SOME MODELS OF GENE CONVERSION FOR TREATING THE EVOLUTION OF MULTIGENE FAMILIES

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ABSTRACT

A simple model of gene conversion presented earlier has been compared with a more general model under the assumption of no bias. The former is based on a simple concept that, by conversion, a gene (or a segment of a gene) is transferred from one locus to another in a multigene family. Intrachromatid symmetric conversion may result in reciprocal exchange of genes within a multigene family, and the previous theory of identity coefficients needs modification when it occurs. The relationship of various parameters of the two models was made clear in formulating the transition equations of identity coefficients. As an example of extending the analyses, a model of preferential conversion that is relevant to the observed uneven polymorphisms of class I genes in the major histocompatibility complex has been investigated. It differs from the biased conversion, in that directional process is through location of genes on the chromosome. It is shown that the model satisfactorily explains the observed data, even though the effect of preferential conversion is difficult to distinguish from that of natural selection.

IN recent years, gene conversion has been considered to play an important role in evolution. Although direct observations of conversions are restricted to fungi which produce meiotic products (tetrads) in asci, data suggesting gene conversion in higher eukaryotic genes are rapidly accumulating (for review, see, BALTIMORE 1981; DOVER 1982; PETES and FINK 1982). Especially when genes are repeated on the chromosome, gene conversion apparently occurs among the gene members with fairly high frequency in the course of evolution (MIYATA et al. 1980; SLIGHTOM, BLECHL and SMITHIES 1980; YAMAWAKI-KATAOKA et al. 1982) and, therefore, is one of the major mechanisms for the observed homogeneity of sequences in some multigene families (NAGYLAKI and PETES 1982; OHTA 1982, 1983a,b). I have been studying the evolution of multigene families from the standpoint of population genetics (for review, see OHTA 1980) and have analyzed a simple model of gene conversion (OHTA 1982). This model was constructed so that the effect of conversion at the level of a population could be studied. The real process of gene conversion is complicated (WHITEHOUSE 1982), and a more realistic, but not yet completely general, model was suggested by NAGYLAKI and PETES (1982). These authors formulated the evolution of a single chromosomal line of a multigene family. In this report, the correspondence between the simple and NAGYLAKI-PETES'
models has been made clear, so that the latter becomes widely applicable. With the simple model, the analyses for complicated cases such as for dispersed multigene families are already available (OHTA and DOVER, 1983). As an extension of such analyses, a model of preferential conversion relevant to some observed polymorphisms of histocompatibility loci is presented. Molecular biology of the antigen is now under intense investigation (for review, see HOOD, STEINMETZ and GOODENOW 1982), and the present analysis gives a theoretical basis for understanding exceptionally high polymorphism at the histocompatibility loci.

COMPARISON OF MODELS

I first consider a single multigene family on a chromosome; a multigene family of \( n \) tandemly arranged genes. Later, discussion will be extended to population genetics, by referring to a recent study of NAGYLAKI (1984) who formulated exact transition equations of identity coefficients. There are two kinds of genes; \( jA \) and \( (n - j)a \) genes, randomly arranged, and unbiased conversion is considered. In the simple model (designated as the \( O \) model, OHTA 1982, 1983a,b), it is assumed that there are \( n\lambda \) conversions per family in one generation, and conversion is assumed to take place between a random pair of genes. Then, each gene is converted with a rate \( \lambda \) by any one of the remaining \( (n - 1) \) genes on the chromosome. Figure 1 represents the \( O \) model.

The more general model by NAGYLAKI and PETES (1982) is slightly modified here and is designated as the \( N-P \) model. In this model, conversion is classified into four classes. Table 1 shows the classes and their probabilities of occurrence in one generation. NAGYLAKI and PETES assumed that exactly one interaction occurs per unit time. Here, let us take one biological generation as a unit time; therefore, the rate of occurrence \( (a_i) \) is much less than unity. In addition, for asymmetric conversion, the cases are classified with respect to which of \( A \) or \( a \) initiates heteroduplex formation with respective probabilities \( b_1 \) and \( c_1 \) for intrachromosomal interactions and \( b_2 \) and \( c_2 \) for sister-chromatid interactions. Furthermore, for each of the four classes, \( u_k \) and \( v_k \) \((k = 1, \ldots, 4)\) are used to define probabilities of resolution of a heteroduplex as \( A \) or \( a \). As in the \( O \) model, interaction is assumed to occur between a random pair of genes from the \( n \) genes. But, in our analyses, only those conversions that occur between nonallelic genes are considered. Because allelic genes are identical between the sister chromatids, the restriction has no effect on the analyses except minor modification of a coefficient, as will be explained later.

