Computational Methods for Exploring the Dynamics of Cancer: The Potential of State Variables for Description of Complex Biological Systems

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Abstract– Observing dynamic patterns in silico and comparing them to experimental data in vitro or in vivo could help us identify and quantify dynamic processes. Since modellers are faced with a high degree of complexity of biological systems, appropriate concepts of system descriptions are needed. The use of state variables is expected to make models applicable to a wider range of the dynamics of biological systems. This is demonstrated by the Multi-Hit-Repair (MHR-) model which is based on a transient dose equivalent. The model calculates the survival of cells irradiated by ionizing radiation and it describes correctly a large variety of radio-biological observations. In addition, the MHR-model is bridging the gap between processes at the molecular or cellular level and tissue dynamics.

1. Introduction

In the last decades, knowledge of molecular aspects of human physiology and pathophysiology has grown enormously. Often, this knowledge is qualitative. Since cellular signaling pathways are embedded in a complex dynamic system and interact with many other pathways, it is difficult to gain quantitative information which can be used to model cellular systems or organisms. Systems biology is addressing this aspect, but the transfer to clinical medicine seems to be difficult. On reason may be the fact that the molecular layer (which is accessible by measurements) is representing the syntactic level of biological systems. The manifestation of biological phenomena responsible for evolutionary processes or environmental interaction takes place at a semantic level. It is important to note that the control (the syntax, so to say) of biomolecular processes is determined (to large extents) by genetic information and some external input which can be regarded as parameters. In biological context, semantics is given by the interaction of the phenotype with its environment (with evolution determining what is "sensible"). The coupling between phenotype (semantics) and genotype (syntax) is known to be non - trivial in both directions. First, many properties of the phenotype emerge from the genotype in a way that is hard to predict by present scientific means. One reason for this is lack of data, but there are additional inherent difficulties when the effect of the combined interaction of molecules, supra-molecular structures and mesoscopic entities (e.g. membranes) have to be computed in a multi - scale simulation. Second, a given phenotype can be realized by a large variety of underlying genetic control schemes and molecules. A simple example are key and lock structures in receptors; There are usually combinatorially many possibilities for the realization of a matching pair. But also more complex processes may be realized by many different reaction networks. This means that methods from reverse engineering cannot be applied, or only with considerable effort. Therefore, the analysis of control processes should happen on the phenotypic level, because there, the connection between organism and environment becomes apparent. The variables we use (the state variables of the system) are chosen to reflect cellular properties and are not necessarily easy to interpret in terms of genomic information.

In clinical medicine, the distinction between disease and illness is a good example for illustrating the relation between a mechanistic view of the loss of functionality (disease) and the clinical manifestation including psychological and psychosomatic aspects. At a first glance, it seems to be hopeless to get access to illness based on a deep, quantitative understanding of underlying processes. But following the idea of describing biological systems at a semantic level, there are some interesting aspects which could help us move forward: Biological systems are complex, sometimes exhibiting non-linear behavior (which is not be chaotic under normal conditions). Assuming a description of the system in terms of continuous variables in phase space, the attractor landscape may consist of different basins of attraction. If malfunction is seen as a dynamic process, disease and illness can be interpreted as a state related to a pathological attractor. A therapeutic intervention could be based on pushing the system to another attractor and /or reshaping the attractor landscape. The main problem for this view is to find an appropriate, quantitative description of the system [1].

Apart from prediction, modelling can help us find adequate descriptions of biological systems—modelling in this sense is a learning tool. A promising approach is the

detection of characteristic dynamic patterns by comparing computer simulations using model systems and experiments in vitro, in vivo — or closer to clinics, in patient. In the following, this aspect will be illustrated by the response of cells to ionizing radiation (cell killing). In contrast to the previous research, we discuss here the use of state variables in the framework of an adapted concept for describing complex biological systems including the aspects of the attractor landscape of such systems.

