Co-evolution of Host and Parasite with Pleiotropy

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Abstract. Host and parasite are locked in a reciprocal relationship, yielding many interesting evolutionary outcomes. Hosts evolve sophisticated defensive strategies to protect themselves against parasites while parasites are expected to develop counter-defensive strategies to increase their infection rate. The matching allele (MA) model frequently results in oscillations of defensive and offensive strategies whereas the gene-for-gene (GFG) model predicts escalation and fixation of host and parasite strategies. Oscillations only occured in the GFG model when defense or offense comes with a cost. Pleiotropy is a form of cost that has been widely accepted in theoretical works and intensively studied in empirical areas. Yet no mathematical model has ever taken the effect of pleiotropy into account. Here, we used a quantitative genetic model to introduce pleiotropy on host traits to illustrate the co-evolution of host defense and parasite offense. In this way, we can track the evolution of defensive strategy with respect to the change of the pleiotropic trait. Furthermore, we would like to show that the GFG model can also produce oscillations of host defense and parasite offense when multiple defensive and offensive strategies are involved.

1 Introduction

Host-parasite relationship is ubiquitous in nature (Poulin (2014),Windsor (1998)). Parasites live on or in their hosts, exploit them and by definition, create harm to the hosts. Hosts therefore are expected to evolve defensive strategies against parasites, which in turn forces the parasites to develop counter-defensive strategies. Host and parasite are thus locked in an antagonistic interaction resulting in many evolutionary consequences. Two conventional outcomes from this co-evolution are (i) the escalation of the parasite virulence and host resistance and (ii) the cyclic evolution of matching virulence and resistance genotypes. Studying the co-evolution of virulence and resistance has been endlessly inspiring for theoretical biologists whose well-known and most classical works are the gene-for-gene (GFG) model and the matching allele (MA) model. Virulence in these two models is viewed as pathogen infectivity.

The GFG model has it foundation laid by Flor (1955) with his research on the resistance of flax and the virulence of its fungal pathogen flax rust (Flor 1955). The idea of the model is that for each resistant allele in the host there is a corresponding and specific virulence allele in the parasite. Such hostile allele of the parasite is considered dominant and universally virulent to the corresponding resistant allele. Parasites that bear the virulent allele are able to infect hosts with the corresponding resistant allele and those with the susceptible alleles, thereby forcing the host to introduce a new resistant allele (Table 1). This newly resistant allele is no longer affected by the old virulent allele whose bearers thereby reduce in number, thus creating a new selection pressure on the parasite. Such antagonistic selection will result in an escalation of host resistance and parasite virulence.

The MA model, on the other hands, assumes that there is no universal virulent allele and infection only occurs when the parasite bears a genotype that matches exactly with the host genotype. In the simplest illustration, a parasite has genotype P1 that can only infect host genotype H1 and genotype P2 that can only infect host genotype H2. As P1 parasite is abundant, the number of H1 host will decrease, leaving spaces for the H2 host that is only infected by P2 parasite. The increase of H2 host now facilitates the rise of its matching P2 parasite, which in turns gives ways to the growth of the H1 host. Eventually, a cycle of the two types of host and parasite's genotypes

will occur in the population.

Gene for gene Model			**Matching allel Model**		
Host \Parasite	V-	vv	**Host \Parasite**	P1	P2
R-	-	+	H1	+	-
rr	+	+	P2	-	+

Table 1: Host-parasite genetic interaction models with one virulent/resistant factor. The sign (+) indicates a successful infection and the sign (-) indicates failure in infection.

A critical difference between the GFG model and the MA model is that without any further assumption, escalating arm races and rapid fixation of virulent and resistant alleles are expected in the GFG model while continual cycles and polymorphism are predicted in the MA model (Agrawal and Lively (2002),Frank (1993),Sasaki (2000)). In nature, fixation of virulence is not ubiquitous and infinite increase of host resistance is nearly impossible because being virulent or resistant is costly (Smchid Hempel (2011)). To defend against parasites, a host needs two investments: the energy to mount a defensive response when infection occurs and the energy to maintain such defensive system even without any interaction with parasites. Similarly, a parasite needs to invest in both maintaining and operating its infectivity. Such energy is withdrawn from the total fixed energy bank that individuals also use to invest in other vital activities such as growing and reproducing. Energy allocated to one task could not be invested in the other, thus resistance and virulence always comes with a cost. Such cost could be simply due to constraint of energy allocation as mentioned above but could also due to pleiotropy, which is a phenomenon where a gene coding for one phenotypic trait affects other seemingly unrelated trait; the evolution of one trait will limit that of the other (Stearns (2010)).

Costly virulence and resistance is among key factors that break the fixation and infinite escalating arm races in the GFG model, maintaining genetic variations of host resistance and parasite virulence similar to the MA model (Leonard (1977), Damgaard (1999), Parker (1994), Seger (1992), Frank (1992), Sasaki et al. (2002)). Thus, GFG model and MA model are rivaled in capturing a common incident in

nature: the diversity of host resistant genotypes and parasite virulent genotypes. All most all the earliest works modeled virulence and resistance using a constant cost imposed on individuals carrying the resistant or virulent allele assuming a monogenic basis (Mode (1958), Frank (1992), Parker (1994), Agrawal and Lively (2002), Luijckx et al. (2013)). Recently, increasing empirical evidences have pointed out that virulence and resistance are more likely quantitative traits (Asea et al. (2009), Kröner et al. (2011), Lan et al. (2015), Luong and Polak (2007a), Luong and Polak (2007b), Polak (2003), Quenouille et al. (2014), Stefansson et al. (2014)). Frank's model (1994) is actually among the few works that treated virulence and resistance as polygenic traits Frank (1994). Although his work could only take into account a maximum of 8 loci due to complexity and cost was introduced as an additive constant whenever a virulent/resistant allele was added. A few other models studied virulence and resistance based on quantitative genetic model however the cost was introduced simply either as a monotonic increase function with respect to phenotypic traits or as a function constantly assuming an intermediate virulence and resistance (Sasaki and Godfray (1999), Gavrilets (1997), Nuismer et al. (2005), Nuismer et al. (2007)).

In this model, we would like to explore the co-evolution of virulence and resistance using quantitative genetic model with the cost introduced in the form of pleiotropic effect. The first aim of the model is to understand the dynamic of the phenotypic resistant and virulent value under both the GFG and MA model. It should be remarked again that here virulence is viewed as a factor that affect infectivity rather than damage to the host. The phenotypic value indicates how many virulent/resistant alleles in a genotype, which should be considered more as how much investment is placed on infectivity/defense. Henceforth, we will use the term defense and offense rather than resistance and virulence to avoid confusion in result interpretation. The second aim of the model is to understand the pleiotropic effect on the dynamic of host defensive phenotypic value. This is another way to introduce cost on host resistance, in which we can track the evolution of defensive strategy following the evolution of the pleiotropic trait. Under the context of quantitative traits, pleiotropy is understood as the genetic overlapping between two quantitative trait loci, one of which controls host defense or parasite offense the other codes for other seemingly unrelated phenotypes (e.g. growth rate, reproduction). Changes of the defensive phenotypic value will lead

to changes of pleiotropic phenotypic value and via versa.

We first worked on a model with a single pair of defensive-offensive traits under the relationship in both GFG and MA models. In this simple version of the model, we expected an escalation of parasite offense and host defense in the GFG model and oscillations of the two traits in the MA model. In fact, some quantitative models on the interaction of host and parasite predicted similar results, although none of them has ever considered the effect of pleiotropy (Nuismer et al. (2005), Nuismer et al. (2007)). We expected that pleiotropy would stabilize the oscillations as the cyclic dynamic of host defense will be constrained by its pleiotropic trait.

Surprisingly, there has been no theoretical work exploring the multiple defensive/offensive strategies yet this phenomenon is common. In fact, a host invests in more than one trait to avoid parasite infection; as such intuitively a parasite is expected to have equal counter-strategies for its successful infection (Smchid Hempel (2011)). For example, host starts escaping from infection by changing behavior to avoid sites where parasites are abundant (Powell et al. (2006), Oi and Pereira (1993)). Once a host interacts with a parasite it mounts a cascade of different immune moleculars involving in detecting and eliminating the parasite; as such parasite also evolves a variety of strategies to hide it self from the host to elevate infectivity (Smchid Hempel (2011)).

Most of the monogenic base models explored the dynamic of single trait interaction (Frank (1992), Parker (1994),Agrawal and Lively (2002), Luijckx et al. (2013)); some of them studied di-allele host interacting with many parasite strains each can be considered a single strategy that has different infectivity on certain host genotype (Seger (1992)). The polygenic base models, however, only explores the single trait interaction probably due the already complexity of the model (Frank (1993), Frank (1994),Sasaki and Godfray (1999), Gavrilets (1997), Nuismer et al. (2005), Nuismer et al. (2007)). Therefore, we would like to introduce one more defensive-offensive strategy on top of the mentioned single-trait-interaction quantitative model to understand the phenotypic dynamic under the multiple defensive – offensive strategies. In each defensive-offensive pair host interacts with parasite by the GFG model. In this extended model, we expected a result similar to the MA model, i.e. cycle of phenotypic traits, even though host-parasite traits interact with each other following

the GFG model.

2 Host-parasite interaction with a single pair of defense - offensive trait

2.1 Model structure

We considered the dynamic of three quantitative traits: host defense x, parasite offense y and host pleiotropic trait u that is genetically correlated with x by a magnitude c (pleiotropy). The traits are assumed to be normally distributed with a constant additive genetic variance $\mathcal{V}_{\mathrm{x}}$, $\mathcal{V}_{\mathrm{y}}$ and $\mathcal{V}_{\mathrm{u}}$. Defensive allele and infectivity allele have equal additive effect on the phenotype (Figure 1C).

Both host and parasite are subjects to two selective forces: (i) stabilizing selection and (ii) selection due to host-parasite interaction or co-evolutionary selection. Stabilizing selection assumes that an individual is at its highest fitness for a trait (i.e. maximal reproduction and lifespan) when the trait is at its optimum value. Thus this selective force always pushes host and parasite traits toward their corresponding optimum values. Contrary, the direction of the co-evolutionary selection depends on the difference between host defense and parasite offense which itself depends on the type of host-parasite interaction.

