The Future of Radiological Protection
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A Proposal for the Application of Mathematical Models that Accurately Approximate Measured Data to Radiation Protection

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Current international consensus on stochastic effect

In the field of radiation protection, current models and concepts
- focus on the total dose of exposure and
- assume that there is no threshold.

- **LNT model** (Linear no-threshold model)
- **LQ model** (Linear quadratic model α/β ratio etc.)
- **ALARA** (As low as reasonably achievable) **principle**
- **DDREF** (Dose and Dose Rate Effectiveness Factor)

Exposure situations for which the current protection system is not appropriate

Situation I : long-term exposure (Low dose-rate)
e.g., High natural radiation area (HNRA),
Fukushima

Situation II : Fractionated exposure (High dose-rate)
e.g., Cancer Treatment,
Astronauts (Multiple

Consequences of overestimating risk assessment

It is true that LNT etc, which assess effects based on total exposure dose, have played an important role to date.
However, it has already become clear that, depending on the circumstances of exposure, they may result in significant social losses.

e.g.,
In Japan, after Fukushima Daiichi NPP accident

- Cost of radioactive decontamination : 6 trillion yen (>46 billion €, >53 billion $)
- Cost of contaminated water : 8 trillion yen
- Cost of compensation to residents : 7.9 trillion yen
- Cost of full bag inspection of all rice : 8 billion yen /year (2012 -2019)
- Thyroid tests for young people & the prefectural health survey are still being conducted.
- Local communities collapsed due to the prolonged evacuation.

Resident return rate in Tomioka Town as of 2019: 7.3%.

Cancer Treatment

- In some situations, the LQ model does not fit.

□ OD9 Prof. Masako BANDO

"Unified Understanding of biological Effects Caused by Radiation - Overcoming LQM Difficulties -"

Space Flight (Multiple Missions, Long Trip …)

- Risk assessment based on total radiation dose may be detrimental to the promising space industry.

Prerequisites for adding a new model in stochastic effect

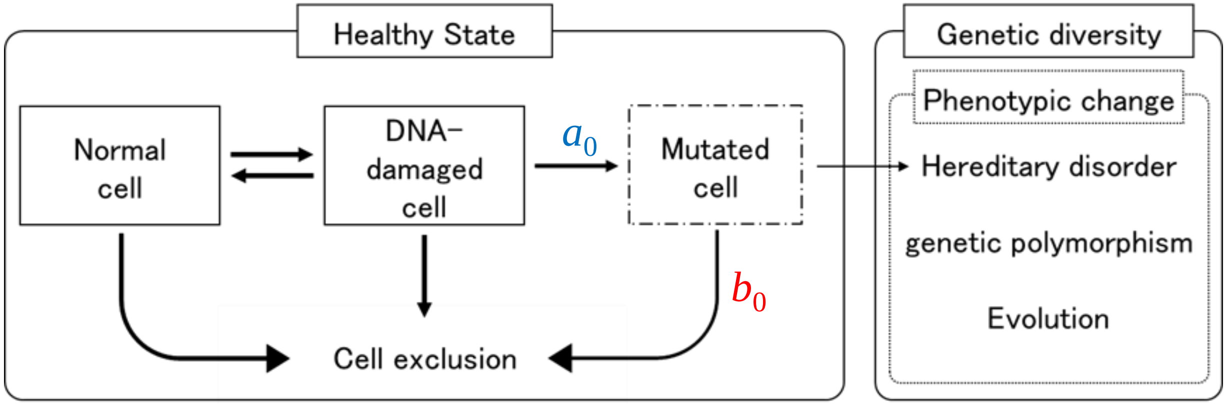
In order to overcome the challenges in irradiated situations,
such as Long-term low dose exposure, Fractionated exposure etc.,

it will be required

- ✔ transcending the dualism of the presence or absence of thresholds,
- ✔ accurately incorporating the dose rate effect.

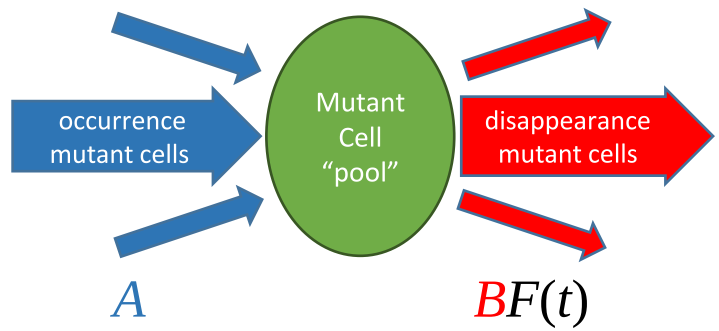
➡ As an example of the new model …

Whack-A-Mole (WAM) Model



$$\frac{dF(t)}{dt} = A - BF(t)$$

$F(t)$: mutation frequency at t



$$A = a_0 + a_1 d$$

d : dose rate   if d = const. (time independent), total dose $D = d \cdot t$

a_0 : spontaneous mutation & proliferation effect [/hour]

a_1 : mutation by the artificial radiation [/Gy]

