IOP | Institute of Physics
Biological Physics Group

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Cover Image: The images show single live bacterial cells showing tracks of single molecules of a DNA-binding protein; the two colours reflect mobile and DNA-bound populations. The imaging was done using PALM on a custom-built microscope. (Mat Stracy).

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Items for the newsletter should be e-mailed to m.peckham@leeds.ac.uk

Editorial

In the December edition, we have a fascinating reflection on laser tweezers and the Nobel Prize in Physics, three meeting reports, a book review, and a reminder of the upcoming meetings. Enjoy reading, and I hope to see you at one of the upcoming conferences!

Professor Michelle Peckham
Newsletter Editor

The Committee

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Honorary Secretary	Mark Wallace *(cross representative with BBS)*
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	Achillefs Kapanidis
	Bartek Waclaw
	Andela Saric

The Chair's commentary

We held the 2018 AGM, and met as a committee, in early December, for the first time in the new IOP headquarters building close to King's Cross. The facility is stunning, the top floor views are in all directions over London roofs. You can see in the picture some strange alien ships / UFOs in the London sky, I have my views of what they had come to do.

The other picture gives a better sense of the architecture. The creatures there are not the aliens, it's just some of us before the meeting.

Moving on. These are strange times, and it seems there could be something positive and unexpected on the funding horizon for biological physics. This week a new scheme was announced by UKRI https://epsrc.ukri.org/funding/calls/physicsoflifecollab/ and we should soon know more. Early impressions are good, this could be the sort of funding arrangement that the physics / life science interface community had argued for over many years.

The year ahead will be nice and busy with several events organised, co-organised or supported by our group. Highlights include Physics of Microorganisms (8thApril, IOP London), a Super-resolution workshop (5thJuly Leeds), our "flagship meeting" Physics Meets Biology (PMB, 9-11th Sept, Oxford), and Quantitative Methods in Gene regulation meeting V (9-10th December, IOP London).

Please do get in touch with the Chair or any of the committee members if you wish to contribute to current activities, and if you have an interest in joining in a more official role in the future. We shall hold the 2019 AGM very likely at the PMB conference in Oxford in September. If you would like to join the committee, the new IOP process apparently requires nominations to arrive 2 months before the AGM. Also, generally please make students and colleagues aware of the IoP Biological Physics group.

Tricks of the light: the remarkable power of laser tweezers to dissect complex biological questions

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On 2 October 2018 Göran Hansson, Secretary General of the Royal Swedish Academy of Sciences, announced that the Nobel Prize in Physics would be jointly awarded to Arthur Ashkin, Gérard Mourou and Donna Strickland, for their "groundbreaking inventions in the field of laser physics". Strickland and Mourou shared one half of the prize for their pioneering work in generating high-intensity, ultra-short optical pulses. The recipient of the other half was Arthur Ashkin for his seminal work leading to the development of optical tweezers, also referred to as 'optical traps' or 'laser tweezers', and their applications to an enormous range of biological systems. As discussed below, laser tweezers are a remarkable class of optical force transduction tools which have had a profound effect in enabling several complex biological questions to be addressed impenetrable using other existing technologies.

The ability to trap particles using laser radiation pressure was demonstrated by Arthur Ashkin while he worked in the Bell Labs almost half a century ago, using a relatively unstable 1D optical trap consisting of two juxtaposed laser beams whose photon flux resulted in equal and opposite forces on a micron sized glass bead (*Ashkin, 1970*). The modern form of the now most commonly employed 3D optical trap design (which Ashkin denoted as a 'single-beam gradient force trap'*, Ashkin, 1986*), results in a net optical force on a refractile, dielectric particle which has a higher refractive index than the surrounding medium, directed approximately towards the intensity maximum of a focused laser beam. The key physics principles that account for the operation of laser tweezers are a testament to the successes of the wave-particle duality model of light; as predicted by quantum mechanics, photons of light carry linear momentum p given by the de Broglie relation which relates this particle property of momentum to the light's wavelength through $p=E/c=hv/c=h/\lambda$, for a wave of energy E, frequency v and wavelength λ where c is the speed of light and h Plank's constant. This momentum results in radiation pressure if photons are scattered from an object, but also if refraction occurs at the point of a photon emerging from an optically transparent particle there is a deviation in beam direction, and thus a change in the momentum vector resulting in an equal and opposite force on the particle, in accordance with Newton's 3rd law. Standard laser tweezers have a Gaussian intensity profile in the vicinity of the laser focus which results in a net force that literally traps the particle in a potential well whose width is limited by the diffraction of light, resulting in a trap diameter in the focal plane of a light microscope of roughly the wavelength of the laser light.

