

Machine learning methods to support personalized neuromusculoskeletal modelling

Author

Saxby, David J, Killen, Bryce Adrian, Pizzolato, C, Carty, CP, Diamond, LE, Modenese, L, Fernandez, J, Davico, G, Barzan, M, Lenton, G, da Luz, S Brito, Suwarganda, E, Devaprakash, D, Korhonen, RK, Alderson, JA, Besier, TF, Barrett, RS, Lloyd, DG

Published

2020

Journal Title

Biomechanics and Modeling in Mechanobiology

Version

Accepted Manuscript (AM)

DOI

[10.1007/s10237-020-01367-8](https://doi.org/10.1007/s10237-020-01367-8)

Downloaded from

<https://hdl.handle.net/10072/395884>

Funder(s)

ARC

Grant identifier(s)

LP150100905

Griffith Research Online

<https://research-repository.griffith.edu.au>

Biomechanics and Modeling in Mechanobiology

Machine learning methods to support personalized neuromusculoskeletal modelling

--Manuscript Draft--

Manuscript Number:		
Full Title:	Machine learning methods to support personalized neuromusculoskeletal modelling	
Article Type:	Review Article	
Keywords:	computational models; biomechanics; artificial intelligence; musculoskeletal	
Corresponding Author:	David John Saxby, PhD Griffith University Gold Coast, Queensland AUSTRALIA	
Corresponding Author Secondary Information:		
Corresponding Author's Institution:	Griffith University	
Corresponding Author's Secondary Institution:		
First Author:	David John Saxby, PhD	
First Author Secondary Information:		
Order of Authors:	David John Saxby, PhD	
	Bryce Alexander Killen, PhD	
	Claudio Pizzolato, PhD	
	Christopher P Carty, PhD	
	Laura Elizebeth Diamond, PhD	
	Luca Modenese, PhD	
	Justin Fernandez, PhD	
	Giorgio Davico, PhD	
	Martina Barzan, PhD	
	Gavin K Lenton, PhD	
	Simao Brito da Luz, PhD	
	Edin Suwarganda, MSc	
	Rami Kristian Korhonen, PhD	
	Jaqueline A Alderson, PhD	
	Thor F Besier, PhD	
	Rod S Barrett, PhD	
	David G Lloyd, PhD	
	Daniel Devaprakesh, MSc	
Order of Authors Secondary Information:		
Funding Information:	Australian Research Council (LP150100905)	Prof David G Lloyd
	Australian Research Council (IC180100024)	Dr David John Saxby
	Queensland Motor Accident Insurance Commission (BioSpine)	Dr Claudio Pizzolato
	BioMedTechHorizons	

	(SLIL_BMTH 07)	Prof David G Lloyd
	Academy of Finland (286526)	Prof Rami Kristian Korhonen
	Academy of Finland (324529)	Prof Rami Kristian Korhonen
	Sigrid Juséliuksen Säätiö	Prof Rami Kristian Korhonen
	IMeasureU Ltd (37122001)	Prof Thor F Besier
	Cleveland Clinic (1R01EB024573)	Prof Thor F Besier
	University of Auckland (3710225)	Prof Thor F Besier
	Imperial College London	Dr Luca Modenese
Abstract:	<p>Many biomedical, orthopaedic, and industrial applications are emerging that will benefit from personalized neuromusculoskeletal models. Applications include refined diagnostics, prediction of treatment trajectories for neuromusculoskeletal diseases, in silico design, development, and testing of medical implants, and human-machine interfaces to support assistive technologies. This review proposes how physics-based simulation, combined with machine learning approaches from big data, can be used to develop high-fidelity personalized representations of the human neuromusculoskeletal system. The core neuromusculoskeletal model features requiring personalization are identified and big data/machine learning approaches for implementation are presented together with recommendations for further research.</p>	

Machine learning methods to support personalized neuromusculoskeletal modelling

¹Saxby DJ[†], ²Killen BA[†], ¹Pizzolato C, ¹Carty CP, ¹Diamond LE, ³Modenese L, ⁴Fernandez J, ^{5,6}Davico G, ¹Barzan M, ¹Lenton G, ¹Brito da Luz S, ¹Suwarganda E, ¹Devaprakash D, ⁷Korhonen R, ⁸Alderson JA, ⁴Besier TF, ¹Barrett RS, ¹Lloyd DG

[†]Equal contribution to the manuscript

¹School of Allied Health Sciences & Menzies Health Institute Queensland, Griffith University, Australia

²Human Movement Biomechanics Research Group, KU Leuven, Belgium

³Imperial College London, United Kingdom

⁴Auckland Bioengineering Institute, University of Auckland, New Zealand

⁵Department of Industrial Engineering, University of Bologna, Italy

⁶Medical Technology Lab, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

⁷Group for Biophysics of Bone and Cartilage, University of Eastern Finland, Finland

⁸University of Western Australia, Australia

Corresponding author:

Dr David J. Saxby

School of Allied Health Sciences & Gold Coast Orthopaedic Research & Education Alliance (GCORE), Menzies Health Institute Queensland, Griffith University, Gold Coast campus, Australia

T: +61755528917 F: +61755528674 E: d.saxby@griffith.edu.au

Abstract

Many biomedical, orthopaedic, and industrial applications are emerging that will benefit from personalized neuromusculoskeletal models. Applications include refined diagnostics, prediction of treatment trajectories for neuromusculoskeletal diseases, *in silico* design, development, and testing of medical implants, and human-machine interfaces to support assistive technologies. This review proposes how physics-based simulation, combined with machine learning approaches from big data, can be used to develop high-fidelity personalized representations of the human neuromusculoskeletal system. The core neuromusculoskeletal model features requiring personalization are identified and big data/machine learning approaches for implementation are presented together with recommendations for further research.

1 Background

Computational biomedicine and artificial intelligence (AI) are scientific fields that developed largely independent of each other over the past four to six decades (Chambers et al. 2016; Coveney et al. 2013; Halilaj et al. 2018; Khoury and Ioannidis 2014; Viceconti et al. 2015). Both computational biomedicine and AI span public health concerns (Sciences 2016), have commercial scope (Saey (2018), 23andMe www.23andme.com; Genos genos.co), and present tremendous potential to realize the, to-date unfulfilled, goal of personalized medicine (Coveney et al. 2013; Esteva et al. 2017; Sciences 2016), the aim of which has been to make mechanistic models of biology personalized to the individual across multiple size-scales to solve clinical issues.

Computational biomedicine is a physics-based approach to modelling multi-scale systems for health (Coveney et al. 2013; Hunter 2016; Hunter et al. 2010; Viceconti and Hunter 2016), while AI is a mathematical approach used to extract features from large information sets (i.e., big data) (Halilaj et al. 2018; Hastie et al. 2009) and/or to search for established patterns in data (Hastie et al. 2009). The utility of AI to computational biomedicine has been criticized because of the complex aetiologies and pathogenesis of diseases (Keyes et al. 2015; Khoury and Galea 2016). Likewise, the explicit object-based behaviour codified in physics-based models results in enormous computational demand when addressing complex problems such as disease mechanisms. The assumption (potentially unfounded) is the ever growing power of modern computing will subdue the problem of computational demand in physics-based modelling (Goranson and Cardier 2013). Potentially, AI can be used to augment physics-based modelling by making it faster to create and perform mechanistic modelling for health applications (Coveney et al. 2013; Hunter 2016; Viceconti and Hunter 2016; Viceconti et al. 2015). The purpose of this paper is to review the contribution of AI methods in personalised physics-based models of human neuromusculoskeletal biomechanics. First, we will begin by outlining computational modelling methods used in human neuromusculoskeletal biomechanics.

1.1 Computational neuromusculoskeletal biomechanics

Computational neuromusculoskeletal biomechanics encompasses physics-based modelling of the complex, multi-scale, non-linear, and dynamic interaction between neural drive to muscles, muscle dynamics, joint kinematics and kinetics, and their effects on the loading experienced by musculoskeletal tissues. Computational neuromusculoskeletal biomechanics aims to understand and manage many neuromusculoskeletal conditions, and to rehabilitate patients and have been used to study

many phenomena ranging from muscle function during locomotion in healthy individuals (Hamner et al. 2010; Killen et al. 2018; Pandy and Andriacchi 2010; Sasaki 2010; Saxby et al. 2016b; Schache et al. 2012; Shelburne et al. 2006; Thelen and Anderson 2006) and those with pathologies (Gerus et al. 2013; Hoang et al. 2019; Konrath et al. 2017; Montefiori et al. 2019a; Saxby et al. 2016a; Shao et al. 2009), to model-driven control of prostheses or rehabilitation robotics (Sartori et al. 2018; Sartori et al. 2016). Other applications include estimation of tissue loading (Kim et al. 2009; Saxby et al. 2016b; Wellsandt et al. 2016) and how this is effected by ergonomic aids (Hall et al. 2019) or occupational demands (Lenton et al. 2018). Musculoskeletal loading (Pena et al. 2006; Shim et al. 2016; Yang et al. 2010) is of particular clinical interest, as loading has mechanistic links to tissue remodelling (Andriacchi et al. 2009; Eskelinen et al. 2019; Gardiner et al. 2016; Myller et al. 2019; Pizzolato et al. 2017a; Smith et al. 2013) (Saxby et al. 2017; Young People With Old Knees Research et al. 2017) and is therefore a logical target for physical therapy.

To translate the power of computational neuromusculoskeletal biomechanics from laboratory settings where almost all research has taken place to clinical or “field” conditions, the models themselves may require high levels of personalization to match the individual, the modelling methods must become fast enough to be of use to the clinician/coach/commander, and the instruments used must be developed into portable and/or body-worn version to “escape the laboratory”. There is general enthusiasm for use of AI in computational neuromusculoskeletal biomechanics, as highlighted in recent reviews (Coveney et al. 2013; Ferber et al. 2016; Halilaj et al. 2018; Hunter et al. 2010; Ku et al. 2015; Viceconti et al. 2015) and original papers (Lee et al. 2019; Peng et al. 2018; Peng et al. 2017). In this review, we will focus on use of big data and AI to make fast personalized computational neuromusculoskeletal biomechanical models.

1.2. Model personalization – a step toward credibility

The answer to the question of how personalized a model should be depends on the research question. A generic model, i.e., one with no particular personalization, is appropriate when studying neuromusculoskeletal phenomena decoupled from the individual/group, investigating motor control principals, or determining simple external biomechanical quantities (e.g., spatiotemporal parameters such as locomotion speed, cadence, etc) which are not particularly sensitive to model personalization. Another example is the study of the dependency of simulated muscle forces on model joint degrees of freedom (Jinha et al. 2006), wherein a generic model without personalization is

adequate. Likewise, if one is demonstrating changes to muscle function by simulating a surgical relocation of muscle attachment, a generic model will perform admirably (Delp et al. 1990). However, if modelling neuromusculoskeletal function of specific individuals/groups the model should properly represent their unique anatomy and neurophysiology.

Throughout the biomechanics literature, the terms “subject-specific” or “patient-specific” are used to describe different levels and aspects of model personalization (Bahl et al. 2019; Barzan et al. 2019; Brito da Luz et al. 2017; Gerus et al. 2013; Kainz et al. 2017a; Marra et al. 2015; Modenese et al. 2018; O'Connor et al. 2018; Wesseling et al. 2016a; Wesseling et al. 2016b), even in cases when minimal personalization was achieved. The level of model personalization in biomechanical studies varies substantially, ranging from using anatomical landmarks identified by skin-surface markers to scale generic models of the underlying musculoskeletal system (O'Connor et al. 2018) to incorporation of complex and subject-specific bone geometry, joint anatomy, and joint function (Barzan et al. 2019; Kainz et al. 2017a; Lenhart et al. 2015; Modenese et al. 2018; Smith et al. 2016; Wesseling et al. 2016a). Studies examining model personalization typically focus on the effects on end-point biomechanical variables (Gerus et al. 2013; Hannah et al. 2017; Lerner et al. 2015; Marra et al. 2015; Modenese et al. 2018; Montefiori et al. 2019a; Wesseling et al. 2016a). Even when simulation accuracy is not reported, an implicit assumption is that a more personalized model has greater physiological and physical plausibility (Bruto da Luz et al. 2017; Hoang et al. 2019; Hoang et al. 2018) or relevance to health state (Anderson et al. 2010; Favre et al. 2016a; Favre et al. 2016b; Smith et al. 2006; Wellsandt et al. 2016), as the individual relationships between anatomy, function, and motor control are, in principle, modelled. However, many previous studies exploring the influence of personalization on model function typically included only one or a small number of personalization features, neglecting others (Gerus et al. 2015; Kainz et al. 2017b; Lerner et al. 2015). The interaction between personalized features has been examined only in few studies (Gerus et al. 2013; Hoang et al. 2018; Navacchia et al. 2017), thus, it is difficult to understand the incremental and likely complex interactions of personalization features and their effects on model outputs.

