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Prediction and prevention of musculoskeletal injury: a paradigm shift in methodology

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Abstract

Traditional methods employed to study musculoskeletal injury mechanisms and joint biomechanics utilise in vivo or in vitro techniques. The advent of new technology and improved methods has also given rise to in silico (computer modelling) techniques. Under the current research paradigm, in vivo, in vitro and in silico methods independently provide information regarding the mechanisms and prevention of musculoskeletal injury. However, individually, each of these methods has multiple, inherent limitations and is likely to provide incomplete answers about multifactorial, complex injury conditions. The purpose of this treatise is to review current methods used to study, understand, and prevent musculoskeletal injury and to develop new conceptual-methodological frameworks that may help create a paradigm shift in musculoskeletal injury prevention research. We term the fusion of these three techniques in simulacra amalgama, or simply in sim, meaning a "union of models done on the likeness of phenomena." Anterior cruciate ligament (ACL) injury will be employed as a model example for the utility and applicability of the proposed, synthesised approach. Shifting the current experimental paradigm to incorporate a multifaceted, multidisciplinary, integration of in vivo, in vitro and in silico methods into the proposed in sim approaches may provide a platform for a more comprehensive understanding of the relationships between complex joint biomechanics and observed injury mechanisms.

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Despite the vast attention devoted to various musculoskeletal injury topics, many methodological and analytical models currently in place are limited in their ability to consistently identify and verify predictive factors. Consequently, a number of contradictory predictive models are present in the musculoskeletal injury literature. For example, a large divide exists between studies that support anterior tibial translation as the primary injury mechanism during an anterior cruciate ligament (ACL) injury event and those that support an abduction/multiplanar mechanism of injury.[1–3] Such controversies make it difficult to determine the most efficacious intervention and prevention strategies.

All studies incur methodological and analytical limitations. While often dismissed as measurement and standard error, it may be that the contradictions in the literature are not due to chance, but rather result from the methodological and analytical limitations associated with common approaches used to study musculoskeletal injuries. It is likely that the inconsistencies in the literature are related to a number of factors. However, we contend that one central and addressable limitation prevalent in the musculoskeletal injury literature is related to the philosophical model of reductionism in which researchers attempt to simplify and reduce a complex phenomenon into its most basic parts and then make inferential leaps to explain how these parts interact to lead to the observed phenomenon. While useful for creating small insights about a phenomenon, a reductionistic approach can also severely limit our abilities to capture the more complex nature of the phenomenon being studied.

The purpose of this treatise is to evaluate the reductionistic characteristics of current methods and analytical techniques used to study musculoskeletal injury, and to propose that an integration of less reductionistic, synthesised study designs and analytical techniques (an approach we term in simulacra amalgama, or simply in sim, meaning a “union of models done on the likeness of phenomena”) can provide a more robust conceptual framework to better understand the relationships between complex joint biomechanics and observed injury mechanisms. It is our contention that in sim approaches have the potential to create a measureable paradigm shift for musculoskeletal injury research and significantly improve our ability to identify risk factors and implement effective prevention programmes.

Many of the methodological limitations and subsequent in sim suggestions we propose are applicable to various musculoskeletal injuries and patient populations. However, we focus on injury to the ACL of the knee in adolescent and young adult athletes as an example literature base to illustrate the need for and potential benefit of drawing upon in sim approaches. ACL injury was chosen because it is an area in musculoskeletal research in which the authors are very familiar as well as an area the authors believe stands to benefit greatly from the application of the proposed suggestions.

ACL INJURY DISRUPTION: AN EXAMPLE OF MUSCULOSKELETAL INJURY

Injury to the ACL of the knee is a common sports injury, which can lead to physical and emotional impairments in the short term and have a high potential to progress to permanent disability in the long term.[4–6] Despite advances in surgical and rehabilitation regimes, currently no postinjury treatment sequences eliminate the risk of progression to knee osteoarthritis after ACL injury.[47–9] The peak number of ACL injuries occur in adolescents and young adults, and the onset of osteoarthritis occurs as early as 10 years or less after injury.[4] Consequently, many athletes in their 20s or early 30s are at high risk of developing knee osteoarthritis. Identification of high-risk athletes and prevention of ACL injury may be our best strategy to reduce risk of osteoarthritis and associated disability in young adults.

In the ACL model, many hypothetical risk factors and injury mechanisms have been proposed and studied extensively. Intrinsic variables such as Q-angle, intracondylar notch width, hormone levels, ligamentous laxity and neuromuscular control deficits are associated with increased ACL injury risk. Likewise a number of extrinsic environmental/social variables such as participation in cutting/jumping sports and contact versus non-contact situations have been theorised as potential mechanisms related to ACL injuries.[1011] It is also well recognised that several feedback mechanisms are associated with a higher rate of injury (eg, a person who sustains an injury to the ACL is at an increased risk for subsequent injury to the reconstructed ACL as well as injury to the ACL in the uninjured leg).[12–15]

Currently, many different techniques are utilised to evaluate risk factors and mechanisms for ACL injury.[16] Methodological approaches in vivo include observational (video analysis of injuries, athlete interviews and questionnaires), clinical (arthroscopic/surgical, clinical imaging and physical exam) and laboratory (motion analysis, electromyography) studies.[116–19] As it is neither ethical nor advisable to apply external loads to a human subject to cause an injury, alternative methods such as in vitro (cadaveric) studies are also a common approach to study injury mechanisms. In more recent years, in silico methods (computer model simulations) have been developed and are being used to explore injury risk factors and mechanisms.

Individually, each of these approaches has provided important contributions to our understanding of how the musculoskeletal system works and identified potential injury mechanisms. However, each approach also has multiple limitations (table 1). Despite the vast attention researchers have devoted to exploring ACL injury mechanisms over the past decade, there is no clear explanation or robust model that powerfully demonstrates how all of the risk factors interact.[16] In fact, few studies demonstrate that the hypothesised risk factors actually increase an athlete's risk for injury. Conflicting, and even contradictory, predictive models are present in the literature.[2320] Moreover, although strong evidence of success for ACL injury neuromuscular training prevention programmes was established almost a decade ago, ACL injury rates remain high for athletes.[2122]

The insufficient and contradictory predictive abilities of the various models in the literature may be the result of a range of factors. Nonetheless, we believe the two underlying philosophical issues (reductionistic study designs and reductionistic data analyses) may be considerably distorting our understanding and ultimately thwarting our ability to develop and implement effective and efficient prevention programmes. These two issues are deeply rooted in the culture of science in general and are prominent across many academic fields of study.

