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 examples 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 Hagedus, 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...
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 inter-related 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):

\[ CV = \frac{\sigma}{\mu} \]  

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; Winmer 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; Schriefe 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 consisting of 354 total 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 (Aissauoi et al., 2011; Al-Jumaily et al., 2011; Alastruey et al., 2011; Bonnet et al., 2011; Brujin et al., 2011; Carminati 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; Druzy 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; Mih ascu et al., 2011; Morbiducci et al., 2011; Oljaca et al., 2011; Palheyan and Gharib, 2011; Rahbar and Moore, 2011; Rankin et al., 2011; Renders et al., 2011; Roddy et al., 2011; Rothstock et al., 2011; Scheps et al., 2011; Speelman et al., 2011; Stevanella et al., 2011; Tovar-Lopez et al., 2011; Trabelsi et al., 2011; Tse et al., 2011; Turnerhill 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; Wong 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.
biomechanical models, separated into major aspects of geometry, material, and boundary conditions.

<table>
<thead>
<tr>
<th></th>
<th>Min</th>
<th>Median</th>
<th>Mean (sd)</th>
<th>Max</th>
<th>n</th>
</tr>
</thead>
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<tr>
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<td>6</td>
<td>27.04 (38.81)</td>
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</tr>
<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>Material</td>
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<td>6.5</td>
<td>8.39 (6.75)</td>
<td>37</td>
<td>54</td>
</tr>
<tr>
<td>Boundary conditions</td>
<td>1</td>
<td>5</td>
<td>8.85 (12.4)</td>
<td>72</td>
<td>53</td>
</tr>
</tbody>
</table>

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Fig. 2. Average (bar) and distribution (dots) of coefficient of variation for various experimentally determined properties of engineered and biological materials (Ellingwood, 1980; Martens et al., 1980; Buckwalter et al., 1994; Myers et al., 1995; Langton et al., 1996; Rho et al., 1997; Hou et al., 1998; Stammberger et al., 1999; Turner et al., 1999; Zysset et al., 1999; Niebur et al., 2000; Ellingwood, 2001; Morgan and Keaveny, 2001; Hess et al., 2002; Bayraktar et al., 2004; Schriefel et al., 2005). Engineering materials and structures typically have coefficients of variation less than 20% (dashed line) (Ellingwood, 1980, 2001; Hess et al., 2002). Measured parameters include apparent density, compressive modulus, shear strength, tensile yield stress, ultimate strength, etc.

3. Results

3.1. Levels of biological variation

A dramatic difference was observed between the levels of variation present in biological materials as compared to engineered materials. Fig. 2 compares coefficient of variation values for numerous material properties of six common materials. All data from each category were combined to produce an average value for each material (bars). As seen in Fig. 2, engineered systems typically have a coefficient of variation less than 20%, while biological systems regularly exhibit coefficients of variation significantly above 20%. For example, the aggregate coefficient of variation for steel is 7.5%. Assuming a normal distribution, 95% of steel samples can thus be expected between 85% and 115% of the mean value. On the other hand, the aggregate coefficient of variation for cartilage is 49.2%, indicating that 95% of measured values may lie between 1.8% and 198% of the mean value, a range that spans two orders of magnitude, similar to the ranges that have been reported for 198% of the mean value, a range that spans two orders of magnitude, similar to the ranges that have been reported for each material (bars). As seen in Fig. 2, engineered systems typically have a coefficient of variation less than 20%, while biological systems regularly exhibit coefficients of variation significantly above 20%. For example, the aggregate coefficient of variation for steel is 7.5%. Assuming a normal distribution, 95% of steel samples can thus be expected between 85% and 115% of the mean value. On the other hand, the aggregate coefficient of variation for cartilage is 49.2%, indicating that 95% of measured values may lie between 1.8% and 198% of the mean value, a range that spans two orders of magnitude, similar to the ranges that have been reported for cartilage permeability (Sander and Nauman, 2003).

