Using Predictive Mathematical Models to Optimise the Scheduling of Anti-Cancer Drugs

By David Orrell and Eric Fernandez at Physiomics

Altering an administration schedule can have a significant effect on drug efficacy, especially when drugs are used in combination. Computer models enable the simulation of thousands of possible schedules for combinations of different drugs – providing a rationale for designing an appropriate schedule, rather than relying on convention, a hunch or trial-and-error.

In recent decades, the explosion of available biological data, combined with a realisation that biological systems can only be understood at the system level rather than in terms of individual proteins or genes, has meant that mathematical models have become an indispensable part of the drug development process. Models are now used by drug developers in a number of different ways. Pharmacokinetic (PK) models simulate the uptake of the drug, and help determine optimal dosage levels. Network analysis is used to trace the complex interactions between proteins in biochemical pathways. Pharmacodynamic (PD) models based on differential equations simulate the various reactions inside the cell, and determine how the network might react to a particular drug therapy.

More complicated models are also being developed, such as large 'multi-scale' models, which are used to simulate how a tumour grows and responds to treatment. Apart from the effect of the drug on biological pathways within individual cells, these models must also take into account many other factors over different scales, such as the diffusion of the drug and nutrients into the tumour, angiogenesis, the necrotic death of cells at the tumour core, and so on.

The ultimate aim of systems biology models in drug development is to optimise drug treatment, improve the success rate of drug trials, and potentially reduce the need for animal experimentation. These goals require that models should be predictive as well as descriptive. However, while systems biology models have proved useful for understanding how drugs affect tumours – an important goal in itself – they suffer from two main problems when it comes to making quantifiable predictions (1).

One is that any mathematical model is only as good as the data on which it is based. Biological data tends to be very noisy and variable, and furthermore is only available for certain molecular species, such as those used as biomarkers, or measures such as tumour volume. This means that there is enormous uncertainty about not just model parameters, but the very structure of the model.

The second problem is that even incomplete models are still highly complicated, with a large number of unmeasurable parameters. Model parameters are therefore underdetermined – the models can be tuned to fit the available data, but are often not very reliable for making predictions. The same problem is found in other fields, such as economic forecasting, where simple models are usually better than complex models for

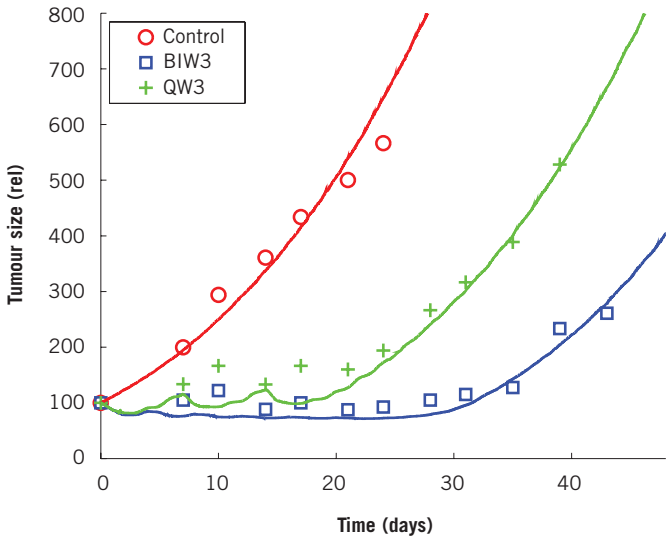

Figure 1: The effect of the aurora kinase inhibitor SNS-314 (shown by points) is accurately simulated in the virtual tumour (lines). Shown are a bi-weekly schedule (blue), a weekly schedule (green) and control (red)

