

Genotoxicity testing in-silico: quantification of the DNA mutation caused by the glycosidic bond hydrolysis

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The goal of the current work is to estimate the missense mutation rates caused by the hydrolysis of the glycosidic bonds between the bases and the DNA backbone. These mutations naturally occur inside the living cells but give origin to innumerable genetic problems, for example, different types of cancers. Computer simulation of the DNA replication and polymerization is used as a tool to measure the rates of this class of mutations. The simulation is built upon the hybrid model of the DNA replication fork that includes polymerases representation and Okazaki segments. Agent based model combined with the Markov chain representation of the polymerase operation represents the essential elements of the biochemical reactions of this process. The DNA polymerization is a stochastic process defined by the Markov chain, while 2nd order chemical kinetics of the glycosidic bonds hydrolysis is represented as stochastic interactions between the agents performing random walk (Brownian motion) in the two-dimensional representation of the chromosomal environment. The estimates of the mutation rates and the investigation of the genotoxicity of water demonstrate the application of this computational system. The influence of water concentration on the missense mutation rate is illustrated for a number of model parameters. The technique presented can be extended at almost no cost to a large class of small molecule genotoxicity testing. Also, the potential application of this tool and method to wider industrial usage is discussed within the context of the mandatory testing of the new chemical and pharmaceutical products for both human consumption and environmental impact.