Global Journal of Pure and Applied Mathematics.
ISSN 0973-1768 Volume 13, Number 11 (2017), pp. 7829-7841

https://dx.doi.org/10.37622/GJPAM/13.11.2017.7829-7841

Stochastic Interpretation for Whack-A-Mole Model

Euich Miztani

JEIN Institute for Fundamental Science (JIFS)
5-14, Yoshida-honmachi, Sakyo-ku, Kyoto, 606-8317, Japan.
Nagoya International High School (NIHS)
1-16, Hiroji-honmachi, Showa-ku, Nagoya, 466-0841, Japan.

Abstract

The Whack-A-Mole Model(WAM) by Manabe et al. has been developed as an alternative model to the Liner No-Threshold model(LNT), because of theoretical defects inherent to the LNT design. Although there are other alternatives to LNT, the merit of WAM is its equivalency to "exponential distribution" in probability theory. This reinforces the adequacy of WAM as an alternative theory to LNT, making it possible to verify it from a legitimate stochastic viewpoint. Before WAM for LNT by Manabe et al., Inamura had derived a solution from differential equation analogous to atomic collapse theory. It matches the data of mutated mice under low-dose rate radiation exposure. Afterward, Manabe et al. derived another similar equation and then indicated the scaling function based on the equation matching mutation data of five different species. However, both of them have some stochastic problems. In this paper, we estimate their models and verify the relationship between the scaling function of WAM and "exponential distribution".

Keywords: Liner No-Threshold model(LNT), Whack-A-Mole Model(WAM), low-dose rate radiation exposure, exponential distribution, cumulative distribution function, probability density function.

AMS subject classification: 60E05, 60G07.

INTRODUCTION

In this study, we focus only on the mutation frequency under low-dose rate radiation exposure. In this condition, we are able to take account not only of damage to the cells by radiation exposure but also of resilience they have. If so, the function of mutation frequency $P(t)$ is not linear like LNT, but an "asymptotic function" approaching some fixed value: because of the individual's recovery, the mutation infrequently occurs as time advances.

Based on such an assumption, Inamura's elaborate equation of mutation frequency $P(t)$ of mice under low-dose rate radiation exposure is derived from a simple differential equation. Now, we assume $P(t)$ is a cumulative distribution function. Letting $N(t)$ be the total number of damaged cells at t under low-dose rate radiation exposure, N_0 total number of normal cells at $t=0$, D the number of damaged cells under low-dose rate radiation exposure per unit time, and μ self-recovery rate of damaged cells per unit time, the differential equation in [1] to derive $P(t)$ is

$$\frac{dN}{dt} = D - \mu N .$$

The solution from the differential equation is

$$N(t) = \frac{D}{\mu}(1 - e^{-\mu t}) .$$

Therefore, the mutation frequency is

$$P(t) = \frac{N(t)}{N_0} = \frac{D}{\mu N_0}(1 - e^{-\mu t}) . \qquad (1)$$

Eq. 1 matches the data of mutated mice under low-dose rate radiation exposure in [1]. However, it has a stochastic problem. We are not sure if $P(t)$ approaches the fixed value 1. In other words, it will never show that the probability of being mutated approaches 100 percent even as time advances long enough because of the value of factor $D/\mu N_0$. Otherwise, we cannot legitimately obtain another important function "probability density function (PDF)".

Likewise, equations of WAM in [2] and [3] have such stochastic problems as in Eq. 1. Therefore, the mutation frequency cannot also obtain the legitimate "PDF" by differentiating the mutation frequency. Also in their papers, it never proves that the mutation frequency $F(t)$ approaches the value 1 at some point in time, considering $F(t)$ as a cumulative distribution function as well as $P(t)$.

However, the scaling function $\Phi(\tau)\left(:=\frac{F(t)-F(0)}{F(\infty)-F(0)}\right)=1-\exp(-\tau)$ where $\tau=(b_0+b_1 d)t$ in [2] is exceptional: like we claimed above, the function obviously approaches the fixed value “1” (: 100 percent) at infinite time, and it appears to be an “exponential distribution”. On the other hand, what the left-hand side suggests is still obscure and seems to be nonsense in probability theory. We think of what the mutation frequency represented by the scaling function suggests from a stochastic viewpoint.

