Hybrid zone dynamics under weak Haldane’s rule

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The ability of genetic isolation to block gene flow plays a key role in the speciation of sexually reproducing organisms. This paper analyses the hybrid zone dynamics affected by “weak” Haldane’s rule, namely the incomplete hybrids inferiority (sterility/inviability) against the heterogametic (XY or ZW) sex caused by a Dobzhansky-Muller incompatibility. Different strengths of incompatibility, dispersal and density-dependent regulation are considered; and the gene flow and clinal structures of allele frequencies in the presence of short-range dispersal (the stepping-stone model) are examined. I show that a weak heterogametic hybrid incompatibility could constitute a substantial barrier that could reduce gene flow and result in non-coincident and discordant clines of alleles. It is found that the differential gene flow is more pronounced under a stronger density-dependent regulation. This study provides a mechanistic explanation for how an adaptive mutation, which may only have a marginal fitness effect, could set a gene up as an evolutionary hot-spot.

Keywords: Dobzhansky-Muller incompatibility, Gene flow, Haldane's rule, Hybrid sterility, Hybrid inviability, Hybrid zone, Speciation.
Hybrids between closely related species of sexually reproduced organisms generally suffer from poor fertility or viability. The question puzzled Darwin himself when formulating his theory of evolution by natural selection was how evolution could maintain inheritable changes to cause hybrid sterility or inviability. Several decades had passed since Bateson (Bateson, 1909, Orr, 1996), Dobzhansky (Dobzhansky, 1937) and Muller (Muller, 1940, Muller, 1942) articulated the evolutionary mechanism that produces such hybrid incompatibility; it is through a process of the establishment of epistatic deficiencies between diverging populations. Detrimental epistasis can be accumulated over time by genetic drifts and/or adaptive mutations in separated populations (Wittbrodt et al., 1989, Ting et al., 1998, Barbash et al., 2003, Presgraves et al., 2003, Brideau et al., 2006, Masly et al., 2006, Phadnis & Orr, 2009) without facing negative selection or “adaptive valley” (Wright, 1988, Gavrilets, 1997). When hybridization occurs, such epistatic interaction could cause sterility or inviability. For instance, from a diallelic ancestral population, an $aabb$ genotype could evolve into $AAbb$ and $aaBB$ genotypes respectively in two separate subpopulations, where the “$A$” or “$B$” allele faces little or no negative selection for their establishment. If “$A$” and “$B$” alleles are incompatible with each other and hybridization occurs, hybrids carrying $AaBb$ genotype will become inferior. This form of reproductive barriers is thus dubbed Dobzhansky-Muller (DM) isolation.

Haldane’s rule represents a major form of BDM isolation in early speciation (Coyne & Orr, 1989, Wu & Davis, 1993, Laurie, 1997). Haldane’s rule indicates that hybridization of closely-related species almost always produces sterile or inviable $F_1$ offspring of the heterogametic sex (male in $XY$ sex determination and female in $ZW$ determination) as opposed to those of the homogametic sex if they are sex-biased. This rule is widely present in almost all taxa investigated (Coyne & Orr, 1998), including mammals, fruit flies, butterflies, birds and many other animals, and dioecious plants (Coyne & Orr, 1989, Wu & Davis, 1993, 2002).
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Laurie, 1997). Heterogametic hybrid sterility/inviability appears to be a critical intermediate step during speciation of many species. However, little is known about the role of a heterogametic hybrid incompatibility in affecting population dynamics (Wang, 2003, Wang & Zhao, 2008). Sex-biased BDM isolation is often the first appeared and a common (if not the most common) form of reproductive isolation in many closely related species pairs, but they have been rarely considered in the theoretical models of speciation with gene flow. The existing theoretical studies on the divergence-with-gene-flow are mainly on the interplays between prezygotic isolation (sexual selection) and ecological differentiations (Dieckmann & Doebeli, 1999, Arnegard & Kondrashov, 2004, Gourbiere, 2004, Van Doorn, 2004, van Doorn et al., 2009, also see Coyne & Orr, 2004, Fitzpatrick et al., 2008, Fitzpatrick et al., 2009).

Hybrid zone analysis provides an excellent system for appreciating the role of Haldane’s rule in population dynamics during speciation (Wang & Zhao, 2008). Theoretical studies on BDM isolation in affecting gene flow and population dynamics were first attempted by Barton & Bengtsson (1986) and Gavrilets (1997). Using heuristic approximation, Bengtsson and Barton (Barton & Bengtsson, 1986) developed a hybrid zone model with BDM isolation and made a first attempt to analyse the neutral gene flow in such a scenario. It was concluded that in the presence of autosome-linked BDM isolation, neutral gene flow could be reduced greatly, but only when it was closely linked to one of the selected alleles. BDM isolation can only constitute a strong barrier to neutral alleles in a hybrid zone when most of them are closely linked to loci under selection (Barton & Bengtsson, 1986). By adapting a more sophisticated fitness matrix, Gavrilets (Gavrilets, 1997) extended the analysis and concluded that epistatic BDM isolation can build up a very strong barrier to neutral gene flow. Gavrilets described in greater detail of the properties of hybrid zones under BDM selection, such as the shapes of clines in relation to strength of selection, migration and linkage. Both of these
models (Barton & Bengtsson, 1986, Gavrilets, 1997) use numerical approximations when
analysing diallelic, autosome-linked epistatic selection. Sex chromosome-linked and sex
dependent selection was not considered.

