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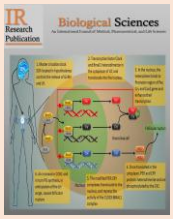

# Mechanobiological Interactions in Microorganisms: Implications for Host-Pathogen Dynamics and Antibiotic Resistance

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ABSTRACT

The interplay between mechanical forces and biological systems, particularly within microorganisms, has emerged as a critical factor influencing pathogen behavior and host-pathogen interactions. This study explores the role of mechanobiology—how mechanical forces such as shear stress, deformation, and surface tension affect microbial dynamics—within the context of infection and antibiotic resistance. This study discusses how mechanical stimuli regulate microbial adhesion, biofilm formation, and virulence, with direct implications for antibiotic resistance. By integrating insights from physics, biology, and microbiology, the study provides a novel perspective on how these forces could influence pathogen survival and resistance mechanisms, such as the formation of protective biofilms or the induction of stress-responsive genetic pathways. While the article offers valuable insights into the mechanobiology of pathogens, it presents several gaps that warrant further investigation. These include the underexplored role of host tissue mechanics in shaping microbial pathogenesis, the genetic adaptations of pathogens to mechanical stresses, and the potential for developing novel therapeutic approaches that target mechanobiological pathways. Future research in this field should aim to bridge the gap between physical forces, microbial genetics, and immune responses, offering new strategies for combating antibiotic-resistant infections. In sum, this study highlights the need for a more integrated approach to understanding microbial infections, one that incorporates the growing field of mechanobiology into conventional therapeutic and preventative paradigms.

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## Introduction

Mechanobiology refers to the study of mechanical forces and their effects on biological systems. In microorganisms, this includes the way physical forces such as shear stress, pressure, and mechanical deformation affect cellular behavior, growth, and survival. Traditionally, microbiology has focused on genetic, biochemical, and environmental factors influencing pathogen virulence. However, in recent years, mechanobiology has emerged as a crucial area of research, recognizing that physical forces play a fundamental role in shaping microbial responses to their environments. For microorganisms, such forces can come from fluid shear in blood or mucus, tissue deformation during infection, or the mechanical properties of surfaces on which they grow (such as epithelial cell membranes or medical devices). These forces can influence key microbial behaviors such as adhesion, biofilm formation, and virulence gene expression, all of which are central to microbial survival and pathogenicity (1).

Recent advances in microscopy, and response to these mechanical cues. For instance, bacteria have evolved mechanosensitive ion channels, which allow them to detect and respond to changes in membrane tension or osmotic pressure. Furthermore, microbial biofilms, which are dense communities of microorganisms encased in a matrix of extracellular polymeric substances, are known to be highly influenced by mechanical forces. The physical pressure exerted by biofilm growth can affect the integrity of the matrix and the cells' ability to adhere to surfaces, thereby influencing the progression of infection (2). However, mechanobiology in microorganisms is a relatively new but growing field that is changing how scientists understand microbial or, pathogen-host interactions, and infection dynamics. The role of mechanical forces in microbial life is now recognized as a critical component of microbial physiology and pathogenicity.

Understanding mechanobiology is crucial for studying host-pathogen dynamics, which refer to the complex interactions between a host's immune system and the invading pathogen. Mechanical forces play a pivotal role in shaping these interactions. During infection, pathogens must navigate the physical barriers of the host, such as epithelial tissues, extracellular matrices, and blood vessels. In many cases, pathogens must also interact with host immune cells, which themselves are influenced by mechanical forces in the tissue microenvironment. One key aspect of host-pathogen interactions is adhesion. Pathogens often utilize specialized structures such as pili, fimbriae, or surface proteins to adhere to host tissues. These adhesive interactions are not only chemically driven but are also influenced by mechanical forces. For instance, the mechanical properties of the host cell surface or extracellular matrix can either enhance or inhibit pathogen adhesion. In addition, pathogens may alter their behavior in response to mechanical cues from the host tissue, such as increased attachment strength in response to shear forces in the bloodstream (3).

Once adhered to a surface, many pathogens form biofilms, which are three-dimensional structures composed of microbial cells and extracellular matrix material. The formation of biofilms is strongly influenced by mechanical forces, including fluid shear forces and the stiffness of the underlying surface (4). These biofilms serve as a protective barrier against host immune responses and antibiotics, contributing to chronic infections and persistent pathogenicity. Changes in tissue stiffness or matrix composition during infection can alter the behavior of immune cells, potentially affecting the outcome of the infection. A growing body of evidence suggests that the physical properties of both the pathogen and the host microenvironment contribute significantly to the dynamics of infection, immune response, and pathogenesis. However, the role of mechanobiology in host-pathogen dynamics is multifaceted. From pathogen adhesion and biofilm formation to immune cell responses, mechanical forces are critical determinants of infection outcomes. A deeper understanding of these forces can lead to more effective strategies for preventing and treating infections.

Antibiotic resistance is one of the most pressing global health challenges, and mechanobiology is starting to reveal new insights into how resistance may develop and persist. Resistance to antibiotics occurs when microorganisms evolve mechanisms to survive or evade the effects of antimicrobial agents. These mechanisms can include the modification of the drug target, active efflux of antibiotics from the cell, or the formation of protective biofilms. Interestingly, recent research suggests that mechanical forces may play a key role in facilitating the development and spread of antibiotic resistance. Biofilm-forming pathogens are often more resilient not only to antibiotics but also to the host immune system. (5). In addition to biofilm formation, mechanical forces in the host microenvironment can also promote resistance through mechanical signaling pathways. For example, increased tissue stiffness, often associated with chronic infections or inflammation, can activate mechanical sensing pathways in bacteria, potentially triggering changes in gene expression that confer resistance. The activation of mechanosensitive ion channels or other mechanoreceptors could lead to the upregulation

of efflux pumps or protective enzymes (6). Furthermore, antibiotic-induced mechanical stress itself can play a role in resistance. The mechanobiological perspective on antibiotic resistance opens up new avenues for intervention. Rather than focusing solely on targeting the genetic or biochemical pathways of resistance, future strategies could explore ways to disrupt the mechanical factors that contribute to biofilm formation, cell survival under stress, and the activation of resistance pathways (7). However, the integration of mechanobiology into the study of antibiotic resistance highlights the complex relationship between mechanical forces, microbial behavior, and treatment outcomes. Understanding how mechanical stress influences resistance mechanisms could provide innovative strategies for combating the growing crisis of antimicrobial resistance.

