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Fixation probability of mobile genetic elements such as plasmids☆

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ABSTRACT

Mobile genetic elements such as plasmids are increasingly becoming thought of as evolutionarily important. Being horizontally transmissible is generally assumed to be beneficial for a gene. Using several simple modelling approaches we show that in fact being horizontally transferable is just as important for fixation as being beneficial to the host, in line with other results. We find fixation probability is approximately $2(s+\beta)$, where s is the increased (vertical) fitness provided by the gene, and β the rate of horizontal transfer when rare. This result comes about because when the gene is rare, almost all individuals in the population are possible recipients of horizontal transfer. The ability to horizontally transfer could thus cause a deleterious gene to become fixed in a population even without hitchhiking. Our findings provide further evidence for the importance and ubiquity of mobile genetic elements, particularly in microorganisms.

1. Introduction

The fixation probability of novel beneficial mutant alleles has been the subject of theoretical attention for nearly a century (Patwa and Wahl, 2008). In asexual populations novel mutations are likely to be particularly important for adaptation because without recombination to otherwise alter gene frequencies or produce beneficial combinations of alleles (Crow and Kimura, 1965; Fisher, 1930; Muller, 1932, 1964) novel mutations are the only way for a population to adapt to its environment. The ability of bacteria to adapt to new environments could be crucial in leading to the evolution of antibiotic resistance, a major public health problem (World Health Organization, 2000). An understanding of fixation probabilities in bacteria is therefore desired, and of the many models relating to fixation probabilities (Patwa and Wahl, 2008), there have been several that explicitly considered bacterial populations, incorporating the effect of clonal interference (Gerrish and Lenski, 1998), and of particular details about bacterial reproduction (Johnson and Gerrish, 2002).

One aspect of bacterial genetics that is believed to be of great importance is the high frequency of mobile genetic elements that spread through a population by horizontal gene transfer (the process of transferring genetic material to neighbouring individuals). Though it has been known about for years (Lederberg and Tatum, 1946; Zinder and Lederberg, 1952), the prevalence, scale, and evolutionary significance of horizontal gene transfer have recently become subjects of great interest (Bergstrom et al., 2000; Bordenstein and Reznikoff, 2005; Goldenfeld and Woese, 2007; Kurland et al., 2003; Ochman et al., 2000; Rankin et al., 2010; Sørensen et al., 2005; Thomas and Nielsen, 2005), and its importance to the evolution of bacteria has been suggested to be huge (Frost et al., 2005; Goldenfeld and Woese, 2007; Ochman et al., 2000).

In this paper, we investigate the fixation probability for a gene that can be transferred horizontally. Horizontal gene transfer mainly occurs in three ways (Bordenstein and Reznikoff, 2005; de la Cruz and Davies, 2000): through transformation, in which naked DNA is taken up from the environment; through transduction, in which bacteriophages integrate DNA into the host chromosome; and through conjugation, in which DNA transfer occurs cell-to-cell, often mediated by plasmids. Plasmids are particularly important in understanding bacterial evolution, frequently encoding traits such as antibiotic resistance and virulence factors, for reasons still imperfectly understood (Eberhard, 1990; Rankin et al., 2010). Reflecting this importance, our model is mainly applicable to plasmid conjugation, since it is based on cell-to-cell transfer of a mobile gene. We consider an idealised system in which a single plasmid enters a population (perhaps from an external species), and see how much its horizontal transferability affects its fixation probability. Our results could also apply to mobile genetic elements more generally, as long as they are transferred horizontally from one host to another at some rate. This could also apply to transposable genes, for example.

Existing calculations of fixation probability for novel horizontally-transferable genes employ continuous time birth–death

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processes (Bichsel et al., 2010; Novozhilov et al., 2005), and the fixation probabilities are calculated as a byproduct of other investigations. In this paper, by contrast, we use two different simple modelling frameworks to approach the problem. Our use of simple models allows us to focus entirely on fixation probability, thus giving it a thorough treatment. By using two different modelling approaches we aim to avoid as much as possible a result that is the artefact of a model rather than the underlying process. Our two methods are branching processes (Haldane, 1927), and diffusion approximations (Kimura, 1962). While the use of diffusion approximations is novel in regard to fixation probabilities for horizontally-transferable genes, both approaches are taken from the classical treatises on fixation probabilities, and have a history of application to such problems more generally (Patwa and Wahl, 2008). Within each approach, we allow for the mutant allele to be transferred both horizontally and vertically. Since the order of life cycle events has been shown to affect fixation probabilities in the past (Johnson and Gerrish, 2002), we also alter the order of events within the life cycle for each approach, investigating both the case where horizontal transfer occurs before vertical transfer, and the contrary case, where vertical transfer occurs before horizontal transfer.

To explain our work, we first describe the common assumptions behind both of our modelling approaches, and then go into details within each approach, outlining first the branching processes and then the diffusion approximations. We provide the details for changing the order of the life cycle within each approach. We then show that all four models lead to the same approximate result, and discuss its importance, connections to previous work, and possible future work.

