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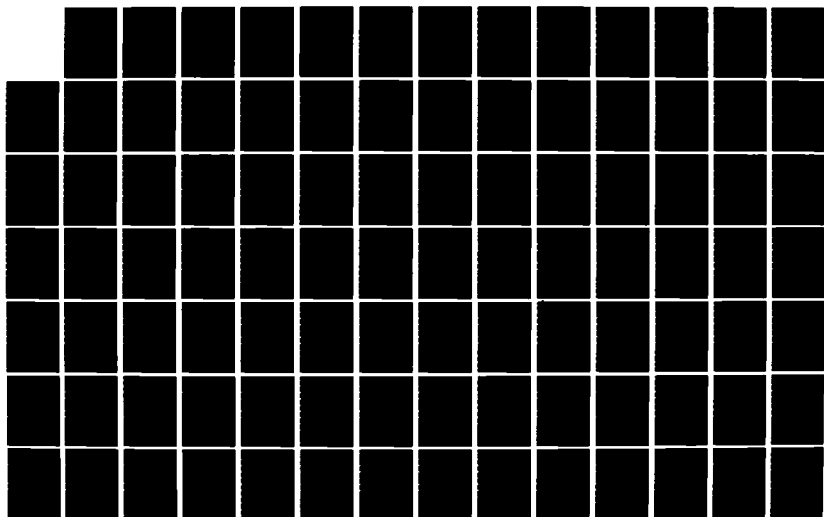
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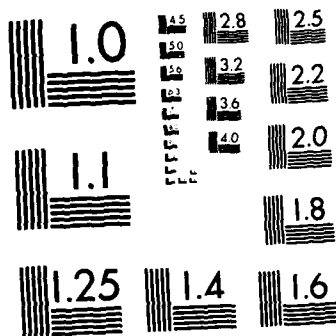
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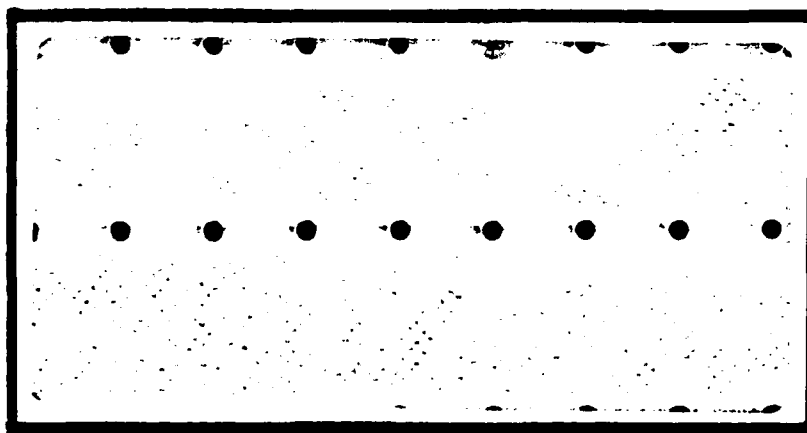




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THE SIMULATION AND ANALYSIS OF AN
EVOLUTIONARY MODEL
OF DEOXYRIBONUCLEIC ACID (DNA)

Captain Richard E. McNally, USAF

LSSR 87-80

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A Monte Carlo simulation model was developed in order to evaluate model predictions with expectations of the evolutionary hypothesis of nearly neutral point mutations. The beta chain of hemoglobin was chosen as the strand of deoxyribonucleic acid(DNA) to be analyzed due to the extensive characterization of point mutations along the 146 amino acids of the protein chain. The nucleotide sequences of human, rabbit and a hypothetical ancestral hemoglobin were used as a starting point in the simulation. Three models of point mutations were tested. Equiprobable mutation from one nucleotide to any of the remaining three nucleotides composing DNA was one model. The second model incorporated observed first order probability of transition from each nucleotide to the remaining three nucleotides composing DNA using observed probabilities from three independent assessments. The third model was an Ising type model employing a probability of nucleotide change based on the nucleotide composition of the nearest neighbors. Use of these models resulted in evidence to suggest that five methods of simulating the mutations in an evolutionary system produced results that primarily differed in the way in which nucleotide changes resulted in a pattern of amino acid changes.

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THE SIMULATION AND ANALYSIS OF AN
EVOLUTIONARY MODEL OF DEOXYRIBONUCLEIC ACID(DNA)

A Thesis

Presented to the Faculty of the School of Systems and Logistics
of the Air Force Institute of Technology

Air University

In Partial Fulfillment of the Requirements for the
Degree of Master of Science in Systems Management

By

Richard E. McNally, BS
Captain, USAF

September 1983

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Captain Richard E. McNally

has been accepted by the undersigned on behalf of the
faculty of the School of Systems and Logistics in partial
fulfillment of the requirements for the degree of

MASTER OF SCIENCE IN SYSTEMS MANAGEMENT

DATE: 28 September 1983

A handwritten signature in cursive script, likely of the undersigned, is written over a horizontal line.

COMMITTEE CHAIRMAN

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My wife and children, for enduring the unending burden of the simulation and writing the thesis deserve far more recognition than these few words here. Without their love and help I would not have finished this work.

Richard E. McNally

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CHAPTER I

INTRODUCTION

Current evidence shows that deoxyribonucleic acid(DNA) is the carrier of genetic information within the nucleus of the cell. In protein synthesis, the DNA is transcribed into a complementary chain of messenger ribonucleic acid(mRNA). The mRNA chain is "read" in the cytoplasm. The reading process involves the incorporation of either an amino acid or the termination of the amino acid chain, depending on the specific three nucleotide sequence of the mRNA chain.

The genetic code which translates the nucleotide triplet into a specific amino acid (or a chain termination signal) has been found to be universal across all species of life so far studied (Epstein, 1966)(Melchar, 1970). The implication is that all forms of life have evolved after the genetic code became fixed in its present form some time in the distant past (Conrad, 1970)(Fox, 1974)(Hartman, 1975)(Jukes, 1973)(Orgel, 1972). The theoretical problem of the origin of life as known on this planet can then be divided into two component parts. First, the problem is to understand the chemistry and exobiology responsible for the development of protocells and the fixation of the genetic code represented by the universality of the genetic code

(Chernavskii, 1975)(Keosian, 1974)(Lacey, 1975)(Mazin, 1975)(Mikelsaar, 1975). The second problem is to understand the mechanisms at work after the fixation of the genetic code. Within this second area fall the mechanisms responsible for the range and diversity of life as observed today (Conrad, 1970)(Geracitano, 1971). The range and diversity is represented by the great number and complexity of species as well as the vast amount of difference observed within each species (Crow, 1970)(Geracitano, 1971)

The evolutionary theories of Darwin and the genetic systems of Mendel have been instrumental in providing a framework for categorizing and understanding many of the processes that have occurred since the fixation of the code. The theories of Darwin and Mendel formed a school of thought which examined phenotype to form generalizations about genotype. This methodology has been continued by the modern population biologists (Jungck, 1971)(Lewontin, 1966)(Ohto, 1971). The main focus is on changes in population statistics as observed and applied using neo-Darwinian theories which emphasize selective advantage, or disadvantage (Epstein, 1967)(Kimura, 1969)(Papentin, 1973)(Richmond, 1970).

After the identification and characterization of the genetic code, many researchers began to look at the phenomenon of evolution from the genotypic level (as represented by amino acid sequence within protein) towards

the phenotypic level. The redundant nature of the genetic code along with known characteristics of DNA enabled certain statistical projections about amino acid sequence and nucleotide sequence to be made. Random point mutations of the DNA chain could yield statistical evidence for changes in the amino acid structure of protein over a time period long enough to reflect evolutionary processes. Such projections lead to surprisingly accurate correlation between predicted time of separation of species and archaeological data (Acher, 1974)(Clarke, 1970). Amino acid differences within species (known as polymorphic proteins) could be partially explained by random point mutations of neutral selection value (Kimura, 1971)(Sueoka, 1961)(Zuckerandl, 1972).

The overall objective of this thesis will be to provide a framework to examine the random mutation hypothesis. From this framework a better understanding of the possibilities and limitations imposed by random mutation can be evaluated. Implications about the evolutionary potential of the information carrying system and the present equilibrium of that system may be possible.

This thesis is written in five chapters. This, the first chapter, has presented a brief introduction to several of the ideas of current interest in evolutionary biology. This section identifies the organization of the remainder of the paper. The second chapter reports the relevant

information gathered during the course of the research into the evolutionary potential of bio-organic information transmitting compounds, the characteristics of mutations occurring within the system, and information on hemoglobin's evolutionary and mutational behavior. The third chapter addresses the methodology to be employed in this thesis. This includes the development of a modeling approach to the point mutation of the DNA sequence responsible for producing viable beta hemoglobin chains as well as the techniques used to evaluate the model's performance and the results on hypothesis testing. The fourth chapter lists the results of analysis I performed on the simulation results obtained. The fifth chapter reflects the conclusions that I have been able to gather from the modeling and analysis results obtained to date.

CHAPTER II

BACKGROUND

The first section will be a quick tutorial of different portions of the information transmission system of cells. This will consist of brief outlines of the compounds and simplified descriptions of the functioning of the system. This section will also include a review of genetic mutations. The second section will contain a bibliographic review of the concept of evolutionary forces at work in the mutation of DNA. Different theories as to the operate mechanism will be discussed as well as some of the implications of these theories.

The chromosomes of organisms are composed of nucleoproteins. Proteins such as histones and nucleic acids comprise the nucleoproteins. The nucleic acids have been associated with the transmission of genetic information while the histones play a role in the stabilization of the compounds and mechanisms involved(Stansfield, 1969)(Stryer, 1975) .

Deoxyribonucleic acid is the repository of genetic information in all eukaryotes. DNA is stabilized into chains thousands of nucleotides long that form a double stranded helix. The backbone of each chain consists of five

carbon sugar compounds oxygenated at the 2' position linked by phosphate to form 5'=>3' phosphodiester linkages. The helix is held together by the interaction of the bases attached to the 1' carbon of the sugar. The paired organic bases found in DNA are the purines adenine(A) and guanine(G) and the pyrimidines thymine(T) and cytosine(C). In normal DNA with unmodified bases, cytosine always pairs with three hydrogen bonds with guanine while adenine always pairs with two hydrogen bonds with thymine. The nucleotide unit consists of the sugar, the phosphate, and the base(Stansfield, 1969)(Stryer, 1975).

Ribonucleic acid(RNA) is another class of nucleic acid. RNA differs from DNA in that the base sugar, again a pentose, does not have an oxygen at the 2' position. RNA is thought of as primarily a single stranded nucleotide, however, the ability of RNA to stabilize itself by forming double and even four stranded chains is thought to play a key role in several of the mechanisms and the results of several thermodynamic considerations. RNA contains the pyrimidine uracil(U) instead of thymine within its structure. RNA is typically much shorter than DNA and is found both within and outside of the cell nucleus(Stansfield, 1969),(Stryer, 1975).

RNA plays a predominate role in protein synthesis. There are three common types of RNA designated as mRNA, tRNA, and rRNA. Messenger RNA, or mRNA, is transcribed from

DNA within the nucleus of the cell and is brought to the cytoplasm. Transfer RNA, or tRNA, is found in the cytoplasm and is active in selectively positioning the appropriate amino acid into the growing protein chain based on the codon of the mRNA carrying the template for protein synthesis. Ribosomal RNA, or rRNA, is actually a class of different molecular weight components with protein components which serve as the binding site for mRNA and tRNA in the translation process(Stansfield, 1969)(Stryer, 1975).

The individual hydrogen bonds linking the bases of the DNA chains are not strong compared to typical covalent chemical bonds such as those that connect the sugar to the phosphate or to the base, however, the large number of bonds form a very powerful and a very stable chain. DNA is replicated with the assistance of enzymes known as DNA-polymerases which assist in the separation of the DNA helix. The two single DNA strands each form a new double stranded DNA helix by the addition of nucleotides in a new second DNA strand which forms in the 5'=>3' direction. The replication of DNA occurs extremely fast. As a practical consideration, single stranded DNA is very rarely found(Stansfield, 1969)(Stryer, 1975).

The nucleotide sequence of DNA is the blueprint for protein synthesis. Proteins form the major structural components of the cell as well as the enzymes necessary to catalyze the biological reactions which are essential for

life as we know it. Proteins are composed of a large number of amino acid residues which forms the primary structure. Proteins form stable secondary and tertiary structures based on the thermodynamic equilibrium of the chain in the ionic environment in which it exists. While the primary structure of the protein may be responsible for the production of an active site in an enzyme, it is the secondary structure which is reflected within the environment which ultimately determines the catalytic ability of the protein. If the ionic or temperature conditions cause the secondary structure to change, the catalytic ability of the enzyme is usually lost. Proteins are comprised of 20 different amino acids as reflected in table 2.1 (Stansfield, 1969) (Stryer, 1975).

Table 2.1
Amino Acids By Decreasing Frequency of Occurance

1	G	Gly	Glycine	11	I	Ile	Ileucine
2	A	Ala	Alanine	12	R	Arg	Arginine
3	L	Leu	Leucine	13	N	Asn	Asparagine
4	S	Ser	Serine	14	Q	Gln	Glutamine
5	V	Val	Valine	15	F	Phe	Phenylalanine
6	K	Lys	Lysine	16	Y	Tyr	Tyrosine
7	T	Thr	Threonine	17	C	Cys	Cysteine
8	E	Glu	Glutamic Acid	18	H	His	Histidine
9	P	Pro	Proline	19	M	Met	Methionine
10	D	Asp	Aspartic Acid	20	W	Trp	Tryptophan

The mRNA is translated by tRNA while being bound by rRNA to form proteins. Each amino acid has an amino group at one end and a carboxyl group at the other. Proteins are

synthesized by the addition of new amino acids at the carboxyl terminal of the growing protein chain based on the "reading" of the mRNA in the 5'=>3' direction. The "reading" of the RNA message is conducted in accordance with the genetic code. The genetic code is a catalog of sixty-four three base codons which form a degenerate reference set for the twenty available amino acids from the four

Table 2.2
Genetic Code

<u>5' DNA 3'</u>	<u>5' RNA 3'</u>	<u>Amino Acid</u>	<u>5' DNA 3'</u>	<u>5' RNA 3'</u>	<u>Amino Acid</u>
AAA	UUU	Phe	GAA	UUC	Phe
TAA	UUA	Leu	CAA	UUG	Leu
AGA	UCU	Ser	GGA	UCC	Ser
TGA	UCA	Ser	CGA	UCG	Ser
ATA	UAU	Tyr	GTA	UAC	Tyr
TTA	UAA	Stop	CTA	UAG	Stop
ACA	UGU	Cys	GCA	UGC	Cys
TCA	UGA	Stop	CCA	UGG	Trp
AAG	CUU	Leu	GAG	CUC	Leu
TAG	CUA	Leu	CAG	CUG	Leu
AGG	CCU	Pro	GGG	CCC	Pro
TGG	CCA	Pro	CGG	CCG	Pro
ATG	CAU	His	GTG	CAC	His
TTG	CAA	Gln	CTG	CAG	Gln
ACG	CGU	Arg	GCG	CGC	Arg
TCG	CCG	Arg	CCG	CGG	Arg
AAT	AUU	Ile	GAT	AUC	Ile
TAT	AUA	Ile	CAT	AUG	Met
AGT	ACU	Thr	GGT	ACC	Thr
TGT	ACA	Thr	CGT	ACG	Thr
ATT	AAU	Asn	GTT	AAC	Asn
TTT	AAA	Lys	CTT	AAG	Lys
ACT	AGU	Ser	GCT	AGC	Ser
TCT	AGA	Arg	CCT	AGG	Arg
AAC	GUU	Val	GAC	GUC	Val
TAC	GUA	Val	CAC	GUG	Val
AGC	GCU	Ala	GGC	GCC	Ala
TGC	GCA	Ala	CGC	GCG	Ala
ATC	GAU	Asp	GTC	GAC	Asp
TTC	GAA	Glu	CTC	GAG	Gly
ACC	GGU	Gly	GCC	GGC	Gly
TCC	GGA	Gly	CCC	GGG	Gly

nucleotide bases available. The code can be seen in Table 2.2.

The attachment of an amino acid to its tRNA is mediated by specific enzymes in a process called activation. The tRNA sequence contains a three nucleotide anticodon which is complementary to the mRNA codon. The tRNA is positioned at the translation site where the rRNA is "reading" mRNA in the 5'=>3' direction. The amino group of the tRNA bound amino acid is brought into a proximal position to the carboxyl group of the growing peptide chain. Enzymes are active in the formation of the peptide bond formed at this site which joins the the amino acid to the protein. The tRNA is released from both its amino acid and the mRNA chain. When the ribosome meets the end of the mRNA or encounters an in-phase termination codon, the protein's primary structure, consisting of the sequence of amino acids is complete. The secondary structure, or the three dimensional structure of the protein, is probably also complete at this point or shortly after release from the ribosome. The secondary structure is created by the formation of three dimensional structures such as the alpha-helix or beta-pleat sheet. Quarternary structures that stabilize the hydrophobic and hydrophillic regions of the protein as well as the formation of internal covalent bonds (such as between cysteine residues). The tertiary structure of multiple proteins may form a quaternary structure. For instance, two alpha and

two beta hemoglobin chains combine to form the functional complex. Any alteration of the final configuration may inactivate the protein(Stansfield, 1969)(Stryer, 1975).

Each tRNA consists of 75 to 80 nucleotides in a specific order. The 3' end of all tRNA's contain the sequence CCA. The 5' end terminates in a guanine residue. Pseudouradic acid, inosinic acid, and a few other modified bases are found in tRNAs. The tRNAs have a characteristic three dimensional four arm stucture with helical sections and single stranded loops. One of the unpaired loops contains the anticodon(Stansfield, 1969)(Stryer, 1975).

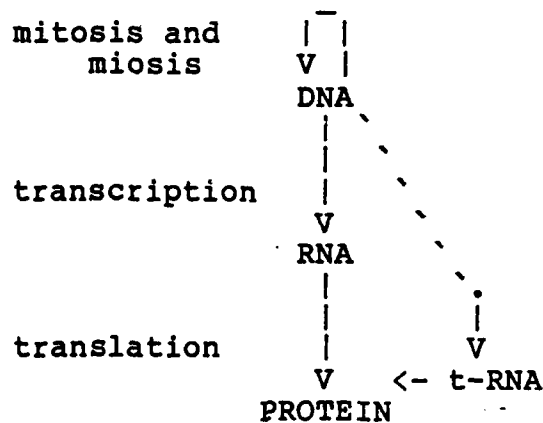


Figure 2.1
Simplified Schematic Of Protein Synthesis

More than 30 different proteins have been associated with rRNA in ribosomes. Three sites conceptually exist on functional ribosomes. A decoding site binds the activated tRNA to the mRNA codon. A condensing site joins the amino

acid to the growing polypeptide chain. An exit site at which the tRNA becomes separated from the protein, mRNA, and ribosome. The tRNA is processed in turn thru all three sites of the ribosome(Stansfield, 1969)(Stryer, 1975).

Most genes are relatively stable and mutation is a very rare event. The average mutation rate has been estimated at one accepted point mutation occurring in million genes. Other genes have mutation rates estimated at one mutation per occurring in ten genes. Mutation at the genotypic level can only be examined directly very recently. Present estimates are directly tied to observations of the proteins produced. When the proteins that are produced cause differences observable in the organism's behavior, a mutation could be identified which caused the change(Stansfield, 1969)(Stryer, 1975).

The majority of mutations are lethal to the organism and result in the death of the organism. The mutant gene, even in the case of lethal effects, are kept at a low frequency with in the population. The effects on the target population and the frequency of the allele can be predicted by modeling techniques used in population genetics. Population genetics have been used to study the transfer of advantageous and neutral alleles within a population. Mutant types produce organism which compete within the ecosystem. Natural selection appears to play an important role in the level of an allele in a population. To date,

all of the population genetic studies that have been conducted rely on phenotypic manifestations. Any genotypic change that occurs in the proteins of an organism can only be evaluated using present techniques when the genotypic change causes a phenotypic change. The hierarchy of information transmission is presented in figure 2.2(Stansfield, 1969)(Stryer, 1975).

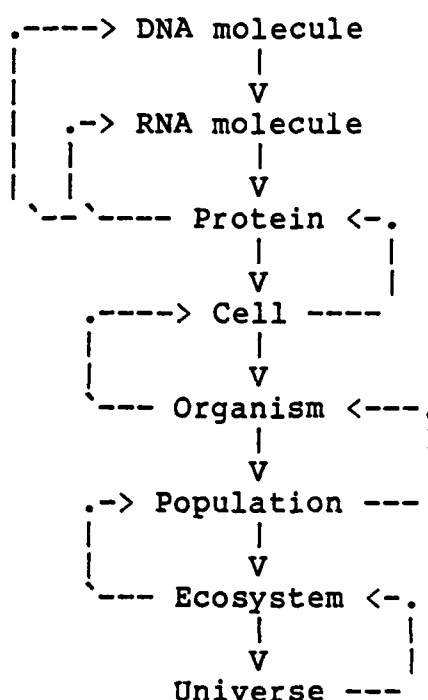


Figure 2.2
Hierarchy Of Biological Information Transfer

There are several types of mutations possible. Each type may be identified by several different sets of terminology which can be used to describe non-exclusive mutation events. When discussing the size of a mutation, the two classifications most used are point and gross. Point

mutations are usually associated with changes at a single nucleotide pair. Gross mutations involve large areas of genetic information. This could describe mutations to multiple nucleotides, an entire gene, or even entire chromosomes(Stansfield, 1969)(Stryer, 1975).

Mutations can also be classified as to quality. Structural mutations affect the nucleotide content of the gene. Substitution mutations, deletion mutations, and insertion mutations, and insertion mutations belong in this category. Transition mutations occur when one purine nucleotide is substituted for another purine or when one pyrimidine is substituted for another pyrimidine. Deletion mutations occur when some part of the gene is lost from the gene. Insertion mutations occur when nucleotides are added to the gene(Stansfield, 1969).

The origin of the mutation is also a source of classification. A mutation is called spontaneous when the origin is unknown. This is the category where the random mutations thought to be important in evolutionary drift. Genetic control mutations are thought to occur when the influence of a specific gene affects one or many other genes. Induced mutations occur when ionizing, noionizing radiation, and chemical mutagens which are not normally included in the environment affects the gene(Stansfield, 1969).

The magnitude of the phenotypic effect is also a

classification scheme for mutation. Some alleles can be distinguished by the frequency with which they mutate. Isoalleles which produce seemingly identical phenotypes when in homozygous or heterozygous combinations, but in combination with other alleles are identifiable. Mutants which affect the viability or the reproductive vigor of the organism can be identified (Stansfield, 1969).

Mutations can be identified by the direction of the phenotypic response. A mutation is considered forward when the normal phenotypic characteristic suddenly becomes an abnormal phenotype. A back mutation is the return to normal phenotype after an abnormal phenotype was observed. Back mutations have been observed to occur either by a change at the initial location within the gene or at a remote site in a different gene (Stansfield, 1969).

Mutations can also be cataloged as to the type of cell. A somatic mutation occurs in the non-reproductive cells of the body. This phenomenon is seen when only a part of the organism demonstrates the effect of the mutation. Gametic mutation occurs in the reproductive cells of the organism and produces an heritable change seen in the following generations of the organism (Stansfield, 1969).

To systematically understand the relationships involved in the mutation of an organism's DNA, it is important to understand the control relationships that exist. Figure 2.3 exemplifies this type of approach.

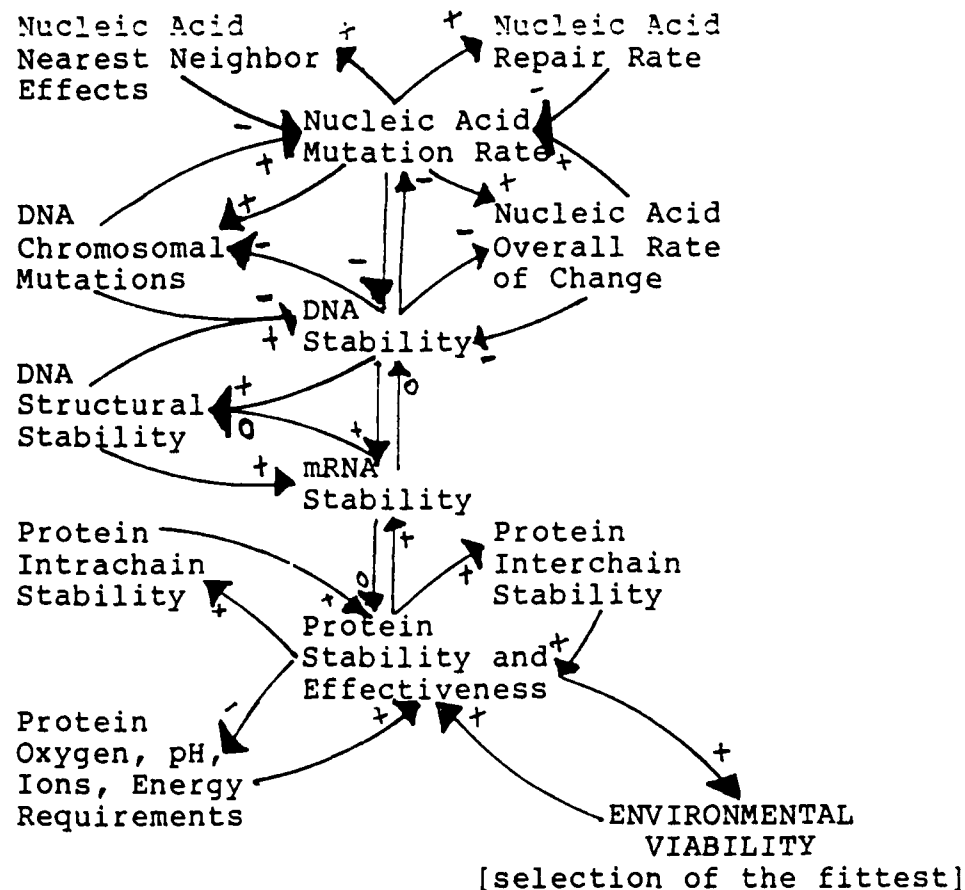


Figure 2.3
Functional Environmental Relationships

In the 1960's it was established that proteins reflected the genotypic content of the gene. This reflection was found to be common across all forms of life according to the genetic code. The amino acid sequence was the result of a specific and ordered sequence of nucleotides in DNA. It is clear that these proteins represent the end products of molecular evolution. The study of amino acid sequences has enabled a new perspective on the study of evolution. These sequences represent a more detailed view

of the phenotype of the organism than is possible from even the most detailed observation of the characteristics of the organism. Atlas of Protein Sequence and Structure edited by Dayhoff and published in 1972 provided a great deal of information on the amino acid sequences of many different proteins and many different species. Because a large quantity of purified protein and the massive labor efforts involved in doing amino acid sequences, the amount of information which can be found is still pretty sparse. Cytochrome C and hemoglobin are the two proteins which have received the most attention. Sequences from many species have been collected for these two proteins.

