

Mathematica Supplement: Host-parasite genome wide association studies and Coevolutionary simulations.

Keeping pace with the Red Queen: identifying the genetic basis of susceptibility to infectious disease. Ailene MacPherson, Sarah P. Otto, and Scott L. Nuismer. Genetics.

```
Clear["Global`*"]
```

We are interested in determining the genetic basis of susceptibility (S) of a host (H) to a parasite (P). We begin by deriving defining three different functions for the susceptibility as a function of host and pathogen genes. These functional forms include the phenotypic-difference model, the phenotypic matching-model, the 2-locus matching-alleles model

Defining Interactions: Deriving expressions for $S(X_H, X_P)$

Phenotypic-Difference model

We begin by considering a host-parasite interaction which is determined by a phenotype z_H in the host and a phenotype z_P in the pathogen. We begin by considering the phenotypes z_H and z_P have the simplest possible genetic basis for a “complex trait”. In particular, suppose they are each determined by two additive loci each with two alleles. If we let $X_S[i]$ be an indicator variable that takes on a value of 0 or 1 depending on the allele present at locus i in species S , and let bSi be the additive effect size of a “1” allele at locus i in species S , we can express the phenotypes of the two species as follows.

$$z_H[XH1_, XH2_] := bH0 + bH1 XH1 + bH2 XH2 + eH;$$

$$z_P[XP1_, XP2_] := bP0 + bP1 XP1 + bP2 XP2 + eP;$$

Here $bH0$ and $bP0$ is the phenotype of an individual with both “0” alleles present.

In the difference phenotype model, host susceptibility (probability of infection) is given by the following function of z_H and z_P :

$$Pdiff[zH_, zP_] := \frac{1}{1 + \text{Exp}[\alpha (zH - zP)]}$$

Assuming that the difference between the host and pathogens phenotypes is small, $(z_H - z_P) \approx 0$, in this case susceptibility can be approximated by the first few terms (2nd order) Taylor series expansion

```
PdiffA[zH_, zP_] :=
  Normal[Series[Pdiff[zH, zP] /. {(zH - zP) -> x}, {x, 0, 2}]] /. x -> (zH - zP)
```

Substituting in z_H and z_P we have an expression for susceptibility becomes.

```
PdiffA[zH[XH1, XH2], zP[XP1, XP2]]

$$\frac{1}{2} - \frac{1}{4} (b_{H0} - b_{P0} + e_H - e_P + b_{H1} X_{H1} + b_{H2} X_{H2} - b_{P1} X_{P1} - b_{P2} X_{P2}) \alpha$$

```

Finally by letting variable X_H be a vector of the host alleles and X_P a vector of the pathogen alleles

```
PdiffX[XH_, XP_] := PdiffA[zH[XH[[1]], XH[[2]]], zP[XP[[1]], XP[[2]]]]
```

The Phenotypic-Matching model

As with the phenotypic-difference model we begin by defining a simple genetic architecture to two traits z_H and z_P as a additive function of two loci in the host and two loci in the pathogen respectively.

```
zH[XH1_, XH2_] := bH0 + bH1 XH1 + bH2 XH2 + eH;
zP[XP1_, XP2_] := bP0 + bP1 XP1 + bP2 XP2 + eP;
```

However now susceptibility has a gaussian form:

```
Pmatch[zH_, zP_] := Exp[-alpha (zH - zP)^2]
```

When we approximate this function with the first 2 terms of the Taylor series about $(z_H - z_P) \approx 0$ we have

```
PmatchA[zH_, zP_] :=
  Normal[Series[Pmatch[zH, zP] /. {(zH - zP) -> x}, {x, 0, 2}]] /. x -> (zH - zP)
```

Substituting in z_H and z_P we have an expression for susceptibility becomes.

```
PmatchA[zH[XH1, XH2], zP[XP1, XP2]]

$$1 - (b_{H0} - b_{P0} + e_H - e_P + b_{H1} X_{H1} + b_{H2} X_{H2} - b_{P1} X_{P1} - b_{P2} X_{P2})^2 \alpha$$

```

Finally by letting variable X_H be a vector of the host alleles and X_P a vector of the pathogen alleles

```
PmatchX[XH_, XP_] := PmatchA[zH[XH[[1]], XH[[2]]], zP[XP[[1]], XP[[2]]]]
```

2-locus Matching-alleles model

For the final model of susceptibility we use an interaction which is explicitly defined to depend on the combination of host and parasite loci present. In particular for a haploid 2-locus host and parasite each of the four host genotypes can be infected by the corresponding genotype in the pathogen. We define IM as a infection matrix which gives the probability of host genotype i being infected by pathogen genotype j , in this case it is simply the 4x4 identify matrix.

```
IM = {{1, 0, 0, 0}, {0, 1, 0, 0}, {0, 0, 1, 0}, {0, 0, 0, 1}};
```

The resulting susceptibility of the host genotype given by the vector X_H by the pathogen genotype X_P is given by:

```
PmamX[XH_, XP_] := IM[[1 + 2 XH[[1]] + XH[[2]], 1 + 2 XP[[1]] + XP[[2]]]]
```

Inferring genetic effects: Deriving analytical expressions for β s

Here we use two different genetic association study designs to infer the genetic basis of susceptibility. In the first design, single-species GWAS, we infer the additive effects and epistatic interaction between the loci of a single species. We arbitrarily chose to focus on the host in this design. The second design, the two-species CoGWAS, infers the additive effects and epistatic interactions between the loci of both species including the interactions between host and pathogen loci. The results attained here are derived analytically and represent the expectations given an infinite sample size. We conclude this section by considering the effect of finite sample sizes.

■ Single-species (Host-Only) GWAS

The Linear Regression Model

In the host-only method we fit susceptibility with a the following linear regression.

```
Pfit1[XH_] :=  $\beta_0 + \beta_{H1} XH[[1]] + \beta_{H2} XH[[2]] + \beta_{H12} XH[[1]] XH[[2]]$ 
```

Here β_{H1} and β_{H2} are the inferred additive effects of the “1” allele at host locus 1 and 2 whereas $\beta_{H[1,2]}$ is the inferred epistatic interaction between the host loci. Finally, $\beta[0]$ is the intercept which approximates the phenotype of a host individual with all “0” alleles.

Using least squares regression to fit susceptibility of the form, $PinfX$, we first calculate the mean squared error. This requires information on the genetic makeup of the host and pathogen populations. In particular, suppose that the frequency of the “1” allele at locus i in species S is given by $pS[i]$ and the linkage disequilibrium between the loci in species S is given by LDS . Assuming Hardy-Weinberg proportions in the host and pathogen the resulting frequency of genotype $xh1, xh2$ in each species is given by:

```
FreqH[XH1_, XH2_] :=  
  pH1XH1 (1 - pH1)(1-XH1) pH2XH2 (1 - pH2)(1-XH2) + (-1)Abs[XH1-XH2] LDH // Simplify
```

```
FreqP[XP1_, XP2_] :=  
  pP1XP1 (1 - pP1)(1-XP1) pP2XP2 (1 - pP2)(1-XP2) + (-1)Abs[XP1-XP2] LDP // Simplify
```

Given these genotype frequencies, if we assume hosts and pathogens come into contact with one another at random and that the probability of infection is given by the function $PinfX$ we can write the mean squared error as:

```
MSE[PinfX_] := Sum[FreqH[XH1, XH2] FreqP[XP1, XP2]  
  (PinfX[{XH1, XH2}, {XP1, XP2}] - Pfit1[{XH1, XH2}])2,  
  {XH1, 0, 1}, {XH2, 0, 1}, {XP1, 0, 1}, {XP2, 0, 1}] // Simplify;
```

We can then solve for β_0 , β_{H1} , β_{H2} , and β_{H12} by minimizing this error. In other words by solving the following equations for $\beta_0, \beta_{H1}, \beta_{H2}$, and β_{H12}

```

Equis[PinfX_] := {D[MSE[PinfX],  $\beta_0$ ] == 0,
  D[MSE[PinfX],  $\beta_{H1}$ ] == 0, D[MSE[PinfX],  $\beta_{H2}$ ] == 0, D[MSE[PinfX],  $\beta_{H12}$ ] == 0};
Vars = { $\beta_0$ ,  $\beta_{H1}$ ,  $\beta_{H2}$ ,  $\beta_{H12}$ };

```

Phenotypic-Difference Model

```

 $\beta_{H0diff}$  = Solve[Simplify[Equis[PdiffX]], Vars] // Flatten

```

```

{ $\beta_0 \rightarrow \frac{1}{4} (2 - b_{H0} \alpha + b_{P0} \alpha - e_H \alpha + e_P \alpha + b_{P1} p_{P1} \alpha + b_{P2} p_{P2} \alpha)$ ,
 $\beta_{H1} \rightarrow -\frac{b_{H1} \alpha}{4}$ ,  $\beta_{H2} \rightarrow -\frac{b_{H2} \alpha}{4}$ ,  $\beta_{H12} \rightarrow 0$ }

```

Plotting these coefficients as a function of pathogen allele frequency $p_{P1}=p_{P2}$

```

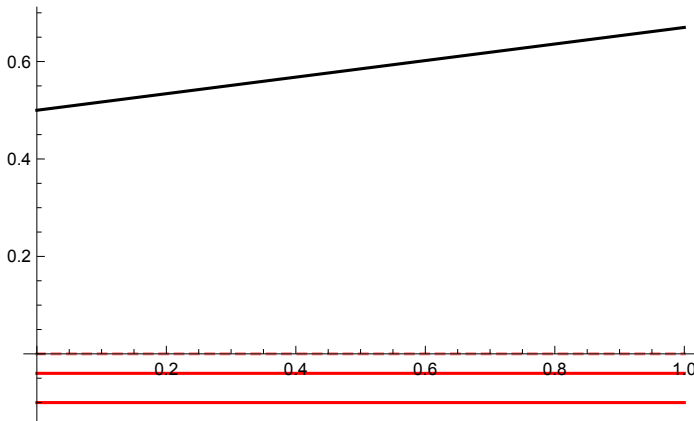
pars = { $\alpha \rightarrow 0.8$ , LDP  $\rightarrow 0$ ,  $b_{H0} \rightarrow 0$ ,  $b_{H1} \rightarrow 0.5$ ,  $b_{H2} \rightarrow 0.2$ ,
   $b_{P0} \rightarrow 0$ ,  $b_{P1} \rightarrow 0.35$ ,  $b_{P2} \rightarrow 0.5$ ,  $e_H \rightarrow 0.0$ ,  $e_P \rightarrow 0.0$ ,  $p_{P1} \rightarrow p_P$ ,  $p_{P2} \rightarrow p_P$ };

```

```

HostOnly = Plot[{ $\beta_0$  /.  $\beta_{H0diff}$  /. pars,
   $\beta_{H1}$  /.  $\beta_{H0diff}$  /. pars,  $\beta_{H2}$  /.  $\beta_{H0diff}$  /. pars,  $\beta_{H12}$  /.  $\beta_{H0diff}$  /. pars},
  {p_P, 0, 1}, PlotStyle -> {Black, Red, Red, Directive[Pink, Dashed]}]

```



Phenotypic-Matching Model

```

 $\beta_{H0match}$  = Solve[Simplify[Equis[PmatchX]], Vars] // Flatten

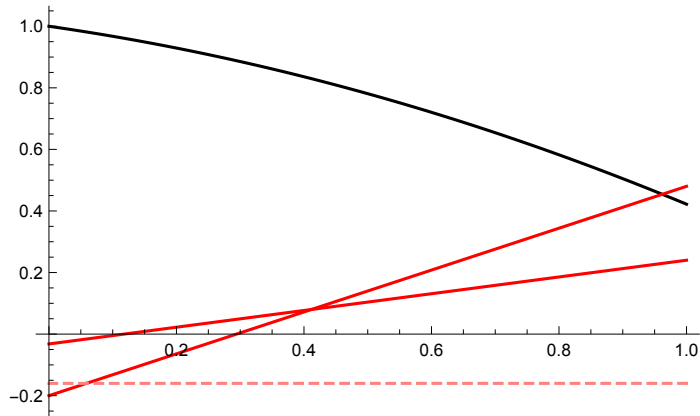
```

```

{ $\beta_0 \rightarrow 1 - b_{H0}^2 \alpha + 2 b_{H0} b_{P0} \alpha - b_{P0}^2 \alpha - 2 b_{H0} e_H \alpha + 2 b_{P0} e_H \alpha - e_H^2 \alpha + 2 b_{H0} e_P \alpha -$ 
   $2 b_{P0} e_P \alpha + 2 e_H e_P \alpha - e_P^2 \alpha - 2 b_{P1} b_{P2} LDP \alpha + 2 b_{H0} b_{P1} p_{P1} \alpha - 2 b_{P0} b_{P1} p_{P1} \alpha -$ 
   $b_{P1}^2 p_{P1} \alpha + 2 b_{P1} e_H p_{P1} \alpha - 2 b_{P1} e_P p_{P1} \alpha + 2 b_{H0} b_{P2} p_{P2} \alpha - 2 b_{P0} b_{P2} p_{P2} \alpha -$ 
   $b_{P2}^2 p_{P2} \alpha + 2 b_{P2} e_H p_{P2} \alpha - 2 b_{P2} e_P p_{P2} \alpha - 2 b_{P1} b_{P2} p_{P1} p_{P2} \alpha$ ,  $\beta_{H1} \rightarrow$ 
   $-2 b_{H0} b_{H1} \alpha - b_{H1}^2 \alpha + 2 b_{H1} b_{P0} \alpha - 2 b_{H1} e_H \alpha + 2 b_{H1} e_P \alpha + 2 b_{H1} b_{P1} p_{P1} \alpha + 2 b_{H1} b_{P2} p_{P2} \alpha$ ,
 $\beta_{H2} \rightarrow -2 b_{H0} b_{H2} \alpha - b_{H2}^2 \alpha + 2 b_{H2} b_{P0} \alpha - 2 b_{H2} e_H \alpha + 2 b_{H2} e_P \alpha +$ 
   $2 b_{H2} b_{P1} p_{P1} \alpha + 2 b_{H2} b_{P2} p_{P2} \alpha$ ,  $\beta_{H12} \rightarrow -2 b_{H1} b_{H2} \alpha$ }

