Appendix A: Finding evolutionarily stable parasite life history strategies

Analysis of the classic non-nested model

The combined Rosenzweig-MacArther, SI model has the following form, assuming that transmission rate β is an unspecified function of virulence v:

$$\begin{aligned}
\frac{\mathrm{dR}}{\mathrm{dt}} &= \rho\, R(t)\left(1-\frac{R(t)}{K}\right)-\frac{f\,R(t)}{h+R(t)}\,(S(t)+Q(t)+Q_m(t)),\\
\frac{\mathrm{dS}}{\mathrm{dt}} &= e\,\frac{f\,R(t)}{h+R(t)}\,(S(t)+Q(t)+Q_m(t))-d\,S(t)\\
&\qquad -(\beta(v)\,Q(t)+\beta(v_m)\,Q_m(t))\,S(t),\\
\frac{\mathrm{dQ}}{\mathrm{dt}} &= \beta(v)\,S(t)\,Q(t)-(d+v)\,Q(t),\\
\frac{\mathrm{dQ}_m}{\mathrm{dt}} &= \beta(v_m)\,S(t)\,Q_m(t)-(d+v_m)\,Q_m(t).
\end{aligned}$$

Whether the mutant parasite can invade depends on its growth rate from rarity (i.e., when $Q_m(t) \approx 0$), when the system with the resident parasite only has reached its asymptotic dynamics.

If the resident-only system goes to an equilibrium, $\left(\hat{R},\, \hat{S},\, \hat{Q}\right)$, the mutant can invade if $\beta(v_m)\,\hat{S}-(d+v_m)>0$. Note that this condition can be rewritten as $\frac{\beta(v_m)}{d+v_m}>\frac{1}{\hat{S}}$. From $\frac{\mathrm{dQ}}{\mathrm{dt}}=0$, this equilibrium is $\hat{S}=\frac{(d+v)}{\beta(v)}$, so the mutant can invade if $\frac{\beta(v_m)}{d+v_m}>\frac{\beta(v)}{d+v}$. Thus evolution will tend to maximize lifetime transmission potential.

If the resident-only system reaches a stable limit cycle with period T, the mutant can invade if $\frac{1}{T}\int_0^T(\beta\,(v_m)\,S(t)-(d+v_m))\,\mathrm{dt}>0$. This can be written as $\beta\,(v_m)\left(\frac{1}{T}\int_0^T S(t)\,\mathrm{dt}\right)-(d+v_m)=\beta(v_m)\,\overline{S}-(d+v_m)>0$, where $\overline{S}$ is the average density of susceptible hosts over the limit cycle. Over the resident-only limit cycle, it must be the case that the per-capita growth rate of infected hosts is 0, that is, $\frac{1}{T}\int_0^T(\beta(v)\,S(t)-(d+v))\,\mathrm{dt}=\beta(v)\left(\frac{1}{T}\int_0^T S(t)\,\mathrm{dt}\right)-(d+v)=0$. This allows us to write $\overline{S}=\frac{(d+v)}{\beta(v)}$. Thus the mutant can invade if $\frac{\beta(v_m)}{d+v_m}>\frac{\beta(v)}{d+v}$, an identical condition to the equilibrium case. This implies that evolution will lead to the same strategy, regardless of the system dynamics.

We can determine this strategy by finding the value of v that maximizes $\frac{\beta(v)}{d+v}$. Taking the derivative of this expression and setting equal to zero, the strategy that maximizes transmission must satisfy $\beta'\,(v)\,(d+v)-\beta(v)=0$. Assuming $\beta(v)=\frac{\beta_0\,v}{1+v}$, the transmission-maximizing v must satisfy $\frac{\beta_0(d-v^2)}{(1+v)^2}=0$, which implies that $v=\sqrt{d}$.