Recently, Wang and Zhao (Wang & Zhao, 2008) developed a recursion model to analyse
hybrid zone structure and gene flow in a more sophisticated scenario – sex-dependent and
sex-chromosome-linked BDM isolation. Different from the earlier hybrid zone models under
BDM isolation (Barton & Bengtsson, 1986, Gavrilets, 1997), this model provides a more
accurate account of the effects of BDM isolation in hybrid zone dynamics. Wang and Zhao’s
model (Wang & Zhao, 2008) separately considers the loci of $X$, $Y$, incompatible autosomes,
and neutral autosomes. The model allows the analysis of various alleles in a hybrid zone both
temporally and spatially. The analysis shows that in the presence of short-range dispersal
(stepping-stone model), a sex-biased hybrid incompatibility is an efficient barrier that
impedes gene flow across hybrid zones. Sex-biased hybrid incompatibilities differ from each
other depending on the sex that they select against, and the chromosomes where the
incompatible alleles are localized (Wang & Zhao, 2008).

The current paper focuses on the effects of “weak” Haldane’s rule or the partial sex-biased
incompatibility that only causes inferiority of one sex in a fraction of carriers ranging from 0
to 100%. Between populations, weak sterility and inviability can arise as incidental
byproducts of divergence, such as adaptive mutations or genetic drifts, which may not be
readily observable in field and laboratory investigations. However, the population dynamics
under such otherwise unnoticeable partial isolation may be important for the formation of
Haldane’s rule (Wang, 2003, Wang & Zhao, 2008). Many questions can be asked, such as,
how efficient a weak incompatibility could be as a genetic barrier; and to what extent it does
affect gene flow and hybrid zone structure; or how it is related to other factors in a hybrid
zone. The dynamics of such system may provide insights for understanding the evolutionary
mechanisms underlying speciation and Haldane’s rule. Here, I quantitatively analyze the influence of such partial incompatibility on the effective dispersal, density distribution, and clinal structure of alleles across a hybrid zone. Variables that are considered also include dispersal and density-dependent regulation.

Definitions and assumptions

Some common assumptions of population genetics are adopted. These include random mating, discrete and non-overlapping generations, finite parental populations and passage of alleles between generations at their probabilities (Endler, 1973, Slatkin, 1973). The parental populations ($H_1$ and $H_2$ in the text, Wang & Zhao, 2008) are geographically separated and genetically distinct.

Sex-biased, two-locus BDM incompatibility. Assume that between two diverging populations, there is inferiority (sterility or inviability) that affects only hybrids of the heterogametic sex. This is caused by detrimental epistatic interaction between two loci (two-locus BDM incompatibility). The two incompatible alleles are localized on the sex chromosome $X_1$ and an autosome $A_2$, which originate from different populations. These alleles cause no fitness loss in their parental populations. The strength of an $X_1A_2$ incompatibility ($\psi$) ranges from 0 to 1, namely that between 0 and 100% of the carriers of a specific sex are inferior (sterile or inviable). I assume that hybrid inferiority is a continuous quantitative trait – each incompatibility causes a fitness loss and produces fewer offspring in average in accordance with its strength ($0 \leq \psi \leq 1$). The rest of the alleles are selectively neutral and confer no fitness effects (loss or gain) in hybrids. In a deme, a fraction of hybrids of affected sex are eliminated according to the strength of incompatibility. All other progeny are equally fit, but subject to further segregation in later generations. For simplicity, we
assume male heterogamety ($XY$) but the results should apply to female heterogametic ($ZW$) species as well.

_Density dependent regulation ($r$)._ In this study, density dependent regulation ($r$) is defined as the ability of a population to adjust its size toward its carrying capacity ($N_0$). The effect of a hybrid incompatibility is not density dependent (see below). However, the reduction of the size caused by the incompatibility leads to a recovery of the deme toward its carrying capacity.

_Gene flow and effective dispersal/migration._ Bengtsson (1985) has provided a clear definition of effective dispersal/migration, “The effective migration rate, $m_e$, is that rate of migration which would have the same evolutionary effect in a population with no genetic barrier as the actual migration rate now has in the population with a barrier.” For short-term dispersal in the stepping stone model (Endler, 1973), dispersal only occurs between neighbouring demes by a dispersal rate $\lambda$. I consider the rate of an allele entering the opposite population across the zone as the “evolutionary effect (Bengtsson, 1985)”. The effective dispersal $\lambda_e$ is defined as the equivalent dispersal under no genetic isolation ($\psi = 0$) that could achieve the same gene flow (the rate of an allele entering the opposite population) in a scenario with a genetic incompatibility ($0 \leq \psi \leq 1$). In other words, the effective dispersal/migration $\lambda_e$ is the product of $\lambda$ multiplied with the ratio of the rate of an allele entering the opposite population in the presence of a genetic barrier (when $0 \leq \psi \leq 1$) to that rate in the absence of a genetic barrier (when $\psi = 0$).

