# Essay: Exploring the Physics of Basic Medical Research

Vahid Sandoghdar
*Max Planck Institute for the Science of Light, Staudtstr. 2, 91058 Erlangen, Germany;*
*Max-Planck-Zentrum für Physik und Medizin, Kußmaulallee 2, 91054 Erlangen, Germany;*
*and Department of Physics, Friedrich-Alexander University Erlangen-Nuremberg, 91058 Erlangen, Germany*

(Received 3 January 2024; published 26 February 2024)

The 20th century witnessed the emergence of many paradigm-shifting technologies from the physics community, which have revolutionized medical diagnostics and patient care. However, fundamental medical research has been mostly guided by methods from areas such as cell biology, biochemistry, and genetics, with fairly small contributions from physicists. In this Essay, I outline some key phenomena in the human body that are based on physical principles and yet govern our health over a vast range of length and time scales. I advocate that research in life sciences can greatly benefit from the methodology, know-how, and mindset of the physics community and that the pursuit of basic research in medicine is compatible with the mission of physics.

*Part of a series of Essays that concisely present author visions for the future of their field.*

DOI: 10.1103/PhysRevLett.132.090001

*Introduction.*—Since the discovery of x rays by Wilhelm Röntgen [1], hospitals and medical centers have benefited from various technologies enabling improved diagnostics and patient care. Prominent examples include the use of nuclear isotopes for functional imaging, x-ray computer tomography (CT), ultrasound imaging, nuclear magnetic resonance imaging (MRI), positron emission tomography (PET), and laser surgery. Indeed, medical technology has become established as a mature field that is offered as university study programs and as such, it continues to innovate and advance.

Physics has had an enormous impact also on fundamental biological research. Quantum mechanics offered a framework for investigating complex features of biological molecules such as DNA, RNA, and proteins, while x-ray diffraction provided insights into their structure. Nuclear magnetic resonance (NMR) spectroscopy, electron microscopy, phase contrast microscopy, fluorescence microscopy, optical trapping, and atomic force microscopy (AFM) are some of the other physical methods that have been crucial in learning about the structure, dynamics, and function of cellular and subcellular entities. For example, AFM and optical tweezers as well as theoretical concepts from polymer physics were used in pioneering works of single-molecule biophysics to explore the mechanical response of isolated DNA and protein molecules [2–4].



Both physicists and life scientists strive to address fundamental scientific challenges in their disciplines and in doing so, they choose model systems for more control in their studies. Just as research in atomic physics and quantum optics has heavily relied on the use of hydrogenic atoms, biologists often study a select group of organisms and cells. *Escherichia coli* (*E. coli*) bacteria, yeast, fruit flies (*Drosophila*), simple worms (*C. elegans*), and small fish (zebrafish) are some of the commonly used model systems because of their genetic simplicity, short reproduction times, and small size. Furthermore, genetically modified mice serve as an important resource for controlled experiments in a mammalian model system. Immortalized human cell lines (e.g., HeLa cells) are also routinely used for model studies.

The approaches of the two disciplines and their working conditions, however, are often quite different. Physicists usually adopt the strategy of reducing and simplifying the problem to a minimal set of parameters that can be understood based on a theoretical foundation. The possibly half-humorous statement by Arthur Schawlow (who shared the Nobel Prize in 1981 for the invention of the laser) in the context of spectroscopy that "a diatomic molecule is one atom too many" conveys this attitude well [5]. Life scientists, on the other hand, embrace the complexity of their systems and attempt to collect multiparameter data, often at the cost of handling nontrivial statistics obtained from a large number of control experiments.

In this Essay, I aim to portray some exciting questions and topics at the interface between physics and *basic* medical research. In particular, I hope to convince the readers, especially those who are less familiar with biophysics, that it will be highly rewarding to engage in medical research,

which is not only of immense social importance but also intellectually enticing. The learning curve and threshold for physicists to become productive in medical research is, notably, much lower than one might fear.

