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## Influence of oxygen on the chemical stage of radiobiological mechanism

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## HIGHLIGHTS

- Creation of the mathematical model.
- Realization of the model with the help of Continuous Petri nets.
- Obtain the time dependence of changes in the concentration of radicals.
- Influence of oxygen on the chemical stage of radiobiological mechanism.

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## ABSTRACT

The simulation of the chemical stage of radiobiological mechanism may be very helpful in studying the radiobiological effect of ionizing radiation when the water radical clusters formed by the densely ionizing ends of primary or secondary charged particle may form DSBs damaging DNA molecules in living cells. It is possible to study not only the efficiency of individual radicals but also the influence of other species or radiomodifiers (mainly oxygen) being present in water medium during irradiation. The mathematical model based on Continuous Petri nets (proposed by us recently) will be described. It makes it possible to analyze two main processes running at the same time: chemical radical reactions and the diffusion of radical clusters formed during energy transfer. One may study the time change of radical concentrations due to the chemical reactions running during diffusion process. Some orientation results concerning the efficiency of individual radicals in DSB formation (in the case of Co60 radiation) will be presented; the influence of oxygen present in water medium during irradiation will be shown, too.

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## 1. Introduction

The radiobiological mechanism is strongly influenced by the presence of oxygen which plays important role in the chemical stage where the radicals (arisen in clusters) react mutually or with other species which are present during irradiation. Oxygen influences the chemical process in two ways: at first it acts as radioprotective substance and secondly it behaves as radiosensitizer, which depends on its concentration. At small concentration the oxygen scavenges the radicals and acts as radioprotective substance. At higher concentrations radicals HO<sub>2</sub> are formed which may react with a molecule DNA and cause its damage; oxygen behaves as radiosensitizer.

The study of the influence of oxygen on the chemical stage of radiobiological mechanism may be very important for

radiotherapy because cancer cells may have different oxygen concentration than healthy cells. Oxygen effect arises mainly when cells are irradiated by low-LET radiation where indirect effect significantly predominates. Direct effect may be in this case practically neglected.

However, the efficient damage of DNA molecule may occur only in a short time after radical cluster formation when radical concentration (diminishing with cluster diffusion) is sufficiently high. At least two single strand breaks (SSB) must be formed in close neighborhood to form double strand break (DSB) that is responsible for DNA damage. SSB arise by chemical reaction of radicals with DNA molecule. This efficiency of individual radicals is then influenced by chemical processes running in corresponding clusters as well as by lowering of non-homogeneous concentrations during radical cluster diffusion.

We proposed already earlier mathematical model making it possible to describe the combined effect of these two processes

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(see Barilla and Lokajčėk (2000) and Barilla et al. (2013)). Recently the given model has been extended by including Petri nets (see Barilla et al. (2014, 2015)), which has made it possible to describe the time evolution of individual radical numbers in corresponding clusters. The model has been applied to experimental data of the yields of individual radicals in anoxic water radiolysis at the instant of cluster formation and at the end of its diffusion. Good agreement has been obtained when we have compared the calculated relation between these values with the measured ones (Barilla et al. (2014, 2015)).

However, the living cells contain usually an amount of oxygen molecules that may influence significantly final biological effect. In this paper we shall analyze the impact of present oxygen molecules on the damage of DNA molecules during the chemical stage of radiobiological process. In such a case the participation of radicals ( $e_{aq}^-$ ,  $H^\bullet$ ,  $OH^\bullet$ ,  $H_3O^+$ ) and associated products ( $H_2$ ,  $H_2O_2$ ,  $O_2^-$ ,  $HO_2^\bullet$ ,  $O_2$ ) is to be taken into account in the corresponding damage of DNA molecule. Their initial yields will be taken from the literature; their estimates in the dependence on energy transfer are included in the most compilations concerning the radiation chemistry of water (see e.g. Beuve et al., 2009; Buxton and Swiatla-Wojcik, 1995; Buxton, 2001, 2004; Hart and Platzman, 1961; Hervé du Penhoat et al., 2000; LaVerne and Pimblott, 1991; Pimblott and Mozumder, 2004; Uehara and Nikjoo, 2006; Watanabe and Saito, 2001). In agreement with Mozumder and Magee (1966), the corresponding radical clusters (at low-LET radiation) will be then described (for the sake of simplicity) as spherically symmetric systems.

As already mentioned we have started to study the corresponding problem earlier, the contemporary result of chemical reactions and cluster diffusion having been described with the help of corresponding differential equations (see Barilla and Lokajčėk (2000); Barilla et al. (2013, 2014, 2015) and also Barilla et al. (2008, 2011)). Our model has been applied to the experimental data obtained for Co60 radiation (see Blok and Loman (1973)). According to the results obtained in radiation chemistry studies the average radical numbers in given clusters should corresponds approximately to transferred energy 300 eV.