When \( Aa \) genes undergo conversion, the products are one of \( AA, Aa, aA \) and \( aa \), with their probabilities of occurrence being given in Table 2. Note

![Figure 1](image-url)
that the meiotic product $Aa$ means no change, whereas $aA$ is the result of both genes being converted. If we assume that conversion is unbiased and that all heteroduplexes are resolved, $b_k = c_k = u_k = v_k = 1/2$ for all $k$. In other words, the four kinds of conversion products are equally likely to occur with probability $1/4$ for symmetric heteroduplexes, and the three kinds occur with probabilities $1/4$, $1/2$ and $1/4$ for asymmetric heteroduplexes. I have considered the correspondence between the two models under this simple condition. Suppose that one interaction occurred between a pair of genes. Note that when the pair is $AA$ or $aa$, no change actually occurs. However, under the condition of no bias in conversion, one can assume that the same process takes place even when $AA$ or $a\bar{a}$ undergo conversion. Also, for sister chromatid interaction, one of the two chromatids is randomly chosen for the next generation. Therefore, for symmetric intrachromatid interaction, the expected number of genes that are converted, given that one $Aa$ interaction occurred, becomes,

$$ g_1 = u_1^2 + v_1^2 + 2u_1v_1 = 1, $$

where the subscript 1 indicates the class number (Table 1). For asymmetric intrachromatid interaction,

$$ g_2 = b_1u_2 + c_1v_2 = \frac{1}{2}, $$

for symmetric sister chromatid interaction,

$$ g_3 = \frac{1}{2} (u_3^2 + v_3^2 + 2u_3v_3) = \frac{1}{2}, $$

and when interaction is asymmetric sister chromatid,
By using these results, we calculate the expected number of genes that are
converted in one generation, \( E(n_{\text{conv}}) \). When conversion is unbiased, one can
assume that the same change takes place even when AA or aa undergoes
conversion in calculating the expected number. Thus we have,

\[
E(n_{\text{conv}}) = a_1 g_1 + a_2 g_2 + a_3 g_3 + a_4 g_4 = a_1 + \frac{a_2}{2} + \frac{a_3}{2} + \frac{a_4}{4}.
\]

The probability that a gene is converted (\( \lambda \)) in one generation becomes,

\[
\lambda = \frac{1}{n} E(n_{\text{conv}}) = \frac{1}{n} \left( a_1 + \frac{a_2}{2} + \frac{a_3}{2} + \frac{a_4}{4} \right).
\]

In the \( O \) model, the theory of probability of gene identity (identity coefficients) has been worked out to study the population dynamics (OHTA 1982, 1983a,b), and an important parameter is \( \alpha \), the rate of decay of genetic variability within a single chromosome of \( n \) genes. It has been shown that

\[
\alpha_0 = \frac{2\lambda}{n-1},
\]

where the subscript \( O \) denotes the \( O \) model. This rate was derived as follows. Consider the probability that two randomly chosen genes are identical (identity coefficient) and its change by conversion. The probability that one of the two genes is converted in one generation is \( 2\lambda \), and in this case, the two genes become identical when one of the two converts the other, \( i.e. \), in the fraction \( 1/(n-1) \) of converted cases. In other words the rate of change of identity coefficient becomes \( 2\lambda/(n-1) \), which is the rate of decay of variability within a chromosome. This statement does not hold for symmetric conversion, since the case of reciprocal exchange of genes, \( aA \) of Table 2, is included. To estimate the rate of decay, such cases have to be subtracted from calculations for intrachromatid conversion. As to the sister chromatid conversion, we assume that one of the two chromatids is randomly chosen for the next generation, and subtraction is not needed. See Figure 2 for such cases. Let

\[
\lambda' = \frac{1}{n} (a_1 g'_1 + a_2 g'_2 + a_3 g'_3 + a_4 g'_4)
\]

