Prediction of changes in the frequency of chromosome aberrations in peripheral blood lymphocytes after radiotherapy

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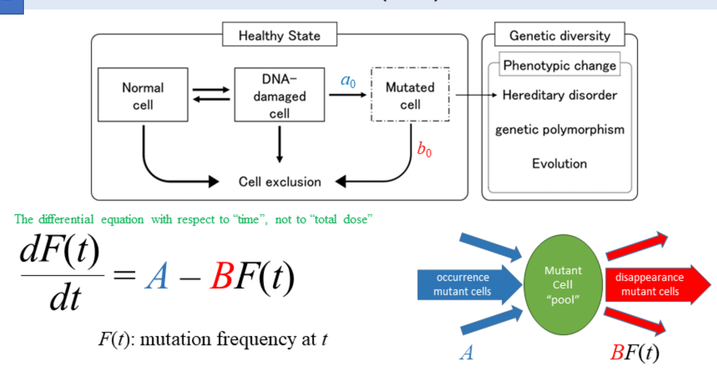
1. Introduction

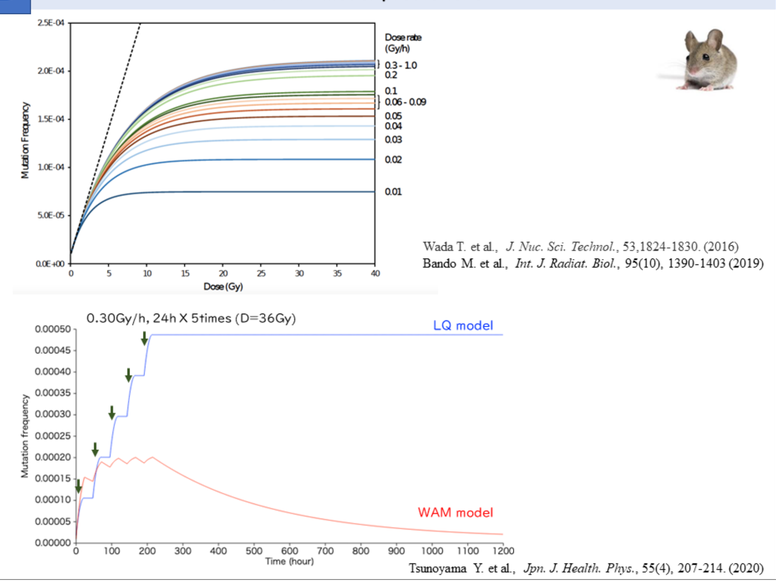
We have already shown that the WAM model (Whack-a-mole model) reproduces very well the measured data obtained in the past irradiation experiments to investigate the genetic effects in various plants and animals [1-4]. The obtained results show that the frequency of mutations in the next generation of irradiated individuals decays with time after irradiation. This binomial mathematical model also has the potential to reproduce a variety of other biological phenomena that vary with time.
Then, in this study, we calculated the parameter sets of the WAM model from the measured data and attempted to reproduce and predict the variation in the frequency of chromosome aberration occurrence in peripheral blood lymphocytes after radiotherapy.

