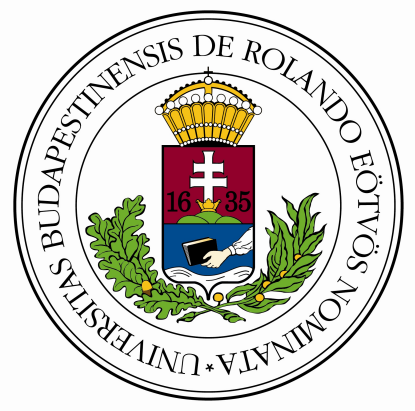

Numerical modelling of the biological effects of ionizing radiation at the tissue level

by

Balázs G. Madas

PhD thesis summary

Eötvös Loránd University
Physics Doctorate School
head: prof. Ferenc Csikor, DSc

Doctoral Program for Statistical Physics, Biological Physics,
and Physics of Quantum Systems
head: prof. Kürti Jenő, DSc

supervisor: dr. Balásházy Imre, DSc
Centre for Energy Research, Hungarian Academy of Sciences

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Introduction

Almost at the time when ionizing radiation was discovered, a question was raised, how this type of radiation affects creatures including humans. In the past hundred years, the increasing number of applications and getting acquainted with biological effects of ionizing radiation supported each other. The increasing number of applications made radiation protection with scientific basis necessary, while getting acquainted with biological effects made it possible. One of the basic principles of radiation protection is the principle of justification, i.e. no unnecessary use of radiation is permitted, which means that the advantages must outweigh the disadvantages. That means that the question "How does it affect humans?" needs not just a qualitative approach but a quantitative one.

Among the research fields related to radiation protection, epidemiology can provide quantitative information on the effects of radiation. In these studies, however, other factors affecting the population cannot be excluded. In addition, their relative importance increases by the decrease of radiation burden. At low doses, therefore, radiation epidemiology cannot answer the question either, how the different effects or their probabilities depend on radiation dose. The lacking knowledge at low doses is recovered by the extrapolation of observation at high doses to the low dose range. However, the extrapolation is questionable, because the mechanisms involved in the progress of harmful effects of radiation are not known. Since data obtained from radiation epidemiology are based not on experiments but on observations, these data cannot uncover these mechanisms. The discovery and understanding of these mechanisms can come from animal experiments and *in vitro* experiments. However, the dose-effect relationships obtained from these experiments are not the same as the dose dependence of human health effects.

Some recent research projects shows that relations between data from experiments in radiation biology and studies in radiation epidemiology should be addressed. One of the ways to do that is to search for relationships between data on different species, however, it is possible that there are no real relationships. The other way is to discover the relationships between the effects at the different levels of biological organization, and so obtain the relations between data from radiation biology and radiation epidemiology. The advantage of the second way is that we can search for surely existing relationships, although it is not easy.

The cellular responses to ionizing radiation are widely investigated both experimentally and theoretically. However, cells are not isolated in the body, but closely interact with each other, and therefore the target of radiation effects is not only the single cell, but also the whole tissue microenvironment. Therefore it is an important question how some cellular responses to ionizing radiation manifest themselves at the tissue level. The aim of this work is to contribute to answer this question.

Although, radiation protection considers different types of radiation, different types of tissues, and different exposure conditions in a unified system, at tissue level effect studies, it is useful to restrict the field of investigation. Therefore, while I strived to draw some general conclusions about the biological effects of radiation, I focussed on the effects of radon progeny, which are the second most important cause of lung cancer after smoking, responsible for the main part of natural radiation burden, and which result in very spatially inhomogeneous dose distribution.

Objectives

One of the main questions of the work comes from the latter property, whether the health effects of different radiation sources and the risks of their applications can be treated in a unified system or not. Firstly, the tissue level effects of locally high doses due to α-radiation as a consequence of spatially inhomogeneous exposure were studied in a small part of the bronchial epithelium. Are there any phenomena observed at the tissue level, which are characteristic exclusively of spatially inhomogeneous exposures or of radon progeny? Then a larger part of the bronchial airways was studied in order to determine the distribution of cellular burdens originating from the activity distribution. Applying a very simple model, it was investigated whether lung cancer risk can be assigned to a specific part of the airways. Finally, it was studied, in which way radiation protection could consider the spatial distribution of radiation burden.

