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Perspective

Connections between physics and metabolism in brain functions

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SUMMARY

Advances in molecular biology have shaped our understanding of cellular biology. Yet, this molecular-centric approach has overshadowed the role of physical processes governing cellular homeostasis. In genetic disorders, particularly inherited metabolic diseases, phenotypic heterogeneity cannot solely be explained by genetic variants. Mechanical properties of cells and tissues may account for this variability, given the interplay between biological and physical cues in metabolic regulations. In July 2024, we organized an international symposium with world experts in physics, chemistry, and neurobiology to explore the physical regulation of brain metabolism in health and disease. Topics included mechanotransduction in neurodevelopment and brain aging, the physics of neurotransmission and cellular trafficking, and emerging methods to model cellular metabolism, analyze single-cell mechanical and transcriptional signals, and track nanoparticles in intact brain tissue. This effort aims to foster an interdisciplinary framework for neuroscience and train scientists across disciplines, while integrating art to stimulate creativity and integrative thinking.

INTRODUCTION

Our understanding of cellular biology has been fundamentally shaped by advances in molecular biology and biochemistry. Over the past decades, hundreds of identified genes were found to be associated with neurological disorders, both in rare and common neurodegenerative disorders, e.g., Parkinson's disease. However, this molecular-centric paradigm of brain functions in health and diseases has overridden one other essential aspect of cellular biology, i.e., physical processes and properties that regulate cellular homeostasis and pathology. Also, cells have often been considered as passive biochemical systems rather than dynamical physical entities. Yet, the laws of physics govern essential biological processes from cell mechanics and membrane and fluid dynamics to thermodynamics, neuronal bioelectrical signaling, and cellular bioenergetics.

In most genetic disorders, particularly in the field of inherited metabolic diseases (IMDs), we are facing the great challenge of phenotypic heterogeneity that cannot solely be explained by genetic variants.[1] So far, we have failed to identify other

biological factors underlying this large phenotypic expression in most IMDs. This poses day-to-day issues for patients' monitoring and treatment, especially for newborn screening programs of most IMDs, for which the early detection of pathogenic variants cannot predict the age of onset, from children to adulthood, and/or disease expressivity. It is plausible that the mechanical properties of cells and tissues may account for part of the phenotypic heterogeneity of IMDs, given the interplay between biological and physical cues in metabolic regulations.

Metabolism indeed plays a central role in *mechanotransduction*, i.e., mechanisms by which cells convert mechanical stimuli into biochemical or electrical signals.[2–4] For example, after a skin injury, nuclear swelling and membrane stretching in epidermal keratinocytes act as mechanical activation signals that trigger the translocation of the cytosolic phospholipase A2 from the nucleoplasm to the nuclear membrane so that arachidonic acid can be released and attract leukocytes to sites for tissue repair.[5] Furthermore, organelles such as the endoplasmic reticulum, the Golgi apparatus, the endo-lysosomal system, and the mitochondria play a central role in mechanotranduction,[6] as they can sense *mechanical forces* through membrane deformation, changes in lipid compositions (Figure 1A), alterations in organelle membrane contact sites, or the cytoskeleton.[7] All these cellular processes are key elements of cellular trafficking, and disorders of cellular trafficking have been recently outlined as a major new category of IMDs.[8]

Mechanical forces, such as *shear stress*, *tension,* and *compression,* can alter cellular metabolism by influencing enzyme activity.[9] More recently, mechanosensitive metabolites, or *mechanometabolites*, have been identified and refer to metabolites whose production, distribution, or function is influenced by mechanical forces within a biological system (Figure 1D).[10,11] For example, tissue and extracellular matrix (ECM) *stiffness* redirects glucose to the polyol pathway and increases intracellular sorbitol concentration, which in turn, promotes biomolecular condensates – i.e., membraneless assemblies that concentrate biomolecules in cells – and cell proliferation.[12] Therefore, sorbitol is a mechanosensitive metabolite enabling protein condensation to control mechano-regulated cellular functions, and *mechanosensitivity*[13] could contribute to the pathophysiology of several IMDs where sorbitol is involved. Another group of mechanosensitive molecules is integrins, a family of adhesion molecules that connect cells to the ECM and actively facilitate communication between the intracellular cytoskeleton and the external environment. Integrins, for instance, modulate neurotransmission by regulating the activity of multiple neuronal transmembrane channels and receptors in response to mechanical stimuli between the cells and the ECM.[14] Various forms of epilepsy have been associated with the increased expression of integrins and ECM proteins.[15]

Electromagnetic forces are other physical forces involved in cell biology. One example is the mitochondrial generation of weak *electromagnetic fields* (EMFs) as byproducts of their biochemical activity. These fields arise due to the movement of charged particles, particularly protons and electrons, within the mitochondrial electron transport chain and across the inner mitochondrial membrane. Mitochondria generated EMFs could play a role in mitochondrial-to-nuclear signaling or even intercellular communication. Dysfunctional mitochondria may alter their EMF patterns, potentially contributing to mechanisms of disease. On the other hand, pulsed EMFs may have therapeutic applications through improved mitochondrial dynamics.[16,17]

As the field of *mechanobiology* continues to develop, exploring the connections between physics and metabolism can provide new insights into the pathophysiology and phenotypic expression of IMDs. This integrative view may also contribute to the development of novel therapeutic approaches within the emerging field of *mechanomedicine*. In that framework, on July 5th, 2024, we organized an international symposium that brought together world experts in physics, chemistry, and neurobiology (Figure S1) to better understand the physical mechanisms underlying brain functions in health and diseases, to foster new collaborations between these sister disciplines and promote "night science," a creative interdisciplinary, hypothesis-generating approach that transcends traditional disciplinary boundaries.

