

# Modelling DNA Damage-Induced Apoptosis

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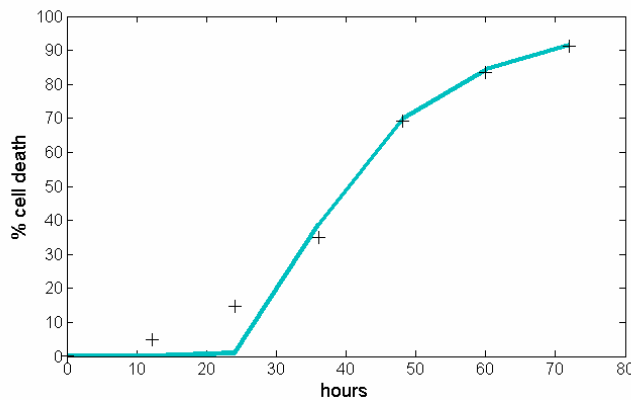
## Introduction

Cancer develops from an initial oncogenic transformation event that creates an imbalance between cell proliferation and cell death. This results in an inappropriate proliferation of cells and the development of a tumour. Various therapeutic strategies are designed to address this balance by intervening at distinct points in the cell cycle, cell death or associated regulatory (growth factor and survival) pathways. Physiomics is developing detailed bottom-up mathematical models of these processes in order to aid mechanistic understanding and assist in the identification and validation of novel therapeutic targets. Here we present some results obtained with our model of the intrinsic pathways of apoptosis, activated by DNA damage. This new model builds on our existing model portfolio that was previously heavily focussed on the cell cycle [1], and has been created through collaboration with ValiRx plc to aid in their research and development of novel therapeutics.

## Cisplatin-Induced Apoptosis of Prostate Cancer LNCaP Cells

We generated a model of the intrinsic pathways of apoptosis from careful evaluation of the available scientific literature. The model includes over 120 reactions and 200 parameters. Once apoptosis is initiated, the response is rapid, occurring within minutes. However, within a population of cells, considerable variation occurs between the time of stimulus and the time of onset of apoptosis. Our completed model therefore contains ordinary differential equations that reflect the average behaviour of a population of cells.

In order to broadly calibrate the input-output characteristics of our model of drug-induced apoptosis, we fitted the model to the published concentration and time-dependence of cisplatin-induced LNCaP cell apoptosis. We simulated caspase 3 activation and related this to cell apoptosis as these two events have been shown to be temporally separated by only a few minutes compared with the time-course for apoptosis of tens of hours [2]. Figure 1 shows the results of our model simulations overlaid with published experimental observations [3]. The results show that within tolerable variances, our model closely follows the experimental observations.



**Figure 1: Time course for cisplatin-induced LNCaP cell apoptosis.** LNCaP cell death was simulated for the experimental conditions reported in Figure 1C in [3]. Simulated results are shown by the solid line whereas published data points are shown by the crosses.

