DoReMi
Integrating Low Dose Research

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Modelling low dose and chronic irradiations

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- Variables of the model
- How it has been implemented
- Brief description of its structure
- Results
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Purpose: to model the effects of low dose rate irradiations on cellular cultures

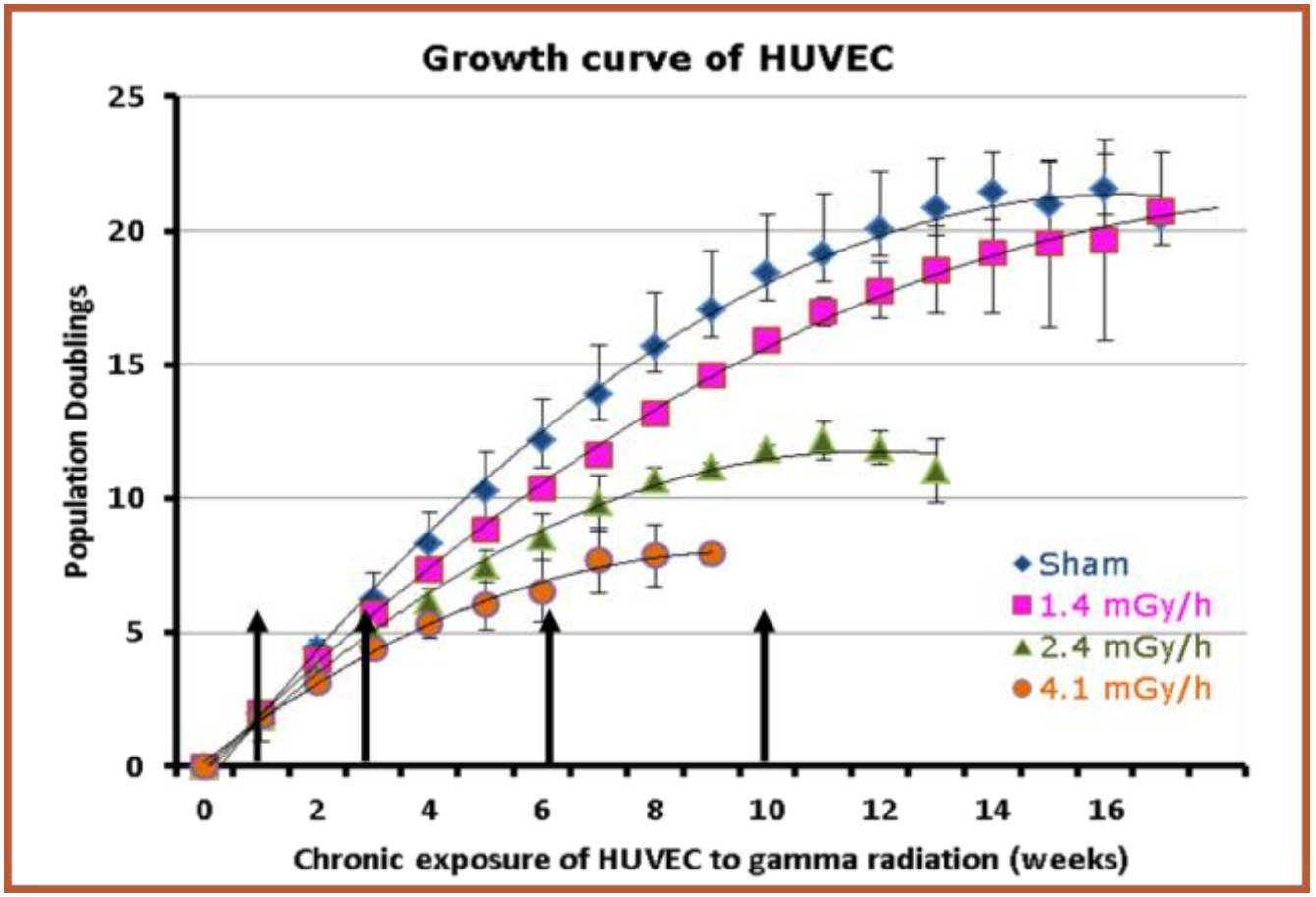
Model initially built to study the adaptive response, with priming doses of the order of 10-100 mGy delivered at dose rates of the order of 10-1000 mGy/h. Now updated to study chronic irradiations at lower dose rates.