PHYSICS AND BRAIN FUNCTIONS

Mechanotransduction is critically important in brain functions, from neurodevelopment and physiology to pathology.[13,18] Eva K. Pillai, from the European Molecular Biology Laboratory in Heidelberg (Germany) and Pasteur Institute in Paris (France), presented an overview of how physical forces shape our nervous system, including the mechanical signals encountered by cells of the nervous system, mechanisms of mechanotransduction, and mechanical regulation of neurodevelopmental processes at multiple scales.[19] She provided examples of how cells translate mechanical signals into biochemical responses, such as the unfolding of cryptic binding sites, the opening of mechano-sensitive ion channels (e.g., changes in membrane curvature or stretching will increase opening of the channel – Figure 1C), and the transport of transcription factors to the nucleus mediated by cell mechanical properties.[20] In stiff environments, cells are stretched out, and these tensile forces are transmitted via the cytoskeleton to the nucleus, which opens the nuclear pore complex and allows facilitated transport of transcription factors between the cytoplasm and the nucleus. Dr. Pillai also illustrated how mechanics impact brain development. At the tissue scale, cortical lamination and folding are driven by mechanical events such as cell migration, differential growth, and tissue buckling.[21,22] Furthermore, the growth and turning behavior of bundled neuronal projections is modulated by tissue stiffness.[19,23] On the cellular scale, in a softer environment, neural stem cell proliferation increases,[24] and upon proliferating, their cell fates are determined by environmental stiffness.[25] On the other hand, at a subcellular level, applying tension to a neurite results in the formation of axons,[26,27] and at an even smaller scale still, mechanical forces play a significant role in synapse formation and plasticity by influencing the structural and functional remodeling of neurons.[28] Broadly, this talk highlighted the profound influence of mechanical forces on brain structure and function, emphasizing mechanotransduction as a fundamental player across multiple biological scales.[12]

Later in life, cells continue to adapt, shape, and respond to their mechanical environment. There is constant feedback

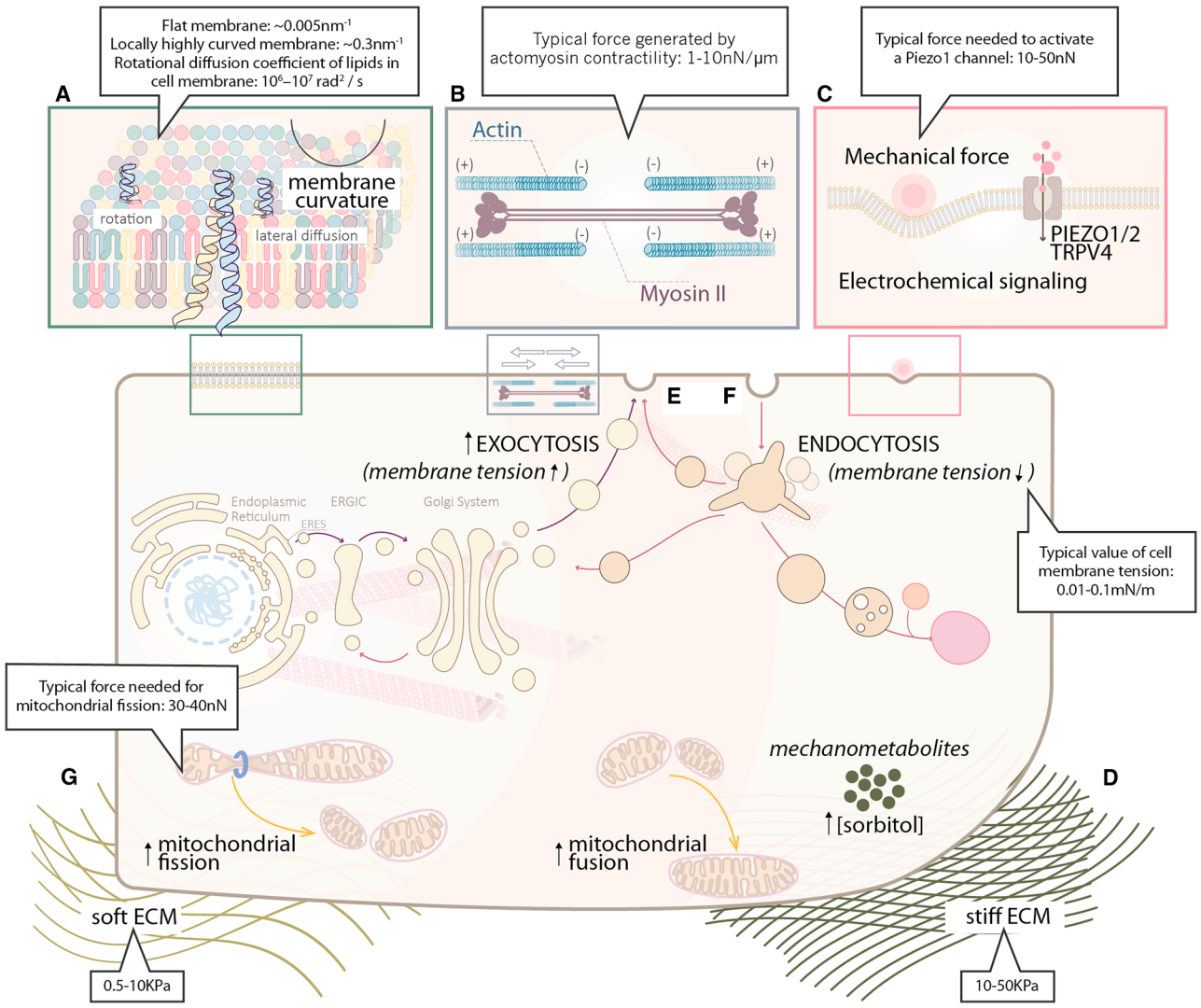

Figure 1. Examples of connections between physics and metabolism in brain functions

(A) Changes in membrane lipid composition influence the rotational and translational diffusion of membrane lipids and proteins as well as membrane curvature and functions, including opening of ion-channels.