```

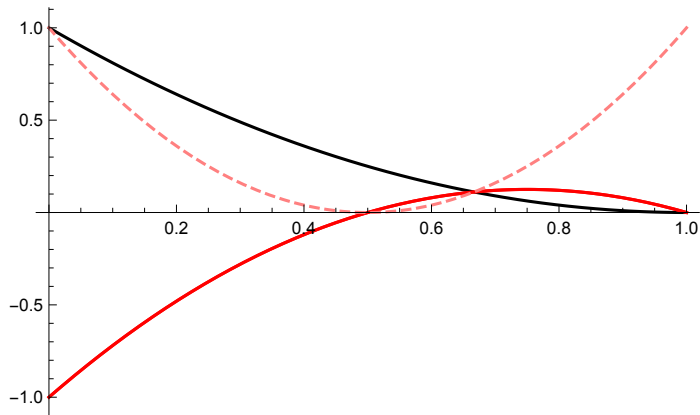
```
HostOnly = Plot[{ $\beta_0$  /.  $\beta_{H0match}$  /. pars,
   $\beta_{H1}$  /.  $\beta_{H0match}$  /. pars,  $\beta_{H2}$  /.  $\beta_{H0match}$  /. pars,  $\beta_{H12}$  /.  $\beta_{H0match}$  /. pars},
  {pP, 0, 1}, PlotStyle -> {Black, Red, Red, Directive[Pink, Dashed]}]
```



Matching-Alleles Model

```
 $\beta_{H0mam} = \text{Solve}[\text{Simplify}[\text{Eqs}[\text{PmamX}]], \text{Vars}] // \text{Flatten}$ 
 $\{\beta_0 \rightarrow 1 + \text{LDP} - pP1 - pP2 + pP1 pP2, \beta_{H1} \rightarrow -1 - 2 \text{LDP} + 2 pP1 + pP2 - 2 pP1 pP2,$ 
 $\beta_{H2} \rightarrow -1 - 2 \text{LDP} + pP1 + 2 pP2 - 2 pP1 pP2, \beta_{H12} \rightarrow 1 + 4 \text{LDP} - 2 pP1 - 2 pP2 + 4 pP1 pP2\}$ 
```

```
HostOnly = Plot[{ $\beta_0$  /.  $\beta_{H0mam}$  /. pars,
   $\beta_{H1}$  /.  $\beta_{H0mam}$  /. pars,  $\beta_{H2}$  /.  $\beta_{H0mam}$  /. pars,  $\beta_{H12}$  /.  $\beta_{H0mam}$  /. pars},
  {pP, 0, 1}, PlotStyle -> {Black, Red, Red, Directive[Pink, Dashed]}]
```



■ Two-species (Host-Pathogen) Co-GWAS

The Linear Regression Model

In the two-species Co-GWAS method we fit susceptibility with a linear regression containing the additive effects from both species, pair-wise epistatic interactions within each species, and pair-wise GxG

interactions between the species.

```
Pfit2[XH_, XP_] :=  $\beta_0 + \beta_{H1} XH[[1]] + \beta_{H2} XH[[2]] + \beta_{H12} XH[[1]] XH[[2]] +$   

 $\beta_{P1} XP[[1]] + \beta_{P2} XP[[2]] + \beta_{P12} XP[[1]] XP[[2]] + \beta_{H1P1} XH[[1]] XP[[1]] +$   

 $\beta_{H1P2} XH[[1]] XP[[2]] + \beta_{H2P1} XH[[2]] XP[[1]] + \beta_{H2P2} XH[[2]] XP[[2]]$ 
```

Once again we can use linear least-squares regression to fit susceptibility of the form PinfX.

```
FreqH[XH1_, XH2_] :=  

 $p_{H1}^{XH1} (1 - p_{H1})^{(1-XH1)} p_{H2}^{XH2} (1 - p_{H2})^{(1-XH2)} + (-1)^{Abs[XH1-XH2]} LDH$  // Simplify
```

```
FreqP[XP1_, XP2_] :=  

 $p_{P1}^{XP1} (1 - p_{P1})^{(1-XP1)} p_{P2}^{XP2} (1 - p_{P2})^{(1-XP2)} + (-1)^{Abs[XP1-XP2]} LDP$  // Simplify
```

```
MSE2[PinfX_] := Sum[FreqH[XH1, XH2] FreqP[XP1, XP2]  

(PinfX[{XH1, XH2}, {XP1, XP2}] - Pfit2[{XH1, XH2}, {XP1, XP2}])2,  

{XH1, 0, 1}, {XH2, 0, 1}, {XP1, 0, 1}, {XP2, 0, 1}] // Simplify;
```

```
Equs2[PinfX_] := {D[MSE2[PinfX],  $\beta_0$ ] == 0, D[MSE2[PinfX],  $\beta_{H1}$ ] == 0,  

D[MSE2[PinfX],  $\beta_{H2}$ ] == 0, D[MSE2[PinfX],  $\beta_{H12}$ ] == 0, D[MSE2[PinfX],  $\beta_{P1}$ ] == 0,  

D[MSE2[PinfX],  $\beta_{P2}$ ] == 0, D[MSE2[PinfX],  $\beta_{P12}$ ] == 0, D[MSE2[PinfX],  $\beta_{H1P1}$ ] == 0,  

D[MSE2[PinfX],  $\beta_{H1P2}$ ] == 0, D[MSE2[PinfX],  $\beta_{H2P1}$ ] == 0, D[MSE2[PinfX],  $\beta_{H2P2}$ ] == 0};  

Vars2 = { $\beta_0$ ,  $\beta_{H1}$ ,  $\beta_{H2}$ ,  $\beta_{H12}$ ,  $\beta_{P1}$ ,  $\beta_{P2}$ ,  $\beta_{P12}$ ,  $\beta_{H1P1}$ ,  $\beta_{H1P2}$ ,  $\beta_{H2P1}$ ,  $\beta_{H2P2}$ };
```

Since the equations can not be solved directly by Mathematica we use the following list of expressions to solve for the β s step by step.

```
EquList[PinfX_] := {D[MSE2[PinfX],  $\beta_0$ ], D[MSE2[PinfX],  $\beta_{H1}$ ],  

D[MSE2[PinfX],  $\beta_{H2}$ ], D[MSE2[PinfX],  $\beta_{H12}$ ], D[MSE2[PinfX],  $\beta_{P1}$ ],  

D[MSE2[PinfX],  $\beta_{P2}$ ], D[MSE2[PinfX],  $\beta_{P12}$ ], D[MSE2[PinfX],  $\beta_{H1P1}$ ],  

D[MSE2[PinfX],  $\beta_{H1P2}$ ], D[MSE2[PinfX],  $\beta_{H2P1}$ ], D[MSE2[PinfX],  $\beta_{H2P2}$ ]}
```

Phenotypic-Difference Model

```
pars = { $\alpha \rightarrow 0.8$ , LDP  $\rightarrow 0$ , bH0  $\rightarrow 0$ , bH1  $\rightarrow 0.5$ , bH2  $\rightarrow 0.2$ ,  

bP0  $\rightarrow 0$ , bP1  $\rightarrow 0.35$ , bP2  $\rightarrow 0.5$ , eH  $\rightarrow 0.0$ , eP  $\rightarrow 0.0$ , pP1  $\rightarrow pP$ , pP2  $\rightarrow pP$ };
```

```
 $\beta_{0sub}$  =  

Solve[(EquList[PdiffX][[1]] // Simplify // Factor) == 0,  $\beta_0$ ] // Simplify // Flatten;
```

```
 $\beta_{H1sub}$  =  

Solve[(EquList[PdiffX][[2]] /.  $\beta_{0sub}$  // Simplify // Factor) == 0,  $\beta_{H1}$ ] // Simplify // Flatten;
```

```
 $\beta_{H2sub}$  =  

Solve[(EquList[PdiffX][[4]] /.  $\beta_{0sub}$  /.  $\beta_{H1sub}$  // Simplify // Factor) == 0,  $\beta_{H2}$ ] // Simplify // Flatten;
```

```

βH12sub =
  Solve[(EquList[PdiffX][[3]] /. β0sub /. βH1sub /. βH2sub // Simplify // Factor) == 0,
    βH12] // Simplify // Flatten;

βP1sub =
  Solve[(EquList[PdiffX][[5]] /. β0sub /. βH1sub /. βH2sub /. βH12sub // Simplify //
    Factor) == 0, βP1] // Simplify // Flatten;

βP2sub =
  Solve[(EquList[PdiffX][[7]] /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub //
    Simplify // Factor) == 0, βP2] // Simplify // Flatten;

βP12sub =
  Solve[(EquList[PdiffX][[6]] /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /.
    βP2sub // Simplify // Factor) == 0, βP12] // Simplify // Flatten;

βH1P1sub =
  Solve[(EquList[PdiffX][[8]] /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /.
    βP2sub /. βP12sub // Simplify // Factor) == 0, βH1P1] // Simplify // Flatten;

βH1P2sub =
  Solve[(EquList[PdiffX][[9]] /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /.
    βP2sub /. βP12sub /. βH1P1sub //
    Simplify // Factor) == 0, βH1P2] // Simplify // Flatten;

βH2P1sub =
  Solve[(EquList[PdiffX][[10]] /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /.
    βP2sub /. βP12sub /. βH1P1sub /. βH1P2sub //
    Simplify // Factor) == 0, βH2P1] // Simplify // Flatten;

βH2P2sub =
  Solve[(EquList[PdiffX][[11]] /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /.
    βP2sub /. βP12sub /. βH1P1sub /. βH1P2sub /. βH2P1sub //
    Simplify // Factor) == 0, βH2P2] // Simplify // Flatten;

```

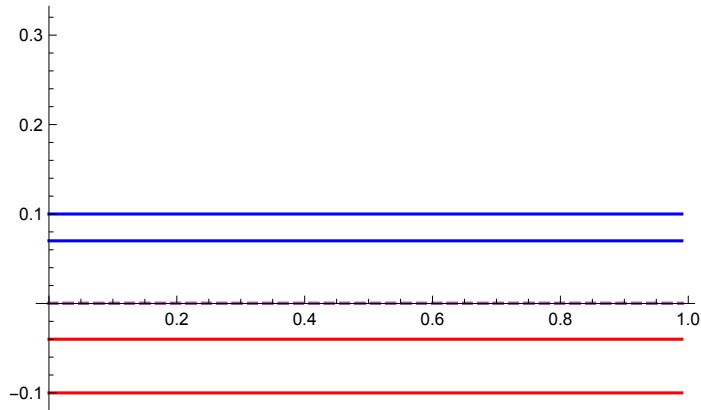
This gives the following solution:

```

sol = Vars2 /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /. βP2sub /. βP12sub /.
  βH1P1sub /. βH1P2sub /. βH2P1sub /. βH2P2sub // Simplify;
βHPdiff = {β0 → sol[[1]], βH1 → sol[[2]], βH2 → sol[[3]], βH12 → sol[[4]],
  βP1 → sol[[5]], βP2 → sol[[6]], βP12 → sol[[7]], βH1P1 → sol[[8]],
  βH1P2 → sol[[9]], βH2P1 → sol[[10]], βH2P2 → sol[[11]]};

```

```
HostPath = Plot[{ $\beta_0$  /.  $\beta$ HPdiff /. pars,  $\beta_{H1}$  /.  $\beta$ HPdiff /. pars,
   $\beta_{H2}$  /.  $\beta$ HPdiff /. pars,  $\beta_{H12}$  /.  $\beta$ HPdiff /. pars,  $\beta_{P1}$  /.  $\beta$ HPdiff /. pars,
   $\beta_{P2}$  /.  $\beta$ HPdiff /. pars,  $\beta_{P12}$  /.  $\beta$ HPdiff /. pars,  $\beta_{H1P1}$  /.  $\beta$ HPdiff /. pars,
   $\beta_{H1P2}$  /.  $\beta$ HPdiff /. pars,  $\beta_{H2P1}$  /.  $\beta$ HPdiff /. pars,  $\beta_{H2P2}$  /.  $\beta$ HPdiff /. pars},
{pP, 0, 0.99}, PlotStyle -> {Black, Red, Red, Directive[Lighter[Red], Dashed],
  Blue, Blue, Directive[Lighter[Blue], Dashed],
  Directive[Lighter[Purple], Dashed], Directive[Purple, Dashed],
  Directive[Lighter[Purple], Dashed], Directive[Lighter[Purple], Dashed]}]
```



Phenotypic-Matching Model

```
 $\beta_{0sub} =$ 
  Solve[(EquList[PmatchX][[1]] // Simplify // Factor) == 0,  $\beta_0$ ] // Simplify // Flatten;
 $\beta_{H1sub} =$ 
  Solve[(EquList[PmatchX][[2]] /.  $\beta_{0sub}$  // Simplify // Factor) == 0,  $\beta_{H1}$ ] // Simplify //
  Flatten;
 $\beta_{H2sub} =$ 
  Solve[(EquList[PmatchX][[4]] /.  $\beta_{0sub}$  /.  $\beta_{H1sub}$  // Simplify // Factor) == 0,  $\beta_{H2}$ ] //
  Simplify // Flatten;
 $\beta_{H12sub} =$ 
  Solve[(EquList[PmatchX][[3]] /.  $\beta_{0sub}$  /.  $\beta_{H1sub}$  /.  $\beta_{H2sub}$  // Simplify // Factor) == 0,
   $\beta_{H12}$ ] // Simplify // Flatten;
 $\beta_{P1sub} =$ 
  Solve[(EquList[PmatchX][[5]] /.  $\beta_{0sub}$  /.  $\beta_{H1sub}$  /.  $\beta_{H2sub}$  /.  $\beta_{H12sub}$  // Simplify //
  Factor) == 0,  $\beta_{P1}$ ] // Simplify // Flatten;
 $\beta_{P2sub} =$ 
  Solve[(EquList[PmatchX][[7]] /.  $\beta_{0sub}$  /.  $\beta_{H1sub}$  /.  $\beta_{H2sub}$  /.  $\beta_{H12sub}$  /.  $\beta_{P1sub}$  //
  Simplify // Factor) == 0,  $\beta_{P2}$ ] // Simplify // Flatten;
```



```

βP12sub =
  Solve[(EquList[PmatchX][[6]] /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /.
    βP2sub // Simplify // Factor) == 0, βP12] // Simplify // Flatten;

βH1P1sub =
  Solve[(EquList[PmatchX][[8]] /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /.
    βP2sub /. βP12sub // Simplify // Factor) == 0, βH1P1] // Simplify // Flatten;

βH1P2sub =
  Solve[(EquList[PmatchX][[9]] /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /.
    βP2sub /. βP12sub /. βH1P1sub //
    Simplify // Factor) == 0, βH1P2] // Simplify // Flatten;

βH2P1sub =
  Solve[(EquList[PmatchX][[10]] /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /.
    βP2sub /. βP12sub /. βH1P1sub /. βH1P2sub //
    Simplify // Factor) == 0, βH2P1] // Simplify // Flatten;

βH2P2sub =
  Solve[(EquList[PmatchX][[11]] /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /.
    βP2sub /. βP12sub /. βH1P1sub /. βH1P2sub /. βH2P1sub //
    Simplify // Factor) == 0, βH2P2] // Simplify // Flatten;

