

# **Uncertainty, Complexity and Interdisciplinarity: The Challenges of Fighting Infectious Diseases**

by Rudi Balling

Infectious diseases have had a major influence on the course of history. More than once, the casualties in wars from infectious diseases outnumbered those from man-made weapons. Up to the end of the 19th century, not much could be done. The development of public health hygiene principles, the discovery of penicillin and the development of vaccines however have dramatically changed this (Nelson and Williams 2007). They were so efficient, that in 1967 the Surgeon General of the United States declared the end of the era of infectious diseases. This was of course too early, as we know by now. Today we are not only faced with newly emerging pathogens, i.e. HIV, SARS or avian influenza, but also with reemerging pathogens, that we thought we had eliminated, such as tuberculosis or malaria (Morens et al. 2004). The most serious of all the problems is the increase in antibiotic resistance (2010). Multi-resistant bacteria are now identified in many hospitals and even the community, sometimes in two-digit percentages. Our antibiotics start to fail and for many of the viruses, i.e. HIV or HCV, we do not have any vaccine or efficient antiviral.

The consequences are very severe. More than 25 million people have died from AIDS during the last 30 years. Respiratory diseases and diarrheal infections have caused more than 5 million deaths, most of them children (Mathers et al. 2009). The SARS epidemic, which spread within a few weeks and caused the shutdown of entire cities, such as Toronto, has demonstrated the vulnerability of our society in times of high mobility. Today Boston, tomorrow Hong Kong or New Delhi, and back to Frankfurt is not an uncommon travel agenda for many people. Viruses often travel along with these passengers. Whereas we enjoy our increased mobility, the global nature of travel and business is one of the major drivers of global infectious disease epidemics and pandemics. Our world is small and for infectious diseases this means that it is easier for them to spread across large distances. In addition to the increased mobility, climate change has the potential to alter the distribution of infectious diseases on our planet. As a result malaria i.e. may spread into geographic areas where it was so far too cold for the parasite to survive (Chaves & Koenraadt 2010)

At the same time that globalization increases the chances of infectious disease transmission, the revolution in information and communication technology opens up new possibilities to fight infectious diseases. It is much easier today than in previous times to set up efficient surveillance programs, supporting early countermeasures. I will briefly discuss the main challenges that we are faced with in our attempt to understand, prevent and treat infectious diseases.

## **Uncertainty**

When we try to predict how many cancer, cardiovascular or neurodegenerative disease patients we will see in our hospitals in 20-30 years from now, the demographics of our population does give us a fairly good estimate. Many Western countries still enjoy an increasing life expectancy. This will be followed by an increase in chronic age related diseases. We already know that in two or three decades the number of Alzheimer and Parkinson's disease patients will be more than double what it is now. We can also predict, that as a result of our changing life style, obesity and diabetes are on the rise. This is not only a problem of western countries, but also of many developing countries (Prentice 2005)

Unfortunately it is much more difficult, if not impossible, to predict when and which infectious disease epidemic will hit the world. HIV was first found in 1981, but then the infection took off rapidly. SARS almost came overnight, without any warning signal (The SARS Commission Interim Report 2004). Scientists had been warning of new influenza viruses for quite some time. Nevertheless, when the swine flu appeared in Mexico and California, the world was not prepared. It is this unpredictability and the stochastic nature of infectious disease emergence, which is the largest challenge that we face. This is somewhat comparable to tsunamis or earthquakes. There is an urgent need to come up with "early warning signals" that can better predict when and which pathogens might emerge (Scheffer et al. 2009).

One of the most promising measures to cope with this uncertainty is the fostering of international relationships between scientists and other professionals. In many cases, when political dialogs have seized or failed, scientists are still able to maintain constructive relations. Some of the unpredictability can be reduced by functioning international personal networks. These can lead to an increase in the quality of infectious disease surveillance, the speed of information flow from one continent to the other or the exchange of key information about the nature of a specific pathogen. Awareness helps to increase preparedness.

## **Complexity**

Almost all diseases are multifactorial and multigenic in nature. It is well known that individual people can differ dramatically in their susceptibility or resistance to infectious disease from each other. Our "genetic background" can have a strong effect on how effectively we are infected, how quickly and efficiently we mount an immune response or whether we become immune after a first infection (Hill 2006). There are more than 20,000 genes in our genome, coding for more than 100,000 proteins. The result is a combinatorial explosion when we try to model and simulate the response of infectious diseases to new drugs or vaccines.

