t = 1

8.2.6.1 Model of microstructure

At t = 1 the microstructure of the scaffold has reached the stage where bone ingrowth guided by the microstructure is being initiated. The microstructure has transitioned towards a vascularized construct that is in the process of balancing the support of directed bone ingrowth with the self-directed degradation kinetics of itself.

Vascularization requires angiogenesis (the formation of blood vessels and capillaries) throughout the scaffold. Stress-shielding is a problem with current implants where there exists a difference in the Young's modulus of the host biological tissue and the implanted graft material (e.g. titanium). This results in the development of scar tissue surrounding the foreign implant. The resulting poor integration between the host's biological tissue and implanted material requires eventual replacement of the implant. This problem is particularly exacerbated in load bearing areas of the human body (e.g. hips).

The newly proliferating bone cells need to reach a critical mass where a body of cells is sufficient to be considered tissue. Groups of bone cells must be guided by the microstructure in a co-ordinated fashion to link with each other to form bone tissue. As the scaffold supports and guides bone regeneration, there is a point at which it hinders further growth due to constricting space.

In order to create further space in which bone tissue can grow into the scaffold itself must be removed in a controllable manner. The ion release profile will be crucial to balance the continued attraction of new cells, the continued co-ordination of the proliferation of existing bone tissue whilst degrading at a rate does not hinder the space available for further bone development.

Therefore the following FRs apply:

FR_9 To **guide** angiogenesis (to provide fully vascularized microstructure)

FR_{10} To **link/join/connect** microstructure bone to host bone (Osseointegration)

FR_{11} To **guide** bone in-growth throughout microstructure

FR_{12} To **remove** microstructure from host body (via resorption)

8.2.6.2 Model of microstructure

For sufficient vascularisation to take place the microstructure needs an optimized capillary network. This prevents regions of dead flow and necrotic cores by ensuring adequate distribution of nutrients. Specific pore body diameters that are separate to previous pore bodies are required. The surface area is an importance parameter in ensuring osseointegration of the biocomposite implant with the host bone in the defect site. The concentration of ionic dissolution products from the bioactive material in the local environment continues to manipulate osteoblasts to proliferate aiding the integration process.

The geometry (shape) of the cluster of pores direct the bone in-growth throughout the microstructure. The textural porosity of microstructure struts is primarily responsible for the degradation kinetics of the microstructure itself. This continues until the microstructure is completely replaced by bone tissue. Based upon these descriptions the following DPs are proposed:

DP_{11} Pore body diameter

DP_{12} Specific surface area

DP_{13} Ionic dissolution concentration

DP_{14} Pore geometry

DP_{15} Textural porosity

The design matrix M_3 is shown below:

$$\begin{Bmatrix} FR_9 \\ FR_{10} \\ FR_{11} \\ FR_{12} \end{Bmatrix} = \begin{bmatrix} X & 0 & 0 & 0 & 0 \\ 0 & X & X & 0 & 0 \\ x & 0 & 0 & X & 0 \\ x & X & 0 & 0 & X \end{bmatrix} \begin{Bmatrix} DP_{11} \\ DP_{12} \\ DP_{13} \\ DP_{14} \\ DP_{15} \end{Bmatrix}$$

The matrix (M_3) indicates that at this time stage the bioresorption of the microstructure has two main effects that both occur at an unknown rate due to an overall increase in porosity. The first, is a negative effect on the overall structural integrity of the scaffold due to a decrease in strength. The second is the variation in flow paths as strut thicknesses are altered, as well as changes to pore body diameters, specific surface area and textural porosity, resulting in unknown variations in both the magnitude and distribution of fluid flow induced wall shear stress.

8.2.7 Matrix 4 (M_4): Design model of a bone tissue scaffold between t = 0 and t = 0.5

M_4 and M_5 are transitory matrices. This is the first of the two transitory matrices. This matrix explores how the couplings change between the M_1 and M_2 design. The purpose of this matrix is to review which FRs from t = 0 instance may still be applicable in the t = 0.5 instance.

$$\begin{Bmatrix} FR_5 \\ FR_6 \\ FR_7 \\ FR_8 \end{Bmatrix} = \begin{bmatrix} x & 0 & 0 & 0 & 0 \\ 0 & X & 0 & 0 & 0 \\ 0 & 0 & x & 0 & 0 \\ 0 & 0 & 0 & ? & ? \end{bmatrix} \begin{Bmatrix} DP_1 \\ DP_2 \\ DP_3 \\ DP_4 \\ DP_5 \end{Bmatrix}$$

In M_4 certain couplings diminish in importance (X to x) whilst two are unknown (as indicated by the '?' symbol). This is due to the transition of external loading forces from cyclic compressions to fluid flow induced wall shear stress, the boundary of which is not yet clearly defined.

8.2.8 Matrix 5 (M_5): Design model of a bone tissue scaffold between t = 0.5 and t = 1

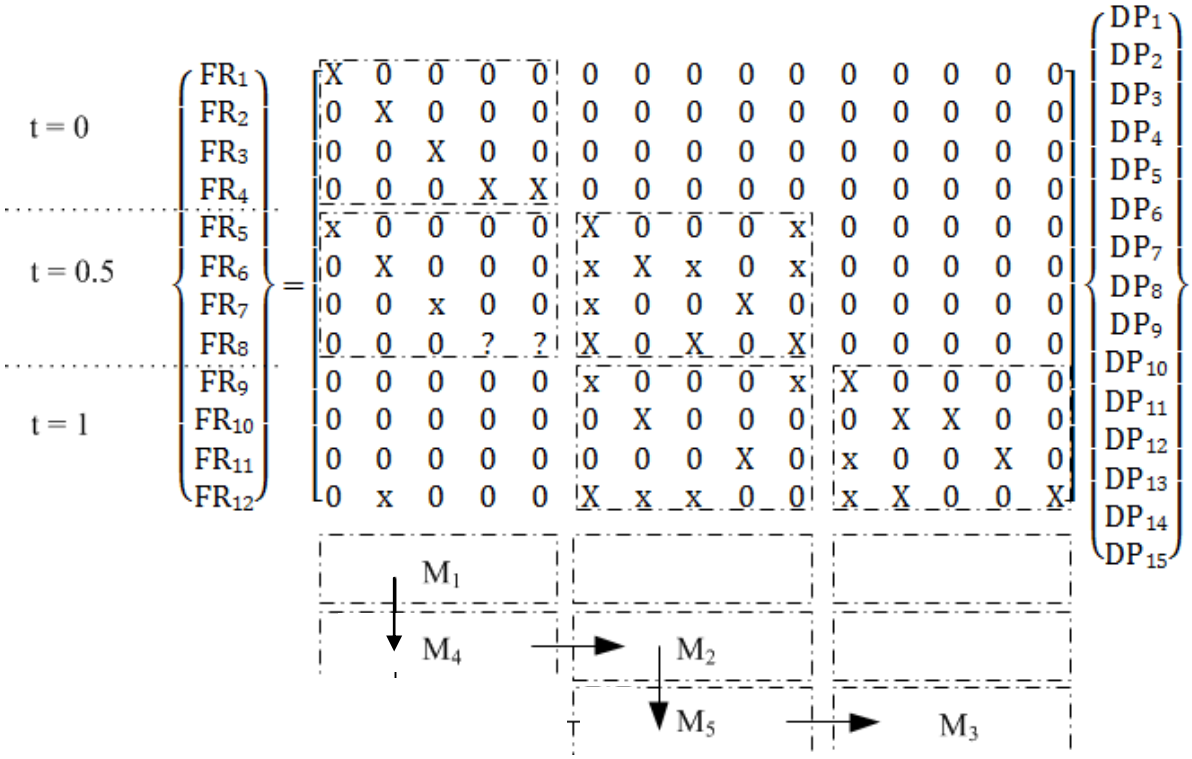
M_5 matrix links M_2 with M_3. The purpose of this matrix is to review which FRs from t = 0.5 instance are would still be applicable in the t = 1 instance

$$\begin{Bmatrix} FR_9 \\ FR_{10} \\ FR_{11} \\ FR_{12} \end{Bmatrix} = \begin{bmatrix} x & 0 & 0 & 0 & x \\ 0 & X & 0 & 0 & 0 \\ 0 & 0 & 0 & X & 0 \\ X & x & x & 0 & X \end{bmatrix} \begin{Bmatrix} DP_5 \\ DP_6 \\ DP_7 \\ DP_8 \\ DP_9 \end{Bmatrix}$$

With M_5, five couplings are removed and one new coupling identified. The new coupling (FR_{12} – DP_7) is due to the fact that that surface roughness is involved with bioresorption kinetics of the microstructure.

8.2.9 Overall design matrix combining all five scaffold designs ($M_1 – M_5$)

The overall design matrix for the time dependent complexity of a bone tissue scaffold is shown below. This matrix is a summary of the FRs of the microstructure compared against all the DPs and how they vary with time. The arrowed sketch below the matrix indicates the order in which the matrices occur due to time. In addition to the incorporation of the three previous matrices 'time-transitional' matrices have also been identified (M_4 & M_5).



The top right area of the matrix includes no couplings. This is due to the fact that the DPs indicated have not yet occurred in relation to time. For example the DPs that are implemented due to fluid perfusion ($DP_6 – DP_{15}$) are assumed to have no relation to the FRs at t = 0 since no fluid is present at this time.

Table 52 summarises the FRs and DPs categorised by time for matrices M_1 to M_3. Time instances are listed in the first column, FRs in the second and DPs in the final column.

8.2.10 Summary of Results

Time	#	Functional Requirements (FRs)	#	Design Parameters (DPs)
t = 0	1	To **distribute** nutrients throughout the microstructure	1	Diffusion path length
	2	To **support** physical handling with adequate "compressive" strength (withstand)	2	Strut thickness
	3	To **distribute** osteoblast/cells (infiltration/migration)	3	Tortuosity*****
	4	To **transfer/distribute** stresses induced by cyclic compressions	4	Pore orientation
			5	Pore geometry
t = 0.5	5	To **regulate** nutrient perfusion throughout microstructure	6	Flow perfusion rate
	6	To **secure** osteogenesis on internal surfaces sites (location)	7	Surface roughness
			8	Pore body diameter
	7	To **regulate** microstructure permeability to osteoblasts/cells*****	9	Pore throat size
	8	To **distribute** fluid flow induced wall shear stress throughout internal surfaces	10	Inlet fluid velocity*****
t = 1	9	To **guide** angiogenesis (to provide fully vascularized microstructure)	11	Pore body diameter
	10	To **link/join/connect** microstructure bone to host bone (Osseointegration)	12	Specific surface area
			13	Ionic dissolution concentration
	11	To **guide** bone in-growth throughout microstructure	14	Pore geometry
	12	To **remove** microstructure from host body (via resorption)	15	Textural porosity

Table 52. Summary of all Functional Requirements and Design Parameters organised by time. The DPs are stated against their corresponding FRs. The FRs and DPs that were not extracted from the previous QFD analysis are indicated with (*).

Figure 18 presents a summary of the relationship between the DPs and their designated FRs. Pore geometry and pore body diameter have both been used twice, but in separate time instances.

8.3 Summary

This chapter presents the results of two descriptive bone tissue scaffold models constructed using AD methodology. The first design is based upon percolation theory. Percolation theory was selected on the basis of its focus upon fluid flow through porous media. Therefore the possibility existed that it may be some relevance to how bone tissue scaffolds function. This design proposed the use of three different lattice designs each with tailored to meet a specific FR of the microstructure.

The second model is based upon time-dependency. This model used time as the metric on which to base scaffold design. This model contains five scaffold designs, each one has a specific role in the co-ordinated objective of bone regeneration. This design model included findings from previous QFD designs.

The next step is to devise a process in which to compare and validate the designs obtained from Chapters 5-8.