The meaning of the effective dispersal ($\lambda_e$) is the same as that the effective migration ($m_e$) defined by (Bengtsson, 1985)(Barton & Bengtsson, 1986), and Gavrilets (Gavrilets, 1997). However, Barton and Bengtsson (Barton & Bengtsson, 1986) and Gavrilets (Gavrilets, 1997)
only considered the flow of neutral markers. In this analysis, the flow of different alleles (X-linked, Y-linked, incompatible autosomal, and neutral autosomal) are considered separately.

**Model**

The Wang and Zhao’s recursion model for short-range dispersal (Wang & Zhao, 2008) is extended for examining the influences of weak incompatibilities on hybrid zone dynamics. I use the stepping-stone model for short-range dispersal (Endler, 1973, Wang & Zhao, 2008). Briefly upon a scenario of secondary contact, a hybrid zone consisting of a chain of “n” demes of equal size is formed by migration of both parental populations (H1 to H2, see Wang & Zhao, 2008); and the migration of mature adults occurs between adjacent demes. In every generation, each deme loses λ (0 ≤ λ ≤ 0.5) of its offspring to migration and at the same time it receives input migration of λ from the adjacent demes (λ/2 on each side). In the either end of the chain, the deme exchanges migrants with the corresponding parental population. The size of each parental population is 100 times that of the hybrid zone.

Four independently localized loci, each with two alleles are considered and denoted X1/X2, Y1/Y2, A1/A2 and C1/C2. All these genotypes are expressed as X_iA_kA_oC_p for females and X_iY_jA_kA_lC_oC_p for males, where i, k, and o represent the maternal origin alleles and j, l, and p represent the paternal origin alleles. This diallelic system consists of 4^3 = 64 possible genotypic combinations of offspring for each sex (Wang & Zhao, 2008). Throughout the paper, the subscripts 1 and 2 represent the population origin of alleles.

The frequency of each genotypic combination of either a sperm or an egg produced in generation t is expressed as \( p_{X_iA_kC_p}^{Q_{perm}} \), \( p_{Y_jA_lC_p}^{Q_{perm}} \) and \( p_{C_oA_p}^{Q_{perm}} \), where q, r, s, t, w, or z represents the population origin of the allele (1 or 2). Accordingly, the frequency of a given genotypic combination in generation t in a hybridizing deme is the product of frequencies of a sperm and an egg (Wang & Zhao, 2008) where:
$u^{(t)} = p_{X_qY_rA_sA_tC_wC_z}^{(t)} \cdot p_{Y_rA_tC_z}^{(t)_{homo}}$  \hspace{1cm} (1) \\

or \\

$v^{(t)} = p_{X_qY_rA_sA_tC_wC_z}^{(t)} \cdot p_{Y_rA_tC_z}^{(t)_{homo}}$  \hspace{1cm} (2) \\

The $u^{(t)}$ or $v^{(t)}$ represents the frequency of a genotype $X_qY_rA_sA_tC_wC_z$ or $X_qY_rA_sA_tC_wC_z$ in males or females in generation $t$ before migration respectively.

The frequencies of genotypic combinations for each sex in a chain of demes in generation $t$ are expressed by $(n \times m)$ matrices $(m = 64)$, $U_0^{(t)}$ (for male) and $V_0^{(t)}$ (for female).

$$U_0^{(t)} = \begin{bmatrix} u_{11}^{(t)} & \cdots & u_{1m}^{(t)} \\ \vdots & \ddots & \vdots \\ u_{n1}^{(t)} & \cdots & u_{nm}^{(t)} \end{bmatrix} \quad \text{and} \quad V_0^{(t)} = \begin{bmatrix} v_{11}^{(t)} & \cdots & v_{1m}^{(t)} \\ \vdots & \ddots & \vdots \\ v_{n1}^{(t)} & \cdots & v_{nm}^{(t)} \end{bmatrix}$$  \hspace{1cm} (3) \\

in which each row vector represents the frequencies of genotype combinations in deme $i$ computed by (1) or (2). The range of $i$ is between 1 to $n$ corresponding to the positions of demes and the range of $j$ is between 1 to $m$ ($m = 64$ in this four loci scenario) corresponding to genotypic combinations.

The size of a compatible genotypic combination in deme $i$ is thus:

$$w^{(t)} = N_i^{(t-1)}u_{i}^{(t)} \quad \text{and} \quad z_{i}^{(t)} = N_i^{(t-1)}v_{i}^{(t)}$$  \hspace{1cm} (4) \\

The size of an incompatible genotypic combination in deme $i$ is:

$$w_{i}^{(t)} = (1-\psi)N_i^{(t-1)}u_{i}^{(t)} \quad \text{and} \quad z_{i}^{(t)} = (1-\psi)N_i^{(t-1)}v_{i}^{(t)}$$  \hspace{1cm} (5) \\

Here, $\psi$ $(0 \leq \psi \leq 1)$ is the strength of an incompatibility. A $\psi$ fraction of an incompatible genotype will be inferior and eliminated in the deme; $(1-\psi)$ will survive.

