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Perspective article

Biological variability in biomechanical engineering research: Significance and meta-analysis of current modeling practices

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ABSTRACT

Biological systems are characterized by high levels of variability, which can affect the results of biomechanical analyses. As a review of this topic, we first surveyed levels of variation in materials relevant to biomechanics, and compared these values to standard engineered materials. As expected, we found significantly higher levels of variation in biological materials. A meta-analysis was then performed based on thorough reviews of 60 research studies from the field of biomechanics to assess the methods and manner in which biological variation is currently handled in our field. The results of our meta-analysis revealed interesting trends in modeling practices, and suggest a need for more biomechanical studies that fully incorporate biological variation in biomechanical models and analyses. Finally, we provide some case study example of how biological variability may provide valuable insights or lead to surprising results. The purpose of this study is to promote the advancement of biomechanics research by encouraging broader treatment of biological variability in biomechanical modeling.

1. Introduction

Biomechanical models have been used to great success in a variety of biomedically relevant applications including the design of advanced prosthetics (2007), orthopedic implants (Keaveny and Bartel, 1993), cardiac tissue modeling (Humphrey and Yin, 1987; Chen and Humphrey, 1998), drug delivery methods (Schuff et al., 2012, 2013), as well as helping to elucidate evolutionary processes (Darwin, 1859; Weiner, 1995). These achievements were based on impressive advances in computational mechanics (Cowin and Hegedus, 1976; Hart et al., 1984; Huiskes and Nunamaker, 1984), the application of mixture theory models to problems in tissue mechanics (Mow et al., 1980; Weinbaum et al., 1994; Cowin et al., 1995, Dickerson et al., 2008), development of elegant physical models (Liang and Mahadevan, 2011), and the integration of modeling with micro and nanoscale experimental methods (Raman et al., 2011).

Future endeavors will eventually integrate muscle biomechanics with metabolic load and neural control, provide an understanding of bone remodeling in the context of both mechanical loading and calcium homeostasis, elucidate the physiological mechanisms necessary to permit the rational design of engineered tissues, and predict the efficacy of therapeutic interventions without the need to perform extensive human trials.

The efficacy of computational models to predict whether or not a medical intervention will be successful often depends on subtle factors operating at the level of unique individuals. While "subject-specific" are useful in some cases, we typically are more interested in trends that can be reliably predicted across a population. However, the ability to predict such behavior is hampered by significant levels of variability that are present in all aspects of human biomechanics, including dimensions and material properties (Saulgozis et al., 1974; van Geemen et al., 2011), stature (Daubes, 1887; Visscher, 2008), function (Brutsaert and Parra, 2006; Tahmoush and Silvious, 2010), and pathological conditions (Drumm et al., 2012). Consequently, much of our future success as biomechanical engineers depends on our ability to quantify and integrate physiological variation into our modeling processes, considering not just an "average" model, but creating models that predict *distributions* of possible outcomes. The purpose of this approach is to stimulate discussion and reflection among the biomechanics research community on the topic of biological variation.

We therefore have examined biological variation in three ways: first by quantifying the general levels of uncertainty in biomechanics

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and comparing these with levels of uncertainty in standard engineering materials; second, by assessing the manner in which biological variability is currently being considered in the biomechanical research community; and third, by providing examples from the literature illustrating ways in which biological variation has affected research results. We conclude with a broad discussion of these interrelated issues.

2. Methods

2.1. Quantifying levels of variation

To quantify levels of variation in biomechanics, and to contrast these levels with those in traditional engineering, we compiled coefficient of variation values for several materials. The coefficient of variation (CV) is commonly used to quantify variation, and is defined as the ratio of the standard deviation (σ) to the mean (μ):

$$CV = \frac{\sigma}{\mu} \quad (1)$$

Low values of CV (e.g. $CV=0.05$) indicate a narrow or "tight" distribution, while values greater than 0.5 indicate a broad distribution. Because the coefficient of variation is non-dimensional, comparisons can be made between different properties of a given material, as well as between different materials. Six common materials were selected for analysis, three of which are engineering materials (aluminum, concrete, and steel), and three of which have biomechanical relevance (bone, cartilage, and wood). Numerous research sources (Ellingwood, 1980; Martens et al., 1980; Buckwalter et al., 1994; Myers et al., 1995; Langton et al., 1996, Rho et al., 1997; Wimmer et al., 1997; Hou et al., 1998; Ladd et al., 1998; Stammberger et al., 1999; Turner et al., 1999; Zysset et al., 1999; Niebur et al., 2000; Morgan and Keaveny, 2001; Hess et al., 2002; Bayraktar et al., 2004; Schriefer et al., 2005) were utilized, and coefficient of variation values were collected for multiple properties of each material.

