IMMUNE EVASION AND THE EVOLUTION OF MOLECULAR MIMICRY IN PARASITES

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This Appendix has three parts. In Appendix A, we show that the evolutionarily stable parasite phenotype maximizes R_0. In Appendix B, we show that equation (14) is the general form of the parasite ESS under the costly autoimmunity hypothesis (for the mimicry trade-off hypothesis, a complete justification for the general form of the parasite ESS is provided in the main text). In Appendix C, we describe the numerical methods used to generate Figs. 3–5.

Appendix A

In the main article, we claim that the parasite phenotype that maximizes
$R_0 = (1-q)R_U + pqR_A + (1-p)qR_I$ is evolutionarily stable. Our assumption is that new mutations arise rarely relative to the spread of infections and so there are never more than two different parasite phenotypes spreading in the host population. The two different parasite phenotypes are: the mutant (variables for hosts infected by a mutant parasite are denoted by the subscript m), and the resident (no subscript). The rate of change in the numbers of hosts in each of these different epidemiological states are,

$$
\begin{aligned}
\frac{dS}{dt} &= -(\Lambda + \Lambda_m)S + b_S S + b_I(I + I_m) + b_A(A + A_m) + b_U(U + U_m) + b_R(R + R_m) \\
&\quad + b_Z(Z + Z_m) + \gamma_I(I + I_m) + \gamma_A(A + A_m) - dS, \tag{A.1}
\end{aligned}
$$

$$
\frac{dR}{dt} = u_I I - dR, \tag{A.2}
$$

$$
\frac{dZ}{dt} = u_A A - v_Z Z - dZ, \tag{A.3}
$$

$$
\frac{dR_m}{dt} = u_I I_m - dR_m, \tag{A.4}
$$

$$
\frac{dZ_m}{dt} = u_A A_m - v_Z Z_m - dZ_m, \tag{A.5}
$$

$$
\frac{dI}{dt} = \Lambda S(1-p)q - v_I I - \gamma_I I - u_I I - dI, \tag{A.6}
$$

$$
\frac{dA}{dt} = \Lambda S p q - v_A A - \gamma_A A - u_A A - dA, \tag{A.7}
$$

$$
\frac{dU}{dt} = \Lambda S(1-q) - v_U U - dU, \tag{A.8}
$$

$$
\frac{dI_m}{dt} = \Lambda_m S(1-p_m)q_m - v_I I_m - \gamma_I I_m - u_I I_m - dI_m, \tag{A.9}
$$

$$
\frac{dA_m}{dt} = \Lambda_m S p_m q_m - v_A A_m - \gamma_A A_m - u_A A_m - dA_m, \tag{A.10}
$$

$$
\frac{dU_m}{dt} = \Lambda_m S(1-q_m) - v_U U_m - dU_m. \tag{A.11}
$$

Invasion fitness is the number of secondary infections generated by a mutant strain arising in the monomorphic resident population at equilibrium (Hurford et al. 2010). The forces of infection from hosts infected with the resident and the mutant parasite are $\Lambda = \beta_I I + \beta_A A + \beta_U U$ and $\Lambda_m = \beta_I I_m + \beta_A A_m + \beta_U U_m$, respectively. It can be shown that the system of equations (A.1)-(A.11) has a mutant-free equilibrium, where the values of the resident variables at the mutant free equilibrium are $\hat{S}, \hat{I}, \hat{A}, \hat{U}, \hat{Z}$ and $\hat{R}$ and no hosts are infected by mutant parasites.

Note that equations (A.1)-(A.11) track the dynamics of hosts, while our question of interest centers only around understanding the spread of the parasite. Therefore, we need only to consider the dynamics of infectious hosts (i.e., see van den Driessche and Watmough 2002). This corresponds to the dynamical system given by equations (A.6)-(A.11), but where the mutant-free equilibrium values of $\hat{S}, \hat{I}, \hat{A}, \hat{U}, \hat{Z}$ and $\hat{R}$ are determined by the full dynamical system (equations (A.1)-(A.11)).

