Biomathematics in the development of personalized medicine in oncology

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Zvia Agur is an internationally known biomathematician whose research focuses on the dynamics of cancer and infectious diseases, and on mathematical methods for identifying improved drug regimens and improved vaccination programs. She is President of the Institute for Medical BioMathematics, Israel, and the Founder, Chairperson and Chief Scientific Officer of Optimata Ltd, Israel. Professor Agur is a former president of the Israeli Society of Theoretical and Mathematical Biology (1995–2001) and a former member of the Board of Directors of the European Society of Mathematical and Theoretical Biology (1996–2002). Her innovative research has won national awards, has been published in a long list of leading scientific journals and is recognized by the academic community worldwide. She serves on the editorial board of several scientific publications, and holds a PhD from the Hebrew University, Jerusalem, and the Université Libre, Brussels.

How did you first get involved in biomathematics & what are the major advances that you have witnessed in your time in the field?

Being interested in both biology and mathematics, I studied biology, as at the time in the 1970s, the two fields of study were exclusive (one could choose either/or). I went on to specialize in genetics and population genetics and while working on my MSc research I understood that, in the science world, there are two kinds of researchers. The first group is those that like to discover new 'continents' – the experimentalists; and the second are those who prefer to holistically understand the complexity of the 'continents' – the theorists. I think these two approaches basically reflect the two different ways that peoples' minds work. When I was doing experimental research, I understood that I belonged to the second group. We theorists try to understand rather than discover. Another example I can give to illustrate this idea is through a puzzle. The people who make up the pieces of a puzzle could be called experimentalists and those that put the pieces together, like in the work I do, are theoreticians. So, I am a theoretician, not an explorer of new frontiers. Already in the early 1970s I was investigating how I could work in theoretical biology, but there were not that many options. One area that was active was mathematical ecology or population dynamics, but it was not yet institutionalized as an acknowledged field. I ended up doing my modeling research in a group of nonlinear dynamics that was part of the Physical Chemistry department. This was carried out in Brussels, as part of a group of those working with Nobel Prize Laureate, Ilya Prigogine.

Physics is the science of the 20th century. Physics is a mature science, since in this field experiments are made for proving a theory. Biology, medicine, physiology, physiological psychology – the realm of the life sciences – have not followed physics in development; they are still based on descriptive experiments with no guidance of an underlying theory.

It was April 1953 before the right mix of technology and personalities resulted in the discovery of the structure and function of DNA. Evolution had finally reached the molecular level. No new laws were found, no new physics. Molecular biology became the great mechanical synthesis of the 20th century. This undoubted triumph has meant that, whereas physicists, from the 1920s onwards, found themselves questioning reductionism, many biologists became and have remained convinced adherents to it. Against the grain, however, some have sought a different, more panoramic view over the landscape of the life sciences. As far back as the 13th century, Leonardo Fibonacci attempted to describe the growth of rabbit populations in terms of mathematical formulae. In our century, the science of ecology has developed rapidly. It is fundamentally opposed to reductionism, seeking instead to explain or 'model' a process in action. There is no appeal to the laws of chemistry or physics, for this would require one to freeze and dismantle the interacting components of the process under study. Instead, ecology looks to mathematical

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formulae to describe the dynamics of the process. This approach is anathema to the experimental biologist, but it is set to revolutionize the practice of biology. A new synthesis of ecology and 'hard' biology, called biomathematics, emerged in the second half of the 20th century within the scientific community. Its role was to study the complexity of biological processes. My own work, which began in the early 1980s, is predicated on the assumption common in physics that the same laws must govern the dynamics of biological systems at all levels of organization. Mathematical formulae describing the growth of rabbit populations, for instance, must also hold true for the behavior of cancer cell populations. Traditionally, experimental biologists working at the microscopic cellular level have developed analytic tools analogous to the stills camera in photography. They are able to view the microworld only as a series of snap shots. Biomathematics formulae effectively animate these shots, allowing us to see the dynamics of the world we are investigating. Such a 'movie' not only contains much more information than a series of stills but it allows the scientist to interact with the system with much greater precision and efficiency. Biomathematics has allowed me to develop and test a wide range of new theories dealing with significant problems of cancer treatment optimization, hitherto beyond the reach of 'snap shot', experimental biology. In my work in the 1980s, I used notions from population dynamics to develop relatively simple formulae to describe the growth patterns of interwoven populations of healthy and cancerous cells; formulae that have resulted in new drug regimens where the toxicity of chemotherapy, formerly such a danger, has been significantly reduced. The power of mathematics here was to prove the universality of the theoretical results. In fact, they justified and encouraged collaboration with cancer research experimentalists, who, not only proved the theory in the lab, but also pinpointed the feasibility and strength of the theory-to-lab arrow. Our research in Optimata Ltd is the first of its kind in using mathematical models for making precise quantitative predictions and for validating these predictions in the clinical setting.

