THE LINKAGE MAP OF BACTERIOPHAGE T4[1]

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RELIABLE estimates of the length of the chromosome of bacteriophage T4 are now available owing to improvements in physical methods, especially autoradiography (CAIRNS 1961) and electron microscopy (KLEINSCHMIDT, LANG, JACHERTS and ZAHN 1962). At the same time, studies of conditional lethal mutants (BENZER 1955; EPSTEIN, BOLLE, STEINBERG, KELLENBERGER, BOY DE LA TOUR, CHEVALLEY, EDGAR, SUSMAN, DENHARDT, and LIELAUSIS 1963) have provided a detailed description of the linkage map of this phage. If these two developments could lead to the establishment of a quantitative relationship between the chromosome and the genetic map of T4, estimates of the physical size of the operational genetic units, the recon and cistron (BENZER 1957), could then be made.

A necessary step in this direction is the construction of a genetic linkage map in which distances between markers are really distances, i.e., like physical distances, are endowed with the property of additivity. In principle, observed recombinant frequencies in a linkage system may be additive *per se* if (a) there is complete positive interference (recombinant frequencies of all magnitudes will be additive) or (b) the recombinant frequencies measured are sufficiently small (whatever the interference relations, multiple exchanges will occur with negligible frequencies in any elementary map interval). The first condition does not apply to T4. Although the second condition is in principle realizable in T4, because of the phenomena of negative interference (NI) (DOERMANN and HILL 1953; VISCONTI and DELBRÜCK 1953) and high negative interference (HNI) (CHASE and DOERMANN 1958; EDGAR and STEINBERG 1958), additivity in T4 is observed only for extremely small map intervals (Figure 1). Thus the construction of a map based on such small intervals would require an extraordinary density of markers.

These considerations led us to attempt the construction of a mapping function for T4, which permits the conversion of recombinant frequencies to distances that are additive. The purpose of this paper is to examine the suitability of various mapping functions for T4 and to present and describe the construction of a genetic map of T4 based on one of these functions. In addition we shall

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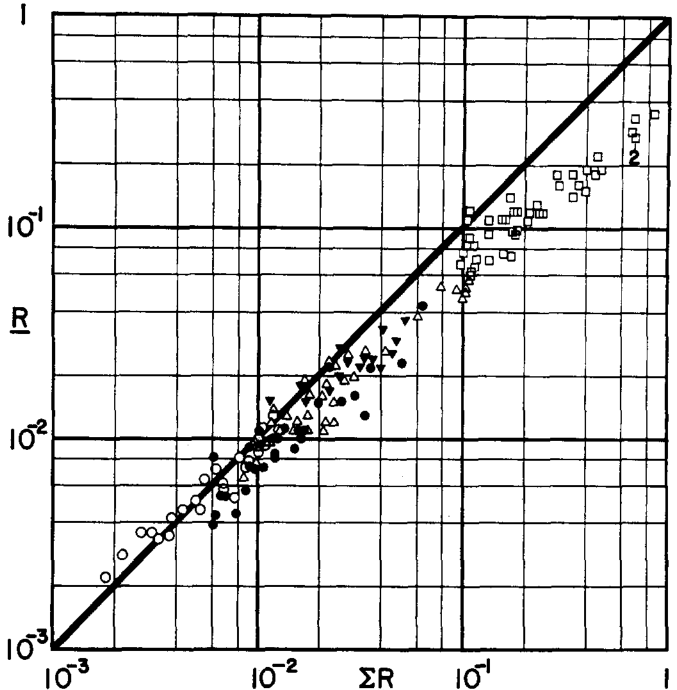


FIGURE 1.—A graphical representation of the degree of additivity of observed recombination values in T4. For a number of different marker pairs, the recombinant frequency observed in a standard cross (STEINBERG and EDGAR 1962) is plotted against the sum of the recombinant frequencies of the elementary intervals between them. Note that additivity of recombinant frequencies (R's) is observed only for R values less than 5×10^{-3}. For a description of the data used in preparing this figure, see Table 1.

discuss the question of correspondence between the genetic map and the chromosome of T4.

PROCEDURES: THE EQUATIONS

Two classes of equations were examined for their usefulness as mapping functions. (1) "Conceptual" equations were constructed which derive from various detailed theories of the mechanism of phage recombination. These were selected, not because of the possible validity of the theories, but because they were developed to account for phage recombination and thus would most likely have suitable features. (2) "Sterile" equations were constructed which were mathematically simple, yet embody the general feature of the "conceptual" equations, i.e. they were designed as "analogues" of the "conceptual" equations.