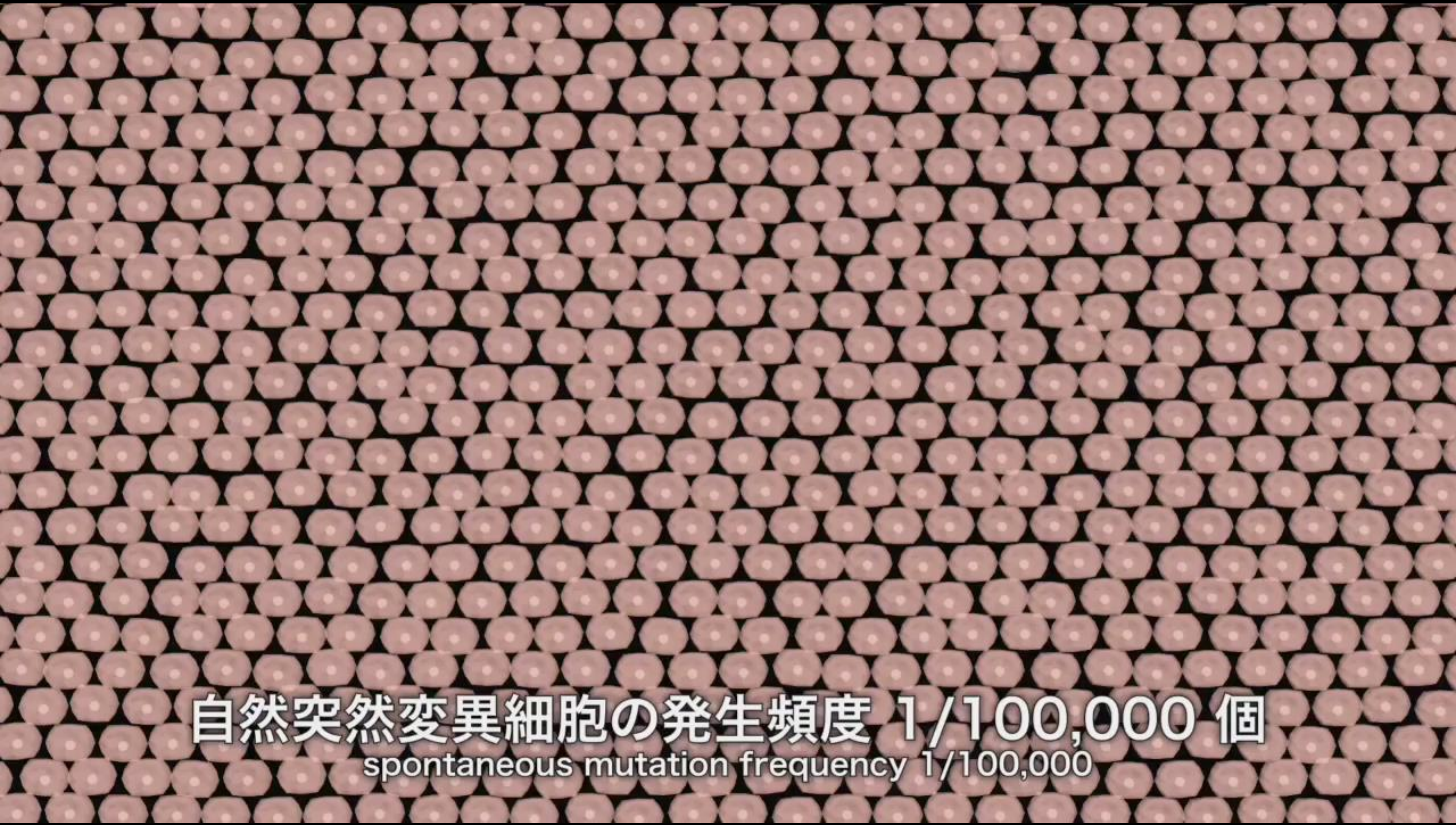
$$B = b_0 + b_1 d$$

b_0 : natural cell death effect [/hour]

b_1 : the effects of cell death by the artificial radiation [/Gy]

The differential equation with respect to "time", not to "total dose"

Wada T. et al., *J. Nuc. Sci. Technol.*, 53,1824-1830. (2016)
Bando M. et al., *Int. J. Radiat. Biol.*, 95(10), 1390-1403 (2019)


自然突然変異細胞の発生頻度 1/100,000 個
spontaneous mutation frequency 1/100,000

William L. Russell (1910-2003)
“The large mouse genetics program”

Mouse spermatogonium were irradiated with X-rays and γ-rays to investigate mutations at seven loci.
More than one million mice were used in this study.

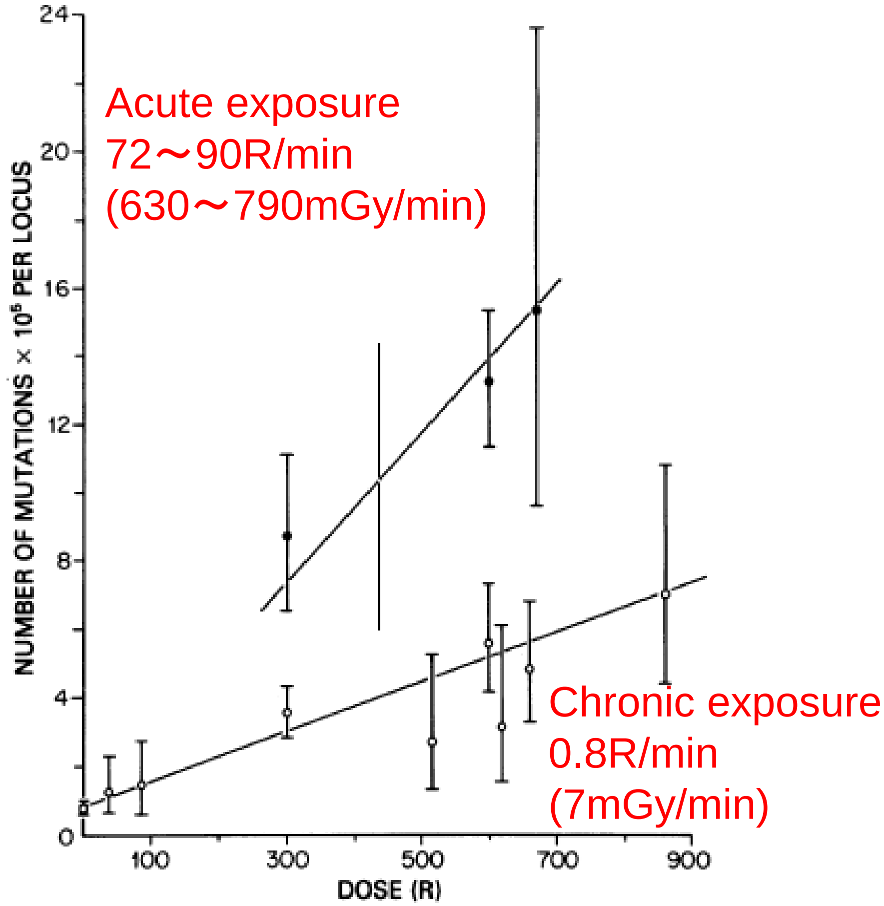
Proc. Natl. Acad. Sci., 79(2), 542-544 (1982)

Mutation frequencies in male mice and the estimation of genetic hazards of radiation in men

