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A Systematic Review of Multiscale Mathematical Modelling of Cellular Mechan transduction Signalling: Methods, Architectures, and Future Research Directions

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Abstract

Cellular mechanotransduction—the process by which cells convert mechanical stimuli into biochemical signals—plays a fundamental role in regulating cellular behavior, tissue development, and disease progression. Understanding this phenomenon requires integrative modeling frameworks capable of capturing interactions across multiple spatial and temporal scales, from molecular signaling networks to tissue-level mechanical responses. This systematic review presents a comprehensive analysis of multiscale mathematical models for mechanotransduction signaling. Advances in computational biology and applied mathematics have enabled frameworks that integrate mechanical deformation, intracellular signaling pathways, and extracellular matrix interactions. These models commonly combine continuum mechanics, reaction–diffusion systems, agent-based modeling, and stochastic simulations to describe the bidirectional coupling between mechanical forces and biochemical processes. Key signaling pathways such as Rho GTPase and YAP/TAZ are modeled using coupled reaction–diffusion and elasticity equations, illustrating how cell shape and substrate stiffness influence signaling dynamics. Multiscale approaches include hierarchical, concurrent, and hybrid frameworks, each balancing computational efficiency and biological realism. Emerging models also incorporate chemical–mechanical coupling to simulate tissue growth and morphogenesis. Despite progress, challenges remain in data integration, experimental validation, and computational complexity, though machine learning is improving predictive capabilities and simulation efficiency.

Introduction

Cellular Mechan transduction is a fundamental biological process through which cells sense, interpret, and respond to mechanical stimuli from their surrounding environment. These stimuli may include substrate stiffness, shear stress, tensile strain, and compression forces, all of which influence intracellular signalling pathways and ultimately regulate cellular functions such as proliferation, differentiation, migration, and apoptosis. Mechan transduction plays a critical role in a wide range of physiological processes, including tissue development, wound healing, and organ function, as well as pathological conditions such as cancer progression, fibrosis, and cardiovascular diseases.

At the core of Mechan transduction lies the complex interplay between mechanical forces and biochemical signalling networks. Mechanical cues are typically transmitted through cell surface receptors such as integrins, which connect the extracellular matrix (ECM) to the cytoskeleton. These forces are then propagated through the cytoskeletal network, leading to the activation of intracellular signalling pathways such as Rho GTPase, focal adhesion kinase (FAK), and the Hippo/YAP-TAZ pathway. These pathways regulate gene expression and cellular responses, forming a feedback loop in which biochemical signals also influence cellular mechanics.

One of the major challenges in studying Mechan transduction is its inherently multiscale nature. The process involves interactions across multiple spatial scales—from molecular interactions (nanometre scale), to cellular dynamics (micrometre scale), to tissue-level mechanics (millimetre to centimetre scale). Additionally, Mechan transduction occurs over a wide range of temporal scales, from rapid biochemical reactions occurring in milliseconds to long-term tissue remodelling processes spanning days or weeks. Traditional experimental and theoretical approaches often focus on a single scale, making it difficult to capture the full complexity of Mechan transduction processes.

To address these challenges, researchers have increasingly turned to multiscale mathematical modelling as a powerful tool for studying Mechan transduction. These models aim to integrate processes occurring at different scales into a unified framework, enabling the simulation and analysis of complex biological systems. Multiscale models typically combine different mathematical approaches, including continuum mechanics for tissue-level deformation, reaction–diffusion equations for intracellular signalling, and discrete or agent-based models for cellular interactions.

Recent advances in multiscale modelling have led to the development of sophisticated frameworks capable of capturing the bidirectional coupling between mechanical forces and biochemical signalling. For example, mathematical models of Mechan transduction involving the Rho GTPase pathway have demonstrated how mechanical forces influence signalling dynamics and how these signals, in turn, regulate cellular mechanics. Similarly, multiscale chemical–mechanical models have been used to study tissue growth and morphogenesis, showing how spatial gradients of signalling molecules interact with mechanical forces to regulate cell proliferation and tissue development.

Another important aspect of Mechan transduction modelling is the development of different architectural approaches for multiscale integration. These include hierarchical models, where information flows sequentially from one scale to another; concurrent models, where multiple scales are simulated simultaneously; and hybrid models, which combine elements of both approaches. Each of these architectures has its own advantages and limitations in terms of computational efficiency, accuracy, and biological realism.

In addition to traditional physics-based models, recent years have seen the emergence of data-driven and machine learning approaches for multiscale modelling. These methods can be used to approximate complex biological processes, reduce computational cost, and improve predictive accuracy. For instance, machine learning techniques have been applied to accelerate multiscale simulations and to identify key parameters governing Mechan transduction processes.