3.2. Meta-analysis of biomechanics models

3.2.1. General observations

A meta-analysis of 60 biomechanics research articles was conducted and analyzed. A tremendous variety in biomechanical models was observed. Models ranged from very simple, idealized descriptions to exceptionally complex models involving over 200 model parameters. In tallying the number of parameters used to define each model, one challenge was the fact that medical images (MRI, CT, optical, etc.) were used as the basis of approximately half (55%) of the studies. Such images provide detailed descriptions of geometric features, but do not consist of a definite number of parameters. As a result, the geometry aspect was split into two components: image-based geometries and idealized geometries. The statistics for the number of parameters used to define biomechanical models are provided in Table 1.

Both the number of parameters used to define biomechanical models, and the number of parameters used to define model aspects (geometry, material, and boundary conditions), exhibited a roughly log-normal distribution. The amount of variation between models, as well as the non-normal distributions in each category makes a description of an “average” biomechanical model difficult. Indeed, the quantitative description of a hypothetical “average” model is perhaps misleading since in cases involving log-normal distributions, the interpretation of a mean value is not as straightforward as it is for normally distributed quantities. For this reason, data regarding the number of model parameters is presented in Table 1 in terms of range, median, mean, and standard deviation. Of these descriptive statistics, median is the most representative value, and is thus emphasized in Table 1. The high degree of variation between models is evident by noticing that the standard deviation is generally greater than the mean for aspects described in Table 1.

3.2.2. Variation by model aspects (geometry, material, and boundary conditions)

Examination of the meta-data revealed several interesting trends in biomechanical modeling practices. The most common method of variation in model parameters was to vary parameters
within one aspect while keeping other aspects fixed throughout the study. Approximately half of the studies used this approach (Fig. 3). We considered that a model aspect is varied when a variation of at least one parameter was performed within the model aspect. Variation of all model aspects was relatively rare; approximately 8% of studies used this approach while the remaining studies held all the features of one or more model aspects fixed throughout the study. Geometric aspects were found to be varied most commonly (in 57% of studies). Boundary conditions were varied in 40% of studies. The least varied model aspect was the material property (in 32% of studies).

3.2.3. Parameter variation within model aspects

To obtain a more detailed description of model variation, variation patterns within each aspect were examined. Relative frequency histograms were used to tabulate the distribution of parameter variation within each aspect, and these distributions were compared to the number of parameters in each aspect. As mentioned previously, the geometry aspect was segmented into idealized and image-based subcategories. Some studies primarily utilized medical images, but then proceeded to parametrically vary certain aspects of the geometry. This approach is evident in histogram 4B, which shows parameter variation in conjunction with medical image-based geometries.

For aspects of idealized geometry, material properties, and boundary conditions, the number of parameters varied within studies appears to be exponentially distributed. In contrast, the number of model parameters is log-normally distributed (as shown by the line plots in Fig. 4A, C, and D). As a result, the median value for parameters varied is much lower than the median value of number of actual model parameters. This suggests that biomechanics studies often utilize an experimental design similar to those used in in vitro medical studies: a select number of parameters are varied in a controlled fashion while the remaining parameters are held fixed.

3.2.4. Variation type

In addition to the number of parameters varied, the type of variation utilized was also of interest. Although many methods exist for experimental design, these can be classified into two broad categories: parametric variation in which one parameter is varied while others are held constant; and simultaneous variation, in which two or more parameters are varied simultaneously. These types of variation were tabulated in terms of relative frequency of occurrence, and segmented by model aspect (Fig. 5).