*Some trends at the interface between physics and life.*—The interdisciplinary interface between physics and biology has many aspects, e.g., the use of physical methods for studying biological processes or investigation of physical phenomena that underlie them. Over the years, terms such as biological physics, biophysics, physical biology, and more recently, physics of life [6,7] have been coined to emphasize one or the other feature. Just as the difference between physical chemistry and chemical physics is not sharp, semantic differentiation of the various efforts at the interface between physics and life has its limits, especially in light of the current drive toward more interdisciplinary research. Investigations in this area have a broad scope, covering a plethora of time and length scales in physical interactions that involve mechanics, electricity, magnetism, heat, etc.

The physics community is generally familiar with electric measurements that elucidated the function of ion channels and action potentials involved in neural signaling and sensory regulations. While the early efforts studied single cells with glass micropipettes and electrodes, nowadays integrated arrays of chip-based nanoelectrodes can be used in combination with microfluidics to map correlations among a large number of signaling events [8]. Furthermore, recent advances in functional MRI (fMRI) and neurophotonics paired with engineered ion-indicating fluorophores provide insight into the workings of the brain in small model animals [9]. Another line of research laboriously combines electron microscopy with nanotechnological techniques, such as focused ion-beam milling, to obtain three-dimensional (3D) sections of the brain [10].

Some of the simple models of the brain put forth by biophysicists have already contributed to the development of deep neural networks used in artificial intelligence and machine learning [11,12]. However, we have a long way ahead to a comprehensive mapping of the brain's blueprint and thus capturing the subtle connectivities among individual neurons. Sophisticated multimodal imaging approaches promise to provide insight into the way information is stored, accessed, and processed in delocalized nodes [13]. An important milestone will be understanding the interplay between the physical (electrical, magnetic, mechanical, and hydrodynamic) and biochemical processes of neurons in relation to their microenvironment and vasculature. Such data will deliver important input for new mathematical models that help elucidate the human connectome.

Another active field of research is *mechanobiology*, which investigates the role of mechanical interactions, addressing questions such as "How is the motion of nanoscopic cellular or extracellular structures actuated? How large are the forces involved? To what extent might mechanical stimuli directly regulate cellular processes?" Although these questions might sound ordinary to physicists, posing such inquiries has been quite new for biologists, who usually consider biochemical and genetic phenomena to be chiefly responsible for life processes.

It is common knowledge that cells contain two-dimensional (2D) organelles of nanometer thickness such as the plasma membrane, which encloses the whole cell. However, cells also contain a sophisticated network of 1D nanostructures decorated by a range of 0D nano-objects such as vesicles and proteins. A motor protein might have a structure that resembles nanoscopic legs and feet, with which it walks on a nanofilament (e.g., myosin on actin) and exerts a force on it. Alternatively, a protein can use a nanofilament as a rail system (e.g., kinesin or dynein on microtubule) to transport loaded vesicles known as cargo [see Fig. 1(a)]. While a biochemist might consider the workings of this system to be the immediate result of chemical bonds and protein conformations, a 21st century physicist could perceive a scenery where nanomachines and nanostructures interact in a physical fashion. By employing techniques imported from optics and nanoscience, researchers have investigated the mechanical properties of these nanomachines individually *in vitro*, e.g., on a glass substrate. Indeed, one of the early feats of single-molecule biophysics was to resolve the individual nanometric steps of a motor protein [7]. Today, AFM and optical tweezers are routinely used to quantify weak forces in the range of a few pico- to nanonewtons [14].

Cellular nanomachines move by taking quantized nanoscopic steps, determined by the molecular graininess of the surface of the nanofilaments. Such nanoscopically confined systems could reveal quantum mechanical properties if they were in the isolated form and at zero temperature. In practice, however, the underlying quantum phenomena are masked by the substantial thermal noise, which is barely smaller than the kinetic energy associated with the process. Contrary to the commonly encountered nanostructures in physics, cellular nanostructures are typically not passive. They are rather constantly powered by biochemical reactions with molecules in their immediate vicinity. The field of *active matter* aims to formulate new statistical physics and hydrodynamics for describing the cooperative and collective behavior of such micro- or nanosystems [15,16], which share some fundamental features with macroscopic phenomena such as bird flocks [7].