Many modern day laser tweezers use near infrared laser sources of wavelengths around a micron, ideal for trapping commercially available microscopic spheres composed of glass or latex/polystyrene. Although single biomolecules themselves cannot be easily optically trapped with any great efficiency (some early laser tweezers experiments toyed with rather imprecise manipulation of chromosomes and other cellular structures), they can be manipulated via such micron sized optically trapped spheres. Such microspheres can be controllably coated in a range of chemicals that can enable specific biological molecules to stick to their surface. These coated microspheres can then be used to probe the forces involved in the activities of these biological molecules, either in isolation or coupled to interactions with other molecules, detected optically through measuring the small displacements in the microsphere position relative to the centre of the laser tweezers force field. Laser tweezers in effect act as a microscopic optical force transduction tool *(Leake, 2016)* which can tease out the tiny piconewton level forces generated in changes in single molecule conformations in real time, with an exceptional sensitivity capable of detecting

molecular displacements down to the sub-nanometre length scale of individual chemical bonds.

These optical force transduction devices have since been applied to very diverse studies in the area of single molecule biology (*Lenn, 2012*), including biomechanical polymers such as nucleic acids and a range of filamentous proteins, as well as intense research of molecular machines, such as those involved in the generation of force in muscle contraction, molecular trafficking inside cells, and those used to enable cells to be motile (*Miller, 2018*). With high stiffness laser tweezers a single biological molecule can be tethered between a trapped microsphere and a microscope coverslip or another independently trapped microsphere, and controllably stretched and relaxed to explore its viscoelastic properties at a single-molecule level, which has given us invaluable insights into the mechanics of molecules such as DNA and RNA and a range of long proteins such as those of muscle tissue (*Leake, 2003*; *Leake, 2004*). Similarly, laser tweezers have been used in a so-called 'dumbbell assay' originally designed to study 'motor protein' interactions between the muscle proteins myosin and actin (*Finer, 1994*), but since utilized to study several different 'linear' motor proteins (motor protein which operate on a linear molecular track) including kinesin, dynein and DNA-protein complexes. Here, the appropriate molecular track can be tethered between two optically-trapped microspheres and is then lowered onto a third surface-bound microsphere coated in motor protein molecules resulting in stochastic interactions during 'power-stokes' of the motor protein against the track, which may be measured by monitoring the displacement fluctuations of the trapped microspheres. Very low stiffness laser tweezers can also be used not to manipulate biomolecules but more as a very high precision positional displacement detector through a process of laser interferometry as a trapped microsphere moves relative to the laser focus. By using the microsphere as a probe attached to the flagella of bacteria it has been possible to monitor individual step-like power-strokes of 'rotary' motor proteins (for which the track is in effect a circle) in the same way as linear motor proteins (*Sowa, 2005*). These most basic of laser tweezers devices have given us huge insights into the *Physics of Life* at the single-molecule level (*Leake, 2013*).

The range of capabilities of laser tweezers have expanded significantly over the past *ca.* decade. The refractive index of the inside of cells is in general heterogeneous, with a mean which is marginally higher than the water-based solution of the external environment. This combined with the fact that cells have a mechanical compliance results in an optical stretching effect in these optical fibre based laser tweezers devices, which has been used to investigate mechanical differences between normal human cells and those which have a marginally different stiffness due to being in a diseased state, such as those involved in cancer (*Gück, 2005*). Also, laser tweezers have been adapted to measure not only force but also molecular *torque*. In standard Gaussian profile laser tweezers there is zero net angular momentum about the optic axis due to the symmetry of the microsphere and the intensity profile of the trap, however rotational asymmetry can be introduced to manipulate and measure angular momentum. For example, two optically trapped microspheres can be fused together to generate a provides a wrench-like 'optical spanner' effect, which has been used for studying the F1-ATPase enzyme (*Pilizota, 2007*), one of the rotary motor proteins which, when coupled to another rotary motor protein called Fo, generates molecules of the 'universal biological fuel' ATP. Another method utilizes the angular momentum properties of light itself. *Laguerre-Gaussian* beams can be generated from higher-order laser modes above the normal symmetrical Gaussian profile used in standard laser tweezers, by either optimizing for higher-order lasing oscillation modes from the laser head or by applying phase modulation optics to the beam path. Combining such asymmetrical beam profiles with the use of circularly polarized light can induce controllable rotation in birefringent particles which can be used to generate torque to study the underlying mechanisms of action of rotary motor, for example in the interactions of certain proteins with DNA (*Forth, 2011*).

