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Employing Mathematical Models to Understand Personalized Medicine

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Abstract

Computational mathematics of personalized medicine has enhanced the amalgamation of complex data from genetics, sequencing, mutations, cellular reactions, interactomes, medications, medication dosing and scheduling, drug reactions and toxicities, and the interpretation of patient responses. This article demonstrates how computational mathematics has furthered the progress of personalized medicine.

Keywords: *Computational Mathematics; Personalized Medicine; Genetics; Pharmacogenomics; Drug Delivery Systems; Interactomes; Mathematical Models*

In addition to the progresses made in sequencing the genetic composition of patients there has been significant progress in computational mathematics of genomic and personalized medicine. The reason is that there are so many genes and proteins involved in personalized medicine, that it is a prerequisite to apply the benefits of computational mathematics. One way to do this is to use mathematical models to study genetics and the gene-environment interactions. Mathematical models are important to interpret the accumulated data in analyzing diseases, genetic mutations, cellular reactions with genes, interactomes, medications, drug reactions and toxicities, beneficial results after the administrations of various medications and regimens, doses of drugs and drug schedules, as well as many x-rays, MRIs, lab tests, and health care professionals. If the practicing clinician is to utilize this information, it should be available on the electronic health record so that it can be of benefit to the patient. As if all of the above were all that was necessary for the clinician to know and analyze, epidemiology problems involving population shifts resulting from epidemics of disease, environmental changes, weather, and wars should be analyzed and available to the treating physicians.

It is helpful to know just how models are constructed so as to be able to use them in personalized medicine. These models can help understand our genetic variation and personalized medicine, by giving us a goal based on assumptions. Although incomplete, mathematical models are explicit about what is included. These models should elucidate information about our genetic system and different combinations of genes. The models are another tool, complement biological investigations, and help to explain results of experiments. It is because there is such a huge amount of data and observations that need to be explained and interpreted, mathematical modeling is so necessary. A great deal of quantitative data is used to detect relationships between genes, diseases, and medications.

In many processes, physical, chemical, or biological, the rate of change of an unknown quantity is related to its current magnitude. The equation relating rate to magnitude is termed a differential equation. Two simple examples of modeling with differential equations, population growth and epidemiology, are given in box 1.

Box 1 Simple biological models using differential equations

Two simple examples are differential equations for population growth are

$$\frac{dP}{dt} = rP$$
$$\frac{dP}{dt} = k(M - P)P.$$

The first equation says, naively, that the rate of population growth is simply proportional to the current number P of organisms. Its solution $P(t) = P_0 \exp(rt)$ predicts exponential growth of the population forever. The second equation, the *logistic model* of population growth, replaces the constant growth rate r with a more realistic growth rate $k(M - P)$ which diminishes as the population P increases, and becomes zero when the carrying capacity M of the environment has been attained. The solution of the logistic model is a sigmoidal curve that approaches M asymptotically as time progresses.
The SIR model for non-lethal diseases divides a population into three groups: members susceptible to a disease, those infected with the disease, and those who have recovered from the disease and are now immune to it. A system of differential equations which describes the infection and recovery process is

$$\frac{dS}{dt} = -\frac{\beta}{N}SI$$
$$\frac{dI}{dt} = \frac{\beta}{N}SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

The sum of the three rates is zero, so that $N = S + I + R$ is not changing. The first of the three equations says that the number of susceptibles is decreasing at a rate proportional the product SI. This is the *law of mass action*, and it is a common assumption in biological models.

Biological systems are complex systems in a particular sense Kitano [1]:

It is often said that biological systems, such as cells, are `complex systems'. A popular notion of complex systems is of very large numbers of simple and identical elements interacting to produce `complex' behaviours. The reality of biological systems is somewhat different. Here large numbers of functionally diverse, and frequently multifunctional, sets of elements interact selectively and nonlinearly to produce coherent rather than complex behaviours.

An illustration of this, the methionine cycle, is given in box 2. One must make a choice about the parameter values in a mathematical model. These choices are made from experimental data, dose-response data, mutation data, and clinical studies Nijhout., *et al* [2]. If there is too much individual variability, then population models might be more accurate.

