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Perspective on "*New and Less New Opportunities For Mathematical Biology as Applied To Biological and Clinical Medicine*"

by JEAN CLAIRAMBAULT

*A*nother conception that makes applications of mathematics quite different from applications of mathematics to sole biology resides in the interventionist nature of medicine ...

This perspective, bouncing from Philip Maini's "*Perspective on The Changing Face of Mathematical Biology*" [1], focuses on the specific case of mathematics as applied to medicine. Philip Maini acknowledges the pioneering work of James D. Murray in Oxford: for sure, this immense founding enterprise with no equivalent worldwide has led, through his stimulating teaching and research, to the training of scores of students, from pure to very applied mathematicians, many of whom have themselves become leading scientists in different fields of mathematical biology.

In other parts of the world, such pioneers were scarce, but little by little, by the virtue of example, scientists coming either from the engineering world or from pure and applied mathematics learnt to know that non-trivial mathematics had been written by some of them, starting from open biology questions, often by transposing methods from physics or chemistry. For instance, reaction-diffusion equations have been studied as providing a theoretical basis for traveling waves of physical phenomena by Kolmogorov, Petrovsky and Piskunov and independently by Fisher (for the spread of a gene in a population), all in 1937, and later a basis for morphogenesis by Turing in 1952. However, James Murray reports (Mathematical Biology 3rd ed., vol. 1, 13.2) that the first discovery of the so-called KPP-Fisher equation is due to the German chemist Luther in 1906, but also that his publication soon sank into oblivion, to be rediscovered later, much later than 1937. The scientific audience likely was not ripe then to catch the scope of this discovery and its potential applications to biology, even though Fick (1855) in the same country had already presented his law of diffusion 50 years earlier. The now classical examples of Hodgkin-Huxley (1952) and later FitzHugh-Nagumo models of action potential propagation (1961, 1962) or Turing instability (1952) came later, on apparently more favorable ground.

What had changed? Maybe the fact that biological phenomena that were until then considered as just being there - the propagation of nerve impulse or the spots on a leopard - were investigated by advanced scientists - physicists or mathematicians - as having in fact a physical basis and hence a mathematical expression. Maybe in about the same way as in the Greek antiquity, presocratic philosophers and the mathematicians among them tried to organize a corpus of pre-existing observations (in particular from Babylon and Egypt) according to rules, some of which could be shown to be more than rules.

The situation in which we are now is indeed somewhat different. In a world where scientists of different disciplines regularly meet in conferences and workshops, and publish jointly in journals in which attention is given to both mathematical modeling and experimental results, it is less likely that breakthrough discoveries may be lost. Furthermore, centers for mathematical biology, and as regards oncology, centers for integrated research on cancer (essentially in the US for the latter) now exist and offer institutional opportunities to exchange knowledge between disciplines, including mathematics and clinical medicine. In the UK, the Mathematics in Medicine Study Group (MMSG) organizes meetings in different locations to model and tackle during 2-3 days problems coming from requests by biologists or physicians. Even in places where such institutions are not yet present, grants coming from international and national calls more and more allow constituting coherent teams of applied mathematicians working in close contact with teams of biologists and - less frequently - physicians.

As Philip Maini stresses, data coming from biological experiments are most often static, i.e., snapshot-like, when we need movie-like data to identify the dynamics of the biological systems under study. Furthermore, a frequent and simplifying underlying assumption is that tissues are homoge-

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[1] http://www.smb.org/publications/newsletter/vol27no1.pdf

neous, genetically and phenotypically, when for instance multilocular samples in the same tumor show that this is frequently not the case, at least in cancer. In biological and medical research teams, people are keen on identifying intracellular signaling pathways - or cell membrane targets upstream of them - searching for so-called *"druggable targets"* to block or enhance them. But the dynamic viewpoint that mathematicians are fond of *"where does this lead to? i.e., what is the asymptotic behavior of the system, controlled or not?"*, is seldom present. However, such a dynamic perspective has always been present in the mind of biologists dealing with evolution, and recently - remembering that, as stated by Theodosius Dobzhansky in 1973, *"Nothing in biology makes sense except in the light of evolution"* - it has also become clear at least for some *cancer* biologists. Some indeed consider cancer as an evolutionary disease, in the sense that cell populations evolve, partly with prescribed rules, partly due to random events and partly under the influence of tissue environmental factors, towards diseased states as populations of multicellular organisms do. In my opinion, this view is about to deeply change our conception of diseases, and in particular of cancer.

Another conception that makes applications of mathematics quite different from applications of mathematics to sole biology resides in the interventionist nature of medicine, that is absolutely irreducible to an applicative branch of biology. Whereas the physicist describes the evolution with time of natural phenomena, and in particular of diseases, the physician is expected to correct them or prevent them, otherwise said to control them. This leads to the idea, not only to apply optimization and optimal control principles to therapeutics, but also to design models of health and disease in tissues and organisms as dynamical systems under physiological control mechanisms that can be corrected when they fail. In this respect, firstly it is necessary to reintroduce physiology at the era of genetics at all levels where physiological regulations occur: intracellular gene regulatory networks, equilibria between competing populations of cells, whole body hormonal regulations, and also between these levels; and secondly, setting such physiological controls and the correction of their disruptions as optimization problems (physiologically solved or to be solved by therapeutic intervention) should foster much more work between physicians and mathematicians specialists of optimal control. This is another opportunity that

I see for the future, and it will make all the more sense as the biological control mechanisms will be more known. Even if they are not known in detail to perform quantitative predictions, qualitative results about optimized therapeutic strategies to combine drugs should prove helpful to clinicians.

Of course, the continuous progress of imagery techniques, at all possible biological levels of observation, from intracellular signaling pathways to whole-body recordings, in a more and more dynamic way, i.e. with space and time resolutions that are driving us from a scenery of poorly defined snapshots to another one of high precision movies, will never exclude the fact that important variables of the dynamic systems under study will remain hidden. This naturally calls for other new mathematical developments, which resort to statistical theory and to inverse problem methods.

Such perspectives, some of them rather recent, together with a growing open-mindedness of biologists and physicians towards mathematics open new tracks to follow for the growing number of mathematicians interested in doing *"mathematics for medicine"*. There are hard problems - and less hard ones - to solve, that will be a source of inspiration for mathematicians and a help to physicians - be it only to provide new ways to ask questions - provided that the initial question is of biological and medical nature, transposable in mathematical settings, and that a collaborative work is performed interactively between members of the two disciplines towards advances in solving them.

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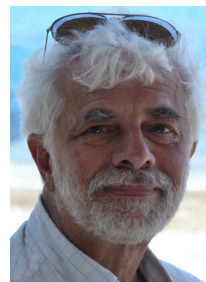
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