

Stochastic Epigenetic Modification as a Parsimonious Mechanism for Origin and Evolution of Heteromorphic Sex Chromosomes in Vertebrates (Supplemental Information)

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1. Stability of ro locus

The mutation $rs \rightarrow ro$ leads to the loss of sex determination function. We have three genotypes in the population: rs/ro , ro/ro and the original rs/rs with frequencies k , w and $z = 1 - (k + w)$, respectively. Tables 1 and 2 list the probabilities of observing each epi-genotype in the population, and the chances of getting each genotype from all the possible crosses, respectively.

genotype	epi-genotype	frequencies in the population	sex
rs/rs	rs^* / rs	$(1 - \rho)(1 - (k + w))$	♂
	rs^* / rs^*	$\rho(1 - (k + w))$	♀
rs/ro	rs/ro^*	$(1 - \rho)k/2$	♂
	rs^*/ro	$(1 - \rho)k/2$	♀
	rs^*/ro^*	ρk	♀
ro/ro	ro/ro^*	$(1 - \rho)w$	♀
	ro^*/ro^*	ρw	♀

Table 1: Genotype / epi-genotype map. ρ is the probability of epigenetic silencing, r and w are the frequencies in the population of the genotypes rs/ro and ro/ro , respectively.

The total frequencies of females and males in the population (Equations 1 and 2), and the relative probabilities for an epi-genotype to be selected as either male or female:

$$Z_f = \sum_i^F P_i = \frac{2\rho + (1 - \rho)(p + 2w)}{2}, \quad (1)$$

$$Z_m = \sum_i^M P_i = \frac{(1 - \rho)(2 - p - 2w)}{2}, \quad (2)$$

where M and F stand for the sets of all possible male and female epi-genotypes, respectively:

$$F = \{rs^*/rs^*, rs^*/ro, rs^*/ro, rs^*/ro^*, ro/ro^*, ro^*/ro^*\}, \quad (3)$$

$\text{♀}/\text{♂}$	rs*/rs	rs/ro*
rs*/rs*	rs/rs (1)	rs/rs ($\frac{1}{2}$) rs/ro ($\frac{1}{2}$)
rs*/ro	rs/rs ($\frac{1}{2}$) rs/ro ($\frac{1}{2}$)	rs/rs ($\frac{1}{4}$) rs/ro ($\frac{1}{2}$) ro/ro ($\frac{1}{4}$)
rs*/ro*	rs/rs ($\frac{1}{2}$) rs/ro ($\frac{1}{2}$)	rs/rs ($\frac{1}{4}$) rs/ro ($\frac{1}{2}$) ro/ro ($\frac{1}{4}$)
ro*/ro	rs/ro (1)	rs/ro ($\frac{1}{2}$) ro/ro ($\frac{1}{2}$)
ro*/ro*	rs/ro (1)	rs/ro ($\frac{1}{2}$) ro/ro ($\frac{1}{2}$)

Table 2: List of all possible crosses. The expected frequencies of the genotypes for each cross are shown in parenthesis.

$$M = \{\text{rs}^*/\text{rs}, \text{rs}/\text{ro}^*\} \quad (4)$$

epi-genotype	probability to be selected	sex
rs*/rs	$2(1 - k - w)/(2 - k - 2w)$	♂
rs/ro*	$k/(2 - k - 2w)$	♂
rs*/rs*	$\rho(1 - (k + w))/Z_f$	♀
rs*/ro	$(1 - \rho)k/2Z_f$	♀
rs*/ro*	$\rho k/Z_f$	♀
ro/ro*	$(1 - \rho)w/Z_f$	♀
ro*/ro*	$\rho w/Z_f$	♀

Table 3: Probability of selecting an epi-genotype in the male and female pool. ρ is the probability of epigenetic silencing, k and w are the frequencies in the population of the genotypes rs/ro and ro/ro, respectively. Z_f is the total frequency of females in the population.

Using the above expression we can estimate the expected genotype frequencies in the next generation for the genotypes rs/ro and ro/ro as

$$p_{t+1} = \frac{\rho(3p_t^2 + 4p_tw_t - 4p_t) + (p_t + 4w_t)(k_t + 4w_t - 2) - 8w_t^2}{Z_t},$$

$$w_{t+1} = \frac{p_t(\rho(p_t + 1) + 4w_t)}{2Z_t}, \quad (5)$$

where $Z = 4Z_f(p - 2(1 - w))$. The expected difference is shown in Equation 6.

$$\Delta k = \frac{\rho(3p_t^2 + 4p_tw_t - 4p_t) + (p_t + 4w_t)(p_t + 4w_t - 2) - 8w_t^2}{Z_t} - p_t, \quad (6)$$

$$\Delta w = \frac{k_t (\rho(k_t + 1) + 4w_t)}{2Z_t} - w, \quad (7)$$

The frequencies in the stationary state can be obtained by setting Δk and Δw (Equations 6, 7) to zero and solving the system of non-linear equations:

$$\begin{cases} \frac{\rho (3k_t^2 + 4k_t w_t - 4k_t) + (k_t + 4w_t) (k_t + 4w_t - 2) - 8w_t^2}{Z_t} - k_t = 0 \\ \frac{k_t (\rho(k_t + 1) + 4w_t)}{2Z_t} - w = 0 \end{cases} \quad (8)$$

