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DEMOGRAPHIC ANALYSIS AND MODELING OF HUMAN POPULATIONS EXPOSED TO IONIZING RADIATION

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1. ABSTRACT

The health effects of ionizing radiation on human populations are often analyzed using epidemiological statistical methods. Because of the complexity of the health consequences of ionizing radiation and the prolonged period during which the consequences emerge, we propose to evaluate these health effects using mathematical models that are based on the best theoretical reasoning and prior biological evidence about disease mechanisms. We believe this will improve the ability of the model to identify health effects and reduce erroneous inferences.

2. INTRODUCTION

The scientific rationale for studying the health of populations exposed to ionizing radiation (IR) is that one can examine the response of cellular genetic and molecular mechanisms to a prevalent exogenous factor, IR, over the long term in a large, rigorously followed, human population. The chronic effects of IR on cellular function, and hence on major chronic disease progression and mortality, is manifested through oxidative and other chemical processes thought to be important. These effects influence carcinogenesis, atherosclerosis, infectious diseases (by affecting immune function), congenital malformations, birth outcomes, male and female reproductive potential, thyroid disease, senescence (involution) and overall mortality and functional loss. By studying human populations exposed to IR that plausibly accelerate morbidity processes and senescence, we may be better able to describe the specific physiological mechanisms involved.

A better understanding of these processes may produce a.) improved treatments of specific diseases by increasing knowledge of cellular and molecular disease mechanisms b.) strategies for intervening in IR-induced injury and c.) increased understanding of the fundamental mechanisms of chronic disease and aging. Major areas of health effects that can be studied are a.) birth outcomes (live births, vs. spontaneous abortions, vs. congenital defects), b.) child health (e.g., immune function) and development, c.) chronic disease risk and d.) changes in senescence and longevity.

These effects must be studied in the context of behavioral and other risk factors, as well as existing chronic disease, to isolate the physical effects of IR – and of the interaction of IR with normal aging processes. It is expected that a.) much of the health burden of low dose IR will not be expressed in terms of cancer but in other lethal (e.g., cardiovascular disease [CVD]) and less lethal, but highly debilitating conditions such as cataracts and psychiatric disorders. Many of these effects can be expected in susceptible sub-populations (e.g., in children of exposed individuals and in pregnant women who are exposed to IR, in the elderly, and in those with chronic illness). At the core of these investigations of low dose IR effects is whether or not they induce special injuries to human cells, injuries so subtle that they do not trigger cell repair mechanisms (1), cell defense mechanisms (e.g., heat shock proteins, hormesis (2)), or induce apoptosis or cell repair while increasing the number of double strand DNA breaks (3).

Studies of the human health effects of low levels of IR (4) are in scientific dispute. For example, chronic low-dose IR from Chernobyl is thought to have increased solid tumor rates in Belarus (5-7) – a health effect not fully recognized in the 2000 United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) Report. Recently, it was confirmed that double strand breaks produced by low dose IR (≤ 1.2 mSv) do not stimulate repair mechanisms (3).

Health effects may be complex enough that a study of the emergence of gross health effects (e.g., mortality, possibly after a lengthy latency period) may require the studied population to become too *large for* individual assessments to be performed frequently enough over time. Such effects may be readily identified only in demographic

(mortality) and population tumor registry data. As an alternative strategy, we propose using the largest human population chronically exposed to IR and applying biologically "sophisticated" or "informed" mathematical models to more efficiently use available health and biomarker data to answer questions about bioregulation of complex biological mechanisms under IR stress and its impact on the population health burden.

3. SOURCES FOR DATA ON EXPOSED POPULATIONS

There are relatively few situations where a large human population has been exposed to measurable doses of IR. First are the cities of Hiroshima and Nagasaki, Japan. When atomic bombs were dropped in 1945, these cities had populations of 310,000 and 250,000 respectively. Approximately 90,000 – 140,000 in Hiroshima and 60,000 – 80,000 people in Nagasaki died immediately or within four months after the bombing. These deaths resulted from: the collapse of houses caused by the blast and from thermal radiation, fires, and radiation exposure. In the 1950 Japanese census, nearly 280,000 persons stated that they "had been exposed" in the two cities.

