

# From the evolution of toxin resistance to virtual clinical trials: the role of mathematical models in oncology

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Sustainable delivery of quality healthcare at affordable cost is a major challenge, especially in oncology. Through interdisciplinary collaboration, researchers can provide new insights into familiar concepts and radically change the ways in which biopharmaceutical and medical studies are conducted and translated into clinical practice. One interdisciplinary approach is 'Virtual R&D', that is, biomedical research and development aided by mathematical models of the human body. This approach has facilitated the development of the 'virtual patient', a clinically validated modeling system that accurately predicts efficacy and toxicity of various oncology drug combinations in individuals and in populations. The use of virtual patients in clinical research will dramatically shorten the period of development of new drugs. Such models can also be used to personalize treatment regimens, substantially reducing the risk of clinical failure. This strategy can improve the quality of healthcare and reduce costs associated with clinical development.

Why has there been so little progress in the war against cancer? In spite of substantial research achievements over the last two decades, an annual cancer death toll of 562,640 was still expected in 2009 in the USA alone [101]. This gap between research progress and clinical results can be accounted for by investigators' reliance on animal models, which are poor at predicting treatment success. Another reason is the excessive focus on the study of intracellular drug interactions, altogether ignoring the effects on the patient as a whole [1]. How can this gap be bridged? Which scientific methods enable accurate prediction of drug-patient interactions?

There is a consensus in the biomedical community that cancer progresses haphazardly and, hence, does not yield to prediction at any level of accuracy. Nevertheless, an oncologist prescribing a treatment must trust his/her own medical education, intuition, experience and the drug developers for predicting how the prescribed treatment will affect disease progression in the patient. However, the human mind is too frail to combine disparate pharmacological and medical information with the dynamic understanding of the multiscale processes taking place in a cancer patient undergoing drug therapy. Oncologists should be aided by tools for integrating vast and diverse biomedical information into a dynamic model that can forecast the patient's response.

Biomathematics is a science that studies biomedical systems by mathematically analyzing their most crucial relationships. Incorporating biological, pharmacological and medical data within mathematical models of complex physiological and pathological processes, the model can coherently interpret large amounts of diverse information in terms of its clinical consequences.

Just as medical books are useful for oncologists, there is a clear advantage in using biomathematical models as a tool for guiding decision-making in oncology. Nevertheless, a declarable mistrust still exists among physicians and cancer researchers in the power of biomathematics to aid their daily work. The aim of this article is to illuminate the influence of mathematical models on medicine, and to show that models can help the oncologist by suggesting improved treatments for individual patients and for patient populations.

## **Biomathematics in medicine: a retrospective view**

Luria and Delbruck developed a simple mathematical model, which deciphered the emergence of toxin resistance in bacteria.

When a population of bacteria is plated onto a substrate containing phages, almost all the bacteria are lysed by the viral toxin except for a few survivors, which give rise to new toxin-resistant

## **Keywords**

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- bevacizumab ■ breast cancer ■ docetaxel
- drug development
- immunotherapy
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colonies. Luria and Delbruck used simple mathematical models to decipher the mechanism that enables these bacteria to develop resistance [2]. They considered two alternative explanations for the acquisition of toxin-immunity in bacteria: resistance is an adaptive mechanism induced by the virus and passed on to the offspring (Lamarckian theory), or, resistance is due to a random mutation, occurring in the bacteria independently of the presence of the virus (Darwinian theory).

Making a few simplifying assumptions, Luria and Delbruck constructed two mathematical models for the distribution of toxin-resistant mutants in bacteria colonies. One of the models embedded the resistance mechanism, satisfying Lamarck's theory, and the other embedded the resistance mechanism that satisfies Darwin's theory. By meticulous laboratory experiments they validated the predictions of one of the models, confirming that bacteria genetics obeys Darwin's theory, and establishing the basis for understanding the evolution of drug resistance.

#### Norton-Simon hypothesis raises awareness to dose density

Chemotherapy is used for treating cancer with variable success. The number of possible chemotherapy schedules is exceedingly large, and trial-and-error clinical testing cannot be exhaustive. In trying to identify efficacious chemotherapy treatments, Larry Norton and Richard Simon constructed a simple mathematical model for relating the efficacy of cytotoxics to the growth dynamics of a tumor. Mathematically, the Norton-Simon model can be written  $N'(t) = f(N(t))(1-d(t))$ , where  $N(t)$  denotes the number of tumor cells at time  $t$ ,  $N'(t)$  is the growth rate of the tumor at time  $t$ ,  $d(t)$  reflects the rate of removal of cells as a result of treatment and  $f$  is a function that describes the growth dynamics of the unperturbed tumor. Norton and Simon assumed that this growth function obeys Gompertz law, and that the rate of tumor regression induced by chemotherapy is proportional to the rate of unperturbed growth of a tumor of that size. Consequently, they argued, to be more efficient, the dose rate of chemotherapy should be increased, for example by decreasing the inter-dosing intervals [3–5].

The Norton-Simon hypothesis has been influential in oncology and has inspired a great deal of clinical investigation. It led to the 'dose-dense' approach to breast cancer chemotherapy, demonstrated in multiple studies to achieve drops in cancer recurrence and death, as the model predicts [6].

Unlike Luria and Delbruck, Norton and Simon did not challenge their initial model predictions by an alternative model of tumor growth, or of drug effect. Can their model be validated? Can it be generalized, for example, to all vascular cancers, or all chemotherapeutic drugs? In the following sections it will be demonstrated that the advantage of dose-dense therapy may depend on the level of tumor angiogenesis and on the kinetic parameters of the chemotherapy-susceptible cancer and host cells.