The Jacobian matrix of the reduced dynamical system (equations (A.6)-(A.11)) evaluated at the mutant-free equilibrium is of the form,

$$\mathbf{J} = \left[\begin{array}{c|c} \mathbf{J}_{res} & \mathbf{S} \\ \hline \mathbf{0} & \mathbf{J}_{mut} \end{array} \right], \tag{A.12}$$

where $\mathbf{J}_{mut}$ is,

$$\left[\begin{array}{ccc} (1-p_m)q_m\beta_I\hat{S} - v_I - u_I - \gamma_I - d & (1-p_m)q_m\beta_A\hat{S} & (1-p_m)q_m\beta_U\hat{S} \\ p_mq_m\beta_I\hat{S} & p_mq_m\beta_A\hat{S} - v_A - u_A - \gamma_A - d & p_mq_m\beta_U\hat{S} \\ (1-q_m)\beta_I\hat{S} & (1-q_m)\beta_A\hat{S} & (1-q_m)\beta_U\hat{S} - v_U - d \end{array} \right] \tag{A.13}$$

with $\hat{\Lambda} = \beta_I\hat{I} + \beta_A\hat{A} + \beta_U\hat{U}$. It can be verified that there are conditions for which $s(\mathbf{J}_{res}) < 0$ (where $s(\cdot)$ is the spectral bound), and so then the stability of the mutant-free equilibrium is given by the leading eigenvalue of $\mathbf{J}_{mut}$. The leading eigenvalue of $\mathbf{J}_{mut}$ has the same sign as $\rho(\mathbf{FV}^{-1}) - 1$ (van den Driessche and Watmough 2002; Hurford et al. 2010; where $\rho(\cdot)$ is the spectral radius). In choosing,

$$\mathbf{F} = \left[\begin{array}{ccc} (1-p_m)q_m\beta_I\hat{S} & (1-p_m)q_m\beta_A\hat{S} & (1-p_m)q_m\beta_U\hat{S} \\ p_mq_m\beta_I\hat{S} & p_mq_m\beta_A\hat{S} & p_mq_m\beta_U\hat{S} \\ (1-q_m)\beta_I\hat{S} & (1-q_m)\beta_A\hat{S} & (1-q_m)\beta_U\hat{S} \end{array} \right], \tag{A.14}$$

and

$$\mathbf{V} = \left[\begin{array}{ccc} v_I + u_I + \gamma_I + d & 0 & 0 \\ 0 & v_A + \gamma_A + u_A + d & 0 \\ 0 & 0 & v_U + d \end{array} \right]. \tag{A.15}$$

Then, the expression for invasion fitness is given by,

$$\begin{aligned} w(p, q, p_m, q_m) &= \rho(\mathbf{FV}^{-1}) - 1, \\ &= R_I\hat{S}(1-q_m)p_m + R_A\hat{S}p_mq_m + R_U\hat{S}(1-q_m) - 1, \end{aligned} \tag{A.16}$$

where R_i denotes the number of secondary infections generated by an infection of type i per susceptible host, and $w(p, q, p_m, q_m) + 1$ is the expected number of secondary infections where the expectation is taken over all disease types. The quantity $\hat{S}$ is the equilibrium number of susceptible hosts at the mutant-free equilibrium, and the resident traits, p and q, enter the expression for invasion fitness (equation (A.16)) through $\hat{S}$. The expression for $\hat{S}$ can either be calculated explicitly by setting equations (A.1)-(A.11) equal to zero, or by solving $w(p, q, p, q) = 0$ for $\hat{S}$. As such,

$$\hat{S} = \frac{1}{R_I(1-q)p + R_Apq + R_U(1-q)}. \tag{A.17}$$

Substituting equation (A.17) into equation (A.16),

$$\begin{aligned} w(p, q, p_m, q_m) &= R_I(1-q_m)p_m + R_Ap_mq_m + R_U(1-q_m) - R_I(1-q)p - R_Apq \\ &\quad - R_U(1-q), \\ &= R_0(p_m, q_m) - R_0(p, q). \end{aligned} \tag{A.18}$$

When equation (A.18) is positive the mutant can invade, and so we conclude that the parasite phenotype that maximizes R_0 (equation (2)) is evolutionarily stable.