Most studies that used parametric variation varied only a small number of parameters. More specifically, 80% of studies in this category varied only one or two parameters (as indicated by the non-shaded region under “parametric variation” in Fig. 5). However, the studies in the simultaneous category exhibited the opposite trend; 74% of studies in this category varied more than two parameters (as indicated by the shaded region under

![Fig. 4. Relative distribution histograms (bars) depicting the number of varied parameters in each aspect. Curves indicate the log-normal distributions for the number of parameters for each corresponding aspect of individual models. Vertical lines indicate the median value for each distribution. Medians at zero indicate that 50% or more of data is within the zero parameter bins. Curve omitted for the image-based geometry because no corresponding distribution is available (see Table 1).](image-url)
“simultaneous” variation, Fig. 5). This was almost exclusively due to the use of multiple medical images in deriving the geometry of the structure. Relatively smaller percentage of studies varied more than two parameters in the aspects of material and boundary condition.

3.2.5. Number of simulations

The number of simulations performed in each study was also tabulated. The number of simulations ranged from 1 to 400, with a median of 11 simulations, a mean of 48.1, and a standard deviation of 103.1. The mode of this data was 1 (22% of all studies involved one simulation).

It is informative to compare the number of simulations to the total number of model parameters. To this end, we define the simulation ratio ($S$) as the ratio of number of simulations ($N_s$) to the number of model parameters ($N_p$):

$$S = \frac{N_s}{N_p}$$

(2)

The simulation ratio allows computational studies to be assessed in relation to the number of model parameters. Overall, 38% of analyzed studies had a simulation ratio higher than 1. The median simulation rate was found to be 0.43 (Fig. 6).

3.2.6. Biological parameters as random variables

Two approaches were used to determine the degree to which biological parameters were treated as random variables. First, we tallied the number of parameters that were referred to in terms of probability distributions or random variables. The 60 reviewed articles utilized a total of 1598 discrete model parameters. Of these, only seven parameters (0.4%) were described in terms of biological variation. In each of these seven cases, parameters were described in terms of biological range (min/max), but the type of distribution was not specified.

Second, we considered the number of cases in which biological variability was incorporated into the study by virtue of the study design. Many studies incorporated the essential features of random variables through the use of image-based geometries. Approximately half of all the studies utilized medical images, and of the image-based models, half again utilized multiple samples in the study design (see the “entire image” column in Fig. 4b). Overall, 30% of all studies incorporated biological variability in this way.

3.2.7. Justifications for fixed parameters

As illustrated in Fig. 4, the most common approach in biomechanics research is to focus on a small number of key parameters, with the remaining parameters fixed throughout the study. We examined the reasons stated for using this approach. The presence or absence of justification for this approach was tabulated for all analyzed studies. We observed that reasons for varying certain parameters were almost always provided, but justification for holding other parameters fixed was uncommon. Overall, 59 out of 60 studies have at least one parameter that was fixed throughout the study. In 90% of studies (53 out of 59), no justification was given for parameter fixation.

4. Discussion

Levels of biological variation are never constant and cannot currently be predicted. Some parameters have narrow distributions (the density of blood for example), while others have very broad distributions (e.g., cartilage stiffness or bone strength). Furthermore, while there are some constants in engineering (specific gravity of water, charge of an electron, etc.), biological constants have proven to be elusive. In fact, the existence of “biological constants” is currently an area of active research and debate (Dhar and Giuliani, 2010). Because of the ubiquity of variation in biological systems, it is useful to conceptualize model parameters in terms of variability. Every biological parameter can be thought of as a random variable with a distinct (though perhaps unknown) probability distribution. In our analysis of biomechanics research studies, the majority of model parameters were fixed throughout the study, while a select number were varied, usually parametrically. However, the practice of viewing model parameters as random variables was not observed in our sampled studies.

Because computational biomechanics research seeks to answer many of the same types of questions as traditional medical research, we can conceptualize biomechanics studies using terminology from medicine and biology. Of all possible experimental
designs, there are a few major types: case studies, in vitro studies, ex vivo studies, and in vivo studies. The level of experimental control is highest for in vitro studies, and lowest in in vivo studies. As a consequence, the in vitro studies provide the advantage to examine relationships between variables in the absence of other effects, but these results cannot be directly generalized at the system level, due to the restrictions imposed by experimental control. On the other hand, in vivo studies provide results that are more easily generalized, but the relationships between parameters may be extremely difficult to detect due to simultaneous variation of many inter-related parameters. Naturally, ex vivo studies lie between the other two methods in terms of control and generalizability.