Another well-known human population exposure is the 1986 Chernobyl Nuclear power plant accident in Ukraine —by far, the worst accident in the history of the nuclear power industry. It led to the acute and chronic radiation exposure of the human population in large areas of the Ukraine, Belarus, and Russia. Until the end of 1991 (the collapse of the USSR) the National Chernobyl Registry in Obninsk included medical and dosimetric data on 659,292 persons, including 284,919 Emergency Accident Workers (8). Since then each country (Russia, Belarus, and the Ukraine) has maintained its own population health registry.

A third major human population exposure is that of Mayak Production Association, the first Russian site for the production and separation of plutonium. It is located in the Southern Ural Mountains, 100 kilometers northwest of Chelyabinsk. The facility's first nuclear reactor and the radiochemical plant for plutonium separation began operation in 1948. The process of plutonium separation resulted in the accumulation of large amounts of highly radioactive liquid waste consisting of mixtures of decaying radionuclides. This was discharged into the Techa-Iset-Irtysh-Tobol river system. From 1949 to 1956, discharges amounted to 76 million m^3 of radioactive waste with total activity of 10^{17} Bq (2.75 million curies) (9) with 124,000 residents of riverside villages exposed. The highest doses were received by 30,136 residents of villages along the Techa River from 1950 to 1960 (10). Data on 30,000 first, second and third generation offspring of the original cohort were also collected. The study now has 50 years of follow-up of the 60,000 persons (parents and offspring). Other studies were done of plant workers.

Fourth, from August 29, 1949 to 1989, 456 above ground and underground nuclear and thermonuclear explosions of nuclear weapons were conducted by the Soviet Union at the Semipalatinsk Nuclear Test Site. Regions of the Northeastern part of Kazakstan were contaminated with high levels of radioactive fallout from tests. Between 1949 and 1962, 1.2 million inhabitants were exposed.

In the U.S. the most serious radiation exposures have been to populations in specific occupations. There have been longitudinal studies of workers at the Hanford nuclear power plant, at the Oak Ridge and Savannah River Nuclear Facilities, of workers at U.S. nuclear shipyards and of uranium miners in the Western U.S. The largest U.S. population exposure has been to residents of Utah and Nevada near the U.S. atomic bomb test range, where a three-fold elevation in leukemia risk was noted (11, 12), and to U.S. soldiers experimentally exposed to radiation during A-bomb tests in Nevada. There are studies of the effects of natural levels of radon gas in houses in the U.S., but the level of exposure is low relative to baseline so that identifying its effect on health has been difficult.

4. STUDIES ON EXPOSED POPULATIONS

The best-known and longest standing scientific study of IR exposure events is the Radiation Effect Research Foundation Studies (RERF) of the survivors of the 1945 Hiroshima and Nagasaki bombs. One limitation of that study is that, although some exposures were of a high level, all were short in duration. Moreover, due to the ravages of W.W. II on Japan, the study could not be fully implemented until approximately seven years after the war, with the consequence that about 2/3 of heavily exposed persons died before the study was fully initiated. Such massive mortality selection means that radiation effects were studied in persons who may have been preferentially resistant to IR effects. One indicator of such temporal selection is that the RERF studies did not find the same significant elevation (~45 fold) of childhood thyroid cancer risks as was found in studies done in Belarus shortly after Chernobyl. Failure to find this effect may have been due to a lower level of radioactive iodine in the A-bomb fallout (13) as well as the bio-selective effects of early mortality (14).

The two Russian events, Chernobyl (with extensive human exposure data for Russia, Belarus and the Ukraine) and Chelyabinsk, may offer the most useful longitudinal data sets to study the full range of IR health effects. The Obninsk registry studies of Chernobyl do not have the primary limitations of the RERF studies because they were started almost immediately after the Chernobyl event of 1986 and because they examined low level, but chronic (as well as acute), radiation exposure from both external and internal sources; furthermore they involve assessment of the effects of the bioaccumulation of long lived radionuclides in the human organism.

In Belarus coverage by a national population-based tumor registry extends up to 20 years before the Chernobyl accident occurred in 1986 – possibly forming a geographic and population across-time control area to better identify the population health effects of IR exposure. However until

2000, there had not been sufficient time for many Chernobyl-related solid tumor and other chronic diseases to become manifest (because the expected latency time for many solid tumors is 15+ years (15,16)). The mean age at exposure of Chernobyl Emergency Accident Workers (EAWs) in 1986 was 33 years – in 2003 the mean age will be 50 years. Consequently new analyses are now needed of the Chernobyl-exposed populations because significant portions of the cohort are just beginning to reach middle age when spontaneous (non-radiation induced) chronic disease prevalence starts to increase rapidly and because it is only now that the time since exposure has been long enough for solid tumor rates to increase (i.e., time since exposure > mean latency).