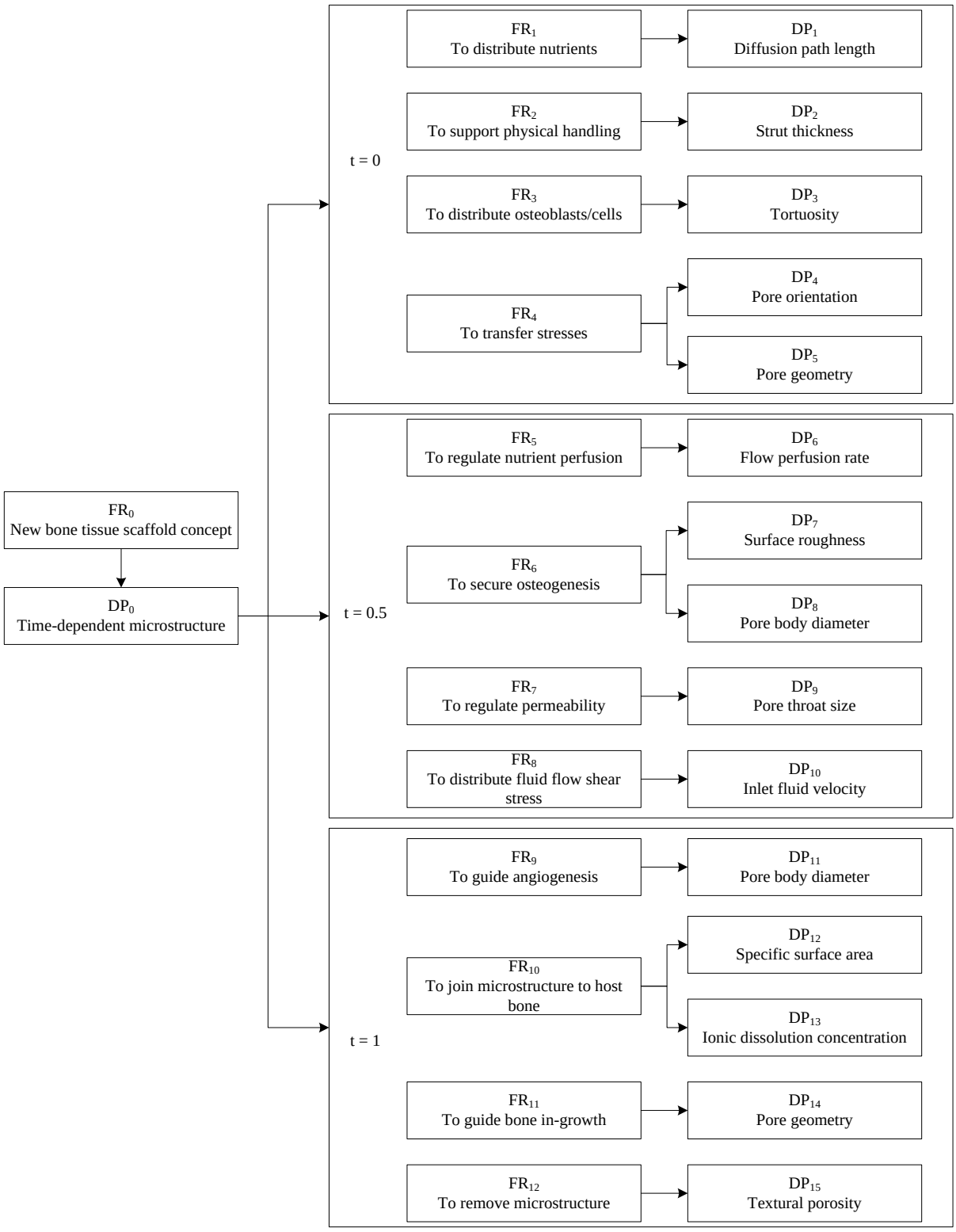


Figure 18. Horizontal tree diagram showing the decomposition of FRs to DPs, organised by time instances. The number of DPs is greater than FRs, which according to AD indicates a redundant design.

9 Results: Validation

This chapter contains the results of the validation of the design outputs by collecting the opinions of regarded experts in an emailed survey. Of the thirty-three surveys sent, at the time of writing four had responded (12% survey response). An additional three had declined to participate.

Despite repeated personalised follow up emails no further participants could be persuaded to participate. Therefore the results contained within this chapter provide an indication as to the future research direction rather than a definitive answer.

The following figures present radar plots based upon averaged feedback scores. Each chart contains the five statements which acted as questions for each design solution. These statements are organised in a clockwise orientation surrounding the chart, with statement one beginning at the twelve o'clock position. Reminders of the statements are shown below.

The scores are presented on a five point scale. One indicates strong disagreement, three is neutral and five strong agreement. The only deviation is the question, 'the solution is…' where one indicates very poor, three, no change and five, very good. The two and four values correspond to the appropriate mid points in opinion.

The statements asked as shown in 4.6.2 were:

1. The design solution could lead to innovation (new or improved product capabilities) in bone tissue scaffold design
2. The content of the design solution enhances current bone tissue scaffold design
3. The solution needs significant improvements
4. I am keen to apply the solution or aspects of it in my future work
5. The solution is….

Figure 19 shows the surveyed response for the design solution from the Quality Function Deployment-TRIZ methodology. All of the responses reside between three and four.

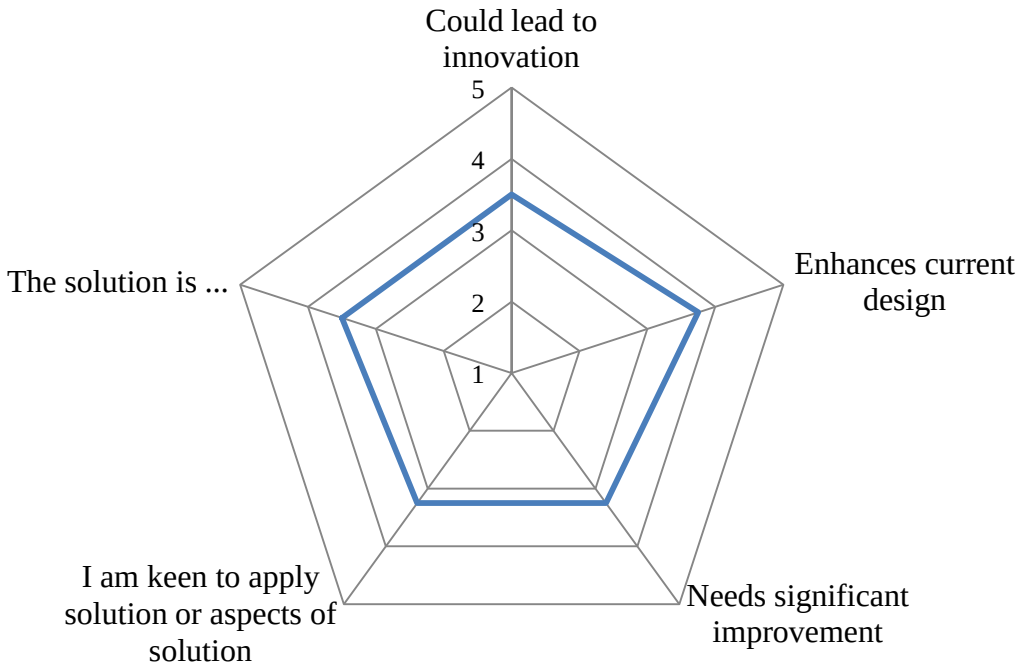


Figure 19. Radar chart for the Quality Function Deployment - TRIZ design solution

Figure 20 shows the responses for the expanded house of quality design solution. For all of the statements except for the need for significant improvement are between 4 and 4.5. The need for significant improvement scored just below 3 (neither agree nor disagree).

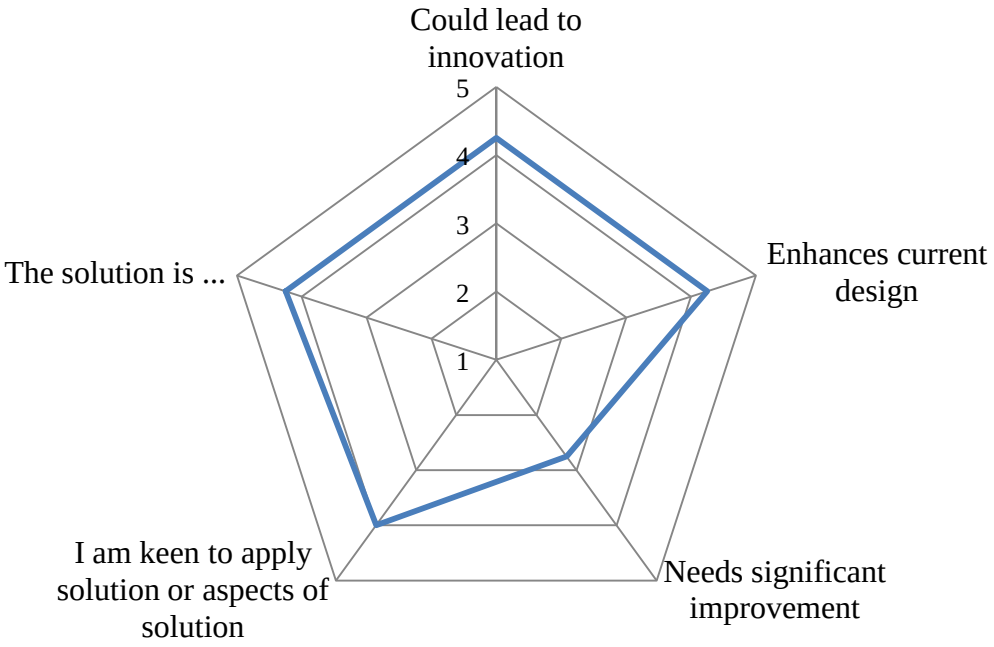


Figure 20. Radar chart for the expanded house of quality design solution

Figure 21 presents the validation scores for the three-dimensional relationship technology chart. For each statement the scores resided between 3 and 3.5.

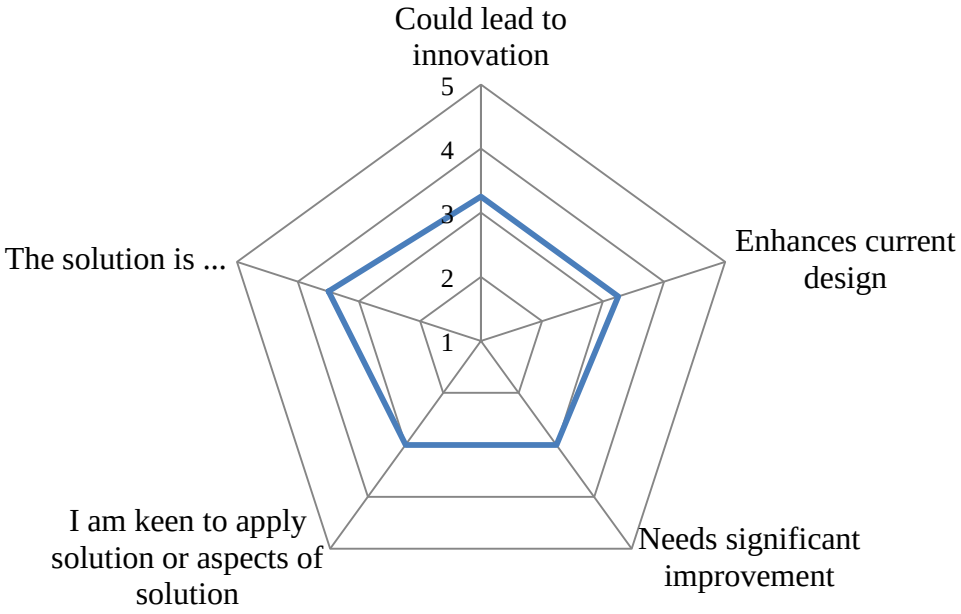


Figure 21. Radar chart for Three-dimensional relationship technology chart design solution

Figure 22 shows the responses for the first part of the time dependent complexity design solution. All statements are between 4 and 4.5 with the exception of statement 3. The need for significant improvement scored approximately 2.5.

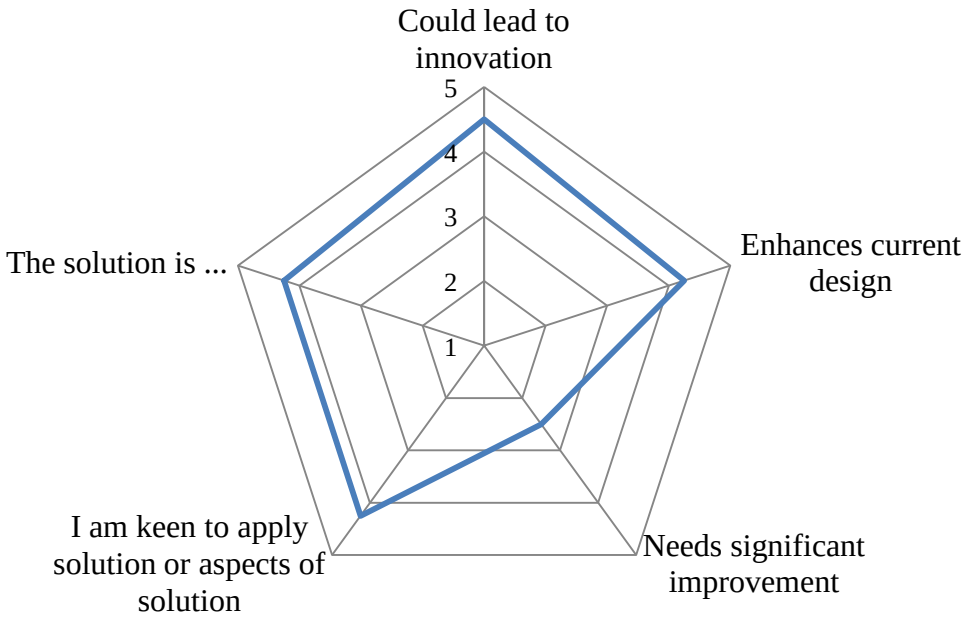


Figure 22. Radar chart for time dependent axiomatic design solution part 1

Figure 23 shows the responses for the second part of the axiomatic time dependent design solution. Statement one scored above four; statements 2, 4 and 5 scored between 3 and 4; and statement three scored below 3.