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#### Make everything as simple as possible, but not simpler

Can the model of Luria and Delbruck be used to predict whether or not a specific pathogen will become resistant to an antibiotic drug, applied, for example, once daily for 1 week in a 4-month cycle? Will the Norton and Simon model be able to predict under which docetaxel regimen a metastatic disease will be stabilized? Certainly not. These models were not designed to solve such quantitative problems and, hence, are too simplistic to predict the effect of specific drug regimens on gene frequency or on vascular tumor progression.

However, any retrievable information yields to mathematical description. Therefore, one can envisage improved drug schedules being provided by mathematical models that are designed for this purpose. For constructing such models the major forces affecting tumor growth dynamics, notably angiogenesis, should be carefully verbalized and translated into mathematical formulae. The 'naked' mathematical model will then be 'dressed up' with parameters, characterizing the case study at hand, and will be numerically calculated in conjunction with the pharmacokinetics and pharmacodynamics (PK/PD) of the particular drug(s). Following model validation, it can be simulated to predict which new drug regimens will yield improved results in a patient or a patient population.

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#### Mathematical models of cancer growth & treatment

Cancer growth and its treatment with chemotherapy have been mathematically modeled since the 1960s. An elaborate and didactic review of the different modeling approaches can be found in a book chapter by Swan [7].

Following Folkman's paradigm concerning the critical role of vascularization in cancer development [8], angiogenesis was incorporated into cancer modeling. The first models of tumor angiogenesis appeared as early as the mid-1970s. These works,

driven by experimental data on cancer progression in animals, accounted for growth and movement of tumor cells and tumor-supporting blood vessels, and their mutual influence [9–11]. A vast body of theoretical work has been developed by different researchers since the early 1990s, along with significant advances in the understanding and detailed characterization of biological processes involved in tumor and blood vessel dynamics. Naturally, these models vary significantly, both in their formulation and in the biological phenomena they represent. In the following sections, we describe one of these mathematical models, which accounts for tumor growth and a detailed angiogenesis process. This model can be singled out from all angiogenesis models by its preclinically and clinically proven accuracy.

The notion that specific cancer therapy regimens that maximize drug efficacy and minimize its toxicity can be suggested *a priori* was introduced by Agur in the 1980s. Agur developed a new treatment optimization method using heuristic optimization of mathematical models for both cancer growth and hematopoietic toxicity [12,13]. This concept is briefly discussed later.

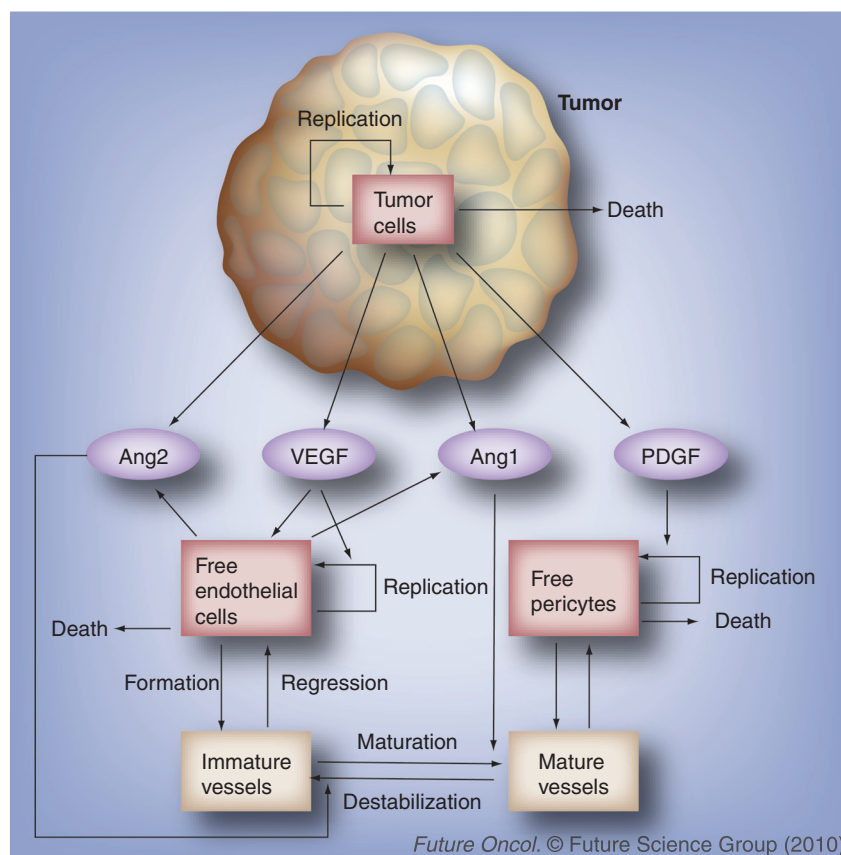
In the 1970s and 1980s, bone marrow hematopoiesis was mainly modeled by relatively simple mathematical models, pioneered by Wichman *et al.*, and Steinbach *et al.* [14,15]. In the 1980s and 1990s, Mackey and others developed simple models of erythropoiesis [16,17], granulopoiesis [18] and thrombopoiesis [19]. Mackey's models were sufficiently simple to be tractable to analysis and therefore could serve for addressing interesting questions about the origin and the dynamics of hematopoietic diseases, such as periodic neutropenia. However, the models were too simple to generate testable quantitative predictions of the effect of different drugs on blood cell counts. The mathematical model for granulopoiesis reviewed here [20] can accurately predict the effect of chemotherapy on individual patients' safety, as validated in metastatic breast cancer patients undergoing docetaxel chemotherapy (see later).

