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Rapidly Evolving Genes and Genetic Systems

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Contents

OUP CORRECTED PROOF – FINAL, 29/5/2012, SPi

OUP CORRECTED PROOF – FINAL, 29/5/2012, SPi

OUP CORRECTED PROOF – FINAL, 29/5/2012, SPi

OUP CORRECTED PROOF – FINAL, 29/5/2012, SPi

OUP CORRECTED PROOF – FINAL, 29/5/2012, SPi

OUP CORRECTED PROOF – FINAL, 29/5/2012, SPi

OUP CORRECTED PROOF – FINAL, 29/5/2012, SPi

OUP CORRECTED PROOF – FINAL, 29/5/2012, SPi

CHAPTER 4

Heterogeneity in neutral divergence across genomic regions induced by sex-specific hybrid incompatibility

Seiji Kumagai and Marcy K. Uyenoyama

4.1 Introduction

Genes introduced into a genomic or environmental context different from the context in which they evolved may induce deleterious effects. Among the best-documented cases are hybrid incompatibility factors, which cause severe disruptions in viability, fertility, morphology, and behavior in interspecific hybrids (Coyne and Orr, 2004; Nosil and Schluter, 2011). Further, adaptation to local ecological conditions may engender divergent selection across environments (Charlesworth et al., 1997; Schluter, 2001). Here, we refer to genes that are neutral in their home context and deleterious in other contexts as incompatibility factors.

4.1.1 Detecting incompatibility factors

Many studies of genomic patterns of variation treat locus-specificity as a hallmark of selection, assuming that demographic history and population structure affect all regions of the genome uniformly (e.g. Akey et al., 2002; Innan et al., 2003). Neutral markers tightly linked to targets of incompatibility selection are expected to show low introgression relative to unlinked markers (Bengtsson, 1985; Barton and Bengtsson, 1986; Navarro and Barton, 2003). Kulathinal et al. (2009) examined genome-wide pairwise nucleotide differences in intraspecific comparisons (different strains of *Drosophila pseudoobscura*) and interspecific comparisons (*D. pseudoobscura* to sister species *D. persimilis* or to outgroup *D. miranda*). This exploration appeared to indicate greater excess of interspecific over intraspecific differences in genomic regions adjacent to known incompatibility factors.

A departure from earlier theoretical expectations is that sex-specific incompatibility can differentially impede introgression of neutral markers even in the absence of physical linkage (Fusco and Uyenoyama, 2011b). This effect derives from associations of genetic regions with sex, in the absence of functional epistasis between targets of selection and neutral markers. For example, deleterious factors tend to be eliminated more slowly from the sex in which they are more benign and neutral markers transmitted primarily or exclusively through one sex experience incompatibility factors predominantly in the context of that sex.

4.1.2 Within-species polymorphisms for incompatibility factors with sex-limited transmission

Chippindale and Rice (2001) detected remarkably strong effects on male fitness of Y chromosomes segregating within a laboratory strain of *Drosophila melanogaster*. Recent analyses have demonstrated pervasive disruptions in expression of genes throughout the genome upon introgression of Y chromosomes between laboratory strains or natural populations (Lemos et al., 2008, 2010; Jiang et al., 2010). Earlier work had documented greater divergence between *D. melanogaster* and *D. simulans* of genes with male-biased expression (Ranz et al., 2003). Male-biased genes contributed disproportionately to those subject to Y-linked regulatory variation (YRV), and YRV genes show greater

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OUP CORRECTED PROOF – FINAL, 24/5/2012, SPi

divergence between *D. melanogaster* and *D. simulans* (Lemos et al., 2008).

Substitution of mitochondrial genomes among strains also induces pervasive changes in expression throughout the *D. melanogaster* genome (Innocenti et al., 2011), with genes with male-biased expression again over-represented among affected genes. The authors suggested that near-complete restriction of mitochondrial transmission through the female line indicates that selection on mitochondrial genomes, driven primarily by their effects on female but not male fitness, may be strongly sexually antagonistic (reviewed by Rice, 1998).