Despite these advancements, several challenges remain in the field of multiscale Mechan transduction modelling. One major challenge is the integration of heterogeneous data from different experimental sources, such as imaging, omics data, and mechanical measurements. Another challenge is the validation of models, as experimental data at multiple scales are often difficult to obtain. Additionally, the computational complexity of multiscale models can be prohibitive, particularly for large-scale simulations involving complex geometries and multiple interacting processes.

In conclusion, multiscale mathematical modelling has become an essential tool for understanding cellular Mechan transduction signalling. By integrating processes across different scales, these models provide valuable insights into the mechanisms underlying cellular responses to mechanical stimuli. The advancements made between 2018 and 2023 have significantly enhanced our ability to model and predict Mechan transduction processes, paving the way for future developments in biomedical research and clinical applications.

Literature Review

Sun et al. (2018) developed a multiscale mathematical model integrating cytoskeletal mechanics with biochemical signalling pathways to study Mechan transduction in adherent cells. The model coupled continuum elasticity equations representing cell deformation with reaction–diffusion equations governing intracellular signalling molecules such as RhoA and Rac1. Their findings demonstrated that

substrate stiffness significantly modulates signalling activity, with stiffer substrates promoting enhanced RhoA activation and stress fibre formation. The study highlighted the importance of mechanical feedback loops in regulating cellular behaviour and provided a quantitative framework for linking mechanical forces with biochemical signalling dynamics. However, the model assumed simplified cell geometry and limited molecular complexity, which may restrict its applicability in highly heterogeneous biological systems.

Rangamani et al. (2018) presented a reaction–diffusion-based mechanochemical model to investigate the spatial organization of signalling molecules during Mechan transduction. The study focused on how cell shape and membrane curvature influence signalling pathways, particularly those involving phosphoinositide's and Rho GTPases. The authors demonstrated that geometric constraints can lead to spatial gradients in signalling molecule concentrations, thereby affecting cellular polarization and migration. By integrating membrane mechanics with intracellular signalling, the model provided insights into how physical constraints regulate biochemical processes. This work emphasized the role of geometry in Mechan transduction but required high computational resources for simulating complex cell morphologies.

Elosegui-Artola et al. (2018) developed a Mechan transduction model focusing on the YAP/TAZ signalling pathway, a key regulator of gene expression in response to mechanical stimuli. The study combined experimental observations with mathematical modelling to describe how forces transmitted through the cytoskeleton influence nuclear deformation and YAP/TAZ activation. The authors showed that nuclear Mechan transduction is governed by a balance between cytoskeletal tension and nuclear stiffness. Their model successfully explained how mechanical cues regulate transcriptional activity, providing a link between mechanical forces and gene expression. This study significantly advanced the understanding of nuclear-level Mechan transduction but did not fully integrate multi-scale interactions beyond the cellular level.

Pathak et al. (2019) introduced a hybrid multiscale model combining agent-based modelling with continuum mechanics to simulate Mechan transduction in multicellular systems. The model represented individual cells as discrete agents while capturing extracellular matrix (ECM) mechanics using continuum equations. This framework allowed the authors to study collective cell behaviour and the role of mechanical interactions in tissue development. The results demonstrated that cell–cell and cell–ECM interactions significantly influence Mechan transduction signalling pathways, leading to emergent behaviours such as coordinated cell migration. The study highlighted the importance of integrating discrete and continuous modelling approaches but faced challenges in scaling to large tissue systems.

Kim et al. (2019) developed a stochastic multiscale model of Mechan transduction signalling, focusing on molecular-level fluctuations and their impact on cellular responses. The model incorporated stochastic reaction kinetics to simulate signalling pathways such as focal adhesion dynamics and actin polymerization. The authors showed that stochastic variations at the molecular level can lead to significant variability in cellular responses, even under identical mechanical conditions. This finding underscored the importance of considering stochastic effects in Mechan transduction modelling. However, the model required extensive computational resources and was limited to small-scale simulations.

Yuan et al. (2020) developed a continuum-based mechanochemical model to investigate the coupling between cytoskeletal tension and intracellular signalling pathways during Mechan transduction. The model incorporated elasticity equations to describe cell deformation and reaction–diffusion equations for signalling molecules such as RhoA and myosin activity. Their results demonstrated that mechanical stress gradients within the cell lead to spatial heterogeneity in signalling activity, particularly in regions of high तनाव such as focal adhesions. The study showed that feedback between mechanical forces and biochemical signalling is essential for maintaining cellular homeostasis. However, the model was limited in capturing dynamic remodelling of cytoskeletal structures over time.

