THE POPULATION BIOLOGY OF BACTERIAL TRANSPOSONS: A PRIORI CONDITIONS FOR MAINTENANCE AS PARASITIC DNA

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Transposable elements are segments of DNA able to move between locations in the DNA of bacteria, plasmids, and phage. They are widespread among the eubacteria (Kleckner 1981; Iida et al. 1983), and related elements can sometimes be found in distantly related bacterial strains (Heffron et al. 1975; Perkins and Youngman 1984; Sawyer et al. 1987). Of particular interest from the perspective of population biology are the conditions responsible for the establishment and maintenance of transposable elements (or transposons) in populations of bacteria. These "existence conditions" (Campbell 1961) have been studied at a theoretical level for eukaryotic transposons (Brookfield 1982; Charlesworth and Charlesworth 1983; Ginzburg et al. 1984; Charlesworth 1985), but since diploidy and meiotic sex are central to this theory, the models employed are not appropriate for the transposons of bacteria.

Two general hypotheses account for the invasion and persistence of transposons in bacterial populations. One is that transposons are "parasitic" or "selfish" DNA (Doolittle and Sapienza 1980; Orgel and Crick 1980), meaning that they are selectively neutral or even deleterious but are maintained in populations by infectious transfer (Campbell 1981). The alternative is that transposons are maintained by selection at either the individual or population level. This selection can be direct selection for transposon-encoded characters (Cohen 1976; Campbell et al. 1977; Biel and Hartl 1983; Hartl et al. 1983; Tanaka et al. 1983) or indirect selection resulting from mutations or from genetic rearrangements caused by transposons (Kleckner 1981; Chao et al. 1983; Chao and McBroom 1985).

In this study, we present and analyze models of the dynamics of transposons in populations of bacteria infected with self-transmissible plasmids. In our analysis of the properties of this model, we give particular consideration to the conditions under which transposable elements can be established and maintained in the absence of selection for transposon-determined characters. We discuss the relevance of these theoretical results to the proposition that extant transposons are maintained as parasitic DNA and to speculations about the evolution of transposable elements.

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BACKGROUND AND DEFINITIONS

Transposable elements.—All known transposons consist of the same basic structure: inverted repeats of DNA flanking one or a few coding regions (Heffron et al. 1979; Foster et al. 1981; Iida et al. 1983). The simplest transposons, the *IS elements* (for insertion sequences), do not code for any known characters other than those needed for transposition. Somewhat more complex transposons, the *Tn elements*, are distinguished from insertion sequences by coding for host-expressed characters, such as resistance to antibiotics (Campbell et al. 1977).

Some transposons replicate when they move, leaving a copy at the original site while inserting at a new site and thus increasing the number of copies of the element in the cell (Klaer et al. 1980; Read et al. 1980; Iida et al. 1983). This is known as *replicative* or *duplicative* transposition. In some cases, transposition may be *conservative*, with transfer from one site to another taking place without an increase in copy number. Our definitions of conservative and replicative transposition are based only on the net effect of a transposition event on the number of copies of the element in a cell, not on molecular mechanisms. Transposons are also known to excise from the genome without leaving a copy elsewhere (Berg 1977; Botstein and Kleckner 1977; Egner and Berg 1981; Iida et al. 1983).

Save for a few exceptions such as the bacteriophage mu (Toussaint and Résibois 1983) and the "conjugative transposons" found in a few genera (Gawron-Burke and Clewell 1982), transposons are not self-transmissible. They can be transmitted between bacterial cells only by hitchhiking on other self-transmissible vectors such as plasmids or phage or by being picked up as free DNA, via transformation. Without such *horizontal transfer*, transposons could not invade populations and be maintained as parasites. But transposons can and do move into new bacterial hosts by hitchhiking on transmissible vectors, particularly plasmids (Cohen 1976; Datta and Hughes 1983; Hawkey et al. 1985).

Plasmids.—In this paper, we restrict our attention to the infectious transfer of transposons by self-transmissible (or *conjugative*) plasmids. These autonomous, extrachromosomal molecules of DNA are ubiquitous among bacteria (Falkow 1975; Bukhari et al. 1977) and are capable of transmitting themselves horizontally in a process called conjugation. During conjugation, a plasmid in a *donor* cell replicates, and a copy is transmitted to a *recipient*. Since many plasmids cause their hosts to exhibit some degree of *surface exclusion*, cells carrying a plasmid make poor recipients. Bacteria can also lose a plasmid by *vegetative segregation*. When cells are infected with copies of the same, or closely related, plasmids, there is competition for replication and the rapid loss of one plasmid type (R. Novick and Hoppensteadt 1978).

Chemostats and plasmid population dynamics.—Our analysis of the population dynamics of transposable elements is restricted to bacteria in mass culture maintained in "equable" habitats, or *chemostats*. A chemostat consists of a reservoir into which nutrients enter at a constant rate that equals the rate at which cells, unused resources, and wastes are washed out (A. Novick 1955; Stewart and Levin 1973, 1977). The population grows at a rate that is a monotonically increasing function of the concentration of the resource in the reservoir (Monod 1949). As

the bacteria increase in density, the concentration of the limiting resource declines, as does the rate of cell growth. Eventually, the rate at which the bacterial population is reproducing equals the rate at which it is washed out, and an equilibrium cell population is maintained. The *fitness* of a population in a chemostat is its rate of cell division; multiple populations in a chemostat have identical washout rates, but their fitnesses can differ.

In order to incorporate plasmid population dynamics into the chemostat model, a *specific conjugation rate*, γ, is used to define the rate of plasmid transfer (Stewart and Levin 1977). If N_D is the donor-cell density, then γ is defined so that $\gamma N_D dt$ is the probability that a recipient cell will receive a plasmid in a short period of time, dt. This is equivalent to saying that the concentration, N_R, of recipient cells is decreased by conjugation at a rate $\gamma N_D N_R$. The concentration of new plasmid-carrying cells (*transconjugants*) is increased at the same rate. Stewart and Levin (1977) also introduced a *segregation rate*, τ, the rate at which plasmid-carrying cells lose their plasmids.