As extensive disruption of expression is likely to be highly deleterious, these examples suggest that polymorphisms for incompatibility factors with sex-limited transmission may induce substantial barriers to introgression among populations of conspecifics. Further, that genes with sex-biased expression diverge at accelerated rates (Ranz et al., 2003) suggests that incompatibility at the intraspecific level as well as the interspecific level may tend to be sex-specific.

In this chapter, we summarize the nature of differential rates of introgression across the genome generated by sex-specific incompatibility. We explore the implications of this process for the inference of population structure.

4.2 Genealogical migration rate

4.2.1 Definition

A number of indices have been proposed to quantify rates of neutral introgression induced by incompatibility factors. The index most widely used in the context of interspecific hybridization (e.g. Barton and Bengtsson, 1986; Navarro and Barton, 2003) is Bengtsson's (1985) 'gene flow factor,' which corresponds to the probability that a foreign marker allele will succeed in transferring to a genomic background free of incompatibility factors. Gavrilets (1997) used the inverse of the equilibrium frequency of a marker allele in a deme in which its existence requires gene flow in opposition to selection. Takahata and Slatkin (1984) studied the rate of replacement of the local neutral marker allele by a foreign allele repeatedly introduced together with an incompatibility factor by one-way migration. Kobayashi et al. (2008) defined 'neutral effective migration rate' in terms of the change in frequency of a foreign allele relative to the difference in frequency of the allele within the deme and among migrants.

Our objective is to characterize the pattern of variation at neutral markers in a genome containing incompatibility factors. Fusco and Uyenoyama (2011a,b) approximated the full, complex process using a structured population model of neutral variation with a migration rate scaled to account for selection targeted to incompatibility factors and crossing-over between the marker and incompatibility loci. The genealogical migration rate (g) corresponds to the parameter of an exponential waiting time density of migration events along a random lineage traced backwards in time:

$$g = m\omega, \tag{4.1}$$

for m the backward migration rate (proportion of the local gamete pool derived from migrants) and ω the relative reproductive rate. For Ω indicating the locations of incompatibility factors, relative reproductive rate $\omega_{\Omega}^{l,s}$ represents the expected number of descendants in a generation far into the future of a neutral marker gene at genomic location l on a gamete (v_m) transmitted by a migrant of sex s, relative to a marker gene on a resident gamete (v_r). It corresponds to the limit

$$\omega_{\Omega}^{l,s} = \lim_{t\to\infty} \frac{v_m(\boldsymbol{ZSG})^t \boldsymbol{e}}{v_r(ZSG)^t e}, \tag{4.2}$$

for $\boldsymbol{Z}$ describing the generation of zygotes from gametes; $\boldsymbol{S}$ selection on zygotes; $\boldsymbol{G}$ the transmission by reproducing zygotes of gametes bearing neutral marker genes; t the number of generations since the focal migration event; and $\boldsymbol{e}$ the vector with all elements equal to 1 (Fusco and Uyenoyama, 2011a). Results of simulations (Fusco and Uyenoyama, 2011b) suggest that for backward migration rates (m) sufficiently low so that the interval between migration events is long relative to the time to convergence of the limit in (4.2), the waiting time to the most recent migration event along a random lineage at the neutral marker locus is indeed well-approximated by an exponential distribution

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with parameter given by the genealogical migration rate (4.1).

