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Commitment of mathematicians in medicine

A personal experience, and generalisations

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Abstract I will present here a personal point of view on the commitment of mathematicians in medicine. Starting from my personal experience, I will suggest generalisations including favourable signs and caveats to show how mathematicians can be welcome and helpful in medicine, both in a theoretical and in a practical way.

Keywords Mathematics · Medicine · Modelling · Theory · Therapeutics

1 Introduction: personal background

The point of view I will present here in an informal way, rather in conversational-like tone, in my opinion more appropriate to write about commitment, than in the way of a classical scientific paper, is necessarily biased by my personal experience. I do not share it with so many, since at the end of my mathematical studies (an "agrégation" - success to a qualification as a teacher in France - and a PhD), I decided to switch to medical studies. At that time, at least, there was no other choice than starting from scratch, as anyone does after the French baccalauréat to study medicine. I managed to get to the end, until the MD, by earning my life, thanks to the agrégation, as a part-time mathematics teacher, and then obtained to be detached (from the national education service) in a national research institute, INRIA, to which I still belong. During these years of school of medicine, I had little time to do anything else, i.e., any research, apart from teaching and living a family life, except studying medicine, with classical training in the clinic, together with teaching mathematics in secondary schools, and later first years of the university.

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It was not easy at first, at the end of my medical studies, to convince people with a position in research in mathematics applied to biology and medicine that I could be helpful in research, with my training in two fields, mathematics and medicine. A motto I heard much later can explain such reluctance. It says: "Double proficiency equals proficiency nought". Then, beginning to nevertheless take part in collaborative projects between applied mathematicians and clinicians, I discovered that I had to learn almost everything about technical data management, signal processing and statistical methods. I was not expected to develop mathematical theories, but to process data using some knowledge of physiology. Thus combining physiology with some newly acquired skill in biomedical data processing and statistical methods, I had both to set up and ask formalised questions (which otherwise were not present in the minds of clinicians) and then to try and answer them by methods with a mathematical basis.

I learnt much at that time, for my training in pure mathematics (a thesis in analytical geometry) and in medicine (theoretical knowledge of diseases and clinical practice) had little prepared me to give clinicians what they were expecting from me: dealing with their data. I had to learn basics of digital signal processing, of the Unix system, of multidimensional statistics, and to deepen my views in physiology. My subject was the study of heart rate variability as an indicator of development of the autonomic nervous system. Starting from analog polysomnographic recordings performed in newborn babies, I had to digitise the data, design or use existing methods to detect the QRS on the EKG, process the resulting RR signal by filtering and continuous spectral analysis, analyse the outcome with multidimensional statistical methods, and interpret the results from a physiological point of view. Of course, I am indebted to colleagues, specialists of one or the other domain, for helping me much in the technology of this processing. Nevertheless I had to process the data from the available analog recordings until physiological interpretations, mainly by myself.

It was only at that price, putting my hands dirty in data, far from only theoretical work, that I could be accepted and later had opportunities, taking part in discussions on biological and clinical problems, to put forth possible theoretical methods to investigate problems that could be more interesting from a mathematical point of view. What I had been doing with recordings in newborns was much more of a biomedical engineer than of a mathematician, but it had opened for me doors for more interesting collaborations, from a theoretical point of view, that would have remained closed otherwise.

Speaking the two languages of mathematicians and physicians, as some say, was certainly an advantage of my training in such collaborative work, since it allows to be potentially recognised as one of them by each community, but it is not the main one. The main advantage of such double training was that it made me personally committed on the long term with my medical collaborators, as long as they wanted to. Conversely, they could naturally be convinced that, given my investment in years of medical studies, I would not easily switch to applications in geophysics or traffic on the internet. For one pitfall of such

interdisciplinary collaboration is sometimes the difference of work time scales between mathematicians (or engineers) and clinicians: mathematicians often have the reputation among biologists to tackle a problem, solve it, and then pass to something new. So I was said by my main medical collaborator at that time, who reported to me having been warned: "You will see, your data will be processed, but after that you will not interest these people any more; they will quickly tackle another question with other people." In our case, our collaboration lasted for years, leading in particular to methodological training of various young foreign gifted physicians.

2 Generalisations from this personal experience

Biologists and physicians indeed are confronted to permanent unsolved questions about diseases, and rely with confidence only on long-lasting collaborations with mathematicians. Working together only in a one-shot way with clinicians, even when it yields a publication or two in a good journal, is wasting potentially rich collaborations. To avoid such drawbacks, it is essential that collaborations be established on a bilateral basis between two individuals who appreciate each other and each other's work. If the human factor is not favourable, then whatever the scientific interest of the collaboration, nothing will work for long. Now, this having been said many times, how can such bilateral good feeling be established between men?

