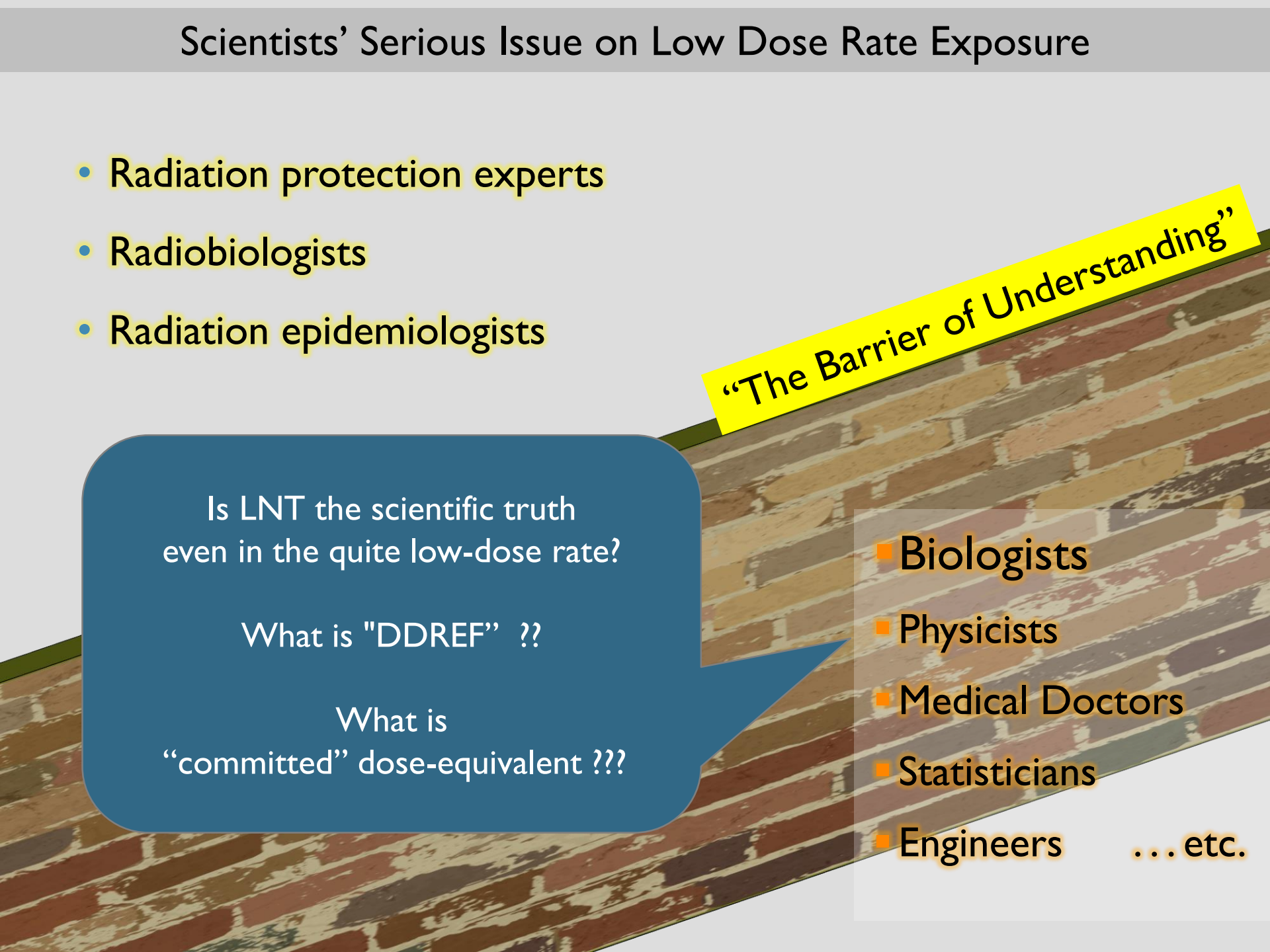
基研研究会「放射線の生体影響解明への
分野横断による挑戦」2019年5月24日

動的平衡を考慮した線量率応答モデル WAM model による遺伝的影響予測

角山　雄一　（京都大学環境安全保健機構RIセンター）
尾上　洋介　（日本大学文理学部情報学科）
鈴木　和代　（京都大学医学部附属病院）
真鍋勇一郎　（大阪大学工学研究科）
髙西　康敬　（埼玉大学理工学研究科）
佐藤　丈　（埼玉大学理工学研究科）
和田　隆宏　（関西大学システム理工学部）
土岐　博　（大阪大学核物理研究センター）
坂東　昌子　（大阪大学核物理研究センター）

Scientists' Serious Issue on Low Dose Rate Exposure

- Radiation protection experts
- Radiobiologists
- Radiation epidemiologists



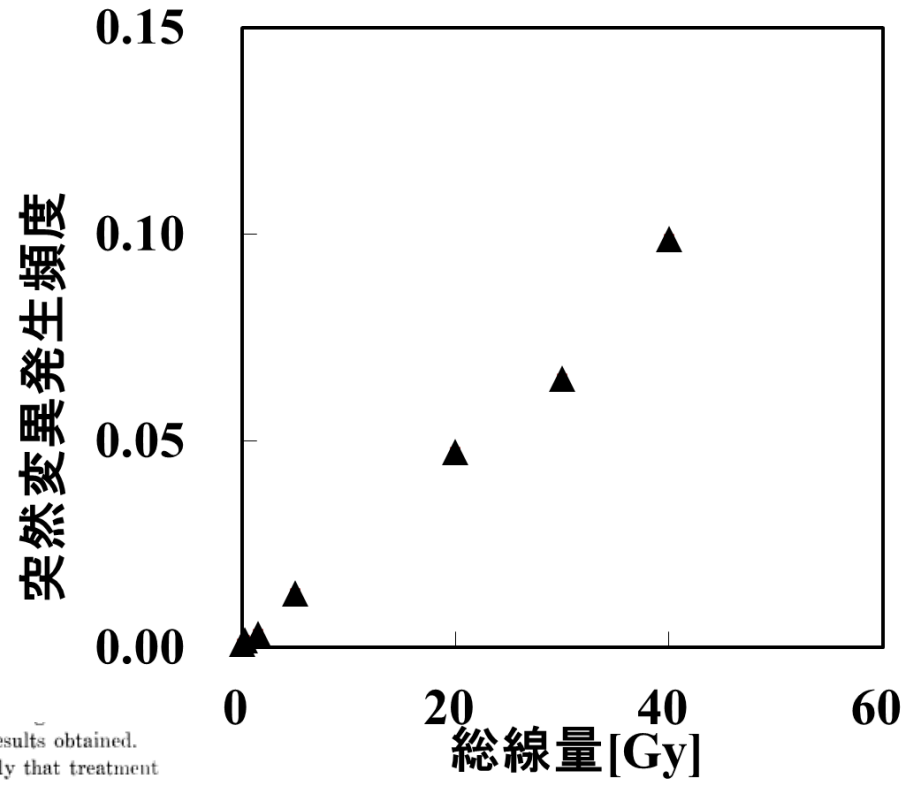
遺伝的影響（キイロショウジョウバエ）

Hermann J. Muller

Hermann J. Muller (1890-1967)

the Nobel Prize in Physiology or Medicine in 1946

キイロショウジョウバエの雄にX線照射
X染色体上における劣性致死突然変異の
発生頻度を調査



Science, Vol. 66, p. 84, 1927

ARTIFICIAL TRANSMUTATION OF THE GENE

Most modern geneticists will agree that gene mutations form the chief basis of organic evolution, and therefore of most of the complexities of living things. Unfortunately for the geneticists, however, the study of these mutations, and, through them, of the genes themselves, has heretofore been very seriously hampered by the extreme infrequency of their occurrence under ordinary conditions, and by the general unsuccessfulness of attempts to modify decidedly, and in a sure and detectable way, this sluggish "natural" mutation rate. Modification of the innate nature of or-

ods employed, or of the individual results obtained.

It has been found quite conclusively that treatment of the sperm with relatively heavy doses of X-rays induces the occurrence of true "gene mutations" in a high proportion of the treated germ cells. Several hundred mutants have been obtained in this way in a short time and considerably more than a hundred of the mutant genes have been followed through three, four or more generations. They are (nearly all of them, at any rate) stable in their inheritance, and most of them behave in the manner typical of the Mendelian chromosomal mutant genes found in organisms generally. The nature of the crosses was such as to be much more favorable for the detection

- LNT仮説のルーツ
- 人工変異原の発見

広島・長崎原爆被ばくと全固形がん発生リスク

LSS（Life Span Study）

RADIATION RESEARCH **168**, 1–64 (2007)

Solid Cancer Incidence in Atomic Bomb Survivors: 1958–1998

D. L. Preston,[a,1] E. Ron,[b] S. Tokuoka,[c] S. Funamoto,[c] N. Nishi,[c] M. Soda,[c] K. Mabuchi[b] and K. Kodama[c]

[a] *Hirosoft International, Eureka, California;* [b] *Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; and* [c] *Radiation Effects Research Foundation, Hiroshima and Nagasaki, Japan*

