



Mini Review

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A Review for Machine Learning Applications in Characterizing Biomaterials and Biological Materials Properties

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Abstract

Characterizing specific mechanical properties for biological materials and biomaterials remains an exciting topic within several research fields. The functionality of biological materials and biomaterials relies on their mechanical properties, such as elastic and shear modulus. While several sophisticated experimental techniques can perform in vivo and in vitro to characterize the material properties, the measurement exhibits a broad uncertainty due to the limitations in diagnostics and experimental randomness. Alternatively, Machine learning approaches evolve as an efficient and striking tool to process a massive amount of complex data sets simultaneously and discover the hidden correlation between the materials structure and dynamic responses. This work briefly reviews the advanced applications of machine learning algorithms in studies of the dynamic behavior of biological materials and the development of biomaterials. It is evident that machine learning approaches can significantly impact the clinical development in biomedical engineering and healthcare.

Keywords: Biological materials; Biomaterials; Machine learning; Material characterization

Abbreviations: ML: Machine Learning; AFM: Atomic Force Microscopy; OT: Optical Tweezers; OCT: Coherence Tomography; OCE: Optical Coherence Elastography; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; SVM: support-vector machines; ANN: Artificial neural networks; CNN Convolutional neural networks; GPs: Gaussian processes; GA: Genetic algorithms; AV: aortic valve

Introduction

Biological materials are natural biocompatible materials present inside living organisms, while biomaterials are typically synthetic and engineered to interact with biological systems. Characterizing mechanical properties of biological materials is crucial for disease diagnosis because the alteration of mechanical properties directly relates to disease progression. For instance, calcified human leaflet becomes severe stiff, leading to aortic stenosis and the cell disease are related to increasing stiffness and adhesiveness [1-2]. Furthermore, the mechanical properties of biomaterials affect their interaction with biological systems [3]. The mechanical properties generally imply elasticity, stiffness and viscosity, quantitatively extracted from experimental measurements. The length scale of biological material and biomaterials can range from nanometer to millimeters, beyond the feasibility of traditional

tension and compression tests. Therefore, multiple advanced probing techniques have been developed and accomplished great success in the past. For instance, Atomic Force Microscopy (AFM) and Optical Tweezers (OT) are utilized in nano- and micrometer-scale detection [4-5]. AFM technique is usually used to measure the cell and tissue viscoelastic properties by correlating the material deformation and the force applied to the indenters. OT utilizes the laser to generate the repulsive force acting on the cell materials and obtain specific mechanical properties. Although those techniques can reach a substantially small scale, they are destructive testing and hardly maintain the physiological environment for cells and tissue. Moreover, the measurement can only perform at single-cell and tissue levels, which is highly time-consuming for cell and tissue screening. Alternatively, Confocal Microscopy, Coherence



Tomography (OCT) and Optical Coherence Elastography (OCE) can generate measurement images in micrometers scales based on the interferometry principle [6-8]. Their applications are limited in the regime between cells and organs; those techniques generally suffer from speckle decorrelation noise, especially for dense tissue materials [9]. Moreover, the living human tissue is limited by availability. Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and ultrasound can perform millimeter-scale measurements to reconstruct the 3D geometric image for further diagnosis and they are non-invasive techniques [10-12]. However, those techniques typically record the material deformation in the vicinity of body fluid and perform a reverse calculation for material properties, such that the knowledge of relative boundary conditions is required. The non- simultaneously measurement of body fluid will also introduce more system uncertainty toward material characterization. Moreover, the rapid development of biomaterials requires the realization of mechanical properties and the understanding of their biocompatibility and their performance within biological systems. For instance, the toxicity of metallic biomaterial, chemical and thermal properties of ceramic biomaterials is within this field's scope [13]. All these requirements bring extra challenges to current experimental measurement.

Alternatively, Machine learning algorithms can overcome those limitations within current experimental techniques. They are more cost-friendly and can achieve a fast analysis of a large amount of data. The data source can either be obtained by experimental measurement or collected from the online database or previous reports. ML has progressively fascinated many researchers over the past two decades, from the application in computer science at the very beginning to broad disciplines such as engineering, biological and medical researches. There are broadly two major categories depending on learning style: supervised and unsupervised learning; while supervised learning requires user- defined labeling for input data, unsupervised learning demands the computer to discover hidden patterns from un-labeled data [14,15]. An ML procedure generally includes input data preparation, model creation, training and predictions. The implementation of the ML model becomes increasingly convenient nowadays with the help of various platforms such as TensorFlow and Sklearn. The most representative ML models include but are not limited to support-vector machines (SVM), Artificial neural networks/Convolutional networks (ANN/CNN), Gaussian processes (GPs), and Genetic algorithms (GA) and Regression analysis, etc. [16-19]. This paper briefly reviews the current state-of-the-art ML algorithms for the applications in biological materials and biomaterials, including multi- physics and multi-scales, natural or synthetic materials.

