PHYSICAL AND MONTE CARLOS SIMULATION OF CONTINUOUS TIME MODEL OF SICKLE CELL ANAEMIA

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Abstract

Sickle Cell Disease (SCD) is a potentially devastating condition that is caused by an autosomal recessive inherited hemoglobinopathy which results in the vaso-occlusive phenomena and hemolysis. Sickle Cell anaemia is the most common form of Sickle Cell Disease. As such, this paper provides an insight on the mathematical transmission dynamics of Sickle Cell Anaemia and develops a physical realistic model. A female dominant renewal equation of birth dynamics was developed for both populations with genotype screening and without genotype screening. By Hardy-Weinberg equation we obtained the frequency of different genotype groups for the physical simulation. Thereafter, Monte Carlos simulation techniques was carried out to justify our position on the renewal equation. We observed that accessible curative measure still stands the only solution to the menace of Sickle Cell Anaemia in our society.

Introduction

Individual genotype **AA, AS, SS, SC** or **AC** differs amongst the world's population [13]. Of interest however, is the fact that genetic mechanism on morphogenetic traits is still not clearly understood as it is seen to occur with variable frequency in different populations and thus useful in evaluating and analyzing evolutionary forces and classification.[4] Meanwhile, marked inter-individual variability in genetic and non-genetic factors has been said to posses the ability to influence the disposition of many endobiotics and xenobiotic affecting health.[11]

Sickle Cell Anaemia which is a genetically transmitted disease is caused by a defective allele (mutant form) of the gene coding for a sub unit of the haemoglobin protein. The Sickle haemoglobin tends to precipitate or "clump together" within the red blood cells after releasing its oxygen. If the clumping is extensive the red blood cell assumes an abnormal sickle shape. These sickle red blood cells plug the blood vessels thus preventing normal red blood cell passage and consequently depriving the tissue of needed oxygen.

Each person has two copies of the gene that determines whether that person has Sickle Cell Anaemia. If both copies are "normal alleles" then only normal haemoglobin is produced **AA**. If one of the two alleles is defective then that person has a mixture of normal and Sickle haemoglobin: a condition known as Sickle Cell trait "**AS**" (Carrier). If both alleles are defective, essentially only sickle haemoglobin is made and the person has Sickle Cell Anaemia "**SS**".

The first case of **SCA** was reported in 1910 on a Jamaican student in the USA.[7] The term **SCA** is a term first used by Mason in 1922 to describe the homozygous state.[14] In 1949, Neel illustrated that **SCA** was transmitted as a recessive gene '**S**'. But it is well known by scientist now that the gene is neither dominant nor recessive but of intermediate penetrance.

The allele causing Sickle Cell Amaemia is found most often in people of African ancestry. It was traced to one family in Ghana (krobo people) in 1670. The "**S**" gene is found mainly where malaria is endemic.[9] It also occurs in people of Mediterranean, Arab, East India, South and Central American ancestry. From the world population of about 7,058, 157,073[20] (No of people officially counted). 5% of world population lives with SCD.[11] mathematically, about 352,907,854 people have haemoglobin disorder "officially counted" while every year 300,000 infants are born with SCD, including 200,000 cases in Africa.[6] Nigeria of about 150 million population with growth rate of 3.2% has prevailing rate of 150,000 offspring per year. Nigeria by the virtue of her population ranks first as a **SCA** endemic country in Africa with annual infant deaths totally around 100,000, 8% of infant

mortality. This alarming infant death related to **SCA** made the authors to carryout mathematical transmission dynamics and its simulations.

Literature Review

Mathematical models of heredity are largely based on one-locus, two allele gene populations, where little or no attempt is made to consider the dynamics of the population and the analysis is somehow probabilistic, accounting of genotype composition of a diploid population. Nevertheless, success approaches have been developed for continuous-time model that laid more emphasis on the dynamics of population of SCA[19]. K. H. Rosen 1983 presented a mathematical model for polygamous system, where he introduced the interaction function (KMF) where M, F, were the male & female population sizes. A new set of functional differential equations modeling heterosexual population dynamics where K was called the polygamy factor was developed by C.O.A Sowunmi in 1993[15]. Here he proved that population renewal is the product of an interaction between the reproductive males and non-gestating reproductive females. C.O.A. Sowunmi and J. M. Tchuenche were the first to use the general interaction function Fij.[9] where Fij contributes the major mathematical background for the formulation of our birth renewal equation. J.M Tchuenche has done a lot in the dynamics of SCA. He is the pioneer mathematician who made use of differential equation to model the disease (SCA). J.M Tchuenche (2000) demonstrated the dynamical behaviour of SCA by a set of first-order non-linear partial differential equation. He also developed the birth renewal equation the same year. General modeling approach which considered the selective advantage of Haemoglobin **(S)** over haemoglobin (**HbA**) was introduced by J. M Tcheunche. The age and character-dependent population dynamics model of genetically transmitted diseases where standard techniques of functional analysis were employed to further simplify and solve the basic equations implicitly in special cases of **SCA** (J. M. Tchuenche 2005) was introduced. Another satisfactory progress on **SCA** was the adequate mathematical picture of pattern of inheritance of the allele "S**S**". Several models had provided solution to the following:

