Dynamical effects of epigenetic silencing of 14-3-3σ expression

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Supplementary Material

A1. Comparison between data used for parameter estimation and model predictions

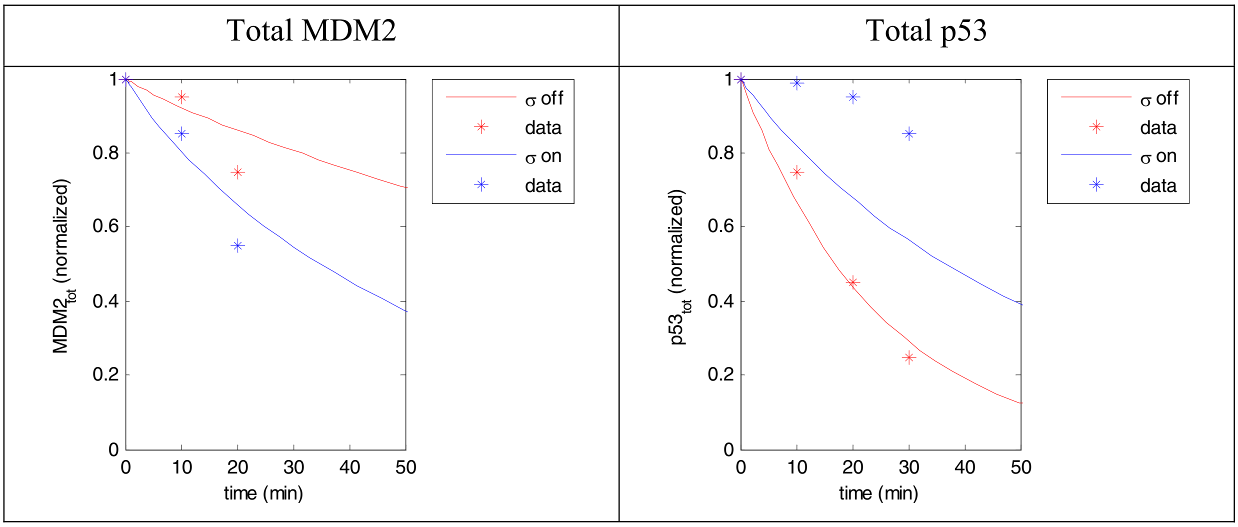

Fig. A1. Comparison between data accounting for half-life of MDM2 and p53 (Yang *et al*. 2003) and the model predictions for experimental conditions where 14-3-3σ is expressed (blue) and not expressed (red). The data correspond to total amounts of protein, that is, the sum of the cytosolic and nuclear fraction.

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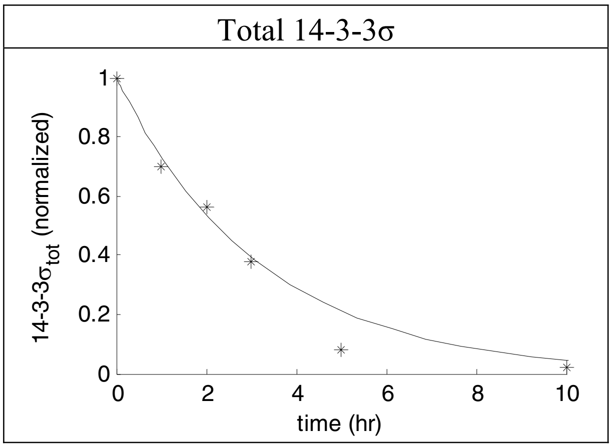


Fig. A2. Comparison between data accounting for half-life of 14-3-3σ (Urano *et al.* 2002) and the model predictions for experimental conditions where proteins involved in 14-3-3σ degradation are normally expressed. The data correspond to total amount of protein, that is, the sum of the cytosolic and nuclear fraction.