In their analysis of the properties of this model, Stewart and Levin (1977) found that a plasmid could invade a population and be maintained if its rate of infectious transfer exceeded its rate of loss from segregation and selection, that is, if

$$\gamma N_R > \alpha f + \tau, \tag{1}$$

where f is the flow rate (h^{-1}) of the chemostat and α is the difference in fitness between plasmid-free and plasmid-carrying cells. Thus, a deleterious plasmid ($\alpha > 0$) can be maintained by transfer if γ is sufficiently high, or a beneficial plasmid ($\alpha < 0$) can be maintained by selection despite a low γ. In either of these cases, there would be an equilibrium with both plasmid-bearing and plasmid-free cells present. Under most conditions plasmid-carrying cells would dominate at this *plasmid equilibrium* (Stewart and Levin 1977).

THE TRANSPOSON MODEL

To incorporate transposon dynamics into the plasmid model of Stewart and Levin (1977), we consider a single clone of bacteria, a single plasmid, and a single transposable element that can reside on either chromosome or plasmid. Since, in the simplest model, each cell can carry only a single plasmid type, we must consider six cell types in order to include all possible combinations of cells with and without plasmids and transposons (fig. 1). In the extended model, we include the possibility of a *heteroplasmid cell* (a cell can carry two different plasmid types), which requires eight cell types (fig. 2). We also developed models based on both conservative and replicative transposition.

Cell types change states by four processes: conjugation, segregation, transposition, and transposon excision (these state changes are indicated by arrows in figs. 1 and 2). There are two types of conjugation: in one, plasmid-free cells acquire a plasmid from any of the plasmid-carrying types; in the other, a plasmid-carrying cell gains a new plasmid to form a heteroplasmid cell (or, in the six-cell case, to replace a resident plasmid). Two types of segregation processes also exist: in one, a cell loses all its plasmids; in the other, a heteroplasmid cell loses one plasmid

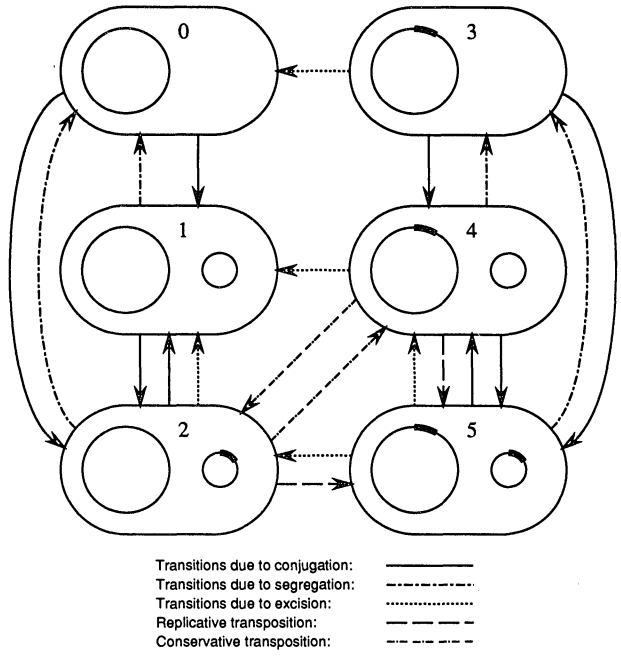

FIG. 1.—Cell types in the six-cell-type model. *Small circles*, Plasmids; *large circles*, chromosomes. The transposon is indicated by a thick section of the plasmid or chromosome. *Arrows*, All cell-transition events. In any one model, transposition was either conservative or replicative, never both. Note that transition events caused by conjugation are indicated by an arrow from recipient to transconjugant, but nowhere do we indicate the donor cell necessary to cause this transition.

type, but not the other. For further details concerning these processes, see Appendix A.

Transposition takes place in plasmid-bearing cells that have a piece of transposon-free DNA (either the chromosome or a plasmid). For example, in the model with eight cell types (fig. 2), cell-type 3 is converted to type 7 by replicative transposition or to type 6 by conservative transposition. Excision is simply the deletion of a single transposon copy, for example, converting cell-type 4 to type 0. Again, further details can be found in Appendix A.

The dynamics of the population density of each cell type are determined by cell division, washout, and all the cell-conversion events just described. These are modeled by a differential equation of the general form

$$dN_i/dt = w_i\psi N_i - fN_i - X_i + Y_i. \qquad (2)$$

Here, N_i is the density (cells $\cdot$ ml^{-1}) of the ith cell type; ψ, the rate (h^{-1}) of cell division of the most fit cell type; w_i, the relative fitness (dimensionless) of the ith cell type; and f (h^{-1}), the washout rate of the chemostat. The rate at which cells of type i are converted into other types is X_i, and Y_i is the total rate at which any other cell types are converted into type i.

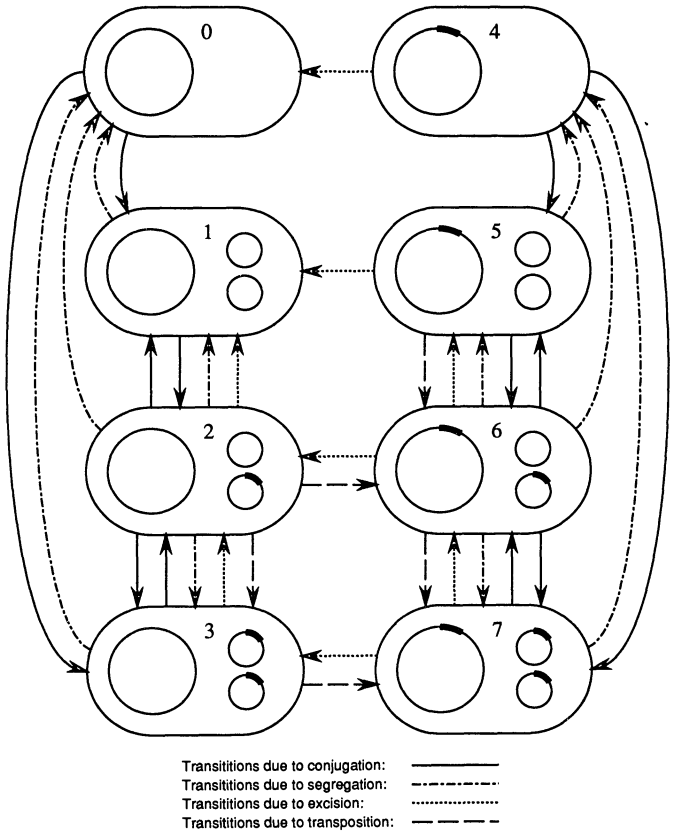

FIG. 2.—Cell types in the eight-cell-type model. Conservative transposition is not shown.