Biological nanostructures are also responsible for many macroscopic phenomena. For instance, nanofilaments form the building blocks of tiny hairlike microstructures, which act as mechanical antennae for activating neurons through their miniscule movements, e.g., in the inner ear or on the skin of fish [17]. Micro- and nanostructures are also being investigated for their optical functionalities (e.g., color) in a wide range of creatures such as insects, birds, and fish [18]. The 2021 Nobel Prize in Physiology honored the discovery that certain ion channels respond to mechanical and thermal

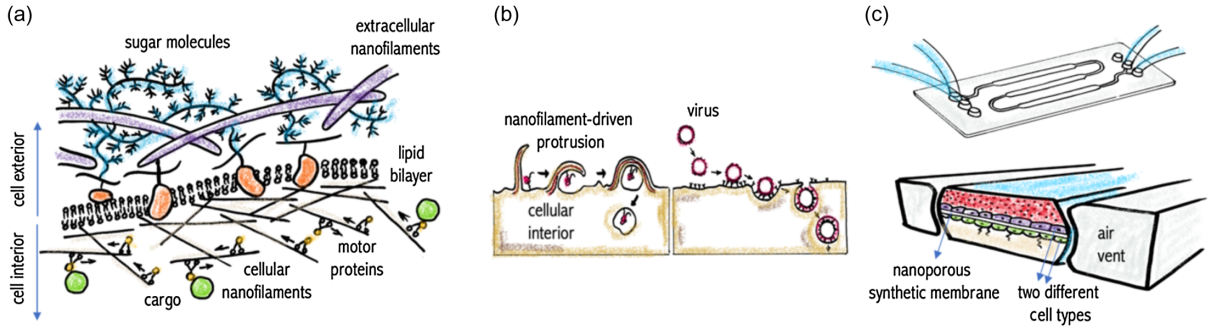


FIG. 1. (a) Nanotubes made of proteins such as actin and tubulin serve as a skeleton for shaping the cell and play essential roles in dynamical processes such as cell locomotion and division. Motor proteins acting as nanomachines interact with various nanotubes to mediate force exertion or to transport cargo. Other nanofilamentous structures such as collagen or fibronectin form the extracellular matrix. (b) Cells use various morphological and mechanical mechanisms for the uptake of proteins, vesicles, and viruses. (c) Chip-based platforms exploit microfluidics and micro- and nanomechanical actuation for an efficient realization of biochemical reactions. These lab-on-chip solutions can mimic physiological tissue, e.g., epithelial and endothelial lung tissues under controlled conditions of air and fluid flow.

stimuli to the skin. It is also known that cells can navigate through concentration gradients, e.g., steered by the secretion of proteins from other cells. Despite these existing clues and evidence, we are still very far from a comprehensive physical understanding of the processes at hand, whereby one of the biggest challenges is the lack of noninvasive *in vivo* measurements down to the cellular scale. Novel nanoscopic pressure gauges, thermometers, and densitometers would greatly help in reaching this goal.

*Physics and medicine.*—The remarkably large number of parameters involved in life processes and their nontrivial dynamic interdependence makes it challenging to extend the lessons of biophysical model studies to the human body. Indeed, medical researchers must often scrutinize the *physiological relevance* of biological investigations performed under controlled conditions. As a result, there is a great need for developing new dedicated methods and concepts suited for *in vivo* examination of fundamental processes of medical significance.

The procedures of performing quantitative and reproducible research are much more demanding in medicine than in physics. First, experimentation as we know from the natural sciences cannot be performed on humans due to ethical concerns. Moreover, clinical trials are very time consuming and expensive. Nevertheless, a great deal of insight can be obtained in the workings of the body in a semi-invasive manner through surgery and autopsy or analysis of bodily fluids such as blood and urine. One can draw a loose analogy between obtaining data from the interior of a functioning human body and the center of a distant galaxy. In both cases, one tries to measure signals and infer their origins over a span of 15–20 orders of magnitude in length and time (see Fig. 2). A stethoscope or an electroencephalogram (EEG) measurement at the surface of the body sets the analog of stellar telescopes observing stars and galaxies. Endoscopes and catheters operate similarly to satellites and space telescopes, namely, they enter the medium of interest. Characterization of fluids extracted from the body could be considered analogous to the study of elementary particles and radiation that reach us from space. In each case, a wealth of physics know-how is employed in devising the instrumentation and interpreting the data.

