

Mathematical Modelling as a Tool for Prediction of Resistance to Targeted Chemotherapy

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Introduction

The development of targeted chemotherapy has been one of the major successes of a genetic approach to the study of cancer. Instead of broadly cytotoxic chemicals, targeting a particular feature associated with cancerous cells, such as a protein product unique to, or overrepresented in cancerous cells. In recent years, targets have included the hybrid Bcr-Abl kinase in Ph+ chronic myelogenous leukaemia (CML), as well as the HER2 receptor associated with a subset of breast cancers¹. Identifying a specific, actionable target found only in cancerous cells theoretically ensures efficacy and minimises cytotoxicity.

However, although such therapies allow for more specific targeting of cancer cells, problems can arise, particularly in the area of resistance². As is the case with antimicrobial resistance, the application of a targeted drug can result in positive selection for tumour cells that lack the drug target, due to underlying heterogeneity in the cell population. This can then lead to resistance, via a variety of mechanisms, as detailed in Figure 1.

Currently, the clinical best practice for managing such cases involves modification of the targeted drug, resulting in the creation of second, and third-generation medicines. However, this simply treats mutation as it arises, and may eventually reach its limit, as is currently observed with antimicrobial resistance. There is therefore a growing interest in the use of mathematical techniques to predict the behaviour of cancers in response to this targeted treatment. The extent to which this evolutionary process is mathematically predictable has consequences for treatment strategies. This poster will detail some of the mathematical approaches to this problem and evaluate their respective strengths and flaws.