### Drug efficacy & toxicity are accurately predicted by multiscale mathematical models

A detailed vascular tumor model can reproduce the clinical scenario and suggest more efficacious regimens.

For identifying improved regimens for cytotoxic and cytostatic cancer drugs, Arakelyan and colleagues studied the impact of angiogenesis on cancer progression, and developed a detailed model of vascular tumor growth. The model takes

account of the molecular-, cellular- and organ-level interactions in cancer cell replication, angiogenesis and vessel maturation. The 'verbal model', namely the algorithm showing the critical forces and effects and their inter-relationships (sketched in a simplified form in FIGURE 1) was translated into mathematical equations, which were, in turn, translated into a computer model. Subsequently, parameter values were estimated and input into the computer model, upon which the model was numerically simulated. In this way the effects of drugs on the growth and decay of both the tumor and the immature and mature blood vessels, and their effect on the induction of an array of relevant growth factors, such as angiopoietin-1, -2, VEGF and PDGF, could be evaluated. The full algorithm is given in Arakelyan *et al.* [21] and in a simplified form in FIGURE 1 and in Agur *et al.* [22]. How the model's equations were derived and how the model parameters were calculated is described in Arakelyan *et al.* [23].

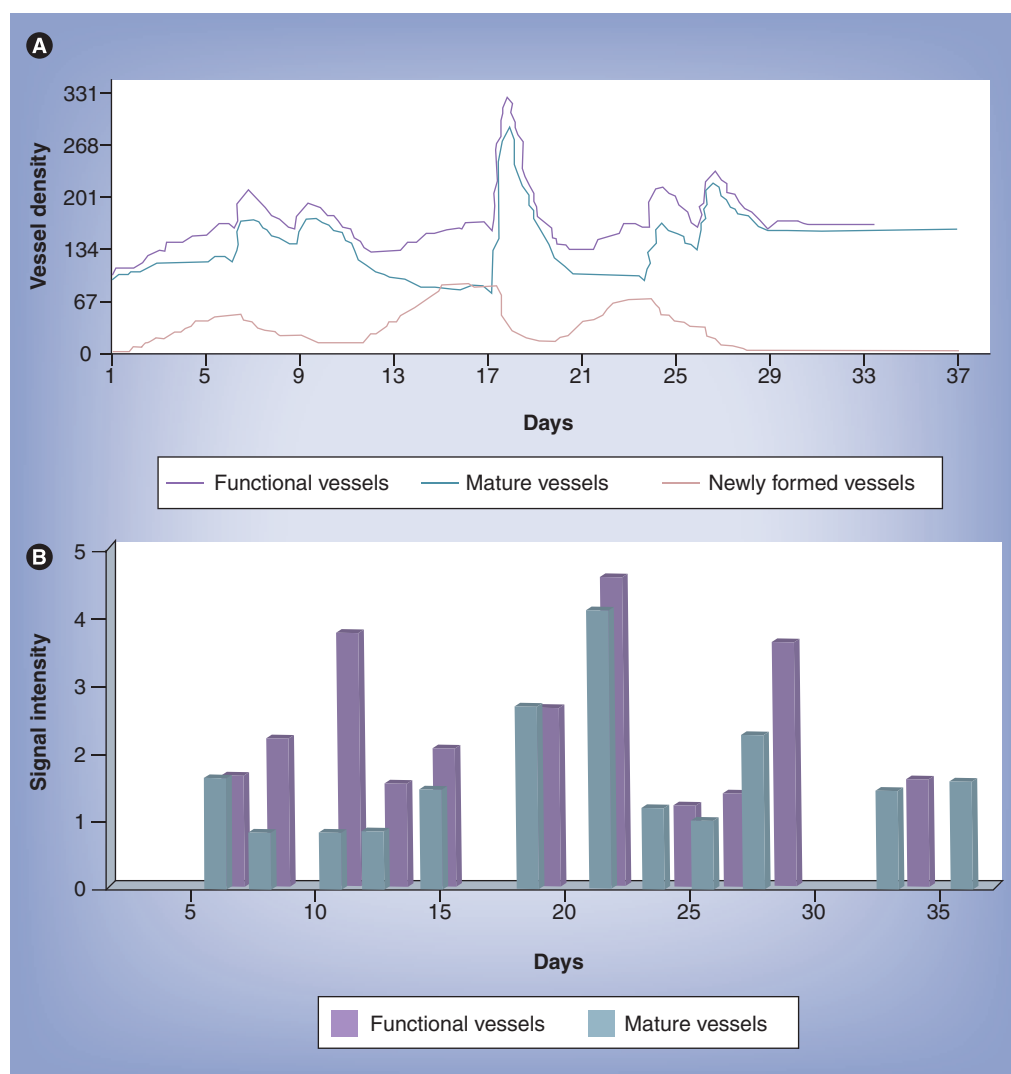


**Figure 1. Vascular tumor growth dynamics.** A schematic description of the multiscale mathematical model as described in [7]. Tissue (yellow), cells (pink) and molecules (purple) interact as marked by the arrows. VEGF and PDGF are secreted by the tumor cells. VEGF binds to endothelial cells and PDGF to pericytes, to generate new and mature blood vessels, respectively, and the ratio of Ang1 and Ang2, secreted both by the tumor and by endothelial cells, affects the stability of the mature vessels. Ang: Angiopoietin.