- How well do bounds capture behavioural features such as long term persistence of the diseases?.
- In which parameter does the model perform best and how relevant are they to the real life situation?.

Migration which is an important demographic parameter has been considered in terms of modeling **SCA** and polygamy (J. M. Tchuenche 2006). Another beauty of population dynamics of the Genetically Transmitted Disease (**SCA**) which takes age, mating behaviour and a physiological factor into account was proposed in the Theoretical population Dynamics Model of a Generically Transmitted Disease (**SCA**) J. M. Tchuenche 2006.

Chelsea Liddell et al (2011) made it critically clear with his mathematical model of sickle cell genome frequency in response to selective pressure from malaria that selection pressure for the carrier gene in the presence of increasing malaria death for either adult or children has higher frequencies of the gene as well as shortened time to reach these frequencies.

Though, with a lot of criticism prices theorem was used as a propagator of the dynamics of the SCA and the prove of the dynamical sufficiency of the model were exercised Vanreelen et al 2012.

Recently, differential impact of sickle cell trait on symptomatic and asymptomatic malaria was introduced where a decreased frequency of S-gene may eventually increase the overall prevalence of both symptomatic and asymptomatic malaria. Hence, the control of symptomatic malaria might result in evolutionary repercussion, despite short-term epidemic logical benefits Eunha Shim et al (2013).

Modeling background

A population is often regarded as a group of individuals that can cross (mate) and give birth to offspring (neonates). Human population differs with respect to their genotype, age, Rhesus factor, physiology etc. Hence they can be classified according to their distinguishable differences. The following assumptions are taken into consideration:

i The entire population has an age structure that spans through (O, L] where L is the life span.

ii A genotype structure composed of three distinct genetic subgroups is duly imposed on the population i.e. normal **AA**, carriers **AS**, and sickles **SS**.

iii Monogamy form of family setting is also assumed.

iv The spread of the population is spatially homogeneous.

v Variables x, y ε $\mathbb{R}_+$ are the independent variables age and time respectively.

Consider below:

Genotype	Sex		Phenotype
	Females	Males	
AA	f_1	m_1	Normal
AS	f_2	m_2	Carriers
SS	f_3	m_3	Sicklers

Suffixes $\boldsymbol{i}$ = 1, j = 2, k = 3 corresponding to:

AA: = 1

AS: = 2

SS: = 3 respectively

$f_{\boldsymbol{i}}$ (x,y) $\geq$ 0 represents the population density of females in group $\boldsymbol{i}$ with age x at time y.

$m_{\boldsymbol{i}}$ (x, y) $\geq$ 0 represents the population density of males in group $\boldsymbol{i}$ with age x at time y.

F_{ij} {[m_i (x,y); f_j (x^1,y)], x,x^1y} – function governing the interaction between males of class 'i' males and females of class 'j'.

δ_{ij}^{k}- Is the probability of getting a neomate of class 'k' from mating between class 'i' males and class 'j' females.

Γ – The probability of acquiring the S gene from any of the parents.

f_i^j – Number of females of class'i' interacting with class 'j'males (Referred to as number of couples) in a monogamous setting.

(a) F_{ij} [(f_i; m_1, m_2, m_3,) α, α^1, y]. In this case, every females at reproductive age has just a life partner and vice-versa.

(b) F_{ij} [(m_i; f_1, f_2, f_3,) α^1, α, y]. This means some males of class 'i'interact with normal females f_1, others with females carriers f_2, and the remaining with sicklers f_3. In this case polygamy may arise. In the sequel we shall refer only to the former.

