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Cytoplasmic Incompatibility and Population Structure

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Wolbachia is a maternally inherited bacterial infection common in many insects. These bacteria cause cytoplasmic incompatibility, in which a cross between an infected male and an uninfected female is sterile. Infected females are always fertile, suggesting that an infected male produces a sterilizing product against which infected females are protected. This sterility trait is an evolutionary puzzle because it acts in males, but males never transmit the parasites. Previous work has suggested that the parasite gains by reducing the fecundity of uninfected females, thereby increasing the relative reproductive rate of infected females. This argument depends on kin selection effects: the parasite in the male does not reproduce, but can aid related parasites in neighbouring females. Formal population genetic models have failed to confirm the verbal kin selection models. Those models assumed pleiotropic gene action whereby incompatibility evolves as a correlated effect of other fitness components. A formal model presented here supports the original kin selection theories. This new model also suggests an explanation for observed variation in the degree of incompatibility among *Wolbachia* strains isolated from *Drosophila simulans*.

Introduction

Wolbachia is a maternally inherited infection found in many insects. These bacteria sometimes cause incompatibility between infected and uninfected mates. A cross between an infected male and an uninfected female is sterile, whereas all other crosses are fertile. This form of sterility is commonly called cytoplasmic incompatibility (for reviews, see Rousset & Raymond 1991; Werren *et al*. 1995; Clancy & Hoffmann 1996).

Possible explanations for the evolution of cytoplasmic incompatibility have been controversial. Hurst (1991) and Rousset & Raymond (1991) suggested that a parasite in a male gains by killing the eggs of uninfected females, thereby increasing the relative reproductive rate of infected females. Thus a parasite in a male does not increase its own reproductive rate, but may increase the reproduction of neighbouring parasites. According to this idea, higher levels of incompatibility evolve as a "selfish" or "spiteful" trait because of potential kin selection benefits to neighbours.

No formal models were presented to support this kin selection explanation. Prout (1994) developed a mathematical model to study the evolutionary forces that influence incompatibility. He concluded that natural selection never directly favours parasite traits that cause the observed pattern of incompatibility. Incompatibility is either a neutral trait of parasites or is favoured because of pieiotropic correlations among parasite traits. Turelli (1994) presented an extensive mathematical treatment that supported Prout's conclusions.

Prout and Turelli's formal models do not address the original ideas about selfish parasites and kin selection as an explanation for incompatibility. Their models implicitly assume that there is no population structure and therefore no potential for kin interactions. I show, with a formal model, that weak

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kin interactions are sufficient to explain the observed patterns of incompatibility.

The Model

I use the method of Taylor & Frank (1996) to account for population structure and kin interactions. The first step is to write a fitness function that describes how biological assumptions influence reproduction

$$w(x,y) = \frac{(1-a-bx)(1-\mu)}{(1-q)^2 + q(1-a-by) + q(1-q)(1-y)}, \quad (1)$$

where the fitness of a parasite in a female, w, depends on the parasite's trait value, x, and the average value of this trait among neighbours with which the infected female interacts, y.

The parasite trait under study, when in a female host, reduces fecundity by an amount bx. All infected females have their reproductive rate reduced by a, thus the focal female's reproductive rate is proportional to $1-a-bx$, as in the numerator. The parasite is vertically transmitted, and there is only one parasite genotype in each host. The probability of transmission is $1-\mu$, that is an infected mother has a fraction μ of her offspring uninfected. Thus, the reproductive rate of a parasite is equal to the reproductive rate of its host female multiplied by $1-\mu$. Transmission probability, $1-\mu$, is uncorrelated with the level of incompatibility, x.

I assume that population regulation occurs within neighbourhoods. Our focal female's fecundity must therefore be compared with the average fecundity in the neighbourhood, given in the denominator of eqn (1). The frequency of infected individuals is q, and I assume that this frequency is the same in both males and females.