Under the GFG model, host-parasite interaction follows a regime such that infection is facilitated when parasite offensive value is higher than host defensive value (Figure 1A – lower panel). Although, increasing the offensive value will not result in infinite increase of infection likelihood. Thus, the infection likelihood $\mathcal{W}_{\mathrm{int}}$ when a host with phenotypic value x interacts with a parasite with phenotypic value y is a sigmoid function of the phenotypic difference between the two traits (Figure 1A)

$$\mathcal{W}_{\mathrm{int(GFG)}}(x, y) = \frac{1}{e^{1+\alpha(x-y)}}$$

α is the sensitivity of the difference between the defensive value and the offensive value. A high value of α indicates that a small rise of offensive value generates significant effect on the infection rate while a small value of α suggests that the

parasite need to increase its offensive value extensively to raise a significant increase in infection. In this GFG model, selection force follows a unique direction, pushing the phenotypic values as high as possible.

On the other hand, under the MA model, host-parasite interaction follows a regime in which similar between offensive and defensive strategy promotes infection likelihood. In this scenario, infection is maximized when parasites have their offensive traits that are literally matched with hosts' defensive traits (Figure 1B). The infection likelihood $\mathcal{W}_{\text{int}}$ when a host with phenotype x interacts with a parasite with phenotype y in this case is a gaussian function of the phenotypic difference between the two traits

$$\mathcal{W}_{\text{int(MA)}}(x, y) = e^{-\alpha(x-y)^2}$$

Selection therefore is able to favor parasites with low defensive and offensive strategy.

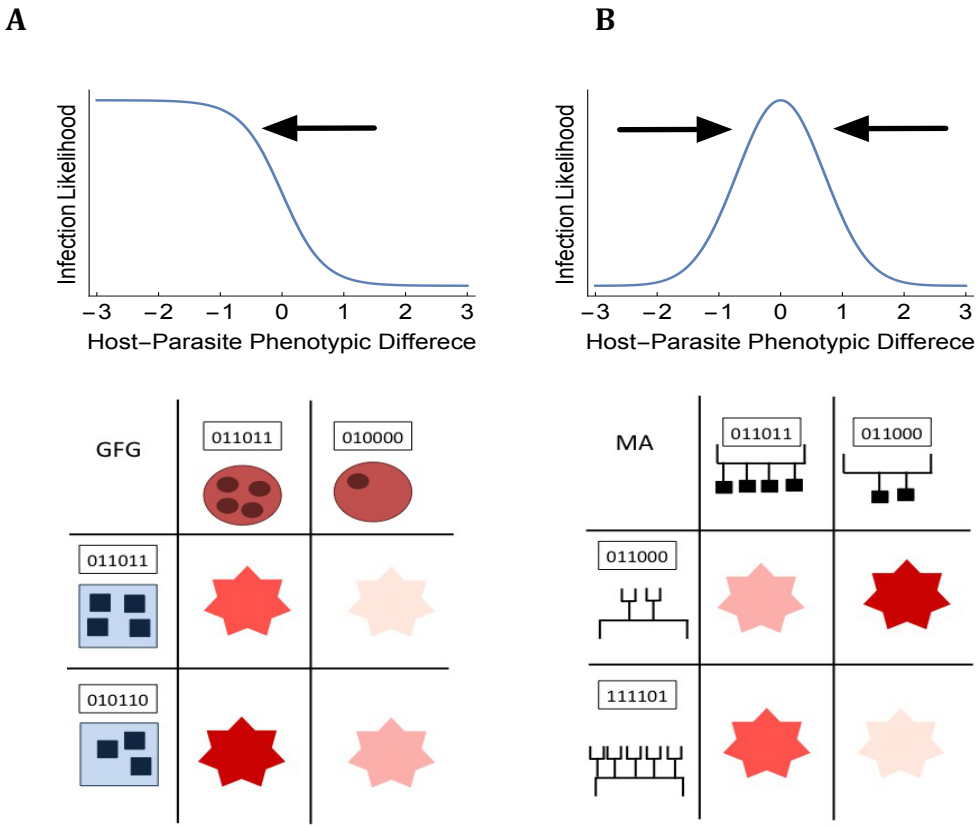

Figure 1: Upper panels: functions of the infection likelihood with respect to host-parasite phenotypic difference, black arrows indicate direction of selection. Lower panels: schematic illustration of genotype-phenotype translation and phenotype-phenotype interaction between hosts and parasites. Gradient of the red color indicates degree of infection, the redder the star the more likely the successful infection. **A** Relationship under the gene-for-gene (GFG) model. **B**. Relationship under the matching allele (MA) model

We next assume that host and parasite each has its own baseline fitness $\mathrm{K_H}$ and $\mathrm{K_P}$ respectively and that the damage to the host ξ_{H} and the benefit to the parasite ξ_{P} resulting from an infection are different. The fitness after an infection is different for host and parasite

$$\mathcal{W}_{\mathrm{intH}}(x, y) = K_{\mathrm{H}} + \xi_{\mathrm{H}}\mathcal{W}_{\mathrm{int}}$$

$$\mathcal{W}_{\mathrm{intP}}(x, y) = K_{\mathrm{P}} + \xi_{\mathrm{P}}\mathcal{W}_{\mathrm{int}}$$

The likelihood of infection is positively correlated with parasite fitness and negatively correlated with host fitness, therefore ξ_{H} is always negative and ξ_{P} is always positive.

The total fitness is the multiplicative result of the fitness from stabilizing selection and that from host-parasite interaction

$$\mathcal{W}_{\mathrm{Htotal}}(x, y, u) = e^{\gamma_{\mathrm{x}}(x-\theta_{\mathrm{x}})} e^{\gamma_{\mathrm{u}}(u-\theta_{\mathrm{u}})^2} \mathcal{W}_{\mathrm{intH}}$$

$$\mathcal{W}_{\mathrm{Ptotal}}(x, y) = e^{\gamma_{\mathrm{y}}(y-\theta_{\mathrm{y}})^2} \mathcal{W}_{\mathrm{intP}}$$

The term $e^{\gamma_i(i-\theta_{\mathrm{i}})^2}$ indicates the fitness resulting from stabilizing selection, where i can represent any of the phenotypic traits, γ_{i} indicates the strength of the stabilizing selection on the corresponding traits. The fitness of the host now depends not only on its defensive phenotypic value x but also the phenotypic value of its pleiotropic trait u.

The evolutionary dynamics of the average phenotypic value of host and parasite's traits follows the breeder's equation: $\frac{d\boldsymbol{v}}{dt} = \mathbf{G}\beta(\boldsymbol{v})$,in which $\boldsymbol{v} = (\overline{x}, \overline{u}, \overline{y})$ is the vector of the average phenotypic values of host and parasite. $\mathbf{G}$ is the additive genetic variance-covariance matrix that is given by

$$\begin{pmatrix} \mathcal{V}_{\mathrm{x}} & c & 0 \\ c & \mathcal{V}_{\mathrm{u}} & 0 \\ 0 & 0 & \mathcal{V}_{\mathrm{y}} \end{pmatrix}$$

where c is the genetic correlation between x and u, whose value ranges from (-1, 1) with 0 corresponding to no genetic correlation and ± 1 corresponding to complete genetic correlation. The sign indicates the direction of the pleiotropic effect on the defensive trait.

$\beta(v)$=(β_{x},β_{u},β_{y}) is the vector of selection gradient that represents the magnitude and the direction of selection acting directly on the corresponding traits, in the context of current host and parasite population with the average phenotypic trait v. β_{x},β_{u},β_{y} is calculated as the derivative of the total fitness function with respect to the corresponding trait at the point of population average phenotypic value, weighted by the mean fitness

$$\beta_{\mathrm{x}} = \frac{1}{\mathcal{W}_{\mathrm{Htotal}}(\overline{x}, \overline{y}, \overline{u})} \frac{\mathcal{W}_{\mathrm{Htotal}}(x, y, u)}{dx}\Big|_{x=\overline{x}}, \beta_{\mathrm{y}} = \frac{1}{\mathcal{W}_{\mathrm{Ptotal}}(\overline{x}, \overline{y})} \frac{\mathcal{W}_{\mathrm{Ptotal}}(x, y)}{dy}\Big|_{y=\overline{y}},$$
$$\beta_{\mathrm{u}} = \frac{1}{\mathcal{W}_{\mathrm{Htotal}}(\overline{x}, \overline{y}, \overline{u})} \frac{\mathcal{W}_{\mathrm{Htotal}}(x, y, u)}{du}\Big|_{u=\overline{u}}$$

Since the fitness functions are different between the GFG model and the MA model, we end up having different forms of the selection gradients for each model

$$\beta_{\mathrm{x(GFG)}} = \frac{\alpha}{1+e^{\alpha(\overline{x}-\overline{y})}} \breve{} \frac{\alpha(K_{\mathrm{H}}+\xi_{\mathrm{H}})}{K_{\mathrm{H}}+e^{\alpha(\overline{x}-\overline{y})}K_{\mathrm{H}}+\xi_{\mathrm{H}}} + 2\gamma_{\mathrm{x}}(\theta_{\mathrm{x}}-\overline{x}) \tag{1}$$

$$\beta_{\mathrm{y(GFG)}} = -\frac{\alpha}{1+e^{\alpha(\overline{x}-\overline{y})}} + \frac{\alpha(K_{\mathrm{P}}+\xi_{\mathrm{P}})}{K_{\mathrm{P}}+e^{\alpha(\overline{x}-\overline{y})}K_{\mathrm{P}}+\xi_{\mathrm{P}}} + \gamma_{\mathrm{y}}(\theta_{\mathrm{y}}-\overline{y}) \tag{2}$$

$$\beta_{\mathrm{u(GFG)}} = 2\gamma_{\mathrm{u}}(\theta_{\mathrm{u}}-\overline{u}) \tag{3}$$

$$\beta_{\mathrm{x(MA)}} = \gamma_{\mathrm{x}}(\theta_{\mathrm{x}}-\overline{x}) - \frac{2(\overline{x}-\overline{y})\alpha\xi_{\mathrm{H}}}{e^{\alpha(\overline{x}-\overline{y})2\alpha}K_{\mathrm{H}}+\xi_{\mathrm{H}}} \tag{4}$$

$$\beta_{\mathrm{y(MA)}} = \gamma_{\mathrm{y}}(\theta_{\mathrm{y}}-\overline{y}) + \frac{2(\overline{x}-\overline{y})\alpha\xi_{\mathrm{P}}}{e^{\alpha(\overline{x}-\overline{y})2\alpha}K_{\mathrm{P}}+\xi_{\mathrm{P}}} \tag{5}$$

$$\beta_{\mathrm{u(MA)}} = 2\gamma_{\mathrm{u}}(\theta_{\mathrm{u}}-\overline{u}) \tag{6}$$

2.2 Mathematical analysis

To find the equilibrium we set the vector $\dfrac{d\boldsymbol{v}}{dt} = \mathbf{G}\beta(\boldsymbol{v}) = 0$. Since the determinant of matrix $\mathbf{G}$ is always non-zero an invertible matrix of $\mathbf{G}$ always exists, therefore the equation can be solved by simply setting the gradient vector $\beta(\boldsymbol{v}) = 0$. As such, we need to solve a system of equations (1), (2), (3) for the GFG model and equations (4), (5), (6) for the MA model. It is clearly seen that by solving equation (3) in the GFG model and equation (6) in the MA model, the equilibrium for the pleiotropic trait u in both models is θ_{u}. Thus, we are left with equations (1) and (2) for the GFG model and equations (4) and (5) for the MA model.