2. Material and Methods

The impact of ionizing radiation can be quantified by clonogenic survival assays, where the surviving fraction $S = N_0 / N$ of irradiated cells (initial number N_0 and N surviving cells) is determined. Typically, the logarithm of the surviving fraction exhibits a linear-quadratic relationship to the absorbed radiation dose D : $\log S(D) = -(\alpha D + \beta D^2)$. This (originally empiric) model was first used by Lea and Catcheside [2] to fit radiation chromosome damage. Theories about DNA lesion formation or cell survival (e.g. Chadwick & Leenhouts [3]) led to mechanistic interpretations of the LQ-model. Such interpretations are problematic since linear-quadratic (LQ)- shaped curves can be produced by different dynamic models. The LQ dose-effect relationship is an often observed dynamic pattern, which by itself does not let us identify a dedicated mechanism or process (in this context, we prefer the term process since biological systems often have an intrinsic plasticity; the term mechanism implies a system with more rigid components similar to a machine). To limit the number of possible structures of models, additional aspects of the dynamics of the cellular response must be taken into account. Dose rate — and cell cycle — dependency, distinct behavior of apoptotic vs. non-apoptotic cell death, low-dose hypersensitivity of some cell lines and synergistic effect of combined application of heat and radiation led to the model structure of the Multi-Hit-Repair (MHR-) model [4]. The model is based on two key ideas: First, it uses a chain of cell populations (Fig.1) which are characterized by the number of radiation induced damages (hits). Cells can shift downward along the chain by collecting hits and upward by a repair process. There is no explicit criterion for lethality of hits. In this model, lethality can be a consequence of too many hits which are reducing the probability of a recovery back to the mitotic cycle. Second, the repair process is governed by a repair probability which depends upon state variables used for a simplistic description of the impact of heat and radiation upon repair proteins. These quantities can be interpreted as a signal transporting summary information about cellular (protein-related) damage and subsequent capability of the repair system. In this sense, state variables are linking between the molecular, syntactic level and a more semantic level, where signals are decoded and converted to information governing cellular control.
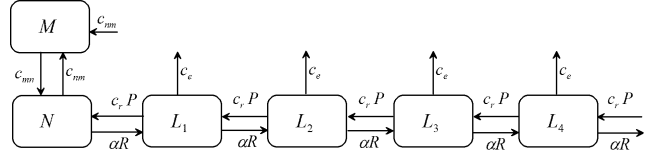

Fig.1. Illustration of the population chain in the MHR model: The model flowchart includes a mitotic cell population (population size M) and vital tumour cells (population size N). The flows (rates) between the populations (with population sizes L_i for populations with i hits) can be found by multiplying the given constants by the corresponding population size (population where the arrow starts). P is the repair probability (according Eq.3), α is a radiation-sensitivity coefficient, R is the radiation dose rate and c_e represents a constant describing the elimination of cell of a population (L_i). For more details see [4].

In the case of the MHR model, the calculation of the state variables follows a simplistic, probabilistic concept without explicit inclusion of underlying molecular processses of damage induction and repair. In the case of the MHR model, two variables of state, Γ and Λ, are used as configuration quantities describing radiation- and heat-induced damages (disorder). The probability of repair P depends upon Γ and Λ: $P = P(\Gamma, \Lambda)$. Moreover, the following approach is used: the repair probability decreases monotonically with increasing values of Γ and Λ. In a first approximation, the following relations may be used:

$$\left[\frac{\partial P}{\partial \Gamma} \right]_{\Lambda = const} = -\mu_\Gamma P$$

$$\left[\frac{\partial P}{\partial \Lambda} \right]_{\Gamma = const} = -\mu_\Lambda P \tag{1}$$

This leads to the following functional dependence:

$$P(\Gamma) = P_\Gamma = e^{-\mu_\Gamma \Gamma}$$
$$P(\Lambda) = P_\Lambda = e^{-\mu_\Lambda \Lambda} \tag{2}$$

In the case of P_Γ and P_Λ being statistically independent, the total probability is given by:

$$\frac{d\Gamma}{dt} = R - \gamma \Gamma \tag{3}$$

The concept using Γ and Λ can be generalized to the framework illustrated in Fig.2. In principle, different levels of a biological system (cellular system embedded in a tissue) correspond to different levels for the description of the system (right part of Fig.2).
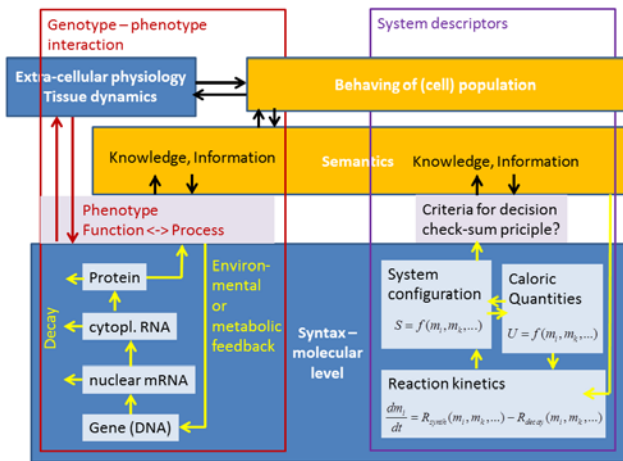
Fig.2. Framework for description of biological systems: left, a more explicit view to the cellular system is illustrated; the right part refers to a possible approach for a corresponding description.
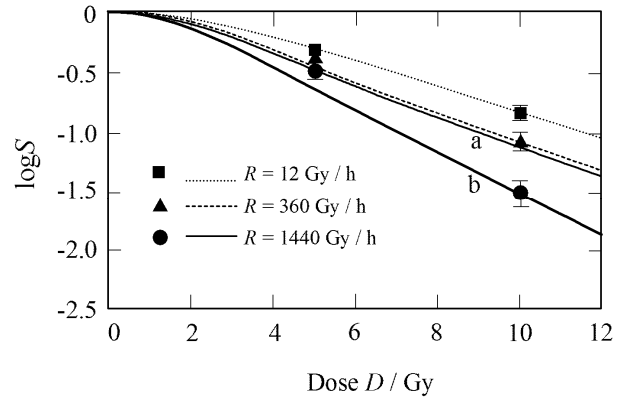

Fig.3. Clonogenic survival of T98G glioblastoma cells at different dose rates: The parameter values for fitting are for 12 -360 Gy/h and for curve (a) with 1440 Gy/h α = 0.27 Gy^{-1}, γ = 1.45 h^{-1}, c_r = 90 h^{-1}, c_e = 19 h^{-1}, μ_Γ = 0.8 Gy^{-1}. In contrast to [4], we explored the conditions for fitting the high dose rate data (curve b); a different set of parameters was found: α = 0.36 Gy^{-1}, γ = 1.45 h^{-1}, c_r = 20 h^{-1}, c_e = 5 h^{-1}, μ_Γ = 0.8 Gy-1.

In Fig.2, system configuration quantities are influencing processes at a higher level, e.g. at the level of cell population. In the MHR-model is the semantics encoded in a repair probability. In contrast to models describing DNA lesions kinetics (e.g. LPL model of Curtis), the MHR model can be used to explore the interaction of populations at the tissue level.

3. Results

The MHR model is able to fit a large variety of experimental data. Linear-quadratic-linear behavior for large doses per fraction [5], apoptotic vs. non-apoptotic cell death [6] and dose rate dependencies as well can be reproduced [7]. With a similar approach (only modelling 2 radiation induced hits and induced repair), also low-dose hypersensitivity can be covered [8]. This range of coverage is remarkable when compared to other existing radiobiological models. Despite this success, changes in the radio-biochemical cascade and as a result, a different dynamic behavior cannot be excluded for very high dose rates or high doses per pulse (as deliverable by new linear accelerators for clinical use with flattening filter free (FFF-) beams). To investigate possible biological effects, Lohse et al. [9] treated glioblastoma cell lines with doses of 5 and 10 Gy. In Fig.3, a fit of the logarithmic survival of T98G glioblastoma cells irradiated at different dose rates is shown. In contrast to the previous work [4], we explored the conditions for fitting the high dose rate data (Fig.3b). By using an evolutionary optimization algorithm, no parameter set could be found that enables a fit for all dose rates. Especially the data point at 10 Gy and a dose rate of 1440 Gy/h cannot be covered by using only one set of parameters.

4. Discussion and Conclusion

The example described in this article illustrates the potential and limitation of a modelling approach using state variables. The simplistic approach using a transient dose equivalent leads to a model structure which covers a large variety of biological observations. One exception is increased cell killing effect of glioblastoma cells at very high dose rates and high dose values per fraction. This may be an indication for a different regime of cell death, related to the triggering of different chemical reactions in the radiobiochemical cascade, severe damage of mitochondria with subsequent energy depletion or destruction of other cellular structures. Using very high doses per radiation pulse seems to drive the cellular systems away from the well-known behavior related to radiation response and cell death. An interesting point relates to the question of how much the model structure must be modified to cover cell death response at very high dose rates. It has to be pointed out that the effect was only observed for the T98G cells which are radio-resistant compared to other tumour cell lines. The observation could be interpreted as a cell-line specific change of dynamic state related to different attractors. The MHR model may cover the cellular dynamics relying upon an attractor of a much more complex system in the case of low or moderate dose rates. When we push the system away from this attractor into another part of the attractor landscape by strong radiation pulses or very high dose rates, we cannot exclude chaotic states.