The second generation of data on information macromolecules has already begun. New techniques for the rapid and automatic sequencing of very small quantities of nucleic acid are now available. Sequencing of mRNA for the hemoglobin chains is now available for use in this study. The sequencing of tRNA have been completed. Using the information from the structure of informational molecules is better than using either observable characteristics or even amino acid sequencing. Proteins reflect the informational structure of the gene far better than any observable characteristic of the organism. The chemistry of the cell is the result in large measure to the functional capability of the available proteins. Amino acid sequences directly reflect the content of the DNA. A single nucleotide change

can result in the placement of a new amino acid into a protein. This amino acid replacement may or may not affect any observable characteristic of the protein. A single amino acid replacement in hemoglobin causes sickle cell anemia. However, since the genetic code is redundant with some amino acids being coded by as many as 6 codons, many changes in nucleic acid result in no change to the primary protein structure. In fact, studies show that the structure of the genetic code is such that most of the changes in nucleotide content either produce the same, or a chemically related amino acid. Another factor to be considered is the existence of multiple genetic loci coding for the same protein. This can result in the production of multiple proteins with the same basic structure and function. The study of the nucleic acid sequence of functional proteins allows a more in-depth view of the phenomenon at work at the genetic level while keeping the product tied to the functional structural requirements placed on the protein chain.

Use of a thorough understanding of the structure-function relationships of proteins together with information available from analysis can result in an understanding of the evolutionary mechanism that is far better than what is commonly known to date. Even the work using these techniques that have been accomplished using the amino acid sequence information has the increased difficulty associated

with the redundancy of the code. Understanding evolutionary mechanics at the level of the protein chain does not directly reflect the process at the level of nucleic acid. For instance, the colinearity of DNA and protein has been presumed for some time now. Most of the information was derived from the translation of mRNA into proteins. When the DNA sequence of the hemoglobin gene was identified, it was found to have a large region of non-coded intervening sequences. Also, recently the discovery of large portions of repeated sequences of DNA identified in mammalian DNA have spurred new questions. Study of the evolutionary impact of random mutation and the effect of processes occurring at the level of the nucleic acids must be conducted using relationships at that level. Using relationships at the amino acid level given the unique information transmission mechanism of the genetic code is likely to give a different perspective of reality.

From an evolutionary viewpoint, the primary structure of a protein is in large part the end point of a biological phenomenon. The secondary structure and binding to cofactors or in the case of hemoglobin, the binding of the heme, to produce a functionally proficient molecule within the cell is the direct result of the primary sequence. Any changes in the primary structure which alters the function of the protein will have very large consequences on the survivability of the cell, and the organism. On the

other hand, many changes at different parts of the protein result in little or no change in the capability of the protein to perform its biochemical function.

For hemoglobin, X-ray crystallographic determinations on the structure of hemoglobin chains from many species show nearly the same tertiary and quaternary structure. Biochemical differences in the oxygen transport capability of the molecule are very small. Since many of the amino acid positions have been observed to have different residues that result in changes that do not affect function, there has been considerable debate on the effect of neutral mutations and the role that random genetic drift may have on the evolutionary process. Changes that are not the result of some selective advantage appear to be occurring throughout the proteins of the cells. Even a protein with the survival requirements that are tied to the functional demands of hemoglobin appear to have a large number of residues that may be changed among several amino acids. Figure 3.2 reflects the variety of residues that a review of the literature suggests as possible. Of note at this time is the use of Figure 3.2. That these amino acids have been found in some of the beta chains of different species is not to say by any stretch of the imagination that all replacements are neutral. In fact, many of these changes have been associated with decreased function of the hemoglobin. Further, many of these residues are only

acceptable when other residues on the chain have already been substituted. Other changes are undoubtedly not acceptable on a survival basis when combined with other changes. Because of the limited nature of detailed functional and survival information on each individual possible change the simplifying assumption made in this study was that all possible combinations would be allowed in this modeling effort.

CHAPTER III

METHODOLOGY

After completing the literature review, it was obvious that there exists strong evidence that point mutations in the amino acid sequences of several different proteins appear to have significant evolutionary patterns that can be studied. The two most commonly characterized, studied, and analyzed protein chains were cytochrome c and hemoglobin. Both consist of protein chains longer than 100 amino acids. Both have had extensive studies of polymorphic variants and of the secondary, and tertiary structures. Many investigators have sequenced both compounds from many different species. Recent work on sequencing the mRNA of the different hemoglobin chains in several species have enabled this study.

The target sequence of the DNA representation of the beta chain of hemoglobin was chosen. The unique availability of this information complemented the existing data on point mutations and amino acid differences among and between different species. Work by Dayhoff and by Fitch to construct hemoglobin ancestral trees based on similarity studies of the amino acid differences between species and between different chains of hemoglobin provided insightful guidance.

For this study, two known mRNA sequences of beta hemoglobin were chosen, that of human and that of rabbit. A third sequence based on the amino acid sequence of an hypothetical ancestral beta hemoglobin chain which should be evolutionary common. Approximately equal numbers of point mutations were accepted into the human and the rabbit chains. The ancestral beta hemoglobin chain was characterized and included in the modeling effort. The ancestral beta hemoglobin I selected to use for this effort was identified as locus 28 in Dayhoff's Atlas of Protein Sequence and Structure.

Table 3.1 presents the DNA representation of the beta hemoglobin chain that were chosen for the present study. Very few point mutations exist in the data between the human and the rabbit DNA. Likewise, there are few point mutations between the ancestral(early) DNA and either the human or the rabbit DNA. In formulating the ancestral nucleotide string, minimizing the differences between existing nucleotides in the human and rabbit DNA was a goal. The ancestral protein string had very few changes in amino acids. If the human and rabbit codon at any particular location was identical and if the ancestral amino acid was that same codon, then the ancestral amino acid was assumed to have the same codon as the other two DNA chains. If the human and rabbit codons were different, then the codon chosen to represent the ancestral codon was chosen to have the minimum number of

nucleotide differences with both chains and still code for the predicted amino acid. If both the human and the rabbit codons were equidistant, then the nearest neighbor nucleotide transition rate was used. The nucleotide chosen for the ancestral codon was that nucleotide that had the highest transition probability to the needed nucleotide. No equivalent probabilities were encountered.

Table 3.1
Beta Hemoglobin DNA

Amino Acid	5'=>3'			Amino Acid	5'=>3'			Amino Acid	5'=>3'		
#	Man	Rabbit	Early	#	Man	Rabbit	Early	#	Man	Rabbit	Early
0	CAT	CAT	CAT	50	AGT	AGA	AGA	100	AGG	AGG	AGG
1	CAC	CAC	CAC	51	AGG	TGC	AGC	101	CTC	CTC	CTC
2	GTG	ATG	ATG	52	ATC	ATT	ATC	102	GTT	GTT	GTT
3	CAG	CAC	CAC	53	TGC	TGC	TGC	103	GAA	GAA	GAA
4	AGT	GGA	GGT	54	AAC	AAC	AAC	104	CCT	CCT	CTT
5	AGG	ACT	AGC	55	CAT	CAT	CAT	105	GAG	GAG	GAG
6	CTC	CTC	CTC	56	GCC	GTT	GCC	106	CAG	CAG	CAG
7	CTC	CTC	CTC	57	GTT	ATT	ATT	107	GCC	GCC	GCC
8	CTT	CTT	CTT	58	AGG	AGG	AGG	108	GTT	GTT	GTT
9	AGA	AGA	AGC	59	CTT	CTT	CTT	109	CAC	CAC	CAC
10	CGC	CGC	CGC	60	CAC	CAC	CAC	110	CAG	CAG	CAG
11	AAC	GAC	AAT	61	CTT	CTT	CTT	111	GAC	AAC	AAC
12	AGT	AGT	AGT	62	AGC	AGC	AGC	112	ACA	AAT	AAT
13	GGC	GGC	GGA	63	ATG	ATG	ATG	113	CAC	CAC	CAC
14	CAG	CAG	CAG	64	GCC	GCC	GCC	114	CAG	CAG	CAG
15	CCA	CAC	CAC	65	CTT	CTT	CTT	115	GGC	AGA	AGC
16	GCC	GCC	GCC	66	TTT	CTT	TTT	116	ATG	ATG	AGG
17	CTT	CTT	CTT	67	CAC	CAC	CAC	117	GTG	ATG	ATG
18	CAC	CAC	CAC	68	GAG	CAG	CAG	118	AAA	AAA	AAA
19	GTT	ATT	ATT	69	ACC	AGC	ACC	119	GCC	GCC	GCC
20	CAC	CAC	CAC	70	GGC	GGC	GGC	120	TTT	TTT	TTT
21	ATC	TTC	TTC	71	AAA	GAA	AAA	121	TTC	TTC	TTC
22	TTC	TTC	TTC	72	ACT	ACT	ACC	122	GAA	GAA	GAA
23	AAC	AAC	AAC	73	ATG	CTC	ATC	123	GGT	AGT	AGT
24	ACC	ACC	ACC	74	GCC	ACC	ACC	124	TGG	AGG	AGG
25	ACC	ACC	ACC	75	CAG	CAG	CAG	125	TGG	CTG	TTC
26	CTC	CTC	CTC	76	AGC	ACT	TTT	126	CAC	CAC	CAC
27	GGC	GGC	GGC	77	GTG	GTG	GTG	127	CTG	CTG	CTG
28	CAG	CAG	CAG	78	CAG	CAG	CAG	128	AGC	AGC	AGC
29	GCC	GCC	GCC	79	GTC	GTC	GTC	129	GGC	GGC	GGC
30	CAT	CCT	CAT	80	GTT	GTT	GTT	130	ATA	ATA	CCA
31	CAG	CAG	CAG	81	GAG	GAG	GAG	131	CTG	CTG	CTG

Table 3.1 Continued

Amino Acid	5'=>3'			Amino Acid	5'=>3'			Amino Acid	5'=>3'		
#	Man	Rabbit	Early	#	Man	Rabbit	Early	#	Man	Rabbit	Early
32	CAG	CAG	CAG	82	CTT	TTT	TTT	132	TTT	CTT	TTT
33	CAC	AAC	AAC	83	GCC	GCC	GCC	133	CAC	CAC	CAC
34	GAC	GAC	GAC	84	GGT	GGT	GTT	134	CAC	CAC	CAC
35	GTA	GTA	GTA	85	AAA	AAA	AAA	135	AGC	AGC	AGC
36	AGG	TGG	AGG	86	GGC	AGC	AGC	136	ACC	ACC	ACC
37	CCA	CCA	CCA	87	TGT	CTT	TTT	137	CAC	CAC	CAC
38	GGT	GGT	GGT	88	CAG	CAG	CAG	138	AGC	GGC	AGC
39	CTG	CTG	CTG	89	ACT	ACT	ACT	139	ATT	ATT	ATT
40	CCT	CCT	CCT	90	CTC	TTC	TTC	140	GGC	GGC	GGC
41	GAA	GAA	GAA	91	CAG	CAG	CAG	141	CAG	CAG	CAG
42	AAA	GAA	AAA	92	GTG	GTG	GTG	142	GGC	AGC	AGC
43	CTC	CTC	GTC	93	ACA	ACA	ACA	143	GTG	GTG	GTG
44	GGA	GGA	GGA	94	GTC	GTC	GTC	144	CTT	TTT	TTT
45	AAA	AAA	AAA	95	CTT	CTT	CTT	145	ATA	GTA	ATA
46	CCC	CCC	CCC	96	CAG	CAG	CAG	146	GTG	GTG	GTG
47	ATC	GTC	ATC	97	GTG	GTG	GTG	147	TTA	TTA	TTA
48	CAG	CAG	CAG	98	CAC	CAC	CAC				
49	GGA	GGA	GGA	99	ATC	ATC	ATC	(BARRALLE, 1977A:1093)			

The model was set up so that all three DNA sequences were run with the same random number stream generating point mutations for each run of the model. The complete model can be found in Appendix A of this report.

Potential point mutations were assessed by comparison of the random number with the assigned probability of a mutation occurring. The probability of a mutation occurring at any nucleotide was dependent upon the structure of the model and the selection of the data coefficient chosen. Three structures were tested for creating point mutation. The first technique is called the random method. If the random number representing the probability of having a point mutation is below the threshold established for having

a mutation, then the mutation was tested for validity/reasonableness. Each nucleotide was assigned an equal probability of becoming changed to any of the other three nucleotides and this was the point mutation tested. Point mutation testing consisted of evaluating whether or not the amino acid that would result from the new codon was possible at that position. Possibility was arbitrarily established in this effort as having the amino acid in question at that position recorded either as a known point mutation, or protein polymorph, or even an amino acid found in one of the other species for which beta hemoglobin protein sequencing had been conducted. See Table 3.2 for a compiled list of acceptable amino acids at each position on the chain.

Table 3.2
Allowable Amino Acid by Position

Beta Hemoglobin Amino Position	Acid	Beta Hemoglobin Amino Position	Acid
1	T,V,M,P,G	74	G,A,D
2	H,L,Q,E,D,N,Y,R	75	L,V,M,I,T
3	L,K,F,W	76	A,N,S,T,H,K,G,Q,E
4	T,S,A	77	H,N,E,Q,D
5	P,D,S,G,E,A,K,N	78	L,P
6	E,A,D,G,K,Q,P,V,S	79	D,N,E
7	E,A,G,D,N,Q,K	80	N,D,K,S
8	K,D,S	81	L,I
9	S,A,N,T,V,D,C,H,G,E	82	K
10	A,T,H,L,E,Q,S	83	G,A,N
11	V,G,I	84	T,A,H
12	T,S,N,A,L,D,R,I,V,K	85	F,Y
13	A,G,T,S,C,N	86	A,S
14	L,S,F,R	87	T,S,K,E,A,Q,N,H
15	W,F,G,S	88	L,R,P
16	G,S,A,D,R	89	S,T

Table 3.2 Continued

Beta Hemoglobin Amino Position	Acid	Beta Hemoglobin Amino Position	Acid
17	K,I,E,H	90	E,Q,K
18	V,K,I,H	91	L,Y,P
19	N,K,H,G,E,Q,A,D	92	H,Y
20	V,A,S,E,L,I,D,G,P	93	C,S
21	D,E,H,A,G,Q,N	94	D,V,N
22	E,D,K,A,N,Q,G	95	K,A,E,Q
23	V,D,A,T,C,I,L	96	L
24	G,L,R,V	97	H,E,R
25	G,K,A,R	98	V,M
26	E,Q,Y,K	99	D,N,H,Y
27	A,H,T	100	P
28	L,P	101	E,Q,A
29	G,A	102	N,K,T,D
30	R,S	103	F
31	L	104	R,K,N
32	L	105	L,R
33	V,L,I	106	L
34	V	107	G
35	Y,F	108	N,D
36	P	109	V,M,S,I,A
37	W,S	110	L,I,F,V
38	T	111	V,D,N,A,I
39	E,R,Q,S	112	C,L,I,S,V,T,H
40	R	113	V,C,E,A
41	F,Y	114	L
42	F,S	115	A,G,S
43	E,S,D,Q,T,A,R	116	H,D,N,R,I,E
44	S,H,T,A,E,Q	117	H,N,R
45	F,L	118	F,L,H
46	G,E	119	G,Q,F,S,K,D
47	D,A,N	120	K,D,N,S,H,E
48	L	121	E,D,Q,N,E,Q,K
49	S,G	122	F
50	T,S,N,D,K	123	T,D,N,S
51	P,A	124	P,I,R
52	D,N,S,H,G,K,E,A	125	P,A,Q,R,E,V,L,G,D,C
53	A	126	V,A,L,M,T,E,C
54	V,I	127	Q,E,L
55	M,L,C	128	A,V,H,S
56	G,N,S,D,A,H	129	A,S,D,Q,E,G,N
57	N,D,A	130	Y,F,H,W,L,D
58	P,A,R	131	Q,E,L
59	K,E,T,M,Q	132	K,A,Q,E
60	V	133	V,M,L,H
61	K,L,N,E,R	134	V,F
62	A,G	135	A,T,C,S,R
63	H,R,Y	136	G,A,D,V

Table 3.2 Continued

Beta Hemoglobin Amino Position	Acid	Beta Hemoglobin Amino Position	Acid
64	G	137	V
65	K,S,A,E	138	A,G,S
66	K,E	139	N,A,D,T,S,H
67	V,A,D,E	140	A
68	L,I	141	L,R
69	P,R,G,T,A,S,D,N,H,V,E,Q	142	A,S,G
70	A,T,S	143	H,S,K,R
71	F,L,I,S	144	K,R,A
72	S,C,G,A,D,K	145	Y,C,H
73	D,E,Q,N	146	H,D

The second structure tested relied on data compiled from three different data sources to address the frequency of any nucleotide being replaced by mutation to the other three. These estimate were derived from different collections of proteins. This structure results in three assessments of nucleotide mutation potential and amino acid possibility assessment. The transition probabilities are listed in Table 3.3.

Table 3.3
DNA Nucleotide Change Frequency

Transition	Dayhoff <u>frequency</u>	Zuckerkandl <u>frequency</u>	Fitch <u>frequency</u>
A=>C	.0244	.0610	.0113
A=>G	.0731	.0360	.0000
A=>T	.0488	.0690	.0602
C=>A	.0122	.0850	.0458
C=>G	.0854	.0980	.0989
C=>T	.2927	.1590	.0960
G=>A	.0610	.0380	.0277
G=>C	.0976	.0920	.0635
G=>T	.0732	.0890	.1995
T=>A	.0366	.0580	.1140
T=>C	.1098	.1210	.1237
T=>G	.0854	.0940	.1694

The third structure conformed to a first order Ising model in which the ordered nucleotide composition of the two nearest neighbors determined what the transition probability at any particular nucleotide site on the genome. Again, amino acid possibility assessment was made before any nucleotide change was allowed to occur. The transition probabilities are listed in Table 3.4.

Table 3.4
DNA Nearest Neighbor Nucleotide Change Frequency

<u>5'=>3'</u>	<u>A=>A</u>	<u>A=>C</u>	<u>A=>G</u>	<u>A=>T</u>	<u>C=>A</u>	<u>C=>C</u>	<u>C=>G</u>	<u>C=>T</u>
A_A	.9946	.00016	.00175	.00349	.00018	.9978	.00180	.00024
A_C	.9901	.00198	.00713	.00079	.00061	.9935	.00427	.00163
A_G	.9957	.00217	.00120	.00193	.00094	.9913	.00126	.00650
A_T	.9872	.00230	.00722	.00328	.00125	.9840	.00847	.00627
C_A	.9948	.00035	.00247	.00247	.00072	.9976	.00168	.00000
C_C	.9901	.00194	.00699	.00097	.00063	.9935	.00440	.00147
C_G	.9947	.00198	.00110	.00221	.00093	.9913	.00124	.00652
C_T	.9874	.00342	.00315	.00603	.00032	.9933	.00260	.00378
G_A	.9946	.00135	.00135	.00270	.00000	.9936	.00260	.00378
G_C	.9900	.00198	.00713	.00079	.00061	.9935	.00427	.00163
G_G	.9947	.00217	.00120	.00193	.00094	.9913	.00126	.00650
G_T	.9872	.00199	.00796	.00284	.00125	.9840	.00847	.00627
T_A	.9947	.00035	.00247	.00247	.00032	.9976	.00208	.00000
T_C	.9901	.00194	.00699	.00097	.00063	.9650	.00440	.00147
T_G	.9947	.00198	.00110	.00221	.00093	.9913	.00124	.00652
T_T	.9872	.00259	.00484	.00536	.00034	.9913	.00394	.00442
<u>5'=>3'</u>	<u>G=>A</u>	<u>G=>C</u>	<u>G=>G</u>	<u>G=>T</u>	<u>T=>A</u>	<u>T=>C</u>	<u>T=>G</u>	<u>T=>T</u>
A_A	.00151	.01389	.9840	.00060	.00311	.00206	.00033	.9945
A_C	.00692	.00053	.9867	.00585	.00101	.00730	.00579	.9859
A_G	.00185	.00238	.9926	.00317	.00152	.00532	.00196	.9912
A_T	.00176	.00821	.9871	.00293	.00137	.01164	.00479	.9822
C_A	.00295	.01263	.9840	.00042	.01333	.00000	.00263	.9840
C_C	.00640	.00049	.9867	.00640	.00053	.00904	.00393	.9865
C_G	.00167	.00215	.9926	.00358	.00157	.00876	.00207	.9876
C_T	.00165	.00660	.9871	.00465	.00072	.00417	.00251	.9926
G_A	.00205	.01231	.9840	.00164	.00467	.00050	.00033	.9945
G_C	.00692	.00053	.9867	.00585	.00101	.00730	.00579	.9859
G_G	.00185	.00228	.9926	.00317	.00152	.00532	.00196	.9912
G_T	.00183	.00879	.9871	.00228	.00123	.01043	.00614	.9822
T_A	.00215	.01354	.9840	.00031	.01333	.00000	.00267	.9840
T_C	.00640	.00049	.9867	.00650	.00101	.00504	.00746	.9865
T_G	.00167	.00215	.9926	.00358	.00231	.00707	.00303	.9876
T_T	.00227	.00765	.9871	.00298	.00072	.00417	.00251	.9926

When the possibility assessment was favorable, the transition is recorded and the new nucleotide will be substituted into the chain. When the possibility assessment did not reveal evidence for the particular amino acid appearing at that position of the hemoglobin chain, the nucleotide will be left without change and the failure to be able to change the nucleotide is recorded.

Many types of information can be recorded from the model. In addition to writing out checks to validate the input data, the model can be used to write out information to trace the point mutations that occurred sequentially from the start of the experiment. The information on transition rates for both amino acids and nucleic acids is output as well as the number of times that possibility assessment did not allow the transition. The number of times that the mutation of a nucleic acid or an amino acid back mutates to an earlier configuration at a location along the chain. Other recorded data includes the similarity of the resulting amino acid sequence with the starting protein chains of human, rabbit, and ancestral beta hemoglobin. The amino acid and nucleotide sequences entered at each location were also put into data files for storage. This information was stored into intermediate files to be used by the Statistical Package for Social Scientists (SPSS) for data analysis and computations.

Statistical tests were used to evaluate the results of the simulation. Linear regression and analysis of variance were used to help understand the relationships that were revealed during the experiment. Review and categorization of the results was used to examine relationships and to determine the applicability of different techniques and the implications of the results of this simulation.

CHAPTER IV

RESULTS

The simulation model used for this study was implemented and tested on the Cyber computer system used by the School of Engineering at the Air Force Institute of Technology. Model verification was conducted. Data collection consisted of 1275 runs of the model on the IBM 370/155 operated by the Human Engineering Division of the Air Force Aerospace Medical Research Laboratory. 425 runs of the model were made for each of the three initial hemoglobin DNA sequences to be examined. The number of iterations selected were randomly determined out of three groups. A stream of random digits between 0 and 9 were used to establish the number of iterations (probability assessment of a mutation at each position along the entire chain) to be used. The three groups were formed by sequentially multiplying the sum of the chosen random digit and 1 by 1, 10, and 1000. This resulted in a stream of iterations which varied between 1 and 1000. Random number streams were generated within the model for the probabilistic determination of a mutation occurring at any location.

Statistical testing of the random digit stream revealed no trends or bias. Verification included examining and

comparing the resultant nucleotide transition frequencies with the transition tables for each of the methods used in the model. There was no observable abnormality and the Chi Square test revealed no significant difference at the 0.05 level. The pattern of changes in amino acids produced in the model appeared to be consistent with the pattern of mutations observed by phenotypic studies of abnormal hemoglobin in vivo. The amino acid mutations produced by the model resulted in primary sequences indistinguishable from primary sequences observed in different species.

Table 4.1
Nucleotide Transition Anova

<u>Transition</u>	<u>Effect</u>	<u>Significance Level</u>
A=>C	Interations	<0.001
	Method	<0.001
A=>G	Interations	<0.001
	Method	<0.001
A=>T	Interations	<0.001
	Method	<0.001
C=>A	Interations	<0.001
	Method	<0.001
C=>G	Interations	<0.001
	Method	<0.001
C=>T	Interations	<0.001
	Method	<0.001
G=>A	Interations	<0.001
	Method	<0.001
	Hemoglobin	<0.01
G=>C	Interations	<0.001
	Method	<0.001
G=>T	Interations	<0.001
	Method	<0.001
T=>A	Interations	<0.001
	Method	<0.001
T=>C	Interations	<0.001
	Method	<0.001
T=>G	Interations	<0.001
	Method	<0.001

The results of the anova used to examine the changes in nucleotides observed in the model can be found in table 4.1.