For c the proportion of females among reproducing migrants, incompatibility loci at genomic locations indicated by Ω induce an overall relative reproductive rate at a neutral marker locus at location l of

$$\bar{\omega}_{\Omega}^{l} = c\omega_{\Omega}^{l,f} + (1-c)\omega_{\Omega}^{l,m}. \quad (4.3)$$

4.2.2 Non-sex-specific incompatibility

While previous analyses of barriers to interspecific introgression have assumed the absence of disfavored incompatibility alleles in pure-species populations, polymorphisms appear to be common in plants (Rieseberg and Blackman, 2010) and are expected to arise among conspecific demes adapted to local ecological conditions. Relative reproductive rate as defined in (4.2) easily accommodates polymorphisms maintained by a balance between selection and migration (Fusco and Uyenoyama, 2011a).

Under purifying or disruptive selection, regimes that promote within-deme monomorphism, genealogical migration rate g (4.1) declines with increasing difference in incompatibility allele frequency between the local gamete pool and gametes transmitted by migrants. In contrast, overdominant selection within demes engenders almost no barrier to introgression, even for very large between-deme differences in equilibrium frequencies of incompatibility alleles. Under meiotic drive opposing purifying selection within demes, relative reproductive rate $\omega_{\Omega}^{l,s}$ (4.2) can exceed unity, signifying that migrants have greater expected numbers of descendants than residents.

4.2.3 Sex-specific incompatibility

Sex-specific incompatibility may reflect differential impairment of the sexes by foreign alleles, linkage to genomic regions transmitted primarily or exclusively through one sex, or differences between the sexes in rates of crossing-over between neutral marker loci and targets of incompatibility selection. For example, incompatibility factors borne on Y chromosomes or mitochondrial genomes (e.g. Lemos et al., 2008; Innocenti et al., 2011), which show maximal associations with sex, differentially impede introgression of neutral markers on autosomes, sex chromosomes, or mitochondria (table 1 of Fusco and Uyenoyama, 2011b).

In general, barriers to neutral introgression engendered by sex-specific incompatibility depend on the locations within the genome of incompatibility loci and neutral marker loci and on the sex of migrants. Table 4.1 provides expressions for relative reproductive rate (4.2) in ZW sex determination systems.

Sex-specificity also causes barriers generated by multiple sex-specific incompatibility factors to depart from earlier expectations. In the absence of sex-specificity, the total barrier to introgression induced by incompatibility factors showing no functional epistasis corresponds to the product of the barriers induced by the factors individually (Barton and Bengtsson, 1986; Fusco and Uyenoyama, 2011b). In contrast, associations with sex developed by multiple sex-specific incompatibility factor influence their joint distribution. Non-epistatic factors with concordant effects on the sexes (e.g. impairing males more than females or higher rates of crossing-over with the neutral marker in females) generate a submultiplicative total barrier (below the multiplicative expectation) and factors with discordant effects a supermultiplicative total barrier (Fusco and Uyenoyama, 2011b). This effect reflects the greater efficiency of selection acting to purge incompatibility factors associated with the same sex (compare Hill and Robertson, 1966; Barton, 1995).

4.3 Applications

We explore some implications of sex-specific incompatibility for patterns of variation across genomic regions.

4.3.1 Mitochondrial introgression

Petit and Excoffier (2009) conducted a literature survey of patterns of interspecific introgression in 37 mammal, bird, and insect species known to have sex-biased dispersal. Their results appeared to indicate a trend opposite to prediction based on sex-biased migration alone: all 16 organisms with

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Table 4.1 Relative reproductive rates under ZW sex determination