Another important questions of the work are, how the effects of ionizing radiation depend on dose, and what kind of relationships there are between the dose dependences of different effects. Firstly, I studied, how mutation induction rate depends on radiation burden, and how cellular effects related to mutagenesis manifest themselves at the tissue level. It is another question what is the significance of the processes which cannot be observed at the cellular level. As an example for that, the effect of accelerated cell turnover due to cell death in mutagenesis was studied.

Methods

Numerical models play an increasingly significant role in the understanding of biological systems and processes. This is partly because of the complexity of the systems, and partly because of the limits of experimental research. Both the human organism as a system and the biological processes induced by radiation are very complex. Numerical models are able to consider the processes taking place at the different levels of biological organization and the interaction between them. For this reason, this work is based on elaboration and application of numerical models.

Firstly, the mathematical model of the bronchial epithelium was elaborated, which consists of six different cell types and considers their cell nucleus and cytoplasm. Then cellular radiation burdens originating from α-radiation were determined with a cell dosimetry model as the function of macroscopic exposure. The outputs of this model are inputs of biological models. The first biological model applied describes mutation induction. Its central assumption is that mutation occurs when a progenitor cell divides with DNA-damage. In the quantification of DNA-damages, spontaneously occurring as well as radiation induced damages were considered and DNA-damage repair was supposed to follow second-order kinetics. Since cell numbers in the tissue has to be kept approximately constant, to fulfil its role, the cell division rate of progenitor cells depends on cell death rate of progenitor and nonprogenitor cells in the neighbouring tissue. However, there is a maximum of cell division rate in the model. Cell survival probability decreases exponentially by the number of α-particles hitting the cell nucleus.

The other biological model is a very simple carcinogenesis model with the assumption that there are two stochastic steps in carcinogenesis. The first is called initiation meaning in this model malignant transformation. Its probability is proportional to cell dose. In this model, the second and final stochastic step in carcinogenesis is promotion meaning the division of an initiated cell. Presuming that cell death forces other cells to divide, promotion probability is proportional to cell division rate. A larger part of the airways was studied with this model. Surviving fractions and a quantity proportional to risk was determined in the smaller tissue units. The effects characteristic of these tissue units were supposed to be independent on each other.

To investigate how inhomogeneous intra-organ distribution of radiation burden could be considered in radiation protection, an alternative way for the determination of effective dose was introduced, organs were divided into smaller tissue units, and weighting factors for these tissue

units were introduced. Absorbed doses and equivalent doses was computed for the tissue units. The biological effects on the different tissue units were supposed to be independent. In order to investigate the macroscopic manifestation of phenomena observed at microscopic level, possibly participating in the induction of stochastic effects, and having non-linear response curve in the low dose range, four basically different functions were defined besides the linear one, which can roughly characterize the dose dependence of some biological responses. These functions were applied in the computation of equivalent dose.

In all the work, I used my colleague, Árpád Farkas's data on deposition distribution of radon progeny and my colleague, István Szőke's data on the distribution of α-tracks. For the computation of data, they had not considered the deposition during exhalation and the mucociliary clearance, so these phenomena are neglected in the above models too.

Results

1. A mathematical model of the bronchial epithelium was developed to study the biological effects of α-particles emitted by inhaled radon progeny. Some of the parameter values characterizing the mathematical model are very close to measured data, while other values are not so precise but still meet the requirements of the present investigation. According to our knowledge, this mathematical model of the bronchial epithelium is the first in the literature that is applicable for the simultaneous quantification of radiation exposure of cells and nuclei in cellular dosimetry calculations. Alpha-particle hits of cell nuclei and cell doses of six different cell types were computed as a function of macroscopic exposure at the most heavily affected parts of deposition hot spots in the bronchial airways (Madas & Balásházy, 2011).

2. The biological consequences of chronic radiation exposures with locally high dose rates were quantified by the adaptation of a mutagenesis and a carcinogenesis model. At the tissue level, mutation induction rate and cancer risk obtained from the model has a completely different dose rate and dose dependence than various cellular dosimetric quantities and individual cells' responses. Mutation induction rate increases monotonically with dose rate. On the basis of the shape of mutation induction curves, three different dose rate ranges can be distinguished (Madas & Balásházy, 2011; Madas et al., 2011).

3. It was found here that acceleration of cell turnover due to cell inactivation is not only a significant contributor to, but a basic determinant of mutation induction in surviving progenitor cells in case of protracted exposures to densely ionizing radiation. This kind of bystander effect is important even at moderate or high doses where classic bystander effects are negligible compared to direct effects (Madas & Balásházy, 2011).