Mathematical analysis and numerical simulations of the model by Arakelyan *et al.* shed important light on vascular tumor dynamics. Analysis suggests that there should be circumstances in which small tumors oscillate in size instead of growing steadily. If such circumstances can be medically replicated then this may be a powerful way of controlling cancer growth [22,24]. Notably, it was suggested that monotherapy by anti-angiogenic drugs alone can slow tumor growth, but cannot altogether eliminate it, and that anti-angiogenesis drugs combined with drugs that target mature vessels may be superior to anti-angiogenic monotherapy [21,25]. These conclusions were later corroborated experimentally [26].

In order to check whether or not the model is a high-fidelity portrayal of vascular tumor growth,

its predictions were experimentally validated [27]. Thus, tumor growth, neovascular maturation and functionality were studied noninvasively by MRI in human epithelial ovarian carcinoma spheroids, xenografted in mice. Individual tumor growth curves were inputted into the model for evaluating the tumor-specific parameters, and predictions of vascular dynamics were compared with the MRI readings. The accuracy of model predictions is demonstrated by the example in FIGURE 2. The model predicts complete maturation of all neovasculatures in a particular tumor within approximately 1 month (FIGURE 2A). Indeed, the experimental results support model predictions quite remarkably and further explain the model-predicted and clinically observed short-term effects of anti-VEGF therapy (FIGURE 2B).



**Figure 2. Prediction accuracy of the vascular tumor growth model.** *In vivo* validation in xenografted human ovary carcinoma spheroids. **(A)** Model predictions of neovascular and mature vessel dynamics in a single tumor. **(B)** Experimental results of neovascular maturation and functionality in the same tumor, measured noninvasively by MRI. Data from [12].

It is often argued that cancer progression in the preclinical setting is a poor indicator of the clinical scenario. Will the mathematical model, which was demonstrated to reflect the tumor dynamics in xenografts, also demonstrate accuracy in modeling clinical results? To answer this question, the accuracy of the mathematical model of vascular tumor dynamics was validated by comparing its predictions to the clinical response of metastatic breast cancer (MBC) patients to docetaxel [YOSEF-HEMO *ET AL.*, UNPUBLISHED DATA].

Clinical and histopathological information was collected from MBC patients treated with tri-weekly docetaxel monotherapy. The patients were randomly divided into a training set, for adjusting patient-specific tumor growth and pharmacodynamic parameters, and a validation set, for validating model predictions of disease progression under individually assigned docetaxel regimens.

The correlation between the predicted and the measured tumor sizes, over the entire treatment, was good ( $R^2 = 0.7$ ;  $p < 0.001$ ), and the predicted accuracy of objective tumor response, assessed by Response Evaluation Criteria In Solid Tumors (RECIST) criteria, was even better (85.7%;  $p < 0.001$ ). For all patients in the trial, the efficacy of the once-weekly schedule was better or equal to that of the bi-weekly or tri-weekly regimens. For 60% of patients it was superior over the three-weekly schedule. For all patients, the bi-weekly regimen was at least as good as the tri-weekly regimen, and in 44% of patients it was superior to it [YOSEF-HEMO *ET AL.*, UNPUBLISHED DATA]. It appears, then, that the mathematical model, combined with patient-specific information, accurately predicts response in docetaxel-treated MBC patients. As such, the model can now be used for planning improved treatments for patients whose response to the originally planned treatment is insufficient.

### What about toxicity?

By the same procedure used for testing the efficacy of drug schedules, one can also test their toxic effects. The benefit of mathematical models for the routine work of the oncologist – having to tailor therapy without compromising the patients' quality of life – is demonstrated in the neutropenia example below.

Neutropenia is a dose-limiting toxicity of many chemotherapeutic drugs, which exert their killing effect on replicating granulocytes in a cell-cycle phase-specific manner. Granulopoiesis models, including an explicit description of the

cell-cycle phase transition in mitotic cells, can be employed for accurately evaluating the risk of chemotherapy-induced neutropenia. The granulopoiesis model, developed by Vainstein *et al.*, has this property and therefore, can faithfully replicate the myelotoxicity of cell-cycle phase-specific drugs, such as docetaxel. A schematic description of this model is found in FIGURE 3 and all model equations in Vainstein *et al.* [20].