We have summarised model personalization into five main categories (Table 1): mathematical definitions (e.g., functions prescribing complex joint kinematics), model parameters (e.g., muscle tendon parameters), anatomy (i.e., external and internal structure), tissue material properties, and (neuro) physiology. All features influence

model performance and their incorporation should be guided by the research question and the credibility the authors require of their results (Viceconti et al. 2020a). If model results will have high levels of influence (e.g., decisively inform a therapy or design) and carry significant consequences (e.g., if wrong, people are harmed or worse), the model is high risk and requires extensive validation and verification (Viceconti et al. 2020b).

Part of validation and verification may involve personalizing the model to the individual. Data needed for personalization may be sourced from laboratory-based motion capture methods and dynamometry (Andriacchi et al. 2009; Astephen et al. 2008; Dempsey et al. 2009; Knoll et al. 2004; Lee et al. 2013), prior literature or cadaveric testing (Lloyd and Besier 2003; Pizzolato et al. 2015; Sartori et al. 2014; Sartori et al. 2012a), and/or medical imaging (Bahl et al. 2019; Marra et al. 2015; Modenese et al. 2018; Wesseling et al. 2016a; Zhang et al. 1999; Zhang et al. 2015). However, establishing robust model personalization involves more than customizing a model to match targets, but doing so in respect of standards and using methods than can be repeated and audited.

To achieve robust model personalization, we need a framework within which to work. Open frameworks, such as the Virtual Physiological Human (Hunter 2016; Hunter et al. 2010; Viceconti and Hunter 2016), are bold and ambitious endeavours enabling users around the world to produce mechanistic models of human physiology. However, the Virtual Physiological Human and other large-scale initiatives are still developing a neuromusculoskeletal system focus, and do not yet encompass what is required for proper personalization. We highlight an existing framework that encompasses, and is built upon, open platforms such as Virtual Physiological Human (Fernandez et al. 2018b; Hunter et al. 2005; Viceconti and Hunter 2016) and OpenSim (Delp et al. 2007; Seth et al. 2018): the Musculoskeletal Atlas Project (Zhang et al. 2015; Zhang et al. 2014), which supports development of personalized neuromusculoskeletal models. It is our hope the Musculoskeletal Atlas Project, or similar initiatives, will serve as rational basis to create and execute personalized models for the wider biomechanics and clinical communities.

Currently, creation of personalized neuromusculoskeletal models is resource intensive, requires considerable technical skills, and is bespoke without standards – although research teams are attempting to codify this process with notable inroads (Modenese et al. 2018). The critical achievement of Modenese and colleagues was a step-by-step procedure for creating musculoskeletal models that minimizes user involvement and quantifies the reliability of a codified workflow (Montefiori et al. 2019b). This ensures different users will create very similar final models from common input imaging data.

Indeed, for personalized models to be widely adopted, especially in clinical fields, the technology used to generate them must be highly automated, hence, the importance of recent work to automate creation of personalized and complex muscle geometries from muscle segmentations obtained from MRI (Modenese and Kohout 2020).

1.3. Machine learning to accelerate neuromusculoskeletal modelling

Machine learning is a subset of AI (Hastie and Tibshirani 2009; Hastie et al. 2009). Herein, we will briefly summarize the classes of unsupervised and supervised machine learning methods, and demonstrate how they may be used to develop, deploy, and refine personalized neuromusculoskeletal models. Although machine learning is undoubtedly a powerful tool for identifying relationships within, and predicting from, data, it assumes no underlying mechanistic representation of the physical system under examination. We may consider machine learning a ‘black box’ of arbitrary, but sophisticated, organization. Many machine learning methods require large quantities of data (i.e., big data) to robustly establish relationships, or use unique data to tune an established machine learning system. This dependency on data presents some problems as phenomena within a system may not be measurable, data may be ill conditioned (Khoury and Ioannidis 2014) and/or not relevant to the problem in question (Bayer and Galea 2015). Machine learning is powerful but needs to be used cautiously as biomechanical data may be ill-conditioned and total reliance on data-driven approaches may have many unpredictable and negative consequences. Furthermore, a narrow focus on data input-to-output relationships in systems that are inherently deterministic seems to be missing the point of causal models.

We contend that physics-based modelling can, in part, help overcome limitations associated with machine learning by creating data reflecting physical and physiological mechanisms. In turn, machine learning can help physics-based modelling by decreasing computational demands in data processing, creating models, and executing analysis, or by reducing need to acquire new experimental data. For example, the finite element analysis (FEA) can be reduced to a surrogate using statistical interpolation of a meaningful sample of outputs – a process often referred to as “Kriging” after statistician Danie Krige. This is relevant because the computational gains of Kriging make FEA outputs such as tissue stresses and strains viable in real-time, as has been demonstrated in impressive fashion recently to understand femur mechanics (Ziaei-poor et al. 2019a; Ziaei-poor et al. 2020; Ziaei-poor et al. 2019b). Real-time capacity is a requirement for future translation to clinical or in-field conditions, where clinicians/coaches/commanders and their patients/athletes/soldiers want immediate feedback about how behavioural

choices influence sub-tissue level mechanics. Once measured and physically modelled data are compiled, an array of machine learning approaches can be used to explore relationships between biomechanical variables, health, and disease states, potentially revealing new and non-intuitive findings.

2 Framework for personalized modelling

The proposed framework to develop and use personalized neuromusculoskeletal models is a combination of (i) multi-modal imaging data, (ii) physics-based modelling, and (iii) machine learning (Figure 1). The framework has five steps: creation, tuning, calibration, validation, and execution, with each step using various imaging modes, physics-based modelling, and machine learning methods.

<Insert Figure 1 about here>

Model creation refers to the generation of model form and function using any data acquired from the individual, such as non-medical motion capture or external body hull imaging, magnetic resonance imaging (MRI), X-ray computed tomography (CT), fluoroscopy, plain and low-dose multi-plane X-ray.

Tuning involves adjusting model features and parameters to achieve anatomical and physiological plausibility. Tuning does not require data from the individual but is informed through cadaveric and/or literature-based data to provide targets and boundaries. Tuning adjusts model parameters to match empirical patterns such as joint kinematics (Brito da Luz et al. 2017), muscle tendon unit (MTU) passive stiffness (van der Krogt et al. 2016), and (MTU) moment arms (Arnold et al. 2000; Rajagopal et al. 2016). Tuning can adjust models to prevent shortcomings such as discontinuities in joint kinematics and interpenetration of musculoskeletal tissues.

Unfortunately, tuning is often a manual process, making it tedious and subjective. Strides are being taken to automate this process robustly. An example is the automated tuning of personalized closed-chain joint mechanisms (Brito da Luz et al. 2017), created through direct segmentation of medical imaging with physical constraints to predict joint motion (Figure 2). As there are errors associated with MRI imaging and processing, and errors in the formulation of the physical constraints (i.e., ligament isometry), the initial personalized closed-chain joint mechanism is ill-conditioned and numerically stiff. The parameters governing these mechanisms (e.g., bone shapes, ligament lengths, etc.) are then tuned, by optimising design variables (e.g., bone shape radii, positions, orientations, etc.), to maximise correlation between closed-chain joint mechanism 6 DOF kinematics

and literature data from cadaveric specimens and/or previously validated models. Importantly, tuning personalized closed-chain joint mechanisms prevents cartilage-into-cartilage penetration and kinematic discontinuities, which are both indications of a physically implausible model.

<Insert Figure 2 about here>

Calibration relies on data measured from the individual to optimize model features. In neuromusculoskeletal biomechanical modelling, parameters governing muscle's excitation to activation dynamics (Buchanan et al. 2004) and/or MTU physiology (Pizzolato et al. 2015) are optimized to minimize error between joint moments estimated via neuromusculoskeletal modelling and corresponding joint moments from inverse dynamics. Likewise, MTU physiological parameters (Walter et al. 2014) or MTU moment arms (Serrancoli et al. 2016) can be adjusted to better predict measured knee contact forces. Further, calibrating FEA continuum material properties can ensure good matching between modelled and measured three-dimensional deformations in tendons (Hansen et al. 2017; Shim et al. 2019b), ligaments (Gardiner and Weiss 2003; Weiss et al. 2002), and cartilage (Keenan et al. 2009; Keenan et al. 2013). Importantly, calibration ensures correspondence between model outputs and experimentally acquired measurements.

Validation involves examining model parameters and derived end-point biomechanical outputs against independent data not used in model creation, tuning, and calibration. Model validation can also be performed by comparing calibrated parameters to surrogate measures from imaging or other assessments. For example, tissue material properties are often quite challenging to directly measure, particularly non-invasively; however, calibration of a FEA model can involve optimizing material properties to match a physics-based target (i.e., measured object deformation) and be validated using proxies of tissue quality from medical imaging (i.e., elastography or specific echo times from MRI).

Many different end-point biomechanical outputs can be used for indirect (e.g., model parameters) or direct (e.g., joint moments, kinematics, and EMG) validation. Furthermore, validation can employ literature-based comparison data, such as instrumented joint implant forces (Bergmann et al. 2001; Fregly et al. 2012; Kutzner et al. 2010), or bone kinematics measured *in vivo* (Benoit et al. 2007; Lafortune et al. 1992; Stagni et al. 2005) and/or from cadavers (Blankevoort et al. 1991). Alternatively, validation can use data collected directly from the individual, for example muscle fascicle kinematics (Gerus et al. 2015), ground reaction forces (Johnson et al. 2019a; Johnson et

al. 2018), joint moments (Lloyd and Besier 2003), joint contact forces from instrumented prosthetic implants (Walter et al. 2014), three-dimensional bone surfaces (Bahl et al. 2019; Davico et al. 2019a; Kainz et al. 2017b; Suwarganda et al. 2019), joint centres (Bahl et al. 2019; Zhang and Besier 2017; Zhang et al. 2015), and EMG (Hoang et al. 2019; Hoang et al. 2018; Lenton et al. 2018; Sartori et al. 2014). As load sharing amongst the many tissues of the body is indeterminate (Crowninshield 1981), it is important to ensure model tuning and calibration are robust to different initial starting conditions (Ong et al. 2019) and to use many sources of validation data to establish a personalized model as valid (Lund et al. 2012). Indeed, validation is essential for establishing model credibility and supporting their use in critical clinical and industrial applications.

Execution refers to the operation of the previously developed neuromusculoskeletal model. Execution results in estimates of end-point biomechanical variables modelled during human function and is often the focus of modelling workflow as it yields mechanistically determined results establishing cause and effect between external biomechanics and internal tissue loading. Each of the previously mentioned steps is vital to ensure model execution produces results in which there can be confidence.

In summary, personalized model generation and operation, as outlined above, relies on literature and data collected from the individual. Subject-specific anatomy and joint models rely on segmentations of medical imaging of bone, cartilage, and ligaments (Modenese et al. 2018; Scheys et al. 2006; Wesseling et al. 2016a), or laboratory-collected kinematic and kinetic data from cadavers (Sancisi et al. 2014; Sancisi and Parenti-Castelli 2011). Segmentation of musculoskeletal tissues is not only time consuming, but image acquisition is also costly, particularly if MRI is used. Additionally, the required imaging facilities may not be accessible to many research teams, so these data are not routinely acquired as part of standard biomechanical data collection. If any models are to be operated in real-world scenarios, data acquired in a traditional motion capture laboratory needs to be alternatively obtained using wearable sensors or via non-invasive means such as image auto-tracking. We propose that both personalized model generation and operation in real-world scenarios can be assisted through big data and machine learning.

2.1. Machine learning to facilitate model personalization

Machine learning methods can facilitate neuromusculoskeletal modelling across five key domains (Table 1). These domains are: i) feature extraction (Diamond et al. 2017; Zhang et al. 2014), (ii) synthesizing data (Bahl et al. 2019; Clouthier et al. 2019; Davico et al. 2019b; Nolte et al. 2016a; Suwarganda et al. 2019; Zhang and Besier 2017), (iii) model

generation (Bahl et al. 2019; Clouthier et al. 2019; Johnson et al. 2019a; Johnson et al. 2018; Nolte et al. 2016b; Zhang and Besier 2017), (iv) execution (Eskinazi and Fregly 2015; Eskinazi and Fregly 2018; Ziaei-poor et al. 2019b), and v) data digitization, processing (Ambellan et al. 2019; Heimann and Meinzer 2009; Liu et al. 2018) and classification (Akhundov et al. 2019). Importantly, machine learning can be applied to measured data (e.g., medical imaging, EMG, ground reaction forces) as well as results of created (e.g., rigid multi-body joint model, tendon mesh) and/or executed (e.g., muscle tendon lengths and moment arms, FEA stresses and strains) models.