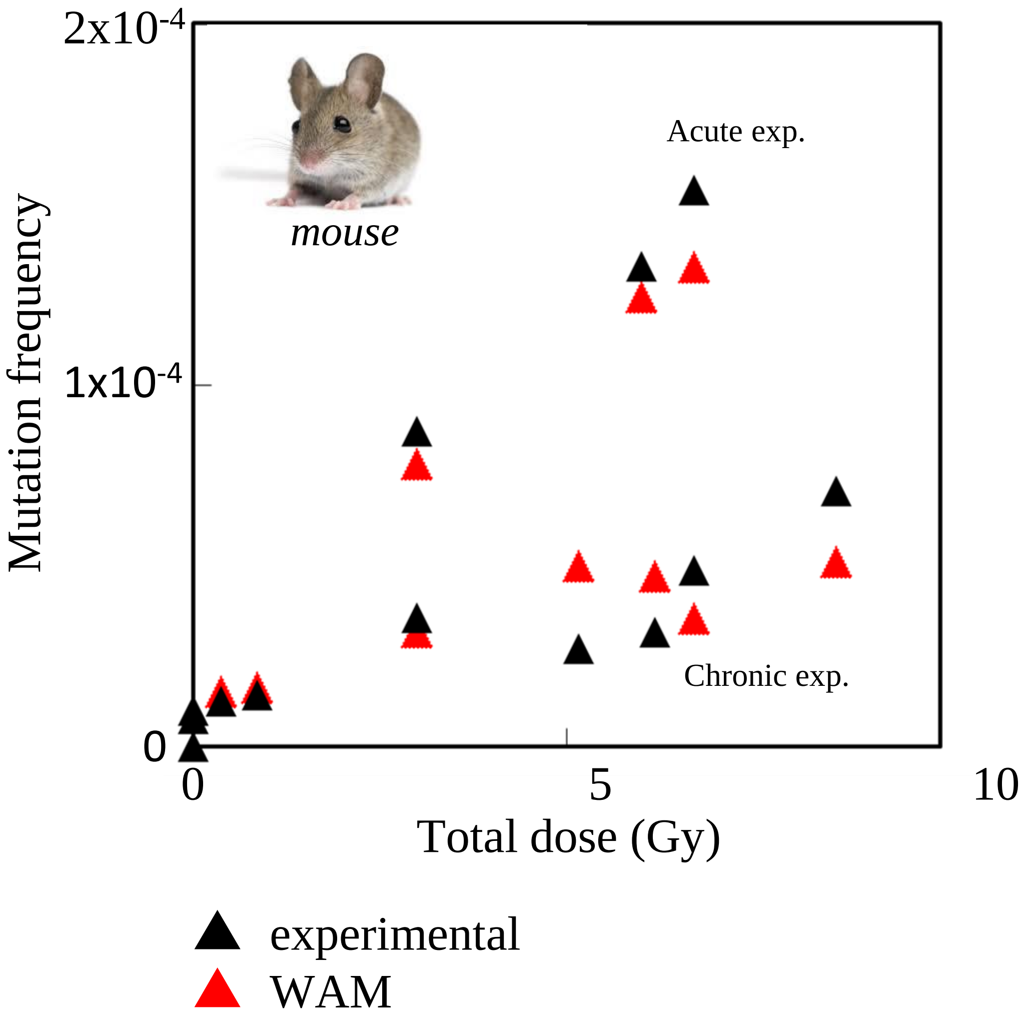
(specific-locus mutations/dose-rate effect/doubling dose/risk estimation)

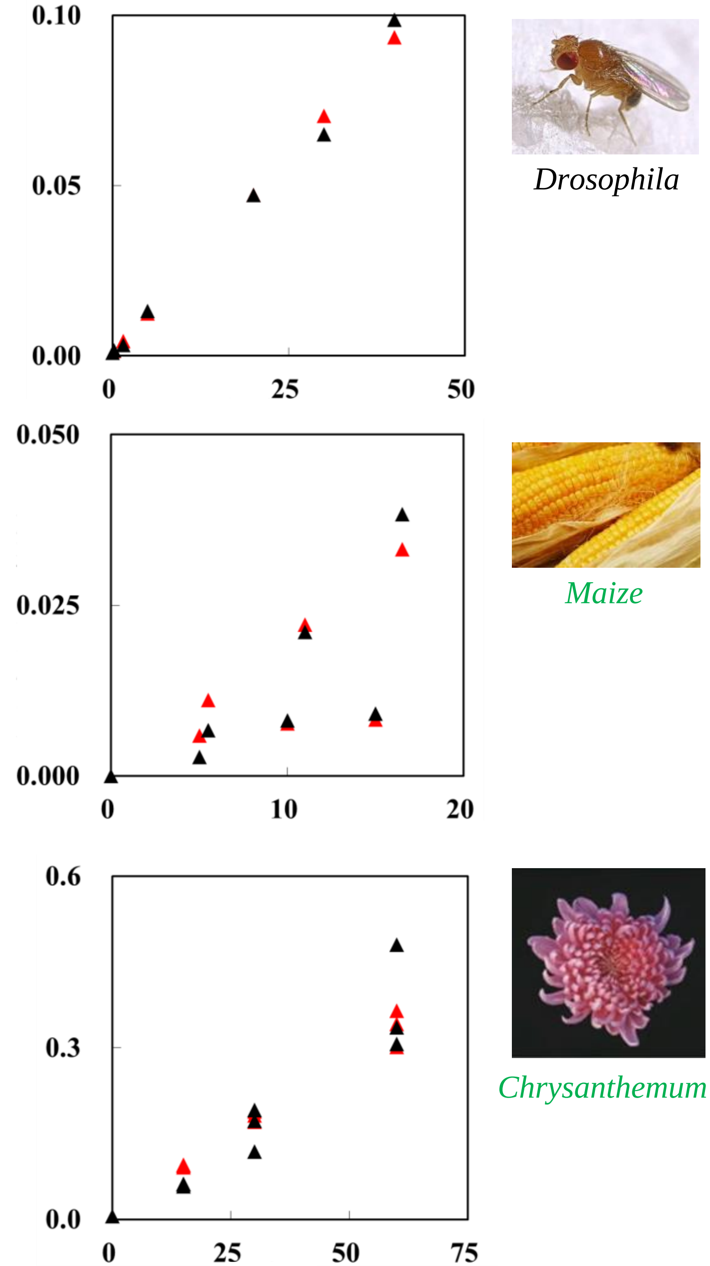
W. L. Russell and E. M. Kelly
Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830