Position[a]		Relative reproductive rate	
Factor	Marker	Female migrant	Male migrant
A	A	$\frac{\sigma_f r_f + \sigma_m r_m}{1-\sigma_f(1-r_f)+1-\sigma_m(1-r_m)}$	$\frac{\sigma_f r_f + \sigma_m r_m}{1-\sigma_f(1-r_f)+1-\sigma_m(1-r_m)}$
A	Z	$\frac{\sigma_m(4+\sigma_f)}{8-\sigma_m(2+\sigma_f)}$	$\frac{2(\sigma_f+\sigma_m)+\sigma_f\sigma_m}{8-\sigma_m(2+\sigma_f)}$
A	W	$\frac{\sigma_f}{2-\sigma_f}$	0
A	mt	$\frac{\sigma_f}{2-\sigma_f}$	0
Z	A	$\frac{4+\sigma_m}{8-\sigma_m(2+\sigma_f)}$	$\frac{2(\sigma_f+\sigma_m)+\sigma_f\sigma_m}{8-\sigma_m(2+\sigma_f)}$
Z	Z	$\frac{2\sigma_m r_m}{2-\sigma_m(1+\sigma_f)(1-r_m)}$	$\frac{\sigma_m(1+\sigma_f)r_m}{2-\sigma_m(1+\sigma_f)(1-r_m)}$
Z	W	1	0
Z	mt	1	0
W	A	$\frac{1}{2-\sigma_f}$	1
W	Z	1	1
W	W	0	0
W	mt	0	0
mt	A	$\frac{\sigma_m}{2-\sigma_f}$	1
mt	Z	σ_m	1
mt	W	0	0
mt	mt	0	0

* Genomic location: autosomal (A), Z-linked (Z), W-linked (W), mitochondrial (mt)

female-biased dispersal showed lower introgression of mitochondrial than nuclear markers and all but two of 21 organisms with male-based dispersal showed higher introgression of mitochondrial markers. Most of the species designated as having female-biased dispersal also had a ZW sex determination system with homogametic (ZZ) males and most of the species with male-biased dispersal had heterogametic (XY or XO) males.

We compare XY and ZW sex determination systems with respect to barriers to mitochondrial introgression induced by incompatibility factors on the Y or W chromosome. A major difference between XY and ZW sex determination systems is the nature of cosegregation of mitochondria with sex. In descendants of a female migrant, the foreign mitochondrial genome, foreign W chromosome, and femaleness show complete cosegregation. In particular, Table 4.1 indicates that a W-linked incompatibility factor completely blocks mitochondrial introgression ($\omega_W^{mt,f} = 0$), while a Y-linked factor presents no barrier at all ($\omega_Y^{mt,f} = 1$). To the extent that incompatibility factors occur on the chromosome held exclusively by the heterogametic sex (Y or W), this comparison suggests greater mitochondrial than nuclear introgression in natural populations with XY but not ZW sex determination systems.

This prediction appears to be consistent with Petit and Excoffier's (2009) finding of higher mitochondrial than nuclear introgression in 13 of the 17 organisms with XY sex determination and in four of the 17 organisms with ZW sex determination. Fur-

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ther, in one of the first empirical observations documenting differential interspecific divergence among genomic regions, Powell (1983) reported that sympatric but not allopatric populations of *Drosophila pseudoobscura* and *D. persilimis* (XY) share mitochondrial genomes despite abundant evidence of nuclear divergence in sympatry as well as allopatry.

4.3.2 Interpreting region-specific F_{ST}

A seminal analysis by Seielstad et al. (1998) revealed striking differences in F_{ST} estimated from autosomal, mitochondrial, and Y-linked variation at a local scale (hundreds of kilometers) among human European populations. They suggested that the large (eightfold) difference in numbers of migrants inferred from mitochondrial and Y-linked variation primarily reflects higher migration rates in females. A number of subsequent studies have based inferences about sex-bias in effective number or migration rate on comparisons of F_{ST} (reviewed by Wilkins, 2006). Exploring sex-bias at the genome scale in global samples has proven to be more complex than anticipated, with some data sets failing to show expected patterns (Wilder et al., 2004), showing conflicting patterns across data sets (Hammer et al., 2008; Keinan et al., 2009; Bustamante and Ramachandran, 2009), or showing no consistent pattern across loci (Garrigan et al., 2007).