(B) Actin and myosin II form contractile actomyosin networks that regulate cell mechanics by producing intracellular tension and coordinating force transmission across the cytoskeleton.

(C) Mechanoreceptors such as PIEZO1/2 and TRPV4, can sense mechanical forces such as pressure, vibration, stretching, and touch in order to convert mechanical signals into electrochemical signaling.

(D) Mechanometabolites are mechanosensitive metabolites whose production, distribution, or function is influenced by mechanical forces. Stiffness of the extracellular matrix (ECM) redirects glucose to the polyol pathway and increases intracellular sorbitol concentration, which promotes cell proliferation.

(E and F) Both endocytosis and exocytosis are very active physical processes. Protein binding plays a critical role in membrane curvature and the formation of tubules/vesicles in the endocytic process. Furthermore, the process of synaptic vesicle priming is an essential determinant of exocytosis and synapse function.

(G) Organelles such as mitochondria are involved in mechanotransduction as they can sense mechanical forces through membrane deformation. For example, mechanical signals such as ECM softness induce mitochondrial fission. Mitochondrial fission is also involved in mechanotransduction, a cellular process called mitochondrial mechanotransduction.

Representative ranges of mechanical and biophysical parameters in cells are indicated in annotation boxes.

between cells and the ECM, which constitutes up to 20% of the brain volume. It contains collagen, which confers mechanical integrity and stiffness, elastic fibers (e.g., elastin), which confer mechanical memory, and proteoglycans and glycosaminoglycans (e.g., hyaluronic acid), which confer viscosity and buffering to tissue. The ECM changes in the brain with aging and disease. Kevin Chalut, from Altos Labs Cambridge Institute of Science in Cambridge (United Kingdom), discussed how a healthy ECM could support brain health, how the ECM changes with age and disease, and evidence that those changes in the matrix lead to loss of function and exacerbate disease states. The starting observation was that stem cells can self-renew and

differentiate, but not in aging. In the brain in particular, aged oligodendrocyte progenitor cells (OPCs) stop proliferating, unlike neonatal OPC, and there are no clear biological factors underlying these differences. Remarkably, aged ECM is much stiffer than neonatal ECM, so that tissue stiffening may drive the loss of function of OPC. Experimentally, this hypothesis is plausible as the authors showed that aged OPCs proliferate on soft hydrogels, similarly to neonatal OPCs, while neither neonatal nor aged OPCs proliferate on stiff hydrogels.[29] RNA sequencing analyses further confirmed that aged OPCs are rejuvenated genome wide on soft hydrogels. The same results were obtained in aged OPC after inhibition of the *mechanoreceptor* PIEZO1,[30,31] a large mechanosensitive ion channel (Figure 1C).[29] Therefore, it is possible to override physiological age by interfering with mechanical signaling through softer ECM or PIEZO1 silencing.

VESICULAR TRAFFICKING AND NEUROTRANSMISSION

Inherited disorders of cellular trafficking have recently been refined into 4 categories[8]: vesicular trafficking (exocytosis and endocytosis – Figure 1E and 1F), membrane contact sites, autophagy, and cytoskeleton trafficking. IMDs affecting neurotransmission encompass both exocytosis and endocytosis and often result in complex neurological phenotypes with movement disorders – predominant hyperkinetic disorders in IMDs mostly affecting exocytosis versus predominant hypokinetic disorders in IMDs affecting, in most cases endocytosis.[8] Fran López Murcia from the Universitat de Barcelona (Spain) addressed exocytosis and presented dynamic regulations of presynaptic function and plasticity in health and disease. The release of neurotransmitters requires the priming and docking of vesicles thanks to the *SNARE* (soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptors) complex. The process of synaptic vesicle priming is an essential determinant of synapse function, strength, and plasticity because it maintains a pool of readily releasable vesicles at any given time and determines the time course of synaptic fatigue and recovery. The corresponding forms of synaptic short-term plasticity determine multiple complex brain functions, from sensory adaptation to working memory. There are 4 states of synaptic vesicle priming and fusion: (i) empty site ready for docking, (ii) site occupied with loosely docked (LS) synaptic vesicles, (iii) site occupied with tightly docked (TS) synaptic vesicles, and (iv) synaptic vesicle fusion.[32] These 4 steps are calcium dependent and are reversible except for synaptic vesicle fusion. Dr. López Murcia exposed a mathematical model that underlies heterogeneity in short-term plasticity among synapses, which is attributed to a distinct proportion of synaptic vesicles residing in the LS and TS states at stimulation onset.[33,34] From a fusion-centric approach of neurotransmitter release, the model has moved to a priming-centric approach that takes into account the heterogeneity of docked/primed synaptic vesicles, and that explains different plasticity among neurons. The families of Munc13 and Munc18 proteins play an important role in synaptic vesicle priming.[35] Pathogenic variants in *Munc18-1* (also called *STXBP1*) are the most common SNAREopathy and lead to a neurodevelopmental disorder with intellectual disability and, in many patients[36] epilepsy and hyperkinetic movements that may evolve toward parkinsonism in older patients. Pathogenic variants in *Munc13* (also called *UNC13A*) also cause a neurodevelopmental encephalopathy comprising epilepsy and movement disorders.[37]