\[
= \frac{1}{2n} \left( a_1 + a_2 + a_3 + a_4 \right),
\]

where \( g'_1 = g_1 - 2u_1v_1 = u_1^2 + v_1^2 = 1/2 \). \( n\lambda' \) is equivalent to \( p + q \) (equations 4b and 4c) of NAGYLAJI and PETES (1982). However, note that the coefficient
(n - 1)/n of their equations for sister chromatid conversion, which is missing here, comes from their assumption that the interaction occurs between random pairs of genes including those at identical sites on the two chromatids. In our case, only those interactions that take place between nonallelic genes are considered. Let $\alpha_{N,P}$ be the rate of decay of genetic variability within a single chromosome under the $N$-$P$ model. Then we have,

$$\alpha_{N,P} = \frac{2\lambda'}{n - 1}. \quad (8)$$

$\alpha_{N,P}$ gives the rate of decay of genetic variability within a chromosome under the $N$-$P$ model.

Next, let us extend our study to the population genetics of multigene families. As before (OHTA 1980, 1983a,b for review), the change of identity coefficients is studied. For intrachromatid gene conversion, NAGYLAKI (1984) derived exact formulas to transform identity coefficients from one generation to the next, when both symmetric and asymmetric conversions occur. In the following, let us relate the present parameters with his formulas. As shown, $\alpha_{N,P}$ gives the rate of decay of genetic variability within a chromosome; therefore, it is the coefficient to give the change of gene identity of a single chromosome, i.e., it corresponds to $\alpha$ of equation (13b) of NAGYLAKI (1984). As to the other coefficients, one can note that, whenever a gene is converted, including the case of reciprocal conversion ($aA$ of Table 2), the identity coefficients change in the same way as the case of asymmetric conversion (see Appendix of OHTA 1983b), and $\lambda$ (equation 5) rather than $\lambda'$ enters into the transition equations as the coefficients. Therefore, $\rho\alpha$ of (13a) and (13c) of NAGYLAKI is $2\lambda/(n - 1)$ in the present notation, and we have the following relationships:

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**Figure 2.**—Hypothetical examples of symmetric conversion that results in reciprocal exchange of genes.
When conversion is asymmetric \((\rho = 1)\), results of numerical studies for the identity coefficients and the time until fixation of a mutant are presented in OHTA (1982, 1983a). NAGYLAKI (1984) carried out extensive numerical calculations for the identity coefficients and the characteristic convergence time when intrachromatid and symmetric conversion may occur, especially when \(\rho = 2, 1.5\) and 1. The reader should refer to these papers for details.

**AN EXTENSION OF THE MODEL: PREFERENTIAL CONVERSION**

In this section, a model of preferential conversion is analyzed. This model was originally suggested by LALANNE et al. (1983) and BREGEGERE (1983) in order to account for exceptionally high polymorphism at loci of histocompatibility loci, i.e., \(H-2\) of mouse and \(HLA\) of man. These loci are located in the chromosomal region called the major histocompatibility complex (MHC). The complex contains three classes of genes; class I includes those of histocompatibility antigens, class II, those for immune response, and class III, those for the complement system (HOOD, STEINMETZ and GOODENOw 1982; ROBERTSON 1982, for review). The class I genes form a multigene family which contains 15–40 members (CAMI et al. 1981; STEINMETZ et al. 1982). From the standpoint of evolutionary genetics, histocompatibility loci are interesting because of their extraordinarily high polymorphism and the explanation that gene conversion or other recombinational mechanisms are the causes (LALANNE et al. 1983; EVANS et al. 1982; LOPEZ DE CASTRO et al. 1982; WEISS et al. 1983; SCHULZE et al. 1983).

A remarkable fact is that the class I family consists of two groups, i.e., histocompatibility antigen loci and differentiation antigen (\(Qa\) and \(Tla\)) loci. Another curious fact is that not all loci belonging to the family of class I genes are equally polymorphic, but that those loci encoding histocompatibility antigens are more polymorphic than the differentiation antigen loci (LALANNE et al. 1983; WEISS et al. 1983). In other words, \(H-2\) loci are much more polymorphic than \(Qa\) and \(Tla\) loci even if both belong to the same class I family of mouse (see Figure 2 of WINOTO, STEINMETZ and HOOD 1983). The model of preferential conversion can explain such observations (BREGEGERE 1983).