The density-dependent regulation of the population/deme size is based on the classic logistic model of population growth (see Hartl & Clark, 1997, page 31) and its strength is
expressed as \( r \) (the intrinsic rate of increase). When the male is the affected sex, the size of
deme \( i \) in generation \( t \) before migration is calculated by:

\[
N_i^{(t)} = \sum_j^m w_j^{(t)} + r \sum_j^m w_j^{(t)} \left( 1 - \frac{\sum_{j=1}^m w_j^{(t)}}{N_0} \right)
\]  

(6)

When the female is the affected sex, the size of deme \( i \) is:

\[
N_i^{(t)} = \sum_j^m z_j^{(t)} + r \sum_j^m z_j^{(t)} \left( 1 - \frac{\sum_{j=1}^m z_j^{(t)}}{N_0} \right)
\]  

(7)

Here, \( N_0 \) is the carrying capacity or the optimal population size. In each generation before
migration, the size of a population will be regulated by \( r \) until the balance is reached to satisfy

\[
N^{(t)} = N^{(t-1)} + rN^{(t-1)} \left( 1 - \frac{N^{(t-1)}}{N_0} \right)
\]  

(Hartl & Clark, 1997). The \( r \) and \( \psi \) together determine the
deme size.

The relative density of a deme before migration is:

\[
\rho = \frac{N^{(t)}}{N_0}
\]  

(8)

Here, \( \rho \) is \( 0 \leq \rho \leq 1 \) and \( N_0 \) is the carrying capacity, which is the same for all demes here.

The proportional sizes of genotypic combinations that will remain in the original demes
after elimination of incompatible offspring are:

\[
W^{(t)} = (1-\lambda) \begin{bmatrix} w_{11}^{(t)} & \cdots & w_{1m}^{(t)} \\ \vdots & \ddots & \vdots \\ w_{sl}^{(t)} & \cdots & w_{sm}^{(t)} \end{bmatrix} \quad \text{and} \quad Z^{(t)} = (1-\lambda) \begin{bmatrix} z_{11}^{(t)} & \cdots & z_{1m}^{(t)} \\ \vdots & \ddots & \vdots \\ z_{sl}^{(t)} & \cdots & z_{sm}^{(t)} \end{bmatrix}
\]  

(9)

The proportional sizes of genotypic combinations that will be migrating in the direction from
\( H_1 \) to \( H_2 \) are:
Here, the first row represents the inputs from $H_1$ with the genotypes $X_1X_1A_1A_1C_1C_1$ for the female and $X_1Y_1A_1A_1C_1C_1$ for the male. The sum of frequencies of either sex equals to 1. We assume that the carrying capacity ($N_0$) is the maximum deme size. The proportional sizes of genotypic combinations that will be migrating in the direction from $H_2$ to $H_1$ are:

\[
W^{(t)}_{\text{mig}1} = \frac{\lambda}{2} \begin{bmatrix} N_0 & 0 & \cdots & 0 \\
\frac{w^{(t)}_{11}}{N_0} & \frac{w^{(t)}_{12}}{N_0} & \cdots & \frac{w^{(t)}_{1n}}{N_0} \\
\vdots & \vdots & & \vdots \\
\frac{w^{(t)}_{n1}}{N_0} & \frac{w^{(t)}_{n2}}{N_0} & \cdots & \frac{w^{(t)}_{nn}}{N_0} 
\end{bmatrix}
\]

and

\[
Z^{(t)}_{\text{mig}1} = \frac{\lambda}{2} \begin{bmatrix} N_0 & 0 & \cdots & 0 \\
\frac{z^{(t)}_{11}}{N_0} & \frac{z^{(t)}_{12}}{N_0} & \cdots & \frac{z^{(t)}_{1n}}{N_0} \\
\vdots & \vdots & & \vdots \\
\frac{z^{(t)}_{n1}}{N_0} & \frac{z^{(t)}_{n2}}{N_0} & \cdots & \frac{z^{(t)}_{nn}}{N_0} 
\end{bmatrix}
\]

(10)

Here, the last row represents the inputs from $H_2$ with the genotypes $X_2X_2A_2A_2C_2C_2$ for the female and $X_2Y_2A_2A_2C_2C_2$ for the male.

Therefore, the proportional sizes of genotypic combinations in the zone after migration are:

\[
W^{(t)}_{\text{mig}2} = \frac{\lambda}{2} \begin{bmatrix} w^{(t)}_{21} & \cdots & w^{(t)}_{2(n-1)} & w^{(t)}_{2n} \\
\frac{w^{(t)}_{n1}}{N_0} & \cdots & \frac{w^{(t)}_{nn}}{N_0} \\
0 & \cdots & 0 & N_0
\end{bmatrix}
\]

and

\[
Z^{(t)}_{\text{mig}2} = \frac{\lambda}{2} \begin{bmatrix} z^{(t)}_{21} & \cdots & z^{(t)}_{2(n-1)} & z^{(t)}_{2n} \\
\frac{z^{(t)}_{n1}}{N_0} & \cdots & \frac{z^{(t)}_{nn}}{N_0} \\
0 & \cdots & 0 & N_0
\end{bmatrix}
\]

(11)

Thus, the frequency of a genotype combination after migration will be:

\[
\omega^{(t)} = \frac{(1-\lambda)w^{(t)}_{x} + \frac{\lambda}{2} \left( w^{(t)}_{x(x+1)} + w^{(t)}_{x(x+1)} \right)}{(1-\lambda)\sum_j w^{(t)}_{x} + \frac{\lambda}{2} \sum_j \left( w^{(t)}_{x(x+1)} + w^{(t)}_{x(x+1)} \right)}
\]