Another way to arrive at the same conclusion is to more explicitly follow the adaptive dynamics approach (Geritz et al. 1997). Letting the invasion fitness $r_m=\beta(v_m)\,\hat{S}-(d+v_m)$ (the equilibrium case) or $r_m=\beta(v_m)\,\overline{S}-(d+v_m)$ (the limit cycle case), possible evolutionarily stable (ES) strategies are given by values of v_m that satisfy $\left(\frac{\mathrm{dr}_m}{\mathrm{dv}_m}\right)_{v_m=v}=0$, where $\left(\frac{\mathrm{dr}_m}{\mathrm{dv}_m}\right)_{v_m=v}$ is the fitness gradient evaluated at the resident strategy. Values of v that cause the fitness gradient to vanish are termed ‘singular strategies’. For the equilibrium case, $\left(\frac{\mathrm{d}r_m}{\mathrm{d}v_m}\right)_{v_m=v} = \beta'(v)\,\hat{S} - 1 = 0$; for the limit cycle case, $\left(\frac{\mathrm{d}r_m}{\mathrm{d}v_m}\right)_{v_m=v} = \beta'(v)\,\overline{S} - 1 = 0$. Since the equilibrium and average densities of susceptible hosts are identical $\left(\hat{S} = \overline{S} = \frac{(d+v)}{\beta(v)}\right)$, we arrive at the expression $\beta'(v)\,(d+v) - \beta(v) = 0$ for the singular strategies, proving that $v = \sqrt{d}$ is a singular strategy. We can further show that this singular strategy is evolutionarily stable by looking at the sign of the second derivative $\left(\frac{d^2 r_m}{\mathrm{d}v_m^{\,2}}\right)_{v_m=v} = \beta''(v)\,\hat{S}$ or $\left(\frac{d^2 r_m}{\mathrm{d}v_m^{\,2}}\right)_{v_m=v} = \beta''(v)\,\overline{S}$. Since $\beta''(v) < 0$ (transmission is a saturating function of virulence), the singular strategy $v = \sqrt{d}$ is guaranteed to be evolutionarily stable.

Analysis of the nested model

With the nested model, the population-level model is the same, but now transmission rate β and virulence v are both functions of the within-host burden $\hat{P}$.

$$
\begin{aligned}
\frac{\mathrm{dR}(t)}{\mathrm{dt}} &= \rho\, R(t)\left(1 - \frac{R(t)}{K}\right) - \frac{f\,R(t)}{h+R(t)}\,(S(t) + Q(t) + Q_m(t)),\\
\frac{\mathrm{dS}(t)}{\mathrm{dt}} &= e\,\frac{f\,R(t)}{h+R(t)}\,(S(t) + Q(t) + Q_m(t)) - d\,S(t)\\
&\quad -\left(\beta(\hat{P})\,Q(t) + \beta(\hat{P}_m)\,Q_m(t)\right) S(t),\\
\frac{\mathrm{dQ}(t)}{\mathrm{dt}} &= \beta(\hat{P})\,S(t)\,Q(t) - \left(d + v(\hat{P})\right) Q(t),\\
\frac{\mathrm{dQ}_m(t)}{\mathrm{dt}} &= \beta(\hat{P}_m)\,S(t)\,Q_m(t) - \left(d + v(\hat{P}_m)\right) Q_m(t).
\end{aligned}
$$

The within-host parasite burden is given by the equilibrium of this model, which models the interaction between within-host energy, E, host immune response, I, and parasites, P.

$$
\begin{aligned}
\frac{\mathrm{dE}(\tau)}{\mathrm{d}\tau} &= \frac{f\,R(t)}{h+R(t)} - r\,E(\tau) - a_B\,E(\tau) - a_I\,f_I\,E(\tau)\,I(\tau)\,P(\tau) - f_P\,E(\tau)\,P(\tau),\\
\frac{\mathrm{dI}(\tau)}{\mathrm{d}\tau} &= \frac{a_B\,E(\tau) + a_I\,f_I\,E(\tau)\,I(\tau)\,P(\tau)}{\epsilon_I} - m_I\,I(\tau),\\
\frac{\mathrm{dP}(\tau)}{\mathrm{d}\tau} &= \frac{f_P\,E(\tau)\,P(\tau)}{\epsilon_P} - f_I\,I(\tau)\,P(\tau) - m_P\,P(\tau).
\end{aligned}
$$

We assume that the resident and mutant parasites differ in their within-host exploitation rate, f_P, which sets up the differences in parasite burden between these two parasite strains. Thus equilibrium parasite burden can be written as a function of exploitation rate and the abundance of resources at time t: $\hat{P}(f_P, R(t))$.