The very high detection sensitivity, spatial precision and high time resolution of laser tweezers predispose them to a broad range of applications for studying the mechanics of biological processes at a single-molecule level. The use of focused laser light in generating an optical trap also facilitates invaluable integration into existing light microscopes, thereby enabling complementary imaging observations not only to visualize trapped microspheres but also to visually detect a range of associated biological structures that may interact with the trapped microsphere, for example utilising various forms of fluorescence microscopy that can illuminate specific features of interest. This use of correlative technology offers enormous potential at combining the breath-taking power of molecular manipulation of laser tweezers with the exceptional imaging precision of the emerging suite of phenomenal super-resolution light microscopy tools. The transformative insights into molecular biomechanics, fundamental to basic biological processes, thanks to the power of laser tweezers, is Ashkin's tremendous legacy to cutting-edge interdisciplinary science at the exciting interfaces between the life and physical sciences.

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Single-molecule bacteriology, Sept 2018, Oxford

Co-Organisers: Achillefs Kapanidis, Meriem el Karoui, Stephan Uphoff and Jie Xiao,

The first "Single-molecule Bacteriology" meeting, took place at Lady Margaret Hall, Oxford on Sept 9-12, 2018. This meeting was also the 84th Harden conference (sponsored by the Biochemical Society). There were 25 invited talks, and a further 23 talks were selected from the abstracts and there were 110 attendees.

The main focus of the meeting was the use of single-molecule experimental methods together with complementary theoretical modeling approaches to understand spatial organization and mechanisms of living bacterial cells. New quantitative in vivo techniques applicable to bacteria, and single-molecule studies of clinical/commercial significance were also covered at the meeting. Many talks focussed on understading the mechanisms that bacteria use to process of nucleic acids, from transcription and translation to CRISPR-based recognition and search processes on the bacterial chromosome.

The opening lecture was given by Professor Taekjip Ha (Johns Hopkins University, Baltimore). Taekjip applies ground-breaking single-molecule fluorescence and force microscopy methods to the understanding of chemistry and biochemistry of nucleic acids. He was awarded the Michael Gait Lectureship award from the Nucleic Acids Group of RSC for his outstanding contributions to the field. Professor Neil Hunter (University of Sheffield),

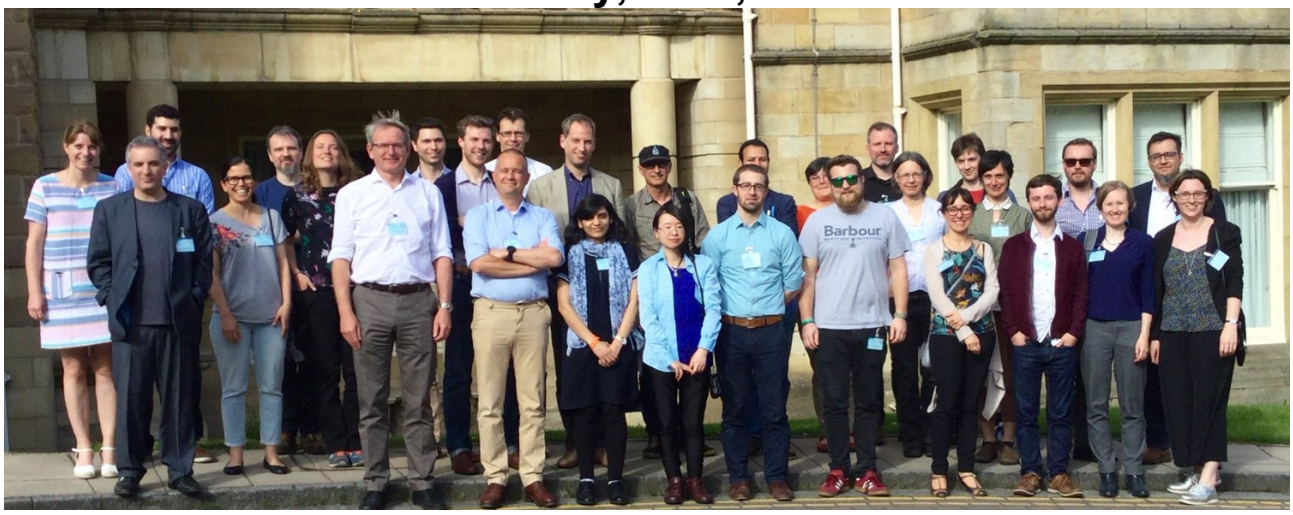
an expert on photosynthetic bacteria, gave the 2018 Biochemical Society Keilin Memorial Prize Lecture,