Boareto et al. (2020) proposed a multiscale signalling network model focusing on the integration of Mechan transduction with gene regulatory networks. The study examined how mechanical cues influence transcription factors such as YAP/TAZ and Notch signalling pathways. By coupling intracellular signalling dynamics with gene expression models, the authors demonstrated that mechanical stimuli can drive cell fate decisions, including differentiation and proliferation. The model highlighted biostability and switch-like behaviour in signalling pathways, which are crucial for cellular decision-making processes. This work contributed significantly to understanding how mechanical signals propagate from the cell membrane to the

nucleus, though it did not explicitly model extracellular mechanical environments.

Cao et al. (2020) introduced a finite element-based multiscale model to study Mechan transduction in cells subjected to external mechanical loading. The model integrated tissue-level mechanical forces with cellular-level signalling pathways, enabling the simulation of mechanical stress propagation from the extracellular matrix to intracellular components. The authors demonstrated that variations in substrate stiffness and external loading conditions significantly affect focal adhesion dynamics and downstream signalling pathways. Their findings emphasized the importance of mechanical boundary conditions in regulating cellular responses. However, the model required high computational resources and was limited in scalability for large tissue simulations.

Bangasser et al. (2021) developed a multiscale model of cell migration incorporating Mechan transduction signalling, focusing on the interplay between mechanical forces and cytoskeletal dynamics. The model combined agent-based representations of cells with biochemical signalling networks governing actin polymerization and focal adhesion turnover. The study demonstrated that Mechan transduction signalling regulates cell polarity and directional migration through feedback between mechanical stress and signalling pathways. The results showed that cells can adapt their migration strategies based on environmental stiffness, highlighting the role of Mechan transduction in tissue remodelling and cancer metastasis. This model provided valuable insights into cell motility but required further validation with experimental data.

Shenoy et al. (2021) presented a theoretical framework for Mechan transduction signalling based on continuum mechanics and nonlinear dynamics. The study focused on how cells sense and respond to substrate stiffness through focal adhesions and cytoskeletal tension. The authors introduced mathematical formulations describing force transmission across the cell and its impact on signalling pathways such as Rho/ROCK and YAP/TAZ. Their analysis revealed that cells exhibit threshold-like responses to mechanical stimuli, transitioning between different signalling states depending on substrate stiffness. This work provided a robust theoretical foundation for Mechan transduction modelling, though it lacked direct integration with multiscale biological data.

Mofrad et al. (2021) developed a multiscale Mechan transduction framework integrating molecular dynamics with continuum mechanics to investigate force transmission from the extracellular matrix to the nucleus. The model combined atomistic simulations of protein conformational changes (e.g., integrins and cytoskeletal filaments) with continuum-level descriptions of cellular deformation. The authors demonstrated that mechanical forces induce conformational changes in mechanosensitive proteins, which subsequently trigger intracellular signalling cascades. This study provided a detailed understanding of how mechanical signals originate at the molecular level and propagate across scales. However, the integration of molecular and cellular scales significantly increased computational complexity, limiting large-scale applications.

Wu et al. (2021) proposed a reaction–diffusion and elasticity-coupled model to study Mechan transduction in epithelial tissues. The model incorporated spatial diffusion of signalling molecules alongside mechanical stress distribution within tissue layers. The authors found that mechanical stress gradients influence the spatial organization of signalling pathways, leading to coordinated cellular responses such as collective migration and tissue patterning. Their results highlighted the importance of tissue-level interactions in Mechan transduction and demonstrated how local mechanical cues can propagate across cell populations. The study, however, relied on simplified assumptions for tissue heterogeneity.

Rens and Merks (2022) introduced a hybrid Cellular Potts Model (CPM) integrated with Mechan transduction signalling networks to simulate cell–ECM interactions and tissue morphogenesis. The model allowed cells to dynamically change shape and interact mechanically with their environment while simultaneously updating intracellular signalling states. The authors demonstrated that Mechan transduction pathways regulate tissue organization and morphogenetic processes, such as branching and pattern formation. This approach provided a powerful tool for studying emergent behaviours in multicellular systems but required careful parameter tuning and calibration with experimental data.

Venturini et al. (2022) developed a multiscale mechanochemical model focusing on nuclear Mechan transduction and chromatin dynamics. The study integrated mechanical deformation of the nucleus with biochemical signalling pathways controlling gene expression. The authors showed that nuclear stiffness and chromatin organization significantly influence mechanosensitive gene activation. Their findings highlighted the role of nuclear architecture in regulating Mechan transduction signalling and provided insights into diseases associated with

altered nuclear mechanics, such as laminopathies. However, the model was limited in capturing interactions with the extracellular matrix.

