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# Compensatory evolution in diploid populations

Motoshi Ichinose [a], Masaru Iizuka [b,*], Tomoyuki Kado [c,1], Masasuke Takefu [d]

[a] Department of Contemporary Liberal Arts, Junior College, Chikushi Jogakuen University, 2-12-1 Ishizaka, Dazaifu-shi, Fukuoka-ken 818-0192, Japan
[b] Division of Mathematics, Kyushu Dental College, 2-6-1 Manazuru, Kokurakita-ku, Kitakyushu 803-8580, Japan
[c] Department of Biology, Graduate School of Sciences, Kyushu University, 4-2-1 Ropponmatsu, Chuo-ku, Fukuoka 810-8560, Japan
[d] Center for Comprehensive Community Medicine, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan

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ABSTRACT

Compensatory mutations are individually deleterious but harmless in appropriate combinations either at more than two sites within a gene or on separate genes. Considering that dominance effects of selection and heterodimer formation of gene products may affect the rate of compensatory evolution, we investigate compensatory neutral mutation models for diploid populations. Our theoretical analysis on the average time until fixation of compensatory mutations shows that these factors play an important role in reducing the fixation time of compensatory mutations if mutation rates are not low. Compensatory evolution of heterodimers is shown to occur more easily if the deleterious effects of single mutants are recessive.



## 1. Introduction

Compensatory mutations are individually deleterious but appropriate combinations of mutants are harmless (Kondrashov et al., 2002; Kulathinal et al., 2004). Many experimental results and those based on phylogenetic-comparative analysis are reported that suggest molecular evolution by compensatory mutations (Bauer et al., 2003; Chelvanayagam et al., 1997; Chen and Stephan, 2003; Clapier et al., 2008; Darrouzet and Daldal, 2003; del Alamo and Mateu, 2005; Duda et al., 2002; Fleck et al., 2003; Gosink et al., 2006; Kirby et al., 1995; Lei et al., 2000; Maisnier-Patin et al., 2002; MacKenzie and Engelman, 1998; McCutchan et al., 2004; Olivares et al., 2007; Paillart et al., 1994; Stephan and Kirby, 1993; Wilson et al., 1992; Yang et al., 2003; Yanofsky et al., 1964). Some of these results are from haploid organisms and the others are from diploid organisms.

Kimura (1985a,b) introduced the compensatory neutral mutation model to investigate the mechanism of molecular evolution by compensatory mutations. To this end, he studied the average time until fixation of the double mutant starting from a population consisting exclusively of the wild type. One of his main results is that the average time until fixation of the double mutant is very long under free recombination and strong selection. He concluded that evolution by compensatory mutations is not a common mechanisms of molecular evolution. More general models are consistent with this conclusion under strong recombination or free recombination when selection is strong (Iizuka and Takefu, 1996; Stephan, 1996). However these models assume haploid populations or genic selection in diploid populations, that is, no dominance in selection for diploid organisms. If deleterious effects of single mutants are recessive, selection against the intermediate deleterious states of single mutants will be less effective and the average time until fixation of the double mutant may be much shorter than that in haploid populations. We investigate the mechanism of molecular evolution by compensatory mutations under such dominance in selection.

In addition to the effects of dominance in selection, there may be a difference between haploid organisms and diploid organisms on the formation of gene products. In haploid organisms, the formation of gene products of monomers and that of heterodimers are essentially the same. However this may not hold for diploid organisms. For example, we consider two sites on two separate genes with states $A_1$ and $A_2$ (resp. $B_1$ and $B_2$) at the first (resp. second) site. The gene product with $A_i$ (resp. $B_j$) is denoted by $\alpha_i$ (resp. $\beta_j$) and they form a heterodimer $\alpha_i\beta_j$. An individual that has two haplotypes $A_1B_2$ and $A_2B_1$ produces not only heterodimers $\alpha_1\beta_2$ and $\alpha_2\beta_1$ but also $\alpha_1\beta_1$ and $\alpha_2\beta_2$ if these gene products associate freely with each other. We will consider the effects of the heterodimer formation on the mechanism of compensatory evolution.

Iizuka and Takefu (1996), Kimura (1985a,b) and Stephan (1996) considered the one-way mutation from the wild types to the mutant types. The effects of back mutation were studied by Higgs (1998), Innan and Stephan (2001) and Michalakis and Slatkin

* Corresponding author.
*E-mail address:* iizuka@kyu-dent.ac.jp (M. Iizuka).