Contributed by William L. Russell, September 21, 1981



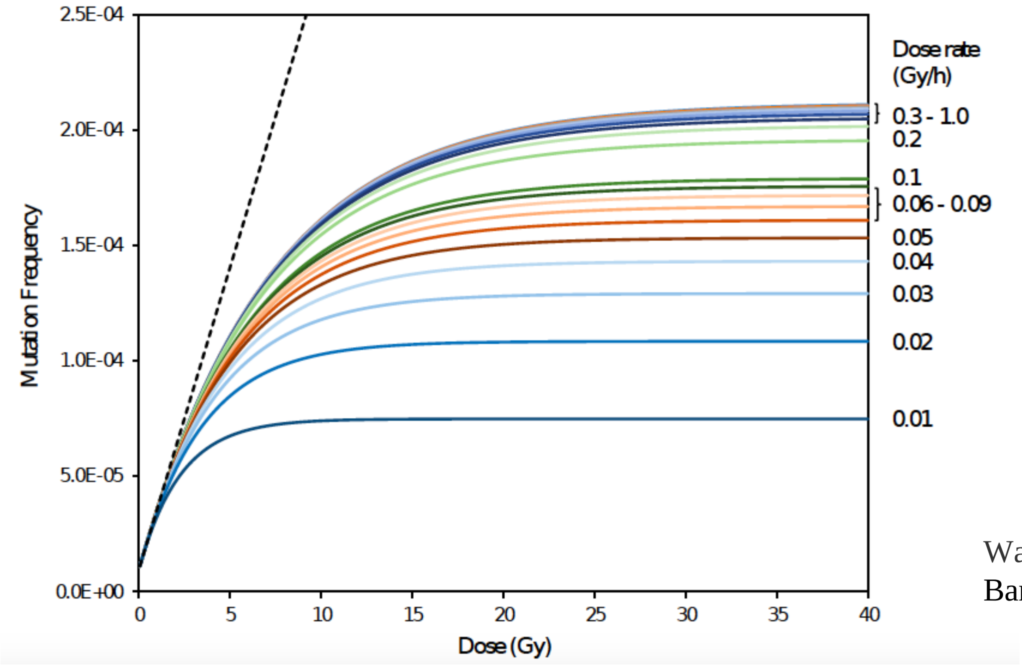
Comparison of WAM-theoretical values and experimental values





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

WAM model predictions



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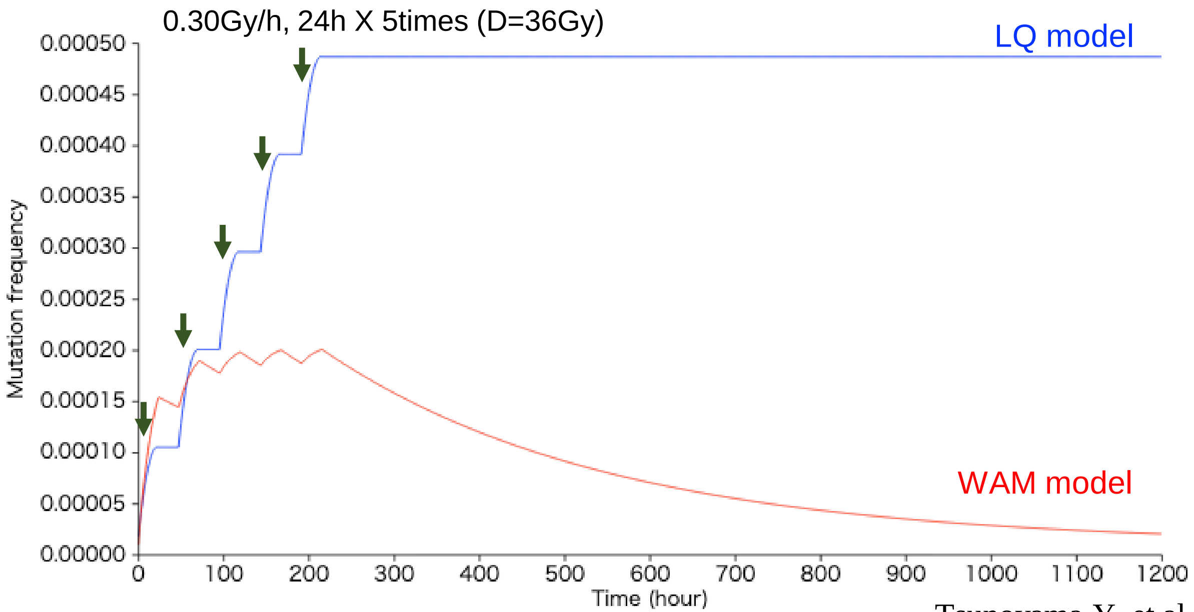
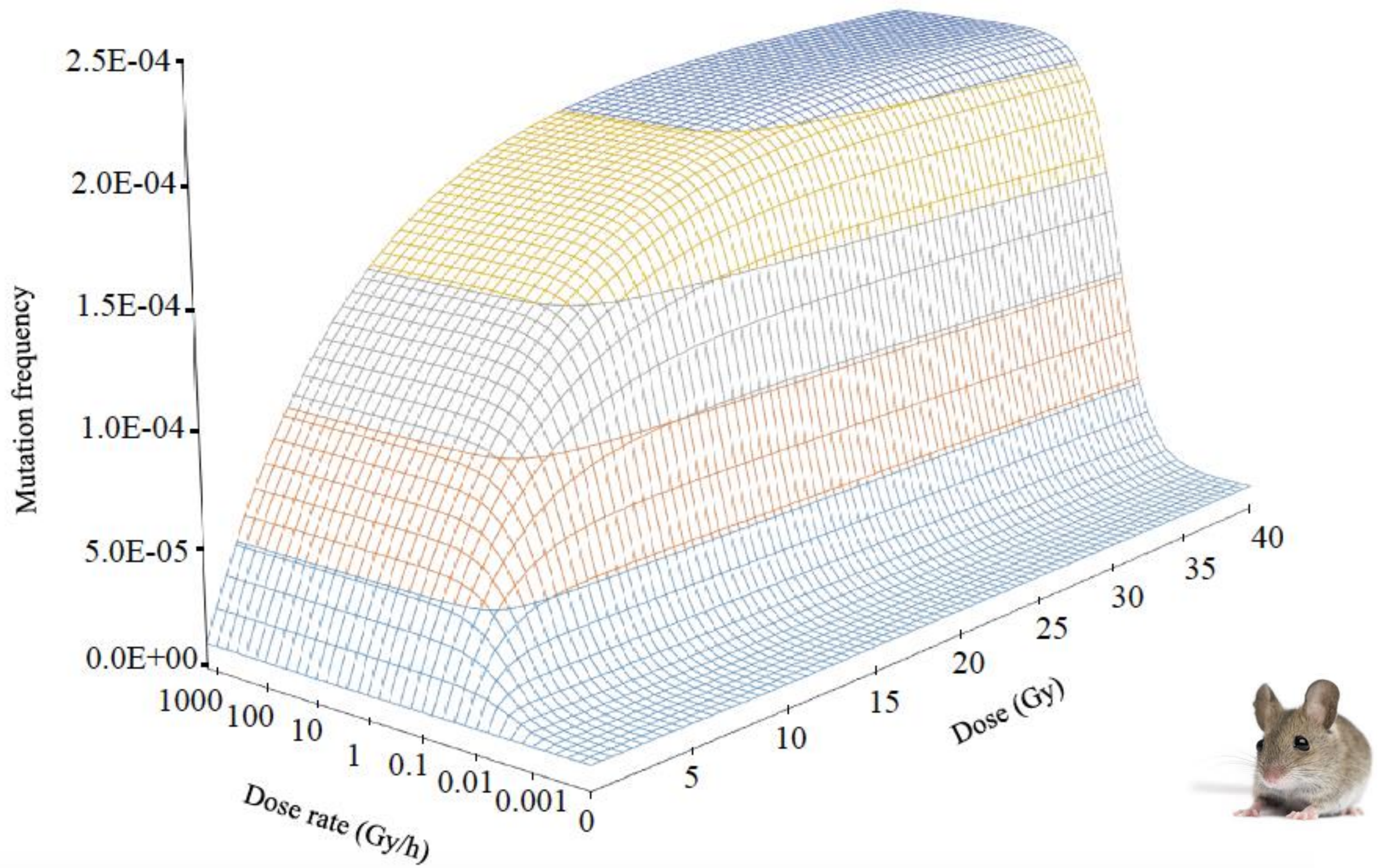