Figure 3 shows the model of preferential conversion. In addition to the usual conversion process of the \(O\) model, a gene belonging to group II is preferentially converted, with rate \(\lambda_p\) per generation, by any one of the genes of group I. Here, group I is for \(Qa\) and \(Tla\) loci, and group II, for \(H-2\) loci. Contrary to \(\lambda\), \(\lambda_p\) is unidirectional, i.e., conversion occurs from group I to group II genes. The model is different from biased or directional conversion. This is because oriented conversion is through location of genes on the chromosome, whereas bias in conversion means disparity between genes themselves such as...
between $A$ and $a$ in the previous section. Let $n$ be the total number of genes in one family, and $n_1$ and $n_2$ be those of groups I and II, respectively ($n = n_1 + n_2$).

With additional conversion of group I to group II genes, the latter becomes more polymorphic than the former. It is straightforward to derive the formulas that give the expected changes of a set of identity coefficients by using the same method as before (OHTA 1982, 1983a,b). The derivation is given in the APPENDIX. To evaluate the polymorphism of the gene family at the level of populations, we define a set of identity coefficients between genes with the relationships as in Figure 3; $f$ is for allelic genes and $C$ for nonallelic genes as before. The first subscript is 1 for group I, $p$ for between groups and 2 for group II, and the second subscript of $C$ is 1 for the same chromosome and 2 for the homologous chromosomes. We assume a randomly mating population of effective size $N$, so that there are $2N$ homologous chromosomes containing the gene family. Let $v$ be the mutation rate as in the KIMURA and CROW (1964) model. The unit used to compare identity may be an amino acid site or a nucleotide site or any DNA region that is smaller than the DNA segment converted at a time. In addition, the gene family is assumed to undergo interchromosomal recombination with rate $\beta$ per adjacent locus $i.e., (n - 1)\beta$ per family per generation through meiosis. Thus the gene family is evolving under the processes of gene conversion, mutation, random genetic drift and interchromosomal recombination.

The formulas to give the change in the set of eight identity coefficients were obtained (see APPENDIX). We ask the question: how much genetic variability does the gene family contain when various forces balance each other? The identity coefficients at equilibrium were obtained by letting their changes be zero. Table 3 gives some examples of interest, obtained numerically. The parameters were chosen so that the results are applicable to the observed polymorphism of histocompatibility loci. The effective population size, $N = 5 \times 10^4$, was based on data of enzyme polymorphism (KIMURA and OHTA 1971; NEI 1975), the number of genes, $n = 32$ with $n_1 = 30$ and $n_2 = 2$ from
TABLE 3

<table>
<thead>
<tr>
<th>$v = 10^{-8}$</th>
<th>Allelic</th>
<th>$v = 10^{-7}$</th>
<th>Allelic</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_\mu/\lambda$</td>
<td>$f_1$</td>
<td>$f_2$</td>
<td>$C$</td>
</tr>
<tr>
<td>0</td>
<td>0.950</td>
<td>0.950</td>
<td>0.829</td>
</tr>
<tr>
<td>1</td>
<td>0.946</td>
<td>0.917</td>
<td>0.817</td>
</tr>
<tr>
<td>2</td>
<td>0.945</td>
<td>0.896</td>
<td>0.811</td>
</tr>
<tr>
<td>3</td>
<td>0.944</td>
<td>0.881</td>
<td>0.808</td>
</tr>
<tr>
<td>4</td>
<td>0.944</td>
<td>0.871</td>
<td>0.808</td>
</tr>
<tr>
<td>5</td>
<td>0.944</td>
<td>0.864</td>
<td>0.808</td>
</tr>
<tr>
<td>10</td>
<td>0.945</td>
<td>0.845</td>
<td>0.811</td>
</tr>
<tr>
<td>20</td>
<td>0.946</td>
<td>0.835</td>
<td>0.816</td>
</tr>
<tr>
<td>30</td>
<td>0.946</td>
<td>0.835</td>
<td>0.819</td>
</tr>
<tr>
<td>40</td>
<td>0.947</td>
<td>0.831</td>
<td>0.820</td>
</tr>
<tr>
<td>50</td>
<td>0.948</td>
<td>0.830</td>
<td>0.822</td>
</tr>
<tr>
<td>100</td>
<td>0.949</td>
<td>0.828</td>
<td>0.824</td>
</tr>
<tr>
<td>200</td>
<td>0.949</td>
<td>0.828</td>
<td>0.826</td>
</tr>
</tbody>
</table>