(13)

and the frequency of a female genotypic combination will be:

\[
\kappa^{(t)} = \frac{(1-\lambda)z^{(t)}_{x} + \frac{\lambda}{2} \left( z^{(t)}_{x(x+1)} + z^{(t)}_{x(x+1)} \right)}{(1-\lambda)\sum_j z^{(t)}_{x} + \frac{\lambda}{2} \sum_j \left( z^{(t)}_{x(x+1)} + z^{(t)}_{x(x+1)} \right)}
\]

(14)

The simulations and graphics used in the figures were generated with MATLAB.
(Code available by request).
Results

Gene flow under a partial sex-biased hybrid incompatibility – effective dispersal

The effective dispersal ($\lambda_e$) represents the strength of gene flow or introgression of an allele. The $\lambda_e$ of alleles on different chromosomes are different as shown in Figure 1. Figure 1 shows the distribution of $\lambda_e$ under the influence of an $X_1A_2$ incompatibility ranging from 0 to 1 ($0 \leq \psi \leq 1$, X-axis) that is in a scenario of a mild density-dependent regulation ($r = 0.05$) and $\lambda = 0.1$ (Figure 1A), 0.2 (Figure 1B) and 0.4 (Figure 1C). It is evident that the introgressions of the incompatible loci ($X$ and $A$) are highly asymmetrical under a weak Haldane’s rule. For instance, in the scenario of $\lambda = 0.4$ (Figure 1C), a 10% ($\psi = 0.1$) $X_1A_2$ incompatibility results in a $\lambda_e$ of $X_1$ and $A_2$ about 0.1060 and 0.158 respectively, and a $\lambda_e$ of $X_2$ and $A_1$ of 0.440 and 0.366 respectively at the “equilibrated point” (2000 generations). The non-incompatible alleles ($X_2$ and $A_1$) have a much higher introgression comparing to their incompatible counterparts ($X_1$ and $A_2$). As shown in Supplementary Figure 1, a higher density-dependent regulation extends the differentiation of introgression between the $X$ and $A$ loci. In a scenario when $r = 0$, $\lambda = 0.4$ and $\psi = 0.2$, the $\lambda_e$ of $X_1$ and $X_2$ would be 0.066 and 0.220 respectively. However, when $r$ increases to 0.1 in the same scenario, the $\lambda_e$ of $X_1$ and $X_2$ would become 0.118 and 0.51 respectively (Supplementary Figure 1A & 1C). Also, the compatible counterparts of the incompatible alleles have a higher tendency to introgress comparing to the alleles at neutral loci when density-dependent regulation is strong. The $\lambda_e$ of these compatible counterparts can be much higher than the actual $\lambda$, but $\lambda_e$ of a neutral allele is always lower than $\lambda$ (Figure 1 and Supplementary Figure 1). A strong flow of non-incompatible alleles ($X_2$ and $A_1$ in this example) would constitute a strong homogenization force causing the collapse of the genetic barrier. Furthermore, a density-dependent regulation could substantially are negatively correlated with the barrier strength against the neutral flow. As shown in Supplementary Figure 1D, under a relatively strong density-dependent
regulation ($r = 0.5$), the introgression of a neutral allele is very close to the scenario with no incompatibility (the reference lines in Supplementary Figure 1D). Interestingly, the trends of $\lambda_e$ of all alleles plateau long before a full strength BDM incompatibility ($\psi = 1$), suggesting that even a milder $X_1A_2$ incompatibility, as low as 20% ($\psi = 0.2$), could mount significant impedance on gene flow that is almost comparable to a 100% incompatibility ($\psi = 1$).

The effective of partial sex-biased incompatibilities on the cline structures of various alleles

Genetic isolation could cause clinal non-coincidence and discordance of alleles in a hybrid zone. I examined the effects of a weak $X_1A_2$ unidirectional incompatibility on the clinal structure in relation to variations of $\psi$, $\lambda$, and $r$. Figure 2 shows some clines of alleles in a number of representative scenarios. It can be seen that an $X_1A_2$ unidirectional incompatibility causes significant clinal non-coincidence and discordance. The cline of a neutral locus is wider, less steep ($P_{C1}$ in Figure 2), and almost symmetrically distributed, but the clines of incompatible loci are steeper, narrower and asymmetrically distributed ($P_{XI}$ and $P_{A1}$ in Figure 2). Figure 2A, B and C show the clines caused by a 10% $X_1A_2$ incompatibility ($\psi = 0.1$). The non-coincidence of clines is rather obvious and significant under the 10% incompatibility but to a lesser extent in comparison with those under a full scale $X_1A_2$ heterogametic incompatibility ($\psi = 1$), which is shown in Figure 2D, E and F. Figure 2 also shows that a stronger density-dependent regulation produces less steep clines of the $Y$ and neutral $C$ loci, similar to those formed through neutral diffusion (Endler, 1973) (Endler, 1977, Barton & Gale, 1993). The clines of $X$ and $A$ are more asymmetrically distributed, in which the $X$ locus shows the most asymmetry. This suggests that a very weak $X_1A_2$ incompatibility under a stronger density-dependent regulation could lead to a pronounced asymmetric introgression of $X$ and $A$ loci, but not in the case of $Y$ and $C$ loci. Among all loci, the cline of the $X$ locus is
the narrowest and steepest, which could likely facilitate faster divergences of $X$-linked loci during speciation.