2. WAM model

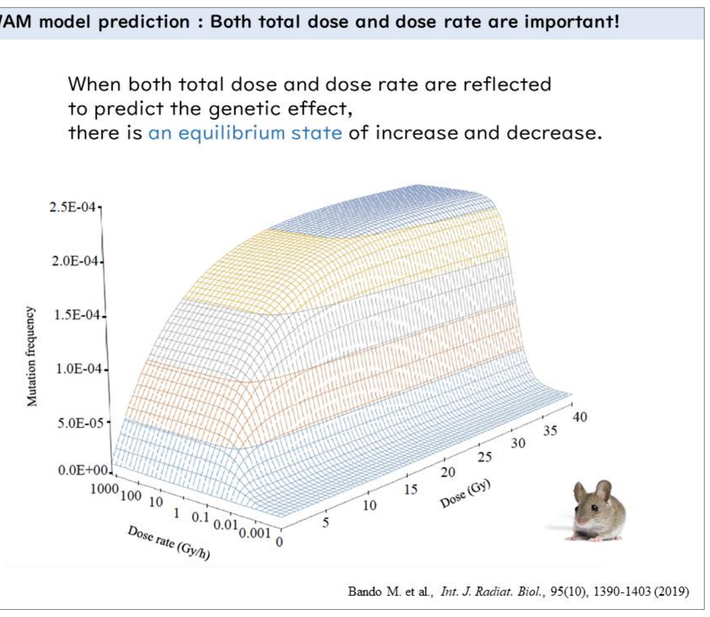
A Whack-A-Mole (WAM) Model



B WAM model predictions



C WAM model prediction : Both total dose and dose rate are important!



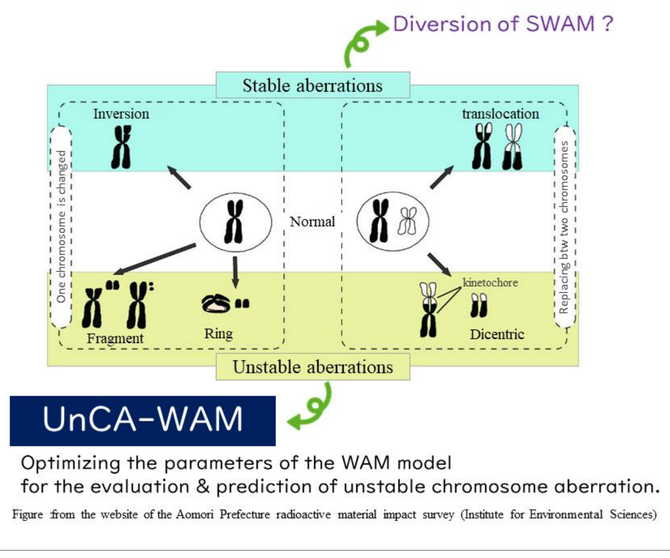
A) The core idea of the WAM model is just two things. (1) A pool of mutant cells is assumed to be the bottleneck. (2)The term of "time" is included in the formula. As a result, we can now calculate the genetic effect in also the cases the dose changes from time to time.

B) The upper graph shows the difference in mutation frequency by dose rate in mice. As the dose rate increases, the mutation rate increases, but it will eventually reach a steady state at any dose rate. The graph below shows a case of fractionated irradiation. The blue line is calculated by use of LQ model, and the red is for the WAM model. In the WAM model, the frequency gradually decreases with the length of time during cooling and after the completion of irradiation.

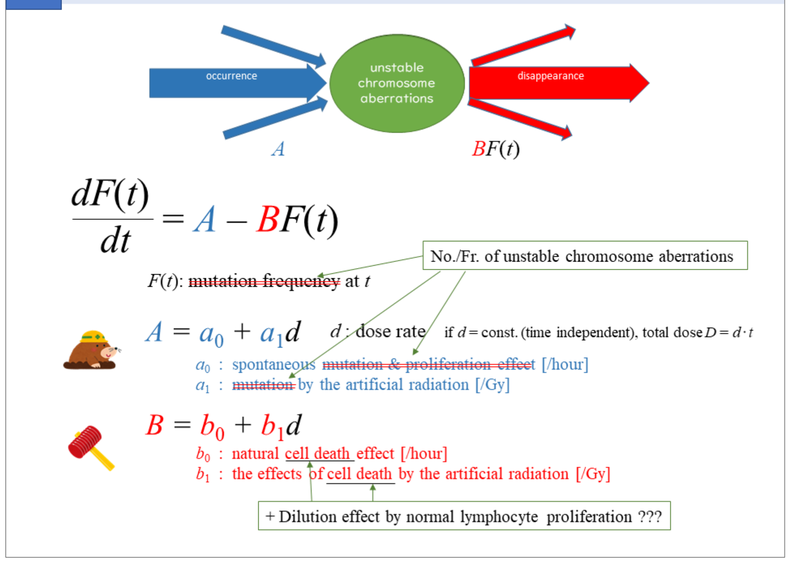
C) 3D graph of total dose, dose rate, and mutation frequency. There is an equilibrium state of increase and decrease of the frequency.