REDUCTIONISTIC TENDENCIES OF STUDY DESIGNS AND ANALYSES

Modern health science literature has been fundamentally shaped by study designs in which it is assumed that the parts of a system can be studied, summed and used to represent the system as a whole.[23–26] For example, with in vitro approaches such as cadaveric testing, it is assumed that observation of the osteokinematics (movement of the bones at the joints in abduction/adduction, flexion/extension and internal/external rotation) and arthrokinematics (small motions occurring at joint surfaces such as glide, slides and rolls) can be used to represent how the tissue and body systems will behave in a living being in a dynamic environment. In other words, the parts of the body and environment are reduced to parts of the musculoskeletal system observed under various laboratory conditions and then generalised back in a way that the behaviour of the parts of the musculoskeletal system is assumed to represent the behaviour of all of the systems of the body during movement.

Philosophically, this could be likened to taking apart a bicycle, thoroughly examining how the handlebars behave and thoroughly examining how the gears work, then assuming because you understand how the parts behave independently, you understand how the bicycle parts will function together as a whole system (fig 1). This approach to understanding how a bicycle works would philosophically be labelled as a reductionist study design.[27,28] Unless each part of the bicycle is the same, and the interactions between them are the same, a reductionistic approach is not likely to give you a complete understanding of how the system functions as a whole and may result in a distorted assumption of how the parts work together to create a movement. At odds with reductionist thinking, an alternative conceptual framework exists in which the notion that a system can be reduced to its parts and still retain the meaning of the whole system is ultimately rejected. Instead, research approaches which are antireductionist in nature are thought to provide richer, more robust and more accurate understandings of the whole.[27,28]

Conventional analytical approaches also tend to be reductionist in nature. Most of the problems related to human health and disease are dynamically and relationally complex. Such problems have typically been approached using correlation-based analytical methods (eg, regression), which are useful for identifying linear relationships but are limited because of their inability to establish and test a web of causal relationships which may include varying weights of variables and feedback loops.[23] While correlation-based methods can be valuable in providing detailed information about various aspects of the problem, used alone they are insufficient for addressing problems that are dynamic (ie, change over time) and complex in terms of the large number of relationships in the system. Even the more complex techniques of multivariate and hierarchical modelling are constrained by similar assumptions as units of analysis are derived from aggregated and averaged data, which assumes that the data are collected on homogeneous subjects (fig 2) that engage in random and relatively equal quantities of mixing (fig 3).[23–26,29–31]

From one perspective, embracing reductionism can be useful, as it helps establish simple explanations and solutions to problems and questions using relatively simple methodological designs and analyses. However, from another perspective, embracing reductionistic study designs is innately problematic. The information that gets obscured or overlooked can lead to overly simplistic understandings and explanations for predicting phenomena. Under the methodological and analytical constraints of reductionistic practice, it is not uncommon to find a large disparity between what seems to be a model of relatively high predictive quality and what actually occurs in "real life."[2331] Although often dismissed as outliers or measurement error, another explanation for such outcomes is that predictive models acquired through conventional approaches are overly simplistic and unable to account for the richness and complexity that truly exists.

The question then becomes: What other options do we have? In general, reductionistic assumptions are so embedded within evidence generation processes because the approaches that we use are inherently socially constructed, psychologically ingrained and subconsciously, sociologically, and politically perpetuated. Researchers are trained to think and carry out studies using conventional methods, and institutional and funding structures are designed to support and reward conventional methods. To a certain extent, acceptance of these assumptions may also be necessary because our methodological and analytical approaches are limited by the technology and computing power that is available to us.

Born out of new advances in technology, and out of recognition and frustration for the limitations of conventional, reductionist approaches, researchers in a variety of fields are developing and adopting what we will broadly refer to as *complex systems modelling and methodologies* or *systems science techniques*. Complex systems-based thinking calls for recognition and reconceptualisation of the assumptions described above and embraces the integration of more powerful methodological and analytical tools such as agent-based modelling, network analyses and dynamic systems analyses.[2329] These innovative methods enable investigators to simultaneously consider the dynamic interaction between and among variables at multiple levels of analysis, and the impact these factors have on the behaviour of a system as a whole. They are complementary in nature to the more conventional methods but allow for a more complex heuristic that elaborates on the information that can be generated from the more simplistic modelling techniques. As such, complex systems modelling and methodologies provide the opportunity to reveal new patterns and insights.[23–26]

In recent years, the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC) and other health-related agencies have increasingly recognised the potential these innovative approaches hold for advancing our understanding of complex health issues.[24–26] Consequently, these agencies are starting to devote a number of resources and training opportunities specifically toward integrating complex systems approaches into public health research and initiatives. For example, in 2007, the NIH Office of Behavioral and Social Sciences, the CDC and other health agencies sponsored a four-part lecture series entitled 2007 Symposia Series on Systems Science and Health (now available in video casts).[24–26] The intention of this symposia series was to introduce systems science methodological approaches to scholars interested in complex health phenomenon.

REDUCTIONISTIC TENDENCIES IN ACL RESEARCH

In essence, ACL injuries are a phenomenon best described by events that entail the interaction between predisposing vulnerabilities (eg, neuromuscular imbalances) and hazard exposures (eg, having the knee in a hazardous position). Injury mechanisms, successful outcomes of therapeutic interventions and the effective implementation of injury prevention strategies are inextricably linked to a complex interaction of anatomical, physiological, psychological (eg, motivation), behavioural (eg, adherence to home exercise programmes) and sociological variables (eg, social support networks, insurance coverage, occupational and recreational activities).[10,11] These risk factors form a system of complex interactions that can ultimately lead to ACL injury. Given the limitations of conventional research designs and analyses described above, we contend that under the current paradigm of ACL research, our ability to understand the role of risk factors is severely constrained by the narrow scope of understanding that simplistic, reductionistic methodological models provide for our "evidence" generation, synthesis and integration processes. Reductionistic designs that focus on one type of data-collection strategy independently (ie, in vivo, in vitro or in silico) and analyses that are linear, static and simplistic in nature only allow researchers to consider the data within the constraints of a reductionist lens. Because of the reductionistic assumptions current methodological models incorporate, we have limited concrete insight into how these variables are structurally linked. As such, our musculoskeletal injury knowledge base could potentially benefit greatly from antireductionist thinking and modelling.