Given those assumptions about frequency of infection, the frequency of matings between uninfected male and female is $(1-q)^2$, and the relative fecundity of the uninfected female is one. Mating pairs with an infected female occur with frequency q, and the relative fecundity of infected females in the neighbourhood is $1-a-by$. Matings between infected males and uninfected females occur at frequency $q(1-q)$. The trait under study causes incompatibility in these matings. The average value of the trait in the neighbourhood is y, so the average fecundity of uninfected females mating with infected males in the neighbourhood is $1-y$.

I study three cases depending on the sign of the parameter b. This parameter is the reduction in the fecundity of an infected female that arises as a correlated trait of the level of incompatibility expressed in males. I emphasize this trait to compare my results with those of Turelli (1994).

In the first case, $b = 0$, incompatibility has no correlated effect on female fecundity. For this assumption Turelli (1994) concluded that selection does not favour incompatibility acting in males. However he implicitly assumed that the coefficient of relatedness among neighbouring males and females is zero, $r = 0$.

The direction of change in incompatibility favoured by selection can be determined by the sign of $\mathrm{d}w/\mathrm{d}x$, where fitness, w, is given in eqn (1). Differentiation is straightforward, and the condition for $\mathrm{d}w/\mathrm{d}x > 0$ is

$$rq(1-q) > 0, \quad (2)$$

which shows that selection favours an increase in incompatibility whenever $r > 0$ and there is some polymorphism in infection status ($q \neq 0$, $q \neq 1$). Here r is the kin selection coefficient of relatedness, and arises in $\mathrm{d}w/\mathrm{d}x$ as the term $\mathrm{d}y/\mathrm{d}x$. This derivative of y with respect to x is the slope of group phenotype on individual genotype, which is the kin selection coefficient of relatedness (Taylor & Frank 1996; under the assumption of a genetically uniform population with rare mutants of small effect). The frequency of infection, q, depends on the level of incompatibility (see below). However, we can treat q as a parameter in this case because our only goal is to show the direction of evolutionary change for a given infection level.

The result in eqn (2) shows that kin selection favours an increase in the level of incompatibility when population regulation occurs at the neighbourhood level. The reason can be seen by inspection of eqn (1). An increase in the incompatibility trait, x, by an amount δ, is associated with an increase in the average incompatibility of neighbours, y, by an amount $r\delta$. If $b = 0$, a rise in y increases fitness whenever there is any polymorphism in infection status.

The second case is $b < 0$, in which incompatibility in males causes a correlated increase in the fecundity of infected females. There does not appear to be any good biological rationale for this assumption, but Turelli (1994) emphasized this case because, under his assumption that $r = 0$, this is the only way he was able to explain the evolution of incompatibility. Using the same method as in the previous case, $\mathrm{d}w/\mathrm{d}x > 0$ is true when $b < 0$ and infected females produce some offspring. The explanation in this case is simple. Selection favours an increase in incompatibility acting in males when incompatibility has a correlated, positive effect on the fecundity of infected females.

The third case is $b > 0$, in which incompatibility causes a correlated decrease in the fecundity of infected females. This case is more interesting because the beneficial effects of incompatibility, proportional to the coefficient of relatedness in the neighbourhood, r, must be compared to the direct reduction in female fecundity, b. The condition for selection to favour an increase in the incompatibility trait, z, is

$$rq(b + 1 - q) > b \tag{3}$$

when the values of a and b are small relative to one, as expected in real situations. Here we must take into account the fact that changes in z will influence the infection frequency, q. The condition for an increase in q is

$$(1 - a - bz)(1 - \mu) > (1 - q)^2 + q(1 - a - bz) + q(1 - q)(1 - z). \tag{4}$$

The left side is the number of infected progeny produced by an infected female, and the right side is the average number of progeny produced by all females. The left and right sides are, respectively, the numerator and denominator from eqn (1), ignoring genetic variation in the incompatibility trait so that $x = y = z$. I ignore genetic variation because I assume throughout that the population is genetically monomorphic except for rare variants of small effect. I also assume that the frequency of infection, q, is the same in all subpopulations.