Sex-bias in migration or effective numbers: A number of methods have been proposed to estimate sex-bias in migration rate or effective number based on genomic patterns of variation (e.g. Hamilton et al., 2005; Hammer et al., 2008; Ramachandran et al., 2008; Ségurel et al., 2008). In particular, low F_{ST} estimated from X-linked (F_{ST}^X) relative to autosomal (F_{ST}^A) markers has been interpreted as indicative of greater numbers of female migrants. For the island model with small rates of mutation relative to migration,

$$F_{ST} = \frac{1}{1 + 4N_e m_e [d/(d-1)]^2}, \tag{4.4}$$

for N_e the effective number of zygotes, m_e the effective rate of migration, and d the number of demes (e.g. Hudson, 1990; Slatkin, 1991). Under sex-biased dispersal or effective numbers,

$$N_e = \frac{4N_f N_m}{N_f + N_m}$$

$$m_e = (m_f + m_m)/2$$

for autosomal marker loci and

$$N_e = \frac{9N_f N_m}{2N_f + 4N_m}$$

$$m_e = (2m_f + m_m)/3$$

for X-linked marker loci, in which N_f and N_m denote effective numbers of female and male reproductives within demes and m_f and m_m female and male backward migration rates.

Ramachandran et al. (2008) addressed the relationship between the ratio of migrant numbers ($M_f/M_m = N_f m_f/(N_m m_m)$) and the proportion of females among reproductives within a deme ($r = N_f/(N_f + N_m)$):

$$\frac{M_f}{M_m} = \frac{r\left[-3\left(\frac{1}{F_{ST}^A} - \frac{1}{F_{ST}^X}\right) + (5-4r)\left(\frac{1}{F_{ST}^X} - 1\right)\right]}{2(1-r)\left[3\left(\frac{1}{F_{ST}^A} - \frac{1}{F_{ST}^X}\right) - (1-2r)\left(\frac{1}{F_{ST}^X} - 1\right)\right]}. \tag{4.5}$$

Sex-specific incompatibility: Here, we explore inferences about sex-biased dispersal or effective numbers that might be drawn from F_{ST} generated under a distinct model: sex-specific incompatibility with sex-independent effective numbers ($N_f = N_m = N/2$) and an overall backward migration rate of m. Under our model,

$$\begin{aligned} F_{ST}^A &= \frac{1}{1 + 4Nm\bar{\omega}_\Omega^A [d/(d-1)]^2} \\ F_{ST}^X &= \frac{1}{1 + 3Nm\bar{\omega}_\Omega^X [d/(d-1)]^2}, \end{aligned} \tag{4.6}$$

for $\bar{\omega}_\Omega^A$ and $\bar{\omega}_\Omega^X$ defined in (4.3). Substitution of these expected values into (4.5) produces

$$\frac{M_f}{M_m} = \frac{r\left[(2-r)\bar{\omega}_\Omega^X - \bar{\omega}_\Omega^A\right]}{(1-r)\left[2\bar{\omega}_\Omega^A - (2-r)\bar{\omega}_\Omega^X\right]}. \tag{4.7}$$

Positivity of the inferred ratio of female to male migrants (M_f/M_m) requires

$$2\bar{\omega}_\Omega^A/(2-r) > \bar{\omega}_\Omega^X > \bar{\omega}_\Omega^A/(2-r),$$

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which reduces, under equal effective numbers of males and females ($r = 1/2$), to

$$\frac{4}{3}\bar{\omega}_{\Omega}^{A} > \bar{\omega}_{\Omega}^{X} > \frac{2}{3}\bar{\omega}_{\Omega}^{A}. \qquad (4.8)$$

Satisfaction of the inequality on the left ensures $F_{ST}^{X} > F_{ST}^{A}$, consistent with lower effective numbers of X-linked than autosomal genes. However, sex-specific incompatibility can induce sufficient greater barriers to neutral introgression of autosomal than X-linked markers to cause F_{ST}^{A} to exceed F_{ST}^{X}.