PROPOSAL FOR IN SIM RESEARCH DESIGN STRATEGIES

In this paper, we refer to antireductionistic, synthesised approaches to the study of musculoskeletal injury phenomena as in sim methodologies. Figure 4 provides a visual interpretation of what we mean by this type of in sim approach. Essentially, an assimilation of the methods in a synergistic manner that utilises in vitro and in vivo methods to optimise and validate in silico techniques will lead to an in sim approach that can overcome many of the experimental limitations associated with independent utilisation of the methods and provide a more clinically acceptable model to study musculoskeletal injury risk factors and mechanisms.

We believe it is the integration of models and overturning of reductionist assumptions that will enable researchers to more accurately capture and closely represent the richness and complexity of what occurs during "real life" injury events. Each methodological approach (in vivo, in vitro and in silico) utilised in musculoskeletal research can independently provide data to address hypotheses about injury risk factors and mechanisms. However, a multifaceted approach and cross-validation process to optimise models could allow for integration of several methods, strengthen the current biomechanical methodology available to study injury mechanisms and lead to a different formalised means to conceptualise study designs and measure and analyse data in musculoskeletal injury research.

As a result of the advancement of a number of analytical approaches, research technology has now reached a point where it is not only possible to conceptualise comprehensive methodological frameworks that integrate in vivo, in vitro and in silico methods but also utilise novel ways to analyse and validate such synthesised, complex conceptualisations of these approaches.[1] The risk for most musculoskeletal injuries is likely multi-factorial. One “ideal and universal” intervention strategy will likely not be identified. Large-scale intervention strategies may be limited to address the most likely injury mechanisms and risk factors. Alternatively, once individuals are identified as “at risk,” advanced tests developed with in sim approaches could be used to identify the magnitude of their risk and ascertain potential intervention strategies. While anatomical subject-specific models are ideal to predict the most accurate stress and strain data, generalised “anatomic” finite element models could be scaled to match appropriate input parameters such as height, strength and laxity of joints, and subject-specific “biomechanical” models could be developed instead. The relationships between structures and changes in magnitude between testing conditions could provide valuable information to help understand, but perhaps not accurately predict, exact ligament, cartilage, and bone stresses and strains.

Integration of in vivo, in vitro and in silico techniques into a new in sim approach could provide an excellent platform to predict risk factors that are important to address and to identify which individuals are most at risk for injury. For example, while there is no current consensus in the literature about the knee movements most likely to cause ACL injury, integration of the methods could help identify the most dangerous postures and potential perturbations likely to cause injury. Furthermore, the consequences of risk factors such as hyperlaxity or neuromuscular deficits on biomechanical parameters (ligament stresses and strains) could be explored in a systematic manner using robust in sim models. This information could be used to establish hypotheses about potential interventions, and the hypotheses could be tested in a simulated environment to determine if the desired effects such as lowering ACL strains could be achieved, prior to undertaking large, expensive prevention studies.[32] Given the nature of the inconsistencies in the literature and the historical use of reductionistic data collection and analytical methods, it is possible that using in sim approaches to study ACL injury could significantly advance our understanding and predictive abilities for identifying individuals at risk for ACL injury.

PROPOSAL FOR IN SIM ANALYTICAL STRATEGIES

Research designs that combine data-collection methods via in sim methods could be analysed using less reductionistic approaches as well. Figure 5 illustrates the differences between a hypothetical causal relationship model using conventional analytical techniques (correlational, regression, factor analyses types of models) and a less reductionistic, more complex model using complex systems analysis techniques (network analyses, dynamic systems analyses). Note that in the less reductionistic model, the web of interrelationships can be modelled and tested between and among variables as well as consider the various weights these variables may carry and the reciprocal and feedback types of relationships that are present within the model.

A complex systems analytical approach necessitates the integration of a variety of data-collection techniques (much like the in sim design strategies discussed in the section above) as well as comprehensive, longitudinal datasets. The creation and analyses of such data sets may allow for the exploration of data in ways that were never considered, or even possible, under the current conventional paradigms. Coupled biomechanical–epidemiological longitudinal data sets are now available that include prospective and retrospective data pertaining to many of the theorised mechanistic variables associated with ACL injuries. Insight of this nature could be very valuable for clinicians in their attempts to minimise hazard exposures and mitigate predisposing vulnerabilities, thereby reducing overall incidence of ACL injury and subsequent long-term sequelae associated with such an injury.

IN SIM METHOD CONSIDERATIONS

We strongly advocate that musculoskeletal injuries for humans be modelled based on the anatomy of live, human subjects. If the geometry is created using live subjects, in vivo biomechanical data such as kinematic, kinetic, electromyography, laxity and strength measures can be used to guide the appropriate selection of material properties, boundary conditions and input data for in silico methods. In vitro data that utilise specimens that best represent the population/subject under investigation should be used to provide supplemental information for the parameters that cannot be determined in vivo. We also advise that initial baseline movement input data for musculoskeletal injury models be determined by in vivo biomechanical data rather than “hypothetical” movement scenarios. Once a baseline condition is established (eg, in our ACL injury scenario, normal landing mechanics from a jump), “hypothetical” conditions such as injury simulations and the roles of hyperlaxity or hypolaxity on ligament stresses and strains can be explored through rigorous sensitivity analyses.

In general, the validation procedures should closely match the situations of interest for simulation studies. In silico modelling of impact scenarios like landing from a jump should utilise validation (both in vitro and in vivo if possible) studies that represent similar conditions. It is also important to demonstrate the validity of in sim models for prediction of internal stresses and strains and external kinematic and kinetic predictions for the task of interest (eg, cutting, jumping and landing). In other words, model validity is task-specific and should not necessarily be considered valid for all tasks. We also strongly recommend that in sim models for musculoskeletal injury be designed to explore mechanisms postulated by observational studies of injuries and not assumed mechanisms of injury. Clearly, the tissue’s primary restraining function may be an important consideration for injury mechanisms; however, the path of most “direct” loading does not necessarily lead to injury.

