

Systems Biology Study of Base Excision Repair Pathway to Improve Therapeutic Gain in Cancer Treatment

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The effectiveness of chemotherapy is related to the DNA damage created by the chemotherapeutic agents. DNA repair pathways repair this damage causing resistance to chemotherapy. Inhibition of DNA repair pathways has been shown to increase the efficacy of DNA damaging agents. Base excision repair (BER) is one of the DNA repair pathways that can reduce the cytotoxicity of alkylating agents. BER is a multiprotein process initiated by a damage specific glycosylase that recognizes and removes damaged or incorrect base pairs. Inhibition of the BER results in increased sensitivity to alkylating agents making it an attractive target for anti-cancer therapy, especially for cancer cells that are resistant to these agents (1).

The efficiency of this inhibition plays an important role in improving the therapeutic efficacy of anticancer agents. The inhibition efficiency is studied computationally in this work. A computational model for the BER from (2) is modified to include inhibition. A system of ordinary differential equations is used to model the enzyme dynamics in BER using Michaelis-Menten kinetics. This model is modified to include MX dynamics using the mass action principle. The kinetic parameters for MX are estimated from experimental data available in the literature (3).

In order to capture the biological variability among individuals for the efficiency of BER, Monte Carlo simulations are conducted using different enzyme concentrations at each iteration. The enzyme concentrations are assumed to have a uniform distribution between 10% and 1000% of the nominal concentration. The initial condition is the amount of initial damage, and the output is the concentration of repaired DNA. The outputs from the Monte Carlo simulations are clustered into three groups: Outputs from a highly efficient BER, medium efficient BER, and inefficient BER. Using the clustered outputs, a decision tree is developed following an approach similar to (4). The decision tree shows possible enzyme concentrations that can be used to classify the efficiency of the BER process for a given individual.

The effectiveness of inhibition depends on the efficiency of the BER. Representative outputs (centroids obtained from the clustering) are used to study the effectiveness of inhibition on high, medium or low efficiency BER. The modified model with MX dynamics is studied through simulation using parameter sets for enzymes that result in high, medium or low efficiency BER. The simulation results have shown that inhibition by the same amount of MX is most effective on the low efficiency BER, and least effective on medium efficiency BER. For a MX concentration of 500 μ M, the steady-state inhibition is 23.5% for highly efficient BER, 21.2% for medium efficient case, and 36% for inefficient BER. For 50 μ M, the inhibition is 3.2%, 2.8%, 5.8% for high, medium and low efficiency cases respectively. Sample outputs of the BER and the inhibited BER are shown in Figure 1.

The computational analysis described here will be validated experimentally. Once validated, it can be used to determine the MX dose that is necessary to obtain the required inhibition effect depending on the BER efficiency profile of the patient.

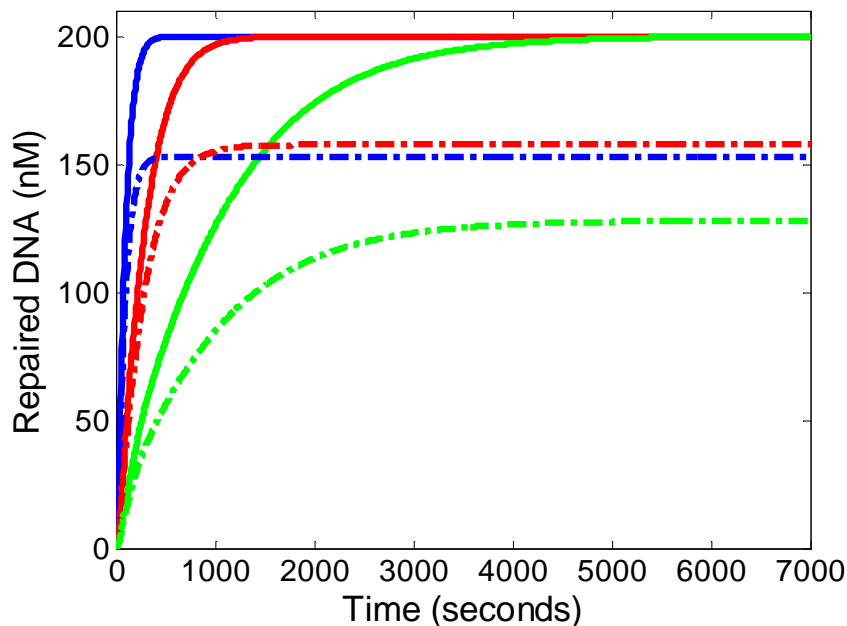


Figure 1: Model outputs for the BER process (solid lines; centroids obtained from clustering) for highly efficient BER (blue line), medium efficient BER (red line), and low efficient BER (green line) compared to the outputs of the MX inhibited BER process of high, medium and low (blue, red and green dotted lines) efficiency.

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