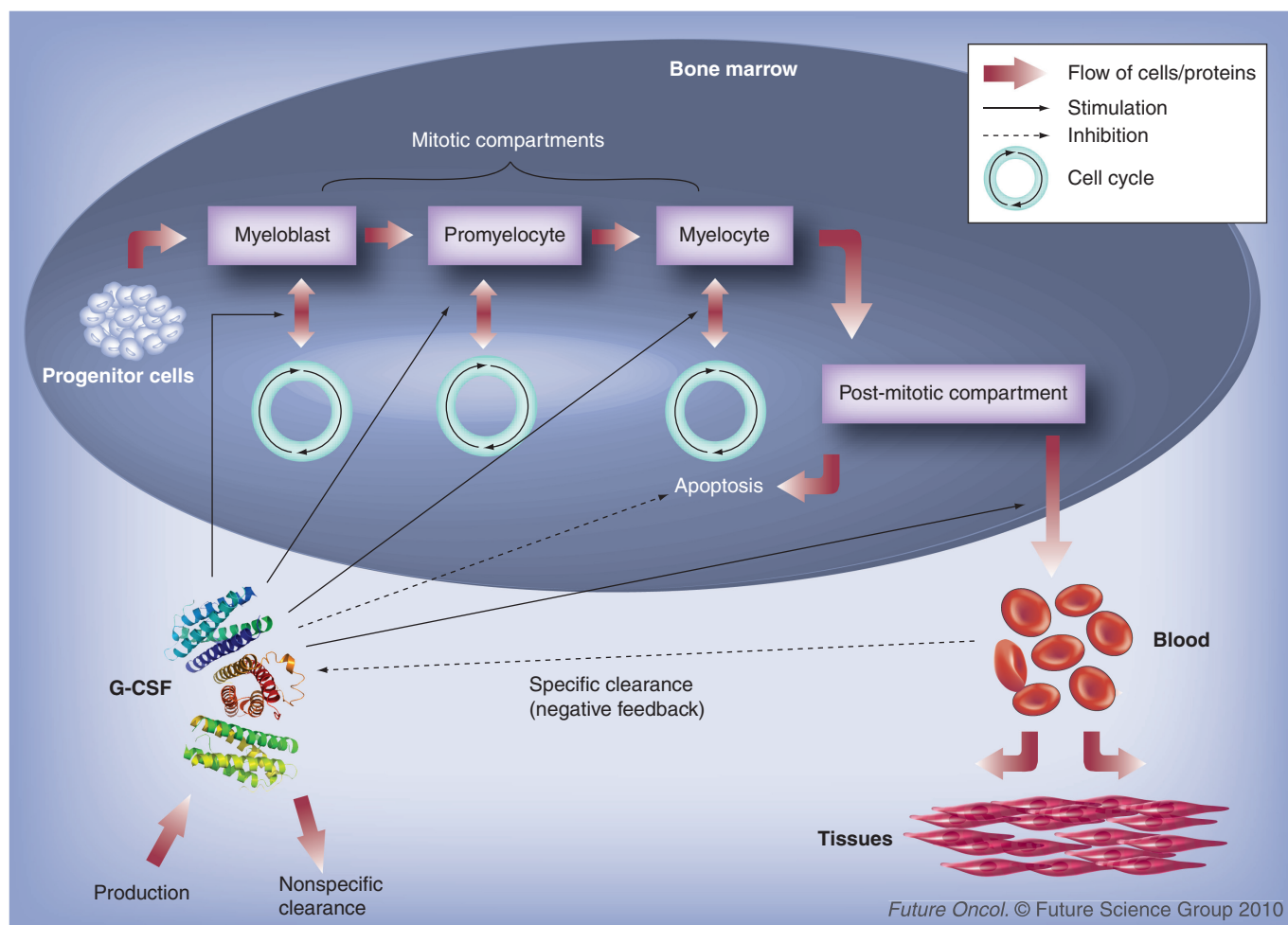
The model of Vainstein *et al.* has been validated by Vainas *et al.* in MBC patients treated with docetaxel monotherapy [VAINAS *ET AL.*, MANUSCRIPT SUBMITTED]. As above, the patient population was divided into a training set, for model calibration to the specific patient-population, and a validation set. The population-adjusted model was simulated in conjunction with the docetaxel PK/PD model, with baseline neutrophil counts and docetaxel schedules of each patient in the validation set serving as inputs for model validation. The model accurately predicted nadir ( $r = 0.99$ ), grade 3/4 neutropenia (86% success) and neutrophil profiles ( $r = 0.63$ ) of individual patients in the validation set (see example in FIGURE 4).

The validated model was then used to identify safe docetaxel and granulocyte colony-stimulating factor (G-CSF) regimens. Weekly docetaxel was found to exert smaller toxicity than the bi-weekly and the tri-weekly regimens, and G-CSF support was found to be optimal if applied 6–7 days post bi- and tri-weekly docetaxel, and 4 days post-weekly high-dose docetaxel. This model can be employed in the clinic. By plugging-in the patient's baseline neutrophil count, the doctor can forecast the day of nadir and the grade of neutropenia and, if required, suggest a safer chemotherapy and G-CSF treatment.

### **A method for improving cancer treatment by increasing drug efficacy while reducing its toxicity**

There is a need to develop ways to give a patient the most efficacious treatment with a reasonable quality of life. We can now determine drug schedules that satisfy this requirement *a priori*. Employing mathematical modeling and operation research methodologies, a method was developed for identifying patient-specific drug schedules that meet specified clinical requirements. The method uses efficacy and toxicity models for calculation of cell death throughout therapy under a large number of potential drug regimens. Search algorithms efficiently identify treatment schedules that represent the optimal treatment, as defined by the efficacy, toxicity and cost criteria, determined by the clinician [13].





**Figure 3. Granulopoiesis model.** A schematic description of the multiscale mathematical model for granulopoiesis developed and fully described mathematically in [14]. Granulopoiesis is described as a pipeline initiated by stem cells inflowing to the myeloblast compartment, then, sequentially, differentiating into promyelocytes, myelocytes and post-mitotic bone marrow cells, and finally released into the blood as mature neutrophils. G-CSF accelerates proliferation, transition through the mitotic compartment and the release of post-mitotic cells into the blood and their apoptosis. G-CSF: Granulocyte colony-stimulating factor.

Using this method two general categories of optimal chemotherapy regimens were identified, depending on the cell-cycle parameters of the chemotherapy-susceptible host and cancer cells, an intensive short treatment, or a series of non-intensive treatments at intervals set by the kinetic parameters of the drug-susceptible cells (dose-dense). It appears, then, that improved chemotherapy schedules can be calculated *a priori* by the use of mathematical models, maximizing drug efficacy while minimizing its toxicity.

#### Treatment personalization

Equipped with the above described treatment optimization method, a new procedure has been developed [28], blending mathematical models and *in vitro* and *in vivo* experiments for personalizing the treatment of cancer patients with combinations of chemotherapy and angiogenesis

inhibitors. The validated method was successfully used to suggest an improved treatment schedule for a mesenchymal chondrosarcoma patient.