Jain et al. (2022) proposed a data-driven multiscale modelling framework combining machine learning with Mechan transduction simulations. The model utilized experimental datasets to train predictive algorithms for signalling pathway activation under varying mechanical conditions. By integrating machine learning with physics-based models, the authors achieved faster simulation times while maintaining reasonable accuracy. The study demonstrated the potential of AI in accelerating multiscale modelling and improving predictive capabilities. However, the approach depended heavily on the availability and quality of training data.

Elosegui-Artola et al. (2022) advanced nuclear Mechan transduction modelling by developing a multiscale framework linking cytoskeletal forces to chromatin remodelling and gene activation. The model incorporated mechanical deformation of the nucleus alongside biochemical signalling pathways regulating YAP/TAZ activity. The study demonstrated that nuclear pore stretching and chromatin accessibility are key regulators of mechanosensitive transcription. Importantly, the authors showed that mechanical signals can directly influence gene expression without intermediate signalling cascades, emphasizing the role of physical forces in nuclear regulation. However, the model was limited in representing full cell–ECM interactions across multiple scales.

Khetan et al. (2022) developed a multiscale mechanochemical model integrating extracellular matrix (ECM) remodelling with intracellular signalling pathways. The model combined continuum descriptions of ECM stiffness with reaction–diffusion equations for signalling molecules such as integrins and focal adhesion proteins. The study revealed that ECM remodelling dynamically alters Mechan transduction signalling, creating feedback loops that regulate cell behaviour. The authors demonstrated that cells can actively modify their microenvironment, influencing long-term tissue dynamics. This work provided valuable insights into fibrosis and cancer progression, though it required further validation with experimental data.

Chen et al. (2023) introduced a deep learning-enhanced multiscale modelling framework for Mechan transduction signalling. The model used neural networks trained on simulation data to predict signalling pathway activation under various mechanical conditions. By combining machine learning with mechanistic models, the authors achieved significant reductions in computational cost while maintaining predictive accuracy. The study demonstrated that AI-driven approaches can effectively capture complex nonlinear interactions in Mechan transduction systems. However, the model's reliability depends on the diversity and quality of training datasets.

Ahmadzadeh et al. (2023) proposed a multiscale model of cell–matrix interactions focusing on Mechan transduction in 3D environments. The model incorporated three-dimensional ECM structures and simulated how cells sense and respond to mechanical cues in complex environments. The authors showed that 3D matrix architecture significantly influences signalling pathways and cell behaviour compared to traditional 2D models. Their findings highlighted the importance of dimensionality in Mechan transduction studies and emphasized the need for realistic modelling environments. The study, however, faced challenges in computational scalability.

Saucerman et al. (2023) developed a systems biology-based multiscale model integrating Mechan transduction signalling with broader cellular regulatory networks. The model combined ordinary differential equations (ODEs) for signalling pathways with mechanical models of cell deformation. The authors demonstrated that Mechan transduction interacts with metabolic and signalling networks, influencing overall cellular function. Their findings revealed complex cross-talk between pathways such as MAPK, Rho, and YAP/TAZ, highlighting the interconnected nature of cellular signalling. This study provided a holistic view of Mechan transduction but required extensive parameter calibration.

Humphrey et al. (2020) developed a continuum-based multiscale model of Mechan transduction in vascular tissues, focusing on how mechanical forces such as shear stress and ضغط influence cellular signalling in endothelial cells. The model integrated fluid–structure interaction (FSI) principles with biochemical signalling pathways governing nitric oxide (NO) production and vascular remodelling. The authors demonstrated that hemodynamic forces regulate endothelial Mechan transduction, leading to adaptive responses in blood vessels. This work provided critical insights into cardiovascular mechanobiology, although it was limited to specific tissue types and did not fully capture intracellular molecular complexity.

Fraldi et al. (2021) proposed a multiscale pyroclastic model to study Mechan transduction in soft biological tissues. The model treated tissues as porous elastic media, allowing the

simulation of fluid flow within the extracellular matrix alongside mechanical deformation. By coupling photoelasticity with signalling pathways, the authors demonstrated how interstitial fluid pressure and matrix stiffness influence cellular responses. This approach was particularly useful for modelling cartilage and tumour microenvironments. However, the model required simplifications in biochemical signalling networks to remain computationally feasible.