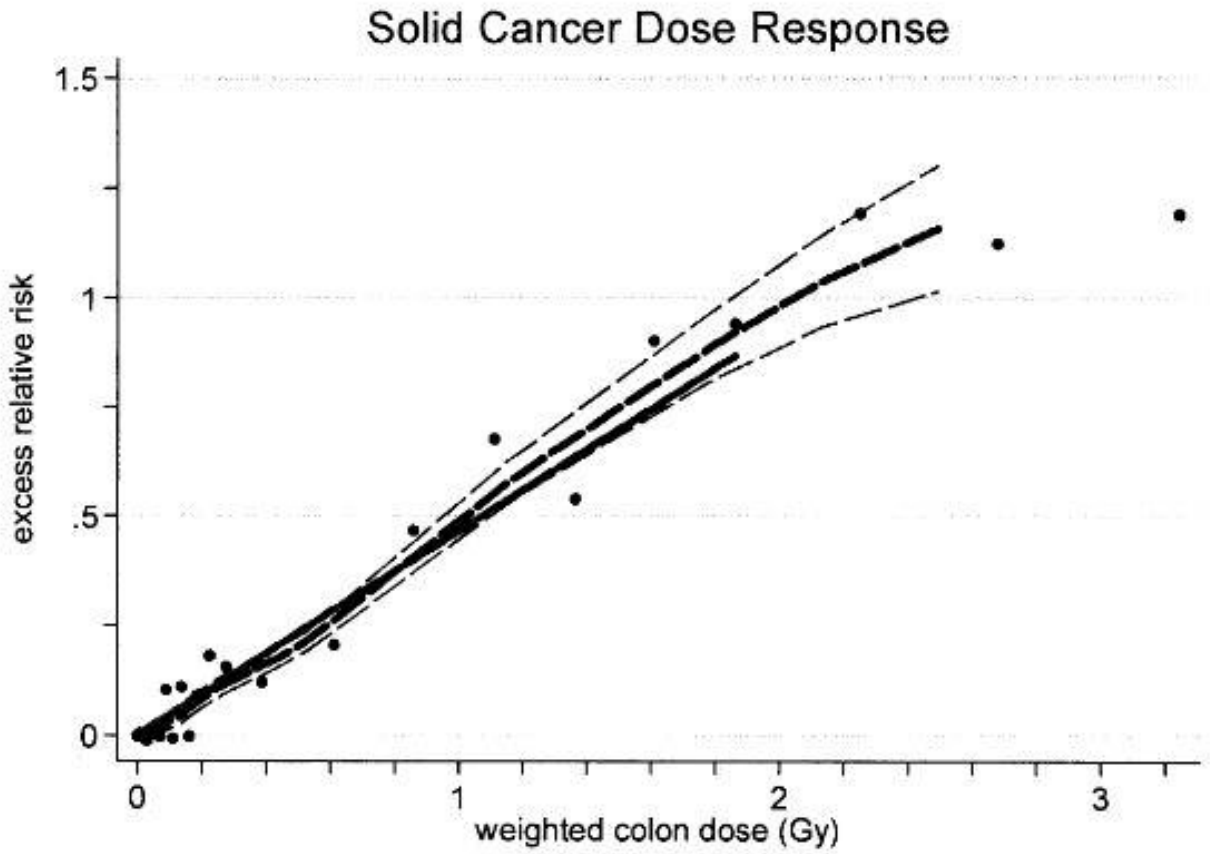


FIG. 3. Solid cancer dose–response function. The thick solid line is

線量・線量率効果係数（Dose and dose-rate effectiveness factor）

LQ（linear-quadratic） model

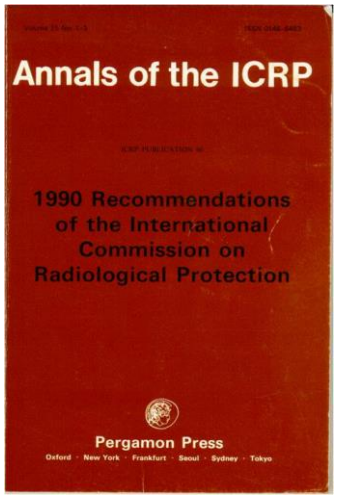
$$E(D) = \alpha D + \beta D^2$$

E : the excess effects

low dose-rate: $\lim_{D \to 0} E(D) \approx \alpha D$

Dose & dose-rate effectiveness factor

DDREF $= (\alpha D + \beta D^2)/\alpha D = 1 + \beta/\alpha \cdot D$



ICRP Pub.60 (1990), Pub.103 (2007) → 2

BEIR Ⅶ委員会（NAS/NRC, 2006） → 1.5

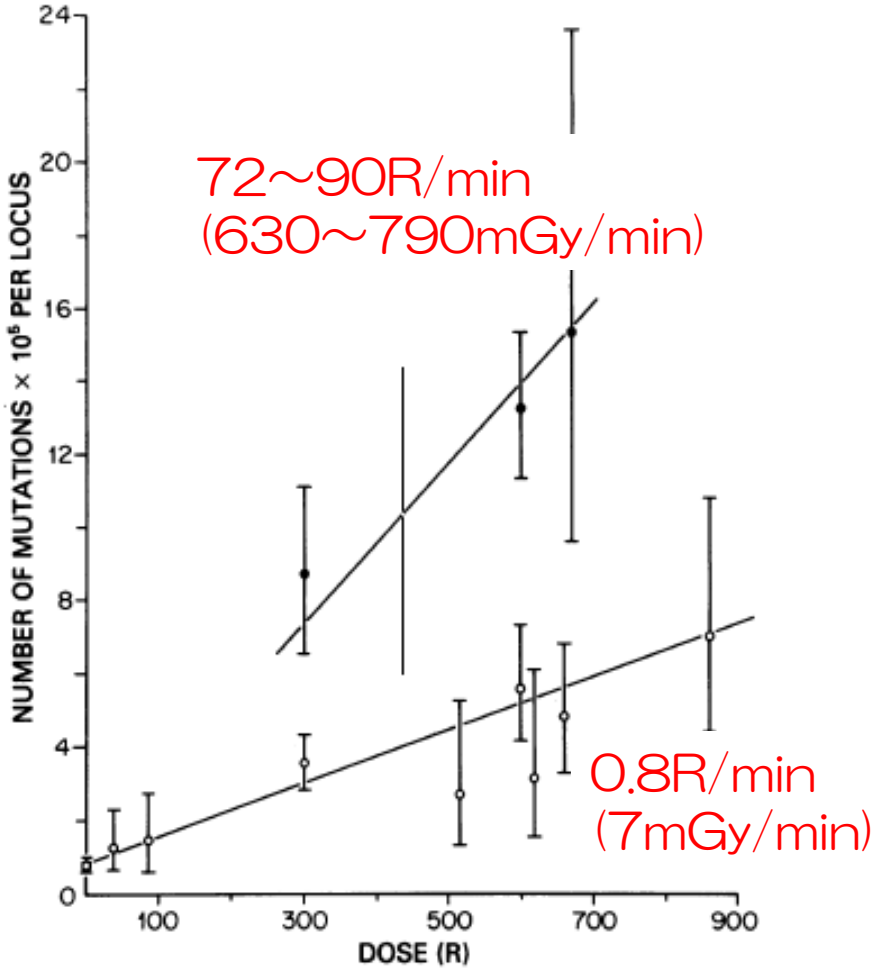
UNSCEAR 1998 → 2～10

線量率効果（マウス・遺伝的影響）

William L. Russell (1910-2003)

“The large mouse genetics program”