While this review has mainly targeted prediction and prevention techniques, in sim approaches could also be useful for diagnosis and treatment as well. One of the most challenging decisions clinicians are forced to make is to determine when it is safe to return to activities of daily living or sports following musculoskeletal injury. Time from injury/surgery is only one variable that can affect a patient’s safe return to activity. Many other variables such as strength, proprioception, implant/hardware strength, hardware fixation and healing properties can affect patient safety for return to activity. In sim studies could evaluate many of these variables and could help provide treatment guidelines and enrich clinical outcome studies. These studies could even be coupled with prediction/prevention models to evaluate potential risk for reinjury.

LIMITATIONS TO INTERPRETATIONS OF IN SIM TECHNIQUES

Although integrated methods that utilise in sim techniques offer many potential benefits for understanding musculoskeletal injury, it is important to mention that all models have experimental shortcomings, and there are often disparities between experimental validation and the mechanical environment during activities. In sim techniques have the unique potential to overcome many of the limitations associated with in vivo, in vitro and in silico methodology as well as the limitations of conventional statistical analyses. While it may not be possible to fully validate high loading rate simulations, models can be used to extend the current knowledge bases about musculoskeletal injury mechanisms and explore working hypotheses about reducing risk for injury without exact stress and strain results for internal musculoskeletal structures. However, we strongly recommend cautious implementation of methods, interpretation and reporting of data.

Researchers and technicians who conduct and report results of in sim techniques should make clinicians and consumers fully aware of the limitations of these methods. Computational modelling and complex systems analyses have the ability to generate large datasets with relative ease and low cost. However, like any scientific hypothesis, it is not possible to fully validate a model, only to invalidate one. Models should be developed and validated to answer specific hypotheses and questions with the research design matching the capabilities of the “validated” model. Extension of models to explore questions with a previously “validated” model may not be appropriate if the validation did not necessarily address the variables under investigation in the new simulation. Propagation of poor use and inappropriate interpretations and applications of the data should be prevented, as applications of these techniques could be dangerous in the clinical setting if clinicians and patients do not consider the limitations of modelling when making clinical decisions.

SUMMARY

The complete understanding of musculoskeletal injury mechanisms and their devastating chronic downstream sequelae is an essential step towards the development of efficacious, efficient and cost-effective techniques for the prevention, diagnosis and treatment of all musculoskeletal injuries. The new in sim approaches that we propose in this review could be used to integrate in vivo, in vitro and in silico techniques, and explore more comprehensive methodological frameworks to improve our understanding of the complex relationships between joint biomechanics and observed joint injury mechanisms. These new in sim approaches can combine the latest developments from in vivo coupled biomechanical epidemiological studies, dynamic-functional MRI imaging, in vitro accurate and precise robotic cadaveric injury simulations and integrated molecular, immunological and biochemical methodologies, with the latest state-of-the-art in silico techniques and analyses to allow for a complete picture of the multiple mechanisms underlying risk of musculoskeletal injury.

While we advise caution with in sim techniques, we still believe that the utility of more complex design and analytical techniques far outweighs the potential problems. We contend that it is increasingly possible to utilise these techniques to generate hypotheses and draw conclusions about musculoskeletal injury risk factors and mechanisms in order to help better predict and prevent musculoskeletal injury. The greatest advances and most significant contributions are likely to come from methodological paradigms that allow us to think, theorise and find appropriate applications that consider the nature of the relationships that exist and what those relationships might indicate about the phenomena we seek to understand but cannot explore using current methodology and technology.

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References

1. Quatman, CE. thesis. University of Toledo; Toledo (OH): 2009. Anterior cruciate ligament injury mechanisms in female athletes: a finite element investigation.
2. Quatman CE, Hewett TE. The anterior cruciate ligament injury controversy: is “valgus collapse” a sex-specific mechanism? Br J Sports Med. 2009; 43:328–35. [PubMed: 19372087]
3. Yu B, Garrett WE. Mechanisms of non-contact ACL injuries. Br J Sports Med. 2007; 41(1 Suppl):i47–51. [PubMed: 17646249]
4. Myklebust G, Bahr R. Return to play guidelines after anterior cruciate ligament surgery. Br J Sports Med. 2005; 39:127–31. [PubMed: 15728687]
5. Freedman KB, Glasgow MT, Glasgow SG, et al. Anterior cruciate ligament injury and reconstruction among university students. Clin Orthop Related Res. 1998; 356:208–12.
6. Freedman, KB.; Glasgow, MT.; Glasgow, SG., et al. The effect of anterior cruciate ligament injury and timing of reconstruction on the academic performance of university students. Annual Meeting of the AAOS, Poster Exhibit; 19–23 March 1998; New Orleans. 1998.
7. Lohmander LS, Englund PM, Dahl LL, et al. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med. 2007; 35:1756–69. [PubMed: 17761605]
8. Gillquist J, Messner K. Anterior cruciate ligament reconstruction and the long-term incidence of gonarthrosis. Sports Med. 1999; 27:143–56. [PubMed: 10222538]
9. Lohmander LS, Ostenberg A, Englund M, et al. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum. 2004; 50:3145–52. [PubMed: 15476248]
10. Hewett TE, Myer GD, Ford KR. Anterior cruciate ligament injuries in female athletes: part 1, mechanisms and risk factors. Am J Sports Med. 2006; 34:299–311. [PubMed: 16423913]
11. Griffin LY, Albohm MJ, Arendt EA, et al. Understanding and preventing noncontact anterior cruciate ligament injuries: a review of the Hunt Valley II meeting, January 2005. Am J Sports Med. 2006; 34:1512–32. [PubMed: 16905673]
12. Salmon L, Russell V, Musgrove T, et al. Incidence and risk factors for graft rupture and contralateral rupture after anterior cruciate ligament reconstruction. Arthroscopy. 2005; 21:948–57. [PubMed: 16084292]
13. Uhorchak JM, Scoville CR, Williams GN, et al. Risk factors associated with noncontact injury of the anterior cruciate ligament: a prospective four-year evaluation of 859 West Point cadets. Am J Sports Med. 2003; 31:831–42. [PubMed: 14623646]