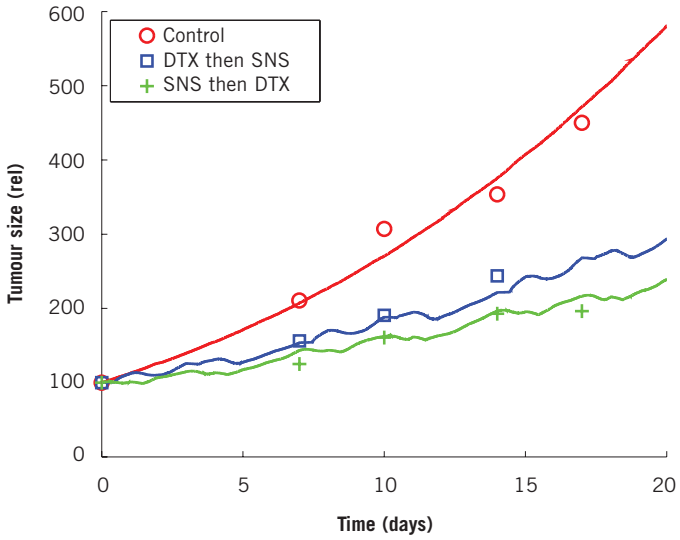

Figure 2: Changing the sequence of administration of two drugs in combination is predicted to have a dramatic effect on tumour growth. The sequential effect is reproduced in the virtual tumour (solid lines). Green and blue lines show the two cases, red line is control

making predictions. In order to address these issues, and deliver tangible benefits to the drug development process, Physiomics has adopted a two-track approach, which we believe combines the advantages of simple and complex models. The idea is to first construct complex descriptive models of networks, and then extract the relevant features of these models to construct simpler agent-based models of cell populations.

As an example of the first, descriptive modelling approach, we have built a detailed model of the cell cycle, including apoptosis. Because cancer cells are rapidly proliferating, anti-cancer drugs usually target proteins that are involved in the cell cycle or promote apoptosis, so this model can be used to visualise and explore the expected effect of the drug on cell growth, division and death.

Such models are in themselves very useful for drug developers: they can be used as a demonstration tool to argue why one drug may be more effective than another, or to determine whether a drug is likely or not to work as expected. However, they are not easy to calibrate against data because they simulate the internal dynamics of a range of proteins inside the cell, which are extremely difficult to measure. Detailed models of this type are therefore less useful for making quantitative predictions about, say, the effect of a drug on tumour growth.

For this type of question, our 'virtual tumour' model adopts an agent-based approach. Each cell in the tumour is described by a separate software agent, which uses a relatively simple set of equations. The aim is to capture the overall effect of the drug on a cell population, rather than the precise processes within each cell. A number of other simplifications are also made. For example, because the propagating cells are located in the periphery of the tumour, it is not necessary to model the central core in detail.

The complexity of the model is thus deliberately constrained so that it can be parameterised with the available data. This data includes PK data for the drug, biomarkers showing the cell population response, and xenograft growth measurements showing how tumour growth is affected. Although the code of each cell is relatively simple, the emergent behaviour of the cell population can be complicated and sometimes counter-intuitive.

SCHEDULES & COMBINATIONS

At Physiomics, one of our main interests is in determining optimal schedules and combinations. Empirical evidence shows that altering a schedule can have a significant effect on drug efficacy. This is especially the case when drugs are used in combination.

As an example, suppose that two drugs target cells are in different stages of the cell cycle. Then the effectiveness of the treatment can depend strongly on the order in which the drugs are taken. This has been demonstrated in numerous pre-clinical and some clinical studies. One Phase II trial compared two schedules involving the anti-cancer agents Cisplatin and Taxol. In the first schedule, Cisplatin was given

just after Taxol, with a 45 to 60 per cent overall response rate. In the second schedule, a 12-hour delay was introduced before administration of Cisplatin. This led to an 80 per cent overall response rate and lower toxicity (2).

The technique of dynamically modelling growing cell populations is ideally suited to the analysis of such timing-related effects. Indeed, a computational approach is necessary because when multiple drugs, doses and administration schedules are considered, the number of possibilities explodes, so it is impossible to test them all in the lab. With computer models, it is possible to perform thousands of simulations if necessary to find the best treatment regimen. These tools therefore provide a means of designing a suitable schedule, as opposed to the other options of relying on convention, a hunch or trial-and-error.

As an example of this approach, Figure 1 shows xenograft growth results for SNS-314 (Sunesis), an Aurora kinase inhibitor (3). A bi-weekly (BIW) schedule has a much greater effect on tumour volume than a weekly schedule (QW). The results of our simulations (solid lines) are in good agreement with the experimental data and capture the schedule dependence.