Note. We are sure that any individual naturally dies before all the cells are mutated, so that it seems to be nonsense to claim 100 percent of cells are mutated at some point in time. However, we should suppose that they survive until all the cells are mutated, because of our discussion in “legitimate” probability theory. It’s not necessarily an eccentric argument. In fact, not only in our discussion here, but also insurance mathematics for example are discussed in a like manner: it often takes the limit of functions unrealistically at infinite time, against the fact that we can never live eternally. We could say it's inevitable to get theoretically right results from a mathematical viewpoint.

The Mutation Frequency of the Scaling Function from a Stochastic Viewpoint

Now, let us think of a couple of differential equations to derive the mutation frequency of WAM in [2]. They consist of differential equations of normal and mutated cells as follows:

$$\frac{1}{N_0}\left(\frac{dN_n(t)}{dt}\right)=R_{nn}\frac{N_n(t)}{N_0}+R_{nm}\frac{N_m(t)}{N_0}=R_{nn}\frac{N_n(t)}{N_0}=R_{nn}, \qquad (2)$$

$$\frac{1}{N_0}\left(\frac{dN_m(t)}{dt}\right)=\frac{dF(t)}{dt}=R_{mn}\frac{N_n(t)}{N_0}+R_{mm}\frac{N_m(t)}{N_0}=R_{mn}+R_{mm}F(t), \qquad (3)$$

where $R_{mn}=a_0+a_1d$ and $R_{mn}=-(b_0+b_1d)$. a_0 and a_1 denote parameters related to mutated cells, b_0 and b_1 related to genetically recovered cells against radiation exposure or dead cells by apoptosis, and *d* related to the irradiation dose for the cells. The former differential function is about a group of normal cells and the latter about mutated within one tissue or organ. For further information, see also [2]. The mutation frequency is derived only from Eq. 3. However, we also evaluate Eq. 2. Although $N_n(t)/N_0=1$ in [2], we consider $N_n(t)/N_0$ as a function $G(t)$ (: not constant) in Eq. 2. So that, Eq. 2 is rewritten as follows,

$$\frac{dG(t)}{dt}=R_{nn}G(t). \qquad (4)$$

Then, let $N_n(t)/N_0$ in Eq. 3 be 1(: constant) according to [2]. Because, the first member R_{mn} should denote mutation rate for all normal cells under low-dose rate radiation exposure, and the second member $R_{mm}F(t)$ which is related to "apoptosis" and "broken cells which die under low-dose rate radiation exposure as well" subtracts from the first member as defined in [2].

Since the solution of Eq. (4) is derived as

$$\int\frac{dG(t)}{G(t)}=\int R_{nn}dt$$

$$\log|G(t)|=R_{nn}t+c,$$

$$\therefore G(t)=C\exp(R_{nn}t), \text{ where } C=e^c.$$

Since there are no mutated cells at $t=0$, $G(0)=1$ (: under no radiation exposure.) Therefore, $C=e^c=1$ and then,

$$G(t)=\exp(R_{nn}t). \qquad (5)$$

Thus, we consider the other frequency $G(t)$ that normal cells keep existing under low-dose rate radiation exposure.

From the second differential equation, another particular solution in [2] is

$$F(t) = F(\infty)(1-\exp(-(b_0 + b_1 d)t)) + F(0)\exp(-(b_0 + b_1 d)t). \quad (6)$$

Now, assuming that the frequency of mutated cells $F(t)$ and therefore the frequency of anti-mutated cells $G(t)$ are complementary events, then $F(0) = 0$ when $G(0) = 1$. $F(0) = 0$ naturally means no mutation without radiation exposure (: we exclude mutation for any other reasons.) So that, $F(t)$ and $G(t)$ are mutually exclusive. Then, $F(t) = 1 - G(t)$.