<Insert Table 1 about here>

Feature extraction (i) – Unsupervised machine learning identifies patterns in data, making use of different clustering and dimensional reduction methods. Regarding musculoskeletal modelling, machine learning has been used to rapidly and automatically process medical imaging to isolate structures of interest. In particular, artificial neural networks have proven particularly effective in medical image processing and have been used in a wide range of applications from automatically determine body composition (Hemke et al. 2020), cartilage pathologies (Liu et al. 2018) and geometries (Nikolopoulos et al. 2020), bone geometries (Ambellan et al. 2019), and muscle volumes (Yeung et al. 2019) and geometries (Ni et al. 2019). Using a dataset of reconstructed anatomical structures or organs exists, statistical shape models have been used to extract features from anatomical data, using principal component analysis (Rodriguez-Florez et al. 2017; Varzi et al. 2015; Williams et al. 2010) to create representations of anatomical tissue with associated principal components for bone (Grant et al. 2020; Suwarganda et al. 2019; Zhang and Besier 2017; Zhang et al. 2014), cartilage (albeit indirectly) (Van Dijck et al. 2018), meniscus (Dube et al. 2018; Vrancken et al. 2014), and other connective tissues (Neubert et al. 2015). Once a statistical shape model has been created using a large sample of tissue morphometries (i.e., big data), weighted principal components can be used to reconstruct morphometry of a novel tissue using minimal (i.e., sparse) data. The capacity to automatically and accurately reconstruct tissue geometries from sparse imaging is an important technical development, as it enhances accessibility of this technology for clinical and research applications.

Analogous to statistical shape models for musculoskeletal tissues, factorisation methods can be used to extract features from measures of muscle activation (i.e., EMG). These EMG features represent the central coordination of multiple muscles and are commonly referred to as a muscle synergy (Chhabra and Jacobs 2006; Ferrante et al. 2016; Neilson

and Neilson 2010). Numerous studies suggest the central nervous system activates muscles in synergy, rather than individually, which reduces the complexity in selecting muscles to activate to produce a movement (d'Avella et al. 2003; Ting and McKay 2007). Muscle synergies can be mathematically quantified using one of many factorisation methods described in literature (Tresch et al. 2006), such as non-negative matrix factorisation (Lee and Seung 1999), Gaussian primitives (Ivanenko et al. 2006), principal component analysis (Diamond et al. 2017; Falck 1983; Soechting and Lacquaniti 1989), and independent component analysis (Kargo and Nitz 2003). Temporal and spatial synergies have been extracted from EMG recordings of many upper- and lower-limb muscles during various movement tasks (e.g., walking, running, upper-limb movement) (Tresch et al. 2006), and muscle synergies have been used extensively in literature to identify differences in motor activity between healthy and pathological populations (e.g., post-stroke (Clark et al. 2010), cerebral palsy (Shuman et al. 2017), Parkinson's disease (Falaki et al. 2017), and spinal cord injury (Perez-Nombela et al. 2017). Although the neurophysiology underpinning muscle synergies is not established, feature extraction from EMG both well represents the CNS recruitment coordination and may be computationally favourable for neuromusculoskeletal modelling.

Synthesising missing data (ii) – In addition to feature extraction, machine learning methods enable synthesis from sparse datasets, once critical features have been extracted from large datasets. Instead of the costly, subjective, and tedious processes of manually segmenting medical imaging to create three-dimensional models of musculoskeletal anatomy, we can deform a template model along the primary modes of shape variation to match the individual. The free and open-source framework the Musculoskeletal Atlas Project Client (MAP) (Zhang et al. 2014) employs principal component analysis scaling as a method to synthesis 3-D bone geometries from sparse data. A principal component analysis scaling is more sophisticated than simple linear scaling (available in most musculoskeletal modelling software) and can accurately reconstruct bone shapes (Bahl et al. 2019; Nolte et al. 2016a; Nolte et al. 2020; Suwarganda et al. 2019; Zhang and Besier 2017; Zhang et al. 2015), but is limited by the variation contained within the training data. For example, large bone reconstruction inaccuracies occur when using an adult statistical shape model to synthesize paediatric data (Davico et al. 2019a). An advantage of the MAP Client is that muscle origin and attachment points/regions from classic computational models and physical models (SOMSO, <https://www.somso.de/en/anatomie/>) are embedded (Zhang et al. 2016). Consequently, when a digital representation of bone is deformed, the attached tissues are also deformed. It is recommended future work focus

on compiling open data as well as statistical shape models of different populations and additional musculoskeletal tissues (e.g., ligaments, cartilages, MTU three-dimensional shapes, origins and insertions).

Like musculoskeletal tissue morphometry, EMG can be reconstructed from muscle synergies (Bianco et al. 2018) as has been done for rigid multi-body neuromusculoskeletal modelling (McGowan et al. 2010; Sartori et al. 2013; Serrancoli et al. 2016; Walter et al. 2014). Furthermore, Sartori et al. (2013) have showed the same synergies could predict joint moments for different tasks. However, the selection of muscle EMGs from which synergies are extracted affects the reconstruction accuracy of missing EMG, so it is recommended large data from many muscles, patient populations, and tasks are collated for analysis.

With more open and complete data, in combination with appropriate machine learning and morphing methods, synthesizing many types of missing data from incomplete data sets is not only possible, but provides many advantages. Specifically, this will enable accurate reconstruction of musculoskeletal geometry with minimal imaging requirements, which eventually translates to faster and cheaper assembly of personalized musculoskeletal models. Moreover, reconstruction of EMG from statistical models may remove the onerous requirement of collecting many EMG signals through laboratory experiments, which is also resource intensive. This would make EMG analysis more viable for routine clinical settings.

Model generation (iii) – Bones, muscles, and articular soft tissues reconstructed using machine learning methods can then be incorporated into high-fidelity subject-specific musculoskeletal models. The combination of population-based machine learning with model personalization is particularly powerful because the same machine learning techniques used to generate population-based statistical models of tissue morphology can also be used to investigate effects model personalization on simulation outputs (Clouthier et al. 2019). Specifically, tissue geometries can be varied systematically along the primary modes of population variance and the effect on model outputs studied. In this way, the variation in model personalization is grounded in empirical quantification of natural variation, rather than numerically techniques (e.g., Montecarlo).

Model execution (iv). Different supervised machine learning methods can overcome limitations of physics-based models such as missing input data, difficulties in creating models, discontinuities in models, and speed of computing. Generally, surrogate models

have no underlying mechanistic model of a system's physics, but rather use mathematical methods that map biomechanical input data to output data.

Recently, Rane and colleagues used a deep-learning approach to train and then independently validate a neural network that used motion capture data (i.e., kinematics, kinetics, and EMG) to predict muscle forces and internal joint loading (e.g., medial knee contact forces) (Rane et al. 2019). Their network predicted the internal biomechanics with excellent accuracy, and, critically, the computations were real-time capable (i.e., <80 ms). The speed of the neural network predictions, which were previously achieved through efficient computational of the equations of motion (Pizzolato et al. 2017b; Pizzolato et al. 2017c; van den Bogert et al. 2013), is quite important, because for modelling to eventually be used in clinical workflows a practical requirement is minimal computational time.

Continuing in the vein, Dao presented predictions of muscle forces from a deep learning method that contains a “long short-term memory” layer in its computational architecture (Dao 2019). Network memory purports to enable a system to learn dynamic relationships by exposing the network to training data exhibiting these dynamic behaviours. In principle, network memory makes the system sensitive to the time history, a dynamic property essential to predict time series and evident in real muscle. Dao demonstrated this method, when coupled with a learning transfer process, could well predict novel muscle forces estimated through static optimization. However, this implementation suffers of the same limitation of static optimization, in that it is unable to account for subject-specific muscle activations, which are known to vary across individuals and control tasks, as well as being affected by training and pathology, thus the generalizability is questionable.

Another recent study into the utility of neural networks has been to use simple two-dimensional ultrasound to estimate muscle states during passive and active contractions (Cunningham and Loram 2020). The authors trained a convolutional neural network based on inputs of joint angle, moment, and EMG with the associated ultrasound image of the muscle. The network achieved approximately 50% accuracy in predicting muscle state (activity, joint angle, joint moment) from any arbitrary ultrasound image. A criticism of their implementation is that isometric and passive tasks were used, neglecting the force-velocity relationships present in muscle force production, which are highly non-linear and dependent on contraction mode (i.e., concentric or eccentric). Likewise, the mapping between a 2D simplification of fibre mechanics to 3D muscle function is a tenuous one, as such the limited network performance is no unexpected. Finally, for muscles that cross two joints, an infinite combination of angles can result in a specific

passive and active force production, thus a simplified model of joint postures (from wearable sensors) could help make solutions unique. The advantage of the approach of Cunningham and Loram is ultrasound sensors are being miniaturized and cheapened at a tremendous pace. In the future, many muscles could be simultaneously tracked using small and cheap body worn arrays, and subsequently used to assess muscle states during dynamic tasks. If accuracy improves, such an approach could limit the reliance on Hill-type or other forms of muscle modelling to estimate muscle state in favour of a measurement passed through a neural network to reveal states.

More broadly, surrogate models (of which we might include the product of machine learning approaches) can be used to avoid difficulties in creating and executing physics-based models through phenomenological interpolating functions. Examples include the use of splines or polynomials fitted to measured muscle tendon lengths and moment arms (Bobbert et al. 1986; Spoor et al. 1990). Indeed, Hill-type muscle models themselves are phenomenological in nature, mapping muscle lengths, velocities and activation to estimate muscle force (Hill 1938; Zajac 1989) through the use of splines, exponential and/or trigonometric functions (Delp et al. 1990; Gordon et al. 1966; Millard et al. 2013; Zajac 1989). Surrogates can also help with problems of muscle geometries, such as when discontinuities exist in muscle-tendon lengths and moment arms. These discontinuities often occur in rigid body musculoskeletal models that use line representations of muscles passing over wrapping surfaces or articulation points that are conditional on states (i.e., via points) (Eskinazi and Fregly 2018; Garner and Pandy 2000; Sartori et al. 2012b). These splines or polynomials can provide 1st or 2nd order differential continuity for the computation of forward simulations of neuromusculoskeletal biomechanical models (Eskinazi and Fregly 2018; Menegaldo et al. 2004; Menegaldo et al. 2006; Sartori et al. 2012b), which is helpful for reducing non-physiological force estimates caused by rapid changes in length (and hence velocities). Moreover, once created, the surrogates representing muscle-tendon unit geometries, can be evaluated in real-time as implemented in an EMG-driven neuromusculoskeletal model (Pizzolato et al. 2017c).

Surrogate methods can also reduce need to execute physics-based models when they are either computationally demanding (e.g., FEA or elasto-structural models) (Eskinazi and Fregly 2018; Ziaeiipoor et al. 2019b) or require peculiar inputs (Eskinazi and Fregly 2018; Johnson et al. 2019c). Surrogates methods, such as partial least-squares regression or deep neural networks, work well on big datasets consisting of input and (labelled) output from physics-based models. For example, to evaluate tissue three-dimensional stress and strain

patterns (outputs from the computationally demanding FEA) from force and boundary conditions (inputs), multiple or partial least-squares regression has been used for muscles (Fernandez et al. 2018a; Wu et al. 2014), tendons (Pizzolato et al. 2019b; Shim et al. 2019a) and bones (Ziaeiipoor et al. 2019b), and deep neural networks for whole joints (Eskinazi and Fregly 2015). Further, by applying convolution neural networks to large datasets of collected and modelled motion capture data, sparse 3-D motion data have been used to estimate ground reaction forces/moments (Johnson et al. 2019a) and joint moments (Johnson et al. 2019b), paving the way forward to use wearable sensors to produce laboratory quality biomechanical data in the real-world (Johnson et al. 2019a; Johnson et al. 2018; Johnson et al. 2019c; Pizzolato et al. 2019a; Pizzolato et al. 2017c).

Data curation, processing, and classification (v) – Experimental data is often acquired in an array of diverse file formats from many different instruments, collectively referred to as “raw data”. Some curation of these data, involving quality checks to ensure ‘data hygiene’, is needed. Digitisation of analogue data from the laboratory (e.g., EMG, ground reaction forces) is a common procedure performed using standard analogue-to-digital conversion methods and will not be discussed here. However, processing of medical imaging data (e.g., MRI, ultrasound) is subjective, time consuming, and tedious. Notably, convolutional neural networks and similar deep learning methods have been used to automatically segment various joint tissues and muscles (Ambellan et al. 2019; Le Troter et al. 2016; van den Noort et al. 2018; Zhou et al. 2018) from medical images. Particularly promising is automatic segmentation of articular cartilages (Ambellan et al. 2019; Chandra et al. 2016; Neubert et al. 2016; Van Dijck et al. 2018; Xia et al. 2014; Yang et al. 2015) using advanced machine learning methods, as cartilage can be quite challenging to image (e.g., hip must be put under traction to delineate acetabular and femoral cartilages, very high resolution scans are required as tissues are small). Automatic and accurate segmentation of medical imaging will prove to be a huge boon to the field as the costs of manual processing of medical imaging is a major barrier to its regular use in computational biomechanics.