Machine Learning Application for Biological Materials

Biological materials typically refer to natural materials that are viable and capable of self-repairing. Human cells, tissue and organ are the most common biological materials. The ML approaches at the cell level focus on the characterization and classification of cell membrane properties under various pathophysiological conditions. Several studies have reported the exciting application of ML in Red Blood Cells (RBC) classification [20-24]. Several experimental techniques are utilized for extracting the cell features that provides input data set for ML purposes. Moreover, various cell types are studied by ML classification, such as circulating tumor cells, lymphoid cells, blast and stem cells, etc. [25-30]. The state-of-the-art ML algorithms, such as Regression analysis, SVM and ANN/CNN, have been employed and discussed in the references. One of the most significant contributions in their work is utilizing the ML method to elucidate the relation between cell morphology and cell disorders, facilitating an efficient screening for cell diseases. Furthermore, ML approaches are applied to estimate the specific elastic properties of the material at the tissue scale, such as the vascular and collagen tissues [31,32]. The random forest regression algorithm and ANN are also utilized to invert the Monte Carlo simulations for the extraction of tissue optical properties [33-35] and improve the awareness of tissue damage mechanisms.

At the organ level, CNN using radio frequency data is adopted to understand the liver and breast deformation [36]. The authors considered a mixture of simulation and experimental results as model inputs. K-Means analysis is also applied to predict the real-time breast tissue deformation based on finite element (FE) simulations [37]; a similar study uses integrated ML approach and FE simulations towards breast deformation in [38]. Their works demonstrate the potential of simulation-based ML approach. The human aortic valve (AV) is the most crucial component inside human body; many researchers have harnessed the power of ML techniques for a robust and efficient AV functional characterization. Specifically, ANN has been utilized to derive the specific constitutive model parameters of the aortic wall [39,40]. The mechanical response of the aorta has also been investigated by CNN and regression analysis [41-43]. For Bioprosthetic valves, ML applications are mainly focused on valve geometric reconstruction and critical geometric decision [44-47]. Moreover, research utilizes the autoencoder-based ML method to optimize the design of transcatheter aortic valves and explores valve deformation behavior [48,49]. The main objective of ML applications in AV is to correlate the AV critical geometric information to its functionality and

bypass the complex and time-consuming computational analysis and clinical experiments. This type of application substantially facilitates a better understanding of AV function and can assist the physician and clinician in the therapy planning.

Machine Learning Application for Bio-materials

Biomaterials play a crucial role in medical applications, such as drug delivery, tissue engineering and medical diagnostics. Characterization of biomaterial properties becomes significant as their interactions with biological systems are highly dependent on their mechanical properties. Though biomaterials have a wide variety, we mainly discuss the ML applications in three popular biomaterials: polymers, metal and ceramic. One of the most outstanding work in ML application of polymer characterization is the Polymer Genome Project [50]. This informatics platform takes polymer key features as input and predicts the corresponding polymer properties based on similarity in the database using GPs, thus waives the necessity for self-design machine learning networks. Many applications for specific polymer material characterization can also be found in the literature such as dielectric polymeric materials characterization using support vector machine [51]; bacterial cytoskeleton polymetric component using decision tree for classification and regression [52]; Quantitative Structure Activity/Property relationships (QSAR/QSPR) integrated with ANN for the surface properties of biodegradable polymers [53]. Another interesting work is utilizing self-organizing maps (SOM) to classify polymer film types since the biomaterial surface properties control the biomaterial interaction with biological systems [54].

For metallic biomaterials, an attractive application of ML in recent years is in medical implant using the high-entropy alloys (HEAs) [55]; several machine learning methods are employed to classify phase status of HEAs and characterize the materials to targeted properties [56-59]. Besides, machine learning algorithms are emerging as a promising tool for evaluating the cytotoxicity of biomaterial nanoparticles. A unified quantitative structure toxicity relationships (QSTR) perturbation model based on ANN has been proposed to assess general cytotoxicity of the nanoparticles [60]; The Decision tree has been utilized to classify cytotoxicity based on cell viability [61]; Similar work using supervised learning method can also be found in [62,63]. Although those machine learning applications are not a direct characterization of metallic biomaterial properties, they explore the feasibility of the ML method to assess the biocompatibility of biomaterials. Another heavily used material for the implant is ceramics due to their light weight and favorable mechanical properties. Nowadays, researchers focus more on ceramic composites whose components are complex such that the

traditional experimental test cannot fully depict their mechanical properties. Instead, machine learning methods can facilitate the development of novel ceramic materials and predict their specific material properties. For instance, linear/nonlinear regression machine learning algorithms and CNN are employed to design bioceramics and bioglass [64,65]. Upon reviewing current progress in the machine learning applications, it is evident that machine learning approaches have a broad range of applications in many aspects of biomaterial development, properties characterization, and material performance assessment.

Summary and Future Expectation

A better understanding of biological materials can also facilitate the development of biomaterials. Meanwhile, ML can assist in the discovery of novel biomaterials. However, the fidelity of a machine learning algorithm is highly dependent on the model architecture, model hyperparameters tuning and input data preparation. The researchers must also carefully validate the integrity of the input parameter metrics to avoid unnecessary system uncertainties. Moreover, machine learning relies on conventional experimental and computational methods for input data collection because it is difficult to establish a comprehensive database for a wide variety of biological materials and biomaterials. However, significant progress has been made in recent years [13]. We expect broader machine learning applications in bio-related material science with the rapid evolution of more sophisticated machine learning networks and more data source availability.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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