Synaptic transmission involves the constant formation of new synaptic vesicles through endocytosis, after their fusion with the plasma membrane. Endocytosis comprises different steps, starting from fast-endophilin mediated endocytosis that is clathrin-independent[38] and involves the deformation of the plasma membrane and formation of a tubule/vesicle. Then, more defined vesicles are formed, coated with clathrin. Patricia Bassereau, from the Curie Institute and Sorbonne University in Paris (France), provided insights on membrane biophysics in the endocytic process. Indeed, the energy required to form a vesicle is a factor of the membrane bending rigidity modulus, but independent of the size of the vesicle. Membrane curvature, though, is modulated by the binding of BAR-domain proteins: the more proteins and the more curved the proteins are, the more the membrane is curved, and the less energy is required.[38] Dr. Bassereau presented biophysical tools that have contributed to understanding the mechanisms by which proteins and membranes cooperate to form small buds and secede them. She detailed an *in vitro* assay based on the formation of a membrane nanotube, using a giant liposome mimicking the plasma membrane or an internal compartment, held by a micropipette, and a bead in an optical trap to pull a membrane tube from the liposome.[39] The radius of the membrane tube changes with the micropipette aspiration. Then, proteins, e.g., BAR-domain proteins, are added to the system. Protein binding, measured by fluorescence, was shown to increase with membrane curvature, with a maximum corresponding to the intrinsic curvature of the ''banana-shape'' of the protein. Thus, the recruitment of these proteins and binding to vesicles is a curvature-matching mechanism where proteins are recruited sequentially to the nascent bud, depending on their shape, contributing to membrane remodeling.[39] Once vesicles have been formed thanks to coating proteins, the next steps of endocytosis involve fission and uncoating with proteins such as LRRK2 and DNAJC6, which are associated with adult and juvenile-onset forms of Parkinson's disease, respectively.[40]

CYTOSKELETON TRAFFICKING

The cytoskeleton is essential to the transport of vesicles and organelles throughout the cell. It consists of a dynamic network of *microtubules* (long tubular polymers of alpha- and beta-tubulin heterodimers), actin filaments, and motor proteins (myosin, dynein, and kinesin) that allow anterograde and retrograde transport of cargoes (Figure 1B). Regarding the microtubule-associated trafficking, pathogenic variants have been identified in genes encoding tubulins[41] (such as *TUBB4A* involved in both a hypomyelinating leukodystrophy and the so-called whispering dysphonia), dyneins (such as *DCTN1* involved in both complex forms of Parkinson's disease and amyotrophic lateral sclerosis), and kinesins (such as *KIF1A*, *KIF1C,* and *KIF5A* involved in spastic paraplegia, cerebellar ataxia, and neurodevelopmental disorders).[42] Anne Straube, from the

Center for Mechanochemical Cell Biology, University of Warwick in Coventry (United Kingdom), summarized current knowledge on microtubule organization in neurons, intracellular transport, and the regulation of microtubule-based motors. Anterograde transport along microtubules is predominantly powered by kinesins and retrograde transport by dyneins. Accordingly, the observation that bidirectional cargo transport occurs cannot be explained theoretically by oppositely directed molecular motors present simultaneously on microtubules. In order for transport cargoes to move in both directions and avoid a "tug-of-war," Prof. Straube proposed a codependency model by which the mutual activation of dynein and kinesin occurs through a shared adapter called HOOK3.[43] In this model, HOOK3 allows to activate both autoinhibited dynein and autoinhibited KIF1C, but (i) KIF1C is partially engaged during transport toward the minus-end of the microtubule so that dynein can drive retrograde transport almost unimpeded and with extended run length; and (ii) dynein is only partially engaged during KIF1C-driven transport toward the plus-end of the microtubule. Since many adapters bind both dyneins and kinesins, this mechanism could be generalized to other bidirectional complexes.[43]

The microtubule-associated protein, Tau, has been identified as a modulator of motor proteins. In Alzheimer's disease, Tau becomes hyperphosphorylated and disengages from microtubules, forming neurofibrillary tangles. Besides their involvement in rare neurogenetic disorders and Alzheimer's disease, Stuart Hameroff, from the University of Arizona in Tucson (USA), addressed the possible role of microtubules in the pathophysiology of other common neurological disorders and implications for treatments. Non-invasive brain stimulation methods such as transcranial magnetic stimulation have shown benefit in the management of pain and psychiatric disorders. Prof. Hameroff conducted a pilot randomized controlled trial using another non-invasive brain stimulation method, transcranial ultrasound. Adult patients presenting with chronic pain experienced improvement in subjective mood after the application of sub-thermal transcranial ultrasound (8 MHz) compared to placebo. The authors hypothesized that ultrasound (megahertz mechanical vibrations for imaging) may have exerted therapeutic benefits by resonating endogenous microtubule megahertz vibrations.[44] Given the role of microtubules in neurodevelopmental disorders, Prof/Hameroff further hypothesized that low intensity transcranial ultrasound may have therapeutic applications in pediatric developmental disorders. Other transcranial ultrasound studies have indeed demonstrated disease-specific therapeutic potential, with low-frequency protocols targeting neurodegenerative disorders and high-frequency parameters effectively alleviating motor symptoms.[45]

THE NEED FOR METHOD DEVELOPMENTS

Our understanding of cell biology and metabolism has been greatly determined by methodological developments. At the beginning of the 20th century, optical microscopy led to the identification of synapses and organelles such as the Golgi apparatus. In the 1960–1970's, electron microscopy uncovered synaptic vesicles and the process of exocytosis/endocytosis in neurotransmission. More recently, *tomography electron microscopy* has allowed analyzing interactions between organelles, including synaptic vesicles, in three-dimensional domains.[46] Furthermore, the progress in *Brillouin microscopy* provides a label-free and contact-less method to characterize the mechanical properties of tissues at the cellular and subcellular scales[47] (Table 1). Accordingly, our understanding of metabolic networks and their connection with mechanical cues will also be driven by new methodological developments. This symposium has illustrated a few promising approaches.