The conceptual equations: We adopted the basic framework of the VISCONTI-DELBRÜCK mating theory VISCONTI and DELBRÜCK 1953; STEINBERG and STAHL 1958) as modified for circular maps by STAHL and STEINBERG 1964 (see companion paper). Of the two models presented by the latter authors, we selected the "open circle model"; not only do recent experiments (STREISINGER, personal communication; THOMAS and RUBENSTEIN 1964; FOSS and STAHL 1963) favor this model over the other one presented by STAHL and STEINBERG, but the open circle model was also more easily modified algebraically to encompass the phenomenon of HNI. Three models for HNI were investigated, each within the open-circle mating framework. We shall call the three HNI models respectively the Modified Bernstein, the Switch and the Exponential Switch.

(a) *The Modified Bernstein Model:* BERNSTEIN (1962) presented an algebraic model for HNI which we have adapted for our purposes. In its adapted form the assumptions underlying the model are these: (1) A single mating may involve either one or two exchanges. The two kinds of matings occur with frequencies α and $1\text{-}\alpha$ respectively. (2) In those matings with two exchanges, the distances between the two exchanges are exponentially distributed. The mean of the distance-distribution is K. It follows (for a chromosome of unit length) that the probability of recombination per mating for two loci separated by a distance D is

$$p_D = \alpha D + 2\,(1\text{-}\alpha)\,K\,(1\text{-}e^{-D/K}).$$

(b) *The Switch Model:* We suppose that a single mating act proceeds according to the following rules: (1) Two chromosomes synapse along a fixed length K. (2) Crossovers then occur within such a "switch region". The crossovers are Poisson-distributed among switch regions with a mean number x of crossovers per switch region.

Now, for a chromosome of unit length,

$$p_D = \frac{1}{2}\,(D\text{-}K)\,(1\text{-}e^{-2x}) + K\,(1\text{-}\frac{1\text{-}e^{-2x}}{2x}) \quad \text{when } D > K,$$

and

$$p_D = \frac{1}{2}\,(K\text{-}D)\,(1\text{-}e^{\frac{-2Dx}{K}}) + D\,(1\text{-}\frac{1\text{-}e^{\frac{-2Dx}{K}}}{\frac{2Dx}{K}}) \quad \text{when } D < K.$$

(c) *The Exponential Switch Model:* We suppose that a mating has the following properties: (1) Two chromosomes synapse in one region. The lengths of those synapsed regions are exponentially distributed with K being the mean length. (2) The mean number of crossovers per switch region is x; among switch regions of a specified length crossovers are Poisson-distributed; the mean number of crossovers among regions of a specified length is proportional to that length.

Now, taking a chromosome of unit length, these assumptions give us

$$p_D = \frac{x}{2x+1}\left[D + \frac{2Kx}{2x+1}\left(1\text{-}e^{-\frac{D}{K}(2x+1)}\right)\right]$$

Each of the three HNI models was used in the Stahl-Steinberg open-circle mating theory in each of two of its forms—

$$(1) \qquad R = 0.45\,[(1\text{-}D)\,(1\text{-}e^{-mp_D}) + D\,(1\text{-}e^{-mp_{1\text{-}D}})]$$

$$(2) \quad R = 0.45\,\left\{(1\text{-}D)\left[1 + \frac{e^{-m_2 p_D}\text{-}e^{-m_1 p_D}}{(m_2 - m_1)\,p_D}\right] + D\left[1 + \frac{e^{-m_2 p_{1\text{-}D}}\text{-}e^{-m_1 p_{1\text{-}D}}}{(m_2 - m_1)\,p_{1\text{-}D}}\right]\right\}$$

These two functions differ only in that the second recognizes the existence of a "spread in maturation" (DOERMANN 1953; VISCONTI and DELBRÜCK 1953) and is, therefore, an average of the first function between limits m_1 and m_2.

The sterile functions: Three sterile functions were examined; we shall call them Functions 1, 2, and 3.

The following "circularized" polynomial (symmetric about $D = 0.5$) was tested:

#1. $R = T + A\ (0.5-D)^2 + B\ (0.5-D)^4 + C\ (0.5-D)^6 + Q\ (0.5-D)^8$

The following two conditions were imposed: $R = 0$ at $D = 0$; and $R = 0.42$ at $D = 0.5$. (0.42 was the maximum recombination value observed by DOERMANN and HILL (1953); see STAHL and STEINBERG 1964.)