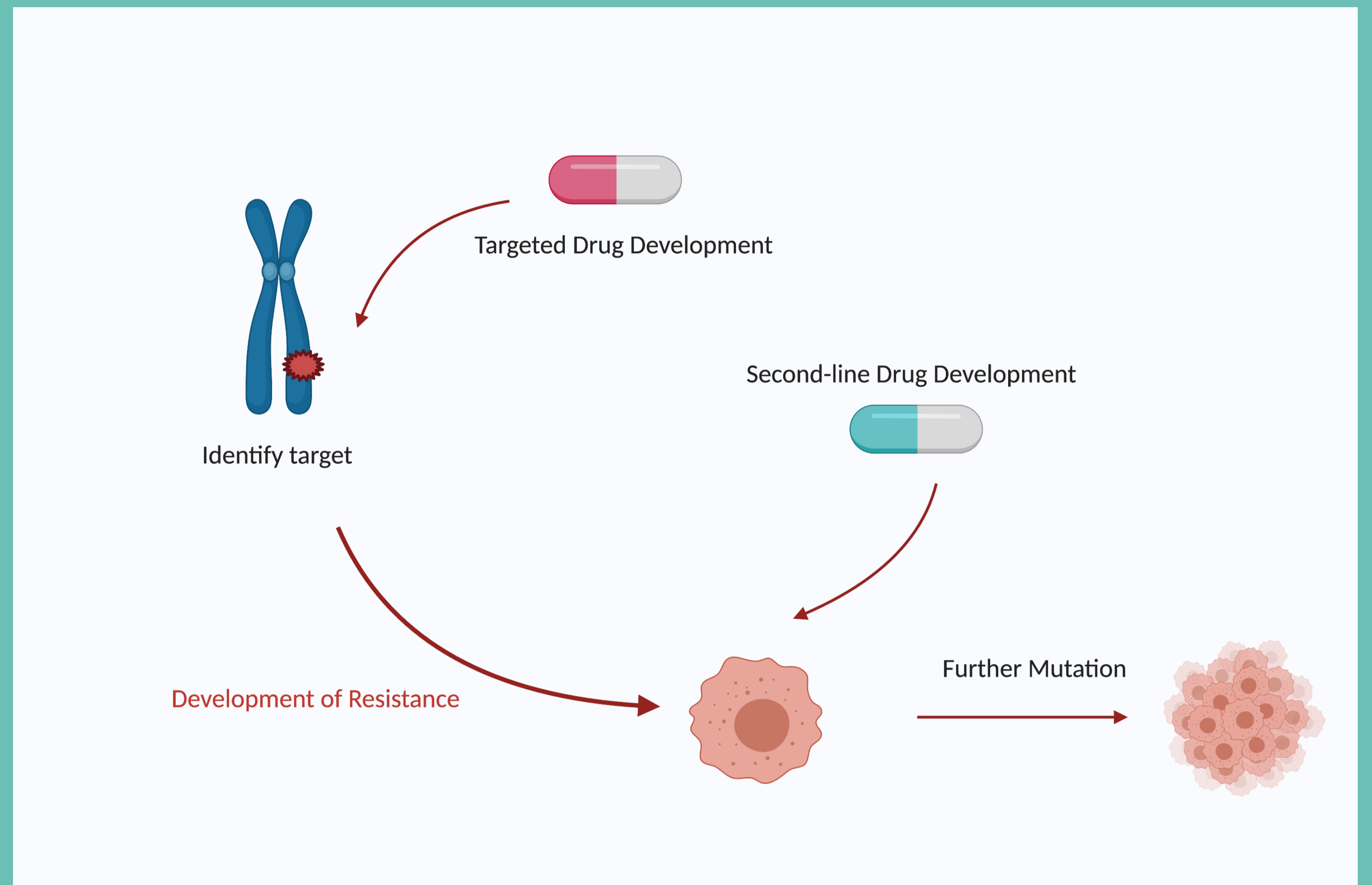


Figure 1: The Success and Challenges of a Targeted Approach to Chemotherapy

Illustration of the process of targeted drug development for cancer treatment. First, a target must be identified that is common to cancerous cells, but not found in healthy cells. This may be identified via a variety of methods, with some older targets being observed cytologically. A first-generation drug is then developed to act at this target, however in some cases, resistance may occur within a subpopulation of cells, which can then proliferate as before. This can occur via mutation resulting in incompatibility between the drug and its target site, or through circumvention of the target through the use of an alternative pathway, with the mechanism employed influencing the development of second and third-line drugs. If a target site mutation is used, the drug may be slightly modified, to some use. However, further mutation and eventual recurrence still occurs in a subset of patients.

Approaches to Mathematical Modelling of Tumour Evolution

A variety of mathematical approaches may be used to understand tumour evolution, with some particularly appropriate to the question of resistance. Models vary in their complexity and scope- assumptions must be made in every model, and no single model can accurately capture all of the detail involved in a complex process such as tumour evolution. Instead, models focusing on specific subsections of the process can provide useful insights, as described in Figure 2.

Systems of ordinary differential equations (ODEs) are commonly used in modelling, however, their deterministic approach results in simplification of complex biological approaches. Stochastic approaches, which account for inherent randomness in the resistance process, may also be used, as discussed in Figure 2. Although stochasticity is an integral aspect of biological systems, in certain cases, deterministic approaches, which are simpler, achieve sufficient detail so as to be of use. In the equations given below⁴, although certain processes, such as cell dissemination and dissemination (dW_1 and dN_1), were modelled stochastically, other processes, such as cell growth (k_g), were approximated using constants, illustrating the role of determinism in simplifying models.

$$dS = k_g \cdot S \cdot \left(1 - \frac{(S+R)}{T_{max}}\right) \cdot dt - u \cdot S \cdot dt - k'_d \cdot S \cdot dt + \sigma_1 \cdot S \cdot dW_1 - q_M \cdot K \cdot S \cdot dN_1$$

$$k'_d = k_d \cdot \frac{C_D}{K_D + C_D}$$

stochastic
stochastic

Where u = mutation probability in one cell division; S = sensitive cells, R = resistant cells, k_g = growth rate constant; k_d = shrinkage rate constant as a result of drug treatment; C_D = drug concentration; K_D = drug concentration that produces 50% of maximum treatment effect; dW_1 = stochastic cell diffusion in a small time interval (Wiener process); dN_1 = stochastic dissemination in a small time interval (Poisson process); σ_1 = diffusion rate; q_M = dissemination rate; K = angiogenesis

Aside from analysing the robustness of a model via techniques such as sensitivity analysis, the results may be assessed by comparison with experimental data.⁵ In this way, even a model that makes assumptions or simplifications about a complex process can be of utility in predicting resistance trends.

Modeling approaches	Resistance mechanisms	Simulation tools	Characteristics
MD simulation	Genetic mechanism	MD simulations	They provide information on the dynamic changes of the drug and conformational changes of the target.
Kinetic models of signaling network	Posttranslational mechanisms	ODEs	They simulate the dynamic changes of the signaling network during drug treatment based on the law of mass action or Michaelis-Menten kinetics.
ODE models of cellular population dynamics	Cellular mechanisms, Microenvironmental mechanisms	ODEs	The growth dynamics of the heterogeneous cellular populations, along with the effects of chemotherapy, are modeled using a system of ODEs.
Stochastic models	Genetic mechanisms, Epigenetic mechanisms, Cellular mechanisms	Stochastic process, SDEs	The stochastic evolution and probability of resistance can be obtained.

Figure 2: Comparison of Mathematical Predictions of Resistance³

A variety of different mathematical models can be used to describe different aspects of the cancer evolution process. This figure illustrates the methods most relevant to this project, as well as some others, for comparison. The use of ODEs to model dynamics at a cellular population level, as well as stochastic approaches to understand the probability of resistance evolving, give a combined picture of various parts of the evolutionary process.

Figure adapted from Sun, X. and B. Hu (2017)

Summary

Modelling the emergence and spread of resistance in cancer cell populations, as well as its implications for clinicians, is complex. A variety of mathematical approaches may be used, each with its own strengths in a particular context. However, though many current models are not yet ready for translation to the clinic, they serve as an indicator of the relevance of such an approach. Biological systems are inherently complex and noisy, and so no model can be said to fully represent even a specific process such as resistance to a given drug. However, it is clear that such a systems approach to cancer therapy has conceptual benefit, which will continue to be realized through increased understanding of the underlying cell biology, as well as through newer modelling techniques.

Acknowledgements

I thank the Laidlaw Undergraduate Research and Leadership Programme for the funding and support necessary to complete the work and my supervisor Adrian Bracken for his guidance.

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