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Review Article

AI-integrated mechanobiology: Predictive modelling of cellular force dynamics in disease

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Abstract

Mechanobiology is now a significant area of study because it tells us how mechanical force influences a cell's or tissue's action as well as how diseases progress. Technological advances in artificial intelligence (AI) and computational modeling allow us to analyze complex multiscale biological systems at a level of detail never before possible. The combination of AI to mechanobiology can be referred to as AI-integrated mechanobiology, which is a revolutionary new approach to forecasting how cells respond to forces and how these force dynamics lead to disease. The authors of this review will take the reader through the present state of mechanotransduction, extracellular matrix (ECM) remodeling, and cytoskeletal production of force and will compare those current mechanobiological approaches with several growing AI-related technologies like machine learning, deep learning, and physics-informed neural networks. Specific emphasis will be placed on creating predictive models that quantify changes in biomechanics through cancer progression, cardiovascular remodeling, fibrotic remodeling, and neurodegenerative disorders. AI will also play a role in creating digital twins, predicting how a tissue would respond to these forces, and developing personalized mechanomedicine. Although impressive progress has been made in mechanobiology and AI integration, gaps in data standardization, model interpretability, and biological scaling continue to exist. This article will summarize the current state of mechanobiology and identify areas of missing knowledge as well as provide insight into how to use mechanobiological, AI-based models for improved clinical diagnostics and new methods for developing innovative therapeutics.

Keywords: Mechanobiology; Artificial Intelligence, Mechanotransduction, Predictive Modelling, Cellular Mechanics, Extracellular Matrix, Digital Twins, Systems Physiology, Mechanomedicine, Deep Learning

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1. Introduction

Mechanobiology is defined as how mechanical forces impact cell or tissue behavior.[1,2] Cells are always measuring and reacting to mechanical signals in their environment, including extracellular matrix (ECM) stiffness, shear stress, and tensile loads, through mechanotransduction.[3,4] Mechanical signals regulate many solid cellular functions, such as cell division, differentiation, movement, and programmed cell death, which are all important for maintaining tissue homeostasis.[5] If any of these processes goes wrong, it can lead to numerous diseases, including all types of cancer, cardiovascular disease, fibrosis, and neurodegeneration.[6–8]

The mechanotransduction pathway consists of multiple signalling pathways that allow integrins, focal adhesion complexes, and cytoskeletal components to convert mechanical stress into biochemical signals.[9,10] Unpredictable mechanosensitive pathways (e.g., the Hippo-YAP/TAZ pathway) directly link changes in physical properties of cells to regulation of transcription by control of gene expression in response to compressive or tensile mechanical forces.[11,12] Moreover, the degradation of the ECM and other changes in ECM composition and thickness will lead to further changes in cellular mechanical properties that contribute to the progression of disease, such as with the microenvironment of tumours and fibrotic tissues.[13,14] All of these findings illustrate the need for a quantitative understanding of how forces change over multiple levels of biological organisation.

Although there have been many improvements made to experimental methodologies such as AFM, TFM and high resolution imaging techniques, mechanobiological systems are still fundamentally complicated and non-linear.[15,16] Many of the conventional analytical methods have not been able to fully represent the dynamic interactions between mechanical forces and the resultant biological reactions. Due to these limitations, there has been an emergence of AI technology as an innovative tool in the modelling of high-dimensional data sets and the discovery of hidden relationships within complex systems.[17,18] The application of both ML and DL techniques have achieved tremendous results in the areas of image analysis, pattern recognition and the predictive modelling of various biomedical applications.[19,20]

The intersection of AI and mechanobiology has developed a new and unique interdisciplinary field which centres around the predictive modelling of cellular force dynamics. The use of AI based models facilitates the incorporation of multiple different types of data, such as mechanical, imaging and omics data sources, to provide a comprehensive model of

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mechanotransduction.[21,22] In particular, the development of hybrid mechanistic-data-driven and physics-informed neural network models represent a new paradigm in the modelling of mechanotransduction, since they embed physical laws into the learning algorithms thereby improving the accuracy and interpretability of the models.[23,24] By allowing for the prediction of force-response relationships in both physiological and pathological states, these models will ultimately advance our understanding of the mechanisms of disease.