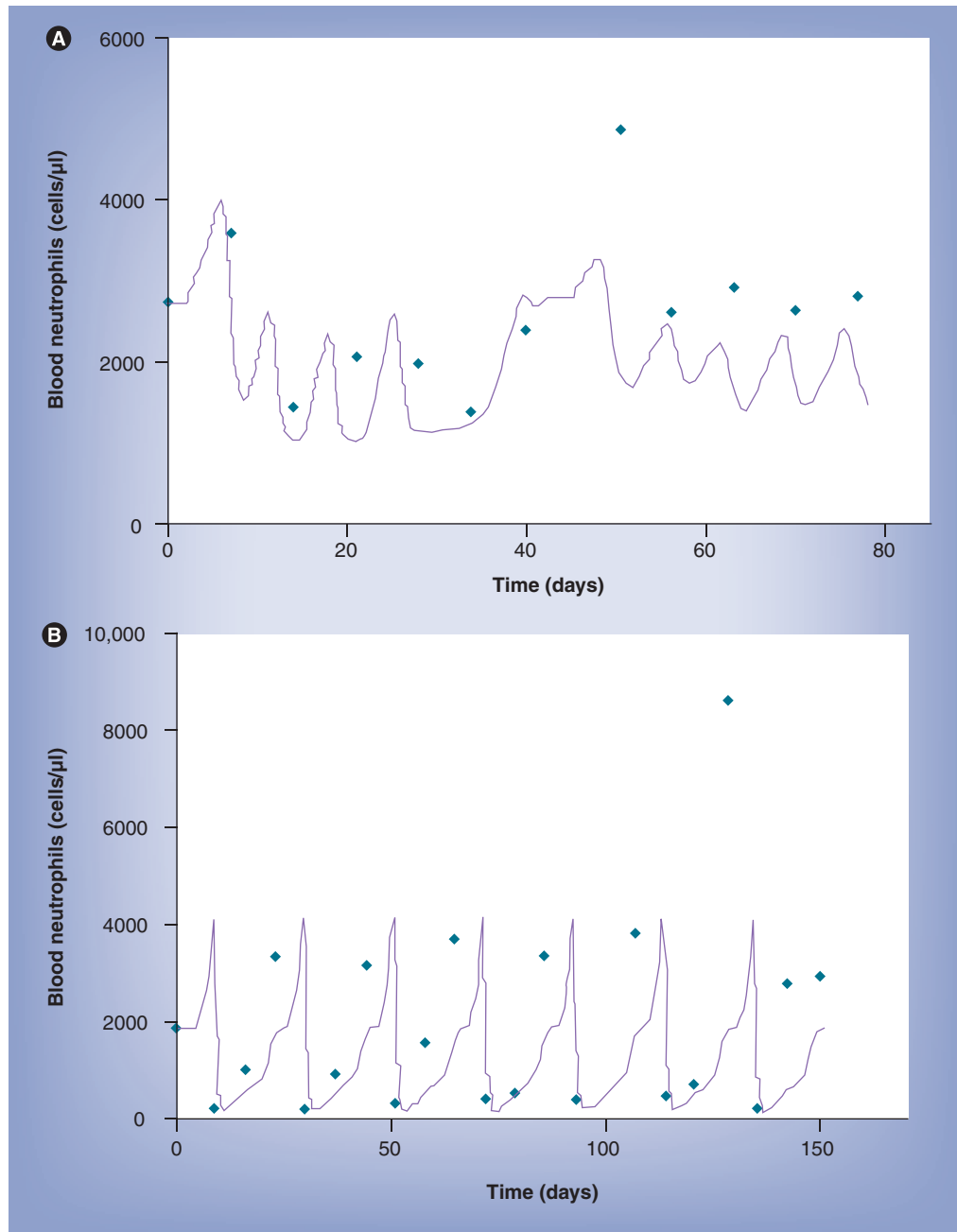
The method is schematically described in Figure 5. Essentially, it involves the construction of personalized disease progression and PK/PD models based on previously published literature and gene-expression analysis of both the patient and the xenografted patient's biopsies. In the first modeling stage, a mathematical model of the xenografted patient biopsies was created. Combined with the PK/PD models, it was tested under a large number of treatment options.

Model predictions were compared with the observed tumor growth inhibition of the xenografted patient's biopsies, which were treated with monotherapy or combination therapies of docetaxel, irinotecan, gemcitabine, doxorubicin,