マウス精原細胞にX線やγ線を照射し
７つの遺伝子座における突然変異を調査。
百万匹以上のマウスを用いた。



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

PNAS, Vol. 79(2), 542-544, 1982

To overcome barriers of understanding …

Theoretical Physicists

Masako
BANDO

Takahiro
WADA

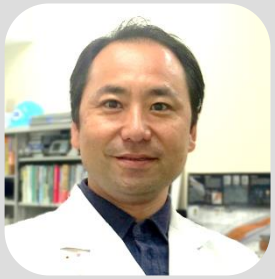
Yuichiro
MANABE

Issei
NAKAMURA

Radiobiologist

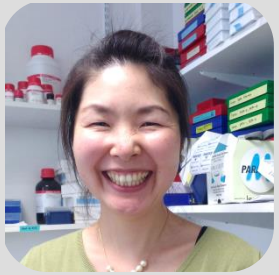
Hiroo
NAKAJIMA

Biologist &
Radi. protect. expert



Yuichi
TSUNOYAMA

Medical Doctor



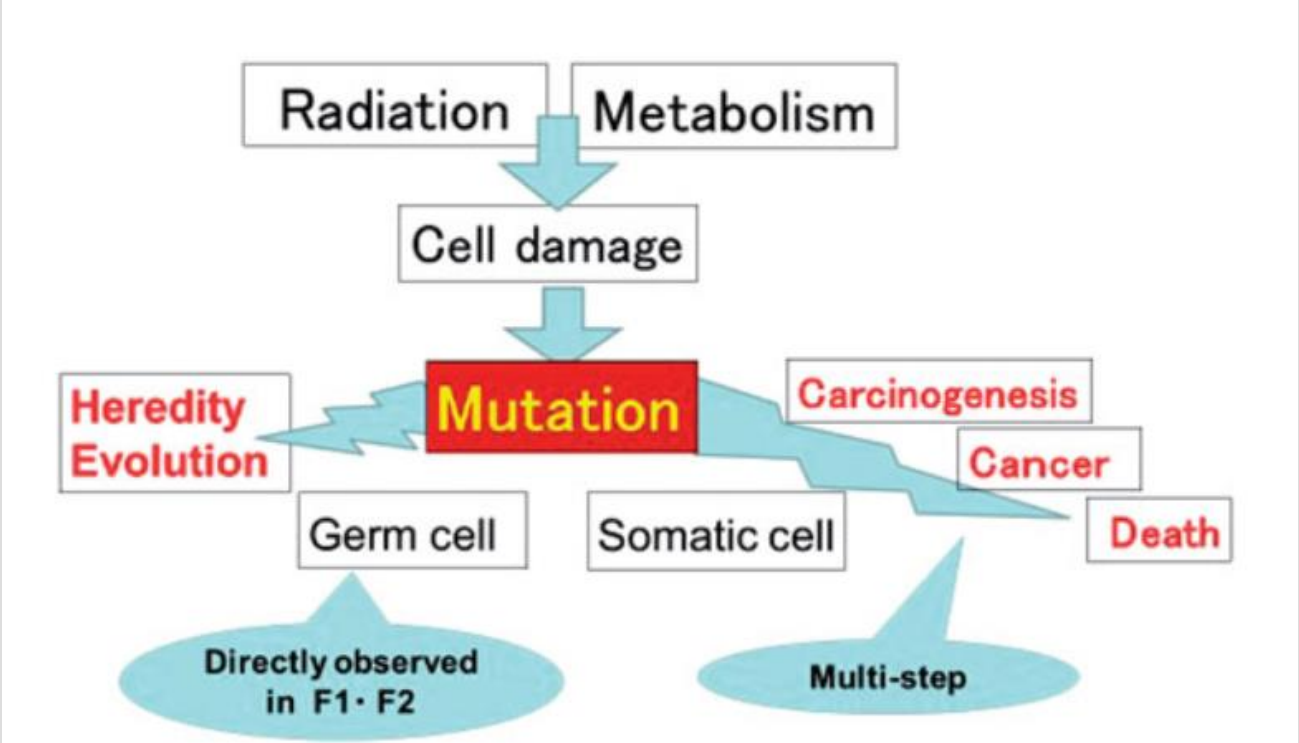
Kazuyo
SUZUKI

Informatician

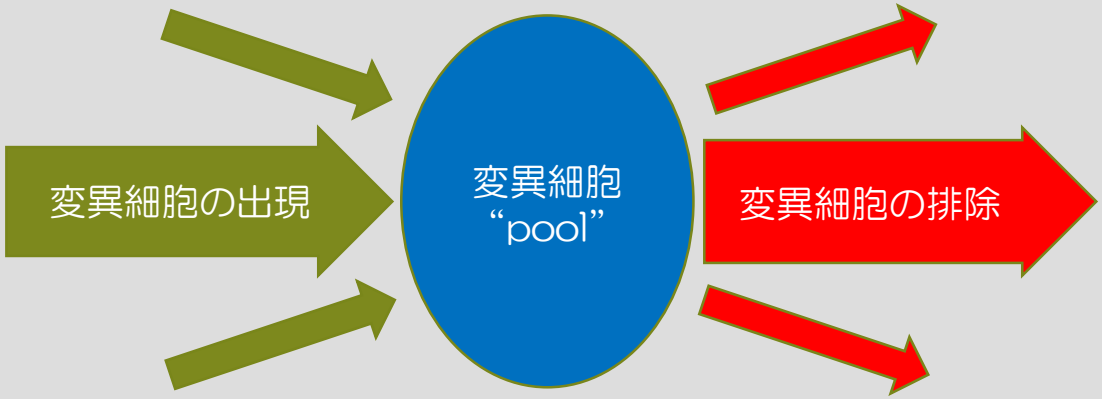
Yosuke
ONOUE

Joe SATO
Yasutaka TAKANISHI
Hiroshi TOKI

Basic concept of the Whack-A-Mole (WAM) Model



Bando M. et al.,
"Study of mutation from DNA to biological evolution."
Int. J. Radiat. Biol. (2019)
in press

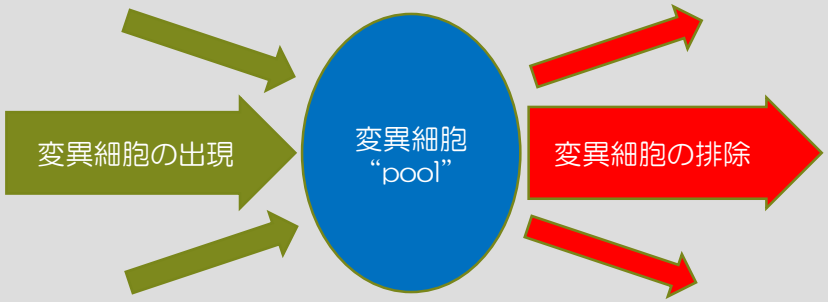


Mole
= Mutant Cell

Whack-A-Mole (WAM) Model

The differential equation with respect to “time”, not to “total dose”

$$\frac{dF}{dt} = A - BF$$



F : 変異発生頻度　$= N_m / N_0$

N_m: 変異細胞数

$$A = a_0 + a_1 d$$

d : 線量率

a_0 : 自然変異とその増加分 [/hour]

a_1 : 追加被ばくによる発生する変異 [/Gy]

$$B = b_0 + b_1 d$$

b_0 : 自然細胞死分 [/hour]

b_1 : 追加被ばくによる細胞死 [/Gy]

Assessing of parameters

マウス

ショウジョウバエ

トウモロコシ

キク

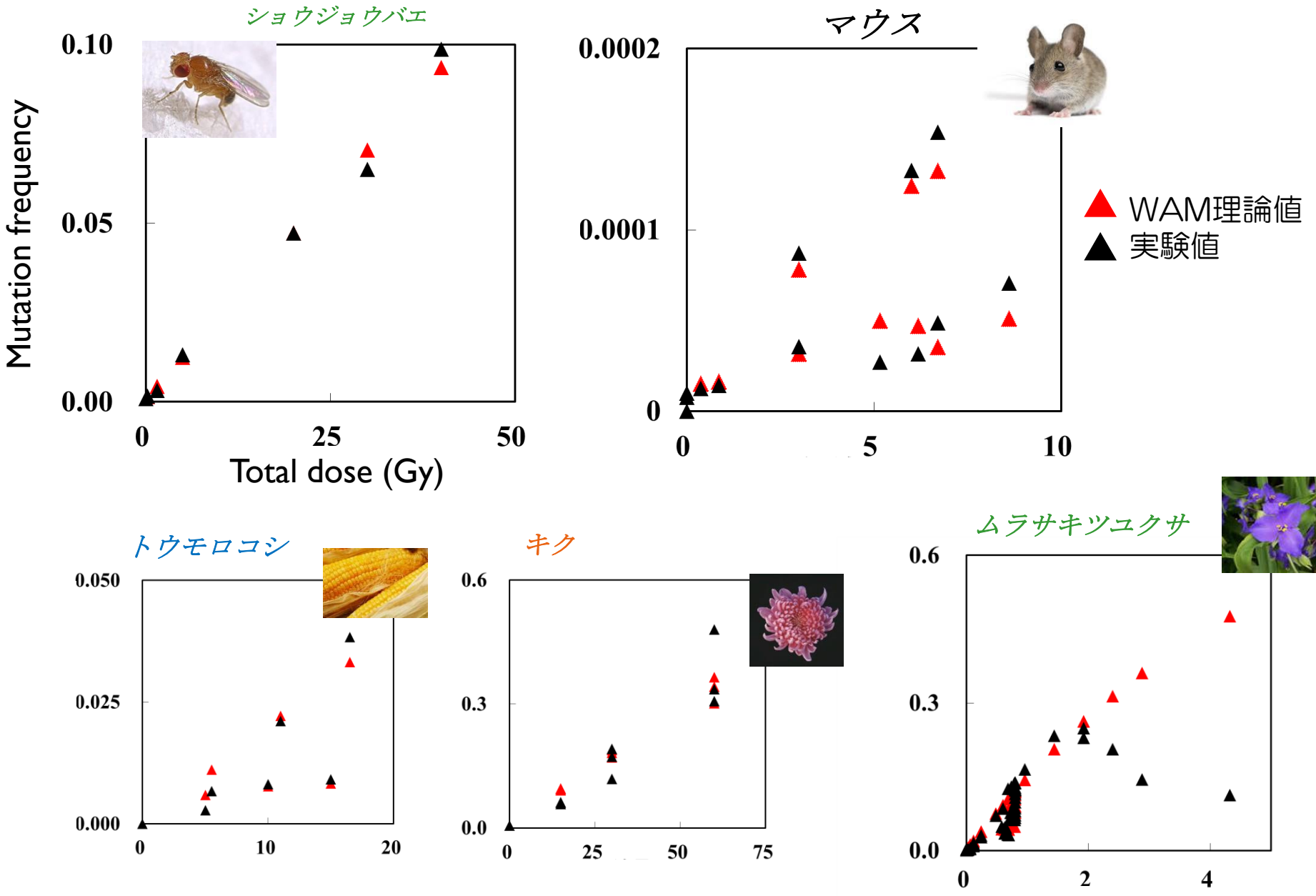
ムラサキツユクサ

experimental data → parameter - fitting

parameter sets（a_0, a_1, b_1, b_2）

	マウス	ショウジョウバエ	トウモロコシ	キク	ムラサキツユクサ
a_0 [1/hour]	3.2E-08	3.5E-05	N.D.	N.D.	2.9E-02
a_1 [1/Gy]	3.0E-05	2.0E-03	2.0E-03	6.5E-03	1.6E-01
b_0 [1/hour]	3.0E-03	1.4E-02	1.8E-01	4.5E-03	6.9E-01
b_1 [1/Gy]	1.4E-01	1.0E-04	N.D.	N.D.	1.6E-01

Comparison of WAM-theoretical values and experimental values



Comparison of WAM-theoretical values and experimental values

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

Proc. Natl. Acad. Sci. USA
Vol. 79, pp. 542–544, January 1982
Genetics

実験値

△ 急照射条件
72 – 90 R/min
(631 – 789 mGy/min)

○ 緩照射条件
<0.8R/min
(<7.0mGy/min)

Comparison of WAM-theoretical values and experimental values

12.5 hours

60 weeks

Mutation Frequency

1.8E-04
1.6E-04
1.4E-04
1.2E-04
1.0E-04
8.0E-05
6.0E-05
4.0E-05
2.0E-05
0.0E+00

0 2 4 6 8 10

Dose (Gy)