Parameters: $\lambda = 2 \times 10^{-6}$, $n_1 = 30$, $n_2 = 2$, $\beta = 2 \times 10^{-5}$ and $N = 5 \times 10^4$.

recent reports (CAMI et al. 1981; STEINMETZ et al. 1982), and recombination rate per adjacent locus, $\beta = 2 \times 10^{-5}$, by considering the physical map of the MHC region (STEINMETZ et al. 1982). Two values of the mutation rate, $v = 10^{-8}$ and $10^{-7}$ were used. The former is appropriate when gene identity is measured by taking an amino acid as a unit (KIMURA and OHTA 1971), and the latter value is appropriate when ten amino acid sites or approximately 30 nucleotide sites are compared for identity. However, in such cases, the situation becomes complicated if recombination occurs within the unit or if the unit is partitioned by conversion. Let us assume here that such cases do not occur. As for conversion rate, I tentatively consider $\lambda = 2 \times 10^{-6}$. For the sets of these parameter values, the nonallelic identity coefficients are all approximately equal, i.e., $C_{11} \approx C_{12} \approx C_{21} \approx C_{22} \approx C_{p1} \approx C_{p2}$, and $C$ in Table 3 represents the common value.

From the table, it can be seen that, when $\lambda_\mu = 0$, $f_1 = f_2$, but as $\lambda_\mu$ gets large relative to $\lambda$, $f_2$ becomes smaller and approaches $C$. In other words, as $\lambda_\mu$ gets larger, allelic identity approaches nonallelic identity for the group II genes. The prediction thus explains the observed polymorphisms of the class I gene family of MHC. In other words, the observed facts that the amino acid identity is approximately 0.9 for allelic products and 0.85 for nonallelic products at H-2 loci (PLOEGH, ORR and STROMINGER 1981), whereas polymorphism is much limited at Qa and Tla loci (LALANNE et al. 1983; WINOTO, STEINMETZ and HOOD 1983), may be easily accounted for by the present model.

DISCUSSION

It is now known that any one of various multigene families is evolving as a set by exchanging genetic information between repeated gene numbers in the
course of evolution. This phenomenon has been called horizontal (Brown and Sugimoto 1973), coincidental (Hood, Campbell and Elgin 1975) or concerted (Zimmer et al. 1980; Krystal et al. 1981; Arnheim 1983) evolution and, more recently, molecular drive (Dover 1982). The nature of genetic diversity contained in the family has to be understood in terms of population genetics. For this purpose, the theory of identity coefficients developed by the present author (Ohta 1980, for review) has proved to be useful. The model of gene conversion (Ohta 1982) can be handled more exactly than that of unequal crossing over (Ohta 1980), and in the previous section, its relationship to the model of Nagylaki and Petes (1982) is clarified.

The models studied here are overly simple given the complicated nature of gene conversion (Whitehouse 1982). Especially, various kinds of bias in conversion may have significant effect on mutant dynamics of multigene family (see Dover 1982, for review). Preferential conversion is one possible kind of such bias. In this case, one needs to assume that the DNA sequence responsible for the preferential conversion is in the region outside the DNA segments that are preferentially converted. The situation might be analogous to the case of the variant switch of surface antigen of Trypanosoma brucei (Pays et al. 1981). The model explains the uneven polymorphism among the loci belonging to the class I gene family of MHC. However, one should be reminded that the effect of preferential conversion is difficult to distinguish from that of natural selection. If some kind of diversifying selection such as overdominance or frequency-dependent selection is at work within the MHC (Bodmer 1979), polymorphisms may be much enhanced, and as a result, uneven polymorphisms may be observed among the loci in a multigene family. In fact, Hedrick and Thompson (1983) found an excess of heterozygosity as compared with the actual number of alleles under the assumption of selective neutrality at HLA loci and suggested that symmetrical balancing selection is at work. In the future, one would need to incorporate both gene conversion and balancing selection into the model.

