today, along with the associated differences in climate, community structure and floristics in areas where they occur (J. Read, R.S.H. & G. S. Hope, manuscript in preparation), supports the hypothesis[7] that early to middle Tertiary climatic conditions in southeastern Australia may have no modern analogue. The co-occurrence of these species in the middle Tertiary may also reflect a more unstable Australian landscape then, as Australia is now one of the few areas inhabited by *Nothofagus* which does not experience recurrent land disturbance[14,15]. Regular disturbance is important for the regeneration of *Nothofagus* species in many communities[16].

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No pure strategy is evolutionarily stable in the repeated Prisoner's Dilemma game

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A knowledge of the conditions under which natural selection can favour cooperative behaviour among unrelated individuals is crucial for understanding the evolution of social behaviour, particularly among humans and other social mammals. In an influential[1-5] series of works, Axelrod[6-10] has argued that reciprocal cooperation is likely to evolve when individual organisms interact repeatedly. This conclusion is based, in part, on an evolutionary analysis of the repeated Prisoner's Dilemma game which indicates that strategies which lead to reciprocal cooperation are evolutionarily stable[1,11]. In this paper, however, we argue that no pure strategy can be evolutionarily stable in this game. This fact casts doubt on several of Axelrod's conclusions about the evolution of reciprocity.

In Axelrod's model, pairs of individuals are sampled from a population and interact repeatedly. The probability that a given pair interacts more than t times is w^t, where $0 < w < 1$. During each interaction individuals choose between cooperation and defection with the incremental effects on the fitness of each individual (T, R, P and S) shown in Table 1. Each individual is further characterized by a strategy which specifies whether it will cooperate or defect during an interaction depending on the sequence of interactions up to that point. Strategies can be fixed rules such as always defect (ALLD), or contingent ones such as TIT FOR TAT (TFT) which cooperates on the first move, and then adopts the behaviour used by the other player during the previous interaction.

Axelrod concludes that when w is sufficiently large, strategies such as TIT FOR TAT which lead to cooperative reciprocity

Table 1 Payoff matrix for the single period Prisoner's Dilemma game

		Choice of player 2	
		Cooperate	Defect
Choice of player 1	Cooperate	R, R	S, T
	Defect	T, S	P, P

Each cell shows the payoffs to the first player and to the second player, separated by commas, of the pair of choices represented by that cell. The dilemma exists if $T > R > P > S$ and $R > (T+S)/2$.

are likely to become common. Such strategies are nice, provokable and forgiving, meaning that they are never the first to defect, punish a defection by another player by immediately defecting, and answer an act of cooperation by another player by immediately cooperating. Axelrod bases this conclusion on three findings: First, nice, provokable and forgiving strategies can increase in frequency in a population in which ALLD is common as long as there is some population structure. Second, computer tournaments indicate that once they get started, nice, provokable, forgiving strategies do extremely well against a wide variety of other strategies. Third, if a nice, provokable, forgiving strategy becomes common in a population where w is sufficiently high, Axelrod argues that it will remain common because such strategies are "collectively stable"[9]. A strategy S_e is collectively stable if for any possible strategy S_i:

$$V(S_e|S_e) \geq V(S_i|S_e) \quad (1)$$

where $V(S_m|S_n)$ means the expected fitness of individuals who use strategy S_m when interacting with individuals using strategy S_n. Axelrod argues that collective stability implies evolutionary stability, so that when a collectively stable strategy is common in a population and individuals are paired randomly, no other rare strategy can invade.

However, collective stability does not imply evolutionary stability. Suppose that a common strategy S_e coexists in a population with $N-1$ rare strategies that are maintained in the population by mutation. Let the frequencies of the N strategies be $p_1, \ldots, p_N$. To be evolutionarily stable, the common strategy, S_e, must have higher expected fitness than any rare invading strategy, S_i (ref. 1). Assuming that interacting individuals pair randomly, this requires:

$$\sum_{j=1}^{N} p_j V(S_e|S_j) > \sum_{j=1}^{N} p_j V(S_i|S_j) \quad (2)$$

If for each i, $V(S_e|S_e) > V(S_i|S_e)$, then S_e is both collectively and evolutionarily stable because $p_e \gg p_j$ $(e \neq j)$. However, if equation (1) is satisfied for each i, but for some i, $V(S_e|S_e) = V(S_i|S_e)$, then S_e is collectively stable but may not be evolutionarily stable. This distinction is important in the repeated Prisoner's Dilemma game because there are many important pairs of strategies for which $V(S_e|S_e) = V(S_i|S_e)$ and $V(S_i|S_i) = V(S_e|S_i)$. For example, any nice strategy has the same expected fitness when interacting with any other nice strategy because neither ever defects. The relative fitness of such pairs of strategies depends on their interaction with other rare strategies. TFT is nice and (assuming w is sufficiently large) collectively stable[10]. Whether it can resist invasion by another nice strategy, for example TIT FOR TWO TATS (TF2T) which allows two consecutive defections before retaliating, depends on how TFT and TF2T do against rare non-nice strategies.