Functions 2 and 3 below were suggested by DR. C. M. STEINBERG.

#2. $R = AD/(D+B) + CD/(D+E)$

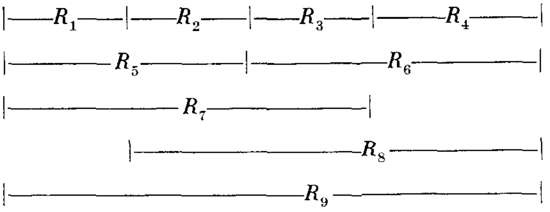
#3. $R = 1/(A+B/\sqrt{D} + C/D)$

In these last two functions, which are not circular, D must be identified with the *shorter* of the two distances between a pair of loci.

PROCEDURES: DETERMINING PARAMETERS

The various equations just described all express R (recombinant frequency) as a function of D (fraction of the total map length). The "conceptual" functions have three independently variable parameters when written in the first form, and four when written in the second, to which numerical values must be assigned. The "sterile" functions have respectively three, four, and three such parameters. With each function we searched for sets of parameter values which would best convert observed recombinant frequencies to additive distances. Electronic computers were used in the search for suitable sets of parameter values. The design of the computer program was as follows:

1. One of the functions was selected.
2. About five numerical values for each of the parameters (giving 625 combinations for the four-parameter cases) were selected. The values were taken such as to extend over the broadest "reasonable" ranges.
3. The computers selected one set of values and solved the equation for $D = 0.5$. If R fell outside of the range 0.42–0.45 that solution was rejected and a new parameter combination was tried. (This step was omitted for equation 1 since the condition that $R = 0.42$ at $D = 0.5$ was already imposed.) Thus, we considered only functions in line with experimental findings, which give a maximum recombination frequency of between 0.42–0.45. (Since the map is circular, R is maximum at $D = 0.5$, half-way round the circle).
4. When a parameter combination was found with a suitable value for R at $D = 0.5$, the computer solved for R at each of the many D-values. The values of D ranged from 10^{-6} to 0.5 in steps increasing geometrically by $\sqrt{2}$.
5. The computer was presented with five matrices of observed recombination values. These matrices are described in Table 1.
6. For each of the experimentally determined R values, the computer determined D by linear interpolation between the nearest calculated points on each side.
7. For each interval, the machine calculated the absolute value of the difference between the D value and the sum of the D values (ΣD) of all the *elementary* intervals out of which it is composed. This difference was then divided by the D value of the interval. By way of illustration, consider five loci for which R values have been measured in all possible combinations, i.e.,



The computer calculated the following:

$$\left|\frac{D_5-(D_1+D_2)}{D_5}\right|, \quad \left|\frac{D_6-(D_3+D_4)}{D_6}\right|, \quad \left|\frac{D_7-(D_1+D_2+D_3)}{D_7}\right|,$$

$$\left|\frac{D_8-(D_2+D_3+D_4)}{D_8}\right|, \quad \left|\frac{D_9-(D_1+D_2+D_3+D_4)}{D_9}\right|.$$

These values are measures of the degree of deviation of the D values from additivity. The "best" set of parameters is that set for which the average value of $\left|\frac{D-\Sigma D}{D}\right|$ is minimal.

It should be noted from the foregoing that in this method of determining "goodness," some data are used more than others. For instance, in the example above, R_1 was used three times while R_3 was used four times and R_5 was used only once.

8. The computer then repeated steps 3 to 7.
9. For each of the ten parameter combinations giving the best additivities the machine printed out the average value of $\left|\frac{D-\Sigma D}{D}\right|$ as well as the R and D values used in its machinations.
10. On the basis of the information obtained, a second, more restrictive set of parameters was

TABLE 1

A summary description of the matrices of mapping data used in Figures 1 to 3 and by the computer in the tests of additivity