For the mutant parasite to be able to invade when the system reaches a stable equilibrium, it must be the case that $\beta\left(\hat{P}\left(f_{\mathrm{Pm}}, \hat{R}\right)\right)\hat{S} - \left(d + v\left(\hat{P}\left(f_{\mathrm{Pm}}, \hat{R}\right)\right)\right) > 0$. Note that this can be rearranged, as in the non-nested case, to $\frac{\beta\left(\hat{P}\left(f_{\mathrm{Pm}},\hat{R}\right)\right)}{d+v\left(\hat{P}\left(f_{\mathrm{Pm}},\hat{R}\right)\right)} > \frac{1}{\hat{S}}$. From $\frac{\mathrm{dQ}}{\mathrm{dt}} = 0$, we have that $\hat{S} = \frac{d+v\left(\hat{P}\left(f_P,\hat{R}\right)\right)}{\beta\left(\hat{P}\left(f_P,\hat{R}\right)\right)}$, implying that the mutant can invade if its lifetime transmission potential exceeds that of the resident strain: $\frac{\beta\left(\hat{P}\left(f_{\mathrm{Pm}},\hat{R}\right)\right)}{d+v\left(\hat{P}\left(f_{\mathrm{Pm}},\hat{R}\right)\right)} > \frac{\beta\left(\hat{P}\left(f_P,\hat{R}\right)\right)}{d+v\left(\hat{P}\left(f_P,\hat{R}\right)\right)}$. Thus we again see that evolution will maximize lifetime transmission potential (or, equivalently, evolution will minimize the abundance of susceptible hosts at equilibrium). Assuming that $\beta(P) = \frac{\beta_0\,P}{\beta_h+P}$ and $v\,(P) = v_0\,P$, the value of f_P that maximizes $\frac{\beta\left(\hat{P}\left(f_P,\hat{R}\right)\right)}{d+v\left(\hat{P}\left(f_P,\hat{R}\right)\right)}$ must satisfy $\hat{P}\left(f_P,\ \hat{R}\right)=\sqrt{\beta_h\, d/v_0}$. In other words, the virulence is equal to $v_0\,\hat{P}=\sqrt{v_0\,\beta_h\,d}$; if $v_0\,\beta_h=1$, the evolutionarily stable virulence will be the same in the non-nested and nested model.

When the system cycles, the mutant parasite can invade if $r_m=\frac{1}{T}\int_0^T\left(\beta\left(\hat{P}(f_{\mathrm{Pm}},\ R(t))\right)S(t)-\left(d+v\left(\hat{P}(f_{\mathrm{Pm}},\ R(t))\right)\right)\right)\mathrm{dt}>0$. It is not possible to simplify this expression any further, as neither the transmission rate or virulence are constant over the cycle: as resources ($R(t)$) cycle, so will parasite burden $\hat{P}(f_{\mathrm{Pm}},\ R(t))$, leading to cycles in both transmission rate and virulence.

Any potential evolutionarily stable strategy must still satisfy the condition $\left(\frac{\mathrm{d}r_m}{\mathrm{d}v_m}\right)_{v_m=v}=0$. For the cycling population, these singular strategies are values of f_P such that the fitness gradient vanishes: $\left(\int_0^T\left(\beta'\left(\hat{P}(f_{\mathrm{Pm}},\ R(t))\right)S(t)-v'\left(\hat{P}(f_{\mathrm{Pm}},\ R(t))\right)\right)\frac{\partial\hat{P}}{\partial f_{\mathrm{Pm}}}\right)\mathrm{dt}\Big)_{f_{\mathrm{Pm}}=f_P}=0$.

To find these strategies, we must resort to numerical simulations. Assuming that $\beta(P)=\frac{\beta_0\,P}{\beta_h+P}$ and $v(P)=v_0\,P$, the fitness gradient is $\int_0^T\left(\frac{\beta_0\,\beta_h}{\beta_h+\hat{P}(f_P,R(t))}\,S(t)-v_0\right)\frac{\partial\hat{P}}{\partial f_{\mathrm{Pm}}}\,\mathrm{dt}$. Below is Mathematica code for the function that computes this fitness gradient, given model parameter values for K, f_P, and d and algorithm values of ‘dt’ (which sets the interval size for the Riemann sum approximation of the integral) and ‘Tsteps’ which determines how long to run the numerical simulation before looking for the limit cycle. A full Mathematica script for generating all of the data used in the figures in the main text can be found in the Dryad repository for this manuscript (**Dryad accession number).**