Infectious diseases caused by pathogens such as bacteria and viruses occur regularly and are treated by physicians quite routinely. Nevertheless, some of the most fundamental questions concerning how a pathogen approaches a cell, how it docks onto it, and how it enters the cell remain unanswered. Advanced label-free microscopy, microfluidics, and nanotechnological methods are currently being employed to investigate pathogen-cell interactions quantitatively. Besides the biochemical and genetic attributes, it is particularly exciting to explore mechanical deformations and cues that influence processes such as engulfment and egress of viruses and vesicles [see Fig. 1(b)].

Our immune system provides a highly complex protection package through the *innate* and *adaptive* immune mechanisms. The former is unspecific and acts as the first line of defense against invading pathogens by recruiting immune cells to active sites via signaling molecules, the cytokines. The responsibility of the adaptive (acquired) immune system is to create a targeted response and to retain memory for specific pathogens so that the body can respond to repeated exposures. The rapid reaction of modern medicine to the COVID-19 pandemic presented a good example of the remarkable progress toward the control of infectious diseases, although the mechanistic and molecular details of the underlying pathogen-cell interactions are still largely not well understood. For example, issues as elementary as the number of required binding sites and the nature of fusion between two lipid membranes remain enigmatic. Similarly, phenomena such as the efficiency of viral infection and its spread from one cell to the next lack satisfactory quantitative explanations. Moreover, the significance of statistical processes such as diffusion, subdiffusion, and nanoscopic confinements involved in cells' uptake of external nano-objects is being debated.