Modeling cellular metabolism

Marta Sales-Pardo, from the Universitat Rovira i Virgili in Tarragona (Spain), presented computational approaches to model cellular metabolism and obtain a more comprehensive insight from metabolic data.[65] Indeed, the use of network science and probabilistic approaches combined with metabolic reconstructions of cellular metabolism can be used to identify how external perturbations affect metabolic pathways globally. Mathematically, the metabolic network can be expressed in a matrix form, i.e., a stoichiometric matrix, to study metabolic fluxes. In 2018, the Recon 3D genome-scale metabolic model reconstruction was achieved, representing over 13,000 metabolic reactions in humans. However, metabolic reconstruction should be context-specific, taking into account both cell type and dynamic metabolic states. Dr. Sales-Pardo used an *in vitro* model of diabetic retinopathy in which the metabolome was compared between cells cultured in high versus normal concentrations of glucose and under hypoxia versus normoxia. With traditional approaches such as volcano plots, significant alterations of metabolites can be identified, but without input from existing knowledge on metabolism. Instead, a full reconstruction of human metabolism allows adding metabolomic data on top of known metabolic networks.[66] These computational system-level network approaches to metabolism can uncover biological alterations not visible at first sight. In the case of the *in vitro* model of diabetic retinopathy, the authors showed that the whole metabolic network is affected by high glucose concentrations, as opposed to being localized in particular pathways of the network. Thus, choosing a system perspective approach implies not disregarding potentially important information on the whole network.

Integrating physics and biology in evolution

Further to system biology, Lee Cronin, from the University of Glasgow (United Kingdom), exposed his new theory of evolution called the *assembly theory* and its applications in explaining evolution in biology, the emergence of complexity, including brain structures, and the ability to process information.[67] Assembly theory provides a new framework to understand selection and evolution that integrates physics and biology. It redefines objects not as particles but by their formation histories. In summary, if there is a complex object that one can find in higher numbers, then it cannot be randomly formed. Assembly theory allows us to describe the possible formation histories of objects,[67] taking objects and cutting them up, and rebuilding blocks such as metabolites.[68] Assembly pathways start with a set of basic building blocks, joining operations, and reuse. The assembly index is the minimum number of steps needed to construct an object

Table 1. Experimental methods allowing to measure the mechanical properties of soft biological tissues *ex vivo* and *in vivo*

Method	Mechanical Quantity	Value range	Tissue types	Force range applied	Strain/indentation	Reference
Atomic Force Microscopy (AFM)	Elastic modulus, viscoelastic properties	~0.1 kPa–100 kPa	Brain, skin, gut, solid tumors, etc.	~10 pN to 100 nN	~0.1 nm to 10 μm	Guimarães et al.,[48] Cho et al.,[49] Shen et al.,[50] Haase and Pelling[51]
Nanoindentation	Elastic modulus, viscoelastic properties	~0.1 kPa to 1 MPa	Brain, liver, gut, solid tumors, etc.	~1 μN to1 mN	~1 nm to 100 μm	Guimarães et al.,[48] Wu et al.[52]
Tensile Testing	Tensile strength, strain, elastic modulus	kPa to MPa	Skin, uterus, esophagus, solid tumors, etc.	~10 μN to 20 N	up to ~150% elongation	Guimarães et al.,[48] Rosalia et al.[53]
Micropipette Aspiration	Cell/tissue deformability, cortical tension.	Several kPa	Cells aggregates or organoids.	nN to μN range (pressure-dependent suction force)	< ~50% deformation of cell membrane	Suresh et al.,[54] Guevorkian and Maître[55]
Tonometry	Tissue stiffness	Pressure ~10–30 mmHg	Eye (cornea, sclera), gut, etc.	mN to N range from calibrated tonometer probe	~0.1 μm–1 μm	Chevalier et al.[56]
Brillouin Microscopy	Longitudinal modulus via frequency shift	~0.1 kPa to 10 MPa	Brain, skin, teeth, bone.	Contactless (optical method)	Negligible	Kabakova et al.,[57] Prevedel et al.[58]
Magnetic Resonance Elastography (MRE)	Shear modulus, tissue stiffness	~1 kPa–100 kPa	Brain, liver, gut, solid tumors.	~1-10 mN (contactless mechanical vibration)	<1% shear strain	Meyer et al.,[59] Muthupillai et al.[60]
Ultrasound Elastography (USE)	Shear modulus, tissue stiffness	~1 kPa–100 kPa	Solid tumors, skin, gut.	~0.1–1 N (probe contact mechanical vibration)	Strain: ~1–20%	Sigrist et al.,[61] Gennisson et al.[62]
Optical Coherence Elastography (OCE)	Elastic modulus, strain, spatial stiffness maps	~0.1 kPa–10 kPa	Skin, eye, gut, solid tumors.	~1 μN to 1 mN (contactless mechanical vibration)	Strain: ~0.1 μm–1 μm ~1–2%	Wijesinghe et al.,[63] Kennedy et al.[64]

This table describes existing experimental methodologies that allow the mechanical properties of soft biological tissues to be measured. For each method, the mechanical quantities measured, and their respective value ranges are provided, along with the force range applied, the resulting strain range, and the tissue types on which the method has been applied.

from its basic parts. It allows us to quantify the "selection needed" to produce that object.[69] From complexity, one can infer how much time in evolution was needed to make that object. Intelligence or biology may take a longer route, but the assembly index is the shortest route to establish that the object was made by evolution and not by chance. For metabolites, the assembly index can be determined experimentally, for example, by mass spectrometry.[68]