## Mechanobiological Principles in Microbial Behavior

### Mechanical forces in microbial environments

Microorganisms live in environments where they are constantly subjected to a variety of mechanical forces. These forces come from both their immediate surroundings and their interactions with host tissues, other microbes, and external factors like fluid flow. Understanding the types of mechanical forces acting on microorganisms is crucial to understanding how they respond to their environments and how they adapt to these physical stresses.

*Shear forces:* In liquid environments, such as the bloodstream or mucosal surfaces, microorganisms are subjected to shear stress from fluid flow. This force acts tangentially to the surface of the microorganism and is crucial in processes like microbial adhesion to surfaces and biofilm formation. For example, bacteria in the bloodstream must withstand the shear forces generated by blood flow to adhere to endothelial cells (8).

*Tensile forces:* These forces are applied perpendicular to a surface, stretching or pulling on the microbial cell. Tensile stress is common during biofilm formation, where cells undergo elongation and rearrangement to form a multilayered structure. Tensile forces can also be generated during bacterial division or when cells migrate across surfaces (9).

*Compressive forces:* Compressive forces occur when microorganisms are subjected to pressures that push them together. These forces are most prominent in biofilm communities, where the cells are packed tightly within an extracellular matrix. (10).

*Cytoskeletal forces:* Microbial cells, particularly bacteria, rely on their internal cytoskeletal components, such as actin filaments and proteins like FtsZ, to maintain cell shape and enable division.

These mechanical forces influence a range of microbial behaviors, from how they adhere to surfaces to how they organize into complex multicellular structures like biofilms. The precise nature and magnitude of these forces can vary dramatically between environments, such as the highly dynamic conditions in human tissues versus more stable environments like soil or water.

### Cellular response to mechanical stress

Microbial cells have evolved sophisticated mechanisms to sense and respond to mechanical stress, ensuring their survival in fluctuating physical environments. These responses are mediated by a combination of mechanosensitive channels, cytoskeletal dynamics, and gene expression pathways that adapt to mechanical cues.

*Mechanosensitive channels:* Many microorganisms have specialized ion channels that sense mechanical stress in their environment. These channels, known as mechanosensitive ion channels (MSCs), open or close in response to changes in membrane tension or mechanical deformation, allowing the cell to adjust its internal environment. For example, in E. coli, the MscL (large mechanosensitive channel) and MscS (small mechanosensitive channel) play critical roles in maintaining osmotic balance under fluctuating external pressures (11).

*Cytoskeletal remodelling:* In response to mechanical stress, microorganisms can reconfigure their internal cytoskeleton, a network of protein filaments that help maintain cell shape, enable movement, and support cellular division. For example, bacterial cells may alter the assembly of actin-like proteins or the polymerization of FtsZ filaments in response to mechanical cues (12).

*Signal transduction pathways:* Mechanical stress can activate intracellular signaling pathways that regulate gene expression and protein synthesis. For example, bacteria can sense the mechanical forces acting on their surface through integrin-like proteins or mechanoreceptors, triggering the upregulation of genes involved in adhesion, stress response, and biofilm formation. In Pseudomonas aeruginosa, mechanical stress has been shown to enhance the expression of virulence factors under specific environmental conditions (13).

*Cellular adaptation to stress:* The response of microorganisms to mechanical stress often involves an adaptation to the environment that allows them to survive or thrive under hostile conditions. For example, biofilm-forming bacteria may become more resistant to mechanical forces as the biofilm grows, with cells within the biofilm adjusting their gene expression to better withstand mechanical disruptions (14).

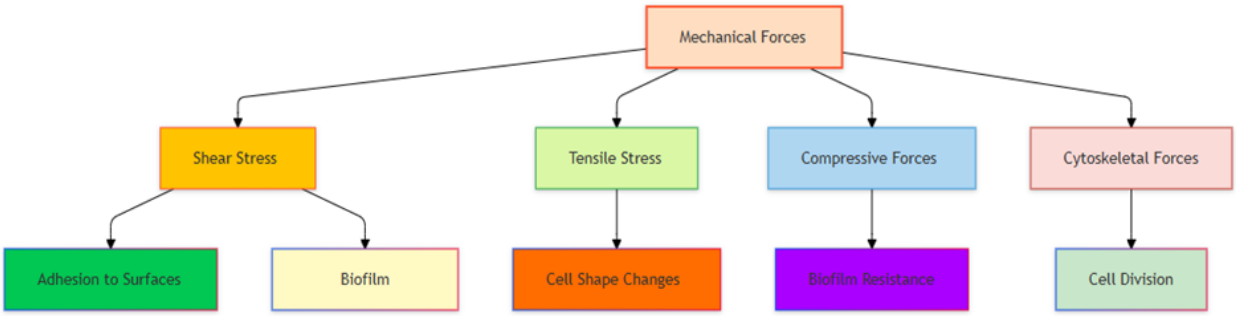


**Figure 1.** Mechanobiological influence on microbial behaviour.

Through these mechanisms, microorganisms can sense and adapt to the mechanical forces they encounter, which are integral to their survival in dynamic environments, including the human body or other ecological niches.