WAM 理論値

△ 急照射条件

● 緩照射条件

実験値

△ 急照射条件

○ 緩照射条件

	Mouse
a_0 [1/hour]	3.24E-08
a_1 [1/Gy]	2.94E-05
b_0 [1/hour]	3.00E-03
b_1 [1/Gy]	1.36E-01

Y. Tsunoyama et al., "Verification of a dose rate-responsive dynamic equilibrium model on radiation-induced mutation frequencies in mice." International Journal of Radiation Biology (2019) in press

Assumption

Time interval from the end of irradiation to the start of mating, only 0.8 R/Gy exposure condition : 2 weeks delay

Y. Tsunoyama et al., "Verification of a dose rate-responsive dynamic equilibrium model on radiation-induced mutation frequencies in mice." International Journal of Radiation Biology (2019) in press

Prediction by WAM model : if dose rate (d) is constant …

Solution of WAM equation

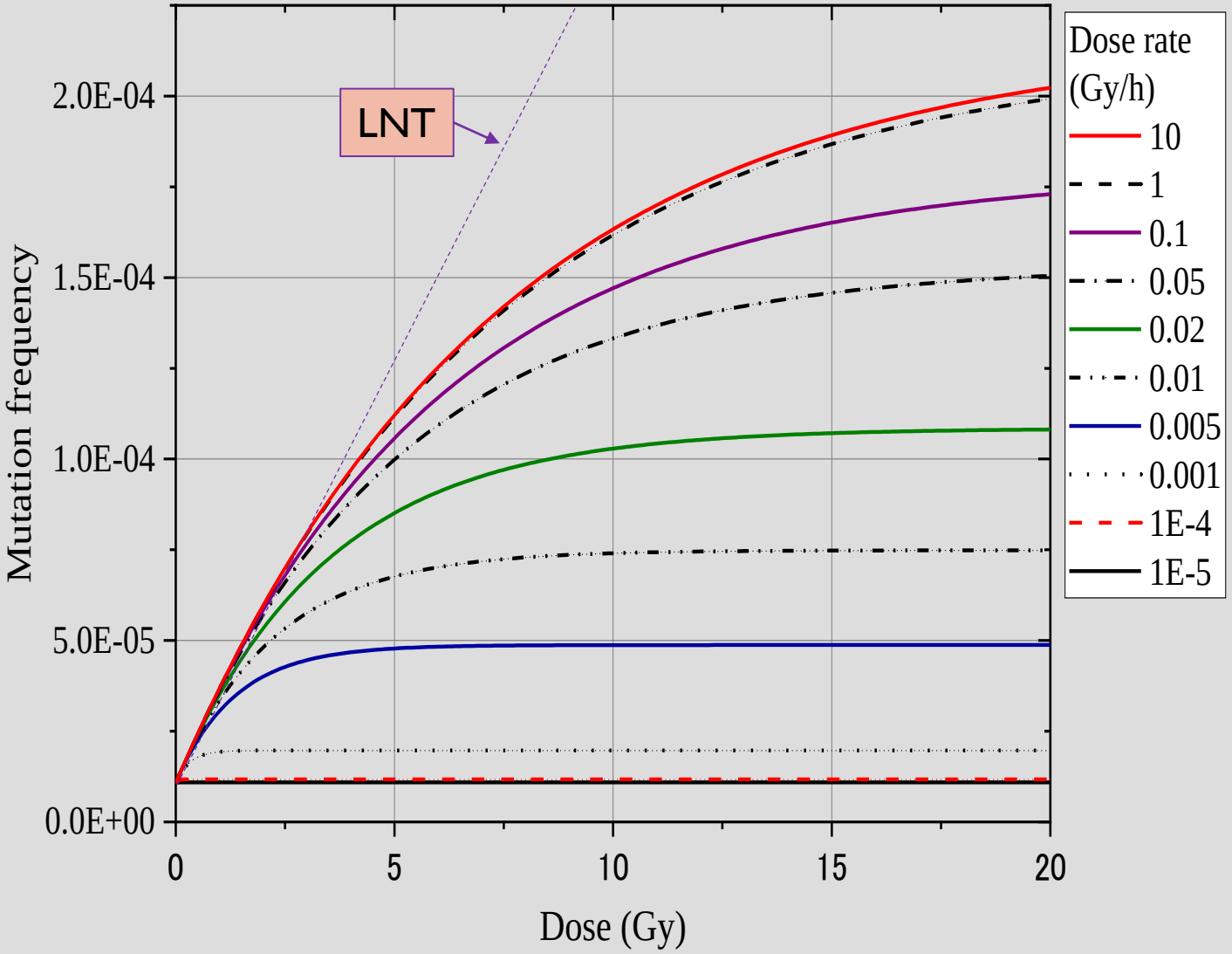
$$\frac{dF(t)}{dt} = A - BF(t) \qquad A = a_0 + a_1 d \qquad B = b_0 + b_1 d$$

$$F(t) = A/B\,(1\text{-}e^{\text{-}Bt}) + F(0)\,e^{\text{-}Bt}$$

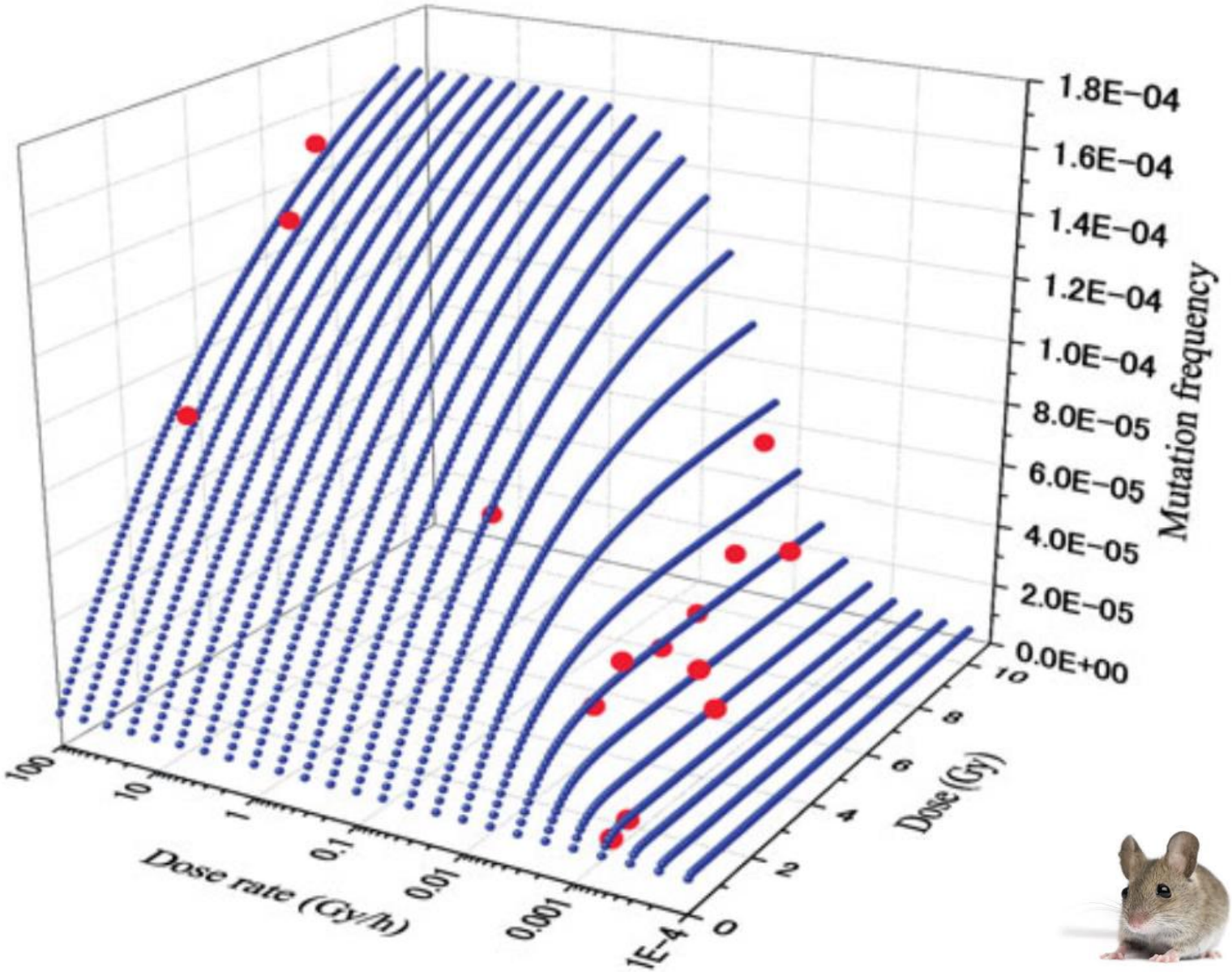
if d is constant - 線量率が長期にわたって一定である場合

$$F(\infty) = A/B = \frac{a_0 + a_1 d}{b_0 + b_1 d}$$

WAM model prediction



T. Wada et al., Journal of Nuclear Science and Technology, 53,1824-1830. (2016)
M. Bando et al., International Journal of Radiation Biology (2019) in press