[1] Present address: Hayama Center for Advanced Studies, The Graduate University for Advanced Studies, Hayama, Kanagawa 240-0193, Japan.

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(1996). We will consider only one-way mutation in this paper. Phillips (1996) considered the compensatory neutral mutation model with some dominance in selection. His results are mainly related to the shifting-balance theory by Wright (1931) and selection schemes are different from those of the present paper (see Section 6).

## 2. The model

We consider two sites with states $A_1$ and $A_2$ (resp. $B_1$ and $B_2$) at the first (resp. second) site in a randomly mating diploid population consisting of $N$ individuals. The states $A_1$ and $B_1$ are wild types and $A_2$ and $B_2$ are mutants. The frequency of the haplotype $A_iB_j$ is denoted by $X_{ij}$. The frequencies in the next generation are determined by mutation, recombination, selection and random genetic drift in this order. We consider the symmetric one-way mutation, that is, $A_1$ and $B_1$ mutate to $A_2$ and $B_2$ with the rate $u$, respectively. The frequency changes from $X_{ij}$ to $Y_{ij}$ by mutations as

$$Y_{11} = (1-2u)X_{11}, \tag{1}$$

$$Y_{12} = uX_{11} + (1-u)X_{12}, \tag{2}$$

$$Y_{21} = uX_{11} + (1-u)X_{21}, \tag{3}$$

$$Y_{22} = X_{22} + uX_{12} + uX_{21}. \tag{4}$$

The recombination rate between the first site and the second site is denoted by $c$. Then the frequency $Y_{ij}$ changes to $Z_{ij}$ by recombination as

$$Z_{ij} = Y_{ij} - c(-1)^{i+j}(Y_{11}Y_{22} - Y_{12}Y_{21}). \tag{5}$$

An individual that has two haplotypes $A_iB_j$ and $A_kB_l$ is denoted by $(A_iB_j, A_kB_l)$. Here we distinguish $(A_iB_j, A_kB_l)$ from $(A_kB_l, A_iB_j)$ if $i \neq k$ or $j \neq l$. Let $w_{ij}^{kl}$ be the relative fitness of an individual $(A_iB_j, A_kB_l)$. The details of selection schemes will be introduced in the next paragraph. The frequency changes from $Z_{ij}$ to $Q_{ij}$ by selection as

$$Q_{ij} = \frac{\sum_{k,l=1}^{2} w_{ij}^{kl} Z_{ij} Z_{kl}}{\bar{W}}, \tag{6}$$

where

$$\bar{W} = \sum_{i,j,k,l=1}^{2} w_{ij}^{kl} Z_{ij} Z_{kl} \tag{7}$$

is the mean fitness of the population. Finally, random genetic drift occurs in a finite population of $N$ diploid individuals subject to the standard assumptions of the Wright–Fisher model.

Now we introduce the selection schemes. Let $\rho_{ij}$ be the gene product that is produced by the genetic information with $A_i$ and $B_j$. We consider two cases for the formation of $\rho_{ij}$. The first case is that $\rho_{ij}$ is a monomer and an individual $(A_iB_j, A_kB_l)$ produces $\rho_{ij}$ and $\rho_{kl}$ with equal proportion. This formation of gene products is referred to as the case of monomer formation. The second case is that $\rho_{ij}$ is a heterodimer $\alpha_i\beta_j$. An individual $(A_iB_j, A_kB_l)$ produces heterodimers $\rho_{ij} = \alpha_i\beta_j$, $\rho_{il} = \alpha_i\beta_l$, $\rho_{kj} = \alpha_k\beta_j$ and $\rho_{kl} = \alpha_k\beta_l$ with equal proportion. This formation of gene products is referred to as the case of heterodimer formation. Note that the heterodimer formation is not the same as recombination between these sites. The heterodimer formation produces a variety of gene products for an individual, whereas recombination produces a variety of types of offspring. Let $c_{ij}^{kl}(m,n)$ be the fraction of $\rho_{mn}$ that is produced by an individual $(A_iB_j, A_kB_l)$. Note that $c_{ij}^{kl}(m,n) = c_{kl}^{ij}(m,n)$. The values of $c_{ij}^{kl}(m,n)$ are presented in Table 1. The values of $c_{ij}^{kl}(m,n)$ for the two formations differ only for $(A_1B_1, A_2B_2)$ and $(A_1B_2, A_2B_1)$. The fitness of an individual that produces only $\rho_{22}$ is assumed to be the same as that of an individual that produces only $\rho_{11}$ and the relative fitness of these individuals is 1. On the other hand, the relative fitness of an individual that produces only $\rho_{12}$, and that of an individual that produces only $\rho_{21}$ are assumed to be $1-s$ with $0 \leqq s < 1$. We consider the following two cases. The first is no dominance where the relative fitness of an individual $(A_iB_j, A_kB_l)$ is