The meeting was well received, and at the end of the meeting, the participants were very enthusiastic about a second meeting. And so, it is very likely that the 2nd "Single-molecule bacteriology" meeting will be held at Oxford in September 2020.

For photographs and comments from the meeting, follow #smolbac on Twitter.

Many thanks to generous sponsorship from the Wellcome Trust and the BBSCR, as well as from academic, industrial, publishing, and industrial sponsors, including the Royal Microscopical Society.

Physics of Life Workshop on ‘Multiscale Mechanics in Biology’ 15-16 May, 2018, Leeds

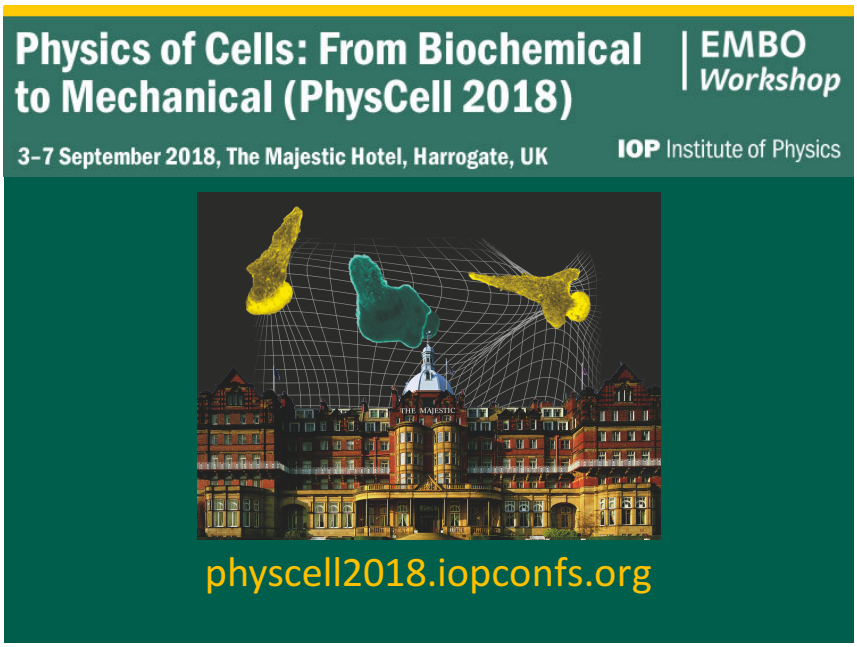


Multiscale mechanics of biological systems has emerged as an exciting area of research and provides enormous opportunities for innovative multidisciplinary basic research and technological advancement. Supported by the EPSRC Physics of Life network we organised a workshop on ‘Multi-scale mechanics in biology: current challenges and potential solutions for healthcare applications’ in Leeds in May 2018. At the workshop, current experimental and theoretical tools for exploring the mechanical properties of biological soft matter, including proteins, polymers, membranes, fibrous networks, cells and tissues were discussed. These discussions were fueled by a series of invited talks by leaders in this area, including Prof Cornelis Storm (Eindhoven) who gave the opening talk on ‘ Strength and Numbers: Modelling the mechanical properties of hierarchical biomaterials’.