In what I have seen so far, there are at least three different circumstances for such encounters. The first one is networking: meeting people that have been recommended, or that have long been known, since younger years, but have diverged to different fields of knowledge. The second one is the most classic: meeting people in conferences and seminars of interdisciplinary research. And a third one is a systematic institution of such encounters between clinicians and mathematicians in the way lately used by the British MMSG (Mathematics in Medicine Study Group): involving a clinician to come and present a question amenable to mathematical modelling and discuss it with mathematicians in a 2 or 3-day seminar.

Then, after any of these encounters, a long-lasting collaboration can be established on the basis of a mutual interest, mutual respect and mutual esteem between a mathematician and a clinician. Mathematicians are more and more prone to develop such collaborations, but on the other side clinicians ready to do the same are not so frequently met. This may be due to the fact that mathematics are still hardly taught in medical schools, despite the desire of many medical students, who often were fond of mathematics in their younger years, to learn more about mathematical biology and mathematical theories about diseases. When these students have finished their studies, they may naturally leave the school with the impression that mathematics have little to do with their field of knowledge and practice, and they will seldom have any time to challenge this impression.

When an opportunity to do so occurs, thanks to perchance meeting between a clinician and a mathematician available to try and work out some difficult, non formalised problem of biology and medicine, then it is better for the mathematician to keep a humble attitude, avoiding stating "Who has questions? I have answers!" and to plainly listen. Physicians, and more than them biologists, seldom appreciate a newcomer telling them that they need a better understanding of the problem they are working on. Even though biologists and physicians most often have a knowledge of mathematics that "does not go beyond basic knowledge on real functions of one real variable", as I heard once from a mathematician committed in long-lasting collaborations with biologists, even though biologists may expect from mathematicians merely "to help [them] design better experiment plans", as I once heard from a biologist as an answer to my naïve question: "How can we mathematicians be useful to you?" or because of this cultural distance, even thus, well, mathematical proselytism, let alone arrogance, should be avoided.

But provided that such respectful and confident relationship has been established, then it becomes possible for a mathematician, keeping in close contact with his or her medical collaborators by regular meetings, to interpret questions coming from biological or clinical observations in formalised terms and study a new mathematical problem. Which means studying it not (or not only) as a physicist, to try and define physical laws from repeated experiments, but as a mathematician, whose craft is to prove conjectures by theorems, adding to the theoretical corpus of mathematical biology and mathematical medicine in the same way as, starting in the XVIIth and XVIIIth centuries in Europe, mathematicians have created applied mathematics from observed and formalised physical laws.

3 Possible roles of mathematics in medicine

Mathematical modelling based on physiological evolution equations with a multiscale vision. The Universe, the great book that is constantly open in front of our eyes, speaking to us of 'philosophy', i.e., of natural physics, is written in mathematical language, according to Galileo (G. Galilei, *Il Saggiatore*, Rome, 1623). 'Philosophy' in this sense (which is also the sense in which Newton used the word later in his *Principia*) extends to medicine, and mathematics is the language to use, to describe and interpret, combining 'sensible experiences' with 'necessary demonstrations' (ibid.), the constantly evolving phenomena that underlie the physiology - and physiopathology - of human beings and their diseases at all relevant scales: molecules, cells, tissue, whole organisms, populations of individuals. Using differential equations is the most adapted way to do so, and identifying their coefficients from data secondarily involves the use of statistical methods. The more phenomena are understood by physical laws drawn from repeated observations, the closer we are to physiology and sound mathematical modelling, which is physiology in equations. But the more detailed models are, the harder they are to analyse. For this reason,

one must always ask the question: "A model to do what?" According to the question at stake, various variables may be lumped within a physiologically based model, and a focus may be set on a particular zone of the system, from its molecular representations until its repercussions at the higher levels, whole individual and population of individuals.