Integrating mechanics and transcriptomics

Physical and biological methodologies can also be integrated experimentally. To illustrate how they can be combined, Adrien Hallou, from the University of Oxford (United Kingdom), presented a new and unique methodology named *spatial mechano-transcriptomics*. This is a new computational framework that enables the joint statistical analysis of mechanical and transcriptional signals at single cell resolution in the context of spatial transcriptomics experiments.[70] Spatial mechano-transcriptomics was applied to study mouse embryogenesis, which is a complex and multiscale process involving different players at different spatial and temporal scales: molecules (e.g., growth factors and morphogens), cells (e.g., adhesion, motility, and contractility), and tissues (e.g., architecture and shape changes driven by mechanical forces). Spatial transcriptomics data were obtained using sequential fluorescence *in situ* hybridization (SeqFISH) on over 400 genes, and full transcriptome information was recovered from single cell RNA sequencing data from the mouse gastrulation atlas.[71] Mechanical forces were derived from image based mechanical force inference, a method that uses cell shapes obtained from image segmentation to infer mechanical forces based on force balance and the *Young-Laplace law*. Applying this combined framework, Dr. Hallou derived both mechanical forces and gene expression from each cell of the developing mouse embryo and identified mechano-associated gene expression profiles that are predictive of cell fate decisions and spatial patterning at the tissue and whole organism level.[70] In the field of IMDs, spatial mechano-transcriptomics could be applied to many models to combine the analyses of mechanical forces at the cellular level with altered gene and signaling pathways. For example, in patients with congenital disorders of glycosylation (CDGs) presenting with *cutis laxa*, mechano-transcriptomics may allow to understand how abnormal cellular

trafficking results in the defective synthesis of elastic fibers and other proteins of the ECM from the skin.[72] Established methods to spatially profile tissue stiffness, such as AFM or nanoindentation (Table 1), could be combined with spatial mechano-transcriptomics to better understand the links between ECM mechanical properties and gene expression. Similarly, newly available spatial metabolomics[73] may also be combined with image based mechanical force inference to provide spatial mechano-metabolomic maps of tissues at cellular resolution.

Bridging functional and molecular brain imaging

It would also be key to bridge functional imaging with molecular imaging to the ultimate sensitivity and resolution of single molecules in action.[74] Physics can contribute to this endeavor through the study of dynamic processes in the brain with nanometer resolutions. Laurent Cognet, from the Institut d'Optique d'Aquitaine in Bordeaux (France), showed how the combination of single-molecule optical microscopy approaches with near-infrared emitting nanoparticles and analytical methods derived from super-resolution microscopy has enabled the shedding of new light on the dynamic molecular organization of brain molecules and structures in health and disease.[75,76] The strategy implied the detection of a single nanoparticle in an intact tissue, that is, a molecule stable enough to be observed for a long time, small enough to have a large diffusion in the extracellular space, and with slow motion so that many data points can be collected. Accordingly, luminescent single-walled carbon nanotubes were selected for their near-infrared emission, where biological tissues are most transparent, and their detection was based on single particle tracking together with the super localization of emitter positions with precisions below 50 nm.[77] These nanosensors were made biocompatible and do not penetrate into cells because they are PEGylated phospholipids.[78] These methods have allowed us to explore the extracellular space that contains the interstitial fluid and the ECM.[79] The ECM is key to convey biochemical signals and intercellular communication and is likely involved in the pathophysiology of IMDs such as CDG, but also mucopolysaccharidoses[80] or congenital disorders of glycosaminoglycan synthesis.[81]

DISCUSSION

Metabolism and cellular mechanics are closely intertwined, so that each should be studied in light of the other to better understand cell and tissue physiology in health and disease. Mechanical forces, sensed through the cytoskeleton or organelles, induce metabolic changes in the cell, which in turn modify the mechanical properties of cells and tissues.[9] Likewise, the cytoskeleton regulates energy metabolism (e.g., actin fiber disassembly causes the release of the actin filament-associated metabolic enzyme aldolase, thereby enhancing glycolysis), while energy metabolism plays a central role in cytoskeletal dynamics.[7] (e.g., ATP molecules are necessary to support transport of motor proteins on microtubules). The dynamic interactions of metabolic enzymes with actin filaments and microtubules are facilitated by the localization of these enzymes to areas of the cell with high energy demand so that the cytoskeleton can respond to metabolic activity and ensure adequate ATP production. We have to approach the interactions between mechanical forces and metabolism as reciprocal regulations whereby metabolic state can alter cellular *mechanosensitivity* and vice versa, a process described as *metabo-reciprocity*. Thus, mitochondrial metabolism and mechanotransduction are closely interconnected (Figure 1G).[82] Mitochondria serve as central hubs that integrate mechanical and metabolic signals, with their morphodynamics adapting to both cues.[83] Mechanical signals, such as ECM stiffness or cell stretching, induce mitochondrial elongation through fusion while suppressing DRP1-mediated fission. Conversely, mitochondrial fission contributes to mechanotransduction in a process termed mitochondrial mechanotransduction (MIME), involving the transcriptional activators YAP and TAZ, which transmit mechanical signals from the cytoskeleton to the nucleus.[82] Understanding these processes is critical for studying cellular metabolism – including intermediary metabolism, lipid trafficking, and organelle function – as well as for explaining phenotypic variability in patients with IMDs.