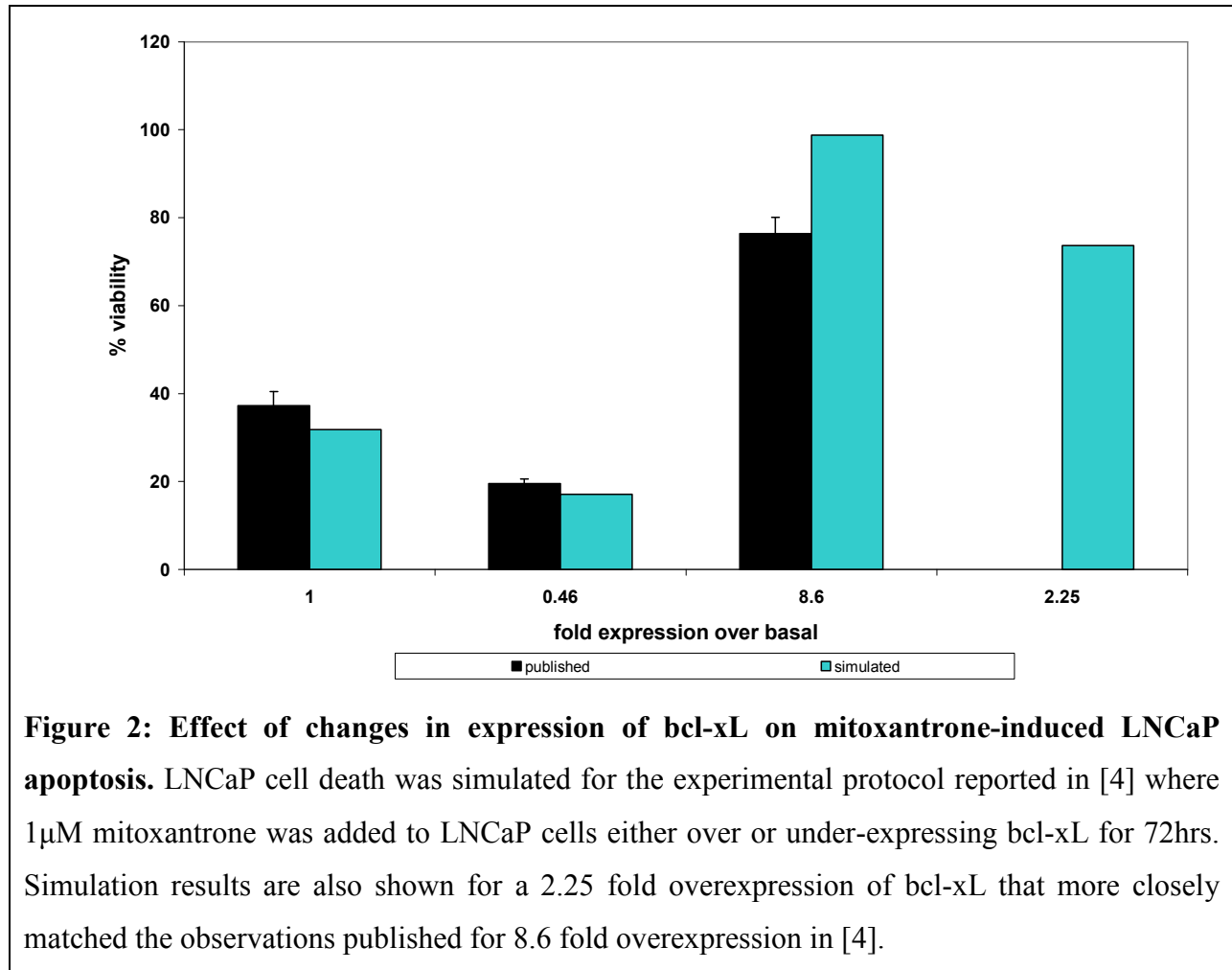
### **The Effect of Changes in Expression of bcl-xL on Mitoxantrone-Induced LNCaP Apoptosis**

Having calibrated the input-output characteristics of our model, we compared our model with experiments that altered the expression level of bcl-xL, a key component of DNA damage-induced apoptosis. Our model required only a little refinement to closely match the published observations for bcl-xL underexpression [4], the results of which are shown in figure 2.

[2] Tyas *et al.*, EMBO Reports (2000) 1(3):266-270

[3] Nomura *et al.*, Urologic Oncology (2004) 22:453-460

[4] Lebedeva I *et al.*, Cancer Res (2000) 60:6052-6060



**Figure 2: Effect of changes in expression of bcl-xL on mitoxantrone-induced LNCaP apoptosis.** LNCaP cell death was simulated for the experimental protocol reported in [4] where 1 $\mu$ M mitoxantrone was added to LNCaP cells either over or under-expressing bcl-xL for 72hrs. Simulation results are also shown for a 2.25 fold overexpression of bcl-xL that more closely matched the observations published for 8.6 fold overexpression in [4].

Our simulation results showed that 8.6-fold overexpression as reported in [4] should have a larger effect on cell viability than was observed. However, simulations with 2.25 fold overexpression or with bcl-xL under-expression matched the observations. It is possible, therefore, that not all over-expressed protein is functional in the experiments where bcl-xL is overexpressed so heavily.

Overall, the results presented here indicate that our model closely parallels published observations for drug-induced LNCaP cell apoptosis. Moreover, they suggest that our model is capable of providing a mechanistic insight into the results of experimental observations and may be used to identify and validate novel therapeutic targets.

[4] Lebedeva I *et al.*, Cancer Res (2000) 60:6052-6060