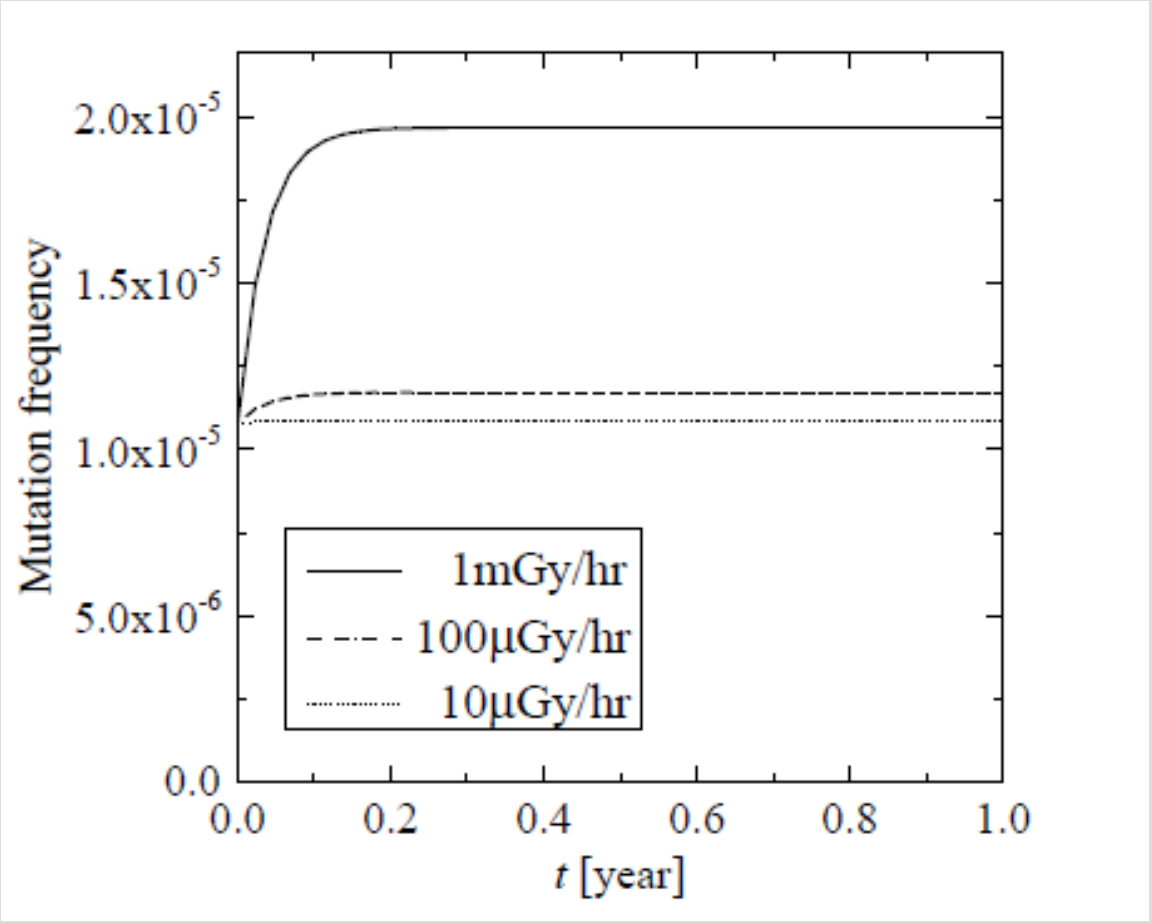


M. Bando et al., "Study of mutation from DNA to biological evolution.", Int. J. Radiat. Biol. (2019) in press

WAM model prediction

	Mouse
a_0 [1/hour]	3.24E-08
a_1 [1/Gy]	2.94E-05
b_0 [1/hour]	3.00E-03
b_1 [1/Gy]	1.36E-01

The parameter sets are given from the “mouse” data.



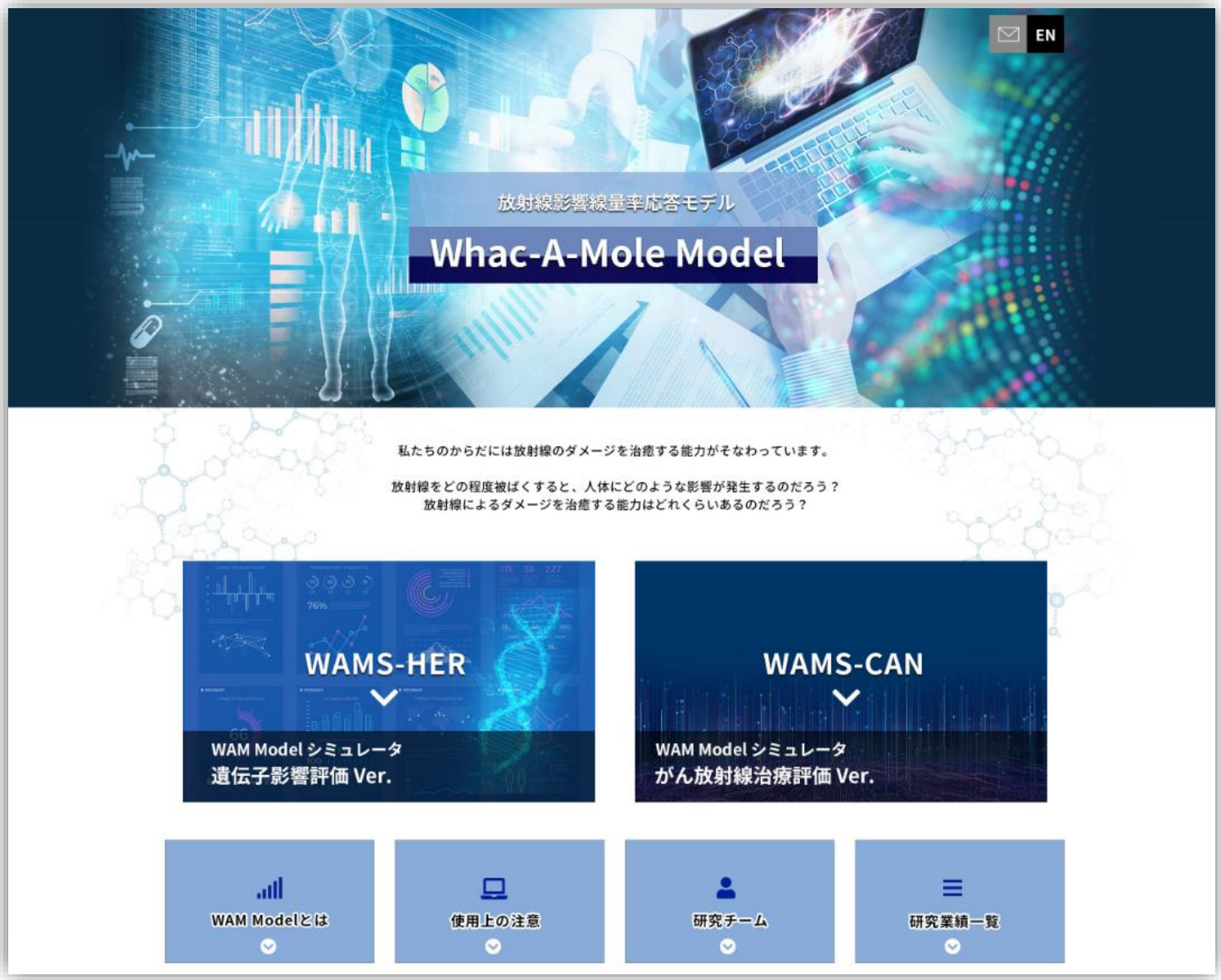
0.1μGy/h, 1μGy/h : the effects are too small to see in this graph.

T. Wada et al., Journal of Nuclear Science and Technology, 53,1824-1830. (2016)

自然突然変異細胞の発生頻度 1/100,000 個

spontaneous mutation frequency 1/100,000

WAM model ポータルサイト　http://radi.rirc.kyoto-u.ac.jp/wam



WAM Simulator

WAM Simulator

https://wamsim.vdslab.jp

WAM Simulator

Parameters

t_{max}

1200

Maximum value of horizontal axis (time (hour))

t_{div}

24

Number of horizontal partitions

F_{max}

0.0002

Maximum value of vertical axis (mutation frequency)

d_{max}

0.1

Maximum value of vertical axis (dose rate (Gy/hour))

Apply

Mutation Frequency

Mutation frequency

0.00020
0.00018
0.00016
0.00014
0.00012
0.00010
0.00008
0.00006
0.00004
0.00002
0.00000