In basic chemostat dynamics, ψ is a function of the resource concentration r. However, with no fitness differences between cell types, r rapidly approaches r_0, where $\psi(r_0) = f$; and the total density of cells, N, approaches $(C - r_0)/\beta$, where C is the concentration of the resource in the input and β is the amount of resource used by a cell for growing and dividing. When there is selection, we may consider an idealized chemostat in which the flow rate is varied slightly. This can be done so that the conditions $r = r_0$ and $N = (C - r_0)/\beta$ are maintained with great stability. No significant differences were observed when we simulated a chemostat with adjusted flow rather than one with a fixed flow rate. Since the transient behavior of r is irrelevant to the questions we are addressing, we make the simplifying assumption throughout that r and N are fixed at their equilibrium values. Further details concerning the justification of this assumption can be found in Appendix A.

The following terms are included in X_i:

(1) *conjugation*, terms of the form $\gamma_{jik}N_iN_j$, where γ_{jik} is the rate constant (ml · cell^{-1} · h^{-1}) for conjugations in which cells of type j transfer a plasmid to type i converting them to type k (k may be the same as j);

(2) *segregation*, terms of the form $\tau_{ij}N_i$, where τ_{ij} is the rate (h^{-1}) at which type i is converted to type j by segregation;
(3) *transposition*, terms of the form $\delta_{ij}N_i$, where δ_{ij} is the rate (h^{-1}) at which transpositions convert cells of type i to those of type j; and
(4) *excision*, terms of the form $\epsilon_{ij}N_i$, where ϵ_{ij} is the rate (h^{-1}) at which excisions convert cells of type i to those of type j.

The same types of terms are included in Y_i. Conjugation terms are of the form $\gamma_{jki}N_jN_k$, where type j is the donor and k the recipient of a conjugation event that creates cell-type i (i.e., k is converted into i). All the other terms include the appropriate rate constant multiplied by N_j, where j is a cell type that can be converted into type i by segregation, transposition, or excision. Note that $\Sigma X_i = \Sigma Y_i$, since the loss of any cell type is accompanied by an identical gain of another.

In most of our analyses, we consider single transposition and excision rates. We also simplify by considering only two segregation rates, one for the loss of all plasmids in a cell (τ_O) and one for the loss of one plasmid type from a heteroplasmid cell (τ_P). Likewise, we allow only two conjugation rates, one for transfer into plasmid-free cells (γ_O) and one for transfer into cells already carrying a plasmid (γ_P).

The equations for our six-cell-type model with replicative transposition are

$$\begin{aligned}
dN_0/dt &= N_0(w_0\psi - f) - \gamma_O N_0(N_1 + N_4) - \gamma_O N_0(N_2 + N_5) \\
&\quad + \tau_O N_1 + \tau_O N_2 + \epsilon N_3, \\
dN_1/dt &= N_1(w_1\psi - f) + \gamma_O N_0(N_1 + N_4) - \tau_O N_1 + \epsilon N_4 + \epsilon N_2 \\
&\quad - \gamma_P N_1(N_2 + N_5) + \gamma_P N_2(N_1 + N_4), \\
dN_2/dt &= N_2(w_2\psi - f) + \gamma_O N_0(N_2 + N_5) - \tau_O N_2 + \epsilon N_5 - \epsilon N_2 \\
&\quad - \delta N_2 - \gamma_P N_2(N_1 + N_4) + \gamma_P N_1(N_2 + N_5), \\
dN_3/dt &= N_3(w_3\psi - f) - \gamma_O N_3(N_1 + N_4) - \gamma_O N_3(N_2 + N_5) \\
&\quad + \tau_O N_4 + \tau_O N_5 - \epsilon N_3, \\
dN_4/dt &= N_4(w_4\psi - f) + \gamma_O N_3(N_1 + N_4) - \tau_O N_4 + \epsilon N_5 - \epsilon N_4 \\
&\quad - \delta N_4 - \gamma_P N_4(N_2 + N_5) + \gamma_P N_5(N_1 + N_4), \\
dN_5/dt &= N_5(w_5\psi - f) + \gamma_O N_3(N_2 + N_5) - \tau_O N_5 - \epsilon N_5 - \epsilon N_5 \\
&\quad + \delta N_4 + \delta N_2 - \gamma_P N_5(N_1 + N_4) + \gamma_P N_4(N_2 + N_5).
\end{aligned} \tag{3}$$

We analyzed the models in order to determine the fate of a transposon introduced at low frequency into a cell-plasmid population at equilibrium. For computer simulations, we used the Euler method; and to estimate the rate of invasion of a transposon when rare, we found the dominant eigenvalue of the linear approximation to the system near the transposon-free equilibrium.

RESULTS

Qualitative Results

Replicating transposons always increased in frequency in a chemostat population at equilibrium, provided that conjugating plasmids were present (fig. 3) and that fitness effects and excision rate were sufficiently small. This was true whether the plasmid was maintained by infectious transfer or by selection favoring plas-