Numerical root finding

The code below calculates the value of the fitness gradient for given values of K, f_P, and d.

```
fitGrad[{thisK_?NumericQ, thisfP_?NumericQ,
   thisd_?NumericQ, thisdt_?NumericQ, Tsteps_?NumericQ}] :=
 Module[{K, B0, Bh, v0, ρ, fs, h, d, es, r, aI, fI, fP, aB, ϵI, m, ϵP, δ, wthn, Pvalue,
   btwn, DOPRIamat, DOPRIbvec, DOPRIcvec, DOPRIevec, DOPRICoefficients, soln, dR,
   dS, dQ, R, S, Q, P, dt, Rt, FirstPeak, SecondPeak, T, PvalueT, grad, Pt, dPt},


  (* Parameters *)
  wthn = {r → 1, aI → 0.1`, fI → 0.1`,
    fP → thisfP, aB → 0.1`, ϵI → 0.1`, m → 0.1`, ϵP → 0.1`, δ → 0.01`};
  btwn = {K → thisK, B0 → 15, Bh → 100, v0 → 0.01, ρ → 1,
    fs → 1, h → 1, d → thisd, es → 0.5};

  (* Within-host parasite abundance from the
    analytical solution of the system {dEdt=0, dIdt=0, dPdt=0} *)
  Pt = (aI fI^2 fP fs^2 R^2 ϵP - fI fP^2 fs h m R ϵI ϵP - fI fP^2 fs m R^2 ϵI ϵP + aI fI fP fs h m R δ ϵI ϵP +
       aI fI fP fs m R^2 δ ϵI ϵP + fP^2 h^2 m^2 δ ϵI^2 ϵP + 2 fP^2 h m^2 R δ ϵI^2 ϵP + fP^2 m^2 R^2 δ ϵI^2 ϵP +
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      aB fI^2 fP fs h R ϵP^2 + aB fI^2 fP fs R^2 ϵP^2 - aI fI^2 fs h r R δ ϵP^2 - aI fI^2 fs r R^2 δ ϵP^2 +
      aB fI fP h^2 m δ ϵI ϵP^2 + 2 fI fP h^2 m r δ ϵI ϵP^2 + 2 aB fI fP h m R δ ϵI ϵP^2 +
      4 fI fP h m r R δ ϵI ϵP^2 + aB fI fP m R^2 δ ϵI ϵP^2 + 2 fI fP m r R^2 δ ϵI ϵP^2 -
      aI fI h^2 m r δ^2 ϵI ϵP^2 - 2 aI fI h m r R δ^2 ϵI ϵP^2 - aI fI m r R^2 δ^2 ϵI ϵP^2 -
      fI fs R √(ϵP^2 (-4 aI fP (h + R) δ (-fP m (h + R) ϵI + aI (fI fs R + m (h + R) δ ϵI))
              (fP m ϵI + fI r ϵP) + (fP (h + R) (fP m ϵI - aB fI ϵP) -
                aI (2 fP m (h + R) δ ϵI + fI (fP fs R + r (h + R) δ ϵP)))^2)) -
      h m δ ϵI √(ϵP^2 (-4 aI fP (h + R) δ (-fP m (h + R) ϵI + aI (fI fs R + m (h + R) δ ϵI))
              (fP m ϵI + fI r ϵP) + (fP (h + R) (fP m ϵI - aB fI ϵP) -
                aI (2 fP m (h + R) δ ϵI + fI (fP fs R + r (h + R) δ ϵP)))^2)) -
      m R δ ϵI √(ϵP^2 (-4 aI fP (h + R) δ (-fP m (h + R) ϵI + aI (fI fs R + m (h + R) δ ϵI))
              (fP m ϵI + fI r ϵP) + (fP (h + R) (fP m ϵI - aB fI ϵP) -
                aI (2 fP m (h + R) δ ϵI + fI (fP fs R + r (h + R) δ ϵP)))^2)))/
    (2 fI fP (h + R) δ (-fP m (h + R) ϵI + aI (fI fs R + m (h + R) δ ϵI)) ϵP^2) /. R →
    R[t];

(* Derivative dP/dfP for calculating the fitness gradient *)
dPt = Simplify[D[Pt, fP] /. wthn /. btwn];
Pt = Simplify[Pt /. wthn /. btwn];

(* Numerical simulation setup *)