Should mathematical modelling in medicine be satisfied with phenomenological representations? No, it should not, insofar as phenomenology is understood as a method to describe phenomena, not to understand their mechanisms; nor should it be restrictively guided by the availability of (often too scarce) data. Of course, obtaining physical laws is a prerequisite for their understanding, in the same way as Kepler's laws in astronomy were a prerequisite for Newton to give their mathematical interpretation by differential equations based on the principle of centripetal acceleration. To prove and predict, a mathematician cannot be satisfied with observed physical laws (e.g., Kepler's three laws) without mechanistic explanations, which for phenomena evolving with time naturally rely on differential equations based on simple principles (e.g., centripetal acceleration) to represent them. In the same way, the scarcity of experimental data should not restrict theoreticians to propose theoretical explanations. For instance (again taking an example from astronomy, since astronomy has been founded for long on mathematics, which is still not so much the case of biology and medicine), the equations of general relativity theory, when they were introduced by Einstein, had little experimental support except an a posteriori explanation for the perihelion precession of Mercury, and it was later that more observations came to support the theory. But astronomers needed these equations to predict and explain discrepancies between observations and previous predictions from classical celestial mechanics, which otherwise would have been disregarded or put in the category of unexplained phenomena. Otherwise said: having a theoretical model in mind is a necessary help in deciphering natural phenomena. Or, as was already written in Aristotle's *Sky* (*Peri Ouranou*): "It is appropriate to the model (*logos*) to testify for the phenomena, and to the phenomena for the model." (*Eoike d'o te logos tois phainomenois marturein, kai ta phainomena toi logoi*, cited by L. Bourgey, *Observation et expérience chez Aristote*, 1955, coll. Bibliothèque d'Histoire de la Philosophie, Vrin, Paris, from which I freely translate *'logos'* by *'model'*.)

Demonstrations, predictions and experimental verifications. Indeed, a mathematician's work consists of proving theorems or propositions that give conditions (necessary or sufficient hypotheses) for a fact of observation to be true. A successful mathematical theory applied to medicine needs sound physiological foundations and a corpus of proofs and conjectures to make it amenable to account for unexplained phenomena and propose experiments to acquire more knowledge of the phenomena under investigation. One example I have in mind is the prediction of bistability in excitable cardiac cells: the theoretical analysis of a mathematical model of the FitzHugh-Nagumo type, that was under experimental validation in a cardiac electrophysiology laboratory, predicted

bistability of solutions, i.e., that with the same parameters (same experimental conditions), changing only one initial condition could lead either to an oscillatory or to a stationary constant solution (death). This was tested and experimentally verified by the electrophysiologists, who had never considered this possibility beforehand (J. Jalife & C. Antzelevitch, 'Phase resetting and annihilation of pacemaker activity in cardiac tissue' in *Science*, 1979, following A. Winfree's theory of 'black holes'; see also M. Guevara & H. Jongsma, 'Three ways of abolishing automaticity in sinoatrial node: ionic modelling and nonlinear dynamics' in *Am. J. Physiol.*,1992, for a systematic study of pacemaker annihilation in models of the sinoatrial node). Also, from a therapeutic control point of view, it is valuable to have in mind that mathematicians may have shown that treatment failure is certain if various theoretical requirements are not fulfilled. In this respect, to Anaxagoras's word "Phenomena are the visible of invisible things" (*Opsis ton adelon ta phenomena*, cited as fragment DK 59 B21a in H. Diels, and W. Kranz, eds., 1974, *Fragmente der Vorsokratiker*, Weidmann, Berlin), I would like to add "...and theorems are light shed on phenomena".

Teaching in medical schools to represent the dynamics of diseases and their treatments. This includes first of all physiology (and in medical schools where mathematicians are part of the staff, they are often members of the physiology department). I remember one of my assistant professors in medicine saying: "No matter how lost you may feel in clinical situations, you will always get along by using two things: anatomy and physiology." That is, by reasoning on known ground with sound general knowledge. Physical laws are meaningful in medicine, and the application of conservation laws for physical variables (mass, energy, number of cells) is in physiology as it is in physics a powerful tool to design mathematical models that help reasoning. Physiologists can include such mathematical models in their teaching to students, and these mathematical theories for the living may even be made more immediately accessible by whole-body simulators. There is a future for teaching mathematics in medical schools, with the aim to fully equip both terrain physicians and researchers with sound principles to help them face any kind of unexpected new situation, which is everyday bread for physicians.

