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	
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	Queensland Motor Accident Insurance Commission (BioSpine)	Dr Claudio Pizzolato
	BioMedTechHorizons	

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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

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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; Ziaei-poor 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.

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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)

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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.