The possibilities of understanding biological systems which span multiple scales, both spatial and temporal, and the challenges involved in bringing this knowledge together into a single multi scale understanding were also explored. This included talks from Robert Ariens (Leeds) on 'Blood clots are covered by a film that protects against infection and cell loss' and Vasileios Vavourakis (University of Cyprus/UCL) on 'The mechanical role of the tumour—host tissue microstructure and microvasculature in interstitial fluid flow and drug delivery'. Daniel Frankel (Newcastle) presented his work on the 'The mechanics of solid cancerous tumours - its role in invasion, metastasis and chemotherapy resistance' and Laurent Blanchoin (Grenoble) on 'Directed Actin Cytoskeleton Self Organization, Contractility and Motility'. Gijsje Koenderink (AMOLF) highlighted the rich information which could be gained from exploring system right across the length scales, in the context of cells and tissue mechanics and Ewa Paluch (UCL/University of Cambridge) presented a fascinating view of 'Cell morphogenesis across scales, from molecular processes to cell surface mechanics'. We learned about a ‘success story’ where knowledge of the physics at each length scale has resulted in novel approaches to solving clinical challenges. In particular, Prof Ruth Wilcox (Leeds) delivered an insightful talk on ‘The mechanics of musculoskeletal tissues and interventions and the rocky road to clinical translation’. During the workshop we discussed some of the current challenges in this area and explored opportunities for collaborative projects to meet those needs.

Workshop Chair: Lorna Dougan (School of Physics & Astronomy, University of Leeds)
Co-organisers: Steve Smye (NIHR/Kings College London), Marlene Mengoni (Engineering, Leeds), Michelle Peckham (Biology, Leeds), David Head (Computing, Leeds)

PhysCell 2018 Conference Report



The EMBO workshop "Physics of Cells: From Biochemical to Mechanical" (PhysCell 2018) took place in Harrogate 3-7th September. 150 participants of 36 different nationalities gathered from 20 different countries of residence, half outside of Europe. Only a couple of participants were prevented from attending by unusually long visa delays (let's hope such problems do not escalate in a post-Brexit UK). Unfortunately, a few people were ill and the dates were difficult for some parents due to their children starting school that week. However, a couple of pre-school children attended the meeting with their parents and were accommodated in family rooms in the venue. The IOP conference office were a great support in hosting this international meeting in the UK for the first time.

Many participants had never been to Yorkshire before and most discovered the delights of the Victorian Spa town of Harrogate for the first time. The Majestic Hotel venue impressed many with its grand old building. It certainly had character, especially with the added complication of ongoing improvement works! All participants were accommodated and fed in the venue and most enjoyed newly refurbished high spec rooms (apart from a few unlucky people in rooms not yet renovated). Many participants were impressed with the food, although some missed the higher quality of wine from their own countries!

The programme covered different aspects of the physics of cells from components such as the cytoskeleton, membrane and nucleus through to processes such as signalling, cell division and migration/swimming. Cell mechanics and adhesion seemed to come into many sessions as the field faces the challenges of elucidating the biochemical and mechanical connections between different cell components and extracellular matrix. The physics of cells ranged from the single molecule level to the tissue and microbial colony levels. The range of topics covered was particularly appreciated by participants (100% of survey respondents felt the topic was adequately covered). The efforts by the organizing committee to include a mix of theoretical as well as experimental approaches worked well.

Discussions were a particular highlight of the meeting with 100% of survey respondents saying there was sufficient time for discussion during the scientific sessions and 94% that there was sufficient time to meet and network with other participants/speakers. 90% acquired useful career contacts/collaborations. The organisers had put much effort into designing the meeting to facilitate discussion and the participants engaged well in this. Offering a free drink to the first student question in discussion sessions provided a fun encouragement to engage younger participants.

During the poster sessions, despite practical issues caused by the hotel staff packing away drinks (including water) too early, participants enthusiastically continued discussing their science until late into the evening continuing the tradition of lively poster sessions that have become a feature of PhysCell.

The conference reflected the young, diverse, international, dynamic community in the field. The gender ratio was better than many physics conferences with 32% of speakers and 44%

of participants identifying as female. There was a healthy range of seniority represented amongst speakers and participants with some great talks and engagement by top professors, new group leaders and PhD students. Participants generally managed well to communicate across discipline and hierarchical barriers establishing a genuine scientific exploration. As described by one survey respondent “active participation of students was successfully encouraged… plenty of time to discuss in formal and informal settings… Age or status did not play any role. This spirit should definitely be kept.”
In the words of another survey respondent, “It was a great conference overall. Definitely one of the best in the world.”
From the excellent bids presented to host the next PhysCell meeting, the international advisory board chose Israel to host PhysCell 2021. We’re looking forward to it already – don’t miss it!

Rhoda Hawkins
University of Sheffield.

