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LETTER TO THE EDITOR

Bacterial cooperation controlled by mobile elements: kin selection and infectivity are part of the same process

Genes involved in bacterial cooperation and virulence are overrepresented on mobile elements (Nogueira *et al.*, 2009). This highlights the importance of gene mobility in bacterial social evolution. We have previously argued that this pattern could emerge due to changes in population genetic structure driven by gene mobility, and drive the evolution of cooperation by kin selection (Nogueira *et al.*, 2009; Rankin *et al.*, 2011). The response of Giraud and Shykoff (2011) proposes 'infectivity' (the infectious transfer of mobile genetic elements— MGEs) as an alternative explanation to that of kin selection. Their argument is similar to one previously proposed by Smith (2001). Smith (2001) suggested that infectivity could promote cooperation by converting phenotypically uncooperative cells into cooperators. Here we argue that infectivity and kin selection are not competing explanations, and can, in fact, act together to promote microbial cooperation (Figure 1).

As we have argued previously (Nogueira *et al.*, 2009; Mc Ginty *et al.*, 2011; Rankin *et al.*, 2011), 'infectivity' (also referred to as 'transmission' for example, Smith, 2001; Rankin *et al.*, 2011) and 'kin selection' are complementary explanations contrary to the claims of Giraud and Shykoff (2011), as infectiousness modifies relatedness (Figure 2 in Nogueira *et al.*, 2009). We can use the Price equation (Price, 1970) to show how this is so. Assuming that transmission (mobile element transfer) takes place before regulation, the change in the frequency p of an MGE in the population is as follows:

$$\underbrace{w\Delta p}_{\text{Change in trait}} = \underbrace{\text{cov}(w_{ij}, p_{ij}^{\text{T}})}_{\text{Selection}} + \underbrace{\text{E}(w_{ij}\Delta p_{ij})}_{\text{Transmission}} \qquad (1)$$

where w_{ij} is the fitness of individual i in patch j, p_{ij}^{T} is the frequency of the MGE in individual i in patch j, after transmission and w and p are the mean fitness and frequency of the MGE across the whole population, respectively. The first term on the right-hand side deals with selection, and the second term of the right-hand side deals with transmission. Equation (1) therefore incorporates both selection and transmission.

Smith's (2001) argument (echoed by Giraud and Shykoff, 2011) depends solely on the transmission term: cooperative genes can increase in frequency as a result of infectious transfer into uninfected cells. Therefore, the transmission effect (Smith, 2001; Giraud and Shykoff, 2011) is essentially a hitch-hiking effect (for example, Barton, 2000; Gardner *et al.*, 2007). As such, it can amplify any gene regardless of whether or not it is social. In fact, as long as the rate of horizontal gene transfer is great enough, transmission can promote the spread of traits that are only temporally beneficial (as in the case of

antibiotic resistance Svara and Rankin, 2011), traits that would otherwise be costly (for example, Lili *et al.*, 2007) or even traits that can potentially drive a population to extinction (for example, Rankin *et al.*, 2010). This would suggest that infectivity, on its own, does not explain that secreted proteins are overrepresented on plasmids, and we would also expect traits that are entirely costly (and thus have no benefit to the host bacteria, or its neighbours) to be equally overrepresented on plasmids.

If transmission occurs before selection in the life cycle of a host-associated bacterial species, gene mobility will also have a substantial effect on the selection term. This will primarily be by increasing the genetic association, at the locus of the plasmid, between two individuals in a local environment. The covariance term in the Price equation can be broken down into the variance and the regression of the genic value of a focal individual and the focal individual's fitness (Frank, 1998):

$$\text{Cov}(w_{ij}, p_{ij}^{\text{T}}) = \text{V}(p_{ij}^{\text{T}})s(w_{ij}, p_{ij}^{\text{T}}) \qquad (2)$$

where $s(w_{ij}, p_{ij}^{\text{T}})$ refers to the selection gradient, and $V(p_{ij}^{\text{T}})$ refers to the variance of the focal gene (after transmission). If transmission is local but competition is global, the selection gradient for a cooperative trait may be written as follows:

$$s(w_{ij}, p_{ij}^{\text{T}}) = BR^{\text{GT}} - C \qquad (3)$$

This is Hamilton's (1964) rule, where B and C are the benefits and costs, respectively, and R^{GT} is the whole-group relatedness, measured after transmission. Our original model demonstrated that gene mobility modifies the selection term due to R^{GT} becoming an increasing function of mobility. Thus, our model implies that non-cooperative MGEs would tend to be selected against due to the population structure (increased relatedness) that their mobility generates. Relatedness is calculated as a coefficient (Orlove and Wood, 1978; Queller, 1992) and, for whole-group relatedness calculated after transmission, can be calculated by