Integrating mechanobiology, metabolism, systems neuroscience, and aging research highlights that mitochondrial dysfunction, disrupted energy metabolism, altered mechanotransduction, and chronic neuroinflammation act synergistically to drive age-related neurological decline.[84] Age-associated changes in tissue stiffness and cytoskeletal mechanics impair mitochondrial trafficking, dynamics, and mitophagy, leading to increased reactive oxygen species (ROS) and energy deficits in neurons and glia. Aging also disrupts metabolic coordination between neurons and glia, reducing ATP production and creating a pro-inflammatory environment that harms synapses and promotes cell death.[85] Microglia respond to these mechanical and metabolic cues by shifting from oxidative phosphorylation to glycolysis, sustaining long-term neuroinflammation and exacerbating neuronal damage.[86] Damaged mitochondria amplify inflammation further through ROS and mitochondrial DNA release, generating a self-perpetuating cycle of metabolic stress, impaired mechanotransduction, and immune activation – a key concept in mechano-immunology of the aging brain.[87] This mechano-metabolic-immune feedback loop shares parallels with cancer biology, where mechanical cues from a stiffened tumor microenvironment drive metabolic reprogramming (e.g., altered mitochondrial dynamics, glycolysis, and ROS signaling) to support cancer cell survival and metastasis.[88] These interconnected processes compromise neural circuits and cognitive function and contribute to neurodegenerative diseases, where mitochondrial loss, metabolic imbalance, altered tissue mechanics, and persistent neuroinflammation collectively drive progressive dysfunction. Clinically, tools such as *magnetic resonance elastography* (MRE) allow the *in vivo* measurement of tissue mechanics (Table 1), linking cellular mechanotransduction to systems-level brain function. Notably, MRE studies have shown that stiffness of regions such as the medial temporal lobe predicts future cognitive decline in Alzheimer's disease more accurately than traditional measures of atrophy amyloid load,[89] highlighting the translational relevance of mechano-metabolic alterations in aging and neurodegeneration.

It is striking that the scientific disciplines of biology, physics, and chemistry have become increasingly compartmentalized in academic training and scientific practice. This divergence can

be attributed to historical differences in their development and methodological approaches, and (necessarily) specialization as we deepened our knowledge of each subject. In the 19th and 20th centuries, advancements in microscopy and molecular biology, both based on advances in physics, accentuated this separation. Yet, understanding complex life processes increasingly demands bridging these disciplinary divides. In 1944, Erwin Schrödinger published "What Is Life?," a scientific book that explores how the laws of physics can explain fundamental biological processes.[90] The key ideas of the book included: (i) living organisms maintain order and resist entropy (disorder) by consuming "negative entropy" (later understood as free energy from the environment); (ii) hereditary information is stored in "an aperiodic crystal," anticipating the discovery of DNA's structure in 1953; (iii) quantum principles may play a role in biological stability and mutations. These ideas anticipated how physics and biology began to converge in the late 20th century with the advent of molecular biology and, more recently, driven by imaging technologies, single cell and spatial genomics, and computational modeling and machine learning.

In our contemporary world, the study of living systems has increasingly been shaped by disciplinary fragmentation, rooted in the modern scientific separation between empirical observation and metaphysical reflection.[91] This fragmentation not only constrains how we understand complexity but also exemplifies what Kuhn identified as the paradigm-driven nature of scientific specialization.[92] Nevertheless, traditions of integrative thought have persisted throughout history. In ancient Greece, Pythagoras asserted the intimate connection between music and mathematics through the laws of harmony, while Euclid's geometry embodied a pursuit of aesthetic and ontological unity. In the Middle Ages and the early modern period, music and astronomy were considered part of mathematics along with arithmetic and geometry, forming the Quadrivium. At the end of the 18th century in Jena, Germany, poets such as Novalis, alongside philosophers and theologians, emphasized the role of feeling as an essential component of experience. In the present day, contemporary scientists and thinkers such as Basarab Nicolescu and Edgar Morin reaffirm the need to transcend disciplinary boundaries and reconnect fragmented knowledge.[93,94] They advocate for a transdisciplinary approach that integrates multiple levels of reality, objective, subjective, and *trans*-subjective, in order to address the complexity of living systems more adequately. Consistent with these integrative perspectives, the symposium on physics and metabolism integrated arts, music, and paintings as key elements to address our quest for understanding the living. Because art is interdisciplinary, encourages thinking outside of conventional frameworks, and has a unique capacity to represent abstract processes (e.g., molecular structures), we wished to explore how the integration of art in science can strengthen our associative thinking and foster creativity in our scientific thought process.[95]

CONCLUDING REMARKS AND THERAPEUTIC PERSPECTIVES

We trust that this first symposium highlighting connections between physics and metabolism in brain functions opened the path to support an integrative view of cell biology in IMDs, structured not only according to intracellular molecular pathways, but also taking into account cellular architecture that is driven by mechanics within cells (i.e., cellular trafficking and mechanics of organelles), across cells, with the ECM (e.g., stiffness), and, more largely, with environmental factors (e.g., temperature, mechanical stimuli, and electromagnetic fields).[96] The possibility to combine mechanical, biochemical, and genomic methodologies in our studies of IMDs will be greatly enhanced by *in vivo* approaches such as MRE or ultrasound elastography, as well as *in vitro* platforms like *mechanomics*.[97]