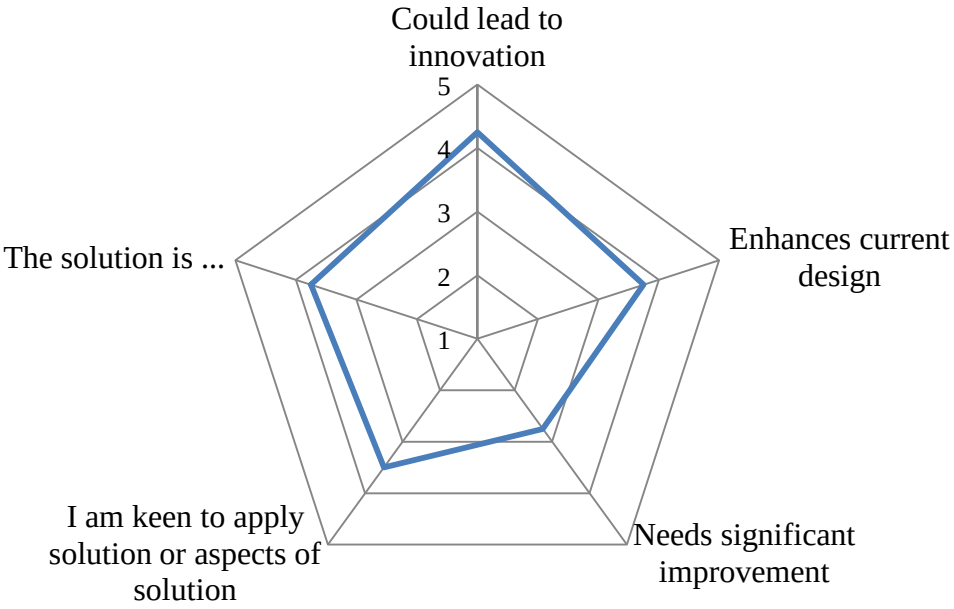


Figure 23. Radar chart for time dependent complexity solution part 2

For comparison Figure 24 contains all of the responses for each of the design solutions superimposed upon one another.

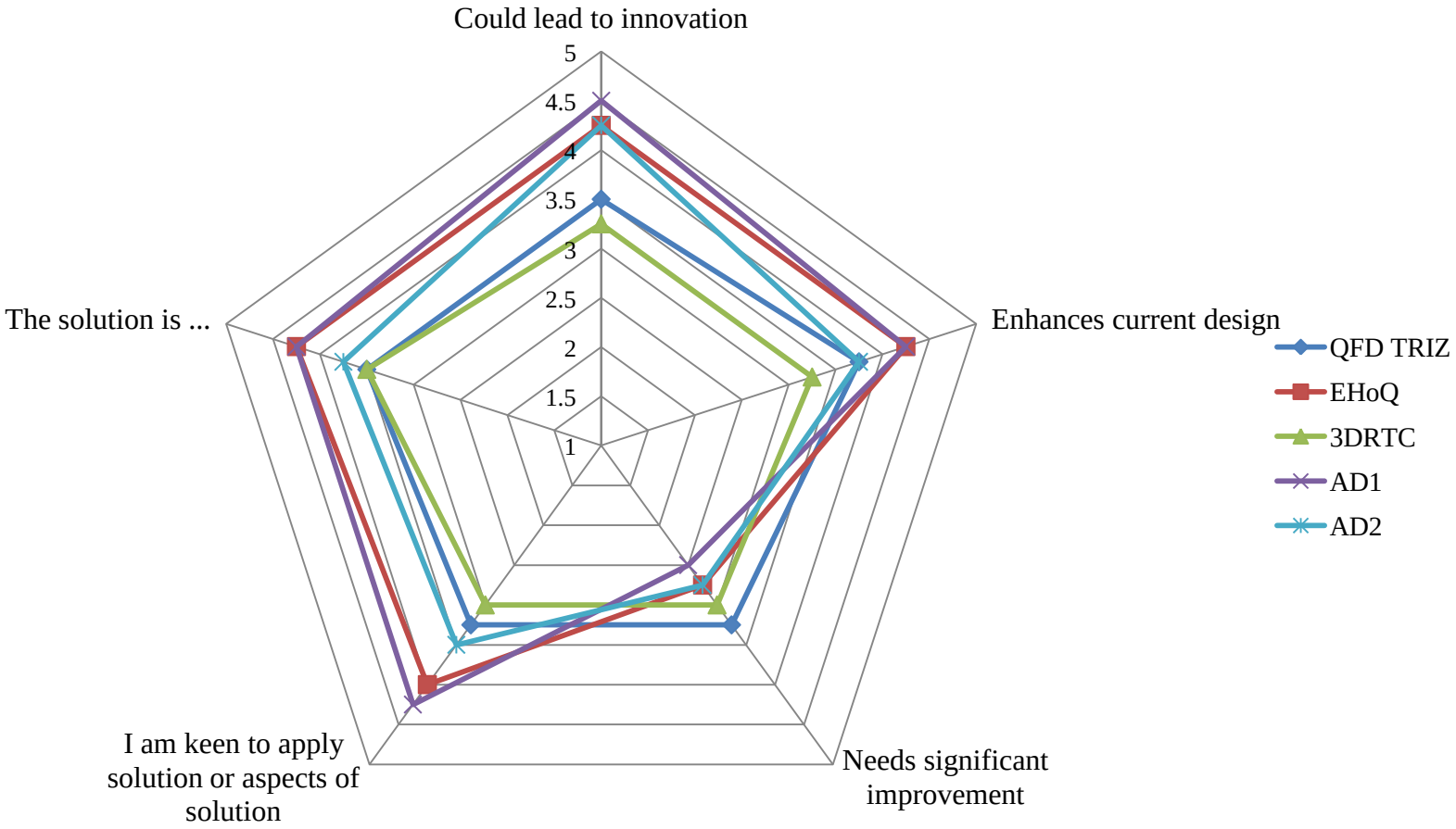


Figure 24. Radar chart containing all the design solution scores. The key identifies which design solutions correspond to which symbols.

This chapter contains the results of the validation process for this thesis. A survey containing the design solutions emailed to regarded experts in the field of tissue engineering, primarily in the UK. Of the thirty-three surveys, four responses were received. The final chart provides the clearest indication of which design solution and hence design methodology will further progress the bone tissue scaffold concept.

10 Discussion

The following section discusses the results in the chapter order in which they were presented. The discussion is divided into five parts. The first four parts correspond to a chapter in the results, whist the final part is a comparison of the techniques used to obtain the results.

10.1 Quality Function Deployment and TRIZ

For the three contradictions shown in Table 19 the following section will discuss various interpretations of the generic TRIZ inventive principles for a Bone Tissue Scaffold.

10.1.1 Coupling 4

"Separation: Separate only necessary part (or property) or remove an interfering part or property from an object or system" (Rantanen and Domb, 2002)

In part some scaffold designs already have this capability with bio-resorbable constituents.

In this context, this leads to the question, can separation of the material properties that contribute towards the overall mechanical characteristics be separated from the material properties that contribute to the bioactive character of the scaffold.

For example, this could be done by a purely organizational approach with parallel struts that run throughout the scaffold in both the vertical horizontal plane, in much the same way that mechanical struts in large buildings are orientated. Potentially this would suggest a two-dimensional approach because of the nature of the load. Woven in-between these load-bearing parallel struts is another material that is solely responsible for the bioactive properties for bone regeneration.

The result is separate materials for those that contribute to the struts, such as by the introduction of polymers with a bioactive component woven throughout in the form of a mesh. A proposal for the potential of three dimensional knitted textile architectures for tissue engineering has discussed by Wintermantel et al., (1996).

Nature also provides potential design solutions. Turtle shells are an example of a multi-scale hierarchy. These structures are able to provide load bearing whilst acting as a reservoir for nutrients (Balani et al., 2011). The multi-scale hierarchy of bone itself is another example of this.

"The other way around: Invert the action(s) used to solve the problem. Make movable parts fixed and fixed parts movable" (Rantanen and Domb, 2002)

In the most literal sense this means choosing between a scaffold to mimic the structure of bone directly, so that the initial tissue formed is the inverse of what is desired, or vice versa, where the scaffold is the opposite of what is desired, so that the initial tissue growth takes the structure of bone itself. This does not appear to be the way in which bone tissue scaffolds are designed currently.

It could be speculated that former design would most likely provide the mechanical integrity whereas the latter would have better cell and fluid distribution. A combination of the two maybe of interest.

"Mechanical interaction substitution: Replace a mechanical method with a sensory method. Use electric, magnetic and electromagnetic fields to interact with the object." (Rantanen and Domb, 2002)

Currently there is difficulty in the immediate application of this principle. A possibility, is that the scaffold microstructure can be manipulated in response to the activation of some type of field. For example a piezo material that is capable of dimensional change, and generating stress, under an applied voltage.

The mechano-transduction effects of mechanical load and fluid wall shear stress are key to bone regeneration. Further exploration into whether cells could be 'tricked' into sensing a load in which course no actual load is required to be transmitted through the scaffold would be a significant advancement for the bone tissue scaffold concept.

10.1.2 Coupling 5

"Periodic action: Instead of continuous actions, use periodic or pulsating actions. If action is already periodic, alter the periodic magnitude or frequency" (Rantanen and Domb, 2002)

This principle is already used in scaffold design in conjunction with *in-vitro* tissue growth strategies.

This consists of inducing stress by either oscillation or vibration. This is currently achieved by designing scaffolds as bioreactors (Wendt et al., 2005; Martin et al., 2004; Wendt et al., 2003; Meyer et al., 2006). These devices act as incubator templates for new tissue within a laboratory environment. Examples of this would be the use of oscillating or rotating flasks containing the scaffold whilst being supplied with a continuous nutrient stream to achieve *in vitro* tissue growth.

Taking this further, scaffolds could also be subjected to 'pulses' in fluid flow perfusion as opposed to vibrations and oscillations. Again in an *ex vivo* environment, scaffolds would be placed within an artificial boundary while being subjected to differing fluid flow regimes in combination with an appropriate cell entrainment velocity.

"Segmentation: Transition to the micro-level. Divide an object or system into independent parts" (Rantanen and Domb, 2002)

This principle is can be immediately applied to bone scaffold design and works well in conjunction with separation.

The scaffold can be segmented into separate zones with the internal geometry of each zone, optimized to create regions of desired fluid flow shear stresses. This is to take advantage of the mechano-transduction mechanism, fluid flow shear stress has on promoting preferred osteoblastic cell linages.

Designers might also consider segmentation of time as a factor. For example whether to primarily focus upon internal stress conditions across the template at an *in-vitro* bone regeneration stage, where it is easier to manipulate fluid flow conditions, and this continues into the *in vivo* phase, or whether once *in vivo*, this becomes a secondary priority.

"Parameter changes: Change an objects physical state (e.g., to a gas, liquid or solid). Change the concentration or consistency. Change the degree of flexibility. Change the temperature" (Rantanen and Domb, 2002)

These are based upon the assumption that the template will have the ability to change from a solid form to liquid via resorption. This occurs via the incorporation of a bioactive material that undergoes ionic dissolution into the scaffold.

However as the solid structure undergoes resorption, the flow paths throughout the template will be altered. This in turn will alter the shear stresses in a random and uncontrollable manner.

Therefore in order to apply this principle the scaffold component materials would have to have a known consistency and controllable ionic dissolution rate.

10.1.3 Coupling 6

"Copying: Instead of an unavailable, expensive or fragile object, use simpler, inexpensive copies" (Rantanen and Domb, 2002)

This strategy could involve the design of a single optimum pore, which has the capability of manipulating the host body into self-replicating itself. This could also involve nano-scale self-assembly machinery to controllably duplicate the pores into a predetermined macrostructure once inside the bone void space.

"Partial or excessive actions: If 100% of a goal is hard to achieve using a given solution method, the problem may be considerably easier to solve by using slightly less or slightly more of the same method" (Rantanen and Domb, 2002)

An example is to saturate the scaffold with cells prior to implantation. Utilizing an *in-vitro* pre-seeding strategy will allow some cells to become entrapped within the tortuous network of the scaffold. If seeding is treated as a bioprocess, the excess cells that initially escape the scaffold are retained in the surrounding fluid to be re-introduced on a continuous basis.

Another solution is the current scaffold composites of bioactive and non-bioactive materials in order to create a mix of replacement and tissue repair.

It may not be necessary to subject the scaffold to the full desired external compression. If the optimum level compromises the integrity of the scaffold, then utilizing a loading regime consisting of a combination of sub optimum compressive forces with a pulsating fluid perfusion flow may be an adequate compromise that still stimulates necessary tissue growth perhaps at the expense of time.

10.1.4 Final design solution

Considering the design strategies outlined above, the question is asked as to how they may come together in a single strategy. A solution may lie in the prioritisation or conjunction of these approaches. TRIZ has no formal route as to how to proceed. It is most likely that prioritisation of design strategies is the most useful as this allows for a single design focus. By incorporating several inventive solutions into a single design there is however a risk of introducing further design contradictions that did not exist previously.