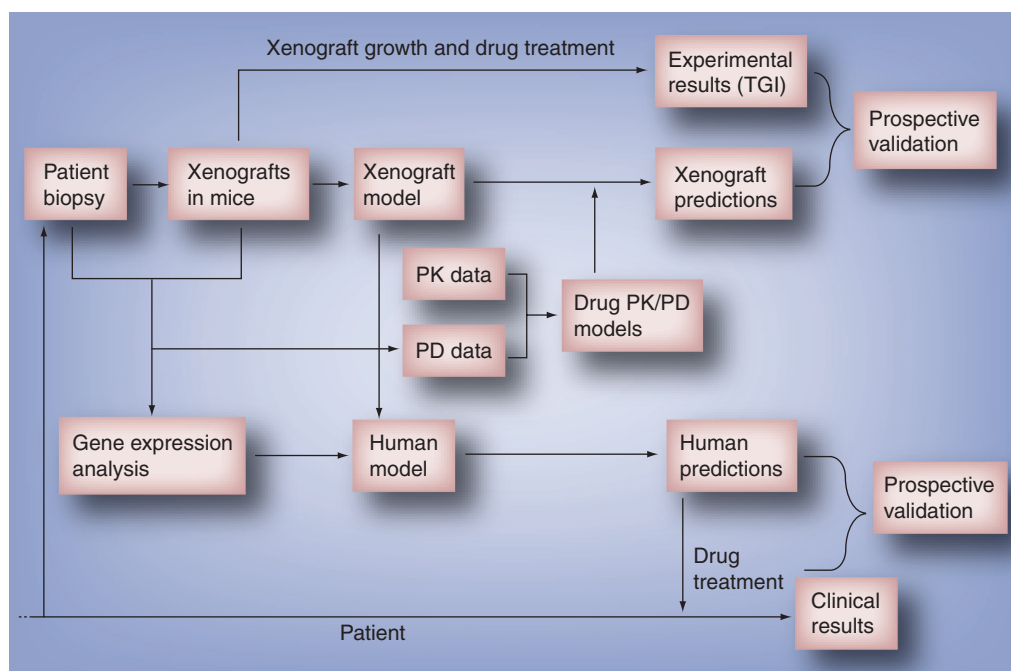
bevacizumab and sorafenib. Results demonstrated the high precision of the models predictions (87.1% accuracy) [28].

Using gene-expression analysis the xenograft model was then scaled up to represent the mesenchymal chondrosarcoma patient. The results of the patient-personalized model suggest that a regimen containing bevacizumab applied intravenously in combination with once-weekly docetaxel would be more efficacious than the

other modeled regimes. The proposed docetaxel regimen was applied to the patient, resulting in temporary tumor stabilization, substantial recovery of blood counts and, for almost 1 year, improved quality of life. The model further suggests that the advantage of weekly docetaxel in the tri-weekly regimen is directly related to the tumor's angiogenesis rate. Further validation of this conclusion may facilitate personalization of solid cancer pharmacotherapy [28].



**Figure 4. Validation of the granulopoiesis/docetaxel model in metastatic breast cancer patients.** Examples of model-predicted neutrophil counts over time (solid lines) compared with the observed neutrophil counts (diamonds) of two metastatic breast cancer patients treated with different docetaxel schedules: **(A)** 25–35 mg/m<sup>2</sup> once weekly, **(B)** 100–75 mg/m<sup>2</sup> tri-weekly. Data from [15].



**Figure 5. Workflow of the combined treatment personalization method.** Growth curves and gene-expression analysis of xenografts, derived from a patient's lung metastasis, served as the basis for creating a mathematical model of mesenchymal chondrosarcoma xenograft progression. The pharmacokinetics and pharmacodynamics of several chemotherapeutic and antiangiogenic drugs were modeled, the model parameters being adjusted by patient-specific chemosensitivity tests. The xenografted animals were treated with various monotherapy and combination schedules, and the mesenchymal chondrosarcoma-xenograft model was computer-simulated under the same treatment scenarios. Observed and predicted TGI results were compared (prospective validation). The mathematical model for xenograft growth was then scaled up to simulate the patient's tumor progression under different treatment schedules. Scaling up was carried out using gene-expression analysis of several key proteins, such as angiopoietin-1, -2, VEGF and others in the patient biopsied lung metastasis. Model predictions were compared with the clinical outcomes (prospective validation). See [17] for further details.

PD: Pharmacodynamics; PK: Pharmacokinetics; TGI: Tumor growth inhibition.

### Virtual clinical trials for streamlining drug development

Despite the growing investment by pharmaceutical companies in medical research, the number of new drugs brought into the market has dropped significantly. If the pharmaceutical industry is to remain at the forefront of medical research and continue helping patients, it must become more innovative in reducing the development time and costs of new therapies.

One strategy is to use 'virtual R&D,' that is, R&D aided by mathematical models of the human body, such as those described above. The use of populations of such 'virtual patients' can dramatically shorten the period of development of new drugs, and substantially reduce the chance of clinical failure, thus saving on the excessive cost of clinical development.

A virtual patient is a collection of mathematical models characterizing the patient's pathology and physiology, and a set of patient-specific

model parameters. When an individual patient has to be virtualized, as in the case described in the previous section, his/her parameters are evaluated using biopsies, blood counts and other tests. In drug development, virtual patients are used to identify potentially successful treatment regimens, which are then introduced. In such cases, a synthetic patient population is created, which is a collection of virtual patients, each characterized by a set of parameters drawn from the distributions of these parameters in the real patient population.

Once a synthetic population of virtual patients is established it can undergo clinical trials much in the same way as the drug treatments were tested in the virtual mesenchymal chondrosarcoma patient (see earlier). The main difference between the two cases lies in the end points of the trial (those employed in the pharmaceutical industry) such as progression-free survival (PFS), objective response rate (ORR) amongst others.



The virtual clinical trial method has been used by Kleiman *et al.* for checking how prematurely shelved, or discontinued, drugs can be rescued. In a theoretical case study of a discontinued drug, ISIS-5132, the virtual clinical trial has demonstrated that by combining ISIS-5132 with a licensed drug, sunitinib malate (Sutent®, Pfizer Inc., NY, USA), the treatment of prostate cancer can be improved,

with more patients reaching PFS at 5 years, as compared with either ISIS-5132 or sunitinib malate monotherapy [29].

### Future perspective

The virtual patient concept does not only apply to cytotoxic and cytostatic monotherapy or combination therapies, but also to immunotherapy, which offers great promise as a new

## Executive summary

### Bench-to-bedside gap in oncology

- Despite substantial achievements in cancer research the death toll owing to the disease is still increasing. This gap must be bridged by scientific methods that enable accurate prediction of drug–patient interactions.