For the greater part of the last three decades, biomathematics has been the stepchild of science. For all those years, biomathematics itself dwelt mainly in ecology and infectious diseases, but very little in cancer and its control. However, the disillusioned postgenomic era has rediscovered biological complexity, renaming it 'system biology'. It seems that, finally, we biomathematicians are becoming legitimate and almost beloved children of the scientific community.

Optimata Ltd is a company involved in developing *in silico* technologies for the development of optimal drug schedules. Could you tell us some more about the aims & goals of Optimata Ltd & what you hope to achieve over the next 6 months & on a more long-term basis?

Over the years of my research, I have been increasingly convinced of the power biomathematics can have in assisting physicians in the decision-making process. This leads to an improved way to treat patients. It was clear to me that, in order to make biomathematics a reality, I would require much more than support from the academic world. By forming a commercial company that carries out large-scale clinical trials, I hope to convince the medical world to join forces with us. Our long-term goal is to transform medicine and drug development from its current state of trial and error practices to scientific-based predictions.

In the next 6 months, we hope to have achieved positive results from the Phase I clinical trials on-going in research hospitals in Europe, where we are testing our technology's ability to accurately predict disease progression for breast and brain cancer. For the long-term, we hope that eventually every clinician and hospital will use our technology for testing treatment options for individual patients. In the interim, we are planning that drug developers will adopt our technology for streamlining drug development.

Can you tell us about the technology that Optimata Ltd has developed over time & how these developments have impacted the pharmaceutical industry & optimization of treatment schedules?

Our technology comprises three main modules. The central module is the virtual patient, who is created to host a disease that is treated with drugs. The virtual patient expresses physiological responses to the treatment at hand. The result is a realistic simulation of foreseen biological and pharmacological events that can be evaluated by a physician or drug developer under any set of parameters for any population of patients.

The second major module is technology we have built that will enable the identification of characteristic parameters for individual patients and thus will help to personalize the virtual patient.

For the third, and perhaps the most exciting module, we have built a tool that will help doctors and drug developers identify the optimal treatment based on requirements set by a drug developer or clinician.

We believe that the awareness of this kind of technology is increasing in the Pharma industry. We have been successful in deciphering previously unknown toxicities of a blockbuster drug whose US FDA approval was revoked when the developer was unable to account for drug toxicity. We have also shown that another drug, thrombopoietin, whose development was halted owing to high immunogenicity, could be nonimmunogenic under a different dosage schedule

Many major Pharma companies are approaching us for assistance in optimizing drug candidates in transition from animal studies to Phase I human studies and through Phase IV.

What are the advantages of using mathematical modeling of disease progression in the development of new technologies?

By modeling disease progression, one can simulate the effect of a drug on the development of the disease and test the efficacy of the drug under an infinite number of schedules and for various patients or patient populations. This allows clinicians to analyze the probability of a drug regimen being able to extinguish a disease or, at the very least, keep the disease under control. Our technologies provide the power for various biomarkers to be checked and to forsee if these biomarkers can represent various endpoints of the disease in question. We can evaluate in advance the potential performance of a drug in development compared with an existing drug on the market and improve the prediction of human efficacy and toxicity of a drug, based on animal trials.