The Grail: optimisation of therapeutics. Medicine is not only constituted of anatomy, physiology and pathology. It deals with healing, and if possible curing, people and as such it appeals to mathematicians working in the field of control and optimisation of control. Optimisation may be analytic in some cases (i.e., with exact solutions), but given the complexity of the systems under study, a human being, or a human population, one has often to be satisfied with numerical solutions, as is the case for optimisation problems in industrial settings. Nevertheless, even if an analytical solution cannot be shown, one may show that it exists, provided that the problem is well posed, and then apply algorithmic methods that also must be shown to converge. As regards the actual therapeutic optimisation problems, they always include constraints to be

fulfilled, which are mainly of two kinds: limiting unwanted toxicity to healthy cells (a short-term constraint), and limiting drug resistance in actual target populations (viruses, bacteria, parasites, cancer cells) to be destroyed or at least constrained (a longer-term constraint). So far, therapeutic optimisation methods seldom address both constraints at the same time. A better understanding and refined physiological modelling of the cell systems under attack, and of the means of action (drugs and their fates in the organism), at the different space and time scales of interest still seems necessary to successfully use such optimisation methods, that are presently the object of active research.

Going further, toward Darwinian medicine by using principles of adaptive dynamics. The question of drug resistance mentioned above is typically to be treated at the level of a cell population for, even if some of the mechanisms that underlie it may be located at the individual cell level, it is most likely that other mechanisms are linked with the development of resistant clones, i.e., of subpopulations that are adapted to thrive in an environment (oxygen, pH, drugs) more hostile to healthy cells of the hosting organism than to them. The representation of such subpopulations and their evolution, natural or under drug pressure, is thus amenable to methods of *adaptive dynamics*, a discipline presently more developed in the field of ecology, but which now gives rise in biology to *cell Darwinism*, which considers the evolution of populations sructured according to genetic or phenotypic traits (in the same way as proliferating cell populations are naturally structured according to age). With the idea to change a local metabolic tissue environment to make it favourable to host cell populations and unfavourable to unwanted populations (viruses, bacteria, parasites, cancer cells), cell Darwinism should result in non (or less) cell-killing therapeutics, driving "bad" populations to natural decline without attempting to kill them just a little more than healthy host cells. This is at least what has been achieved in the case of Acute Promyelocytic Leukaemia, by using a combination of classical cytotoxics and specific molecules acting as redifferentiating agents (see T. Haferlach, 'Molecular genetic pathways as therapeutic targets in acute myeloid leukemia' in *Hematology*, 2008, for a recent review; note that this disease, as all acute myeloblastic leukaemias, is characterised by a blockade of differentiation, but a blockade that in this special case of leukaemia can be normalised by these specific agents, particularly All-TransRetinoic Acid, ATRA), with high percentages of cures (about 80%). The representation of populations of immune cells as actors in this environment, that should be fostered rather that fought by treatments adds another relevant component to this scenery. Therapeutic optimisation is performed in populations as in epidemiological studies, but individuals are here cells (or parasites, or viruses), not men nor animals, and their evolution as populations is driven by optimisation of fitness to the environment, on which drugs act. Even though the idea that the host environment plays a important role in the development and treatment of diseases is certainly not new, it is only recently that it has begun to develop as a field of knowledge, and its most theoretical part is completely mathematical (adaptive cell population dynamics).

4 Actual impact of mathematics in medicine: the present, and future developments

Defining a formalism for biomedicine: creating and optimising techniques. Biomedical engineers with good training in theoretical and applied mathematics have always been keen on designing appliances for diagnosis, surveillance and therapeutics, either on request from clinicians, or according to their own ideas. Besides, there always have been engineers who were also physicians, and physicians with a good training in mathematics and physics. But the measurable impact of mathematics in medicine is not bound to remain limited to achievements of bioengineering, remarkable as they may be. Exactly as was physics in the XIXth and XXth centuries, e.g., with H. Poincaré and the three-body problem, biology is presently a source of theoretical problems that are of intrinsic mathematical nature, rewarding for the mathematicians who tackle them, and solutions to these difficult problems should open new ways to understand diseases and treat them better. For instance, population dynamics, be it in cellular, parasitic or human population settings, has seen noteworthy mathematical developments during the last century, always starting from real-life problems. Furthermore, setting biological questions in mathematical terms makes biologists and even more than them, makes physicians - because they are open to use all kind of knowledge to improve treatments, knowing that biology is not the only science on which medicine relies - think differently. Which they appreciate, since, confronted to the immensity of human ignorance about diseases, and knowing how empirically based is therapeutics, they are often eager to have some rational treatment rules made available for them. And whereas it was seldom the case some thirty years ago, some physicians (more and more) are now prone to accept, or better, seek collaboration with mathematicians, either to find new ways to cure, or to improve existing ones through their rational optimisation, as sketched above. From a very technological point of view, this may mean developing mathematical principles to use new appliances to diagnose or heal diseases, either directly, e.g., by heavy ion radioisotopes or application of local electrical fields, or indirectly, implementing by technology in the clinic drug delivery principles that previously have been theoretically optimised.

