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# Towards a quantitative understanding of the DNA damage response through data-driven dynamical modeling

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Among the most important proteins regulating homeostasis is the transcription factor p53, primarily known for its function to maintain genomic stability, regulate transient and permanent cell cycle arrest and apoptosis. Activated p53 transcriptionally regulates the expression of many proteins, among which are MDM2, p21 and BTG2. MDM2 functions as a direct inhibitor of p53 by targeting it for ubiquitination, whereas the proteins p21 and BTG2 are known for their regulatory function in cell cycle arrest. Although the general wiring of the molecular interactions in the DNA damage response (DDR) is well known, this is not the case for its detailed quantitative dynamics. An aspect that is not fully understood includes the relative importance of p21 and BTG2 in determining cell cycle arrest. Moreover, it is unclear whether DDR dynamics differs between cell lines compared to primary cells, which may affect cancer susceptibility.

Therefore, we developed a computational dynamical model that describes the dynamics of DDR regulator p53 and targets MDM2, p21 and BTG2, and applied it to time-lapse imaging data of HepG2 reporter cells of these components. With this model, we first generated simulations of virtual primary human hepatocytes (PHHs) and compared the results to transcriptomics data for PHH donor samples. Our analysis showed that model-based extrapolation from HepG2 to PHH can be done for some DDR elements, yet our analysis also reveals that such extrapolation is inaccurate for the regulator MDM2. Second, we studied the quantitative relation between protein expression and cell cycle arrest, by extending our DDR computational model with the cell cycle. We calibrated model parameters to cell cycle data acquired with HepG2-FUCCI reporter cells, thus determining the importance of p21 and BTG2 in their stimulation of G1 and G2 cell cycle arrest. The protein dynamics could predict the G2 cell cycle arrest in HepG2 cells treated with cisplatin.

In conclusion, our work illustrates the relevance of studying pathway dynamics in addition to gene expression comparisons, which allows a quantitative understanding of pathway dynamics, and supports translation of cellular responses from cell lines to primary cells.

**Keywords:**
DNA damage response; cell cycle; computational modelling; HepG2 cells; primary human hepatocytes.