## Mechanisms of adhesion and biofilm formation

Adhesion to surfaces and the subsequent formation of biofilms are critical processes in microbial pathogenesis and persistence. Mechanical forces play an essential role in both processes, influencing how microorganisms attach to host tissues or inert surfaces and how they form multicellular communities.

*Adhesion mechanisms:* Microorganisms employ a variety of mechanisms to adhere to surfaces, and these processes are often governed by mechanical forces. For instance, bacteria utilize fimbriae, pili, and adhesins—surface proteins that facilitate strong attachment to host cells or abiotic surfaces. These adhesins undergo conformational changes in response to mechanical stress, enhancing their binding capacity. The mechanical properties of the surface itself, such as stiffness and roughness, can also influence the strength of adhesion. On softer or more flexible surfaces, bacteria may be able to adhere more firmly, as seen in the attachment of Streptococcus pneumoniae to lung epithelial cells (15).

*Biofilm formation:* Once adhered, many microorganisms form biofilms, which are clusters of microbial cells embedded in a self-produced extracellular matrix (ECM) of polysaccharides, proteins, and nucleic acids. Biofilm formation is a highly regulated process that is significantly influenced by mechanical forces. For example, fluid shear forces can help organize the biofilm structure by influencing the distribution and movement of cells within the matrix (16). As the biofilm matures, cells within it experience a range of mechanical stresses, such as compression from surrounding cells and tension from the extracellular matrix. These stresses can cause changes in biofilm architecture, such as increased matrix production or the formation of microchannels to facilitate nutrient and waste transport (17).

*Mechanical properties of biofilms:* The mechanical properties of biofilms, such as their stiffness and resistance to external forces, are key factors in their persistence and resistance to antibiotics. Biofilms often exhibit viscoelastic properties, meaning they behave both like a solid and a liquid under different conditions. The stiffness of the biofilm matrix can affect the cells' resistance to shear forces and antimicrobial agents. For instance, more rigid biofilms are harder to penetrate by antibiotics or immune cells, which contributes to their enhanced resistance (18). Moreso, biofilm formation is regulated by quorum sensing, a cell-density-dependent communication system that can be influenced by mechanical forces within the biofilm. Increased tension or pressure within the biofilm matrix can modulate the expression of genes involved in biofilm maintenance and virulence (19). Figure 1 illustrates the core mechanobiological principles that govern microbial behavior. It highlights the interplay between mechanical forces and microbial cellular responses, including cell migration, growth, and biofilm formation. Various external forces such as shear stress, compressive forces, and matrix stiffness impact the microbial cellular mechanics, influencing gene expression, motility, and virulence factors.

## Host-Pathogen Interactions and Mechanical Forces

### Physical interactions between pathogens and host tissues

The physical interactions between pathogens and host tissues are essential for the initiation of infection and its progression. Microorganisms typically encounter host tissues through physical barriers such as the epithelial lining of the skin, mucosal membranes, or endothelial cells. The initial step in host invasion involves adhesion, where microbial cells attach to host surfaces using specialized proteins, pili, and other surface structures that interact directly with host cell receptors or extracellular matrix components.

Mechanical forces, such as shear stress from blood or mucus flow, can significantly affect this adhesion process. For example, bacteria in the bloodstream, such as Streptococcus pneumoniae or Escherichia coli, must overcome the shear forces of blood flow to attach to endothelial cells or tissues at infection sites (20). These forces not only facilitate the attachment but also influence the strength of the interaction between pathogen and host, with stronger mechanical attachment often enhancing virulence.

In addition to adhesion, physical penetration or invasion of host tissues is a critical process in pathogenesis. Certain pathogens, such as Salmonella or Shigella, use specialized secretion systems to inject virulence factors into host cells, often using mechanical forces to induce cellular uptake. These forces can deform host cell membranes and enable pathogen internalization. Mechanical cues also play a role in the migration of immune cells, such as macrophages or neutrophils, toward the site of infection, which can either limit or promote pathogen survival depending on how well pathogens evade or manipulate these physical responses (21). Thus, physical interactions between pathogens and host tissues, mediated by mechanical forces, are key to microbial adhesion, invasion, and immune evasion.

### Impact of host tissue mechanics on pathogenesis

The mechanical properties of host tissues—including their stiffness, elasticity, and the presence of physical barriers—greatly influence the outcome of infections. Tissue mechanics refer to the properties of the host environment that influence cell behavior, including migration, adhesion, and tissue remodelling. These properties can affect pathogen-host interactions at multiple levels, from immune cell recruitment to pathogen adhesion and the ability to form biofilms.

*Tissue stiffness:* Pathogens, particularly in chronic infections, encounter changes in tissue stiffness that influence their ability to persist. In conditions like fibrosis, cancer, or inflammation, tissue becomes stiffer due to the remodelling of the extracellular matrix (ECM). This stiffness can alter the behavior of both the host and the pathogen. For instance, increased stiffness in tissue can enhance bacterial adhesion and biofilm formation. Studies have shown that bacteria like Pseudomonas aeruginosa exhibit increased biofilm formation in stiffer environments, which may contribute to chronic infections, such as those in cystic fibrosis patients (22). Furthermore, stiffened tissues can create microenvironments that promote the survival and persistence of biofilm-associated pathogens, which are often resistant to immune clearance and antimicrobial therapy.

*Extracellular matrix (ECM) remodelling:* The ECM, composed of collagen, elastin, and other structural proteins, provides mechanical support to tissues and plays a role in tissue integrity. During infection, ECM remodelling occurs, and this process can create niches for microbial colonization and biofilm formation. Infected tissues often exhibit altered ECM properties, making it easier for pathogens to invade or maintain chronic infections. Moreover, pathogens can manipulate host cell signalling pathways to influence ECM remodelling, thereby creating an environment conducive to infection (23).

