AN INFERRED CHIASMA MAP OF *DROSOPHILA MELANOGASTER*

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SUMMARY

The chiasma map of *D. melanogaster* is inferred from the genetic map, giving correspondences between physical and genetic locations. Crossing-over is reduced near the centromere and telomeres. If chiasmata occur preferentially near the telomere they must be distal to genetic loci. A precept of Bridges and Morgan is discussed, which *Drosophila* genetics neglected but chromosome mapping in other organisms should follow.

1. INTRODUCTION

A *chiasma map* gives the distribution of observed or inferred chiasmata in relation to cytological markers. On the assumption of a precise correspondence between sites of chiasmata and crossing-over the chiasma map is a genetic map which integrates cytological and genetic observations. *Drosophila* is unusual in presenting great difficulty for cytological observation on meiosis but a wealth of genetic information from which the distribution of chiasmata can be inferred, free of uncertainty about preanaphase terminalisation and loss. This distribution for oogenesis may be relevant to other organisms like man where meiotic observations (on spermatogenesis) can be made more easily than in *Drosophila* but not so precisely that movement and loss can be neglected with assurance, and where genetic data are insufficient to infer the distribution of chiasmata (Morton *et al.*, 1976).

2. THEORY

We assume that the distribution of crossing-over on a chromosome arm is compound,

$$f(x) = A\beta_1(x) + (1-A)\beta_2(x) \quad (0 \leq A \leq 1)$$

where $\beta_i(x)$ is a simple beta density function

$$\beta_1(x) = \frac{(C+D+1)!}{C!D!} x^C(1-x)^D \quad (C, D > -1)$$

$$\beta_2(x) = \frac{(2E+F+1)!}{E!(E+F)!} x^E(1-x)^{E+F} \quad (E > -1, F > -1-E).$$

Capital letters denote parameters and $0 \leq x < 1$ is the relative distance of a point on the physical chromosome arm measured from the centromere.

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This distribution is extremely flexible and was chosen to give a good fit to chromosome arms of less than 100 cmo, which have an average of 2 chiasmata. If distance is measured in salivary bands, then the value of x_j corresponding to the c_j th band from the left telomere is

$$x_j = \begin{cases} 1 - c_j/C_l & \text{for the left arm} \\ (c_j - C_l)/C_r & \text{for the right arm} \end{cases}$$

where C_l , C_r are the number of bands in the left and right arms, respectively (Bridges, 1942). Then the expected genetic locus corresponding to x_j is

$$z_j = \begin{cases} L_l \left[1 - \int_0^{x_j} f(x) dx \right] & \text{for the left arm} \\ L_l + L_r \int_0^{x_j} f(x) dx & \text{for the right arm} \end{cases}$$

where L_l and L_r are the genetic lengths of the left and right arms respectively.

Arm length is only approximate. An independent estimate is

$$L = \frac{w_t}{\int_0^x f(x) dx}$$

where t is the terminal locus on the arm and w_t is its location on the genetic map.

We used the cytogenetic maps of Lindsley and Grell (1968), assigning approximate locations to genetic markers known to lie in an interval. For example, the *dor* locus which has a step function that extends from band 1F1 to band 2A2 was assigned to band 1F3 for our calculations. Where an interval on the genetic map corresponds to a cytogenetic step function, we placed the terminal loci at the extremes and ignored intermediate loci. For example, 21 loci from *pl* to *sd* have the step function 13B2 to F17: we placed *pl* in 13B2, *sd* in 13F17, and omitted the other 19 loci.

Parameters of the beta distribution are estimated by minimising the discrepancy between observed and expected map segments. By analogy with a likelihood ratio the function to be minimised is taken to be

$$Q = \sum_{j=1}^N \Delta w_j \ln (\Delta w_j / \Delta z_j)$$

where $\Delta w_j = w_j - w_{j-1}$, an observed segment of the genetic map (map distance between loci j and $j-1$), and $\Delta z_j = z_j - z_{j-1}$, its expected value. This criterion gives appropriate weight to small and large values of Δw_j , unlike the usual quadratic form.