The anova revealed that both the method being used to generate transition probabilities and the number of iterations of the model has a consistently significant effect on the transition of a nucleotide to one of the other three possible nucleotides. Hemoglobin starting chain was only found significant for the transition of guanine to adenine.

The results of the anova conducted to examine the transitions between amino acids can be found in table 4.2.

Table 4.2
Amino Acid Transition Anova

Transition	Effects (Significance Level)		
	<u>Iterations</u>	<u>Method</u>	<u>Hemoglobin</u>
G=>A	<0.001	<0.001	
G=>S	<0.001	<0.001	
G=>V	<0.001	<0.001	
G=>E	<0.001	<0.001	<0.001
G=>D	<0.001	<0.001	<0.05
G=>R	<0.001	<0.001	
G=>C	<0.001	<0.001	
G=>W	<0.001		
A=>G	<0.001	<0.001	
A=>S	<0.001	<0.001	
A=>V	<0.001	<0.001	
A=>K	<0.001	<0.001	
A=>T	<0.001	<0.001	
A=>E	<0.001	<0.001	<0.05
A=>P	<0.001	<0.001	<0.001
A=>D	<0.001	<0.001	<0.001
A=>R	<0.001	<0.001	<0.001
A=>M	<0.001	<0.001	<0.001
L=>S	<0.001	<0.001	
L=>V	<0.001	<0.001	
L=>P	<0.001	<0.001	<0.001
L=>I	<0.001	<0.001	
L=>R	<0.001	<0.001	
L=>Q	<0.001	<0.001	
L=>F	<0.001	<0.001	
L=>H	<0.001	<0.001	

Table 4.2 Continued

Transition	Effects (Significance Level)		
	<u>Interactions</u>	<u>Method</u>	<u>Hemoglobin</u>
L=>M	<0.001	<0.001	<0.001
L=>W	<0.001	<0.001	
S=>G	<0.001	<0.001	
S=>A	<0.001	<0.001	
S=>L	<0.001	<0.001	
S=>T	<0.001	<0.001	
S=>P	<0.001	<0.01	<0.001
S=>I	<0.001	<0.001	
S=>R	<0.001	<0.001	
S=>N	<0.001	<0.001	<0.001
S=>F	<0.001	<0.001	
S=>Y	<0.001	<0.001	
S=>C	<0.001	<0.001	
S=>W	<0.001	<0.001	
V=>G	<0.001	<0.001	
V=>A	<0.001	<0.001	
V=>L	<0.001	<0.001	
V=>E	<0.001	<0.001	<0.05
V=>D	<0.001	<0.001	
V=>I	<0.001	<0.001	<0.001
V=>F	<0.001	<0.001	
V=>M	<0.001	<0.01	
K=>A	<0.001	<0.001	
K=>T	<0.001	<0.001	
K=>E	<0.001	<0.001	
K=>I	<0.001	<0.001	<0.05
K=>R	<0.001	<0.001	
K=>N	<0.001	<0.001	
K=>Q	<0.001	<0.001	
K=>M	<0.001	<0.001	
T=>A	<0.001	<0.001	
T=>S	<0.001	<0.001	<0.001
T=>K	<0.001	<0.001	<0.001
T=>P	<0.001	<0.001	<0.05
T=>I	<0.001	<0.001	
T=>R	<0.001	<0.001	
T=>N	<0.001	<0.001	
F=>G	<0.001	<0.001	
F=>A	<0.001	<0.001	
F=>V	<0.001	<0.001	
F=>K	<0.001	<0.001	
F=>D	<0.001	<0.001	<0.001
F=>Q	<0.001	<0.001	
P=>A	<0.001	<0.001	<0.001
P=>L	<0.001	<0.001	
P=>S	<0.001	<0.001	<0.001
P=>T	<0.001	<0.001	
P=>R	<0.001	<0.001	

Table 4.2 Continued

Transition	Effects (Significance Level)		
	<u>Interactions</u>	<u>Method</u>	<u>Hemoglobin</u>
P=>Q	<0.001	<0.001	
P=>H	<0.001	<0.001	
D=>G	<0.001	<0.001	
D=>A	<0.001	<0.001	
D=>V	<0.001	<0.001	
D=>E	<0.001	<0.001	
D=>N	<0.001	<0.001	
D=>Y	<0.001	<0.001	
D=>H	<0.001	<0.001	
I=>L	<0.001	<0.001	
I=>S	<0.001	<0.001	<0.05
I=>V	<0.001	<0.001	
I=>K	<0.001	<0.001	<0.001
I=>T	<0.001	<0.001	
I=>N	<0.001	<0.001	
I=>F	<0.001	<0.001	
I=>M	<0.001	<0.01	
R=>G	<0.001	<0.001	<0.05
R=>A	<0.001	<0.001	
R=>L	<0.001	<0.001	
R=>S	<0.001	<0.001	
R=>K	<0.001	<0.001	<0.05
R=>T	<0.001	<0.001	
R=>P	<0.001	<0.001	
R=>I	<0.001	<0.01	
R=>Q	<0.001	<0.001	<0.01
R=>C	<0.001	<0.001	<0.05
R=>H	<0.001	<0.001	
R=>M	<0.001	<0.001	
R=>W	<0.001	<0.001	
N=>S	<0.001	<0.001	
N=>K	<0.001	<0.001	
N=>T	<0.001	<0.001	<0.05
N=>D	<0.001	<0.001	
N=>I	<0.001	<0.001	
N=>Y	<0.001	<0.05	
N=>H	<0.001	<0.001	
Q=>L	<0.001	<0.001	
Q=>K	<0.001	<0.001	
Q=>E	<0.001	<0.001	
Q=>P	<0.001	<0.001	<0.001
Q=>R	<0.001	<0.001	
Q=>H	<0.001	<0.001	
F=>L	<0.001	<0.001	
F=>S	<0.001	<0.001	
F=>V	<0.001	<0.001	
F=>I	<0.001	<0.001	
F=>Y	<0.001	<0.001	

Table 4.2 Continued

Transition	Effects (Significance Level)		
	<u>Iterations</u>	<u>Method</u>	<u>Hemoglobin</u>
F=>C	<0.001	<0.001	<0.05
Y=>S	<0.001	<0.001	
Y=>D	<0.001	<0.001	
Y=>N	<0.001	<0.001	
Y=>F	<0.001	<0.05	
Y=>C	<0.001	<0.001	<0.001
Y=>H	<0.001	<0.001	
C=>G	<0.001	<0.001	
C=>S	<0.001	<0.001	<0.001
C=>R	<0.001		
C=>F	<0.001	<0.001	
C=>Y	<0.001	<0.001	
H=>L	<0.001	<0.001	
H=>P	<0.001	<0.001	
H=>D	<0.001	<0.001	
H=>R	<0.001	<0.001	
H=>N	<0.001	<0.001	
H=>Q	<0.001	<0.001	
H=>Y	<0.001	<0.001	
M=>A	<0.001	<0.001	
M=>L	<0.001	<0.001	
M=>V	<0.001	<0.001	
M=>K	<0.001		<0.001
M=>I	<0.001		
M=>R	<0.001	<0.01	<0.05
W=>G		<0.001	
W=>L	<0.001	<0.001	
W=>S	<0.001	<0.001	
W=>R	<0.001	<0.001	

As is seen in examining the results of the nucleotide anova, both the number of iterations of the chain and the method of assessing the transition probabilities resulted in overwhelmingly significant effects. Hemoglobin was found to be a significant effect for several of the amino acid transitions.

Table 4.3 presents information on the frequency of the transits observed in the position and iteration averaged values of the nucleotide.

Table 4.3
Average Nucleotide Transition Frequency

	Random	Dayhoff	Zuckerkandl	Fitch	Nearest-Neighbor
Allowed Change	49.43	117.90	108.75	111.55	43.94
Repeated Change	6.70	38.45	36.27	38.03	6.34
Rejected Change	211.58	542.46	526.98	530.59	197.91

Table 4.4 contains the results from the regression of the value of the positioned averaged transition of nucleotides.

Table 4.4
Average Nucleotide Transition Regression

Intercept/ Slope	Random	Dayhoff	Zuckerkandl	Fitch	Nearest-Neighbor
Allowed Change	1.311	3.144	5.296	3.434	2.236
Repeated Change	.2254	.5375	.4846	.5064	.1953
Rejected Change	-1.515	-7.924	-6.721	-6.073	-1.454
Change	.0385	.2172	.2013	.2108	.0365
Rejected Change	-2.160	0.000	0.396	-2.531	-2.792
Change	1.160	2.944	2.858	2.894	1.089

In these tables, the variable that tracks allowed change is incremented every time that a nucleotide change produces a reasonable amino acid at the particular amino acid position coded for by the nucleotide. Repeated change refers to any nucleotide change for which the nucleotide previously had the same base at some earlier time during the run of the model. Rejected change is incremented whenever the proposed nucleotide transition would result in the coding of an amino acid residue that has not been previously

associated with any of the polymorphs, abnormal hemoglobin variants, or species with sequenced hemoglobin in Atlas of Protein Sequence and Structure at that particular location.

Table 4.5 presents information on the frequency of the transitions observed in the position and iteration averaged values of the amino acid residues.

Table 4.5
Average Amino Acid Transition Frequency

	Random	Dayhoff	Zuckerkandl	Fitch	Nearest-Neighbor
Accepted Change	42.38	105.40	97.97	100.45	41.12
Repeated Amino Acid	49.42	117.87	108.75	111.55	43.94

Table 4.6 contains the results from the regression of the value of the positioned averaged transition of amino acid residues.

Table 4.6
Average Amino Acid Transition Regression

Intercept/ Slope	Random	Dayhoff	Zuckerkandl	Fitch	Nearest-Neighbor
Accepted Change	1.837	1.972	4.527	2.772	2.065
Repeated Amino Acid	.2177	.5553	.5017	.5244	.2097
	1.311	3.144	5.256	3.434	2.236
	.2254	.5375	.4846	.5064	.1953

In the two preceeding tables, accepted changes are the result of nucleotide changes that were compatible with coding for accepted amino acids at the appropriate position. The repeated amino acid line of the tables presents that subset of the accepted amino acid changes that result in an

amino acid that was previously found during a particular simulation run at the same position of the protein chain.

Table 4.7 contains a listing of the regression of transition frequency as a function of interaction listed by nucleotide position.

Table 4.7
Nucleotide Transition Regression

Intercept/ Slope Position	Allowed Change None Seen	Repeated Change No Repeats	Rejected Change None Rejected
1			
2	0.0240	-0.0160	0.0679
	0.0015	0.0004	0.0056
3	-0.0291	-0.0287	0.1318
	0.0016	0.0007	0.0055
4	-0.0094	-0.0033	-0.0235
	0.0001	0.0000	0.0025
5	-0.0410	-0.0259	0.1093
	0.0015	0.0006	0.0058
6	0.0438	-0.0035	-0.2064
	0.0018	0.0002	0.0054
7	None Seen	No Repeats	0.1686
			0.0022
8	-0.0214	-0.0014	0.0231
	0.0008	0.0000	0.0059
9	-0.0260	-0.0125	0.0624
	0.0004	0.0002	0.0060
10	-0.0033	-0.0004	0.0386
	0.0000	0.0000	0.0034
11	0.0463	-0.0016	0.0294
	0.0009	0.0000	0.0081
12	0.0039	0.0016	-0.0365
	0.0002	0.0001	0.0076
13	-0.0000	No Repeats	-0.0456
	0.0000		0.0015
14	0.0608	-0.0176	-0.1250
	0.0011	0.0005	0.0066
15	0.0999	0.0016	-0.0358
	0.0012	0.0001	0.0056
16	0.0885	-0.0000	-0.0540
	0.0008	0.0000	0.0028
17	-0.0087	-0.0074	-0.0406
	0.0004	0.0002	0.0050

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
18	0.0653 0.0005	0.0018 0.0001	-0.1654 0.0068
19	-0.0018 0.0010	-0.0100 0.0005	-0.0092 0.0011
20	0.1507 0.0011	-0.0000 0.0000	-0.0907 0.0068
21	-0.0056 0.0018	-0.0084 0.0010	0.1703 0.0066
22	-0.1228 0.0030	-0.0770 0.0015	0.0410 0.0018
23	-0.0120 0.0034	-0.0818 0.0017	0.1544 0.0076
24	-0.0360 0.0008	-0.0111 0.0003	-0.0565 0.0098
25	-0.0072 0.0001	-0.0012 0.0000	-0.0216 0.0008
26	0.0145 0.0014	-0.0117 0.0006	-0.0622 0.0046
27	-0.0066 0.0009	-0.0056 0.0002	0.0551 0.0041
28	None Seen	No Repeats	-0.0043 0.0022
29	0.0470 0.0010	-0.0080 0.0002	-0.1331 0.0062
30	0.0580 0.0004	No Repeats	-0.1106 0.0064
31	None Seen	No Repeats	-0.0449 0.0022
32	0.0382 0.0006	0.0004 0.0000	0.0196 0.0062
33	-0.0041 0.0006	-0.0087 0.0003	-0.0257 0.0065
34	None Seen	No Repeats	-0.0902 0.0021
35	None Seen	No Repeats	0.0538 0.0056
36	None Seen	No Repeats	-0.1616 0.0077
37	None Seen	No Repeats	-0.0440 0.0009
38	0.0010 0.0001	-0.0006 0.0000	-0.1044 0.0066
39	-0.0454 0.0029	-0.0504 0.0013	0.0850 0.0045
40	None Seen	No Repeats	-0.0331 0.0007
41	-0.0200 0.0007	-0.0086 0.0002	-0.0003 0.0045

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
42	-0.0136 0.0025	-0.0366 0.0012	-0.0745 0.0054
43	None Seen	No Repeats	-0.0008 0.0059
44	0.0485 0.0018	-0.0188 0.0007	0.1758 0.0067
45	-0.0143 0.0009	-0.0099 0.0003	0.0086 0.0062
46	-0.0230 0.0008	-0.0179 0.0004	0.0039 0.0013
47	0.0643 0.0021	-0.0200 0.0010	0.0545 0.0069
48	-0.0003 0.0014	-0.0084 0.0008	0.1020 0.0052
49	None Seen	No Repeats	-0.0427 0.0047
50	-0.0459 0.0014	-0.0284 0.0006	0.1272 0.0062
51	0.0556 0.0011	No Repeats	-0.1116 0.0058
52	-0.0207 0.0007	-0.0015 0.0002	-0.0292 0.0006
53	-0.0170 0.0020	-0.0166 0.0003	-0.0175 0.0059
54	-0.0414 0.0011	-0.0234 0.0005	-0.0246 0.0080
55	0.0093 0.0002	- 0.0008 0.0000	-0.0321 0.0026
56	-0.0248 0.0015	-0.0234 0.0008	-0.1041 0.0060
57	0.0978 0.0030	-0.0309 0.0009	-0.0850 0.0065
58	0.0073 0.0001	-0.0000 0.0000	-0.0464 0.0021
59	0.0567 0.0006	-0.0062 0.0001	0.0215 0.0041
60	-0.0192 0.0018	-0.0311 0.0008	0.0449 0.0058
61	None Seen	No Repeats	0.0108 0.0019
62	0.0709 0.0031	-0.0555 0.0013	-0.0782 0.0054
63	-0.0170 0.0016	-0.0309 0.0008	-0.1159 0.0073
64	None Seen	No Repeats	-0.0460 0.0032
65	-0.0080 0.0002	-0.0037 0.0001	-0.1562 0.0093

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change No Repeats	Rejected Change
66	-0.0012 0.0000		-0.0388 0.0066
67	-0.0048 0.0009	-0.0020 0.0003	-0.0175 0.0007
68	-0.0118 0.0007	-0.0123 0.0002	0.0030 0.0034
69	0.0984 0.0071	-0.1056 0.0043	-0.0030 0.0023
70	-0.0008 0.0004	0.0036 0.0001	-0.0262 0.0014
71	0.1193 0.0019	0.0130 0.0008	0.1506 0.0057
72	-0.0215 0.0014	-0.0206 0.0008	0.0155 0.0071
73	-0.0243 0.0009	-0.0087 0.0002	0.0186 0.0030
74	0.0513 0.0030	-0.0567 0.0012	0.0511 0.0055
75	-0.0412 0.0024	-0.0480 0.0009	0.0079 0.0045
76	-0.0247 0.0015	-0.0045 0.0004	0.0776 0.0030
77	0.0231 0.0030	-0.0635 0.0015	0.0330 0.0057
78	-0.0161 0.0040	-0.0832 0.0022	-0.1682 0.0040
79	-0.0025 0.0000	-0.0012 0.0000	0.0136 0.0014
80	-0.0425 0.0037	-0.0814 0.0019	0.0052 0.0043
81	-0.0317 0.0017	-0.0180 0.0007	0.0401 0.0066
82	-0.0375 0.0011	-0.0117 0.0002	-0.0416 0.0008
83	0.0044 0.0015	-0.0135 0.0002	-0.0184 0.0065
84	-0.0378 0.0010	-0.0258 0.0004	0.0981 0.0071
85	-0.0293 0.0019	-0.0279 0.0009	-0.0482 0.0023
86	0.1172 0.0022	-0.0174 0.0010	-0.1215 0.0068
87	-0.0129 0.0025	-0.0441 0.0011	-0.0985 0.0068
88	None Seen	No Repeats	0.1238 0.0023
89	0.0008 0.0020	-0.0185 0.0004	-0.0172 0.0078

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
90	0.0103 0.0022	-0.0301 0.0010	0.1865 0.0045
91	-0.0019 0.0000	-0.0006 0.0000	0.0537 0.0011
92	-0.0115 0.0009	-0.0161 0.0004	0.0829 0.0036
93	-0.0110 0.0002	-0.0129 0.0002	0.1076 0.0061
94	None Seen	No Repeats	-0.0673 0.0021
95	-0.0244 0.0017	-0.0132 0.0003	0.0683 0.0054
96	-0.0507 0.0011	-0.0299 0.0005	-0.0461 0.0063
97	-0.0031 0.0001	-0.0012 0.0000	-0.0704 0.0017
98	-0.0032 0.0013	-0.0161 0.0005	-0.0433 0.0045
99	-0.0260 0.0010	-0.0134 0.0005	-0.0892 0.0061
100	None Seen	No Repeats	-0.0051 0.0002
101	0.0060 0.0020	-0.0186 0.0006	-0.1118 0.0046
102	0.0193 0.0014	-0.0160 0.0004	0.0385 0.0078
103	None Seen	No Repeats	0.0145 0.0048
104	0.0115 0.0002	0.0066 0.0001	-0.0791 0.0069
105	0.0018 0.0001	-0.0000 0.0000	0.0456 0.0050
106	-0.0428 0.0015	-0.0257 0.0006	-0.0138 0.0004
107	0.0480 0.0020	-0.0164 0.0008	0.0581 0.0041
108	0.1660 0.0043	-0.0615 0.0018	0.0822 0.0056
109	None Seen	No Repeats	-0.0484 0.0039
110	-0.0518 0.0015	-0.0382 0.0008	0.0015 0.0061
111	0.0393 0.0013	-0.0025 0.0000	-0.0255 0.0046
112	0.0048 0.0001	No Repeats	-0.0139 0.0015
113	0.0685 0.0017	0.0114 0.0003	0.0073 0.0044

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
114	0.0153	-0.00562	0.0671
	0.0004	0.0003	0.0104
115	None Seen	No Repeats	0.1773
			0.0018
116	0.1958	0.0077	0.0145
	0.0033	0.0015	0.0044
117	-0.0411	-0.0272	0.0012
	0.0012	0.0007	0.0077
118	0.0024	No Repeats	-0.0328
	0.0000		0.0027
119	0.0034	-0.0031	0.0030
	0.0006	0.0001	0.0095
120	0.0483	-0.0113	0.0680
	0.0013	0.0007	0.0052
121	-0.0025	-0.0012	-0.0068
	0.0000	0.0000	0.0031
122	-0.0298	-0.0171	-0.0125
	0.0008	0.0004	0.0036
123	0.0313	-0.0221	-0.0510
	0.0019	0.0009	0.0057
124	None Seen	No Repeats	0.0522
			0.0025
125	None Seen	No Repeats	0.0283
			0.0037
126	0.0588	-0.0720	0.1128
	0.0041	0.0020	0.0038
127	0.0136	-0.0017	0.0274
	0.0003	0.0000	0.0023
128	0.0323	-0.0015	-0.0116
	0.0016	0.0002	0.0063
129	-0.0127	-0.0066	-0.0463
	0.0006	0.0002	0.0062
130	None Seen	No Repeats	-0.0294
			0.0043
131	-0.0121	No Repeats	0.0221
	0.0012		0.0058
132	-0.0031	No Repeats	-0.0117
	0.0001		0.0039
133	None Seen	No Repeats	0.0003
			0.0040
134	None Seen	No Repeats	0.0621
			0.0065
135	None Seen	No Repeats	0.0969
			0.0058
136	-0.0979	-0.0439	0.0279
	0.0030	0.0012	0.0010
137	0.0893	0.0101	-0.1334
	0.0015	0.0005	0.0069

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
138	-0.0012 0.0000	No Repeats	-0.0873 0.0092
139	None Seen	No Repeats	-0.0189 0.0033
140	-0.0158 0.0009	-0.0131 0.0005	-0.1156 0.0086
141	0.0316 0.0007	-0.0031 0.0001	-0.0570 0.0069
142	-0.0161 0.0004	No Repeats	0.0626 0.0027
143	-0.0155 0.0004	-0.0006 0.0000	0.1275 0.0058
144	-0.0050 0.0003	No Repeats	0.0674 0.0064
145	None Seen	No Repeats	-0.0049 0.0001
146	0.0024 0.0000	-0.0000 0.0000	-0.1568 0.0083
147	0.0146 0.0001	-0.0000 0.0000	-0.0180 0.0069
148	None Seen	No Repeats	0.0566 0.0015
149	0.0000 0.0000	No Repeats	-0.1345 0.0084
150	None Seen	No Repeats	-0.1076 0.0064
151	None Seen	No Repeats	-0.0176 0.0010
152	0.0123 0.0003	-0.0008 0.0001	0.0670 0.0051
153	0.0403 0.0013	-0.0188 0.0003	0.0262 0.0058
154	-0.1360 0.0042	-0.1065 0.0020	0.0043 0.0010
155	0.0227 0.0004	-0.0039 0.0001	-0.0897 0.0080
156	0.0131 0.0003	-0.0023 0.0001	-0.0663 0.0067
157	-0.0483 0.0018	-0.0279 0.0008	0.1042 0.0005
158	-0.0027 0.0001	-0.0017 0.0000	-0.0748 0.0079
159	0.0774 0.0025	-0.0260 0.0016	0.1247 0.0049
160	0.0030 0.0001	-0.0000 0.0000	0.0218 0.0014
161	0.0267 0.0001	No Repeats	0.0038 0.0064

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
162	None Seen	No Repeats	-0.1115 0.0080
163	None Seen	No Repeats	0.1657 0.0081
164	None Seen	No Repeats	0.0346 0.0050
165	None Seen	No Repeats	0.0589 0.0082
166	-0.0004 0.0000	No Repeats	-0.0295 0.0023
167	0.0034 0.0029	-0.0623 0.0017	0.0002 0.0042
168	0.0102 0.0009	-0.0217 0.0003	-0.0905 0.0072
169	None Seen	No Repeats	-0.0571 0.0047
170	None Seen	No Repeats	0.0160 0.0080
171	None Seen	No Repeats	-0.0512 0.0091
172	None Seen	No Repeats	-0.0643 0.0020
173	-0.0638 0.0022	-0.0636 0.0016	-0.0292 0.0075
174	0.0895 0.0010	No Repeats	-0.0263 0.0072
175	0.1249 0.0008	No Repeats	-0.1250 0.0042
176	0.0502 0.0009	-0.0190 0.0003	-0.1460 0.0076
177	None Seen	No Repeats	-0.0490 0.0078
178	-0.0098 0.0001	-0.0061 0.0001	0.0098 0.0025
179	-0.0241 0.0006	-0.0037 0.0001	-0.0352 0.0061
180	0.0324 0.0007	No Repeats	0.0907 0.0078
181	None Seen	No Repeats	-0.0440 0.0028
182	0.0275 0.0010	-0.0019 0.0000	0.0128 0.0071
183	-0.0119 0.0014	-0.0050 0.0005	0.0982 0.0061
184	-0.0883 0.0027	-0.0407 0.0009	0.0233 0.0014
185	0.0773 0.0012	-0.0019 0.0000	-0.1211 0.0069