Therefore an alternative design would be based upon optimizing the scaffold for one particular requirement, rather than trying to satisfy all requirements and achieving sub-satisfactory levels across the board. The scaffold could be designed for optimum mechanical properties or optimum fluid flow induced shear stress and not for bioactivity.

This is the endpoint of the combination of Quality Function Deployment and TRIZ.

10.2 Reapplication of Quality Function Deployment

The following section of the discussion discusses the results from Chapter 6, the expanded house of quality methodology. The results are discussed in order of presentation in Chapter 6.

10.2.1 The Design Requirements

The microstructure design requirements consisted of parameters identified from six different domains of research (Table 20). These domains are porosity theory, bioresorption kinetics, osteogenesis, porous material characteristics, mechano-transduction and fabrication.

Porosity theory combines different scales of porosity; macroscale (<10 µm), mesoscale (1-10 µm), and nanoscale. The nanoscale level of porosity dictates primarily the adhesive properties of the scaffold to cells whereas the macroscale level dictates the internal geometry void spaces in which the cells will proliferate. Since the scales are intrinsically linked this presents a significant design challenge in combining the optimums.

Bioresorpion kinetics dictate firstly the ion dissolution profile of the scaffold material and secondly the level of ion accumulation in the major organs. These mechanics will initially attract the cells to the local environment and over time then become responsible for the removal of the scaffold material entirely.

Osteogenesis processes are the organic part of the scaffold and are responsible for the regeneration of bone. These processes are for which the porosity theory parameters and bioresorpion kinetics must be optimized for. The bioresorption kinetics attract the cells to the local environment due to favourable ion concentrations, and the nanoscale porosity allows sites of attachment for the bone cells. The meso and macroscale then provide the long term site geometry for the cells to proliferate into, eventually becoming bone tissue.

Mechano-transduction mechanisms of fluid flow become vital in the effective mass transfer of nutrients via continuous perfusion and providing ideal wall shear stress for the correct osteoblast lineages.

Fabrication design requirements incorporate the production aspect of the scaffold. For a product to be viable it must be mass producible under strict regulatory compliance to the relevant regulatory authority.

Finally the material characteristics are those that result from the porous nature of the scaffold. These metrics are characterised when the final validated scaffold product is fabricated. To a certain extent it may be impossible to design for a certain compressive strength or stiffness, due to their intrinsic nature other than by the initial selection of a certain material.

10.2.2 Relationship matrix

The relationship matrix is the link between the customer requirements to the design requirements. By expanding upon this stage (Figure 13) compared to the previous house of quality (Figure 13) a greater level of detail is presented about the link between the literature voice of the customer and the literature design requirements. The value that this brings to this process is the greater level of confidence in the subsequent absolute importance values. A greater number of comparisons require a greater overall consideration of the interactions that may or may not take place.

10.2.3 Absolute Importance

The absolute importance values for the corresponding design requirements are presented along the foot of Figure 13. As previously stated, the top five design requirements identified by the expanded house of quality were; Fluid flow mediated wall shear stress (399), pore body diameter (390), strut thickness (390), Textural porosity (384) and pore throat diameter (346). These numbers are the relative importance ratings. The value of this process is the confidence that these design requirements were identified by following a repeatable methodology. If readers do not agree with these design requirements, then at least one is able to verify the route by which they were scored. This achieves a repeatability characteristic which is not present in current scaffold design concepts.

10.2.4 Engineering Targets

The scaffold engineering targets are summarised with supporting references in Table 20. The difficulty for scaffold designers in interpreting this data is identifying a single value. The variations are due to the authors carrying out research into scaffolds with differing aims and objectives.

Taking into account the number of different pore body diameters as well as pore throat sizes, it may be beneficial to move away from the traditional view of pores and interconnects. Rather than having the complexity of what looks like a bimodal pore scaffold design with difference pore throat diameters acting as interconnects, an easier alternative would be to combine the pore bodies with pore throats into a series of continuous trans-microstructure channels. These channels would have a controllable tortuosity in order to create a set wall shear stress under fluid perfusion conditions.

A structure consisting of repeating spiral tubular membranes in parallel could be a potential design. Circular spiral columns as manufactured by femtosecond laser microfabrication may be a potential design candidate (Seet et al., 2006).

In order to achieve the desired flow conditions for bone regeneration the scaffold would be seeded with cells and incubated in a bioreactor design. This would enable the effective manipulation of perfusion, whether it is continuous or pulsatile as well as controlling the rate. At this stage this seems the only method of being able to achieve the identified perfusion rates and wall shear stresses. Achieving cyclic compression under these bioreactor conditions would require a hydraulic piston-like incubator that could exert a controllable pressure regimen. At this time it is not certain of this is possible.

Taking into account the above, the choice of biomaterial in terms of resorption kinetics would be shortlisted to one that is one that can be safely excreted by the kidneys, has a controllable ion dissolution profile and is suitable for processing by a microfabrication technique.

10.2.5 Couplings

From the roof of the house of quality in Figure 14 the quantity of the couplings further indicate the complexity of the scaffold microstructure design task. The groupings of the couplings reveal several trends. Firstly that the osteogenic processes and material characteristics are coupled to porosity parameters, and secondly that the bioresorption kinetics are also coupled to osteogenic processes. These all take the form of positive couplings as was expected.

The only strong negative couplings occur between the porosity theory parameters themselves. This is due to the conflict between the struts of the pores and the dimensions of the internal voids themselves. Larger void spaces results in smaller struts and vice versa. This is likely to be a design problem since the large struts are integral to the overall strength and stiffness of the scaffold itself but large struts also mean smaller dimensions available to fluid flow and tissue growth.

10.2.6 Summary

An initial interpretation of the range of targets presented in Table 20 indicates the complexity of a ‘one size fits all’ scaffold design concept. Especially since multiple values are presented for several design requirements. This is of interest as it moves the design concept towards a ‘moment of design’ paradigm. This means designing for a particular moment in time in which the scaffold should be able to fulfil the purpose of which it is asked.

This suggests that a more practical approach to scaffold microstructure design is to design for a specific moment of application. This would involve the addition of a third set of attribute statements in the form of design strategies. For example, should a design strategy be based upon the practical aspect of its initial handling and application as an 'off-the shelf' product for use in a medical theatre. Designing for ease of handling and the practically issues may actually be more important in terms of producing a viable commercial entity rather than a product that has the necessary biological efficacy but is simply impractical for everyday handling or requires specific storage conditions whose costs may be unacceptable.

Examples include design strategies based solely upon maintaining integrity when physically being handled by surgeons without failure (crumbling), or providing a range of overall shapes that allow the surgeon to physically cut into and manipulate the external dimensions for the unpredictable nature of the medical defect (similar to tearing a stamp from a book of stamps along designated pre-perforated lines).

Another possibility is the provision of generic 'off-the shelf bone'. The scaffolds are seeded with cells and a ready supply of bone is ready in the form of a bone bank. There is also the possibility of the microstructure that is optimised for fabrication based upon the need for proof of consistency in reproducibility for validation. This design is not optimized for bone regeneration but that for a business strategy that believes that a slight improvement in what is currently available and cheap to validate and manufacture would be more profitable.

In order to take the scaffold design concept further, additional tools are required that organise the design requirements into a viable overall design strategy. Again the value or the reapplication of this process is seen when compared to the previous house of quality in Figure 12. The identified couplings provide greater specificity than in the previous iteration. The benefits are two-fold. Firstly, of the greater clarity of the interactions based upon tangible engineering design requirements and, secondly, in the greater user-confidence of the robustness by which the couplings shown were identified (Table 21 to Table 48).

10.3 Three-dimensional relationship technology chart

This section discusses the findings of the three-dimensional relationship technology chart order of presentation in Chapter 7.

10.3.1 Step 1: Collecting the customer demanded quality

In order to apply the three-dimensional relationship technology chart a previous methodology for collecting the customers' demanded quality statements is required. The attribute statements that were originally identified and validated as critical-to-satisfaction statements in Chapter 5, renamed as customer requirements in Chapter 6 and subsequently used as the customers' demanded quality in Chapter 7 were the foundation on which this scaffold design method is based upon.

10.3.2 Step 2: Creating the design strategies

This method allowed the introduction of a third set of hypothetical attribute statements in the form of design strategies. These strategies were constructed with a clear methodology, each with the clear intension of a different focus for the bone tissue scaffold problem.

The advantage of this introduction is a further refinement of design in the mind of both the designer and customer. This is a deliberate bias towards deciding 'what it is' that the microstructure of the scaffold 'needs' to deliver. This allows for an additional discussion between the designer and customer to see firstly if the customer agrees with the strategy, secondly if it is one that they which to pursue and finally, if they were originally aware of this strategy at all. The latter part is the most important because the customer may see additional value for their product that was not previously recognised.

10.3.3 Step 3: Selecting the design requirements

The selection and exclusion of design requirements was done to reduce the overall complexity of the design problem and manoeuvre the microstructure deliberately towards the material science domain. Specifically porosity theory and fluid flow mechanics. This was due to the presumption that these design requirements can be readily manufactured for.

The contribution of this step is the reduction in the scope of the design problem for the designer. The method and criteria on which exclusions were made are clearly shown, which allows subsequent designers to clearly identify what the design output was based upon. This is an important factor for any future redesigns, as the number of design requirements could be expanded or reduced as required in order to create an alternative microstructure.

10.3.4 Steps 4 & 5: Three-dimensional relationship technology chart

The construction of the chart has value for several reasons. Firstly the clear methodology and scoring system allows the designer to talk the customer through how the 'effectiveness' ratings for each design requirement was made. This allows for adjustments and opinions of experts to change where necessary. Secondly the customer is presented with four design options, and for each, which are the suggested most effective design requirements.

For the gene up-regulation strategy, strut thickness, fluid flow induced wall shear stress and pore body diameter are the three most effective design requirements. For nutrient distribution, strut thickness, pore throat diameter and pore body diameter are the most effective. For both cell proliferation and cell distribution, textural porosity, strut thickness and pore throat diameter were the most effective.

Strut thickness was common to all design strategies. This indicates that the design of microstructure should focus on designing the struts surrounding the pores rather than the pores themselves. These struts are the solid part of the internal microstructure. One solution is the control of the degree of truncation of the struts when the pores are being introduced into the microstructure.

Textural porosity is the most effective design requirement for both cell proliferation and cell distribution. This is due to the significance of nano-scale porosity in regards to cell attachment at the cell-scaffold surface interface. The diameter of the pore throats is key in providing unhindered transport of cells throughout the microstructure. Too small a diameter would result in the accumulation of cells resulting in necrotic cores.

Based upon the above, it could be speculated that the only design that could provide an adequate internal microstructure would be a gyroid structure or membrane. These structures have no straight lines and can be described as triply periodic. This minimal surface microstructure could provide a controllable pore throat size for cell distribution. Another potential advantage of this design might be a constant fluid flow induced wall shear stress distribution in comparison to designs that have more rigid angled pore channels.

The value of the three-dimensional relationship technology chart is to establish a clear dialogue between the customer and designer by the designer presenting the design information visually so that it can readily be analysed and critiqued by the customer in a constructive manner. This allows for a better working relationship between the customer and designer and is likely to result in proactive product development.

However the application of three-dimensional relationship technology charts appears to be uncommon. It is unclear as to whether this is due to it being an unknown design tool or whether designers do not value its contribution to design methodology. The absence of any direct criticism suggests the former. No references could be found for literature reviews on three-dimensional relationship technology charts. This indicates that the tool is not in common usage and hence no comment can be made in context to its validity from peer reviewed sources.

Another problem is with the values produced by the chart itself. The scoring system was based upon a 1-5 ranking, as followed by the case study. However this produces ordinal data and not ratio data. This means that there is a risk of interpreting the values in the chart as ratios. The numbers indicated can only provide an 'effectiveness' and nothing else. A better method might be to use the analytical hierarchy process (AHP) to rank the values. This would produce ratio values. Therefore, one could then make more meaningful direct comparisons between design requirements. This means that if the value was twice that of another then it is twice as good. With the current method this comparison cannot be made.

10.4 Axiomatic Design

The following section is divided into four parts. The first part will discuss the findings of the percolation theory based bone tissue scaffold design. The second part discusses the time-dependent model. The third part is a comparison of the two designs. The final part of the discussion is a critique of the Axiomatic Design methodology itself.

10.4.1 Percolation design analysis

The application of percolation theory to design a porous scaffold is novel in the bone tissue scaffold domain. Percolation theory is typically applied from the perspective of characterising flow in a wide range of porous structures from soils to rocks.

The proposition of a separate percolation threshold for each function requirement (FR) maintains the independence axiom. That is that variation in one parameter influences one parameter only by design. In order to accommodate these differing percolation thresholds into one single design it is likely that the scaffold would have to be segmented into zones, each with one of the designated percolation thresholds. These zones would have to be mutually exclusive as to prevent unwanted conduction of flow.

