# Dynamical modelling of DNA damage-dependent NF-kB activation

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Environmental factors as well as intracellular processes continuously damage DNA. The degree of DNA damage determines cell fate, DNA repair and survival or in case of irreparable damage senescence or apoptosis to prevent malignant transformation. Since chemotherapy also causes DNA damage, understanding the decision making process is not only important in terms of tumor formation but also in terms of treatment and occurrence of resistant tumor cells. The decision whether damaged DNA is repaired or cell death is induced is thought to be determined by a complex regulatory network that controls the activity of the oncogene NF-κB and the tumor suppressor p53. In order to analyse the complex regulatory network we aim to develop a dynamical mathematical model that predicts cell fate decisions based on the activation status of NF-κB and p53.

As a first step, we defined sub-modules of the overall signaling cascade. We developed differential equation models for the modules describing the recognition of DNA double strand breaks (DSBs) by the sensor proteins PARP-1 and MRN, the subsequent posttranslational modification of the IKK subunit IKKγ in the nucleus as well as the formation of a high molecular cytosolic complex which is required for an additional modification of IKKγ. The subsequent activation of the IKK complex results in NF-κB activation. After combining all individual models, we performed a sensitivity analysis on all parameters of the overall model. The results of this analysis revealed that the strength of γ-irradiation, which is used to generate DSBs, can have an impact on parameter sensitivity. Therefore, in case of tumor therapy, the efficiency of applied inhibitors targeting components of this pathway, could be affected by the irradiation strength.