Journal of Physics and Chemistry of Solids 78 (2015) 127–136

Contents lists available at ScienceDirect

Journal of Physics and Chemistry of Solids

journal homepage: www.elsevier.com/locate/jpcs

Applying Petri nets to modeling the chemical stage of radiobiological mechanism

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ARTICLE INFO

Article history:
Received 31 July 2014
Received in revised form
20 November 2014
Accepted 25 November 2014
Available online 27 November 2014

Keywords:
Radiation damage
Organic compounds
Critical phenomena
Defects

ABSTRACT

The chemical stage represents important part of radiological mechanism as double strand breaks of DNA molecules represent main damages leading to final biological effect. These breaks are formed mainly by water radicals arising in clusters formed by densely ionizing ends of primary or secondary charged particles in neighborhood of a DNA molecule. The given effect may be significantly influenced by other species present in water, which may depend on the size and diffusion of corresponding clusters. We have already proposed a model describing the corresponding process (i.e., the combined effect of cluster diffusion and chemical reactions) running in individual radical clusters and influencing the formation probability of main damages (i.e., DSBs). Now a full number of corresponding species will be considered. With the help of Continuous Petri nets it will then be possible to follow the time evolution of corresponding species in individual clusters, which might be important especially in the case of studying the biological effect of very low-LET radiation. The results in deoxygenated water will be presented; the ratio of final and initial contents of corresponding species being in good agreement with values established experimentally.

1. Introduction

Any ionizing particle incident into a biological object (and having sufficient energy) may have significant influence on the life of a corresponding cell. The basic effect may be represented by the formation of SSB or DSB (single or double strand breaks) in individual DNA molecules. The whole radiobiological mechanism consists then always of three stages: physical, chemical and biological. While the physical stage (corresponding to energy transfer to irradiated medium) is known quite well the actual characteristics of two other stages often influencing the corresponding biological effect very substantially are still rather open.

As in water medium the direct effect of incident particles may be practically fully neglected the chemical stage always represents important part of the corresponding mechanism. The given damages in DNA molecules are caused by radicals arising in clusters from water molecules by densely ionizing track ends of individual ionizing particles in the neighborhood of individual molecules. Especially in the case of low-LET radiation the final biological effect may be rather strongly influenced by the presence of some other species in corresponding water medium; oxygen being one of the most important species.

The individual radicals present in a cluster may always form one SSB that may be practically quickly repaired in individual DNA molecules. More efficient DSB may be also repaired in diploid cells but the repair time is much greater. Consequently, at greater radiation doses a greater number of these DSBs may be formed in individual DNA molecules, which may lead to destroying corresponding molecules and eventually to even killing of diploid cells. The number of efficient radicals in individual clusters may then be influenced (lowered or heightened) by the presence of other species in corresponding water medium. Then the efficiency of DSB formation lowers quickly by cluster diffusion.

Great attention has been devoted to estimating the initial yields of radicals and ions (e^-_{aq}, $H^\bullet$, $OH^\bullet$, H_3O^+) and associated products (OH^-, H_2, H_2O_2, O_2^-, $HO_2^\bullet$) in the time when the clusters have been formed; see different compilations concerning the radiation chemistry of water (e.g. [10,11,15–17,19,24–26,8]).

For low-LET radiation the radical clusters of different sizes may be formed according to the energy of secondary electrons that are responsible for cluster formation. According to Mozumder and Magee [18] the excitation energy values of efficient clusters lie in the interval from several tens of eV to 500 eV. In the radiation chemistry research the average number corresponding to different energy values has been established. However, it is possible to say that until now the efficiency of different clusters in DSB formation and of different radiomodifiers (in final biological effect) has not been sufficiently evaluated.

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http://dx.doi.org/10.1016/j.jpcs.2014.11.016
0022-3697/

We have started to study the corresponding problem already earlier, the contemporary result of chemical reactions and cluster diffusion having been described with the help of corresponding differential equations (see [3–7]). The average excitation energy of efficient clusters (in the case of Co60 radiation [6]) should be approximately 300 eV (estimated according to results obtained in radiation chemistry studies). We should ask, however, how the efficiency of corresponding individual clusters changes in dependence on their sizes. And further, whether the distribution of radicals in all clusters corresponds to average size when the radicals are formed in diverse processes requiring different excitation energy values? Or how does the corresponding efficiency evolve during cluster diffusion if the interaction with DNA molecules occurs some time after cluster formation?

These questions may be studied with the help of Continuous Petri nets that have been introduced by us recently [7]. It has been demonstrated in the case of 100 eV clusters arising in deoxygenated water that the average yields of individual radicals in the time of cluster formation and at the end of cluster diffusion correspond well to the evolution values described with the help of Petri nets. In this paper we shall try to derive some further characteristics that might contribute to the solution of the mentioned problems.