Fig. 4.1 shows the ratio of female to male migrants (4.7) inferred from values of F_{ST}^{A} and F_{ST}^{X} expected to arise in response to a sex-specific Y-linked incompatibility factor that reduces the viability of its carriers to $\sigma_m = 0.5$ (solid) or to $\sigma_m = 0.8$ (dashed). For increasing proportions of females among reproducing migrants (c), the inferred M_f/M_m uniformly *decreases*. Because X-linked marker genes borne by a male migrant are transmitted only to factor-free daughters, Y-linked incompatibility factors induce no barrier to their introgression ($\bar{\omega}_{Y}^{X} = 1$). In contrast, autosomal markers transmitted to sons of a male migrant suffer reductions in fitness induced by the Y-linked factor, implying

$$\bar{\omega}_{Y}^{A} = c + (1 - c)/(2 - \sigma_m)$$

(from table 1 of Fusco and Uyenoyama, 2011b). Strong incompatibility ($\sigma_m < 2/3$) can cause F_{ST}^{A} to

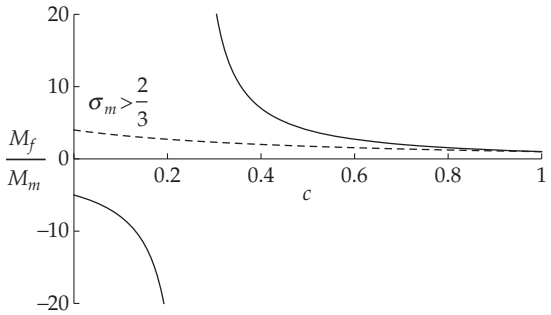

Figure 4.1 Ratio of numbers of female to male migrants (M_f/M_m) inferred from values of F_{ST}^{A} and F_{ST}^{X} expected under sex-specific incompatibility induced by Y-linked incompatibility factors as a function of the proportion of females among migrants (c). The solid lines represent the effects of a factor that reduces the viability of its carriers to $\sigma_m = 0.5$ and the dashed line to $\sigma_m = 0.8$.

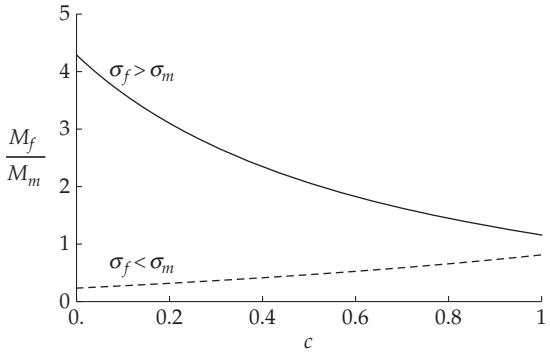

Figure 4.2 Ratio of numbers of female to male migrants (M_f/M_m) inferred from values of F_{ST}^{A} and F_{ST}^{X} expected under sex-specific incompatibility induced by an autosomal factor that reduces the viability of its female and male carriers to σ_f and σ_m as a function of the proportion of females among migrants (c). The solid line corresponds to $\sigma_f = 0.6$ and the dashed line to $\sigma_f = 0.4$, under the constraint $\sigma_f + \sigma_m = 1$.

exceed F_{ST}^{X} (violation of the left inequality of (4.8)) for sufficiently low c, in spite of the higher effective number of autosomal genes. This effect generates a discontinuity in the inferred M_f/M_m ratio, as exemplified by the hyperbola in Fig. 4.1 ($\sigma_m = 0.5$).

Fig. 4.2 illustrates trends in the inferred M_f/M_m (4.7) under sex-specific incompatibility due to an autosomal factor that reduces the viability of its female (σ_f) and male (σ_m) carriers relative to factor-free individuals ($1 > \sigma_f, \sigma_m$). To maintain a fixed total amount of selection across the comparison, we imposed the constraint $\sigma_f + \sigma_m = 1$. Fig. 4.2 indicates that the inferred M_f/M_m increases with the proportion of females among reproducing migrants (c) only for factors that impair females more than males ($\sigma_m > \sigma_f$).