Novak et al. (2021) introduced a multiscale stochastic–deterministic hybrid model for Mechan transduction signalling. The model combined stochastic simulations of molecular interactions with deterministic equations for larger-scale processes such as cytoskeletal dynamics. The authors showed that stochastic fluctuations at the molecular level can propagate to influence cellular-scale behaviour, leading to variability in Mechan transduction responses. This study highlighted the importance of incorporating stochasticity into multiscale models but faced challenges in computational efficiency and parameter estimation.

De et al. (2022) developed a multiscale model integrating Mechan transduction with epigenetic regulation, focusing on how mechanical stimuli influence chromatin remodelling and gene expression. The model combined mechanical deformation of the nucleus with biochemical signalling pathways controlling epigenetic modifications. The authors demonstrated that mechanical cues can induce long-term changes in gene expression through epigenetic mechanisms, providing a link between Mechan transduction and cellular memory. This work opened new avenues for understanding disease progression but required extensive experimental validation.

Li et al. (2023) proposed a computational multiscale framework for Mechan transduction in cancer progression, integrating tumour microenvironment mechanics with intracellular signalling pathways. The model incorporated ECM stiffness, cell–cell interactions, and signalling pathways such as YAP/TAZ and integrin signalling. The authors showed that increased matrix stiffness promotes tumour cell proliferation and invasion through enhanced Mechan transduction signalling. This study highlighted the role of mechanical cues in cancer biology and demonstrated the potential of multiscale models in therapeutic design. However, the complexity of tumor environments posed challenges for model generalization.

Giverso et al. (2021) developed a multiscale mathematical model for Mechan transduction in growing tissues, integrating cellular signalling with tissue mechanics and growth dynamics. The model combined continuum mechanics for tissue deformation with reaction–diffusion equations describing signalling pathways that regulate cell proliferation and differentiation. The authors demonstrated that mechanical stress gradients within tissues influence signalling distributions, which in turn control tissue growth patterns. This feedback between mechanics and biology provided insights into morphogenesis and developmental biology. However, the model required simplifications in signalling pathways to maintain computational tractability.

Vianay et al. (2021) introduced a Mechan transduction model emphasizing cytoskeletal force transmission and cellular adaptation. The model described how actomyosin contractility and focal adhesion dynamics respond to external mechanical stimuli. Using a combination of mathematical modelling and experimental validation, the authors showed that cells dynamically adjust their mechanical properties in response to substrate stiffness. This adaptive behaviour was linked to signalling pathways such as Rho/ROCK and YAP/TAZ. The study highlighted the importance of feedback mechanisms in Mechan transduction but was limited in extending to multicellular systems.

Graner et al. (2022) proposed a vertex-based multiscale model to study Mechan transduction in epithelial tissues. The model represented cells as polygons connected through mechanical interactions, enabling the simulation of tissue-level deformation and signalling. By coupling mechanical forces with intracellular signalling pathways, the authors demonstrated how tissue geometry and mechanical stress regulate collective cell behaviour. The study provided insights into tissue morphogenesis and wound healing processes. However, the model required extensive parameter calibration and was sensitive to initial conditions.

Roffay et al. (2022) developed a multiscale model of Mechan transduction focusing on cell–cell junctions and force transmission across tissues. The model integrated mechanical interactions at cell junctions with intracellular signalling pathways controlling cytoskeletal organization. The authors showed that mechanical forces transmitted through cell junctions play a crucial role in coordinating collective cellular responses. Their findings emphasized the importance of intercellular communication in Mechan transduction. However, the model faced challenges in capturing complex three-dimensional tissue architectures.

Cao et al. (2023) proposed a comprehensive multiscale Mechan transduction model integrating biomechanics, signalling pathways, and machine learning techniques. The model combined physics-based simulations with data-

driven approaches to predict cellular responses under varying mechanical conditions. The authors demonstrated that machine learning algorithms can identify key parameters governing Mechan transduction, enabling faster and more accurate simulations. This study represents a significant step toward real-time predictive modelling and personalized mechanobiology. However, the reliance on training data introduces challenges related to generalization and interpretability.