```

This gives the following solution:

```

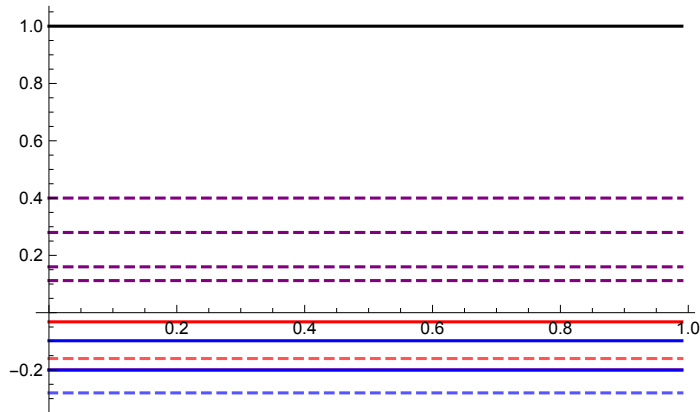
sol = Vars2 /. β0sub /. βH1sub /. βH2sub /. βH12sub /. βP1sub /. βP2sub /. βP12sub /.
  βH1P1sub /. βH1P2sub /. βH2P1sub /. βH2P2sub // Simplify;
βHPmatch = {β0 → sol[[1]], βH1 → sol[[2]], βH2 → sol[[3]], βH12 → sol[[4]],
  βP1 → sol[[5]], βP2 → sol[[6]], βP12 → sol[[7]], βH1P1 → sol[[8]],
  βH1P2 → sol[[9]], βH2P1 → sol[[10]], βH2P2 → sol[[11]]};

```

```

HostPath =
Plot[{\beta0 /. \betaHPmatch /. pars, \betaH1 /. \betaHPmatch /. pars, \betaH2 /. \betaHPmatch /. pars,
  \betaH12 /. \betaHPmatch /. pars, \betaP1 /. \betaHPmatch /. pars, \betaP2 /. \betaHPmatch /. pars,
  \betaP12 /. \betaHPmatch /. pars, \betaH1P1 /. \betaHPmatch /. pars, \betaH1P2 /. \betaHPmatch /. pars,
  \betaH2P1 /. \betaHPmatch /. pars, \betaH2P2 /. \betaHPmatch /. pars}, {pP, 0, 0.99},
PlotStyle -> {Black, Red, Red, Directive[Lighter[Red], Dashed], Blue, Blue,
  Directive[Lighter[Blue], Dashed], Directive[Purple, Dashed], Directive[
  Purple, Dashed], Directive[Purple, Dashed], Directive[Purple, Dashed]}]

```



Matching-Alleles Model

```

\betaH2P2sub = FullSimplify[Flatten[Solve[EquList[PmamX][[11]] == 0, \betaH2P2]]];
\betaH2P1sub = FullSimplify[
  Flatten[Solve[Simplify[EquList[PmamX][[3]] /. \betaH2P2sub] == 0, \betaH2P1]]];
\betaH1sub = FullSimplify[
  Flatten[Solve[Simplify[EquList[PmamX][[4]] /. \betaH2P2sub /. \betaH2P1sub] == 0, \betaH1]]];
\betaH12sub = FullSimplify[Flatten[
  Solve[Factor[EquList[PmamX][[2]] /. \betaH2P2sub /. \betaH2P1sub /. \betaH1sub] == 0, \betaH12]]];
\betaP2sub = FullSimplify[Flatten[Solve[Factor[
  EquList[PmamX][[1]] /. \betaH2P2sub /. \betaH2P1sub /. \betaH1sub /. \betaH12sub] == 0, \betaP2]]];
\betaP1sub = FullSimplify[
  Flatten[Solve[Factor[EquList[PmamX][[6]] /. \betaH2P2sub /. \betaH2P1sub /. \betaH1sub /.
    \betaH12sub /. \betaP2sub] == 0, \betaP1]]];
\betaH1P2sub = FullSimplify[
  Flatten[Solve[Factor[EquList[PmamX][[7]] /. \betaH2P2sub /. \betaH2P1sub /. \betaH1sub /.
    \betaH12sub /. \betaP2sub /. \betaP1sub] == 0, \betaH1P2]]];

```

```

βP12sub = FullSimplify[
  Flatten[Solve[Factor[EquList[PmamX][[5]] /. βH2P2sub /. βH2P1sub /. βH1sub /.
    βH12sub /. βP2sub /. βP1sub /. βH1P2sub] == 0, βP12]]];

βH1P1sub = FullSimplify[Flatten[
  Solve[Factor[EquList[PmamX][[9]] /. βH2P2sub /. βH2P1sub /. βH1sub /. βH12sub /.
    βP2sub /. βP1sub /. βH1P2sub /. βP12sub] == 0, βH1P1]]];

β0sub = FullSimplify[Flatten[
  Solve[Factor[EquList[PmamX][[8]] /. βH2P2sub /. βH2P1sub /. βH1sub /. βH12sub /.
    βP2sub /. βP1sub /. βH1P2sub /. βP12sub /. βH1P1sub] == 0, β0]]];

βH2sub =
  FullSimplify[Flatten[Solve[Factor[Simplify[EquList[PmamX][[10]]] /. βH2P2sub /.
    βH2P1sub /. βH1sub /. βH12sub /. βP2sub /. βP1sub /.
    βH1P2sub /. βP12sub /. βH1P1sub] /. β0sub] == 0, βH2]]];

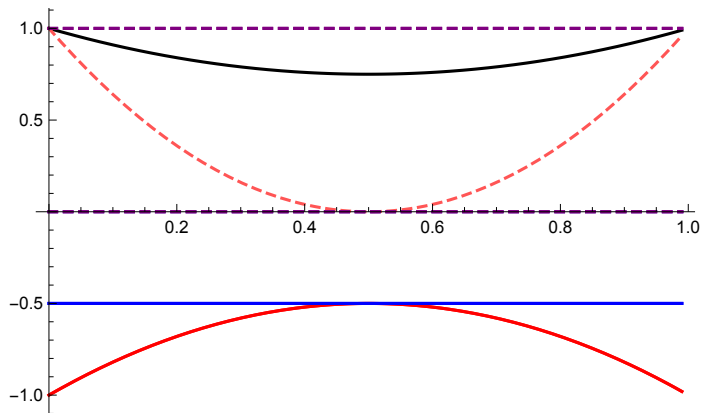
sol = Simplify[
  Vars2 /. βH2P2sub /. βH2P1sub /. βH1sub /. βH12sub /. βP2sub /. βP1sub /. βH1P2sub /.
    βP12sub /. βH1P1sub /. β0sub /. βH2sub];
βHPmam = {β0 → sol[[1]], βH1 → sol[[2]], βH2 → sol[[3]], βH12 → sol[[4]],
  βP1 → sol[[5]], βP2 → sol[[6]], βP12 → sol[[7]], βH1P1 → sol[[8]],
  βH1P2 → sol[[9]], βH2P1 → sol[[10]], βH2P2 → sol[[11]]];

Unlike the phenotypic-matching and phenotypic-difference model the β coefficients here depend on the
host allele frequencies and linkage disequilibrium.

parsH = {pH1 → 0.5, pH2 → 0.5, LDH → 0};

```

```
HostPath = Plot[{ $\beta_0$  /.  $\beta$ HPmam /. pars /. parsH,
   $\beta_{H1}$  /.  $\beta$ HPmam /. pars /. parsH,  $\beta_{H2}$  /.  $\beta$ HPmam /. pars /. parsH,
   $\beta_{H12}$  /.  $\beta$ HPmam /. pars /. parsH,  $\beta_{P1}$  /.  $\beta$ HPmam /. pars /. parsH,
   $\beta_{P2}$  /.  $\beta$ HPmam /. pars /. parsH,  $\beta_{P12}$  /.  $\beta$ HPmam /. pars /. parsH,
   $\beta_{H1P1}$  /.  $\beta$ HPmam /. pars /. parsH,  $\beta_{H1P2}$  /.  $\beta$ HPmam /. pars /. parsH,
   $\beta_{H2P1}$  /.  $\beta$ HPmam /. pars /. parsH,  $\beta_{H2P2}$  /.  $\beta$ HPmam /. pars /. parsH}, {pP, 0, 0.99},
  PlotStyle -> {Black, Red, Red, Directive[Lighter[Red], Dashed], Blue, Blue,
    Directive[Lighter[Blue], Dashed], Directive[Purple, Dashed], Directive[
      Purple, Dashed], Directive[Purple, Dashed], Directive[Purple, Dashed]}
```



Variance explained: Simulating R^2 across pathogen allele frequencies

We begin by constructing a function that simulates a sample of interacting hosts and pathogens given an arbitrary susceptibility function. We then use this function to simulate samples for each susceptibility function, fit the data with the host only or the two-species model, and calculate the variation explained.

■ Simulating a sample

For a host a pathogen populations with a particular genetic composition (as specified by the vectors of haplotype frequencies h_H and h_P) we can simulate a sample of size n . Given a particular infection model PinfX the following function generates such a sample where column 1: 1 if host is infected 0 if not infected, column 2: allele present at first host locus (X_{H1}), column 3: allele present at second host locus (X_{H2}), column 4: allele present at first parasite locus (X_{P1}), and column 5: allele present at second parasite locus (X_{P2}).

```
pars2 = { $\alpha$  -> 2, LDP -> 0, bH0 -> 0, bH1 -> 0.5,
  bH2 -> 0.2, bP0 -> 0, bP1 -> 0.5, bP2 -> 0.35, eH -> 0.0, eP -> 0.0};
```

```

sim[hH_, hP_, n_, PinfX_] := Block[{rand, rand2, s, out, pinf}, out = {};
  For[s = 1, s ≤ n, s++,
    rand = RandomReal[]; rand2 = RandomReal[];
    (*Host and Pathogen Genotypes*)
    If[rand < hH[[1]], (*host is 00*)
      If[rand2 < hP[[1]], (*path is 00*)AppendTo[out, {0, 0, 0, 0}],
        If[rand2 < hP[[1]] + hP[[2]], (*path is 01*)AppendTo[out, {0, 0, 0, 1}],
          If[rand2 < hP[[1]] + hP[[2]] + hP[[3]],
            (*path is 10*)AppendTo[out, {0, 0, 1, 0}],
            (*path is 11*)AppendTo[out, {0, 0, 1, 1}]]];
      If[rand < hH[[1]] + hH[[2]], (*host is 01*)
        If[rand2 < hP[[1]], (*path is 00*)AppendTo[out, {0, 1, 0, 0}],
          If[rand2 < hP[[1]] + hP[[2]], (*path is 01*)AppendTo[out, {0, 1, 0, 1}],
            If[rand2 < hP[[1]] + hP[[2]] + hP[[3]],
              (*path is 10*)AppendTo[out, {0, 1, 1, 0}],
              (*path is 11*)AppendTo[out, {0, 1, 1, 1}]]];
        If[rand < hH[[1]] + hH[[2]] + hH[[3]], (*host is 10*)
          If[rand2 < hP[[1]], (*path is 00*)AppendTo[out, {1, 0, 0, 0}],
            If[rand2 < hP[[1]] + hP[[2]], (*path is 01*)AppendTo[out, {1, 0, 0, 1}],
              If[rand2 < hP[[1]] + hP[[2]] + hP[[3]],
                (*path is 10*)AppendTo[out, {1, 0, 1, 0}],
                (*path is 11*)AppendTo[out, {1, 0, 1, 1}]]];
          (*host is 11*)
          If[rand2 < hP[[1]], (*path is 00*)AppendTo[out, {1, 1, 0, 0}],
            If[rand2 < hP[[1]] + hP[[2]], (*path is 01*)AppendTo[out, {1, 1, 0, 1}],
              If[rand2 < hP[[1]] + hP[[2]] + hP[[3]],
                (*path is 10*)AppendTo[out, {1, 1, 1, 0}],
                (*path is 11*)AppendTo[out, {1, 1, 1, 1}]]];
        ]];
    (*Host infection Status*)
    rand = RandomReal[];
    pinf =
      PinfX[{out[[s, 1]], out[[s, 2]]}, {out[[s, 3]], out[[s, 4]]}] /. pars2 // N;
    AppendTo[out[[s]], pinf]
  ];
  out
]

```

Next we construct a function that simulates the data and then fits the data with linear models ranging from a model with only additive host effects through the complete 2 species Co-GWAS. This function outputs a vector of R^2 values for each linear model. The variable x is an arbitrary variable which can be used to easily plot the variance explained as quantity “ x ” changes. In particular we will use “ x ”=pathogen allele frequency ($x=hP[[3]]+hP[[4]]$), and “ x ”=time ($x=t$).

```

SimR2[hH_, hP_, n_, PinfX_, x_] :=
Block[{simDat, simDat2, out, lm1, lm2, lm3, lm4, lm5, pP},
  simDat = sim[hH, hP, n, PinfX];
  (*Fitting additive effects only*)
  lm1 = LinearModelFit[
    Transpose[Join[Transpose[simDat[[ ;; , 1 ;; 2]]], {simDat[[ ;; , 5]]}],
    {xh1, xh2}, {xh1, xh2}];
  (*Fitting additive and epistatic effects*)
  lm2 = LinearModelFit[Transpose[
    Join[Transpose[simDat[[ ;; , 1 ;; 2]]], {simDat[[ ;; , 1]] * simDat[[ ;; , 2]],
    {simDat[[ ;; , 5]]}], {xh1, xh2, xh12}, {xh1, xh2, xh12}];
  (*Fitting host-additive, host-epistatic, and parasite-additive effects*)
  lm3 = LinearModelFit[Transpose[
    Join[Transpose[simDat[[ ;; , 1 ;; 2]]], {simDat[[ ;; , 1]] * simDat[[ ;; , 2]],
    Transpose[simDat[[ ;; , 3 ;; 4]]], {simDat[[ ;; , 5]]}],
    {xh1, xh2, xh12, xp1, xp2}, {xh1, xh2, xh12, xp1, xp2}];
  (*Fitting host-additive, host-epistatic, parasite-additive,
  and parasite-epistatic effects*)
  lm4 = LinearModelFit[Transpose[Join[Transpose[simDat[[ ;; , 1 ;; 2]]],
    {simDat[[ ;; , 1]] * simDat[[ ;; , 2]], Transpose[simDat[[ ;; , 3 ;; 4]]],
    {simDat[[ ;; , 3]] * simDat[[ ;; , 4]]}, {simDat[[ ;; , 5]]}],
    {xh1, xh2, xh12, xp1, xp2, xp12}, {xh1, xh2, xh12, xp1, xp2, xp12}];
  (*Fitting host-additive, host-epistatic, parasite-additive,
  and parasite-epistatic effects, GxG interactions*)
  lm5 = LinearModelFit[Transpose[Join[Transpose[simDat[[ ;; , 1 ;; 2]]],
    {simDat[[ ;; , 1]] * simDat[[ ;; , 2]], Transpose[simDat[[ ;; , 3 ;; 4]]],
    {simDat[[ ;; , 3]] * simDat[[ ;; , 4]]}, {simDat[[ ;; , 1]] * simDat[[ ;; , 3]]},
    {simDat[[ ;; , 1]] * simDat[[ ;; , 4]]}, {simDat[[ ;; , 2]] * simDat[[ ;; , 3]]},
    {simDat[[ ;; , 2]] * simDat[[ ;; , 4]]}, {simDat[[ ;; , 5]]}],
    {xh1, xh2, xh12, xp1, xp2, xp12, xh1p1, xh1p2, xh2p1, xh2p2},
    {xh1, xh2, xh12, xp1, xp2, xp12, xh1p1, xh1p2, xh2p1, xh2p2}];
  {{x, lm1["RSquared"]}, {x, lm2["RSquared"]}, {x, lm3["RSquared"]},
  {x, lm4["RSquared"]}, {x, lm5["RSquared"]}}
]