Another problem regarding the evolution of multigene families is the elimination of deleterious mutations that are known to be constantly occurring in the course of evolution (Breggeger 1983). The effectiveness of natural selection for eliminating these mutations is dependent on the variance of the number of deleterious mutants among the genomes. Parameters such as conversion rate (a) and recombination rate (\( \beta \)) are considered to play a decisive role on the effectiveness just as in case of accumulation of selfish DNA (Ohta 1983c), and so we need further investigation of these details.

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**APPENDIX: TRANSITION EQUATIONS OF IDENTITY COEFFICIENTS FOR THE MODEL OF PREFERENTIAL CONVERSION**

In addition to changes due to various processes as in the $O$ model (see Appendix, OHTA 1983b), identity coefficients, $C_21$, $C_22$, $f_3$, $C_31$ and $C_32$, are transformed by preferential conversion from group I genes to group II genes. For example, $f_3$ changes by preferential conversion according to the following formula,

$$\Delta_{\text{conv}} f_3 = 2\lambda_y (C_{32} - f_3) \quad (A1)$$
where $\Delta_{\text{conv}}(\cdot)$ is the expected change by preferential conversion. Changes of other coefficients are similarly expressed. Let $\mathbf{x}$ be the following vector,

$$\mathbf{x} = (f_1, C_{11}, C_{12}, f_2, C_{21}, C_{22}, C_{p1}, C_{p2}).$$  \hfill (A2)

Then the equation to give the change of $\mathbf{x}$ becomes as follows, by using the following notation.

$$s = \frac{n_1}{n - 1}$$

$$s' = \frac{n_1 - 1}{n - 1}$$

$$t = \frac{n_2}{n - 1}$$

$$t' = \frac{n_2 - 1}{n - 1}$$

$$\alpha_1 = \frac{2\lambda}{n_1 - 1}$$

$$\alpha_2 = \frac{2\lambda}{n_2 - 1}$$

\[
\Delta \mathbf{x} = \begin{bmatrix}
    a_{11} & 0 & 2\lambda s' & 0 & 0 & 0 & 0 & 2\lambda t \\
    0 & a_{22} & 0 & 0 & \frac{n_1}{3} & \beta & 0 & \alpha t \\
    \alpha_{15} & \frac{1}{2N} & a_{25} & 0 & 0 & 0 & 0 & \alpha_{11} \\
    0 & 0 & 0 & a_{44} & 0 & 2\lambda s' & 0 & 2\lambda_p + 2\lambda_s \\
    0 & 0 & 0 & a_{55} & \frac{n_2}{3} & \beta & 2\lambda_p + \alpha_{55} & 0 \\
    0 & 0 & 0 & \alpha_{54} & \frac{1}{2N} & a_{66} & 0 & 2\lambda_p + \alpha_{55} \\
    0 & \lambda_p + \lambda t' & 0 & 0 & \lambda t' & 0 & a_{77} & \frac{n}{2} & \beta \\
    \frac{\lambda}{n-1} & 0 & \lambda_p + \lambda t' & \frac{\lambda}{n-1} & 0 & \lambda t' & \frac{1}{2N} & a_{88} & 0 \\
\end{bmatrix}
\]

$$\begin{bmatrix}
    \frac{1}{2N} \\
    \frac{1}{2N} \\
    0 \\
    0 \\
    \frac{2\lambda}{n-1} \\
\end{bmatrix}$$

\[
\mathbf{x} + \begin{bmatrix}
    \frac{1}{2N} \\
    \frac{1}{2N} \\
    0 \\
    0 \\
    \frac{2\lambda}{n-1} \\
\end{bmatrix}
\]

where

$$a_{11} = -\frac{1}{2N} - 2\lambda(s' + t) - 2v, a_{22} = -\alpha_1(s' + t) = -\frac{n_1}{3} - \beta - 2v, a_{55} = -\alpha_3(s' + t) = -\frac{1}{2N} - 2v, a_{44} = -\frac{1}{2N} - 2\lambda_p - 2\lambda(s + t') - 2v, a_{66} = -2\lambda_p - 2v, a_{54} = -\frac{1}{2N} - \alpha_2(t' + s) - 2v, a_{77} = -\lambda_p - \lambda(s + t) = -\frac{n}{2} - \beta - 2v, a_{88} = -\lambda_p - \frac{1}{2N} - \lambda(s + t) - 2v.$$

and