Symbol Figures 1–3	Type of mutant	Number of elementary intervals	Number of nonelementary intervals (=No. of points in Figures 1–3)	Range of recombination percentages of elementary intervals	Recombination percentage of largest nonelementary interval	Source of data
○	*rIIA*	8	24	0.05–0.25	1.1	LIELAUSIS and HARTWELL, unpublished
△	*rIIA*	16	35	0.29–1.2	5.7	EDGAR, FEYNMAN, KLEIN, LIELAUSIS and STEINBERG 1962
●	*rIIB*	13	30	0.24–0.91	4.3	EDGAR *et al*, 1962
▼	*ts*, intragenic crosses	6	15	0.49–1.6	3.7	BERNSTEIN, DENHARDT, and EDGAR 1964
□	*ts*, intergenic crosses	16	44	4.5–7.5	35.0	EDGAR and LIELAUSIS 1964 and unpublished

The matrices were chosen for their possession of the following properties: (1) Each matrix spans a large distance; (2) all of the elementary intervals and most, at least, of the possible nonelementary intervals had been measured; (3) the matrices overlap (with one exception) and among themselves span most of the scale of observable recombination percentages; (4) no two of the five matrices contain any crosses in common; (5) all markers in the matrices have low, finite reversion rates.

offered to the computer, and steps 3 to 9 were repeated. The entire procedure was reiterated until no substantial improvement appeared likely.

RESULTS

Before presenting the results of the computer calculations, we must make two qualifying comments. Although the results presented below are the best fits which we found, in all cases fits almost as good were obtained with appreciably different combinations of parameter values. Furthermore, since the parameter values tested are but a sample of all those possible, there is no guarantee that the "best fits" which we found are, in fact, the best fits obtainable with the functions employed.

TABLE 2

"Best" parameter values and the degree of additivity of map distances obtained with the functions tested

Function	Parameter values	Average deviation
Modified Bernstein (3 parameter)	$m = 26$ $K = 2.0 \times 10^{-3}$ $\alpha = 0.3$	0.249
Modified Bernstein (4 parameter)	$m_1 = 8$; $m_2 = 45$ $K = 1.8 \times 10^{-3}$ $\alpha = 0.3$	0.251
Switch (3 parameter)	$m = 32$ $K = 6.6 \times 10^{-3}$ $x = 3$	0.250
Switch (4 parameter)	$m_1 = 9$; $m_2 = 20$ $K = 1.4 \times 10^{-2}$ $x = 3$	0.250
Exponential Switch (3 parameter)	$m = 30$ $K = 6.7 \times 10^{-3}$ $x = 2.5$	0.250
Exponential Switch (4 parameter)	$m_1 = 10$; $m_2 = 55$ $K = 6.5 \times 10^{-3}$ $x = 2$	0.250
Function 1	$A = -3$ $B = 6$ $C = 36$	0.319
Function 2	$A = 3.0 \times 10^{-2}$ $B = 2.0 \times 10^{-3}$ $C = 0.55$; $E = 0.16$	0.247
Function 3	$A = 0.60$ $B = 1.10$ $C = 0.05$	0.247

Of the functions tested, only Function 1 gave an average deviation from additivity which was conspicuously inferior. The average deviations obtained may be compared with 0.508, the average deviation from additivity of the observed recombination frequencies to which the functions are fitted.

In Table 2 are presented the "best" parameter values, along with the average deviations from additivity, for each of the functions tested. The sets of crosses used to test the functions are those for which the R vs ΣR relationships are given in Figure 1. All the functions except Function 1 achieved essentially equally good fits. The success of the fitting procedure may be judged from the plots of D vs ΣD for two of the functions (Figures 2 and 3). Those functions for which good fits were obtained achieved their almost equally good fits in slightly different manners. For each "good" function the average deviation from additivity for each of the five sets of crosses separately is shown in Table 3. The fits are satisfactory with a large part of the residual deviation reflecting experimental variability in the determination of R values (see EDGAR 1958).

As pointed out in the companion paper, the circularity of the T4 map permits an extension of the additivity test. The experimentally determined R values for sets of adjacent regions circumscribing the map can be (graphically) converted to D values. The degree to which the sum of the derived D values approaches unity is a measure of the "goodness" of a particular mapping function. For each of the functions which gave good fits to the previous additivity test, the results