```

■ Fitting different interaction Models

Phenotypic-Difference Model

For host haplotype frequencies {0.25,0.25,0.25,0.25} and a sample size of 5000 the parameters given in pars we can simulate model fits as pathogen allele frequency $pP1=pP2=pP$.

```
pars
```

```
{ $\alpha \rightarrow 0.8$ , LDP  $\rightarrow 0$ , bH0  $\rightarrow 0$ , bH1  $\rightarrow 0.5$ , bH2  $\rightarrow 0.2$ , bP0  $\rightarrow 0$ ,  
bP1  $\rightarrow 0.35$ , bP2  $\rightarrow 0.5$ , eH  $\rightarrow 0.$ , eP  $\rightarrow 0.$ , pP1  $\rightarrow$  pP, pP2  $\rightarrow$  pP}
```

```
VarExp[pP_] :=
```

```
SimR2[{0.25, 0.25, 0.25, 0.25}, {(1 - pP)2 + LDP /. pars, (1 - pP) pP - LDP /. pars,  
(1 - pP) pP - LDP /. pars, (pP)2 + LDP /. pars}, 5000, PdiffX, pP]
```

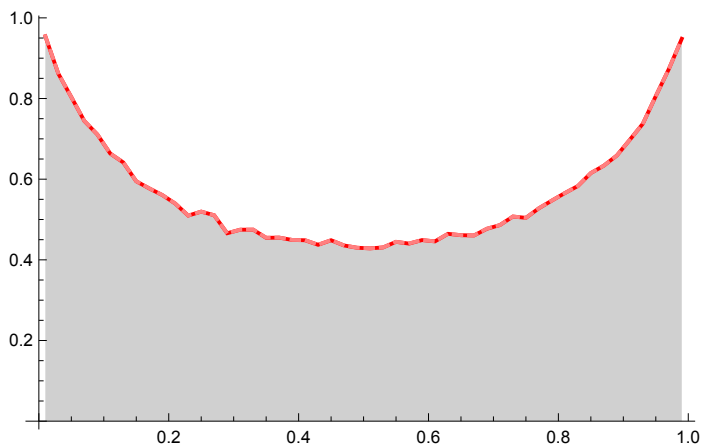
```
R2table = Table[VarExp[in], {in, 0.01, 0.99, 0.02}];
```

LinearModelFit: The rank of the design matrix 6 is less than the number of terms 7 in the model. The model and results based upon it may contain significant numerical error.

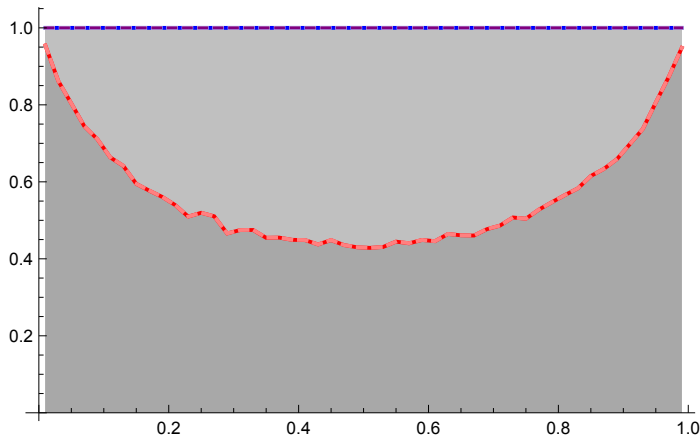
LinearModelFit: The rank of the design matrix 10 is less than the number of terms 11 in the model. The model and results based upon it may contain significant numerical error.

Plotting the variance explained by the host-only model

```
HostOnly = ListLinePlot[{R2table[[ ; ; , 1]], R2table[[ ; ; , 2]]},  
PlotStyle  $\rightarrow$  {{Red, Thick}, {Pink, Thick, Dashed}},  
Filling  $\rightarrow$  Axis, FillingStyle  $\rightarrow$  Directive[Gray, Opacity[0.2]]]
```



```
HostPath = ListLinePlot[{R2table[[ ; ; , 1]], R2table[[ ; ; , 2]],
  R2table[[ ; ; , 3]], R2table[[ ; ; , 4]], R2table[[ ; ; , 5]]},
  PlotStyle -> {{Red, Thick}, {Pink, Thick, Dashed}, {Blue, Thick},
    {LightBlue, Thick, Dashed}, {Purple, Dashed}},
  Filling -> Axis, FillingStyle -> Directive[Gray, Opacity[0.2]]]
```



Phenotypic-Matching Model

For host haplotype frequencies $\{0.25, 0.25, 0.25, 0.25\}$ and a sample size of 5000 the parameters given in pars we can simulate model fits as pathogen allele frequency $pP1=pP2=pP$.

pars

```
{ $\alpha \rightarrow 0.8$ , LDP  $\rightarrow 0$ , bH0  $\rightarrow 0$ , bH1  $\rightarrow 0.5$ , bH2  $\rightarrow 0.2$ , bP0  $\rightarrow 0$ ,
  bP1  $\rightarrow 0.35$ , bP2  $\rightarrow 0.5$ , eH  $\rightarrow 0.$ , eP  $\rightarrow 0.$ , pP1  $\rightarrow pP$ , pP2  $\rightarrow pP$ }
```

VarExp[pP_] :=

```
SimR2[{0.25, 0.25, 0.25, 0.25}, {(1 - pP)2 + LDP /. pars, (1 - pP) pP - LDP /. pars,
  (1 - pP) pP - LDP /. pars, (pP)2 + LDP /. pars}, 5000, PmatchX, pP]
```

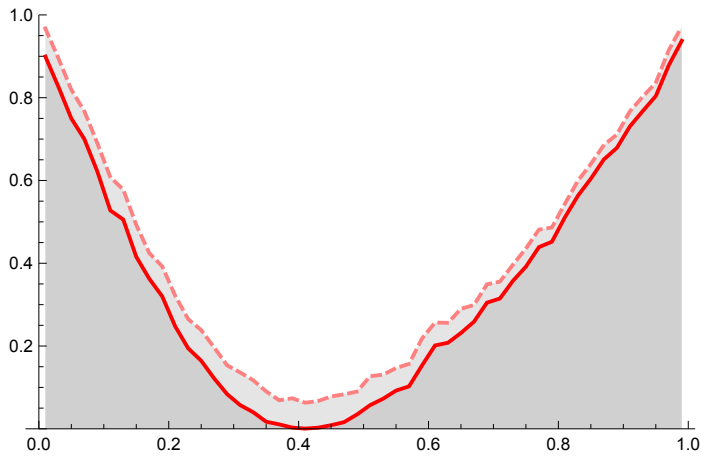
```
R2table = Table[VarExp[in], {in, 0.01, 0.99, 0.02}];
```

LinearModelFit: The rank of the design matrix 6 is less than the number of terms 7 in the model. The model and results based upon it may contain significant numerical error.

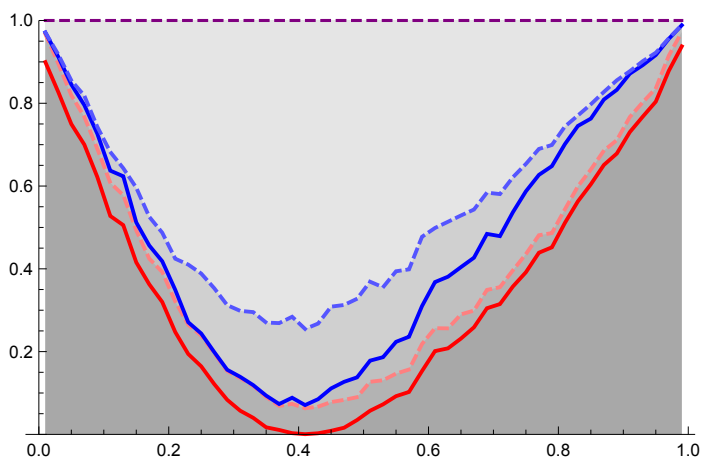
LinearModelFit: The rank of the design matrix 10 is less than the number of terms 11 in the model. The model and results based upon it may contain significant numerical error.

Plotting the variance explained by the host-only model


```
HostOnly = ListLinePlot[{R2table[[ ; ; , 1]], R2table[[ ; ; , 2]]},
  PlotStyle -> {{Red, Thick}, {Pink, Thick, Dashed}}, Filling -> Axis,
  FillingStyle -> Directive[Gray, Opacity[0.2]], PlotRange -> {0, 1}]
```



```
HostPath = ListLinePlot[{R2table[[ ; ; , 1]], R2table[[ ; ; , 2]],
  R2table[[ ; ; , 3]], R2table[[ ; ; , 4]], R2table[[ ; ; , 5]]},
  PlotStyle -> {{Red, Thick}, {Pink, Thick, Dashed}, {Blue, Thick},
  {Lighter[Blue], Thick, Dashed}, {Purple, Dashed}}, Filling -> Axis,
  FillingStyle -> Directive[Gray, Opacity[0.2]], PlotRange -> {0, 1}]
```



Matching-alleles model

For host haplotype frequencies $\{0.25, 0.25, 0.25, 0.25\}$ and a sample size of 5000 the parameters given in pars we can simulate model fits as pathogen allele frequency $pP1=pP2=pP$.

pars

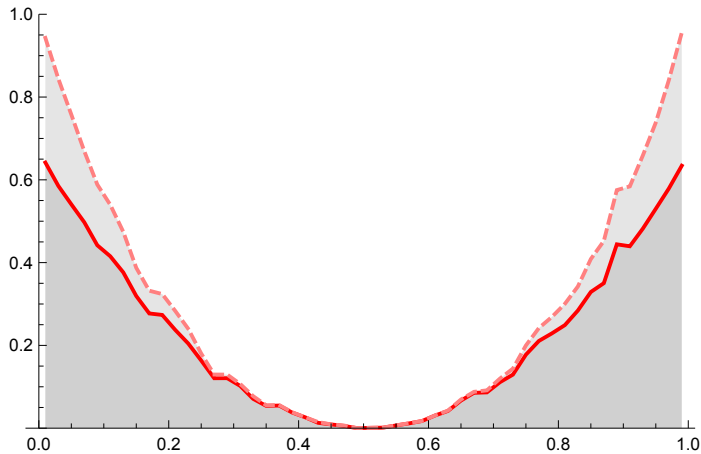
```
{ $\alpha \rightarrow 0.8$ , LDP  $\rightarrow 0$ , bH0  $\rightarrow 0$ , bH1  $\rightarrow 0.5$ , bH2  $\rightarrow 0.2$ , bP0  $\rightarrow 0$ ,
  bP1  $\rightarrow 0.35$ , bP2  $\rightarrow 0.5$ , eH  $\rightarrow 0.$ , eP  $\rightarrow 0.$ , pP1  $\rightarrow pP$ , pP2  $\rightarrow pP$ }
```

```
VarExp[pP_] := SimR2[{0.25, 0.25, 0.25, 0.25}, {(1 - pP)2 + LDP /. pars,
  (1 - pP) pP - LDP /. pars, (1 - pP) pP - LDP /. pars, (pP)2 + LDP /. pars}, 5000, PmamX, pP]
```

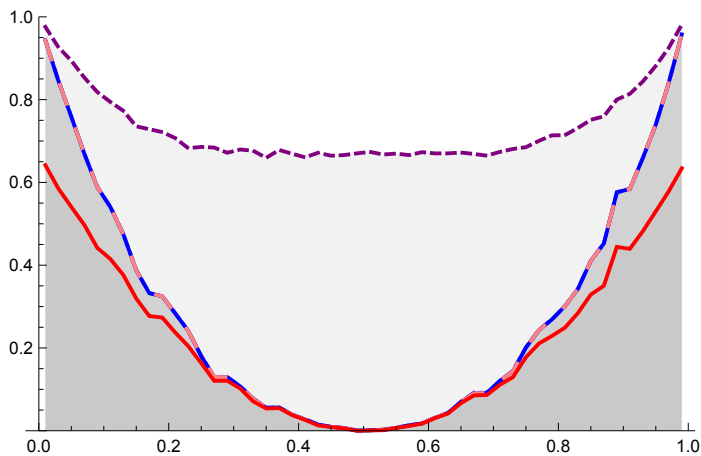
```
R2table = Table[VarExp[in], {in, 0.01, 0.99, 0.02}];
```