Artificial neural networks have tremendous potential to aid neuromusculoskeletal modelling as a tool to classify data quality, such as EMG. Normally, EMG is assessed at the time of acquisition and when intended for use in post-processing through visual inspection from a trained operator. The operator is looking for high signal to noise, minimal DC-offset, phasic muscle activation during common cyclic tasks (e.g., walking), and quiet signal when the muscle is at rest. This is time consuming, subjective, and

requires trained and experienced personnel. Akhundov and colleagues (2019) used AlexNet CNN to classify >47,000 novel EMG signals into quality bins with >98% accuracy and negligible false classifications. Their work is an example of how machine learning, deployed as an open software tool, can accelerate processing of large data sets at human-like accuracy levels.

3 Recommendations and future directions

A large amount of time is required to collect data (e.g., medical imaging), and build the resulting personalized musculoskeletal models due to the highly manual (Valente et al. 2017) or semi-automated workflows that require human interventions (Modenese et al. 2018; Scheys et al. 2006). The manual nature of model personalization means many model features are influenced by the user's knowledge and expertise, as well as the repeatability of the workflow itself. Consequently, many personalized models are bespoke, acceptable only for technical academic literature. However, when performed in a robust manner, personalized models can inform mission critical applications, such design of parts for installation in the body or assisting vital functions and can provide insight into function following medical procedures (Taddei et al. 2012). These models come with the promise to assist and inform medical procedures, develop biomedical devices, be human-machine-interfaces, and solve other real-world clinical problems. If these promises are to be realised, model creation steps must be automated, and this requires robust vetting and documentation to meet regulatory requirements.

Although there are commercial software platforms that can be used, we believe the endeavour to generate and operate neuromusculoskeletal models will require large scale international collaboration. Consequently, we advocate the use of open data, tools, and software that are readily customisable and available for widespread adoption with the different software and associated models capable of interaction. To this ideal, the previously introduced MAP, with its Database, Query, and Client, provides a lightweight but powerful open-source framework with solutions to many of these problems. Notably, the MAP client a highly automated framework for development of rigid multi-body models compliant with OpenSim and solid meshes for subsequent FEA modelling. This will enhance interaction between anatomical modelling, multi-body simulation and analysis, and FEA.

There are several features of the MAP Client (the workflow tool of MAP) that are essential for engagement with the biomechanics community. First, its dependent software libraries are freely available (<https://github.com/MusculoskeletalAtlasProject/mapclient>),

but require more contributions with updates and user modifications. Second, the underlying software libraries are written or wrapped in Python, which means they are cross-platform, widely supported (<https://simtk.org/projects/map>), and without requirement for expensive user licenses. Third, the MAP Client workflows are organized through a graphical canvas where users link plugins that perform computational steps. In this way, workflows can be exchanged between different groups without the need to customize code. Fourth, as many computational steps are standard (e.g., opening a file type, serializing data, etc.), there are many plugins already available for use from the user community (<https://github.com/mapclient-plugins>), which reduces the burden on researchers to program their own workflows. Fifth, because the MAP Client can interact with the native MAP Database, the user gains access to a large database of bone geometries already processed into a statistical shape model. This means that with limited subject-specific data (e.g., skin surface markers and/or limited medical imaging), the user can create accurate personalized bone geometries by reconstructing the principal components to fit these subject-specific anatomical points and readily print an OpenSim model informed from this geometry. An important endeavour going forward will be to continue to contribute dataset of the different musculoskeletal tissues, such as cartilages, muscles, and ligaments, to MAP and expand the dataset to specific populations such as paediatrics or those with known musculoskeletal conditions.

Computational biomechanics is a rich and rewarding discipline, but not without challenges. If the promise of personalized medicine in the domain of physical therapy has not been realized to date, this failure resides in part with the scientists and engineers producing technology and establishing the causal mechanisms of pathology. Indeed, the limited uptake of our technologies by the clinical community is, in part, because we have failed to produce a compelling product. What is needed is a technology that is unified, simple to use, robust, fast, and accessible such that it may be applied to myriad examples of neuromusculoskeletal conditions that clinicians treat only a daily basis. Despite shortcomings to date, the present conditions are ideal for the field of biomechanics to move forward and bring these new technologies to address real-world problems.

In this narrative, we have outlined currently available methods to rapidly generate high-fidelity personalized models with limited involvement of the human operator. We have outlined the software frameworks that can be used to personalize a model from the perspectives of form and function. The developers of free and open-source software are typically open to work with those who would like to make contributions to their ongoing

development. Machine learning methods have the capacity to drive down costs associated with data acquisition (e.g., less medical imaging, reduced instrument requirements in laboratories, etc.), rapidly accelerate model creation processes, and launch us out of the confines of the laboratory and into real-world settings.

Taken together, personalized neuromusculoskeletal models will soon be able to estimate, in real-time, internal tissue strains in the real world (e.g., during field-based practice, work-tasks, or military operations) with minimal imposition on humans (e.g., sensor-integrated garments). Independently, the required technologies exist: machine learning to predict human motion and external loading using trivial measurements (Johnson et al. 2019a; Johnson et al. 2018), computational methods to estimate real-time applied tissue loading (Pizzolato et al. 2017c) and internal tissue strains, and sensor integrated garments to measure biological signals. What remains is to intelligently and robustly integrate these different technologies into a usable package for research and clinical use. The integrated package will shortly be a reality and we hope any of our clinical colleagues reading this paper will seize the opportunity to use cutting-edge technology to help their clientele.

Conflicts of Interest

Authors Lloyd, Barrett, and Besier have received research grant funding from the Australian Research Council (LP150100905). Authors Lloyd, Saxby, and Carty have received research grant funding from the Australian Research Council (IC180100024). Authors Pizzolato, Lloyd, Diamond, and Saxby have received research grant funding from the Queensland Motor Accident Insurance Commission (BioSpine). Authors Lloyd and Saxby have received research grant funding from the MTPConnect BioMedTechHorizons (SLIL_BMTH 07). Author Korhonen holds research grant funding from the Academy of Finland (#'s 286526 and 324529) and Sigrid Juselius Foundation. Author Besier hold research grant funding from IMeasureU Ltd (#37122001), Cleveland Clinic (#1R01EB024573), Auckland Bioengineering Institute MedTech (#3710225). Luca Modenese was funded by an Imperial College Research Fellowship granted by Imperial College London.

References

- Akhundov R, Saxby DJ, Edwards S, Snodgrass S, Clausen P, Diamond LE (2019) Development of a deep neural network for automated electromyographic pattern classification J Exp Biol 222 doi:10.1242/jeb.198101
- Ambellan F, Tack A, Ehlke M, Zachow S (2019) Automated segmentation of knee bone and cartilage combining statistical shape knowledge and convolutional neural networks: Data from the Osteoarthritis Initiative Medical image analysis 52:109-118 doi:10.1016/j.media.2018.11.009
- Anderson DD, Iyer KS, Segal NA, Lynch JA, Brown TD (2010) Implementation of discrete element analysis for subject-specific, population-wide investigations of habitual contact stress exposure J Appl Biomech 26:215-223
- Andriacchi T, Koo S, Scanlan SF (2009) Gait Mechanis Influence Healthy Cartilage Morphology and Osetoarthritis of The Knee Journal of Bone and Joint Surgery 91:95-101
- Arnold AS, Sallinas S, Hakawa DJ, Delp SL (2000) Accuracy of Muscle Moment Arms Estiamted from MRI-Based Musculoskeletal Models of the Lower Extremity Computer Aided Surgery 5:108-119
- Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ, Hubley-Kozey CL (2008) Gait and neuromuscular pattern changes are associated with differences in knee osteoarthritis severity levels J Biomech 41:868-876 doi:10.1016/j.jbiomech.2007.10.016
- Bahl JS et al. (2019) Statistical shape modelling versus linear scaling: Effects on predictions of hip joint centre location and muscle moment arms in people with hip osteoarthritis J Biomech 85:164-172 doi:10.1016/j.jbiomech.2019.01.031
- Barzan M et al. (2019) Development and validation of subject-specific pediatric multibody knee kinematic models with ligamentous constraints J Biomech 93:194-203 doi:10.1016/j.jbiomech.2019.07.001
- Bayer R, Galea S (2015) Public Health in the Precision-Medicine Era N Engl J Med 373:499-501 doi:10.1056/NEJMp1506241
- Benoit DL, Ramsey DK, Lamontagne M, Xu L, Wretenberg P, Renstrom P (2007) In vivo knee kinematics during gait reveals new rotation profiles and smaller translations Clin Orthop Relat Res 454:81-88 doi:10.1097/BLO.0b013e31802dc4d0
- Bergmann G, Deuretzbacher G, Heller M, Graichen F, Rohlmann A, Strauss J, Duda GN (2001) Hip contact forces and gait patterns from routine activities J Biomech 34:859-871

- Bianco NA, Patten C, Fregly BJ (2018) Can Measured Synergy Excitations Accurately Construct Unmeasured Muscle Excitations? *J Biomech Eng* 140 doi:10.1115/1.4038199
- Blankevoort L, Kuiper JH, Huiskes R, Grootenboer HJ (1991) Articular contact in a three-dimensional model of the knee *J Biomech* 24:1019-1031
- Bobbert MF, Huijing PA, van Ingen Schenau GJ (1986) A model of the human triceps surae muscle-tendon complex applied to jumping *J Biomech* 19:887-898 doi:10.1016/0021-9290(86)90184-3
- Brito da Luz S, Modenese L, Sancisi N, Mills PM, Kennedy B, Beck BR, Lloyd DG (2017) Feasibility of using MRIs to create subject-specific parallel-mechanism joint models. *Journal of Biomechanics* 53:45-55
- Buchanan TS, Lloyd DG, Manal K, Besier TF (2004) Neuromusculoskeletal modeling: estimation of muscle forces and joint moments and movements from measurements of neural command *J Appl Biomech* 20:367-395
- Chambers DA, Feero WG, Khoury MJ (2016) Convergence of Implementation Science, Precision Medicine, and the Learning Health Care System: A New Model for Biomedical Research *JAMA* 315:1941-1942 doi:10.1001/jama.2016.3867
- Chandra SS et al. (2016) Fast automated segmentation of multiple objects via spatially weighted shape learning *Physics in medicine and biology* 61:8070-8084 doi:10.1088/0031-9155/61/22/8070
- Chhabra M, Jacobs RA (2006) Properties of synergies arising from a theory of optimal motor behavior *Neural computation* 18:2320-2342 doi:10.1162/neco.2006.18.10.2320
- Clark DJ, Ting LH, Zajac FE, Neptune RR, Kautz SA (2010) Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke *J Neurophysiol* 103:844-857 doi:10.1152/jn.00825.2009
- Clouthier AL, Smith CR, Vignos MF, Thelen DG, Deluzio KJ, Rainbow MJ (2019) The effect of articular geometry features identified using statistical shape modelling on knee biomechanics *Med Eng Phys* 66:47-55 doi:10.1016/j.medengphy.2019.02.009
- Coveney PV, Diaz-Zuccarini V, Graf N, Hunter P, Kohl P, Tegner J, Viceconti M (2013) Integrative approaches to computational biomedicine *Interface Focus* 3:20130003-20130003 doi:ARTN 20130003
10.1098/rsfs.2013.0003

- Crowninshield RD (1981) The Prediction of Forces in Joint Structures: Distribution of Intersegmental Resultants Exercise and Sports Science Reviews 9:159-182
- Cunningham RJ, Loram ID (2020) Estimation of absolute states of human skeletal muscle via standard B-mode ultrasound imaging and deep convolutional neural networks Journal of the Royal Society, Interface 17:20190715 doi:10.1098/rsif.2019.0715
- d'Avella A, Saltiel P, Bizzi E (2003) Combinations of muscle synergies in the construction of a natural motor behavior Nat Neurosci 6:300-308 doi:10.1038/nn1010
- Dao TT (2019) From deep learning to transfer learning for the prediction of skeletal muscle forces Med Biol Eng Comput 57:1049-1058 doi:10.1007/s11517-018-1940-y
- Davico G, Pizzolato C, Killen BA, Barzan M, Suwarganda E, Lloyd DG, Carty CP (2019a) Reconstruction of paediatric lower limb bones using statistical shape modelling for musculoskeletal modelling Biomechanics and Modeling in Mechanobiology:(In Press)
- Davico G, Pizzolato C, Killen BA, Barzan M, Suwarganda EK, Lloyd DG, Carty CP (2019b) Best methods and data to reconstruct paediatric lower limb bones for musculoskeletal modelling Biomech Model Mechanobiol doi:10.1007/s10237-019-01245-y
- Delp SL et al. (2007) OpenSim: open-source software to create and analyze dynamic simulations of movement {IEEE} Trans Biomed Eng 54:1940-1950 doi:10.1109/TBME.2007.901024
- Delp SL, Loan J, Hoy MG, Zajac FE, Topp EL, Rosen JM (1990) An interactive graphics-based model of the lower extremity to study orthopaedic surgical procedures IEEE Transactions on Biomedical Engineering 37:757-767
- Dempsey AR, Lloyd DG, Elliott BC, Steele JR, Munro BJ (2009) Changing sidestep cutting technique reduces knee valgus loading The American journal of sports medicine 37:2194-2200 doi:10.1177/0363546509334373
- Diamond LE, Van den Hoorn W, Bennell KL, Wrigley TV, Hinman RS, O'Donnell J, Hodges PW (2017) Coordination of deep hip muscle activity is altered in symptomatic femoroacetabular impingement Journal of orthopaedic research : official publication of the Orthopaedic Research Society 35:1494-1504 doi:10.1002/jor.23391
- Dube B, Bowes MA, Kingsbury SR, Hensor EMA, Muzumdar S, Conaghan PG (2018) Where does meniscal damage progress most rapidly? An analysis using three-