4. A threshold of daily tissue dose for chronic exposures to α-particles was found, at which the tissue regeneration capacity of progenitor cells is exhausted (i.e., they cannot divide frequently enough to replace inactivated cells). I pointed out that the response of the tissue to the protracted exposure to high dose rate radiation can be progenitor cell hyperplasia to enhance the local tissue regeneration capacity. Since the computed threshold dose rate is lower than values possibly characteristic of the deposition hot spots of the airways of former uranium miners, the exhaustion of local tissue regeneration capacity and local hyperplasia provide a possible explanation of the inverse dose-rate effect (which disappears at low-dose rates or low cumulative doses) observed in the epidemiology of lung cancer among uranium miners (Madas & Balásházy, 2011).

5. Some of the output values of the mutagenesis model are in good agreement with the results of other experiments without any parameter tuning. In other cases where existing experimental results are not appropriate to verify model predictions, new experiments were proposed (Madas & Balásházy, 2011).

6. With the example of radon progeny, it was shown that inhomogeneity in radiation burden cannot be and need not be considered in the current system of radiation protection, because the relationship between absorbed dose, equivalent dose, effective dose and nominal risk are linear. It is suggested that nonlinearity in low dose effects is less significant in case of inhaled radon progeny than in case of radiation sources producing spatially homogeneous exposures (Madas & Balásházy, 2012).

Conclusions

The results showed that modelling at the tissue level can enhance our knowledge about the biological effects of ionizing radiation, but at the same time pointed out the necessity of investigations at even higher levels of biological organization. The results demonstrate the obvious but not well-known fact that the LNT model applied in radiation protection cannot be disproved or underpinned on the basis of studies of cellular effects.

The contribution of accelerated cell turnover to mutation induction suggests that the radiation burden of differentiated cells play a role in carcinogenesis induced by radon progeny, which is not considered by dosimetric models applied in radiation protection. The significance of accelerated cell turnover suggests that on the basis of experiments on cell cultures mutation induction rate can be considerably underestimated in case of multicellular organisms chronically exposed to densely ionizing radiation. The monotonically increasing mutation induction rate as the function of dose rate challenges the conclusions of several epidemiological studies that the effect of radon progeny on mutation induction (called initiation) can be neglected besides their effect on the proliferation of already mutated cells (promotion).

Based on the spatial distribution of cellular burdens and the exhaustion of local regeneration capacity of the tissue, it can be hypothesised that lung cancer formation among uranium miners exposed to high radon progeny concentrations is driven by completely different mechanisms than carcinogenesis induced by such radiation burdens which are not characterized by chronic, high dose rate. It is suggested that the risk of harmful health effects of radon progeny cannot be properly estimated without considering the spatial inhomogeneity, but it is not possible in the frame of the current radiation protection system.

Publications supporting the thesis statements

Madas, B.G., Balásházy, I., 2011. Mutation induction by inhaled radon progeny modeled at the tissue level. Radiat Environ Biophys 50, 553–570.

Madas, B.G., Balásházy, I., Farkas, Á., Szőke, I., 2011. Cellular burdens and biological effects on tissue level caused by inhaled radon progenies. Radiat Prot Dosim 143, 253–257.

Madas, B.G., Balásházy, I., 2012. Possible consequences of inhomogeneous suborgan distribution of dose and the linear no-threshold dose-effect relationship. In: 13th International Congress of the International Radiation Protection Association: Living with Radiation - Engaging with Society. Glasgow, Scotland, 13-18 May, 2012. Paper TS1a.6. pp. 1-9.

Further publications in the topic of the thesis

Balásházy, I., Farkas, Á., Madas, B.G., Hofmann, W., 2009. Non-linear relationship of cell hit and transformation probabilities in a low dose of inhaled radon progenies. J Radiol Prot 29, 147–162.

Farkas, Á., Hofmann, W., Balásházy, I., Szőke, I., Madas, B.G., Moustafa, M., 2011. Effect of site-specific bronchial radon progeny deposition on the spatial and temporal distributions of cellular responses. Radiat Environ Biophys 50, 281–297.

Szőke, I., Farkas, Á., Balásházy, I., Hofmann, W., Madas, B.G., Szőke, R., 2012. 3D-modelling of radon-induced cellular radiobiological effects in bronchial airway bifurcations: Direct versus bystander effects. Int J Radiat Biol 88, 477–492.