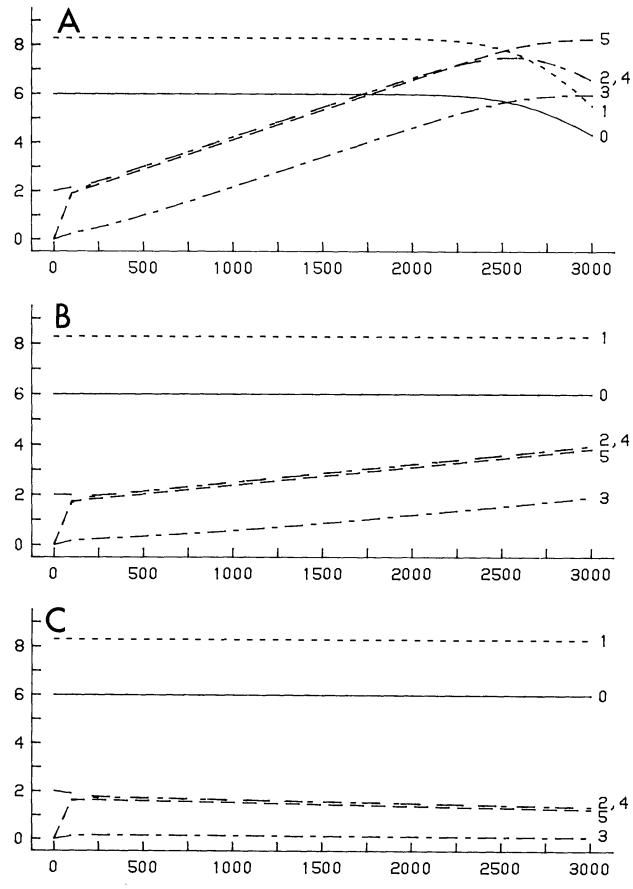

FIG. 3.—Changes in cell populations after transposon-bearing cells are introduced at low frequency into a chemostat containing cells and plasmids at equilibrium; six-cell-type model with replicative transposition. Vertical axis is the log of cell density; horizontal axis is the time in hours. The cell types are indicated by numbers. Conditions are favorable for invasion of the transposon, with the rates of plasmid turnover and of transposition both set unrealistically high for the sake of illustration. In all three runs, $\gamma_O = 10^{-9}$, $\gamma_P = 10^{-10}$, $\tau = 10^{-3}$, $f = 0.2$, $\delta = 10^{-2}$, $\epsilon = 0$. *A*, No cost to transposon. *B*, Fitness of transposon-bearing cells is 98% that of transposon-free cells; the transposon invades, but more slowly. *C*, Fitness is 97%, and the transposon fails to invade. In each case, the transposon achieves its characteristic invasion rate after about 200 h.

mid-bearing cells. Resetting the transposition rate to zero always prevented invasion, demonstrating that the ability to transpose allowed invasion. Fitness costs imposed by the transposon reduced the rate of invasion, and beyond a certain cost, invasion did not occur; generally, this cost was exceedingly small. Excision could also prevent invasion.

In contrast, a conservative transposon never increased in frequency if neutral; if cells carrying that element suffered any fitness cost, it was eventually eliminated

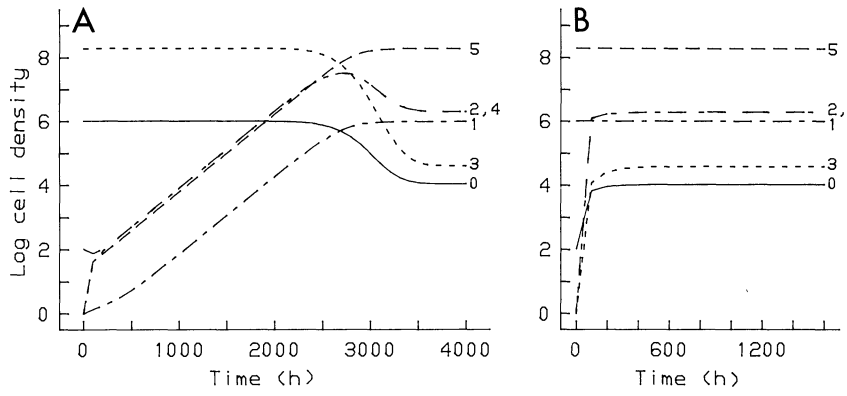

FIG. 4.—Equilibrium between transposon-bearing and transposon-free cells with a nonzero excision rate ($\epsilon > 0$). The parameter values are the same as in figure 3, except that $\epsilon = 10^{-4}$ and there is no fitness effect of the transposon. *A*, The transposon starts at a density of 10^2 and rises to become dominant, but all six cell types are maintained. *B*, Transposon-free cells start at a density of 10^2 and rise to reach the same equilibrium as in *A*.

from the population. In Appendix B, we provide a general proof that a conservative transposon cannot invade or be maintained as a strict parasite.

For all numerical runs in which the transposon could invade, the cell population eventually reached a new equilibrium with the transposon present (fig. 4). If the excision rate and fitness differences were zero, then at equilibrium all cells carried the transposon; but if there was either a positive excision rate or some cost to the carriage of the transposon, then both transposon-bearing and transposon-free cells were maintained. We have not been able to prove that maintenance of the transposon ensures a unique and stable equilibrium point; however, one can provide a compelling argument that transposons that can invade will persist.

Quantitative Results

Invasion rate.—In all simulations, an inoculum of transposon-bearing cells was introduced into a chemostat where transposon-free cells were in conjugation-segregation-selection balance. At the start of all runs of both the six- and eight-cell models, the frequencies of transposon-bearing cell lines fluctuated for a relatively short period. After this adjustment period, all transposon-bearing cells increased (or decreased) exponentially until they became sufficiently numerous to affect the transposon-free cells by taking up a significant amount of the resource (fig. 3). During this exponential growth phase, the different transposon-bearing cell types all had the same growth rate, which we call I_c, the *characteristic rate of invasion* of the transposon. (For a conservative transposon, I_c was never positive.) For reasons explained in Appendix B, the characteristic rate of invasion and the relative frequencies of the transposon-bearing cell types during exponential growth were independent of their initial frequencies. In all our analyses, we use the characteristic rate of invasion as our measure of a transposon's ability to invade.

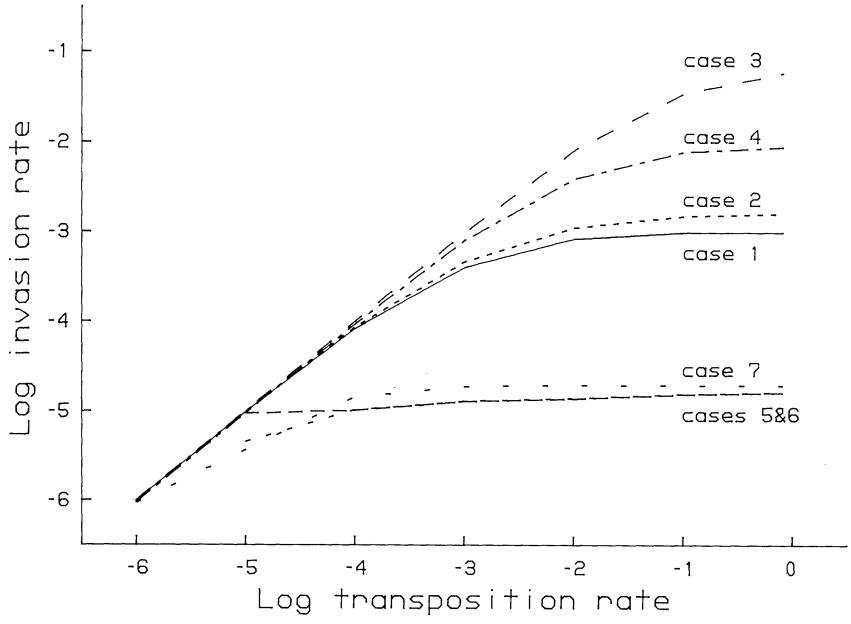

FIG. 5.—Characteristic invasion rate of a transposon as it varies with transposition rate in the eight-cell-type model. Each line represents one set of segregation and conjugation parameters. At low transposition rates, the lines all converge, but they separate to the right; the higher lines are cases with higher plasmid turnover. In all cases, $\epsilon = 0$ and bearing a transposon incurs no cost. Cases 1–6, plasmid maintained by transfer. Case 7, plasmid maintained by fitness, with plasmid-carrying cells having a 5% fitness advantage over plasmid-free cells.