The hybrid sink effects of weak incompatibilities

To better appreciate the fitness effect of a weak $X_A X_B$ heterogametic incompatibility, the density depression in a hybrid zone as a consequence of elimination of inferior hybrids was examined. The zone here acts as a “sink” because the production of inferior hybrids results in an inward net flow of migrants towards the centre of the zone (the hybrid sink effect) (Barton, 1980, Barton & Bengtsson, 1986). Distribution of relative density ($0 \leq \rho \leq 1$) across a hybrid zone is the function of the incompatibility strength ($\psi$), dispersal rate ($\lambda$), and density-dependent regulation ($r$). Figure 3 shows the distribution of relative density across a hybrid zone in different scenarios at equilibrium. The density distribution in the zone displays an asymmetrical, “V” shape depression.

In this 10 deme scenario, if density-dependent regulation is absent ($r = 0$), the lowest depression point is at deme 5; if density-dependent regulation is present ($r = 0.05$ or 0.2), the lowest depression point shifts to further left to deme 4. This suggests that the asymmetrical pressure increases when density-dependent regulation is larger. The density depression is more pronounced when the strength of the incompatibility is higher, density-dependent regulation is lower, or dispersal rate is ($\lambda$) is higher (Figure 3). There is a good correlation between the density distribution and the percentages of inferior offspring produced in a hybrid zone in each generation at equilibrium (See Supplementary Figure 2).

Next, I examined the relationship between the density depression and the strength of density-dependent regulation ($X$-axis). Figure 4 shows the equilibrated density of Deme No.5 in response to the varying $r$ values with a 5, 10, 30 or 100% incompatibility strength ($\psi = 0.05, 0.1, 0.3$ or 1) and 10 or 40% dispersal ($\lambda = 0.1$ or 0.4). A strong density-dependent
regulation can almost entirely compensate for the depression caused by an $X_1A_2$ incompatibility (Figure 3 and Figure 4). The analysis here also suggests that when density-dependent regulation is relatively weak, a weak $X_1A_2$ heterogametic incompatibility ($\psi \ll 1$) could still be a rather efficient barrier and causes a substantial density depression (Figure 3A, 3B and 4). However, if density-dependent regulation is strong and the $r$ value is large ($r > 0.2$), even a full strength heterogametic incompatibility ($\psi = 1$) would only cause an insignificant density depression (Figure 4). Density-dependent regulation is an important factor in regulating the density and the size of demes in a hybrid zone.
Discussion

The current paper is an attempt to examine the role of a weak BDM incompatibility in a hybrid zone system. It provides a more quantitative account of how “slightly lessened fertility (see ‘Charles Darwin's letters: a selection, 1825-1859’Darwin & Burkhardt, 1998)” caused by weak sex-biased inferiority (i.e. weak Haldane’s rule) could contribute to the genetic divergence and potentially the establishment of complete reproductive isolation during speciation. The gene frequency changes and gene flow between diverging populations during speciation are at the heart of population genetics. I found that a weak sex-biased hybrid incompatibility can profoundly affect gene flow past a hybrid zone. A weak, sex-biased BDM incompatibility provides a) a significant reinforcement pressure to drive further divergence of population; and b) a substantial drive of the asymmetrical flow of incompatible loci (Figures 1), which leads to significant clinal non-coincidence and discordance (Figure 2).

The impedance of the flow of incompatible genes across a hybrid zone is no surprising. Such gene flow usually results in abrupt clines (Barton & Gale, 1993). It is interesting, however, that such impedance can be achieved through a weak, sex-biased BDM incompatibility. As shown in Figure 1, a weak incompatibility with 10-20% (ψ = 0.1-0.2) strength is sufficient to confer a significant reduction of gene flow across a hybrid zone of an incompatible allele. The effective dispersal of most alleles under a 20% incompatibility is close to that of a full strength sex-biased incompatibility (Figure 1). Such reduced gene flow results in characteristic clinal structures in the hybrid zone. The width, steepness and spatial distribution of allele clines (Figure 2) are similar, but to lesser extent, to those under a full strength incompatibility (Wang & Zhao, 2008). Furthermore, a weak compatibility can also cause a substantial density depression in the hybrid zone that is only moderately shallower than a full strength sex-biased incompatibility (Figure 3). In essence, a hybrid zone in the presence of weak sex-biased BDM isolation would act like a filter: it selectively blocks the
exchange of incompatible ones (e.g. $X_1$ and $A_2$ in an $X_1A_2$ incompatibility) and at the same
time, allows almost free exchange of neutral loci similar to that through neutral diffusion ($P_{C_j}$
in Supplementary Figure 1C and 1D). The introgression of non-incompatible alleles, such as
the $X_2$ and $A_i$ in the case of $X_iA_2$ incompatibility, would be higher than that of neutral alleles
(Supplementary Figure 1C and D). The most affected loci by a weak Haldane’s rule are on
the $X$ chromosomes. These trends are more pronounced when density-dependent regulation is
high.