- dimensional shape models on data from the Osteoarthritis Initiative Osteoarthritis and cartilage 26:62-71 doi:10.1016/j.joca.2017.10.012
- Eskelinen ASA, Mononen ME, Venalainen MS, Korhonen RK, Tanska P (2019) Maximum shear strain-based algorithm can predict proteoglycan loss in damaged articular cartilage Biomech Model Mechanobiol 18:753-778 doi:10.1007/s10237-018-01113-1
- Eskinazi I, Fregly BJ (2015) Surrogate modeling of deformable joint contact using artificial neural networks Med Eng Phys 37:885-891 doi:10.1016/j.medengphy.2015.06.006
- Eskinazi I, Fregly BJ (2018) A computational framework for simultaneous estimation of muscle and joint contact forces and body motion using optimization and surrogate modeling Med Eng Phys 54:56-64 doi:10.1016/j.medengphy.2018.02.002
- Esteva A, Kuprei B, Novoa RA, Ko J, Swetter SM, Blau HM, Thrun S (2017) Dermatologist-level classification of skin cancer with deep neural networks Nature 542:115-118
- Falaki A, Huang X, Lewis MM, Latash ML (2017) Motor equivalence and structure of variance: multi-muscle postural synergies in Parkinson's disease Experimental brain research 235:2243-2258 doi:10.1007/s00221-017-4971-y
- Falck B (1983) Automatic analysis of individual motor unit potentials recorded with a special two channel electrode. University of Turku,
- Favre J, Clancy C, Dowling AV, Andriacchi TP (2016a) Modification of Knee Flexion Angle Has Patient-Specific Effects on Anterior Cruciate Ligament Injury Risk Factors During Jump Landing Am J Sport Med 44:1540-1546 doi:10.1177/0363546516634000
- Favre J, Erhart-Hledik JC, Chehab EF, Andriacchi TP (2016b) Baseline ambulatory knee kinematics are associated with changes in cartilage thickness in osteoarthritic patients over 5 years J Biomech 49:1859-1864 doi:10.1016/j.jbiomech.2016.04.029
- Ferber R, Osis ST, Hicks JL, Delp SL (2016) Gait biomechanics in the era of data science J Biomech 49:3759-3761 doi:10.1016/j.jbiomech.2016.10.033
- Fernandez J, Mithraratne K, Alipour M, Handsfield G, Besier T, Zhang J (2018a) Towards rapid prediction of personalised muscle mechanics: integration with diffusion tensor imaging Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization:1-9

- Fernandez JF et al. (2018b) Musculoskeletal Modelling and the Physiome Project. In: Pivonka P (ed) Multiscale Mechanobiology of Bone Remodeling and Adaptation, vol 578. CISM International Centre for Mechanical Sciences, vol CISM International Centre for Mechanical Sciences. Springer Nature, pp 123-174. doi:10.1007/978-3-319-58845-2_3
- Ferrante S et al. (2016) A Personalized Multi-Channel FES Controller Based on Muscle Synergies to Support Gait Rehabilitation after Stroke Front Neurosci 10:425 doi:10.3389/fnins.2016.00425
- Fregly BJ, Besier TF, Lloyd DG, Delp SL, Banks SA, Pandy MG, D'Lima DD (2012) Grand challenge competition to predict *in vivo* knee loads Journal of orthopaedic research : official publication of the Orthopaedic Research Society 30:503-513 doi:10.1002/jor.22023
- Gardiner BS, Woodhouse FG, Besier TF, Grodzinsky AJ, Lloyd DG, Zhang L, Smith DW (2016) Predicting Knee Osteoarthritis Ann Biomed Eng 44:222-233 doi:10.1007/s10439-015-1393-5
- Gardiner JC, Weiss JA (2003) Subject-specific finite element analysis of the human medial collateral ligament during valgus knee loading Journal of orthopaedic research : official publication of the Orthopaedic Research Society 21:1098-1106 doi:10.1016/S0736-0266(03)00113-X
- Garner BA, Pandy MG (2000) The Obstacle-Set Method for Representing Muscle Paths in Musculoskeletal Models Comput Methods Biomech Biomed Engin 3:1-30 doi:10.1080/10255840008915251
- Gerus P, Rao G, Berton E (2015) Ultrasound-based subject-specific parameters improve fascicle behaviour estimation in Hill-type muscle model Comput Methods Biomech Biomed Engin 18:116-123 doi:10.1080/10255842.2013.780047
- Gerus P et al. (2013) Subject-specific knee joint geometry improves predictions of medial tibiofemoral contact forces J Biomech 46:2778-2786 doi:10.1016/j.jbiomech.2013.09.005
- Goranson HT, Cardier B (2013) A two-sorted logic for structurally modeling systems Prog Biophys Mol Biol 113:141-178 doi:10.1016/j.pbiomolbio.2013.03.015
- Gordon AM, Huxley AF, Julian FJ (1966) The variation in isometric tension with sarcomere length in vertebrate muscle fibres J Physiol 184:170-192
- Grant TM et al. (2020) Development and validation of statistical shape models of the primary functional bone segments of the foot PeerJ 8:e8397 doi:10.7717/peerj.8397

- Halilaj E, Rajagopal A, Fiterau M, Hicks JL, Hastie TJ, Delp SL (2018) Machine learning in human movement biomechanics: Best practices, common pitfalls, and new opportunities *J Biomech* 81:1-11 doi:10.1016/j.jbiomech.2018.09.009
- Hall M, Diamond LE, Lenton GK, Pizzolato C, Saxby DJ (2019) Immediate effects of valgus knee bracing on tibiofemoral contact forces and knee muscle forces *Gait Posture* 68:55-62 doi:10.1016/j.gaitpost.2018.11.009
- Hamner SR, Seth A, Delp SL (2010) Muscle contributions to propulsion and support during running *J Biomech* 43:2709-2716 doi:10.1016/j.jbiomech.2010.06.025
- Hannah I, Montefiori E, Modenese L, Prinold J, Viceconti M, Mazza C (2017) Sensitivity of a juvenile subject-specific musculoskeletal model of the ankle joint to the variability of operator-dependent input *Proceedings of the Institution of Mechanical Engineers H* 231:415-422
- Hansen W, Shim VB, Obst S, Lloyd DG, Newsham-West R, Barrett RS (2017) Achilles tendon stress is more sensitive to subject-specific geometry than subject-specific material properties: A finite element analysis *Journal of Biomechanics* 56:26-31 doi:10.1016/j.jbiomech.2017.02.031
- Hastie T, Tibshirani R (2009) Unsupervised Learning. In: *The Elements of Statistical Learning*. Springer Series in Statistics. Springer, New York, NY. doi:0.1007/978-0-387-84858-7_14
- Hastie T, Tibshirani R, Friedman J (2009) Overview of supervised Learning. In: *The Elements of Statistical Learning*. Springer Series in Statistics. Springer, New York, NY. doi:0.1007/978-0-387-84858-7_14
- Heimann T, Meinzer HP (2009) Statistical shape models for 3D medical image segmentation: a review *Medical image analysis* 13:543-563 doi:10.1016/j.media.2009.05.004
- Hemke R, Buckless CG, Tsao A, Wang B, Torriani M (2020) Deep learning for automated segmentation of pelvic muscles, fat, and bone from CT studies for body composition assessment *Skeletal radiology* 49:387-395 doi:10.1007/s00256-019-03289-8
- Hill AV (1938) The heat of shortening and the dynamic constants of muscle *Proc R Soc Ser B-Bio* 126:136-195 doi:DOI 10.1098/rspb.1938.0050
- Hoang HX, Diamond LE, Lloyd DG, Pizzolato C (2019) A calibrated EMG-informed neuromusculoskeletal model can appropriately account for muscle co-contraction in the estimation of hip joint contact forces in people with hip osteoarthritis *Journal of Biomechanics* 83:134-142 doi:10.1016/j.jbiomech.2018.11.042

- Hoang HX, Pizzolato C, Diamond LE, Lloyd DG (2018) Subject-specific calibration of neuromuscular parameters enables neuromusculoskeletal models to estimate physiologically plausible hip joint contact forces in healthy adults *J Biomech* 80:111-120 doi:10.1016/j.jbiomech.2018.08.023
- Hunter P (2016) The Virtual Physiological Human: The Physiome Project Aims to Develop Reproducible, Multiscale Models for Clinical Practice *IEEE Pulse* 7:36-42 doi:10.1109/MPUL.2016.2563841
- Hunter P et al. (2010) A vision and strategy for the virtual physiological human in 2010 and beyond *Philos Trans A Math Phys Eng Sci* 368:2595-2614 doi:10.1098/rsta.2010.0048
- Hunter P, Smith N, Fernandez J, Tawhai M (2005) Integration from proteins to organs: the IUPS Physiome Project Mechanisms of ageing and development 126:187-192 doi:10.1016/j.mad.2004.09.025
- Ivanenko YP, Poppele RE, Lacquaniti F (2006) Spinal cord maps of spatiotemporal alpha-motoneuron activation in humans walking at different speeds *J Neurophysiol* 95:602-618 doi:10.1152/jn.00767.2005
- Jinha A, Ait-Haddou R, Herzog W (2006) Predictions of co-contraction depend critically on degrees-of-freedom in the musculoskeletal model *J Biomech* 39:1145-1152 doi:10.1016/j.jbiomech.2005.03.001
- Johnson WR, Alderson J, Lloyd D, Mian A (2019a) Predicting Athlete Ground Reaction Forces and Moments From Spatio-Temporal Driven CNN Models {IEEE} *Trans Biomed Eng* 66:689-694 doi:10.1109/TBME.2018.2854632
- Johnson WR, Mian A, Donnelly CJ, Lloyd D, Alderson J (2018) Predicting athlete ground reaction forces and moments from motion capture *Med Biol Eng Comput* 56:1781-1792 doi:10.1007/s11517-018-1802-7
- Johnson WR, Mian A, Lloyd DG, Alderson JA (2019b) On-field player workload exposure and knee injury risk monitoring via deep learning *Journal of Biomechanics* Submitted
- Johnson WR, Mian A, Lloyd DG, Alderson JA (2019c) On-field player workload exposure and knee injury risk monitoring via deep learning *J Biomech* 93:185-193 doi:10.1016/j.jbiomech.2019.07.002
- Kainz H, Carty CP, Maine S, Walsh HPJ, Lloyd DG, Modenese L (2017a) Effects of hip joint centre mislocation on gait kinematics of children with cerebral palsy calculated using patient-specific direct and inverse kinematic models *Gait & Posture* 57:154-160 doi:10.1016/j.gaitpost.2017.06.002

- Kainz H, Hoang HX, Stockton C, Boyd RR, Lloyd DG, Carty CP (2017b) Accuracy and Reliability of Marker-Based Approaches to Scale the Pelvis, Thigh, and Shank Segments in Musculoskeletal Models J Appl Biomech 33:354-360 doi:10.1123/jab.2016-0282
- Kargo WJ, Nitz DA (2003) Early skill learning is expressed through selection and tuning of cortically represented muscle synergies The Journal of neuroscience : the official journal of the Society for Neuroscience 23:11255-11269
- Keenan KE, Kourtis LC, Besier TF, Lindsey DP, Gold GE, Delp SL, Beaupre GS (2009) New resource for the computation of cartilage biphasic material properties with the interpolant response surface method Comput Methods Biomech Biomed Engin 12:415-422 doi:10.1080/10255840802654319
- Keenan KE, Pal S, Lindsey DP, Besier TF, Beaupre GS (2013) A viscoelastic constitutive model can accurately represent entire creep indentation tests of human patella cartilage J Appl Biomech 29:292-302
- Keyes KM, Smith GD, Koenen KC, Galea S (2015) The mathematical limits of genetic prediction for complex chronic disease J Epidemiol Community Health 69:574-579 doi:10.1136/jech-2014-204983
- Khoury MJ, Galea S (2016) Will Precision Medicine Improve Population Health? JAMA 316:1357-1358 doi:10.1001/jama.2016.12260
- Khoury MJ, Ioannidis JP (2014) Medicine. Big data meets public health Science 346:1054-1055 doi:10.1126/science.aaa2709
- Killen BA, Saxby DJ, Fortin K, Gardiner BS, Wrigley TV, Bryant AL, Lloyd DG (2018) Individual muscle contributions to tibiofemoral compressive articular loading during walking, running and sidestepping J Biomech 80:23-31 doi:10.1016/j.jbiomech.2018.08.022
- Kim HJ, Fernandez JW, Akbarshahi M, Walter JP, Fregly BJ, Pandy MG (2009) Evaluation of predicted knee-joint muscle forces during gait using an instrumented knee implant Journal of orthopaedic research : official publication of the Orthopaedic Research Society 27:1326-1331 doi:10.1002/jor.20876
- Knoll Z, Kiss RM, Kocsis L (2004) Gait adaptation in ACL deficient patients before and after anterior cruciate ligament reconstruction surgery Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology 14:287-294 doi:10.1016/j.jelekin.2003.12.005