2. Model

We assume a large population of bacteria with a fixed size N. We suppose that the bacterial life cycle has distinct periods of growth and division, with division being instantaneous. Fitness is genetically determined. We define two genotypes, the wild type and the mutant. We suppose that the mutant begins at a very low frequency. Because of its initial scarcity, there is some probability that stochastic demographic fluctuations might make the mutant type go extinct over the long term. We calculate the probability that this stochastic extinction does not occur, and refer to this as the probability of fixation of the mutant gene.

The novelty of our work is that the mutant gene can be transferred horizontally. This means that its frequency can increase through horizontal transfer in addition to increasing via its affect on the survival and reproduction of its bearers ("vertical transfer"). We therefore need to incorporate both these processes into our models. For mathematical tractability we investigate horizontal and vertical transfers as distinct phases. To minimise the possibility that this assumption unduly informs our results, we alter the order of these events, analysing the situation when horizontal transfer occurs before vertical, and when it occurs after. Thus our two different life cycles are as follows: (1) horizontal transfer, then vertical transfer (i.e. selection and breeding), then census the genotypes, and (2) vertical transfer (i.e. selection and breeding), then horizontal transfer, then census the genotypes. Investigating both of these possibilities minimises the likelihood of our results being an artefact of the life cycle assumptions, especially important since in reality horizontal and vertical transfers are not distinct, discrete phases.

2.1. Branching process

For our branching process approach, we break the vertical transfer portion of the life cycle into survival and breeding periods (Johnson and Gerrish, 2002). The survival period comes first, followed by breeding, which is assumed to be instantaneous. All individuals that make it through the survival period reproduce, transforming from a single mother cell to two clonal daughter cells. If we denote the probability that a mutant individual makes it through the survival period by p, then the number of copies of the mutant gene produced by that individual via vertical transfer will be a random variable that can be zero (if the mutant does not survive, probability $1-p$), or two (if the mutants survives and therefore reproduces, probability p). The mean number of copies from vertical transmission is therefore $2p$. If the mutant allele is beneficial we can follow the standard approach (Haldane, 1927; Johnson and Gerrish, 2002; Patwa and Wahl, 2008), and define the expected (vertical) fitness of a mutant as $1+s$ for some s, meaning $p=(1+s)/2$. To analyse the model we utilise probability generating functions (PGFs). In the case of vertical transfer, the PGF is $v(y)=(1-p)+py^2$ (Parzen, 1962).

For horizontal transfer, the mass action principle is typically used to approximate the spread of the horizontally-transferable elements (Ross, 1915). Given a proportion x of individuals bearing the gene, this states that the number of horizontal transfer events will be proportional to $x(1-x)$. Then for some transfer rate β the expected number of transfers per individual is $\beta(1-x)$. We could model the number of transfers by a single individual as a Poisson distribution with this mean, but presuming that $\beta \ll 1$, the chance of more than one horizontal transfer event is very unlikely, and we can instead approximate this distribution by a Binomial distribution with a single trial. We incorporate this into our branching process framework by further supposing that $x \approx 0$ (at least for the portion of time where the gene could be lost by stochastic fluctuations), so that the probability of success of the single Binomial trial is β (for our branching process approach to be valid the horizontal transmission cannot depend on $(1-x)$ since the fates of each individual in the population are assumed to be independent). Then the number of additional copies of the mutant gene produced by a single individual via horizontal transfer is a random variable that can be zero (if horizontal transfer does not occur, probability $1-\beta$) or one (if horizontal transfer does occur, probability β). The PGF for horizontal transfer is then $h(y)=(1-\beta)y+\beta y^2$.

We start with a single mutant individual. Combining the two types of transfer will result in a random variable X describing the number of offspring descending from this individual at the next census, where "offspring" here means bearers of the mutant allele due to either vertical or horizontal transfer by the individual in question. This variable will have PGF $m(y)$. We denote by $Q(t)$ the probability that a single copy of the mutant allele present at time t in the population is ultimately lost (Johnson and Gerrish, 2002). Assuming that the population is sufficiently large and mutant alleles sufficiently rare (at least while stochastic extinction is a threat) so that different copies of the mutant allele act independently of one another, a single copy present at time t has the same probability of eventually being lost as a single copy at time $t+1$, so consequently $Q(t)=Q(t+1)=Q$ for all t, and we can say that the probability of extinction given i copies of the allele is Q^i (Haldane, 1927; Parzen, 1962). The standard branching process procedure (Haldane, 1927; Parzen, 1962) then gives the probability of the mutant being lost from the population as the solution to

$$Q = m(Q) \tag{1}$$

in the neighbourhood of zero (Haldane, 1927). We solve this, substitute in $p=(1+s)/2$, and then calculate $P=1-Q$, the probability that the mutant allele does not go extinct. This expression is generally messy and complicated, so we simplify matters by taking a Taylor series approximation of it when $s^2 \approx 0$, $\beta^2 \approx 0$, neglecting higher-order terms in s and β, and getting an approximate expression for the probability of fixation of the mutant allele starting from a single copy.