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
186	-0.0589 0.0023	-0.0611 0.0015	-0.0389 0.0051
187	None Seen	No Repeats	0.0635 0.0027
188	-0.0569 0.0015	-0.0272 0.0007	0.1970 0.0068
189	0.0085 0.0012	-0.0000 0.0000	-0.1098 0.0086
190	None Seen	No Repeats	-0.0767 0.0017
191	0.0103 0.0021	-0.0487 0.0010	0.0366 0.0079
192	0.1047 0.0010	-0.0025 0.0001	-0.0567 0.0076
193	None Seen	No Repeats	-0.0023 0.0042
194	0.0596 0.0020	0.0001 0.0010	-0.0832 0.0064
195	0.1308 0.0028	0.0005 0.0015	0.0830 0.0043
196	None Seen	No Repeats	-0.0677 0.0031
197	0.0279 0.0007	No Repeats	-0.0426 0.0062
198	0.0033 0.0000	No Repeats	0.0568 0.0073
199	None Seen	No Repeats	0.0939 0.0016
200	0.0695 0.0010	-0.0160 0.0003	0.1742 0.0051
201	-0.0487 0.0027	-0.0597 0.0012	-0.0813 0.0065
202	None Seen	No Repeats	0.0721 0.0021
203	None Seen	No Repeats	0.1042 0.0060
204	None Seen	No Repeats	0.0227 0.0063
205	None Seen	No Repeats	-0.0614 0.0012
206	-0.0604 0.0012	-0.0418 0.0007	-0.1538 0.0056
207	0.0591 0.0010	0.0038 0.0001	-0.0358 0.0057
208	-0.0050 0.0001	-0.0000 0.0000	0.1785 0.0016
209	-0.0353 0.0013	-0.0025 0.0000	-0.1131 0.0065

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
210	-0.0037 0.0001	-0.0000 0.0000	0.1737 0.0105
211	0.0587 0.0008	No Repeats	-0.0441 0.0026
212	0.0036 0.0020	-0.0033 0.0005	0.1166 0.0039
213	0.0227 0.0005	-0.0055 0.0001	0.0342 0.0054
214	None Seen	No Repeats	-0.0617 0.0029
215	-0.0044 0.0003	-0.0041 0.0001	-0.0722 0.0079
216	0.0032 0.0001	0.0006 0.0000	-0.0016 0.0092
217	0.0673 0.0004	No Repeats	-0.0636 0.0024
218	0.0352 0.0023	-0.0260 0.0011	0.0754 0.0050
219	None Seen	No Repeats	-0.0539 0.0075
220	-0.0006 0.0000	No Repeats	0.0300 0.0010
221	0.0853 0.0013	-0.0021 0.0001	-0.0740 0.0064
222	None Seen	No Repeats	0.0138 0.0089
223	-0.0218 0.0004	-0.0043 0.0001	0.0336 0.0005
224	-0.0173 0.0010	-0.0012 0.0000	0.0278 0.0052
225	-0.0203 0.0004	-0.0043 0.0001	0.1336 0.0061
226	-0.0385 0.0014	-0.0183 0.0004	-0.0539 0.0019
227	0.0575 0.0020	-0.0188 0.0007	-0.0251 0.0051
228	0.0086 0.0017	-0.0319 0.0009	0.0011 0.0053
229	0.1118 0.0008	No Repeats	-0.0748 0.0024
230	-0.0426 0.0021	No Repeats	-0.0756 0.0058
231	-0.0610 0.0010	-0.0240 0.0004	0.0754 0.0053
232	None Seen	No Repeats	-0.0244 0.0005
233	-0.0052 0.0012	-0.0272 0.0007	0.0196 0.0054

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
234	0.0018 0.0001	-0.0000 0.0000	0.1055 0.0074
235	0.1115 0.0008	No Repeats	-0.0544 0.0020
236	0.0212 0.0021	-0.0388 0.0008	-0.0008 0.0057
237	-0.0128 0.0015	-0.0138 0.0006	-0.0029 0.0068
238	None Seen	No Repeats	-0.0862 0.0036
239	0.0503 0.0003	No Repeats	0.0482 0.0059
240	0.0567 0.0009	No Repeats	-0.0165 0.0089
241	None Seen	No Repeats	0.0661 0.0012
242	-0.0192 0.0005	-0.0092 0.0002	-0.0165 0.0063
243	-0.0069 0.0028	-0.0366 0.0015	0.0291 0.0060
244	0.1090 0.0012	-0.0106 0.0002	-0.0427 0.0043
245	-0.0006 0.0001	-0.0031 0.0001	0.0361 0.0077
246	0.0151 0.0021	-0.0364 0.0011	0.0180 0.0070
247	None Seen	No Repeats	-0.0540 0.0024
248	0.0278 0.0023	-0.0532 0.0014	-0.0539 0.0061
249	0.1042 0.0016	-0.0125 0.0009	0.0667 0.0068
250	0.0433 0.0009	-0.0056 0.0002	0.0712 0.0017
251	-0.0128 0.0007	-0.0062 0.0003	0.0619 0.0085
252	0.0044 0.0066	-0.1361 0.0043	0.1065 0.0047
253	None Seen	No Repeats	-0.0007 0.0021
254	0.0263 0.0008	No Repeats	0.0280 0.0064
255	-0.0025 0.0000	No Repeats	0.0929 0.0055
256	-0.0590 0.0024	-0.0272 0.0007	0.0659 0.0014
257	0.0016 0.0033	-0.0710 0.0021	-0.0398 0.0078

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
258	0.0244 0.0003	-0.0030 0.0002	0.1344 0.0077
259	0.0031 0.0012	-0.0028 0.0004	-0.0296 0.0011
260	0.0635 0.0020	-0.0269 0.0007	-0.0279 0.0050
261	0.0181 0.0014	-0.0016 0.0008	0.0407 0.0055
262	0.0100 0.0002	No Repeats	0.0595 0.0014
263	-0.0146 0.0007	-0.0044 0.0002	0.0470 0.0049
264	-0.0138 0.0006	-0.0037 0.0001	0.1057 0.0053
265	None Seen	No Repeats	-0.0393 0.0018
266	-0.0394 0.0016	-0.0296 0.0007	0.0148 0.0074
267	0.0940 0.0011	No Repeats	-0.0816 0.0060
268	-0.0196 0.0008	-0.0075 0.0003	0.0810 0.0023
269	0.0746 0.0019	-0.0157 0.0006	0.0216 0.0083
270	-0.0587 0.0024	-0.0326 0.0009	0.0085 0.0037
271	0.0018 0.0001	-0.0000 0.0000	0.0003 0.0016
272	-0.0365 0.0010	-0.0173 0.0004	-0.0072 0.0061
273	-0.0032 0.0002	0.0018 0.0000	0.1048 0.0067
274	-0.0055 0.0001	-0.0025 0.0000	0.1639 0.0062
275	-0.0684 0.0016	-0.0382 0.0008	-0.0214 0.0067
276	0.0464 0.0028	-0.0467 0.0009	-0.1743 0.0064
277	-0.0031 0.0001	No Repeats	0.0102 0.0015
278	0.0307 0.0009	-0.0049 0.0001	-0.1415 0.0075
279	0.0174 0.0007	-0.0031 0.0001	0.0851 0.0064
280	0.0052 0.0004	-0.0032 0.0003	-0.0254 0.0043
281	0.0054 0.0002	-0.0013 0.0001	-0.0052 0.0073

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
282	0.0263 0.0003	-0.0001 0.0001	0.0268 0.0086
283	-0.0917 0.0027	-0.0519 0.0013	-0.0296 0.0026
284	-0.0096 0.0004	-0.0111 0.0002	-0.0727 0.0078
285	0.0521 0.0011	-0.0019 0.0000	0.0460 0.0062
286	-0.0333 0.0006	-0.0142 0.0003	-0.0176 0.0008
287	0.0239 0.0006	No Repeats	0.0028 0.0050
288	0.0012 0.0006	-0.0002 0.0003	0.0568 0.0068
289	0.0029 0.0002		0.0349 0.0015
290	0.0871 0.0012	-0.0063 0.0006	-0.0435 0.0072
291	0.0277 0.0021	-0.0204 0.0005	-0.1257 0.0064
292	None Seen	No Repeats	None Rejected
293	-0.0031 0.0001	No Repeats	-0.0365 0.0062
294	None Seen	No Repeats	-0.0480 0.0077
295	-0.0694 0.0017	-0.0306 0.0006	-0.0664 0.0025
296	0.0285 0.0009	-0.0032 0.0003	0.0524 0.0059
297	0.0152 0.0018	-0.0111 0.0003	-0.0036 0.0051
298	-0.0752 0.0018	-0.0253 0.0005	0.0278 0.0014
299	0.0287 0.0038	-0.0833 0.0028	0.0422 0.0071
300	-0.0024 0.0000	No Repeats	-0.0675 0.0097
301	0.0152 0.0001	0.0073 0.0000	-0.0368 0.0036
302	-0.0028 0.0026	-0.0418 0.0008	-0.0783 0.0047
303	0.0338 0.0002	No Repeats	0.1787 0.0068
304	None Seen	No Repeats	0.1483 0.0037
305	-0.0605 0.0028	-0.0408 0.0012	0.2168 0.0051

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
306	0.0735 0.0011	-0.0012 0.0000	-0.0665 0.0072
307	None Seen	No Repeats	-0.0701 0.0033
308	None Seen	No Repeats	0.0412 0.0045
309	None Seen	No Repeats	-0.0844 0.0050
310	None Seen	No Repeats	-0.0115 0.0034
311	0.0236 0.0005	-0.0007 0.0001	0.1183 0.0076
312	0.0518 0.0009	-0.0058 0.0001	0.0973 0.0059
313	None Seen	No Repeats	-0.0492 0.0021
314	-0.0051 0.0006	No Repeats	-0.1122 0.0056
315	-0.0265 0.0005	-0.0129 0.0002	-0.0200 0.0049
316	-0.0051 0.0002	No Repeats	-0.0074 0.0017
317	-0.0140 0.0009	-0.0049 0.0001	0.0091 0.0044
318	-0.0087 0.0003	-0.0019 0.0000	-0.0980 0.0046
319	None Seen	No Repeats	-0.0302 0.0014
320	-0.0631 0.0020	-0.0482 0.0012	0.1247 0.0090
321	0.0503 0.0016	No Repeats	0.0285 0.0060
322	-0.0061 0.0001	-0.0025 0.0000	0.0015 0.0053
323	-0.0392 0.0012	-0.0222 0.0004	0.0051 0.0093
324	0.0892 0.0027	-0.0199 0.0006	-0.0600 0.0071
325	None Seen	No Repeats	-0.0241 0.0013
326	0.0308 0.0000	0.0024 -0.0000	0.0139 0.0061
327	0.0440 0.0013	0.0018 0.0001	-0.0036 0.0048
328	0.0158 0.0001	0.0037 0.0000	0.1169 0.0035
329	0.0060 0.0008	-0.0006 0.0000	0.0770 0.0058

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
330	-0.0332 0.0006	-0.0190 0.0003	-0.0158 0.0044
331	-0.0004 0.0000	No Repeats	-0.0160 0.0002
332	-0.0047 0.0001	-0.0008 0.0000	0.0086 0.0051
333	-0.0039 0.0001	-0.0010 0.0000	-0.1022 0.0088
334	None Seen	No Repeats	0.0168 0.0026
335	-0.0013 0.0001	-0.0025 0.0001	-0.0469 0.0054
336	0.0610 0.0008	0.0024 0.0000	-0.0624 0.0070
337	None Seen	No Repeats	-0.0726 0.0015
338	0.0040 0.0000	No Repeats	-0.1484 0.0048
339	0.0285 0.0012	No Repeats	-0.0120 0.0065
340	-0.0062 0.0001	-0.0025 0.0001	0.0007 0.0007
341	-0.0320 0.0007	-0.0135 0.0002	0.0629 0.0043
342	0.1032 0.0011	No Repeats	-0.0902 0.0069
343	None Seen	No Repeats	-0.0382 0.0012
344	0.0295 0.0004	0.0073 0.0000	0.0270 0.0058
345	0.0053 0.0000	0.0012 0.0000	-0.0122 0.0065
346	None Seen	No Repeats	-0.0716 0.0022
347	None Seen	No Repeats	-0.1222 0.0070
348	0.0070 0.0000	No Repeats	-0.0690 0.0075
349	-0.0102 0.0001	-0.0023 0.0000	0.1705 0.0035
350	0.0407 0.0011	No Repeats	0.0660 0.0050
351	-0.0078 0.0001	-0.0025 0.0000	0.0692 0.0076
352	None Seen	No Repeats	-0.0065 0.0015
353	0.0207 0.0005	-0.0037 0.0000	-0.0244 0.0062

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
354	0.0140 0.0010	-0.0074 0.0001	-0.0329 0.0078
355	None Seen	No Repeats	-0.0504 0.0018
356	-0.0327 0.0008	-0.0210 0.0004	-0.0633 0.0077
357	0.0201 0.0005	No Repeats	-0.0385 0.0065
358	None Seen	No Repeats	-0.0317 0.0041
359	0.0027 0.0005	-0.0012 0.0000	0.0626 0.0063
360	None Seen	No Repeats	-0.0661 0.0067
361	None Seen	No Repeats	0.0702 0.0017
362	0.0669 0.0014	-0.0049 0.0001	0.0364 0.0080
363	-0.0593 0.0015	-0.0334 0.0009	-0.0735 0.0061
364	-0.0393 0.0006	-0.0141 0.0002	0.0122 0.0022
365	-0.0681 0.0014	-0.0412 0.0007	0.1755 0.0047
366	0.0102 0.0006	No Repeats	-0.0432 0.0081
367	-0.0572 0.0020	-0.0222 0.0006	0.0192 0.0018
368	0.0600 0.0024	-0.0098 0.0005	-0.0194 0.0040
369	0.0006 0.0000	No Repeats	-0.0320 0.0082
370	None Seen	No Repeats	-0.0357 0.0012
371	0.0256 0.0017	-0.0317 0.0008	0.0276 0.0059
372	0.1330 0.0020	-0.0068 0.0004	-0.0480 0.0068
373	-0.0046 0.0001	-0.0045 0.0001	0.0115 0.0016
374	0.0559 0.0019	-0.0218 0.0007	-0.1633 0.0047
375	0.0299 0.0004	-0.0010 0.0000	0.0766 0.0065
376	0.0000 0.0000	No Repeats	-0.0319 0.0019
377	-0.0047 0.0008	0.0012 0.0001	-0.0238 0.0046

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
378	0.0054	0.0048	0.0630
	0.0002	0.0001	0.0074
379	0.0446	No Repeats	-0.0548
	0.0008		0.0020
380	0.0073	-0.0426	-0.0435
	0.0019	0.0010	0.0066
381	-0.0236	-0.0265	0.0968
	0.0012	0.0006	0.0063
382	-0.0037	No Repeats	-0.0182
	0.0001		0.0030
383	0.0069	-0.0012	0.0723
	0.0001	0.0000	0.0079
384	0.0839	-0.0783	0.0225
	0.0034	0.0017	0.0053
385	-0.0066	-0.0012	-0.0946
	0.0001	0.0000	0.0019
386	0.0582	-0.0149	-0.0679
	0.0024	0.0004	0.0045
387	-0.0417	-0.0348	0.0773
	0.0014	0.0008	0.0077
388	None Seen	No Repeats	0.0324
			0.0050
389	-0.0061	No Repeats	-0.1540
	0.0001		0.0078
390	None Seen	No Repeats	0.0833
			0.0075
391	None Seen	No Repeats	-0.1154
			0.0041
392	-0.0245	-0.0246	0.1098
	0.0016	0.0008	0.0077
393	0.0738	-0.0006	0.1109
	0.0013	0.0000	0.0068
394	-0.0166	-0.0151	0.0813
	0.0004	0.0002	0.0068
395	-0.0133	-0.0078	-0.1425
	0.0010	0.0001	0.0086
396	-0.0448	-0.0279	-0.0011
	0.0011	0.0005	0.0061
397	None Seen	No Repeats	-0.0155
			0.0018
398	0.0556	-0.0006	-0.0729
	0.0009	0.0001	0.0058
399	0.0006	-0.0000	-0.1685
	0.0001	0.0000	0.0069
400	None Seen	No Repeats	-0.0020
			0.0003
401	None Seen	No Repeats	-0.0000
			0.0056

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
402	None Seen	No Repeats	-0.2218 0.0102
403	-0.0093 0.0002	-0.0043 0.0001	-0.0291 0.0007
404	-0.0219 0.0007	-0.0068 0.0001	0.0720 0.0065
405	0.0561 0.0011	-0.0012 0.0000	0.0662 0.0044
406	None Seen	No Repeats	-0.0081 0.0005
407	0.0619 0.0007	0.0036 0.0000	-0.1284 0.0058
408	-0.0309 0.0010	-0.0124 0.0004	0.0727 0.0071
409	-0.0500 0.0011	-0.0117 0.0002	-0.0215 0.0006
410	-0.0215 0.0011	-0.0735 0.0002	-0.0077 0.0006
411	-0.0946 0.0030	-0.0704 0.0017	-0.1072 0.0052
412	-0.0364 0.0008	-0.0148 0.0004	0.0179 0.0088
413	-0.0569 0.0021	-0.0250 0.0008	-0.0182 0.0006
414	0.0473 0.0033	-0.0557 0.0017	-0.0364 0.0077
415	-0.0221 0.0003	-0.0135 0.0002	-0.0686 0.0034
416	0.0290 0.0000	0.0024 0.0000	-0.0758 0.0073
417	0.0952 0.0013	-0.0000 0.0001	0.0352 0.0058
418	-0.0184 0.0003	-0.0074 0.0001	-0.0277 0.0022
419	0.0102 0.0018	-0.0222 0.0005	-0.0072 0.0059
420	-0.0181 0.0015	-0.0307 0.0005	-0.1104 0.0078
421	None Seen	No Repeats	-0.0450 0.0029
422	0.0582 0.0007	-0.0037 0.0001	0.0813 0.0069
423	0.0048 0.0001	No Repeats	0.0086 0.0087
424	None Seen	No Repeats	-0.0207 0.0010
425	-0.0118 0.0004	-0.0089 0.0002	-0.0347 0.0076

Table 4.7 Continued

Intercept/ Slope Position	Allowed Change	Repeated Change	Rejected Change
426	None Seen	No Repeats	-0.0663 0.0067
427	0.0180 0.0001	No Repeats	-0.1183 0.0039
428	-0.0213 0.0003	-0.0123 0.0002	0.0793 0.0072
429	0.0042 0.0001	No Repeats	-0.0209 0.0055
430	None Seen	No Repeats	-0.0503 0.0034
431	-0.0312 0.0024	-0.0472 0.0012	0.0322 0.0056
432	0.1037 0.0006	No Repeats	0.1043 0.0073
433	None Seen	No Repeats	0.0396 0.0040
434	0.0256 0.0014	-0.0154 0.0003	-0.0015 0.0063
435	0.0067 0.0013	-0.0166 0.0002	-0.0364 0.0044
436	None Seen	No Repeats	0.0054 0.0027
437	-0.0265 0.0017	-0.0315 0.0007	-0.1455 0.0071
438	-0.0147 0.0002	-0.0098 0.0001	0.0123 0.0081

Table 4.8 contains the regression analysis by position for the transition of amino acid residues as a function of iteration.

Table 4.8
Amino Acid Transition Regression

Intercept/ Slope Amino Acid	Ancestral Change	Accepted Human Change	Rabbit Change	Reverse Change
1	0.0425 0.0009	0.0425 0.0009	0.0425 0.0009	-0.0051 0.0031
2	0.0526 0.0012	0.0526 0.0012	0.0526 0.0012	-0.0066 0.0034
3	0.6671 0.0003	0.3180 0.0004	0.6671 0.0003	-0.0474 0.0012

Table 4.8 Continued

Intercept/ Slope	Accepted			Reverse
Amino Acid	Ancestral Change	Human Change	Rabbit Change	Change
4	0.3793	0.3793	0.6724	0.0470
	0.0008	0.0008	0.0000	0.0012
5	0.7315	0.7919	0.7503	0.1607
	0.0005	0.0004	0.0004	0.0023
6	0.1434	0.1434	0.1434	0.1450
	0.0012	0.0012	0.0012	0.0017
7	0.1525	0.1525	0.1525	0.1433
	0.0010	0.0010	0.0010	0.0039
8	0.0870	0.0870	0.0870	-0.1708
	0.0012	0.0012	0.0012	0.0072
9	0.6741	0.3623	0.3623	0.0008
	0.0002	0.0001	0.0001	0.0024
10	0.1155	0.1155	0.1155	0.1051
	0.0011	0.0011	0.0011	0.0014
11	0.6670	0.3694	0.3694	0.0341
	0.0001	0.0005	0.0005	0.0013
12	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
13	0.6688	0.3580	0.3580	-0.0440
	0.0004	0.0002	0.0002	0.0029
14	0.0356	0.0356	0.0356	-0.0335
	0.0005	0.0005	0.0005	0.0032
15	0.0635	0.0635	0.0635	0.0342
	0.0008	0.0008	0.0008	0.0027
16	0.0888	0.0888	0.0888	0.0411
	0.0008	0.0008	0.0008	0.0043
17	0.0556	0.0556	0.0556	0.0097
	0.0011	0.0011	0.0011	0.0026
18	0.0170	0.0170	0.0170	-0.0791
	0.0012	0.0012	0.0012	0.1038
19	0.1349	0.1349	0.1349	0.0823
	0.0013	0.0013	0.0013	0.0047
20	0.0805	0.0805	0.0805	0.0447
	0.0010	0.0010	0.0010	0.0025
21	0.4308	0.7365	0.4308	0.0539
	0.0008	0.0004	0.0008	0.0046
22	-0.0031	-0.0031	-0.0031	-0.0093
	0.0001	0.0001	0.0001	0.0002
23	0.1762	0.1762	0.1762	0.0818
	0.0010	0.0010	0.0010	0.0086
24	0.1565	0.1565	0.1565	0.0969
	0.0007	0.0007	0.0007	0.0037
25	0.1565	0.1565	0.1565	-0.0142
	0.0012	0.0012	0.0012	0.0062
26	0.1970	0.1970	0.1970	-0.0177
	0.0010	0.0010	0.0010	0.0085

Table 4.8 Continued

Intercept/ Slope Amino Acid	Accepted			Reverse
	Ancestral Change	Human Change	Rabbit Change	Change
27	0.0762	0.0762	0.0762	-0.0766
	0.0011	0.0011	0.0011	0.0054
28	0.0491	0.0491	0.0491	-0.0709
	0.0009	0.0009	0.0009	0.0036
29	0.1765	0.1765	0.1765	0.0750
	0.0011	0.0011	0.0011	0.0066
30	0.7279	0.3740	0.3740	0.01110
	0.0004	0.0008	0.0008	0.0042
31	0.0170	0.0170	0.0170	-0.0243
	0.0003	0.0003	0.0003	0.0013
32	0.0190	0.0190	0.0190	-0.0752
	0.0007	0.0007	0.0007	0.0027
33	0.0170	0.0170	0.0170	-0.0323
	0.0004	0.0004	0.0004	0.0023
34	0.0884	0.0884	0.0884	0.0253
	0.0014	0.0014	0.0014	0.0034
35	0.0020	0.0020	0.0020	0.0133
	0.0001	0.0001	0.0001	0.0003
36	0.2160	0.2160	0.2160	0.1712
	0.0012	0.0012	0.0012	0.0078
37	0.0442	0.0442	0.0442	-0.0125
	0.0012	0.0012	0.0012	0.0028
38	0.0719	0.0719	0.0719	0.0886
	0.0010	0.0010	0.0010	0.0021
39	0.1794	0.1794	0.1794	0.1547
	0.0008	0.0008	0.0008	0.0044
40	0.0766	0.0766	0.0766	0.0541
	0.0008	0.0008	0.0008	0.0021
41	0.0504	0.0504	0.0504	-0.0010
	0.0007	0.0007	0.0007	0.0028
42	0.1457	0.1457	0.1457	0.0588
	0.0011	0.0011	0.0011	0.0041
43	0.6605	9.6146	9.6146	0.0331
	0.0004	0.0007	0.0007	0.0025
44	-0.0121	-0.0121	-0.0121	-0.0152
	0.0012	0.0012	0.0012	0.0013
45	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
46	0.0714	0.0714	0.0714	-0.0097
	0.0009	0.0009	0.0009	0.0045
47	0.0372	0.0372	0.0372	0.0159
	0.0006	0.0006	0.0006	0.0016
48	-0.0121	-0.0121	-0.0121	-0.0366
	0.0012	0.0012	0.0012	0.0011
49	0.0146	0.0146	0.0146	0.0170
	0.0000	0.0000	0.0000	0.0001

Table 4.8 Continued

Intercept/ Slope Amino Acid	Accepted Ancestral Change	Accepted Human Change	Accepted Rabbit Change	Reverse Change
50	0.3333	0.6667	0.3333	0.0000
	0.0000	0.0000	0.0000	0.0000
51	0.3753	0.7054	0.3753	0.0525
	0.0002	0.0003	0.0002	0.0016
52	0.3634	0.3634	0.7116	-0.1003
	0.0002	0.0002	0.0004	0.0048
53	0.0806	0.0806	0.0806	0.0264
	0.0004	0.0004	0.0004	0.0044
54	0.0267	0.0267	0.0267	0.0297
	0.0001	0.0001	0.0001	0.0002
55	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
56	0.4010	0.4010	0.6562	0.0132
	0.0007	0.0007	0.0001	0.0038
57	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
58	0.0937	0.0937	0.0937	0.0257
	0.0010	0.0010	0.0010	0.0033
59	0.2034	0.2034	0.2034	0.1751
	0.0012	0.0012	0.0012	0.0017
60	0.0282	0.0282	0.0282	-0.0015
	0.0008	0.0008	0.0008	0.0015
61	0.0275	0.0275	0.0275	0.0156
	0.0009	0.0009	0.0009	0.0024
62	0.0823	0.0823	0.0823	0.0700
	0.0011	0.0011	0.0011	0.0062
63	0.0085	0.0085	0.0085	-0.0484
	0.0012	0.0012	0.0012	0.0027
64	0.1735	0.1735	0.1735	0.1149
	0.0012	0.0012	0.0012	0.0031
65	0.1442	0.1442	0.1442	0.1903
	0.0008	0.0008	0.0008	0.0048
66	0.0299	0.0299	0.0299	0.0312
	0.0006	0.0006	0.0006	0.0007
67	0.1097	0.1097	0.1097	0.0208
	0.0012	0.0012	0.0012	0.0036
68	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
69	0.3827	0.3827	0.6649	-0.0013
	0.0008	0.0008	0.0001	0.0022
70	-0.0290	-0.0290	-0.0290	-0.0440
	0.0012	0.0012	0.0012	0.0016
71	0.1141	0.1141	0.1141	0.0850
	0.0013	0.0013	0.0013	0.0033
72	0.6660	0.3345	0.3345	-0.0012
	0.0002	0.0001	0.0001	0.0004