Based on our analysis, the experimental approach most common in the field of biomechanics is the in vitro type, as illustrated in Figs. 4 and 5. Studies in our field are focused on key parameters and relationships. They seek to provide understanding in areas where little information and knowledge exists, and in these situations, in vitro studies are the most appropriate choice. However, advances in computational power now provide the opportunity to use experimental designs that mimic ex vivo, and in vivo studies. This approach is exciting and has tremendous potential but is not commonly applied in biomechanics research studies.

To encourage this approach, we suggest the use of terminology that supports the concept of biological variation in computational modeling: “instances”, “virtual sample” and “virtual individuals.” An instance is any fully defined computational model (i.e., all model parameters have been assigned as discrete numerical value), though the manner in which they are assigned may be controlled and limited. A virtual sample is formed as a collection of instances of a computational model. Finally, a virtual individual (or virtual human subject (Cook, 2009)) is a special case in which an instance of a model is obtained by allowing each parameter to take on values that reflect patterns of natural biological variation. In other words, no parameters are explicitly fixed, but are allowed to vary according to their respective probability distributions. Because very few parameters are directly controlled, this approach mirrors in vivo research methods, as suggested by the name itself.

There are practical reasons why the in vitro approach is most common. One limiting factor in biomechanics research is the lack of distribution data for many biological parameters. While mean and standard deviation data is available for many biomedical parameters, this information alone is incomplete unless the relevant studies have specifically investigated the distribution of this parameter to ensure that it is actually normally distributed. Furthermore, many biological parameters have not yet been measured. Probability distributions for these parameters are thus unknown. This however does not preclude the application of stochastic methods which can be used even in the absence of experimental data. In the following section, we highlight three studies in which biological variation has revealed surprising or insightful results in biomechanics research.

4.1. Examples

The first example illustrates how the consideration of biological variation can be used to gain important insight, even in the absence of experimental data. The vibratory characteristics of the vocal folds have been a subject of study for many decades (Titze, 2006). Because the vocal folds are a complex structure consisting of multiple layers of transversely isotropic tissue, few material measurements are available. As a result, models of this structure are often based on assumptions or estimates of material properties. This practice is common in biomechanics owing to the difficulty in measuring mechanical properties of various tissues. Even though not all material properties of this system have been measured, stochastic sensitivity analysis was applied to a detailed vocal fold model in which all relevant geometric and materials properties were varied using Monte Carlo and other techniques (Cook, 2009; Cook et al., 2009). This study revealed that the longitudinal shear modulus is one of the most influential factors affecting the vibratory characteristics of the vocal folds. Due to lack of experimental data on this property, a single value for the longitudinal shear modulus had been used in all prior modeling studies (Alipour et al., 2011). The inclusion of biological variation in a vocal fold model, combined with powerful computational tools, led to the identification of an important feature that had been previously obscured because of the lack of experimental data and biological variation.

Another example illustrates the use of sensitivity analysis to develop patient-specific calibration tools. The success of chemotherapeutic treatments and the potential efficacy of nanoparticle-based therapies depend on a number of factors including geometric (capillary length, diameter, density, and plasma skimming layer thickness), material properties (tissue permeability, fluid conductivity through the vessels, plasma viscosity, and the like), and boundary conditions (arteriole pressure, venule pressure, osmotic pressure gradients, and tissue pressure). Previous studies examined a handful of variables at a time (Jain and Baxter, 1988), leading to the conclusion that the tissue pressure was one of the most important variables, but a complete assessment of all the aforementioned variables was daunting due to a lack of data for calibration. Schuff et al. (2012, 2013) demonstrated one of the benefits of statistical sensitivity analysis, by characterizing which variables have the biggest effect on the ultimate response of the computational model. Their data demonstrated that the penetration of small molecules into the extravascular space depends not only on the tissue pressure, but also the capillary density, pressure difference between the arteriole and venule sides, and the properties of the vascular wall. More importantly, incorporating biological variability into the model and assessing the effects of the critical variables allowed calibration of the model to individual patients.