Infectious diseases are the result of extremely complex interactions between two evolving genomes, that of the host and that of the pathogen. These interactions are strongly influenced by environmental factors, such as nutrition or stress situations. For this reason it is not sufficient to only know the components of a complex system such as an emerging infection (Boshof & Barry 2007). The design and development of new vaccines or antivirals requires

an understanding of the entire system, especially the topology and dynamics of the underlying molecular and cellular networks. It is currently impossible to predict the behavior of a pathogen to evolutionary pressure, such as chemotherapy.

As a result of the human genome project and the technological advances in DANN sequencing, transcriptome, proteome and metabolome analysis, we have made great progress in identifying most of the components in the human body and importantly of the pathogens that infect us. However we are far away from an understanding the mechanisms of infectious disease pathogenesis. Without this understanding we cannot expect to be able to design efficient drugs that not only kill or slow down the pathogen, but that also avoid the development of antibiotic resistance.

### **Systems Biology: One way to deal with the complexity**

Biomedical research during the last 50 years has been very successful by focusing on increasingly smaller parts of the systems and by an attempt to reduce complexity by an analytical approach. We now realize that this approach is limited if we want to understand and predict the behavior of entire multiscale emerging systems, such as those that we find in living organisms. Complex systems such as infectious diseases often show a highly nonlinear behavior. It is for this reason that we now see a strong interest in systems biology (Sturdevand et al. 2010).

Systems biology is not only looking at the components, but is trying to address the characteristics of the entire system. Systems approaches have been very successful in engineering, social sciences and many other disciplines. This approach is now also moving into the life sciences, mainly because of the revolution in genomics. A key factor was the development of technology to sequence DNA. Within a decade, the cost of sequencing an entire human genome has come down from tens of millions of dollars into the range of a few thousand dollars. This trend will continue and has also moved into the high-throughput generation of RNA expression data. Single molecule sequencing and Mass-Spec based proteomics and metabolomics will further accelerate the transformations in biology and biomedicine.

It will not be long before genomic sequencing will become a commodity and, as a result, constitute an integral part of biomedical research, medical routine diagnostics and therapeutics. (Shendure & Ji 2008). These developments will have a great potential to improve our understanding of the mechanisms of infectious diseases. This will guide future vaccine and antiviral drug design and enable the development of effective public health policies and measures (Ye 2010). The challenge however will be whether and how we are able to transfer these technologies to the developing world. Rapid DNA sequences of pathogens at the “point of care” has a tremendous potential, but as described requires a rather high tech environment, which is often not available in less developed countries.

### **Interdisciplinarity**

High-throughput functional genomics and genetics need to be combined with information technology, mathematics, computational biology and engineering approaches. It is a combination of experimental and theoretical approaches that will be necessary to describe, analyse and predict the behaviour of complex biological systems. Most of the currently trained biologists do not have an adequate training in mathematics, statistics or physics, which is required for a successful modelling and simulation of infectious diseases. It will be necessary to change the curriculum of the next generation of students (Wingreen & Botstein 2006). Biological systems and human diseases can only be understood by a highly interdisciplinary approach. This will not be restricted to the classical natural sciences such as biology, chemistry or physics, but also needs to encompass an understanding of our climate and the changes we observe through the social sciences, psychology and economy.

Research in life sciences has undergone another change within the last decade. Collaboration and resource sharing have become an important element not only in the design and implementation of the experiments per se, but also in the establishment of large scale, capital and human resource rich infrastructure. Top-notch infrastructure is a key attractor for becoming and staying competitive on an international level. As a result of the progress in sequencing the human genome, the analysis of biological systems has largely been driven by efforts to automate and miniaturize individual assays. This has led to "Big Biology" -- laboratories which are characterized by major capital investments, i.e. in robotics, automatic imaging capture devices and IT infrastructure. The costs for equipment and human resources to operate and manage high throughput-infrastructure are substantial and the replacement cycles become shorter and shorter. As mentioned before we need to come up with solutions how to enable developing countries to participate in the potential and opportunities in the biotechnological and biomedical area.