14. Pinczewski LA, Lyman J, Salmon LJ, et al. A 10-year comparison of anterior cruciate ligament reconstructions with hamstring tendon and patellar tendon autograft: a controlled, prospective trial. Am J Sports Med. 2007; 35:564–74. [PubMed: 17261567]
15. Wright RW, Dunn WR, Amendola A, et al. Risk of tearing the intact anterior cruciate ligament in the contralateral knee and rupturing the anterior cruciate ligament graft during the first 2 years after anterior cruciate ligament reconstruction: a prospective MOON cohort study. Am J Sports Med. 2007; 35:1131–4. [PubMed: 17452511]
16. Quatman CE, Quatman CC, Hewett TE. A "plane" explanation of non-contact anterior cruciate ligament injury mechanisms: a systematic review. Sports Medicine. 2009 (Under Review).
17. Robertson, DGE. Research methods in biomechanics. Champaign: Human Kinetics; 2004.
18. Shimokochi Y, Shultz SJ. Mechanisms of noncontact anterior cruciate ligament injury. J Athl Train. 2008; 43:396–408. [PubMed: 18668173]
19. Krosshaug T, Andersen TE, Olsen OE, et al. Research approaches to describe the mechanisms of injuries in sport: limitations and possibilities. Br J Sports Med. 2005; 39:330–9. [PubMed: 15911601]
20. van den Bogert AJ, McLean SG. Comment on "A stochastic biomechanical model for risk and risk factors of non-contact anterior cruciate ligament injuries. J Biomech. 2009; 42:1778–9. author reply 1780–2. [PubMed: 19481754]
21. Agel J, Arendt EA, Bershadsky B. Anterior cruciate ligament injury in national collegiate athletic association basketball and soccer: a 13-year review. Am J Sports Med. 2005; 33:524–30. [PubMed: 15722283]
22. Hewett TE, Ford KR, Myer GD. Anterior cruciate ligament injuries in female athletes: part 2, a meta-analysis of neuromuscular interventions aimed at injury prevention. Am J Sports Med. 2006; 34:490–8. [PubMed: 16382007]
23. Mabry PL, Olster DH, Morgan GD, et al. Interdisciplinarity and systems science to improve population health: a view from the NIH Office of Behavioral and Social Sciences Research. Am J Prev Med. 2008; 35(2 Suppl):211–24S.
24. Mabry, P.; Milstein, B.; Sterman, J., et al. NIH. Systems methodologies for solving real-world problems: applications in public health. 2007. National Institute of Health: Symposia Series on Systems Science and Health.
25. Faust, K. NIH. Systems network analysis: using connections and structures to understand and change health behaviors. 2007. National Institute of Health Symposia on Systems Science and Health.
26. Homer, J.; Richardson, G. NIH. System dynamics modeling: population flows, feedback loops and health. 2007. National Institute of Health Symposia Series on Systems Science and Health.
27. Nagel T. Reductionism and antireductionism. Novartis Found Symp. 1998; 213:3–10. discussion 10–14, 73–5. [PubMed: 9653712]
28. Rose S. What is wrong with reductionist explanations of behaviour? Novartis Found Symp. 1998; 213:176–86. discussion 186–92, 218–121. [PubMed: 9653723]
29. Wasserman, S.; Faust, K. Social network analysis: methods and applications. Cambridge: Cambridge University Press; 1994.
30. Scott, J. Social network analysis: a handbook. 2. Thousands Oaks: Sage; 2000.
31. Sternman J. Learning from evidence in a complex world. Am J Public Health. 2006; 96:505–14. [PubMed: 16449579]
32. Quatman, CE.; Kiapour, A.; Ford, KR., et al. Reduced knee abduction loads at landing decrease ACL strains in athletes at high risk for ACL injury. American Orthopaedic Society for Sports Medicine Annual Meeting; Keystone, Colorado, USA. 9–12 July 2009;

What is already known on this topic

- Under the current research paradigm, in vivo, in vitro and in silico methods independently provide information regarding the mechanisms and prevention of musculoskeletal injury.
- However, individually, each of these methods has multiple, inherent limitations and is likely to provide incomplete answers about multifactorial, complex injury conditions.

What this study adds

A proposal that an integration of less reductionistic, synthesised study designs and analytical techniques (an approach termed in sim meaning a “union of models done on the likeness of phenomena”) can provide a more robust conceptual framework to better understand the relationships between complex joint biomechanics and observed injury mechanisms.

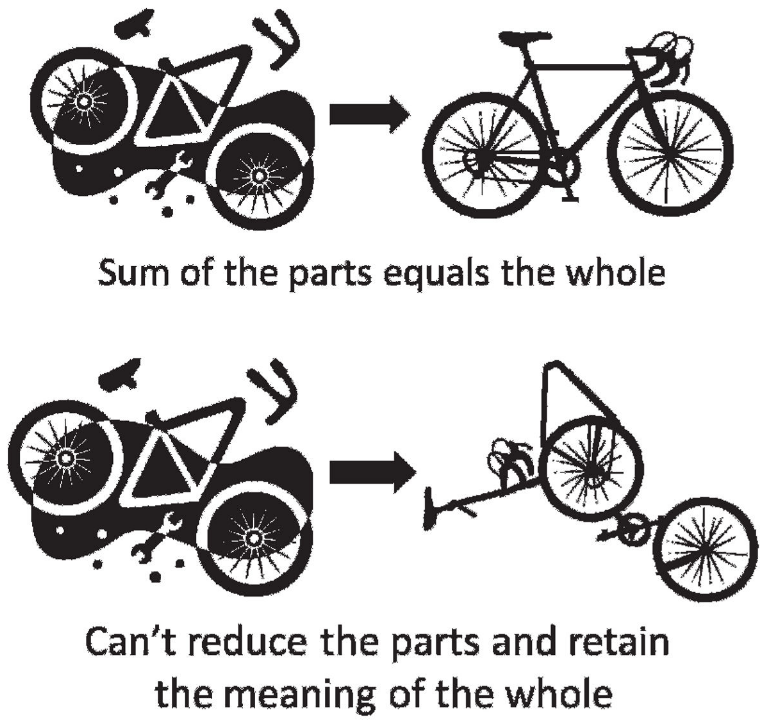

Figure 1.
Reductionistic study design assuming that examination of each of the parts independently (such as examining bicycle parts) will indicate how the parts interact and function as a whole. In contrast, unless each of the parts is the same and the interactions between them are the same, a reductionistic approach is unlikely to give a complete picture and understanding of how the system functions as a whole.