Let $a = 0$ to highlight the relative roles of b and r. Assuming that b and μ are small relative to one, eqn (3) and eqn (4) can be written as

$$q^2 - q(1 + b) + b/r < 0 \tag{5}$$

$$q^2 - q(1 + b) + b + \mu/z < 0 \tag{6}$$

where the top inequality sets the condition for an increase in z and the bottom inequality sets the condition for an increase in q. These inequalities allow one to sketch a phase plane for the joint dynamics of z and q.

The equilibrium $z^* = q^* = 0$ is locally stable. An internal, locally attracting point may also exist when $r > 4b$. There are two cases. If $r < b/(b + \mu)$, then there is an internal equilibrium at

$$z^* = \frac{r\mu}{b(1 - r)} \tag{7}$$

$$q^* \approx \frac{1 + \sqrt{1 - 4b/r}}{2}. \tag{8}$$

This situation is shown in the left panel of Fig. 1. If $r > b/(b + \mu)$, then

$$z^* = 1 \tag{9}$$

$$q^* \approx 1 - b - \mu. \tag{10}$$

This type of equilibrium is shown in the right panel of Fig. 1. Comparing the left and right panels of Fig. 1 shows that incompatibility, z^*, increases as the transmission efficiency of the symbiont, $1 - \mu$, declines. As the symbiont is lost more frequently from hosts, higher μ, the polymorphism in infection status, $q^*(1 - q^*)$, increases. Incompatibility is advantageous only in matings between infected males and uninfected females, thus an increase in the polymorphism of infection enhances the benefit of high incompatibility.

The internal equilibrium, when it exists, is shown in Fig. 2. The infection tends to be absent or at high frequency, as shown in the lower row for the equilibrium value of q. The level of incompatibility varies over a wide range, influenced by all three parameters, b, r, and μ. The transmission efficiency, μ, appears to cause the most pronounced effects on the level of incompatibility. This analysis is only meant as a rough, qualitative guide to the complex

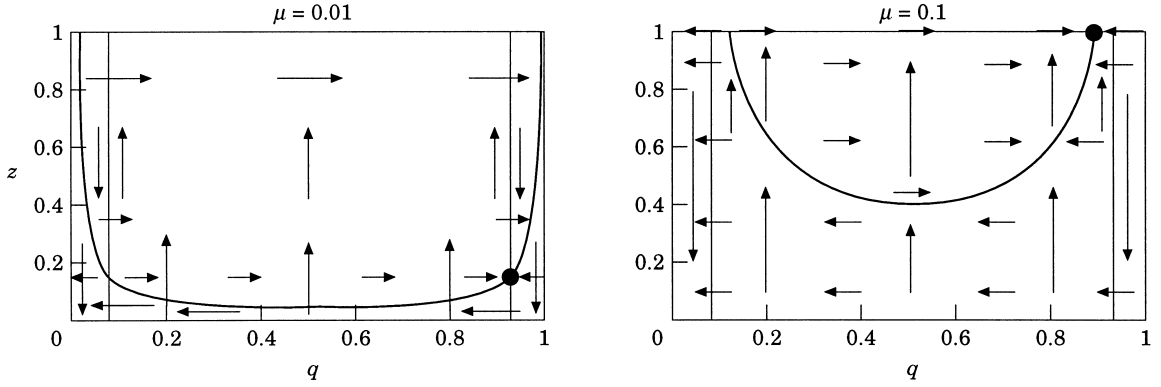

FIG. 1. Joint dynamics of the frequency of infected individuals, q, and the level of incompatibility, z. These plots were made from eqn (5) and eqn (6). The parameters used are $a = 0$, $b = 0.005$, and $r = 0.07$. The two vertical lines separate regions in which z is favoured to increase or decrease. The curve separates regions in which q is increasing or decreasing.