The two variables x and y in the remaining equations locates both inside and outside of the exponential terms, which make it difficult for an analytical solution. We thus evaluated the equilibrium approximately by graphical method. First, we reduced the system of two remaining equations of two variables (x and y) into one equation of two variables (x and y). Since the explicit equilibrium value of x and y separately is not as important as the difference between the two values, we then substitute the two variables with a new variable $\overline{z} = \overline{x} - \overline{y}$. This new variable $\overline{z}$ is not only directly related to the infection likelihood as well as host and parasite fitness, it also makes the equations simpler. We then approximate the equation assuming very weak stabilizing

selection ($\gamma_{\mathrm{x}} \approx 0, \gamma_{\mathrm{y}} \approx 0$) and very small host lost and parasite gain ($\xi_{\mathrm{H}} \approx 0, \xi_{\mathrm{P}} \approx 0$) to archive a simple equation that is easier to solve by graphical method as followed

$$\alpha \frac{\frac{\xi_{\mathrm{H}}}{\gamma_{\mathrm{H}} K_{\mathrm{H}}} + \frac{\xi_{\mathrm{P}}}{\gamma_{\mathrm{y}} K_{\mathrm{P}}}}{4(1 + Cosh(\bar{z}\alpha)} = \bar{z} - \theta x + \theta y \;\; under GFG model \tag{7}$$

$$-e^{\alpha \bar{z}^2} z\alpha \left(\frac{\xi_{\mathrm{H}}}{\gamma_{\mathrm{x}} K_{\mathrm{H}}} + \frac{\xi_{\mathrm{P}}}{\gamma_{\mathrm{y}} K_{\mathrm{P}}} \right) = \bar{z} - \theta x + \theta y \;\; under MA model \tag{8}$$

The right term of the equation is always a line with slope of 1 and an intercept of $-\theta_{\mathrm{x}} + \theta_{\mathrm{y}}$; the left term of the equation is a curve whose form depends on the parameter value; the intersect of the line and the curve is the equilibrium we need to find. By varying the parameter value, we estimated the number and the value of the equilibrium graphically. We performed bifurcation analysis to explore the model behavior.

2.3 Result

2.3.1 Gene for gene model

The key result of the GFG model is the escalating arm races of host defense and parasite offense. Due to the cost introduced by stabilizing selection, these values do not rise indefinitely but level off at their own stable equilibrium state. Pleiotropic effect does not qualitatively alter the model dynamic.

When there is no genetic correlation between x and u (no pleiotropy c=0), the change of host defensive value depends on two elements: (i) the deviation from its optimum value (θ_{x}) and (ii) the parasite offensive value (y). As such solely the balance between fitness from stabilizing selection and fitness from host-parasite interaction affects the speed to the equilibrium point. Therefore, host defensive value and parasite offensive value reach their equilibrium rapidly (Figure 2B). When pleiotropy is introduced, i.e. c$\neq$ 0, the change of host defensive value relies on another factor beside the mentioned ones: (iii) the phenotypic value of the pleiotropic trait u. A change in the phenotypic value of the pleiotropic trait u drags along the alteration of host defensive value, which itself may be pulled away from the optimum value or become much lower than the parasite infectivity value. Consequently, introducing pleiotropy requires many

more adjustments for the host to meet all the fitness balances, which prolongs the time to reach the equilibrium (Figure 2B, 2C).

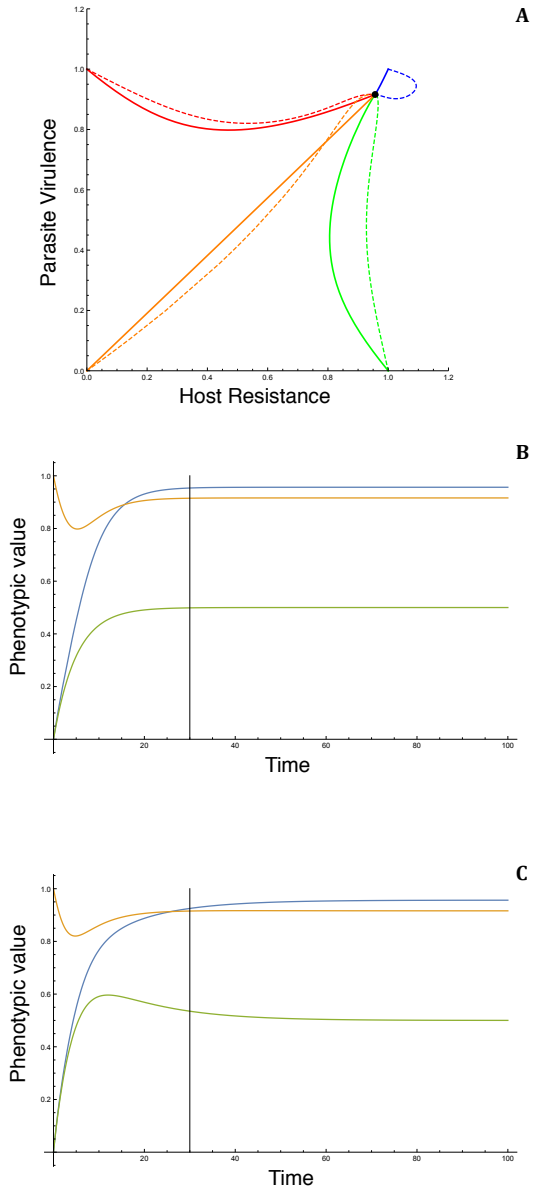

Figure 2: **A**. Parametric plot of offensive and defensive phenotypic value. Thick lines represent cases where c=0, dot lines represent cases where c=0.65. Different colors correspond to different initial values. **B**, **C** Time series of defensive and offensive phenotypic values with and without pleiotropy (c = 0,c = 0.65 respectively). Blue line represents defensive value, orange line represents infectivity value, green line represents pleiotropic value. The vertical black line shows a delay to reach equilibrium in the case of pleiotropy.

Remarkably, in all cases the equilibrium where host evolves a higher defensive value

than parasite offensive value is guaranteed. This is the unique stable equilibrium when all things are equal between host and parasite (e.g $\theta_{\mathrm{x}} = \theta_{\mathrm{y}}, \xi_{\mathrm{H}} = \xi_{\mathrm{P}}$). However, under dissimilar optimum values and unequal host lost and parasite gain, sometimes more than one equilibrium scenario exists where host occasionally evolves lower defensive value than parasite offensive value. The emergence of multi-equilibrium tightly link to the variation of the sensitivity value α (Figure 3). There is a threshold for α such that if α is smaller than the critical value $\alpha*$ there always existed one equilibrium regardless of how much host lost and parasite gain. If α exceed $\alpha*$ then depending on the magnitude of host lost and parasite gain, two to three equilibrium will occur. In other words, when a small shift of phenotypic values yields enough change in infection likelihood, host and parasite start to have more than one defensive – counter-defensive strategy.