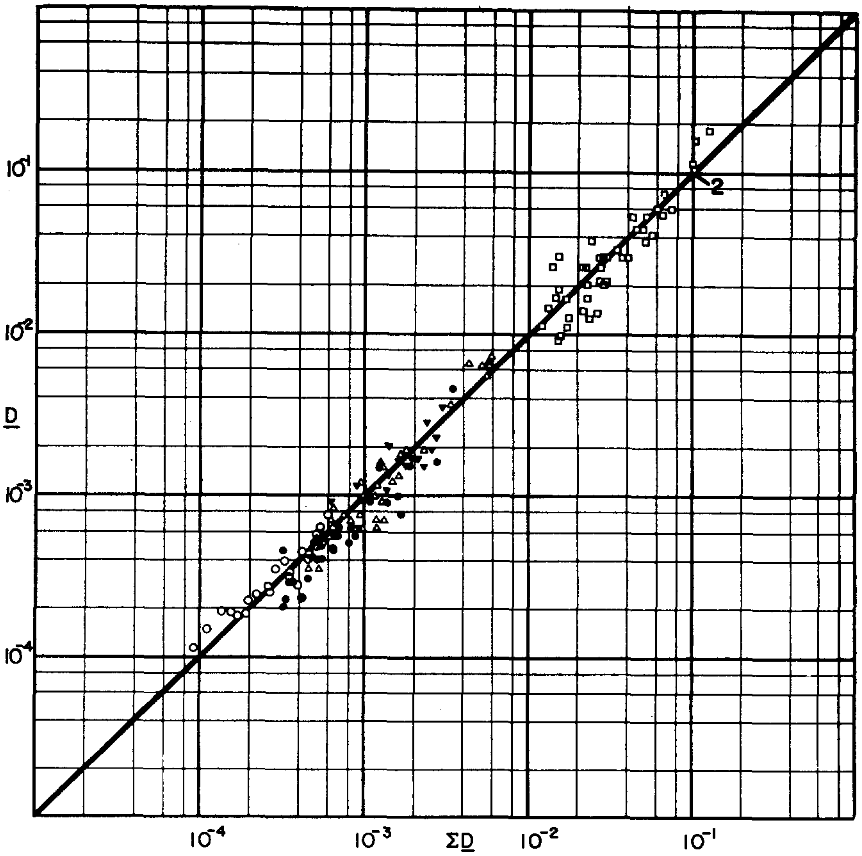


FIGURE 2.—Degree of additivity of map distances obtained by application of the 4-parameter Switch Function. For a description of the data used in preparing this figure, see Table 1.

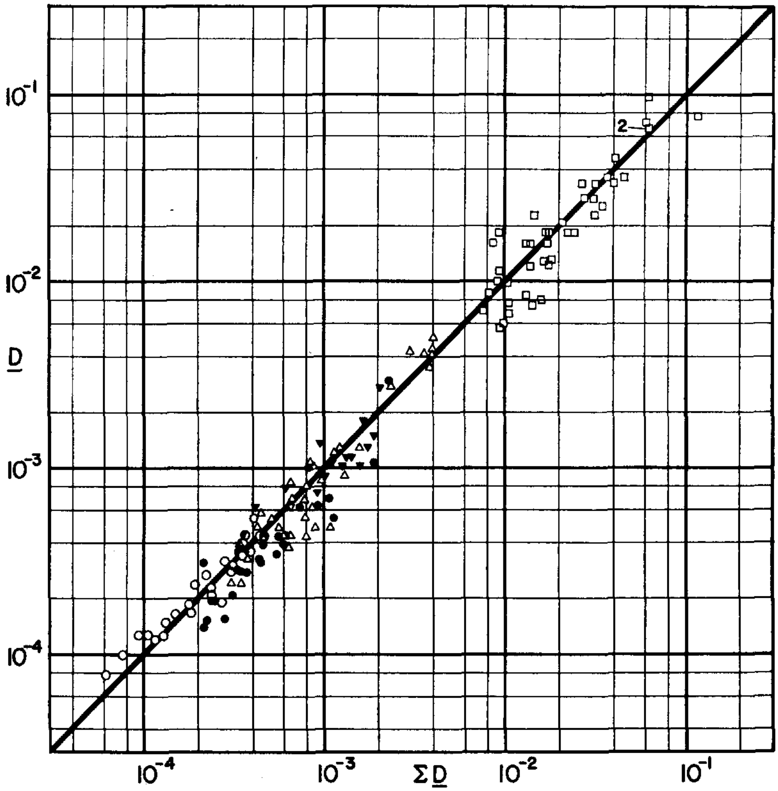


FIGURE 3.—Degree of additivity of map distance obtained by application of the 4-parameter Exponential Switch Function. For a description of the data used in preparing this figure, see Table 1.

of such "circular additivity" tests are given in Table 4. Not only is the logic of the circular additivity test semi-independent of the additivity tests used to select parameter values, but the data used are almost entirely independent as well. For these reasons, we find the fits to circular additivity most gratifying.