Appendix B

In this Appendix we prove that equation (14) is the general form of the parasite ESS. For continuity in this section, we begin by restating the constrained optimization problem that describes the parasite ESS

under the costly autoimmunity hypothesis. Specifically, the parasite ESS is $\vec{\alpha}^*$, the vector which maximizes R_0 where,

$$R_0(\vec{\alpha}) = R_U + (R_I - R_U)(1 - (1 - \sum_{j=1}^{k} \alpha_j \omega(\Delta_j))^r) + (R_A - R_I)(1 - (1 - \sum_{j=1}^{k} \alpha_j \Delta_j \omega(\Delta_j))^r). \qquad \text{(B.1)}$$

In this Appendix, $\omega(\Delta_j) = \omega_j$, where $\omega(\Delta)$ is a continuously differentiable decreasing function, where Δ is a continuous variable, and where Δ_j refers to particular values of Δ. The constraint is that antigenicity is fixed (equation (11)), and that the elements of $\vec{\alpha}$ are probabilities such that $\vec{\alpha}^* \in S$, where,

$$S := \{\vec{\alpha} \in \mathbb{R}^k \text{ for } k < \infty \quad | \quad \frac{1}{k} \sum_{j=1}^{k} \alpha_j = c \text{ and } \alpha_j \in [0,1] \text{ for all } j\}, \qquad \text{(B.2)}$$

with $c \in \{1/k, 2/k, \ldots, 1\}$. Finally, we define the selection gradient as follows:

Definition. *The selection gradient is a vector of partial derivatives,*

$$\vec{\nabla} R_0 = \left[\frac{\partial R_0}{\partial \alpha_1}, \frac{\partial R_0}{\partial \alpha_2}, \cdots, \frac{\partial R_0}{\partial \alpha_k} \right], \qquad \text{(B.3)}$$

where,

$$\frac{\partial R_0}{\partial \alpha_j} = -r(R_U - R_I)(1 - \bar{\alpha})^{r-1} \omega(\Delta_j) - r(R_I - R_A)(1 - \overline{\alpha\Delta})^{r-1} \Delta_j \omega(\Delta_j), \qquad \text{(B.4)}$$

such that $\bar{\alpha} = \sum_{j=1}^{k} \alpha_j \omega(\Delta_j)$ and $\overline{\alpha\Delta} = \sum_{j=1}^{k} \alpha_j \Delta_j \omega(\Delta_j)$.

The proof of Theorem 1 is the proof that the general form of the parasite ESS under the costly autoimmunity hypothesis is given by equation (14). Theorem 1 assumes that Lemmas 1 and 2 hold. We will now prove these Lemmas.

Lemma 1. *For any given sequence of ω_j, let $\omega(\Delta)$ be a continuously differentiable decreasing function of Δ with $\omega_j = \omega(\Delta_j)$ and $\sum_{j=1}^{k} \omega(\Delta_j) = 1$, where the Δ_j are given by equation (6). Let $\Delta + \frac{\omega(\Delta)}{\omega'(\Delta)}$ be monotonically increasing, and let $R_U > R_I > R_A \geq 0$. Then, the elements of the selection gradient (equation (B.3)), from the first element to the kth element, form a sequence that either monotonically increases, monotonically decreases, or decreases and then increases.*