Tsunoyama Y. et al., *Jpn. J. Health. Phys.*, 55(4), 207-214. (2020)

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

When both total dose and dose rate are reflected
to predict the genetic effect,
there is an equilibrium state of increase and decrease.



Bando M. et al., *Int. J. Radiat. Biol.*, 95(10), 1390-1403 (2019)

Development & Application of WAM model

Genetic effect

High accuracy WAM model, WAM prediction simulator

- An empirical study is currently underway in Japan.
  Research and Survey Project on Radiation Health Effects
  by the Ministry of the Environment in Japan
  "Analysis of Radiation Effects and Mutagenesis Mechanisms Based on Ultrasensitive Mutation Detection in Mice and Cells Exposed to Long-term Low Doses."
- WAMSIM (WAM model simulator)
  http://radi.rirc.kyoto-u.ac.jp/wam/en/

Cancer Treatment

S-WAM (Seesaw WAM model)

: WAM model + Cell growth effect & volume effect

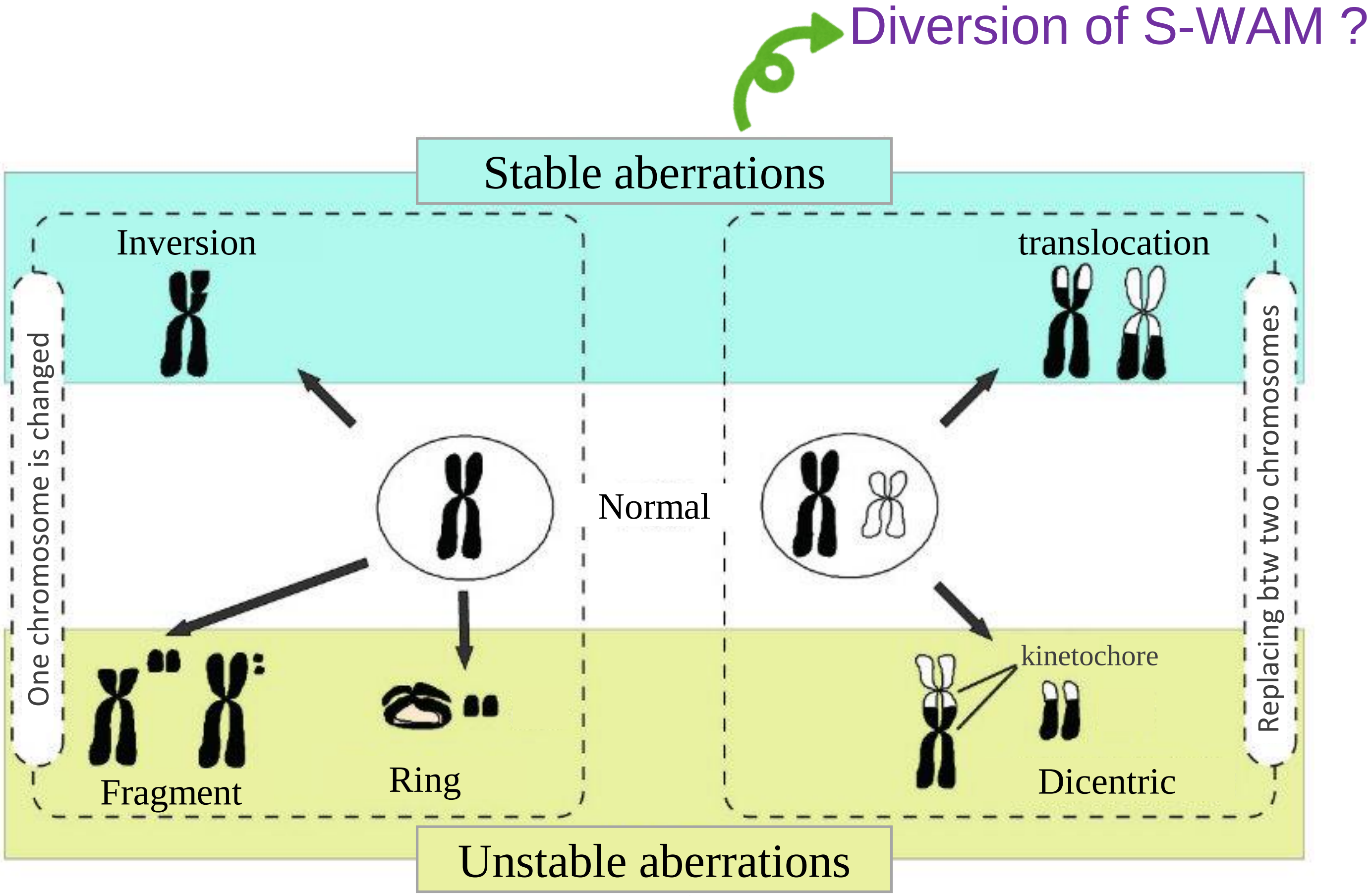
- An empirical study is currently underway at
  Osaka International Cancer Institute, Japan.
  Bando M. et al., *Int. J. Radiat. Biol.*, 97(2), 228-239 (2021) & OD9

