Literature Review: Design of Experiments in Cartilage Properties Research

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I. ABSTRACT

Design of Experiments (DOE) is often used in engineering as a method for determining the influence of one or more factors on the outcome of an experiment. In this paper, an analysis will be done of six papers that use DOE methods and include a property of cartilage as a factor to see what kind of factorial analysis is done, and if the properties of cartilage were significant. To do this, information from 163 articles that cited Statistical Methods in Finite Element Analysis by Dar et al. was collected, and six articles were identified for this literature review [1]. The type of factorial design was found in the article's "methods" section, and the statistical significance was found using ANOVA results. It was found that four out of the six articles had done two experiments, and, out of the ten total experiments, 90% used a Fractional Factorial design method. Out of the six articles, 66.7% found a property of cartilage to be a significant factor. The information from this report was used to determine efficient factorial designs and can be used to design experiments involving the properties of cartilage.

II. INTRODUCTION

The Design of Experiments (DOE) is a statistical method, frequently used in engineering, to determine the important variables of a process and the optimal conditions those variables should be under [2]**.** Specific statistical methods for designing experiments are called Fractional Factorial designs, which allow for a large number of variables to be analysed more efficiently and typically at a lower cost than using a full factorial approach [1] [3]**.** Using a full factorial approach would involve testing all possible combinations of factor levels. This type of design would be useful for experiments with a low number of factors and levels. It can also provide more information on interactions between factors. However, a higher number of factors and levels make this kind of test impractical and inefficient. Utilizing a Fractional Factorial design is a solution to this. Fractional Factorial designs reduce the number of test runs by operating under the principle that at some point, higher order interactions will most likely become insignificant [4], [5]. There are many different types of Fractional Factorial designs, including Box-Behnken, Plackett-Burman, Resolution III, IV, and V, and Taguchi [5] [6].

Once a factorial design has been selected and performed, the results can be analysed using probabilistic analysis. An Analysis of Variance (ANOVA) is popularly used for analysing factorial designs, this gives the percentage of contribution to the total sum of squares (TSS) of each factor [5], [7]. Therefore it can be used to identify significant factors. [3]

In Statistical Methods in Finite Element Analysis, Fazilat H. Dar explains the effectiveness of the Taguchi design and probabilistic analysis in the field of biomechanics, specifically biomechanical Finite Element Modeling.[6] Finite Element Analysis (FEA) is a computer-based method used for stress analysis when factors are too complicated for analytical methods [2]. Since the publishing of this article, it has been cited 163 times. (using data from Scopus as of 3 August, 2021). In these 163 articles, six articles that include properties of cartilage as a factor in their experiments were selected for this literature review.

This review aims to investigate the types of factorial designs these articles used, as well as the number of articles in which properties of cartilage are a significant factor. The purpose of this is to summarize the different ways one may apply DOE to cartilage research in the field of Biomechanical Engineering.

III. METHODS

For this literature review, we collected the 163 papers that cited Dar et al. [1]. and attempted to find information relating to their Design of Experiments. Out of 163 papers, we were able to access 147, 24 of which were deemed "non applicable". The information extracted from the papers included:

- Whether or not they used FEA
- Number of input variables
- Number of runs
- Whether it is a full factorial or Fractional Factorial (and details)
- Whether or not all raw data is present
- Number of output factors
- % of significant input on each output
- Average of %

Once the information had been collected, the search was narrowed down to articles in which properties of cartilage were a factor in their factorial design. This resulted in the collection and analysis of 6 articles. This analysis included the following criteria:

- Type of factorial design
- Whether or not finite element analysis was used
- Number of input factors
- Number of output factors
- Whether or not cartilage was a significant factor
- Percentage of main factor related to cartilage

The six articles were:

- A finite element model of an idealized diarthrodial joint to investigate the effects of variation in the mechanical properties of the tissues- Dar & Aspen [7]
- Finite element analysis of the meniscus: The influence of geometry and material properties on its behaviour- Meakin et al. [8]
- Sensitivities of medial meniscal motion and deformation to material properties of cartilage, meniscus and meniscal attachments- Yao et al. [9]
- Determining the most important cellular characteristics for fracture healing using design of experiments methods- Isaksson et al. [10]
- Sensitivity of tissue differentiation and bone healing predictions to tissue properties- Isaksson et al. [11]
- Mechanobiological simulations of peri-acetabular bone ingrowth: a comparative analysis of cell-phenotype specific and phenomenological algorithms- Mukherjee & Gupta [12]

The information from these articles was then used to determine which factorial design each experiment used, and whether or not properties of cartilage were a significant factor.