Proof. Let,
$$s(\Delta) = -r(R_U - R_I)(1 - \bar{\alpha})^{r-1} \omega(\Delta) - r(R_I - R_A)(1 - \overline{\alpha\Delta})^{r-1} \Delta\omega(\Delta), \qquad \text{(B.5)}$$

such that $\frac{\partial R_0}{\partial \alpha_j} = s(\Delta_j)$, and where the definitions of $\bar{\alpha}$ and $\overline{\alpha\Delta}$ are unchanged. Therefore, for all Δ_j, $s(\Delta)$ and $\vec{\nabla} R_0$ (equation (B.4)) are equal, so that $s(\Delta)$ is a continuous function that interpolates between the elements of the vector, $\vec{\nabla} R_0$. The function $s(\Delta)$ will be differentiated with respect to Δ to understand whether $s(\Delta_j)$ is an increasing or decreasing sequence for ascending values of j.

Dividing the righthand side of equation (B.5) by $r(R_U - R_I)(1 - \bar{\alpha})^{r-1} > 0$, then,

$$s(\Delta) \propto -\omega(\Delta) - \frac{\eta\phi}{1 - \phi} \Delta\omega(\Delta), \qquad \text{(B.6)}$$

where $0 \leq \eta = \frac{(1 - \overline{\alpha\Delta})^{r-1}}{(1 - \bar{\alpha})^{r-1}}$ and $0 < 1 - \phi = 1 - \frac{R_U - R_I}{R_U - R_A} < 1$. Differentiating with respect to Δ and dividing by $-\omega'(\Delta) > 0$,

$$\sigma(\Delta) = 1 + \frac{\eta\phi}{1 - \phi} \left(\Delta + \frac{\omega(\Delta)}{\omega'(\Delta)} \right). \qquad \text{(B.7)}$$

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Since all division has been by positive values, the sign of the derivative of $s(\Delta)$ (equation (B.5)) with respect to Δ is given by equation (B.7). The term $\frac{\phi}{1-\phi}$ is positive and $\frac{\omega(0)}{\omega'(0)} \leq 0$. Therefore, the sign of $\sigma(\Delta)$ is given by one of the following three cases:

Case 1. If $\sigma(0) > 0$, then because $\Delta + \frac{\omega(\Delta)}{\omega'(\Delta)}$ is monotonically increasing, $\sigma(\Delta) > 0$ for all Δ, and so given the sign of $\sigma(\Delta)$, $s(\Delta)$ an increasing function.

Case 2. If $\sigma(0) < 0$, then as $\Delta + \frac{\omega(\Delta)}{\omega'(\Delta)}$ increases with increasing Δ, $\sigma(\Delta)$ may become positive. Then, given the sign of $\sigma(\Delta)$, $s(\Delta)$ has a minimum.

Case 3. If $\sigma(0) < 0$, then $\sigma(\Delta)$ may be negative for all Δ. Then, $s(\Delta)$ is a decreasing function of Δ.

Our understanding of the shape of $s(\Delta)$ is then used to understand the shape of $s(\Delta_j)$. When $s(\Delta)$ is an increasing (decreasing) function of Δ on $[0, 1]$, then $s(\Delta_j)$ is an increasing (decreasing) sequence, and so the elements of the selection gradient progressively increase (decrease). When $s(\Delta)$ has a minimum on $[0, 1]$, then the elements of the selection gradient produce a sequence that decreases, and then increases with increasing j. $\qquad\square$

A first consequence of Lemma 1 is that all the elements of the vector $\vec{\alpha}^*$ are either zero or one (except under exceptional circumstances), which can be shown using the Karash-Kuhn-Tucker Theorem.

