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MODELING OF DNA DAMAGE IN G2/M REGULATORY NETWORK WITH ROBUSTNESS STUDY

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ABSTRACT

A mathematical modeling of regulatory network for G2/M phase transition influenced by different intensities of DNA damage is performed. The modeling framework contains the sub-modules of p53-Mdm2 feedback loop and G2/M phase transition process. To investigate the robustness of the regulatory network, a sensitivity analysis of kinetic parameters in the modeling framework is implemented so as to select the most significant kinetic parameters, which are relevant to key proteins involved in the G2/M phase transition. Kinetic parameters related to preMPF, MPF, Cdc25, aCdc25, iCdc25Ps216/14-3-3, iCdc25, Wee1, Wee1P, p53 and Mdm2 that play significant roles in affecting peak time of MPF. Those parameters are identified to be the most sensitivity kinetic parameters in the G2/M regulatory network from our simulated results. Moreover, the statistical hypothesis testing is employed to evaluate the influence of perturbations on the G2/M regulatory network. The results indicate that G2/M regulatory network is robust to DNA damage signal when perturbations are very small. The robustness of the G2/M network decreases as the DNA damage signal increases, which is in consistent with the experimental observations [1, 2]. The work of investigating sensitivity parameters and their effects under different DNA damage conditions may help us with better understanding of the robustness of G2/M regulatory network in the cell cycle.

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