Box 2 Methionine metabolism

A more complex example of modeling biological systems is DNA methylation, which affects gene expression. It is one function of the methionine cycle. The article **?** presents a mathematical model of methionine metabolism. The model consists of a system of four ordinary differential equations in the four unknown concentrations of the substrates methionine (MET), S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), and homocysteine (HCY). The equation for the concentration of MET is

$$\frac{d}{dt}[MET] = MET_{in} + V_{MS} + V_{BHMT} - V_{MATI} - V_{MATIII}, \tag{1}$$

which says that the rate of change of the concentration of the substrate methionine (MET) consists of an exogenous flow MET_{in} into the cycle from dietary proteins augmented by conversion of HCY into MET catalyzed either by the enzyme Betaine:homocysteine methyltransferase (BHMT) or the enzyme Methionine synthase (MS), and decremented by the conversion of methionine into SAM catalyzed by the enzymes MAT-I or MAT-III (Methionine adenosyltransferase). A statement such as (1) is a conservation law, in this case conservation of mass. Such laws often constitute the starting point for deriving differential equations. *Continued on the next page.*

Box 2 Methionine metabolism (continued)

In (1) the influx MET_{in} is assumed known, but the four fluxes denoted with Vs all depend upon the unknown concentrations of one or more of the substrates, thus making it a differential equation. The Michaelis-Menten formula for the rate at which a simple catalytic reaction takes place is

$$v = \frac{V_{max}[S]}{[S] + K_M}. \tag{2}$$

where $[S]$ is the concentration of the substrate, V_{max} is the maximum rate the reaction approaches asymptotically with increasing concentration, and K_M is the concentration at which v is half of V_{max}. The Vs in (1) are more complicated than (2) because, among other reasons, of the long range allosteric effects of SAM on the methionine cycle and the interacting folate cycle. Thus, for instance, V_{BHMT} is (2) with $[S] = [HCY]$ scaled by a decaying exponential factor representing the inhibitory effects of increasing SAM and SAH. Comparing the solutions of the system of differential equations with the allosteric effects turned on or off indicates that the effects buffer the rate of DNA methylation against fluctuations in MET_{in}.

Even with genetic mutations and the changing environment, the regulatory mechanisms keep our health systems functional. Many of the metabolic systems contain homeostatic mechanisms that must be taken into account. One example would be the stabilization of dopamine in synapses. The concentration of dopamine in the extra-cellular space is maintained by a balance between the release from the terminal and the uptake by the dopamine transporters. If the concentration of dopamine decreases, then tyrosine hydroxylase is increased. A model has been developed to explain this reaction. Parkinson's disease occurs when there is a decline of the dopamine in the striatum leading to the death of dopamine neurons in the substantia nigra.

Mathematical models can also show that these homeostatic mechanisms stabilize critical phenotypes. For example, a large number of defective genes persist in the human body, but the homeostatic mechanisms reduce their effect at the phenotypic level.

Precision or personalized medicine and computational oncology are relatively new ends made possible in part by the use of in silico analyses Barbolosi., *et al* [4]. The application of this concept to the diagnosis and treatment of cancer has contributed to the analysis of large datasets relating to complex signaling networks Powathil., *et al* [5]. Huge databases of information on intracellular pathways aid in

the understanding of the inter-relationships between complex biological processes which improve tumor classification, tumor growth and progression, and tumor response to many drugs and their targets Agur., *et al* [6]. Computational oncology also focuses on optimizing the dosing and scheduling of anticancer therapies. Physicians cannot do this task efficiently by the bedside. Choosing the best treatment for any patient is a much more complicated task because of the large number of potential drug combinations and the variety of drug schedules and sequences. Combining antiangiogenic therapies with cytotoxic agents requires an understanding of the toxicity-efficacy balance. The multikinase inhibitor sorafenib, which has antiangiogenic effects, promotes tumor growth in pediatric patients with a progressive low grade glioma. Acceleration of the metastatic process can follow treatment with sunitinib in renal cell carcinoma Ebos., *et al.* [7] and bevacizumab in patients with breast cancer Mollard., *et al* [8].

Therapeutic drug monitoring (TDM) is the measurement of drug levels in patients to check if the dose is accurate. This is the first step towards developing a computational approach for the treatment allocation at the patient's bedside. No mathematical model can be established without an accurate comprehensive knowledge of the dose-exposure relationships Beumer [9]. Mostly, weight and body surface area have been used to tailor dosing for individuals. Population studies are mandatory to determine if dose individualization is required to increase the efficacy-toxicity balance. Other models can be developed to identify better regimens for scheduling, dosing, and sequencing in order to achieve maximal efficiency in reducing tumor size or growth of metastatic lesions while maintaining neutrophil levels above a certain level. These approaches require a skilled work force to design and build mathematical models and they will need computer coding in mathematical languages Bruno., *et al* [10]. Specific models can be built to prevent the disruption of the haematopoietic chain by cytotoxic agents Bruno., *et al* [10].