Plotting the variance explained by the host-only model

```
HostOnly = ListLinePlot[{R2table[[ ; ; , 1]], R2table[[ ; ; , 2]]},
  PlotStyle -> {{Red, Thick}, {Pink, Thick, Dashed}}, Filling -> Axis,
  FillingStyle -> Directive[Gray, Opacity[0.2]], PlotRange -> {0, 1}]
```



```
HostPath = ListLinePlot[{R2table[[ ; ; , 5]], R2table[[ ; ; , 4]],
  R2table[[ ; ; , 3]], R2table[[ ; ; , 3]], R2table[[ ; ; , 1]]},
  PlotStyle -> {{Purple, Thick, Dashed}, {Lighter[Blue], Thick, Dashed},
  {Blue, Thick}, {Pink, Thick, Dashing[{0.03, 0.07 - 0.03}]}, {Red, Thick}},
  Filling -> Axis, FillingStyle -> Directive[Gray, Opacity[0.1]], PlotRange -> {0, 1}]
```



Coevolution: Simulating Coevolution

■ Phenotypic-difference Model

Allele Frequencies over time

```
pars3 = {tmax → 1000, r → 0.5, α → 0.2, ξH → 0.5, ξP → 0.5, bH0 → 0,
  bH1 → 3, bH2 → 2, bP0 → 0, bP1 → 4, bP2 → 1, eH → 0.0, eP → 0.0, μ → 0.001};
```

Here we let the susceptibility determine the probability of infection of a host with phenotype z_H by a pathogen with phenotype z_P . If infected hosts suffer a fitness cost ξ_H and pathogens a fitness increase ξ_P . Let's denote the frequency of the host genotype $\{X_{H1}, X_{H2}\}$ and pathogen genotype $\{X_{P1}, X_{P2}\}$ in generation t by $f_H[X_{H1}, X_{H2}, t]$ and $f_P[X_{P1}, X_{P2}, t]$ respectively. The fitness of the host genotype $\{X_{H1}, X_{H2}\}$ and pathogen genotype $\{X_{P1}, X_{P2}\}$ in generation t then is given by:

$$W_H[X_{H1}_-, X_{H2}_-, t_-] := \text{Sum}[f_P[X_{P1}, X_{P2}, t] (1 - \xi_H \text{Pdiff}[z_H[X_{H1}, X_{H2}], z_P[X_{P1}, X_{P2}]]) , \{X_{P1}, 0, 1\}, \{X_{P2}, 0, 1\}]$$

The average host fitness at time t is given by:

$$W_{H\text{avg}}[t_-] := \text{Sum}[f_H[X_{H1}, X_{H2}, t] W_H[X_{H1}, X_{H2}, t], \{X_{H1}, 0, 1\}, \{X_{H2}, 0, 1\}]$$

Hence the relative fitness of host genotype $\{X_{H1}, X_{H2}\}$ is given by:

$$w_H[X_{H1}_-, X_{H2}_-, t_-] := \frac{W_H[X_{H1}, X_{H2}, t]}{W_{H\text{avg}}[t]}$$

Similarly we can calculate the recursion equation for the change in parasite genotype frequencies. The absolute fitness of genotype $\{X_{P1}, X_{P2}\}$ is given by

$$W_P[X_{P1}_-, X_{P2}_-, t_-] := \text{Sum}[f_H[X_{H1}, X_{H2}, t] (1 + \xi_P (\text{Pdiff}[z_H[X_{H1}, X_{H2}], z_P[X_{P1}, X_{P2}]]) , \{X_{H1}, 0, 1\}, \{X_{H2}, 0, 1\}]$$

The average pathogen fitness is:

$$W_{P\text{avg}}[t_-] := \text{Sum}[f_P[X_{P1}, X_{P2}, t] W_P[X_{P1}, X_{P2}, t], \{X_{P1}, 0, 1\}, \{X_{P2}, 0, 1\}]$$

The relative fitness

$$w_P[X_{P1}_-, X_{P2}_-, t_-] := \frac{W_P[X_{P1}, X_{P2}, t]}{W_{P\text{avg}}[t]}$$

```
Module[{Htmp, Ptmp, t}, ListH = {}; ListP = {};
  (*Inializing*)
  AppendTo[ListH, {0.24, 0.25, 0.27, 0.24}];
  AppendTo[ListP, {0.23, 0.25, 0.27, 0.25}];
  For[t = 1, t ≤ tmax /. pars3, t++,
    Htmp =
```

```

{fH[0, 0, t]  $\frac{WH[0, 0, t]}{WHavg[t]}$ , fH[1, 0, t]  $\frac{WH[1, 0, t]}{WHavg[t]}$ , fH[0, 1, t]  $\frac{WH[0, 1, t]}{WHavg[t]}$ , fH[1, 1,
t]  $\frac{WH[1, 1, t]}{WHavg[t]}$ } /. {fH[0, 0, t] → ListH[[t, 1]], fH[1, 0, t] → ListH[[t, 2]],
fH[0, 1, t] → ListH[[t, 3]], fH[1, 1, t] → ListH[[t, 4]]} /.
{fP[0, 0, t] → ListP[[t, 1]], fP[1, 0, t] → ListP[[t, 2]],
fP[0, 1, t] → ListP[[t, 3]], fP[1, 1, t] → ListP[[t, 4]]} /. pars3;
Htmp = {Htmp[[1]] (Htmp[[1]] + (Htmp[[2]] + Htmp[[3]]) + (1 - r) Htmp[[4]]) +
r Htmp[[2]] Htmp[[3]],
Htmp[[2]] (Htmp[[2]] + (Htmp[[1]] + Htmp[[4]]) + (1 - r) Htmp[[3]]) +
r Htmp[[1]] Htmp[[4]],
Htmp[[3]] (Htmp[[3]] + (Htmp[[1]] + Htmp[[4]]) + (1 - r) Htmp[[2]]) +
r Htmp[[1]] Htmp[[4]],
Htmp[[4]] (Htmp[[4]] + (Htmp[[2]] + Htmp[[3]]) + (1 - r) Htmp[[1]]) +
r Htmp[[2]] Htmp[[3]]
} /. pars3;
AppendTo[ListH,
{(1 -  $\mu$ )2 Htmp[[1]] +  $\mu$  (1 -  $\mu$ ) Htmp[[2]] + (1 -  $\mu$ )  $\mu$  Htmp[[3]] +  $\mu$ 2 Htmp[[4]],
 $\mu$  (1 -  $\mu$ ) Htmp[[1]] + (1 -  $\mu$ )2 Htmp[[2]] +  $\mu$ 2 Htmp[[3]] + (1 -  $\mu$ )  $\mu$  Htmp[[4]],
(1 -  $\mu$ )  $\mu$  Htmp[[1]] +  $\mu$ 2 Htmp[[2]] + (1 -  $\mu$ )2 Htmp[[3]] +  $\mu$  (1 -  $\mu$ ) Htmp[[4]],
 $\mu$ 2 Htmp[[1]] + (1 -  $\mu$ )  $\mu$  Htmp[[2]] +
 $\mu$  (1 -  $\mu$ ) Htmp[[3]] + (1 -  $\mu$ )2 Htmp[[4]]} /. pars3];
Ptmp = {fP[0, 0, t]  $\frac{WP[0, 0, t]}{WPavg[t]}$ , fP[1, 0, t]  $\frac{WP[1, 0, t]}{WPavg[t]}$ , fP[0, 1, t]  $\frac{WP[0, 1, t]}{WPavg[t]}$ ,
fP[1, 1, t]  $\frac{WP[1, 1, t]}{WPavg[t]}$ } /. {fH[0, 0, t] → ListH[[t, 1]], fH[1, 0, t] →
ListH[[t, 2]], fH[0, 1, t] → ListH[[t, 3]], fH[1, 1, t] → ListH[[t, 4]]} /.
{fP[0, 0, t] → ListP[[t, 1]], fP[1, 0, t] → ListP[[t, 2]],
fP[0, 1, t] → ListP[[t, 3]], fP[1, 1, t] → ListP[[t, 4]]} /. pars3;
Ptmp = {Ptmp[[1]] (Ptmp[[1]] + (Ptmp[[2]] + Ptmp[[3]]) + (1 - r) Ptmp[[4]]) +
r Ptmp[[2]] Ptmp[[3]],
Ptmp[[2]] (Ptmp[[2]] + (Ptmp[[1]] + Ptmp[[4]]) + (1 - r) Ptmp[[3]]) +
r Ptmp[[1]] Ptmp[[4]],
Ptmp[[3]] (Ptmp[[3]] + (Ptmp[[1]] + Ptmp[[4]]) + (1 - r) Ptmp[[2]]) +
r Ptmp[[1]] Ptmp[[4]],
Ptmp[[4]] (Ptmp[[4]] + (Ptmp[[2]] + Ptmp[[3]]) + (1 - r) Ptmp[[1]]) +
r Ptmp[[2]] Ptmp[[3]]
} /. pars3;
AppendTo[ListP,
{(1 -  $\mu$ )2 Ptmp[[1]] +  $\mu$  (1 -  $\mu$ ) Ptmp[[2]] + (1 -  $\mu$ )  $\mu$  Ptmp[[3]] +  $\mu$ 2 Ptmp[[4]],
 $\mu$  (1 -  $\mu$ ) Ptmp[[1]] + (1 -  $\mu$ )2 Ptmp[[2]] +  $\mu$ 2 Ptmp[[3]] + (1 -  $\mu$ )  $\mu$  Ptmp[[4]],
(1 -  $\mu$ )  $\mu$  Ptmp[[1]] +  $\mu$ 2 Ptmp[[2]] + (1 -  $\mu$ )2 Ptmp[[3]] +  $\mu$  (1 -  $\mu$ ) Ptmp[[4]],
 $\mu$ 2 Ptmp[[1]] + (1 -  $\mu$ )  $\mu$  Ptmp[[2]] +

```

```

       $\mu (1 - \mu) P_{tmp}[[3]] + (1 - \mu)^2 P_{tmp}[[4]] \} /. pars3];$ 
```

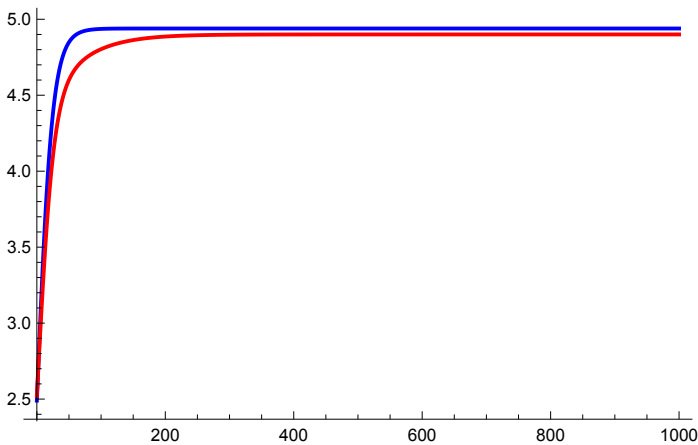
```

];
ListHDiff = Transpose[ListH];
ListPDiff = Transpose[ListP];
pHList = {ListHDiff[[1]] + ListHDiff[[3]], ListHDiff[[2]] + ListHDiff[[4]],
  ListHDiff[[1]] ListHDiff[[4]] - ListHDiff[[2]] ListHDiff[[3]]};
pPList = {ListPDiff[[1]] + ListPDiff[[3]], ListPDiff[[2]] + ListPDiff[[4]],
  ListPDiff[[1]] ListPDiff[[4]] - ListPDiff[[2]] ListPDiff[[3]]};
]
```

Plotting the expected values of zH and zP over time.

```

zHList = Transpose[{Table[t, {t, 0, tmax /. pars3}],
  Sum[ListHDiff[[2 XH2 + XH1 + 1]] zH[XH1, XH2], {XH1, 0, 1}, {XH2, 0, 1}] /. pars3}}];
zPList = Transpose[{Table[t, {t, 0, tmax /. pars3}],
  Sum[ListPDiff[[2 XP2 + XP1 + 1]] zP[XP1, XP2], {XP1, 0, 1}, {XP2, 0, 1}] /. pars3}}];
ZPlot = ListLinePlot[{zHList, zPList},
  PlotRange -> All, PlotStyle -> {{Blue, Thick}, {Red, Thick}}]
```



Effect Sizes over time

Host-only GWAS

β_{H0diff}

$$\left\{ \beta_{H0} \rightarrow \frac{1}{4} (2 - b_{H0} \alpha + b_{P0} \alpha - e_H \alpha + e_P \alpha + b_{P1} p_{P1} \alpha + b_{P2} p_{P2} \alpha), \right.$$

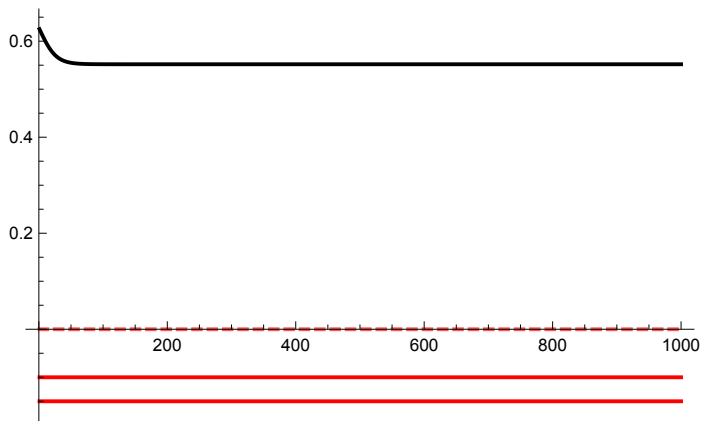
$$\left. \beta_{H1} \rightarrow -\frac{b_{H1} \alpha}{4}, \beta_{H2} \rightarrow -\frac{b_{H2} \alpha}{4}, \beta_{H12} \rightarrow 0 \right\}$$

```

PlotH0diff =
  {Table[{t,  $\beta_0$ } /.  $\beta_{H0diff}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]], pP2  $\rightarrow$  pPlist[[2, t]],
    LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
  Table[{t,  $\beta_{H1}$ } /.  $\beta_{H0diff}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]], pP2  $\rightarrow$  pPlist[[2, t]],
    LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
  Table[{t,  $\beta_{H2}$ } /.  $\beta_{H0diff}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
    pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
  Table[{t,  $\beta_{H12}$ } /.  $\beta_{H0diff}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
    pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}];

ListLinePlot[PlotH0diff,
  PlotStyle  $\rightarrow$  {Directive[{Thick, Black}], Directive[{Thick, Red}],
  Directive[{Thick, Red}], Directive[{Thick, Lighter[Red], Dashed}]}}