In Section 2 the influence of changing concentrations due to cluster diffusion dependence on chemical reactions running in individual clusters will be derived. The system of all processes running in clusters will be represented with the help of Continuous Petri nets in Section 3. Main characteristics provided with the help of Petri nets and the comparison with experimental data will be presented in Section 4. Some concluding remarks will be introduced in Section 5.

2. Mathematical model of processes running in diffusing clusters

The corresponding mathematical model of chemical stage has started from the assumption that the given process is mediated by diffusing radical clusters containing non-homogeneous concentrations of individual species [19]. And macroscopic laws have been used to describe the diffusion of radiation-induced objects and concentration changes caused by different chemical reactions. In developing the given mathematical model we have come out of the prescribed diffusion model of the radiation track proposed by Schwartz [21]. In contrast to the solution published by Schwarz, we have converted our mathematical model to the solution of ordinary differential equations, which has significantly accelerated the simulation process.

To establish the influence of the cluster diffusion (on corresponding concentration changes) we shall assume for simplicity that this diffusion goes in a limited spherical volume [19]. The time dependence of the diffusion process may then be described with the help of partial differential equations:

$$\frac{\partial c_i}{\partial t} = D_i \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial c_i}{\partial r}\right), \tag{1}$$

where $c_i(r, t)$ represent the time dependences of concentration distributions of individual species i and r denoting the distance from the cluster center. By solving this equation one obtains

$$c_i(r, t) = \frac{N_i}{8\sqrt{(\pi D_i t)^3}} \exp\left(-\frac{r^2}{4D_i t}\right), \tag{2}$$

where N_i is the (initial) number of species i in the cluster, D_i are corresponding diffusion coefficients and t is the time from the start of the diffusion in the theoretical center of the given cluster. The average cluster radius then equals

$$\bar{r}_i(t) = \frac{1}{N_i}\int_0^\infty r c_i(r, t) 4\pi r^2 \, dr \tag{3}$$

or

$$\bar{r}_i(t) = \frac{\pi}{2\sqrt{(\pi D t)^3}} \int_0^\infty r^3 \exp\left(-\frac{r^2}{4Dt}\right) dr, \tag{4}$$

and the time dependence of the cluster volume may then be defined as

$$V_i(t) = \frac{4}{3}\pi \bar{r}_i^3(t) \tag{5}$$

or

$$V_i(t) = \frac{256}{3}\sqrt{\left(\frac{D_i^3 t^3}{\pi}\right)}. \tag{6}$$

One can see from the last equation that the volumes occupied by individual diffusing species at a given time are practically independent of the number of corresponding species, depending only on their diffusion coefficients.

Differentiating Eq. (6) we obtain

$$\frac{dV_i(t)}{dt} = 128\sqrt{\left(\frac{D_i^3 t}{\pi}\right)}. \tag{7}$$

The given formulas (6) and (7) may be accepted as sufficient for characterizing the influence of diffusion process at least in the first approximation (even if the cluster diffusion will not go in fully spherically symmetrical way).

As the size of cluster is small (about tens of nm), the concentration profile of radicals in clusters may be assumed to be Gaussian, and it is then possible to introduce average cluster concentrations $\bar{c}_i(t)$ of individual species:

$$\bar{c}_i(t) = \frac{N_i(t)}{V_i(t)}, \tag{8}$$

where $N_i(t)$ is the number of corresponding chemical species in a cluster in a given instant and $V_i(t)$ describes the time dependence of cluster volume established according to Eq. (6), which may be regarded as sufficient approximation for simulating the dynamics of chemical processes in diffusing clusters.

The average concentration change of individual chemical substances at any time may then be then given as the sum of two processes (diffusion + chemical reactions). One can write

$$\frac{d\bar{c}_i(t)}{dt} = -\frac{\bar{c}_i}{V_i}\frac{dV_i}{dt} - \sum_j k_{ij}\bar{c}_i(t)\bar{c}_j(t) + \sum_{j,k\neq i} k_{jk}^{(i)}\bar{c}_j(t)\bar{c}_k(t). \tag{9}$$

The first term of the right-hand side of the system of ordinary differential equations (9) 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, respectively. Using Eq. (8) one obtains the system of ordinary differential equations:

$$\frac{dN_i(t)}{dt} = -\sum_j k_{ij}\frac{N_i(t)N_j(t)}{V_j(t)} + V_i(t)\sum_{j,k\neq i} k_{jk}^{(i)}\frac{N_j(t)N_k(t)}{V_j(t)V_k(t)}, \tag{10}$$

Eq. (10) together with Eq. (7) describes the dynamics of chemical reactions at any time t when the influence of cluster diffusion is respected. Chemical reactions are influenced by diffusion processes causing a concentration change of individual particles