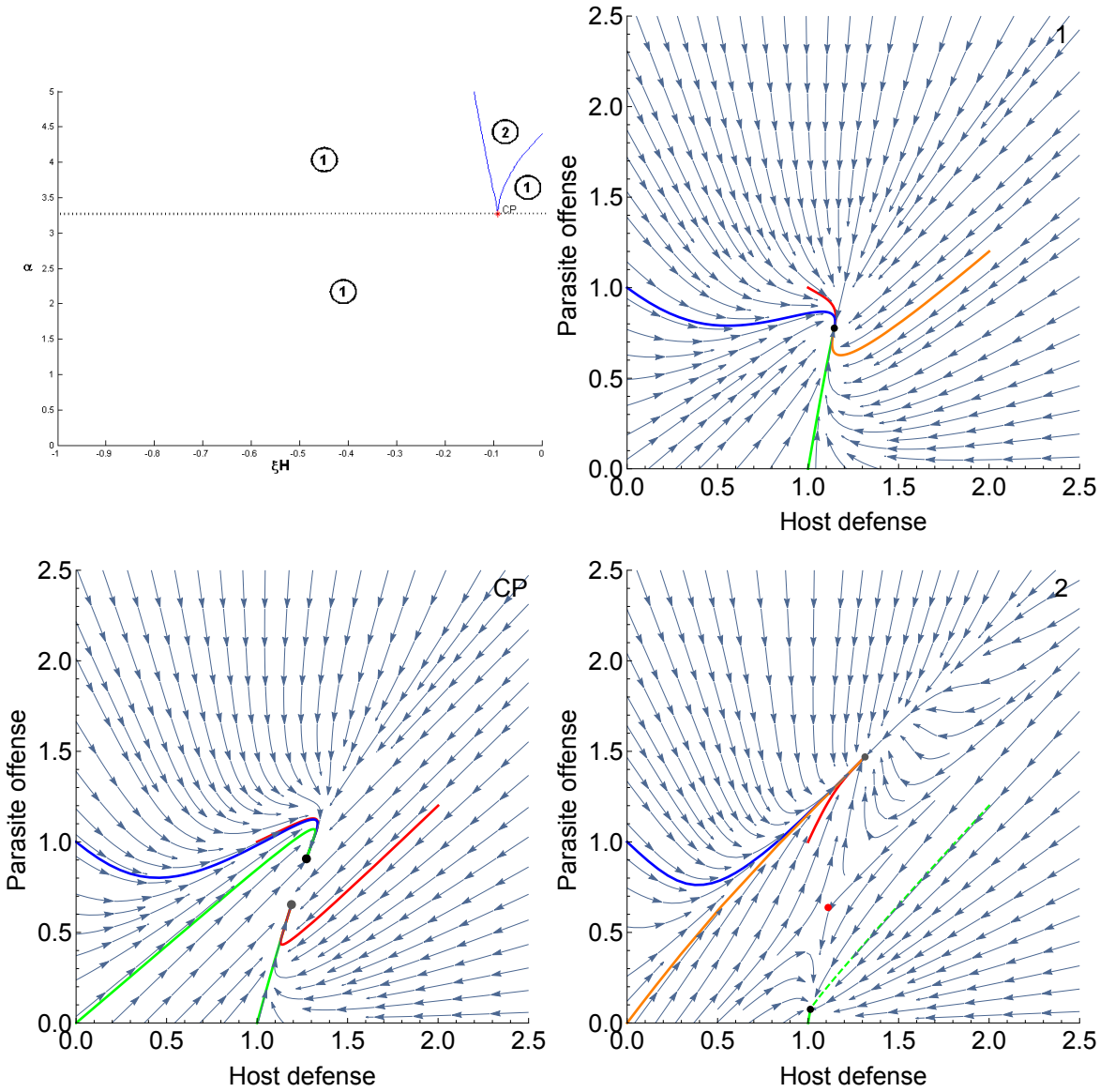

Figure 3: Bifurcation diagram that shows different equilibrium regions. The dot line indicate the threshold for α so that 2 or more equilibrium could occur. Region 1 phase lane diagram when a unique stable equilibrium exist (α = 2.5,ξ_H= -0.056,ξ_P = 0.334). Region 2 phase lane diagram when three equilibrium exist (α = 5,ξ_H = -0.056,ξ_P = 0.334).Cursp point (CP) phase line diagram when two equilibrium exist (α = 3.3,ξ_H = -0.0913,ξ_P = 0.334) .

There are two situations where the host will evolve a smaller defensive value than the parasite offensive value. First, optimum defensive value is greater than optimum offensive value, damage to the host is small enough, and benefit for the parasite is large enough. In such a case, if initially the host defensive value is smaller than the

parasite offensive value then due to the enormous benefit gain the parasite will keep its high infectivity value regardless of its large deviation from the optimum value while the host will keep its low defensive value close to the optimum value as it suffers little from the infection. This case describes a parasite population that could exploit their host greatly but leave very small damage.

Second, the optimum defensive value is smaller than optimum offensive value, the damage to the host is large enough, and the benefit gain by the parasite is small enough. In this case, if initially the host defensive value is higher enough than the parasite offensive value then the huge benefit from escaping from the parasite helps it retain at that value despite the distance from the optimum value. On the other hand, if the host starts with a lower defensive value than the parasite offensive value, the cost to invest in the defensive system could not compensate the divergence from the optimum value. The host thus stays at a low defensive value. This scenario should correspond to situations where it might be more beneficial to invest in other strategies such as reproduction rather than defensive system to ensure population survival.

2.3.2 Matching allel model

The MA model is different from the GFG model in its regime of interaction such that a high offensive value does not ensure high likelihood of infection and via versa. As mentioned above, the critical requirement for a successful infection under this type of interaction is the phenotypic match between parasite offense and host defense. Thus, hosts can escape from parasites by either making their defensive value higher or lower than the parasite offensive value. In other words, selection can go in two directions (Figure 1B-upper panel), generating many evolutionary outcomes.

In our MA model, there are 3 key parameters that determine the qualitative change of the dynamic of host and parasite phenotypic traits: the sensitivity of host-parasite phenotypic difference (α), and strength of stabilizing selection on both host and parasite ($\gamma_{\mathrm{x}}, \gamma_{\mathrm{y}}$). Following are cases in which we observed qualitative change of the model dynamic.

a. Equally strong stabilizing selection on host and parasite

Strong stabilizing selection will impose intense force on phenotypic traits toward optimum values, although how near the traits will reach the optimums will depend heavily on a key parameter α. Under a low sensitivity of host-parasite phenotypic difference (small α), i.e. a small mismatch of infectivity value from defensive value yields little decrease in infection likelihood, host and parasite phenotypic traits evolve to the optimum values ($x \to \theta_{\mathrm{x}}, y \to \theta_{\mathrm{y}}$), which is the unique equilibrium point under this condition. In an example, when we set an equal optimum value for host defense and parasite offense we always reach the equilibrium where $x = \theta_{\mathrm{x}}, y = \theta_{\mathrm{y}}$ even though the parasite offensive value matches completely with the host defensive value, i.e. hosts are under maximum likelihood of infection. In this case, the cost paid for diverting from the optimum value is much greater than the benefit gain from escaping from infection (Figure 4B). However, as the sensitivity increases (big α), i.e. a small mismatch of infectivity value from defensive value is enough for a significant reduction of infection likelihood, hosts are more ready to escape from parasites. In this case, the equilibrium where host defense entirely matches with parasite offense becomes unstable and two other stable equilibrium emerge on the opposite sites of the unstable equilibrium (Figure 4C). One extreme is where host defensive value is negative and smaller than parasite offensive value, the other is where host defensive value is positive and greater than parasite offensive value. The host can go in either direction depending on its initial values but in any case it represents only one escaping strategy: to create enough mismatches between host defensive value and parasite offensive value.

When we introduce pleiotropy, it only changes the model dynamic quantitatively such that it also prolongs the time for host and parasite to reach their optimum value (Figure 5).

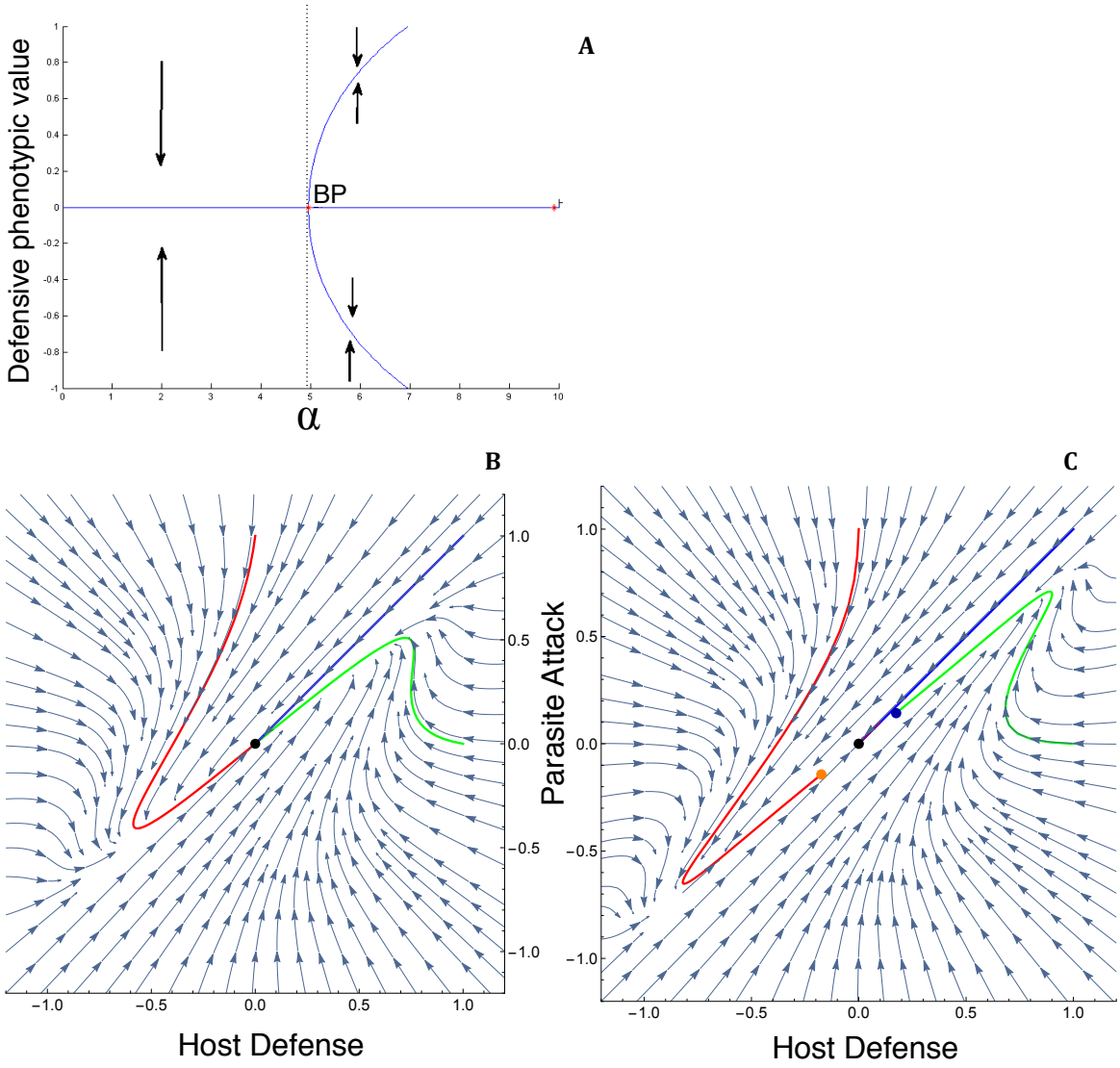

Figure 4: **A**. Pitchfork bifurcation with α as the varying parameter. Dot line indicates the threshold of α , arrows indicate direction to the equilibrium. **B**. Phase lane diagram when a unique equilibrium exists ($\alpha = 2.5$). **C**. Phase lane diagram where three equilibrium exist ($\alpha = 5$).