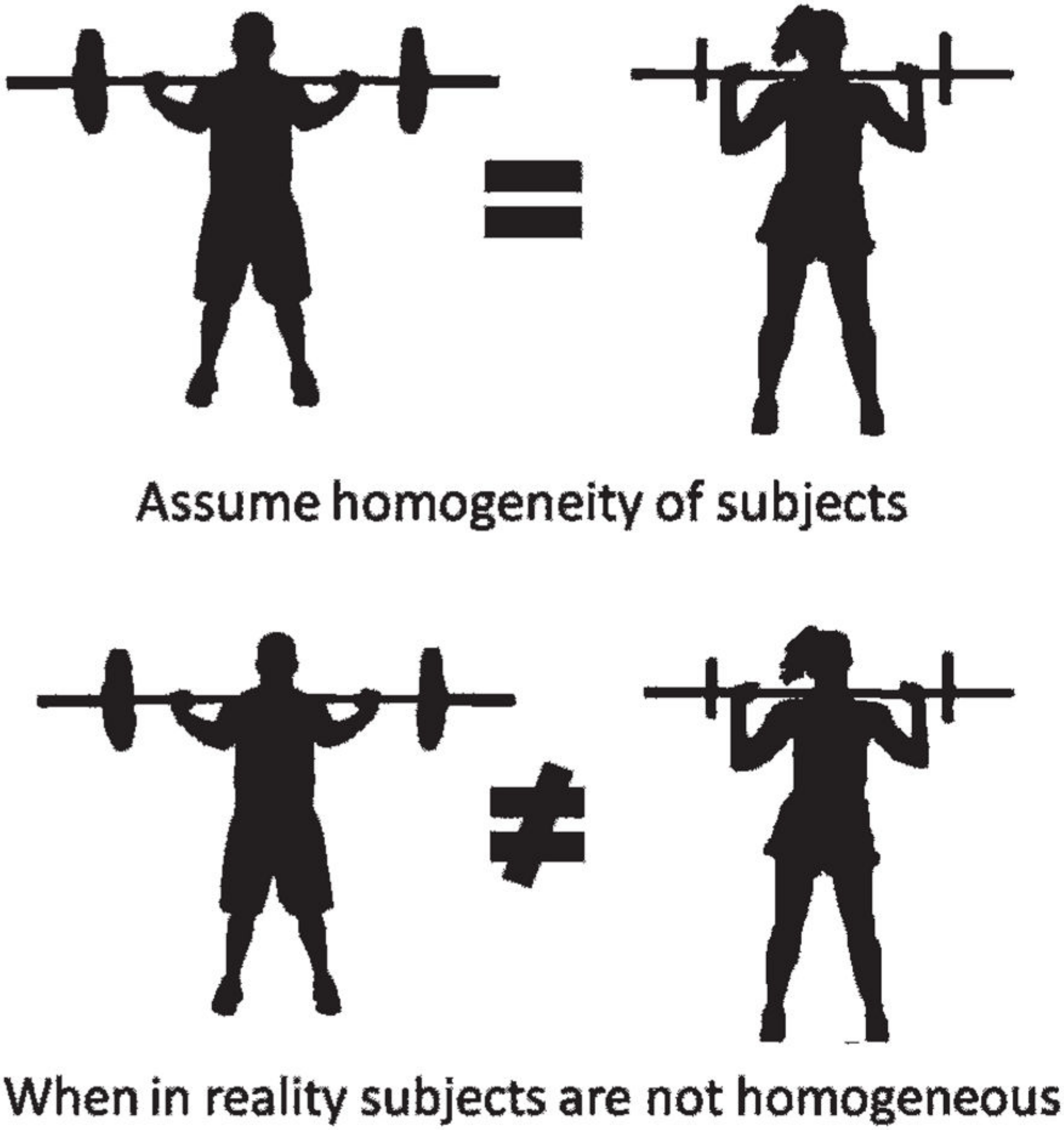

Figure 2.
Study assuming that the subjects are homogeneous (sex does not affect the variables being investigated), when in reality sex differences affect the outcome.

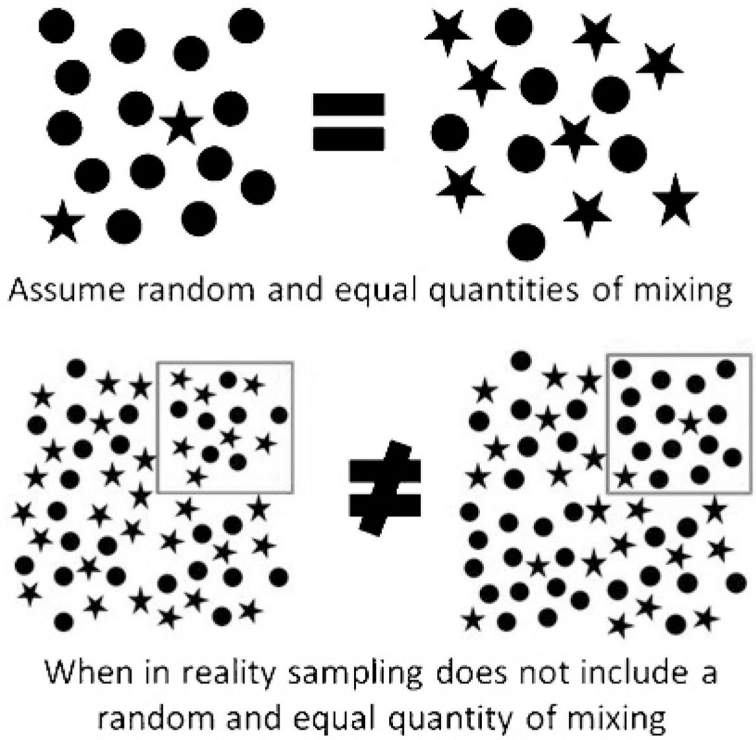

Figure 3.