```



Host-Pathogen Co-GWAS

β_{HPdiff}

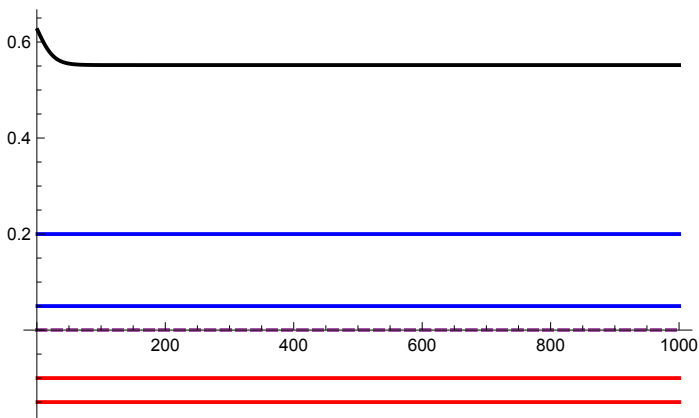
$$\left\{ \beta_0 \rightarrow \frac{1}{4} (2 - b_{H0} \alpha + b_{P0} \alpha - e_H \alpha + e_P \alpha), \beta_{H1} \rightarrow -\frac{b_{H1} \alpha}{4}, \beta_{H2} \rightarrow -\frac{b_{H2} \alpha}{4}, \beta_{H12} \rightarrow 0, \right. \\
 \left. \beta_{P1} \rightarrow \frac{b_{P1} \alpha}{4}, \beta_{P2} \rightarrow \frac{b_{P2} \alpha}{4}, \beta_{P12} \rightarrow 0, \beta_{H1P1} \rightarrow 0, \beta_{H1P2} \rightarrow 0, \beta_{H2P1} \rightarrow 0, \beta_{H2P2} \rightarrow 0 \right\}$$

PlotHPdiff =

```
{Table[{t,  $\beta_0$ } /.  $\beta_{H0}$ diff /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]], pP2  $\rightarrow$  pPlist[[2, t]],
  LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H1}$ } /.  $\beta_{HP}$ diff /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]], pP2  $\rightarrow$  pPlist[[2, t]],
  LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H2}$ } /.  $\beta_{HP}$ diff /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H12}$ } /.  $\beta_{HP}$ diff /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{P1}$ } /.  $\beta_{HP}$ diff /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{P2}$ } /.  $\beta_{HP}$ diff /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{P12}$ } /.  $\beta_{HP}$ diff /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H1P1}$ } /.  $\beta_{HP}$ diff /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H1P2}$ } /.  $\beta_{HP}$ diff /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H2P1}$ } /.  $\beta_{HP}$ diff /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H2P2}$ } /.  $\beta_{HP}$ diff /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}]]];
```

ListLinePlot[PlotHPdiff, PlotStyle \rightarrow

```
{Directive[{Thick, Black}], Directive[{Thick, Red}], Directive[{Thick, Red}],
Directive[{Thick, Lighter[Red], Dashed}], Directive[{Thick, Blue}],
Directive[{Thick, Blue}], Directive[{Thick, Lighter[Blue], Dashed}],
Directive[{Thick, Lighter[Purple], Dashed}],
Directive[{Thick, Lighter[Purple], Dashed}], Directive[
{Thick, Lighter[Purple], Dashed}], Directive[{Thick, Lighter[Purple], Dashed}]]]
```



Variance Explained over time

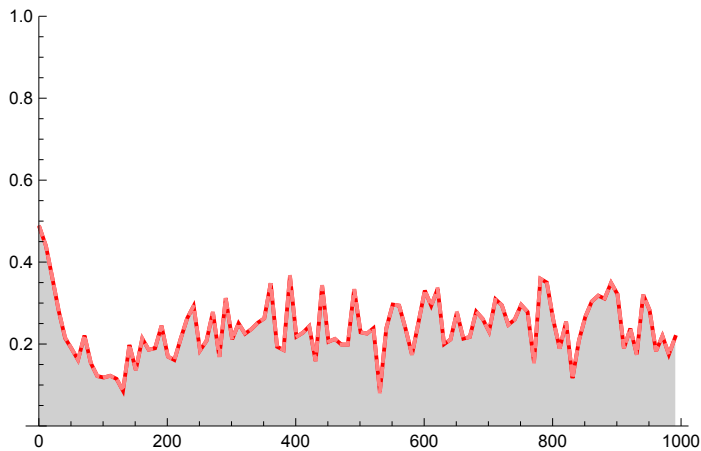
We can use the `sim` and `SimR2` functions from above.

```
R2table = Table[SimR2[ListHDiff[[] ;; , t]], ListPDiff[[] ;; , t], 1000, PdiffX, t],
  {t, 1, tmax /. pars3,  $\frac{tmax /. pars3}{100}$ }]];
```

- ... **LinearModelFit**: The rank of the design matrix 3 is less than the number of terms 4 in the model. The model and results based upon it may contain significant numerical error.
- ... **LinearModelFit**: The rank of the design matrix 5 is less than the number of terms 6 in the model. The model and results based upon it may contain significant numerical error.
- ... **LinearModelFit**: The rank of the design matrix 6 is less than the number of terms 7 in the model. The model and results based upon it may contain significant numerical error.
- ... **General**: Further output of `LinearModelFit::rank` will be suppressed during this calculation.

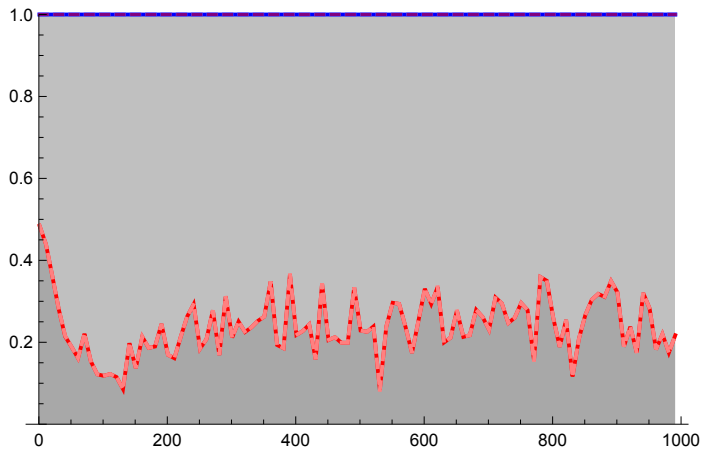
Host-only GWAS

```
HostOnly = ListLinePlot[{R2table[[] ;; , 1]], R2table[[] ;; , 2]},
  PlotStyle → {{Red, Thick}, {Pink, Thick, Dashed}}, Filling → Axis,
  FillingStyle → Directive[Gray, Opacity[0.2]], PlotRange → {0, 1}]
```



Host-Pathogen Co-GWAS

```
HostPath = ListLinePlot[{R2table[[ ; ; , 1]], R2table[[ ; ; , 2]],
  R2table[[ ; ; , 3]], R2table[[ ; ; , 4]], R2table[[ ; ; , 5]]},
  PlotStyle -> {{Red, Thick}, {Pink, Thick, Dashed}, {Blue, Thick},
    {Lighter[Blue], Thick, Dashed}, {Purple, Dashed}}, Filling -> Axis,
  FillingStyle -> Directive[Gray, Opacity[0.2]], PlotRange -> {0, 1}]
```



■ Phenotypic-matching Model

Allele Frequencies over time

```
Pars3 = {tmax -> 1000, r -> 0.5, alpha -> 0.2, xiH -> 0.5, xiP -> 0.5, bH0 -> 0,
  bH1 -> 3, bH2 -> 2, bP0 -> 0, bP1 -> 4, bP2 -> 1, eH -> 0, eP -> 0, mu -> 0.001};
```

```
WH[XH1_, XH2_, t_] := Sum[
  fP[XP1, XP2, t] (1 - xiH Pmatch[zH[XH1, XH2], zP[XP1, XP2]]), {XP1, 0, 1}, {XP2, 0, 1}]
```

The average host fitness at time t is given by:

```
WHavg[t_] := Sum[fH[XH1, XH2, t] WH[XH1, XH2, t], {XH1, 0, 1}, {XH2, 0, 1}]
```

Hence the relative fitness of host genotype $\{XH1, XH2\}$ is given by:

$$wH[XH1_, XH2_, t_] := \frac{WH[XH1, XH2, t]}{WHavg[t]}$$

Similarly we can calculate the recursion equation for the change in parasite genotype frequencies. The absolute fitness of genotype $\{XP1, XP2\}$ is given by

```
WP[XP1_, XP2_, t_] := Sum[fH[XH1, XH2, t] (1 + xiP (Pmatch[zH[XH1, XH2], zP[XP1, XP2]])),
  {XH1, 0, 1}, {XH2, 0, 1}]
```

The average pathogen fitness is:

WPavg[t_] := Sum[fP[XP1, XP2, t] WP[XP1, XP2, t], {XP1, 0, 1}, {XP2, 0, 1}]

The relative fitness

$$wP[XP1_, XP2_, t_] := \frac{WP[XP1, XP2, t]}{WPavg[t]}$$

Module[{Htmp, Ptmp, t}, ListH = {}; ListP = {};

(*Inializing*)

AppendTo[ListH, {0.24, 0.25, 0.27, 0.24}];

AppendTo[ListP, {0.23, 0.25, 0.27, 0.25}];

For[t = 1, t ≤ tmax /. pars3, t++,

Htmp =

$$\left\{ fH[0, 0, t] \frac{WH[0, 0, t]}{WHavg[t]}, fH[1, 0, t] \frac{WH[1, 0, t]}{WHavg[t]}, fH[0, 1, t] \frac{WH[0, 1, t]}{WHavg[t]}, fH[1, 1, t] \frac{WH[1, 1, t]}{WHavg[t]} \right\} /. \{fH[0, 0, t] \rightarrow ListH[[t, 1]], fH[1, 0, t] \rightarrow ListH[[t, 2]],$$

$$fH[0, 1, t] \rightarrow ListH[[t, 3]], fH[1, 1, t] \rightarrow ListH[[t, 4]]\} /.$$

$$\{fP[0, 0, t] \rightarrow ListP[[t, 1]], fP[1, 0, t] \rightarrow ListP[[t, 2]],$$

$$fP[0, 1, t] \rightarrow ListP[[t, 3]], fP[1, 1, t] \rightarrow ListP[[t, 4]]\} /. pars3;$$

$$Htmp = \{Htmp[[1]] (Htmp[[1]] + (Htmp[[2]] + Htmp[[3]]) + (1 - r) Htmp[[4]]) + r Htmp[[2]] Htmp[[3]],$$

$$Htmp[[2]] (Htmp[[2]] + (Htmp[[1]] + Htmp[[4]]) + (1 - r) Htmp[[3]]) + r Htmp[[1]] Htmp[[4]],$$

$$Htmp[[3]] (Htmp[[3]] + (Htmp[[1]] + Htmp[[4]]) + (1 - r) Htmp[[2]]) + r Htmp[[1]] Htmp[[4]],$$

$$Htmp[[4]] (Htmp[[4]] + (Htmp[[2]] + Htmp[[3]]) + (1 - r) Htmp[[1]]) + r Htmp[[2]] Htmp[[3]]$$

} /. pars3;

AppendTo[ListH,

$$\left\{ (1 - \mu)^2 Htmp[[1]] + \mu (1 - \mu) Htmp[[2]] + (1 - \mu) \mu Htmp[[3]] + \mu^2 Htmp[[4]], \right. \\ \mu (1 - \mu) Htmp[[1]] + (1 - \mu)^2 Htmp[[2]] + \mu^2 Htmp[[3]] + (1 - \mu) \mu Htmp[[4]], \\ (1 - \mu) \mu Htmp[[1]] + \mu^2 Htmp[[2]] + (1 - \mu)^2 Htmp[[3]] + \mu (1 - \mu) Htmp[[4]], \\ \left. \mu^2 Htmp[[1]] + (1 - \mu) \mu Htmp[[2]] + \mu (1 - \mu) Htmp[[3]] + (1 - \mu)^2 Htmp[[4]] \right\} /. pars3;$$

$$Ptmp = \left\{ fP[0, 0, t] \frac{WP[0, 0, t]}{WPavg[t]}, fP[1, 0, t] \frac{WP[1, 0, t]}{WPavg[t]}, fP[0, 1, t] \frac{WP[0, 1, t]}{WPavg[t]}, \right.$$

$$\left. fP[1, 1, t] \frac{WP[1, 1, t]}{WPavg[t]} \right\} /. \{fH[0, 0, t] \rightarrow ListH[[t, 1]], fH[1, 0, t] \rightarrow$$

$$ListH[[t, 2]], fH[0, 1, t] \rightarrow ListH[[t, 3]], fH[1, 1, t] \rightarrow ListH[[t, 4]]\} /.$$

$$\{fP[0, 0, t] \rightarrow ListP[[t, 1]], fP[1, 0, t] \rightarrow ListP[[t, 2]],$$

$$fP[0, 1, t] \rightarrow ListP[[t, 3]], fP[1, 1, t] \rightarrow ListP[[t, 4]]\} /. pars3;$$

$$Ptmp = \{Ptmp[[1]] (Ptmp[[1]] + (Ptmp[[2]] + Ptmp[[3]]) + (1 - r) Ptmp[[4]]) + r Ptmp[[2]] Ptmp[[3]],$$