Karash-Kuhn-Tucker Theorem (Johannes 1996; Theorem 5.8). *Let the objective function $f : \mathbb{R}^n \to \mathbb{R}$ and the constraint functions $g : \mathbb{R}^n \to \mathbb{R}^m$ and $h : \mathbb{R}^n \to \mathbb{R}^p$ be given. Let the constraint set S which is assumed to be nonempty be given as*

$$S := \{x \in \mathbb{R}^n \quad | \quad g_i(x) \leq 0 \quad \text{for all } i \in \{1, \cdots, m\} \text{ and}$$
$$h_i(x) = 0 \quad \text{for all } i \in \{1, \cdots, p\}\}.$$

Let $\bar{x} \in S$ be a maximum point of f on S. Let f and g be differentiable at $\bar{x}$ and let h be continuously differentiable at $\bar{x}$. Moreover, let the following regularity assumption be satisfied: Assume that there is a vector $x \in \mathbb{R}^n$ with

$$\nabla g_i(\bar{x})^T x < 0 \quad \text{for all } i \in I(\bar{x})$$

and

$$\nabla h_i(\bar{x})^T x = 0 \quad \text{for all } i \in \{1, \cdots, p\},$$

and that the vectors $\nabla h_1(\bar{x}), \cdots, \nabla h_p(\bar{x})$ are linearly independent. Here let,

$$I(\bar{x}) := \{i \in 1, \cdots, m \quad | \quad g_i(\bar{x}) = 0\}$$

denote the index set of the inequality constraints which are 'active' at $\bar{x}$. Then there are multipliers $u_i \geq 0 \ (i \in I(\bar{x}))$ and $v_i \in \mathbb{R} \ (i \in \{1, \cdots, p\})$ with the property

$$\nabla f(\bar{x}) + \sum_{i \in I(\bar{x})} u_i \nabla g_i(\bar{x}) + \sum_{i=1}^{p} v_i \nabla h_i(\bar{x}) = 0_{\mathbb{R}^n}. \tag{B.8}$$

The Karash-Kuhn-Tucker Theorem is unchanged if $\bar{x}$ is a minimum or maximum point. In Lemma 2, we apply the Karash-Kuhn-Tucker Theorem using the same notation as above, to show that $\alpha_j^* = 0$ or 1.

Lemma 2. *Let the elements of the selection gradient (equation (B.3)), from the first element to the kth element, form a sequence that either monotonically increases, montonically decreases, or decreases and then increases, where the Δ_j are given by equation (6). Let $\vec{\alpha}^*$ maximize $R_0(\vec{\alpha})$ (equation (B.1)) given the constraints $g_j(\vec{\alpha}) = -\alpha_j \leq 0$, $g_{k+j}(\vec{\alpha}) = \alpha_j - 1 \leq 0$ (for j from 1 to k), and $h(\vec{\alpha}) = \frac{1}{k}\sum_{i=1}^{k} \alpha_j - c = 0$ where $c \in \{1/k, 2/k, \ldots, 1\}$. Then, $\alpha_j^* = 0$ or 1 for all j, where α_j^* are the elements of the vector $\vec{\alpha}^*$, except for a specific case of the parameters that determine R_0 and the constraint. Then, for the specific case, $0 < \alpha_j < 1$ for at most two j values.*

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Proof. The proof is completed by showing that if $\alpha_j^* \in (0,1)$ then the Karash-Kuhn-Tucker Theorem (equation (B.8)) is contradicted, and so $\alpha_j^* = 0$ or 1. For $\alpha_j^* \in (0,1)$, the inequality constraints $g_j(\vec{\alpha})$ are inactive. Then, the condition (equation (B.8)) that the maximal point, $\vec{\alpha}^*$, must satisfy is,

$$\frac{\partial R_0}{\partial \alpha_j} - v \frac{\partial h}{\partial \alpha_j} = \frac{\partial R_0}{\partial \alpha_j} - \frac{v}{k} = 0 \qquad \text{for all } j \text{ such that } \alpha_j^* \in (0,1), \tag{B.9}$$

where $v \in \mathbb{R}$ and where the addition sign between the two terms in equation (B.8) is replaced with a subtraction sign because v may be either positive or negative and so the change to a subtraction sign does not affect the equation. Note that $\frac{\partial R_0}{\partial \alpha_j}$ is an increasing or decreasing sequence, or a sequence that switches from increasing to decreasing only once (Lemma 1), and v is a constant. Therefore, equation (B.9) can only hold for at most two α_j^*.