DISCUSSION

Results of the fitting operation: Among the conceptual equations, the addition of a parameter to account for spread in maturation did not result in improved additivity. This might be a consequence of the fact that most of the data used to test the functions involved short intervals, for which the averaged function is approximately the same as the function evaluated at an average value of m. (In the case of the Modified Bernstein functions, a slightly better additivity was obtained with the three parameter equation than with the averaged, four parameter, equation. This is an example of the limitation of the trial-and-error aspect of our search for "best" parameter values.)

In contrast to the conceptual functions which ignore maturation spread, a

TABLE 3

Average deviations from additivity of the separate sets of mapping data for each of the "good" functions

Data set: Symbol in Figures 1 to 3: No. of points:	Close *rII* ○ 24	*rIIA* △ 35	*rIIB* ● 30	Close *ts* ▼ 15	Loose *ts* □ 44
Modified Bernstein (3 parameter)	0.130	0.228	0.372	0.224	0.257
Modified Bernstein (4 parameter)	0.130	0.233	0.366	0.218	0.263
Switch (3 parameter)	0.130	0.236	0.370	0.222	0.255
Switch (4 parameter)	0.130	0.235	0.369	0.218	0.258
Exponential Switch (3 parameter)	0.130	0.237	0.367	0.218	0.256
Exponential Switch (4 parameter)	0.130	0.227	0.369	0.221	0.264
Function 2	0.136	0.230	0.318	0.193	0.292
Function 3	0.174	0.200	0.299	0.201	0.306
Uncorrected data	0.132	0.435	0.464	0.369	0.846

The average deviations from additivity for the observed R values are given in the last line. Number of points is the number of individual tests of $\left|\frac{D-\Sigma D}{D}\right|$ (or $\left|\frac{R-\Sigma R}{R}\right|$ for the uncorrected data) upon which the average deviations are based; it is the same as the number of entries of the corresponding symbol in Figures 1 to 3.

TABLE 4

Summary of circular additivity tests

Number of intervals	Small *ts* 48	Large *ts* 19	Amber 39	Average deviation from unity —
Modified Bernstein (3 parameter)	1.213	1.137	1.326	0.225
Modified Bernstein (4 parameter)	1.165	1.198	1.395	0.253
Switch (3 parameter)	0.6384	0.5966	0.6933	—0.357
Switch (4 parameter)	1.335	1.247	1.457	0.346
Exponential Switch (3 parameter)	0.7990	0.7411	0.8658	—0.198
Exponential Switch (4 parameter)	0.8251	0.7730	0.8999	—0.167
Function 2	1.399	1.474	1.669	0.514
Function 3	1.408	1.699	1.873	0.660

The tests in the first two columns are based on selected crosses involving pairs of temperature-sensitive mutants (EDGAR and LIELAUSIS 1964 and unpublished). The first column has used the smallest intervals for which R values have been reliably determined. The intervals in the second column are on the average about 2½ times (in D units) as large as those in the first; only a few entries are common to both columns. The tests in the third column are based on crosses involving pairs of amber mutants (EPSTEIN *et al.*, unpublished). The last column gives the average deviation from unity of the three sets of data. Values close to zero are "good" values.

function which did not account for HNI (the open circle mating theory of STAHL and STEINBERG 1964, Equation 6 of companion paper) was examined along with the functions described here and proved to be highly inadequate. A deviation from additivity of 0.408 was the best found.

Although the sterile functions fared slightly better on their linear additivity tests than did the conceptual ones, the latter functions did better on the circular

TABLE 5

Estimates of total map length

Function	Total map length (percent)*
Modified Bernstein (3 parameter)	2,030
Modified Bernstein (4 parameter)	2,050
Switch (3 parameter)	4,370
Switch (4 parameter)	2,070
Exponential Switch (3 parameter)	3,420
Exponential Switch (4 parameter)	2,970
Function 2	1,850
Function 3	1,880

* Map lengths were obtained by graphically determining the R values at $D=10^{-5}$ and multiplying those values by 10^5.

ones. Thus, there appears to be little to choose among the various functions examined.