$$Ptmp[[2]] (Ptmp[[2]] + (Ptmp[[1]] + Ptmp[[4]]) + (1 - r) Ptmp[[3]]) +$$

```

    r Ptmp[[1]] Ptmp[[4]],
    Ptmp[[3]] (Ptmp[[3]] + (Ptmp[[1]] + Ptmp[[4]]) + (1 - r) Ptmp[[2]]) +
    r Ptmp[[1]] Ptmp[[4]],
    Ptmp[[4]] (Ptmp[[4]] + (Ptmp[[2]] + Ptmp[[3]]) + (1 - r) Ptmp[[1]]) +
    r Ptmp[[2]] Ptmp[[3]]
  } /. pars3;
AppendTo[ListP,
  {(1 -  $\mu$ )2 Ptmp[[1]] +  $\mu$  (1 -  $\mu$ ) Ptmp[[2]] + (1 -  $\mu$ )  $\mu$  Ptmp[[3]] +  $\mu$ 2 Ptmp[[4]],
   $\mu$  (1 -  $\mu$ ) Ptmp[[1]] + (1 -  $\mu$ )2 Ptmp[[2]] +  $\mu$ 2 Ptmp[[3]] + (1 -  $\mu$ )  $\mu$  Ptmp[[4]],
  (1 -  $\mu$ )  $\mu$  Ptmp[[1]] +  $\mu$ 2 Ptmp[[2]] + (1 -  $\mu$ )2 Ptmp[[3]] +  $\mu$  (1 -  $\mu$ ) Ptmp[[4]],
   $\mu$ 2 Ptmp[[1]] + (1 -  $\mu$ )  $\mu$  Ptmp[[2]] +
   $\mu$  (1 -  $\mu$ ) Ptmp[[3]] + (1 -  $\mu$ )2 Ptmp[[4]]} /. pars3];
];
ListHMatch = Transpose[ListH];
ListPMatch = Transpose[ListP];
]

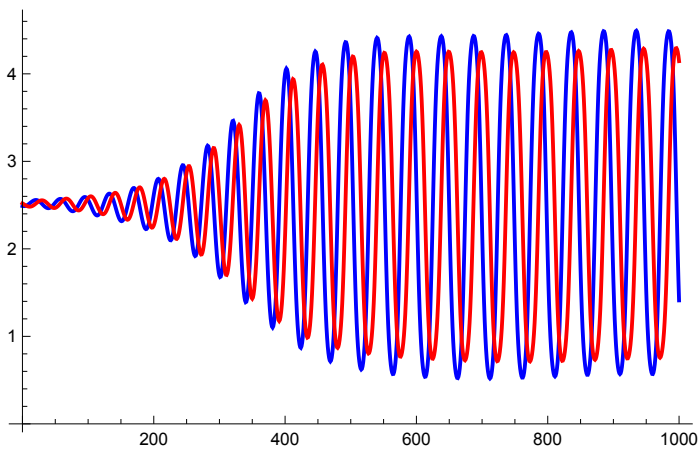
pHList = {ListHMatch[[1]] + ListHMatch[[3]], ListHMatch[[2]] + ListHMatch[[4]],
  ListHMatch[[1]] ListHMatch[[4]] - ListHMatch[[2]] ListHMatch[[3]]};
pPList = {ListPMatch[[1]] + ListPMatch[[3]], ListPMatch[[2]] + ListPMatch[[4]],
  ListPMatch[[1]] ListPMatch[[4]] - ListPMatch[[2]] ListPMatch[[3]]};

Plotting the expected values of zH and zP over time.

zHList = Transpose[{Table[t, {t, 0, tmax /. pars3}],
  Sum[ListHMatch[[2 XH2 + XH1 + 1]] zH[XH1, XH2], {XH1, 0, 1}, {XH2, 0, 1}] /. pars3}];
zPList = Transpose[{Table[t, {t, 0, tmax /. pars3}],
  Sum[ListPMatch[[2 XP2 + XP1 + 1]] zP[XP1, XP2], {XP1, 0, 1}, {XP2, 0, 1}] /. pars3}];

ZPlot = ListLinePlot[{zHList, zPList},
  PlotRange → All, PlotStyle → {{Blue, Thick}, {Red, Thick}}]

```



Effect Sizes over time

Host-only GWAS

$\beta_{H0match}$

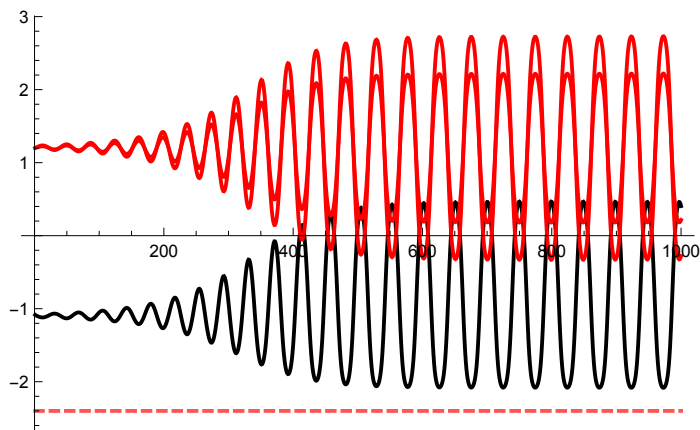
$$\left\{ \begin{aligned} \beta_{H0} &\rightarrow 1 - b_{H0}^2 \alpha + 2 b_{H0} b_{P0} \alpha - b_{P0}^2 \alpha - 2 b_{H0} e_H \alpha + 2 b_{P0} e_H \alpha - e_H^2 \alpha + 2 b_{H0} e_P \alpha - \\ &2 b_{P0} e_P \alpha + 2 e_H e_P \alpha - e_P^2 \alpha - 2 b_{P1} b_{P2} LDP \alpha + 2 b_{H0} b_{P1} p_{P1} \alpha - 2 b_{P0} b_{P1} p_{P1} \alpha - \\ &b_{P1}^2 p_{P1} \alpha + 2 b_{P1} e_H p_{P1} \alpha - 2 b_{P1} e_P p_{P1} \alpha + 2 b_{H0} b_{P2} p_{P2} \alpha - 2 b_{P0} b_{P2} p_{P2} \alpha - \\ &b_{P2}^2 p_{P2} \alpha + 2 b_{P2} e_H p_{P2} \alpha - 2 b_{P2} e_P p_{P2} \alpha - 2 b_{P1} b_{P2} p_{P1} p_{P2} \alpha, \beta_{H1} \rightarrow \\ &- 2 b_{H0} b_{H1} \alpha - b_{H1}^2 \alpha + 2 b_{H1} b_{P0} \alpha - 2 b_{H1} e_H \alpha + 2 b_{H1} e_P \alpha + 2 b_{H1} b_{P1} p_{P1} \alpha + 2 b_{H1} b_{P2} p_{P2} \alpha, \\ \beta_{H2} &\rightarrow - 2 b_{H0} b_{H2} \alpha - b_{H2}^2 \alpha + 2 b_{H2} b_{P0} \alpha - 2 b_{H2} e_H \alpha + 2 b_{H2} e_P \alpha + \\ &2 b_{H2} b_{P1} p_{P1} \alpha + 2 b_{H2} b_{P2} p_{P2} \alpha, \beta_{H12} \rightarrow - 2 b_{H1} b_{H2} \alpha \end{aligned} \right\}$$

PlotH0match =

```
{Table[{t,  $\beta_{H0}$ } /.  $\beta_{H0match}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]], pP2  $\rightarrow$  pPlist[[2, t]],
  LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H1}$ } /.  $\beta_{H0match}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H2}$ } /.  $\beta_{H0match}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H12}$ } /.  $\beta_{H0match}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}];
```

ListLinePlot[PlotH0match,

```
PlotStyle  $\rightarrow$  {Directive[{Thick, Black}], Directive[{Thick, Red}],
  Directive[{Thick, Red}], Directive[{Thick, Lighter[Red], Dashed}]}
```



Host-Pathogen Co-GWAS

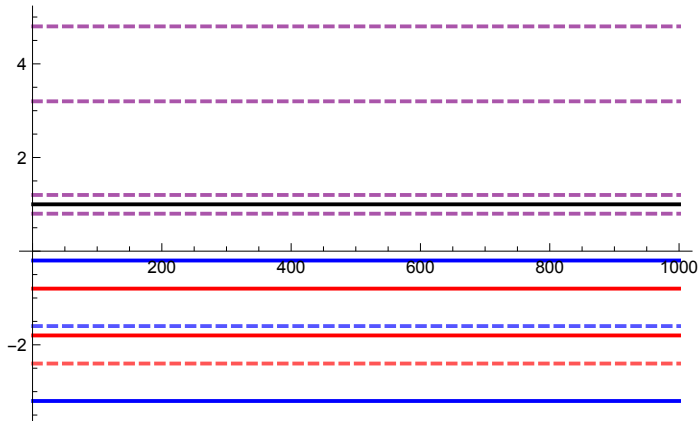
β HPMatch

$$\begin{aligned} \{\beta_0 &\rightarrow 1 - bH_0^2 \alpha - bP_0^2 \alpha - eH^2 \alpha + 2 bP_0 (eH - eP) \alpha + 2 eH eP \alpha - eP^2 \alpha + 2 bH_0 (bP_0 - eH + eP) \alpha, \\ \beta_{H1} &\rightarrow -bH_1 (2 bH_0 + bH_1 - 2 (bP_0 - eH + eP)) \alpha, \beta_{H2} \rightarrow -bH_2 (2 bH_0 + bH_2 - 2 (bP_0 - eH + eP)) \alpha, \\ \beta_{H12} &\rightarrow -2 bH_1 bH_2 \alpha, \beta_{P1} \rightarrow -bP_1 (-2 bH_0 + 2 bP_0 + bP_1 - 2 eH + 2 eP) \alpha, \\ \beta_{P2} &\rightarrow -bP_2 (-2 bH_0 + 2 bP_0 + bP_2 - 2 eH + 2 eP) \alpha, \beta_{P12} \rightarrow -2 bP_1 bP_2 \alpha, \\ \beta_{H1P1} &\rightarrow 2 bH_1 bP_1 \alpha, \beta_{H1P2} \rightarrow 2 bH_1 bP_2 \alpha, \beta_{H2P1} \rightarrow 2 bH_2 bP_1 \alpha, \beta_{H2P2} \rightarrow 2 bH_2 bP_2 \alpha \end{aligned}$$

PlotHPmatch =

```
{Table[{t,  $\beta_0$ } /.  $\beta$ HPMatch /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]], pP2  $\rightarrow$  pPlist[[2, t]],
  LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H1}$ } /.  $\beta$ HPMatch /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H2}$ } /.  $\beta$ HPMatch /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H12}$ } /.  $\beta$ HPMatch /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{P1}$ } /.  $\beta$ HPMatch /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{P2}$ } /.  $\beta$ HPMatch /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{P12}$ } /.  $\beta$ HPMatch /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H1P1}$ } /.  $\beta$ HPMatch /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H1P2}$ } /.  $\beta$ HPMatch /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H2P1}$ } /.  $\beta$ HPMatch /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
Table[{t,  $\beta_{H2P2}$ } /.  $\beta$ HPMatch /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}];
```

```
ListLinePlot[PlotHPmatch, PlotStyle →
  {Directive[{Thick, Black}], Directive[{Thick, Red}], Directive[{Thick, Red}],
  Directive[{Thick, Lighter[Red], Dashed}], Directive[{Thick, Blue}],
  Directive[{Thick, Blue}], Directive[{Thick, Lighter[Blue], Dashed}],
  Directive[{Thick, Lighter[Purple], Dashed}],
  Directive[{Thick, Lighter[Purple], Dashed}], Directive[
  {Thick, Lighter[Purple], Dashed}], Directive[{Thick, Lighter[Purple], Dashed}]]]
```



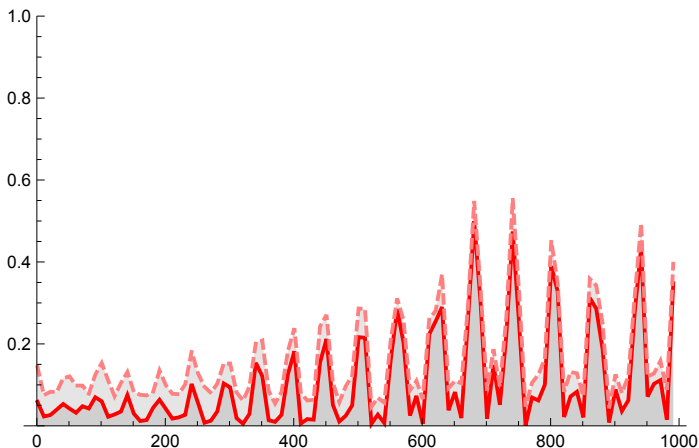
Variance Explained over time

We can use the `sim` and `SimR2` functions from above.

```
R2table = Table[SimR2[ListHMatch[[] ; ; , t]], ListHMatch[[] ; ; , t], 1000, PmatchX, t],
  {t, 1, tmax /. pars3,  $\frac{tmax /. pars3}{100}$ }]];
```

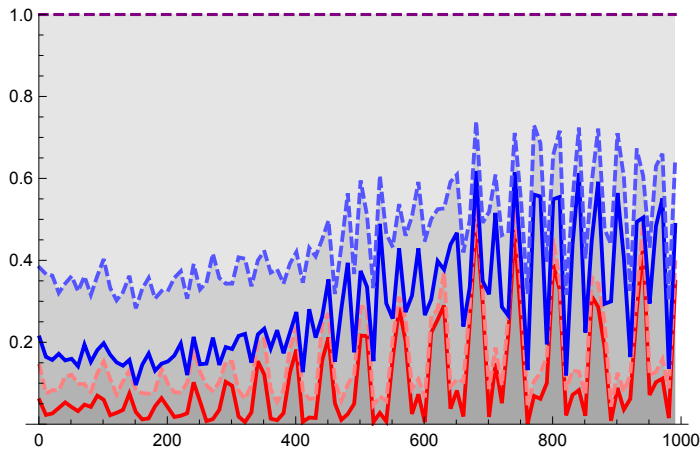
Host-only GWAS

```
HostOnly = ListLinePlot[{R2table[[] ; ; , 1]], R2table[[] ; ; , 2]],
  PlotStyle → {{Red, Thick}, {Pink, Thick, Dashed}}, Filling → Axis,
  FillingStyle → Directive[Gray, Opacity[0.2]], PlotRange → {0, 1}]
```



Host-pathogen Co-GWAS

```
HostPath = ListLinePlot[{R2table[[ ; ; , 1]], R2table[[ ; ; , 2]],
  R2table[[ ; ; , 3]], R2table[[ ; ; , 4]], R2table[[ ; ; , 5]]},
  PlotStyle -> {{Red, Thick}, {Pink, Thick, Dashed}, {Blue, Thick},
    {Lighter[Blue], Thick, Dashed}, {Purple, Dashed}}, Filling -> Axis,
  FillingStyle -> Directive[Gray, Opacity[0.2]], PlotRange -> {0, 1}]
```



■ Matching-alleles Model

Allele Frequencies over time

```
Pars3 = {tmax -> 1000, r -> 0.5, alpha -> 0.2, xiH -> 0.5, xiP -> 0.5, bH0 -> 0,
  bH1 -> 3, bH2 -> 2, bP0 -> 0, bP1 -> 4, bP2 -> 1, eH -> 0, eP -> 0, mu -> 0.001};
```

```
WH[XH1_, XH2_, t_] :=
```

```
Sum[fP[XP1, XP2, t] (1 - xiH PmamX[{XH1, XH2}, {XP1, XP2}]), {XP1, 0, 1}, {XP2, 0, 1}]
```

The average host fitness at time t is given by:

```
WHavg[t_] := Sum[fH[XH1, XH2, t] WH[XH1, XH2, t], {XH1, 0, 1}, {XH2, 0, 1}]
```