$$w_{ij}^{kl} = c_{ij}^{kl}(1,1) + (1-s)c_{ij}^{kl}(1,2) + (1-s)c_{ij}^{kl}(2,1) + c_{ij}^{kl}(2,2). \tag{8}$$

The second is that deleterious effects of single mutants are completely recessive, that is, the relative fitness of an individual $(A_iB_j, A_kB_l)$ is

$$w_{ij}^{kl} = \begin{cases} 1, & \text{if } c_{ij}^{kl}(1,1) + c_{ij}^{kl}(2,2) > 0 \\ 1-s, & \text{if } c_{ij}^{kl}(1,1) + c_{ij}^{kl}(2,2) = 0. \end{cases} \tag{9}$$

By these assumptions, we have $0 < w_{ij}^{kl} \leq 1$, $w_{11}^{11} = w_{22}^{22} = 1$ and $w_{12}^{12} = w_{21}^{21} = 1-s$. These fitness interactions are diploid versions of the compensatory neutral mutation model introduced by Kimura (1985a,b).

By the formation of $\rho_{ij}$ and dominance in selection, we have the following four selection schemes. Monomer formation with no dominance, heterodimer formation with no dominance, monomer formation with completely recessive effects of single mutants, heterodimer formation with completely recessive effects of single mutants are referred to as selection schemes 1, 2, 3 and 4, respectively. The relative fitness of an individual $(A_iB_j, A_kB_l)$ is presented in Table 2 for these selection schemes. Note that $w_{ij}^{kl} = w_{kl}^{ij}$ by definition. Selection scheme 1 is essentially the same as the compensatory neutral mutation models for a haploid population and selection parameter $s$ in this paper corresponds to $2s$ in the compensatory neutral mutation models of Iizuka and Takefu (1996), Kimura (1985a,b) and Stephan (1996). The symmetry that $w_{ij}^{kl} = w_{ji}^{lk}$ holds for our model. Stephan (1996) discussed the effects of asymmetry of two deleterious haplotypes for the haploid case.

Kimura (1985a,b) did a computer simulation of the Wright–Fisher model, a numerical analysis of diffusion models and an analytical approximation for a diffusion model to study the average time until fixation of the double mutant $A_2B_2$. The same approximation was employed by Stephan (1996). Iizuka and Takefu (1996) investigated the average time until fixation by numerical analysis of diffusion models. The approximation introduced by Kimura (1985a,b) is not applicable for the case of completely recessive effects of single mutants since the

**Table 1**
Values of $c_{ij}^{kl}(m,n)$

| | $(m,n)=(1,1)$ | $(m,n)=(1,2)$ | $(m,n)=(2,1)$ | $(m,n)=(2,2)$ |
|---|---|---|---|---|
| $c_{11}^{11}(m,n)$ | 1 | 0 | 0 | 0 |
| $c_{11}^{12}(m,n)$ | 0.5 | 0.5 | 0 | 0 |
| $c_{11}^{21}(m,n)$ | 0.5 | 0 | 0.5 | 0 |
| $c_{11}^{22}(m,n)$[a] | 0.5 | 0 | 0 | 0.5 |
| $c_{11}^{22}(m,n)$[b] | 0.25 | 0.25 | 0.25 | 0.25 |
| $c_{12}^{12}(m,n)$ | 0 | 1 | 0 | 0 |
| $c_{12}^{21}(m,n)$[a] | 0 | 0.5 | 0.5 | 0 |
| $c_{12}^{21}(m,n)$[b] | 0.25 | 0.25 | 0.25 | 0.25 |
| $c_{12}^{22}(m,n)$ | 0 | 0.5 | 0 | 0.5 |
| $c_{21}^{21}(m,n)$ | 0 | 0 | 1 | 0 |
| $c_{21}^{22}(m,n)$ | 0 | 0 | 0.5 | 0.5 |
| $c_{22}^{22}(m,n)$ | 0 | 0 | 0 | 1 |

[a] Monomer formation.
[b] Heterodimer formation.