Chromosome aberrations

UnCA-WAM

: Optimized WAM model for unstable chromosome aberrations

UnCA-WAM overview

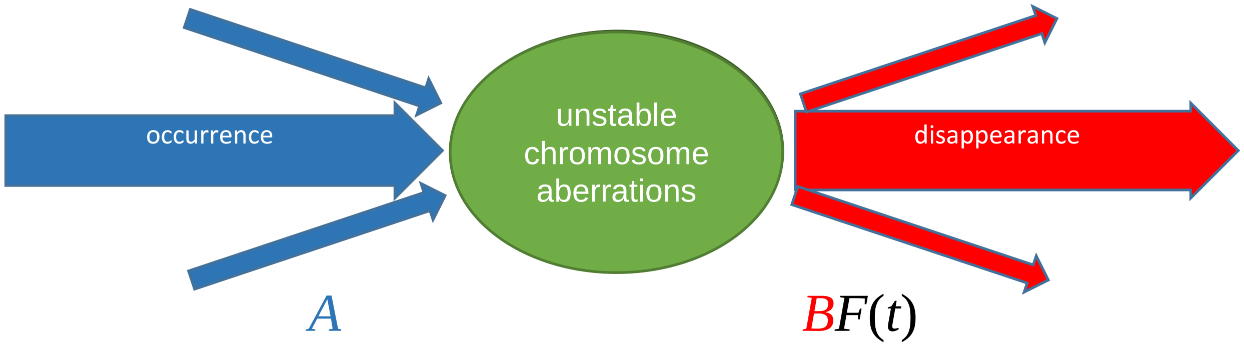


UnCA-WAM

Optimizing the parameters of the WAM model
for the evaluation & prediction of unstable chromosome aberration.

Figure :from the website of the Aomori Prefecture radioactive material impact survey (Institute for Environmental Sciences)

WAM to UnCA-WAM



$$\frac{dF(t)}{dt} = A - BF(t)$$

No./Fr. of unstable chromosome aberrations

$F(t)$: ~~mutation frequency~~ at t

$$A = a_0 + a_1 d$$

d : dose rate   if d = const. (time independent), total dose $D = d \cdot t$

a_0 : spontaneous ~~mutation & proliferation effect~~ [/hour]

a_1 : ~~mutation~~ by the artificial radiation [/Gy]

$$B = b_0 + b_1 d$$

b_0 : natural cell death effect [/hour]

b_1 : the effects of cell death by the artificial radiation [/Gy]

+ Dilution effect by normal lymphocyte proliferation ???

"Lymphocyte lifetime: Determination by elimination rate of chromosome aberration in radiotherapy patients"

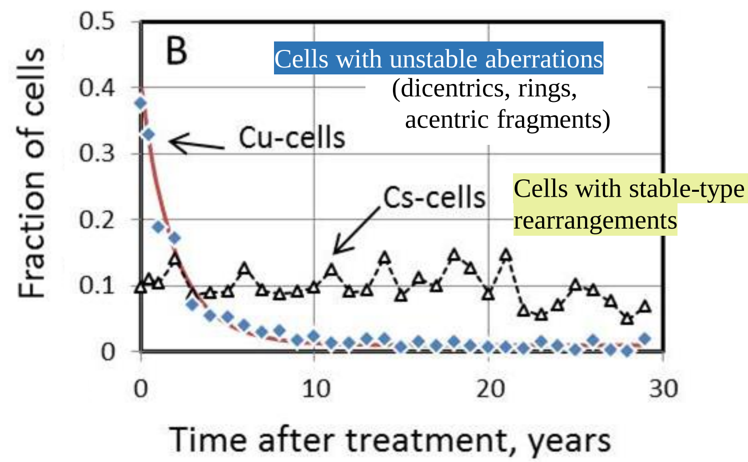
Human Radiation Cytogenetics Archives, RNC, Kyoto Univ.
[B] **Buckton et al. 1978** (40-50 h culture)
Analysis in 58 patients treated X-rays for ankylosing spondylitis. Irradiation was applied along the spinal strip field to give a total skin dose of 1,500, 2,000 or 2,500 rads (15, 20 or 25 Gy) in 10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

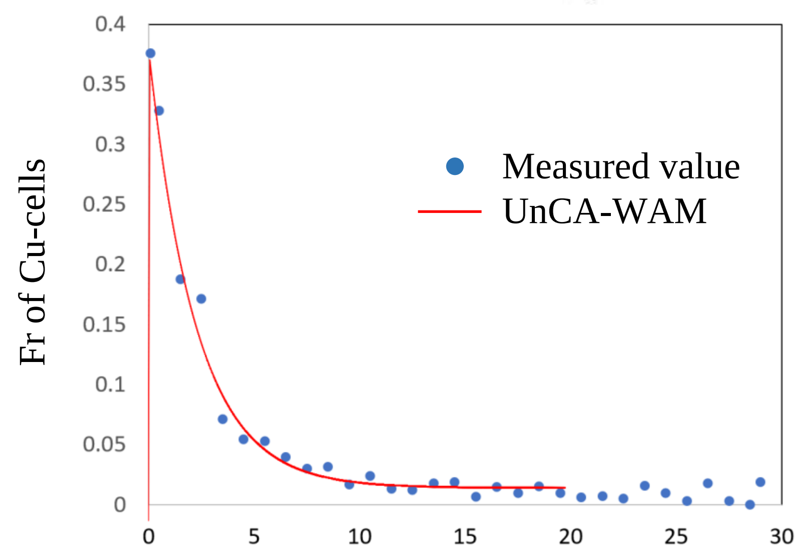
[B] Buckton et al. 1978 (40-50 hour culture)

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.