3. RESULTS

Estimates of genetic arm lengths are in extremely good agreement with conventional values (tables 1 and 2). There is a highly significant deficiency of crossing-over near the centromere and telomeres ($\chi^2_0 = 16.7$) and the distribution is asymmetrical ($\chi^2_0 = 101.0$). Fitting only one beta function

TABLE 1
Parameters of chromosome arms (Bridges, 1942)

	Arm						Total
	X	2L	2R	3L	3R	4	
Number of salivary bands	1011	803	1136	884	1178	137	5149
Number of loci used for map	52	18	23	11	18	4	126
Physical length in μ	414	370	446	424	519	46	2219
Genetic length, L, in cmo	66.0	55.0	53.0	47.8	58.5	3.0	283.3

($A = 0$) is inadequate ($\chi^2_{16} = 37.6$), implicating at least a second beta function. Mather (1936) made this observation and attributed it to chiasma localisation, with interstitial regions of interference. Alternatively, as discussed below, the reluctance of *Drosophila* geneticists to revise the genetic map may have created spurious saltations.

The maxima are estimated to be at $C/(C+D)$ and $E/(2E+F)$, the modes of the beta functions (table 2). If chiasmata occur preferentially near the telomere, they must be distal to genetic loci (fig. 1). This is strongly suggested by chromosome 4, which has virtually no crossing-over in the distal regions of the physical map. A terminal chiasma might be postulated to

TABLE 2
Estimates and tests of hypotheses

Hypothesis		X	2L	2R	3L	3R	4	Total
Uniform distribution ($A = E = F = 0$)	Q	0.164	0.142	0.090	0.191	0.171	0.017	0.775
Symmetry ($A = F = 0$)	Q	0.148	0.127	0.084	0.183	0.169	0.013	0.724
Homogeneity ($A = 0$)	Q	0.147	0.085	0.051	0.072	0.055	0.005	0.415
	E	0.394	1.043	0.699	1.874	1.161	6.334	—
	F	-0.054	-0.680	-0.558	-1.458	-1.080	-2.901	—
Heterogeneity	Q	0.123	0.068	0.040	0.026	0.043	0.000	0.300
	d.f.	47	13	18	6	13	1*	98
	A	0.876	0.800	0.803	0.644	0.849	0.828	—
$C/(C+D)$		0.403	0.853	0.815	0.575	1.000	0.655	—
$E/(2E+F)$		0.861	0.327	0.157	0.920	0.403	—	—
	L	66.1	55.0	53.1	47.8	58.5	3.1	283.6

* Assuming $C = D = 0$.

Testing for uniform distribution: $\chi^2_6 = (0.775 - 0.724)/(0.300/98) = 16.7$

Testing for symmetric distribution: $\chi^2_6 = (0.724 - 0.415)/(0.300/98) = 101.0$.

Testing for $A = 0$: $\chi^2_{16} = (0.415 - 0.300)/(0.300/98) = 37.6$.

account for regular disjunction of this chromosome, whose genetic length is only 0.2 cmo in diploids and 3.1 cmo in diplo-4 triploids. Suppression of distal crossing-over would then be evidence that terminal chiasmata show interference with medial chiasmata.

4. DISCUSSION

Both physical and genetic locations are subject to errors. Most physical assignments are not to a single band, but to an interval covered by a deletion. Genetic locations are computed as sums of small distances, each with some

error of estimation, perhaps biased due to differential viability and incomplete penetrance, and only in the limit strictly additive. Since an approximate relation between the physical and genetic maps may be of interest, the genetic location for the rightmost salivary band in each conventional region has been estimated (table 3) by integrating the beta distribution up to that band, using formula 26.5.4 of Abramowitz and Stegun (1965).