An autosomal factor induces relative reproductive rates at markers on a separate autosome and on the X-chromosome of

$$\omega_{A}^{A,f} = \omega_{A}^{A,m} = \frac{\sigma_f + \sigma_m}{4 - \sigma_f - \sigma_m}$$

$$\omega_{A}^{X,f} = \frac{2(\sigma_f + \sigma_m) + \sigma_f\sigma_m}{8 - \sigma_f(2 + \sigma_m)}$$

$$\omega_{A}^{X,m} = \frac{\sigma_f(4 + \sigma_m)}{8 - \sigma_f(2 + \sigma_m)}$$

(from table 1 of Fusco and Uyenoyama, 2011b). Under the constraint $\sigma_f + \sigma_m = 1$, the relative reproductive rate at the unlinked autosomal marker ω_{A}^{A}

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reduces to 1/3. For incompatibility factors causing greater impairment of females than males ($\sigma_f < \sigma_m$), X-linked markers introgress at lower rates than autosomal markers, with $\omega_A^{X,m} < \omega_A^{X,f} < \omega_A^A$. This relation reflects a stronger association of the X-chromosome with females, the sex more impaired by incompatibility. The association between femaleness and the X-linked marker strengthens with higher proportions of male migrants, which transmit the X-linked marker exclusively to daughters. The inferred ratio of numbers of female to male migrants (4.7) increases with increasing c (decreasing proportion of male migrants), although it indicates a male-bias in migrant number ($M_f/M_m < 1$) even for c exceeding 1/2.

For incompatibility factors causing greater impairment of males than females ($\sigma_f > \sigma_m$), however, the inferred ratio M_f/M_m *declines* with increasing proportions of female migrants (solid line in Fig. 4.2). In this case, X-linked markers introgress at higher rates than autosomal markers ($\omega_A^{X,m} > \omega_A^{X,f} > \omega_A^A$), with the dependence on c reflecting the strengthening of the association of the X-linked marker with femaleness as the proportion of male migrants increases. Inferences based on (4.7) would indicate uniformly higher numbers of female migrants ($M_f/M_m > 1$), even for c less than 1/2.

These examples illustrate that sex-specific incompatibility can induce differential rates of introgression across the genome, especially among regions that differ in their cosegregation with sex. Associations between incompatibility factors and neutral markers derive not from functional epistasis but rather from an association of each class of loci with sex. Ignoring sex-specific incompatibility may cause patterns in F_{ST} across the genome to be misinterpreted with respect to the existence or direction of sex-bias in effective number or dispersal.

4.4 Conclusions

In *Drosophila*, the model system for speciation in which key genetic and epigenetic mechanisms have been best-characterized, various lines of evidence have now well established that genes with male-limited or male-biased expression diverge at accelerated rates (e.g. Civetta and Singh, 1998; Ranz et al., 2003). Even at the intraspecific level, transfer between populations of genomic regions with sex-limited transmission can cause pervasive disruptions of expression of genes throughout the genome (Lemos et al., 2008; Innocenti et al., 2011).

Rapidly evolving sex-specific hybrid incompatibility can generate heterogeneity in neutral divergence across genomic regions. The locus-specific nature of the induced barriers to introgression derive not from physical linkage to incompatibility factors but rather from associations between sex and neutral markers and between sex and targets of sex-specific selection (Fusco and Uyenoyama, 2011b). As such associations arise even in the absence of linkage, a single sex-specific incompatibility factor can induce locus-specific patterns of neutral divergence across genomic regions. We suggest that the locus-specific nature of barriers to introgression both between species and between conspecific populations induced by sex-specific incompatibility may affect inferences regarding sex-biased dispersal and selection.

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OUP CORRECTED PROOF – FINAL, 24/5/2012, SPi

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