	γ_O	γ_P	τ_O	τ_P		γ_O	γ_P	τ_O	τ_P
Case 1	10^{-9}	10^{-13}	10^{-3}	0.04	Case 5	10^{-9}	10^{-13}	10^{-5}	0.04
Case 2	10^{-9}	10^{-11}	10^{-3}	0.04	Case 6	10^{-11}	10^{-13}	10^{-5}	0.20
Case 3	10^{-9}	10^{-9}	10^{-3}	0.04	Case 7	10^{-13}	10^{-13}	10^{-3}	0.44
Case 4	10^{-9}	10^{-13}	10^{-2}	0.04					

Invasion rate and transposition rate.—Over a range of values, the I_c of a replicative transposon increased with the rate at which that element moved within cells. Eventually, however, increases in transposition rate no longer affected the I_c of a transposon (fig. 5).

The importance of plasmid dynamics.—At low transposition rates, plasmid parameters became irrelevant to the invasion rate of a replicative transposon. At the lowest rate of transposition that we examined (10^{-6}), varying plasmid parameters over several orders of magnitude did not alter the characteristic invasion rate of the transposon. At higher transposition rates, however, the rate of plasmid spread became increasingly important: transposons invaded more rapidly in populations infected by plasmids that had higher conjugation and segregation rates. In fact, at high transposition rates, the I_c of a transposon was exactly equal to a simple index of plasmid movement that we call *plasmid turnover*. We define this as the probability that a randomly chosen cell in the population will acquire a new

plasmid during the course of an hour. At equilibrium in a plasmid-bearing population, the plasmid turnover equals the sum of the products of the densities of available recipients and the appropriate conjugation-rate parameter for those recipients.

If a plasmid had a low conjugation rate (10^{-13}) and was maintained in the population by selection, the rate at which the transposon invaded was extremely low (fig. 5). This was due to a very low plasmid turnover rate when the conjugation rate was so low. Even in this situation, at low transposition rates the I_c of the transposon converged to a value similar to that obtained for any other set of plasmid parameters.

Allowing two different plasmid types to coexist in a cell had negligible effect on the I_c of a transposon regardless of transposition rate. Despite adding the opportunity of inter-plasmid transposition, the invasion rate of a transposon was nearly identical in the six- and eight-cell-type models with the same parameter values.

Effect of costs borne by the transposon.—If cells harboring a transposon had lower fitness than transposon-free cells, the transposon's invasion rate declined from the neutral case (in which there was no cost). For any set of parameters, a unique value of the cost, which we call the sustainable cost (C_s), just prevented invasion. When invasion occurred without cost (I_0), the sustainable cost could be predicted. In fact,

$$C_s = I_0/f, \tag{4}$$

where f is the chemostat's flow rate or the mean growth rate of cells in the chemostat. Flow rate appears in this equation because of our original choice of units: we defined invasion rate in terms of absolute time (per hour), but relative fitness is dimensionless. Since I_0 is never more than the transposition rate, and is often just equal to it, we make the following generalization: a transposon cannot invade if it reduces fitness by an amount approximately equal to its transposition rate, measured per generation rather than per hour.

Effect of spontaneous excision.—If a transposon suffered spontaneous excision, its rate of invasion decreased. The relationship between loss rate and invasion rate was roughly linear, and a sufficiently high rate of excision prevented invasion.

Effect of cell density.—All our analyses were carried out at a constant total cell density, but we can evaluate the effect of altering density by using some of the conclusions stated above. Transposition is independent of density, but plasmid turnover is directly proportional to cell density. Since plasmid turnover limits a transposon's invasion rate when transposition rate is high, altering density could lead to proportional changes in invasion. In other words, at low cell densities, invasion rates would be reduced, but only if transposition rates were high enough that plasmid turnover limited invasion rates.

DISCUSSION AND CONCLUSIONS

The results of our analysis indicate that under certain conditions transposable genetic elements can become established and will be maintained in bacterial

populations, even when the elements confer a disadvantage on their hosts. In order for this "parasitic DNA" to exist, transposition must be replicative and plasmid transfer must take place. Under no conditions can conservative transposons become established without augmenting the fitness of their host cell or plasmid.

These qualitative results could be interpreted to mean that there are (or have been) transposons that are pure parasites, but we hesitate to champion this position. Indeed, according to what is currently known about the rates of transposition and plasmid transfer in bacterial populations, it seems unlikely that transposons could become established as parasites. Published values of transposition rates are nearly always less than 10^{-3} per hour, and typical rates are 10^{-5}–10^{-7} (Heffron et al. 1977; Foster et al. 1981; Kleckner 1981; De La Cruz and Grinsted 1982; Isberg and Syvanen 1982; Peterson et al. 1982; Iida et al. 1983; Meyer et al. 1983; Schmidt and Klopfer-Kaul 1984). Moreover, plasmid transfer rates, which can also be critical to establishment, are generally quite low. The plasmid parameter that is important to a transposon is what we defined as plasmid turnover, or the rate at which average cells acquire fresh plasmids. In general, this can be estimated as the product of conjugation rate and cell density, and we believe that this will usually be about 10^{-3} or lower. Although transfer-rate constants of 10^{-9} ($ml \cdot cell^{-1} \cdot h^{-1}$) and higher have been reported for derepressed plasmids (Levin et al. 1979; Freter et al. 1983), wild-type plasmids are normally repressed for conjugative pili synthesis and transfer at rates of 10^{-12} or lower. Furthermore, in populations at equilibrium with conjugative plasmids, plasmid-free cells would be relatively few (Stewart and Levin 1977), and the rate of plasmid transfer would be even further reduced by surface exclusion. Even if cell densities are often as high as 10^9 per milliliter, plasmid turnover rates would usually be quite low.