- Konrath JM, Saxby DJ, Killen BA, Pizzolato C, Vertullo CJ, Barrett RS, Lloyd DG (2017) Muscle contributions to medial tibiofemoral compartment contact loading following ACL reconstruction using semitendinosus and gracilis tendon grafts Plos One 12 doi:ARTN e0176016
10.1371/journal.pone.0176016
- Ku JP, Hicks JL, Hastie T, Leskovec J, Re C, Delp SL (2015) The mobilize center: an NIH big data to knowledge center to advance human movement research and improve mobility J Am Med Inform Assoc 22:1120-1125 doi:10.1093/jamia/ocv071
- Kutzner I et al. (2010) Loading of the knee joint during activities of daily living measured in vivo in five subjects Journal of Biomechanics 43:2164-2173
- Lafortune MA, Cavanagh PR, Sommer HJ, 3rd, Kalenak A (1992) Three-dimensional kinematics of the human knee during walking J Biomech 25:347-357
- Le Troter A et al. (2016) Volume measurements of individual muscles in human quadriceps femoris using atlas-based segmentation approaches. Magnetic Resonance Materials in Physics, Biology and Medicine 29:245-257
- Lee DD, Seung HS (1999) Learning the parts of objects by non-negative matrix factorization Nature 401:788-791 doi:10.1038/44565
- Lee MJ, Lloyd DG, Lay BS, Bourke PD, Alderson JA (2013) Effects of different visual stimuli on postures and knee moments during sidestepping Med Sci Sports Exerc 45:1740-1748 doi:10.1249/MSS.0b013e318290c28a
- Lee S, Park M, Lee K, Lee J (2019) Scalable muscle-actuated human simulation and control ACM Transactions on Graphics (TOG) 38:73
- Lenhart RL, Kaiser J, Smith CR, Thelen DG (2015) Prediction and Validation of Load-Dependent Behavior of the Tibiofemoral and Patellofemoral Joints During Movement Ann Biomed Eng 43:2675-2685 doi:10.1007/s10439-015-1326-3
- Lenton GK, Bishop PJ, Saxby DJ, Doyle TLA, Pizzolato C, Billing D, Lloyd DG (2018) Tibiofemoral joint contact forces increase with load magnitude and walking speed but remain almost unchanged with different types of carried load Plos One 13:e0206859 doi:10.1371/journal.pone.0206859
- Lerner ZF, DeMers MS, Delp SL, Browning RC (2015) How tibiofemoral alignment and contact locations affect predictions of medial and lateral tibiofemoral contact forces Journal of Biomechanics 48:644-650 doi:10.1016/j.jbiomech.2014.12.049

- Liu F et al. (2018) Deep Learning Approach for Evaluating Knee MR Images: Achieving High Diagnostic Performance for Cartilage Lesion Detection *Radiology* 289:160-169 doi:10.1148/radiol.2018172986
- Lloyd DG, Besier TF (2003) An EMG-driven musculoskeletal model to estimate muscle forces and knee joint moments in vivo *J Biomech* 36:765-776 doi:10.1016/s0021-9290(03)00010-1
- Lund ME, de Zee M, Andersen MS, Rasmussen J (2012) On validation of multibody musculoskeletal models *Proc Inst Mech Eng H* 226:82-94 doi:10.1177/0954411911431516
- Marra MA, Vanheule V, Fluit R, Koopman BH, Rasmussen J, Verdonchot N, Andersen MS (2015) A subject-specific musculoskeletal modeling framework to predict in vivo mechanics of total knee arthroplasty *J Biomech Eng* 137:020904 doi:10.1115/1.4029258
- McGowan CP, Neptune RR, Clark DJ, Kautz SA (2010) Modular control of human walking: Adaptations to altered mechanical demands *J Biomech* 43:412-419 doi:10.1016/j.jbiomech.2009.10.009
- Menegaldo LL, de Toledo Fleury A, Weber HI (2004) Moment arms and musculotendon lengths estimation for a three-dimensional lower-limb model *J Biomech* 37:1447-1453 doi:10.1016/j.jbiomech.2003.12.017
- Menegaldo LL, de Toledo Fleury A, Weber HI (2006) A 'cheap' optimal control approach to estimate muscle forces in musculoskeletal systems *J Biomech* 39:1787-1795 doi:10.1016/j.jbiomech.2005.05.029
- Millard M, Uchida T, Seth A, Delp SL (2013) Flexing computational muscle: modeling and simulation of musculotendon dynamics *J Biomech Eng* 135:021005 doi:10.1115/1.4023390
- Modenese L, Kohout J (2020) Automated Generation of Three-Dimensional Complex Muscle Geometries for Use in Personalised Musculoskeletal Models *Ann Biomed Eng* doi:10.1007/s10439-020-02490-4
- Modenese L, Montefiori E, Wang AQ, Wesarg S, Viceconti M, Mazza C (2018) Investigation of the dependence of joint contact forces on musculotendon parameters using a codified workflow for image-based modelling *Journal of Biomechanics* 73:108-118 doi:10.1016/j.jbiomech.2018.03.039
- Montefiori E et al. (2019a) An image-based kinematic model of the tibiotalar and subtalar joints and its application to gait analysis in children with Juvenile Idiopathic Arthritis. *Journal of Biomechanics* *Journal of biomechanics* 85:27-36

- Montefiori E et al. (2019b) An image-based kinematic model of the tibiotalar and subtalar joints and its application to gait analysis in children with Juvenile Idiopathic Arthritis *J Biomech* 85:27-36 doi:10.1016/j.jbiomech.2018.12.041
- Myller KAH, Korhonen RK, Toyraas J, Salo J, Jurvelin JS, Venalainen MS (2019) Computational evaluation of altered biomechanics related to articular cartilage lesions observed in vivo *Journal of orthopaedic research : official publication of the Orthopaedic Research Society* 37:1042-1051 doi:10.1002/jor.24273
- Navacchia A, Kefala V, Shelburne KB (2017) Dependence of Muscle Moment Arms on In Vivo Three-Dimensional Kinematics of the Knee *Ann Biomed Eng* 45:789-798 doi:10.1007/s10439-016-1728-x
- Neilson PD, Neilson MD (2010) On theory of motor synergies *Human movement science* 29:655-683 doi:10.1016/j.humov.2009.10.005
- Neubert A, Fripp J, Engstrom C, Schwarz D, Weber MA, Crozier S (2015) Statistical shape model reconstruction with sparse anomalous deformations: Application to intervertebral disc herniation *Computerized medical imaging and graphics : the official journal of the Computerized Medical Imaging Society* 46 Pt 1:11-19 doi:10.1016/j.compmedimag.2015.05.002
- Neubert A et al. (2016) Automatic segmentation of the glenohumeral cartilages from magnetic resonance images *Medical physics* 43:5370 doi:10.1118/1.4961011
- Ni R, Meyer CH, Blemker SS, Hart JM, Feng X (2019) Automatic segmentation of all lower limb muscles from high-resolution magnetic resonance imaging using a cascaded three-dimensional deep convolutional neural network *Journal of medical imaging (Bellingham, Wash)* 6:044009 doi:10.1117/1.jmi.6.4.044009
- Nikolopoulos FP, Zacharaki EI, Stanev D, Moustakas K (2020) Personalized Knee Geometry Modeling Based on Multi-Atlas Segmentation and Mesh Refinement *IEEE Access* 8:56766-56781
- Nolte D, Kit Tsang C, Yu Zhang K, Ding Z, Kedgley AE, Bull AMJ (2016a) Non-linear scaling of a musculoskeletal model of the lower limb using statistical shape models *Journal of Biomechanics* 49:3576-3581
- Nolte D, Ko ST, Bull AMJ, Kedgley AE (2020) Reconstruction of the lower limb bones from digitised anatomical landmarks using statistical shape modelling *Gait Posture* 77:269-275 doi:10.1016/j.gaitpost.2020.02.010
- Nolte D, Tsang CK, Zhang KY, Ding Z, Kedgley AE, Bull AMJ (2016b) Non-linear scaling of a musculoskeletal model of the lower limb using statistical shape models *J Biomech* 49:3576-3581 doi:10.1016/j.jbiomech.2016.09.005

- O'Connor JD, Rutherford M, Bennett D, Hill JC, Beverland DE, Dunne NJ, Lennon AB (2018) Long-term hip loading in unilateral total hip replacement patients is no different between limbs or compared to healthy controls at similar walking speeds *Journal of Biomechanics* 80:8-15 doi:10.1016/j.jbiomech.2018.07.033
- Ong CF, Geijtenbeek T, Hicks JL, Delp SL (2019) Predicting gait adaptations due to ankle plantarflexor muscle weakness and contracture using physics-based musculoskeletal simulations *PLoS Comput Biol* 15:e1006993 doi:10.1371/journal.pcbi.1006993
- Pandy MG, Andriacchi TP (2010) Muscle and joint function in human locomotion *Annu Rev Biomed Eng* 12:401-433 doi:10.1146/annurev-bioeng-070909-105259
- Pena E, Calvo B, Martinez MA, Doblare M (2006) A three-dimensional finite element analysis of the combined behavior of ligaments and menisci in the healthy human knee joint *J Biomech* 39:1686-1701 doi:10.1016/j.jbiomech.2005.04.030
- Peng XB, Abbeel P, Levine S, van de Panne M (2018) Deepmimic: Example-guided deep reinforcement learning of physics-based character skills *ACM Transactions on Graphics (TOG)* 37:143
- Peng XB, Berseth G, Yin K, Van De Panne M (2017) Deeploco: Dynamic locomotion skills using hierarchical deep reinforcement learning *ACM Transactions on Graphics (TOG)* 36:41
- Perez-Nombela S et al. (2017) Modular control of gait after incomplete spinal cord injury: differences between sides *Spinal Cord* 55:79-86 doi:10.1038/sc.2016.99
- Pizzolato C, Lloyd DG, Barrett RS, Cook JL, Zheng MH, Besier TF, Saxby DJ (2017a) Bioinspired Technologies to Connect Musculoskeletal Mechanobiology to the Person for Training and Rehabilitation *Frontiers in computational neuroscience* 11:96 doi:10.3389/fncom.2017.00096
- Pizzolato C, Lloyd DG, Sartori M, Ceseracciu E, Besier TF, Fregly BJ, Reggiani M (2015) CEINMS: A toolbox to investigate the influence of different neural control solutions on the prediction of muscle excitation and joint moments during dynamic motor tasks *J Biomech* 48:3929-3936 doi:10.1016/j.jbiomech.2015.09.021
- Pizzolato C et al. (2019a) Finding the sweet spot via personalised Achilles tendon training: the future is within reach *British journal of sports medicine* 53:11-12 doi:10.1136/bjsports-2018-099020
- Pizzolato C, Reggiani M, Modenese L, Lloyd DG (2017b) Real-time inverse kinematics and inverse dynamics for lower limb applications using OpenSim *Comput*

- Pizzolato C, Reggiani M, Saxby DJ, Ceseracciu E, Modenese L, Lloyd DG (2017c) Biofeedback for Gait Retraining Based on Real-Time Estimation of Tibiofemoral Joint Contact Forces IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society 25:1612-1621 doi:10.1109/TNSRE.2017.2683488
- Pizzolato C, Shim V, Besier TF, Devaprakash D, Barrett RS, Lloyd DG Real-time estimation of localised Achilles tendon strain using a multiscale EMG-informed neuromusculoskeletal model. In: XXVII Congress of the International Society of Biomechanics, Calgary, Canada, July 31-August 4 2019b.
- Rajagopal A, Dembia CL, DeMers MS, Delp DD, Hicks JL, Delp SL (2016) Full-Body Musculoskeletal Model for Muscle-Driven Simulation of Human Gait {IEEE} Trans Biomed Eng 63:2068-2079 doi:10.1109/TBME.2016.2586891
- Rane L, Ding Z, McGregor AH, Bull AMJ (2019) Deep Learning for Musculoskeletal Force Prediction Ann Biomed Eng 47:778-789 doi:10.1007/s10439-018-02190-0
- Rodriguez-Florez N et al. (2017) Statistical shape modelling to aid surgical planning: associations between surgical parameters and head shapes following spring-assisted cranioplasty Int J Comput Assist Radiol Surg 12:1739-1749 doi:10.1007/s11548-017-1614-5
- Saey TH (2018) What genetic tests from 23andMe, Veritas and Genos really told me about my health vol 193.
- Sancisi N, Baldisserri B, Parenti-Castelli V, Belvedere C, Leardini A (2014) One-degree-of-freedom spherical model for the passive motion of the human ankle joint Med Biol Eng Comput 52:363-373 doi:10.1007/s11517-014-1137-y
- Sancisi N, Parenti-Castelli V (2011) A New Kinematic Model of the Passive Motion of the Knee Inclusive of the Patella J Mech Robot 3:1-7 doi:Artn 041003
10.1115/1.4004890
- Sartori M, Durandau G, Dosen S, Farina D (2018) Robust simultaneous myoelectric control of multiple degrees of freedom in wrist-hand prostheses by real-time neuromusculoskeletal modeling J Neural Eng 15:066026 doi:10.1088/1741-2552/aae26b
- Sartori M, Farina D, Lloyd DG (2014) Hybrid neuromusculoskeletal modeling to best track joint moments using a balance between muscle excitations derived from