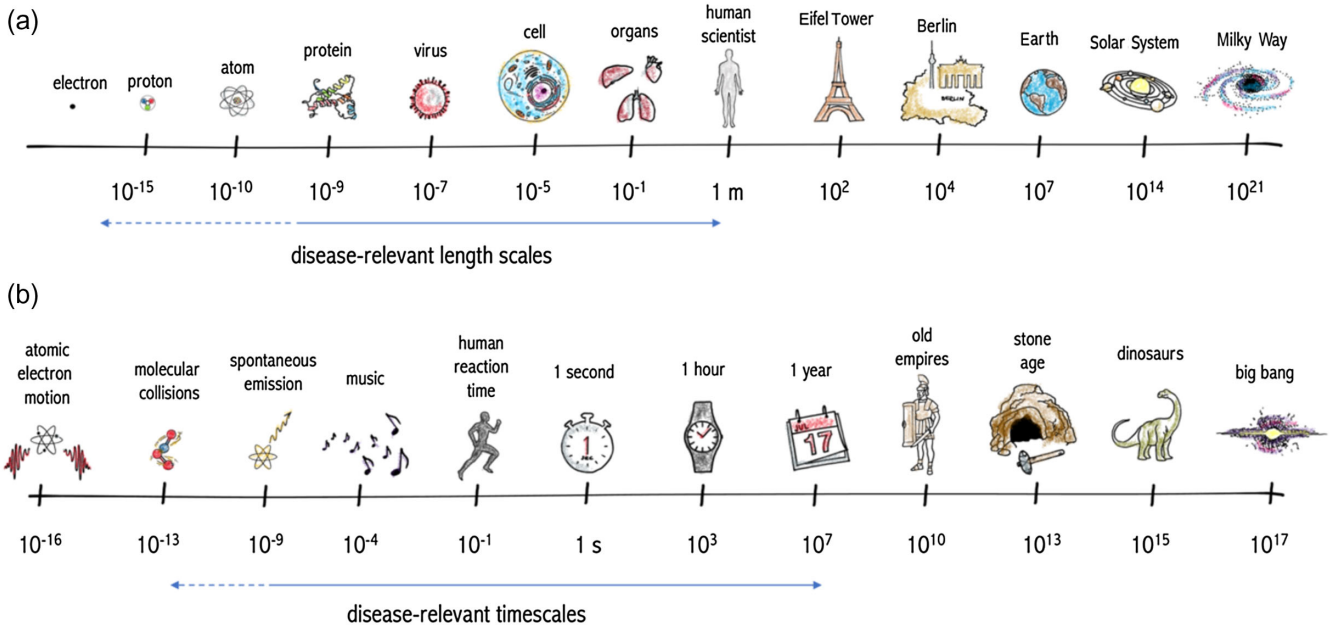


FIG. 2. Length and time scales in nature. (a) On a logarithmic scale, the size of the human body is about midway between subatomic particles and the Milky Way. (b) Let us argue that 1 second is about the smallest timescale that we comfortably feel and that makes a difference in our daily lives. At an estimated age of the order of 10 billion years, the development of the Universe has been $10^{17}$ times slower, whereas electronic processes that underlie (bio)chemical reactions can reach subfemtosecond scales, e.g., $10^{-16}$. From another interesting perspective, we may compare the timescales of the development of pathological diseases (years, $10^{7}$ s) with the timescale for the encounter of two proteins during diffusion ($10^{-8}$ s). Here, I have assumed a diffusion constant of 100 $\mu m^2/s$ and a surface area of the order of 10 $nm^2$ for a protein. Such a rough estimate also yields a temporal span of 15 orders of magnitude.

Pathological illnesses such as cancer and neurodegenerative diseases pose a more formidable challenge than infectious diseases. Over the past decades, we have witnessed impressive progress in early diagnosis and cure of cancer, but the disease remains a mystery and continues to take in the order of 10 million lives each year, with a steadily increasing trend [19]. It is now known that the existence of a tumor is often not what causes death, but it is its metastasis that poses a life threat. In other words, whatever genetic or biochemical phenomenon initiates a tumor, it may not ultimately determine the cancer's deadly effect. Today, physical phenomena are believed to play a key role in the development of cancer [20,21]. For example, migration and spread of tumor cells rely on the molecular machinery of cytoskeletal filaments and motor proteins described above. Moreover, metastasis is currently being examined as a phase transition between a solid state (cells stay where they are) and a fluid state (cells start to move and flow). Ideas from game theory that have been applied to social and economic interactions have also been proposed for understanding tumor formation [22]. From a mechanistic point of view, the stiffness of cancer cells and the properties of the extracellular matrix surrounding them are currently being scrutinized as decisive features [23]. Sensitive methods for monitoring and quantifying movements, forces, stress, stiffness, pH, and oxygen concentration over various length and time scales will be invaluable for unraveling the mysteries of cancer.

Neurodegenerative diseases such as Parkinson's, Alzheimer's, and multiple sclerosis have also been a subject of active research, and other less frequent variations continue to be identified. In many cases, there is evidence that morphological and mechanical anomalies such as aggregation and plaque formation directly correlate with the disease pathology. In some other cases, motor neurons, which are the longest cells in our body and command some of our motoric behavior directly from the brain, malfunction. This could, e.g., happen if the myelin sheath that shields an axon from electrical interference with its environment becomes faulty. Efforts in many laboratories employ physical methods, such as superresolution microscopy, AFM, or electron microscopy, to identify and characterize nanoscopic features that are associated with protein aggregation and neuronal dysfunction [24,25].

A currently plausible hypothesis for the growing number of chronic disease patients is our aging society. The emerging field of *geroscience* investigates this complex topic [26]. It is known that somatic cells typically divide a finite number of times (on the order of 40–60 times) before they enter senescence, a state where they no longer divide [7]. Thus, one can depict aging as a process in which the odds of cellular malfunction rise with age [27]. Although the details of such errors are not understood, it is believed that the production of harmful radicals (highly reactive atoms and molecules) plays a role in accumulating memory

as cells divide. There is a great demand for dedicated statistical physics concepts that account for the resulting type of decay. However, to steer such studies, we first need novel experimental methods to elucidate cellular and tissue processes with sufficient temporal resolution over days and months. Its social and human consequences aside, the systematic extension of mammalian life is now believed to be well within reach [26].

