WHAT'S NEXT IN MECHANOBIOLOGY: Missing tools related to the physics of the system

The mechanobiology field has spread out remarkably over the last years, due notably to the development of elaborated methods to probe and quantify the forces exerted by cells and tissues at different scales. However, lots remains to be understood in this interdisciplinary field and novel exciting questions are emerging for which answers will probably require a broader range of expertise. In this editorial, we will therefore review the current challenges we identified over the mechanobiology round table session at the last Mifobio meeting and the leads to explore to meet these needs.

A central element to mechanobiology is the understanding of how cells probe their extracellular environment and exert traction forces to mediate different cellular responses. Scientists have thus rapidly developed a wide variety of efficient tools to measure cell substrate interactions. **On the contrary, measuring intercellular forces turns out to remain challenging**. Great effort has recently been made in that direction by characterizing cell-cell forces from cell substrate interactions, by using molecular FRET sensors or by incorporating deformable probes directly inside the tissue. **Even though these methods have proven very useful, they are still limited in terms of their spatial resolution, sensitivity or range of forces measured**. Alternative strategies have been developed through ***in silico*** **modeling to infer intercellular forces** from cell shape analysis, however these approaches don't give access to direct measurements of forces. A new lead to pursue could be acoustic microscopy in order to fill this gap. This technique indeed offers a potential tool to measure cell physical properties, in particular the tightness of cell-cell junction, in a standardized, robust and versatile manner (rigidity, compressibility, volume) both *in vitro* and *in vivo*. Complementary efforts have also been suggested in the development of alternative techniques to directly image molecular tensions not only a cellular interfaces but also directly within the cytoskeletal machinery. **In this way optical tension probes such as FRET sensors appear as a path to follow.**

Other important questionings have recently been introduced in the mechanobiology field due to the viscoelastic nature of the biosystems. Among them, the mechanical **impact of dissipation in biological processes** and its origins are started to be questioned as they appear as key parameters to understand force generation. **Dissipation, which at that scale essentially originates from friction,** for example plays a key role in cell migration processes. It has indeed been proposed that cells might adapt their friction to the substrate in order to make their migratory behavior more flexible while encountering different microenvironments such as matrix composition. **Characterizing the origins of friction and identifying tools to measure it would probably help us understand better its mechanical impact in biosystems**. **The question of dissipation appears intimately related to the question of energy consumption of the system and thus to its metabolism,** a field in which our knowledge remains rather limited. For example, there is accumulating evidence that there is a limited amount of energy for a given system but how it is shared between different cellular events and how this energy distribution is orchestrated spatiotemporally is still unknown. Additionally, we still have no clue about the mechanisms involved in energy limitation (rate of each reaction?) and to what extent that relates to the homeostatic state of the system itself.

Despite the acknowledged importance of energy dissipation, interrogating the metabolic machinery within bio-systems appears quite challenging because the existing tools are really limited and/or unknown from scientists of the mechanobiology field. **At the scale of human, RMN approaches related to glucose consumption have been mostly developed while for *in vitro* approaches, a few groups are currently developing FRET sensors to image and quantify glucose related consumption. Alternatively, microcalorimetry, a sensitive technique that enables the measurement of small heat changes** in small volumes, could also represent a potential solution to measure the dissipation of energy at the entire bio-system scale , however preventing access to the local consumption measurement. ATP uncaging or otpogenetics with new probes directed toward metabolic entities could also constitute complementary approaches.

In conclusion, the identification of missing tools to address the unmet needs in the mechanobiology field highlighted a more important and generic point: the necessity of establishing more cross bridges between distant disciplines in science. As exemplified for the questions of inter-cellular force measurement or energy dissipation, some expertise may not be present or incomplete in the directly concerned field but may be found in others (fluorophore activity reporters field, acoustic field, metabolic field…). The future might thus involve a recast of the research institutes based on different teams bringing complementary expertise and working at different scales to reach a common objective.