A FORMULA TO PREDICT THE TRANSMISSION FREQUENCY OF ACENTRIC FRAGMENTS*

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ABSTRACT

A formula, based on the Poisson distribution of radiation-induced chromosomal deletions, was derived to predict the frequency of transmission of acentric fragments between subsequent mitoses. The frequency of deletions observed in the $i^{\text{th}} + 1$ division subsequent to fragment distribution at the i^{th} division anaphase is independent of the cell death resulting from fragment loss. Further, the transmission frequency of chromosome acentric fragments is mathematically equal to the fragment frequency observed in the $i^{\text{th}} + 1$ generation divided by the mean fragment frequency in the i^{th} generation. The formula was also extended to chromatid deletions.

FORMULAE derived by CARRANO and HEDDLE (1972) permit prediction of radiation-induced chromosome aberration frequencies at any given mitosis from known aberration frequencies at the first mitosis. One of the formulae implies that in the absence of asymmetrical exchange aberrations the frequency of chromosome acentric fragments observed in subsequent divisions is not influenced by cell death between divisions. The reason for this independence of fragment frequency and cell survival was not readily apparent. Consequently, this analysis was undertaken to extend this finding by using a more direct derivation of a formula to describe chromosome fragment transmission and to extend the formula to the transmission of chromatid deletions. WOLFF (1961), EVANS (1962), and BENDER (1969) provide excellent reviews on the origin and nature of these aberrations in relation to the cell life cycle.

DERIVATION

Two parameters are defined for this analysis:

1. T , the probability that a chromosome deletion (acentric fragment) will be transmitted as a whole to one daughter nucleus (assumption 2 below); transmission to either one or the other daughter nucleus being $2T$; and
2. P , the probability that a cell will survive to a subsequent mitosis after losing a chromosome acentric fragment.

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TABLE 1

Probabilities of events associated with chromosome fragment transmission

Parent	Events*		Binomial probability	Frequency	Probability of each event
	daughter 1	daughter 2			
			2T	-	2T
			1-2T	-	1-2T
			$(2T)^2$	1	$2T^2$
				1	$2T^2$
			$2(2T)(1-2T)$	-	$4T(1-2T)$
			$(1-2T)^2$	-	$(1-2T)^2$
			$(2T)^3$	1	$2T^3$
				3	$6T^3$
			$3(2T)^2(1-2T)$	1	$6T^2(1-2T)$
				1	$6T^2(1-2T)$
			$3(2T)(1-2T)^2$	-	$6T(1-2T)^2$
			$(1-2T)^3$	-	$(1-2T)^3$

* The fragments have been replicated in the daughter cells as would be observed at metaphase. Fragments are assumed to be transmitted without splitting.

In addition, the following assumptions are made:

1. Radiation-induced chromosomal deletions are distributed according to a Poisson distribution at the first post-irradiation division (WOLFF 1961).
2. A chromosome terminal deletion or isochromatid deletion passes as a whole to one or the other daughter nucleus or is lost, i.e., only one of the daughters can receive a particular fragment, and if it does there will be two identical paired fragments (four chromatids) at the next mitosis (SASAKI and NOR-

MAN 1967) (Table 1). Single chromatid deletions can, of course, only be transmitted to one daughter nucleus or be lost.

3. The probability that a cell will survive the loss of f fragments is P^f .
4. Cells with chromosomal deletions do not contain other aberrations that would prevent their passage to subsequent mitoses.

Table 1 illustrates the probabilities of all events associated with fragment transmission for cells containing one, two, or three isochromatid fragments per cell. The analysis is readily extended to higher fragment frequencies. The probabilities that the two daughter cells will receive 0, 1, . . . f fragments from a parent possessing f fragments is given by the binomial expansion of $[2T + (1-2T)]^f$ where $2T$ is the probability of fragment transmission to either daughter cell and $1-2T$ is the probability of non-transmission to either daughter.

The distribution of fragments in each daughter cell must also be considered. For example, progeny cells receiving three fragments from the parent cell might have all three fragments in one cell or two fragments in one cell and one in the other. The relative frequency of these events is 1:3 respectively. The probability of each event is thereby determined.

As stated in the assumptions, a cell losing f fragments has a probability of survival P^f . For purposes of comparison, the two extreme values of P will be considered here, i.e., $P = 0$ or 1.0. The Poisson distribution is given by

$$\frac{e^{-m}m^f}{f!}$$

where m is the average number of fragments per cell and f the number of fragments in any given cell. Table 2 shows this distribution for the first four classes of cells containing 0, 1, 2, or 3 fragments. If the fragment is transmitted as a whole, only paired fragments will be observed at the next division so that only cells containing 0, 2, 4, . . . f_{even} fragments will be observed after replication of the fragment in the intervening DNA synthesis period. Each class of cells in the i^{th} division, i.e., those containing 0, 1, 2, . . . f fragments, will contribute to both the survival and number of fragments in its progeny cells. This contribution can be calculated from the formula:

$$N_{i+1} = \sum_{\text{all } e} N_i P^f n_e q_e, \quad (1)$$

where N_{i+1} is the frequency of cells produced in the $i^{\text{th}} + 1$ generation for a particular class of the Poisson distribution; N_i is the frequency of cells present in the i^{th} generation for a particular class of the Poisson distribution; P^f is the probability of a daughter cell surviving after losing f fragments; n_e is the number of daughter cells produced by an event, e , for each class of the Poisson distribution; and q_e is the probability of the event occurring for each class.