Table 4.8 Continued

Intercept/ Slope Amino Acid	Accepted			Reverse
	Ancestral Change	Human Change	Rabbit Change	Change
73	0.4418	0.4418	0.6212	0.1025
	0.0008	0.0008	0.0001	0.0027
74	0.0860	0.0860	0.0860	0.0847
	0.0012	0.0012	0.0012	0.0013
75	-0.0112	-0.0112	-0.0112	-0.0594
	0.0010	0.0010	0.0010	0.0019
76	0.7060	0.7009	0.7093	0.0275
	0.0040	0.0001	0.0004	0.0051
77	0.1225	0.1225	0.1225	0.0383
	0.0013	0.0013	0.0013	0.0039
78	0.0343	0.0343	0.0343	-0.0034
	0.0004	0.0004	0.0004	0.0015
79	0.1927	0.1927	0.1927	0.1199
	0.0012	0.0012	0.0012	0.0044
80	0.1069	0.1069	0.1069	0.1069
	0.0012	0.0012	0.0012	0.0012
81	0.0460	0.0460	0.0460	-0.0261
	0.0006	0.0006	0.0006	0.0033
82	0.1869	0.1869	0.1869	0.1234
	0.0012	0.0012	0.0012	0.0035
83	0.1624	0.1624	0.1624	0.1321
	0.0008	0.0008	0.0008	0.0039
84	0.1999	0.1999	0.1999	0.0035
	0.0009	0.0009	0.0009	0.0082
85	0.0263	0.0263	0.0263	0.0239
	0.0008	0.0008	0.0008	0.0008
86	0.1196	0.1196	0.1196	-0.0329
	0.0005	0.0005	0.0005	0.0060
87	0.4162	0.6755	0.4162	0.0847
	0.0007	0.0001	0.0007	0.0047
88	0.0121	0.0121	0.0121	-0.0185
	0.0007	0.0007	0.0007	0.0015
89	0.0958	0.0958	0.0958	0.0546
	0.0011	0.0011	0.0011	0.0028
90	0.0853	0.0853	0.0853	-0.0037
	0.0012	0.0012	0.0012	0.0051
91	-0.0142	-0.0142	-0.0142	-0.0379
	0.0004	0.0004	0.0004	0.0012
92	0.1009	0.1009	0.1009	-0.0276
	0.0012	0.0012	0.0012	0.0045
93	0.0604	0.0604	0.0604	-0.0450
	0.0013	0.0013	0.0013	0.0017
94	0.0227	0.0227	0.0227	0.0369
	0.0002	0.0002	0.0002	0.00081
95	0.0598	0.0598	0.0598	-0.0491
	0.0013	0.0013	0.0013	0.0043

Table 4.8 Continued

Intercept/ Slope	Accepted			Reverse
Amino Acid	Ancestral Change	Human Change	Rabbit Change	Change
96	0.0239	0.0239	0.0239	-0.0081
	0.0006	0.0006	0.0006	0.0018
97	0.1635	0.1635	0.1635	0.1170
	0.0012	0.0012	0.0012	0.00351
98	-0.0031	-0.0031	-0.0031	-0.0031
	0.0001	0.0001	0.0001	0.00018
99	0.0698	0.0699	0.0699	-0.0258
	0.0012	0.0012	0.0012	0.0044
100	0.1185	0.1185	0.1185	-0.0490
	0.0004	0.0004	0.0004	0.0056
101	0.1067	0.1067	0.1067	0.0462
	0.0013	0.0013	0.0013	0.0029
102	0.0747	0.0747	0.0747	0.0130
	0.0011	0.0011	0.0011	0.0039
103	0.0000	0.0000	0.0000	Not Repeated
	0.0000	0.0000	0.0000	
104	0.7410	0.3444	0.3444	0.0753
	0.0004	0.0005	0.0005	0.0015
105	-0.0045	-0.0045	-0.0045	-0.03160
	0.0006	0.0006	0.0006	0.0011
106	-0.0142	-0.0142	-0.0142	-0.0308
	0.0012	0.0012	0.0012	0.0014
107	0.0721	0.0721	0.0721	-0.0129
	0.0012	0.0012	0.0012	0.0036
108	0.1210	0.1210	0.1210	0.0439
	0.0013	0.0013	0.0013	0.0039
109	0.0681	0.0681	0.0681	0.0748
	0.0013	0.0013	0.0013	0.0013
110	0.0090	0.0090	0.0090	-0.0115
	0.0007	0.0007	0.0007	0.0015
111	-0.0031	-0.0031	-0.0031	-0.0091
	0.0001	0.0001	0.0001	0.0002
112	0.3921	0.6656	0.3921	0.0597
	0.0008	0.0000	0.0008	0.0009
113	0.0322	0.0322	0.0322	0.0325
	0.0012	0.0012	0.0012	0.0013
114	0.1032	0.1032	0.1032	0.0650
	0.0011	0.0011	0.0011	0.0019
115	0.3327	0.3327	0.6867	0.0347
	0.0001	0.0001	0.0003	0.0005
116	0.3263	0.3333	0.3333	0.0070
	0.0000	0.0000	0.0000	0.0000
117	0.0406	0.0406	0.0406	0.0227
	0.0011	0.0011	0.0011	0.0013
118	0.0467	0.0467	0.0467	0.0347
	0.0011	0.0011	0.0011	0.0015

Table 4.8 Continued

Intercept/ Slope Amino Acid	Accepted			Reverse Change
	Ancestral Change	Human Change	Rabbit Change	
119	0.0201	0.0201	0.0201	-0.0127
	0.0005	0.0005	0.0005	0.0013
120	0.0052	0.0052	0.0052	0.0027
	0.0005	0.0005	0.0005	0.0005
121	0.0817	0.0817	0.0817	0.0076
	0.0011	0.0011	0.0011	0.0028
122	0.0102	0.0102	0.0102	-0.0972
	0.0006	0.0006	0.0006	0.0027
123	0.0776	0.0776	0.0776	0.0034
	0.0012	0.0012	0.0012	0.0044
124	0.1779	0.1779	0.1779	0.1586
	0.0012	0.0012	0.0012	0.0037
125	0.7112	0.7073	0.6611	0.0811
	0.0004	0.0004	0.0001	0.0024
126	-0.0095	-0.0095	-0.0095	0.0006
	0.0006	0.0006	0.0006	0.0010
127	0.1023	0.1023	0.1023	0.0283
	0.0013	0.0013	0.0013	0.0039
128	0.1918	0.1918	0.1918	0.0872
	0.0010	0.0010	0.0010	0.0036
129	0.0812	0.0812	0.0812	0.0099
	0.0013	0.0013	0.0013	0.0038
130	0.6646	0.3292	0.3292	-0.0061
	0.0000	0.0001	0.0001	0.001
131	0.0887	0.0887	0.0887	0.0493
	0.0011	0.0011	0.0011	0.0028
132	0.0036	0.0036	0.0036	-0.0747
	0.0009	0.0009	0.0009	0.0025
133	0.0563	0.0563	0.0563	0.0562
	0.0007	0.0007	0.0007	0.0010
134	0.0000	0.0000	0.0000	No Repeats
	0.0000	0.0000	0.0000	
135	0.0611	0.0611	0.0611	0.0250
	0.0011	0.0011	0.0011	0.0020
136	0.0552	0.0552	0.0552	0.0310
	0.0007	0.0007	0.0007	0.0017
137	-0.0034	-0.0034	1.0034	-0.1809
	0.0007	0.0007	0.0007	0.0049
138	0.1073	0.1073	0.1073	-0.0088
	0.0006	0.0006	0.0006	0.0054
139	0.0983	0.0983	0.0983	0.1021
	0.0012	0.0012	0.0012	0.0016
140	0.0708	0.0708	0.0708	-0.0263
	0.0012	0.0012	0.0012	0.0035
141	0.0703	0.0703	0.0703	0.0630
	0.0007	0.0007	0.0007	0.0008

Table 4.8 Continued

Intercept/ Slope Amino Acid	Accepted		Reverse	
	Ancestral Change	Human Change	Rabbit Change	Change
142	-0.0006	-0.0006	-0.0006	-0.0118
	0.0001	0.0001	0.0001	0.0004
143	0.0222	0.0222	0.0222	0.0010
	0.0002	0.0002	0.0002	0.0005
144	0.1261	0.1261	0.1261	0.0725
	0.0012	0.0012	0.0012	0.0030
145	0.0794	0.0794	0.0794	0.0323
	0.0013	0.0013	0.0013	0.0027
146	0.0071	0.0071	0.0071	-0.0413
	0.0009	0.0009	0.0009	0.0020

Table 4.9 shows the number of amino acid residues that remain the same as the starting hemoglobin.

Table 4.9
Hemoglobin Similarity

Starting Hemoglobin	Number of amino acids similar to:					
	Ancestral		Rabbit		Human	
	Intercept	Slope	Intercept	Slope	Intercept	Slope
Ancestra	135.7737	-.1239	118.4503	-.1057	119.3220	-.1071
Rabbit	118.1745	-.1075	136.0249	-.1208	123.2636	-.1078
Human	119.1841	-.1083	123.5119	-.1077	136.0913	-.1202
Combined	124.3775	-.1132	125.9957	-.1114	126.2256	-.1117

Table 4.10 takes the process one step further by presenting the hemoglobin similarity regression for each of the methods used in this study.

Table 4.10
Hemoglobin Similarity Regression

Intercept/ Slope	Random	Dayhoff	Zuckerkandl	Fitch	Nearest- Neighbor
Ancestral Starting Hemoglobin					
Ancestral	141.09	131.85	131.95	133.12	140.86
	-.1178	-.1392	-.1268	-.1334	-.1031
Rabbit	122.85	114.99	115.28	116.08	123.05
	-.1002	-.1181	-.1098	-.1137	-.0869
Human	123.83	115.78	116.23	116.90	123.88
	-.1015	-.1189	-.1103	-.1155	-.0893
Rabbit Starting Hemoglobin					
Ancestral	122.81	114.55	115.03	115.76	122.72
	-.1023	-.1194	-.1114	-.1147	-.0894
Rabbit	141.36	132.04	132.95	133.49	140.79
	-.1139	-.1340	-.1256	-.1137	-.1014
Human	127.79	119.66	120.08	121.08	127.69
	-.1016	-.1204	-.1120	-.1159	-.0892
Human Starting Hemoglobin					
Ancestral	123.86	115.55	115.96	116.80	123.75
	-.1032	-.1210	-.1110	-.1167	-.0894
Rabbit	127.97	119.90	120.43	121.43	127.83
	-.1008	-.1213	-.1119	-.1165	-.0881
Human	141.27	132.10	132.04	133.56	141.15
	-.1146	-.1341	-.1235	-.1292	-.0991

Table 4.11 presents the final tabular results examined in this effort. The amino acid residues similarity to the starting hemoglobins is used in a regression by iterations for each position of each of the three starting hemoglobins.

Table 4.11 Amino Acid Similarity Regression						
Amino Acid	Ancestral		Human		Rabbit	
	Intercept	Slope	Intercept	Slope	Intercept	Slope
1	.9575	-.0009	.9575	-.0009	.9575	-.0009
2	.9474	-.0012	.9474	-.0012	.9474	-.0012
3	.3329	-.0003	.6820	-.0004	.3329	-.0003
4	.6207	-.0008	.6207	-.0008	.3276	-.0000
5	.2685	-.0005	.3081	-.0004	.2497	-.0004
6	.8566	-.0012	.8566	-.0012	.8566	-.0012

Table 4.11 Continued

Amino Acid	Ancestral		Human		Rabbit	
	Intercept	Slope	Intercept	Slope	Intercept	Slope
7	.8475	-.0010	.8475	-.0010	.8475	-.0010
8	.9130	-.0012	.9130	-.0012	.9130	-.0012
9	.3259	-.0002	.6377	-.0001	.6377	-.0001
10	.8845	-.0011	.8845	-.0011	.8845	-.0011
11	.3330	-.0001	.6306	-.0005	.6306	-.0005
12	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
13	.3312	-.0004	.6420	-.0002	.6420	-.0002
14	.9644	-.0005	.9644	-.0005	.9644	-.0005
15	.9365	-.0008	.9365	-.0008	.9365	-.0008
16	.9112	-.0008	.9112	-.0008	.9112	-.0008
17	.9444	-.0011	.9444	-.0011	.9444	-.0011
18	.9830	-.0012	.9830	-.0012	.9830	-.0012
19	.8651	-.0013	.8651	-.0013	.8651	-.0013
20	.9195	-.0010	.9195	-.0010	.9195	-.0010
21	.5692	-.0008	.2635	-.0004	.5692	-.0008
22	1.0031	-.0001	1.0031	-.0001	1.0031	-.0001
23	.8238	-.0010	.8238	-.0010	.8238	-.0010
24	.8941	-.0007	.8941	-.0007	.8941	-.0007
25	.8435	-.0012	.8435	-.0012	.8435	-.0012
26	.8030	-.0010	.8030	-.0010	.8030	-.0010
27	.9238	-.0011	.9238	-.0011	.9238	-.0011
28	.9509	-.0009	.9509	-.0009	.9509	-.0009
29	.8235	-.0011	.8235	-.0011	.8235	-.0011
30	.2721	-.0004	.6260	-.0008	.6260	-.0008
31	.9830	-.0003	.9830	-.0003	.9830	-.0003
32	.9810	-.0007	.9810	-.0007	.9810	-.0007
33	.9830	-.0004	.9830	-.0004	.9830	-.0004
34	.9116	-.0014	.9116	-.0014	.9116	-.0014
35	.9970	-.0001	.9970	-.0001	.9970	-.0001
36	.7840	-.0012	.7840	-.0012	.7840	-.0012
37	.9558	-.0012	.9558	-.0012	.9558	-.0012
38	.9281	-.0010	.9281	-.0010	.9281	-.0010
39	.8206	-.0008	.8206	-.0008	.8206	-.0008
40	.9234	-.0008	.9234	-.0008	.9234	-.0008
41	.9496	-.0007	.9496	-.0007	.9496	-.0007
42	.8543	-.0011	.8543	-.0011	.8543	-.0011
43	.3395	-.0004	.6146	-.0007	.6146	-.0007
44	1.0121	-.0012	1.0121	-.0012	1.0121	-.0012
45	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
46	.9286	-.0009	.9286	-.0009	.9286	-.0009
47	.9628	-.0006	.9628	-.0006	.9628	-.0006
48	1.0121	-.0012	1.0121	-.0012	1.0121	-.0012
49	.9854	-.0000	.9854	-.0000	.9854	-.0000
50	.6667	-.0000	.3333	-.0000	.6667	-.0000
51	.6247	-.0002	.2946	-.0003	.6247	-.0002
52	.6366	-.0002	.6366	-.0002	.2884	-.0004
53	.9194	-.0004	.9194	-.0004	.9194	-.0004
54	.9733	-.0001	.9733	-.0001	.9733	-.0001

Table 4.11 Continued

Amino Acid	Ancestral		Human		Rabbit	
	Intercept	Slope	Intercept	Slope	Intercept	Slope
55	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
56	.5990	-.0007	.5990	-.0007	.3438	-.0001
57	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
58	.9063	-.0010	.9063	-.0010	.9063	-.0010
59	.7966	-.0012	.7966	-.0012	.7966	-.0012
60	.9718	-.0008	.9718	-.0008	.9718	-.0008
61	.9725	-.0009	.9725	-.0009	.9725	-.0009
62	.9177	-.0011	.9177	-.0011	.9177	-.0011
63	.9915	-.0012	.9915	-.0012	.9915	-.0012
64	.8265	-.0012	.8265	-.0012	.8265	-.0012
65	.8558	-.0008	.8558	-.0008	.8558	-.0008
66	.9701	-.0006	.9701	-.0006	.9701	-.0006
67	.8903	-.0012	.8903	-.0012	.8903	-.0012
68	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
69	.6173	-.0008	.6173	-.0008	.3351	-.0001
70	1.0290	-.0012	1.0290	-.0012	1.0290	-.0012
71	.8859	-.0013	.8859	-.0013	.8859	-.0013
72	.3340	-.0002	.6655	-.0001	.6655	-.0001
73	.5582	-.0008	.5582	-.0008	.3788	-.0001
74	.9140	-.0012	.9140	-.0012	.9140	-.0012
75	1.0112	-.0010	1.0112	-.0010	1.0112	-.0010
76	.2940	-.0040	.2991	-.0001	.2907	-.0004
77	.8775	-.0013	.8775	-.0013	.8775	-.0013
78	.9657	-.0004	.9657	-.0004	.9657	-.0004
79	.8073	-.0012	.8073	-.0012	.8073	-.0012
80	.8931	-.0012	.8931	-.0012	.8931	-.0012
81	.9540	-.0006	.9540	-.0006	.9540	-.0006
82	.8131	-.0012	.8131	-.0012	.8131	-.0012
83	.8376	-.0008	.8376	-.0008	.8376	-.0008
84	.8001	-.0009	.8001	-.0009	.8001	-.0009
85	.9737	-.0008	.9737	-.0008	.9737	-.0008
86	.8804	-.0005	.8804	-.0005	.8804	-.0005
87	.5838	-.0007	.3245	-.0001	.5838	-.0007
88	.9879	-.0007	.9879	-.0007	.9879	-.0007
89	.9042	-.0011	.9042	-.0011	.9042	-.0011
90	.9147	-.0012	.9147	-.0012	.9147	-.0012
91	1.0142	-.0004	1.0142	-.0004	1.0142	-.0004
92	.8991	-.0012	.8991	-.0012	.8991	-.0012
93	.9396	-.0013	.9396	-.0013	.9396	-.0013
94	.9773	-.0002	.9773	-.0002	.9773	-.0002
95	.9402	-.0013	.9402	-.0013	.9402	-.0013
96	.9761	-.0006	.9761	-.0006	.9761	-.0006
97	.8365	-.0012	.8365	-.0012	.8365	-.0012
98	1.0031	-.0001	1.0031	-.0001	1.0031	-.0001
99	.9302	-.0012	.9301	-.0012	.9301	-.0012
100	.8815	-.0004	.8815	-.0004	.8815	-.0004
101	.8933	-.0013	.8933	-.0013	.8933	-.0013
102	.9253	-.0011	.9253	-.0011	.9253	-.0011

Table 4.11 Continued

Amino Acid	Ancestral		Human		Rabbit	
	Intercept	Slope	Intercept	Slope	Intercept	Slope
103	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
104	.2590	-.0004	.6556	-.0005	.6556	-.0005
105	1.0045	-.0006	1.0045	-.0006	1.0045	-.0006
106	1.0142	-.0012	1.0142	-.0012	1.0142	-.0012
107	.9279	-.0012	.9279	-.0012	.9279	-.0012
108	.8790	-.0013	.8790	-.0013	.8790	-.0013
109	.9319	-.0013	.9319	-.0013	.9319	-.0013
110	.9910	-.0007	.9910	-.0007	.9910	-.0007
111	1.0031	-.0001	1.0031	-.0001	1.0031	-.0001
112	.6079	-.0008	.3344	-.0000	.6079	-.0008
113	.9678	-.0012	.9678	-.0012	.9678	-.0012
114	.8968	-.0011	.8968	-.0011	.8968	-.0011
115	.6673	-.0001	.6673	-.0001	.3133	-.0003
116	.3263	-.0000	.6667	-.0000	.6667	-.0000
117	.9594	-.0011	.9594	-.0011	.9594	-.0011
118	.9532	-.0011	.9532	-.0011	.9532	-.0011
119	.9799	-.0005	.9799	-.0005	.9799	-.0005
120	.9948	-.0005	.9948	-.0005	.9948	-.0005
121	.9183	-.0011	.9183	-.0011	.9183	-.0011
122	.9898	-.0006	.9898	-.0006	.9898	-.0006
123	.9224	-.0012	.9224	-.0012	.9224	-.0012
124	.8221	-.0012	.8221	-.0012	.8221	-.0012
125	.2888	-.0004	.2922	-.0004	.3389	-.0001
126	1.0095	-.0006	1.0095	-.0006	1.0095	-.0006
127	.8977	-.0013	.8977	-.0013	.8977	-.0013
128	.8082	-.0010	.8082	-.0010	.8082	-.0010
129	.9188	-.0013	.9188	-.0013	.9188	-.0013
130	.3354	-.0000	.6708	-.0001	.6708	-.0001
131	.9113	-.0011	.9113	-.0011	.9113	-.0011
132	.9964	-.0009	.9964	-.0009	.9964	-.0009
133	.9437	-.0007	.9437	-.0007	.9437	-.0007
134	1.0000	0.0000	1.0000	0.0000	1.0000	0.0000
135	.9389	-.0011	.9389	-.0011	.9389	-.0011
136	.9448	-.0007	.9448	-.0007	.9448	-.0007
137	1.0034	-.0007	1.0034	-.0007	1.0034	-.0007
138	.8927	-.0006	.8927	-.0006	.8927	-.0006
139	.9017	-.0012	.9017	-.0012	.9017	-.0012
140	.9292	-.0012	.9292	-.0012	.9292	-.0012
141	.9297	-.0007	.9297	-.0007	.9297	-.0007
142	1.0006	-.0001	1.0006	-.0001	1.0006	-.0001
143	.9778	-.0002	.9778	-.0002	.9778	-.0002
144	.8739	-.0012	.8739	-.0012	.8739	-.0012
145	.9206	-.0013	.9206	-.0013	.9206	-.0013
146	.9919	-.0009	.9919	-.0009	.9919	-.0009

CHAPTER V

CONCLUSIONS

The generalizability of results from this work is restricted due to the limited availability of sequence data for protein generating sequences. The DNA sequencing data for human alpha, beta, and sigma hemoglobin; for mouse alpha and beta hemoglobin; and for rabbit alpha and sigma hemoglobin is currently known. Until the sequencing data from a wide variety of different proteins from a large cross-section of different species, the full implication of the use of these techniques will be difficult to completely evaluate.

The review of the literature revealed a great deal of literature relative to the possible shemes for the evolution of DNA. Literature from basic fields of study have not yet converged. Literature being produced in the field of population genetics have addressed the dynamics of phenotypic introduction and propogation of mutations in the genetic material of the organism. The general results from the work in the field to date is that mutations resulting in neutral, or nearly neutral advantage to the survival of an organism in the environment are not supportable from the frequency of mutations observed when compared to the best

models of the rate of acceptance of this type of mutation. This effort found in almost all cases an order of magnitude higher rejection than acceptance, even using the extremely lax criteria used in this effort for acceptance.

The molecular biologists have found evidence for several effects that suggest that many of the mutations that are expected to be found in the primary sequence of amino acids in protein should result in selectively neutral mutations. Further, studies which relate the differences in the primary sequence of proteins such as hemoglobin, cytochrome c, and fibrinogen suggest a constant rate of amino acid replacement for each protein which provides evolutionary relationships between species which agrees well with the phylogenic relationships that have been previously established. This strongly suggests that neutral mutations would be expected to be the primary mechanism involved. Some of the assumptions used for estimating the transition probabilities of amino acid may be suspect. Use of the nucleotides sequences instead of the amino acid sequences as the methodology adapted in this effort should avoid these same difficulties and was the motivating force for the selection of the modeling technique chosen in this effort.

Information theory and the application of information theory have been applied to information on the evolutionary system. Involvement of this field to the problems existing in the genetic system have not had a large impact to date.

The genetic code and the redundancies of the system have been successfully evaluated. Application to the mutation of amino acid sequences have not provided significant insight into the behavior of the system. More basic information provided from nucleotide mutation behavior should allow further analysis in this area with a better prospect for success. Recent information that has been obtained in studies of the chemical and physical characteristics of the nucleic acid found in organisms has changed many ideas about possible interactions that may be occurring. The observation of multiple repeated sequences of nucleotides in the DNA of eukaryotes and the finding of intervening sequences within the gene that codes for DNA will have to be understood and incorporated into future work.

Also, the field of chemical physics has yielded information on chain stability caused by the ratio of guanine and cytosine and the stabilization of mRNA by the formation of autocomplementary regions and the formation of loops offer potential for understanding the selective advantage of nucleotide changes that result in amino acid point mutations which do not appear to have selective advantage when examined on the basis of protein function.

The fields of study involved in trying to understand the underlying mechanisms does not appear to have been incorporated into a systematic framework necessary for the evaluation of system performance. This thesis effort is

an attempt to try to evaluate the system by examining the output produced by several different sets of inputs with different methods of modeling system performance, since the underlying mechanisms were uncharacterized. Estimates of the transition probabilities were obtained from three different sources as well as assumed to be completely random. The output of the system was characterized at the nucleotide level and at the level of the amino acid. The output of the system was "locked" in place by constraining the acceptable amino acids at each position of the chain to those residues that have been characterized in previous studies. This artificial constraint was an attempt to restrict the model to a domain that would be evolutionary significant. In other words, this was a primitive attempt to collectively model the possibility of random mutation resulting in selective advantage at the nucleotide and the amino acid level. As a better understanding of mechanisms that have physical significance is formulated, more detailed modeling of the process will be possible.