Applying the TRIZ solution 'the other way around/inversion' to the lattice design, the mechanical strength properties are provided by the inverse of the open lattice network bonds and sites created by FR_2 and FR_3. Another possible TRIZ solution is the use of 'nesting'. This means placing an object inside another. This indicates a design hierarchy of porosity scales. The percolation threshold for each FR may be achieved by designing differing scales of porosity to accomplish their tasks.

10.4.2 Time dependent complexity design

10.4.2.1 Matrix analysis

When utilizing time as a variable the microstructure was divided into three distinct matrices. For M_1 the design parameters are dedicated towards the maintenance of mechanical integrity. It is intended that the t = 0 phase describes the point at which fabrication ends to the moment that it is selected to be used in a medical theatre or laboratory (depending in *in vivo* or *in vitro* tissue growth strategy). This is indicated by the inclusion of strut thickness, pore orientation and pore geometry.

The remaining parameters, diffusion path length and tortuosity describe what occurs at the point of immersion of the scaffold in either simulated body fluid (SBF) or blood. Passive transport mechanisms such as diffusion dictate the transport of nutrients and tortuosity indicates the relationship between the microstructure and its relationship with the cells that are to seed it.

For M_2 the introduction of the fluid phase adds couplings to the microstructure. DP_6 and DP_{10} are the most coupled DPs, with four and three respectively. This was expected since the literature supports fluid flow as an important attribute in achieving the desired mechano-transduction mechanisms for ideal osteoblast differentiation.

Whilst Axiomatic Design theory emphasises the importance of the independence axiom, in this time instance it could be speculated that the purpose of the microstructure is to provide ‘optimized couplings’ rather than the alternative uncoupled ideal.

At M_3 the emphasis is upon achieving the balance between the bioresorption of the microstructure and the guided growth of bone tissue. The dissolution ions themselves are intended to provide a local environment that encourages osteoblast proliferation. This local environment consists of a concentration of bioactive ions that stimulates cell proliferation but not concentrated enough to result in apoptosis (cell death).

The design parameters reflect the desire for structural dissolution and guided bone in-growth. The reuse of pore geometry as a design parameter in M_3 allows for uncoupling from the pore geometry in M_1. This indicates an anisotropic microstructure as at least two types of pore geometries are required.

10.4.2.2 Design improvements

To advance the microstructure of the bone tissue scaffold using Axiomatic Design, the following section proposes ways to 'manage' the couplings in the design parameters particularly for the t= 0.5 time instance. This is because of the significance of fluid flow on the relationship between the microstructure and the cells within it.

A possibility that is worthy of investigation is to manipulate the viscosity of the fluid phase. This assumes an *in vitro* bone regeneration strategy was being used. Investigation of electrorheological fluids which can alter their viscosity based upon electric fields may be a possibility. Therefore the viscosity of the simulated body fluid could be manipulated if required. A fluid with a lower viscosity may be able to permeate the microstructure and provide improved nutrient and cell distribution for a lower given inlet velocity and perfusion rate, than a fluid of higher viscosity. This in turn will lead to alteration in the distribution of wall shear stress within the microstructure. A fluid with lower viscosity would also be beneficial if the microstructure needed to maintain mechanical integrity in the previous time instance (t = 0) was of particularly tortuous design.

The introduction of an additional functional requirement may also help decouple the t = 0.5 time instance. An example would be 'to support the distribution of cells throughout the microstructure". This could be achieved by the application of a wetting agent, prior to cell seeding, in order to reduce the surface tension within the microstructure. This may benefit the system by reducing the number or extent of the couplings in this system. This is dependent on the current level of hydrophobicity or hydrophilicity of the microstructure.

10.4.3 Comparison

The initial percolation theory model presents an over simplistic view of the bone tissue scaffold concept. This model is an isotropic material view of the bone tissue scaffold concept. This design is based upon control over the particle arrangements and packing. The division of FRs by time in the second model presents a model with greater complexity but it appears to be closer to reality. The time-dependent model, shows, in a clearer fashion, what should occur in each time instance. The advantage of the first model is that scaffold designers may be readily able to begin a manufacturing step in order to assess the designs viability compared to the second model.

10.4.4 Critique of Axiomatic Design

It appears inescapable that the design of the ideal microstructure for a bone tissue scaffold cannot maintain the independence axiom from an Axiomatic Design perspective. The relationship between the design parameters that create the microstructure are intrinsically linked to the flow of fluid throughout itself. Whilst the addition of fluid flow appears at first to act as a 'coupling medium' it is these couplings that are of benefit in the generation of the necessary mechano-transduction mechanisms, which are required for preferential osteoblast differentiation.

The combination of both the ideal microstructure, from the perspective of acting as a template for cellular adhesion and subsequently bone in-growth, and an ideal microstructure that is optimised for generating the desired fluid-flow-induced wall shear stresses are of vital importance.

The advantage of utilizing Axiomatic Design to analyse the time-dependent nature of the scaffold simplifies the design process into three separate stages. Firstly, without cells, secondly the seeding the microstructure with cells and finally, directing the tissue growth. This allows the production of three separate microstructural designs based upon time. From this system of interest, the transition to and from the mid time instance (i.e. $t < 0.5$, $t = 0.5$ and $t > 0.5$) also revealed two additional scaffold designs. It can be speculated that in order to expand upon the relationships within this system of interest identified by Axiomatic Design that further unconsidered domains of research need to be considered (the unknown-unknowns).

10.5 Future perspectives for the bone tissue scaffold design concept

Based upon the discussion of the finding for the different design methodologies the future of the scaffold concept could be dependent on the implementation of design quality. The amount of primary research data in this field has more than exceeded a point of critical mass to implement industry applied total quality management (TQM) techniques and quality function deployment. According to Shiba et al., 1993, the foundation of TQM is to "enhance product design, eliminate defects and reduce costs".

MIT's Sloan School of Management actively encourages the application of QFD to those who seek to become leaders in industry. Future scaffold designers need not be left behind by significant developments outside their sphere of research. Rather by embracing the aspects of quality in order to co-ordinate the large amount of empirical research available to them, this would better develop their own understanding of the scaffold concept with also the perspective to achieving fabrication viability.

10.6 Validation

This section discusses the responses to the survey from the experts in tissue engineering. The discussion is organised by the statements asked in the survey with a final section discussing the overall findings. The Quality Function Deployment – TRIZ (QFD-TRZ), expanded house of quality, three-dimensional relationship technology chart (3DRTC) and time-dependent Axiomatic Design were all presented. The percolation theory based design was not included in the survey. The time-dependent design was presented in two parts. All references to part one and part two refer to the time-dependent design and not the axiomatic percolation theory model.

The design solution could lead to innovation (new or improved product capabilities)in bone tissue scaffold design

The first part of the time-dependent Axiomatic Design solution was selected as the design that could lead to innovation with the highest rating of 4.5. In joint second place was the expanded house of quality and second time-dependent Axiomatic Design solution. The QFD-TRIZ design scored 3.5, in fourth, and finally the three-dimensional relationship technology chart with 3.3. Both the QFD-TRZ and 3DRTC are still within in the neither agree nor disagree bounds.

These results showed that despite the literature review in Chapter 2 indicating the TRIZ was a useful design methodology for innovation, the tissue engineering experts indicated that the both the Axiomatic Design solutions and expanded house of quality solution could lead to innovation. Two possible explanations exist. The first is that the thorough decomposition and analysis of the system of interest (bone tissue scaffold) that both provide, is more likely to lead to innovation because of the clarity of understanding of which factors and parameters dictate and influence one another in the system.

The second is that the unspecific nature of TRIZ itself in the field of scaffold design makes it difficult to directly interpret the relevance of solutions without applying varying levels of speculation. If the TRIZ solutions and principles were entirely reworked for scaffold design and tissue engineering, then experts may elevate TRIZs status as a tool to drive innovation in bone tissue scaffold design.

3DRTC was considered the least innovative of the five proposed design solutions. It is likely that the design methodology is better suited as a management decision making aid in support of assigning different technologies based upon demands by the customer rather than an innovative design methodology in itself. The absence of literature for this design methodology seems to support its unpopularity.

The content of the design solution enhances current bone tissue scaffold design

Axiomatic time-dependent design, part one, and expanded house of quality came joint top with 4.3. QFD-TRIZ and Axiomatic Design part two came joint third with 3.8. 3DRTC came last with 3.3.

The expanded house of quality design solution provided an extensive list of scaffold design requirements accompanied by precise engineering targets for each. In some cases more than one target was provided. Therefore it is likely that designers can readily assess, firstly, if they agree with the specific design requirement itself and, secondly, if the engineering target was viable or not. This pragmatic approach to presenting a detailed list of targets contrasts to the joint top Axiomatic Design solution. The first Axiomatic Design solution presented the use of time to divide scaffold function and design. The novelty of this design solution may have contributed to its joint top status.

The second Axiomatic Design solution was the execution of the proposed first design which was joint third with the QFD-TRIZ design. The placing of these indicates that the design solutions still offer a possibility of enhancing the bone tissue scaffold concept.

The scores for the 3DRTC resulted in a neutral average score. Further refinement and explanation of this design solution and potentially the methodology itself may be required for experts to value its contribution to further the bone tissue scaffold concept.

The solution needs significant improvements

The design in need of significant improvement was the QFD-TRIZ design with a score of 3.3. The second design in need of improvement was the 3DRTC. The expanded house of quality and part two of the axiomatic design solution scored 2.8. Axiomatic Design part one came last with a score of two.

The neutral response to the QFD-TRIZ design solution indicated this as the design solution of the five presented that needed the most significant improvement. This is may be due to two factors. The first is that TRIZ it its current generic presentation requires intensive speculation by the experts themselves prior to making an informed assessment of the design. The second factor is that the house of quality coupling and matrix analysis was performed at too high a level of abstraction to make a useful design contribution.

The 3DRTC remained in the neither agree nor disagree category. Further work is required in terms of the methodology and the solution itself is required to generate an improved solution.

The lack of agreement with the statement for the remaining designs indicates that they are closer to a potential manufacturing step than the previously mentioned solutions.

I am keen to apply the solution or aspects of it in my future work

The design solution most popular was the axiomatic time-dependent part one with 4.3. This was followed by expanded house of quality (4), axiomatic time-dependent design part 2 (3.5), QFD-TRIZ (3.3) and finally 3DRTC (3).

The positive response for the top two design solutions indicates the potential that the design methodologies offer to the bone tissue scaffold concept. A more detailed analysis of precisely what parts of the design solutions the tissue engineering experts were indicating would be the most logical next step.

The remaining three design solutions whilst, they did not receive a negative response, require further clarification as to what was lacking in these design solutions.

The solution is….

Axiomatic time-dependent solution part one and the expanded house of quality came joint top with 4.3. Axiomatic time-dependent solution part two came third (3.8) with the remaining two designs scoring 3.

Generally the Axiomatic Design solutions and the expanded house of quality were well received by the tissue engineering experts. Further work is required to redevelop the QFD-TRIZ and 3DRTC design solutions in order to convince the experts of their value to the bone tissue scaffold design concept

Summary

Based upon the visual representation of the radar charts it is clear that both the axiomatic time-dependent design part one and the expanded house of quality were indicated as the most positive design solutions. This was followed by the second part of the time-dependent axiomatic design solution. Both the Quality Function Deployment-TRIZ solution and three-dimensional relationship technology chart were the least popular solutions.

However based upon the four responses for the survey the validation provides an indication of the popularity for the design solutions rather than a conclusive review of the field of tissue engineering in its entirety.

11 Conclusions

The following section presents the thesis findings in order of the research objectives. The contribution to knowledge and broader implications are stated.

1. Findings from the multi-tiered literature review:
    a. The following design methodologies were identified for consideration; Quality Function Deployment, TRIZ, three-dimensional relationship technology chart and Axiomatic Design
    b. No reason was found to exclude the application of the design methodologies listed above

2. The second literature review identified the current state of the art in bone tissue scaffold design as:
    a. Design based upon computer image design followed by solid free form fabrication technique
    b. No formal design methods were currently in use
    c. Design decisions were based upon what can physically be designed, based upon the fabrication technologies available to the researchers, rather than what should be designed regardless of whether or not the technologies exist
    d. In some cases, the arguments for key design decisions were not stated

3. The Quality Function Deployment – TRIZ findings:

    a. The literature voice of the customer consisted of three customer attribute statements, based upon the criteria of living tissue, which were validated by a small survey if experts
    b. The literature critical-to-satisfaction (CTS) statements consisted of nine attribute statements for bone tissue scaffolds and were validated by the same group of experts
    c. The most important CTS statements identified by the house of quality were: Act as a template for three dimensional bone growth, is biocompatible and be sterlizable and meet regulatory requirements
    d. The roof of the house of quality identified both positive and negative design conflicts between the criteria for living tissue and bone tissue scaffold CTS attribute statements. These were the subject of the TRIZ analysis
    e. The most interesting TRIZ findings were: separation and segmentation
    f. Limitations in the QFD-TRIZ methodology were identified as:
        i. The non-specific nature of the TRIZ solutions, leading to speculation rather than concrete design conflict resolutions
        ii. No safeguard against the unintended generation of further design conflicts by the resolution of the identified conflicts
        iii. No process for combining all the identified TRIZ design solutions into a single design

A contribution to knowledge of this design method is that TRIZ was shown to be a method to solve design conflicts in the bone tissue scaffolds. The visual nature of the co-ordination of information presented enables the design solution to be subject to immediate discussion. However the design solution occurs at an abstract level that may not be specific enough in terms of details for scaffold designers.

