COMMENT

Mechanobiology by the numbers: a close relationship between biology and physics

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Abstract | Studies of mechanobiology lie at the interface of various scientific disciplines from biology to physics. Accordingly, quantification and mathematical modelling have been instrumental in fuelling the progress in this rapidly developing research field, assisting experimental work on many levels.

The origins of mechanobiology can be traced back to early interests in development and cell migration — two phenomena that rely on cell shape changes and forces[1]. However, the field as such emerged only 20 years ago, spurred by the experimental observation that integrin-based cell–matrix adhesions (known as focal adhesions) are mechanosensitive and can grow in size in stiff environments and under mechanical force. From the viewpoint of physics, these findings are surprising because supramolecular assemblies are expected to dissociate rather than strengthen under force, and thus this discovery led to the development of a large body of mathematical models that explore potential mechanisms[2].

Since those early days of mechanobiology, the application of physics and modelling has become an integral part of many studies in this field, in parallel with similar developments in the field of cell migration. Such quantitative approaches assist experimental work on various levels. First, by putting numbers on the relevant processes, mathematical models help the community to build intuition about potential mechanisms that underlie cellular mechanosensation; second, mathematical models can serve as data integrators, enabling the interpretation of sometimes counterintuitive or even contradictory experimental data; and third, mathematical models can generate truly novel understanding of biological phenomena by suggesting hypotheses that motivate the next experiments.

An instructive example of the importance of numbers in mechanobiology is provided by the pioneering experiments of Pelham and Wang[3], who discovered that tissue cells on soft elastic substrates are less spread and show increased motility and more irregular focal adhesions than on stiff elastic, glass or plastic substrates. The lowest stiffness investigated in that study — defined by the Young's modulus of the polymer substrate — was around 5 kPa, and later it was shown in many other studies to be the typical threshold value for this phenotypic switch in cell morphology and organization. At that time, however, the result that cells respond in such a strong manner to substrate stiffness was completely novel and there was even some uncertainty about the stiffness measurement. Yet, the validity of a stiffness threshold around 5 kPa can be supported by physics arguments. Pelham and Wang already noted that the stiffness response of cells is strongly connected to the dynamics of focal adhesions, which we now consider the tactile organs of cells and which have a typical size of microns. On the scale of a single focal adhesion, a threshold stiffness of 5 kPa would correspond to a force of 5 kPa μm^2 = 5 nN, and this magnitude of force was later found experimentally to be generated by single focal adhesions[4]. Another validation of the obtained threshold value is provided by the consideration that for stiffness sensing, cells would have to calibrate their stiffness measurement against some internal reference value. To a first approximation, this can only be their own stiffness, which has been measured with atomic force microscopy to be around 5 kPa, in good agreement with predictions from models that apply principles of polymer physics to the cytoskeleton.

Progress in mechanobiology is strongly supported by the development of new technologies, in particular novel methods to measure forces[5]. The most widely used technique in this field is traction force microscopy on soft elastic substrates, which was initially developed as a tool to convert deformations of the cellular environment into estimates of the cellular traction forces. More recently, this approach was combined with modelling that imposed specific assumptions regarding the mechanics of cells, for example the biophysical properties of the stress fibres at focal adhesions. Thus, traction force microscopy is now on its way to becoming a correlative technique that can integrate different kinds of data into one common framework.

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As a final example of the usefulness of mathematical models in mechanobiology, let us consider the question of how the lamellipodium of a spreading or migrating cell could sense physical force. Although many mechanosensitive molecules are involved in the regulation of lamellipodia extension, there is also the theoretical possibility that the interplay between growth, branching and capping of actin filaments under mechanical load could lead to global changes in the cytoskeleton that are not necessarily tied to a specific molecular player, but rather governed by the statistics of a dynamical system. This was suggested by several theoretical studies before but has only very recently been confirmed experimentally with correlative electron tomography.

As seen from the above examples, the most important benefit of mathematical modelling is not the emergence of a single universal model that can provide a complete understanding of mechanobiology, as is sometimes the case in other areas of physics, but the gradual development of a toolbox for mechanobiological thought and practices that provides a basis for new discoveries by evoking questions that go beyond genetics and biochemistry. This integration with physics was essential for mechanobiology to grow beyond the field of cell adhesion and cover the physical aspects of the cytoskeleton, the genome and the extracellular matrix, which have all proved to be mechanosensitive in one way or the other. Mechanobiology continues to develop as a research discipline at a very fast pace, and quantification and mathematical models, together with new technologies, are sure to constitute important elements to further advance this exciting and important field.

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Competing interests statement
The author declares no competing interests.