IV. RESULTS

A. Overview

The analysis of these six articles found that four out of six featured two experiments: a preliminary screening experiment and a more targeted experiment (Table 1) [7], [9]–[11]. It was also found that, out of ten total experiments, a full factorial design was only used once. All articles utilized FEA to perform their experiments. Using ANOVA results from the articles, it was concluded that cartilage/properties of cartilage were significant factors 66.7% (4/6) of the time (Figure 1). The following sections will offer more in-depth analyses of each article.

Table 1

Article	Author/Date	Number of input variables	Type of factorial design
1	Dar/2003	7	Full Factorial
		11	Fractional Factorial
2	Meakin/2003	10	Fractional Factorial
3	Yao/2006	7	Taguchi
			Resolution V
4	Isaksson/2008	26	Resolution IV
		10	Taguchi
5	Isaksson/2009	24	Resolution IV
		7	Box-Behnken
6	Mukherjee/2017	20	Plackett-Burman

The six articles analyzed in this review are listed along with the number of input variables in each of their experiments and the type of factorial design.

B. Dar/2003

This article was used to find the effect the mechanical properties had on different materials in a diarthrodial joint. The output factors included the von Mises stress in the articular cartilage, calcified cartilage, subchondral bone plate, and the cancellous bone. This article contained a full factorial screening experiment, which was used to identify the sensitivity of the response variables, as well as any significant interactions. They found that there were no significant interactions between the factors. For the additional Fractional Factorial design, they included four more variables: changes in the Poisson's ratios of cartilage, the zone of calcified cartilage (ZCC), the subchondral bone plate, and the cancellous bone. They identified four main factors across all four outputs: the Young's modulus of articular cartilage, thickness of articular cartilage, the Young's modulus of subchondral bone, and the Young's modulus of the subchondral bone plate. Factors involving cartilage made up 50% of the main factors.

C. Meakin/2003

This article aimed to determine the effect of geometrical and material properties on the behavior of the meniscus under axial compression. A two-level Fractional Factorial experiment was used. The effects of ten factors were investigated on six output factors: axial displacement, radial displacement, axial stress, radial stress, circumferential stress, and shear stress. Out of all outputs, eight influential factors were identified, 25% of which were the Young's modulus and Poisson's ratio of cartilage. While these were part of the main factors, all material properties in this study were considered less important than geometry.

D. Yao/2006

This article's aim was to find the effect of materials on meniscus motion. This was measured by the effect of the factors on the ability of the FEM to reproduce experimentally measured meniscus motion and deformation after a 45N load is placed. They used two tests, a Taguchi design and a Resolution V. Both of them used the same seven factors on three output factors: volume error, volume error due to deformation, and volume error due to translation. These tests found that cartilage properties (Young's modulus and Poisson's ratio) were not significant.

E. Isaksson/2008

This paper was used to determine the most important cellular characteristics for bone healing. A Resolution IV screening experiment with 26 factors was used to find the most important factors. Ten variables were identified, three of which were properties of cartilage. In the article, the significant factors of the second test, a Taguchi design, were not clearly defined. So, for the purpose of this review, it was determined that ⅔ of the cartilage properties were significant.

F. *Isaksson/2009*

This article outlined the effect of tissue properties on bone healing and tissue differentiation. They used two tests, a Resolution IV design with 24 factors and a Box-Behnken design with 7 factors. The article stated that the modulus of cartilage was the only highly influential factor, therefore making up 100% of significant factors. Two out of the three significant interactions investigated involved the Young’s modulus of cartilage.

G. *Mukherjee/2017*

The purpose of this article was to determine the effect of cell-phenotype and phenomenological algorithms on peri-acetabular bone growth. This article had one experiment with twenty variables, arranged in a Plackett-Burman design. They studied the impact of these factors on the spatial distribution of peri-acetabular bone ingrowth. The properties of cartilage were considered not significant.

V. DISCUSSION

The two criteria that were analyzed for this report were the type of factorial design used, and the significance of cartilage-related factors.