p(0) : spontaneous frequency = 0.011





UnCA-WAM : Application to the biological effect assessment in Astronauts

Cytogenet Genome Res 103:40–46 (2003)
DOI: 10.1159/000076288

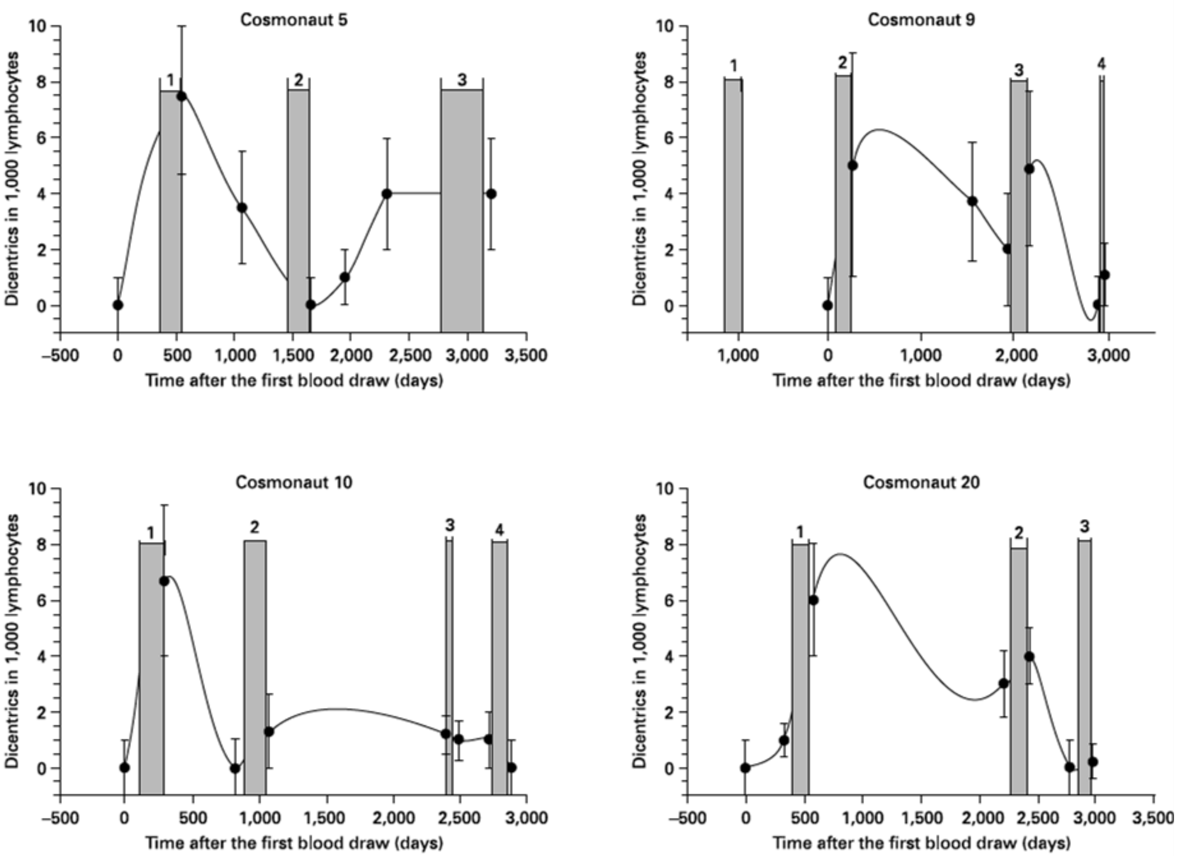
Cytogenetic and Genome Research

Chromosome aberration dosimetry in cosmonauts after single or multiple space flights

M. Durante,[a] G. Snigiryova,[b] E. Akaeva,[c] A. Bogomazova,[b] S. Druzhinin,[d] B. Fedorenko,[d] O. Greco,[e] N. Novitskaya,[b] A. Rubanovich,[c] V. Shevchenko,[c] U. von Recklinghausen,[f] and G. Obe[f]

[a] Department of Physics, University Federico II, Napoli (Italy);
[b] Russian Research Center of Roentgenology and Radiology, Ministry of Health, Moscow (Russia);
[c] Vavilov Institute of General Genetics, Russian Academy of Sciences, Moscow (Russia);
[d] State Research Center of Russian Federation, Institute of Biomedical Problems, Russian Academy of Sciences, Moscow (Russia);
[e] Radiation Oncology Department, Karmanos Cancer Center, Detroit, MI (USA);
[f] Department of Genetics, University of Essen, Essen (Germany)

Durante M., et al.,
Cytogenet. Genome Res., 103, 40–46 (2003)



● : Dicentrics in 1,000 lymphocytes
■ : time spent in space

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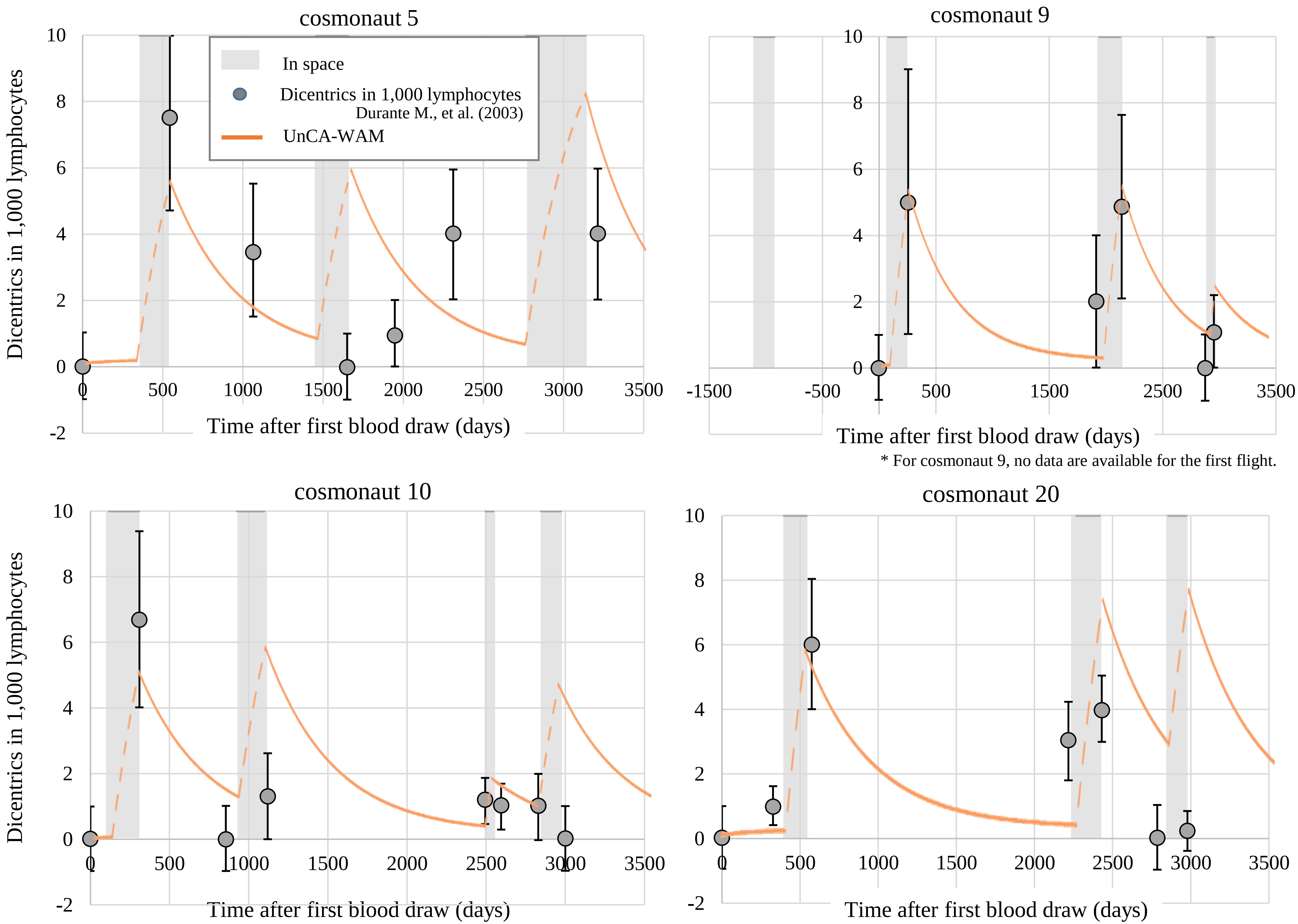