Review "some critical questions in biological physics – a guided tour around the bugbears" by Thomas Waigh

Defining and explaining Biological Physics keeps me busy in strategy committees and dinners, and sometimes wakes me up at night. As scientists we are all prone to tunnelling into questions and working away at them until we gain pleasure from some understanding or decide to shelve the problem for some other more interesting one. Let's say this represents process digging forwards. If you practice biological physics you realise there's an extra challenge: as well as digging forwards you are constantly having to prop up sideways and behind you because the rest of physics, and sometimes biology, presses in! This is all the more frustrating because (if you are already a biological physicist) you can see how scientifically fertile the landscape is around you, and how much more physics should invest there. We have not yet nucleated a sufficiently stable community, one which is recognisable and appreciated by the rest of science. This is exactly what *Some critical questions in biological physics* by Thomas Waigh is about.

There have been a handful of textbooks recently that form excellent platforms for undergraduate or graduate teaching in biological physics: *Physical biology of the cell*, 2nd ed., Rob Phillips *et al*. (2012) covers cell biology in the language of soft and statistical physics, and contains a wealth of useful course material; *Physical models of living systems*, Phil Nelson (2014) is, I find, a crystalline pitch for the value and meaning of doing physics in the world of life; *Biophysics: Searching for Principles*, William Bialek (2012) gives a sense of how deep physics can go in terms of understanding signal processing in living systems, and *An Introduction to Systems Biology*, Uri Alon (2006) is a classic entry point, typically much appreciated by physicists, showing how it is possible to be quantitative about living systems. I believe that these books together define what is today biological physics: the contribution that methods from statistical, nonlinear and condensed matter physics can bring to biology, often enabling entirely new biological questions to be posed and addressed. These books are mostly written by theoreticians, and there is of course a complement of knowledge and books based around techniques. One should not forget that, as a result of evolutionary complexity, biology is not a subject that can be tackled by theory abstracted from experimental data.

Some critical questions in biological physics is quite a unique book. Firstly, it is written in a very personal style: you can imagine that the author is writing in a direct and informal language pitching the field to prospective graduate students, or to his departmental colleagues out of frustration, or simply trying to rationalise what the community has achieved and where it is headed. Waigh's own career and experiences are central to the topics covered in this book, which gives the text a personal connecting thread I. happened to enjoy this approach but, if you are looking for a more unbiased style, you will not like it. Secondly, Waigh is an experimentalist who has had a successful career deploying imaging, scattering, spectroscopy and rheological tools across soft and biological systems. This gives the author a different point of view from the textbooks listed above. Instead of gathering our current understanding into a systematic framework, Waigh takes stock of open problems, mostly connected to experimental challenges, looking for new tools or experimental design. In essence, he is calling for innovative clever practitioners within physics.

Waigh has crafted a structure that makes the book very accessible: there are 18 chapters, each of which begins with a roughly 10 page essay with introductory and advanced references, followed by a few pages of "Technical details" explaining specialised terms and the underlying physics, with some further references. My favourites are the chapter on the 21 types of mucins in a human, and that on the challenges of gene delivery, but I enjoyed most of them and you are presented with material ranging from molecular motors to cell membranes, the role of physical chemistry, and regulation of gene expression. Don't expect to learn any physics here, nor all the necessary biology to start working on these problems. The value of this book is to highlight, in a clear and straightforward way, a number of frontiers

where physicists can join biological physics and help to tackle important open biological questions. This book should be read by non-biological physicists in order to get an appreciation of what the field is about, and perhaps to transition into it. It is also a pleasure to read from within biological physics, and you will find yourself constantly challenged to see if you can claim one of the lollipops promised by the author in return for sorting out his bugbears! The main fault is the price: that the only number in this book which is off by an order of magnitude.

Note: this review is based on a version published by Physics Today in the December 2018 issue, with permission.

Pietro Cicuta is Professor of Biological Physics in Cambridge at the Cavendish Laboratory; he lectures a 4th year Biological Physics course and currently chairs the IOP Biological Physics group.

Upcoming Meetings

Physics of Micro-organisms 8 April 2019

MMC (incorporating EMAG) Manchester July 1-4th 2019

Super-resolution Workshop on Friday July 5th University of Leeds.
(Organisers: Susan Cox and Michelle Peckham)

Physics meets Biology 9-11 September, 2019. Oxford
Organisers: Andrew Turberfield, Achillefs Kapanidis, Bartlomiej Waclaw, Thomas Waigh, Michelle Peckham