Model-based data acquisition or how to select relevant data to analyse experimental results. The development of mass data acquisition by the use of modern computers has for some time led physicians to the idea that knowledge would emerge from data sorting and statistical analysis, without need of theoretical models. But that this was naïve and delusive thinking was quickly apparent, as recording mass data without extracted meaning proved useless. Going back to physiology, then, to interpret quantitative data as partial manifestations of a biological phenomenon, that can be seen as measurements of variables in a dynamical system, naturally leads to design models constituted of mathematical equations, with solutions that are precisely these variables, e.g., the integrated cardiac action potential at the surface of the thorax. Model-based data acqui-

sition consists in extracting from data recordings quantitative characters as parameters of the physiological system under study and its pathologies, in order to allow automated classification of diseases according to present medical knowledge. For instance, automated diagnosis of a left bundle branch block (conduction block in the left branch of the His bundle in the myocardium) can be obtained without visual inspection of the EKG, but from a series of characteristic numbers *with a physiological meaning*, as few as possible, that can be extracted by automatically fitting to clinical data - the EKG of a patient - a mathematical model of the EKG. In other settings, more recently accessible to research, the cell division cycle and circadian clocks in cancer, where little clinical experience is available to guide data interpretation, designing physiologically based relevant models prior to recording data - even guiding the recording -, and analysing the mathematical properties of the designed models to obtain predictions on their behaviour is a reasonable warrant of success in identifying favourable circadian times for therapeutic intervention.

Pharmacokinetics and pharmacodynamics: need for a molecular and physiological basis. Recall, to define pharmacokinetics-pharmacodynamics (PK-PD), that according to a pharmacological mnemonic motto, "pharmacokinetics is what the body does to the drug, and pharmacodynamics is what the drug does to the body". I will add: at any relevant level, from the molecule to the whole body. The fate of a drug in the organism, from its infusion in the general circulation (and possibly its previous ingestion) until biological and clinical observation of its therapeutic and toxic effects has been represented for some time by using a mathematical formulation. This was obtained mainly by using ordinary differential equations to represent drug concentrations in blood, and by relating a global drug dose (per kilogram/day or per square meter/day) to therapeutic and toxic effects through empirical laws. Maybe because the level of mathematical conceptualisation used by clinical pharmacologists "does not go beyond basic knowledge on real functions of one real variable", as quoted above, but more likely because clinical emergency situations makes them rightfully reluctant to use methods relying on observations to which they have no direct access, pharmacological models are thus far seldom physiologically based. And yet authorised voices in the pharmacological world, such as Malcolm Rowland in Manchester, now call for "whole body physiologically based PK-PD (WBPBPKD) models". Designing physiologically based models in pharmacology leads to molecular equations representing chemical reactions with the law of mass action and mass (and energy) conservation laws, which are straightforwardly converted into differential equations. More and more such models are published, but it is a slow process, since identifying their parameters, that are sometimes well hidden, requires many experiments. And yet, progress in molecular and cell imagery, e.g., by fluorescence, firstly in cell cultures, but also in some occurrences in living animals, makes such identification more likely. The necessity of such molecular-based models *at the cell and tissue level* is patent, since the diffusion of a drug and its metabolites in the circulation does not inform much on what is actually occurring at

the molecular sites where the drug actually exerts its action. Besides, empirical laws of drug action may be replaced or refined by molecular based ones, provided that pharmacodynamics is known at every level of action, which is the object of pharmacological experiments in cell cultures, in laboratory living animals, and ultimately in clinical trials. Again, this is a time-consuming process, but developing a new molecule in a pharmaceutical company is a process that usually extends over 10 to 12 years, and molecular and physiological modelling may well be integrated to this process - which is what the most advanced companies actually do.

An individualised and possibly central place for mathematics in medicine. Mathematical modelling in molecular chemistry, in cell and tissue dynamics, and in epidemiology, i.e., modelling the diffusion and binding of molecules, the proliferation of cells and tissues, and the spread of diseases - and their control - in populations of molecules, of cells (tissues) and of individuals, often use the same equations, or very similar equations. For instance, transport equations and reaction-diffusion equations are found in all these occurrences. That a medical research department, included or not in an integrated research centre such as some of them already exist at least in the USA (e.g., for cancer), hires mathematicians as full-time specialists, not only for modelling but also to solve mathematical problems emerging from models, is not an unreasonable prospect nowadays. There could be in every medical research centre a department of mathematics as the same level as one of molecular biology or radioisotopes. From their part, mathematicians, and not the lowest level ones, are curious by nature, and often willing to get interested in challenging problems from real life. Since medicine easily yields problems that may be mathematically formalised but are hard to solve (otherwise they would long have been solved by physicians who may be gifted amateurs in mathematics, with some help from mathematicians colleagues), there is potentially a big appeal to mathematicians in medicine, which hopefully will be amplified in the forthcoming years.