There were several interesting observations that can be made regarding the results of the modeling effort. All of the transition frequencies were based upon estimates of an accepted amino acid change in 10,000,000 years for a protein 140 residues long. The data in table 4.6 reflects that using the Dayhoff transition frequencies resulted in the highest acceptance of new amino acid residues while the

nearest-neighbor transition frequencies resulted in the lowest acceptance rate. The random data was nearly identical with the nearest-neighbor rate. All three simple transition methodologies, Dayhoff, Zuckerkandl, and Fitch were very close to having the same rate of accepting a mutation. The rate at which a previous amino acid residue was back mutated to a residue that was already at the same position was very high and uniform across methods. 99% of all accepted mutations using the random transition probabilities resulted in a back mutation. 97%, 96%, and 95% were the respective back mutation rate for Dayhoff, Zuckerkandl, and Fitch. Nearest-neighbor back mutations accounted for 93% of the accepted mutations. This extremely high percentage of back mutations at the amino acid level was not expected before this analysis was begun. Table 4.4 for the nucleotide transition regression sheds some light on the situation. All five methods resulted in the acceptance of only 15% to 16% of the nucleotide changes. Of the nucleotide changes that did occur, 17%, 44%, 42%, 42%, and 19% of the changes were backmutations. The rates of transition are nearly the same for allowing nucleotide changes as for accepting amino acid changes. At first thought, it would appear that some form of the wobble hypothesis of Crick might provide the answer. The wobble hypothesis has been applied to the degenerate pairing of the third nucleotide of mRNA to tRNA in a manner which preserves

the reliability of obtaining the same amino acid in the peptide chain. When the data from table 4.7 is examined, no significant trend of either allowing, repeating, or rejecting nucleotide based upon the position in the codon can be found to support a wobble relationship in the mutations at the DNA level. Upon further investigation, the relationship between nucleotide transition frequency and amino acid transition frequency are tied in two cycles. The amino acids acceptable at any particular position typically form a small subset of the 20 residues possible. As a result, nucleotides changes are allowed at any of the positions in the codon with few restrictions, but after a very few resulting changes in amino acids, they begin repeating. The repetitive cycling of amino acids was much higher than anticipated by any of the literature. Most of the literature dealing with the evolutionary fixation of mutations in amino acids did not reflect the high degree of repetition that was found to exist at the amino acid level.

Interestingly enough, the method used in the simulation proved to be the driver for the type of repetition seen. The repetition cycles were very dependent on the position. At one end of the spectrum was the use of the random method. Most of the repeats observed were simple back mutations at the third position in the DNA codon. As the transitions of the nucleotides is more controlled such as in the nearest-neighbor approach, repeats of amino acids occur more often

only after cycles of two, three, or sometimes even more changes in the amino acid residue. These cycles are found to regularly repeat. The structured transition probabilities of the three methods seemed to be intermediate in behavior. Some two and three cycle transition patterns were seen, but they were not regularly repeated as were the transitions observed with the nearest-neighbor method.

This difference in mutational patterns depending on the non-random transition probabilities seems to paint a different picture of the process of evolution. The fixation of a point mutation may be part of an equilibrium searching mechanism important in the survival of the organism. The strength of the Ising model used with the nearest-neighbor transition probabilities and the allowable amino acid replacements may enable the organism to control random genetic drift and neutral mutations at the protein level to control the stability of the DNA and the RNA chains. The ability to control the guanine-cytosine content of DNA is important in the information potential of DNA. It is also important in the stability of the chain to denaturalization from heat as well as ion levels. It controls the rate of chain separation. These physical properties of the DNA chain have been shown to follow the same behavior and performance as would be expected from an Ising model.

Much further work needs to be done. Further identification of more DNA from more species and for

different proteins needs to be conducted. With a larger database, more closure on the process of evolution may be examined. DNA from species of very distant, or non-existent, connection to the environment would be instrumental in identifying several points. An opportunity to use DNA sequences from species found around the hydrogen sulfide vents on the ocean floor in the Atlantic and the Pacific oceans has high potential to shed light on many of the theories existing in the field of evolutionary biology.