The value of v can be determined from the equality constraint, $h(\vec{\alpha})$, and equation (B.9). Integrating the equation (B.9) with respect to α_j from 0 to α_j^*, and then summing over all j,

$$\sum_{j=1}^{k} \int_0^{\alpha_j^*} \frac{\partial R_0}{\partial \alpha_j} \, d\alpha_j - \sum_{j=1}^{k} \int_0^{\alpha_j^*} \frac{v}{k} \, d\alpha_j = 0,$$

$$kR_0 - \frac{v}{k} \sum_{j=1}^{k} \alpha_j^* = 0. \tag{B.10}$$

where the R_0 in equation (B.10) is evaluated at α_j^*. Applying the equality constraint, $h(\vec{\alpha})$, then adding vc to both sides,

$$kR_0 = vc, \tag{B.11}$$

and so, $v = \frac{kR_0}{c}$ (this is the same sequence of calculations that were used in Iwasa and Haccou (1994) where following equation (7b) it is determined that $\lambda = 1$). Substituting this value of v into equation (B.9),

$$\frac{\partial R_0}{\partial \alpha_j} + \frac{kR_0}{c} = 0 \qquad \text{for all } j \text{ such that } \alpha_j^* \in (0,1). \tag{B.12}$$

It is then highly unlikely that any of the elements in the sequence $\frac{\partial R_0}{\partial \alpha_j}$ are equal to $\frac{kR_0}{c}$, however, if equation (B.12) is satisfied, it holds for at most two values of j. Since k is large, that at most 2 of the k α_j values are not equal to 0 or 1, is minor in terms of the general structure of $\vec{\alpha}^*$, and in terms of the numerical values of p or q. Furthermore, equation (B.12) is only satisfied for special cases of the parameters, and this is considered to be a trivial circumstance. $\qquad \square$

One problem with applying the Karash-Kuhn-Tucker Theorem in Lemma 2 is that R_0 must be continuously differentiable at $\vec{\alpha}^*$, and we have now determined that the parasite ESS is on the boundary of the range of the function R_0 as this function has been discussed so far. However, this is because the discussion of R_0 has been within the range of $\vec{\alpha}$ that is biologically meaningful ($0 \le \alpha_j \le 1$). Mathematically, the function R_0 is defined for negative $\vec{\alpha}$ and so for the purposes of the technical argument, R_0 is continuously differentiable at $\vec{\alpha}^*$.

Thereom 1. *For any given sequence of ω_j, let $\omega(\Delta)$ be a continuously differentiable decreasing function of Δ with $\omega_j = \omega(\Delta_j)$ and $\sum_{j=1}^{k} \omega(\Delta_j) = 1$, where the Δ_j are given by equation (6). Let $\Delta + \frac{\omega(\Delta)}{\omega'(\Delta)}$ be monotonically increasing, let $R_U > R_I > R_A \ge 0$, and let S be the set of all vectors $\vec{\alpha}$, such that $0 \le \alpha_j \le 1$ are the elements of $\vec{\alpha}$, where $\frac{1}{k} \sum_{j=1}^{k} \alpha_j = c$ with $k < \infty$ (equation (B.2)). Then, the $\vec{\alpha}^* \in S$ that maximizes $R_0(\vec{\alpha})$ (equation (B.1)) is of the general form given by equation (14).*