Most previous studies of Chernobyl workers were performed too soon after exposure and adult populations (low base line risk and few events) still too young to identify solid tumor risk. Indeed, recently in the study of Ukrainian EAWs, mortality rates for non-cancer causes of death have begun to increase; dramatic elevations of mental disorders are also being recorded (17). Furthermore, previous studies often did not include children, wives, or the elderly – crucial groups for investigating susceptible populations.

5. BIOLOGICAL MECHANISMS OF RADIATION DAMAGE

To understand the biological mechanisms by which IR affects population health, one must realize that the human organism is a complex multi-level system and that IR operates at the most basic molecular level within individual cells. Cellular effects would not be understandable without realizing that they are organized into highly differentiated, complex, communicating tissue systems whose functioning and interactions may be disturbed by dysfunction caused by radiation in specific tissues (e.g., thyroid or pituitary gland).

One of the first issues in conducting such analyses is the quantification of radiation dose. One of the basic measures of radiation is its energy. Radiation is also characterized by its type (for example, α, β or γ). α radiation reflects the effects of a Helium nucleus and, due to a relatively large particle mass, is extremely damaging to tissue, but has little tissue penetrance. Hence to cause damage, radionuclides must be chemically incorporated into tissues. β radiation are electrons that have modest tissue penetrance. γ radiation has higher energy but, because photons are massless, may impart less of that energy to tissue (i.e., it has lower biological efficacy). Also significant is neutron radiation of relatively high mass, but which is chargeless.

Though energy is one measure of radiation, in physiological studies it is often adjusted for the biological efficacy of energy transfer to tissue. This biological energy transfer measure is called the Sievert (Sv) and is defined as absorbed radiation dose (ratio between the absorbed energy by an object and its mass, called the Gray, Gy) multiplied by a biological efficacy coefficient. The problem with the Sievert is that the mechanism by which the radiation produces its effects is absorbed in the measures (i.e., the biological efficacy factor), making it tautological. This is problematic for the assessment of low doses of certain types of radiation, such as α radiation. It is less important for γ and β radiation because the biological efficacy coefficient for them is approximately equal to one; and the Sievert coincides with the Gray.

For example, Reference (1) describes three models in which low dose effects may occur. One is a "no" threshold model which says there is damage done at all energy levels, but that it cannot be detected below a certain level or that monitoring and repair mechanisms can correct its effects. Another model is the adaptive response (or hormesis) model, which suggests that in repairing damage, the cell is somehow made more fit by inducing repair mechanisms such as Heat Shock Protein (HSP). The third "bystander" model suggests that, through cellular communication (possibly by IL-8, cytokine generated by cells under oxidative stress), the distress of exposed cells is communicated to non-irradiated cells. Of interest is the direct confirmation of this concept in a recent article, which indicated that double strand breaks of nuclear DNA produced by low level IR was not repaired unless the energy was above 1.2 mSv (3).

The study of the internal structure of the cell is important. Nuclear DNA has extensive error monitoring and repair mechanisms. Mitochondrial DNA has few. The mitochondria is the energy production center of the cell and hence produces normally high levels of reactive oxygen species (ROS) – and even more so when damaged (e.g. due to electron "leakage"). Thus, the mitochondria should be more sensitive to exogenous sources of stress such as IR. Because of the high metabolic activity of the brain, this feature of cell structure should be considered in determining the effect of radiation on the cell – especially in terms of neurodegeneration. In this regard IR may produce the same type of stress, ROS, which stimulates many aging processes (18).

In studying the effects of IR on tissue, the differential radio-sensitivity of tissue types must be acknowledged. One tissue system known to be radiosensitive is bone marrow, and derivatively, immune function. Bone marrow sensitivity is a result of the rapid rate of cell division in marrow, meaning that high proportions of cells are in a radiosensitive state (DNA replicating) in which DNA is more susceptible to radiation damage. The gastrointestinal (GI) tract is also a cell tissue system that has a high rate of division and is sensitive to radiation effects.