Main variables and processes present in the model

- DNA damage of two different classes: sub-lethal and lethal
- DNA damage induction directly by radiation and by radicals (indirect damage)
- Efficiency of DNA damage repair
- Radicals production and scavenging
- Modulation of repair efficiency by senescence and by radiation

We want in particular compare with the results obtained concerning the effect of chronic irradiations with different dose rates on the proliferative senescence and premature senescence of HUVEC (primary human umbilical vein endothelial) cells. The study of these cells has been the subject of the Task 7.3 of DoReMi, aimed at performing a “feasibility study towards a system biology approach of radiation response of the endothelium”.

Specifically, our purpose is to compute, based on the output of our model, the growth curve, to be compared with that obtained with the experiments performed at Stockholm University (leader of Task 7.3).



Population doublings of the HUVEC cells used in the task 7.3 of DoReMi: sham and three irradiated samples at different dose rates:
1.4 mGy/h, 2.4 mGy/h, 4.1 mGy/h.

Replicative senescence

It is the essentially irreversible loss of replicative capability

- Telomeres shortening
- Stress such as:
    - DNA damage
    - Excessive mitogenic stimulations
    - Chromatin perturbation

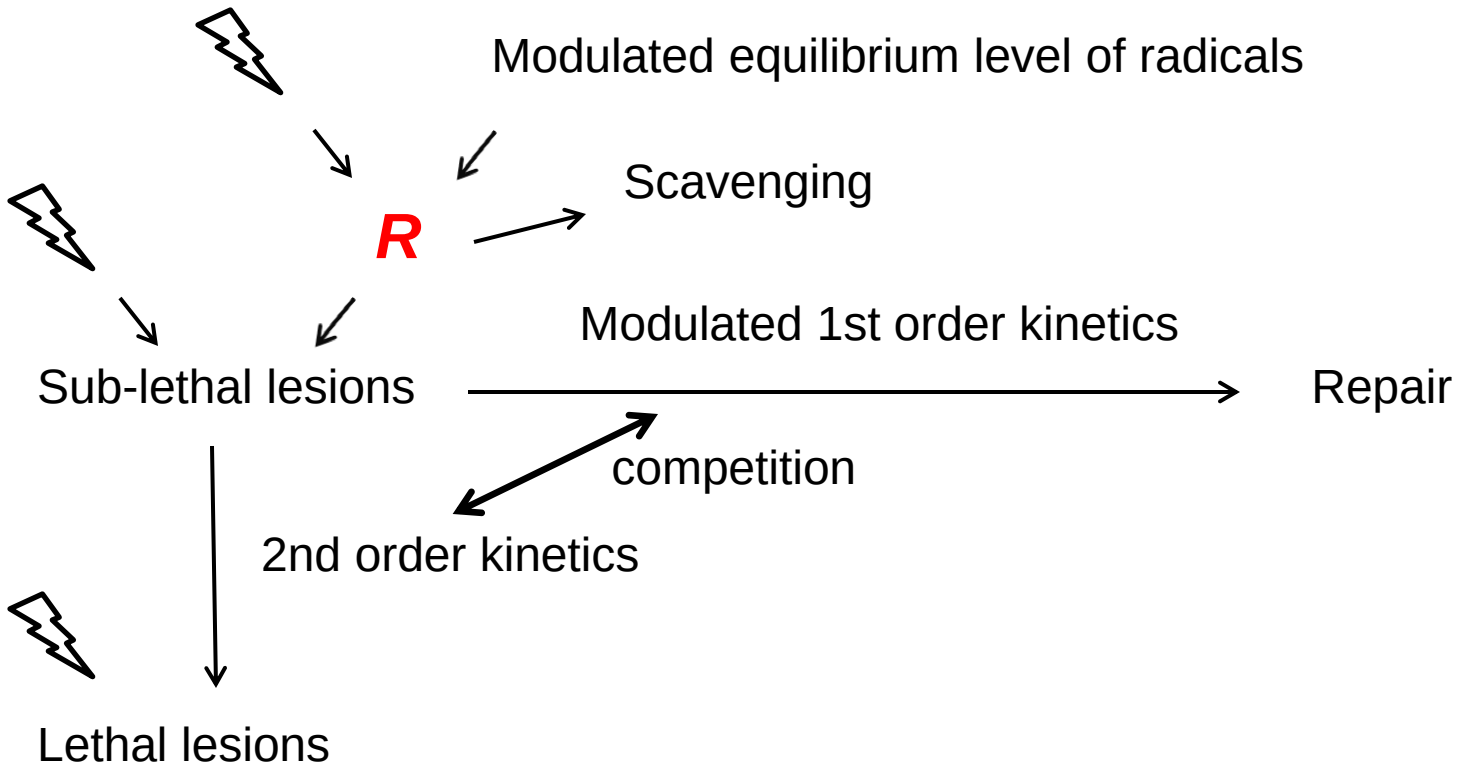
Associated with

- Equilibrium shift between ROS and antioxidant defences, leading to an increase of damage on macromolecules
- Decrease of efficiency of pathways of DNA repair

The mentioned association between senescence, and aging in vivo, and the oxidation shift in the redox state of the cells does not imply that damage by radicals is the only cause.

In our model, which has a limited number of variables, we assume the radicals (and the anti-oxidant enzymes) and the efficiency of DNA repair damage as the primary actors.

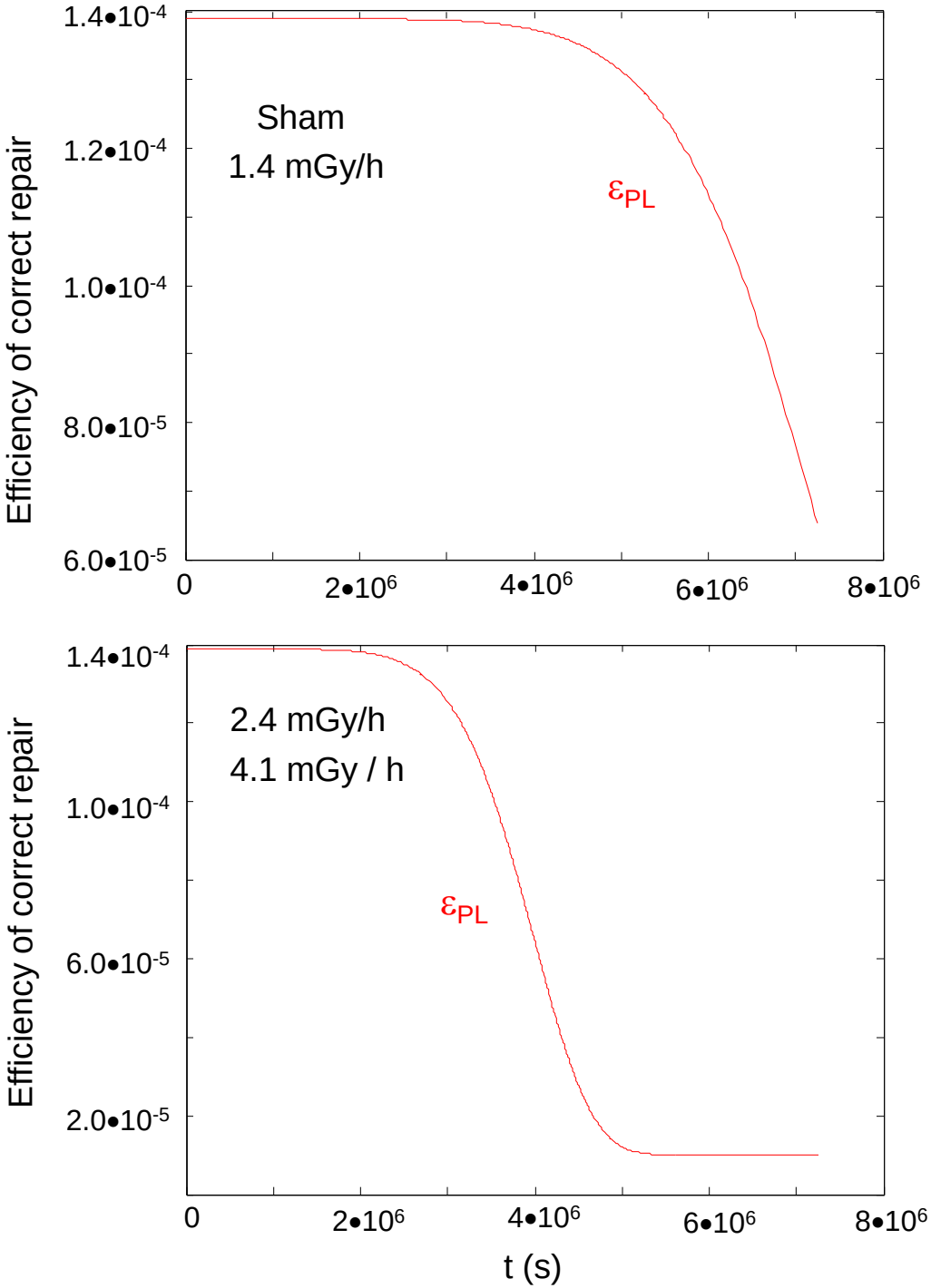
Also, the stress represented by ionizing radiation is not assumed to trigger different senescence causes, but to modulate the same variables, inducing a premature senescence.