With extremely low transposition and plasmid turnover rates, the force behind the maintenance and spread of a parasitic transposon (i.e., its maximum rate of invasion) would also be extremely low. This has led us to doubt that prokaryotic transposable elements are parasites, for several reasons. First, any cost a transposon carried would probably be sufficient to counteract such weak forces; it is likely that transposons often reduce fitness by more than their transposition rates. Second, the pressures maintaining transposons as parasites would be so small that genetic drift could overwhelm them. (This depends on effective population size, which we hesitate to discuss here; see Levin 1981.) Finally, we doubt that forces on the order of 10^{-5} can be responsible for the entire evolution of elaborate DNA organisms like transposons.

We acknowledge, however, that any positive invasion rate, no matter how small, can lead to fixation of a gene if maintained long enough in enough populations. We doubt only the generality of the parasitic-DNA hypothesis; we suggest that most bacterial transposable elements are not parasites, but must at times contribute to the fitness of their hosts.

The strength of this conclusion depends on the reality and generality of our analysis. We certainly do not believe that the simplistic model presented here represents a precise analogue of the population dynamics of transposons and

conjugative plasmids, but we do believe that the conclusions drawn from this analysis are useful. In essence, the issue of primary concern is the rate at which transposons move between plasmids and chromosomes and the rate at which the plasmid vectors move between cells. Whether the bacteria are maintained in an equable habitat (chemostats), are confronted with feast and famine (serial transfer; Koch 1971; Stewart and Levin 1973), or are maintained as colonies on surfaces (Goguen 1980) should have little effect on these rates. For these reasons, we believe that the conclusions drawn here would hold under any condition in which the transposon is infectiously transmitted by plasmids.

Restricting this consideration to infectious transfer by plasmid vectors also limits the generality of our treatment. Transposons can be infectiously transferred as free DNA (transformation) or by phage vectors (transduction), but in both cases, transposition would be conservative, since the donor cell must die in order to exchange the transposon. We thus find it unlikely that either process could favor the invasion of a transposon. We also restricted our model by considering only the presence or absence of transposons and not their copy number. Many insertion-sequence elements exist in many copies per cell (Sawyer et al. 1987), and variation in copy number could cause variation in excision and transposition rates. However, we feel justified in ignoring such variation for three reasons. First, we are considering whether transposons can penetrate populations of cells, and replication within a cell is not relevant to this question (except that it affects parameters). Second, since excision rate was set to zero in most of our analyses, varying copy number would have little impact. Finally, transposition rate would probably decline as copy number increased (because most transposons repress their own transfer to some degree; Kleckner 1981); thus, our conclusion about the ineffectiveness of transposition would only be strengthened if we considered the buildup of copies within a cell.

A further limitation is that our analysis was restricted to populations at equilibrium with plasmids. It might seem that rather different conclusions would be drawn if we considered the invasion of transposons in populations not at equilibrium. If a transposon moved onto a plasmid that was invading a plasmid-free population, the transposon would be swept to fixation in that population, but thereafter it would gradually decrease in frequency. We conjecture, however, that a transposon that cannot be maintained in any one plasmid population could not persist by perpetually hitchhiking onto new plasmids, but such nonequilibrium systems should be more thoroughly analyzed.

The primary implication of this theoretical consideration is that extant transposons are maintained by either continuous or intermittent selection favoring their carriage. This can be direct selection for transposon-encoded characters, such as antibiotic resistance or other undetermined phenotypes (Biel and Hartl 1983) or indirect selection resulting from their mutagenic effect (Chao et al. 1983). This mutator hypothesis is attractive in that it does not require the transposon to carry genes other than those needed for transposition, but its generality remains unclear.

If transposons cannot be maintained by infectious transfer, but only by increasing host fitness, why do they transpose? One possibility is that this mobility enables transposons (and plasmids as well) to expand their host range. By hitch-

hiking they can move from their present host to another strain or species that occupies a somewhat different habitat. This begs the question, then, of why certain genes are carried on transposons but most are not. The only sorts of genes that could succeed by host-range expansion are genes that are useful but not often found in bacterial cells. Drug-resistance genes fit this criterion, and we believe that the unknown functions that give certain transposons a fitness edge (Biel and Hartl 1983) must also.

Another possibility is that transposition is the accidental by-product of some other function, such as the regulation of gene action. There are many analogies between the flip-flop mechanisms responsible for antigenic shifts and the mechanisms of transposition (Silverman and Simon 1983). Alternatively, contemporary transposons could be relics of a previous function, such as the integration and excision mechanism of temperate bacterial viruses. It is not difficult to imagine that extant transposons evolved from self-transmissible but transposon-like elements such as mu or the conjugating transposons (Gawron-Burke and Clewell 1982; Toussaint and Résibois 1983). Since the transposon would be vertically transmitted as either a degenerate prophage or a degenerate gene regulator, there would be secondary selection for these elements to acquire characters that augment the fitness of their host bacteria.

We have argued against the notion that prokaryotic transposons are "selfish DNA." In contrast, Hickey (1982) demonstrated that parasitic transposons can rapidly increase in frequency in populations of sexual organisms. In his model, however, the transposition rate was 1.0, since it occurred in every gamete, and genome mixing (sex in his model, plasmid turnover in ours) was not a limiting factor, since it occurred once for each organism in each generation. Given the high rates of transposition and genome mixing that Hickey used, our model would also predict a high rate of invasion. In fact, it would exactly agree with Hickey's analysis. Transposition rates in eukaryotes may be much higher than in prokaryotes, for Kidwell (1983) has demonstrated the rapid invasion of P elements into *Drosophila* strains in the last 40 years. Since transposons are not known to benefit their eukaryotic hosts in the way they benefit prokaryotes, it seems quite likely that they have evolved as parasites in eukaryotes but not in prokaryotes.

SUMMARY

We have theoretically and quantitatively analyzed the population dynamics of transposable elements in populations of bacteria and plasmids. Computer simulations were used to describe populations of cells with and without plasmids and transposons. Plasmids could enter new cells during conjugation events, and transposons could enter new pieces of DNA (either a plasmid or the chromosome) by transposition. Because both processes could be reversed, either element could be lost from a cell.

The model demonstrates that a conservative transposon cannot increase in frequency by transposition alone but that a replicating one can. Plasmid transfer is necessary as the vehicle by which transposons penetrate new cells. The rate at which a selectively neutral transposon increases in frequency is limited by trans-

position rate or plasmid turnover rate, whichever is smaller. A fitness cost greater than this maximum invasion rate results in the elimination of the transposon from the population.