The central nervous system (CNS) was thought not to be sensitive to IR because of a low rate of cell division. Only recently was it determined (19, 20) that stem cells function in the human brain at all ages. However, because the CNS is an area of high metabolic activity producing a high endogenous level of ROS and there may be frequent reformulation of synaptic connections due to protein

metabolism, the assumption that the CNS is radio insensitive might be incorrect. Thus CNS may be sensitive to IR directly and not just by affecting the arterial endothelium.

The liver, lung, kidney, and pancreas are relatively radio resistant, with most damage occurring because of effects on connective (stromal) tissue and the endothelium of small blood vessels feeding those tissues. Some tissues have higher sensitivity because of the chemical attractiveness of an ingested radionuclide. For example, due to its chemical similarity to calcium Sr_{90} is attracted to and incorporated into bone. Radioactive iodine is picked up by the thyroid preferentially. Damage to the organism may result from secondary and tertiary mechanisms such as altered thyroid hormone status – especially in growing children. A tissue where radiation effects may become symptomatic rapidly due to ROS generation is the optic lens (early cataracts).

What is unclear is how age related processes affect the radio sensitivity of tissue. From the perspective that cells in the elderly often divide more slowly, they may be less radiosensitive. From the perspective of the declining efficiency of stress-protective mechanisms (sulfhydrals, heat shock proteins) to: 1.) prevent proteins unfolding due to thermal stress and 2.) repair systems and apoptosis, the elderly may be more susceptible to radiation-induced damage. Theoretically, radiation can generate an acceleration of senescent physiological changes – especially those dimensions related to free radical damage and glycation of macromolecules. In Ukrainian EAWs, younger workers (under age 45) showed greater acceleration of senescent processes than older workers (21).

Clearly the "deep" hierarchal system of equations necessary to describe damage occurring at several levels of biological complexity is going to be intricate. In part this is an intrinsic limitation of collecting certain types of measures from intact living systems. For example, the effects of lipid peroxidation on nuclear and cellular membrane functions of ion transport are a subtle physiological process that is difficult to measure. What is needed is a strategy to identify the positive and negative feedbacks within the homeostasis/hormesis of the cells in complex living organisms (2).

6. FORMAL CONSTRUCTION OF A "DEEP" (MULTIPLE LAYERS OF BIOLOGICAL ORGANIZATION) RADIATION DAMAGE MODEL

To study the effects of IR on population health, we need a model that describes the dynamics of the health and mortality of an individual. To do this we developed a model based on the well known FPK equation (22) for a diffusion process and describing both the dynamics of multiple risk factors (i.e., state variables in J-dimensional state space) and of mortality (estimable from longitudinal studies of human risk factor changes and mortality {23)). Parameters of that model can be used to calculate life table functions dependent on multi-covariate diffusion processes (24). The initial model assumed linear state variable dynamics, an initial multi-variate normal distribution of risk factors, and a quadratic mortality function. Maximum likelihood (ML) procedures for estimating parameters of that model are discussed in Reference (16).

Manton *et al*., (25) eliminated the model's restriction to Gaussian diffusion processes by assuming that each of the J-1 state variables operating in a convexly constrained/bounded diffusion process was Bernoulli-distributed, with probability mass renormalization in each life table "projection" interval (26-29). They further generalized the model by making the quadratic hazard a function of an age-dependent mortality function (such as the Gompertz or Weibull (30)).

This model was used to analyze the Framingham Heart Study (46-year follow up), the Framingham Offspring Study (20-year follow-up), the Honolulu Heart Study, and the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) studies – all longitudinally followed human populations with measures selected from chronic disease risk factor measures (e.g., serum cholesterol; systolic blood pressure) (31). Exploiting the biological richness of the models' parameter space makes it possible to combine data set experiences by capturing population differences in specific parameters (e.g., study-dependent initial conditions; age by initial state variable interactions). Thus, scale invariance, and hence robustness, may be achieved by using theoretically motivated parameter constraints. This has been used to compare risk factor dynamics and mortality, both in longitudinal studies studied cross-nationally (32) and in risk factor surveys studied cross-nationally (33).

