BIOENGINEERING AND MEDICAL-SURGICAL SCIENCES

AMMIN - Decoding Emergent Functions in Cells: A Multiscale Mechanobiology Framework Linking Models and Experiments

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Context of the research activity	This research explores neuronal mechanobiology through an interdisciplinary, multiscale approach that integrates experimental and computational modelling. It aims to understand how mechanical forces and molecular interactions regulate brain development and function across scales, shaping neuronal architecture, plasticity, and their alterations in pathological conditions.
	Multiscale neuro-mechanobiology is an interdisciplinary research area that investigates brain development and function through mechanical forces at the molecular, cellular, and tissue levels. These forces contribute to neuronal circuit formation and adult brain plasticity, integrating with biochemical and genetic signals that regulate neurodevelopment. Malfunctions in these mechanisms can lead to neurological disorders. During neurodevelopment, proliferation, migration, axon formation, and synaptogenesis generate mechanical signals that shape cerebral morphogenesis through mechano-transduction pathways. Locally, microenvironmental stiffness, intracellular tension, and adhesion forces influence neuronal differentiation. Globally, tissue deformation contributes to brain topography. These processes span multiple length and time scales, requiring integrated theoretical and experimental tools. The specialized architecture of neurons—from dendrites to synaptic spines to axons—underpins their function. Microscopic changes, such as spine remodeling and dendritic outgrowth, directly affect synaptic transmission and plasticity. The cytoskeleton, composed of microtubules, actin filaments, and neurofilaments, links morphology to functionality. Motor proteins, crosslinkers, stabilizers, and regulators modulate these networks. Investigating their structure-function relationships reveals how mechanical properties emerge from molecular organization, connecting cell biomechanics to functional development. Long-term synaptic stability, and thus memory, may depend on persistent cytoskeletal rearrangements. Some theories even suggest consciousness may rely on the mechanical and organizational properties of

Objectives	individual neurons. The research integrates experimental analyses (e.g., biochemical assays, microscopy) with in silico modeling (e.g., molecular dynamics, docking, coarse-grained models). The experiments may involve neuronal cultures on 2D substrates with adjustable stiffness and 3D hydrogels or scaffolds with specific properties. Custom bioreactors deliver controlled mechanical stimuli replicating physiological or pathological cues. High-resolution imaging and tools like optical tweezers, stretchable substrates, and AFM will be considered to measure cellular and subcellular forces. Substrate mechanics will be characterized via multiscale testing (nanoindentation, rheology, compression) under normal and perturbed conditions (e.g., pharmacological stimulation, genetic modification). Electro-mechanical interactions can also be examined, focusing on how electric and electromagnetic fields affect neurons and cytoskeletal proteins known to be field-sensitive (e.g., tubulin, MAPs, actin, integrins), highlighting the role of ionic conduction in neurobiology. The methodological framework would be of interest for genetically-based neurodevelopmental or neurodegenerative conditions where loss-of-function mutations disrupt intracellular trafficking and cytoskeletal integrity, especially in motor neurons. These pathological models offer insight into how molecular deficits alter mechanical responsiveness, affecting neuronal structure, polarity, and resilience. In this connection, patient-derived iPSC models and targeted perturbations of endosomal and cytoskeletal pathways help identify mechanobiological vulnerabilities and therapeutic opportunities. Bioinformatics and multiscale modeling, including AI-assisted data analysis and generation, will integrate experimental results on functional patterns, disease mutations, and post-translational modifications affecting neuronal function. The research will follow an iterative cycle of simulation, validation, and prediction across scales from single proteins to networks. This synergistic approach, combining bioengineering, biomechanics, bioinformatics, and bionanotechnology, aims to establish a quantitative framework linking mechanical cues, mutations, and structural changes to cellular behavior and network connectivity. It will extend to pathological contexts, clarifying how mechanical dysfunction and abnormal protein interactions contribute to disease progression. A deeper understanding of subcellular organization could illuminate higher-order functions like memory, perception, and consciousness. The project offers a flexible and personalised development path shaped by the synergy among participating partners (Politecnico di Torino, Kansai Medical University, and others) and the candidate's background. It reflects modern bioengineering's integration of theory and experimentation to tackle complex, interdisciplinary challenges.

Skills and competencies for the development of the activity	This project is ideal for individuals with experience in bioengineering, biotechnology, neuroscience, molecular biology, or computational sciences. Key skills may encompass interest or experience in experimental neurobiology (such as cell culture, microscopy, and molecular assays), molecular modeling, bioinformatics, AI-driven data analysis, bioreactor design, and mechanical characterization. An interdisciplinary approach and a desire to learn across various fields are crucial.