How do you measure the mechanical forces generated by single cells? What are the cues that guide cell migration? What are the interactions between cells that account for cooperative behaviors among cells? To answer these and many other basic questions about biological function, we must have the right tools. Mathematicians have perhaps the ultimate tool in science developed and honed over centuries. Given the ancient roots of our interest in biology and the human body, it is not surprising that mathematics was applied early to explore the complexity of life. Science has advanced based on the development of new tools (engineering). In this respect, physiologists are often at the forefront, both in developing the tools themselves (biomedical engineers) and as early adopters of advanced technologies to explore life. The “modern” microscope was first developed in the 16th and 17th centuries and resulted from a general interest in the field of optics. Robert Hooke and Antonie van Leeuwenhoek were early adopters of this novel technology, effectively using this new tool to define cells as the basis of biological structure. More recently, microscopy was coupled with mechanical engineering to develop novel tools for measuring the traction forces generated by single cells on the extracellular matrix surrounding them. In Physiology, we examine a range of topics related to life’s functions, and in this issue we comment on two major themes: Physiology by the Numbers and Technological Advancement.

**Physiology by the Numbers:**

**Physiological Complexity Addressed by the Physiome Project**

According to the IUPS long-range planning committee, “Physiology is the study of the functions and integrative processes of life at all levels of structural complexity between the molecular level and that of the whole organism. It includes all organisms, and frames function in evolutionary, environmental, ecological and behavioral contexts. It embraces a cross-disciplinary approach to modern science, through which physiologists aim to achieve translation of this knowledge into human health” (http://www.iups.org/reports/long-range-plan/). Physiology thus reveals the integrative processes of life by studying structure/function relations at spatial scales from genes and proteins to whole organisms, and in particular by studying biophysical mechanisms based on molecular properties, anatomical structure, and environmental influences.

Fifty years of intense focus on the molecular mechanisms underpinning life have yielded a wealth of information that has the potential to radically improve healthcare. Yet, as genome-wide association studies (GWAS) have shown so dramatically, knowledge of gene expression and molecular mechanisms alone is insufficient to explain phenotype at the physiological scale. The “bottom up” approach is extremely valuable, but it does not address the question of how evolution has exploited these molecular systems to create the ~400 highly structurally organized cell types in the mammalian body or, at a higher scale, the kidney nephrons, liver sinusoids, cardiac sheets, lung alveoli, colon crypts, and myriad of other anatomical structures where function depends critically on the 3D organization of those cells to serve a particular physiological purpose. Clearly, knowledge of these molecular mechanisms must be combined with information regarding environmental influences and then integrated into anatomically based physiological processes that span multiple spatial and temporal scales. Physiology is the discipline that integrates molecular and cellular biology into an understanding of phenotype at the intact organism level, but, as in every other area of complex quantitative science, it must be supported by the systematic development of anatomical and physiological databases and the use of mathematical models that are closely tied to experimental data in their formulation and validation.

Mathematics is the language of quantitative science and provides the means to deal quantitatively with highly complex processes that link molecular mechanisms at the nanometer scale to integrated organ function at the meter scale. At its best, physiology has always involved the development of new instrumentation (often the prerequisite for new observations), experimental measurements, and the mathematical modeling needed to interpret these measurements in light of physical laws. The big change that recently occurred (in the last decade or so) is our ability to solve these complex equations (often based on physical principles such as conservation of mass, or energy, or momentum, or charge, etc.) with computational techniques applied to physiological models that capture anatomical structure as well as molecular detail. This emerging field of computational physiology is closely allied with biomedical engineering and with the Physiome Project.

The concept of a Physiome Project was originally presented in a report from the Commission on Bioengineering in Physiology to the IUPS Council at the 32nd World Congress in Glasgow in 1993. The term “physiome” comes from “physio” (life) + “ome” (as a whole) and with the goal of an holistic approach to computational physiology. Importantly, the Physiome Project has led the development of modeling standards. The satellite workshop “On designing the Physiome Project” was held in Petrovoretz, Russia, following the 33rd IUPS World Congress in St. Petersburg in 1997. Subsequently, the first symposium on the Physiome Project was held at the 34th IUPS World Congress in Christchurch, New Zealand, in 2001 and at every IUPS World Congress thereafter.