4. The second application of Quality Function Deployment consisted of an expanded house of quality. The following findings were identified:

    a. Thirty two design requirements (DR) were identified from the following areas of research; porosity theory, bioresorption theory, osteogenesis, materials science, mechano-transduction and fabrication processing
    b. Fifty two design conflicts identified by the roof of the house of quality
    c. A limitation identified in this method was that it lacked a process for the re-organisation and recombination the identified DRs into a single master design for a bone tissue scaffold
    d. Clear presentation of engineering targets for each associated DR enabling scaffold designers to begin planning the manufacturing step

A contribution to knowledge of this work in the domain of bone tissue scaffolds is the generation of the detailed list of DRs and engineering targets. This enables scaffold designers to readily begin assessing the feasibility of the engineering targets as to whether or not they are able manufacture that DR with the available fabrication techniques. The design detail presented in this design is greater than the first QFD design which occurred at a higher level of abstraction.

5. The three-dimensional relationship technology chart presented a design methodology capable for aiding in decision making for the bone tissue scaffold concept

    a. The following design strategies were proposed; up-regulation of genes, effective distribution of nutrients, guided cell proliferation and uniform cell distribution
    b. Based upon the up-regulation and effective distribution of nutrient design strategies, the strut thickness was identified as the most effective design requirement
    c. Based upon the guided cell proliferation and uniform cell design strategies, textural porosity was identified as the most effective design requirement
    d. Design strategies were reached by a clear design methodology, which can be readily critiqued by a ‘customer’
    e. The “customer” is able to re-evaluate the microstructure design, prior to the implementation of the fabrication process, adding value to the overall design process

The most significant contribution to knowledge for this design methodology is the identification of the effectiveness of individual design requirements in relation to an overall scaffold design strategy. The visual aspect of this design method is intended to be appealing when presented to the ‘customer’, thereby readily enabling discussion of potential talking points. By its presentation of alternative designs, it allows the ‘customer’ to make an informed decision as to whether or not one strategy is more viable than another.

6. The first Axiomatic Design analysis used percolation theory. The findings are as follows:

    a. Percolation model suggested three functional requirements (FRs): to provide mechanical strength, to distribute cells and to provide locations for cells
    b. Percolation model design parameters (DPs) based upon isotropic properties with percolation threshold was identified as the critical parameter
    c. Microstructure design was dependent on three different percolation thresholds with an ranked hierarchy to satisfy the initial functional requirements
    d. The percolation thresholds were dictated by control of both the site co-ordination numbers and lattice particle arrangement: Face-centred cubic, body-centred cubic and diamond arrangements were suggested

    The second Axiomatic Design broke the analysis into time segments. The findings are as follows:

    e. For the second model a tractable design solution was obtained by the introduction of time as a constraint and three time instances were proposed
    f. Whilst changes were required to the standard methodology for the application of axiomatic design for the time dependent model, it was deemed necessary in order to show a comprehensive attempt at design, since no prior example or template existed to build upon
    g. In difference to the percolation model, the functional requirements varied with time
    h. The majority of microstructure design parameters were extracted from percolation and porosity theory
    i. Three design matrices; the first at (t = 0) is closest to the independence axiom with five couplings and also revealed redundant design (number of DPs > FRs)

j. The second matrix (t = 0.5) identified eleven couplings so the independence axiom can no longer be maintained, at this phase fluid is a factor in the microstructure system of interest
k. The third matrix (t = 1) found eight couplings, therefore the independence axiom cannot be maintained
l. The design matrices revealed fluid to act as a coupling medium within the microstructure
m. Two transitory design matrices revealed indicating previous unknown couplings from the three matrices above
n. Percolation theory model simplistic compared to time-dependent model, the latter is more likely to be closer to the bone regeneration process itself

A contribution to knowledge for this design solution is to design a bone tissue scaffold with the inherent time-dependent nature of biological systems in mind. Previous scaffold designs state the desire for functions that have an assumed time dependency without stating at what point in the bone regeneration process 'should' that function be executed. By focusing on time itself the scaffold design problem is subjected to an alternative design perspective of which there is value.

7. The validation of the design outputs by a survey of expert opinion indicated the following:

    a. Future work should focus upon the both the application of Axiomatic Design, specifically due to the time-dependent nature of biological systems, and the expanded house of quality approach
    b. The TRIZ parameters and solutions should be re-written according to the state of the art in tissue scaffold design in order to move TRIZ closer to the practical usage for tissue scaffold designers
    c. The neutral feedback of the three-dimensional relationship technology chart indicates that improvement is required in both the design output and development of the methodology itself in order for practical usage
    d. Formal design methodologies have a role in developing the bone tissue scaffold further

A contribution to knowledge of the validation process is that formal design methodologies identified, from alternative industries, have a role to play in developing the bone tissue scaffold concept. Time-dependent design, is an area that future scaffold design should focus upon.

Based upon the research outputs achieved by the selection and application of these formal design methodologies it has been shown that there is a potential role for these methodologies in both bone tissue scaffold design and tissue scaffold design in general. The clear presentation of the design as well as the information the design was implemented on provides external viewers the ability to readily critique or identify areas of improvement. This clarity in presenting the design process as well as the reasoning and justification behind design decisions is often absent in traditional scaffold design research publications.

A future direction for bone tissue scaffold design research is repeated applications of both QFD and Axiomatic Design along with other potential design methodologies such as Design for X, in order identify if similar customer requirement, functional requirements and design parameters are generated as well as their respective priority ratings. One of the difficulties with QFD is the collection of enough opinions from technical experts to validate and score the various attribute statements in the House of Quality process. It may only be possible to collect the necessary information at large gatherings of experts such as at tissue scaffold conferences. The process of physically interacting with participants also makes it difficult for people to refuse to participate.

The design methodologies have incorporated the voice of the customer with literature sources and derived an insight into the level of detail and engineering targets that the future processing technologies would need to be able to satisfy in order to manufacture a prototype. Manufacturing processes are traditionally presented in the form of a process stream with employees proactively identifying and analysing key performance indicators throughout the development of the product. By applying a formal design methodology potential and unforeseen manufacturing problems may be more readily solved by clearly being able to alter the engineering targets of one or more of the design requirements or design parameters. It may also be the case that future research identifies design requirements to be irrelevant or of greater significance than first realised.

In summary the knowledge gained by the application and research output of formal design methodologies is but the first step that provides a foundation on which bone tissue scaffold research and manufacture should proceed. The next steps in the QFD and AD process are to investigate process and manufacturing techniques that can satisfy, control and manufacture the identified design requirements and design parameters.

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13 Appendices

13.1 Appendix A: Critical-to-satisfaction analysis

Appendix A contains the critical-to-satisfaction (CTS) statements extracted from the literature as the voice of the customer.

13.1.1 Critical-to-satisfaction statements

The details of these CTSs and the papers which included them were analysed. The literature CTSs are listed below:

- CTS_1 = Act as template for three dimensional bone growth
- CTS_2 = Resorbs at the same rate as bone is repaired
- CTS_3 = Is biocompatible (non-toxic)
- CTS_4 = Composed of a bioactive material (class A/B)
- CTS_5 = Surface properties promote cell adhesion
- CTS_6 = Exhibit mechanical properties that match host bone
- CTS_7 = Transmit fluid stress across itself
- CTS_8 = Transmit compressive stress
- CTS_9 = Have a fabrication process that allows scaffold to fit a differing range of geometries
- CTS_{10} = Be sterilizable and meet regulatory standards

In order to achieve (CTS_1) a high porosity is needed for cell seeding, ingrowth, vascularization and diffusion of nutrients. An overall porosity of 90% is ideal with a pore size within a critical range of 100 – 200 µm (Jones et al., 2004a; Freyman et al., 2001; Hulbert et al., 1972). The lower bound is dependent on cell size (20 µm) and the upper bound is associated to the specific surface area. It has been observed however that scaffolds with pore sizes of 300 – 500 µm range result in faster osteoconductivity than those in the 50 – 100 µm range (Chang et al., 2000). Overall porosity due to average pore size, is linked to the rate at which cells are able to perfuse the scaffold. It is clear that a porous architecture allows the scaffold to act as a delivery vehicle for cells and aid in the repair of bone defects (Goshima et al., 1991).

The optimum conditions for vascularization of scaffold have not been determined. The rate of capillary growth may be too slow to provide the required nutrients for cells within the scaffold, resulting in inhibited tissue growth in the scaffold core resulting in a necrotic core (Silva et al., 2006; Checa and Prendergast, 2010). For scaffolds with pore sizes ranging from 150 – 710 μm, cell and tissue growth reached has been observed to reach a maximum penetration depth of approximately 200 μm over a 56 day period. It was concluded that diffusion limitations were the cause for not exceeding this penetration depth (Ishaug-Riley et al., 1998).

The ion release profile (CTS_5) is linked to the scaffolds ability for bone cells to attach to the scaffold surface (CTS_2) and hence enable direct bonding to bone (Gough et al., 2004; Ohura et al., 1991). The rate of ion release is related to the textural porosity of the scaffold (Jones et al., 2006b). This in turn alters the attraction of osteoblast cells to the scaffold surface.

The bioactive nature of the scaffold (CTS_3) is directly related to the composition of the scaffold material. Foamed sol-gel derived binary-system glasses have been shown to be Class A bioactive materials (Sepulveda et al., 2002c; Jones et al., 2007; Jones et al., 2004a; Jones and Hench, 2004; Jones and Hench, 2003b; Saravanapavan and Hench, 2001; Saravanapavan and Hench, 2003a; Saravanapavan and Hench, 2003b; Martinez et al., 2000). These materials are both osteoproductive and osteoconductive. The properties include rapid bonding to bone, enhanced bone proliferation and bonding to soft connective tissue (Hench et al., 1999). Bioactive materials have been shown to improve the long term survivability of prosthetic implants (Hench et al., 1999). The capability of the scaffold to form a hydroxyl-apatite (HA) crystalline phase is crucial to support *in vivo* bioactivity (Lukito et al., 2005; Newport et al., 2007; FitzGerald et al., 2007). The ability of the scaffold to bond to bone is important. This is related to the surface chemistry of the scaffold (Jones et al., 2006).

The biocompatible property of the scaffold (CTS_4) is linked closely to the dissolution products of the scaffold (CTS_5) and (CTS_6). The scaffold must not illicit a toxic response on implantation, and as ion dissolution takes place, the ionic products must also be non-toxic. Animal studies have confirmed that the ionic products of bioactive glass monitored over a 7 month period after implantation, were excreted harmlessly in the urine with no evidence of saturation of silicon, in the major organs such as the kidneys (Lai et al., 2002; Lai et al., 2005).

In the case of (CTS_5) and (CTS_6) the rate of dissolution is an important attribute. If the scaffold rate of dissolution is too rapid then the ionic concentrations are too high to be effective. If the rate of dissolution is too slow the ion concentrations are not high enough to stimulate cellular proliferation and differentiation (Hench, 2006). The ionic products of bioactive glasses have shown to up-regulate gene-expression of human osteoblasts (Xynos et al., 2001).

The scaffold has to maintain mechanical integrity (CTS_7) to resist handling during implantation as well as the loading conditions *in vivo* (Freyman et al., 2001). Much work has been carried out on the manufacturing process to optimize the compressive strength of bioactive foam scaffolds (Jones and Hench, 2003a; Jones et al., 2004b). Currently bioactive glass scaffolds can achieve a compressive strength of 2.26 MPa (Jones et al., 2006a) which is within the lower limit of the compressive strength of trabecular bone (2 – 12 MPa) (Jones et al., 2006a). This has been achieved by altering the sintering property of the bioactive glass foam to 800 ˚C from 600 ˚C that has been previously used (Sepulveda et al., 2002a).

Load transfer (CTS_8) is important since the pattern of fracture healing in bones depends on the mechanical environment at the fracture site (Sarmiento et al., 1977a; Sarmiento et al., 1977b; McKibbin, 1978). Experimental studies have indicated that the application of load, influences tissue differentiation and conclude that there is an optimum loading regimen for enhancing fracture healing. Studies performed on sheep have shown that the controlled application of axial micromovement, at a loading regime that is osteogenic in intact bones, applied daily, improves healing (Goodship and Kenwright, 1985). Therefore any external mechanical stimuli influence must be transferred to local mechanical stresses inside a scaffold to impact on local bone tissue regeneration. It has been shown that cyclic compression has an effect on local bone formation in a 3D scaffold seeded with bone cells (Baas et al., 2009).