Using the criterion of evolutionary stability changes several of Axelrod's important results. First, when w is large enough, TFT can be invaded even though it is nice, provokable and forgiving. Assume that strategies are transmitted according to a haploid genetic model[1,12,13] and that one-way mutation maintains SUSPICIOUS TIT FOR TAT (STFT), which defects on the first interaction and then plays TFT, in the population. Then TF2T can invade TFT whenever $V(\text{TF2T}|\text{STFT}) > V(\text{TFT}|\text{STFT})$. When w is large enough, this inequality is always

satisfied because the more tolerant TF2T induces STFT to cooperate, whereas the provokable TFT becomes involved in an endless sequence of reprisals. Second, strategies like TF2T which are not provokable can persist in a population at high frequency. If w is sufficiently large, the only population configuration in this system that is locally stable is a mixture of TF2T and STFT. The frequency of TF2T at this equilibrium, $\hat{p}$, is given by

$$\hat{p} \approx \frac{(1-w)S + wR - P}{(1-w)(T+S-R) + wR - P} \quad (3)$$

Thus as w increases, the equilibrium frequency of TF2T approaches one. For the parameter values used in Axelrod's tournaments, $\hat{p} = 0.9863$. Thus a population fixed for a nice, but intolerant morph (TIT FOR TAT) is replaced by a population which is a mixture of a nice, tolerant morph (TF2T) and a suspicious and somewhat exploitative morph (STFT). Finally, if w is large enough, ALLD can be invaded without population structure. For example, STFT can invade a population in which ALLD is common and in which TF2T is maintained by one-way mutation. Neither ALLD nor STFT are ever the first to cooperate; when paired they both defect during every interaction. Thus, their relative fitness depends on how each fares against TF2T. For w large enough, STFT has a higher expected payoff against TF2T than does ALLD, because STFT can be induced to cooperate whereas ALLD cannot. Thus, STFT can invade ALLD. The only stable equilibrium in this popuation is the mixture of TF2T and STFT given by equation (3). Although the results in this paragraph assume that rare variants are maintained by mutation, similar results obtain if rare variants are maintained by non-heritable phenotypic variation, or if they are due to repeated small perturbations in a model without mutation or phenotypic variation.

In fact, no strategy whose behaviour during interaction t is uniquely determined by the history of the game up to that point is evolutionarily stable if

$$w > \min[(T-R)/(T-P), (P-S)/(R-S)] \quad (4)$$

where min denotes the smaller of the two values in brackets. To prove this, let S_e be a collectively stable strategy and let S_1 be a distinct strategy which nonetheless behaves exactly the same way on each interaction with S_e as S_e does against itself. This implies that $V(S_1|S_e) = V(S_e|S_e) = V(S_e|S_1) = V(S_1|S_1)$. Thus, if a third strategy S_x exists in the population, S_e can be invaded by S_1 if $V(S_1|S_x) > V(S_e|S_x)$. Because S_e and S_1 are distinct, there must be some sequence of moves, A, during interactions $1, \ldots t-1$ such that S_e and S_1 react differently to S_x for the first time on move t. There are two possibilities. First, suppose S_e defects and S_1 cooperates on move t. Let S_2 be the strategy that generates the sequence A in response to both S_e and S_1, cooperates on move t, and then defects forever in response to defection by S_e and cooperates forever in response to cooperation by S_1 on move t. S_e can be invaded by S_1 whenever:

$$V(S_1|S_2) - V(S_e|S_2) \geq w^{t-1}(R-T) + w^t(R-P)/(1-w) > 0 \quad (5)$$

or $w > (T-R)/(T-P)$. Next, let S_3 be a strategy which behaves exactly like S_2 for the first $t-1$ moves, defects on move t, and then defects forever in response to S_e's defection and cooperates forever in response to cooperation by S_1 on move t. In this case S_e can be invaded by S_1 whenever $w > (P-S)/(R-S)$. The second possibility is that S_e cooperates and that S_1 defects on move t. A similar argument shows that S_e can be invaded by S_1 for any value of w. This result can be understood in terms of Axelrod's insight that if w is large enough, no strategy can be best against all opponents. When two strategies interact with each other the same way that they do with themselves, their relative fitness depends on their interactions with other strategies. Because neither strategy can be best against every possible third strategy, no pure strategy can resist invasion by any combination of strategies.

This result does not mean that nice, provokable, forgiving strategies like TFT cannot persist in real populations. In reality, mutation and phenotypic variation will not generate every possible combination of invading strategies. Thus, whether nice, provokable and forgiving strategies can persist at high frequency in real populations will depend on the actual mix of rare non-nice strategies maintained in the population by mutation and phenotypic variation. For example, consider a population in which TFT is common, and STFT and ALLD are maintained by mutation. If the frequency of ALLD is low relative to STFT at mutation-selection equilibrium, TF2T can invade such a population. If, on the other hand, ALLD is relatively more common, TF2T cannot invade. Thus, TFT may or may not persist depending on the relative rates at which mutation creates the two non-nice variants. More generally our results suggest that the nature of the selective forces that shape ongoing, potentially altruistic social interactions depends on the distribution of rare variants that are created by mutation, environmental variation and other processes that maintain phenotypic variation. Although it seems likely that cooperative strategies will predominate when ongoing interactions persist over long periods of time, the nature of the contingent strategies that enforce this cooperation may depend on the kinds of non-adaptive varation that are present.

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Adjuvant-free IgG responses induced with antigen coupled to antibodies against class II MHC

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The generation of strong serological responses to protein antigens in experimental animals usually requires the use of potent adjuvants, most of which cannot be used in human or veterinary vaccines because of deleterious side effects[1,2]. Attempting to circumvent this problem, we have assessed an adjuvant-free antigen-delivery system based on the hypothesis that antigen coupled to monoclonal antibodies (mAbs) specific for class II major histocompatibility complex (MHC) determinants should be 'targeted' onto antigen-presenting cells, thus facilitating recognition by helper T cells[3]. We found that the biotin-binding protein avidin[4] could generate a serological response in mice, without adjuvant, when injected coupled to a biotinylated anti-class II MHC mAb. Equivalent amounts of avidin mixed with the non-biotinylated form of the same mAb failed to elicit a response. A targeting effect was demonstrated at low levels of injected conjugate because only mice bearing the appropriate class II antigens responded. Responses were also seen with a protein antigen other than avidin, offering a new, adjuvant-free approach to subunit vaccine construction.

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