Artificial Intelligence (AI) and mechanobiology integrated into oncology have proven to be beneficial in predicting how tumors will progress by using models to analyze the stiffness of the extracellular matrix (ECM) and the forces that cells exert on the ECM.[25] In the same fashion, the use of computational models incorporating the forces of hemodynamics within cardiovascular physiology has helped with predicting vascular remodeling and the formation of atherosclerotic plaques.[26] There are now also AI-based models that simulate the stiffening of tissue due to fibrotic diseases and how stiffened tissue causes changes in cellular signaling pathways.[27] More recently, the concept of the "digital twin," a virtual duplicate of a biological system, provides a mechanism for personalizing mechanobiological predictions while optimizing treatment options.[28,29]

These advancements have provided the current understanding of mechanobiology; however, there are many challenges to the broader implementation of AI-based mechanobiology. Some challenges include quality and standardization issues with existing data; difficulties in integrating multiple data types at different scales; and concerns regarding how interpretable AI predictions will be and how AI models will be clinically validated in terms of their therapeutic efficacy.[30] Addressing these challenges is crucial to translating computational discoveries into practical clinical applications. This review will present an overview of the state of the art of the integration of AI and mechanobiology, in particular utilizing predictive modeling methods regarding the dynamics of forces at the cellular level for various diseases. This article combines ideas from biomechanics, systems physiologic, and artificial intelligence to illustrate the latest ideas about how mechanobiology and AI could eventually advance precision medicine and mechanomedicine.

2. Mechanotransduction Pathways and Cellular Force Dynamics

A central component of the way that cells acknowledge and react to physical stimulus, mechanotransduction, starts at the cell's outer membrane where the integrin receptors associate together linking the cell's internal cytoskeleton to the outside extracellular matrix (ECM).[9,10] When a cell receives a mechanical stimulus, the integrins cluster and form focal adhesion complexes that activate several different signalling pathways, including those that involve the focal adhesion kinase (FAK), Src family kinases and Rho GTPases.[10,11]

The cytoskeleton, which is made up of actin filaments, microtubules and intermediate filaments, transmits forces that are present within the cell. Actomyosin contractility generates traction forces that result in cells migrating and organizing into tissues.[5,12] These traction forces can be dynamically changed by the stiffness of the ECM, which is a bi-directional feedback mechanism between the cell and its surrounding microenvironment.[13] One of the best studied mechanosensitive pathways is the Hippo-YAP/TAZ signalling pathway, acting as a molecular switch that links mechanical inputs to gene outputs.[11,12] When there is a high level of mechanical loading or substrate stiffness YAP/TAZ can move from the cytoplasm to the nucleus and activate genes involved in proliferation and survival. Conversely, low mechanical loading causes YAP/TAZ to remain in the cytoplasm and be unable to activate transcriptional genes.[12]

Measuring the Impact of Forces on Cells: Impacts of Forces on Cells through YAP/TAZ and Ion Channels - In addition to YAP/TAZ being a major regulator of cellular responses to forces, mechanosensitive ion channels (e.g. Piezo1) and nuclear mechanotransductive mechanisms have also emerged as important regulators of cellular responses to forces [6,7]. Nuclear deformation induced by the cytoskeletal forces exerted on it can directly influence both the organization of chromatin and transcriptional activities, further integrating mechanical and biochemical signaling.[8] Collectively these pathways highlight the fundamental multiscale nature of force transmission from mechanical forces at the molecular level, through the cellular level and into tissue level forces. Collectively, the quantitative characterisation of these dynamics is vital to understanding the pathophysiology of disease and forms the basis for computational modelling approaches.

3. Artificial Intelligence in Mechanobiology

The application of AI in mechanobiology provides solutions to the difficulties in the handling and understanding of biomechanical systems which are high-order, complex and high-dimensional. Traditional modelling approaches that have performed simplistically based on assumptions have been unable to accurately define non-linear interactions and multiscale dependencies [17,18]. AI methodologies are able to overcome these limitations by discovering the underlying patterns in the data through automated analyses.

4. Machine Learning and Deep Learning

When classification of biomechanical phenotypes and prediction of biological cells response to mechanical stimuli, algorithm such as support vector machine, random forest and clustering have all been illustrated in the application of ML[19]. The extraordinary performance of deep learning (DL) through Convolutional Neural Networks (CNN) has been illustrated through high-resolution imaging datasets (i.e. traction force microscopy and live cell imaging) [20]. Convolutional Neural Networks afford:

1. Automated quantification of cellular central forces,
2. Detection of subtle variations in cellular morphology, and
3. Predictions of mechanobiological states across different environments.

5. Physics-Informed Neural Networks (PINNs)

An example of recent advancement in the area of AI in biomechanics is the development of a new breed of Neural Network called PINNs which integrates physical laws into the learning process (ie. conservation of momentum, equations of elasticity) [23,24]. This is especially important, as modeled predictions will be a reflection of current biomechanical principles. Application of PINNs include:

1. Modeling of stress-strain relationships in soft tissues;
2. Simulating interaction between fluids and structures within the vascular system; and
3. Predicting how forces will propagate within the cellular network.

6. Hybrid Mechanistic-AI Models

Hybrid models combined mechanistic equations with AI-based learning methods to provide the best of both worlds with their respective strengths: interpretability and predictive powers [21,22]. Hybrid mechanisms and AI hybrid models are especially beneficial when there is only partial knowledge of mechanisms of the system or process.