3. From WAM to UnCA-WAM

D UnCA-WAM overview



E WAM to UnCA-WAM



D) Chromosome aberrations increase in proportion to the exposed dose. Unstable type aberrations cannot be duplicated because of their chromosomal structure. For this reason, the number of cells with such aberrations (Cu cells) decreases with time dependent manner after exposure.

E) In order to divert the WAM model for the calculation of unstable chromosome aberration frequencies, each parameter in the WAM model needs to be redefined. In the mathematical model for calculating the frequency of unstable chromosome aberrations (UnCA-WAM)
a0: spontaneous aberration, a1: the aberration caused by irradiation, b0: the spontaneous disappearance of lymphocytes, and b1: the disappearance of lymphocytes caused by irradiation. b0 may include the dilution effect of normal lymphocyte proliferation.

4. Results

F UnCA-WAM parameters

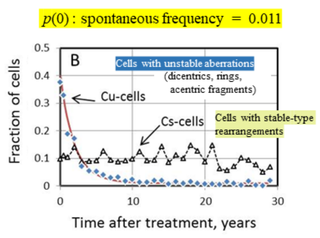
"Lymphocyte lifetime: Determination by elimination rate of chromosome aberration in radiotherapy patients"
Human Radiation Cytogenetics Archives, RNC, Kyoto Univ.

[B] **Buckton et al. 1978** (40-50 h culture)
Analysis in 58 patients treated X-rays for ankylosing spondylitis. Irradiation was applied along the spinal strip field to give a total skin dose of 1,500, 2,000 or 2,500 rads (15, 20 or 25 Gy) in 10 fractions in 12 to 14 days.

[B] Buckton et al. 1978 (40-50 hour culture)

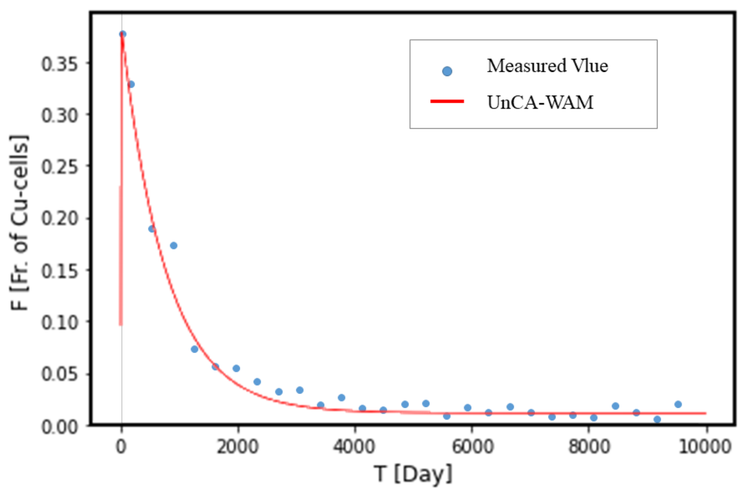
Post-RT[a] (yr)	No. of cells	No. of Dicentric	No. of Rings	No. of Acentrics	No. of Cu-cells[b]	No. of Cs-cells[c]
<0.08	1,375	446	57	230	517	135
0.08-0.5	930	263	39	169	305	103
0.5-1.5	1,097	168	13	116	206	113
1.5-2.5	350	46	6	24	60	49
2.5-3.5	393	24	3	15	28	34
3.5-4.5	990	38	8	30	54	89
4.5-5.5	1,812	83	4	46	96	164
5.5-6.5	1,336	44	10	23	53	170
6.5-7.5	2,043	55	3	34	62	190
7.5-8.5	1,422	39	11	19	45	124
8.5-9.5	1,410	18	6	10	24	128
9.5-10.5	1,575	26	2	25	38	155
10.5-11.5	1,320	10	2	9	18	165
11.5-12.5	960	8	1	7	12	87
12.5-13.5	935	14	2	7	17	87
13.5-14.5	991	10	1	14	19	142
14.5-15.5	1,350	4	1	5	9	115
15.5-16.5	1,150	11	1	6	17	128
16.5-17.5	830	8	1	3	8	82
17.5-18.5	1,340	8	2	15	21	197
18.5-19.5	920	4	1	4	9	117
19.5-20.5	980	5	0	3	6	86
20.5-21.5	550	3	0	3	4	81
21.5-22.5	380	0	1	0	2	24
22.5-23.5	810	4	2	7	13	45
23.5-24.5	510	3	0	1	5	36
24.5-25.5	325	0	0	1	1	33
25.5-26.5	225	2	0	0	4	21
26.5-27.5	300	0	0	0	1	23
27.5-28.5	200	0	0	0	0	10
>29	260	5	0	1	5	18