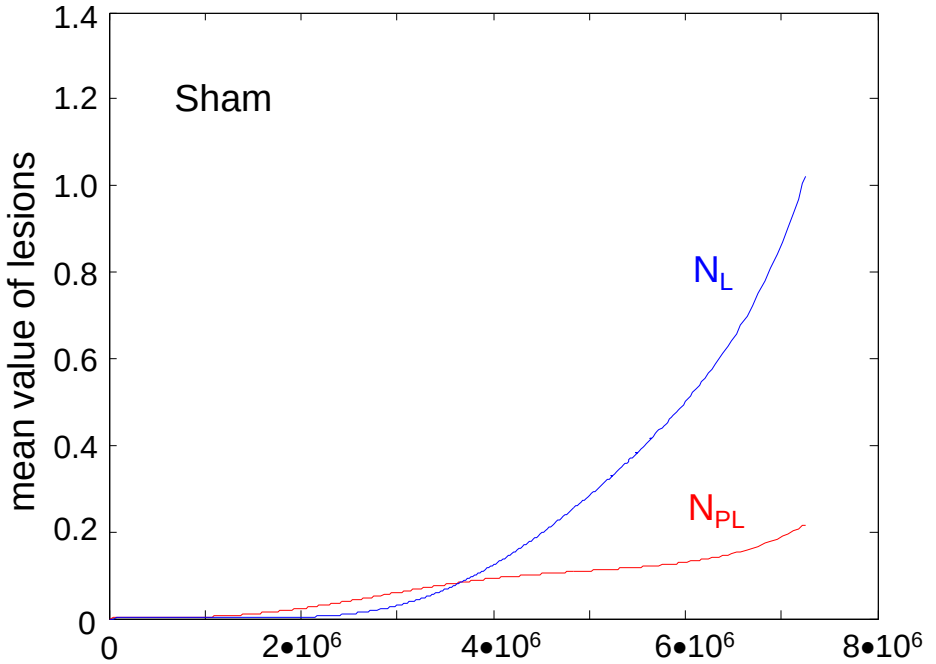


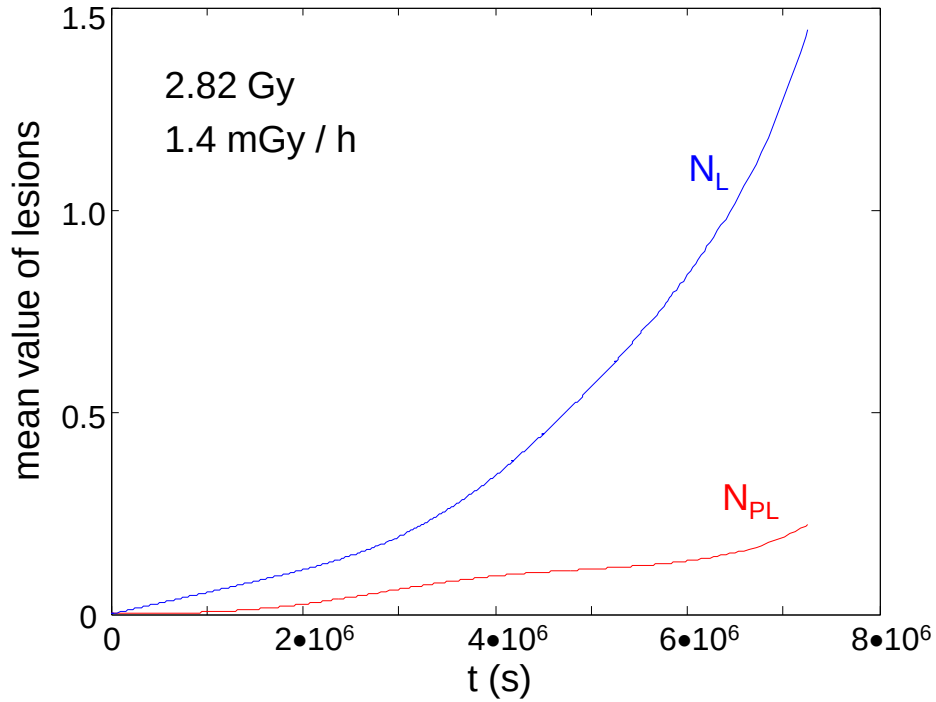