Based on our definition in probability theory mentioned above, let us think of the scaling function $\Phi(\tau)$ in [2]. We denote it $\varphi(t)$ to emphasize within it the function of *t*. The scaling function derived from Eq. 6 is

$$\varphi(t) = \frac{F(t) - F(0)}{F(\infty) - F(0)} = 1 - \exp(-(b_0 + b_1 d)t). \quad (7)$$

However, we are also able to cast Eq. 6 into another equation as follows:

$$\frac{F(t) - F(\infty)}{F(0) - F(\infty)} = \exp(-(b_0 + b_1 d)t). \quad (8)$$

Let Eq. 8 be $\psi(t)$. Now, considering $1 - \psi(t)$,

$$1 - \psi(t) = 1 - \frac{F(t) - F(\infty)}{F(0) - F(\infty)} = \frac{F(0) - F(\infty) - (F(t) - F(\infty))}{F(0) - F(\infty)} = \frac{F(0) - F(t)}{F(0) - F(\infty)} = \frac{-(F(t) - F(0))}{-(F(\infty) - F(0))}$$

$$= \frac{F(t) - F(0)}{F(\infty) - F(0)} = \varphi(t) = 1 - \exp(-(b_0 + b_1 d)t). \quad (9)$$

Therefore, $\varphi(t)$ and $\psi(t)$ are mutually exclusive (: $\varphi(t) = 1 - \psi(t)$). Then, let us consider Eq. 8. Since $F(0) = 0$ as we defined it from a stochastic viewpoint, the left

hand side is expanded as follows.

$$(\psi(t) =)1-\frac{F(t)}{F(\infty)}\text{, where } F(\infty)=\frac{a_0+a_1 d}{b_0+b_1 d} \text{ in [2].} \qquad (10)$$

Now, given that $F(\infty)=1$: it indicates that all normal cells are mutated under low-dose rate radiation exposure at "infinite time" in probability theory. In other words, growth of mutated cells and digression of the cells will reach equilibrium at infinite time: growth of mutated cells concretely stops. Such a suggestion from $F(\infty)$ does not contradict claims of WAM (: see also [2].) Then, Eq. 10 is $1-F(t)$. Therefore,

$$1-F(t)=G(t). \qquad (11)$$

From Eq. 11, we know the unknown of the exponential in Eq. 5: $R_{nn}=-(b_0+b_1 d)$. It is natural that $G(t)=\exp(-(b_0+b_1 d)t)$ is the "decreasing function" of normal cells under low-dose rate radiation exposure, for $F(t)$ is the "increasing function" of mutated cells under radiation exposure.

Since $\varphi(t)=1-\psi(t)$ from Eq. 9, we can say $\varphi(t)=F(t)$ in the same conditions mentioned above(: If $F(0)=0$ and $F(\infty)=1$), then

$$\varphi(t)=\frac{F(t)-F(0)}{F(\infty)-F(0)}=\frac{F(t)-0}{1-0}=F(t)=1-\exp(-(b_0+b_1 d)t). \qquad (12)$$

Likewise, Eq. 6 is

$$F(t)=F(\infty)(1-\exp(-(b_0+b_1 d)t))+F(0)\exp(-(b_0+b_1 d)t)=1-\exp(-(b_0+b_1 d)t).$$

Therefore, from (9), (11), and (12),

$$\varphi(t)=1-\psi(t)=F(t)=1-G(t)=1-\exp(-(b_0+b_1 d)t). \qquad (13)$$

The scaling function $\varphi(t)$ thus results in $F(t)=1-\exp(-(b_0+b_1 d)t)$, then we can state that the mutation frequency $F(t)$ is "exponential distribution" in probability theory.

Another Derivation of the Differential Equation of WAM

Let $F(t)$ be an "exponential distribution". Then, let us think of the probability in a very short period of time from t to $t+h$. It is as follows.

$$F(t+h)-F(t). \qquad (14)$$

On the other hand, assuming that in a case which no event happens by t and then happens in h, the probability is

$$(1-F(t))F(h), \qquad (15)$$

where $1-F(t)$ is a complimentary event of $F(t)$ (: nothing happens via t) and $F(h)$ is a probability that happens during h.

The probability by Eq. 14 is eventually the same as Eq. 15 from the "memoryless property of exponential distribution". So, as a result, since Eq. 14 is equal to Eq. 15,

$$F(t+h)-F(t)=(1-F(t))F(h). \qquad (16)$$

Dividing by h and taking the limit approaching 0 on both sides of Eq. 16,

$$(\frac{dF(t)}{dt}=)\lim_{h\to 0}\frac{F(t+h)-F(t)}{h}=(1-F(t))\lim_{\Delta x\to 0}\frac{F(h)}{h},$$

$$\therefore f(t)=(1-F(t))f(0). \qquad (17)$$

Putting $f(0)=\lambda$, Eq. 17 is

$$f(t)=\lambda-\lambda F(t). \qquad (18)$$

Now, let us remember the differential equation of WAM mentioned above (: Eq. 3 and see also [2]), it is as follows.