*Inflammation and host tissue deformation:* Inflammatory responses also induce mechanical changes in tissues. For example, during inflammation, increased vascular permeability can lead to swelling and tissue deformation. Pathogens can exploit these changes to facilitate their migration into deeper tissue layers or to evade immune responses. In addition, certain pathogens like Listeria monocytogenes can hijack host cell cytoskeletal elements, deforming the cell membrane to promote their internalization (24).

Thus, the mechanical properties of the host tissue not only affect pathogen invasion but can also shape the pathogen's persistence, virulence, and resistance to treatment.

### Role of shear stress, cell deformation, and rigidity in infection

Mechanical forces such as shear stress, cell deformation, and rigidity are central to the processes of microbial adhesion, biofilm formation, and host invasion during infection. These forces play crucial roles in determining how pathogens interact

with host tissues and how host cells respond to infection.

*Shear stress:* As mentioned earlier, pathogens in dynamic environments, like the bloodstream or respiratory tract, are constantly exposed to shear forces exerted by flowing fluids. Shear stress can impact microbial adhesion to host cells and tissues. Cell-stretching devices: advances and challenges in biomedical research and live-cell imaging. Moreso, shear forces can influence the gene expression of pathogens involved in biofilm formation and virulence. Pathogens that resist shear forces are more likely to establish chronic infections, as seen in conditions like endocarditis, where bacteria adhere to heart valve surfaces despite constant blood flow (25).

*Cell deformation:* During infection, host cells can be deformed by the physical forces generated by pathogens or the immune system. For example, pathogens like Shigella and Salmonella can use mechanical forces to invade host cells by inducing membrane ruffling, which is a form of cellular deformation. These bacteria often use actin polymerization to generate the force needed to deform host cell membranes and allow bacterial uptake (26). Similarly, mechanical forces can lead to alterations in the behavior of immune cells. For instance, the deformation of endothelial cells during inflammation can enable the migration of immune cells to the site of infection, facilitating a host response to infection (27).

*Rigidity and biofilm formation:* The rigidity of the surface or tissue matrix to which bacteria attach can influence their ability to form biofilms. Bacteria sense the stiffness of the substrate via mechanosensitive proteins or cytoskeletal elements. On rigid surfaces, bacterial cells tend to aggregate and form biofilms more effectively, which enhances their resistance to antimicrobial treatment. This behavior is particularly important in chronic infections, where biofilm formation protects pathogens from immune responses and antibiotics. In contrast, softer substrates might lead to different forms of microbial behavior, such as more transient attachment or less structured colony formation (28).

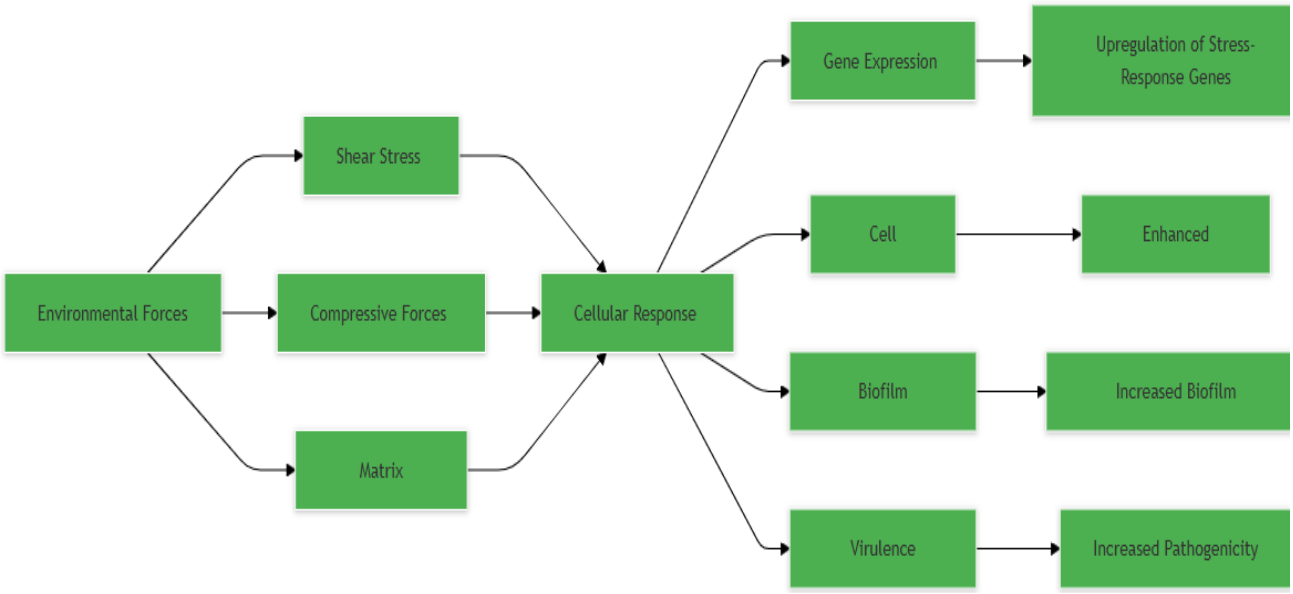


**Figure 2.** Mechanobiology of antibiotic resistance: mechanical forces shaping resistance mechanisms.

## Mechanobiology of Antibiotic Resistance

### Mechanisms of resistance induced by mechanical forces

Mechanical forces can influence the ability of pathogens to resist antibiotics by triggering changes in cellular structures, metabolism, and gene expression. These forces can be encountered during the microbial interaction with host tissues, in biofilms, or response to external mechanical stressors like fluid flow or substrate stiffness.