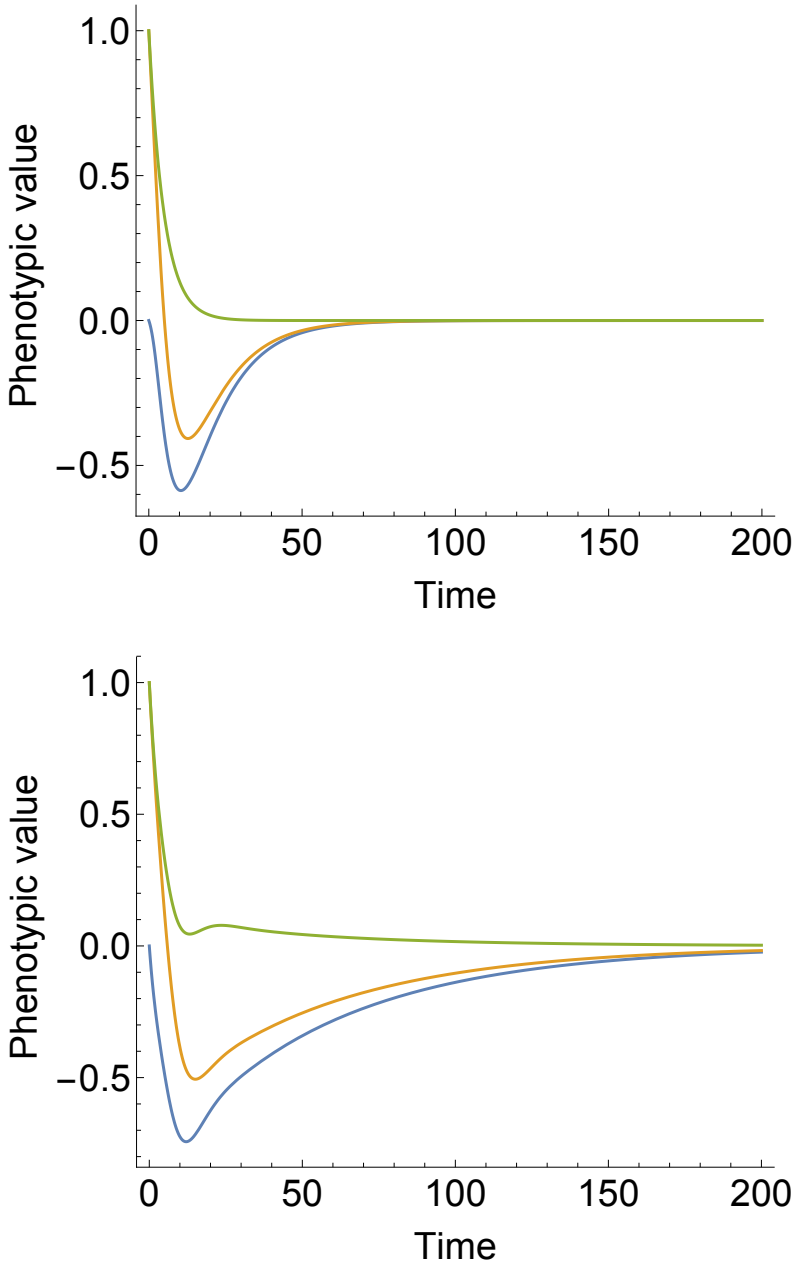

Figure 5: Time series of phenotypic value. Blue line: host defense, orange line: parasite offense, green line: host pleiotropic trait. **A**. No pleiotropy c = 0. **A**. Pleiotropy introduced c = 0.65.

b. Weak stabilizing selection on host and parasite

As we relax the stabilizing selection on hosts and parasites, many interesting evolutionary outcomes occured. Since hosts and parasites are less consrtained by reaching their optimum value, their phenotypic values are freer to co-vary. The magnitude and difference between stabilizing selective forces on host and parasite now play a more important role than the sensitivity α in determining the model dynamic.

Following a branching point with respect to the variation of the two stabilizing selective forces, we observed a Bogdanov-Taken point (Figure 6). The Bogdanov-Taken point indicates the birth and death of a limit cycle. The hopf curve originated from this BP point and the branching line divide our model dynamic into 3 different regions: (i) a unique stable equilibrium, (ii) a stable periodic cycle, (iii) two stable equilibrium and a saddle node (Figure 6).

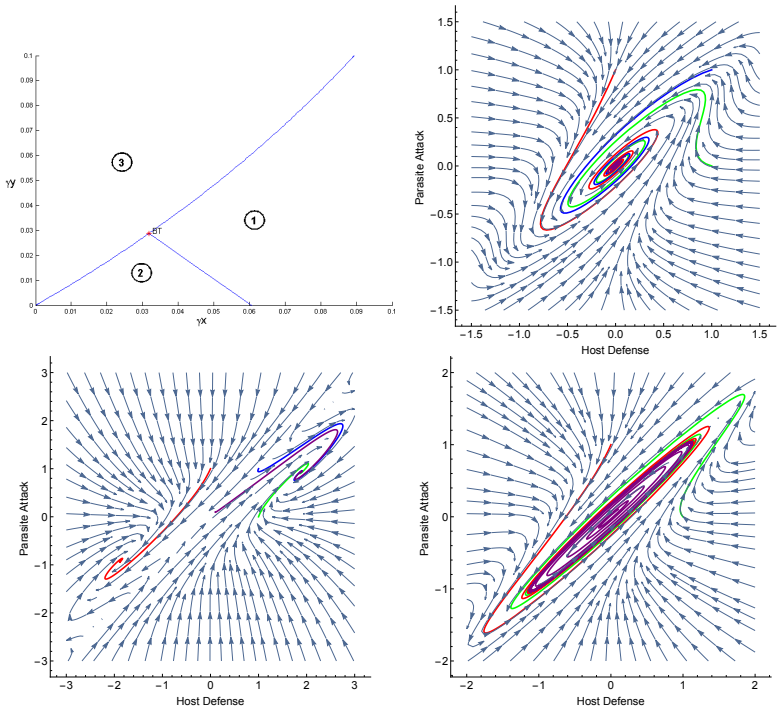

Figure 6: Figure 6. Bifurcation diagram with γ_x and γ_y as the varying parameters. Region 1: convergence of oscillation toward a unique equilibrium. Region 2: an unstabl1e limit cycle exists. Region 3: two stable equilibrium and a saddle node exist.

When stabilizing selection on host is stronger than stabilizing selection on parasite, it gives the host less choices to defend against the parasite. Although the magnitude of the stabilizing selection is not strong enough to lead the host value directly to the optimum, it eventually force the oscillation of the trait to converge into that optimum value, which is also the unique equilibrium. The stronger the force, the faster it drags the host value toward the optimum (Region 1). However, if the selective force on host is more and more relax (but still stronger than stabilizing selection on parasite) this unique equilibrium will become unstable and a stable limit cycle appears; or the host value is allowed to co-vary with the parasite value, creating oscillations of the two phenotypic traits (Region 2). On the other hands, if stabilizing selection on parasite is greater than that on host, the parasite infectivity value is pushed toward its optimum value while it is not necessary for the host. Thus, the host always reaches either of the two existing equilibrium where its is able to evolve mistmatches between its defensive value and the parasite offensive value (Region 3).

Under weak stabilizing selection, pleiotropic effect generates a variety of interesting results. In the case of a unique equilibrium, or when host is able to evolve only one defensive strategy, if a non-zero genetic correlation is introduced the oscillation of host defensive value is constrained by the stabilizing selective force on the pleiotropic trait. Therefore both host defensive value and the pleiotropic value are pushed toward the equilibrium (Figure 7A).

Interestingly in the cases where more than one equilibrium exists, or when there are many possibilities to escape from parasites, introducing pleiotropy actually makes the dynamic more complicated. It should be remarked again that under this situation stabilizing selection on host defense is more relaxed; the equilibrium where the host defensive value stays at the optimum becomes unstable, the host can either evolve a higher or lower defensive value than the optimum value to escape from the parasite. However, due to pleiotropy when the defensive value diverts farer away from the optimum, the evolution of the pleiotropic trait tends to pull it back to the optimum; and since the optimum is unstable the defensive trait is again pushed away from the optimum, generating oscillation. Because there are two directions to which the defensive value could go, there exist two limit cycles depending on the initial values (Figure 7B).

3 Host-parasite interaction with two pairs of defensive-offensive traits

3.1 Model structure

We extended the previous model by considering that host has two defensive strategies x_1 and x_2 against the corresponding offensive strategies y_1 and y_2 of the parasite. Each defensive and offensive trait in a pair interacts with each other following the GFG model. The fitness of host and parasite after infection are given by

$$\mathcal{W}_{\mathrm{intH}}(x_1, y_1, u_1, x_2, y_2, u_2) = K_{\mathrm{H}} + \xi_{\mathrm{H}} \left(\frac{\mathcal{W}_{\mathrm{int1}}{}^{\varphi \mathrm{xy}}) + \mathcal{W}_{\mathrm{int2}}{}^{\varphi \mathrm{xy}}}{2} \right)^{\varphi \mathrm{xy}}$$

$$\mathcal{W}_{\mathrm{intP}}(x_1, y_1, x_2, y_2) = K_{\mathrm{P}} + \xi_{\mathrm{P}} \left(\frac{\mathcal{W}_{\mathrm{int1}}{}^{\varphi \mathrm{xy}}) + \mathcal{W}_{\mathrm{int2}}{}^{\varphi \mathrm{xy}}}{2} \right)^{\varphi \mathrm{xy}}$$

where $\mathcal{W}_1(x_1, y_1, u_1, x_2, y_2, u_2) = \frac{1}{1+e^{\alpha 1(x_1 - y_1)}}$ and $\mathcal{W}_2(x_1, y_2, x_2, y_2) = \frac{1}{1+e^{\alpha 2(x_2 - y_2)}}$ represents the infection likelihood of each defense-infectivity pair. The term $\left(\frac{\mathcal{W}_{\mathrm{int1}}{}^{\varphi \mathrm{xy}}) + \mathcal{W}_{\mathrm{int2}}{}^{\varphi \mathrm{xy}}}{2} \right)^{\varphi \mathrm{xy}}$ indicates the net infection likelihood of a host bearing two defensive values x_1 and x_2 in the interaction with a parasite with two offensive values y_1 and y_2. The parameter φxy determines whether the average fitness lost to the host after an infection is a geometrical mean or an arithmetic mean. The total fitness of host and parasite are given by

$$\mathcal{W}_{\mathrm{Htotal}}(x_1, y_1, u_1, x_2, y_2, u_2) = e^{-\beta \left(\frac{\kappa_1 x_1{}^{2\varphi \mathrm{x}} + \kappa_2 x_2{}^{2\varphi \mathrm{x}} + \nu_1 u_1{}^{2\varphi \mathrm{x}} + \nu_2 u_2{}^{2\varphi \mathrm{x}}}{\kappa_1 + \kappa_2 + \nu_1 + \nu_2} \right)^{\frac{1}{\varphi \mathrm{x}}}} \mathcal{W}_{\mathrm{intH}}(x_1, y_1, u_1, x_2, y_2, u_2)$$

$$\mathcal{W}_{\mathrm{Ptotal}}(x_1, y_1, x_2, y_2) = e^{-\beta \left(\frac{\lambda_1 y_1{}^{2\varphi \mathrm{y}} + \lambda_2 y_2{}^{2\varphi \mathrm{y}}}{\lambda_1 + \lambda_2} \right)^{\frac{1}{\varphi \mathrm{y}}}} \mathcal{W}_{\mathrm{intP}}(x_1, y_1, x_2, y_2)$$