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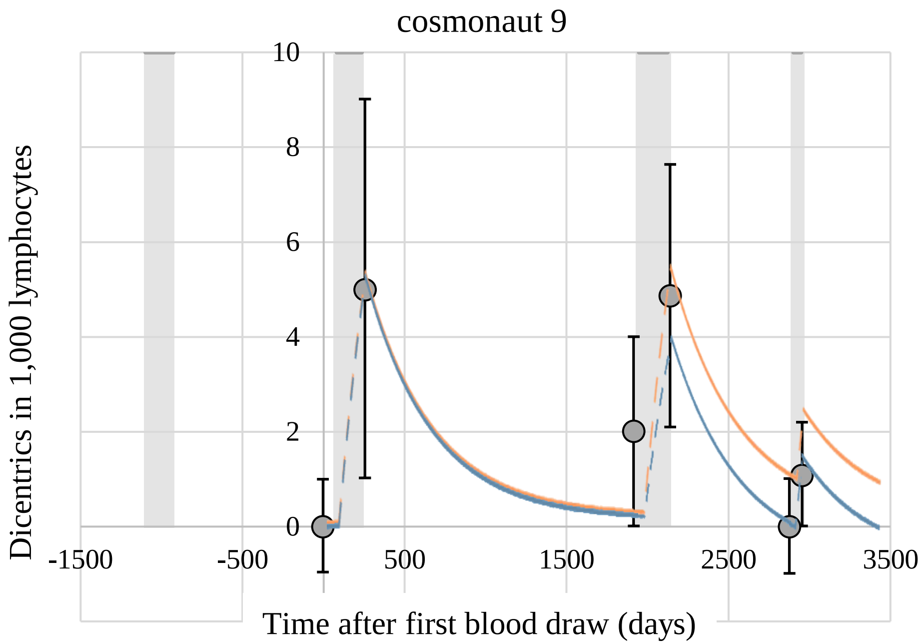
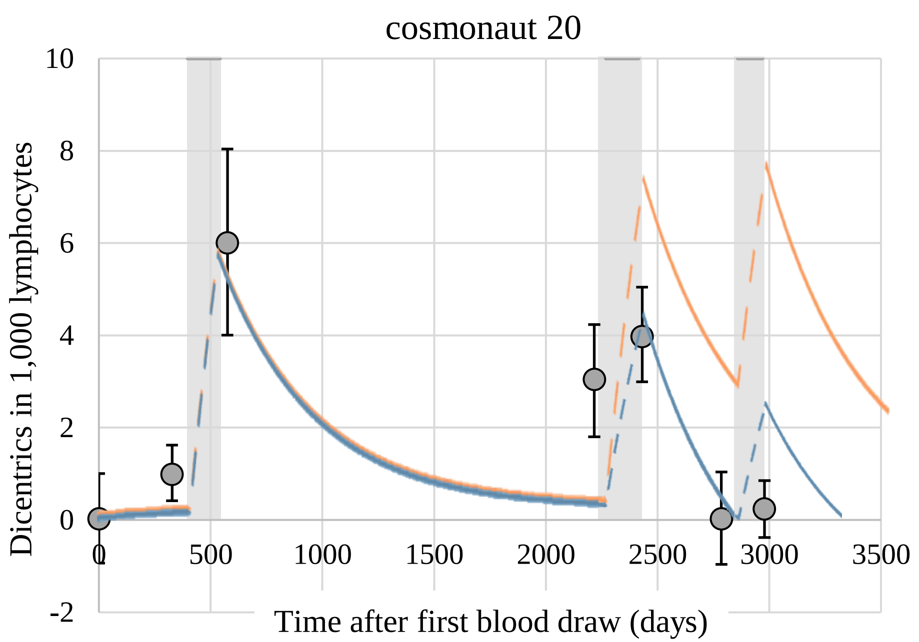
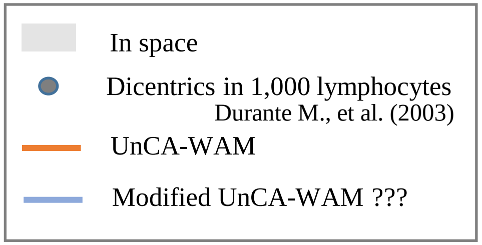


* For cosmonaut 9, no data are available for the first flight.





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[e] Radiation Oncology Department, Karmanos Cancer Center, Detroit, MI (USA);
[f] Department of Genetics, University of Essen, Essen (Germany)

Conclusions

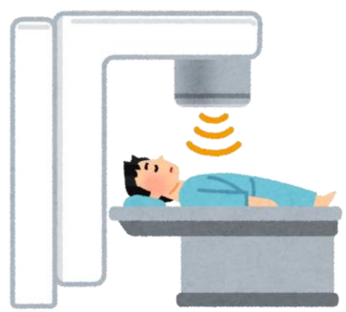
- In the first flight, a significant increase is observed for long-term missions.
- In multiple space missions, no significant correlation was observed between frequencies of dicentrics or translocations in their lymphocytes and the integral duration of space sojourns or absorbed dose.
- The frequencies of dicentrics or translocations decline rapidly in the time interval between two space flights, and the yield of stable translocations after repeated missions is similar to background values.

Challenges in incorporating mathematical models into risk assessment

The application of the ALARA principle will be limited depending on the situation.

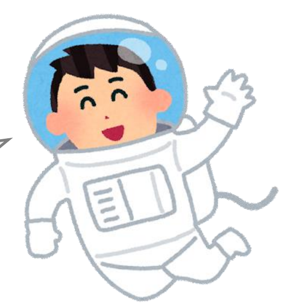
➡ We need to use different models for risk prediction and effect assessment depending on the situation.

Acute exposure	Fractionated exposure	Chronic exposure
One time Extremely high dose High dose rate	Multiple time High dose High dose rate	Long-time Low dose Low dose rate



LNT, LQM	S-WAM, UnCA-WAM etc.	WAM etc.

Isn't it time for us to use "differential equations" to assess risk?



Thank You!

ふくしまから
はじめよう。
Future From Fukushima.