Another fascinating feature of our complex body is its ability to regenerate, e.g., in the case of an open wound. However, except for very few cases such as the liver, organ regrowth does not take place in the human body. This begs the question as to whether there is a fundamental limitation to regeneration. Stem cell research has introduced hope toward this vision, but there is also emerging physics research. For example, mechanical [28] and electric [29] cues are being investigated, and topological defects in actin fibers have been proposed as sites for morphogenesis [30]. On the experimental front, a very fruitful avenue in regeneration research is offered by the organ-on-chip technology [see Fig. 1(c)], where a combination of synthetic and natural materials is employed to emulate various organs at the microtissue level on a chip [31,32]. This general approach delivers one of the most physics-compatible platforms, where one can incorporate a large number of measurement and stimulation access points in a fairly controlled manner. An additional important advantage of the organ-on-chip technology is a reduced need for animal samples. Another promising effort in the same vein concerns the *in vitro* development of organoids, 3D cell arrangements that recapitulate various aspects of certain *in vivo* organ tissues, e.g., from the brain, gut, kidney, etc. [33]. Different engineering strategies are currently being pursued to facilitate the growth of organoids as well as their proliferation and maturation.

*Outlook.*—Biomedical research continues to progress in its conventional realm based on the *central dogma of molecular biology*, which states that the information encoded in the DNA is transferred to RNA, in turn determining the structure and function of proteins and with that the behavior of our cells. Researchers indicate, however, that our health condition is also steered by a wide range of physical processes in many direct and indirect ways. A strong engagement from the physics community would boost the ongoing efforts to unveil these phenomena. To achieve this goal, we need to *measure, interpret, and control*, as we are used to doing in basic physics research.

Fundamental medical research of the future will greatly benefit from quantitative characterization of the concentrations of vital molecules and compounds such as oxygen, vitamins, hormones, glucose, proteins, metabolites (e.g., ATP), and ions (e.g., sodium and potassium) as well as temperature, pressure, stress, tension, viscosity, and electromagnetic fields inside the body, both at the macroscopic (organs and tissues) and microscopic (cellular and subcellular) levels. Some of these measurements are already accessible, but as is often the case in physics, a higher precision in biomedical measurements will also allow one to ask more subtle questions, opening doors to new hypotheses.

Recent advances in nanoscience, optics, and biological physics have launched many efforts for mapping various quantities of interest with submicrometer spatial resolution in cell culture. For example, changes in the fluorescence spectrum, excited-state lifetime, or spin transitions of molecules and other quantum emitters can be related to the modifications of physicochemical quantities in their local environment [34,35]. Studies on live cell cultures under controlled conditions also promise to shed much-needed light on many outstanding biomedical questions within the next decade. For instance, repeated imaging of single viruses throughout their interaction with a cell under physiologically controlled conditions as well as the reaction of the surrounding immune cells at high spatiotemporal resolution promises to facilitate a first-principles understanding of viral and bacterial infections. Furthermore, advances in lab-on-chip technologies will accelerate quantitative studies and reduce the need for animal research.

While cell culture measurements remain invaluable, the road ahead requires sensitive noninvasive measurements in animal models and, ideally, in the human body. Novel methods for high-throughput characterization of conventional medical samples such as urine or blood extracts with molecular sensitivity will continue to play an important role. Moreover, microscopy and spectroscopy through the eye can be used for natural access to the interior of the body, especially to the brain and the central nervous system [36]. Improvements in sensitivity as well as spatiotemporal resolution of existing technologies such as magnetic resonance imaging will also hold promise to pair with new methodologies such as deep-tissue optical imaging and photoacoustic microscopy [37,38] to generate high-resolution maps of the distribution and gradients of the vital biochemical factors and physical parameters in the body. In addition, these parameters can be monitored in real time in the artery, joints, intestine, lung, mouth, etc., through microendoscopy and implanted miniaturized mechanical, electronic, magnetic, or optical sensors.

A significant complication in the way of characterizing the medical condition of human beings is the large heterogeneity of the key parameters even within a healthy population. Personalized medicine promises a new paradigm for the characterization and documentation of the health of individuals. Here, an impressive wave of developments in wearable electronics is providing access to some of the essential factors on or under the skin [39]. However, the staggeringly large number of factors and parameters that cooperate in a living body makes it dauntingly impractical to explain life processes based on a catalog and map of individual molecules. Interpreting the results and establishing

causal relations and correlations will, hence, be a major research task that lies ahead. Machine learning and artificial intelligence will certainly play a pivotal role in tackling this challenge. In addition, there is immense potential for new theoretical approaches and models. Indeed, it is not unthinkable that complex life processes are founded on a mathematical paradigm that is yet to be formulated.