APPENDIX

APPENDIX A
PROGRAM SOURCE LISTING

PROGRAM SOURCE LISTING

```

00005  PROGRAM (COMPUTERANDOM MUTATIONS FOR BETA Hb)
00010      INTEGER E,F,K
00020      DIMENSION NA(438,50),MA(146,50)
00030      DIMENSION NULL(438),PCT(438)
00040      DIMENSION NCOUNT(4,4),MCOUNT(28,28)
00050      DIMENSION MCRIT(146,14)
00060      DIMENSION MGC(16,4),N(450),M(150),NP(450,4),
00061      1MP(150,4)
00070      DIMENSION T(64,3)
00080      DIMENSION NR(438),MR(150),MCH(150),MCR(150),
00081      1MCA(150)
00090      IXS=9636
00110      CALL HB(NP)
00120      CALL GC(MGC)
00130      CALL INIT1(NP,MP,MGC)
00190      CALL AAAR(MCRIT)
00191      DO 1001 INTE=1,3
00192      IF (INTE.EQ.1) INTER=700
00193      IF (INTE.EQ.2) INTER=40
00194      IF (INTE.EQ.3) INTER=6
00200      CALL INIT(IX,IXS,F,E,N,INTER,NCOUNT,MCOUNT,NULL,
00210      1NA,MA,M,MGC,NP,NIP,NR,MR,MP,IH,MCH,MCR,MCA)
00220      DO 10 L=1,INTER
00230      DO 20 I=2,438
00240      CALL TRAN1(NUC,I,INTER,N,IX)
00250      IF (NUC.EQ.N(I)) GO TO 20
00260      CALL MUTATE(I,MCRIT,NULL,NUC,NCOUNT,MCOUNT,NA,
00270      1MA,N,M,MGC,E,F,NR,MR)
00280      20 CONTINUE
00290      10 CONTINUE
00300      PRINT 2
00310      METH=1
00320      CALL OUT(M,N,NA,MA,NULL,MCOUNT,NCOUNT,IH,IXS,
00330      1METH,INTER,NR,MR,MCH,MCR,MCA,MP)
00340      DO 30 K=1,3
00350      CALL INIT(IX,IXS,F,E,N,INTER,NCOUNT,MCOUNT,NULL,
00360      1NA,MA,M,MGC,NP,NIP,NR,MR,MP,IH,MCH,MCR,MCA)
00370      DO 40 L=1,INTER
00380      DO 50 I=2,438
00390      CALL TRAN2(NUC,I,INTER,N,K,IX)
00400      IF (NUC.EQ.(N(I))) GO TO 50
00410      CALL MUTATE(I,MCRIT,NULL,NUC,NCOUNT,MCOUNT,NA,
00420      1MA,N,M,MGC,E,F,NR,MR)
00430      50 CONTINUE
00440      40 CONTINUE
00450      IF (K.EQ.1) PRINT 3

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00460      IF (K.EQ.1)  METH=2
00470      IF (K.EQ.2)  PRINT 4
00480      IF (K.EQ.2)  METH=3
00490      IF (K.EQ.3)  PRINT 5
00500      IF (K.EQ.3)  METH=4
00510 C      CALL RESULT(M,N,NA,MA,NULL,MCOUNT,NCOUNT)
00520      CALL OUT(M,N,NA,MA,NULL,MCOUNT,NCOUNT,IH,IXS,
00530      1METH,INTER,NR,MR,MCH,MCR,MCA,MP)
00540      30 CONTINUE
00550      CALL INIT(IX,IXS,F,E,N,INTER,NCOUNT,MCOUNT,NULL,
00560      1NA,MA,M,MGC,NP,NIP,NR,MR,MP,IH,MCH,MCR,MCA)
00570      CALL TP(T)
00580      DO 60 L=1,INTER
00590      DO 70 I=2,438
00600      CALL TRAN3(NUC,I,INTER,N,T,IX)
00610      IF (NUC.EQ.(N(I))) GO TO 70
00620      CALL MUTATE(I,MCRT,NULL,NUC,NCOUNT,MCOUNT,NA,
00630      1MA,N,M,MGC,E,F,NR,MR)
00640      70 CONTINUE
00650      60 CONTINUE
00660      PRINT 6
00670      METH=5
00680 C      CALL RESULT(M,N,NA,MA,NULL,MCOUNT,NCOUNT)
00690      CALL OUT(M,N,NA,MA,NULL,MCOUNT,NCOUNT,IH,IXS,
00700      1METH,INTER,NR,MR,MCH,MCR,MCA,MP)
00710      1001 CONTINUE
00715      1000 CONTINUE
00750      2 FORMAT (16H0RANDOM MUTATION)
00760      3 FORMAT (42H0NUCLEOTIDE DEPENDENT MUTATION-
00761      1ZUKERKANDL)
00770      4 FORMAT (36H0NUCLEOTIDE DEPENDENT MUTATION-FITCH)
00780      5 FORMAT (38H0NUCLEOTIDE DEPENDENT MUTATION-
00781      1DAYHOFF)
00790      6 FORMAT (36H0NEAREST NEIGHBOR DEPENDENT MUTATION)
00810      STOP
00820      END
10010      SUBROUTINE HB(NP)
10020      DIMENSION NP(450,4)
10030      DO 10 I=1,450
10040      NP(I,1)=0
10050      NP(I,2)=0
10060      NP(I,3)=0
10070      10 CONTINUE
10110      NP(436,1)=2
10120      NP(437,1)=1
10130      NP(438,1)=2
10140      NP(433,1)=3
10141      NP(433,2)=1
10142      NP(433,3)=1
10150      NP(434,1)=4
10160      NP(435,1)=3
10169      NP(430,1)=2

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10170	NP(431,1)=1
10180	NP(432,1)=3
10181	NP(432,2)=2
10182	NP(432,3)=2
10190	NP(427,1)=1
10200	NP(428,1)=3
10210	NP(429,1)=4
10220	NP(424,1)=1
10230	NP(425,1)=3
10231	NP(425,2)=2
10240	NP(426,1)=3
10241	NP(426,2)=4
10242	NP(426,3)=2
10250	NP(421,1)=2
10260	NP(422,1)=4
10270	NP(423,1)=2
10280	NP(418,1)=2
10290	NP(419,1)=4
10300	NP(420,1)=2
10310	NP(415,1)=2
10320	NP(416,1)=4
10330	NP(417,1)=4
10340	NP(412,1)=1
10350	NP(413,1)=3
10360	NP(414,1)=1
10362	NP(414,3)=2
10370	NP(409,1)=2
10380	NP(410,1)=3
10390	NP(411,1)=2
10400	NP(406,1)=1
10401	NP(406,2)=3
10410	NP(407,1)=1
10420	NP(408,1)=2
10422	NP(408,3)=4
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10450	NP(405,1)=4
10460	NP(400,1)=3
10470	NP(401,1)=3
10480	NP(402,1)=2
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10500	NP(398,1)=1
10510	NP(399,1)=3
10520	NP(394,1)=2
10530	NP(395,1)=2
10540	NP(396,1)=1
10550	NP(391,1)=3
10560	NP(392,1)=2
10570	NP(393,1)=2
10580	NP(388,1)=2
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10600	NP(390,1)=4
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10620	NP(386,1)=1
10630	NP(387,1)=2
10640	NP(382,1)=3
10641	NP(382,2)=1
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10650	NP(383,1)=4
10660	NP(384,1)=4
10670	NP(379,1)=2
10680	NP(380,1)=1
10690	NP(381,1)=2
10700	NP(376,1)=1
10701	NP(376,2)=4
10702	NP(376,3)=4
10710	NP(377,1)=4
10720	NP(378,1)=2
10730	NP(373,1)=4
10740	NP(374,1)=4
10750	NP(375,1)=2
10760	NP(370,1)=1
10770	NP(371,1)=1
10780	NP(372,1)=2
10790	NP(367,1)=1
10800	NP(368,1)=2
10810	NP(369,1)=2
10820	NP(364,1)=1
10830	NP(365,1)=2
10840	NP(366,1)=2
10850	NP(361,1)=2
10860	NP(362,1)=4
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10880	NP(358,1)=3
10890	NP(359,1)=3
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10910	NP(355,1)=2
10920	NP(356,1)=1
10930	NP(357,1)=3
10940	NP(352,1)=3
10950	NP(353,1)=2
10960	NP(354,1)=2
10970	NP(349,1)=2
10980	NP(350,1)=1
10981	NP(350,2)=2
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11000	NP(346,1)=2
11010	NP(347,1)=1
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11030	NP(343,1)=2
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11050	NP(345,1)=3
11060	NP(340,1)=2

11061	NP(340,2)=1
11062	NP(340,3)=1
11070	NP(341,1)=1
11080	NP(342,1)=2
11090	NP(337,1)=3
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11330	NP(313,1)=1
11331	NP(313,1)=3
11340	NP(314,1)=1
11350	NP(315,1)=1
11360	NP(310,1)=2
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11370	NP(311,1)=4
11380	NP(312,1)=2
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11400	NP(308,1)=3
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11420	NP(304,1)=1
11430	NP(305,1)=1
11440	NP(306,1)=1
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11470	NP(303,1)=2
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11490	NP(299,1)=4
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11570	NP(289,1)=1
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11620	NP(288,1)=3
11621	NP(288,2)=2
11622	NP(288,3)=2
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11650	NP(285,1)=2
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11660	NP(280,1)=4
11670	NP(281,1)=3
11680	NP(282,1)=2
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11720	NP(274,1)=2
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11782	NP(268,3)=1
11790	NP(269,1)=4
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11810	NP(265,1)=1
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11870	NP(259,1)=2
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11920	NP(258,1)=4
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AD-A134 488

THE SIMULATION AND ANALYSIS OF AN EVOLUTIONARY MODEL OF
DEOXYRIBONUCLEIC ACID (DNA) (U) AIR FORCE INST OF TECH
WRIGHT-PATTERSON AFB OH SCHOOL OF SYST... R E MCNALLY

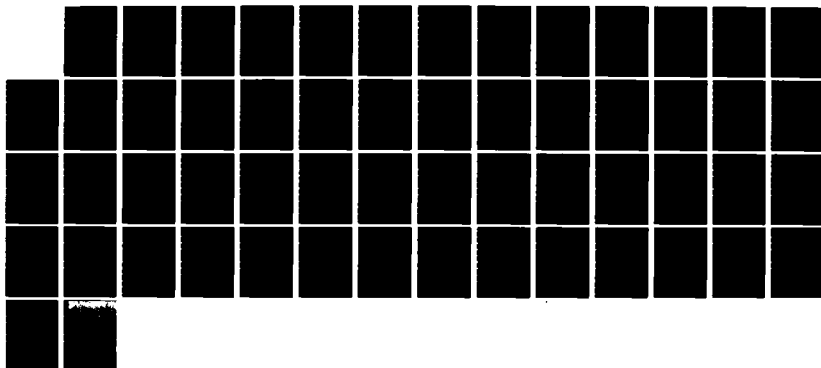
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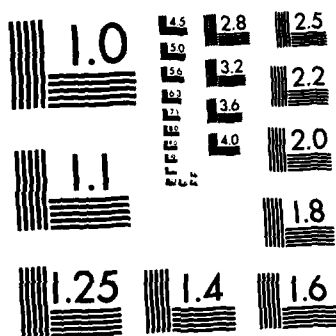
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NL





MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

11960	NP(250,1)=1
11970	NP(251,1)=4
11980	NP(252,1)=3
11990	NP(247,1)=3
12000	NP(248,1)=2
12110	NP(249,1)=2
12020	NP(244,1)=2
12030	NP(245,1)=4
12040	NP(246,1)=4
12050	NP(241,1)=4
12051	NP(241,2)=2
12060	NP(242,1)=4
12070	NP(243,1)=4
12080	NP(238,1)=2
12090	NP(239,1)=1
12100	NP(240,1)=2
12110	NP(235,1)=3
12111	NP(235,2)=2
12112	NP(235,3)=2
12120	NP(236,1)=1
12130	NP(237,1)=3
12140	NP(232,1)=1
12150	NP(233,1)=2
12151	NP(233,2)=3
12160	NP(234,1)=2
12170	NP(229,1)=3
12180	NP(230,1)=3
12190	NP(231,1)=2
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12210	NP(227,1)=1
12211	NP(227,2)=3
12220	NP(228,1)=1
12230	NP(223,1)=1
12240	NP(224,1)=2
12250	NP(225,1)=4
12252	NP(225,3)=2
12260	NP(220,1)=1
12261	NP(220,2)=2
12270	NP(221,1)=4
12280	NP(222,1)=2
12290	NP(217,1)=3
12291	NP(217,2)=1
12292	NP(217,3)=1
12300	NP(218,1)=2
12310	NP(219,1)=2
12320	NP(214,1)=2
12330	NP(215,1)=1
12340	NP(216,1)=3
12350	NP(211,1)=1
12352	NP(211,3)=4
12360	NP(212,1)=3
12361	NP(212,2)=2

12362	NP(212,3)=4
12370	NP(213,1)=2
12371	NP(213,2)=4
12372	NP(213,3)=4
12380	NP(208,1)=3
12390	NP(209,1)=4
12400	NP(210,1)=3
12410	NP(205,1)=2
12420	NP(206,1)=1
12430	NP(207,1)=3
12440	NP(202,1)=3
12450	NP(203,1)=4
12460	NP(204,1)=2
12470	NP(199,1)=3
12480	NP(200,1)=4
12490	NP(201,1)=4
12500	NP(196,1)=3
12510	NP(197,1)=1
12520	NP(198,1)=3
12530	NP(193,1)=2
12531	NP(193,2)=4
12532	NP(193,3)=4
12540	NP(194,1)=4
12550	NP(195,1)=4
12560	NP(190,1)=3
12570	NP(191,1)=2
12580	NP(192,1)=2
12590	NP(187,1)=3
12600	NP(188,1)=3
12610	NP(189,1)=4
12620	NP(184,1)=1
12630	NP(185,1)=1
12640	NP(186,1)=1
12650	NP(181,1)=3
12651	NP(181,2)=1
12652	NP(181,3)=1
12660	NP(182,1)=3
12670	NP(183,1)=2
12680	NP(178,1)=4
12681	NP(178,2)=2
12690	NP(179,1)=3
12691	NP(179,2)=4
12692	NP(179,3)=4
12700	NP(180,1)=4
12710	NP(175,1)=2
12720	NP(176,1)=1
12730	NP(177,1)=3
12740	NP(172,1)=1
12750	NP(173,1)=2
12760	NP(174,1)=4
12770	NP(169,1)=2
12771	NP(169,2)=4

12772	NP(169,3)=4
12780	NP(170,1)=4
12790	NP(171,1)=2
12800	NP(166,1)=2
12810	NP(167,1)=1
12820	NP(168,1)=3
12830	NP(163,1)=3
12840	NP(164,1)=4
12850	NP(165,1)=3
12860	NP(160,1)=1
12870	NP(161,1)=2
12880	NP(162,1)=1
12890	NP(157,1)=3
12900	NP(158,1)=4
12910	NP(159,1)=2
12920	NP(154,1)=2
12930	NP(155,1)=4
12940	NP(156,1)=4
12950	NP(151,1)=2
12960	NP(152,1)=1
12970	NP(153,1)=3
12980	NP(148,1)=3
12990	NP(149,1)=4
13000	NP(150,1)=3
13010	NP(145,1)=2
13020	NP(146,1)=1
13030	NP(147,1)=2
13040	NP(142,1)=1
13050	NP(143,1)=4
13060	NP(144,1)=2
13070	NP(139,1)=1
13080	NP(140,1)=3
13090	NP(141,1)=3
13100	NP(136,1)=2
13110	NP(137,1)=4
13120	NP(138,1)=2
13130	NP(133,1)=3
13140	NP(134,1)=4
13150	NP(135,1)=4
13160	NP(130,1)=3
13170	NP(131,1)=1
13180	NP(132,1)=1
13190	NP(127,1)=2
13200	NP(128,1)=2
13202	NP(128,3)=4
13210	NP(129,1)=4
13220	NP(124,1)=3
13230	NP(125,1)=1
13240	NP(126,1)=3
13250	NP(121,1)=2
13260	NP(122,1)=1
13270	NP(123,1)=3

13280	NP(118,1)=3
13290	NP(119,1)=2
13300	NP(120,1)=2
13310	NP(115,1)=3
13320	NP(116,1)=4
13330	NP(117,1)=4
13340	NP(112,1)=2
13350	NP(113,1)=1
13360	NP(114,1)=2
13370	NP(109,1)=2
13380	NP(110,1)=1
13390	NP(111,1)=3
13400	NP(106,1)=3
13401	NP(106,2)=1
13402	NP(106,3)=1
13410	NP(107,1)=1
13420	NP(108,1)=2
13430	NP(103,1)=1
13440	NP(104,1)=2
13441	NP(104,2)=1
13442	NP(104,3)=1
13450	NP(105,1)=1
13451	NP(105,2)=4
13452	NP(105,3)=4
13460	NP(100,1)=2
13470	NP(101,1)=1
13480	NP(102,1)=2
13490	NP(97,1)=2
13500	NP(98,1)=1
13510	NP(99,1)=3
13520	NP(94,1)=3
13521	NP(94,2)=1
13522	NP(94,3)=1
13530	NP(95,1)=3
13531	NP(95,2)=2
13540	NP(96,1)=2
13550	NP(91,1)=1
13560	NP(92,1)=4
13562	NP(92,3)=2
13570	NP(93,1)=3
13580	NP(88,1)=3
13581	NP(88,2)=1
13582	NP(88,3)=1
13590	NP(89,1)=4
13600	NP(90,1)=3
13610	NP(85,1)=1
13620	NP(86,1)=1
13630	NP(87,1)=1
13640	NP(82,1)=3
13650	NP(83,1)=2
13660	NP(84,1)=2
13670	NP(79,1)=4

13680	NP(80,1)=4
13690	NP(81,1)=4
13700	NP(76,1)=4
13710	NP(77,1)=4
13720	NP(78,1)=2
13730	NP(73,1)=3
13740	NP(74,1)=1
13750	NP(75,1)=1
13760	NP(70,1)=3
13761	NP(70,2)=1
13762	NP(70,3)=1
13770	NP(71,1)=3
13780	NP(72,1)=4
13790	NP(67,1)=4
13791	NP(67,2)=1
13792	NP(67,3)=1
13800	NP(68,1)=3
13810	NP(69,1)=3
13820	NP(64,1)=4
13821	NP(64,2)=2
13830	NP(65,1)=3
13831	NP(65,2)=4
13832	NP(65,3)=4
13840	NP(66,1)=3
13842	NP(66,3)=2
13850	NP(61,1)=2
13860	NP(62,1)=1
13870	NP(63,1)=2
13880	NP(58,1)=2
13890	NP(59,1)=4
13900	NP(60,1)=3
13910	NP(55,1)=1
13920	NP(56,1)=3
13930	NP(57,1)=2
13940	NP(52,1)=3
13950	NP(53,1)=3
13960	NP(54,1)=2
13970	NP(49,1)=1
13972	NP(49,3)=2
13980	NP(50,1)=4
13982	NP(50,3)=2
13990	NP(51,1)=1
14000	NP(46,1)=2
14010	NP(47,1)=4
14020	NP(48,1)=3
14030	NP(43,1)=4
14031	NP(43,2)=2
14040	NP(44,1)=4
14050	NP(45,1)=4
14060	NP(40,1)=2
14070	NP(41,1)=1
14080	NP(42,1)=2

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14090      NP(37,1)=2
14100      NP(38,1)=1
14110      NP(39,1)=2
14120      NP(34,1)=1
14121      NP(34,2)=3
14130      NP(35,1)=3
14140      NP(36,1)=2
14150      NP(31,1)=1
14160      NP(32,1)=2
14170      NP(33,1)=2
14180      NP(28,1)=2
14190      NP(29,1)=1
14200      NP(30,1)=2
14210      NP(25,1)=1
14220      NP(26,1)=3
14230      NP(27,1)=2
14240      NP(22,1)=1
14250      NP(23,1)=4
14260      NP(24,1)=4
14270      NP(19,1)=3
14280      NP(20,1)=3
14290      NP(21,1)=2
14300      NP(16,1)=2
14310      NP(17,1)=1
14320      NP(18,1)=3
14330      NP(13,1)=3
14331      NP(13,2)=1
14332      NP(13,3)=1
14340      NP(14,1)=3
14350      NP(15,1)=2
14360      NP(10,1)=3
14370      NP(11,1)=4
14380      NP(12,1)=3
14390      NP(7,1)=2
14391      NP(7,2)=4
14392      NP(7,3)=4
14400      NP(8,1)=4
14410      NP(9,1)=4
14420      NP(4,1)=1
14421      NP(4,2)=3
14430      NP(5,1)=4
14440      NP(6,1)=1
14450      NP(1,1)=3
14460      NP(2,1)=4
14470      NP(3,1)=3
14480      DO 20 I=1,438
14490      IF(NP(I,2) .EQ. 0) NP(I,2)=NP(I,1)
14500      IF(NP(I,3) .EQ. 0) NP(I,3)=NP(I,1)
14510      20 CONTINUE
14520      RETURN
14530      END
23440      SUBROUTINE GC(MGC)

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23450	DIMENSION MGC(16,4)
23460	MGC(1,1)=15
23470	MGC(2,1)=17
23480	MGC(3,1)=4
23490	MGC(4,1)=16
23500	MGC(5,1)=3
23510	MGC(6,1)=20
23520	MGC(7,1)=4
23530	MGC(8,1)=25
23540	MGC(9,1)=15
23550	MGC(10,1)=17
23560	MGC(11,1)=4
23570	MGC(12,1)=16
23580	MGC(13,1)=3
23590	MGC(14,1)=25
23600	MGC(15,1)=4
23610	MGC(16,1)=25
23620	MGC(1,2)=5
23630	MGC(2,2)=1
23640	MGC(3,2)=2
23650	MGC(4,2)=10
23660	MGC(5,2)=5
23670	MGC(6,2)=1
23680	MGC(7,2)=2
23690	MGC(8,2)=8
23700	MGC(9,2)=5
23710	MGC(10,2)=1
23720	MGC(11,2)=2
23730	MGC(12,2)=10
23740	MGC(13,2)=5
23750	MGC(14,2)=1
23760	MGC(15,2)=2
23770	MGC(16,2)=8
23780	MGC(1,3)=3
23790	MGC(2,3)=12
23800	MGC(3,3)=9
23810	MGC(4,3)=18
23820	MGC(5,3)=3
23830	MGC(6,3)=12
23840	MGC(7,3)=9
23850	MGC(8,3)=14
23860	MGC(9,3)=3
23870	MGC(10,3)=12
23880	MGC(11,3)=9
23890	MGC(12,3)=18
23900	MGC(13,3)=3
23910	MGC(14,3)=12
23920	MGC(15,3)=9
23930	MGC(16,3)=14
23940	MGC(1,4)=11
23950	MGC(2,4)=4
23960	MGC(3,4)=7

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23970      MGC(4,4)=13
23980      MGC(5,4)=19
23990      MGC(6,4)=12
24000      MGC(7,4)=2
24010      MGC(8,4)=6
24020      MGC(9,4)=11
24230      MGC(10,4)=4
24040      MGC(11,4)=7
24050      MGC(12,4)=13
24060      MGC(13,4)=11
24070      MGC(14,4)=12
24080      MGC(15,4)=7
24090      MGC(16,4)=6
24100      RETURN
24110      END
40010      SUBROUTINE INIT1(NP,MP,MGC)
40020      DIMENSION NP(450,4),MP(150,4),MGC(16,4)
40025      DO 10 I=1,3
40030      J=146
40040      12 J3=J*3
40050      J31=J3-1
40060      J32=J3-2
40070      NIP=4*NP(J32,2)+NP(J31,2)-4
40080      MP(J,2)=MGC(NIP,NP(J3,2))
40090      J=J-1
40100      IF (J.GE.1) GO TO 12
40105      10 CONTINUE
40110      RETURN
40120      END
50010      subroutine init3(np,mp,mgc)
50020      DIMENSION NP(450,4),MP(150,4),MGC(16,4)
50030      J=146
50040      12 J3=J*3
50050      J31=J3-1
50060      J32=J3-2
50070      NIP=4*NP(J32,3)+NP(J31,3)-4
50080      MP(J,3)=MGC(NIP,NP(J3,3))
50090      J=J-1
50100      IF (J.GE.1) GO TO 12
50110      RETURN
50120      END
60010      SUBROUTINE AAAR(MCRIT)
60020      DIMENSION MCRIT(146,14)
60030      MCRIT(1,3)= 7
60040      MCRIT(1,4)=19
60050      MCRIT(1,5)= 9
60060      MCRIT(1,6)= 1
60070      MCRIT(1,7)=25
60080      MCRIT(2,2)=10
60090      MCRIT(2,3)=12
60100      MCRIT(2,4)=18
60110      MCRIT(2,5)= 3

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60120	MCRIT(2,6)=14
60130	MCRIT(2,7)= 8
60140	MCRIT(2,8)=25
60150	MCRIT(2,9)=13
60160	MCRIT(2,10)=16
60170	MCRIT(3,2)= 3
60180	MCRIT(3,3)= 6
60190	MCRIT(3,4)=15
60200	MCRIT(3,5)=20
60210	MCRIT(3,6)=25
60220	MCRIT(4,2)= 7
60230	MCRIT(4,3)= 4
60240	MCRIT(4,4)= 2
60250	MCRIT(4,5)=25
60260	MCRIT(5,2)= 9
60270	MCRIT(5,3)=10
60280	MCRIT(9,5)=13
60290	MCRIT(12,11)= 5
60300	MCRIT(13,2)= 2
60310	MCRIT(12,7)= 3
60320	MCRIT(12,8)=10
60330	MCRIT(12,9)=12
60340	MCRIT(12,10)=11
60350	MCRIT(13,3)= 1
60360	MCRIT(13,4)= 7
60370	MCRIT(13,5)= 4
60380	MCRIT(13,6)=17
60390	MCRIT(13,7)=13
60400	MCRIT(14,2)= 3
60410	MCRIT(9,6)= 7
60420	MCRIT(9,7)= 5
60430	MCRIT(9,8)=10
60440	MCRIT(9,9)=17
60450	MCRIT(9,10)= 1
60460	MCRIT(9,11)=14
60470	MCRIT(10,2)= 2
60480	MCRIT(10,3)= 7
60490	MCRIT(10,4)=18
60500	MCRIT(10,5)= 3
60510	MCRIT(10,6)=14
60520	MCRIT(10,7)= 4
60530	MCRIT(10,8)= 8
60540	MCRIT(11,2)= 5
60550	MCRIT(11,3)= 1
60560	MCRIT(11,4)=11
60570	MCRIT(11,5)= 3
60580	MCRIT(11,6)=14
60590	MCRIT(11,7)= 4
60600	MCRIT(11,8)= 8
60610	MCRIT(12,2)= 6
60620	MCRIT(12,3)= 7
60630	MCRIT(12,4)= 4

60640	MCRIT(12,5)=13
60650	MCRIT(12,6)= 2
60660	MCRIT(5,4)= 4
60670	MCRIT(5,5)= 1
60680	MCRIT(5,6)= 8
60690	MCRIT(5,7)= 2
60700	MCRIT(5,8)= 6
60710	MCRIT(5,9)=25
60720	MCRIT(6,2)= 4
60730	MCRIT(6,3)= 8
60740	MCRIT(6,4)= 2
60750	MCRIT(6,5)=10
60760	MCRIT(6,6)= 1
60770	MCRIT(6,7)= 6
60780	MCRIT(6,8)=14
60790	MCRIT(6,9)= 9
60800	MCRIT(6,10)= 5
60810	MCRIT(6,11)=25
60820	MCRIT(7,2)= 8
60830	MCRIT(7,3)= 2
60840	MCRIT(7,4)= 1
60850	MCRIT(7,5)=10
60860	MCRIT(7,6)=21
60870	MCRIT(7,7)=13
60880	MCRIT(7,8)=14
60890	MCRIT(7,9)= 6
60900	MCRIT(8,2)= 6
60910	MCRIT(8,3)=10
60920	MCRIT(8,4)= 4
60930	MCRIT(9,2)=18
60940	MCRIT(9,3)= 4
60950	MCRIT(9,4)= 2
60960	MCRIT(14,3)= 4
60970	MCRIT(14,4)=15
60980	MCRIT(14,5)=12
60990	MCRIT(15,2)=20
61000	MCRIT(15,3)=15
61010	MCRIT(15,4)= 1
61020	MCRIT(15,5)= 4
61030	MCRIT(16,2)= 1
61040	MCRIT(16,3)= 4
61050	MCRIT(16,4)= 2
61060	MCRIT(16,5)=10
61070	MCRIT(16,6)=12
61080	MCRIT(17,2)= 6
61090	MCRIT(17,3)=11
61100	MCRIT(17,4)= 8
61110	MCRIT(17,5)=18
61120	MCRIT(18,2)= 5
61130	MCRIT(18,3)= 6
61140	MCRIT(18,4)=11
61150	MCRIT(18,5)=18

61160	MCRIT(19,2)=13
61170	MCRIT(19,3)= 6
61180	MCRIT(19,4)=18
61190	MCRIT(19,5)=21
61200	MCRIT(19,6)= 1
61210	MCRIT(19,7)=14
61220	MCRIT(19,8)= 8
61230	MCRIT(19,9)= 2
61240	MCRIT(19,10)=10
61250	MCRIT(20,2)= 5
61260	MCRIT(20,3)= 2
61270	MCRIT(20,4)= 4
61280	MCRIT(20,5)= 8
61290	MCRIT(20,6)= 3
61300	MCRIT(20,7)=11
61310	MCRIT(20,8)=10
61320	MCRIT(20,9)= 1
61330	MCRIT(20,10)= 9
61340	MCRIT(21,2)=10
61350	MCRIT(21,3)= 8
61360	MCRIT(21,4)=13
61370	MCRIT(21,5)=18
61380	MCRIT(21,6)= 2
61390	MCRIT(21,7)= 1
61400	MCRIT(21,8)=14
61410	MCRIT(21,9)=13
61420	MCRIT(21,10)= 8
61430	MCRIT(22,2)= 8
61440	MCRIT(22,3)=10
61450	MCRIT(22,4)= 6
61460	MCRIT(22,5)= 2
61470	MCRIT(22,6)=13
61480	MCRIT(22,7)=14
61490	MCRIT(23,2)= 5
61500	MCRIT(23,3)=10
61510	MCRIT(23,4)= 2
61520	MCRIT(23,5)= 7
61530	MCRIT(23,6)=17
61540	MCRIT(23,7)=11
61550	MCRIT(23,8)=25
61560	MCRIT(23,9)= 3
61570	MCRIT(24,2)= 1
61580	MCRIT(24,3)= 3
61590	MCRIT(24,4)=12
61600	MCRIT(24,5)= 5
61610	MCRIT(25,2)= 1
61620	MCRIT(25,3)= 6
61630	MCRIT(25,4)= 2
61640	MCRIT(25,5)=12
61650	MCRIT(26,2)= 8
61660	MCRIT(26,3)=14
61670	MCRIT(26,4)=16

61680	MCRIT(26,5) = 6
61690	MCRIT(27,2) = 2
61700	MCRIT(27,3) = 18
61710	MCRIT(27,4) = 7
61720	MCRIT(28,2) = 3
61730	MCRIT(28,3) = 9
61740	MCRIT(29,2) = 1
61750	MCRIT(29,3) = 2
61760	MCRIT(30,2) = 12
61770	MCRIT(30,3) = 4
61780	MCRIT(31,2) = 3
61790	MCRIT(32,2) = 3
61800	MCRIT(33,2) = 5
61810	MCRIT(33,3) = 3
61820	MCRIT(33,4) = 11
61830	MCRIT(34,2) = 5
61840	MCRIT(35,2) = 16
61850	MCRIT(35,3) = 15
61860	MCRIT(36,2) = 9
61870	MCRIT(37,2) = 20
61880	MCRIT(37,3) = 4
61890	MCRIT(38,2) = 7
61900	MCRIT(39,2) = 14
61910	MCRIT(39,3) = 12
61920	MCRIT(39,4) = 8
61930	MCRIT(39,5) = 4
61940	MCRIT(40,2) = 12
61950	MCRIT(41,2) = 15
61960	MCRIT(41,3) = 16
61970	MCRIT(42,2) = 15
61980	MCRIT(42,3) = 4
61990	MCRIT(43,2) = 8
62000	MCRIT(43,3) = 4
62010	MCRIT(43,4) = 10
62020	MCRIT(43,5) = 14
62030	MCRIT(43,6) = 7
62040	MCRIT(43,7) = 2
62050	MCRIT(43,8) = 12
62060	MCRIT(44,2) = 4
62070	MCRIT(44,3) = 18
62080	MCRIT(44,4) = 7
62090	MCRIT(44,5) = 14
62100	MCRIT(44,6) = 2
62110	MCRIT(44,7) = 8
62120	MCRIT(45,2) = 15
62130	MCRIT(45,3) = 3
62140	MCRIT(46,2) = 1
62150	MCRIT(46,3) = 8
62160	MCRIT(47,2) = 10
62170	MCRIT(47,3) = 2
62180	MCRIT(47,4) = 13
62190	MCRIT(48,2) = 3

62200	MCRIT(49,2) = 4
62210	MCRIT(49,3) = 1
62220	MCRIT(50,2) = 7
62230	MCRIT(50,3) = 4
62240	MCRIT(50,4) =13
62250	MCRIT(50,5) =10
62260	MCRIT(50,6) = 6
62270	MCRIT(51,2) = 9
62280	MCRIT(51,3) = 2
62290	MCRIT(52,2) =10
62300	MCRIT(52,3) =13
62310	MCRIT(52,4) = 4
62320	MCRIT(52,5) =18
62330	MCRIT(52,6) = 1
62340	MCRIT(52,7) = 6
62350	MCRIT(52,8) = 8
62360	MCRIT(52,9) = 2
62370	MCRIT(53,2) = 2
62380	MCRIT(54,2) = 5
62390	MCRIT(54,3) =11
62400	MCRIT(55,2) =19
62410	MCRIT(55,3) = 3
62420	MCRIT(55,4) =17
62430	MCRIT(56,2) = 1
62440	MCRIT(56,3) =13
62450	MCRIT(56,4) = 4
62460	MCRIT(56,5) =10
62470	MCRIT(56,6) = 2
62480	MCRIT(56,7) =18
62490	MCRIT(56,8) =25
62500	MCRIT(57,2) =13
62510	MCRIT(57,3) =10
62520	MCRIT(57,4) = 2
62530	MCRIT(58,2) = 9
62540	MCRIT(58,3) = 2
62550	MCRIT(58,4) =12
62560	MCRIT(58,5) =25
62570	MCRIT(59,2) = 6
62580	MCRIT(59,3) = 8
62590	MCRIT(59,4) = 7
62600	MCRIT(59,5) =25
62610	MCRIT(59,6) =19
62620	MCRIT(59,7) =14
62630	MCRIT(60,2) = 5
62640	MCRIT(61,2) = 6
62650	MCRIT(61,3) = 3
62660	MCRIT(61,4) =13
62670	MCRIT(61,5) = 8
62680	MCRIT(61,6) =12
62690	MCRIT(62,2) = 2
62700	MCRIT(62,3) = 1
62710	MCRIT(63,2) =18

62720	MCRIT(63,3)=12
62730	MCRIT(63,4)=16
62740	MCRIT(64,2)= 1
62750	MCRIT(65,2)= 6
62760	MCRIT(65,3)= 4
62770	MCRIT(65,4)= 2
62780	MCRIT(65,5)= 8
62790	MCRIT(66,2)= 6
62800	MCRIT(66,3)= 8
62810	MCRIT(67,2)= 5
62820	MCRIT(67,3)= 2
62830	MCRIT(67,4)=10
62840	MCRIT(67,5)= 8
62850	MCRIT(68,2)= 3
62860	MCRIT(68,3)=11
62870	MCRIT(69,2)= 8
62880	MCRIT(69,3)=12
62890	MCRIT(69,4)= 9
62900	MCRIT(69,5)= 1
62910	MCRIT(69,6)= 7
62920	MCRIT(69,7)= 2
62930	MCRIT(69,8)= 4
62940	MCRIT(69,9)=10
62950	MCRIT(69,10)=13
62960	MCRIT(69,11)=18
62970	MCRIT(69,12)= 5
62980	MCRIT(69,13)=14
62990	MCRIT(70,2)= 2
63000	MCRIT(70,3)= 7
63010	MCRIT(70,4)= 4
63020	MCRIT(71,2)=15
63030	MCRIT(71,3)= 3
63040	MCRIT(71,4)=11
63050	MCRIT(71,5)= 4
63060	MCRIT(72,2)= 4
63070	MCRIT(72,3)=17
63080	MCRIT(72,4)= 1
63090	MCRIT(72,5)= 2
63100	MCRIT(72,6)=10
63110	MCRIT(72,7)=13
63120	MCRIT(73,2)=10
63130	MCRIT(73,3)= 8
63140	MCRIT(73,4)=14
63150	MCRIT(73,5)=13
63160	MCRIT(73,6)= 4
63170	MCRIT(74,2)= 1
63180	MCRIT(74,3)= 2
63190	MCRIT(74,4)=10
63200	MCRIT(75,2)= 3
63210	MCRIT(75,3)= 5
63220	MCRIT(75,4)=19
63230	MCRIT(75,5)=11

63240	MCRIT(75,6) = 7
63250	MCRIT(76,2) = 2
63260	MCRIT(76,3) = 13
63270	MCRIT(76,4) = 4
63280	MCRIT(76,5) = 7
63290	MCRIT(76,6) = 18
63300	MCRIT(76,7) = 6
63310	MCRIT(76,8) = 1
63320	MCRIT(76,9) = 14
63330	MCRIT(76,10) = 8
63340	MCRIT(77,2) = 18
63350	MCRIT(77,3) = 13
63360	MCRIT(77,4) = 8
63370	MCRIT(77,5) = 14
63380	MCRIT(77,6) = 10
63390	MCRIT(77,7) = 14
63400	MCRIT(78,2) = 3
63410	MCRIT(78,3) = 9
63420	MCRIT(79,2) = 10
63430	MCRIT(79,3) = 8
63440	MCRIT(79,4) = 13
63450	MCRIT(80,2) = 13
63460	MCRIT(80,3) = 10
63470	MCRIT(80,4) = 6
63480	MCRIT(80,5) = 4