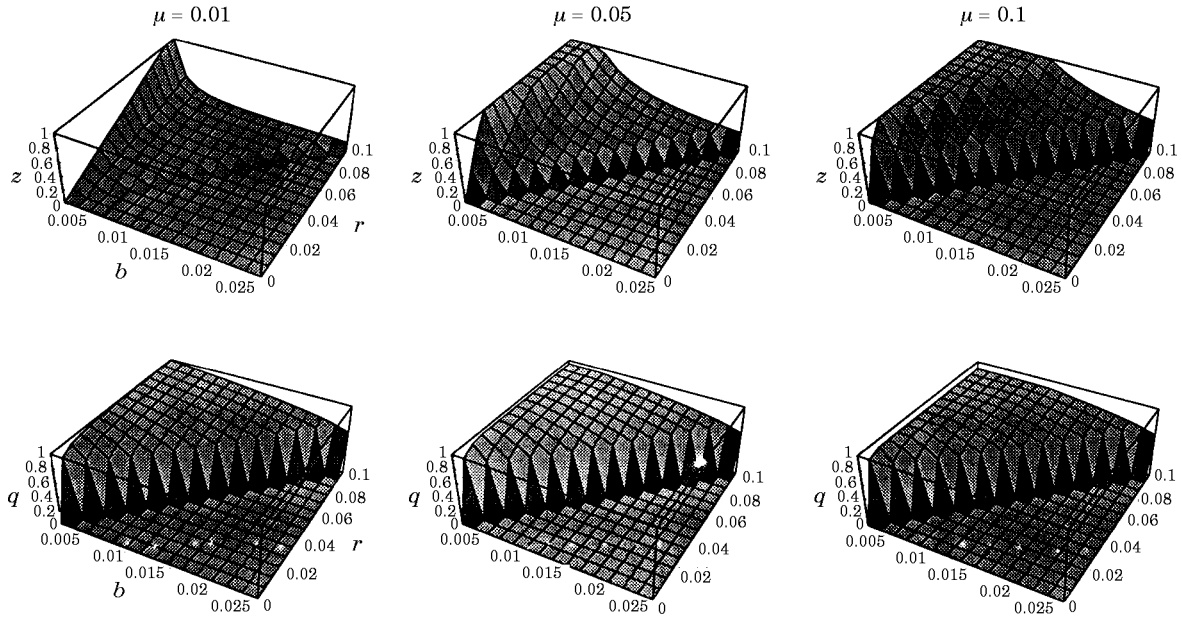

FIG. 2. Internal equilibrium values of the frequency of infected individuals, q, in the lower row, and the level of incompatibility, z, in the upper row.

dynamics of this system. The main point is that relatedness, r, can strongly influence selection of incompatibility.

Prout (1994) and Turelli (1994) implicitly assumed that $r = 0$. Given that assumption, it is not surprising that they concluded kin selection does not favour incompatibility. I have shown that the simple condition $r > 0$ is sufficient to favour incompatibility when there is no genetic correlation between incompatibility expressed in infected males and reduced fecundity expressed in infected females (the parameter $b = 0$). When there is a correlation, $b > 0$, kin selection influences incompatibility, but the net selective effect depends on the relative magnitudes of relatedness, r, negative effects on female fecundity, b, transmission efficiency, μ, and the frequency of infection, q. The direction of selection can shift toward higher or lower incompatibility as these factors change in magnitude.

Shifts in the direction of selection may explain the fact that strains of *Drosophila simulans* from Madagascar harbour *Wolbachia* variants that do not cause cytoplasmic incompatibility (Rousset & Solignac 1995), whereas *D. simulans* from other locations have *Wolbachia* infections that cause the standard pattern of incompatibility (Clancy and Hoffmann 1996).

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