*Mechanical stress induces protective mechanisms:* Mechanical forces can activate stress response pathways that help bacteria survive in hostile environments, including those exposed to antibiotics. For example, shear forces in blood vessels or respiratory tracts can trigger the activation of mechanosensitive ion channels, which help

bacteria adjust to osmotic pressure and maintain cell integrity (29). Such responses can not only help bacteria endure physical stresses but also modulate antibiotic susceptibility. When exposed to mechanical forces, some bacteria upregulate genes related to stress resistance, such as those involved in DNA repair, protein chaperoning, and the production of efflux pumps, which are involved in expelling antibiotics from the cell (30).

*Altered cell wall and membrane properties:* Mechanical forces can also influence the structural properties of the bacterial cell wall and membrane, making them less susceptible to antibiotic penetration. For example, bacterial cells exposed to continuous shear forces may alter the composition of their cell wall or outer membrane proteins, reducing the ability of antibiotics, such as beta-lactams or polymyxins, to reach their target sites (31). Furthermore, mechanical deformation can induce membrane remodeling, a phenomenon observed in bacteria like E. coli, which may make the cell less permeable to antibiotics or increase resistance to membrane-targeting agents (32).

*Biofilm formation and antibiotic resistance:* The formation of biofilms is a well-established mechanism by which pathogens resist antibiotics, and mechanical forces are critical in this process. Shear stress, for example, has been shown to promote biofilm formation in certain pathogens by affecting the ability of cells to adhere to surfaces and by triggering gene expression pathways that promote extracellular matrix production (33). Once biofilms are established, bacteria within these communities exhibit heightened resistance to antimicrobial agents due to reduced penetration of antibiotics, altered metabolic states, and the protective effects of the biofilm matrix itself.

Thus, mechanical forces contribute to antibiotic resistance by inducing protective cellular responses, altering structural components, and facilitating biofilm formation.

## Role of biofilms in resistance to antimicrobials

Biofilm formation is one of the most significant factors contributing to antibiotic resistance in pathogenic microorganisms. Biofilms are structured communities of bacteria embedded in a self-produced extracellular matrix that protects from external stresses, including antibiotics and immune system attacks. Mechanical forces play a pivotal role in biofilm formation and maintenance, which in turn contributes to microbial resistance to antibiotics.

*Shear stress and biofilm formation:* Shear forces, which occur in dynamic environments like the bloodstream or during the movement of fluids across mucosal surfaces, can directly affect the formation and architecture of biofilms. For instance, bacteria exposed to shear stress on a surface are more likely to aggregate and form biofilms compared to those exposed to static conditions. This is particularly evident in pathogens like Pseudomonas aeruginosa and Staphylococcus aureus, which use mechanical signals to initiate biofilm formation (34). The flow of fluids helps in the spatial distribution of bacteria and can lead to the formation of microcolonies and the secretion of an extracellular matrix that encases the microbial community.

*Biofilm matrix and antibiotic protection:* The extracellular matrix (ECM) of biofilms, which consists of polysaccharides, proteins, and extracellular DNA, acts as a physical barrier, preventing antibiotic molecules from penetrating deep into the biofilm. Furthermore, the matrix protects bacterial cells by promoting metabolic heterogeneity within the biofilm. Cells in the deeper layers of the biofilm are often in a slow-growing or dormant state, which makes them less susceptible to antibiotics that target actively dividing cells, such as beta-lactams or aminoglycosides (35). Furthermore, bacteria in biofilms are more likely to exhibit increased expression of efflux pumps, which actively pump out antibiotics from the cell, further enhancing resistance (36).

*Quorum sensing in biofilms:* Quorum sensing (QS), a process where bacteria communicate via signaling molecules, plays a critical role in biofilm formation and maintenance. Mechanical forces, including shear stress, can influence quorum sensing pathways, thereby regulating the expression of genes involved in biofilm formation and antibiotic resistance. For example, shear stress has been shown to upregulate QS pathways in P. aeruginosa, leading to increased biofilm production and resistance to antibiotics like ciprofloxacin (37). The mechanical properties of the biofilm, including its rigidity and cohesiveness, contribute to its ability to resist antimicrobial treatment, as biofilms formed under high-shear stress conditions are often more difficult to disrupt and eradicate.

## Mechanical stress and genetic adaptations in pathogens

Mechanical stress can drive genetic adaptations in pathogens, contributing to the emergence of antibiotic resistance. The exposure of pathogens to physical forces—whether from fluid flow, tissue deformation, or biofilm formation—induces changes in the genetic landscape of microbial populations that can increase their survival and resistance to antibiotics.

*Mechanosensitive gene regulation:* Mechanical forces can activate mechanosensitive (MS) channels that influence gene expression and trigger cellular pathways linked to stress responses, repair mechanisms, and resistance. For example, bacterial cells exposed to mechanical stress from shear forces may alter gene expression in ways that promote resistance to antibiotics. In E. coli, exposure to mechanical forces such as fluid shear stress has been shown to upregulate genes related to cell envelope biogenesis, repair pathways, and efflux pumps (38). These changes allow bacteria to better withstand environmental stresses and survive exposure to antibiotics.

*Horizontal gene transfer:* In biofilms and during infection, pathogens can exchange genetic material, including antibiotic resistance genes, through horizontal gene transfer (HGT). Mechanical forces in biofilm environments, such as shear stress, can promote HGT by facilitating the transfer of plasmids or other mobile genetic elements between bacteria (39). For example, in biofilms under flow conditions, bacteria may more readily exchange genetic material that confers resistance to antibiotics, which accelerates the spread of resistance genes within microbial communities.