An interactome is the whole set of molecular interactions in a particular cell. This refers to the interactions among molecules such as among proteins known as protein-protein interactions (PPI), but can refer to genetic interactions Sanchez., *et al* [11]. Another interactome is the protein-DNA interactome or the gene regulatory network formed by transcription factors, chromatic regulatory proteins, and their target genes. The interaction of genes may affect the function of other genes. A genetic mutation may be harmless, but when it interacts with another harmless gene, the result could be lethal. The goals of these genetic networks are to develop a functional map of the cell's processes, drug target identification, and to predict the function of some other genes Wikipedia [12]. There are numerous ways to analyze the properties of an interactome such as studying the topology of its interactions and focus on the role of the proteins in the interactions. PPIs from one organism can be used to predict interactions among homologous proteins in another organism. The topology of an interactome can be used to make a prediction based on the reaction to the removal of proteins (nodes) or interactions (edges) caused by genetic mutations. Then drug targets and biomarkers of diseases can be identified. Viral interactomes are connected to their host interactomes forming virus-host interaction networks Navratil., *et al* [13]. Some of the human (mammalian) viruses include: Human varicella zoster virus, Chandipura virus, Epstein-Barr virus, Hepatitis C virus, Hepatitis E virus, Herpes simplex virus, Kaposi's sarcoma associated herpes virus, and Murine cytomegalovirus. Some of the bacterial interactomes include: *Helicobacter pylori, Campylobacter jejuni, Treponema pallidum, Escherichia coli, Mesorhizobium loti*, *Mycobacterium tuberculosis, Mycoplasma genitalium, Synechocystis*, and *Staphylococcus aureus*.

The size of protein interaction networks in different organisms correlates with their biological complexity. The number of interactions in humans is about 650,000 Stumpf., *et al* [14]. There are extensive protein interaction network (PIN) datasets in humans and these are useful tools for the analysis of functional evolutionary properties.

Protein-protein interactions mediate all biological processes Lage [15]. There are several large scale methods to map functional associations between genes such as through gene expression correlations, text mining associations, protein-protein interactions, synthetic lethality relationships, as well as many data sets which are viewed as networks where genes are represented as nodes and nodes are connected by edges. Genes exert their function by collaborating with other genes in molecular networks. These represent molecular machines, cellular structures, or signaling pathways. Common and rare diseases are driven by genomic and environmental influences. Thus protein-protein interaction networks are a powerful resource to elucidate biological systems affected by disease Rossin., *et al* [16]. Genes

involved in similar phenotypes often interact physically at the level of proteins in humans. There are more than 800 linkage intervals already reported. Proteins for which the corresponding gene is known to be involved in a disease are identified and some are involved in different disorders. Ataxia related proteins interact with each other to a much higher degree than one would expect by random Lim., *et al* [17].

Mathematics is needed in personalized medicine just to process the vast numbers and amounts of data involved. For example, up to ten different proteins are associated with a single human gene. The number of proteins in a cell is far greater than the number of its genes. Humans are thought to have 20,000 to 50,000 genes and the number of proteins range from 80,000 to 400,000. The proteins are the molecular motors, signaling substances, and antennas. Hopefully, the study of the proteomes will detect just that one faulty gene that may trigger disorders such as cancer, Alzheimer's or Parkinson's disease. (Rosch, H., From Genome to Interactome) What is needed is more information about the numerous interactions between the proteins as there are about 130,000 paired interactions.

At the 3rd International Congress on Personalized Medicine 26 - 29 June, 2014, in Prague, Czech Republic, a panel discussed the issue of integrating the vast amount of genomic information, chemical laboratory data, radiological and clinical knowledge into the patient's electronic health record so that oncology health professionals could actually utilize all that is available. Some of this information characterizes the myriad cancer types and their sensitivities to treatment. Machine learning algorithms and CDS (Clinical Decision Support) software may help harness the cancer genomic information so that doctors can chart the treatment course more efficiently Warner., *et al* [18].

It is important to understand metabolic networks in terms of their function in the organism and in relation to the data we already have. We need to gather the information from biochemistry, genomics, microarray experiments, network analysis, and simulation. Then we need to make this information comprehensible in biological terms, which will require computational analysis Chao [19].

Any discussion of the influence of mathematics on personalized medicine should include Magnetic Resonance Imaging. Two major applications of the MRI are blood flow imaging and quantification and functional neuroimaging. One of the major advances due to mathematics and physics is the improvement in the resolution of brain images. Radio-frequency coils constitute the essential means of stimulating the spin systems and are the entrance for the sensing of MRI data (https://www.ncbi.nlm.nih.gov/books/NBK 232486). The MRI builds up a map of tissue types and integrates this information to create 2-D and 3-D models with a mathematical formula known as the Fourier transform. The mathematical data is converted into a picture Gould [20]. Although the issue of treatment results has been adumbrated above, this is the issue that it all comes down to in the final analysis. Does the disease originate from a known specific genetic defect? Do all of the tests confirm that connection? Will the medication prescribed really be effective with the dose and schedule recommended? How do we know that the treatment suggested will be effective for this patient who lives in this population in this particular location? Computational mathematics can be very helpful in elucidating these questions.

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