0 100 200 300 400 500 600 700 800 900 1000 1100 1200

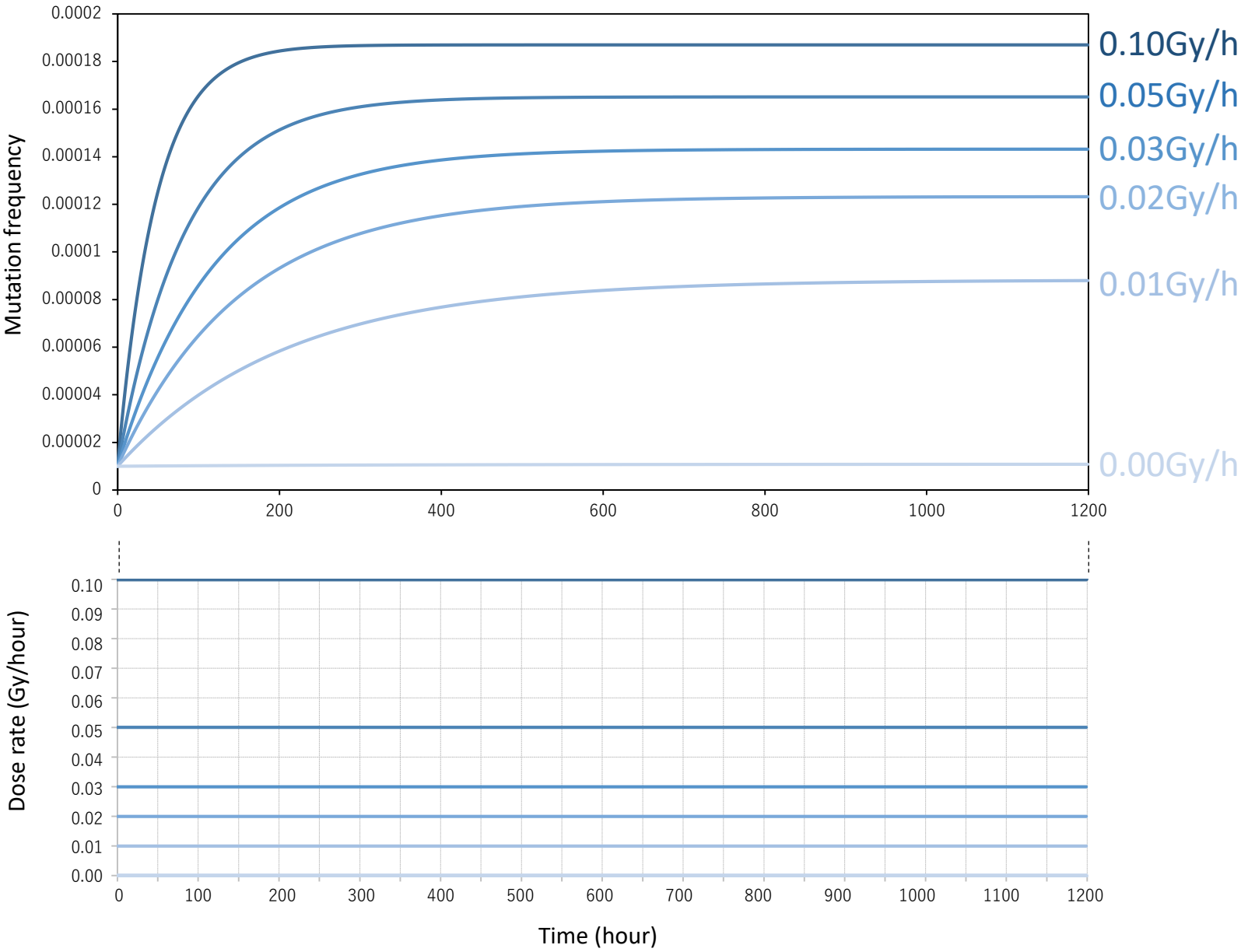
Time (hour)

Add Line export CSV export SVG export PNG

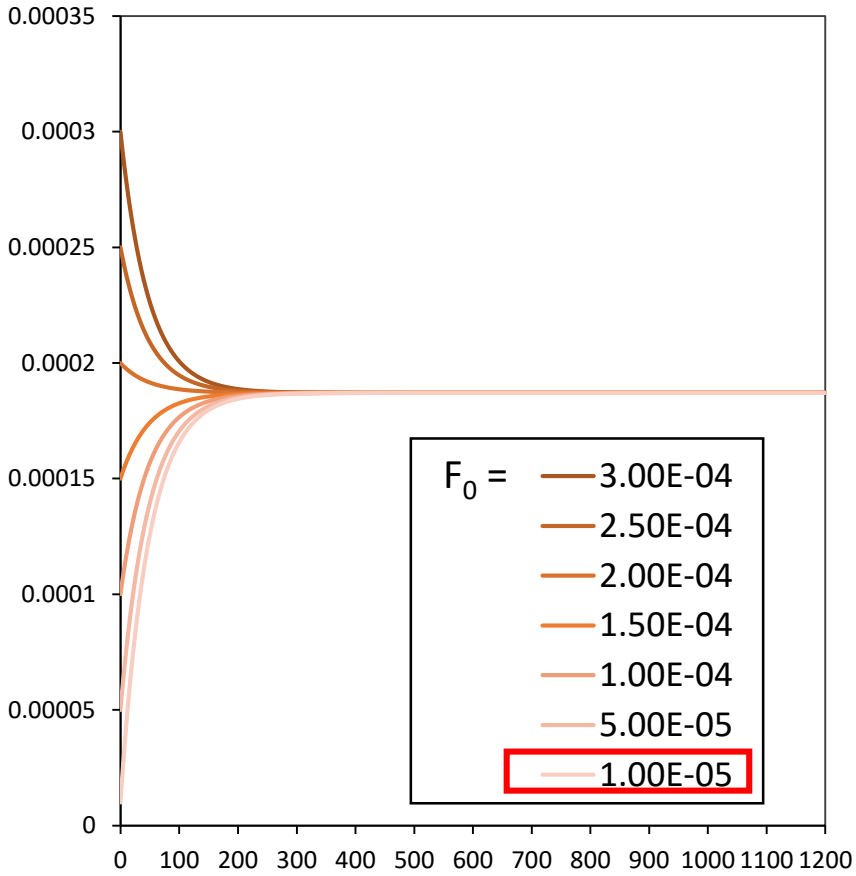
Whack-A-Mole (WAM) Model Simulator

The simulator solves a following differential equation:

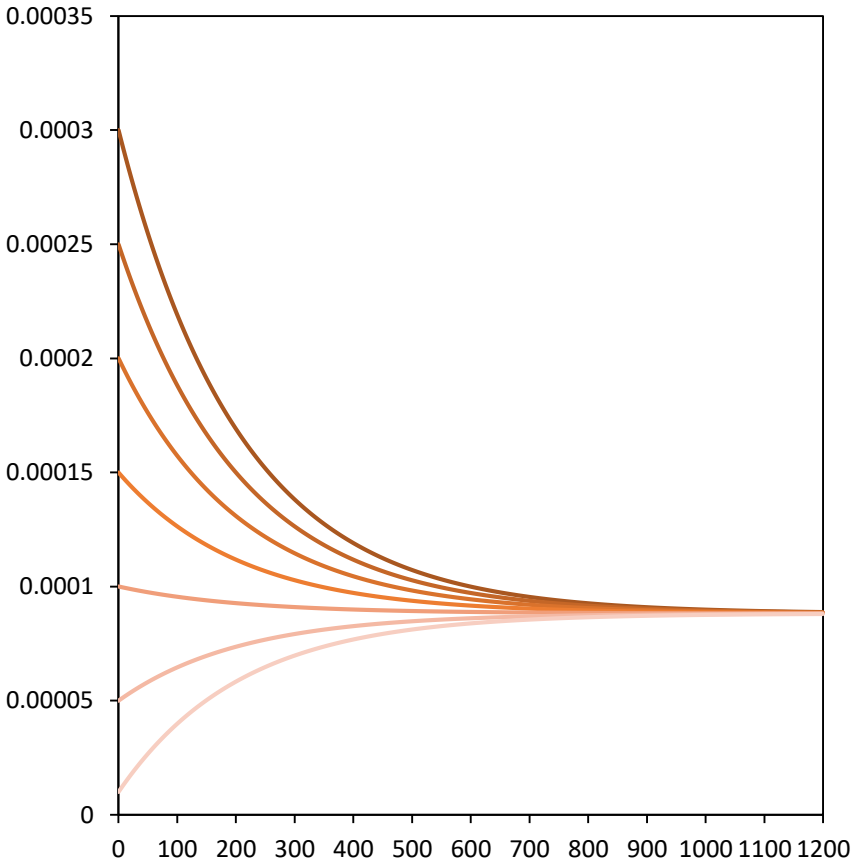
$$\frac{F(t)}{dt} = A(t) - B(t)F(t)$$


Mutation frequency
0.0002
0.00018
0.00016
0.00014
0.00012
0.0001
0.00008
0.00006
0.00004
0.00002
0
0
200
400
600
800
1000
1200
0.10Gy/h
0.05Gy/h
0.03Gy/h
0.02Gy/h
0.01Gy/h
0.00Gy/h
Dose rate (Gy/hour)
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
Time (hour)