*Adaptation to environmental stresses:* Chronic exposure to mechanical stress, such as that encountered in host tissues or during biofilm development, can lead to adaptive mutations that enhance bacterial fitness under stressful conditions. These mutations often involve genes associated with antibiotic resistance, such as those encoding for efflux pumps, biofilm matrix components, or altered cell wall synthesis (40). The genetic adaptation of pathogens to mechanical stress not only enhances their resistance to antibiotics but also allows them to thrive in hostile environments, including those where antibiotics are present. Figure 2 below illustrates how mechanical forces such as shear stress, compressive forces, and matrix stiffness influence microbial resistance to antibiotics. It highlights the role of these forces in promoting bacterial adaptation, including increased mutation rates, biofilm formation, efflux pump activation, and gene expression changes.

## Current Research and Experimental Insights

### Experimental models in mechanobiology

Various experimental models have been developed to study the mechanobiology of microorganisms, particularly focusing on how mechanical forces influence microbial behavior, biofilm formation, and pathogenesis. These models allow researchers to replicate the mechanical stresses found in natural environments and to investigate their effects on microbial physiology and antibiotic resistance.

*Microfluidic models:* Microfluidic systems have become a prominent tool in mechanobiology research. These systems can simulate dynamic fluid environments and expose microbial populations to controlled shear stress, mimicking conditions in blood flow or mucus layers. Microfluidic devices are often used to study biofilm formation under flow conditions, track microbial motility, and test antimicrobial efficacy in biofilm models. For example, microfluidic chambers have been used to study Pseudomonas aeruginosa biofilms under varying shear stress, revealing how fluid dynamics influence biofilm structure and resistance to antibiotics (41).

*Atomic force microscopy (AFM):* AFM is a powerful tool used to study the mechanical properties of single bacterial cells and biofilms. By applying forces at the nanoscale, AFM can measure changes in cell stiffness, the forces required for bacterial adhesion, and interactions between pathogens and host cells. AFM has been used to measure the mechanical properties of biofilms and identify how their rigidity contributes to antibiotic resistance (42). This tool allows researchers to understand how bacteria respond to mechanical forces and adapt their surface structures to survive.

*3D Tissue culture models:* Advanced 3D tissue culture systems, such as organ-on-a-chip platforms, have been developed to replicate the mechanical properties of human tissues and to study the interactions between pathogens and host cells under physiologically relevant conditions. These models allow researchers to study the deformation of host tissues due to infection, the role of mechanical forces in immune cell migration, and the impact of antibiotic treatments on biofilm dynamics in a more in vivo-like environment (43).

### Key findings from studies on microbial biofilms

Biofilm research has been one of the most active areas in mechanobiology, as biofilm formation is crucial for the persistence of infections, particularly those that are resistant to antibiotics. Key findings from recent studies highlight how mechanical forces influence biofilm development, structure, and resistance.

*Shear stress promotes biofilm formation:* One of the key findings in biofilm research is that fluid shear stress plays a critical role in the initiation and maturation of biofilms. Studies have shown that bacteria exposed to shear forces, such as those found in the bloodstream or within the airways,

exhibit enhanced biofilm formation compared to those grown under static conditions. For instance, Staphylococcus aureus and Pseudomonas aeruginosa have been shown to form more robust biofilms under flow conditions (44). This biofilm formation is partly attributed to changes in bacterial gene expression, including upregulation of matrix-forming genes like those for exopolysaccharides.

*Biofilm architecture and antibiotic resistance:* The architecture of microbial biofilms is another critical factor influencing antibiotic resistance. Biofilms exhibit complex heterogeneity in terms of cell density and metabolic activity. Cells at the periphery of biofilms are more active and metabolically active, while those in deeper layers are often dormant or slow-growing, making them less susceptible to antibiotics that target actively dividing cells (45). Moreover, the extracellular matrix (ECM) acts as a physical barrier that restricts the diffusion of antimicrobial agents into the deeper layers of the biofilm (46).

*Mechanosensitive pathways in biofilms:* Recent studies have uncovered how mechanical forces, such as shear stress or cell deformation, influence the expression of genes involved in biofilm formation and antibiotic resistance. For example, Pseudomonas aeruginosa exposed to shear stress upregulates genes related to matrix production and antibiotic resistance, such as those encoding efflux pumps (47). This highlights the role of mechanosensitive pathways in enhancing biofilm formation and the pathogen's ability to resist antimicrobial treatment.

*Impact of substrate stiffness on biofilm formation:* The mechanical properties of the surface on which biofilms form also influence their structure and resistance. Studies have shown that biofilms tend to form more compact and dense structures on rigid surfaces compared to soft substrates. This increased density contributes to enhanced antibiotic resistance due to the reduced penetration of antimicrobial agents (48). This observation has implications for designing materials and surfaces that can inhibit biofilm formation in clinical and industrial settings.

## Case studies of mechanobiological interactions in pathogenesis

Several case studies have illustrated the crucial role of mechanical forces in pathogen-host interactions and the progression of infectious diseases. These case studies highlight how mechanical stress influences pathogen behavior, infection dynamics, and immune responses, as well as how pathogens adapt to mechanical challenges in the host environment.

*Case study 1: Streptococcus pneumoniae and pneumococcal disease*

In Streptococcus pneumoniae infections, the bacterium must navigate mechanical forces, such as the shear stress generated in the respiratory tract during coughing or breathing. These forces influence the bacteria's ability to adhere to and invade respiratory epithelial cells. A study by (49) demonstrated that shear stress in the airways increases the expression of surface adhesins in S. pneumoniae, which enhances bacterial adhesion to the epithelial cells and facilitates colonization. This interaction contributes to the pathogenesis of pneumonia and other pneumococcal diseases.

*Case study 2: Staphylococcus aureus and biofilm formation in chronic wounds*

In chronic wounds, the mechanical environment plays a key role in the development of Staphylococcus aureus biofilms. Wounds are often exposed to fluctuating mechanical forces due to movement, pressure, and fluid flow, which promote biofilm formation and increase bacterial resistance to antibiotics. A study by (50) showed that shear stress and mechanical strain on the wound surface significantly enhanced biofilm production by S. aureus, leading to chronic infection and difficulty in eradication despite antibiotic therapy. This case highlights the role of mechanical forces in chronic infections and the challenges they pose in clinical management.