2.2. Assessing the role of biological variation in biomechanics research

An extensive meta-analysis was performed based on research articles published in Journal of Biomechanics in the year 2011. This year included 16 issues comprising a total of 354 research articles. Other article types (perspective, review, letter to editor, and short communications) were excluded from our analysis. Of the 354 total research articles, 158 articles involved computational modeling to some degree. Articles were sampled randomly ($n=60$) from these 158 articles. These articles are indicated in the references section by the dagger symbol (Aissaoui et al. (2011); Al-Jumaily et al. (2011); Alastruey et al. (2011); Bonnet et al. (2011); Bruijn et al. (2011); Carnelli et al. (2011); Chaichana et al. (2011); Chong et al. (2011); Cox et al. (2011); de Tullio et al. (2011); de Vaal et al. (2011); Di Martino et al. (2011a, 2011b); Drury et al (2011); Dvinskikh et al. (2011); Ferrara et al. (2011); Gonçalves Coelho et al. (2011); Henak et al. (2011); Henderson et al. (2011); Johnson et al. (2011); Khalil et al. (2011); Kociolek and Keir (2011); Konala et al. (2011); Labrosse et al. (2011); Landsberg et al. (2011); Lin, C.-J. et al. (2011); Lin, C.-L. et al. (2011); Liu et al. (2011); Manda et al. (2011); Martelli et al. (2011); Mihaescu et al. (2011); Morbiducci et al. (2011); Olgac et al. (2011); Pahlevan and Gharib (2011); Rahbar and Moore (2011); Rankin et al. (2011); Renders et al. (2011); Roddy et al. (2011); Rothstock et al. (2011); Scheys et al. (2011); Speelman et al. (2011); Stevanella et al. (2011); Tovar-Lopez et al. (2011); Trabelsi et al. (2011); Tse et al. (2011); Turnbull et al. (2011); van der Giessen et al. (2011); Varghese et al. (2011); Vavourakis et al. (2011); Vetter et al. (2011); Waanders et al. (2011); Wang and Li (2011); Weaver et al. (2011); Willemet et al. (2011); Wilson et al. (2011); Winkel and Schleichardt (2011); Wong and Tang (2011); Wood et al. (2011); Yu et al. (2011)).

Each article selected for inclusion was reviewed thoroughly and corresponding data were recorded in a database. The database fields were chosen based on a criterion of objectivity: only features which could be objectively determined were included in this study. Data was collected for each paper in aspects such as: the number of reported parameters in the modeled system; the statistical distribution of each parameter; the number of parameters varied (and held constant); the technique(s) used for varying model parameters; the source(s) of parameter values; the total number of simulations performed; and the type of validation performed, just to name a few.

Variation techniques were classified into two broad categories: parametric variation (i.e. one parameter varied while all others held constant); and simultaneous variation of two or more parameters. In both cases, the number of varied parameters was also recorded. Where relevant, all information was parsed into aspects of geometry, material, and boundary conditions. The resulting database consisted of 35 fields: 25 numeric fields and 10 nominal (i.e. typographic) fields.

An example of the type and structure of data collected is shown in Fig. 1. This figure depicts the most relevant type of data collected from one of the sampled articles. Note that each model was decomposed into aspects of geometry, material, and boundary conditions, and parameter counts in each area were recorded along with number of simulations. Additional information is provided in the supplementary material associated with this article (available online).

In presenting meta-analysis data, relative frequency histograms are used extensively to summarize trends. For ease of interpretation and to facilitate comparison between charts, all histogram results were normalized by the total number of studies (60 studies) and the term "overall relative frequency" was used to describe this approach.

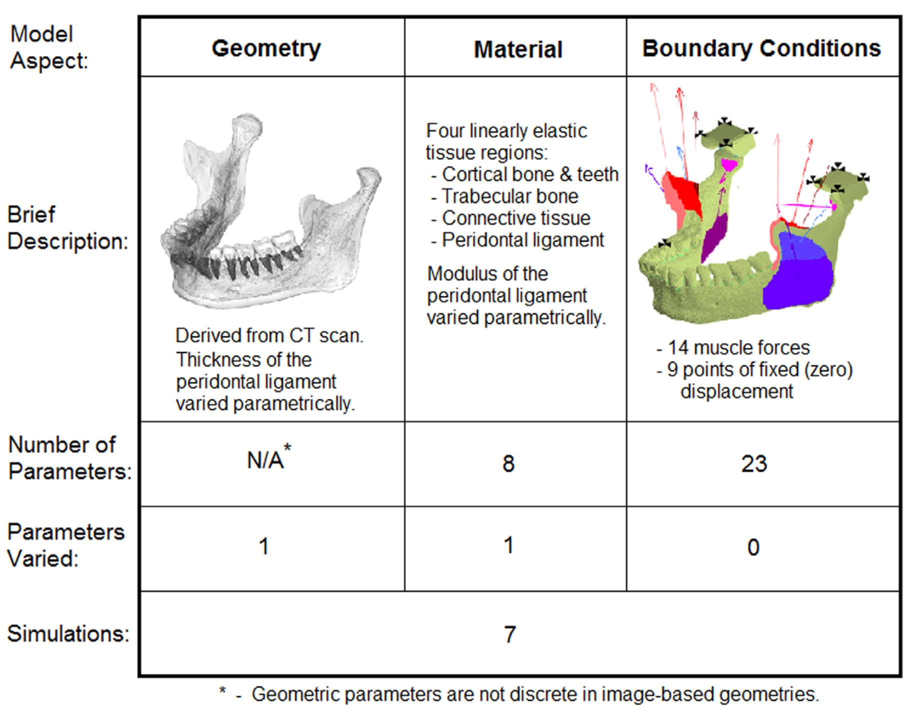

Fig. 1. A sampling of data collected from a study involving the human mandible (Gröning et al., 2011), and an illustration of how this data was organized according to model aspect.