The interaction of state variable dynamics and mortality is described by extending the FPK equation for a probability distribution function, *f(x)*,

[1]

$$\frac{\partial f(x)}{\partial t} = -\sum_j \frac{\partial}{\partial x_j}\left[u(x,t) f(x)\right] + \frac{1}{2}\left[\sum_j \sum_{j'} \sigma^0_{jj'}(x,t) \frac{\partial^2 f(x)}{\partial x_j \partial x_{j'}}\right] - \mu(x,t) f(x),$$

where $x \equiv x_i(t)$ is the *j*-element vector of measurements (state variables) for individual *i*. The first term describes regression or drift (*u(x,t)*), the second diffusion ($\sigma^0(x,t)$), and the third mortality ($\mu(x,t)$).

Equation [1] describes the change in the probability distribution function (pdf) for a population in which the evolution of an individual's state and survival probability *S(x)* is described by two random walk equations (23)

[2]

$$dx = u_0(x,t)\,dt + \sigma(x,t)\,dw(t),$$

and

[3]

$$dS(x) = -\mu(x,t) \cdot S(x) \cdot dt,$$

where *w(t)* is Wiener's process. These equations describe the future values of *x* and $S(x)$.

In discrete time the stochastic process model requires linear Markovian dynamics, Gaussian diffusion and quadratic mortality. The equations corresponding to (2) and (3) for a population are,

[4]

$$x_{t+1} = u_0 + Rx_t + \varepsilon_{t+1},$$

and,

[5]

$$\mu(x_t) = \mu_0 + q^T x_t + x_t^T Q' x_t.$$

Scalar μ_0, vectors u_0 and *q*, and matrices *A* and Q' are estimated by ML. The first generalization made the hazard dependent on a function of age representing unmeasured state variables affecting survival (29) or,

[6]

$$\mu(t) = \mu(x_t) F(t).$$

Selection of the age-dependent function *F(t)* depends on theoretical arguments (e.g., Strehler-Mildvan specialized their model using a Gompertz ($e^{\theta t}$). Rosenberg *et al*., (34) used a Weibull (t^{m-1}) to model the thermodynamics of protein denaturation.

An important generalization of the model is to include fertility. A number of theoretical models of aging imply a theoretical linkage of fertility and longevity – and hence of the rate of physiological aging change (35,36). This is because reproduction and growth are viewed as competitors for energy with processes of cell maintenance in lower organisms. This concept leads to the view of caloric restriction as a way of increasing longevity by lowering oxidative stress. However, humans are far more complex than these organisms (e.g., in terms of tissue receptors for IGF-1, insulin and GH) so that caloric restriction may operate in quite different ways (37).

Since a human population is usually non-homogeneous, we need to divide it into several groups (compartments) with similar characteristics. Such a concept is used to construct so-called compartmental models (38). Within each compartment, parameters of the model vary smoothly while they can be qualitatively different in distinct compartments. Two natural compartments in a population are males and females. It is reasonable to distinguish them by introducing an additional gender-specific index *g*. Let $f_d(x,t,g) \equiv f_d(\cdot)$ be the probability density function for $x(t)$ for state *d* at time *t* for a male (*g=m*) or female (*g=f*) state space. We will use this design to model the multi-dimensional correlation of mortality and senescence with reproduction and growth and to determine how that multi-dimensional correlation function might be affected by IR. Then we have (39):

[7]

$$\frac{\partial f_d(\cdot)}{\partial t} = -\Psi\left(u_j, \sigma^0_{jj'}, f_d(\cdot)\right) + \sum_{k \neq d} \lambda_{kd}(x) f_k(x,g) - f_d(\cdot) \sum_{k \neq d} \lambda_{dk}(x) - \mu(x,g,t) f_d(\cdot)$$
$$+ \delta(x_1) \sum_{k=1}^{d} \sum_{k'=1}^{d} \int_{X_f} \int_{X_m} dx_f dx_m G_d\left(x, x_f, x_m, g\right) B_{kk'}\left(x_f, x_m\right) f_k\left(x_f, f, t\right) f_{k'}\left(x_m, m, t\right)$$

, where

[8]

$$\Psi\left(u_j, \sigma^0_{jj'}, f(\cdot)\right) = \sum_j \frac{\partial}{\partial x_j}\left[u_j f(\cdot)\right] + \frac{1}{2}\left[\sum_j \sum_{j'} \sigma^0_{jj'} \frac{\partial^2 f(\cdot)}{\partial x_j \partial x_{j'}}\right]$$

and $u = u(x,t), \sigma^0 = \sigma^0(x,t)$.