The real question is how relevant these trends are to genetic divergence and speciation. It
is conceivable that a hybrid zone (tension zone) with a sex-biased isolation is highly unstable
and mobile, because of asymmetric gene flow and incomplete isolation. Maintaining such a
hybrid zone would have to involve other selection forces. For instance, a hybrid zone could
be stabilized if alleles related to BDM isolation have selective advantages in their own
respective localities; or when it coincides with density troughs and/or habitat boundaries with
environmental differentiations, which is indeed often the case in nature (Hewitt, 1988, Rice &
Hostert, 1993). The population dynamics described in this study may be indicative of how
sex-biased BDM incompatibilities is established and preserved during speciation.

Studies on diverse taxa have shown that natural selection caused by habitat shifts and
environmental changes can lead to extremely rapid genetic divergence and ecological
segregation, such as soapberry bugs (Carroll, 1997; Carroll, 2003), threespine
sticklebacks (Schluter, 1996, Albert et al., 2008, Berner et al., 2009), cichlids (Barluenga et
al., 2006), Neotropical guppies (Reznick et al., 1997), island lizards (Losos et al., 1997), and
rainforest passerines (Smith et al., 1997). For instance, after the introduction of an alternative
host into North America in less than 100 generations, the “derived-type” soapberry bugs
($Jadera hematoloma$) had evolved epistatic incompatibilities from the “ancestral-type”
(Carroll et al., 2003). The “derived-type” and “ancestral-type” were genetically diverged in
the feeding morphology, growth rate, survival and fecundity (Carroll et al., 1997). In threespine sticklebacks, the analysis of neutral microsatellites markers indicate that adaptive divergence and partial reproductive isolation often coexist between two parapatric populations (Berner et al., 2009). In these fish, some genomic regions, including the sex-determining chromosome region, have the largest effect on adaptive traits by QTL analysis, suggesting a rapid fixation of adaptive mutations and uneven divergence of different chromosomal regions (Albert et al., 2008); ecological selection also drove rapid evolution of extrinsic postzygotic isolation (Gow et al., 2007) and prezygotic isolation (Boughman et al., 2005) between benthic and limnetic sticklebacks.

In recent years, many hotspot genes and mutations have been discovered (Stern & Orgogozo, 2009). The evolutionary changes in the hotspots are often associated with specific adaption (ffrench-Constant et al., 1998, Wichman et al., 1999, Shindo et al., 2005); and/or with sex-biased incompatibility and Haldane’s rule in various species pairs (Wittbrodt et al., 1989, Ting et al., 1998, Barbash et al., 2003, Presgraves et al., 2003, Brideau et al., 2006, Masly et al., 2006, Mihola et al., 2009, Phadnis & Orr, 2009, Tang & Presgraves, 2009).

These studies support the notion that the rapid evolution of isolating mechanisms is not merely the by-products of genetic drifts or neutral divergence, as many once believed, in environments with high ecological differentiations in sympatry or parapatry (Carroll et al., 1997, Reznick et al., 1997, Orr & Smith, 1998, Wang, 2003, Wang & Zhao, 2008).

The interplays between adaptation and reproductive isolation hold the key for the evolution of sexually reproducing organisms (Butlin et al., 2008, Fitzpatrick et al., 2008). In light of the current analysis, one can speculate that in a highly differentiated environment, the adaptive changes in subpopulations would more likely be preserved during speciation, if they happen to cause hybrid inferiority. This mechanism may have led to the dominance of BDM isolation and Haldane’s rule. This population dynamics provides a glimpse of how a
speciation gene comes into being at an early stage of population divergence. In a megapopulation consisting of many clades with complex environmental differentiations, an adaptive mutation could set the gene up as a hotspot that initiates a runaway evolutionary process toward more complete reproductive isolation. With such dynamics, local adaptation and postzygotic isolation could promote each other during genetic divergence and population differentiation. This model may also be extended to test some controversial issues in evolutionary biology. For instance, whether or not secondary contact is a prerequisite for the formation of hybrid zone and species; whether or not hybrid zones are the sites of ‘reinforcement’ (Dobzhansky, 1940) – the evolution of prezygotic barriers to gene exchange in response to selection against hybrids (Harrison, 1993). These are the fundamental questions in the field of population genetics that remain controversial for many years (Paterson, 1978, 1982; Butlin, 1987, 1989).

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**Figure 1.** The effective dispersal ($\lambda_e$) of different alleles in a scenario of $r = 0.05$ with dispersal of (A) $\lambda = 0.1$; (B) $\lambda = 0.2$; and (C) $\lambda = 0.4$. The strength of an $X_1A_2$ heterogametic incompatibility varies from 0 to 1 ($X$-axis). The horizontal dotted line in each panel is the reference line, which represents a scenario of no genetic incompatibility between two parental populations.

**Figure 2.** The non-coincident and discordant clines of the representative loci, $X$, $Y$, $A$ and $C$ across a hybrid zone consisting of 10 demes with different density-dependent regulations ($r$) and barrier strengths ($\psi$ – caused by an $X_1A_2$ heterogametic incompatibility) at 40% dispersal ($\lambda = 0.4$). (A) $r = 0$, $\psi = 0.1$; (B) $r = 0.05$, $\psi = 0.1$; (C) $r = 0.4$, $\psi = 0.1$; (D) $r = 0$, $\psi$ = 1; (E) $r = 0.05$, $\psi = 1$; (F) $r = 0.4$, $\psi = 1$.