Estimates of total map lengths: Each of the functions provides an estimate in recombination units of the total map length for T4. The estimates are obtained by extrapolating the linear region of each function to D equal one. They correspond to the map distances of classical genetics in that the units refer to recombination units obtained at distances sufficiently short that the values themselves manifest additivity. These estimates are presented in Table 5; they range from slightly less than 2,000 map units to slightly more than 4,000 map units. A comparison of Tables 4 and 5 reveals that there is a correlation between degree of deviation from circular additivity and total map length. These properties are plotted against each other in Figure 4. We conclude from that plot that our best estimate of the total map length of T4, as derived from the data employed is 2,500 map units.

Comparisons of map lengths and chromosome dimensions: The original purpose of determining a mapping function for T4 was for its use in correlating

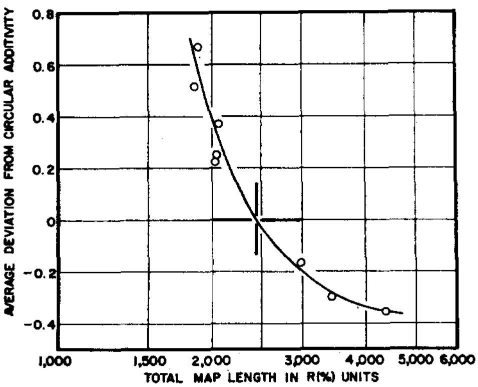


FIGURE 4.—The correlation between fit to circular additivity and total map length for the eight "good" mapping functions. It appears that somewhere there is a function which would fit the circular additivity test perfectly and would yield a total map length close to 2500 percent.