As a final example, Lee and Piazza (2009) observed that the foot and ankle geometry of sprinters (track athletes) was noticeably different from that of the general population. As compared to the general population, sprinters were found to have a significantly shorter calcaneus, longer toes, and longer fascicles of the lateral gastrocnemius. Rather than providing a mechanical advantage to sprinters, these factors actually produce a mechanical disadvantage, in terms of force and leverage. However, a complete analysis of the entire system (geometry, muscular contraction rates, and dynamic interactions between these factors), revealed that particular geometric configurations enable faster running, due to advantages in terms of speed and energy transfer. The authors concluded that, to some extent, an individual’s potential to become a world-class sprinter is determined by biological variation. While running ability can be refined by training, a person without the “sprinter’s heel” may never be an outstanding runner, regardless of training.

4.2. Paradigm shift

The above examples illustrate ways in which the inclusion of biological variation can provide insights in biomechanics research. Looking outside of the biomechanics community, we observed that high levels of variation in other fields have initiated important paradigm shifts and new techniques have been developed to deal with the consequences of variation. In the past 10–20 years, several engineering fields have shifted from a deterministic design methodology to a more sophisticated approach that considers the effects of random variation. For example, steel construction building codes were previously based on an extensive set of safety factors to account for uncontrolled variation in material, geometry,
and loading (1972). Revised standards (Ellingwood, 2001) are based on stochastic methods which can be used to quantify risk, which is not possible by using safety factors. Second, the rapidly changing field of computer chip manufacturing has also recently undergone a similar transition. For many years, computer chips were designed using a methodology known as static timing analysis. This method was used to compute the performance of chip designs, assuming constants for the rates of various internal processes (Kirkpatrick and Clark, 1966; Hitchcock et al., 1982). As the size of integrated circuits has become progressively smaller, however, variations in production have become more influential. This has required the development of statistical static timing analysis, which considers statistical distributions of internal chip processes (Orshansky and Keutzer, 2002). Thus, in both steel construction and chip design, a consideration of variation has led to engineering methods which provide more accurate design methodologies for the overall system. Biomechanics as a field has not yet undergone a transition from a deterministic to a statistical paradigm. Such a transition will likely be needed if biomechanical models are to continue to increase in accuracy and relevance to the scientific and healthcare fields, especially regulatory bodies. The need for this transition is illustrated by a comparison between levels of variation in engineered and biological systems (Fig. 2), as well as the understanding that in biology, all variables are inextricably connected.

Numerous methods have been developed for assessing the effects of variation on model behavior. These include sensitivity analysis techniques (Saltelli et al., 2009), reliability analysis (Haldar and Mahadevan, 2000a), and stochastic modeling (Haldar and Mahadevan, 2000a, 2000b; Buzzard and Xiu, 2011). Among these, Monte Carlo analysis may be the most popular, due to its ease of implementation and flexibility. For examples of this technique applied in biomechanics, see Gentle (2003), Kalos and Whitlock (2008) and Ackland et al. (2012), among others.