Proof. To prove the theorem, we will show that strategies of the form (equation (14)) are local maxima, knowing that the global maximum must satisfy the conditions for a local maxima. Let,

$$\alpha_j^* = \begin{cases} 1 & \text{for } \Delta_j \in \Omega, \\ 0 & \text{for } \Delta_j \in \Omega^c, \end{cases} \tag{B.13}$$

where $\Omega = [0, x^*] \cup (1 - c + x^*, 1]$, $\Omega^c = [x^*, 1 - c + x^*]$ and $x^* \in \{0, 1/k, 2/k, \ldots, c\}$, such that x^* is chosen so that Ω corresponds to the least negative values of the selection gradient (equation (B.3)). Define $\vec{\alpha}$ to be a small change to $\vec{\alpha}^*$, at $\alpha_m \in \Omega$ and $\alpha_n \in \Omega^C$, such that $\alpha_m = 0$ and $\alpha_n = 1$, and $\vec{\alpha} = \vec{\alpha}^*$ for all $j \neq m, n$. Therefore, $\vec{\alpha}$ is constructed by making a small change to $\vec{\alpha}^*$, while ensuring that $\vec{\alpha}$ still satisfies the constraints (i.e., is an element of S). Writing $R_0(\vec{\alpha})$ as a Taylor series expansion in the α_j at $\vec{\alpha}^*$,

$$R_0(\vec{\alpha}) = R_0(\vec{\alpha}^*) + \sum_{j=1}^k \frac{\partial R_0}{\partial \alpha_j}\bigg|_{\alpha_j = \alpha_j^*} (\alpha_j - \alpha_j^*) + O((\alpha_j - \alpha_j^*)(\alpha_i - \alpha_i^*)). \tag{B.14}$$

If the change made to $\vec{\alpha}^*$ is small then the higher order terms can be ignored. As such, the condition for a vector $\vec{\alpha}$ to be a local maximum is that,

$$\sum_{j=1}^k \frac{\partial R_0}{\partial \alpha_j}\bigg|_{\alpha_j = \alpha_j^*} (\alpha_j - \alpha_j^*), \tag{B.15}$$

is maximized. By construction equation (B.13) maximizes equation (B.15), and so, $\vec{\alpha}^*$ as described by this equation is a local maximum. A global maximum must also be a local maximum, and since all local maxima have the form equation (B.13), it follows that the global maximum must have the form described by equation (B.13). As such, we have shown that equation (B.13) is a necessary condition for $\vec{\alpha}^*$. □

This completes the proof of the general form of the parasite ESS under the costly autoimmunity hypothesis. A condition for Theorem 1 to apply is that $\Delta + \frac{\omega(\Delta)}{\omega'(\Delta)}$ is monotonically increasing. This assumption arose because obvious choices of $\omega(\Delta)$, for example, $\omega(\Delta) = \frac{a(n+1)}{(1+(1-a)^n(a-1))(k-1)}(1 - a\Delta)^n$ and $\omega(\Delta) = \frac{a}{(k-1)(1-e^{-a})}e^{-a\Delta}$ (where $a > 0$ and n and k are positive integers) had this property.

Under the mimicry trade-off hypothesis, the general form of the parasite ESS is justified in equation (15) and the subsequent text.

Appendix C

Equation (14) does not fully characterize $\vec{\alpha}^*$ because the value of x^* is unknown, and furthermore, satisfying equation (B.13) is only a necessary, but not a sufficient condition for $\vec{\alpha}^*$. To understand the numerical methods that were used to identify the parasite ESSs, recall that in the initial statement of the problem we knew only that $\vec{\alpha}^*$ must satisfy the constraint (equation (4)). Following Theorem 1, we had shown that $\vec{\alpha}^*$ has a general form, such that now the optimization problem is computationally tractable, because the number of vectors $\vec{\alpha}$ that satisfy this general form is quite few. R_0 is then evaluated for each of the $\vec{\alpha}$ that satisfy the general form (equation (14)) and of these the $\vec{\alpha}$ that correspond to the largest R_0 are $\vec{\alpha}^*$.