The ability to control bodily factors in a deterministic manner highlights an ultimate goal of medical practice that aims at finding cures for diseases. Efforts based on microrobotics and nanomedicine have recently brought about very promising results [40]. For instance, as used in some COVID-19 vaccines, synthetic lipid vesicles or viruslike particles can be used as a nanocontainer for delivering therapeutic substances to specific locations in the body. Moreover, magnetic nanorobots are used to clear clogged pathways in the brain or heart, camera capsules are employed to image the inner parts of the digestive system, and multifunctional microendoscopes are applied not only to image but also to deliver chemicals or induce electrical stimuli locally to tumors or inflammatory regions of the tissue.

The human body comprises a wide range of secrets down to the subatomic level. Understanding our health from first principles will require quantitative measurements, analysis, and theoretical interpretation. I consider this mission to be very much in line with the physics agenda and would like to advocate that physicists of any background and specialty delve into different topics and aspects of basic medical research, be it through the development of novel methods, sophisticated theoretical analysis, implementation of artificial intelligence algorithms, or simply through their drive to break down complex questions to smaller fundamental modules—the *physics mindset*. Multidisciplinary approaches are, indeed, not foreign to the history of physics, featuring polymaths such as Hermann von Helmholtz, who was a thought leader in both physics and physiology. I believe by embracing complexity and breadth, 21st century physics will be in an excellent position to advance medicine.

I thank David Albrecht, Stephan Götzinger, Jahangir Nobakht, Alexandra Schambony, Ashley Shin, and Alexey Shkarin for helpful comments on the manuscript and Susanne Viezens for preparing the artwork. I am also thankful for a Visiting Miller Professorship at the University of California at Berkeley, during which the foundation of this article was set. Importantly, I am grateful to the Max Planck Society for continuous and generous financial support, which has allowed my group to branch out from our traditional area of quantum nano-optics to biomedical research.

**Vahid Sandoghdar**

Vahid Sandoghdar is a director at the Max Planck Institute for the Science of Light and the founder of the Max-Planck-Zentrum für Physik und Medizin, a joint research center for fundamental medical research with physical and mathematical methods. Born in Tehran (Iran), Professor Sandoghdar studied at the University of California at Davis and obtained his Ph.D. in atomic physics from Yale University. After a postdoctoral stay at the École Normale Supérieure in Paris, he moved to the University of Konstanz in Germany to start a new line of research that combined single-molecule spectroscopy, scanning probe microscopy, and quantum optics. In 2001, he took on a professorship at ETH in Zurich, Switzerland. In 2011, he joined the Max Planck Society and became the Alexander von Humboldt Professor at the Friedrich-Alexander University in Erlangen, Germany. Sandoghdar's work has been honored with the Quantum Electronics and Optics Prize of the European Physical Society (2023).

[1] https://www.aps.org/publications/apsnews/200111/history.cfm.
[2] P. Cluzel, A. Lebrun, C. Heller, R. Lavery, J-L. Viovy, D. Chatenay, and F. Caron, Science **271**, 792 (1996).
[3] S. B. Smith, Y. Cui, and C. Bustamante, Science **271**, 795 (1996).
[4] J. P. Junker, F. Ziegler, and M. Rief, Science **323**, 633 (2009).
[5] In New Scientist, vol. **92**, issue 1276 (October 22), p. 225 (1981).
[6] S. W. Grill and H. Chaté, Phys. Rev. Lett. **123**, 130001 (2019).