Study assumptions that the subjects are randomly mixed in equal quantities (eg, at risk and not at risk subjects), may or may not be valid.

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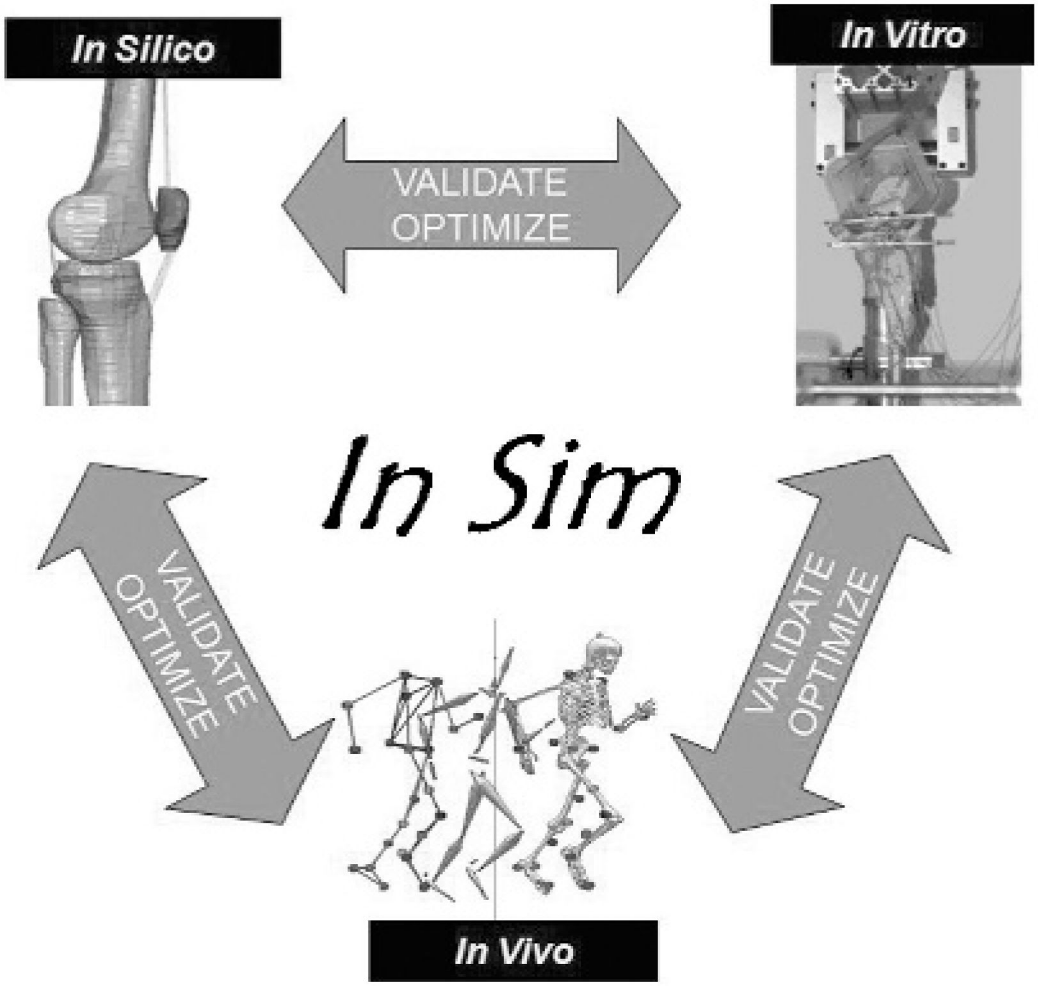

Figure 4.
Integration of in vivo, in vitro and in silico methods as a comprehensive in sim methodological framework to study musculoskeletal injury.