We cannot affirm with certainty that a woman aged x will marry a man aged x^1. This is a problem that takes into cognizance numerous factors that cannot be controlled mathematically. We have therefore modified the interaction function F_{ij} to suit our case where the population is subdivided into three groups; namely, **AA, AS** and **SS.** Our two-sex mixing function F_{ij} can be defined as:

$$F_{ij} \coloneqq F_{ij} \{[f_i (\alpha, y); m_j ((\alpha^1, y)]; \alpha, \alpha^1, y\}.$$

Where F_{ij} is a positive real-valued function and has compact support with respect to (α, α^1). The reproductive age of females spans the interval $[w_{f_r}, w_{f_s}]$ and $[w_{m_r}, w_{m_s}]$ for males. Hence;

Supp $F_{ij} \leq [w_{f_r}, w_{f_s}]$ x $[w_{m_r}, w_{m_s}]$

<u>Results of the Different mating patterns</u>

The techniques employed to derive the results of mating placed more emphasis on the individuals than the genetics.

The possible outcome of the interactions could produce[2]

Normal individuals:

F_{11} $[(f_1; m_1), \alpha, \alpha^1, y]$

F_{12} $[(f_1; m_2), \alpha, \alpha^1, y]$

F_{22} $[(f_2; m_2), \alpha, \alpha^1, y]$

Carriers:

F_{12} $[(f_1; m_2), \alpha, \alpha^1, y]$

F_{13} $[(f_1; m_3), \alpha, \alpha^1, y]$

F_{22} $[(f_2; m_2), \alpha, \alpha^1, y]$

F_{23} $[(f_2; m_3), \alpha, \alpha^1, y]$

Sicklers:

F_{22} $[(f_2; m_2), \alpha, \alpha^1, y]$

F_{23} $[(f_2; m_3), \alpha, \alpha^1, y]$

F_{33} $[(f_3; m_3), \alpha, \alpha^1, y]$

The probabilities of acquiring the gene from either parents are the same, this point is worth noting, because this is what implies $F_{ij} = F_{ji}$, since

Derivation of birth equation:

For $x \in (O, L]$ $0 \leq \delta_{ij}^k \leq 1$ and the compactness of the support of F_{ij}; the birth equations are given below:

$$\boldsymbol{B}_{1(y)} = \int_0^\infty \int_0^\infty (\delta_{11}^{(1)} F_{11} + \delta_{12}^{(1)} F_{12} + \delta_{22}^{(1)} F_{22})\, d\propto d\propto^{\iota} \ldots\ldots\ldots\ldots\ldots\ldots \text{(i)}$$

$$\boldsymbol{B}_{2(y)} = \int_0^\infty \int_0^\infty (\delta_{12}^{(2)} F_{12} + \delta_{13}^{(2)} F_{13} + \delta_{22}^{(2)} F_{22} + \delta_{23}^{(2)} F_{23})\, d\propto d\propto^{\iota} \ldots\ldots\ldots\ldots\ldots\text{(ii)}$$

$$\boldsymbol{B}_{3(y)} = \int_0^\infty \int_0^\infty (\delta_{22}^{(3)} F_{22} + \delta_{23}^{(3)} F_{23} + \delta_{33}^{(3)} F_{33})\, d\propto d\propto^{\iota} \ldots\ldots\ldots\ldots\ldots\ldots\text{(iii)}$$

And

$$\beta = \sum_{n=1}^{3} \mathcal{B}_n(y)$$

Properties of $B_n(y)$

1. $B_n(y)$ is well defined and non negative $F_{ij} > 0$. Human beings are a good example of birth flow population in which birth occur continuously over the time interval.
2. $B_{n(y)}$ is a first degree homogeneous function of its arguments i.e $B_n K F_{ij(y)} = KB_n F_{ij(y)}$.
3. $B_{n(y)} = 0$ for any population in which either male or female is absent.

Now if genotype screening is duly imposed on the model (i.e the relative activities between AS x AS, AS x SS, and SS x SS become zero). Hence, we have the birth equation as given below:

$$\hat{B}_1(y) = \int_0^{\propto} \int_0^{\propto} (\delta_{11}^{(1)} F_{11} + \delta_{12}^{(1)} F_{12})\, d\propto\, d\propto^1 < B_{1(y)} \ldots\ldots\ldots\ldots\ldots\ldots\text{(iv)}$$

$$\hat{B}_2(y) = \int_0^{\propto} \int_0^{\propto} (\delta_{12}^{(2)} F_{12} + \delta_{13}^{(2)} F_{13})\, d\propto\, d\propto^1 < B_{2(y)} \ldots\ldots\ldots\ldots\ldots\ldots\text{(v)}$$

$$\hat{B}_3 = 0 \ldots\ldots\ldots\ldots\ldots\ldots\text{(iv)}$$

From (iv), (v) and (vi) there will be no birth of sicklers, there is drastical decline in the birth equation and there is abundant of **AS** in the population.

