In the past two decades, the field of biophysics has witnessed tremendous progress. In 2000, Bill Clinton presented the first draft of the human genome. Techniques to sequence DNA rapidly improved, the power of computers exploded, and the cost of whole-genome sequencing rapidly fell. The parts lists of many organisms quickly became available. But life does not reside in the genes or the proteins: it arises from the interactions between them. As a result, the accumulation of data exploded. This has pushed quantitative modelling to unprecedented heights, and the interaction between experiments and theory has become tighter than ever before. Concepts from physics, such as fluctuations, phase separation and criticality, have been invoked to explain the design and behavior of biological systems. Techniques from mathematics and computer sciences have been applied increasingly to analyze experimental data. These trends have swept all the different fields at the wide interface between physics and biology, from microbiology, cell biology, immunology to neuroscience.

And yet, as we wrote in our ICAM proposal, we believe we have arrived at a crossroad. On the one hand, the different subfields become increasingly specialized. On the other hand, the increasing amounts of data pose challenges and create opportunities that are common to all these different fields. The overarching question of our workshop, The Future of the Physics of Life, is whether the future of the interaction between experiment and theory will be a continuation of existing approaches or whether fundamentally new routes will be taken.

For our workshop, we identified four focus areas, and the program of our workshop followed these. We will therefore present this report along the lines of these focus areas, and then end with a few concluding remarks.

Focus area: Coarse-grained versus molecular mechanistic modelling

The first focus area was coarse-grained versus molecular modelling. What is the role of coarse-grained versus detailed molecular modelling? Do they serve distinct purposes, or does modelling inherently become more fine-grained as more data becomes available? How do we connect the dynamics at different scales in biological systems? Are there general laws in the spirit of macroscopic thermodynamics?

A prime example of the latter is provided by the bacterial growth laws identified by Terry Hwa and coworkers. We were therefore very happy that Terry Hwa was willing to kick-start our workshop. In this talk, he first summarized his earlier work that beautifully demonstrates that the allocation of resources in metabolic networks can be explained via a few basic principles, built on the idea of supply and demand: if the nutrient quality or abundance is high, less resources need to be invested into the metabolic sectors that turn the nutrients into amino-acids; more resources can therefore be devoted into building ribosomes, so that the cell can grow faster. These ideas can be captured in coarse-grained protein allocation models, which quantitatively describe how the protein allocation varies with the growth rate. The power of these coarse-grained models is thus not only that they allow for quantitative predictions, but also that they can elucidate the design logic of these systems. Yet, *how* the cell controls the allocation at the molecular level cannot be explained by these models. This question inherently calls for a more detailed and molecular, mechanistic model. In the second part of his talk, he then presented the recent and on-

going work in his group, in which they developed a molecular, mechanistic model that can describe how the cell controls the size of the different metabolic sectors. His work is thus a beautiful and unique demonstration of how the dynamics at different scales can be connected.

In his after-dinner talk Bill Bialek also addressed the question of how dynamics at different scales can be connected. In physics, the classic example of coarse-graining details at the microscopic scale, generating interactions at larger length and time scales, is renormalization group theory. Bialek showed how ideas from renormalization group theory can be applied to neuronal networks. The trick was that the "neighboring spins and interactions" that are integrated out first are determined based on the strength of the pairwise neuronal correlations, which are not necessarily nearest neighbor interactions. Bialek showed that this trick made it possible to apply the machinery of renormalization group theory to integrate out interactions, describing dynamics at larger length and timescales.

Christoph Zechner showed how another well-studied phenomenon in physics, liquid-liquid phase separation, can be used for cellular function, namely to reduce gene expression noise. Yet, here the question of how behavior at the higher cellular scale – phase separation – arises from interactions at the lower molecular scale remains pertinent. The cell is a highly multi-component mixture, and what all the possible phase separation scenarios are, and how they should be identified and described, remains a highly challenging question.

Massimo Vergassola ended this session with a beautiful talk on how to navigate in turbulent flows, a notoriously difficult multiscale problem. Using ideas from reinforcement learning, he derived optimal navigation strategies and showed how these depend on, for example, the level of turbulent fluctuations.