Equation [7] represents the distribution of the risk factors and discrete states, given an initial state. This is similar to FPK equations for continuous processes [1], though we allow a person to move between compartments. The last term in [7] represents the growth of probability mass through birth. Integration is over male and female state space, with the kernel fertility function $B_{kk'}\left(x_f, x_m\right)$ modeled in a similar fashion to mortality (i.e., an age/time dependent quadratic form (39)). Function $G_d\left(x, x_f, x_m, g\right)$ describes the state space distribution for male and female newborns for state *d*. Initially it can be modeled as a product of Gaussian distributions of deviations of risk factors from means, which can be functions of parent states *d*. Dirac's delta–function $\delta(x_1)$ reflects that newborns have zero age ($x_1 = 0$). Coefficients λ_{kd} and λ_{dk} represent rates of redistribution between compartments.

The central methodological question is how to model the inter-related systems linking physiological, tissue and cell parameters, and nuclear and mitochondria DNA and RNA in a way that preserves structural information about molecular dynamics. One strategy is to generalize a mixed effects regression model [4] as,

[9]

$$x_{t+1} = u + \left(R + C_y y_t\right) x_t + \gamma_y y_t + \varepsilon_{t+1},$$

where *x* is the vector of individual organism's level health measures, as described above, and *y* is the vector of measures of the physiological functioning of specific tissue systems. In distributed effect models, *R* would be the response parameter for person *i*. This parameter has some specific distributions, such as the gamma (40). Instead, we model the distribution of effects over individuals empirically as the field effects ($C_y y$) in the interaction term. Thus the effect C_y is modulated over the distribution of *y*, where *y* is the tissue-specific functional capacity for the i^{th} person who has the state vector *x*.

This model is then projected down to the cellular/molecular level by a tissue specific function,

[10]

$$y_{t+1} = u_y + \left(R_y + C_z z_t\right) y_t + \Lambda_z z_t + \varepsilon_{t+1},$$

where z is a vector of molecular kinetic parameters, which may include indices of the topology of specific biochemical structures and which represents the new stochastic field effects for molecular activity within cells (41). The system of equations represents a three-fold convolution of multi-variate distribution functions. Full information on estimates of parameters would involve evaluations of complex integrals across the various levels.

Due to reactions with the host molecule, (e.g., Sr_{90} competes with Calcium for binding sites in bones or myocardium), it is in the mechanisms involving z, their diffusion over tissue systems (e.g., thyroid, pituitary or gonads), and their interactions over the biological fields (reflected in $C_z y$) we need to describe the effects of IR in terms of energy transfer or, as for a specific nuclide, the energy transfer for a nuclide embedded in an organic chemical structure.

Theoretically, one way to represent such biological "deep" structures (despite a paucity of direct molecular information) is to specify the effects of radiation in terms of individual factors (for example, IR may increase the uncertainty of accurate genetic transmission of information). This may be done by affecting one, or more, genes in the cell's nucleus. This genetic "discrete" failure model may be described by the Weibull hazard process (42) so that the effects of radiation on overall mortality might be described as,

[11]

$$\mu = \left(x^T Q x\right) \alpha_S(D)\, t^{m-1},$$

where α is a scale factor that changes as a function of dose, D, Gy; $x(t)$ is the stochastic state dynamic process described above. In practice, the process may involve both nuclear and mitochondrial DNA, so that two linked failure processes might be written,

[12]

$$\mu = \left(x^T Q x\right)\left[\alpha_N(D)\, t^{m_N - 1}\right]\left[\alpha_{mt}(D)\, t^{m_{mt}-1}\right]$$

.

Equation [12] implies that the integral over the DNA_{mt} and DNA_N failure processes is independent and that their time path may be described by Weibull functions with different scale (α) and shape (m) parameters, with scale parameters as a function of the intensity of radiation exposure D. The difference in the parameters is likely due to the greater simplicity of the DNA_{mt}, with fewer error monitoring and repair functions (43, 44) and with a mutation rate 1000 times that of DNA_N. Also of significance is that there are multiple mitochondria in each cell and that the mitochondria provide the energy for the cell to function through oxidative reactions so that the density of ROS in mitochondria is high. The m_N and m_{mt} represent the genetic errors that have to occur before nuclear or mitochondrial dysfunction occurs. Since they refer to discrete genetic changes, each of these can be modeled as a function of IR dose and other cell traits.