a) Time after radiation therapy (years).
b) Cu-cells: cells with unstable aberrations (dicentrics, rings, acentric fragments).
c) Cs-cells: cells with stable-type rearrangements only.

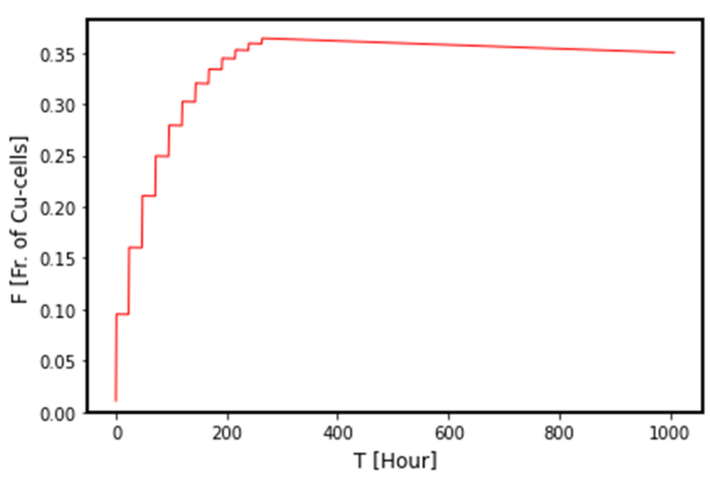


parameter	WAM	UnCA-WAM
a_0	3.24E-08	6.00E-07
a_1	2.94E-05	5.20E-02
b_0	3.00E-03	5.45E-05
b_1	1.36E-01	1.36E-01

G Medical data and UnCA-WAM simulation results



H UnCA-WAM simulation results



F) Parameter values obtained from measured medical data by Buckton *et al*. The values of a0, a1, and b0 are very different from those of WAM.

G) Comparison of the value of the frequency of cells with unstable chromosome aberrations (Cu-cells) obtained by calculation using the UnCA-WAM model with the value of the measured data. The calculation was made assuming that 20 Gy was irradiated during treatment. The model reproduced the measured values very well.

H) This graph expands the graph in Figure G from the start of irradiation to one month after the completion of irradiation. In this treatment, 20 Gy is irradiated in 12 days (1.67 Gy per day). During the 24h cooling time and the term after irradiation, the chromosomal aberrations are almost unchanged. However, after all the fractionated irradiation were completed, the aberrations decreased with time.

References: 1) Manabe Y. et al., *J. Phys. Soc. Jpn.*, 84m 044002. (2015)
2) Wada T. et al., *J. Nuc. Sci. Technol.*, 53,1824-1830. (2016)
3) Bando M. et al., *Int. J. Radiat. Biol.*, 95(10), 1390-1403 (2019)
4)Tsunoyama Y et al., *Int. J. Radiat. Biol.*, 95(10), 1414-14020 (2019)