The importance of combination scheduling is illustrated by Figure 2, which shows a simulation of the combination between SNS-314 and Docetaxel (Taxotere, Sanofi-aventis). The results predict that just altering the timing between the administration of defined doses of the two drugs will have a significant effect on the synergy between the two compounds. This sequencing effect was again observed in animal studies.

As another example, a major pharmaceutical company recently provided us with data for two drugs (compounds are undisclosed for confidentiality reasons). The data consisted of xenograft growth and biomarker information for the drugs taken individually. We were asked to predict xenograft

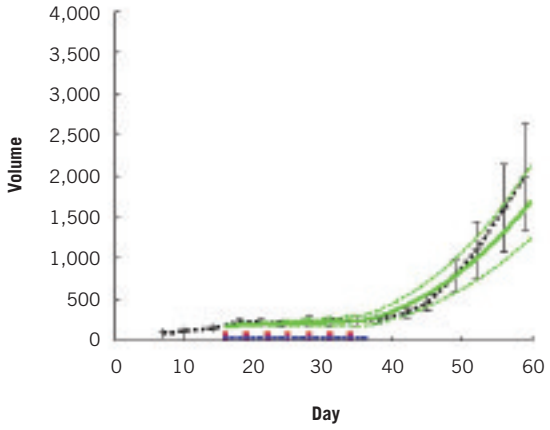

Figure 3: The green lines show our prediction, along with estimated upper and lower bounds. The black lines show the actual average xenograft growth, along with 5 and 95 percentile error bounds. Schedules for the two drugs are indicated in red and blue on the bottom axis

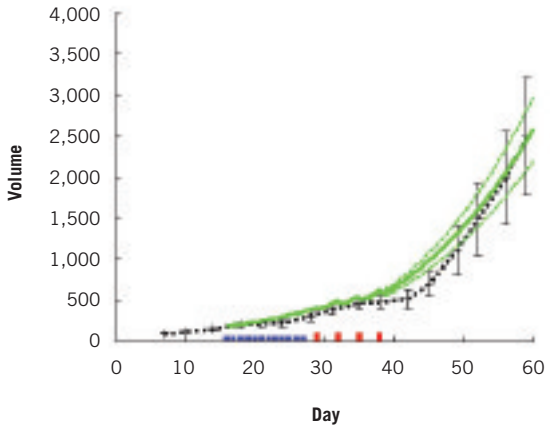

Figure 4: As for Figure 3, but the drugs are taken sequentially

growth when the two separate drugs were used in two different combinations. Our predictions were then compared against experimental data in a single-blind test.

Figures 3 and 4 show the results for the two different schedules. In Figure 3, the two drugs are administered in parallel, while in Figure 4 they are taken sequentially. The black lines show the average xenograft growth, while the green lines show our prediction, along with estimated upper and lower bounds. The predictions are in good agreement with the experimental data, and again accurately capture the schedule dependency.

As mentioned above, an advantage of the computational approach is that we can quickly simulate thousands of possible schedules for combinations of different drugs. This allows our partners to prioritise the most effective drug combinations and the best schedules for validation *in vivo*. Drugs we have worked with include cell-cycle inhibitors and apoptotic agents.

Another factor to be considered in scheduling is the time of day at which the drugs are taken, which turns out to have a major effect on both the efficacy and toxicity of a range of drugs, including anti-cancer agents. Chronotherapy studies have shown that tolerability can vary in mice and rats by as much as 10-fold for more than 35 anti-cancer drugs, including standard-of-care treatments like 5-FU and Docetaxel (4). Physiomics was a key member of the TEMPO project, funded by the European Union, in which we used our models to determine an optimal chronotherapeutic schedule for the drug Seliciclib (Cyclacel) (5).

To conclude, Physiomics has developed a set of system biology models to aid with the drug discovery process. The models combine disparate data, at the cell and tumour level, into a consistent picture, and leverage them to make testable predictions about tumour response. Mathematical models may never replace animal or human trials, but as in other branches of science they promise to make experiments far more efficient, effective and informative.

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