$$f(t)=dF(t)/dt=A-BF(t), \qquad (19)$$

where $A=a_0+a_1d$ and $B=b_0+b_1d$. However, since we conclude that

$F(\infty) := \int_0^\infty f(t)dt = 1$ in our stochastic definition, Eq. 19 at $t = \infty$ is

$$\left.\frac{dF(t)}{dt}\right|_{t=\infty} = 0 = A - BF(\infty) = A - B ,$$

$$\therefore A = B \quad (\text{or} \quad F(\infty) = A/B \quad \text{in a sense.}) \qquad (20)$$

At $t = 0$ is

$$\left.\frac{dF(t)}{dt}\right|_{t=0} = f(0) = A - BF(0) = A . \qquad (21)$$

Then, Eq. 18 is equivalent to Eq. 19(: Eq. 3.)

Thus, we verified that the differential equation of WAM is derived also from the "memoryless property of exponential distribution".

Furthermore, solving the differential equation Eq. 18,

$$\int \frac{1}{1-F(t)} dF(t) = \int \lambda dt . \quad \therefore -\log|1-F(t)| = \lambda t + c \Leftrightarrow F(t) = 1 - e^{-c} e^{-\lambda t} ,$$

where *c* is an integral constant. We can obtain $c = 0$ in the condition of $F(0) = 0$. Therefore,

$$F(t) = 1 - e^{-\lambda t} . \qquad (22)$$

Then, differentiating Eq. 22,

$$f(t) = \lambda e^{-\lambda t} . \qquad (23)$$

From Eq. 23, we can confirm that $f(0) = \lambda e^{-\lambda 0} = \lambda$ (: see the process from Eq. 17 to 18.) Then, $f(0) = \lambda = A = B$ (: from Eq. 20 to 21.)

These Eqs. 22 and 23 naturally denote cumulative distribution function and probability density function of "exponential distribution".

CONCLUSIONS

Our discussion mentioned above is faithfully based on probability axioms thus. In other words, there are 3 stochastic claims in the process of results:

1. The mutation frequency $F(t)$ is necessarily ranged from 0 to 1.

2. The frequency $G(t)$ that normal cells keep existing under low-dose rate radiation exposure is the complementary event of $F(t)$: $G(t) = (F(t))^c = 1 - F(t)$.

In other words, $F(t)$ and $G(t)$ are "mutually exclusive".

3. From the claims 1 and 2 mentioned above, at $t = 0$, then $F(0) = 0$ and $G(0) = 1$. Contrarily, at $t = \infty$, then $F(\infty) = 1$ and $G(\infty) = 0$.

From our stochastic interpretation of WAM, we can find another function behind the scaling function: differentiating it with respect to *t*, we can naturally obtain the *probability density function* $f(t)$ as follows.

$$f(t) = F'(t) = \varphi'(t) = \frac{d}{dt}(1 - e^{-\lambda t}) = \lambda e^{-\lambda t}, \qquad (24)$$

where $\lambda = b_0 + b_1 d$. The mean μ and variance σ^2 are therefore

$$\mu = 1/\lambda = \frac{1}{b_0 + b_1 d} \text{ and } \sigma^2 = 1/\lambda^2 = \frac{1}{(b_0 + b_1 d)^2}. \qquad (25)$$

NOTATIONS

Cumulative Distribution Function for a Particular Case as Tradescantia

It is known that mutation data of tradescantia fairly yields as time advances (: see [2].) Tradescantia cells are so vulnerable to radiation exposure that the whole cells under low-dose rate radiation exposure decrease with duration. Since Eq. 13 doesn't match the data for such a reason, we should think of another differential equation for it.