*Case study 3: Salmonella enterica and intestinal invasion*

During Salmonella infections, mechanical forces in the intestinal epithelium, such as those generated by peristalsis and tissue deformation, contribute to pathogen invasion. A study by (51) demonstrated that Salmonella enterica uses its type III secretion system to inject virulence factors into epithelial cells, which is facilitated by the mechanical deformation of host cell membranes. Moreover, the physical stress from intestinal peristalsis can increase the permeability of the intestinal epithelium, enabling Salmonella to cross into deeper tissues and establish systemic infection. This case illustrates how mechanical forces in the host can directly influence pathogen invasion and virulence.

## Research Gaps and Future Directions

### Gaps in understanding host-pathogen mechanical interactions

While the role of mechanical forces in microbial behavior is increasingly recognized, the interaction between mechanical forces and host-pathogen dynamics is still not fully understood. Several key gaps in our understanding need to be addressed:

*Mechanisms of pathogen sensing of mechanical forces:* One critical area of research is understanding how pathogens sense and respond to mechanical forces in the host environment. While some pathogens have well-characterized mechanosensitive channels (e.g., E. coli), the full range of mechanosensory in pathogens remains unknown. For example, how do pathogens respond to mechanical deformation or tension in host tissues, such as during inflammation or tissue remodeling? Furthermore, the specific molecular mechanisms by which mechanical forces influence gene expression and virulence remain poorly understood (52). More research is needed to uncover the cellular pathways that are activated by mechanical stress in pathogens, and how these *pathways contribute to virulence and resistance*.

*Host tissue response to infection-induced mechanical stress:* The impact of infection on host tissue mechanics is another understudied area. Pathogen invasion often leads to tissue remodelling, changes in stiffness, and altered mechanical properties of infected tissues, yet how these changes influence the immune response and infection progression remains unclear. For instance, infections like tuberculosis or pneumonia involve significant changes in lung tissue mechanics, but the consequences of these mechanical alterations on immune cell migration, pathogen clearance, or chronicity of infection have not been fully explored (53).

*Cellular crosstalk in mechanical interactions:* Another major gap is understanding the cellular and molecular cross-talk between host cells (e.g., epithelial, endothelial, and immune cells) and pathogens under mechanical stress. How do immune cells respond to pathogen-induced mechanical forces during infection? Research into the mechanical interactions between pathogens and immune cells (e.g., neutrophils or macrophages) is still in its infancy, and understanding these interactions could have important implications for improving immune responses or targeting specific microbial virulence factors (54).

## Need for multidisciplinary approaches in mechanobiology

Mechanobiology is an inherently interdisciplinary field that combines concepts from microbiology, physics, engineering, and materials science. To address the complexity of host-pathogen interactions and antibiotic resistance, a more integrated, multidisciplinary approach is required.

*Integration of engineering and microbiology:* There is a growing need for collaboration between engineers, microbiologists, and clinicians to develop advanced experimental models that better replicate the mechanical conditions in vivo. For instance, microfluidic systems and organ-on-a-chip platforms have proven useful for simulating mechanical forces in a controlled setting, but they often lack the full complexity of host tissues. Future research could focus on improving the physiological relevance of these models by incorporating additional mechanical and biological factors, such as immune cell dynamics or tissue stiffness (55). Combining physical principles with microbiological studies will be key to creating more accurate models of infection.

*Computational modelling:* Computational approaches, such as finite element modelling (FEM), are increasingly being used to simulate the mechanical environment during infection, including tissue deformation and fluid flow dynamics. However, these models need to be refined to better capture the mechanical feedback between pathogens and the host tissue, particularly during biofilm formation and chronic infections. Computational models could also predict how bacterial cells experience mechanical stress under different conditions and how this affects their virulence and resistance mechanisms. Integrating experimental data from microfluidic models, AFM, and 3D tissue culture systems into computational frameworks will allow for more predictive and mechanistic studies of host-pathogen interactions (56).

*Collaboration between basic and clinical Research:* Bridging the gap between basic mechanobiology research and clinical application is crucial for translating findings into therapeutic strategies. For example, understanding how mechanical forces influence antibiotic resistance mechanisms in biofilms could lead to new treatment strategies targeting mechanical pathways. However, clinical trials that examine the effects of manipulating mechanical forces on infection outcomes are still limited. Multidisciplinary collaborations between laboratory-based scientists, clinical researchers, and pharmaceutical developers will be essential to push mechanobiological findings toward clinical application (57).

## Potential for targeting mechanobiological pathways in therapy

There is increasing recognition that targeting mechanobiological pathways offers a promising avenue for developing new therapeutic strategies for treating infections, particularly those caused by antibiotic-resistant pathogens. By modulating mechanical forces within the host or the pathogen, it may be possible to prevent biofilm formation, reduce virulence, or enhance the efficacy of existing antibiotics.

*Targeting biofilm mechanics:* As discussed earlier, biofilms are a major contributor to antibiotic resistance, and mechanical forces play a critical role in their formation and persistence. Therapeutic strategies that disrupt the mechanical properties of biofilms could have significant clinical benefits. For example, agents that alter the stiffness or structure of the biofilm matrix, such as enzymes that degrade extracellular polymeric substances (EPS) or small molecules that affect biofilm integrity, could make bacteria more susceptible to antibiotics (58). Moreso, mechanical disruption of biofilms using techniques like acoustic waves, laser treatments, or nanomechanical forces could offer a non-antibiotic-based approach to tackling chronic infections.