Because there is extensive data supporting threshold models for the effects of radiation, we take into account feedback representing adaptation of the physiological functioning of an organism to the change of the environmental conditions (including radiation). Hence, we project the effect of the physiological parameters to the mini (tissue) and micro (cellular, molecular) levels. This requires coupling equations [9] and [10],

[13]

$$x_{t+1} = u_x + \left(R_x + C_y y_t\right) x_t + \gamma_y y_t + \varepsilon_{t+1},$$
$$y_{t+1} = u_y + \left(R_y + C_z z_t\right) y_t + \Lambda_z z_t + B x_t + \varepsilon_{t+1}.$$

The cellular multiplicity of mitochondria and the energy dependence of nuclear functions on mitochondrial function should also be recognized in the model structure. Estimation of those equations will be complicated in that the likelihood function will involve actions at multiple distinct levels of organization. It is also crucial to determine how that organization will be built into the functions.

Thus, each individual is comprised of a structured system of tissues; each tissue system is a structured system of cells and inter-cellular connections; and each cell is a structured set of molecular and inter-related kinetic trajectories. Then, state dynamic equations for x are replaced with the deep structure equations similar to [13]. To complete the model we explicitly specify [7] for IR exposed populations.

At the beginning we can assume that the population is homogeneously exposed to radiation. Therefore, we can separate groups of healthy persons, persons subject to conventional cancers, and persons with radiation-induced cancers, and then allow transitions between the three main compartments (since individuals can become ill or recover) to produce,

[14]

$$\frac{\partial f_H}{\partial t} = -\Psi\left(u_j, \sigma^0_{jj'}, f_H\right) - \sum_l \left(\alpha_l + \alpha_l^R\right) f_H + \sum_l \left(\beta_l f_l^C + \beta_l^R f_l^R\right) + \Upsilon_H - \mu(x,g,t) f_H$$

,

[15]

$$\frac{\partial f_l^C}{\partial t} = -\Psi\left(u_j, \sigma^0_{jj'}, f_l^C\right) + \alpha_l f_H - \beta_l f_l^C - \mu_l^C(x,g,t) f_l^C + \Upsilon_C$$

,

[16]

$$\frac{\partial f_l^R}{\partial t} = -\Psi\left(u_j, \sigma^0_{jj'}, f_l^R\right) + \alpha_l^R f_H - \beta_l^R f_l^R - \mu_l^R(x,g,t) f_l^R + \Upsilon_R$$

,

and the fertility function is

$$\Upsilon_w = \delta(x_1) \sum_k \sum_{k'} \int_{X_f} \int_{X_m} dx_f dx_m G_w\left(x, x_f, x_m, g\right) B_{kk'}\left(x_f, x_m\right) f_k\left(x_f, f, t\right) f_{k'}\left(x_m, m, t\right).$$

Here $w = H, C, R$; k and k' runs over discrete states as H, C, R and l; g is the gender parameter (m for males and f

for females); $u = u(x,t)$; $\sigma^0 = \sigma^0(x,t)$ and $f \equiv f(x,g,t)$. Operator $\Psi(\cdot)$ is given by [8]. Index "C" means conventional and "R" indicates radiation-induced cancers. α (α^R) is the spontaneously (radiation-induced) cancer rate; β (β^R) is the rate of recovery after spontaneous (radiation-induced) cancer. Index *l* runs over specific cancers (or, more generally, causes of death).

On the organism level the radiation-induced cancer rate α^R can be represented as $\alpha^R = \alpha \cdot ERR$, where the additional cancer risk *ERR* (the Excess Relative Risk) depends on the IR dose and age (x_1) at exposure as,

[17]

$$ERR(D,x_1) = \frac{D}{D_0}\exp\left(-\frac{x_1 - 25}{\tau}\right).$$

Here risk parameters D_0 and τ might be taken as $D_0 = 2.2$ Gy (males), $D_0 = 1.3$ Gy (females) and $\tau = 38.5$ years (45). In general, coefficients with the index "R" depend on the risk factors *x*, which reflect the effect of the radiation exposure on cellular/molecular levels as described by [13]. Other coefficients are, generally, age- and time-dependent. In the case of a non homogeneous radiation dose, we separate subpopulations with nearly homogeneous doses. Then, for each of these compartments a system of equations similar to [14] – [16] has to be written or, if appropriate, an IR field effects interaction may limit the model to one system of equations. The latter is preferable if information is limited and theoretical insights about mechanisms are to be generated.