Ultimately, these integrative approaches hold the potential to develop therapeutics that not only bypass deficient metabolic pathways but also compensate for altered metabolism by enhancing cellular and ECM mechanics. Therapeutic strategies targeting brain disorders increasingly focus on this interplay between ECM mechanics, cellular metabolism, and mechanotransduction. ECM-targeted interventions include the enzymatic remodeling of inhibitory components (e.g., chondroitin sulfate proteoglycans in perineuronal nets) to enhance synaptic plasticity,[98] as well as biomaterial scaffolds[99] and glycosaminoglycan-based hydrogels[100] that restore matrix stiffness, provide mechanical support, modulate neuroinflammation, and facilitate neuronal integration and regeneration. Modulation of matrix metalloproteinases and their inhibitors further balances ECM remodeling, synaptic formation, and immune responses.[101] Complementary metabolic approaches aim to restore glucose homeostasis, taking advantage of the tight coupling between ECM mechanics, post-translational modifications, and neuronal signaling.[102] Beyond structural and metabolic support, mechanotransduction- and transport-targeted strategies offer additional therapeutic avenues. Sonogenetic stimulation via ectopic mechanosensitive channel expression combined with focused ultrasound enables precise temporal and spatial control of neuronal activity, offering a non-invasive route to restore function in disorders such as vision loss.[103] Similarly, multivalent modulation of blood-brain barrier transport via LRP1-targeting polymersomes enhances amyloid β clearance and improves cognition in Alzheimer's models,[104] demonstrating that restoring mechanical and trafficking dynamics at the cellular interface can have systemic therapeutic effects. We are entering a new era in the study of IMDs, i.e., mechanometabolism,[11] which promises to enrich our field through greater interdisciplinarity while uncovering new dimensions of human health and disease.

Methodological overview

This Perspective synthesizes scientific concepts, discussions, and emerging hypotheses presented during the international symposium "Connections between Physics and Metabolism in Brain Functions" held on July 5th, 2024, at Sant Joan de Deu hospital (Barcelona).

No new experimental procedures were performed.

The figures and tables were created using conceptual models derived from published literature and symposium presentations.

GLOSSARY

Assembly theory: This is a framework used to understand the complexity and origin of molecular structures by analyzing the minimal steps required to build a given molecule from simpler components. It may be used in the context of origin-of-life studies and systems chemistry to assess the informational content and the likelihood of a molecule forming naturally.
Brillouin microscopy: It refers to an optical imaging technique that measures the mechanical properties of biological tissues – e.g., stiffness or elasticity – by detecting how light interacts with microscopic acoustic vibrations inside the sample (Table 1).
Compression: A mechanical force that occurs when an object is pressed or squeezed, resulting in a decrease in volume or length. In biology, it affects cellular shape, structure, and signaling.
Electromagnetic force: A fundamental force in physics describing the interaction between electrically charged particles, combining electric fields and magnetic fields into a unified theory.
Electromagnetic fields: Regions of space where electric and magnetic forces interact. These fields can influence biological systems, especially those involving ions or charged molecules.
Magnetic resonance elastography: A non-invasive imaging technique that uses MRI to measure the stiffness or elasticity of tissues by analyzing their response to mechanical vibrations (Table 1).
Mechanical forces: Physical forces such as tension, compression, and shear that affect cells and tissues. These forces influence cell behavior, development, and disease progression.
Mechanobiology: An interdisciplinary field studying how mechanical forces influence biological systems at molecular, cellular, and tissue levels.
Mechanomedicine: The application of mechanical principles to diagnose, monitor, or treat diseases. It bridges mechanobiology with clinical practice.
Mechanometabolites: Metabolic products that are produced or regulated in response to mechanical stimuli, linking physical forces with cellular metabolism (Figure 1D).
Mechanometabolism: The study of how mechanical forces influence cellular and tissue metabolism, playing a role in development, homeostasis, and disease.
Metabo-reciprocity: Reciprocal regulation whereby metabolic state can alter cellular mechanosensitivity and vice versa.
Mechanomics: A systems biology approach to understanding how mechanical forces regulate gene expression, signaling pathways, and overall cellular behavior.
Mechanoreceptors: Mechanoreceptors are specialized sensory cells or nerve endings that respond to mechanical stimuli such as pressure, vibration, stretching, and touch. They play a crucial role in the somatosensory system, allowing organisms to perceive physical changes in their environment and within their own bodies (Figure 1C).
Mechanosensitivity: The ability of cells or tissues to detect and respond to mechanical stimuli, often through specialized receptors or structural elements.
Mechanotransduction: The process by which cells convert mechanical signals into biochemical responses, allowing them to adapt to their physical environment.
Microtubules: Cylindrical components of the cytoskeleton made of tubulin, playing a key role in maintaining cell shape, transport, and mechanosensing.
Shear stress: A type of mechanical force that occurs when layers of fluid or tissue move parallel to each other, causing deformation. It's critical in blood flow and endothelial function.
SNARE: SNARE (Soluble NSF Attachment Protein Receptor) proteins are essential components of the cellular machinery responsible for vesicle fusion. They mediate the docking and merging of vesicles with target membranes, such as in neurotransmitter release at synapses or during intracellular trafficking, ensuring precise delivery of cargo within cells.
Spatial mechano-transcriptomics: An advanced technique that combines spatial transcriptomics with mechanical analysis to study how mechanical forces affect gene expression in specific tissue regions.
Stiffness: A biomechanical property which denotes the resistance to deformation when subjected to mechanical stress (Table 1).
Tension: A pulling force applied to an object or tissue that can elongate or stretch it. Tension affects cell signaling and structural integrity.
Tomography electron microscopy: A 3D imaging method using electron microscopy to reconstruct the ultrastructure of cells or tissues at high resolution by combining multiple angled images.
Young-Laplace law: A physical principle that describes the relationship between surface tension, pressure, and curvature in structures like bubbles or biological membranes.

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AUTHOR CONTRIBUTIONS

Conceptualization, F.M. and A.G.C.; investigation, P.B., K.C., L.C., L.C., S.H., F.J.L.M., E.K.P., M.S.P., A.S., and A.H.; writing—original draft, F.M., A.D.O.S., and A.G.C.; writing—review and editing, L.P.P., J.R.C., P.B., K.C., L.C., L.C., S.H., F.J.L.M., E.K.P., M.S.P, A.S., and A.H.; funding acquisition, J.R.C. and A.G.C.; supervision, F.M., J.R.C., and A.G.C.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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