*Modulating host tissue mechanics:* Another promising area for therapeutic intervention involves modulating the mechanical properties of host tissues to prevent infection or enhance the immune response. For example, targeting the stiffness of tissue matrices could make it more difficult for pathogens to adhere or invade. Strategies that influence extracellular matrix remodeling, such as inhibiting matrix metalloproteinases (MMPs) or other enzymes involved in tissue degradation, could reduce pathogen entry or tissue colonization (59). Similarly, approaches that improve immune cell migration and function by altering the mechanical properties of the tissue could enhance the host's ability to clear infections.

*Inhibition of mechanosensitive pathways:* As mechanosensitive channels and pathways are crucial in the survival and virulence of many pathogens, targeting these pathways represents another potential therapeutic strategy. For example, blocking mechanosensitive channels or proteins involved in stress-induced antibiotic resistance (e.g., those that regulate efflux pump activity) could sensitize bacteria to antibiotics. Inhibiting bacterial mechanosensing could also impair their ability to form biofilms or invade host tissues. Moreso, modulating host cell mechanosensors may improve immune cell function during infections or facilitate the clearance of pathogens (60).

*Combining mechanobiology with existing therapeutics:* One of the most promising future directions is combining mechanobiological approaches with traditional antibiotic therapies to overcome resistance. By using mechanical force-based strategies to disrupt biofilms or modulate the mechanical properties of the host or bacterial cells, it may be possible to enhance the activity of existing antibiotics or reduce the likelihood of resistance development. For instance, antibiotics could be paired with agents that increase biofilm permeability or reduce the mechanical stiffness of bacterial cell walls, thereby enhancing the drug's efficacy (61).

## Conclusion

The study of mechanobiology has provided valuable insights into how mechanical forces influence both microbial behavior and host-pathogen interactions. It has become clear that mechanical stress plays a significant role in pathogen virulence, biofilm formation, and antibiotic resistance. Pathogens can sense and respond to mechanical forces in their environment, which impacts their ability to adhere to host tissues, form biofilms, and evade immune responses. Furthermore, the mechanical properties of host tissues—such as stiffness and deformation—can affect infection progression and the effectiveness of immune defenses, highlighting the complex interplay between pathogens and host environments. Understanding these mechanobiological interactions opens new possibilities for therapeutic strategies. Targeting the mechanical properties of biofilms could be an effective way to enhance the action of antibiotics, as mechanical disruption of biofilm structures may make pathogens more susceptible to treatment. Similarly, modulating the mechanical characteristics of host tissues could help prevent pathogen adhesion and invasion, potentially reducing the severity of infections. Moreover, by integrating mechanobiology with existing antibiotic therapies, new treatments could be developed to overcome the challenges posed by multidrug-resistant bacteria. Looking ahead, the field of mechanobiology offers exciting potential for addressing long-standing challenges in infection management. A deeper understanding of how mechanical forces affect host-pathogen dynamics could lead to the development of personalized, more effective therapies for chronic and resistant infections. Future research should focus on bridging the gap between basic mechanobiological principles and clinical applications, with an emphasis on designing therapies that target the mechanical pathways involved in infection and resistance. Through interdisciplinary collaboration, new treatment paradigms that harness the power of mechanobiology may significantly improve patient outcomes in the fight against infectious diseases.

## Contribution of authors

- Shuaib Sauda Bello conceptualized and led the research on the mechanobiological interactions in microorganisms, particularly focusing on the implications for host-pathogen dynamics and antibiotic resistance. She contributed to drafting and revising the manuscript, ensuring the integration of mechanobiological principles in microbial behavior, host-pathogen interactions, and antibiotic resistance mechanisms.
- Olaitan Lateefat Salam contributed to the study of mechanical forces in microbial environments, specifically how these forces influence microbial behavior. She also played a key role in the analysis of the physical interactions between pathogens and host tissues, as well as their implications in the pathogenesis of infections.
- Shehu-Alimi Elelu focused on exploring the mechanisms of adhesion and biofilm formation in microorganisms. He provided insights into the role of shear stress, cell deformation, and rigidity in the infection process and the development of antibiotic resistance. Additionally, he analyzed the relationship between mechanical stress and genetic adaptations in pathogens.
- Ganiyat Omotayo Ibrahim reviewed the current experimental models used in mechanobiology, particularly about microbial biofilms. She provided a comprehensive overview of case studies of mechanobiological interactions in pathogenesis, contributing to the discussion on the implications of these interactions for antibiotic resistance.
- Idowu Afeez Temitope contributed to the analysis of experimental models in mechanobiology, focusing on the development of new models for studying microbial behavior under mechanical stress. He also provided critical insights into the potential clinical applications of mechanobiological research, particularly in the treatment of infections.
- Miracle Uwa Livinus explored the impact of host tissue mechanics on pathogenesis, focusing on how mechanical forces influence the infection process and contribute to antibiotic resistance. She provided key insights into how shear stress and cell deformation affect pathogen-host interactions.
- Alege Abdulraheem Lateefat worked on identifying the research gaps in understanding host-pathogen mechanical interactions. She contributed to the discussion on the need for multidisciplinary approaches in mechanobiology and the potential for targeting mechanobiological pathways in therapy to address antibiotic resistance.
- Musa Ojeba Innocent focused on the role of biofilms in resistance to antimicrobials, analyzing how biofilm formation contributes to the persistence of infections. He also reviewed the current research and experimental findings in mechanobiology and their implications for overcoming antibiotic resistance.
- Mustapha Abdulsalam contributed to identifying the future directions in mechanobiology research, particularly in the integration of mechanical forces in the study of microbial resistance mechanisms. He provided insights into how these findings could be applied to therapeutic interventions and the potential for targeting mechanobiological pathways in clinical settings.

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## Conflict of Interest

The authors declared no conflict of interest.

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## Data Availability

Not available

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