An analysis of the types of factorial design found a total of seven different factorial designs across all six articles. Fractional Factorial designs were used the majority of the time (90%), with two out of nine designs being described as a generic Fractional factorial design. The other Fractional designs included Taguchi, Resolution IV and V, Box-Behnken, and Plackett Burman. The only time a full factorial design was used within the articles for this review was in a preliminary screening test, to identify any significant interactions between factors. No interactions were found [7]. The only article that highlighted significant interactions involving cartilage in their experiments was Isaksson/2009, which used a Resolution IV and a Box-Behnken factorial design. Isaksson stated that their Box-Behnken design “Allowed [them] to independently estimate all factors, quadratic factors and two factor interactions.”. This allowed them to examine two-factor interactions in 62 runs instead of 2187 needed for a full factorial [11]**.** Yao et al. used a Resolution V design in their Central Composite Design, which allowed them to assess two-factor interactions as well, and it was found that there were three significant interactions. This was found in 81 runs, instead of a full factorial 128 [9]. In contrast to this, Mukherjee chose to use a Plackett-Burman design, which purposefully neglects the interactions in order to focus on the main effects of the control factors [12]. Meakin et al. used a resolution V and assumed the interactions would be negligible, which, determined by an ANOVA, was true [8]. Isaksson/2008 used a Taguchi design for their higher level experiment, which they admitted was not an efficient way for identifying interactions [10]. From these statistics, it can be concluded that using a Box-Behnken or Resolution IV design can be an efficient way to identify two-way interactions while still reducing the number of tests done.

The second part of this report was the significance of the properties of cartilage as a factor. Out of six articles, four found properties of cartilage to be significant, and ¾ of those included Young’s modulus of cartilage as a significant factor (Figure 1). Dar & Aspen identified the Young’s modulus of articular and calcified cartilage as having a significant effect on the Von Mises Stress, as well as the thickness of cartilage [7]**.** Meakin et al. found that the Young's modulus of cartilage had a significant effect on the axial displacement of the meniscus [8]. Unlike Meakin and Dar, Isaksson et al. (2009) found that the Young's modulus of cartilage had a significant effect on multiple outputs: time to complete healing, amount of bone formation at early, mid, and late stages, interfragmentary movements at early and mid-stages, and stiffness at mid-phase [11].

There were two articles in which the properties of cartilage were not significant. Mukherjee & Gupta found that the proliferation and differentiation of mesenchymal stem cells, the proliferation of osteoblasts, and the matrix formation of bone tissue had significant effects on the time to attain equilibrium in bone ingrowth [12]. Yao et al. identified the initial strain of meniscal horn attachments, liner modulus of meniscus peripheral attachments, and the ratio of meniscal moduli in the circumferential and transverse directions, as well as multiple two-factor interactions as significant. They had significant effects on the ability of the FEM to reproduce experimentally measured meniscus motion and deformation after a 45N load is placed [9].

The average significance of a property of cartilage throughout all six papers was 40.63%, data from Isaksson/2008 was not included, as there were no specified p-values so we were unable to determine statistical significance.

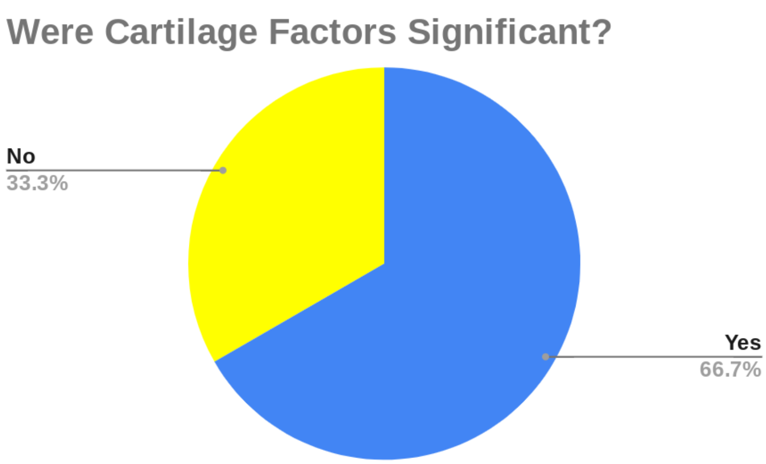

Figure 1: Pie chart showing the percentage of articles in which cartilage factors were significant.

Within the articles reviewed, one used a full factorial analysis, with the other five using some type of Fractional Factorial analysis. It was concluded that Resolution IV and Box-Behnken designs were efficient in identifying main factors, as well as identifying significant two-way interactions. Four out of the six articles had a property of cartilage as a significant factor, with the majority of which including the Young's Modulus of cartilage. The purpose of this report was to analyse articles that cited Dar et al. and also had properties of cartilage as a factor. This information can be used to design experiments involving the properties of cartilage. More research could be done analysing articles using factorial designs that did not cite Dar et al. [1]**.**

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