First, let us derive the equation from the stochastic viewpoint as well. Letting $P_n(t) = e^{-At}$ be the probability of normal cells as time advances, it is derived from the differential equation as follows:

$$\frac{dP_n(t)}{dt} = \frac{1}{N_0}\left(\frac{dN_n(t)}{dt}\right) = -AP_n(t), \qquad (26)$$

where the initial condition is 1. The mutated cells $P_m(t) = 1 - P_n(t) = 1 - e^{-At}$. However, since "the whole number of cells under low-dose rate radiation exposure decrease with duration", we should consider the probability of surviving cells under the radiation exposure $P_s(t) = e^{-Bt}$. It is derived from the differential equation as follows:

$$\frac{dP_s(t)}{dt} = \frac{1}{N_0}\left(\frac{dN_s(t)}{dt}\right) = -BP_s(t), \qquad (27)$$

where $N_s(t)$ is the number of surviving cells and initial condition is N_0. The probability of dead cells is $P_d(t) = 1 - P_s(t) = 1 - e^{-Bt}$. Therefore, the virtual mutation frequency $H(t)$ is as follows:

$$H(t) = P_s(t)P_m(t) = e^{-Bt}(1 - e^{-At}). \qquad (28)$$

This $H(t)$ is what we would like to obtain for the mutation frequency of tradescantia.

Let us scrutinize it further. Since the virtual probability of normal cells is $P_s(t)P_n(t) = e^{-Bt}e^{-At} = e^{-(A+B)t}$, the whole event is naturally as follows:

$$P_s(t)P_m(t) + P_s(t)P_n(t) + P_d(t) = e^{-Bt}(1 - e^{-At}) + e^{-(A+B)t} + 1 - e^{-Bt} = 1. \qquad (29)$$

Secondly, let us think of the differential function for the mutation frequency of tradescantia $H(t)$ as follows:

$$\frac{dH(t)}{dt} = AI(t) - BH(t), \qquad (30)$$

where $I(t)$ is supposed to be a reduction function by the mutation data of tradescantia. This is analogous to Eq. 3(: see also [2].) The solution should be naturally Eq. 28. It is verified by differentiating it on both sides as follows:

$$\frac{dH(t)}{dt} = -Be^{-Bt}(1 - e^{-At}) + e^{-Bt}(Ae^{-At}) = Ae^{-(A+B)t} - BH(t). \qquad (31)$$

Putting $I(t) = e^{-(A+B)t} (= P_s(t)P_n(t))$, Eq. 31 is equal to Eq. 30.

Furthermore, in fact, it is theoretically natural that $H(t) \approx F(t)$ if the value of *B* is considerably small.

Note. Although the author is not sure of the relevance and reason at this time, the graph of $H(t)$ is remarkably similar to a graph illustrating the growth of leukemia after radiation exposure by the atomic bombing of Hiroshima and Nagasaki. Therefore, this stochastic model could be applicable to the modeling of leukemia.

Open Problems

1. Labeling t_1, t_2, ... , t_n as individual becomes mutated in the elapsed time, let them take time intervals $U_n = t_n - t_{n-1}$. From the property of the Poisson process (also from "exponential distribution"), the mean of U_n is,

$$\overline{U}_n (= 1/\lambda) = 1/B \text{, where } B = b_0 + b_1 d \text{.} \qquad (32)$$

We will be able to compare the theoretical value to the experimental data based on the statistical analyses.

2. Assuming that the mutation frequency $F(t)$ of WAM can be measured by "exponential distribution", we are immediately able to apply it to the formula of the Poisson process. Supposing the number of individuals $B(:= b_0 + b_1 d)$ become mutated on average per unit time, then the probability $P(n)$ with the number of individuals $N(t) = n$ which is mutated in t is naturally given by,

$$P\{N(t) = n\} = \frac{(Bt)^n}{n!} e^{-Bt} \text{, where } (\lambda =) B = b_0 + b_1 d \text{.} \qquad (33)$$

The probability obtained by setting values of n and t arbitrarily is also comparable to experimental mutation data in the elapsed time.

3. Let us think of WAM based on "exponential distribution" discussed above under fractionated irradiation. Letting probability density frequency (: PDF) of mutation frequency "for normal cells" under irradiation be p_{2i-1} and under "no" irradiation p_{2i}, they are denoted as follows:

$$p_{2i-1} = B \exp(-B(t_{2t-1} - t_{2t-2})) \text{, where } B = b_0 + b_1 d \text{,} \qquad (34)$$

$$p_{2i} = b \exp(-b(t_{2i} - t_{2i-1})) \text{, where } b = b_0 \text{.} \qquad (35)$$