- electromyograms and optimization J Biomech 47:3613-3621
doi:10.1016/j.jbiomech.2014.10.009
- Sartori M, Gizzi L, Lloyd DG, Farina D (2013) A musculoskeletal model of human locomotion driven by a low dimensional set of impulsive excitation primitives Frontiers in computational neuroscience 7:79 doi:10.3389/fncom.2013.00079
- Sartori M, Lloyd DG, Farina D (2016) Neural Data-Driven Musculoskeletal Modeling for Personalized Neurorehabilitation Technologies IEEE Transactions on Biomedical Engineering 63:879-893
- Sartori M, Reggiani M, Farina D, Lloyd DG (2012a) EMG-driven forward-dynamic estimation of muscle force and joint moment about multiple degrees of freedom in the human lower extremity Plos One 7:e52618
doi:10.1371/journal.pone.0052618
- Sartori M, Reggiani M, van den Bogert AJ, Lloyd DG (2012b) Estimation of musculotendon kinematics in large musculoskeletal models using multidimensional B-splines J Biomech 45:595-601
doi:10.1016/j.jbiomech.2011.10.040
- Sasaki K Muscle Contributions To The Tibiofemoral Joint Contact Force During Running. In: Rocky Mountain Bioengineering Symposium & Internatioanl ISA Biomedical Sciences Instrumentation Symposium, Laramie, Wyoming, 2010.
- Saxby DJ et al. (2016a) Tibiofemoral Contact Forces in the Anterior Cruciate Ligament-Reconstructed Knee Med Sci Sports Exerc 48:2195-2206
doi:10.1249/MSS.0000000000001021
- Saxby DJ et al. (2017) Relationships Between Tibiofemoral Contact Forces and Cartilage Morphology at 2 to 3 Years After Single-Bundle Hamstring Anterior Cruciate Ligament Reconstruction and in Healthy Knees Orthopaedic journal of sports medicine 5:2325967117722506 doi:10.1177/2325967117722506
- Saxby DJ et al. (2016b) Tibiofemoral contact forces during walking, running and sidestepping Gait Posture 49:78-85 doi:10.1016/j.gaitpost.2016.06.014
- Schache AG, Dorn TW, Blanch PD, Brown NA, Pandy MG (2012) Mechanics of the human hamstring muscles during sprinting Med Sci Sports Exerc 44:647-658
doi:10.1249/MSS.0b013e318236a3d2
- Scheys L, Jonkers I, Loeckx D, Maes F, Spaepen A, Suetens P (2006) Image based musculoskeletal modeling allows personalized biomechanical analysis of gait Lect Notes Comput Sc 4072:58-66

- Sciences TAoM (2016) Improving the health of the public by 2040. The Academy of Medical Sciences,
- Serrancoli G, Kinney AL, Fregly BJ, Font-Llagunes JM (2016) Neuromusculoskeletal Model Calibration Significantly Affects Predicted Knee Contact Forces for Walking J Biomech Eng-T Asme 138:1-11 doi:Artn 081001
- 10.1115/1.4033673
- Seth A et al. (2018) OpenSim: Simulating musculoskeletal dynamics and neuromuscular control to study human and animal movement PLoS Comput Biol 14:e1006223 doi:10.1371/journal.pcbi.1006223
- Shao Q, Bassett DN, Manal K, Buchanan TS (2009) An EMG-driven model to estimate muscle forces and joint moments in stroke patients Comput Biol Med 39:1083-1088 doi:10.1016/j.compbimed.2009.09.002
- Shelburne KB, Torry MR, Pandy MG (2006) Contributions of muscles, ligaments, and the ground-reaction force to tibiofemoral joint loading during normal gait Journal of orthopaedic research : official publication of the Orthopaedic Research Society 24:1983-1990 doi:10.1002/jor.20255
- Shim V, Pizzolato C, Fernandez JW, Zhang J, Besier TF, Barrett RS, Lloyd DG Combining finite element analysis with a machine learning technique for rapid prediction of subject-specific Achilles tendon tissue stress. In: XXVII Congress of the International Society of Biomechanics, Calgary, Canada, July 31-August 4 2019a.
- Shim VB, Besier TF, Lloyd DG, Mithraratne K, Fernandez JF (2016) The influence and biomechanical role of cartilage split line pattern on tibiofemoral cartilage stress distribution during the stance phase of gait Biomech Model Mechanobiol 15:195-204 doi:10.1007/s10237-015-0668-y
- Shim VB et al. (2019b) Influence of altered geometry and material properties on tissue stress distribution under load in tendinopathic Achilles tendons - A subject-specific finite element analysis J Biomech 82:142-148 doi:10.1016/j.jbiomech.2018.10.027
- Shuman BR, Schwartz MH, Steele KM (2017) Electromyography Data Processing Impacts Muscle Synergies during Gait for Unimpaired Children and Children with Cerebral Palsy Frontiers in computational neuroscience 11:50 doi:10.3389/fncom.2017.00050

- Smith AJ, Lloyd DG, Wood DJ (2006) A kinematic and kinetic analysis of walking after total knee arthroplasty with and without patellar resurfacing *Clin Biomech* 21:379-386 doi:10.1016/j.clinbiomech.2005.11.007
- Smith CR, Lenhart RL, Kaiser J, Vignos MF, Thelen DG (2016) Influence of Ligament Properties on Tibiofemoral Mechanics in Walking *The journal of knee surgery* 29:99-106 doi:10.1055/s-0035-1558858
- Smith DW et al. (2013) A conceptual framework for computational models of Achilles tendon homeostasis *Wiley interdisciplinary reviews Systems biology and medicine* 5:523-538 doi:10.1002/wsbm.1229
- Soechting JF, Lacquaniti F (1989) An assessment of the existence of muscle synergies during load perturbations and intentional movements of the human arm *Experimental brain research* 74:535-548
- Spoor CW, van Leeuwen JL, Meskers CG, Titulaer AF, Huson A (1990) Estimation of instantaneous moment arms of lower-leg muscles *J Biomech* 23:1247-1259 doi:10.1016/0021-9290(90)90382-d
- Stagni R, Fantozzi S, Cappello A, Leardini A (2005) Quantification of soft tissue artefact in motion analysis by combining 3D fluoroscopy and stereophotogrammetry: a study on two subjects *Clin Biomech* 20:320-329 doi:<http://dx.doi.org/10.1016/j.clinbiomech.2004.11.012>
- Suwarganda EK et al. (2019) Minimal medical imaging can accurately reconstruct geometric bone models for musculoskeletal models *Plos One* 14 doi:ARTN e0205628
10.1371/journal.pone.0205628
- Taddei F, Martelli S, Valente G, Leardini A, Benedetti MG, Manfrini M, Viceconti M (2012) Femoral loads during gait in a patient with massive skeletal reconstruction *Clin Biomech (Bristol, Avon)* 27:273-280 doi:10.1016/j.clinbiomech.2011.09.006
- Thelen DG, Anderson FC (2006) Using computed muscle control to generate forward dynamic simulations of human walking from experimental data *J Biomech* 39:1107-1115 doi:10.1016/j.jbiomech.2005.02.010
- Ting LH, McKay JL (2007) Neuromechanics of muscle synergies for posture and movement *Curr Opin Neurobiol* 17:622-628 doi:10.1016/j.conb.2008.01.002
- Tresch MC, Cheung VC, d'Avella A (2006) Matrix factorization algorithms for the identification of muscle synergies: evaluation on simulated and experimental data sets *J Neurophysiol* 95:2199-2212 doi:10.1152/jn.00222.2005

- Valente G, Crimi G, Vanella N, Schileo E, Taddei F (2017) nmsBuilder: Freeware to create subject-specific musculoskeletal models for OpenSim *Comput Methods Programs Biomed* 152:85-92 doi:10.1016/j.cmpb.2017.09.012
- van den Bogert AJ, Geijtenbeek T, Even-Zohar O, Steenbrink F, Hardin EC (2013) A real-time system for biomechanical analysis of human movement and muscle function *Med Biol Eng Comput* 51:1069-1077 doi:10.1007/s11517-013-1076-z
- van den Noort F, van der Vaart CH, Grob ATM, van de Waarsenburg MK, Slump CH, van Stralen M (2018) Deep learning enables automatic quantitative assessment of the puborectalis muscle and the urogenital hiatus in the plane of minimal hiatal dimensions *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* doi:10.1002/uog.20181
- van der Krogt MM, Bar-On L, Kindt T, Desloovere K, Harlaar J (2016) Neuro-musculoskeletal simulation of instrumented contracture and spasticity assessment in children with cerebral palsy *J Neuroeng Rehabil* 13:64 doi:10.1186/s12984-016-0170-5
- Van Dijck C, Wirix-Speetjens R, Jonkers I, Vander Sloten J (2018) Statistical shape model-based prediction of tibiofemoral cartilage *Comput Methods Biomech Biomed Engin*:1-11 doi:10.1080/10255842.2018.1495711
- Varzi D, Coupaud SAF, Purcell M, Allan DB, Gregory JS, Barr RJ (2015) Bone morphology of the femur and tibia captured by statistical shape modelling predicts rapid bone loss in acute spinal cord injury patients *Bone* 81:495-501 doi:10.1016/j.bone.2015.08.026
- Viceconti M, Hunter P (2016) The Virtual Physiological Human: Ten Years After *Annu Rev Biomed Eng* 18:103-123 doi:10.1146/annurev-bioeng-110915-114742
- Viceconti M, Hunter P, Hose R (2015) Big data, big knowledge: big data for personalized healthcare *IEEE J Biomed Health Inform* 19:1209-1215 doi:10.1109/JBHI.2015.2406883
- Viceconti M, Juarez MA, Curreli C, Pennisi M, Russo G, Pappalardo F (2020a) Credibility of In Silico Trial Technologies-A Theoretical Framing *IEEE J Biomed Health Inform* 24:4-13 doi:10.1109/jbhi.2019.2949888
- Viceconti M, Pappalardo F, Rodriguez B, Horner M, Bischoff J, Musuamba Tshinanu F (2020b) In silico trials: Verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products *Methods (San Diego, Calif)* doi:10.1016/j.ymeth.2020.01.011

- Vrancken AC et al. (2014) 3D geometry analysis of the medial meniscus--a statistical shape modeling approach *Journal of anatomy* 225:395-402 doi:10.1111/joa.12223
- Walter JP, Kinney AL, Banks SA, D'Lima DD, Besier TF, Lloyd DG, Fregly BJ (2014) Muscle synergies may improve optimization prediction of knee contact forces during walking *J Biomech Eng* 136:021031 doi:10.1115/1.4026428
- Weiss JA, Gardiner JC, Bonifasi-Lista C (2002) Ligament material behavior is nonlinear, viscoelastic and rate-independent under shear loading *J Biomech* 35:943-950
- Wellsandt E, Gardiner ES, Manal K, Axe MJ, Buchanan TS, Snyder-Mackler L (2016) Decreased Knee Joint Loading Associated With Early Knee Osteoarthritis After Anterior Cruciate Ligament Injury *The American journal of sports medicine* 44:143-151 doi:10.1177/0363546515608475
- Wesseling M, De Groote F, Bosmans L, Bartels W, Meyer C, Desloovere K (2016a) Subject-specific geometrical detail rather than cost function formulation affects hip loading calculation *Computer Methods in Biomechanics and Biomedical Engineering* 19:1475-1488
- Wesseling M, De Groote F, Meyer C, Corten K, Simon JP, Desloovere K, Jonkers I (2016b) Subject-specific musculoskeletal modelling in patients before and after total hip arthroplasty *Computer Methods in Biomechanics and Biomedical Engineering* 19:1683-1691
- Williams TG et al. (2010) Anatomically corresponded regional analysis of cartilage in asymptomatic and osteoarthritic knees by statistical shape modelling of the bone *IEEE Trans Med Imaging* 29:1541-1559 doi:10.1109/TMI.2010.2047653
- Wu T, Martens H, Hunter P, Mithraratne K (2014) Emulating facial biomechanics using multivariate partial least squares surrogate models *Int J Numer Method Biomed Eng* 30:1103-1120 doi:10.1002/cnm.2646
- Xia Y, Chandra SS, Engstrom C, Strudwick MW, Crozier S, Fripp J (2014) Automatic hip cartilage segmentation from 3D MR images using arc-weighted graph searching *Physics in medicine and biology* 59:7245-7266 doi:10.1088/0031-9155/59/23/7245
- Yang NH, Nayeb-Hashemi H, Canavan PK, Vaziri A (2010) Effect of frontal plane tibiofemoral angle on the stress and strain at the knee cartilage during the stance phase of gait *Journal of orthopaedic research : official publication of the Orthopaedic Research Society* 28:1539-1547 doi:10.1002/jor.21174