Since both transposition and plasmid turnover rates are generally extremely low in natural populations of bacteria, usually below 10^{-3} and often 10^{-5} to 10^{-7} per cell per hour, we argue that transposons would be ineffective as parasites of bacteria. We thus argue against the generality of the hypothesis that transposons are parasitic DNA in prokaryotes. It is more likely that most transposons are currently maintained in populations and invade new strains by augmenting the fitness of their hosts.

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APPENDIX A

The Equations

In these appendixes we confine the discussion to the model with eight cell types, but only minor notational changes are needed to make the discussion apply to the simpler six-cell-type model.

In the systems that we are investigating, complex interactions occur among the cell types. To obtain the equations needed to investigate the way in which such systems behave, one must make assumptions about processes that are known only in outline. To do this, we seek the simplest assumptions that are consistent with known facts.

In most of the argument it is more convenient to think in terms of cell numbers than of cell concentrations. For this reason, we assume throughout that we are dealing with a chemostat of unit volume. However, all the equations are valid for chemostats of arbitrary size, and the arguments apply equally well to such chemostats if one simply inserts the words "per milliliter" at appropriate places.

In the initial discussion we also assume that, because selection is not operating, the growth rate ψ and the flow rate f are equal.

Consider first the excision terms. Assume that each transposon-bearing replicon is subject to the possible loss of the transposon at a loss rate of ϵ. Let $\epsilon_{ij}N_i$ be the rate at which cells of type i are converted to cells of type j by such loss. In cells of type 4, the only possible excision event is the loss of the transposon from the chromosome and the resulting cell will be of type 0. Thus, $\epsilon_{40} = \epsilon$. By contrast, a cell of type 3 will become a cell of type 2 when either of its plasmids loses its transposon; thus, $\epsilon_{32} = 2\epsilon$. A cell of type 6 also has two replicons that bear transposons, but since the two losses result in different metamorphoses, $\epsilon_{62} = \epsilon_{65} = \epsilon$. Similar reasoning yields $\epsilon_{21} = \epsilon_{51} = \epsilon_{73} = \epsilon$ and $\epsilon_{76} = 2\epsilon$. All other ϵ_{ij} are zero and will be ignored.

Conservative transposition is considered in Appendix B.

For replicative transposition, we assume that any given transposon replicates—with the duplicate integrating into a transposon-free replicon—at a rate δ. Since a duplicate transposon in a cell of type 2 might move either to the chromosome or to the other plasmid, $\delta_{23} = \delta_{26} = \frac{1}{2}\delta$. The same kind of argument yields $\delta_{56} = \delta$ and $\delta_{37} = \delta_{67} = 2\delta$. All other δ_{ij} are zero.

Since the rate at which cells lose all their plasmids is a measurable biological parameter that does not appear to be significantly affected by the presence or absence of the transposons, we assume a single rate, τ_O, for such segregation events. Thus, $\tau_{10} = \tau_{20} = \tau_{30} = \tau_{54} = \tau_{64} = \tau_{74} = \tau_O$.

Segregation events whereby a heteroplasmid cell produces a cell that contains only one type of plasmid are of an entirely different character. R. Novick and Hoppensteadt (1978) suggested that such segregations are often the result of random replication and random partitioning of the plasmids. The following calculations are based on the simplest case of the Novick and Hoppensteadt model.

Consider a short period of time, dt, during which fN_2dt cells of type 2 are washed out of the chemostat and an equal number divide. We imagine that in the dividing cells each of the plasmids replicates and that the four plasmids now in each cell are partitioned at random, two to each daughter cell. There are three equally likely ways in which four objects can be divided into two sets of two objects each. In one of these, the transposon-bearing plasmids are paired with each other; in this case, the transposon-free plasmids, of necessity, go together to the other daughter cell. In the other two cases, each transposon bearer is paired with one or the other of the transposon-free plasmids. Thus, on the average, of six original cells, three are gone. The others have produced six daughter cells, of which one carries two transposon-free plasmids, one carries two transposon-bearing plasmids, and four carry one transposon-bearing and one transposon-free plasmid. Therefore, during the period dt, this process results in an increase of $\frac{1}{6}fN_2dt$ cells of type 1 at the expense of cells of type 2. Let $\tau_P = f/6$. In the equations, the process is represented by terms $\tau_{ij}N_i$, where $\tau_{21} = \tau_{23} = \tau_{65} = \tau_{67} = \tau_P$.

For conjugation events, it may be helpful to be explicit about the distinction between concentrations and numbers, even though it does not affect the equations.

Consider first the case in which the recipient is plasmid-free. Let N_i be the concentration of plasmid-carrying cells of type i (i = 1,2,3,5,6,7), and let N_j be the number of plasmid-free cells of type j (j = 0,4). We assume that during a short period, dt, there will be $\gamma_O N_i N_j dt$ conjugation events in which a cell of type i transmits one of its plasmids to a cell of type j. If the donor cell carries both transposon-bearing and transposon-free plasmids, we assume that they are transmitted with equal frequency. This implies that events of this kind, whereby a cell of type j (j = 0,4) is converted to a cell of type k (k = 1,2,3,5,6,7) by receiving a plasmid from a donor of type i, occur at a rate $\gamma_{ijk}N_iN_j$, where

$$\gamma_{ijk} = \begin{cases} \gamma_O & \text{if } i = 1,3,5, \text{ or } 7 \\ \gamma_O/2 & \text{if } i = 2 \text{ or } 6 \end{cases}.$$

There are 16 terms of this type. Note that $\gamma_{202} = \gamma_{646} = 0$, since heteroplasmid cells donate only a single plasmid at a time. Moreover, some conjugations do not result in any change of cell type. Since these do not affect the equations, we set $\gamma_{ijk} = 0$ whenever $j = k$.