Let us remark that the second member $b_1 d$ on the right-hand side of B denotes the total dose of radiation, so that the member $b_1 d$ is left out of b. Since fractionated irradiation is to alternate "irradiation" and "no irradiation", the mutation frequency under fractionated irradiation we'd like to obtain will be given by Eqs. 34 and 35 over time. Now, let the mutation frequency under irradiation from time 0 to t_1 be P_1. From Eq. 34, it is denoted as follows:

$$P_1 = \int_0^{t_1} B \exp(-Bs) ds = -\exp(-Bt_1) - (-1) = 1 - \exp(-Bt_1). \qquad (36)$$

Let the mutation frequency under "no" irradiation from time t_1 to t_2 be P_2 according to Eq. 35 be

$$P_2 = \int_{t_1}^{t_2} b \exp(-bs) ds = -\exp(-bt_2) - (-\exp bt_1) = \exp(-bt_1) - \exp(-bt_2). \qquad (37)$$

Likewise, P_3 under irradiation, P_4 under no irradiation, ... , P_{2n-1}, and P_{2n} at last. They are naturally denoted as follows:

$$P_3 = \exp(-Bt_2) - \exp(-Bt_3), \quad P_4 = \exp(-bt_3) - \exp(-bt_4), \ldots,$$
$$P_{2n-1} = \exp(-Bt_{2n-2}) - \exp(-Bt_{2n-1}), \quad P_{2n} = \exp(-bt_{2n-1}) - \exp(-bt_{2n}).$$

We can obtain the mutation frequency under fractionated irradiation after $2n$ times P^{2n} is the summation of the equations above:

$$P^{2n} = P_1 + P_2 + ,...,+ P_{2n-1} + P_{2n}$$

$$= 1 - \exp(-Bt_1) + \exp(-bt_1) - \exp(-bt_2) + ... + \exp(-Bt_{2n-2}) - \exp(-Bt_{2n-1}) + \exp(-bt_{2n-1}) - \exp(-bt_{2n}).$$

Since $B = b_0 + b_1 d$ and $b = b_0$,

$$P^{2n} = 1 + \exp(-b_0 t_1)\{1 - \exp(-b_1 dt_1)\} - \exp(-b_0 t_2)\{1 - \exp(-b_1 dt_2)\} + ...$$
$$+ \exp(-b_0 t_{2n-1})\{1 - \exp(-b_1 dt_{2n-1})\} - \exp(-b_0 t_{2n})\{1 - \exp(-b_1 dt_{2n})\}$$

$$= 1 + \sum_{k=1}^{n} \exp(-b_0 t_{2k-1})\{1 - \exp(-b_1 dt_{2nk-1})\} - \sum_{k=1}^{n} \exp(-b_0 t_{2k})\{1 - \exp(-b_1 dt_{2k})\}. \qquad (38)$$

ACKNOWLEDGEMENTS

I would like to acknowledge Prof. Wolfgang Weiss who is a former chair of UNSCEAR. I have privately kept in touch with him and he has always encouraged and advised me in this research since I met him at his lecture meeting titled Opportunities and Challenges in Low Dose Risk Research held at Kyoto University on May 28, 2015. I also appreciate my colleague Steven McLellan at Nagoya International High School, who voluntarily and patiently listened to my explanations of this research and offered me significant suggestions and opinions for English expression.

REFERENCES

[1] Takashi Inamura, Journal of the Physical Society of Japan, 66, 2011

[2] (Takashi Inamura, Journal of the Physical society of Japan (Japanese version,) vol. 66, 2011) The Japanese article written by the author is: http://jein.jp/images/announcement/activity-report/symposium/nbp2012-discussion3.pdf

[3] Y. Manabe, T. Wada, Y. Tsunoyama, H. Nakajima, I. Nakamura, and M. Bando, Whack-A-Mole Model: Towards unified description of biological effect caused by radiation-exposure, Journal of the Physical Society of Japan, April 15, 2015, Vol. 84, No. 4 (https://arxiv.org/abs/1411.4132)

[4] T. Wada, Y. Manabe, I. Nakamura, Y. Tsunoyama, H. Nakajima, M. Bando, Dose and dose-rate dependence of mutation frequency under long-term exposure -- A new look at DDREF from WAM model -- , Journal of Nuclear Science and Technology, 53(11), Pages 1824-1830, April 06, 2016 (https://arxiv.org/abs/1503.00227)