It has also been proposed, that two main biophysical stimuli: tissue shear stress and interstitial fluid flow influence tissue differentiation (Claes and Heigele, 1999; Lacroix et al., 2002). The basis of this proposal is that fluid flow through a structure induces shear stress along the interface between the fluid and the structure. As tissue differentiation progresses, mechanical changes occur on the cells in the interfacial tissue. It is this transition of biophysical stimuli that controls the tissue differentiation sequence and leads to the creation of a "mechano-regulatory pathway (Prendergast et al., 1997). Mechano-regulatory modeling has produced simulations that are similar to histological observations (Lacroix and Prendergast, 2002). Fluid-structure interaction, whilst widely integrated into engineering disciplines, such as aeronautics, is relatively overlooked in terms of its potential in biomechanics (Blecha et al., 2010).

13.2 Appendix B: Percolation theory

This section contains additional information results as of the analysis of the percolation theory literature from 4.5.2.1

Figure 25 was intended to be an alternative iteration of the bone tissue scaffold concept, based upon the assumption that bacterial transport through soil under conditions of torrential rain was similar to osteoblast perfusion through the microstructure as analysed by Axiomatic Design. The intention was to finally be able to create a unifying concept that considered all parameters on all scales of interactions.

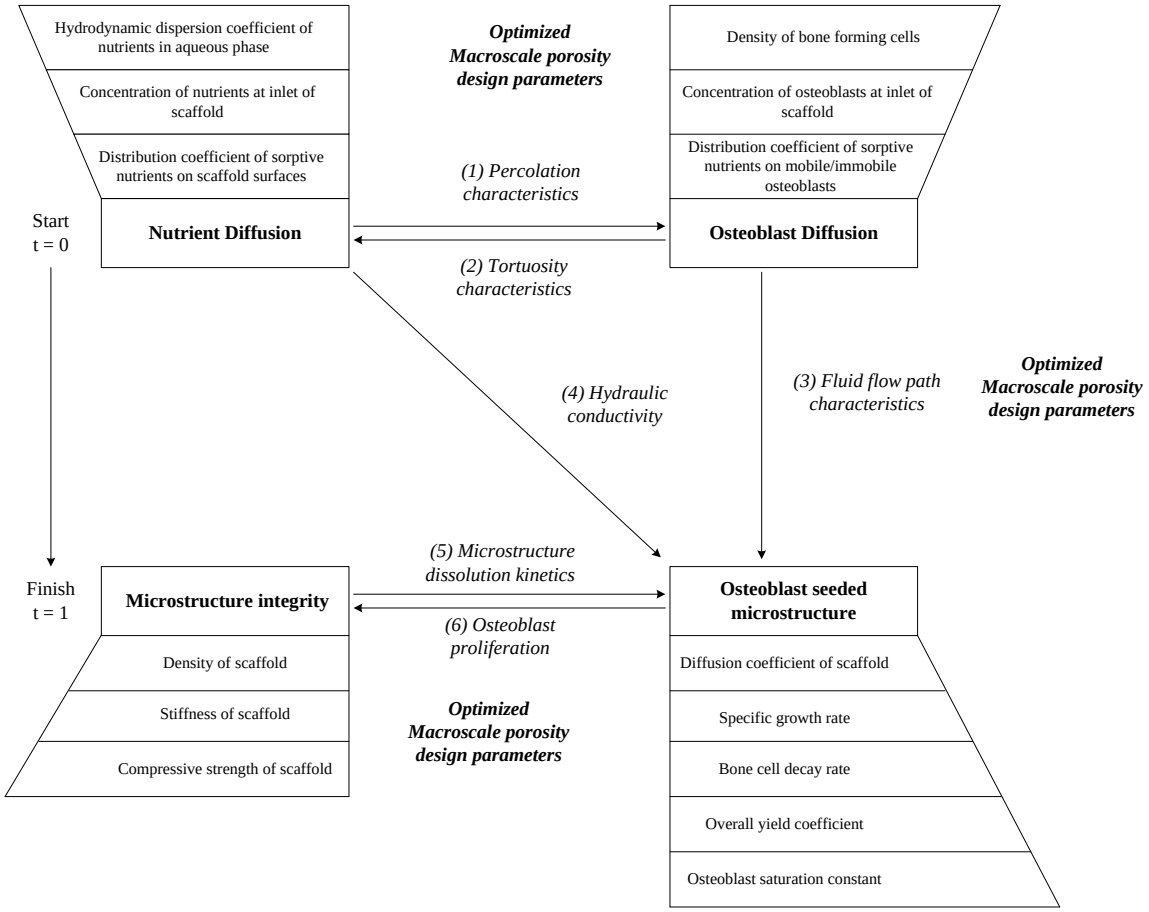

Figure 25. Unifying concept for the design of microstructure based upon bacterial transport and growth in soil. A summary of the interacting parameters at both the macro and micro-porous scale and how the microstructure porosity design parameters would have to be continually optimized with time. The numbered characteristics are discussed in the supporting text.

The following is a brief discussion of the intension of Figure 25. At t = 0, passive diffusive processes dictate nutrient flux and osteoblast migration. During this stage the scaffold has been immersed in fluid containing osteoblasts and nutrients. The flow conditions are laminar and the corresponding Reynolds number applied.

At (1) the percolation is responsible for ensuring nutrient transport to the osteoblasts within the scaffold and con currently (2) the degree of tortuosity of the channels within the microstructure influence the diffusion of osteoblasts throughout the microstructure. The list of parameters attached to nutrient diffusion and osteoblast diffusion are a summary of the important interactions that occur below the macro-porous level. These are the parameters that it are assumed to be important but cannot directly be influenced by the design of the microstructure at this scale of porosity. It is intended that mathematical proof be researched to identify whether or not the interactions listed, firstly interact with one another, and secondly how porosity affects them.

During the transition from t = 0 to t = 1, it is assumed that the diffusive interactions no longer take prominence. Rather, the hydraulic conductivity, a characteristic related to permeability, and flow path characteristics supersede diffusion. The flow regime in (3) and (4) shifts from laminar flow towards turbulent flow. It has been identified that relationship between porosity and fluid flow results in wall shear stress, which has the desired mechano-transduction effect for osteoblast differentiation, the optimum design parameters at this stage are based upon maximizing this process.

At t = 1, it is assumed that osteoblasts have effectively seeded the microstructure and reached a point of sufficient critical mass, that the term bone can be used. At this point the most important relationships in the microstructure are between the mechanical integrity and the rate at which bone in-growth occurs. (5) refers to the desired dissolution of the scaffold material.

The dissolution ions of which have a positive influence on maintaining a local environment that stimulates continued osteoblast proliferation and osteoblast adhesion.

However a balance has to be maintained between the gradual decline in integrity with the regenerating bone incrementally taking over the load bearing responsibilities as indicated by (6). The corresponding material properties of that are of interest in maintaining structural integrity are listed.

It was intended that the relationship between these material metrics, the life cycle of osteoblast (growth and decay), as well as combining the interaction of nutrients was required to fully complete the bone tissue design concept.

13.3 Appendix C: Validation survey

This appendix presents the survey used in the validation process of the thesis.

Introduction and Instruction

Context

I am contacting you, with this request for you to take part in a survey, because you are involved in the research field of tissue engineering. I hope that your participation in this survey will make a contribution to knowledge in the field of scaffold design. Answering the sixteen survey statements below should only take a few minutes of your time.

Why a survey?

In my work I have selected and then applied formal design methodologies to the design of bone tissue scaffolds. The purpose of this survey is to subject the potential design solutions, resulting from my work, to the scrutiny of regarded experts.

Because the design methods, and their inputs, differ, their outputs also differ, in both detail and the level of abstraction. Though it is difficult to do so, I would like you to try to consider the design solutions obtained from each method in isolation from each other.

Instructions

For each design solution five statements are posed in the form of a questionnaire. The survey is designed so that answers are selected by a tick box method (left click the box to tick it). Each statement requires only one response. The views of the participants will be held anonymously.

Once completed please remember to save changes prior to uploading and attaching to an email. If there are any additional comments that you wish to make on any aspect of the survey, then please feel free to voice your thoughts on the last page of the survey. Any and all contributions would be gratefully received.

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Design solution 1

[Solution one was achieved by Quality function deployment (QFD) and Theory of Inventive Solutions (TRIZ)]

- Two parameters are described as ‘coupled’ when variation in one has an effect on another
- A coupling may be described as ‘negative’ if as a result of an increase in a desired parameter there is a decrease in another desired parameter

The first design method identified three negative couplings in a design analysis of a bone tissue scaffold. The final part of the design method speculates as to how these couplings could be resolved. Table 53 below describes the coupling, the parameters affected (increase and decrease) and the potential design principles that could be applied to resolve the issue.

Statement of coupling	Relationship		Applicable Principles	Suggested solutions
Preferred increase in the template porosity for desired bone cell penetration and bone in-growth but results in a compromise to Stiffness	↑	*Template for 3D bone growth*	2. Separation 13. The other way around 28. Mechanical interaction substitution	Woven load bearing struts/ Knitted textile architecture/ Biomimicry (turtle shells)/ Piezo material/
	↓	*Mechanical properties match host bone*		
Desired increase in template porosity by random pore anisotropy but leads to creation of zones of random fluid shear stresses	↑	*Template for 3D bone growth*	19. Periodic action 1. Segmentation 35. Parameter changes	Fluid phase pulses/ Zone optimization/ Phase consistency
	↓	*Transmit fluid stress*		
Desired increase in template porosity leads to increased potential for microcracking when under compression	↑	*Template for 3D bone growth*	26. Copying 16. Partial or excessive actions	Self-replicating pore/ Cyclic loading and fluid flow regime manipulation
	↓	*Transmit compressive stress*		

Table 53. Potential design solutions for uncoupling the design conflicts.

After analysing the design solution, please tick the relevant box (left click on box) which best describes your answer to the following statements:

1. *The design solution could lead to innovation (new or improved product capabilities) in bone tissue scaffold design*

Strongly agree	Agree	Neither disagree nor agree	Disagree	Strongly disagree
☐	☐	☐	☐	☐

2. *The content of the design solution enhances current bone tissue scaffold design*

Strongly agree	Agree	Neither disagree nor agree	Disagree	Strongly disagree
☐	☐	☐	☐	☐

3. *The solution needs significant improvements*

Strongly agree	Agree	Neither disagree nor agree	Disagree	Strongly disagree
☐	☐	☐	☐	☐

4. *I am keen to apply the solution or aspects of it in my future work*

Strongly agree	Agree	Neither disagree nor agree	Disagree	Strongly disagree
☐	☐	☐	☐	☐

5. *The solution is….*

Very good	Good	No change	Poor	Very poor
☐	☐	☐	☐	☐

Design solution 2

[Solution two was achieved by application of Quality function deployment but to a greater level of detail than the previous attempt in order to reduce the level of abstraction]

- A design requirement is an identified parameter that 'should be' incorporated into the microstructure design of a bone tissue scaffold

The second formal design method worked at a lower hierarchy of design. The output of this design method was a list of design requirements and for each, a suggested engineering target value for a bone tissue scaffold (Table 54).

	Design Requirement (DR)	**Target Value**
1	Open porosity	85-89%
2	Pore body diameter	2 – 20 µm ; 100 - 300 µm (bimodal)
3	Pore throat size	10 - 50 µm
4	Strut thickness	394 ; 646 µm
5	Pore geometry (shape)	Cube ; hexagonal prism ; tubular ; spherical ; cylindrical
6	Pore orientation	Cubic ; hexagonal ; Gyroid stacking
7	Specific surface area	107.4 – 122.7 m^2/g ; 126 – 164 m^2/g
8	Surface roughness	10 – 100 nm
9	Textural porosity	2 – 50 nm

10	Rate of ion dissolution	Positive gene-expression profile on osteoblasts
11	Ion dissolution concentration	Positive gene-expression profile on osteoblasts
12	Accumulation in major organs	Negligible Parts Per Million in major organs
13	Rate of excretion in urine	1.8 mg/day (rabbits); 24 to 28 weeks
14	Osteoinduction	Yes
15	Osteoconduction	300 µm pores optimal
16	Osseointegration	Yes
17	Osteoblast infiltration	10 µm/min
18	Osteoblast proliferation	Proliferation rate: 20 hours (doubling time)
19	Osteoblast/cell adhesion	Surface roughness 10-100 nm
20	Osteoblast apoptosis	35 cells/mm (Unwanted :undiluted dissolution products)
21	Mass transfer of nutrients	Cellular/substrate parameters
22	Neovascularization / angiogenesis	33 µm/h (rate of vessel growth); 100 µm (O_2 diffusion distance)
23	Compressive strength	86 ± 5 MPa (Composite –PDLLA)
24	Stiffness (young's modulus)	5MPa
25	Fracture toughness	-
26	Flow perfusion rate	0.1 – 0.5 ml/min ; 0.08 – 0.89 ml/min (Glucose); 0.51 – 1.23 ml/min (Oxygen)
27	Fluid flow mediated wall shear	1.5 – 12 dyn/cm^2 ; 6 dyn/cm^2 = Nitric Oxide

	stress	release rate of 9.8 nmol.h^{-1}.mg $protein^{-1}$ *(Continuous vs pulsatile perfusion)*
28	Cyclic compression	500 – 5000 microstrain
29	Cyclic compression induced fluid flow	1.5%, 1Hz, 1 hour daily / static
30	Personalized external geometry	Computer-Aided Design
31	Mass producible	RP/SFF fabrication technologies
32	FDA approved	Yes

Table 54. Identified design requirements and target engineering values

After analysing the design solution, please tick the relevant box (*left click on box*) which best describes your answer to the following statements:

1. *The design solution could lead to innovation (new or improved product capabilities) in bone tissue scaffold design*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

2. *The content of the design solution enhances current bone tissue scaffold design*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

3. *The solution needs significant improvements*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

4. *I am keen to apply the solution or aspects of it in my future work*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

5. *The solution is….*

Very good	**Good**	**No change**	**Poor**	**Very poor**
☐	☐	☐	☐	☐

Design solution 3

[Solution three was achieved by application of the Three Dimensional Relationship Technology Chart design methodology]

The third design method was based upon hypothetical design strategies which are described below. The design method identified three design requirements from Table 55 that are the 'most important' in relation to the corresponding design strategy.