Hypothesis-driven versus data-driven modelling

Looking back at the history of the modelling of arguably the best characterized cellular systems in biology, the E. coli chemotaxis system and the cyanobacterial circadian clock, reveals that the canonical models for these systems have been established via concept- or hypothesis-driven modelling. Yet, the wealth of data has prompted the development and application of data-driven Bayesian modelling. Will the future of biophysics be driven by this type of "hypothesis-free" modelling? And does this even exist? Is this even possible? Or does model building always entail developing hypotheses, making assumptions about what is important?

In his talk, Aaron Dinner gave a glimpse on what the future might bring, using the cyanobacterial clock as a model system. In particular, he showed how data-driven modelling can be combined by more conventional modelling. The human mind is still essential to define the space of possible models, but then data-driven, Bayesian modelling is becoming a powerful tool to develop concrete models within this space. Interestingly, this led to a new, as yet unidentified mechanism for generating a non-linear activation of the central clock protein, but the abstraction from the data, necessary to identify the generic mechanism, still required the human mind.

This was also the message of the talk by Thierry Emonet, who presented their recent work on olfaction. Machine learning, Bayesian modelling are very important tools, but the big leap forward was made by old-fashioned hypothesis-driven research. Using an elegant experimental setup for optogenetic stimulation, they could precisely control the spatial pattern of olfactory stimuli experienced by freely behaving animals, which led to the surprising discovery that flies can sense not only the intensity but also the spatial motion of odors.

Multicellular systems

In the past two decades, physicists made many seminal contributions through work on unicellular organisms, primarily because these were easier to manipulate experimentally. However, as the interface between physics and biology has grown over the past two decades, physicists have been venturing into biological systems of increasing complexity, and beyond canonical model systems. Some of the major themes that emerge are collective behavior, morphogenesis, and transport processes – how do populations of cells manage to process information, generate the necessary spatial structures to build up an anatomy, and carry out organism-scale functions in the real world?

Arup Chakraborty gave a most impressive talk on the application of ideas from statistical physics to the development of vaccination strategies. He described a new strategy based on broadly neutralizing antibodies (bnAbs), which have the potential to protect against highly mutable pathogens. In this strategy, antigens are administered sequentially, in such a way that the total level of frustration increases. Furthermore, the capacity to evolve bnAbs depends sensitively and non-monotonically on the level of frustration. This work relies on a beautiful interplay between ideas from biophysics, evolution, learning and immunology.

Toby Kiers described biophysical experiments that are mapping morphogenesis and transport in a non-canonical multicellular system – arbuscular mycorrhizal fungi (AMF), which grow underground and engage in symbiotic trade with plant roots. These community-level nutrient trade and transport dynamics play a major role in the global carbon cycle, but the underlying mechanisms remain largely unknown. The new data demonstrate how fungal morphogenesis implements a traveling-wave growth strategy, and that the carbon acquired through nutrient trade with plants appear to be transported efficiently by leveraging liquid-liquid phase separation within fungal hyphae.

Karen Alim described results on how vasculature – a key feature of multicellular systems enabling long-range transport – responds and adapts to varying environmental conditions over space and time, in the soil microbe *Physarum polycephalum*. This organism is a unique model to study vascular morphogenesis and adaptation, and her work demonstrates how experiment and theory can be combined to uncover basic design principles of the flow networks that implement transport in multicellular systems, including dynamic remodeling of their network architecture.

Katharina Sonnen described experimental results demonstrating signaling oscillations during embryonic development and adult tissue homeostasis. Through elegant fluorescence experiments *in vivo*, she demonstrated how temporal regulation of the segmentation clock plays a critical role in the biogenesis of vertebrae in developing mouse embryos.

Jeroen van Zon described imaging experiments that enable lineage tracking in intestinal organoids. By combining 3D imaging with computational analysis, he demonstrated how lineage correlations across mother-, daughter-, sister-, cousin-cells, can be mapped to cell fate decisions in a developing tissue.

Optimality

In the past two decades, the idea that biological systems have been optimized has gained much traction. In his talk, Gasper Tkacik pushed this idea to new heights. Using in-silico evolution, he showed that the gap-gene developmental system of the fruit fly can be predicted from the premise that this system has been optimized to maximize the transmission of positional information. The in-silico evolution procedure generated multiple outcomes, but the observed system was among them. Moreover, its positional information was the highest.