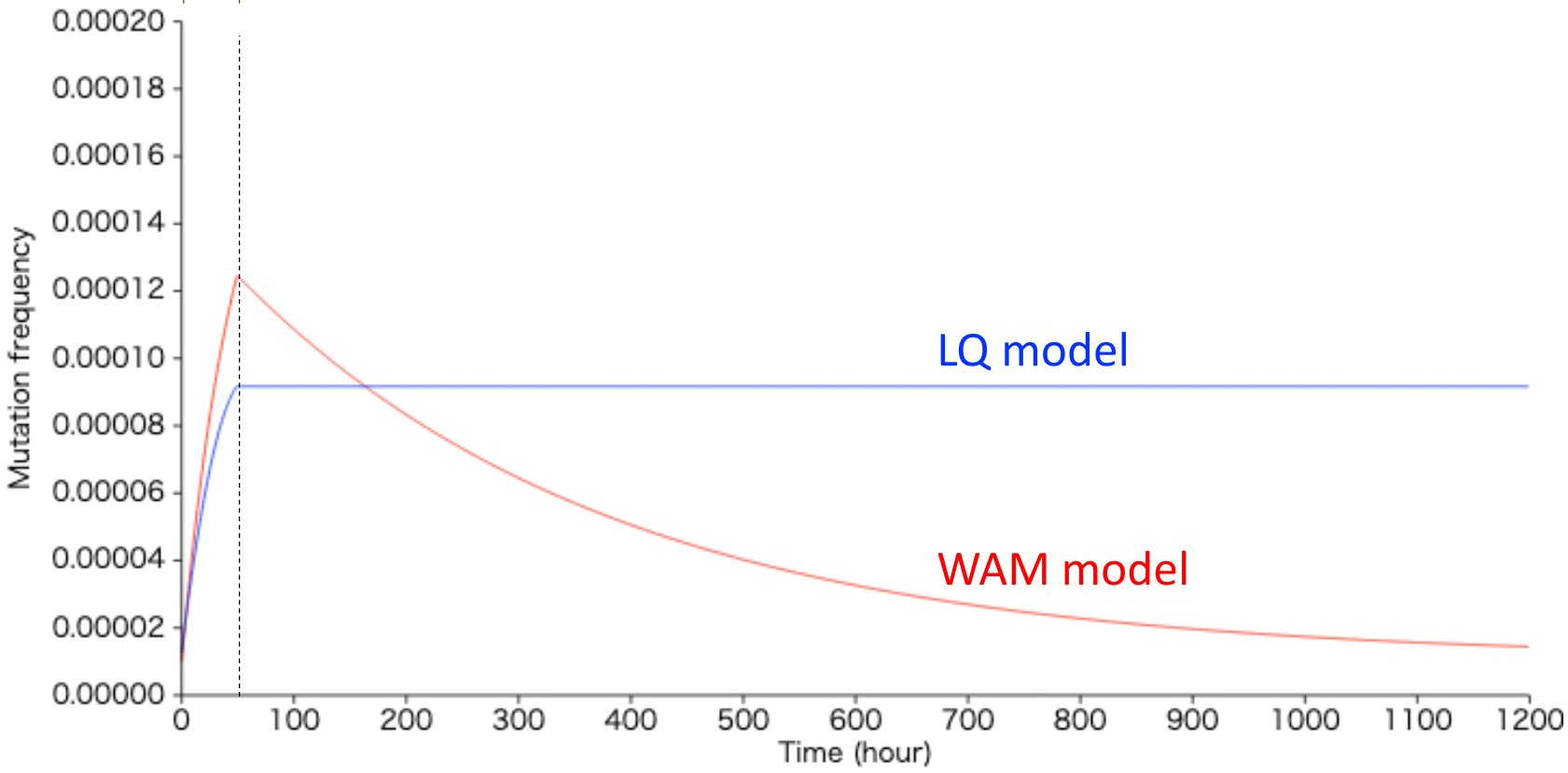
Dose rate = 0.1Gy/h



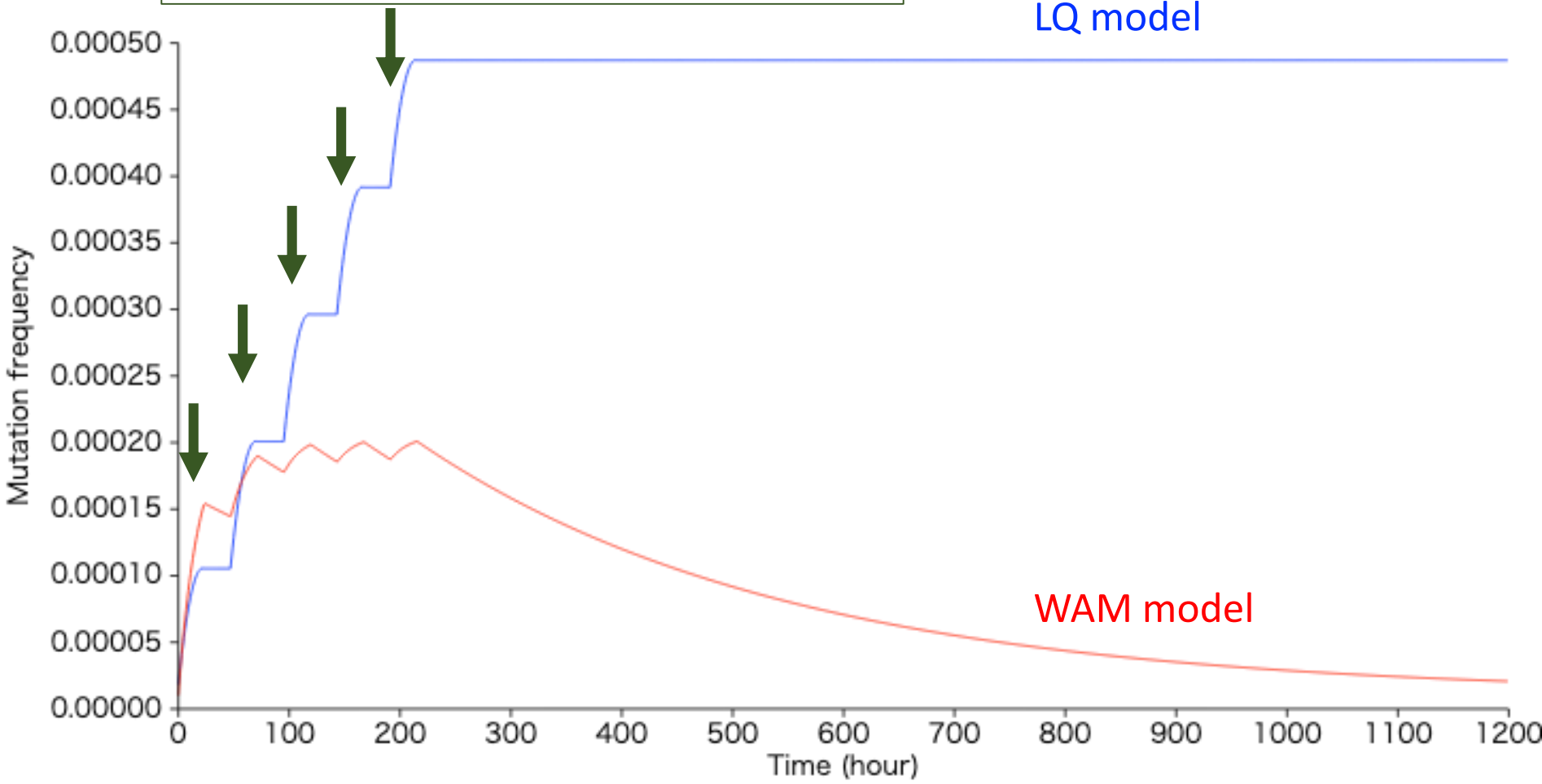
Dose rate = 0.01Gy/h

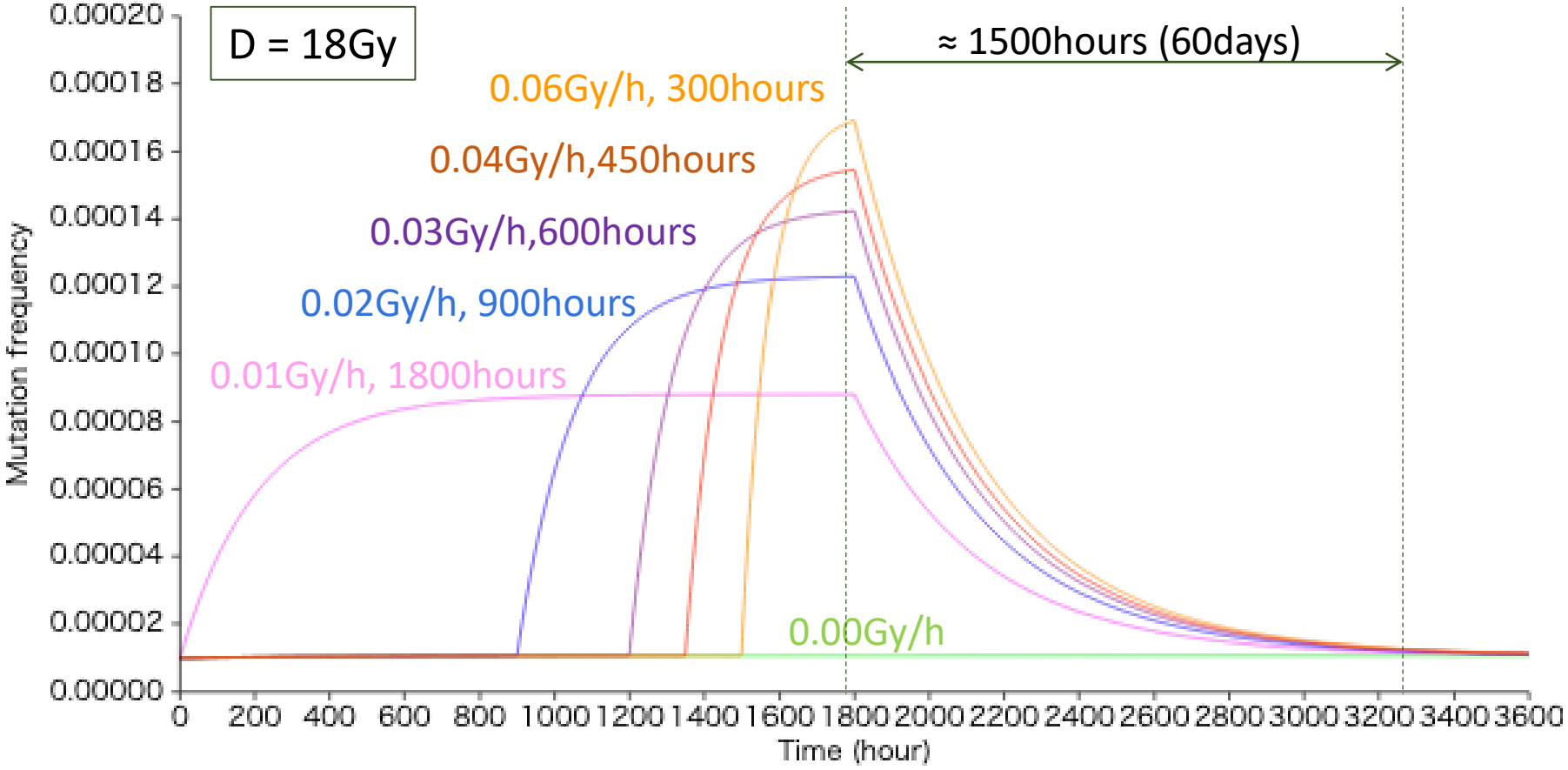


0.10Gy/h, 50h (D=5Gy)