**Figure 3.** The relative density depression in an equilibrated hybrid zone ($t = 2000$) consisting of 10 demes with the various strengths ($\psi$) of an $X_1A_2$ heterogametic incompatibility and different density-dependent regulation, (A and D. $r = 0$; B and E. $r = 0.05$; and C and F. $r = 0.2$). In each panel, the alternate lines from top to bottom represent the strength of an $X_1A_2$ heterogametic incompatibility of $\psi = 0.05$, 0.1, 0.2, 0.3, 0.5 or 1.

**Figure 4.** The equilibrated density distribution in Deme No.5 under different density-dependent regulation in a scenario of 10 demes with different strengths of an $X_1A_2$ heterogametic incompatibility ($\psi = 0.05$, 0.1, 0.3 and 1) and dispersal (A) $\lambda = 0.1$ (B) $\lambda = 0.4$.

**Figure 5.** The population density over time (generations) in the Deme No.5 with different strength of BDM incompatibility ($\psi$). From top to bottom, the alternate lines from top to bottom represent a $\psi$ value of 0.05, 0.1, 0.2, 0.3, 0.5 or 1, respectively.
Supplementary Figure 1. The effective dispersal ($\lambda_e$) of different alleles in scenarios of $(\mathbf{A}) r = 0$, $(\mathbf{B}) r = 0.05$, $(\mathbf{C}) r = 0.1$, and $(\mathbf{D}) r = 0.5$ with 40% dispersal ($\lambda = 0.4$) and the strength ($\psi$) of an $X_A X_B$ heterogametic incompatibility varying from 0 to 1 ($X$-axis). The horizontal dotted line in each panel is the reference line representing a scenario of no incompatibility, in which there is no genetic isolation between parental populations.

Supplementary Figure 2. The percentage of inferior offspring under a complete $X_A X_B$ heterogametic incompatibility ($\psi = 1$) in each generation at equilibrium. The variations of parameters are: $r = 0$, 0.05, and 0.2; $\lambda = 0.05$, 0.2 and 0.4.

Supplementary Figure 3. The time (generations) required for establishing equilibrium under a weak $X_A X_B$ heterogametic incompatibility. The cutoff of equilibration is set at the 1% collective size of all 10 demes. The hybrid zone with a size change smaller than the cutoff between generations is considered at equilibrium. Here, the strength of the incompatibility ($\psi$) varies from 0 to 1 ($X$-axis). Dispersal of 10, 20 and 40% ($\lambda = 0.1$, 0.2 and 0.4) are considered. $(\mathbf{A}) r = 0$; $(\mathbf{B}) r = 0.05$; $(\mathbf{B}) r = 0.1$; and $(\mathbf{C}) r = 0.5$. 
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Figure 1: Strength of $X_1A_2$ incompatibility ($\psi$) for $\lambda = 0.1$, $\lambda = 0.2$, and $\lambda = 0.4$. The graphs show the relationship between $\lambda$, $X_1$, $Y$, and $A$ loci for different values of $\lambda$. The x-axis represents the strength of $X_1A_2$ incompatibility ($\psi$) and the y-axis represents the values of the loci. The plots are divided into three categories based on $\lambda$ values: A) $\lambda = 0.1$, B) $\lambda = 0.2$, and C) $\lambda = 0.4$. Each category contains subplots for different loci ($\lambda_1$, $\lambda_2$, $\lambda_3$, $\lambda_4$, $\lambda_5$, $\lambda_6$).
Figure 2

Allele frequencies (P)

A. $r = 0$

B. $r = 0.05$

C. $r = 0.4$

D. $r = 0$

E. $r = 0.05$

F. $r = 0.4$
Figure 3

A. $r = 0, \lambda = 0.1$

B. $r = 0.05, \lambda = 0.1$

C. $r = 0.2, \lambda = 0.1$

D. $r = 0, \lambda = 0.4$

E. $r = 0.05, \lambda = 0.4$

F. $r = 0.2, \lambda = 0.4$

Densities $\rho (\lambda)$ for different values of $\varphi$: $\varphi = 0.05$, $\varphi = 0.1$, $\varphi = 0.2$, $\varphi = 0.3$, $\varphi = 0.5$, $\varphi = 1$.

Deme No. vs Density $\rho$ for various scenarios.
Figure 4

A. $\lambda = 0.1$

B. $\lambda = 0.4$
Figure 5

A. \( r = 0, \lambda = 0.1 \)

B. \( r = 0.05, \lambda = 0.1 \)

C. \( r = 0.2, \lambda = 0.1 \)

D. \( r = 0, \lambda = 0.4 \)

E. \( r = 0.05, \lambda = 0.4 \)

F. \( r = 0.2, \lambda = 0.4 \)
Strength of $X_1 A_2$ incompatibility ($\psi$)
Supplementary Figure 2

A. $r = 0$

B. $r = 0.05$

C. $r = 0.2$

Percent of inferior progeny

Deme
A. $r = 0$

B. $r = 0.05$

C. $r = 0.1$

D. $r = 0.5$