7. Digital Twins and Multiscale Modelling

In the field of mechanobiology, the notion of digital twins refers to computer representations of living systems, which has been rapidly expanding [28,29]. Digital twins facilitate the following functions by using patient-specific information:

1. Simulating how a disease will develop
2. Predicting how a given patient will respond to a treatment
3. Modeling how forces affect individual patients

Collectively, these tools represent a shift toward precision mechanomedicine—where treatment plans are individualized based on patients' unique biomechanical profiles.

8. Mechanobiology Applications of AI in the Management of Disease

8.1. Cancer development and tumor environment

Cancer is inherently a mechanobiological disease, characterized by changes in ECM stiffness (increased leukocyte contractility), and aberrant signaling of mechanical force.[6,25] Using AI-based models, researchers have been able to:

1. Evaluate the likelihood of a tumour invading nearby tissues based on the elasticity of its surroundings
2. Examine how heterogeneous (inhomogeneous, varying in composition) the tumour microenvironment is and how certain pathologies (cancer) develop
3. Find biomarkers of metastases

Deep Learning (DL) techniques have developed models for predicting how tumours develop in a very accurate way by combining information from images and the biomechanical properties of cells.[20,25]

1. Evaluate the likelihood of a tumour invading nearby tissues based on the elasticity of its surroundings
2. Examine how heterogeneous (inhomogeneous, varying in composition) the tumour microenvironment is and how certain pathologies (cancer) develop
3. Find biomarkers of metastases

Keywords include mechanical forces (fluid mechanics)—shear and cycled stress. AI-generated models of blood vessel mechanics have increased the accuracy with which researchers predict:

1. How atherosclerotic plaques will form
2. How the endothelium will work
3. How blood vessel remodelling will occur

Fluid dynamics and wall mechanics have been captured in these models to assist researchers in understanding both the timeline of development of a disease as well as intervention strategies.

8.2. Fibrosis and tissue stiffening

Fibrotic diseases have too much deposition of ECM leading to tissue stiffness and developing gradually [13,27]. AI modeling has been used to:

1. Dimulate feedback loops between ECM stiffness and cellular activity.
2. Predict the progression of organ fibrosis.
3. Evaluate potential antifibrotic therapies.

As such, these models show the significance of mechanical feedback in creating and maintaining pathological states.

8.3. Neurodegenerative disease

There is some emerging evidence to suggest that neurodegenerative disease may be mediated through changes in brain tissue mechanics.[7,8] Some ways AI-integrated mechanobiology has been/ is being developed for neurodegenerative disease include:

1. Modeling changes in brain stiffness;
2. Modeling mechanotransduction for neuronal cells; and
3. Predicting disease progression with respect to Alzheimer's Disease.

Although the field is still in its infancy, it represents an exciting area of research.

9. Challenges/Limitations

Despite recent advances in mechanobiological models using AI and machine learning methodologies, there are still many challenges that exist. These include but are not limited to the following:

1. **Data heterogeneity:** Lack of standardized datasets across different experimental platforms will make generalizing the use of models difficult.[30]
2. **Multiscale integration:** Difficulty with the integration of molecular, cellular, and tissue-level data.
3. **Model interpretability:** Many of the new deep learning models function as "black boxes," which creates difficulty in translating findings into clinical settings.[18]
4. **Validation and translation:** There is limited clinical validation of AI-based mechanobiological models.

To address these challenges, multidisciplinary collaboration and standardized frameworks will be required.

9.1. Future directions and emerging opportunities

*F*rom the coming together of many technological and scientific fields:

1. **Explainable AI (XAI):** Greater interpretable predictive models.
2. **Real-time Biomechanical Monitoring:** Coupling to wearable/implantable sensors.
3. **3D Bioprinting and Tissue Engineering:** Combining mechanobiological models and engineered tissues.
4. **Precision Mechanomedicine:** Personalized therapeutic approaches based on biomechanical profiling.
5. **Integrating Multi-Omics:** Combining mechanical signals with genomic, proteomic, and metabolomic data.

Additionally, the development of complete digital twins capable of modelling an entire organ system would provide a long-term objective that could have profound clinical implications.[28,29]

10. Discussion

The integration of mechanobiology and AI marks a significant paradigm shift in the way biomedical research is performed. The integration of Mechanobiology with AI enables the transformation of mechanobiological systems from descriptive observations to predictive quantitative models of force dynamics within the cells. The inherent multiscale, nonlinear, and adaptive characteristics of mechanobiological systems have created significant challenges when attempting to develop analytical methods for these systems[17,18] The integration of AI-based methodologies enables the identification and description of complex interactions between mechanical signals and cellular responses, thus furthering our understanding of disease pathophysiology.