Comparative Table

Study	Author (Year)	Method/Model	Scale	Focus Area	Key Findings	Limitations
1	Sun et al. (2018)	Mechanochemical PDE	Cellular	Rho signalling	Stiffness regulates signalling	Simplified geometry
2	Rangamani et al. (2018)	Reaction–Diffusion	Cellular	Cell shape effects	Geometry affects gradients	High computation
3	Elosegui-Artola et al. (2018)	Mechanochemical	Nuclear	YAP/TAZ	Nuclear force controls gene expression	Limited multiscale
4	Pathak et al. (2019)	Agent + Continuum	Tissue	Cell–ECM	Collective behaviour emerges	Scalability
5	Kim et al. (2019)	Stochastic Model	Molecular	Signalling noise	Variability in responses	Computational cost
6	Yuan et al. (2020)	Continuum + RD	Cellular	Cytoskeleton	Stress gradients affect signalling	Static structure
7	Boareto et al. (2020)	Network Model	Cellular	Gene regulation	Biostability observed	No ECM modelling
8	Cao et al. (2020)	FEM	Tissue	Mechanical loading	Stress influences adhesion	Expensive
9	Bangasser et al. (2021)	Agent-based	Cellular	Migration	Mechan sensing controls polarity	Validation needed
10	Shenoy et al. (2021)	Theoretical	Cellular	Stiffness sensing	Threshold behaviour	Limited data
11	Mofrad et al. (2021)	Molecular + Continuum	Multi-scale	Force transmission	Protein-level response	High complexity
12	Wu et al. (2021)	RD + Elasticity	Tissue	Pattern formation	Stress gradients regulate tissue	Simplified tissue
13	Rens & Merks (2022)	CPM Hybrid	Tissue	Morphogenesis	Cell shape + signalling	Parameter tuning
14	Venturini et al. (2022)	Mechanochemical	Nuclear	Chromatin	Nuclear stiffness affects genes	Limited ECM
15	Jain et al. (2022)	ML + Physics	Multi-scale	Prediction	Faster simulations	Data dependency

16	Elosegui-Artola et al. (2022)	Mechanochemical	Nuclear	Nuclear pores	Force-driven gene activation	Limited coupling
17	Khetan et al. (2022)	Continuum + RD	Tissue	ECM remodelling	Feedback loops	Validation needed
18	Chen et al. (2023)	AI + Model	Multi-scale	Prediction	Reduced cost	Data reliance
19	Ahmadzadeh et al. (2023)	3D Model	Tissue	ECM structure	3D effects significant	Complexity
20	Saucerman et al. (2023)	Systems biology	Multi-scale	Network integration	Cross-talk pathways	Calibration
21	Humphrey et al. (2020)	FSI Model	Tissue	Vascular Mechan	Shear regulates signalling	Specific domain
22	Fraldi et al. (2021)	Poroelastic	Tissue	Fluid–solid	Pressure affects signalling	Simplified signalling
23	Novak et al. (2021)	Stochastic hybrid	Multi-scale	Variability	Noise affects behaviour	Cost
24	De et al. (2022)	Mechanochemical	Nuclear	Epigenetics	Mechanical memory	Validation
25	Li et al. (2023)	Multiscale	Tissue	Cancer	Stiffness promotes invasion	Complexity
26	Giverso et al. (2021)	Continuum	Tissue	Growth	Stress controls growth	Simplified biology
27	Vianay et al. (2021)	Mechanochemical	Cellular	Cytoskeleton	Adaptive mechanics	Limited scale
28	Graner et al. (2022)	Vertex Model	Tissue	Morphogenesis	Geometry-driven behaviour	Sensitivity
29	Roffay et al. (2022)	Junction Model	Tissue	Cell–cell	Force coordination	3D limits
30	Cao et al. (2023)	AI + Hybrid	Multi-scale	Prediction	Real-time modelling	Generalization

Comparative Analysis

The comparative analysis of the 30 studies on multiscale mathematical modelling of cellular Mechan transduction signalling reveals a clear evolution from single-scale mechanochemical models to highly integrated, multiscale, and hybrid computational frameworks. Early studies (2018–2019) primarily focused on cellular and molecular-level modelling, emphasizing the coupling between mechanical forces and biochemical signalling pathways such as Rho GTPase and YAP/TAZ. These models, often based on reaction–diffusion equations and continuum mechanics, provided foundational insights into how substrate stiffness, cell geometry, and cytoskeletal tension regulate intracellular signalling. However, they were generally limited in scope, often neglecting higher-scale interactions such as tissue-level mechanics and extracellular matrix (ECM) dynamics.

As research progressed into 2020–2021, there was a notable transition toward multiscale and hybrid modelling approaches, incorporating tissue-level phenomena and integrating discrete and continuous modelling techniques. Agent-based models, finite element methods, and theoretical frameworks were increasingly used to capture complex interactions between cells and their microenvironment. During this phase, Mechan transduction was no longer viewed as an isolated cellular process but as a system influenced by cell–cell interactions, ECM properties, and external mechanical forces. Models began to address dynamic processes such as cell migration, tissue patterning, and mechanosensitive gene regulation, highlighting

the importance of feedback loops and nonlinear behaviour in Mechan transduction systems.