N_{PL} ≡ #(sub-lethal lesions)

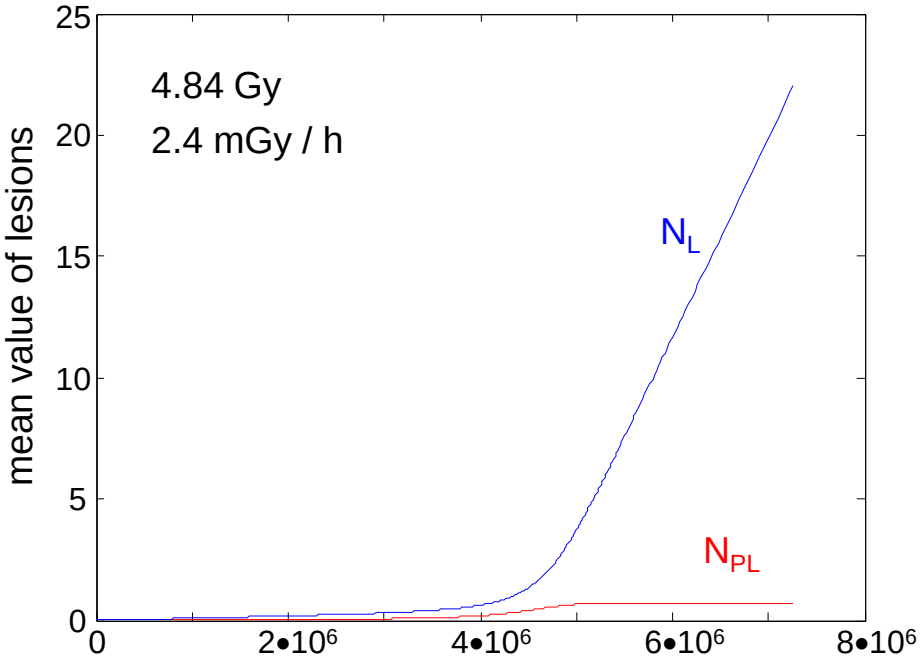
N_L ≡ #(lethal lesions)