Aleksandra Walczak described an analysis of collective dynamics in flocking birds and socially interacting mice. Analyzing a statistical mechanical model of starling flocks, she showed that the collective dynamics demonstrate entropy production when motion is coupled with interactions, and suggested an approach to detecting the departure from equilibrium statistics from steady-state distributions. In addition, she showed an analysis of social interactions in mice. She showed that a maximum-entropy spin model trained on the steady-state distribution of experimental data could recapitulate also dynamics when a generalized Glauber dynamics framework was employed.

Discussion

In the Discussion section at the end, led by Sander Tans and Erik van Nimwegen, we returned to the overarching questions of the workshop. It became clear that connecting the descriptions across levels remains challenging. Hwa gave a beautiful example where this is possible, but how general this is remains to be seen. Everyone also agreed that machine learning and data-driven and Bayesian modelling will become even more important, but also that conventional, hypothesis driven research remains critically important. Indeed, the biggest leaps forward, as Hwa's, Dinner's, Emonet's and Chakraborty's talks demonstrated, were induced by the creativity and the conceptual power of the human mind. More generally, these talks showed that taking time to reflect on the bigger picture and question is vital to make progress.

Concerning the big versus small data question, people agreed that both are important, but what is even more important is the quality of the data. Big data becomes a problem when the quality is not high. Bialek and Hwa both remarked that physicists have much to contribute in this respect, not only in analyzing data but also in producing high quality quantitative data.

There was a long discussion about optimality. Toby Kiers pointed out that biologists are trained to focus on the complexity of organisms, the interactions between them, and the environment they live in, and hence tend to be extremely cautious, perhaps even skeptical, about claims that one thing or another has been optimized. Many organisms do indeed live in a highly fluctuating environment, which is often not even stationary. How to define

optimality in these cases, let alone whether it can be reached, remains an inspiring question for the years to come. What is clear is that optimality gives a useful guiding perspective on the design logic of biological systems.

A topic that arose through the ensuing discussion was how best to train young researchers entering the field. Interestingly, some young participants expressed excitement / positive sentiment regarding new multidisciplinary education programs (e.g. Bionanoscience at TU Delft), whereas a number of senior participants (Chakhraborty/Bialek) emphasized their believe that a solid foundation in disciplinary training is essential to be successful in interdisciplinary work later in one's career.

There was also a shared feeling that in the coming years, the trend towards studying more complex, multicellular systems will continue. Also the interaction with medicine will probably tighten, as Chakraborty's talk also showed.

Impact

Connecting dynamics / descriptions across scales remains a timely topic for the years to come. The example of Hwa's work will certainly inspire others to develop similar cross-scale descriptions in many other systems. The presentations by Vergassola, Dinner and Emonet exemplify how machine-learning / data-driven modelling can augment conventional hypothesis-driven modelling to develop understanding of increasingly complex biological systems. The talk of Tkacik will inspire the application of optimality principles to other biological systems (both unicellular and multicellular). Talks by Alim and Kiers demonstrated how completely new biophysics can be uncovered in unconventional model organisms. The talk by Chakhraborty provides an inspiring example of how biophysics of multicellular systems has matured to the extent that it has a direct impact on medicine / development of vaccination strategies.

Collaborations

The meeting led to multiple new collaborations. Ten Wolde and Emonet developed new interactions regarding information transmission in the *E. coli* chemotaxis system. Ten Wolde and Dinner have been in contact regarding the cyanobacterial circadian clock. Emonet and Sonnen forged links to analyze developmental dynamics in space and time. Kiers, Shimizu and Alim have been discussing how to connect their respective observations of fluid transport in their contrasting vascular systems. There was ample time for discussion, which also helped to set up new collaborations.

Concluding remarks

The workshop was a big success. The talks were outstanding. The poster session was also very lively. With 110 attendees, the number of participants was higher than we had hoped for. Apart from one speaker, all speakers agreed that their talk will be made publicly available. Everyone agreed that this was indeed an exceptionally inspiring meeting, which will initiate new research, establish new connections between topics and questions, and generate new collaborations.