63490	MCRIT(81,2) = 3
63500	MCRIT(81,3) = 11
63510	MCRIT(82,2) = 6
63520	MCRIT(83,2) = 2
63530	MCRIT(83,3) = 1
63540	MCRIT(83,4) = 13
63550	MCRIT(84,2) = 7
63560	MCRIT(84,3) = 2
63570	MCRIT(84,4) = 18
63580	MCRIT(85,2) = 15
63590	MCRIT(85,3) = 16
63600	MCRIT(86,2) = 2
63610	MCRIT(86,3) = 4
63620	MCRIT(87,2) = 7
63630	MCRIT(87,3) = 4
63640	MCRIT(87,4) = 6
63650	MCRIT(87,5) = 14
63660	MCRIT(87,6) = 2
63670	MCRIT(87,7) = 8
63680	MCRIT(87,8) = 18
63690	MCRIT(87,9) = 13
63700	MCRIT(88,2) = 3
63710	MCRIT(88,3) = 12
63720	MCRIT(88,4) = 9
63730	MCRIT(89,2) = 4
63740	MCRIT(89,3) = 7
63750	MCRIT(90,2) = 8

63760	MCRIT(90,3)=14
63770	MCRIT(90,4)= 6
63780	MCRIT(91,2)= 3
63790	MCRIT(91,3)=16
63800	MCRIT(91,4)= 9
63810	MCRIT(91,5)=25
63820	MCRIT(92,2)=18
63830	MCRIT(92,3)=16
63840	MCRIT(92,4)=25
63850	MCRIT(93,2)=17
63860	MCRIT(93,3)= 4
63870	MCRIT(93,4)=25
63880	MCRIT(94,2)=10
63890	MCRIT(94,3)= 5
63900	MCRIT(94,4)=13
63910	MCRIT(95,2)= 6
63920	MCRIT(95,3)= 2
63930	MCRIT(95,4)=25
63940	MCRIT(95,5)= 8
63950	MCRIT(95,6)=14
63960	MCRIT(96,2)= 3
63970	MCRIT(97,2)=18
63980	MCRIT(97,3)=14
63990	MCRIT(97,4)=12
64000	MCRIT(98,2)= 5
64010	MCRIT(98,3)=19
64020	MCRIT(99,2)=10
64030	MCRIT(99,3)=13
64040	MCRIT(99,4)=18
64050	MCRIT(99,5)=16
64060	MCRIT(100,2)= 9
64070	MCRIT(101,2)= 8
64080	MCRIT(101,3)=14
64090	MCRIT(101,4)= 2
64100	MCRIT(102,2)=13
64110	MCRIT(102,3)=10
64120	MCRIT(102,4)= 6
64130	MCRIT(102,5)= 7
64140	MCRIT(103,2)=15
64150	MCRIT(104,2)=12
64160	MCRIT(104,3)= 6
64170	MCRIT(104,4)=13
64180	MCRIT(105,2)= 3
64190	MCRIT(105,3)=12
64200	MCRIT(106,2)= 3
64210	MCRIT(107,2)= 1
64220	MCRIT(108,2)=13
64230	MCRIT(108,3)=10
64240	MCRIT(109,2)= 5
64250	MCRIT(109,3)=19
64260	MCRIT(109,4)= 4
64270	MCRIT(109,5)=11

64280	MCRIT(109,6) = 2
64290	MCRIT(110,2) = 3
64300	MCRIT(110,3) = 11
64310	MCRIT(110,4) = 15
64320	MCRIT(110,5) = 5
64330	MCRIT(111,2) = 5
64340	MCRIT(111,3) = 21
64350	MCRIT(111,4) = 2
64360	MCRIT(111,5) = 11
64370	MCRIT(112,2) = 17
64380	MCRIT(112,3) = 11
64390	MCRIT(112,4) = 4
64400	MCRIT(112,5) = 5
64410	MCRIT(112,6) = 18
64420	MCRIT(112,7) = 11
64430	MCRIT(113,2) = 5
64440	MCRIT(113,3) = 17
64450	MCRIT(113,4) = 8
64460	MCRIT(113,5) = 2
64470	MCRIT(114,2) = 3
64480	MCRIT(115,2) = 2
64490	MCRIT(115,3) = 1
64500	MCRIT(115,4) = 4
64510	MCRIT(116,2) = 18
64520	MCRIT(116,3) = 10
64530	MCRIT(116,4) = 12
64540	MCRIT(116,5) = 7
64550	MCRIT(116,6) = 8
64560	MCRIT(116,7) = 13
64570	MCRIT(117,2) = 18
64580	MCRIT(117,3) = 13
64590	MCRIT(117,4) = 12
64600	MCRIT(118,2) = 15
64610	MCRIT(118,3) = 3
64620	MCRIT(118,4) = 18
64630	MCRIT(119,2) = 1
64640	MCRIT(119,3) = 14
64650	MCRIT(119,4) = 15
64660	MCRIT(119,5) = 4
64670	MCRIT(119,6) = 6
64680	MCRIT(119,7) = 10
64690	MCRIT(120,2) = 6
64700	MCRIT(120,3) = 10
64710	MCRIT(120,4) = 13
64720	MCRIT(120,5) = 4
64730	MCRIT(120,6) = 18
64740	MCRIT(120,7) = 8
64750	MCRIT(121,2) = 8
64760	MCRIT(121,3) = 10
64770	MCRIT(121,4) = 14
64780	MCRIT(121,5) = 13
64790	MCRIT(121,6) = 6

64800	MCRIT(122,2)=15
64810	MCRIT(123,2)= 7
64820	MCRIT(123,3)=10
64830	MCRIT(123,4)= 4
64840	MCRIT(123,5)=13
64850	MCRIT(124,2)= 9
64860	MCRIT(124,3)=11
64870	MCRIT(124,4)=12
64880	MCRIT(125,2)= 9
64890	MCRIT(125,3)= 2
64900	MCRIT(125,4)=14
64910	MCRIT(125,5)=12
64920	MCRIT(125,6)= 8
64930	MCRIT(125,7)= 5
64940	MCRIT(125,8)= 3
64950	MCRIT(125,9)= 1
64960	MCRIT(125,10)=10
64970	MCRIT(125,11)=17
64980	MCRIT(126,2)= 5
64990	MCRIT(126,3)= 2
65000	MCRIT(126,4)= 3
65010	MCRIT(126,5)=19
65020	MCRIT(126,6)= 7
65030	MCRIT(126,7)= 8
65040	MCRIT(126,8)=17
65050	MCRIT(127,2)=14
65060	MCRIT(127,3)= 8
65070	MCRIT(127,4)= 3
65080	MCRIT(128,2)= 2
65090	MCRIT(128,3)= 5
65100	MCRIT(128,4)=18
65110	MCRIT(128,5)= 4
65120	MCRIT(129,2)= 2
65130	MCRIT(129,3)= 4
65140	MCRIT(129,4)=10
65150	MCRIT(129,5)=14
65160	MCRIT(129,6)= 8
65170	MCRIT(129,7)= 1
65180	MCRIT(129,8)=13
65190	MCRIT(130,2)=16
65200	MCRIT(130,3)=20
65210	MCRIT(130,4)=18
65220	MCRIT(130,5)= 3
65230	MCRIT(130,6)=15
65240	MCRIT(130,7)=10
65250	MCRIT(131,2)=14
65260	MCRIT(131,3)= 8
65270	MCRIT(131,4)= 3
65280	MCRIT(132,2)= 6
65290	MCRIT(132,3)= 2
65300	MCRIT(132,4)=14
65310	MCRIT(132,5)= 8

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65320      MCRIT(133,2) = 5
65330      MCRIT(133,3) = 19
65340      MCRIT(133,4) = 3
65350      MCRIT(133,5) = 18
65360      MCRIT(134,2) = 5
65370      MCRIT(134,3) = 15
65380      MCRIT(135,2) = 2
65390      MCRIT(135,3) = 7
65400      MCRIT(135,4) = 17
65410      MCRIT(135,5) = 4
65420      MCRIT(135,6) = 12
65430      MCRIT(136,2) = 1
65440      MCRIT(136,3) = 2
65450      MCRIT(136,4) = 10
65460      MCRIT(136,5) = 5
65470      MCRIT(137,2) = 5
65480      MCRIT(138,2) = 1
65490      MCRIT(138,3) = 2
65500      MCRIT(138,4) = 4
65510      MCRIT(139,2) = 13
65520      MCRIT(139,3) = 2
65530      MCRIT(139,4) = 10
65540      MCRIT(139,5) = 7
65550      MCRIT(139,6) = 4
65560      MCRIT(139,7) = 18
65570      MCRIT(140,2) = 2
65580      MCRIT(141,2) = 3
65590      MCRIT(141,3) = 12
65600      MCRIT(142,2) = 2
65610      MCRIT(142,3) = 4
65620      MCRIT(142,4) = 1
65630      MCRIT(143,2) = 18
65640      MCRIT(143,3) = 4
65650      MCRIT(143,4) = 6
65660      MCRIT(143,5) = 12
65670      MCRIT(144,2) = 6
65680      MCRIT(144,3) = 12
65690      MCRIT(144,4) = 2
65700      MCRIT(145,2) = 16
65710      MCRIT(145,3) = 17
65720      MCRIT(145,4) = 18
65730      MCRIT(146,2) = 18
65740      MCRIT(146,3) = 10
65750      RETURN
65760      END
70080      SUBROUTINE INIT(IX,IXS,F,E,N,INTER,NCOUNT,
70090      1MCOUNT,NULL,NA,MA,M,MGC,NP,NIP,NR,MR,MP,IH,
70091      1MCH,MCR,MCA)
70100      INTEGER E,F
70110      DIMENSION NA(438,50),MA(146,50),NULL(438),
70111      1PCT(438),NCOUNT(4,4)
70120      DIMENSION MCOUNT(28,28),MGC(16,4),N(450),M(150),

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70121      1NP(450,4)
70130      DIMENSION NR(438),MR(146),MP(150,4),MCH(150),
70131      1MCR(150),MCA(150)
70140      IX=IXS
70150      E=1
70160      F=1
70170      MCH(147)=0
70180      MCR(147)=0
70190      MCA(147)=0
70200      N(439)=2
70210      DO 13 I=1,4
70220      DO 13 J=1,4
70230      NCOUNT(I,J)=0
70240      13 CONTINUE
70250      DO 14 J=1,28
70260      DO 14 I=1,28
70270      MCOUNT(I,J)=0
70280      14 CONTINUE
70290      DO 15 I=1,438
70300      NULL(I)=0
70310      NA(I,1)=1
70320      NR(I)=0
70330      PCT(I)=0.000
70340      DO 151 J=2,50
70350      NA(I,J)=0
70360      151 CONTINUE
70370      15 CONTINUE
70380      DO 141 I=1,146
70390      MA(I,1)=1
70400      MR(I)=0
70410      M(I)=MP(I,IH)
70420      MCH(I)=0
70430      MCR(I)=0
70440      MCA(I)=0
70450      DO 1411 J=2,50
70460      MA(I,J)=0
70470      1411 CONTINUE
70480      141 CONTINUE
70490      DO 101 I=1,438
70500      N(I)=NP(I,IH)
70510      101 CONTINUE
70520      DO 1011 I=1,146,7
70530      1011 CONTINUE
70540      RETURN
70550      END
80010      SUBROUTINE TRANF(A,B1,B2,B3,C1,C2,C3,D1,D2,D3,E1,
80011      1E1,E2,E3,K)
80020      INTEGER K
80030      A=0.3971
80040      IF (K.EQ.2) GO TO 20
80050      IF (K.EQ.3) GO TO 30
80060 C *****FROM ZUCKERKANDL(1971)*****

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80070      C1=0.061
80080      C2=0.097
80090      C3=0.166
80100      D1=0.085
80110      D2=0.183
80120      D3=0.342
80130      E1=0.038
80140      E2=0.130
80150      E3=0.219
80160      B1=0.058
80170      B2=0.179
80180      B3=0.273
80190      GO TO 40
80200      20 CONTINUE
80210 C *****FROM FITCH(1967)*****
80220      C1=0.0113
80230      C2=0.0113
80240      C3=0.0715
80250      D1=0.0458
80260      D2=0.1447
80270      D3=0.2407
80280      E1=0.0277
80290      E2=0.0912
80300      E3=0.2907
80310      B1=0.1140
80320      B2=0.2377
80330      B3=0.3971
80340      GO TO 40
80350      30 CONTINUE
80360 C *****FROM DAYHOFF-P.226*****
80370      C1=0.0244
80380      C2=0.0975
80390      C3=0.1463
80400      D1=0.0122
80410      D2=0.0976
80420      D3=0.3903
80430      E1=0.0610
80440      E2=0.1586
80450      E3=0.2318
80460      B1=0.0366
80470      B2=0.1464
80480      B3=0.2318
80490      40 RETURN
80500      END
90010      SUBROUTINE TRAN1(NUC,I,INTER,N,IX)
90020      DIMENSION N(450)
90030      NUC=N(I)
90040      B=0.066666667
90050      C=0.033333333
90060      CALL RANDOM (IX,P)
90070      IF (P.GT.0.1) GO TO 33
90080      IF (P.LE.0.0) GO TO 33

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90090      IF (P.GE.B)   GO TO 31
90100      IF (P.LE.C)   GO TO 32
90110      N(I)=N(I)+1
90120      GO TO 33
90130      31 N(I)=N(I)+2
90140      GO TO 33
90150      32 N(I)=N(I)+3
90160      33 CONTINUE
90170      IF (N(I).GE.5) N(I)=N(I)-4
90180      RETURN
90190      END
100010      SUBROUTINE MUTATE(I,MCRIT,NULL,NUC,NCOUNT,
100020      IMCOUNT,NA,MA,N,M,MGC,E,F,NR,MR)
100030      INTEGER E,F
100040      DIMENSION NA(438,50),MA(146,50),NULL(438),
100041      INCOUNT(4,4)
100050      DIMENSION MCOUNT(28,28),MCRIT(146,14),N(450)
100060      DIMENSION MGC(16,4),NR(438),MR(146),M(150)
100070      JIN=1+((I-1)/3)
100080      J3=3*JIN
100090      J31=J3-1
100100      J32=J3-2
100110      NIP=4*N(J32)+N(J31)-4
100120      IF (M(JIN).EQ.MGC(NIP,N(J3))) GO TO 30
100130      50 ICRIT=JIN
100140      K=1
100150      DO 51 IC=2,14
100160      IF (MGC(NIP,N(J3)).EQ.MCRIT(ICRIT,IC)) K=2
100170      51 CONTINUE
100180      IF (K.EQ.2) GO TO 34
100190      NULL(I)=NULL(I)+1
100200      N(I)=NUC
100210      GO TO 30
100220      34 CONTINUE
100230      NCOUNT(NUC,N(I))=NCOUNT(NUC,N(I))+1
100240      MCOUNT(M(JIN),MGC(NIP,N(J3)))=MCOUNT(M(JIN),
100241      IMGC(NIP,N(J3)))+1
100250      E=NA(I,1)+1
100260      IF (E.GE.50) E=50
100270      NA(I,E)=NUC
100280      IP1=0
100290      DO 130 IP=2,50
100300      IPIT=NA(I,IP)
100310      IF (IPIT.EQ.N(I)) IP1=1
100320      130 CONTINUE
100330      NA(I,1)=NA(I,1)+1
100340      F=MA(JIN,1)+1
100350      IF (F.GE.50) F=50
100360      1 MA(JIN,F)=M(JIN)
100370      IP2=0
100380      DO 131 IP=2,50
100390      IPIT=MA(JIN,IP)

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100400      IF (IPIT.EQ.M(JIN)) IP2=1
100410 131  CONTINUE
100420      MA(JIN,1)=MA(JIN,1)+1
100430      M(JIN)=MGC(NIP,N(J3))
100440 30   CONTINUE
100450      IF (IP1.EQ.1) NR(I)=NR(I)+1
100460      IF (IP2.EQ.1) MR(JIN)=MR(JIN)+1
100470      IP1=0
100480      IP2=0
100490      RETURN
100500      END
110010      SUBROUTINE OUT(M,N,NA,MA,NULL,MCOUNT,NCOUNT,
110020      1HB,IXS,METH,INTER,NR,MR,MCH,MCR,MCA,MP)
110030      DIMENSION NA(438,50),MA(146,50),NULL(438),
110031      1PCT(438)
110040      DIMENSION NCOUNT(4,4),MCOUNT(28,28),N(450),
110041      1M(150)
110050      DIMENSION NR(438),MR(146),MCH(150),MCR(150),
110051      1MCA(150)
110060      DIMENSION MP(150,4)
110070      DO 1000 I=1,21
110080      MCOUNT(I,21)=MCOUNT(I,25)
110090      MCOUNT(21,I)=MCOUNT(25,I)
110100      MCOUNT(21,21)=MCOUNT(25,25)
110110      DO 1001 J=1,21
110120      IVAL=MCOUNT(I,J)
110130      WRITE (10,100) (HB,METH,IXS,INTER,IVAL)
110140 1001 CONTINUE
110150 1000 CONTINUE
110160      DO 1002 I=1,4
110170      DO 1003 J=1,4
110180      IVAL=NCOUNT(I,J)
110190      WRITE (11,100) (HB,METH,IXS,INTER,IVAL)
110200 1003 CONTINUE
110210 1002 CONTINUE
110220      DO 1005 I=1,438
110230      NA(I,1)=NA(I,1)-1
110240      IVAL=NA(I,1)
110250      WRITE (13,100) (HB,METH,IXS,INTER,IVAL)
110260 1005 CONTINUE
110270      DO 1006 I=1,438
110280      IVAL=NR(I)
110290      WRITE (14,100) (HB,METH,IXS,INTER,IVAL)
110300 1006 CONTINUE
110310      DO 1007 I=1,146
110320      IVAL=MR(I)
110330      WRITE (15,100) (HB,METH,IXS,INTER,IVAL)
110340 1007 CONTINUE
110350      DO 1004 I=1,438
110360      IDEM1=I
110370      IVAL=NULL(I)
110380      WRITE (12,100) (HB,METH,IXS,INTER,IVAL)

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110390 1004 CONTINUE
110400      DO 1 J=1,3
110410      DO 2 I=1,146
110420      IF (MP(I,J).EQ.M(I)) GO TO 3
110430      GO TO 2
110440      3 IF (J.EQ.1) MCH(I)=1
110450      IF (J.EQ.2) MCR(I)=1
110460      IF (J.EQ.3) MCA(I)=1
110470      2 CONTINUE
110480      1 CONTINUE
110490      MCH(147)=0
110500      MCR(147)=0
110510      DO 4 I=1,146
110520      MCH(147)=MCH(147)+MCH(I)
110530      MCR(147)=MCR(147)+MCR(I)
110540      MCA(147)=MCA(147)+MCA(I)
110550      4 CONTINUE
110560      DO 5 I=1,147
110570      WRITE (20,100) (HB,METH,IXS,INTER,MCH(I))
110580      WRITE (21,100) (HB,METH,IXS,INTER,MCR(I))
110590      WRITE (22,100) (HB,METH,IXS,INTER,MCA(I))
110600      5 CONTINUE
110610 100 FORMAT (10X,I2,1X,I2,1X,I8,1X,I6,1X,I8)
110620      RETURN
110630      END
120010      SUBROUTINE RANDOM(IX,P)
120020      IY=IX*1220703125
120030      IF(IY)3,4,4
120040      3 IY=IY+2147483647+1
120050      4 RN=IY
120060      RN=RN*0.4656613E-9
120070      P=24.3*RN-10.
120080      IX=IY
120090      RETURN
120100      END
130010      SUBROUTINE RESULT(M,N,NA,MA,NULL,MCOUNT,NCOUNT)
130020      DIMENSION NA(438,50),MA(146,50),NULL(438),
130021      1PCT(438)
130030      DIMENSION NCOUNT(4,4),MCOUNT(28,28),N(450),
130031      1M(150)
130040      IXS=3513
130050      PRINT 38,(M(J),J=1,146)
130060      PRINT 45,((MCOUNT(I,J),I=1,25),J=1,25)
130070      PRINT 391
130080      PRINT 39,(N(I),I=1,438)
130090      PRINT 44,((NCOUNT(I,J),I=1,4),J=1,4)
130100      PRINT 421
130110      DO 40 I=1,438
130120      NA1=NA(I,1)
130130      IF (NA1.EQ.1) GO TO 40
130140      IF (NA1.GE.50) NA1=50
130150      PRINT 42,I,(NA(I,J),J=1,NA1)

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130160      40 CONTINUE
130170          PRINT 431
130180          DO 41 I=1,146
130190              MA1=MA(I,1)
130200              IF (MA1.EQ.1) GO TO 41
130210              IF (MA1.GE.25) MA1=25
130220              PRINT 43,I,(MA(I,J),J=1,MA1)
130230      41 CONTINUE
130240          PRINT 551
130250          DO 56 I=1,438,6
130260              IF (NULL(I).EQ.0) GO TO 56
130270              PRINT 55,I,NULL(I),NULL(I+1),NULL(I+2),
130280              1NULL(I+3),NULL(I+4),NULL(I+5)
130290      56 CONTINUE
130300          PRINT 531
130310          DO 54 I=1,438
130320              PCT(I)=100.*NA(I,1)/(NA(I,1)+NULL(I))
130330      54 CONTINUE
130340          DO 52 I=1,438,6
130350              PRINT 53,I,PCT(I),PCT(I+1),PCT(I+2),PCT(I+3),
130351              1PCT(I+4),PCT(I+5)
130360      52 CONTINUE
130370      36 FORMAT (15H00N INTERATION ,I7,10H POSITION ,I4,
130380              16H FROM ,I2,4H TO ,I2)
130390      37 FORMAT (4H AA ,I3,14H CHANGED FROM ,I2,4H TO ,
130391              1I2)
130400      38 FORMAT (20I3)
130410      39 FORMAT (30I2)
130420      42 FORMAT (I4,2X,I2,49I3)
130430      43 FORMAT (I4,2X,I2,24I5)
130440      44 FORMAT (26H0NUCLEID ACID CHANGE TABLE/15X,2HTO/
130441              16H FROM ,3X,1HA,
130450              13X,1HC,3X,1HG,3X,1HT/3X,1HA,2X,4I4/3X,1HC,2X,
130451              14I4/3X,1HG,2X,4I4/
130460              13X,1HT,2X,4I4)
130470      45 FORMAT (25H0 AMINO ACID CHANGE TABLE/39X,2HTO/
130471              16H FROM ,
130480              11HG,2X,1HA,2X,1HL,2X,1HS,2X,1HV,2X,1HK,2X,1HT,
130481              12X,1HE,2X,1HP,
130490              12X,1HD,2X,1HI,2X,1HR,2X,1HN,2X,1HQ,2X,1HF,2X,
130491              1HY,2X,1HC,2X,
130500              11HH,2X,1HM,2X,1HW,12X,4HSTOP/2H G,2X,25I3/2H A,
130501              12X,25I3/2H L,
130510              12X,25I3/2H S,2X,25I3/2H V 2X,25I3/2H K,2X,25I3/
130511              12H T,2X,25I3/
130520              12H E,2X,25I3/2H P,2X,25I3/2H D,2X,25I3/2H I,2X,
130521              125I3/2H R,2X,
130530              125I3/2H N,2X,25I3/2H Q,2X,25I3/2H F,2X,25I3/
130531              12H Y,2X,25I3/2H C,
130540              12X,25I3/2H H,2X,25I3/2H M,2X,25I3/2H W,2X,25I3/
130550              14X,25I3/4X,25I3/4X,25I3/4X,25I3/1X,4HSTOP,25I3)
130560      53 FORMAT(I4,6F10.3)

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130570      55 FORMAT (I4,6I5)
130580      381 FORMAT(21H0STARTING AMINO ACIDS/)
130590      382 FORMAT(19H0ENDING AMINO ACIDS/)
130600      391 FORMAT(21H0ENDING NUCLEIC ACIDS/)
130610      421 FORMAT (34H0 NUCLEOTIDE MUTATIONS BY POSITION//
130611          15H NA ,5HQUNT/)
130620      431 FORMAT (34H0 AMINO ACID MUTATIONS BY POSITION//
130621          15H AA ,5HQUNT/)
130630      531 FORMAT (29H0PERCENT ACCEPTABLE MUTATIONS/)
130640      551 FORMAT (46H0 COUNT OF DISALLOWED MUTATIONS BY N
130641          1A POSITION)
130650          RETURN
130660          END
140010      SUBROUTINE TRAN2(NUC,I,INTER,N,K,IX)
140020          INTEGER K
140030          DIMENSION N(450)
140040          NUC=N(I)
140050          CALL RANDOM (IX,P)
140060          IF (P.LT.0.0) GO TO 341
140070          CALL TRANF(A,B1,B2,B3,C1,C2,C3,D1,D2,D3,E1,E2,
140071          1E3,K)
140080          IF (P.GT.A) GO TO 341
140090          NUC=N(I)
140100          IF (NUC.EQ.1) GO TO 31
140110          IF (NUC.EQ.2) GO TO 32
140120          IF (NUC.EQ.3) GO TO 33
140130          IF (P.GE.B3) GO TO 341
140140          IF (P.LE.B1) N(I)=N(I)-1
140150          IF (P.GE.B2) N(I)=N(I)+1
140160          N(I)=N(I)-2
140170          GO TO 341
140180      31 IF (P.GE.C3) GO TO 341
140190          N(I)=N(I)+2
140200          IF (P.LE.C1) N(I)=N(I)-1
140210          IF (P.GE.C2) N(I)=N(I)+1
140220          GO TO 341
140230      32 IF (P.GE.D3) GO TO 341
140240          N(I)=N(I)+1
140250          IF (P.LE.D1) N(I)=N(I)-2
140260          IF (P.GE.D2) N(I)=N(I)+1
140270          GO TO 341
140280      33 IF (P.GE.E3) GO TO 341
140290          N(I)=N(I)-1
140300          IF (P.LE.E1) N(I)=N(I)-1
140310          IF (P.GE.E2) N(I)=N(I)+2
140320      341 CONTINUE
140330          RETURN
140340          END
150010      SUBROUTINE TP(T)
150020          DIMENSION T(64,3)
150030          T(1,1)=.0540
150040          T(1,2)=.0016

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150050	T(1,3)=.0191
150060	T(2,1)=.0990
150070	T(2,2)=.0198
150080	T(2,3)=.0911
150090	T(3,1)=.0530
150100	T(3,2)=.0217
150110	T(3,3)=.0337
150120	T(4,1)=.1280
150130	T(4,2)=.0230
150140	T(4,3)=.0952
150150	T(5,1)=.0270
150160	T(5,2)=.0018
150170	T(5,3)=.0198
150180	T(6,1)=.0650
150190	T(6,2)=.0061
150200	T(6,3)=.0488
150210	T(7,1)=.0870
150220	T(7,2)=.0094
150230	T(7,3)=.0220
150240	T(8,1)=.1600
150250	T(8,2)=.0125
150260	T(8,3)=.0972
150270	T(9,1)=.1600
150280	T(9,2)=.0151
150290	T(9,3)=.1540
150300	T(10,1)=.1330
150310	T(10,2)=.0692
150320	T(10,3)=.0745
150330	T(11,1)=.0740
150340	T(11,2)=.0185
150350	T(11,3)=.0423
150360	T(12,1)=.1290
150370	T(12,2)=.0176
150380	T(12,3)=.0997
150390	T(13,1)=.0550
150400	T(13,2)=.0311
150410	T(13,3)=.0517
150420	T(14,1)=.1410
150430	T(14,2)=.0101
150440	T(14,3)=.0831
150450	T(15,1)=.0890
150460	T(15,2)=.0152
150470	T(15,3)=.0684
150480	T(16,1)=.1780
150490	T(16,2)=.0137
150500	T(16,3)=.1301
150510	T(17,1)=.0530
150520	T(17,2)=.0035
150530	T(17,3)=.0282
150540	T(18,1)=.0990
150550	T(18,2)=.0194
150560	T(18,3)=.0893

150570	T(19,1)=.0530
150580	T(19,2)=.0198
150590	T(19,3)=.0308
150600	T(20,1)=.1260
150610	T(20,2)=.0342
150620	T(20,3)=.0657
150630	T(21,1)=.0240
150640	T(21,2)=.0072
150650	T(21,3)=.0240
150660	T(22,1)=.0650
150670	T(22,2)=.0063
150680	T(22,3)=.0503
150690	T(23,1)=.0870
150700	T(23,2)=.0930
150710	T(23,3)=.0217
150720	T(24,1)=.0870
150730	T(24,2)=.0032
150740	T(24,3)=.0292
150750	T(25,1)=.1600
150760	T(25,2)=.0295
150770	T(25,3)=.1558
150780	T(26,1)=.1330
150790	T(26,2)=.0640
150800	T(26,3)=.0689
150810	T(27,1)=.0740
150820	T(27,2)=.0167
150830	T(27,3)=.0382
150840	T(28,1)=.1290
150850	T(28,2)=.0165
150860	T(28,3)=.0825
150870	T(29,1)=.1600
150880	T(29,2)=.1333
150890	T(29,3)=.1333
150900	T(30,1)=.1350
150910	T(30,2)=.0053
150920	T(30,3)=.0957
150930	T(31,1)=.1240
150940	T(31,2)=.0157
150950	T(31,3)=.1033
150960	T(32,1)=.0740
150970	T(32,2)=.0072
150980	T(32,3)=.0489
150990	T(33,1)=.0540
151000	T(33,2)=.0135
151010	T(33,3)=.0270
151020	T(34,1)=.0990
151030	T(34,2)=.0198
151040	T(34,3)=.0912
151050	T(35,1)=.0530
151060	T(35,2)=.0217
151070	T(35,3)=.0337
151080	T(36,1)=.1280

151090	T(36,2) = .0199
151100	T(36,3) = .0995
151110	T(37,1) = .0270
151120	T(37,2) = .0000
151130	T(37,3) = .0221
151140	T(38,1) = .0650
151150	T(38,2) = .0061
151160	T(38,3) = .0488
151170	T(39,1) = .0870
151180	T(39,2) = .0094
151190	T(39,3) = .0220
151200	T(40,1) = .1600
151210	T(40,2) = .0125
151220	T(40,3) = .0972
151230	T(41,1) = .1600
151240	T(41,2) = .0205
151250	T(41,3) = .1486
151260	T(42,1) = .1330
151270	T(42,2) = .0692
151280	T(42,3) = .0745
151290	T(43,1) = .0740
151300	T(43,2) = .0185
151310	T(43,3) = .0423
151320	T(44,1) = .1290
151330	T(44,2) = .0183
151340	T(44,3) = .1062
151350	T(45,1) = .0550
151360	T(45,2) = .0467
151370	T(45,3) = .0517
151380	T(46,1) = .1410
151390	T(46,2) = .0101
151400	T(46,3) = .0831
151410	T(47,1) = .0880
151420	T(47,2) = .0152
151430	T(47,3) = .0684
151440	T(48,1) = .1780
151450	T(48,2) = .0123
151460	T(48,3) = .1666
151470	T(49,1) = .0530
151480	T(49,2) = .0035
151490	T(49,3) = .0283
151500	T(50,1) = .0990
151510	T(50,2) = .0194
151520	T(50,3) = .0893
151530	T(51,1) = .0530
151540	T(51,2) = .0198
151550	T(51,3) = .0308
151560	T(52,1) = .1280
151570	T(52,2) = .0259
151580	T(52,3) = .0743
151590	T(53,1) = .0240
151600	T(53,2) = .0032

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151610      T(53,3)=.0240
151620      T(54,1)=.0650
151630      T(54,2)=.0063
151640      T(54,3)=.0503
151650      T(55,1)=.0870
151660      T(55,2)=.0093
151670      T(55,3)=.0217
151680      T(56,1)=.0870
151690      T(56,2)=.0034
151700      T(56,3)=.0428
151710      T(57,1)=.1600
151720      T(57,2)=.0215
151730      T(57,3)=.1569
151740      T(58,1)=.1330
151750      T(58,2)=.0640
151760      T(58,3)=.0689
151770      T(59,1)=.0740
151780      T(59,2)=.0167
151790      T(59,3)=.0382
151800      T(60,1)=.1290
151810      T(60,2)=.0227
151820      T(60,3)=.0992
151830      T(61,1)=.1600
151840      T(61,2)=.1333
151850      T(61,3)=.1333
151860      T(62,1)=.1350
151870      T(62,2)=.0101
151880      T(62,3)=.0605
151890      T(63,1)=.1240
151900      T(63,2)=.0231
151910      T(63,3)=.0938
151920      T(64,1)=.0740
151930      T(64,2)=.0072
151940      T(64,3)=.0489
151950      RETURN
151960      END
160080      SUBROUTINE TRAN3(NUC,I,INTER,N,T,IX)
160090      DIMENSION N(450),T(64,3)
160100      CALL RANDOM (IX,P)
160110      NUC=N(I)
160120      IF (P.LT.0.0) GO TO 341
160130      IA=I+1
160140      IB=I-1
160150      IT=N(IA)+4*(N(I)-1)+16*(N(IB)-1)
160160      IF (P.GE.T(IT,1)) GO TO 341
160170      NUC=N(I)
160180      IF (NUC.EQ.1) GO TO 31
160190      IF (NUC.EQ.2) GO TO 32
160200      IF (NUC.EQ.3) GO TO 33
160210      IF (P.LE.T(IT,2)) N(I)=N(I)-1
160220      IF (P.GE.T(IT,3)) N(I)=N(I)+1
160230      N(I)=N(I)-2

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160240      GO TO 341
160250      31 N(I)=N(I)+2
160260          IF (P.LE.T(IT,2)) N(I)=N(I)-1
160270          IF (P.GE.T(IT,3)) N(I)=N(I)+1
160280      GO TO 341
160290      32 N(I)=N(I)+1
160300          IF (P.LE.T(IT,2)) N(I)=N(I)-2
160310          IF (P.GE.T(IT,3)) N(I)=N(I)+1
160320      GO TO 341
160330      33 N(I)=N(I)-1
160340          IF (P.LE.T(IT,2)) N(I)=N(I)-1
160350          IF (P.GE.T(IT,3)) N(I)=N(I)+2
160360      341 CONTINUE
160370      RETURN
160380      END

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