$$R^{\text{GT}} = \frac{\text{Cov}(p_{\text{o}}^{\text{T}}, p_{\text{G}}^{\text{T}})}{\text{Cov}(p_{\text{o}}^{\text{T}}, p_{\text{o}}^{\text{T}})}, \qquad (4)$$

where p_{o}^{T} refers to the genic value of a focal individual (whether it carries the plasmid or not), measured after transmission, whereas R^{GT} refers to the average genic value in the local economic neighbourhood, measured after transmission.

It is important to consider that relatedness is always measured at the locus of interest, and, even if our presentation was at times overly brief, is always properly calibrated to the appropriate reference population (for example, Gardner and West, 2004). In our case the locus of interest is characterised by a specific degree of local transmission or mobility (high for MGEs, low for
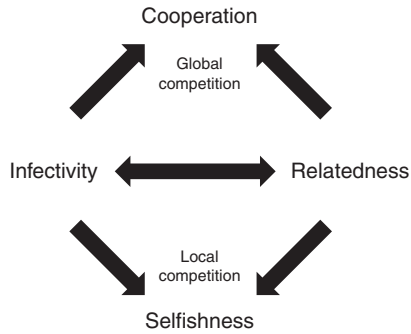
Figure 1 The interaction between relatedness and infectivity. Relatedness and infectivity are complimentary explanations for the evolution of plasmid-carried cooperation. Fundamentally, the scale of competition will influence whether genes are cooperative or not. Infectivity can increase relatedness, and higher relatedness can mean that there is less scope for infectivity. Thus there is the potential for feedbacks between the two mechanisms.

chromosomal transfer 'cold-spots' Nogueira et al., 2009). Given local transmission, it is clear that gene mobility will affect relatedness. Thus there are two ways in which genetic relatedness can be generated in our model: the first is through direct, vertical, inheritance (which is independent of gene mobility) and the second is through horizontal gene transfer itself. If, for maximal simplicity, we assume a life cycle where n individuals colonise a patch, then gene transfer occurs among offspring before they interact and then all disperse to form new patches (that is, there is full migration), relatedness will be $1/n$ in the absence of transmission (for example, Taylor, 1992). However, it is clear that, because we measure relatedness at the locus of interest, HGT will increase the number of local cells, which carry the MGE and thus increase local relatedness, relative to the rest of the population. Relatedness, after transmission, can be given as

$$R^{GT} = \frac{1}{n} + f(\beta, p, n) \qquad (5)$$

where $f(\beta, p, n)$ is a function describing the influence of initial colonisers and transmission rates on relatedness (which will always be positive if $\beta > 0$, $n > 1$ and $p < 1$). As we assume competition (for new patches) between individuals in other patches, our relatedness calculations (Nogueira et al., 2009) are appropriate for the 'economic neighbourhood' referred to in Giraud and Shykoff (2011). The existence of any additional within-patch structuring (for instance, because of receptor-mediated discrimination between MGE carriers and non-carriers, as alluded to by Giraud and Shykoff, 2011) would only act to increase the amplifying effect of gene mobility on the selection term in equation (1). As we show in Figure 1, kin selection and transmission are not rival explanations, but are complementary. In our original article, we neglected to discuss the issue of the scale of competition in our model (Frank, 1998; West et al., 2002), simply assuming that we had global competition, where individuals interacted locally, but competed globally. Depending on the life cycle, and particularly on the scale of competition, increased transmission will either promote cooperation, in the case where competition takes place between patches, or will promote selfishness, in the case where competition takes place within patches (Figure 1). However, it is clear from our work that if interactions take place within a patch, and

competition is global, this will favour plasmids which code for cooperation (Nogueira et al., 2009; Rankin et al., 2011).

An important limitation of the infectivity argument (Smith, 2001; Giraud and Shykoff, 2011) is that it does not consider the possibility that transmission also amplifies non-cooperative genes (discussed in Nogueira et al., 2009; Mc Ginty et al., 2011). Although the model of Smith looked at infectivity as a mechanism to promote cooperation, he did not consider the fact that other plasmids could persist in the population that do not carry genes for cooperation. The infectivity argument breaks down when there are multiple plasmids in the population that are incompatible with each other (that is, a single cell cannot be infected with >1 plasmid). In a recent paper (Mc Ginty et al., 2011), it was shown that if there are incompatible plasmids that do not carry a gene for the production of public goods, these will outcompete plasmids that do produce the public good within a well-mixed patch. In fact, the only way that plasmid-carried cooperation could persist in such a context was in a patch-structured population, highlighting the importance of spatial structure in promoting plasmid-carried cooperation.