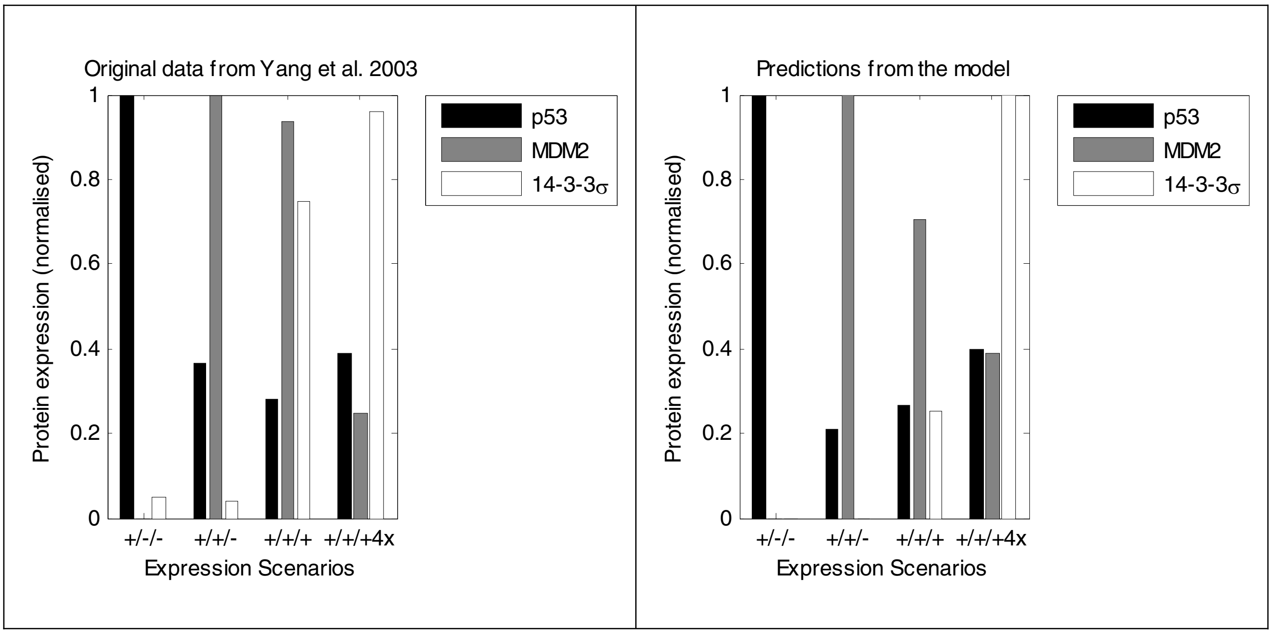


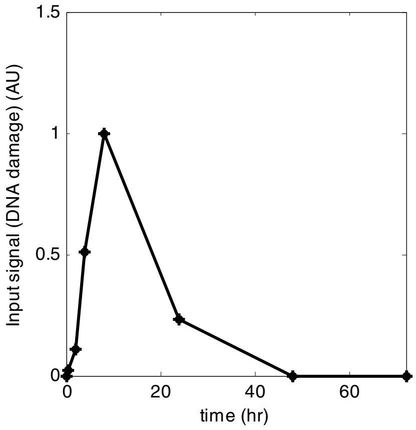
Fig. A3. Comparison between data accounting for dynamics of the system under different conditions of expression for the three proteins (Yang *et al.* 2003) and the model predictions. In both figures, black bar corresponds to total p53 expression level, gray bar represents MDM2 expression and white bar is for 14-3-3σ. Data from four scenarios are shown: 1) only p53 is expressed, +/-/-; 2) p53 and MDM2 expressed, +/+/-; 3) the three proteins expressed, +/+/+; and 4) the three proteins expressed with overexpression for 14-3-3σ, +/+/+4x.

A2. Model parameters

Table1. Model parameter values

Parameter	*Value*	*Parameter*	*Value*
γ_1	7.2411	γ_2	2
τ	0	γ_0	25
k_{0po53}	0.0083	k_{dp53c}	0.0333
k_{ip53}	0.0897	k_{ep53}	0.0247
k_{dp53n}	0.0535	k_{0m2}	0.0094
k_{dm2c}	0.0527	k_{im2}	0.0910
k_{em2}	0.0195	k_{dm2n}	0.0548
k_{0sg}	0.0013	k_{dsgc}	0.0069
k_{isg}	0.2336	k_{esg}	0.7008
g_{met}	2	g_{ind}	1
g_{am2}	1	g_{a53}	1

A3. Effect of time delay in the dynamics of the system



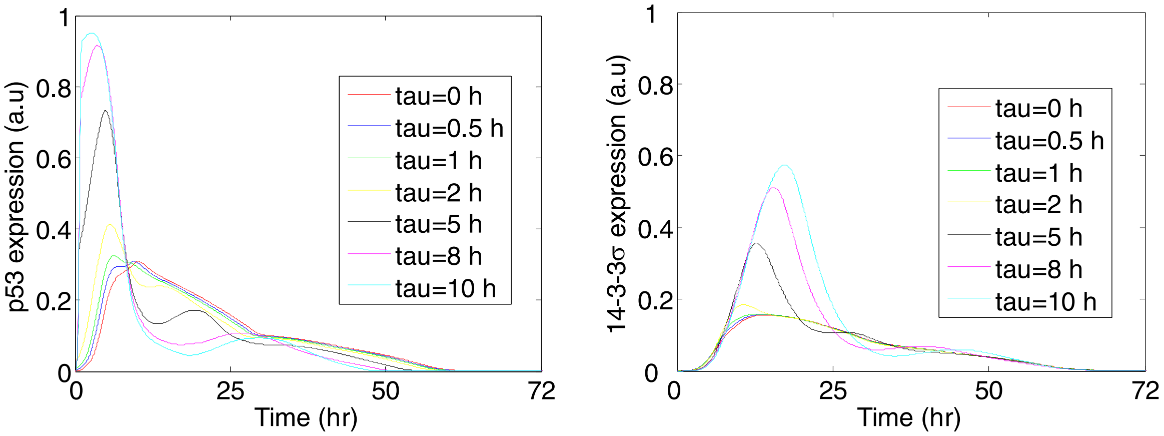


Figure A3.1 Simulation of the dynamics for total p53 and 14-3-3σ with a stimulation similar to the one in Figure 2 when different values of time-delay are considered in the p53-mediated protein expression. Simulations were performed using the Matlab solver for delayed differential equations '*dde23*'. The figure suggests that for small physiologically feasible time-delay in the p53-mediated protein expression (smaller than 2 hours) the dynamics of the system is not affected when time-delay is considered. Longer (unfeasible) time-delay provokes changes in the intensity of the signal peak in both proteins. Further analysis indicates that the model does not show sustained oscillations for a wide interval of values in the system input signal and the level of *14-3-3σ* gene methylation in the original parameterisation of the model (data not shown).

A4. Methylation status of 14-3-3σ in the different cell lines used

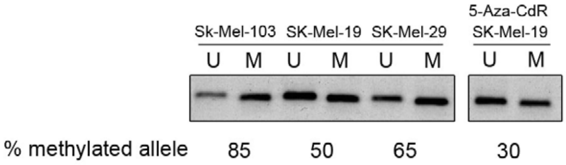


Figure A4.1. The methylation status of 14-3-3σ in the different cell lines used in our work was tested by methylation-specific PCR (U, unmethylated allele; M, methylated allele).