FIG. 1.—Chiasma distribution inferred in *D. melanogaster* from physical locations of genetic loci. ●, centromere; —, single beta distribution; ----, double beta distribution.

The correspondence of the two maps is illustrated in table 4. Band y lying in an interval between bands x and z , with assigned map locations w_x and w_z , is estimated to have location.

$$w_y = w_x + (y - x)(w_z - w_x)/(z - x)$$

and conversely

$$y = x + (w_y - w_x)(z - x)/(w_z - w_x).$$

In the worst example the assigned and estimated map locations differ by 2.3 cmo or 38 bands (table 4). However, most estimates are more reliable,

TABLE 3
A chiasma map of D. melanogaster

Chromosome 1			Chromosome 2L			Chromosome 2R		
Band	Physical locus <i>c</i>	Genetic locus <i>w</i>	Band	Physical locus <i>c</i>	Genetic locus <i>w</i>	Band	Physical locus <i>c</i>	Genetic locus <i>w</i>
1F4	40	0.5	21F3	31	2.1	41F11	837	55.1
2F6	87	1.9	22F4	65	4.8	42F3	887	55.9
3F9	136	6.7	23F6	103	8.0	43F9	935	57.2
4F14	188	12.9	24F8	141	11.2	44F12	982	58.8
5F6	244	16.8	25F5	187	15.0	45F8	1035	60.7
6F11	290	19.5	26F7	233	18.8	46F11	1094	62.6
7F10	358	23.8	27F7	270	21.7	47F18	1163	64.5
8F10	422	28.1	28F5	315	25.0	48F11	1215	65.9
9F13	475	31.9	29F8	350	27.5	49F15	1273	67.4
10F11	538	36.4	30F6	394	30.4	50F9	1345	69.5
11F8	604	41.3	31F5	432	32.7	51F13	1407	71.9
12F7	654	45.1	32F4	460	34.2	52F11	1472	75.1
13F18	724	50.2	33F5	508	37.0	53F13	1537	79.0
14F6	773	53.6	34F5	557	48.2	54F6	1592	82.8
15F9	818	56.7	35F12	601	51.5	55F13	1650	87.5
16F8	867	59.8	36F11	654	53.1	56F17	1709	92.5
17F3	910	62.2	37F6	698	54.0	57F11	1782	98.9
18F5	960	64.6	38F6	743	54.7	58F8	1829	102.8
19F6	992	65.7	39F3	773	54.9	59F8	1869	105.5
20F4	1011	66.1	40F6	803	55.0	60F5	1939	108.1

Chromosome 3L			Chromosome 3R			Chromosome 4		
Band	Physical locus <i>c</i>	Genetic locus <i>w</i>	Band	Physical locus <i>c</i>	Physical locus <i>w</i>	Band	Physical locus <i>c</i>	Physical locus <i>w</i>
61F8	33	0.1	81F6	890	47.8	101F7	42	0.2
62F6	83	11.3	82F11	932	47.8	102F17	137	3.1
63F7	129	17.9	83F4	976	47.9			
64F5	198	20.4	84F16	1039	48.2			
65F11	252	23.1	85F16	1130	49.0			
66F6	327	28.0	86F11	1200	50.3			
67F4	384	32.0	87F15	1275	52.9			
68F8	430	35.2	88F9	1339	56.3			
69F7	472	38.0	89F4	1407	60.5			
70F7	524	41.1	90F11	1456	63.5			
71F5	554	42.6	91F13	1503	66.1			
72F4	585	44.0	92F13	1571	69.7			
73F4	625	45.4	93F14	1633	73.0			
74F4	654	46.2	94F6	1701	76.9			
75F11	709	47.2	95F15	1768	81.2			
76F3	748	47.5	96F14	1855	87.5			
77F5	786	47.7	97F11	1917	92.6			
78F4	824	47.8	98F14	1972	97.4			
79F6	855	47.8	99F11	2027	102.7			
80F9	884	47.8	100F5	2062	106.3			

even in chromosomal regions that are sparsely mapped. Discrepancies must be partly due to errors in map assignments: for example, it would be surprising if *rst* and *N* lying only 3 bands apart have a map distance of 1.3 cmo as reported.