One of the major observations from this review is that there is a bidirectional relationship between mechanical forces and biochemical signals in relation to both health and disease. Mechanotransduction processes (particularly with respect to integrins, cytoskeletal remodeling and YAP/TAZ signaling) are key to linking the mechanical structure of the extracellular environment with the cellular decision-making process.[9–12] AI-based models have improved our ability to quantify these relationships, allowing us to produce predictive patterns of some of these mechanisms that could not have been identified by traditional experimental methods. For example, predictive models that incorporate ECM stiffness and traction force dynamics have shown promise in predicting the behavior of tumors and their ability to invade and metastasise.[25] This demonstrates that mechanical variables are not simply a characteristic of the disease, but are instead active components of the pathology.

Another important observation is that hybrid modelling methods (particularly those that combine physics informed principles with data-driven learning) are becoming increasingly relevant. Purely data-driven AI models are powerful, but often provide limited interpretability and may not generalise beyond the data on which they were trained. In contrast, physics-informed neural networks (PINNs) and hybrid mechanistic-AI frameworks provide a more robust alternative because they combine established biomechanical laws with predictive models.[23,24] This technique not only increases accuracy but also increases biological feasibility, which is essential for clinical applications. Simulating stress-strain correlations, fluid-structure interactions, and transmission of forces throughout the body emphasizes the use of these models as a decision-support tool in clinical practice.

The development of AI-integrated mechanobiology across all types of diseases has enhanced its ability to serve as a translational tool. In cancer research, integrating biomechanical variables into predictive models has revealed complexities in tumor heterogeneity and developing resistance to therapy.[20,25] In cardiovascular disease research, AI-enabled modeling of hemodynamic forces has enhanced the risk assessment process and has helped improve predictions regarding vascular remodeling [26]. Examples of the relationship between increases in ECM stiffness and cellular activation, as seen in fibrotic diseases, are now able to be simulated quantitatively with AI-derived models.[27] Emerging applications for neurodegenerative diseases indicate that changes in tissue mechanical properties may provide early indicators of disease onset, requiring additional verification.[7,8]

Despite the potential of these ideas, numerous limitations must be resolved. A key limitation is the lack of standardization and quality of the available datasets that include biomechanical, imaging, and molecular data.[30] As different methods and result collection techniques can cause vast discrepancies regarding the same experiment, this reduces the ability of AI models to be reconstructed and the ability to generalize the results of AI models. Additionally, combining multiscale data from molecular interactions to organ mechanics will continue to be challenging and will require sophisticated computer science frameworks, as well as multiple disciplines of expertise.

A second challenge is the ability to understand AI models, particularly deep-learning AI systems that act as "black boxes".[18] In clinical applications, the inability to understand the predictions made by the model could impede adoption and raise ethical concerns regarding the use of AI. Thus, the development of explainable artificial intelligence (XAI) is essential for establishing trust, transparency, and adherence to regulatory requirements. Furthermore, a rigorous process of clinical validation through prospective studies will be required before their reliability and usefulness can be confirmed for real-world applications of AI-based mechanobiological models.

Digital twins are one of the most promising future directions in the field. Digital twins provide the ability to integrate patient-specific data and identify individualised disease trajectories as well as therapeutic responses.[28,29] This fits closely with the goals of precision medicine to enable the ability to use biomechanical profiling to design an individualised intervention for each patient. However, before digital twins can be implemented at scale, advances will be necessary in data integration, computational performance, and regulatory frameworks. More broadly, AI-nautical mechanobiology supports interdisciplinary partnerships across biology, physics, engineering, and data science, which serve to advance the field of AI.

The success of this area will hinge on the establishment of standardized protocols, shared would be data repositories and collaborative networks for research. Ethical issues regarding data privacy, algorithmic bias and clinical accountability must all be managed effectively in order for the deployment of systems to occur responsibly.

11. Conclusion

In conclusion, while AI-integrated mechanobiology has already shown tremendous promise in enhancing our understanding of how cells respond to force, the full clinical effects of AI-integrated mechanobiology can only be realised by eliminating the current methodological and translation barriers to progress. Continued innovation in computational modelling and rigorous experimental validation will be needed to fully realise the potential of this relatively new field. AI-integrated mechanobiology provides a transformative way to understand and predict the cellular response to mechanical forces associated with health and disease. By connecting advances in biomechanics, computational modelling and artificial intelligence, this interdisciplinary field provides novel ways to identify complex biological processes. While challenges related to data integration, model interpretability and clinical validation remain, continuous advancements will ultimately provide a bridge between scientific knowledge and clinical application. Ultimately, the implementation of AI guided mechanobiology within a clinical setting will have the potential to be transformative for diagnostic, prognostic and therapeutic interventions, laying the groundwork for a new era of precision mechanomedicine.

12. Source of Funding

None.

13. Conflict of Interest

None.

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