The terms in the exponential indicates the average fitness lost an individual suffers when its phenotypic values deviate from the optimum values; the terms *varphi*x and *varphi*y also indicates what type of average fitness lost is used. β is the strength of stabilizing selection on all host traits with κ_1, κ_2,ν_1 and ν_2 as the weight that the selection places on the corresponding traits; γ is the strength of stabilizing selection on all parasite traits with λ_1 and λ_2 as the weight that the selection places on the corresponding traits. Here, the parameter φi (where i could be x, y or xy) is a critical parameter that strongly affects the dynamic of the model. φi ranges from 0 to 1,

where the value 0 indicates that an unbalanced investment in any phenotypic trait does not create severe lost (i.e. small cost due to inappropriate investment) while the value 1 indicates that any neglectedness of investment in one phenotypic trait yields serious damage (i.e. high cost due to inappropriate investment). Inappropriate investment could be a large deviation from optimum values and a lower phenotypic value than that of the enemy. In other words, an individual should better invest in all traits if φi reaches 1 and can focus on one trait if *varphi*i reaches 0 (Figure 8).

Similar to the simple version of the GFG model the dynamic of the phenotypic value follows the breeder's equation: $\frac{d\boldsymbol{v}}{dt} = \mathbf{G}\beta(\boldsymbol{v})$,in which $\boldsymbol{v} = (\overline{x}, \overline{u}, \overline{y})$, in which now the vector of the average phenotypic value of the population is $\boldsymbol{v}$=(x_1,x_2,y_1,y_2,u_1, u_2), the additive genetic variance-covariance matrix is

$$\begin{pmatrix} \mathcal{V}_{\mathrm{x_1}} & 0 & 0 & 0 & c_1 & 0 \\ 0 & \mathcal{V}_{\mathrm{x_2}} & 0 & 0 & 0 & c_2 \\ 0 & 0 & \mathcal{V}_{\mathrm{y_1}} & 0 & 0 & 0 \\ 0 & 0 & 0 & \mathcal{V}_{\mathrm{y_2}} & 0 & 0 \\ c_1 & 0 & 0 & 0 & \mathcal{V}_{\mathrm{u_1}} & 0 \\ 0 & c_2 & 0 & 0 & 0 & \mathcal{V}_{\mathrm{u_2}} \end{pmatrix}$$

and the vector of selection gradient is $\beta(v)$=($\beta_{\mathrm{x_1}}$,$\beta_{\mathrm{x_2}}$,$\beta_{\mathrm{y_1}}$,,$\beta_{\mathrm{y_2}}$,,$\beta_{\mathrm{u_1}}$,,$\beta_{\mathrm{u_2}}$) .

3.2 Numerical analysis and result

a. Escalation of defensive and offensive traits under strong stabilizing selection

To find the equilibrium of the system, we need to solve the system of 6 ordinary differential equations (ODE) derived from the above breeder's equation. Since the total fitness function is composed of quadratic and exponential terms, it results in a system of complex ODEs that could not be solved analytically. We then evaluated and analyzed the system numerically; we only focused on the model dynamic with one equilibrium.

By running simulation under many different initials, we found a unique stable equilibrium, where host always evolves higher defensive values than parasite offensive

values (Figure 9), when we set the condition similar to the simple GFG version, that is, all optimum values are the same, host and parasite have an equal baseline fitness, host lost is equal to parasite gain, infection sensitivity is small enough, and average fitness is multiplicative (φi=1). Pleiotropy does not have a strong effect in this complex model as it does in the simple GFG model (Figure 8).

b. Oscillations are guaranteed under weak stabilizing selection

Next, we tracked this equilibrium by varying some parameters of interest to study the model behavior. We observed oscillations of the phenotypic values in many situations. Remarkably, the strength of stabilizing selection plays a very important role in creating the cycle, such that weak stabilizing selection facilitates oscillations (Figure 9). Interestingly, the role of stabilizing selection on host defense (β) and on parasite offense (γ) is unequal. Weak stabilizing selection on parasite seems to be more important in promoting oscillations than weak stabilizing selection on host.

Under the condition of weak stabilizing selection on both host and parasite, the baseline fitness of parasite K_P become one critical factor influencing oscillations, such that the smaller the base line fitness the easier it is for cycle existence. This condition indicates the population of holoparasite, i.e. parasite that requires a host to reproduce and grow. If parasite is rather independent of their host (high base line fitness), which should referred to populations of facultative parasites, oscillations will only occur under strong stabilizing selection on hosts (Figure 11, Figure 12A).

c. Multiplicative mean fitness lost conditionally promotes oscillations

The multiplicative mean fitness lost is another key element influencing oscillations under weak stabilizing selection on both host and parasite. When the mean fitness lost is multiplicative (i.e. $\varphi x = \varphi y = \varphi xy = 1$) it means that either a slight inferior defensive values than parasite offensive value and a small deviation from the optimum values yields enormous lost to the host. Therefore, the host not only need to invest in both defensive traits to effectively protect itself against the parasite but also need to put effort in pushing all their traits to the optimum values. Multiplicative fitness is thus an important condition for oscillations. Initially, host begins to raise both of its defensive values to escape from parasite infectivity; the parasite offensive values also rise along to catch up with the hosts. On the quest of increasing their values, parasite and host traits are deviated from the optimum value, thus at the point when benefit for host from escaping from infectivity and benefit for parasite from racing with host no longer compensate for the lost imposed by stabilizing selection, all traits will be pushed back to the optimum. As the rise and fall of the two strategies are not synchronized, in the process of decreasing toward the optimum values the host becomes vulnerable to the parasite at some points. Therefore the host is urged to increase their defensive values again.

If the mean fitness lost is no longer multiplicative (i.e. φi reaches 0) then oscillations cease because as either trait of the host reaches close enough to its optimum value and archives a good distance from parasite offensive value there is no need to concern about the state of the remaining traits (Figure 12A).

When stabilizing selection on host increases, the condition of multiplicative mean fitness lost for the existence of oscillation reverses, such that oscillation occurs only when mean fitness lost is not multiplicative. It should be noted that due to some calculation constrain, we could not vary the parameter φx, thus in any circumstances this parameter is set at 1 and only φy and φxy are set at a small value, i.e. he host requires all of its traits at the optimum value, the parasite only need one of its infectivity value at equilibrium and the host only needs to invest in one defensive strategy (Figure 12B). In this case, initially the host needs to raise only one of the defensive values while leaving other close to the optimum even though it is smaller

than parasite infectivity value. At some point, due to strong stabilizing selection on host, the rising defensive value is pulled back toward the optimum while the corresponding infectivity value stays at its high value due to weak stabilizing selection on parasite. Therefore, selection force from host-parasite interaction begins to raise the remaining defensive value up and having the decreasing defensive value near the optimum again. Following this routine, in the dynamic of the oscillation, we always observe at any point of time, there is only one defensive value higher than the corresponding infectivity value and the other value close to the optimum (Figure 12B).

Pleiotropy does not have a strong effect in this model, however it does stabilize the cyclic dynamic or at least make the period last longer. When pleiotropy is introduced, the deviation away from the optimum value of the defensive traits is constrained by the pleiotropic traits, thereby all traits tend to converge into an equilibrium (Figure 12).

4 Dicussion

In general, our results are in congruent with previous models, that is, with respect to the single trait models escalating arm races are favorable under the GFG model and oscillations occur under many conditions of the MA model (Nuismer et al. (2007), Nuismer et al. (2005)). These result indicate the robustness of the defensive-offensive dynamic regardless of the genetic basis, suggesting that the evolution of host defense and parasite offense could be studied without concerning about genetic assumptions. More importantly, we showed a critical role of pleiotropic effect in the MA model, such that it stabilized the cyclic evolution of the traits (but note that this is not always the case).

We further showed that our extended GFG model with two pairs of defensive-offensive traits actually produced oscillations under many combinations of parameters, indicating that the GFG interaction could result in consequences similar to the MA interaction. Undoubtedly, a great many models have shown oscillation was feasible in the GFG model. However, frequency-dependence, density-dependence or demographic introduction is compulsory factors for such cyclic evolution aside cost for defense and offense (Leonard (1977), Frank (1993), Damgaard (1999), Sasaki et al. (2002), **?**). Our extended GFG model showed that the involvement of two defensive – offensive strategies, which is common in nature, is enough to create oscillations – an indication of polymorphism for defensive and offensive strategies.

Therefore, our model affirms and strengthens the compatibility of the GFG model and the MA model in explaining the diversity of host defense and parasite offense. Conventional presumptions considered GFG model was best fitted for the plant-pathogen system while MA model explained best the animal-parasite system. Recent studies showed that the interaction of host and parasite might be a mix of both models albeit a lack of empirical evidences (Dybdahl et al. (2014), Agrawal and Lively (2002),Agrawal and Lively (2003)). Empirical supports for the GFG model and the MA model are rare because the interaction of a single host-parasite system in nature is more complex than in these abstract model and varies greatly among species. Specific models for specific species are required to best illustrate and predict the consequence of host-parasite interaction with respect to the corresponding host-parasite system.