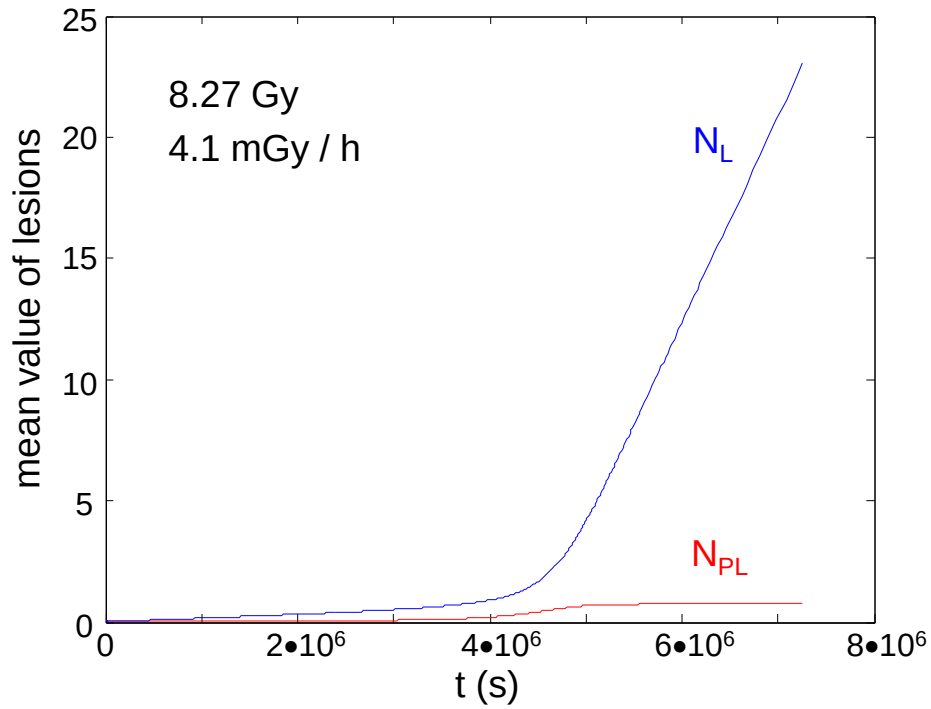
Fraction of non-senescent cells = exp[- N_L]


Efficiency of correct repair
1.4•10-4
1.2•10-4
1.0•10-4
8.0•10-5
6.0•10-5
Sham
1.4 mGy/h
εPL
0
2•10⁶
4•10⁶
6•10⁶
8•10⁶
Efficiency of correct repair
1.4•10-4
1.0•10-4
6.0•10-5
2.0•10-5
2.4 mGy/h
4.1 mGy / h
εPL
0
2•10⁶
4•10⁶
6•10⁶
8•10⁶
t (s)


Sham
mean value of lesions
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
N_L
N_{PL}
0
2•10^6
4•10^6
6•10^6
8•10^6