The example illustrated in this article is not comparable to the much more complex situation in vivo or in patient. However, it is interesting to see that the use of a simplistic approach using state variables in the MHR model enables a more or less correct description of the radiation induced response of cells (as long as the dose rate range is limited). In addition, the model is a cell population based. This is important since dynamic pro-

cessses such as competition, nutrient stress, oxygenation and vascularization, immune response etc. may override intrinsic cellular radiation sensitivity in some situations [10]. In this sense, the MHR-model is bridging the gap between the molecular or cellular level and tissue dynamics.

The concept of state variables refers to the approach of thermodynamics known in statistical thermodynamics. While we know how to calculate analytically the entropy or temperature of an ideal gas or crystal, we could not expect the same for determining state variables of biological systems with a heterogeneous, highly compartmentalized structure. Therefore, algorithmic (in-silico) approaches should be investigated for gaining a more solid basis for this concept. In addition, interesting information theoretic and thermodynamic aspects of biological systems may lead to more concise ideas about the relationship between entropy-like state variables and information in general and in biological systems in particular [11,12].

References

[1] R.M. Füchslin, A. Dzyakanchuk, D. Flumini, H. Hauser, K.J. Hunt, R.H. Luchsinger, B. Reller, S. Scheidegger, R. Walker, "Morphological Computation and Morphological Control: Steps Toward a Formal Theory and Applications", *Artificial Life*, vol. 19, No. 1: 9–34. 2013.

[2] D.E. Lea, D.G. Catcheside, "The mechanism of induction by radiation of chromosome aberrations in Transcendentia, " *J. Genet.,* vol.44, pp.216-245, 1942.

[3] K.H. Chadwick, H.P. Leenhouts,"A molecular theory of cell survival, " *Phys. Med. Biol.*, vol.18, pp.78-87, 1973.

[4] S. Scheidegger, H.U. Fuchs, K. Zaugg, S. Bodis, R.M. Füchslin,"Using State Variables to Model the Response of Tumour Cells to Radiation and Heat: A Novel Multi-Hit-Repair (MHR-) Approach," *Computational and Mathematical Methods in Medicine*, http://dx.doi.org /10.1155/2013/587543, 2013.

[5] M. Guerrero, X.A. Li, "Extending the linear-quadratic model for large fraction doses pertinent to stereotactic radiotherapy," *Phys. Med. Biol.* vol.49, pp.4825-4835, 2004.

[6] P. Harrigan Hardenberg, P. Hahnfeldt, L. Hlatky, C. Takemoto, A. Shimamura, G. McGill, C.Y. Fung, S. Bodis, D.E. Fisher, "Distinct mathematical behavior of apoptovic vs. non-apoptotic tumor cell death," *Int. J. Radiat. Oncol. Bio. Phys.,* vol.43(3), pp.601-605, 1999.

[7] R.L. Wells, J.S. Bedford, "Dose rate effects in mammalian cells.IV. Repairable and nonrepairable damage in noncyclic C3H10T1/2 cells," *Radiat. Res.* vol.94, pp.105-134, 1983.

[8] S. Scheidegger, R.M. Füchslin, "Kinetic model for dose equivalent – an efficient way to predict systems response of irradiated cells," *Proc. of ASIM 2011* (full papers, ISBN 978-3-905745-44-3), 2011.

[9] I. Lohse, S. Lang, J. Hrbacek, S. Scheidegger, S. Bodis, N. Sanchez-Macedo, J. Feng, U.M. Lütolf, K. Zaugg, "Effect of high dose per pulse flattening filter – free beams on cancer cell survival," *Radiother. Oncol.* vol.101, pp.226-232, 2011.

[10] S. Scheidegger, G. Lutters, S. Bodis, "Computer simulation of oxygenation and growth inhibition of tumours during fractionated radiotherapy: Exploration of the dynamic system behavior," *Radiother. Oncol.* vol.95, Suppl.1, pp.512, 2010

[11] P.A. Corning, S.J. Kline, "Thermodynamics, Information and Life Revisited, Part I: `To Be or Entropy'," *Systems Research and Behavioral Science*, *Syst Res* vol.15, pp.273–295, 1998.

[12] P.A. Corning, S.J. Kline, "Thermodynamics, Information and Life Revisited, Part II: `Thermoeconomics' and `Control Information'," *Systems Research and Behavioral Science, Syst Res* vol.15, pp.453–482, 1998.