Our model is a conceptual model and should be used as a guide to understand the possible evolutionary outcomes of a host-parasite interaction. Interestingly, our model results captured some natural observations, particularly in the brood parasite system.

For example, the village weavers that live in Africa have shown an increase in rejection rate to cuckoo's eggs from 13.8% to 89.3% in 16 years (Robert and Sorci (1999)). Magpie population in Japan had developed the aggressiveness and egg rejection behavior since cuckoo was introduced in the region (Ornithol (1990)). These examples are demonstrations of escalating host resistance as a measure to defend against parasitic cuckoos.

Hosts however do not always increase their resistance, for example reed warblers under some conditions accept common cuckoo's egg instead of rejecting them because they run the risk of making errors by rejecting their own eggs (**?**). Sometimes, when parasitic bird do not evict host's eggs, i.e. the host gets the chance to raise both of its nestlings and those of the parasite, hosts are less likely to develop rejection. In our model, when the cost to invest in defensive trait is too high or when parasites yield little harm hosts might evolve a lower defensive value.

As mentioned above, hosts and parasites normally have more than one defensive-offensive strategy. For example, magpies can protect themselves against parasitic cuckoos by nest defense or parasitic egg rejection. Natural observations have shown that magpies that are good at recognizing the parasite and the parasitic eggs, thus normally have higher rejection rate, have a lower rate of nest defense and via versa (Stahl and Bishop (2000)). This example is a nice demonstration for the extended GFG model in which host only need to invest in one defensive strategy.

Our models stand as a nice explanation for the above empirical evidences, however, like other mathematical work, they have some constrains considering model assumptions. First, our quantitative genetic model assumes that each added allele has equal effect on the phenotype whereas it is very common that some alleles have strong effects and other have minor effects. Second, our model did not take into account the spatial structure of host population and assumed that host and parasite individuals encounters randomly while this is highly not the case in nature. In fact,

ecological effects have strong implication on the evolution of resistance and virulence traits (Damgaard (1999), Sasaki et al. (2002), Thrall and Burdon (2006)). Defensive ability becomes a wasteful investment for individuals in the absent of parasite, thus ecological factors also play no less an important role than genetic factors in driving the evolution of host defense and parasite offense. Studying the evolution of host-parasite interaction under one context without the other might lead to missing of interesting dynamic.

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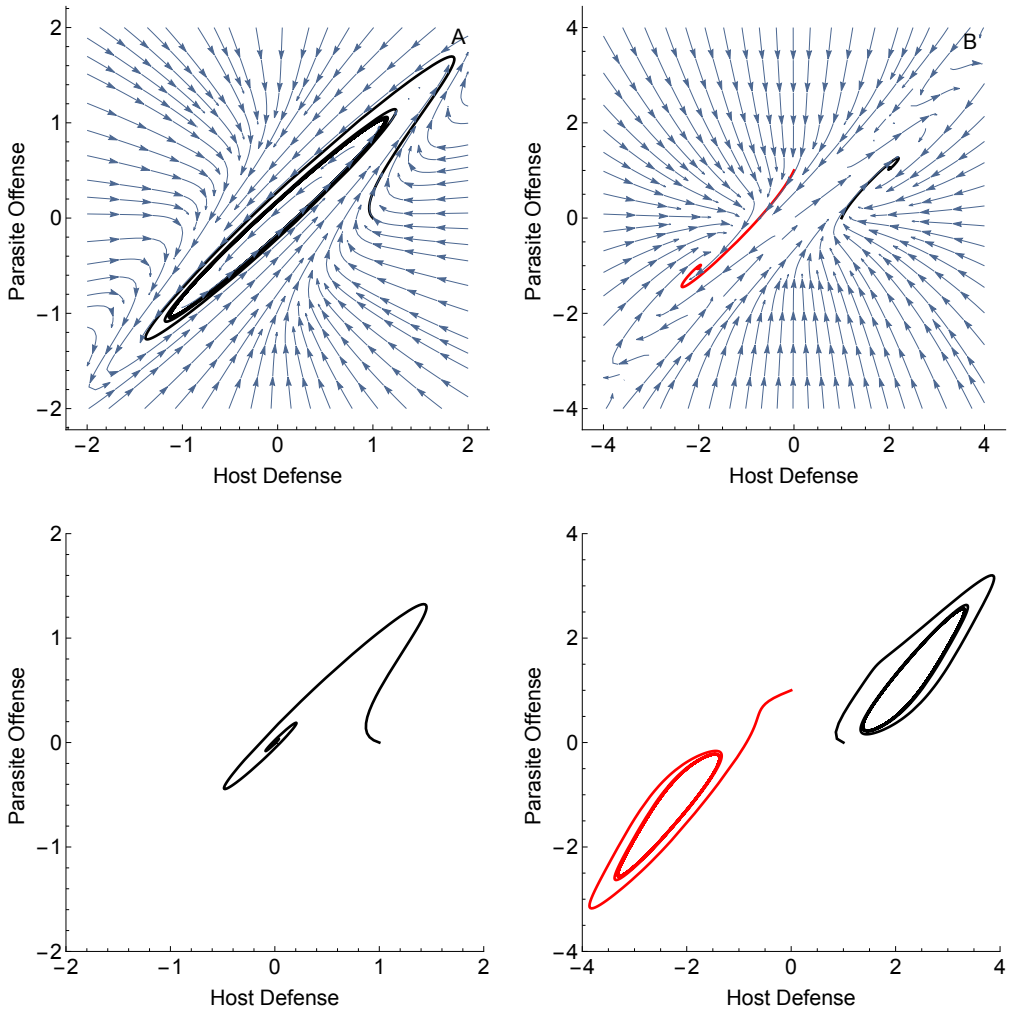

Figure 7: Pleiotropic effect on the model dynamic. The upper panels represent the dynamic when there is no pleiotropy and the lower panels represent the dynamic when pleiotropy is introduced. **A**. effect when there is one limit cycle around an unstable equilibrium (c = 0.35). **B**. effect when there is two stable equilibrium (c = 0.65).

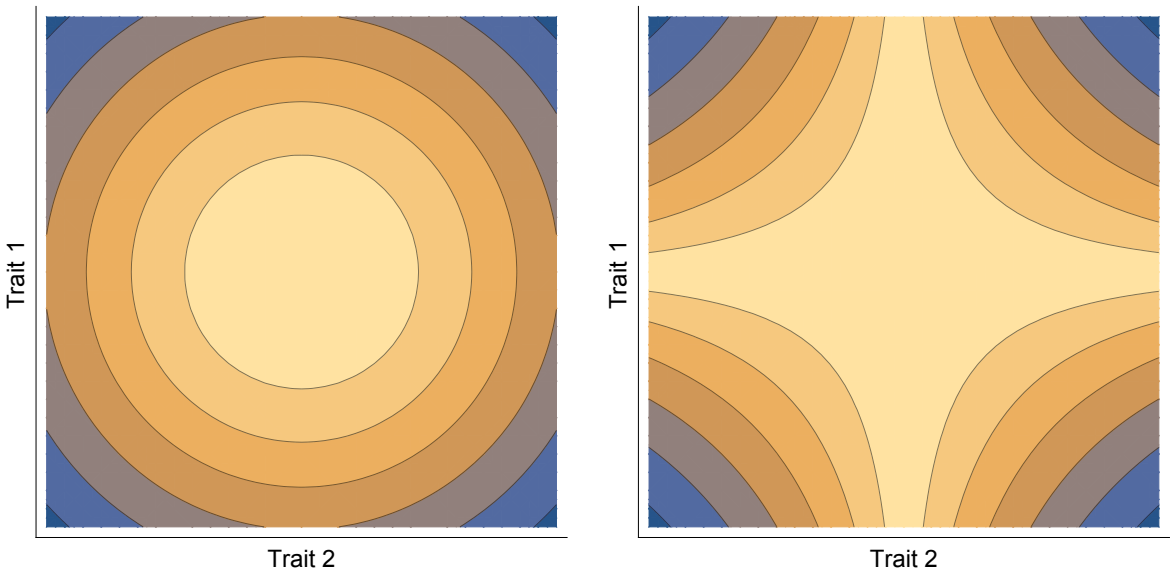

Figure 8: An illustration of arithmetic mean and geometric mean. Left panel arithmetic mean fitness lost (φi = 1). Right panel geometric mean fitness loss (φi = 0) (i indicate either xy, x or y. The lighter the color the higher the fitness.

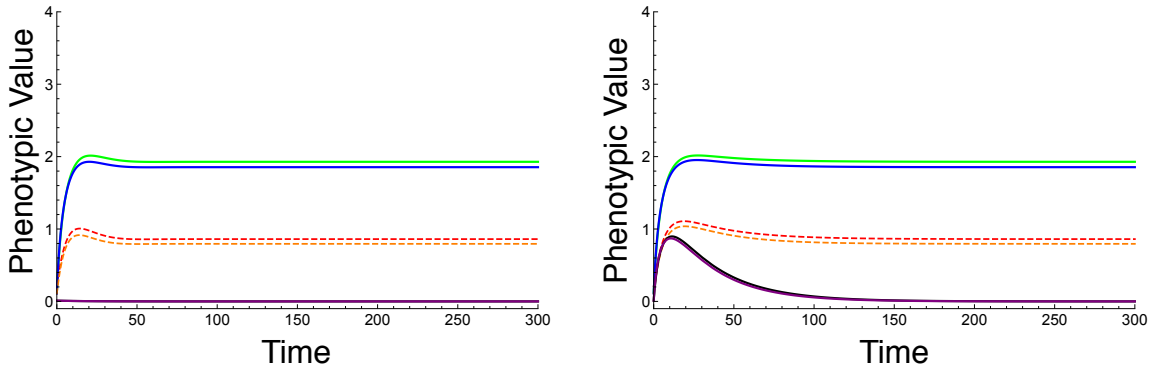

Figure 9: Time series of the phenotypic values. Thick lines: Host phenotypic value, dot lines: parasite phenotypic values. Green, blue: host defensive traits, black, purple: host pleiotropic traits. Left panel No pleiotropy c=0. Right panel pleiotropy introduced c=0.65.