Over the last 6 years, the Virtual Physiological Human (VPH) project (created by the Information and Communication Technologies (ICT) division of the European Commission under the Framework 7 program) developed a modeling infrastructure for computational physiology with a particular focus on the clinical application of computational modeling. The motivations for the VPH project are to improve our quantitative understanding of physiological and pathophysiological processes and to provide a rational basis for healthcare decisions. Since the IUPS Physiome Project and the European VPH project have similar aims, they are now collectively referred to as the VPH/
Physiome project. The VPH/Physiome project infrastructure includes 1) minimum information standards, 2) markup language encoding of data, models, and simulation protocols, 3) model curation, 4) metadata annotation via bio-ontologies that assign biological and biophysical meaning to the model parameters, 5) workflows that facilitate the demonstration of model reproducibility, 6) data and model repositories, based on the data and model encoding standards, and 7) freely available, open-source software for authoring, visualizing, running, and analyzing the models. The key goal is to create a modeling infrastructure in which a model, together with its input data, can be verified and run automatically to generate a guaranteed output. The creation of modeling infrastructure is essential for the effective use of models and software in both drug and medical device approval processes (e.g., with the FDA), and in applications to clinical diagnosis, surgical planning, and medical treatment. The VPH/Physiome infrastructure is closely aligned with clinical applications and has a strong focus on tools for model-based interpretation of clinical images as well as the techniques for the personalization of models in a clinical setting. The markup languages developed under the VPH/Physiome project are CellML (for biophysically based lumped parameter models) and FieldML (for spatially varying fields) (http://www.cellml.org). The markup language SBML deals specifically with reaction systems (http://www.sbml.org), and SED-ML is also being developed for encoding simulation protocols (http://www.sed-ml.org).

As elsewhere, the key to progress in the biomedical field is the right combination of data-driven, physics-driven, and computationally driven science. The bottom up molecular systems biology approach has been largely data driven, whereas “top down” bioengineering approaches have been largely physics driven. These complementary approaches are more closely integrated in the new discipline of computational physiology based on the emerging markup languages with their associated databases. One of the key factors in the success of molecular biology has been the availability of well organized databases of DNA sequence data, protein structure, etc. The physiology community needs to support these global efforts to build computational physiology tools and the databases of physiological data and models that adhere to the community encoding standards.

Technical Advances: Mechanobiology, Remodeling, and Regeneration: How Tools Transform the Question

This issue of *Physiology* highlights reports taken from topic areas and levels of integration that at first glance might seem incongruous but come together nonetheless in impressive fashion to illustrate common features that teach important lessons. Here, we highlight three reports related to tissue remodeling. These reports focus on the extracellular matrix and its role in migration and proliferation of the isolated fibroblast (4), collective migration of the cellular monolayer (5), and destruction of lung tissue in emphysema (3). Differences notwithstanding, in each of these systems and at a variety of levels, we see that physical forces and mechanical properties of cells and tissues prove to be pivotal. In each of these systems, moreover, recent advances in basic science were made possible only through technological advances in the laboratory. Although each report clearly illustrates how technological advances help us to answer a pressing question, each illustrates as well how the technology can lead to a new biological question that otherwise would not have been conceived and asked. Just as a question can beget a new technology, so too a technology can beget a new question. That being the case, what technologies do we need but do not yet have? And what new questions might they spawn?

A longstanding technical challenge in mechanobiology is that physical forces are plugged into cell signaling in manifold ways, but the forces themselves and their distributions are invisible. In 1980, Harris, Wild, and Stopak showed that, even if forces are invisible, their biological effects are not, the simplest demonstration being the manner in which a cell exerts traction forces that can wrinkle a silicone rubber membrane. Through a series of technological advances since that time—in soft substrate technology, imaging, and mathematics—we can now image and quantify at a high level of resolution the distribution of stress (force per unit area) that a cell exerts upon its substrate, the stress that an integrated monolayer exerts upon is substrate, and even the stress that each cell within the monolayer exerts on its immediate neighbors across cell-cell junctions (2, 5). Associated stretch of particular stress-bearing molecules can now be measured for encoding simulation protocols (http://www.sed-ml.org).

These technologies go well beyond anything we might have imagined only 10 years ago. But, as always, they do not go far enough and leave unfilled gaps. For example, although the FRET tension sensors (1) provide a readout of the localized relative stretch of a stress-bearing molecule of interest, they report neither the direction of stretch nor the forces supported by more than a single molecular species. In contrast, recent stress microscopy technologies (2, 5) measure local magnitude and direction of force, and thus define the complete local stress tensor but provide no details whatsoever concerning the molecules exerting those forces. This gap is important, for example, within a seemingly homogeneous cellular monolayer, where there arise spontaneously dynamic heterogeneities in space and in time of the intercellular stress (2), but these dynamic heterogeneities have yet to be related to any particular molecular species. New technologies that assess the full stress state together with decomposition of that stress across the spectrum of contributing stress-exerting molecules would transform how we design experiments, open new routes to pursuing previously unanswerable questions, and precipitate new questions. Such a spectrum-analyzer, as it were, that could decompose stress components across molecular species would bridge the gap between current molecular FRET and continuum stress imaging, and thereby yield unprecedented insight into the molecular pathways that control mechanotransduction and resulting gene expression events.

There exists no fundamental reason that such a technology might not be on the horizon. That being the case, one can imagine experiments with different classes of applied stresses—whether by tissue stretch, fluid shear, osmotic compression, cellular contraction, tissue growth, or injury—that could be taken together
with existing mRNA sequencing and gene expression profiling technologies. Such experiments would almost surely identify unanticipated stress response pathways. In the topic areas of growth, remodeling, and regeneration, the synergies and the new questions that would be spawned are exciting to contemplate.

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References