- Yang Z et al. (2015) Automatic bone segmentation and bone-cartilage interface extraction for the shoulder joint from magnetic resonance images *Physics in medicine and biology* 60:1441-1459 doi:10.1088/0031-9155/60/4/1441
- Yeung S, Fernandez JW, Handsfield GG, Walker C, Besier TF, Zhang J (2019) Rapid muscle volume prediction using anthropometric measurements and population-derived statistical models *Biomech Model Mechanobiol* doi:10.1007/s10237-019-01243-0
- Young People With Old Knees Research T et al. (2017) Relationships Between Tibiofemoral Contact Forces and Cartilage Morphology at 2 to 3 Years After Single-Bundle Hamstring Anterior Cruciate Ligament Reconstruction and in Healthy Knees *Orthopaedic journal of sports medicine* 5:2325967117722506 doi:10.1177/2325967117722506
- Zajac FE (1989) Muscle and tendon: properties, models, scaling, and application to biomechanics and motor control *Crit Rev Biomed Eng* 17:359-411
- Zhang H, Totterman S, Perucchio R, Lerner AL Magnetic Resonance Image Based 3D Poroelastic Finite Element Model of Tibio-menisco-femoral Contact. In: 23rd Proceedings of the American Society of Biomechanics, 1999. pp 198-199
- Zhang J, Besier TF (2017) Accuracy of femur reconstruction from sparse geometric data using a statistical shape model *Comput Methods Biomech Biomed Engin* 20:566-576 doi:10.1080/10255842.2016.1263301
- Zhang J, Fernandez J, Hislop-Jambrich J, Besier TF Lower Limb Bone Shape and Pose Estimation from Sparse Landmarks Using an Articulated Shape Model. In: *Computer Method in Biomechanics and Biomedical Engineering (CMBBE)*, Montreal, Canada, 2015.
- Zhang J, Fernandez J, Hislop-Jambrich J, Besier TF (2016) Lower limb estimation from sparse landmarks using an articulated shape model *J Biomech* 49:3875-3881 doi:10.1016/j.jbiomech.2016.10.021
- Zhang J et al. The MAP Client: User Friendly Musculoskeletal Modelling Workflows. In: Bello F, Cotin S (eds) *International Symposium on Biomedical Simulation*, Strasbourg, France, 2014. Springer, pp 182-192
- Zhou Z, Zhao G, Kijowski R, Liu F (2018) Deep convolutional neural network for segmentation of knee joint anatomy *Magn Reson Med* 80:2759-2770 doi:10.1002/mrm.27229

- Ziaeipoor H, Martelli S, Pandy M, Taylor M (2019a) Efficacy and efficiency of multivariate linear regression for rapid prediction of femoral strain fields during activity Med Eng Phys 63:88-92 doi:10.1016/j.medengphy.2018.12.001
- Ziaeipoor H, Taylor M, Martelli S (2020) Population-Based Bone Strain During Physical Activity: A Novel Method Demonstrated for the Human Femur Ann Biomed Eng doi:10.1007/s10439-020-02483-3
- Ziaeipoor H, Taylor M, Pandy M, Martelli S (2019b) A novel training-free method for real-time prediction of femoral strain J Biomech 86:110-116 doi:10.1016/j.jbiomech.2019.01.057

Figure 1

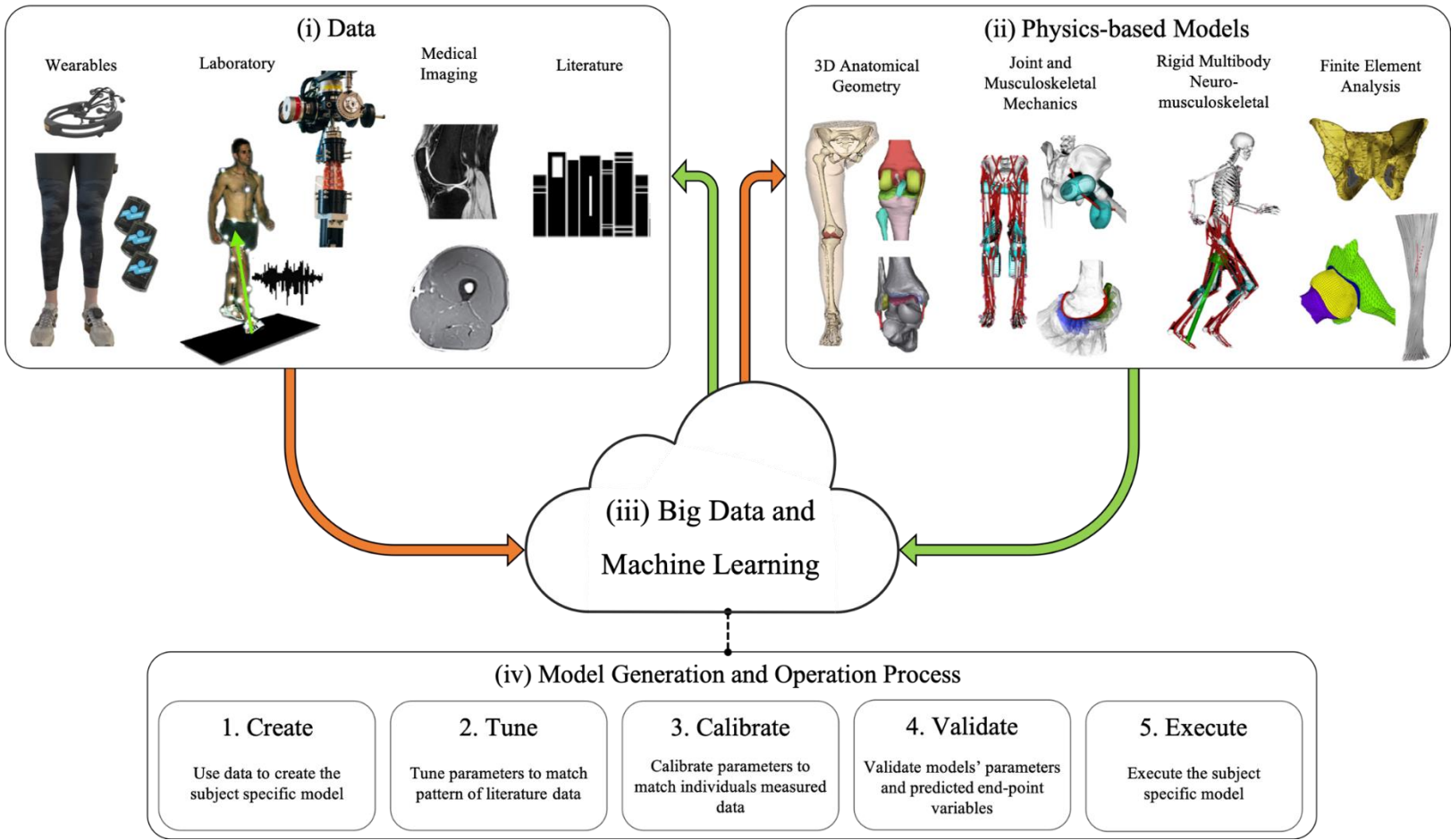


Figure 2

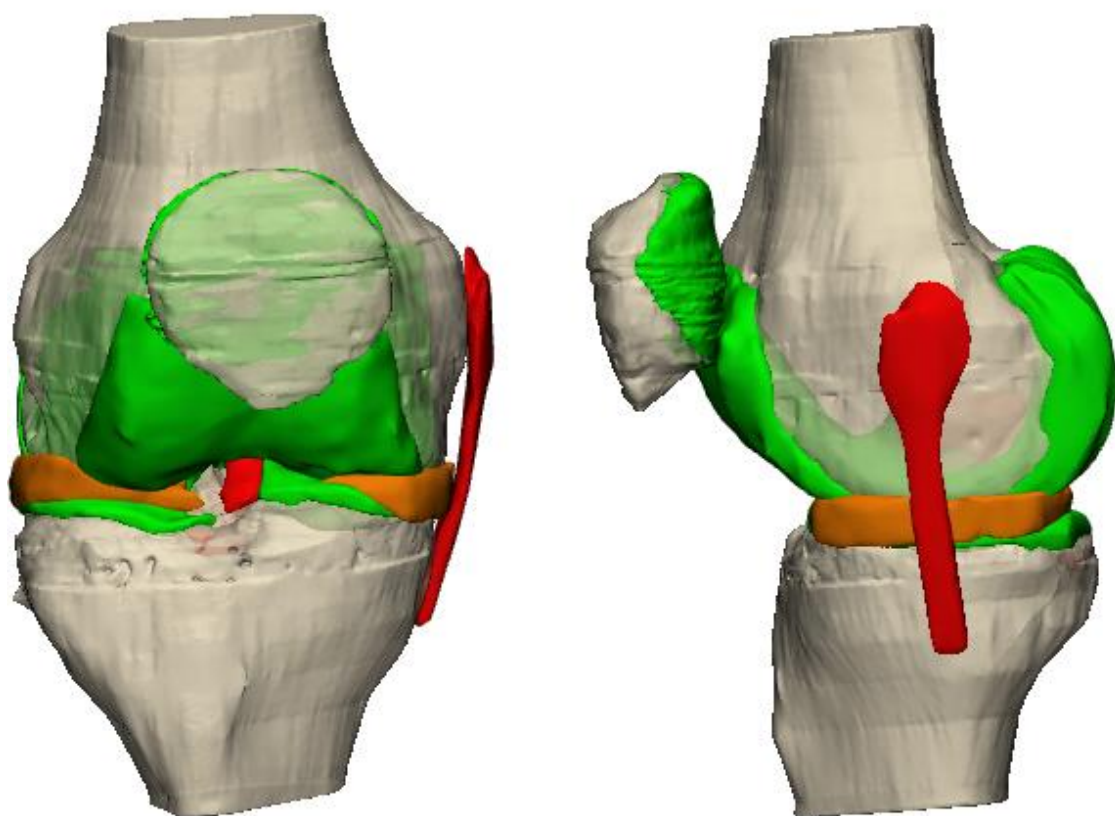


Table 1

Model Personalisation Feature	Feature Extraction	Synthesising Missing Data	Model Generation	Model Execution	Data Digitisation and Processing
<i>1. Segmental and Skeletal</i>					
†Underlying mechanical model	MLSR	-	-	MLSR	-
*Morphometry	PCA	PCA	PCA	-	CNN, PCA
‡Mechanical model parameters	MLSR	MLSR	MLSR	MLSR	-
<i>2. Musculotendon Unit</i>					
†Underlying mechanical model	PLSR	-	-	PLSR	-
*Morphometry	PCA, B-Splines, Polynomials	PCA	PCA	B Splines, Polynomials	CNN, PCA
‡Mechanical model parameters	-	-	-	-	-
<i>3. Joint</i>					
†Underlying mechanical model	Splines, DNN	-	-	Splines, DNN	-
*Morphometry	PCA	PCA	PCA	-	-
‡Mechanical model parameters	-	-	-	-	-
<i>4. Muscle Activation Patterns</i>					
	NNMF, GP	NNMF, GP	-	NNMF, GP	CNN
<i>5&6. Movement and External loading</i>					
	CNN, PCA, PLSR	CNN, PCA, PLSR	-	CNN, PCA, PLSR	-

†-CNN=Convolution neural network; DNN=Deep neural network; PCA=Principle component analysis; MLSR= Multivariate least squares regression; PLSR= Partial least squares regression; NNMF= Non-negative matrix factorisation; GP=Gaussian primitives

†Underlying mechanical model concerns the type of mechanical model (e.g., rigid multi-body, finite element method, Hill-type muscle model) and data produced (e.g., kinematics, forces, tissue stress and strain)

*Morphometry regards the static quantitative three-dimensional external and internal anatomical structural model representation

‡Mechanical model parameters pertain to parameters that define how the mechanical model operates (e.g., Young's modulus, Poisson's ratio, tendon slack length, and muscle optimal fibre length)

[Click here to view linked References](#)

Figure captions

Figure 1. Schematic representation of the proposed framework to develop and use subject-specific neuromusculoskeletal models. Schematic shows each of the five steps to generate and operate models from the different forms of input data.

Figure 2. (A) Anterior and (B) medial view of three-dimensional reconstruction of the tibiofemoral joint with detailed segmentations of the bones (cream), cartilage (green), ligaments (red), and menisci (orange). This model is used for rapid development of a close-chain mechanism of subject-specific knee motion.