Genet. Res., Camb. (1962), **3**, *pp.* 328–330
Printed in Great Britain

SHORT NOTE

Mate-killer (*mu*) particles in *Paramecium aurelia*: the metagon division hypothesis

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(*Received* 1 *May* 1962)

Mate-killer (*mu*) particles in *Paramecium aurelia* depend on the presence of the dominant genes M_1 or M_2; but, on elimination of these genes, there is a delay of 8–15 fissions before most of the daughter cells lose their particles, the loss in any cell occurring abruptly. To explain this delay, Gibson & Beale (1962) postulated that the *mu* particles depend on intermediary particulate elements (metagons), which are themselves maintained or produced by the *M* genes. On elimination of the *M* genes, the metagons cease to be formed in the dividing cells and are passively diluted out during subsequent fissions. Any cell which does not inherit a single metagon rapidly destroys its *mu* particles. The *M* genes are assumed to maintain a large number of metagons in the cell, although a single one of these elements is assumed to be able to maintain the normal complement of *mu* particles.

If, immediately after loss of its M gene or genes, a cell has N metagons, and these are randomly distributed at each subsequent fission without either multiplication or destruction, then after n fissions a fraction $\{1-(\frac{1}{2})^n\}^N$ of the cells is expected to lack metagons (and therefore *mu* particles). On this hypothesis, M_2 must maintain about 1000 metagons, and M_1 and M_2 jointly about 1500 metagons in the cell; but the trend in the frequencies of 'empty' cells at successive fissions shows significant deviations from that expected, in both these cases (Reeve, 1962). This suggests that the metagons are not simply eliminated by passive dilution during cell fission, but there is some other factor, and the question arises whether any simple modification of the passive-dilution hypothesis will give a satisfactory fit to the data.

We consider here the hypothesis, among those listed by Reeve (loc. cit.), that the metagons are randomly distributed at each fission but any metagon has a constant small probability of dividing into two during any interfission period. Whether or not it is biologically reasonable, this hypothesis has the advantage of being amenable to mathematical formulation.

Let N be the initial number of metagons, and let $p = 1-q$ be the probability that any particular metagon divides in a given interfission period. It is assumed that a metagon can divide only once in a single interfission period, but may divide again in a subsequent period, and that the division of one metagon does not influence the probability of other metagons in the same cell dividing simultaneously.

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Then the probability $P_1(t)$ that a daughter cell from the first fission contains t metagons is the probability that it receives r from the parent cell and that $(t-r)$ of these divide into two, summed for all r not greater than t. This probability is

$$P_1(t) = \sum_{r \leqslant t} \frac{1}{2^N} \binom{N}{r} \binom{r}{t-r} p^{t-r} q^{2r-t} \tag{1}$$

This expression is the coefficient of x^t in the expansion of

$$\{F(x)\}^N = (\tfrac{1}{2} + \tfrac{1}{2}qx + \tfrac{1}{2}px^2)^N \tag{2}$$

A cell emerging with t_1 particles from the first fission can give rise to a daughter in the second fission with t_2 particles if it passes on r_1, of which $t_2 - r_1$ divide. The total probability of a cell at the second fission ending with t_2 metagons is thus

$$P_2(t_2) = \sum_{t_1} \sum_{r_1} P_1(t_1) \frac{1}{2^{t_1}} \binom{t_1}{r_1} \binom{r_1}{t_2 - r_1} p^{t_2 - r_1} q^{2r_1 - t_2} \tag{3}$$

where summation is over all possible t_1 and r_1. This is the coefficient of x^{t_2} in the expansion of

$$\{F_2(x)\}^N = \{F(F(x))\}^N \tag{4}$$

obtained by substituting $x = (\frac{1}{2} + \frac{1}{2}qx + \frac{1}{2}px^2)$ in (2). Evidently the probability of finding a cell with t metagons after n fissions is the coefficient of x^t in $F_n(x)^N$, and the frequency of empty cells after n fissions is the corresponding coefficient with $t = 0$.

$F_n(x)$ is a polynomial of degree 2^n in x and of degree $2^n - 1$ in p, and rapidly becomes very cumbersome as n increases, so an algebraic method of estimating N and p from a given set of observations of the frequencies of empty cells at successive fissions is not feasible. Instead, a solution was obtained using the Elliott 401 Digital Computer at Rothamsted Experimental Station. Let the coefficient of x^0 in $F_n(x)$ be $Q_n(p)$, where $Q_n(p)$ is a polynomial in p. Then

$$Q_{n+1}(p) = \tfrac{1}{2} + \tfrac{1}{2}(1-p)\, Q_n(p) + \tfrac{1}{2}pQ_n(p)^2 \tag{5}$$

The maximum likelihood estimates of N and p were obtained numerically, using a routine which computed the logarithm of the likelihood for any given values of N and p. If T_n cells were tested in the nth generation and A_n were found to be empty, the function to be maximised is

$$L(p, N) = N \sum_n A_n \log Q_n(p) + \sum_n (T_n - A_n) \log \{1 - Q_n(p)^N\} \tag{6}$$

The maximum was found by an iterative procedure in which initial estimates p_0 and N_0 were improved by using the maximum of the second degree approximation to the function. When the process converged, the second degree approximation provided large sample estimates of the variances and covariance of p and N.

Maximum likelihood estimates of N and p for the one- and two-factor cases (loss of gene M_2 and of $M_1 + M_2$, respectively) discussed by Gibson and Beale (1962, Tables 1 and 3) are compared with the corresponding estimates assuming $p = 0$, in Table 1.

Compared with the assumption of no metagon division, χ^2 for goodness of fit is reduced about 10-fold, and the data for both cases are perfectly compatible with the hypothesis that the metagons are randomly distributed at each cell fission but each metagon has a 1 in 5 chance of dividing during any interfission period. It is interesting that N is much the same for the two cases (if we assume a common p-value of 0·204, N is estimated as 250

https://doi.org/10.1017/S0016672300035096 Published online by Cambridge University Press

Table 1. *Estimates based on frequencies of 'empty' cells after fissions* 8–15

(*a*) Metagon division hypothesis: maximum likelihood estimates of N and p:

	N	p	χ^2	D.F.
One-factor case:	286 ± 73	$0{\cdot}184 \pm 0{\cdot}037$	4·13	6
Two-factor case:	275 ± 71	$0{\cdot}223 \pm 0{\cdot}037$	6·68	6

(*b*) Corresponding estimates assuming no division of metagons ($p = 0$):

	N	p	χ^2	D.F.
One-factor case:	1090 ± 70	—	40·8	7
Two-factor case:	1480 ± 92	—	82·9	7

for the one-factor and 310 for the two-factor case), and the data are not consistent with the hypothesis that two factors maintain twice as many metagons in the cell as one factor (χ^2 about 60, with 14 degrees of freedom).

The mathematical consequences of a system in which hereditary particles are dividing at a different rate from that of the host carrying them are, perhaps, of some intrinsic interest, and we hope to give a more detailed analysis of this system elsewhere. At present, it should be emphasised that the results of Table 1 do not prove that the metagon-division hypothesis is the correct one, although the improvement in fit on adding a single parameter (p) is striking. On this hypothesis, the data are only consistent with a p of at least 0·15, and experimental tests of whether the metagons do divide with anything like this frequency should put the hypothesis effectively to the test.

Erratum: In one or two places in Gibson & Beale (1962), the word 'mesosome' appears instead of 'metagon'. The name of the particles was changed from 'mesosome' to 'metagon' during the proof stage of their paper, when prior use was claimed for 'mesosome', and the proof correction was imperfect.

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