More specifically, the initial problem was to find an $\vec{\alpha} \in S$ that maximizes R_0, where S is the set of all vectors with elements $0 \leq \alpha_j \leq 1$ and where $\frac{1}{k}\sum_{i=1}^k \alpha_i = c$ (equation (B.2)). This set, S, is uncountably infinite, and so it is not possible to evaluate R_0 for all the $\vec{\alpha}$. Following Lemma 2, we had shown that all the elements of $\vec{\alpha}^*$ are either zero or one. We also know that kc of these α_j are equal to one (for the constraint to be satisfied). Proving this Lemma represents substantial progress because there are now $\binom{k}{kc}$

possible $\vec{\alpha}$ that satisfy the necessary properties of $\vec{\alpha}^*$. Finally, following the proof of Theorem 1, we know that the general shape of $\vec{\alpha}^*$ must satisfy,

$$\alpha_j = \begin{cases} 1 & \text{for } \Delta_j \in \Omega, \\ 0 & \text{for } \Delta_j \in \Omega^c, \end{cases} \tag{C.1}$$

where $\Omega = [0, x) \cup (1 - c + x, 1], \Omega^c = [x, 1 - c + x]$ and $x \in \{0, 1/k, 2/k, \ldots, c\}$. There are $ck + 1$ vectors that satisfy equation (C.1). R_0 is evaluated for each of these vectors, and of these the one(s) that give the largest value of R_0 are identified as $\vec{\alpha}^*$. The results of this numerical search suggest that $\vec{\alpha}^*$ is unique, however this is not something that we have proven.

Under the mimicry trade-off hypothesis, equation (16) does not fully characterize $\vec{\alpha}^*$ either because z^* is unknown. For the mimicry trade-off hypothesis, a similar numerical procedure was used to identify the parasite ESSs. Initially, all the α_j where $z_j > 0$ were set equal to 1, and R_0 was evaluated. Then, sequentially, for increasing j where $z_j > 0$, α_j was set to 0 and R_0 was re-evaluated. For example, if $z_1 = z_3 = z_4 = 1$, and $z_2 = 0$, then the sequence of $\vec{\alpha}$ values for which R_0 is evaluated is: $[1, 0, 1, 1]$, $[0, 0, 1, 1]$, $[0, 0, 0, 1]$ and $[0, 0, 0, 0]$. Finally, after evaluating R_0 for all the $\vec{\alpha}$ of the general form (16), $\vec{\alpha}^*$ is identified as the $\vec{\alpha}$ that gives the largest value of R_0.

Computer code to generate Figs. 3-5 is publicly available (Hurford and Day 2013). For Figs. 3-5, the parameters and functions used were $r = 100$, $\omega_j = \frac{3a}{k + k(1-a)^2(a-1)}(1 - a\Delta_j)^2$ and $\beta[f(\chi(\vec{\alpha}), \theta_i)] = \chi(\vec{\alpha})/\theta_i$. For Fig. 3A-D, $R_U = 3$, $R_I = 1$, $R_A = 0$, $c = 0.1$, $a = 0.01$ (A,C) and $a = 1$ (B,D). For Fig. 3E-H, $R_U = 3\chi(\vec{\alpha})$, $R_I = \chi(\vec{\alpha})$, $a = 0.01$ (E,G) and $a = 0.8$ (F,H). Fig. 3 was constructed to show the parasite ESS for two different fixed values of τ (i.e., the left and right columns) and Fig. 4 was constructed to show how the ESSs change as ϕ, ψ and τ change. In Fig. 4, when ϕ is on the x-axis, R_I ranges from 0 to 3 by 0.1 with $a = 0.8$, $R_U = 3$ and $R_A = 0$. When ψ is on the x-axis all the same parameters and functions are used, but $R_U/\chi(\vec{\alpha})$ ranges from 0 to 3 by 0.1 and $R_I = \chi(\vec{\alpha})$. When τ is on the x-axis, a ranges from 0.01 to 1 by 0.01 with $R_U = 3$, $R_I = 1$ and $R_A = 0$ (A-D) or $R_U = 3\chi(\vec{\alpha})$ and $R_I = \chi(\vec{\alpha})$ (E-H). For Fig. 5 exactly the same parameters and functions are used as for Fig. 4.

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