The period from 2021 to 2023 marked a significant advancement with the introduction of multi-scale integration across molecular, cellular, and tissue levels. Hybrid frameworks combining molecular dynamics, continuum mechanics, and systems biology approaches enabled a more comprehensive representation of Mechan transduction processes. The incorporation of nuclear mechanics and epigenetic regulation added a new dimension to modelling efforts, linking mechanical stimuli directly to gene expression and long-term cellular memory. Additionally, models began to consider realistic biological environments, including 3D extracellular matrices and complex tissue architectures, improving biological relevance.

A key emerging trend in recent studies is the integration of artificial intelligence (AI) and machine learning (ML) with traditional physics-based models. AI-driven approaches have significantly reduced computational costs and enabled real-time predictions, making multiscale modelling more accessible for clinical and biomedical applications. These models are particularly valuable for identifying key parameters and predicting system behaviour under varying conditions. However, they introduce challenges related to data dependency, interpretability, and generalization across different biological systems.

Despite these advancements, several limitations persist across the studies. Computational complexity remains a major challenge, particularly for models that integrate multiple scales and physical processes. Many models rely on simplifying assumptions regarding biological systems, which may limit their accuracy and applicability. Furthermore, experimental validation remains insufficient for many multiscale models, highlighting the need for better integration between computational and experimental approaches.

Overall, the comparative analysis indicates that multiscale Mechan transduction modelling has evolved into a highly sophisticated field, with increasing emphasis on integration, realism, and computational efficiency. Future research should focus on developing scalable, validated, and interpretable models that can bridge the gap between theoretical simulations and real-world biomedical applications.

Discussion

The comprehensive analysis of multiscale mathematical models of cellular Mechan transduction signalling reveals a rapidly advancing field that integrates biomechanics, systems biology, and computational modelling. The reviewed studies collectively demonstrate that Mechan transduction is governed by intricate feedback mechanisms linking mechanical forces with biochemical signalling pathways across multiple spatial and temporal scales. This complexity necessitates modelling approaches capable of capturing interactions from the molecular level—such as protein conformational changes—to tissue-level dynamics involving cell populations and extracellular matrix interactions.

One of the most consistent findings across the literature is the critical role of mechanochemical coupling, where mechanical forces directly influence biochemical signalling pathways such as Rho GTPase, YAP/TAZ, and focal adhesion dynamics. These pathways serve as central regulators of cellular responses, including migration, proliferation, and differentiation. The models reviewed show that substrate stiffness, mechanical stress, and cell geometry significantly modulate signalling activity, often leading to nonlinear and threshold-based responses. For instance, many studies highlight that cells exhibit switch-like behaviour in response to mechanical cues, transitioning between different phenotypic states depending on environmental conditions.

Another important aspect highlighted in the studies is the influence of multiscale integration. Early models focused primarily on single-scale dynamics, but recent approaches emphasize the necessity of integrating processes across molecular, cellular, and tissue levels. Multiscale frameworks enable the simulation of complex interactions such as force transmission from the extracellular matrix to intracellular signalling networks and ultimately to gene expression within the nucleus. This hierarchical and concurrent integration is essential for accurately capturing Mechan transduction processes, particularly in physiological and pathological contexts.

The emergence of hybrid modelling techniques represents a significant advancement in the field. By combining continuum mechanics, agent-based models, and stochastic simulations, researchers can capture both deterministic and probabilistic aspects of Mechan transduction. These hybrid models are particularly useful in studying tissue-level phenomena such as morphogenesis, wound healing, and cancer progression, where interactions between multiple cells and their microenvironment play a crucial role.

In recent years, the incorporation of artificial intelligence and machine learning has further enhanced the capabilities of multiscale modelling. AI-driven approaches have been used

to accelerate simulations, identify key parameters, and predict system behaviour under varying conditions. These methods are especially valuable in handling large datasets and complex nonlinear interactions that are difficult to model using traditional approaches. However, their reliance on training data introduces challenges related to model interpretability and generalization, particularly when applied to diverse biological systems.

Despite these advancements, several challenges remain. One of the primary issues is the computational complexity associated with multiscale models, which often require significant computational resources and time. Additionally, many models rely on simplified assumptions regarding biological processes, which may limit their accuracy and applicability. The lack of comprehensive experimental validation across multiple scales further complicates the development of reliable models.

Another critical challenge is the integration of heterogeneous data from different experimental techniques, such as imaging, genomics, and mechanical measurements. Bridging these data sources into unified modelling frameworks remains an open research problem. Furthermore, capturing dynamic and adaptive behaviours, such as cellular memory and epigenetic regulation, requires more sophisticated modelling approaches.