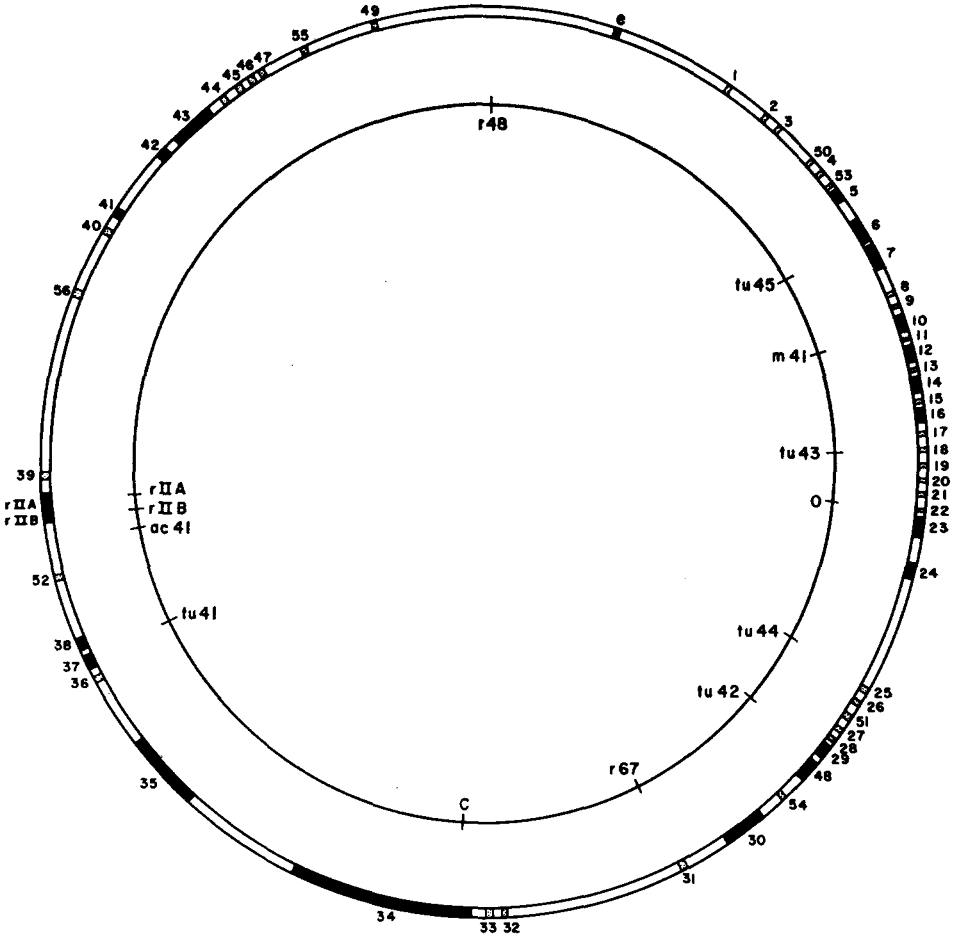


FIGURE 5.—A map of T4D. Gene numbering follows that given by EPSTEIN *et al.* (1963) and EDGAR, DENHARDT and EPSTEIN 1964, and includes additional genes. The map was constructed using recombination data presented in previous publications (EDGAR and LIELAUSIS 1964; EDGAR, DENHARDT and EPSTEIN 1964) and unpublished. R values were converted to D values using the 4-parameter Switch Function. The elemental D values were proportionately adjusted such that $\Sigma D = 1$, then converted to degrees of arc for map construction. Filled areas indicate minimal lengths for genes. Dotted areas indicate location of genes for which no intragenic mapping data are available. The inner circle indicates the relative locations of standard markers as determined by EDGAR, DENHARDT and EPSTEIN 1964.

genetical and physical lengths. (We remind the reader that we are concerned not with the degree of (or lack of) mathematical elegance of either our functions or our fitting procedure but only with the usefulness of the result of constructing a T4 linkage map in which distances are additive.) Although the mapping functions we have found give adequate additivity relations for the data used for their solution, we do not know if such relations are uniform over the genome. Further, we have at present no way of determining if at every point on the genome there

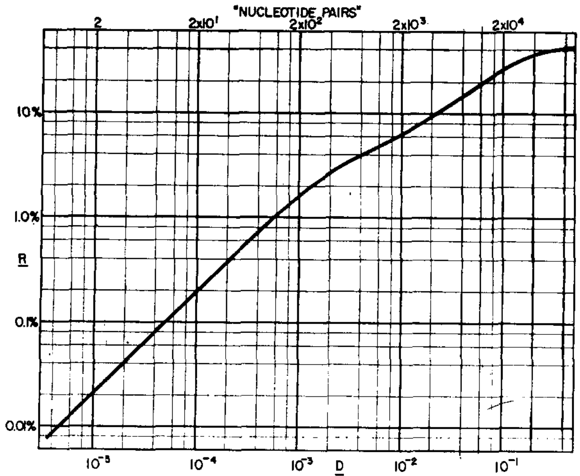


FIGURE 6.—The 4-parameter Switch Function evaluated at the "best" values for its parameters. D is distance on a map of unit length; R is observed frequency of recombinants; "Nucleotide Pairs" is the number of nucleotide pairs corresponding to D under the assumptions that the total nucleotide-pair content of T4 is 2×10^5 and that there is a strict proportionality between map distances and physical distances.

is a constant correspondence between physical and genetic lengths. However, one observation can be made concerning the degree to which the use of our mapping functions might have any validity at all. The T4-evoked lysozyme is one polypeptide containing about 150 amino acids (TSUGITA, TERZAGHI, and STREISINGER, personal communication; and see DREYER 1959). It seems likely, assuming a coding ratio of three nucleotide pairs per amino acid, (see CRICK, BARNETT, BRENNER, and WATTS-TOBIN 1961) that the *e* cistron, which determines the structure of lysozyme, contains about 450 nucleotide pairs. This corresponds to 2.25×10^{-3} of the length of the entire chromosome. For a given mapping function, this assumed "D" value can be converted to an R value and compared with the R value experimentally determined. STREISINGER and NEWTON (personal communication) have observed 3 percent recombination between the outermost markers of the *e* cistron. For each of the mapping functions which gives a total map length greater than 2,000 and less than 3,000 map units the predicted R value is compared in Table 6 with the observed value. We observe that there is a pleasant correspondence between map distance as measured by our best mapping functions and physical distance as measured by another line of inquiry.

A map for T4: Figure 5 is a map of T4 constructed with the aid of the four-parameter Switch Function (Figure 6).

We are grateful to MR. JAMES LO who substituted for one of us (J.S.) as computer operator in the final stages of this work. DR. C. M. STEINBERG not only responded to our call for sterile functions, but was most constructive in his criticism of our manuscript as well.

TABLE 6

Comparison of T4 map with T4 chromosome

Function	Recombination frequency for most distant *e* mutants: $\hat{R}$ value corresponding to $D=2.25\times10^{-3}$
Modified Bernstein (3 parameter)	3.2%
Modified Bernstein (4 parameter)	3.1%
Switch (4 parameter)	2.9%
Exponential Switch (4 parameter)	3.9%
Corresponding observed recombination frequency	3%

SUMMARY

Mapping functions for T4 have been constructed and fitted to data. They indicate a total map length of about 2,500 recombination units and suggest a pleasing degree of correspondence between map distances and physical distances.

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