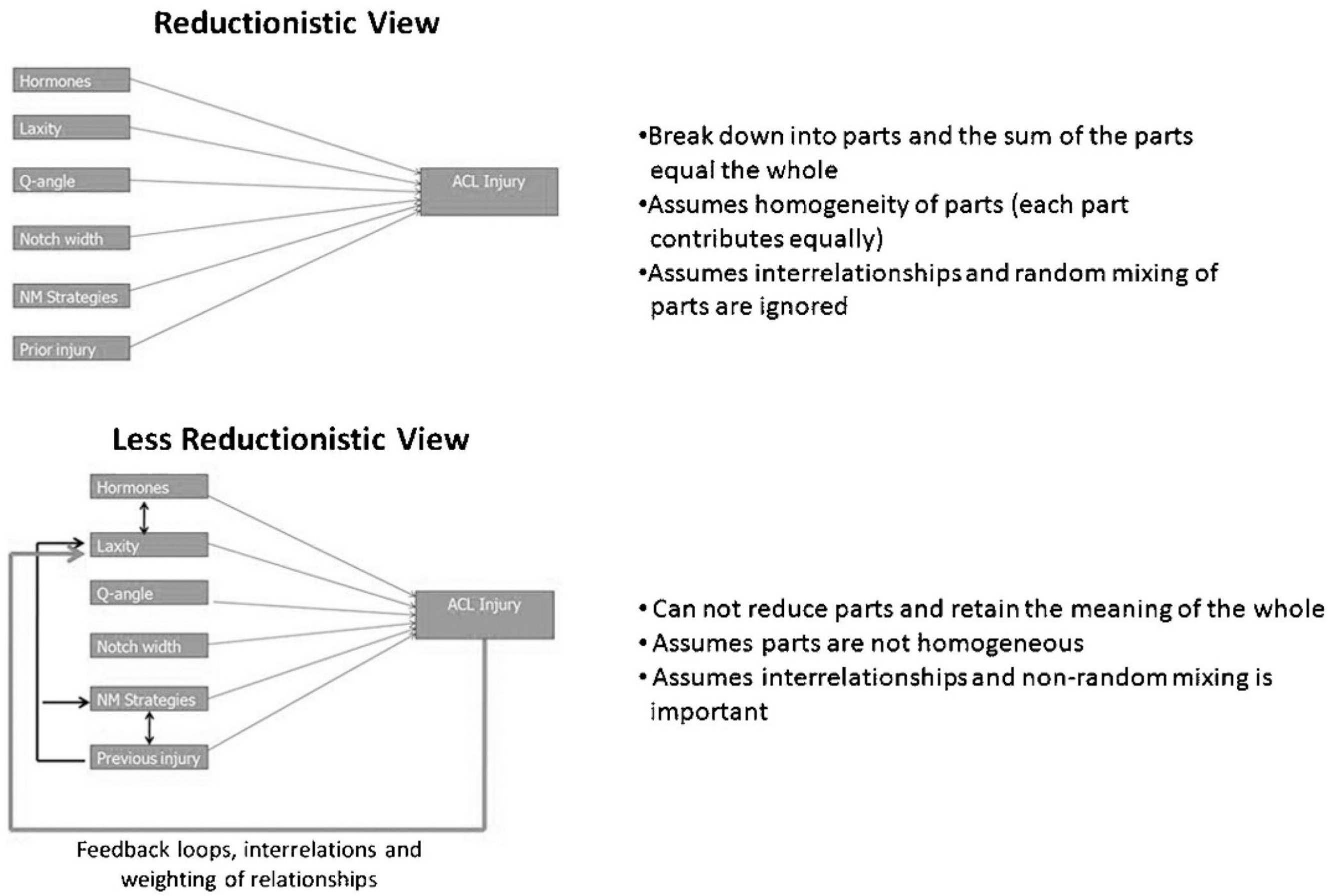

Figure 5.

Assumption of a simple, linear relationship between variables, a reductionistic view. In reality, many of the variables may influence each other, have a greater influence on the dependent variable or provide feedback to other variables. ACL, anterior cruciate ligament; NM, neuromuscular.

Table 1

Advantages and limitations of the various investigational methods

Data-collection method	Examples	Advantages	Limitations	Applications in ACL research
In vivo	Observational: questionnaires, video, interviews	Direct observation or description of injury mechanism	• Cannot determine internal structure stresses/strains • Questionnaire/ interview: subjective and dependent on athletes ability to recall event • Video: limited by quality of video, camera angles available and observer's ability to describe event	Description of inciting event (contact or non-contact, type of sporting activity), gross position of knee, trunk, lower extremity during injury
	Clinical: arthroscopic, imaging, physical exam	• lesions associated with injury, strain gauges on internal joint structures, analyse anatomical restraints—functional-dynamic imaging such as MRI or roentgen stereogrammetric analysis techniques offer enhanced ability to visualise internal structures during dynamic weight-bearing activities • Accuracy, precision, reliability of data acquisition continuous to improve	• Do not directly analyse injury mechanism • Postinjury pathology and associated biomechanical effects may not be reliable indicators of actual injury mechanisms • Arthroscopic: not ethical for healthy subjects, may affect proprioception or cause joint impingement, expensive • Imaging: possible radiation exposure, expensive • Physical exam: often subjective and highly variable differences between subjects	• Strain gauges placed on ACL during arthroscopy provide information about ACL strains during external loads • Bone bruise locations may provide evidence for injury mechanisms • Posterior tibial slope calculated from images may be associated with ACL injury • Lachman's, pivot shift, knee arthrometer data provide evidence of biomechanical effects of ACL deficiency • Functional-dynamic images help identify osteokinematics and ACL changes that occur during weight-bearing tasks
	Laboratory: motion analysis, electromyography	• Mimic specific movements that	• Do not replicate actual injury;	• Identify sex differences in

Data-collection method	Examples	Advantages	Limitations	Applications in ACL research
		occur during injury • Estimate both kinematics and net kinetics at joint during high-risk movements • Coupled biomechanical–epidemiological studies provide predictive tools about injury risk factors (allows for both correlation and prediction of musculoskeletal injury)	rather estimate total joint biomechanics during high-risk movements • Difficult to reproduce or even approximate the strains and stresses that occur in internal joint structures (ligaments, cartilage, bones) • Unethical to try to produce injury in laboratory	landing/cutting mechanics that may be associated with ACL injury • Identify biomechanical/ neuromuscular variables associated with ACL injury
In vitro	Robotic, quasistatic, dynamic	• Identify passive biomechanical characteristics of joint motions • Direct injury studies possible • Quantify multiple degree of freedom kinematics of joints • Measure ligament and joint articulation contact forces	• Age of specimens (may differ significantly from the population of interest) • Difficult to reproduce dynamic joint motions and neuromuscular contributions to motion during injury conditions • Expensive and injury studies often require a large number of specimens to reproduce injury mechanisms • Orientation of loading, rate of loading and age of specimen may have significant effects on musculoskeletal failure loads	• ACL strains and biomechanical parameters during different external loading parameters provide evidence of how ACL injuries may occur • Cadaveric ACL injury may occur during anterior tibial shear, abduction, knee hyperextension and many combined loads • Biomechanical consequences of ACL deficiency
In silico	Phenomenological, anatomical, rigid, finite element, quasistatic, dynamic, stochastic, inverse simulation, forward simulation	• Estimate internal joint biomechanics • In vivo biomechanical data can be used as input for geometric models to analyse movements	• Due to complexity of joints, models are simplified • Certain assumptions are necessary about material properties, boundary	• ACL injury simulations for various tasks • Identification of possible strategies to lower ACL injury risk • Extension of coupled

Data-collection method	Examples	Advantages	Limitations	Applications in ACL research
		• Can be used to extend motion analysis data to relate ground reaction forces and kinematics to ligament, cartilage and bone forces • Can be used to simulate injury mechanisms • Parametric/ sensitivity studies possible • Relatively inexpensive if equipment is readily available • Accuracy, precision, reliability of data acquisition continuous to improve	conditions and anatomy • Models must be validated (ideally by in vivo and in vitro data) which can be difficult without adequate material property characteristics available for the population of interest • Not currently possible to validate high loading rate/ injury simulations	biomechanical–epidemiological motion analysis data to relate ground reaction forces and external loading conditions to ACL strains

ACL, anterior cruciate ligament.