Two models of DNA damage repair

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***Short Abstract* — This work presents a modification of an existent model of DNA damage repair under in-vivo conditions. The modified model contains terms that are responsible for DNA damage after irradiation stop. With this modification the model of repair DNA is able to better fit to the experimental data in comparison to the existent model.**

***Keywords* — ordinary differential equations, DNA damage repair, mathematical modeling**

I. The Initial Model

The initial model of DNA single and double strand breaks repair in circular minichromosome under in-vivo conditions is a system of four ordinary differential equations [1]:

$$\begin{cases} \frac{dS}{dt} = Ks \cdot CssB + INH \cdot Kd \cdot L \\ \frac{dCssB}{dt} = INH \cdot Kds \cdot LssB - Ks \cdot CssB \\ \frac{dLssB}{dt} = -INH \cdot Kds \cdot LssB - Ksd \cdot LssB \\ \frac{dL}{dt} = Ksd \cdot LssB - INH \cdot Kd \cdot L \end{cases}$$

Variables *S*, *CssB*, *LssB*, *L* are concentrations of particular DNA forms: supercoiled, linear, linear with single strand breaks and circular with single strand breaks, respectively. Parameters *Ks*, *Kd*, *Ksd*, *Kds* mean kinetic constants for particular repair pathways and *INH* is logic variable that takes 1 or 0 values depending on conditions (with or without inhibition of double strand break repair).

In order to estimate parameters of the model a data obtained from experiments done at Laval University is used. In this experiments the repair of irradiated viral DNA present in the Raji cells was examined. The data contains measurements done through time for the supercoiled form (which means the repaired DNA - variable *S* in the model), and the total linear form (*L*+*LssB* in the model) under two conditions:

- normal (variable *INH* take 1),
- when arrested double strand breaks repair (variable *INH* take 0).

Detailed information about the experiment and the data are presented in work [1].

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Parameters of the model were estimated (optimized in least square sense) based on the experimental data. The obtained fit was satisfactory and good enough for example to gain the information about unmeasurable variables. However, there was visible discrepancy between the data and the model at the initial part of the simulation.

II. The Modified Model

We obtained better fit of the model by adding some new terms to the initial model that are responsible to the DNA damage after irradiation stop (in the early stage of the repair). This effect may be caused by radiation excited molecules or by the DNA repair system that cuts the DNA in the initial phase of the repair. The modified model contains system of five ordinary differential equations:

$$\begin{cases} \frac{dS}{dt} = Ks \cdot CssB + INH \cdot Kd \cdot L - Ox \cdot S \\ \frac{dCssB}{dt} = INH \cdot Kds \cdot LssB - Ks \cdot CssB + Ox \cdot S - Ox \cdot CssB \\ \frac{dLssB}{dt} = -INH \cdot Kds \cdot LssB - Ksd \cdot LssB + Ox \cdot CssB \\ \frac{dL}{dt} = Ksd \cdot LssB - INH \cdot Kd \cdot L \\ \frac{dOx}{dt} = -Kox \cdot Ox \end{cases}$$

The last equation in the system explains the decreasing through time effect of "secondary" DNA damages. The constant parameter *Kox* tells us how quickly the effect is decreasing.

The numerical parameter estimation of this model is done by using the adjoint sensitivity analysis [2] and MATLAB environment.

III. Conclusion

The better fit of the modified model indicates that there exist in cells some factors that cause DNA damages after stopping the irradiation.

Additionally, the values of estimated parameters in the modified model indicate the likely repair pathways of DNA damages (first repair double strand breaks then repair single strand breaks).

References

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