Hence the relative fitness of host genotype {XH1,XH2} is given by:

$$wH[XH1_, XH2_, t_] := \frac{WH[XH1, XH2, t]}{WHavg[t]}$$

Similarly we can calculate the recursion equation for the change in parasite genotype frequencies. The absolute fitness of genotype {XP1,XP2} is given by

```
WP[XP1_, XP2_, t_] :=
```

```
Sum[fH[XH1, XH2, t] (1 + xiP (PmamX[{XH1, XH2}, {XP1, XP2}]))], {XH1, 0, 1}, {XH2, 0, 1}]
```

The average pathogen fitness is:

```
WPavg[t_] := Sum[fP[XP1, XP2, t] WP[XP1, XP2, t], {XP1, 0, 1}, {XP2, 0, 1}]
```

The relative fitness

$$wP[XP1_, XP2_, t_] := \frac{WP[XP1, XP2, t]}{WPavg[t]}$$

```
Module[{Htmp, Ptmp, t}, ListH = {}; ListP = {};
(*Inializing*)
AppendTo[ListH, {0.24, 0.25, 0.27, 0.24}];
AppendTo[ListP, {0.23, 0.25, 0.27, 0.25}];
For[t = 1, t ≤ tmax /. pars3, t++,
Htmp =
{fH[0, 0, t]  $\frac{WH[0, 0, t]}{WHavg[t]}$ , fH[1, 0, t]  $\frac{WH[1, 0, t]}{WHavg[t]}$ , fH[0, 1, t]  $\frac{WH[0, 1, t]}{WHavg[t]}$ , fH[1, 1,
t]  $\frac{WH[1, 1, t]}{WHavg[t]}$ } /. {fH[0, 0, t] → ListH[[t, 1]], fH[1, 0, t] → ListH[[t, 2]],
fH[0, 1, t] → ListH[[t, 3]], fH[1, 1, t] → ListH[[t, 4]]} /.
{fP[0, 0, t] → ListP[[t, 1]], fP[1, 0, t] → ListP[[t, 2]],
fP[0, 1, t] → ListP[[t, 3]], fP[1, 1, t] → ListP[[t, 4]]} /. pars3;
Htmp = {Htmp[[1]] (Htmp[[1]] + (Htmp[[2]] + Htmp[[3]]) + (1 - r) Htmp[[4]]) +
r Htmp[[2]] Htmp[[3]],
Htmp[[2]] (Htmp[[2]] + (Htmp[[1]] + Htmp[[4]]) + (1 - r) Htmp[[3]]) +
r Htmp[[1]] Htmp[[4]],
Htmp[[3]] (Htmp[[3]] + (Htmp[[1]] + Htmp[[4]]) + (1 - r) Htmp[[2]]) +
r Htmp[[1]] Htmp[[4]],
Htmp[[4]] (Htmp[[4]] + (Htmp[[2]] + Htmp[[3]]) + (1 - r) Htmp[[1]]) +
r Htmp[[2]] Htmp[[3]]
} /. pars3;
AppendTo[ListH,
{(1 - μ)2 Htmp[[1]] + μ (1 - μ) Htmp[[2]] + (1 - μ) μ Htmp[[3]] + μ2 Htmp[[4]],
μ (1 - μ) Htmp[[1]] + (1 - μ)2 Htmp[[2]] + μ2 Htmp[[3]] + (1 - μ) μ Htmp[[4]],
(1 - μ) μ Htmp[[1]] + μ2 Htmp[[2]] + (1 - μ)2 Htmp[[3]] + μ (1 - μ) Htmp[[4]],
μ2 Htmp[[1]] + (1 - μ) μ Htmp[[2]] +
μ (1 - μ) Htmp[[3]] + (1 - μ)2 Htmp[[4]]} /. pars3];
Ptmp = {fP[0, 0, t]  $\frac{WP[0, 0, t]}{WPavg[t]}$ , fP[1, 0, t]  $\frac{WP[1, 0, t]}{WPavg[t]}$ , fP[0, 1, t]  $\frac{WP[0, 1, t]}{WPavg[t]}$ ,
fP[1, 1, t]  $\frac{WP[1, 1, t]}{WPavg[t]}$ } /. {fH[0, 0, t] → ListH[[t, 1]], fH[1, 0, t] →
ListH[[t, 2]], fH[0, 1, t] → ListH[[t, 3]], fH[1, 1, t] → ListH[[t, 4]]} /.
{fP[0, 0, t] → ListP[[t, 1]], fP[1, 0, t] → ListP[[t, 2]],
fP[0, 1, t] → ListP[[t, 3]], fP[1, 1, t] → ListP[[t, 4]]} /. pars3;
Ptmp = {Ptmp[[1]] (Ptmp[[1]] + (Ptmp[[2]] + Ptmp[[3]]) + (1 - r) Ptmp[[4]]) +
r Ptmp[[2]] Ptmp[[3]],
Ptmp[[2]] (Ptmp[[2]] + (Ptmp[[1]] + Ptmp[[4]]) + (1 - r) Ptmp[[3]]) +
r Ptmp[[1]] Ptmp[[4]],
```



```

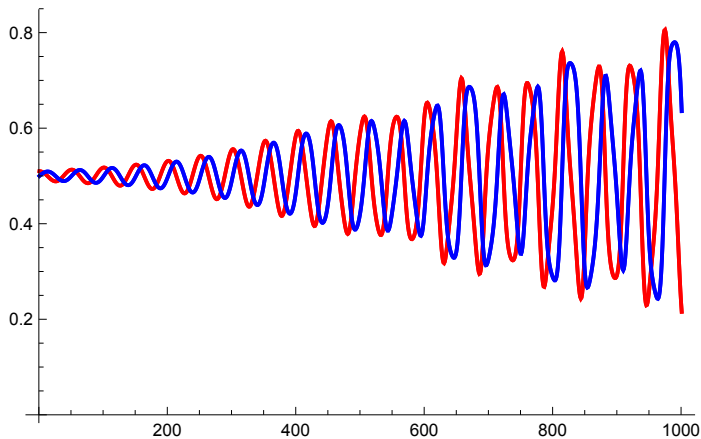
Ptmp[[3]] (Ptmp[[3]] + (Ptmp[[1]] + Ptmp[[4]]) + (1 - r) Ptmp[[2]]) +
r Ptmp[[1]] Ptmp[[4]],
Ptmp[[4]] (Ptmp[[4]] + (Ptmp[[2]] + Ptmp[[3]]) + (1 - r) Ptmp[[1]]) +
r Ptmp[[2]] Ptmp[[3]]
} /. pars3;
AppendTo[ListP,
{(1 - μ)2 Ptmp[[1]] + μ (1 - μ) Ptmp[[2]] + (1 - μ) μ Ptmp[[3]] + μ2 Ptmp[[4]],
μ (1 - μ) Ptmp[[1]] + (1 - μ)2 Ptmp[[2]] + μ2 Ptmp[[3]] + (1 - μ) μ Ptmp[[4]],
(1 - μ) μ Ptmp[[1]] + μ2 Ptmp[[2]] + (1 - μ)2 Ptmp[[3]] + μ (1 - μ) Ptmp[[4]],
μ2 Ptmp[[1]] + (1 - μ) μ Ptmp[[2]] +
μ (1 - μ) Ptmp[[3]] + (1 - μ)2 Ptmp[[4]]} /. pars3];
];
ListHMAM = Transpose[ListH];
ListPMAM = Transpose[ListP];
]

pHlist = {ListHMAM[[1]] + ListHMAM[[3]], ListHMAM[[2]] + ListHMAM[[4]],
ListHMAM[[1]] ListHMAM[[4]] - ListHMAM[[2]] ListHMAM[[3]]};
pPlist = {ListPMAM[[1]] + ListPMAM[[3]], ListPMAM[[2]] + ListPMAM[[4]],
ListPMAM[[1]] ListPMAM[[4]] - ListPMAM[[2]] ListPMAM[[3]]};

Plotting the allele frequencies over time

PPlot = ListLinePlot[{pHlist[[1, ;;]], pHlist[[1, ;;]],
pPlist[[1, ;;]], pPlist[[1, ;;]]}, PlotRange → All,
PlotStyle → {{Red, Thick}, {Red, Thick}, {Blue, Thick}, {Blue, Thick}}]

```



Effect Sizes over time

Host-only GWAS

β_{H0mam}

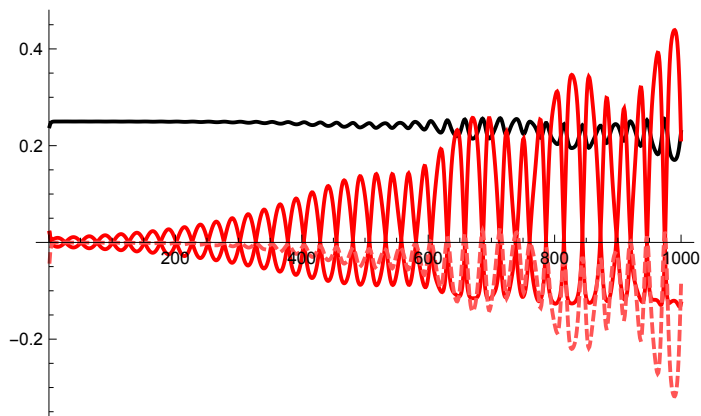
$\{\beta_0 \rightarrow 1 + LDP - pP1 - pP2 + pP1 pP2, \beta_{H1} \rightarrow -1 - 2 LDP + 2 pP1 + pP2 - 2 pP1 pP2,$
 $\beta_{H2} \rightarrow -1 - 2 LDP + pP1 + 2 pP2 - 2 pP1 pP2, \beta_{H12} \rightarrow 1 + 4 LDP - 2 pP1 - 2 pP2 + 4 pP1 pP2\}$

PlotH0mam =

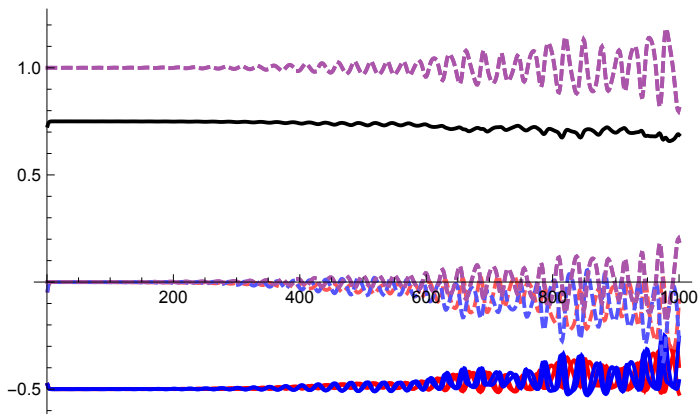
```
{Table[{t,  $\beta_0$ } /.  $\beta_{H0mam}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]], pP2  $\rightarrow$  pPlist[[2, t]],
  LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
  Table[{t,  $\beta_{H1}$ } /.  $\beta_{H0mam}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]], pP2  $\rightarrow$  pPlist[[2, t]],
  LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
  Table[{t,  $\beta_{H2}$ } /.  $\beta_{H0mam}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}],
  Table[{t,  $\beta_{H12}$ } /.  $\beta_{H0mam}$  /. pars3 /. {pP1  $\rightarrow$  pPlist[[1, t]],
  pP2  $\rightarrow$  pPlist[[2, t]], LDP  $\rightarrow$  pPlist[[3, t]]}, {t, 1, tmax /. pars3}];
```

ListLinePlot[PlotH0mam,

```
PlotStyle  $\rightarrow$  {Directive[{Thick, Black}], Directive[{Thick, Red}],
  Directive[{Thick, Red}], Directive[{Thick, Lighter[Red], Dashed}]}
```




```
ListLinePlot[PlotHPmam, PlotStyle →
  {Directive[{Thick, Black}], Directive[{Thick, Red}], Directive[{Thick, Red}],
  Directive[{Thick, Lighter[Red], Dashed}], Directive[{Thick, Blue}],
  Directive[{Thick, Blue}], Directive[{Thick, Lighter[Blue], Dashed}],
  Directive[{Thick, Lighter[Purple], Dashed}],
  Directive[{Thick, Lighter[Purple], Dashed}], Directive[
  {Thick, Lighter[Purple], Dashed}], Directive[{Thick, Lighter[Purple], Dashed}]]]
```



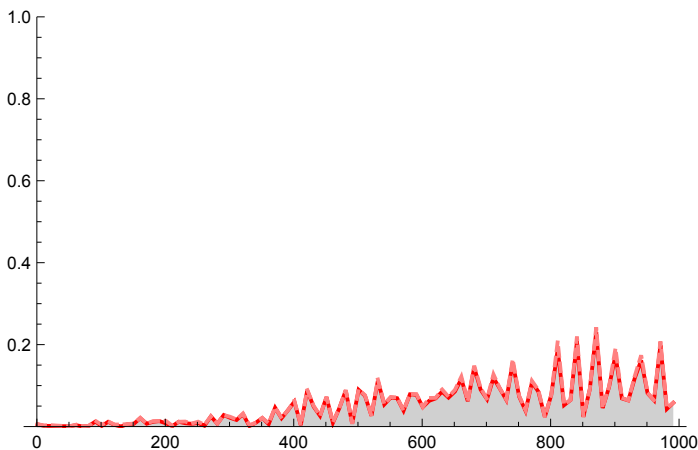
Variance Explained over time

We can use the `sim` and `SimR2` functions from above.

```
R2table = Table[SimR2[ListHMAM[[ ; ; , t]], ListHMAM[[ ; ; , t]], 1000, PmamX, t],
  {t, 1, tmax /. pars3,  $\frac{tmax /. pars3}{100}$ }]];
```

Host-only GWAS

```
HostOnly = ListLinePlot[{R2table[[ ; ; , 1]], R2table[[ ; ; , 2]]},
  PlotStyle → {{Red, Thick}, {Pink, Thick, Dashed}}, Filling → Axis,
  FillingStyle → Directive[Gray, Opacity[0.2]], PlotRange → {0, 1}]
```



Host-pathogen Co-GWAS

```
HostPath = ListLinePlot[{R2table[[ ; ; , 1]], R2table[[ ; ; , 2]],  
  R2table[[ ; ; , 3]], R2table[[ ; ; , 4]], R2table[[ ; ; , 5]]},  
  PlotStyle → {{Red, Thick}, {Pink, Thick, Dashed}, {Blue, Thick},  
    {Lighter[Blue], Thick, Dashed}, {Purple, Dashed}}, Filling → Axis,  
  FillingStyle → Directive[Gray, Opacity[0.2]], PlotRange → {0, 1}]
```