2.82 Gy
1.4 mGy / h
mean value of lesions
1.5
1.0
0.5
0
N_L
N_{PL}
0
2•10^6
4•10^6
6•10^6
8•10^6
t (s)


4.84 Gy
2.4 mGy / h
mean value of lesions
N_L
N_{PL}
0
5
10
15
20
25
0
2•10^6
4•10^6
6•10^6
8•10^6


8.27 Gy
4.1 mGy / h
mean value of lesions
N_L
N_{PL}
0
5
10
15
20
25
0
2•10^6
4•10^6
6•10^6
8•10^6
t (s)

M(t) = number of cells at time *t*

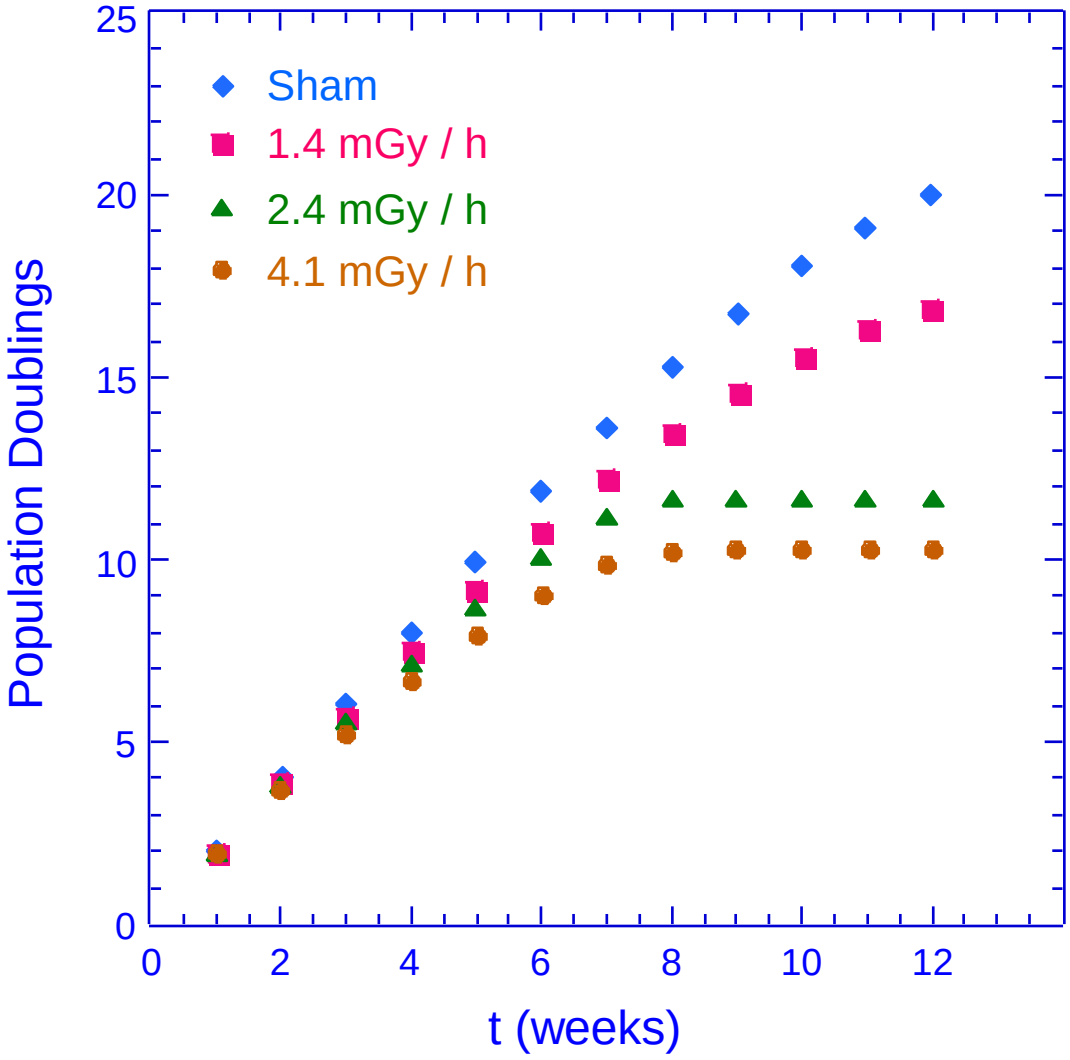
$$\frac{\mathrm{d}M}{\mathrm{d}t} = ap(t)M(t) \qquad a = \frac{\ln 2}{t_2}$$