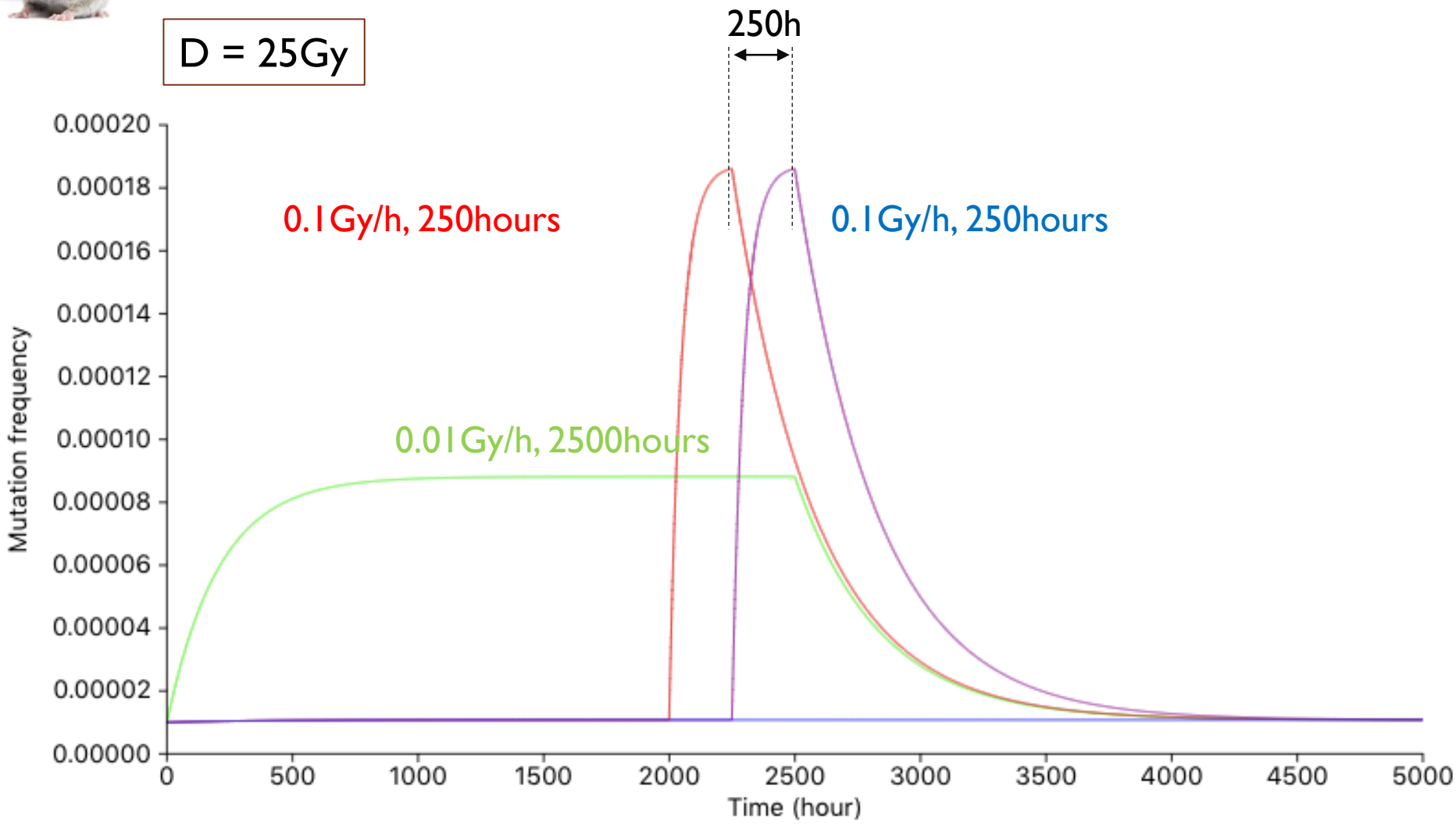


0.30Gy/h, 24h X 5times (D=36Gy)

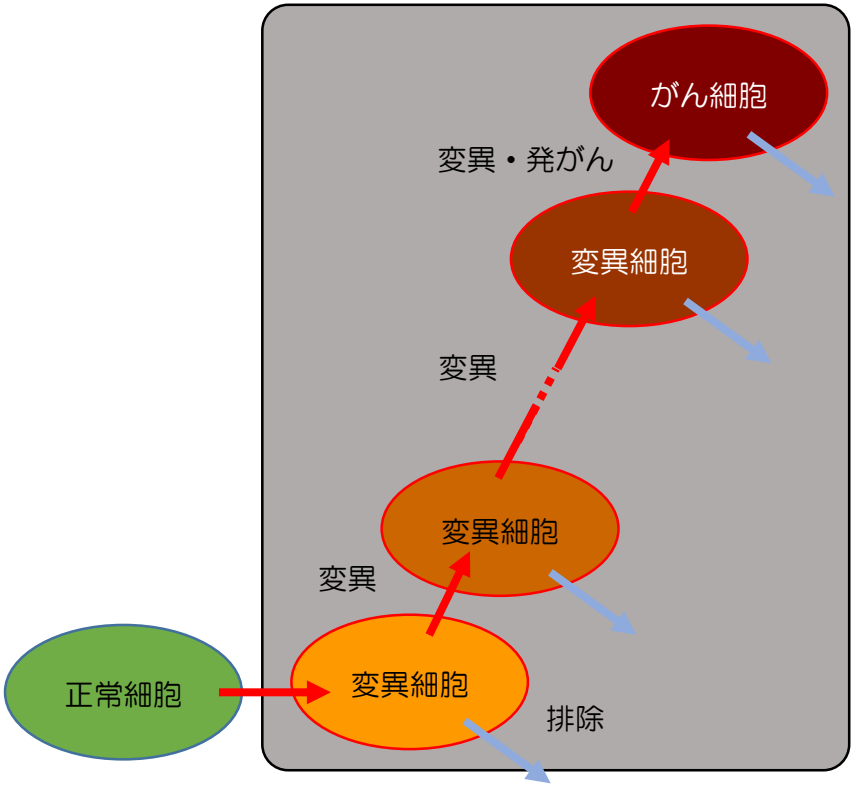


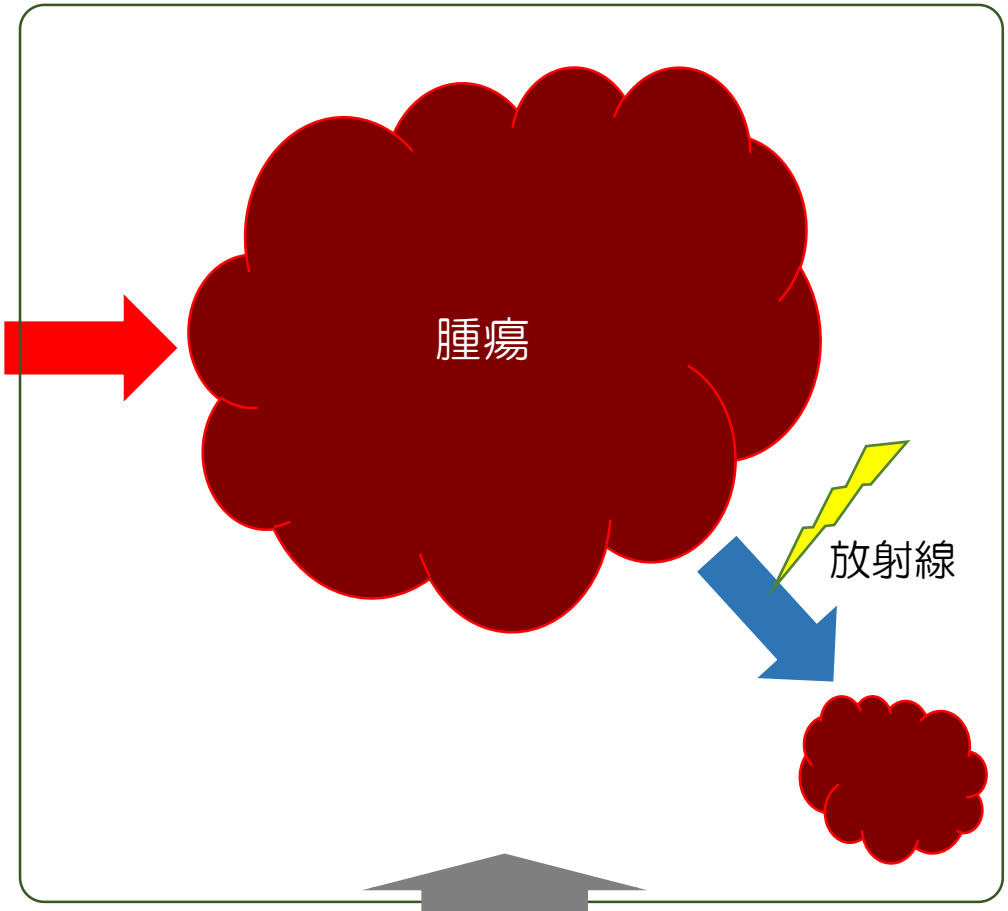

D = 18Gy
≈ 1500hours (60days)
0.06Gy/h, 300hours
0.04Gy/h,450hours
0.03Gy/h,600hours
0.02Gy/h, 900hours
0.01Gy/h, 1800hours
0.00Gy/h
Mutation frequency
0.00020
0.00018
0.00016
0.00014
0.00012
0.00010
0.00008
0.00006
0.00004
0.00002
0.00000
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600 2800 3000 3200 3400 3600
Time (hour)

D = 25Gy


250h
0.1Gy/h, 250hours
0.1Gy/h, 250hours
0.01Gy/h, 2500hours
Mutation frequency
0.00020
0.00018
0.00016
0.00014
0.00012
0.00010
0.00008
0.00006
0.00004
0.00002
0.00000
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
Time (hour)

WAM model は、がん放射線治療効果の予測にも応用可能





Thank you for your attention.