If plasmid-carrying cells have a tendency to exclude new homogenic plasmids, we must use a different specific conjugation-rate constant, γ_P, for conjugations in which the recipient cell already carries plasmids. When such a conjugation takes place, we imagine that the mechanisms that regulate copy number will result in the elimination of some plasmids. Since the details of the process are obscure, we adopt the simplest rule. Suppose the recipient contains two plasmids and receives one more by conjugation. If all three plasmids are of the same kind, the transconjugant will contain two plasmids of that kind. Otherwise, one-third of all transconjugants will contain only plasmids of the majority kind, and the other two-thirds will contain plasmids of both kinds. There are 32 such nonzero conjugation terms, $\gamma_{ijk}N_iN_j$, but each γ_{ijk} fits one of four simple patterns:

$$\gamma_{ijk} = \begin{cases} \gamma_P/3 & \text{if } i = 2 \text{ or } 6 \text{ and } j = 1,3,5, \text{ or } 7; \\ 2\gamma_P/3 & \text{if } i = 3 \text{ or } 7 \text{ and } j = 1 \text{ or } 5 \\ & \quad \text{or if } i = 1 \text{ or } 5 \text{ and } j = 3 \text{ or } 7; \\ \gamma_P/3 & \text{if } i = 1,3,5, \text{ or } 7 \text{ and } j = 2 \text{ or } 6; \\ \gamma_P/6 & \text{if } i = 2 \text{ or } 6 \text{ and } j = 2 \text{ or } 6. \end{cases}$$

(At a quick glance, there appear to be only 28 cases in this list, but when both cells include both kinds of plasmid, two values of k are possible for each i,j.)

Such term-by-term analysis makes it easy to write down the differential equations for replicative transposons:

$$\frac{dN_i}{dt} = \psi(r)w_iN_i - fN_i + \sum_{j,k=0}^{7} \gamma_{jki}N_jN_k - \sum_{j,k=0}^{7} \gamma_{jik}N_jN_i + \sum_{j=0}^{7} \delta_{ji}N_j - \sum_{j=0}^{7} \delta_{ij}N_i + \sum_{j=0}^{7} \epsilon_{ji}N_j - \sum_{j=0}^{7} \epsilon_{ij}N_i, \tag{A1}$$

where w_i is the relative growth rate of the ith cell type.

In all the calculations, interest centers on the effects of the transposon. For that reason, it is helpful to make minor changes in the model if they simplify the equations and eliminate extraneous influences. In a chemostat with a steady inflow of nutrients, the resource level has a stabilizing effect. As the following mathematical analysis shows, that means that fluctuations in the resource concentration can be ignored and the dimensionality of the system can be reduced, without significantly affecting the computations that are of interest.

The chemostat equation for the concentration of the resource is

$$\frac{dr}{dt} = f(C - r) - \sum_{i=0}^{7} \beta w_i\psi(r)N_i, \tag{A2}$$

where β is the amount of resource used by a cell during the time needed for cell division. If we add to equation (A2) β times each of the eight equations encompassed by (A1), we see that, thanks to all the cancellations,

$$\frac{d}{dt}\left(r + \beta \sum_{i=0}^{7} N_i\right) = f\left[C - \left(r + \beta \sum_{i=0}^{7} N_i\right)\right]. \tag{A3}$$

It follows that the hyperplane

$$r + \beta \sum_{i=0}^{7} N_i = C \tag{A4}$$

is a strongly stable invariant manifold. Thus, it is reasonable in studying the population dynamics to restrict our attention to those systems that satisfy equation (A4).

Now add the equations (A1) and substitute from equation (A4). The result is

$$\frac{dr}{dt} = -\beta \sum_{i=0}^{7} w_iN_i\left[\psi(r) - f \sum_{i=0}^{7} N_i \Big/ \sum_{i=0}^{7} w_iN_i\right]. \tag{A5}$$

If there is no selection, one might as well take all the w_i to be one. In that case, the submanifold $r = r_0$, where r_0 is the solution of $\psi(r_0) = f$, is also strongly stable, and we may confine our attention to solutions where $r = r_0$.

When we wish to study selection, we consider an idealized chemostat where the flow rate, f, is controlled in such a way that

$$f = \psi(r_0) \sum_{i=0}^{7} w_iN_i \Big/ \sum_{i=0}^{7} N_i. \tag{A6}$$

With this small change in the equations, $r = r_0$ is again a stable invariant submanifold.

If we make allowance for cell deaths resulting from transposition events that interfere

with the action of essential genes—or for the possibility that the ratio of the resource uptake rate to the population growth rate varies among cell types—equation (A6) must be modified. If the flow rate is adjusted according to the modified equation, $r = r_0$ will again be a stable invariant manifold, but the cell densities will no longer satisfy the constraint, ΣN_i is constant, that comes from equation (A4). If the initial population and resource are not too far from their equilibrium values and if the new effects are small, equation (A4) will be satisfied approximately.

In theory, the justification for taking $r = r_0$ is that we can regard equations for fixed-flow chemostats as slightly perturbed variants. In practice, the justifications are (1) that no significant differences are observed when we simulate one rather than the other and (2) that the resource concentration in laboratory chemostats quickly stabilizes to a value that closely approximates that predicted by theory.

APPENDIX B

Conditions for the Establishment of a Transposon

This appendix deals with two related questions. Why is it that a transposon achieves a characteristic invasion rate and that all transposon-bearing cell types increase in frequency at that same rate? Why cannot conservative transposons invade a habitat where transposon-free plasmids are established, unless the transposon conveys a selective advantage?

When a small inoculum of transposon-bearing cells is introduced into a chemostat where plasmid-free and plasmid-carrying cells are in conjugation-segregation balance, it will be some time before the new cell types are numerous enough to have a significant effect on the resident cell populations. Thus, when studying the rate at which the newcomers increase or decrease in numbers, we may treat the concentrations of the resident types as constant. Moreover, the terms in the equations that represent conjugation between two of the rare transposon-bearing types involve products of two relatively small numbers and are negligible compared to the remaining terms.

Treating N_0 and N_1 as constants and ignoring terms involving products $N_i \times N_j$, where $i,j > 1$, leaves a system of homogeneous, linear, differential equations with constant coefficients, in the variables $N_2, N_3, \ldots, N_7$. It follows that, to a good approximation, the solutions are sums of exponentials. The terms that involve the largest exponent will soon dominate the others, and transposon-bearing cell types will all increase at the rate given by this largest exponent. Further, their relative frequencies will approach the ratios determined by the coefficients in those dominant terms.

This argument not only explains why there is a characteristic invasion rate, it also provides a basis for a formal proof that, in this model, unselected, conservative transposons cannot invade an established plasmid-carrying population.

The conclusion is hardly surprising, since the definition of conservative transposition is that the number of transposons is unchanged by transposition events. Since the number is increased by cell division and by conjugation events, it is conceivable that these might enable a conservative transposon to survive without a selective advantage. However, detailed analysis of the equations shows that when conjugation is balanced by segregation, the gain of transposons through conjugation equals their loss through segregation. Population increase through cell division is balanced by loss through washout. If there is any transposon loss through excision, the number of transposons must steadily decline.

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