In Barilla et al. (2014, 2015) Continuous Petri nets have been then used to simulate time dynamics of chemical stage under anoxic conditions. The changes of individual radical numbers during cluster diffusion have been established and initial and final values have been compared to yield obtained in chemical studies of corresponding water analysis.

In this paper we shall analyze the influence of oxygen on the dynamics of the chemical stage of water radiolysis under various oxygen concentrations to establish how individual radicals may contribute to DNA damage in different cases. It might help in understanding better the so called oxygen effect that may play important role in cancer radiotherapy.

The mathematical model based on using Continuous Petri nets and described earlier in studying processes in deoxygenated water medium will be extended to include processes running at oxygen presence. Only main formulas and model extension will be presented; all necessary details may be found in the paper Barilla et al. (2015). The changing concentrations of individual radicals in diffusing clusters at different oxygen concentrations will be presented.

## 2. Extended model including oxygen influence at different concentrations

The general mathematical model of the chemical stage of radiobiological mechanism has been derived in our previous

papers (see Barilla et al. (2014, 2015)). In this paper only short survey will be done. The model starts from the assumption that the given process (damaging DNA molecule) is mediated by diffusing radical clusters containing non homogeneous concentrations of individual species (see Pimblott and Mozumder (2004)).

The model has been based on the assumption that the cluster evolution has been determined by diffusion coefficients of corresponding radicals and the numbers of these radicals have been changing during this diffusion by chemical reactions running inside any cluster. The beginning of the given process has been given by the volume  $V_i(t=0)=V_0$  of the cluster and by the numbers of corresponding radicals  $N_i(t=0)$ .

These initial values will be chosen on the basis of earlier results obtained by fitting the effect on formation of DSB in DNA solved in corresponding water medium in comparison to published results obtained in studying water analysis.

It is then possible to define the concentrations of individual radicals

$$\bar{c}_i(t) = \frac{N_i(t)}{V_i(t)}, \quad (1)$$

and to express the corresponding derivatives as common effect of cluster diffusion and chemical reactions running in the cluster

$$\frac{d\bar{c}_i(t)}{dt} = -\frac{\bar{c}_i}{V_i} \frac{dV_i}{dt} - \sum_j k_{ij} \bar{c}_i(t) \bar{c}_j(t) + \sum_{j,k \neq i} k_{jk}^{(i)} \bar{c}_j(t) \bar{c}_k(t), \quad (2)$$

where  $k_{ij}$  is rate coefficient of reaction species  $i$  with species  $j$ . The first term of the right-hand side of the system of ordinary differential Eq. (2) represents the diffusive contribution to the evolution of  $c_i$ , while the second and third terms represent removal and production of species  $i$  by chemical reactions. Using Eq. (1) one may rewrite Eq. (2) as

$$\frac{dN_i(t)}{dt} = - \sum_j k_{ij} \frac{N_i(t)N_j(t)}{V_j(t)} + V_i(t) \sum_{j,k \neq i} k_{jk}^{(i)} \frac{N_j(t)N_k(t)}{V_j(t)V_k(t)}. \quad (3)$$

The diffusion change of average volumes of individual radicals has been then derived as sphere symmetrical diffusion starting from the center of corresponding cluster:

$$\frac{dV_i(t)}{dt} = 128 \sqrt{\left( \frac{D_i^3 t}{\pi} \right)}, \quad (4)$$

where volume  $V_0$  represents the starting size of corresponding radical cluster and  $D_i$  is diffusion coefficient.

Two last systems of equations may be then solved if one uses the values of corresponding diffusion coefficients and reaction rates (see Tables 1 and 2). In this paper only the final equations of the mathematical model has been shown; a more detailed derivation has been done in Barilla et al. (2014, 2015).

**Table 1**  
Diffusion coefficients (Hervé du Penhoat et al., 2000).

Substance	Diffusion coefficient (nm <sup>2</sup> ns <sup>-1</sup> )	Species amount	Designation of diff. coefficients
1. H <sup>•</sup>	7.0	$N_H$	$D_H$
2. OH <sup>•</sup>	2.2	$N_{OH}$	$D_{OH}$
3. $e_{aq}^-$	4.9	$N_e$	$D_e$
4. H <sub>3</sub> O <sup>+</sup>	9.5	$N_{H_3O^+}$	$D_{H_3O^+}$
5. OH <sup>-</sup>	5.3	$N_{OH^-}$	$D_{OH^-}$
6. H <sub>2</sub>	5	$N_{H_2}$	$D_{H_2}$
7. H <sub>2</sub> O <sub>2</sub>	2.2	$N_{H_2O_2}$	$D_{H_2O_2}$
8. O <sub>2</sub> <sup>-</sup>	1.8	$N_{O_2^-}$	$D_{O_2^-}$
9. HO <sub>2</sub> <sup>•</sup>	2.3	$N_{HO_2}$	$D_{HO_2}$

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