Clearly chiasmata are not distributed uniformly along the physical map. The hypothesis that density of structural loci is inversely proportional to

chiasma frequency is contradicted by the genetic map, where loci cluster in regions of low crossing-over. Therefore a uniform distribution of loci on the genetic map is only a crude approximation, and should not be incorporated into linkage analysis as some Bayesians do (Renwick, 1971).

A double beta distribution of chiasmata gives a reasonable fit to the genetic map and may be useful to estimate genetic and physical locations. While mixtures of more than two distributions may improve the accuracy of the map, a double distribution gives an adequate fit and avoids convergence problems involved in estimating many parameters (*e.g.* 8 for a triple distribution). If the chiasma distribution were observed instead of deduced, it would be feasible to distinguish arms with one chiasma from those with more, making the double distribution still more acceptable (Morton *et al.*, 1976).

TABLE 4
Correspondence between physical and genetic locations

Marker	Chromosome arm	Physical location	Band y	Assigned genetic location w_y	Estimated genetic location	Estimated band
<i>z</i>	X	3A3	90	1.0	2.2	57
<i>rst</i>	X	3C4	105	1.7	3.7	80
<i>N</i>	X	3C7	108	3.0	4.0	98
<i>B</i>	X	16A1-2	820	57.0	56.8	823
<i>ex</i>	2L	21C3	15	0.1	1.0	2
<i>Ly</i>	3L	70A3-5	476	40.5	38.2	514
<i>ss</i>	3R	89C1-2	1376	58.5	58.6	1375

The classical *Drosophila* geneticists used crude empirical mapping functions, but they had a clear conception of what they were doing: "The serial order of the loci is the most important information represented by the map. . . . The distances between loci are also represented, but this type of information is by no means so unquestionable as is the serial order. The serial order can be established absolutely, except in those cases where the loci of recessives are so close together that double recessives are too difficult to obtain. . . . As new data accumulate it becomes advisable occasionally to discard the old map completely, as far as distances are concerned, and to calculate a new map, considering all the data simultaneously" (Bridges and Morgan, 1923).

Unfortunately two circumstances have made *Drosophila* geneticists honour this counsel in the breach. First, the linkage map soon came to include hundreds of loci, and the three-point backcrosses which alone could establish the order of closely linked genes became prohibitively tedious. Secondly, as the theoretical interest of extending the linkage map decreased, data were no longer published in detail. Consequently the old linkage map has been extended but not corrected. For example, the distance between *ru* and *se* is still taken as 26.0 cmo (Lindsley and Grell, 1968) just as it was estimated by Bridges and Morgan without correction for multiple crossing-over, and the intervening loci have been forced into an interval that is presumably underestimated. This may create spurious irregularities in the chiasma map. Perhaps such systematic errors are negligible relative to biases due to differential viability and variations in map distance with maternal age and genotype. However, it may be hoped that the linkage map

of man will be developed according to the precept of Bridges and Morgan, so that data collected laboriously and expensively will be accessible for subsequent reanalysis. The mooted convention of publishing lod scores for recombination values of 0.1 and 0.3 only (McKusick and Edwards, 1975) is hardly adequate for that purpose.

After the manuscript of the present paper was submitted for publication we learned through correspondence with Professor Lindsley of a paper by Lindsley and Sandler (in press). Their plots of loci on the chiasma map agree substantially with our continuous distributions, including the peak of recombination in DNA-rich bands near the white locus on the X chromosome. Even when expressed relative to DNA content, the chiasma distribution is markedly reduced near the telomeres and centromeres.

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