This non-linear system admits a trivial solution $O(k_0 = 0, w_0 = 0)$; to obtain the other solutions of the system we observe that it will converge to a sex ratio equal to 0.5 (in the stationary state we will have $Z_f^{ss} = Z_m^{ss} = 0.5$)

$$Z_f^{ss} = \frac{2\rho + (1 - \rho)(k + 2w) - 1}{2} = 0, \quad (9)$$

and solving for k we obtain

$$k = \frac{1 - 2w(1 - \rho) - 2\rho}{1 - \rho}; \quad (10)$$

by substituting k in the second equation of Equations 8 and solving for w we obtain two solutions:

$$\begin{aligned} w_1 &= \frac{1 + 2\rho^3 - 3\rho^2 - \sqrt{2(1 - \rho)^3}}{2(\rho - 1)^3}, \\ w_2 &= \frac{1 + 2\rho^3 - 3\rho^2 + \sqrt{2(1 - \rho)^3}}{2(\rho - 1)^3}; \end{aligned} \quad (11)$$

we then substitute in Equations 10, 11 to obtain

$$\begin{aligned} k_1 &= \frac{2 + 2\rho^2 - 4\rho - \sqrt{2(1 - \rho)^3}}{(1 - \rho)^3}, \\ k_2 &= \frac{2 + 2\rho^2 - 4\rho + \sqrt{2(1 - \rho)^3}}{(1 - \rho)^3}. \end{aligned} \quad (12)$$

2. Further evolution of the sex determination locus

$$\begin{aligned} q_{t+1} &= \frac{2g_t p_t \rho - g_t p_t (\rho - 1) + 4g_t \rho z_t + 2q_t p_t \rho - q_t p_t (\rho - 1) + 4q_t \rho z_t}{8Z_t}, \\ p_{t+1} &= \frac{\Lambda_t (1 - \rho) + p_t (\beta q_t + \alpha g_t) - 4g_t \rho (\Theta_t) - 4w_t [g_t (\rho - 2) + q_t (2\rho - 1)]}{Z_t}, \\ w_{t+1} &= \frac{(2g_t + p_t (1 - \rho)) (p_t (\rho + 1) + 4w_t)}{16Z_t}, \\ g_{t+1} &= \frac{(g_t + q_t) (p_t (\rho + 1) + 4w_t)}{8Z_t}, \end{aligned} \quad (13)$$

with $Z = Z_f Z_m$, $\Lambda = r^2 (3\rho + 1) + 4pw (\rho + 2) - 2p (2\rho + 1) - 8w (1 - w)$, $\Theta = (1 - g_t - q_t)$
 $\alpha = 1 - 4\rho^2 + 5\rho$, and $\beta = 1 - 4\rho^2 + \rho$.

$\text{♀}/\text{♂}$	rs^*/rs	rs/ro^*	rs/xs^*	ro/xs^*
rs^*/rs^*	rs/rs (1)	rs/rs ($\frac{1}{2}$) rs/ro ($\frac{1}{2}$)	rs/rs ($\frac{1}{2}$) rs/xs ($\frac{1}{2}$)	rs/ro ($\frac{1}{2}$) rs/xs ($\frac{1}{2}$)
rs^*/ro	rs/rs ($\frac{1}{2}$) rs/ro ($\frac{1}{2}$)	rs/rs ($\frac{1}{4}$) rs/ro ($\frac{1}{2}$) ro/ro ($\frac{1}{4}$)	rs/rs ($\frac{1}{4}$) rs/xs ($\frac{1}{4}$) rs/ro ($\frac{1}{4}$) ro/xs ($\frac{1}{4}$)	rs/ro ($\frac{1}{4}$) rs/xs ($\frac{1}{4}$) ro/ro ($\frac{1}{4}$) ro/xs ($\frac{1}{4}$)
rs^*/ro^*	rs/rs ($\frac{1}{2}$) rs/ro ($\frac{1}{2}$)	rs/rs ($\frac{1}{4}$) rs/ro ($\frac{1}{2}$) ro/ro ($\frac{1}{4}$)	rs/rs ($\frac{1}{4}$) rs/xs ($\frac{1}{4}$) rs/ro ($\frac{1}{4}$) ro/xs ($\frac{1}{4}$)	rs/ro ($\frac{1}{4}$) ps/xs ($\frac{1}{4}$) ro/ro ($\frac{1}{4}$) ro/xs ($\frac{1}{4}$)
ro^*/ro	rs/ro (1)	rs/ro ($\frac{1}{2}$) ro/ro ($\frac{1}{2}$)	rs/ro ($\frac{1}{2}$) ro/xs ($\frac{1}{2}$)	ro/ro ($\frac{1}{2}$) ro/xs ($\frac{1}{2}$)
ro^*/ro^*	rs/ro (1)	rs/ro ($\frac{1}{2}$) ro/ro ($\frac{1}{2}$)	rs/ro ($\frac{1}{2}$) po/xs ($\frac{1}{2}$)	ro/ro ($\frac{1}{2}$) ro/xs ($\frac{1}{2}$)

Table 4: Possible crosses. The expected frequencies of the genotypes for each cross are shown in parenthesis.