DOPRIamat = {{1/5}, {3/40, 9/40}, {44/45, -56/15, 32/9},
   {19 372/6561, -25 360/2187, 64 448/6561, -212/729},
   {9017/3168, -355/33, 46 732/5247, 49/176, -5103/18 656},
   {35/384, 0, 500/1113, 125/192, -2187/6784, 11/84}};
DOPRIbvec = {35/384, 0, 500/1113, 125/192, -2187/6784, 11/84, 0};
DOPRIcvec = {1/5, 3/10, 4/5, 8/9, 1, 1};
DOPRIevec = {71/57 600, 0, -71/16 695, 71/1920, -17 253/339 200, 22/525, -1/40};
DOPRICoefficients[5, p_] := N[{DOPRIamat, DOPRIbvec, DOPRIcvec, DOPRIevec}, p];
(* Numerically solve the system *)
soln = NDSolve[{R'[t] == (ρ R[t] (1 - R[t]/K) - (fs R[t] (Q[t] + S[t]))/(h + R[t]) /. btwn),
    S'[t] == (-d S[t] - (B0 P Q[t] S[t])/(Bh + P) +
          (es fs R[t] (Q[t] + S[t]))/(h + R[t]) /. P → Pt /. wthn /. btwn),
    Q'[t] == (-(d + P v0) Q[t] + (B0 P Q[t] S[t])/(Bh + P) /. P → Pt /. wthn /. btwn),
    R[0] == 1/2, S[0] == 0.1, Q[0] == 0.1}, {R, S, Q},
   {t, 0, Tsteps}, Method → {"ExplicitRungeKutta", "DifferenceOrder" → 5,
     "Coefficients" → DOPRICoefficients, "StiffnessTest" → False},
   AccuracyGoal → Infinity, PrecisionGoal → 12];
```

```
 (* Check for parasite extinction *)
 If[(Q[Tsteps] /. soln)⟦1⟧ < 10^-12, Return["parasite extinction"],
  (* Compute the fitness gradient *)
  grad = If[Abs[((R[Tsteps] - R[Tsteps - 1]) /. soln)[[1]]] < 10^-6,
    (* If the system has gone to an equilibrium *)
    ((((B0 Bh)/(Bh + Pt)^2 S[t] - v0) dPt) /. wthn /. btwn /. t → Tsteps /. soln)⟦1⟧,
    (* If the system is cycling *)
    dt = thisdt;
    Rt = Table[(R[t] /. soln)⟦1⟧, {t, Tsteps - 200, Tsteps - 100, dt}];
    (* Find the first peak of the cycle *)
    FirstPeak = Tsteps - 200 + Position[Rt, Max[Rt]]⟦1, 1⟧ dt;
    (* Find the next peak *)
    Rt = Table[(R[t] /. soln)⟦1⟧, {t, FirstPeak, Tsteps, dt}];
    (* Compute the cycle period *)
    T = Position[
        Table[(Rt⟦t⟧ - Rt⟦t + 1⟧)/(Rt⟦t + 1⟧ - Rt⟦t + 2⟧), {t, 1, Length[Rt] - 2}], _? (# < 0 &)]⟦2, 1⟧ dt;
    (* Next peak *)
    SecondPeak = FirstPeak + T;
    (* Check to make sure the system is not in damped oscillations *)
    If[Abs[((R[FirstPeak] - R[SecondPeak]) /. soln)⟦1⟧] < 10^-5,
     (* If the system has reached stable cycling attractor
      compute the average fitness gradient over the cycle *)
     1/T Total[Table[((((B0 Bh)/(Bh + Pt)^2 S[t] - v0) dPt) /. wthn /. btwn) /. soln,
          {t, FirstPeak, SecondPeak, dt}] dt]⟦1⟧,
     (* If still in damped oscillations towards an equilibrium *)
     "Damped oscillations"]
   ];
  Return[grad]
 ]
]
```