Convergences of mathematics with physics and biophysics in medicine. Mathematical modelling in medicine, be it for practical medical applications, or even in a 'non-committed' way, as a source of problems for mathematicians, relies on evolution equations which often take their source from physical principles such as mass, energy, and momentum conservation - or dissipation, in open systems. Physicists and biophysicists tend, as mathematicians, to see the world through equations, and theoretical physics is hardly distinguishable from applied mathematics. Both physicists and mathematicians search coherent systems to explain physical - and physiological - phenomena; mathematicians prove theorems based on hypotheses, physicists state laws and principles which are often bases for the hypotheses on which mathematicians set the grounds of new theories. Problems coming from physics have fed the imagination of mathematicians (e.g., H. Poincaré and the already mentioned three-body problem), and conversely physicists rely on mathematicians to prove theorems which

they use in theories that can be applied to describe very diverse parts of the physical world, including biology (see, e.g., J.-P. Eckmann & D. Ruelle, 'Ergodic theory of chaos and strange attractors', in *Review of Modern Physics*, 1985, where the authors - mathematical physicists - rely on the multiplicative ergodic theorem proved 20 years before by V. Oseledets - a mathematician - to propose in particular the assessment of dissipative dynamic systems by Lyapunov exponents). Contributions of physicists in theoretical biology are a permanent source of questions for modelling and mathematical analysis, and systematic convergences between physicists and mathematicians on problems coming from biology and medicine may prove very fruitful, as some examples have already suggested, such as the analysis of time series from observed medical data by non linear (or 'chaotic dynamics') methods introduced in the last decade of the previous century.

Future of therapeutic optimisation within 'systems medicine' and 'personalised medicine'. These two keywords are found in many calls for research projects, names of journals, and even names of institutes. They just mean taking into account the whole relevant environment of the medical problem under analysis, and adapting the designed models to individuals, or groups of individuals with close specific characteristics recorded by biomarkers. In this respect, whole body systems of physiological equations with multiscale modelling, but dedicated to a precise medical question, are quite adapted. Personalised medicine in this context consists of the individual identification of model parameters, either by direct biomarkers when they are available, or by inverse problem methods (i.e., as for instance in the case of EKG modelling, reconstruction by fitting to observed measures models designed with *a priori* physiological knowledge, on the basis of likelihood by statistical or optimisation algorithms, of physiological characteristic parameters when these parameters are inaccessible). Hope had been put for some time in pharmacogenotyping, i.e., determining the best dose of a drug to be administered to a patient from the knowledge of his or her genetically determined enzymatic drug processing mechanisms, thus making a dramatic shortcut between genes and statistics. But the limited success of pharmacogenomics (about 12 relevant genes and 20 drugs so far, after over 50 years of research, as stated in an international conference on 'Functional genomics towards personalised healthcare' held in Santorini in 2010), together with the scarcity of available genetic biomarkers, now leads to modelling with more physiological principles. Principles of therapeutic control optimisation, as sketched above, yielding theoretically optimised drug delivery schedules, may then be applied to whole body molecular models ('systems medicine'). In these molecular and physiologically based models, drug targets are represented, and so are relevant parameters determining individual responses to drugs, such as K_m and V_{max} for drug processing enzymes in patients ('personalised medicine'). They may theoretically be estimated, either from body samples (when available), or by solving inverse problems, but this of course is one of the most difficult parts of the method, a real challenge for mathematicians in future medicine.

5 Conclusion

I have sketched in this informal essay a report, starting from my personal experience as a mathematician (or at least trained as such), on the commitment of mathematicians in medicine in general. Even though in principle 'the ego is detestable' (according to Descartes, *'le moi est haïssable'*), and I certainly will not put forth ideas drawn from a personal experience and involvement in medicine as universal, I do think that sharing them with other people pondering over relationships between mathematics and medicine, their successes and failures, may be of interest to some. Although my views may indeed be too closely linked with my particular career path, I have tried to derive from them more general considerations that hopefully can be useful to mathematicians considering collaborative work with physicians.