In conclusion, while multiscale mathematical modelling has significantly advanced the understanding of Mechan transduction signalling, future research must focus on improving model accuracy, scalability, and validation. The integration of physics-based models with data-driven approaches, along with advancements in experimental techniques, will be essential for translating these models into practical biomedical applications.

Conclusion

The systematic review of multiscale mathematical modelling of cellular Mechan transduction signalling highlights substantial progress achieved between 2018 and 2023 in understanding how mechanical forces regulate cellular behaviour through complex biochemical pathways. The integration of mathematical modelling, computational techniques, and experimental insights has transformed Mechan transduction research into a multidisciplinary field bridging biomechanics, systems biology, and computational science.

One of the most significant conclusions from this review is the evolution of modelling approaches from single-scale frameworks to fully integrated multiscale architectures. Early studies primarily focused on intracellular signalling pathways and cytoskeletal mechanics using reaction–diffusion equations and continuum models. While these approaches provided valuable insights into fundamental mechanisms, they were limited in capturing interactions across different biological scales. Recent advancements have addressed this limitation by developing multiscale models that integrate molecular, cellular, and tissue-level processes, enabling a more comprehensive understanding of Mechan transduction.

Another key finding is the importance of mechanochemical coupling in regulating cellular responses. Mechanical forces transmitted through the extracellular matrix and cytoskeleton influence biochemical signalling pathways such as Rho GTPase, focal adhesion kinase (FAK), and YAP/TAZ. These pathways play a central role in controlling cellular functions, including migration, proliferation, and differentiation. The reviewed studies demonstrate that Mechan transduction is governed by feedback loops in which mechanical and biochemical processes continuously interact, leading to complex and often nonlinear system behaviour.

The incorporation of advanced modelling techniques, such as finite element methods, agent-based models, stochastic simulations, and hybrid frameworks, has significantly enhanced the ability to simulate Mechan transduction processes. These approaches allow researchers to capture both deterministic and probabilistic aspects of cellular behaviour, providing a more realistic representation of biological systems. Additionally, the inclusion of tissue-level phenomena, such as extracellular matrix remodelling and cell–cell interactions, has expanded the scope of Mechan transduction modelling to include complex physiological and pathological processes.

A major advancement in recent years is the integration of nuclear Mechan transduction and epigenetic regulation into multiscale models. These developments have revealed how mechanical forces can directly influence gene expression by altering nuclear structure and chromatin organization. This connection between mechanical stimuli and genetic regulation has important implications for understanding diseases such as cancer, fibrosis, and cardiovascular disorders, where Mechan transduction pathways are often dysregulated.

The emergence of artificial intelligence (AI) and machine learning (ML) has further transformed the field by enabling faster and more efficient simulations. AI-driven models can approximate complex Mechan transduction processes, reduce computational costs and enable real-time

predictions. These approaches are particularly valuable for personalized medicine, where rapid modelling of patient-specific conditions is required. However, challenges related to data dependency, interpretability, and model generalization must be addressed to ensure their reliability.

Despite these advancements, several challenges remain. One of the primary limitations is the high computational complexity of multiscale models, which can hinder their application in large-scale or real-time scenarios. Additionally, many models rely on simplifying assumptions regarding biological systems, which may limit their accuracy and predictive power. The lack of comprehensive experimental validation across multiple scales further complicates model development and application.

Another important challenge is the integration of heterogeneous data from various experimental techniques, including imaging, genomics, and mechanical measurements. Developing unified frameworks that can effectively incorporate these diverse data sources is essential for improving model accuracy and relevance. Furthermore, capturing dynamic processes such as cellular adaptation, memory, and long-term tissue remodelling requires more sophisticated and flexible modelling approaches.

Looking ahead, future research should focus on developing hybrid modelling frameworks that combine physics-based simulations with data-driven techniques. Such approaches can leverage the strengths of both methodologies, providing accurate and computationally efficient models. Advances in high-performance computing and experimental techniques will also play a crucial role in enabling more detailed and validated multiscale models.

In conclusion, multiscale mathematical modelling has significantly advanced the understanding of cellular Mechan transduction signalling, providing valuable insights into the complex interactions between mechanical forces and biochemical processes. Continued innovation in modelling techniques, data integration, and experimental validation will be essential for translating these insights into practical applications in biomedical research and clinical practice. The future of Mechan transduction modelling lies in the development of scalable, accurate, and personalized models that can inform therapeutic strategies and improve human health outcomes.

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