The following design strategies were created:

5. The up-regulation of the genes in order to stimulate the osteogenic processes via manipulation of fluid flow
6. Effective distribution of nutrients in order to maintain cell population viability via perfusion parameters (convective transport supersedes diffusion limitations)
7. Guided cell proliferation in order to stimulate bone regeneration via optimized cell sites
8. Uniform cell distributions in order to maximise cell infiltration (to prevent necrotic cores) via optimized cell channels

	Scaffold design strategy	Design Requirements		
		Primary	**Secondary**	**Tertiary**
1	Up-regulation	Strut thickness	Wall shear stress	Pore body diameter
2	Nutrient distribution	Strut thickness	Pore throat diameter	Pore body diameter
3	Cell proliferation	Textural porosity	Strut thickness	Pore throat diameter
4	Cell distribution	Textural porosity	Strut thickness	Pore throat diameter

Table 55. A summary of the most important design requirements for each design strategy

After analysing the design solution, please tick the relevant box (*left click on box*) which best describes your answer to the following statements:

1. *The design solution could lead to innovation (new or improved product capabilities) in bone tissue scaffold design*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

2. *The content of the design solution enhances current bone tissue scaffold design*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

3. *The solution needs significant improvements*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

4. *I am keen to apply the solution or aspects of it in my future work*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

5. *The solution is….*

Very good	**Good**	**No change**	**Poor**	**Very poor**
☐	☐	☐	☐	☐

Design solution 4

[Solution four was achieved by application of Axiomatic Design methodology]

The fourth design method used time as a metric in the design process (Figure 26). The design revolved around designing the optimum scaffold for three separate time instances. In each time instance the desired properties of the scaffold are stated in the form of functional requirements (FRs).

The time instances are described as follows:

- t = 0 : Scaffold is void of cells
- t = 0.5 : Scaffold is seeded with cells
- t = 1 : Cells within scaffold have reached a point of critical mass that they can be termed bone tissue

The design solution describes what the bone tissue scaffold should be doing in each time instance (Figure 26).

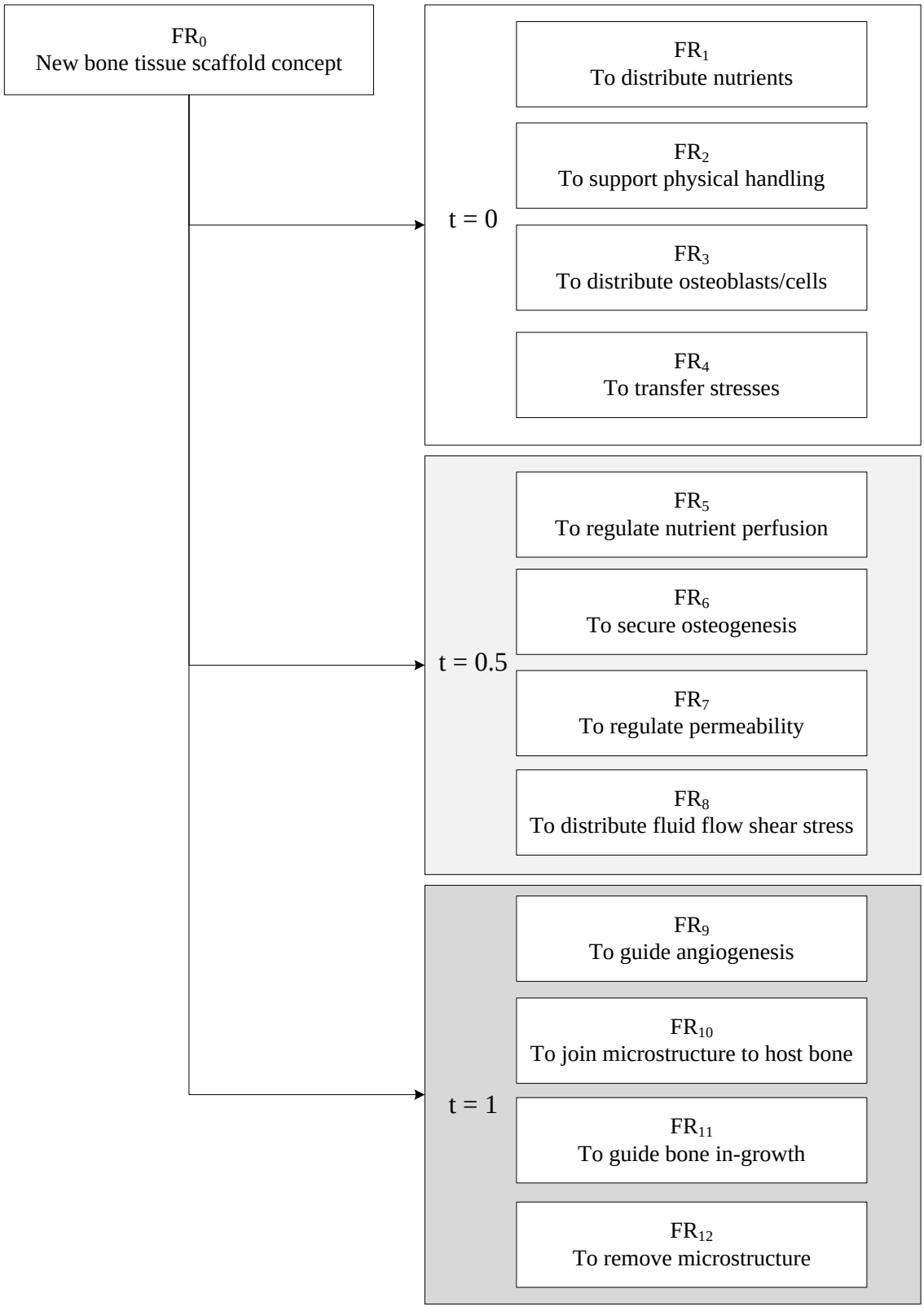

Figure 26. Tree diagram showing the key functional requirements organised by time instances.

After analysing the design solution, please tick the relevant box (left click on box) which best describes your answer to the following statements:

1. *The design solution could lead to innovation (new or improved product capabilities) in bone tissue scaffold design*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

2. *The content of the design solution enhances current bone tissue scaffold design*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

3. *The solution needs significant improvements*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

4. *I am keen to apply the solution or aspects of it in my future work*

Strongly agree	**Agree**	**Neither disagree nor agree**	**Disagree**	**Strongly disagree**
☐	☐	☐	☐	☐

5. *The solution is….*

Very good	**Good**	**No change**	**Poor**	**Very poor**
☐	☐	☐	☐	☐

Design solution 5

[Solution five was achieved by application of Axiomatic Design methodology]

This design solution (Figure 27) shows how, in each of the three time instances, the functional requirements (FRs) are to be satisfied by scaffold design parameters (DPs)

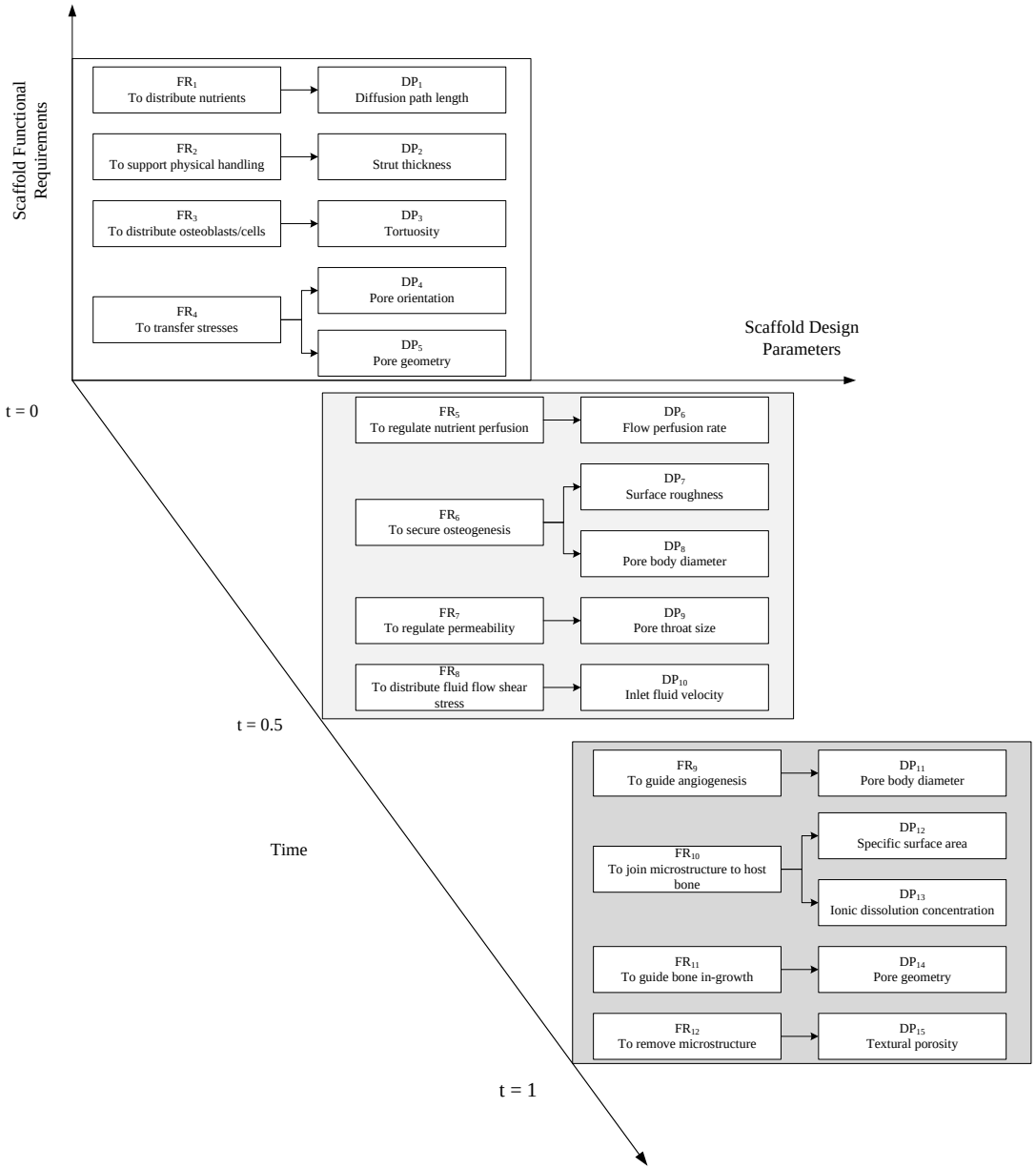

Figure 27. Scaffold microstructure design parameters vary due to a change in functional requirements for three time instances from Figure 26.

After analysing the design solution, please tick the relevant box (*left click on box*) which best describes your answer to the following statements:

1. *The design solution could lead to innovation (new or improved product capabilities) in bone tissue scaffold design*

Strongly agree	Agree	Neither disagree nor agree	Disagree	Strongly disagree
☐	☐	☐	☐	☐

2. *The content of the design solution enhances current bone tissue scaffold design*

Strongly agree	Agree	Neither disagree nor agree	Disagree	Strongly disagree
☐	☐	☐	☐	☐

3. *The solution needs significant improvements*

Strongly agree	Agree	Neither disagree nor agree	Disagree	Strongly disagree
☐	☐	☐	☐	☐

4. *I am keen to apply the solution or aspects of it in my future work*

Strongly agree	Agree	Neither disagree nor agree	Disagree	Strongly disagree
☐	☐	☐	☐	☐

5. *The solution is….*

Very good	Good	No change	Poor	Very poor
☐	☐	☐	☐	☐

Please remember to save changes to the document, so that your box ticks are recorded, prior to uploading the survey. Thank you for taking the time to respond.

If there is anything that you would like to add, please use the space below: