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Interdisciplinarity as both Necessity and Hurdle for Progress in the Life Sciences

Abstract

The ability to sequence the genome of entire organisms has produced a fundamental change in the scientific practice of the life sciences. With the Omics revolution, biologists working with cellular systems have become dependent on the support of and collaboration with other disciplines. Following the identification and characterization of cellular components in the context of bioinformatics, the focus has shifted in recent years to the study of mechanisms that determine the functioning of cells in terms of gene regulatory networks, signal transduction and metabolic pathways. This shift of focus towards an understanding of functional activity and therefore towards cellular processes required methodologies from systems theory and thus expertise from other fields than computer science and physics. Since then, the term 'systems biology' has become associated with an interdisciplinary approach that realizes a practice of data-driven modelling and model-driven experimentation. With systems biology, mathematical models have become a central element in the formulation of biological arguments and as a consequence, a new quality of interdisciplinary collaboration has become necessary. The "modeller" or "theoretician" no longer plays a simple supportive role. Instead, the construction and analyses of the models require both – the "experimentalist" and "modeller" to meet at "eye level", pursue a common question, and rely upon each other. The present text discusses the practice of systems biology with respect to the hurdles and opportunities provided by interdisciplinary collaborations in this field. The main conclusion is that truly interdisciplinary collaborative efforts are a necessity for progress in the life sciences but these efforts are hampered by academic structures and practices that prevent these projects from succeeding.

1. The emergence of systems biology

The ability to sequence the genomes of organisms has produced a fundamental change in the scientific practice of the life sciences. Genome projects have generated large-scale data sets, which required databases to store information about sequences, structures, and auxiliary information about the gene and proteins in question. In addition to the computational infrastructure that stores the data and the provision of interfaces to access the information, tools and algorithms were

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needed to analyse the data. To this end, predominantly statistical and machine learning techniques were employed, thereby attracting computer scientists and physicists to the life sciences. While computer scientists have often cast themselves in a supportive, software-developing role in which biological questions are of secondary interest, the skilled application of tools and algorithms to answer biological question has turned many biologists into “bioinformaticians”. One possible explanation for the success of physicists in the biological sciences may be seen in their training – they are competent in mathematical modelling, not afraid of theory but at the same time they do not mind “getting their hands dirty” with experimental data, which they know to process with statistical tools. In systems biology, a similar argument can be made about control engineers, who are trained to combine mathematical modelling with experimental data and “real-world” problems.

With the genomics revolution, biologists have thus become dependent on the support of and collaboration with other disciplines. Genomics and bioinformatics has focussed on the identification and molecular characterization of cellular components. It quickly became apparent that from the components themselves one cannot fully understand their function. This triggered a shift of focus towards the study of interactions and an understanding of mechanisms that underly cell function (e.g. cell growth, proliferation, differentiation and apoptosis). The study of functional activity as processes that are realized by gene regulatory networks, signal transduction pathways and metabolic networks requires techniques to model dynamical systems.

The fact that cell functions are driven by spatio-temporal processes is crucial for the emergence of systems biology. While statistical and computational techniques (including machine learning) took centre stage in bioinformatics, the shift of focus towards an understanding of functional activity and processes required methodologies from systems theory. This need introduced many (control) engineers to the biological sciences. The use of systems-theoretic approaches in molecular and cell biology, mostly focussing on intracellular pathways and networks, has now become an active area of research under the umbrella of ‘systems biology’. The practice of systems biology is characterized by a close integration of “theory” and “experiment”, of data-driven modelling and model-driven experimentation. The role of mathematical models is changing from a supportive to a central role in formulating and arguing a biological hypothesis. As a consequence, a new quality of interdisciplinary collaboration has become necessary. The “modeller” or “theoretician” no longer plays a simple supportive role in which a deeper understanding of the biological context is secondary. Instead, the “experimentalist” and “modeller” have to meet at “eye level”, pursue a common question, and rely upon each other for their mutual success. The remainder of the present text discusses the practice of systems biology with respect to the hurdles and opportunities for interdisciplinary approaches.

Truly interdisciplinary, large-scale, and multinational projects are essential for progress in the life sciences. The complexity of cells and systems made up of cells does not leave us a choice. We shall here argue that the biggest hurdle for progress may not be funding or technical limitations, but the personal relationships and dependence of members in interdisciplinary teams. In many instances the risk of failure in a project is *not* related to the science or scientific approach, but is more often a consequence of personal problems between project leaders, often as a consequence of the current academic system and how this system hinders interdisciplinarity.

2. True interdisciplinarity

Any definition of interdisciplinarity already harbours some difficulties. Experts differentiate between trans-, inter- and cross-disciplinarity. What we will refer to in the present text, focussing on the practice of systems biology, is interdisciplinarity understood as a means to answer questions by teams of experts from different disciplines *and* which could otherwise not be answered. We therefore speak about the collaboration of at least two experts from different fields of research. In a truly interdisciplinary project, the team members meet "at eye-level", sharing a passion for *one and the same* research question – with either of them having only a small or no chance of succeeding on their own. This is the crucial point – a blessing and a curse at the same time. Because all team members share an interest in the same question but approach it from different angles, this collaboration has the greatest potential for finding an answer or novel solution. At the same time, however, the participants in such a truly interdisciplinary team will depend on each other, on their ability and compatibility.

Interdisciplinarity is a key element in large-scale research projects. However, the inevitable loss of independence in a truly interdisciplinary project provides an enormous challenge to the realization of large-scale research projects in the life sciences. At present, many projects in the life sciences that may be considered "large scale" efforts are more often than not characterized by redundancy and a strong degree of independence of the partners. In such projects each partner contributes a piece to a puzzle but the search for and description of that piece is something the partner can do fairly independent of other partners and with only infrequent interactions. In such large-scale projects, data and models are not integrated at the level of experiments; instead, the results of subprojects, the interpretation of individual works are being integrated at an intellectual level, through discourse and joint publications.

The genome projects are also examples of large-scale collaborative efforts in the life sciences but in these projects the dependency of partners is limited. Here the costs for the hardware and infrastructure, the desire to conduct a comprehensive study, as well as the wish to share the data amongst a large group of users are the main motivations for collaboration.

Health research provides an example of an area where there is an obvious need for integration of research efforts, not just between groups or across disciplinary boundaries, but also across countries. In recent years, funders of research in the life sciences have realized the importance of interdisciplinary research and have established a large number of programmes to promote interdisciplinary collaborations. Systems biology and systems biology approaches have emerged in this period of unprecedented opportunities for interdisciplinary projects. The complexity of cellular systems makes a joint collaborative, truly interdisciplinary effort necessary. As will be discussed below, this however requires that the environment, including the academic structures, are supportive of such efforts. The present situation is one in which large-scale projects do not pursue an integration of results at the level of experiments. This is because the coordination of such projects would require an elaborate strategy and top-down steering to ensure that the extra effort required is not a hurdle.

From a scientific point of view, the development towards truly interdisciplinary projects in biology and medicine may be seen as necessary but it should also be recognized that the scientific effort has to be preceded and anticipated by an enormous effort of the funding bodies and academic system. Interdisciplinary projects not only imply an additional effort by the scientists but also a greater effort in their administration, evaluation and coordination. For the purpose of the present essay, we shall however focus on our experiences as scientists and what we consider the biggest hurdle for progress in systems biology, respectively systems medicine.

3. Apparent interdisciplinarity

New funding programmes that support interdisciplinary efforts in systems biology are a temptation to anyone who seeks funding for his/her research. The many existing interpretations of the nature of systems biology are, in part, also a reflection of the creativity of scientists to attract funding. The re-labelling of one's own work as "systems biology" without ever changing the scientific approach presents a serious threat to progress in the life sciences. The need for interdisciplinary approaches, like systems approaches and mathematical and computational modelling, is a consequence of and response to biological complexity. The misuse of the term "systems biology" for pseudo-collaborative projects undermines the real added value of interdisciplinarity. A point in case is the boundary between bioinformatics and systems biology. Bioinformatics approaches are characterized by the use of algorithms, say for sequence analysis, structure prediction and the use of databases, machine learning techniques and statistical techniques. There is a focus on macromolecules and if networks are considered, then temporal aspects do not play a role. In contrast, systems biology has emerged from the realization that cell functions are driven by networks of genes and proteins interacting in time and space, leading to the view that the functioning of cells is an intrinsically dynamic phenomenon. Once one accepts that a cell function, say apoptosis, is a nonlinear dynamical process, then the theory of dynamical systems should or must enter the scene. A subtle but important difference between bioinformatics and systems biology is thus the perspective, that is, the focus on individual components vs. dynamical networks. For this reason different people are attracted to the fields: in bioinformatics, mostly computer scientists and biologists can be found, while in systems biology the theory of dynamical systems is more important and hence engineers and applied mathematicians will feel more at home. However, with the broad range of problems and due to the fact that many approaches are complementary, it is difficult to draw clear boundaries.

The point is that biological complexity forces us to expand our set of tools, and sometimes a change in how we pursue a problem become necessary. To ensure that such change is implemented, may require some top-down steering to put pressure upon scientists to change their practice. While one would naively imagine scientists to choose whatever is best for answering their scientific problem, in reality decisions are more closely linked to administrative and formal requirements for career progression. There is also an inherent resistance to change if it is accompanied by an additional effort. As will be discussed below, in systems biology the collaboration of experimentalists with modellers usually implies more costly and more time-consuming experiments. Mechanistic models of cell functions require sufficiently rich, quantitative datasets, the need for replicates and increased precision to quantify the uncertainty in experiments; this can strain the relationship in any interdisciplinary partnership. Mathematical modelling represents however not only a natural language with which to integrate data at various levels, the theory of dynamical systems becomes a necessity when dealing with complex dynamical phenomena. Conventional models of medical and biological explanation rely primarily on verbal reasoning and are only suited for dealing with mechanisms that involve small numbers of components and short chains of causality. The value of modelling is then that is necessitates the statement of explicit hypotheses, a process which often enhances comprehension of the biological system and can uncover critical points where understanding is lacking. Simulations can then reveal hidden patterns and/or counter-intuitive mechanisms. Theoretical thinking and mathematical modelling thus constitute powerful tools to integrate and make sense of biological and clinical information being generated and, more importantly, to generate new hypotheses that can then be tested in the laboratory.

Biomedicine is an area in which the need for truly interdisciplinary and integrative large-scale efforts is most obvious. Many diseases are spatio-temporal phenomena that occur across multiple levels of structural and functional organization of the human body. Understanding diseases requires an integration of data from the cellular level to the physiology of an organ. Another dimension is the need for an integration of experimental systems, merging results from studies on cell cultures, genetic/mouse models and patient data. The data themselves can be generated with a range of technologies, each of which is often a specialization with its own community, journals etc. At present there is no experience with such comprehensive, large-scale projects of an interdisciplinary nature.

Only “truly interdisciplinary” projects are likely to provide a high degree of innovation, a “more valuable” publication output (publications that would otherwise not have been achieved and which are published in journals with a higher impact). Most importantly, truly interdisciplinary projects increase the chance of solving complex problems. Research funders and decision-makers should care (more) about recognizing “real” interdisciplinarity. Freeloaders (as reputed as they might be) should be dropped.

4. Learning from physics

In September 2008, after decades of work and bringing together thousands of scientists from hundreds of institutes, universities and laboratories from more than eighty countries, a particle accelerator called the “Large Hadron Collider” or LHC was launched. The project cost some billions of Euros and is dedicated to the question of whether there is such thing as the Higgs boson – an elementary, hypothetical particle. What this project demonstrates is a culture in which large teams collaborate on a joint project and in which many subprojects are mutually dependent. Physicists dare to make their own success dependent upon the other project partners, technicians and designers of the devices. These collaborative efforts are born out of a necessity dictated by the complexity of the problem at hand. Besides an organizational and communication structure, such projects require persistence and a lot of money, too. Physicists have thus succeeded in convincing the general public and politicians of the importance of their goals.

Comparing large-scale research projects in physics with those in the life sciences, the difference becomes apparent. In the European Union, the largest projects in health research are funded with a maximum of 12 million Euros – this is less than the costs to repair the particle accelerator that broke down right after its launch in September 2008. Projects in the life sciences are usually funded for three years, very rarely for more than five years. Everyone who wants to initiate a comprehensive, multinational disease research project will realize that 12 million Euros is not a lot of money to develop new drugs and therapies – certainly not in three years. Furthermore, existing large-scale projects in the life sciences, on a national and international level, are usually designed in a way that the subprojects are pretty much independent of each other – the risks and the fear of failure is perceived as too high. This is true for biologists and biomedical scientists themselves as well as for the cooperation with theoreticians. No one would consider research on diseases less important and less complex than the search for the Higgs-boson and yet this is what the current practice implies: we lack a realistic strategy and approach to tackle diseases by developing a culture for truly interdisciplinary large-scale projects in the life sciences.

The technological developments in the life sciences make it necessary for computer scientists, mathematicians, physicists and engineers to get involved. Not only the frequently quoted "flood of data", but the complexity of the processes looked at, create new areas research, among which systems biology and synthetic biology have generated considerable interest. The fact that cell functions are nonlinear dynamic processes means that they cannot be analysed by common sense and intuition – as highly developed these faculties might be. It therefore becomes necessary for "modellers" to get involved, to use mathematical modelling as an extension of common sense into the realm of complex systems. This requires a new quality of cooperation, starting from the design of the experiments and ending with the interpretation of data. A partnership like this comes along with some potential for trouble, further discussed below.

5. Systems biology should not be a discipline but an "approach"

No one will doubt that understanding any disease is less complex than the proof for the existence of the Higgs boson that the physicists are striving for. A comprehensive disease project requires the combination of a range of technologies to generate data, the comparison of different experimental systems to compare the results and the integration of results over a wide range of spatio-temporal scales – from the molecular and subcellular level to the physiology of an organ. The large quantities of data and their heterogeneous sources motivate the cooperation with bioinformaticians, while the nonlinearity and the dynamical aspects of cellular phenomena requires systems theoretical approaches. In biomathematics and theoretical biology, groups working on a theoretical basis have been inspired by biology for decades. However, theory and experiment never really intertwined. Now, systems biology gives reason for hope to develop models from experimental data and to use models for the design of new experiments.

Systems biology should not to be understood as a new discipline, but as a new *approach* to examine complex cellular systems. Mathematical methods are used as tools to support common sense and the excellent intuition of an experimentalist in analyzing non-linear, dynamical processes. The process of modelling in itself, and the discussion about what to measure and how, are valuable and help to formulate hypotheses and new experiments with which they can be tested. It is exactly this dialogue that benefits from the different views and different training of the scientists involved. This dialogue is also a reason why this interdisciplinary approach is so exciting and inspiring.

Because systems biology is not a discipline, there are no "systems biologists" either. There are medical scientists, biologists, physicists, mathematicians, control engineers and computer scientists realizing a systems biology approach by their cooperation. To make this work, "only" three things are necessary: [i] specialists from different fields of research, [ii] mutual respect and a basic appreciation of each others work, and [iii] the interest in a joint or shared scientific question that will be solved by meeting one another at "eye-level". This list suggests that the appeal and the risks of interdisciplinary research depend on interpersonal, even psychological factors.

One of us took part in initiating the first international journal on systems biology and fought vehemently for a distinction between bioinformatics and systems biology (albeit always pointing out their complementarity). Unfortunately, it is still necessary to promote systems biology separately to avoid true interdisciplinarity ending prematurely and freeloaders using it as a "buzzword". If systems biology prevails as a new view, a new approach – mathematical modelling being accepted as integral part in answering biological questions – we would not mind if the term "systems biology" disappears as a research field, in the names of departments, or in the names of research institutes. The goal is to answer biological and biomedical questions and recognizing the complexity of cellular systems; this requires a change of practice. The notions of 'systems biology' or 'systems medicine' serve as a vehicle to induce this change.

6. Missing the wood for the trees

To solve important, exciting, scientific questions, generalist-specialists are needed: specialists who dare to look over the edge. This is against the idea that the solution of a complex problem requires specialists only, that is, scientists who spend all of their time concentrating on one single question.

If we are serious about the investigation of diseases, the promotion of true interdisciplinarity will be necessary. The large number of funding programmes available all over the world should provide strong encouragement for interdisciplinary research. However, researchers have to ask themselves at which point they should give up specialization. We would recommend starting to broaden their horizon with the masters degree at the earliest. Interdisciplinarity thrives on the encounter of different views and expertise. Assuming that training in the individual disciplines spans several years, the expertise of two different areas can be hardly reconciled in one person. Specialization is a recipe for success, in nature with plants and animals, as in economies and science. At the beginning of a career it is important to become an expert in a single discipline, to distinguish oneself from the big crowd in order to win the race for university positions and to successfully obtain research funds.

A prime example in which a high degree of specialization and individual effort appears to be common is mathematics. In mathematics, extreme forms of specialization are considered as necessary precondition to succeed. A look at the mathematical highlights of the last few years reveals another facet, though. Although the solution of the Poincaré conjuncture by the Russian mathematician Grigori Yakovlevich Perelman was the result of a focused work during several years by a single person, it was still necessary to combine the results of a range of mathematical research areas to prove it. Geniuses often appear as experts by means of extreme specialization. If one takes a closer look, however, they quite often reveal themselves as generalists in their field of specialization. Fermat's Theorem was supposed to be one of the biggest mathematical problems that could not be solved for several centuries, until Andrew Wiles found the proof in 1995 – after decades of work. His proof, however, compiled and created results in a large number of areas in mathematics. Andrew Wiles is a generalist-specialist, as were Albert Einstein and Leonardo da Vinci. Linus Pauling and Max Delbrück are renowned examples from the life sciences. For Perelman and Wiles, it was necessary to have an extraordinary command of many areas of mathematics. Many curricula vitae of great scientists prove the fact that the look beyond the boundaries of their own specialty does not do any harm.

Truly interdisciplinary large-scale research efforts requires both: the combination of specialists from different disciplines and generalist-specialists. The question for how we can progress in the life sciences has thus also consequences for training researchers.

7. Science evaluation as a threat for interdisciplinarity

With the ever finer branching of the sciences into new disciplines, we must be careful not to miss the wood for the trees. The wood is the nature of complex systems. The complexity of nature makes an interdisciplinary, e.g., systems biological approach, absolutely necessary. For funders such interdisciplinarity must have a high priority and because of the risks involved special attention is required.

But also for universities, "true" interdisciplinary harbours an important potential for success. Interdisciplinarity contributes towards the creation of "critical mass" when it comes to attracting grants for large(r) research projects. Especially for small universities, in which departments tend to be small too, interdisciplinarity is a mechanism to build competitive teams, to have success with larger proposals and to increase international visibility. The trend towards dissolving disciplinary boundaries could be used as an opportunity because in small universities there often are ways to shortcut physical and communication obstructions.

The big funders for research, like the National Institutes of Health (NIH), the European Union and many national funding bodies, have recognized that interdisciplinary is necessary but also that the initiation of such collaborations has its problems. In particular the spatial separation, that is, the opportunity for researchers to meet and get to know each other, and the often very different working languages and cultures, can be a hurdle. What funders have recognized is also true for universities: disciplinary boundaries must be overcome systematically. This includes the creation of opportunities during which professors, PhD students and postdocs from different areas can get to know each other. Such get-togethers however have to be actively organized and moderated – the usual form of seminars are not sufficient.

Once new project partners have met and a collaboration has been established, the spatial separation of laboratories can be overcome with, for example, videoconferences that are already common practice in international projects. The common research problem, which is equally exciting to all partners, should make it easy to overcome such practical problems. Another, much bigger problem lurks in the publication of results. Two difficulties come together here: the authorship and the often very different cultures in judging the contributions in the list of authors. If, for example, two professors – one from an experimental group and one theoretical group – collaborate, one can end up with two more postdocs and two more PhD students in the list of authors. How does one rank the names? With the usual project duration of three to four years, it will not be easy to generate enough manuscripts to keep everyone happy, to ensure everyone gets the credit (s)he deserves through an appropriate position in the list of authors. Ideally, the collaboration leads to publications in journals from both fields. Theoretically one could then increase the overall “output”. In practice this usually looks different.

In biology and medicine the impact factor of journals plays an important role for in career development. While for most researchers in the medical sciences an impact factor of over 10 is aimed at, for theoretical and mathematical journals the impact factors are far lower, for various reasons to do with the different cultures in these fields. The judgement of interdisciplinary grant applications is often done in relation to the applicant’s publications and impact factors of the journals under consideration. At present there is a lack of understanding and appreciation for the different citation cultures and one would expect that various project ideas suffer from poor judgement of the reviewers. Because it should be quality over quantity, it has become common practice to consider the number of citations a paper has received. The Hirsch-(h)-index is very popular and easy to determine for any scientist on the Internet. With all these efforts to evaluate, to quantify, we scientists have accepted the situation in which our efforts and work is reduced to a single number! It is impossible to imagine this for any other part of society, but in science many decisions are taken without a closer look at and discussion of someone’s CV. Instead, formulas and counting and indices are used. Encouraging interdisciplinary research requires a strategy and academic structures that avoid pitfalls such as those described here.

8. Summary and conclusions

In summary, a big enemy of interdisciplinarity, and thereby the biggest hindrance to the solution of important scientific questions, is (i) factors in interpersonal relations, (ii) the judgement of authorships in joint publications and (iii) the quantitative evaluation of scientific performance with formulas and indices. Other problems, like physical separation of groups or finding a common language, can, once the collaboration is initiated, be overcome.

There is however no doubt that interdisciplinarity is necessary – not only for science and the solution of important problems, but also for universities to build critical mass. For the young scientist who has specialized during his training, an interdisciplinary orientation offers opportunities to enrich personal experience and to build a career on a broader basis with possibly more opportunities and choices.

With interdisciplinarity comes, above all, the requirement for a greater effort and an increased risk for failure. True interdisciplinarity requires a longer time frame to realize preliminary results; it is hard, or often impossible, to complete a doctoral thesis within three years and the more "leaders" are involved, the greater the potential for conflicts.

There are thus, on the surface, few reasons speaking *for* interdisciplinarity, but those are after all most important. As universities realize the importance of interdisciplinary collaborations to generate the required critical mass for grant applications, interdisciplinarity also provides opportunities for young scientists. Above all, the problems we are trying to solve depend on graduates, postdocs and academics deciding – after years of intense specialization – to take a look beyond their own field.

Compared to the established disciplines, interdisciplinarity is an extreme sport, which requires most of all persistence, risk taking and a long-term effort. Extreme sports, like the practice of systems biology, involves going from one failure to the next without loosing enthusiasm, thereby however pushing the boundaries of what can be achieved. Extreme sports are not for everyone but those who are made for it derive a great deal of satisfaction from it, achieving things that would otherwisenot be possible.

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