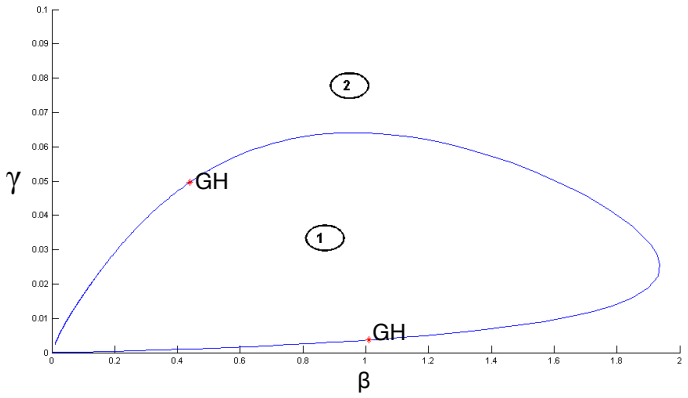

Figure 10: Bifurcation graph tracking the Hopf line with respect to β and γ. Region 1: limit cycle of the phenotypic traits. Region 2: Unique stable equilibrium.

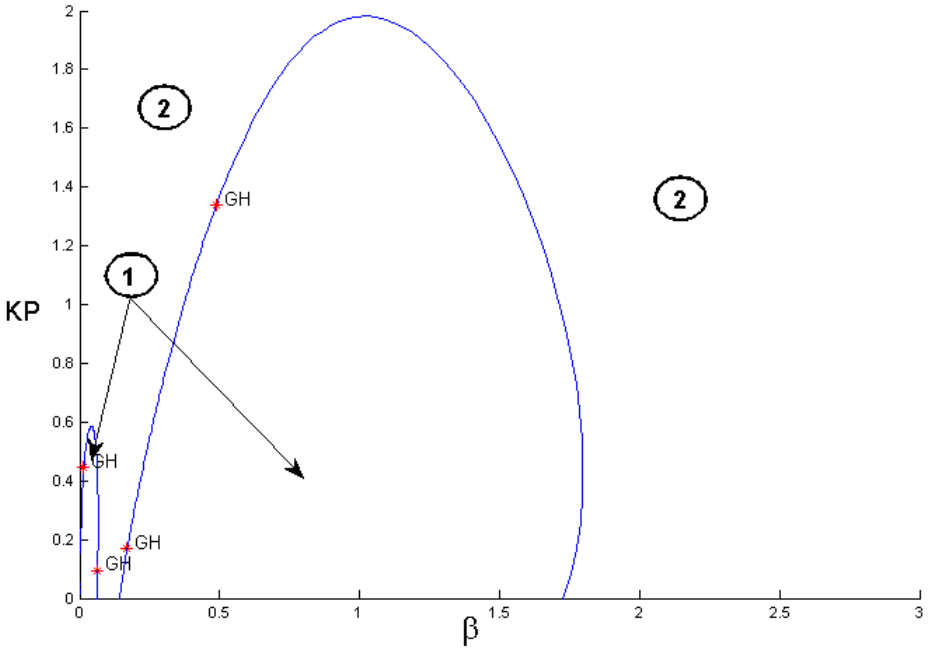

Figure 11: Bifurcation graph tracking the Hopf line with respect to β and K_{P}. Region 1: limit cycle of the phenotypic traits. Region 2: Unique stable equilibrium.

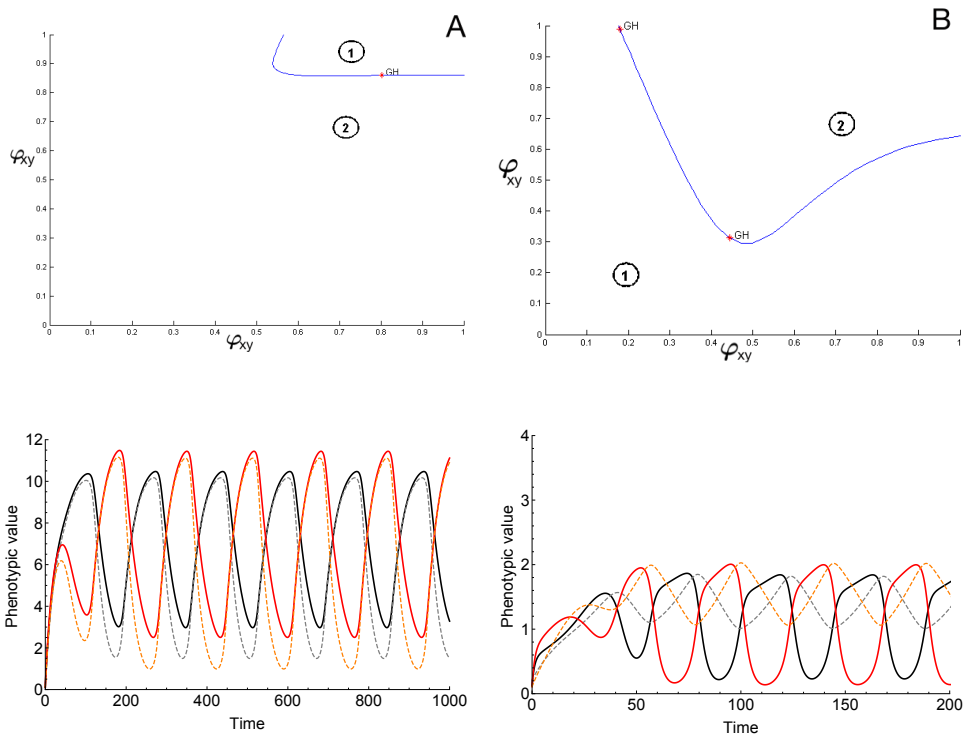

Figure 12: Bifurcation graph tracking the hopf point with respect to φxy and φx and time series of the phenotypic values in region 1. Region 1: limit cycle of the phenotypic traits. Region 2: unique equilibrium. **A**. Weak stabilizing selection on both host and parasite. **B**. Weak stabilizing selection on parasite only.

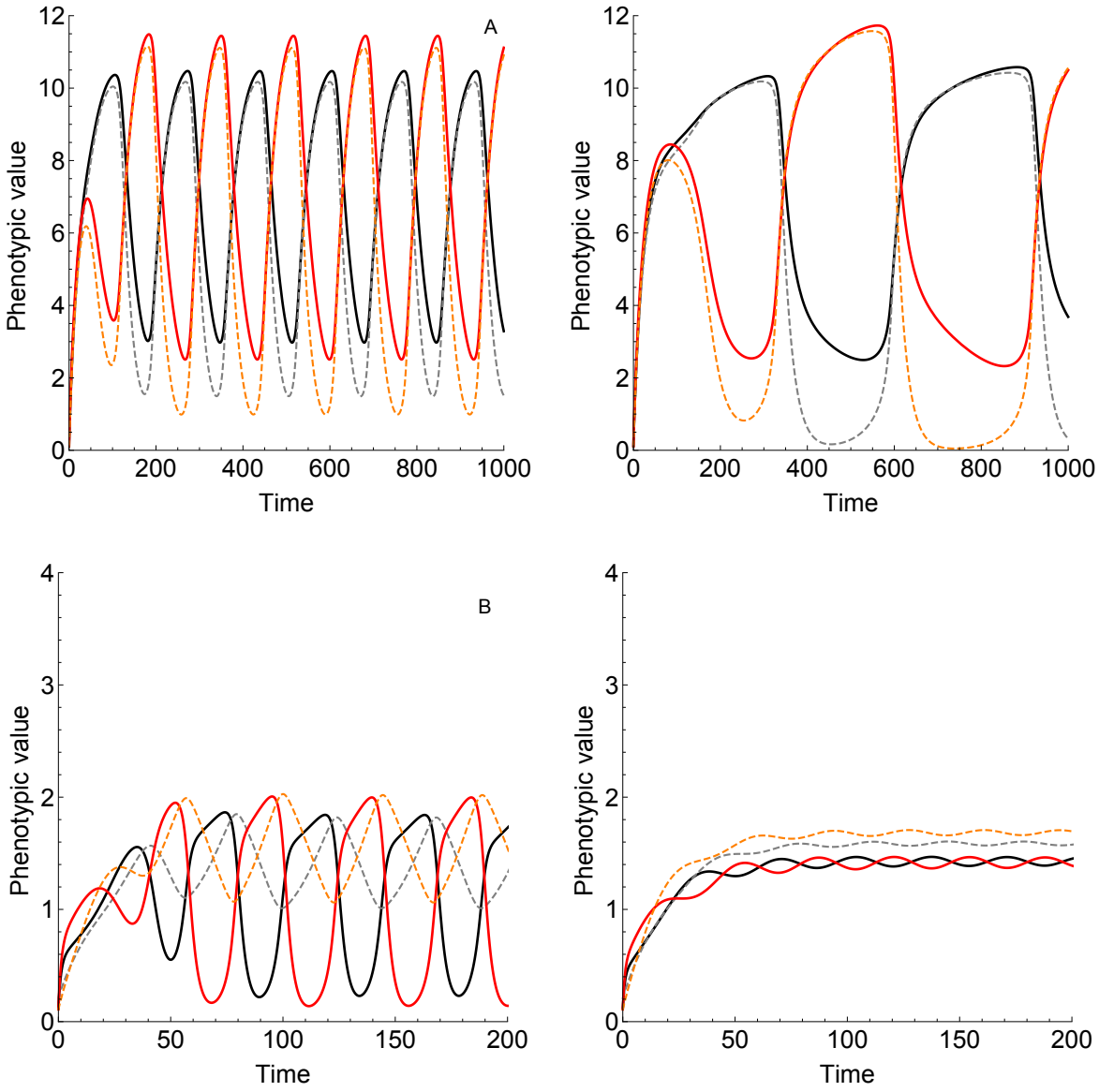

Figure 13: Time series of phenotypic traits and the effect of pleiotropy. Upper panels weak stabilizing selection on both hosts and parasites. Lower panels strong stabilizing selection on host and weak stabilizing seletion on parasite. **A**. Model dynamic without pleiotropy. **B**. Model dynamic with pleiotropy.