We now introduce a new conceptual framework for evaluating biomechanical models. It is evident from the meta-analysis data that many biomechanical models are sufficiently complex that a thorough analysis involving all model parameters may beyond the scope of a single research paper. Modern computational tools support the creation of extremely large, highly complex models. These models are powerful tools if we understand the many interactions that take place within the model. The results of our analysis show that typical biomechanics studies involve approximately 10 simulations for every 18 model parameters. Because an n-parameter model potentially exhibits \( n^2/2 - n \) interactions between pairs of parameters, a typical 18-parameter model may have 144 such interactions. However, most studies in the biomechanics literature rely on fewer simulations than the number of model parameters, with the typical (median) number of simulations being 10. It is clear that 10 simulations are insufficient to understand either the primary effects of each of the 18 model parameters or the 144 potential interactions between model parameters. The quadratic relationship between interactions and the number of parameters is a tremendous problem, especially for models involving a large number of parameters. As a consequence, we suggest that many biomechanics models may be “over-developed.” In other words, these models are so complex, and require a computational expense that precludes the quantification of each parameter's effect on the model. The authors feel that the issue of model development merits attention because the tendency in all areas of research is to build upon previous efforts. The introduction of a single over-developed model could lead to additional over-developed models as the new model is expanded upon, combined with other models, etc.

Finally, we consider the conclusions that are drawn from our biomechanical models. In performing the meta-analysis described above, we noticed that while the in vitro approach is most common, the corresponding limitations of this approach are seldom addressed. In fact, conclusions are often stated in general terms even though the majority of model parameters were fixed throughout the study. Experimental designs that incorporate only a small number of parameters (in vitro) can obviously obscure important features. That certain relationships exist in a controlled situation cannot be argued, but whether or not such relationships persist and are detectable when all other variables are considered cannot be concluded from an in vitro study; these questions can be answered by simultaneous variation of all model parameters.

5. Conclusions

Levels of biological variation were quantified, a meta-analysis of biomechanics research studies was performed, and examples illustrating the effects of biological variation in biomechanics research were discussed. The meta-analysis provided a high-level overview of modeling practices in biomechanics, with an emphasis on biological variation. Each study was analyzed to determine the number of model parameters in each essential aspect (geometry, material properties, and boundary conditions). In addition, data was collected regarding study design, variation type, definition of variables, etc. The conclusions of this study are as follows:

1. The dominant approach in performing biomechanical research using biomechanical models is similar to in vitro studies: a few select model parameters are typically varied while the majority of model parameters are held fixed. Overall, 92% of all studies are based on an experimental design in which at least one major aspect (geometry, material properties, or boundary conditions) is held constant throughout the study.

2. The parameters of biomechanical models are not often conceptualized as random variables. Consideration of model parameters as random variables may be useful in shifting the paradigm in biomechanics towards a perspective that more comprehensively addresses biological variation.

3. Biomedical imaging is currently the most successful avenue for including natural biological variation in biomechanical simulations. Multiple medical images were used in 30% of biomechanical modeling studies. We anticipate that this figure will continue to rise with the improvement of image processing software and image acquisition tools.

4. Biomechanical models may currently have a tendency toward over-development. Most models rely upon fewer simulations than the number of model parameters, and are focused on varying a minority of model parameters.

5. Consideration of biological variation has been shown (anecdotally) to lead to useful, sometimes counter-intuitive, or unexpected results. This approach is not currently common in biomechanics research.

6. We recommend the increased use and application of methods for incorporating biological variation in biomechanical models, including sensitivity analysis techniques such as Monte Carlo methods, etc.

It is the authors’ hope that the data and analysis included in this study will encourage the biomechanics research community to broaden the current scope of modeling practices. While in vitro experimental designs will always be an essential component of biomechanics research, we feel that more attention can and should be paid to the issues of biological variation, biomechanical parameters as random variables, and interactions between model parameters. As has occurred in other research fields, this approach
will significantly improve the quality and robustness of biomechanics research, eventually leading to increased understanding and improvement of human well-being as biomechanical research becomes increasingly useful and relevant.

Conflict of interest statement

None of the authors have any conflict of interest to report.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jbio mech.2014.01.040.

References


Wong, H.C., Tang, W.C., 2011. Finite element analysis of the effects of focal adhesion mechanical properties and substrate stiffness on cell migration. J. Biomech. 44 (6), 1046–1050 (†).