There are a number of other explanations for why we observe that secreted proteins are carried on plasmids that were not explored, either in our review, or in the response of Giraud and Shykoff (2011). For example, genes carried by high-copy-number plasmids may potentially be expressed at higher dosages than single genes carried on the chromosome. This could be a simple mechanism to amplify a given gene. Additionally, if a gene is only occasionally required, or is needed only in certain environments, then plasmid-carried genes are favoured over chromosomally carried genes (Svara and Rankin, 2011). This is especially true in the case of antibiotic resistance, where there is often a heterogenous application of drugs, which may potentially select for plasmid-carried resistance genes (for example, Svara and Rankin, 2011). However, neither these explanations, nor infectivity, can be applied to any gene, not necessarily genes with social effects, and thus neither help to explain why secreted proteins in particular are overrepresented on plasmids. Although non-social genes can also be promoted under most of these mechanisms, kin selection, where horizontal gene transfer increases local relatedness, represents a simple mechanism, which can exclusively explain why genes coding for social traits are specifically overrepresented on plasmids.

MGEs code for a wide range of different genes, and many factors are likely to influence which genes are carried on mobile elements and why (Rankin et al., 2011). As we have argued here, it is likely that both transmission (directly, on a transient local scale) and kin selection (modified by horizontal gene transfer) will have a role in the ecology and evolution of mobile element driven cooperation. Rather than being competing theories, they both help to explain in a complementary manner why so many social genes are transmitted horizontally.

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References

Barton NH (2000). Genetic hitchhiking. *Philos Trans R Soc Lond B Biol Sci* **355**: 1553–1562.

Frank SA (1998). *Foundations of Social Evolution*. Princeton University Press: Princeton.

Gardner A, West SA (2004). Spite and the scale of competition. *J Evol Biol* **17**: 1–9.

Gardner A, West SA, Barton NH (2007). The relation between multilocus population genetics and social evolution theory. *Am Nat* **169**: 207–226.

Giraud T, Shykoff JA (2011). Bacterial cooperation controlled by mobile elements: kin selection versus infectivity. *Heredity* (e-pub ahead of print 27 July 2011; doi:10.1038/hdy.2011.57).

Hamilton WD (1964). The genetical evolution of social behaviour. I & II. *J Theor Biol* **7**: 1–52.

Lili LN, Britton NF, Feil EJ (2007). The persistence of parasitic plasmids. *Genetics* **177**: 399–405.

Mc Ginty SE, Rankin DJ, Brown SP (2011). Horizontal gene transfer and the evolution of bacterial cooperation. *Evolution* **65**: 21–32.

Nogueira T, Rankin DJ, Touchon M, Taddei F, Brown SP, Rocha EPC (2009). Horizontal gene transfer of the secretome drives the evolution of bacterial cooperation and virulence. *Curr Biol* **19**: 1683–1691.

Orlove MJ, Wood CL (1978). Coefficients of relationship and coefficients of relatedness in kin selection—covariance form for rho formula. *J Theor Biol* **73**: 679–686.

Price GR (1970). Selection and covariance. *Nature* **227**: 520–521.

Queller DC (1992). A General-model for kin selection. *Evolution* **46**: 376–380.

Rankin DJ, Bichsel M, Wagner A (2010). Mobile DNA can drive lineage extinction in prokaryotic populations. *J Evol Biol* **23**: 2422–2341.

Rankin DJ, Rocha EPC, Brown SP (2011). What traits are carried on mobile elements, and why? *Heredity* **106**: 1–10.

Smith J (2001). The social evolution of bacterial pathogenesis. *Proc R Soc Lond B Biol Sci* **268**: 61–69.

Svara F, Rankin DJ (2011). Why is antibiotic resistance over-represented on plasmids? *BMC Evol Biol* **11**: 130.

Taylor PD (1992). Altruism in viscous populations—an inclusive fitness model. *Evol Ecol* **6**: 352–356.

West SA, Penn I, Griffin AS (2002). Cooperation and competition between relatives. *Science* **296**: 72–75.