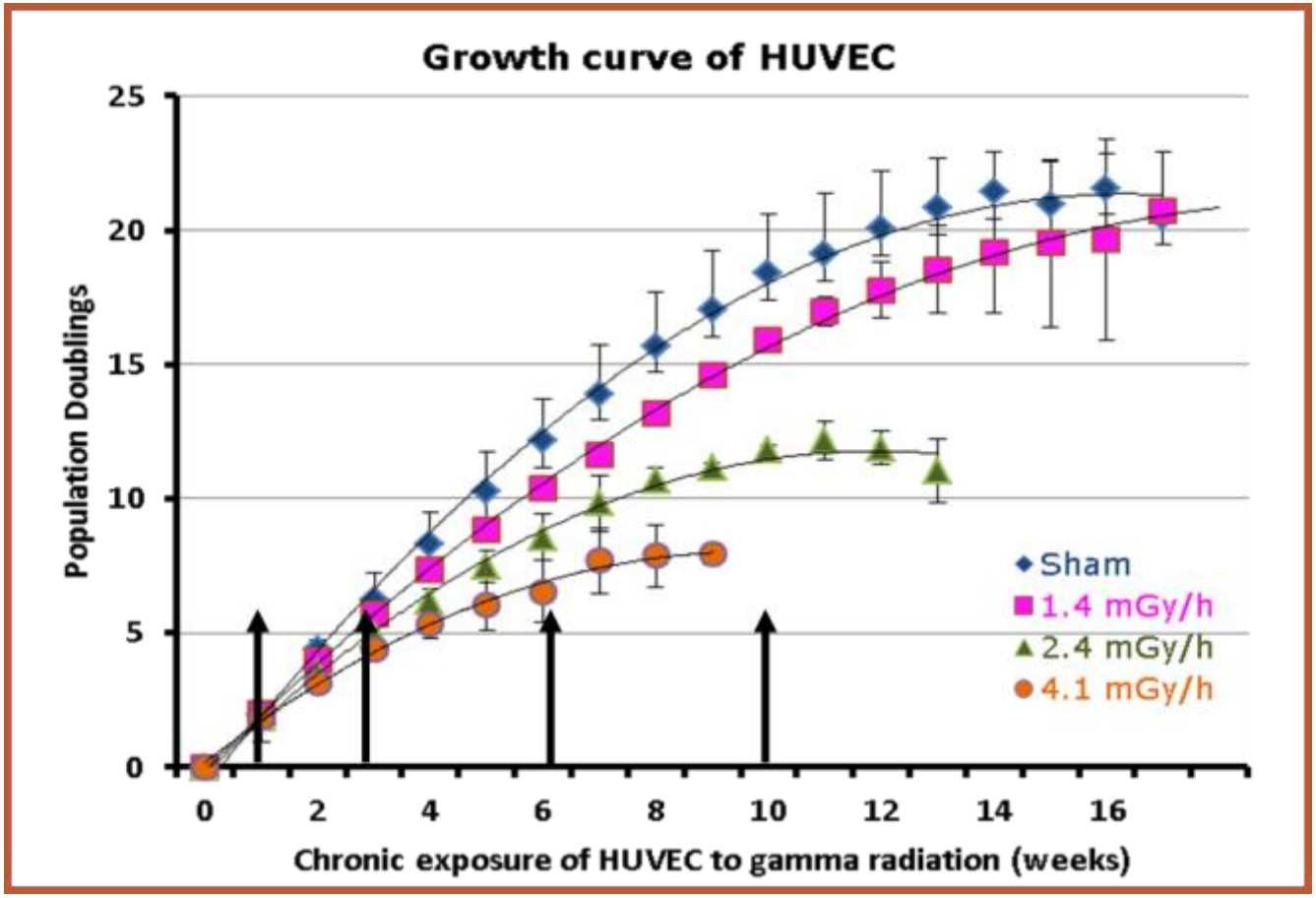
t_2 = doubling period (taken to be 3.5 days)

$$p(t) = \exp[-N_L(t)]$$

If no damage *p(t)* = 1: unperturbed exponential growth

Population doublings = $\log_2 \frac{M(t)}{M(0)} = \frac{1}{t_2}\int_0^t \mathrm{d}t' p(t')$


Sham
1.4 mGy / h
2.4 mGy / h
4.1 mGy / h
Population Doublings
t (weeks)
0
5
10
15
20
25
0
2
4
6
8
10
12


Growth curve of HUVEC
Population Doublings
25
20
15
10
5
0
0
2
4
6
8
10
12
14
16
Chronic exposure of HUVEC to gamma radiation (weeks)
Sham
1.4 mGy/h
2.4 mGy/h
4.1 mGy/h

Summary

- Replicative senescence described by a progressive increase of the level of radical production and a progressive decrease of repair efficiency
- Chronic low-dose rate irradiation enhances these processes
- Non-senescent cells are those without lethal damage
- Comparison with experimental growth curves of HUVEC cells.

Perspectives

- Introduce different structures for endogenous damage and radiation induced damage
- More detailed study of the roles of redox shift and repair efficiency
- Introduce cell signalling
- Previous points require a substantial extension of the model