As a result of the increasing efficiency in genomics, proteomics and metabolomics, we are currently witnessing an explosion in the amount of data derived from biological experiments and clinical research. This requires the development of new bioinformatics tools (Homer et al. 2010). The challenge of data rich biology and medicine is not only in pattern recognition, but becomes increasingly a problem in data security, data handling and data archiving. Currently the increase in the amount of data production greatly exceeds our capacity to store data. Individual institutions are not able to maintain the fast and expensive cycles in equipment and infrastructure necessary for genomic, proteomic or bioinformatics analysis of biological data. For this reason it is necessary to share technology platforms, i.e. in bioinformatics, high throughput fast sequencing, proteomics or metabolomics, which serve not only a few research centres, but also increasingly a larger number of research institutes, i.e. within a region, a country or even beyond. This asks for new modes of international cooperation.

## **Outlook**

Infectious diseases will never be completely eliminated. It will always be an arms race, driven by evolutionary forces, between the infected host and the infecting pathogen. Uncertainty and complexity are the hallmarks of infectious diseases. Our best counterattack is probably the

ability to work across disciplinary boundaries in order to understand in detail the underlying mechanisms. Maybe we will discover and understand general rules of complexity and new ways to dissect complexity. This will not only be relevant for biology and infectious diseases, but will touch upon many other areas.

## References:

- Boshoff, H.I. & Barry III, C.E. (2007)  
Systems Biological Approaches in Infectious Diseases  
Progress in Drug Research, Vol. 64  
Birkhäuser Verlag, Basel, Boston, Berlin
- Boucher, H., Miller, L.G. & Razonable, R.R. (2010)  
Serious infections caused by methicillin-resistant staphylococcus aureus  
Clin. Infect. Dis. 51, S183-S197
- Chaves. L.F. & Koenraadt, C.J. (2010)  
Climate change and highland malaria: fresh air for a hot debate  
Qart. Rev. Biol. 85, 27-55
- Campbell, J. A. (2004)  
The SARS Commission Interim Report  
<http://www.fas.org/irp/threat/cbw/sars-ontario.pdf>
- Hill, A.V.S. (2006)  
Aspects of genetic susceptibility to human infectious diseases  
Ann. Rev. Genetics 40, 469-486
- Homer, D.S., Pavesi, G., Castrignano, T., De Meo, P.D., Liuni, S., Sammeth, M., Picardi, E. & Pesole, G. (2010)  
Bioinformatics approaches for genomics and post genomics applications of next-generation sequencing  
Brief. Bioinform. 11, 181-197
- Mathers, C.D., Boerma, T. & Ma Fat, D. (2009)  
Global and regional causes of death  
Br. Med. Bull. 92, 7-32
- Morens, D.M., Folkers, G.K. & Fauci, A.S. (2004)  
The challenge of emerging and reemerging infectious diseases  
Nature 430, 242-249
- Nelson K.E. & Williams C.F. (2007)  
Infectious Disease Epidemiology, Theory and Practice  
Jones and Bartlett Publishers  
ISBN-13:978-0-7637-2879-3
- Prentice, A. (2005)  
The emerging epidemic of obesity in developing countries.  
Int. J. Epidem. 35, 93-99
- Scheffer et al. (2009)  
Early-warning signals for critical transitions

Nature 461, 53-59

Shendure, J. & Ji, H. (2008)  
Next-generation DNA sequencing  
Nature Biotechnology 26, 1135-1145

Sturdevand, D.E., Virtaneva, K., Martens, C., et al. (2010)  
Host-microbe interaction systems biology: lifecycle transcriptomics and comparative genomics  
Future Microbiol. 5, 205-219

Wingreen, N. & Botstein, D. (2006)  
Back to the future: education for systems-level biologists  
Nat. Rev. Mol. Cell Biol. 7, 829-832

Yan, Q. (2010)  
Immunoinformatics and systems biology methods for personalized medicine  
Methods. Mol. Biol. 662, 203-220

- ◆ Rudi Balling is director of the Luxembourg Centre for Systems Biomedicine.
- ◆ This is an unedited version of a lecture given at the OCF conference session on Global Health and Molecular Medicine in Hannover.