### Drug–patient interactions can be predicted

- Drug–patient interactions can be predicted by incorporating biological, pharmacological and medical data within mathematical models of complex physiological and pathological processes.
- Physicians and drug developers still tend to mistrust the ability of biomathematics to aid their daily work, despite the success of concepts developed by simple mathematical models, such as ‘dose-dense therapy’.

### Mathematical models predicting efficacy & toxicity have been validated

- Validation of a mathematical model of vascular tumor growth under chemotherapeutic and antiangiogenic drug treatment has demonstrated high prediction accuracy, both in xenograft experiments (87.2%) and in metastatic breast cancer patients (85.7%).
- Validation of a mathematical granulopoiesis model demonstrates good precision in predicting which patients will develop grade III/IV neutropenia under docetaxel chemotherapy (86%), including prediction of the day and level of nadir ( $r = 0.99$ ). This model suggests safe chemotherapy and granulocyte colony stimulating factor (G-CSF) treatment schedules for individual patients.
- The metastatic breast cancer models suggest that the once-weekly docetaxel regimen is superior to other regimens, both in efficacy and in preventing neutropenic toxicity.

### The virtual patient concept

- Employing mathematical modeling and operation research, an optimization method has been developed for identifying patient-specific drug schedules that meet both efficacy and safety requirements.
- Equipped with this optimization method, the virtual patient concept has been developed, by which the mathematical models are adjusted to reflect individual patients, and an improved treatment is then tailored *a priori*.

### Treatment personalization in monotherapy & combination drug therapy & in immunotherapy

- This concept has been successfully employed in a treatment personalization case study of a metastatic chondrosarcoma patient. The model predicts tumor shrinkage of xenografted patient’s biopsies under a large array of combinations of antiangiogenic and chemotherapeutic drugs. Administration of the model-recommended treatment to the patient resulted in stable metastatic disease and relief of pancytopenia.
- Preclinically validated mathematical models for cytokine immunotherapy with IL-21 suggest improved regimens of this drug, and models of cellular immunotherapy of malignant glioma and prostate cancer show potential in personalized cellular immunotherapy and suggest a new concept of in-trial personalization.

### Virtual clinical trials

- Virtual clinical trials, including populations of virtual patients, have been simulated to test alternative treatment schedules, both for drugs in development and for discontinued drugs.
- Virtual clinical trials of a licensed drug, sunitinib malate, in combination with a discontinued drug, ISIS-5132, suggest a new combination treatment for prostate cancer, resulting in more patients reaching progression-free survival at 5 years, as compared with either sunitinib malate or ISIS-5132 monotherapy.

### Future perspective

- The virtual patient concept has already begun to be employed by oncologists for aiding their prognostic decision-making, and by drug developers conducting virtual clinical trials to focus their clinical studies on the most promising candidates, patient populations and treatment schedules.
- To increase the applicability and precision of treatment personalization methods, systems biology-processed information should be integrated with mathematical models of the complex biological and pathological processes involved. In this way diverse patient data, extracted from genetic, gene expression and other levels of biological organization, will be coherently embedded in terms of their effects on the clinical scenario.
- Patients’ survival, considered the most reliable cancer end point, cannot be mathematically modeled, owing to lack of knowledge about a definitive underlying survival mechanism. Deciphering the major determinants of survival will allow the development of mathematical models for predicting patients’ survival under specific drug regimens. This will aid focusing on drug regimens predicted to increase patients’ survival and thus contribute to improving the rate of drug approval by regulatory authorities.

dimension in cancer treatment. Mathematical models can aid in selecting the most appropriate patients and in optimizing immunotherapeutic regimens for individual patients. For example, preclinically validated mathematical models for cytokine immunotherapy with IL-21 suggest improved regimens of this drug, in particular, dose fractionation [30–32], and models for cellular immunotherapy of malignant glioma demonstrate the potential for personalized cellular immunotherapy and the power of mathematical models in tailoring individual immunotherapy schedules [33,34]. A model for prostate cancer cellular immunotherapy, validated by Phase IIa clinical trial results, suggests a new methodology for in-trial immunotherapy personalization [35].

Oncologists have already begun to employ virtual patients to aid their prognostic decision-making and drug developers already perform virtual clinical trials for focusing clinical studies on the most promising candidates, patient populations and treatment schedules. The transition to using virtual patients in the healthcare industry is imminent, but not easy. New approaches will have to be adopted, integrating deep medical understanding with tools for processing complex biological dynamics. We are entering the golden age of interdisciplinary science.

Major modelling challenges still remain. To increase the applicability and precision of the available treatment personalization methods, multilevel genetic network maps and experimental and clinical information should be integrated

with mathematical models of the complex biological and pathological processes involved in cancer growth and therapy. This integration is necessary for coherently embedding large amounts of diverse data, extracted from different levels of biological organization.

Patient survival is considered the most reliable cancer end point, and when studies can be conducted to adequately assess survival, it is usually the preferred end point. However, there are difficulties inherent in survival studies, such as long follow-up periods, or subsequent cancer therapies, potentially confounding the survival analysis. Survival is believed to be affected by immunological and neuroendocrine factors, or some health-related behavior. However, no knowledge exists about a definitive critical underlying survival mechanism. Such knowledge is indispensable for constructing a mathematical model to predict the relative contribution of specific drug regimens to patient survival. This will be instrumental in improving the drug approval rate.

# Financial & competing interests disclosure

The author has founded and has shares in Optimata Ltd (Ramat Gan, Israel), which has developed virtual patient models. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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