[7] National Academies of Sciences, Engineering, and Medicine, *Physics of Life* (The National Academies Press, Washington DC, 2022), 10.17226/26403.
[8] M. Cerina, M. C. Piastra, and M. Frega, Prog. Biomed. Eng. **5**, 032002 (2023).
[9] A. S. Abdelfattah *et al.*, Neurophotonics **9**, 013001 (2022).
[10] G. Knott, H. Marchman, D. Wall, and B. Lich, JNeurosci **28**, 2959 (2008).
[11] J. J. Hopfield, Proc. Natl. Acad. Sci. U.S.A. **79**, 2554 (1982).
[12] A. Decelle, Physica (Amsterdam) **631A**, 128154 (2023).
[13] S. Weisenburger and A. Vaziri, Annu. Rev. Neurosci. **41**, 431 (2018).
[14] C. J. Bustamante, Y. R. Chemla, S. Liu, and M. D. Wang, Nat. Rev. Methods Primers **1**, 26 (2021).
[15] M. C. Marchetti, J. F. Joanny, S. Ramaswamy, T. B. Liverpool, J. Prost, M. Rao, and R. A. Simha, Rev. Mod. Phys. **85**, 1143 (2013).
[16] M. J. Bowick, N. Fakhri, M. C. Marchetti, and S. Ramaswamy, Phys. Rev. X **12**, 010501 (2022).
[17] A. J. Hudspeth, Nat. Rev. Neurosci. **15**, 600 (2014).
[18] K. Vynck, R. Pierrat, R. Carminati, L. S. Froufe-Perez, F. Scheffold, R. Sapienza, S. Vignolini, and J. J. Saenz, Rev. Mod. Phys. **95**, 045003 (2023).
[19] https://www.who.int/news-room/fact-sheets/detail/cancer.
[20] F. M. White, R. A. Gatenby, and C. Fischbach, Cancer Res. **79**, 2107 (2019).
[21] V. Gensbittel, M. Kräter, S. Harlepp, I. Busnelli, J. Guck, and J. G. Goetz, Develop. Cell. **56**, 164 (2020).
[22] Y. Zheng, Y. Sun, G. Torga, K. J. Pienta, and R. H. Austin, Biophys. Rev. Lett. **15**, 171 (2020).
[23] S. Ishihara and H. Haga, Cancers **14**, 1049 (2022).
[24] C. Werner, M. Sauer, and C. Geis, Chem. Rev. **121**, 11971 (2021).
[25] M. Martinez-Miguel, W. Tatkiewicz, M. Köber, N. Ventosa, J. Veciana, J. Guasch, and I. Ratera, *Insoluble Proteins*, edited by E. Garcia Fruitos and A. Aris Giralt, Methods in Molecular Biology Vol. 2406 (Humana Press, Totowa, NJ, 2022), Chap. 29.
[26] B. K. Kennedy *et al.*., Cell **159**, 709 (2014).
[27] P. B. Medawar, *An Unsolved Problem of Biology* (H. K. Lewis, London 1952); reprinted in *The Uniqueness of the Individual*, 2nd Revised Edition (Dover, New York, 1981), pp. 28–54.
[28] T. O. Josephson and E. F. Morgan, Front. Physiol. **14**, 1232698 (2023).
[29] M. Verdes, K. Mace, L. Margetts, and S. Cartmell, Curr. Opin. Biotechnol. **75**, 102710 (2022).
[30] Y. Maroudas-Sacks, L. Garion, L. Shani-Zerbib, A. Livshits, E. Braun, and K. Keren, Nat. Phys. **17**, 251 (2021).
[31] D. Huh, Y-S. Torisawa, G. A. Hamilton, H. J. Kim, and D. E. Ingber, Lab Chip **12**, 2156 (2012).
[32] C. M. Leung *et al.*, Nat. Rev. Methods Primers **2**, 33 (2022).
[33] Z. Zhao *et al.*, Nat. Rev. Methods Primers **2**, 94 (2022).
[34] O. S. Wolfbeis, Chem. Soc. Rev. **44**, 4743 (2015).
[35] N. Aslam, H. Zhou, E. K. Urbach, M. J. Turner, R. L. Walsworth, M. D. Lukin, and H. Park, Nat. Rev. Phys. **5**, 157 (2023).
[36] A. London, I. Benhar, and M. Schwartz, Nat. Rev. Neurosci. **9**, 44 (2013).
[37] L. Wang and S. Hu, Science **335**, 1458 (2012).
[38] S. Yoon, M. Kim, M. Jang, Y. Choi, W. Choi, S. Kang, and W. Choi, Nat. Rev. Phys. **2**, 141 (2020).
[39] H. C. Ates, P. Q. Nguyen, L. Gonzalez-Macia, E. Morales-Narváez, F. Güder, J. J. Collins, and C. Dincer, Nat. Rev. Mater. **7**, 887 (2022).
[40] F. Soto and R. Chrostowski, Front. Bioeng. Biotechnol. **6**, 179 (2018).