In addition to drugs, mathematical modeling can also impact on other technologies, such as medical devices, where there are various exciting options. Some existing devices, for example, those enabling precise diagnosis, can be connected to our disease progression mathematical models, enabling the prediction of optimal treatment of individual patients. Currently, there are several options in proteomics technology that analyze cellular pathological events. Putting together the sophistication of proteomics with disease models empowers clinicians to simulate special patient parameters under specific treatment regimens. This combination will certainly improve our ability to predict disease progression.

In the area of genomics, the technology exists to produce disease/patient genetic profiles. Specific profiles have been discovered, but current medical practices do not offer an integrated way of decision-making based on the patient's specific gene profiles. We allow science to jump from the gene profile into parameters that affect a whole cascade of events, which lead to the actual patient undergoing a treatment. One can input a specific oncological profile into the elaborate mathematical models, simulate the adapted model and match available treatments to that profile.

There is a lot of optimism & interest in healthcare in the postgenomic era as we progress towards a more personalized approach in medicine. To what extent are individualized therapies emerging in cancer healthcare?

Individualized therapies are emerging in cancer healthcare. My opinion is that we should probably distinguish between the genome of the disease and the genome of the patient. What's unique about cancer progression is that the genome of the disease is not stable – there is an ongoing somatic evolution – and so the disease genome is changing constantly. Therefore, I believe, that apart from a few crucial mutations, the study of the disease genome itself may have a lesser impact in cancer than in other diseases. However, this area is evolving tremendously and we believe that, if plugged in a model that simulates downstream processes, genomic information may increase our capacity to tailor treatments to the patient. AstraZeneca, for example, has a drug, Iressa®, which was found to be of little effect in the world's general population but highly effective in small fractions of certain patient populations. Japan was one of these places. By making the above liaison between genomic information and the Virtual Patient Engine, one can tailor efficacious treatment not only to the best responders but also to others. Through doing this, there is the possibility of checking the genomes of each individual and selecting the most efficient drug for any particular person. But we, and others, are still in the research stage in this area. At this time, we believe that using virtual patients is still the best way to go about this process.

How does the innovative 'Virtual Patient Engine' model work & how can it be applied to the optimization of cancer therapies?

We get the initial information about the patient from tests carried out routinely when he or she is first admitted to the clinic. Before treatment, various patient clinical tests are conducted. We feed this information into the computer, which turns data, such as sex, age, tumor size or biomarkers, into parameters that will feed the virtual patient (or clone of that patient) in a computer. We take real flesh and blood information to build the virtual patient. Once we have done this, the Virtual Patient Engine examines various treatment options and makes recommendations to the physician. Of course, this all starts with the physician plugging in preferred treatment end points and outcomes desired from the treatment. We offer a convenient way for doctors to use computers in their decision making.

Optimata Ltd has recently formed a collaboration with the University of Nottingham, UK, to carry out a clinical trial aimed at improving the treatment of breast cancer by providing patients with individualized therapies; can you update us on the progress of the trial & what the anticipated outcome will be?

The Nottingham City Hospital is testing the adequacy of our technology for improving the treatment of breast cancer. We recently received an award from Cancer Research UK and The National Cancer Research Institute UK on the design of our upcoming Phase II trials. We decided to conduct the clinical trials and model them in the same way as is normally carried out in the Pharma industry. Phase I checks for toxicity and Phase II checks the efficacy of the drug. In our case, we are obviously not testing a specific drug, but in Phase I are checking the accuracy of prediction of the Virtual Patient Engine on breast cancer patients. Results from Phase I are expected in approximately 2 months.

What do you envisage as the major obstacles in the field of oncological personalized medicine in the near future?

Measurements of pathology are not as precise as they should be and, owing to their cost, are not carried out as frequently as they could be. In addition, a big obstacle is the lack of knowledge about the adequacy of various biomarkers to precisely describe the disease status of patients. Moreover, pharmacogenomics enables a better tailoring of treatments to the patient, which means a smaller patient population for each drug in development. However, drug development itself has not improved in efficacy. Development is lengthy and costly. Paradoxically, it becomes less cost-effective to develop drugs that are better suited for specific patients. So a major obstacle is that even if a personalized treatment can be found for the patient, at the present stage, the process is too costly to justify clinical trials of such drugs. We hope to change that.

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