For example, consider the contribution of those cells with one fragment in the i^{th} division to cells in the $i^{\text{th}} + 1$ division. The frequency of cells in the one class of the i^{th} division, according to the Poisson distribution of this class to the zero

TABLE 2

Distribution of chromosome fragments at division i and $i+1$ for maximum ($P=1.0$) and minimum ($P=0$) cell survival after fragment loss

No. fragments (i^{th} div)	0	1	2	3
Frequency (i^{th} div)	e^{-m}	$e^{-m}m$	$\frac{e^{-m}m^2}{2!}$	$\frac{e^{-m}m^3}{3!}$
Contributing class (i^{th} div)	No. fragments ($i^{\text{th}} + 1$ division)			
	0	2	4	6
Frequency of cells contributed to $i^{\text{th}}+1$ division ($P=1.0$)				
0	$2e^{-m}$			
1	$2me^{-m}(1-T)$	$2mTe^{-m}$		
2	$\frac{2m^2e^{-m}(1-T)^2}{2!}$	$\frac{4m^2Te^{-m}(1-T)}{2!}$	$\frac{2m^2T^2e^{-m}}{2!}$	
3	$\frac{2m^3e^{-m}(1-T)^3}{3!}$	$\frac{6m^3Te^{-m}(1-T)^2}{3!}$	$\frac{6m^3T^2e^{-m}(1-T)}{3!}$	$\frac{2m^3T^3e^{-m}}{3!}$
$\sum_{f=0}^{\infty}$	$2e^{-mT}$	$2mTe^{-mT}$	$\frac{2m^2T^2e^{-mT}}{2!}$	$\frac{2m^3T^3e^{-mT}}{3!}$
Frequency of cells contributed to $i^{\text{th}}+1$ division ($P=0$)				
0	$2e^{-m}$			
1		$2mTe^{-m}$		
2			$\frac{2m^2T^2e^{-m}}{2!}$	
3				$\frac{2m^3T^3e^{-m}}{3!}$
$\sum_{f=0}^{\infty}$	$2e^{-m}$	$2mTe^{-m}$	$\frac{2m^2T^2e^{-m}}{2!}$	$\frac{2m^3T^3e^{-m}}{3!}$

class in the $i^{\text{th}} + 1$ division then becomes (using Table 1, equation (1) and assuming $P = 1$):

$$N_{i+1} = me^{-m}(1)(1)(2T) + me^{-m}(1)(2)(1-2T)$$

or

$$N_{i+1} = 2me^{-m}(1-T) \quad (2)$$

Similarly, the contribution of cells in the one class in the i^{th} division to the frequency of cells in the two class in the $i^{\text{th}} + 1$ division is:

$$N_{i+1} = me^{-m}(1)(1)(2T) = 2mTe^{-m}. \quad (3)$$

These values are illustrated in Table 2 with the values similarly obtained for all other classes. The lower portion of Table 2 lists the values obtained when $P = 0$. The summation of each class at the $i^{\text{th}} + 1$ division is the result of the arrangement of the individual terms into an infinite series.

The fragment frequency at the $i^{\text{th}} + 1$ division can now be calculated for each value of P , from the formula,

$$F_{i+1} = \frac{\sum_{f=1}^{\infty} fn_f}{\sum_{f=0}^{\infty} n_f}; \quad (4)$$

where F_{i+1} is the fragment frequency at the $i^{\text{th}} + 1$ division; f is the number of fragments in each class of the Poisson distribution; and n_f is the sum of the frequency of cells with f fragments. For $P = 1.0$ this becomes:

$$F_{i+1} = \frac{2(2mTe^{-mT}) + 4(2m^2T^2e^{-mT}/2!) + 6(2m^3T^3e^{-mT}/3!) + \dots}{2e^{-mT} + 2mTe^{-mT} + 2m^2T^2e^{-mT}/2! + 2m^3T^3e^{-mT}/3! + \dots}$$

which reduces to

$$F_{i+1} = 2mT. \quad (5)$$

For $P = 0$ this becomes:

$$F_{i+1} = \frac{2(2mTe^{-m}) + 4(2m^2T^2e^{-m}/2!) + 6(2m^3T^3e^{-m}/3!) + \dots}{2e^{-m} + 2mTe^{-m} + 2m^2T^2e^{-m}/2! + 2m^3T^3e^{-m}/3! + \dots}$$

which also reduces to

$$F_{i+1} = 2mT. \quad (6)$$

DISCUSSION

The fragment frequency observed at the $i^{\text{th}} + 1$ division is independent of whether or not the cell losing a fragment survives after the i^{th} division. The observed frequency, F_{i+1} is merely the product of the transmission frequency, $2T$, and the fragment frequency, m , at the i^{th} division. Consequently, the transmission frequency of chromosome deletions and isochromatid deletions can be readily calculated if their frequency in the population is known for any two successive generations. The transmission of chromatid deletions can also be calculated by modifying the formula such that:

$$2T = \frac{2F_{i+1}}{m}, \quad (7)$$

where F_{i+1} is now the frequency of chromosome deletions observed in the $i^{\text{th}} + 1$ division derived from the transmission of chromatid deletions with a mean frequency of m in the i^{th} division (EVANS and SCOTT 1964). Of course, the mean

fragment frequencies must be ascertained only in cells which contain no aberrations which affect their survival or alter the fragment distribution in the $i^{\text{th}} + 1$ generation. Such chromosomal aberrations might include dicentrics or other asymmetrical exchanges.

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