Epidemiological data are usually collected during several surveys conducted at fixed times in which physiological variables are measured and diagnoses (according to, for example, ICD-10 classification) are identified. These data are treated by maximizing the likelihood and fitting parameters in models that describe covariate dynamics and risks of mortality or radiation-induced disease incidence as a function of covariate dynamics. Likelihood construction must also reflect the specifics of data collection, (e.g., if time intervals between measurements cannot be fixed and there is missing data). In this case a stochastic process model may be used. Stochastic differential equations for incidence, mortality, and changes of risk factors can deal with missing data and allow use of exact dates of birth and death – or other censoring events (28),

$$\mu(x(t),t) = \mu_0(t) + 2b(t)x(t) + x^*(t)B(t)x(t),$$

and

$$dx(t) = \left[a_0(t) + a_1(t)x(t)\right]dt + a_2(t)\,dW_t.$$

These equations describe changes only in second order moments. As non-linear terms are added into the dynamic equations we can better model non-gaussian diffusion by introducing the second and higher order moment spaces into the dynamic equations by defining interaction terms as in Reference (31).

The resulting likelihood is,

[18]

$$L = \prod_{i=1}^{N}\hat{\mu}\left(\tau_i,\hat{x}(\tau_i)\right)^{\delta_i}\exp\left(-\int_0^{\tau_i}du\hat{\mu}\left(u,\hat{x}_i(u)\right)\right)\prod_{j=1}^{k_i}f\left(x_i\left(t_j\right)\mid\hat{x}_i\left(t_{j-1}\right)\right),$$

where $f\left(x_i\left(t_j\right)\mid\hat{x}_i\left(t_{j-1}\right)\right)$ is a density that is conditional on prior observations, τ_i are ages of events, δ_i indicate censoring, t_j are observation times, and $\hat{x}_i\left(t_j\right)$ are discrete jumps observations *i* and *j* run: a.) over individuals and b.) examinations of each individual. The equation

$$\hat{\mu}(\hat{x}(t),t) = m^*(t)B(t)m(t) + 2b(t)m(t) + tr\left[B(t)\gamma(t)\right] + \mu_0(t)$$

has the sense of a right-continuous mortality rate (28).

By generalizing the Cameron-Martin equations (28), vector $m(t)$ and matrix $\gamma(t)$ are defined by systems of ordinary differential equations at intervals $\left[t_j,t_{j+1}\right)$.

$$\frac{dm(t)}{dt} = a_0(t) + \left[a_1(t) - 2b(t)\right]m(t) - 2\gamma(t)B(t)m(t), \qquad m\left(t_j\right) = \hat{x}\left(t_j\right),$$
$$\frac{d\gamma(t)}{dt} = a_1(t)\gamma(t) + \gamma(t)a_1^*(t) + a_2(t)a_2^*(t) - 2\gamma(t)B(t)\gamma(t), \qquad \gamma\left(t_j\right) = 0.$$

Assumptions about the time dependence of $a_{0,1,2}(t)$, $b(t)$, and $B(t)$ are needed, (e.g., a Gompertz dependence for hazard parameters). Birth can be considered as a risk with the same approach used for parameter estimation. Genetic information can be included in the dynamics and mortality functions generalized to non-Gaussian diffusion and nonlinear dynamics. By introducing this information as an interaction with other variables, we introduce nonlinear dynamics into the system, (i.e., dynamics differ between different genotypes and in specific ways with specific physiological parameters). Thus, such longitudinal population data allow us to perform a wide range of studies to discover correlations among the physiological mechanisms of genotype, age, radiation and disease incidence.

7. CONCLUSION

We have developed a general analytic model to study the effects of IR on human population health. This model is constructed to be consistent with "deeper" biological mechanisms. It links (through a multi-dimensional correlation function, reproduction, and growth processes) with senescence – a dynamic equilibrium suggested by several models of human aging and their evolutionary interpretations. We believe that such approaches will greatly expand the insights available with

the extant rare data in longitudinal health changes in human populations exposed to IR.

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