Physical simulation of the model

This will help to clarify the biological process behind the mathematical model. To reduce the complexity of the generation gene pool, two alleles namely HbA (normal allele) and HbS (sickle cell allele) haemoglobin of males and non gestating reproductive females were only taken into account.

We used beads of different colours to represent alleles. The births are simulated by randomly drawing beads from the gene pool. For each generation number of individuals with each of three possible allele combination (namely **AA, AS, SS** are obtained $F_{ij} = F_{ji}$ i.e. AS and SA are indistinguishable.) were drawn

According to Adeyinka Falusi (Haematologist) the President Sickle Cell Hope Alive Foundation (SCHAF) January, 2014 and Segun Ashimolowo (Haematologist) June, 2014.

"Nigeria has about 5 million people with SS genotype, 40 million with AS genotype and about 66-72% with AA genotype"[1]. Mathematically, Nigeria accounts for ¾ of people living with SCD globally.

Hence the generation gene pool constitutes alleles which replicates the genotypic population of Nigeria. The population size of the gene pool is taken to be 3136 alleles. This represents the initial genetic make up of a reproductive non-gestating female and male adults. Hence, in the gene pool we have 2640 **A** alleles and 496 **S** alleles. That is, 1568 reproductive couples are considered.

Let P be the frequency of the allele "(**A**)" in the population and let q be the frequency of the allele "**S**" in the population. By Hardy-Weinberg equation $p^2 + 2pq + q^2$ we obtained the frequency of each generation.

Generation / trial	**AA**		**AS**		**SS**	
	NO.	**Frequency**	**NO.**	**Frequency**	**NO.**	**Frequency**
1	1111	69%	412	28%	45	3%
2	1073	75%	468	23%	27	2%
3	1021	70%	504	27%	43	3%
4	1071	68%	450	29%	47	3%
5	1112	70%	415	27%	41	3%
6	1116	70%	410	27%	42	3%
7	1113	69%	411	28%	44	3%

Domain = $\{P: 0 \leq P \leq 1\}$ and Range = $\{ B: 0 \leq B \leq 1568\}$

From the above table, we realized that an average of 70% neonates will be **AA**, 27% **AS** and 3% **SS**.

Simulation by Monte Carlos Technique

The results of the physical simulation model created the basis for the application of Monte Carlos Technique.

We simulated for number of births of different genotypes namely **AA, AS** and **SS**. Considering 156 couples which is about 10% of the couples under consideration in physical simulation model (strictly under monogamy setting). Hence, the next 156

neonates were simulated for seven generations/trials, while the random numbers were generated by SPP (Smith's Statistical Package).

Genotype	Probability	Cumulative Probability	Tag –Numbers
AA	0.69	0.69	0-68
AS	0.28	0.97	69-96
SS	0.03	1.00	97 -

Couple's Number	Random Numbers							Genotype						
	1^{st} $Gen/_{trial}$	2^{nd} $Gen/_{trial}$	3^{rd} $Gen/_{trial}$	4^{th} $Gen/_{trial}$	5^{th} $Gen/_{trial}$	6^{th} $Gen/_{trial}$	7^{th} $Gen/_{trial}$	1^{st} $Gen/_{trial}$	2^{nd} $Gen/_{trial}$	3^{rd} $Gen/_{trial}$	4^{th} $Gen/_{trial}$	5^{th} $Gen/_{trial}$	6^{th} $Gen/_{trial}$	7^{th} $Gen/_{trial}$
1.	59	42	4	97	70	42	3	AA	AA	AA	SS	AS	AA	AA
2.	80	66	98	82	88	63	82	AS	AA	SS	AS	AS	AA	AS
3.	2	98	3	74	36	56	29	AA	SS	AA	AS	AA	AA	AA
4.	7	43	66	12	29	49	15	AA	AA	AA	AA	AA	AA	AA
5.	52	0	24	74	94	3	31	AA	AA	AA	AS	AS	AA	AA
6.	73	37	49	10	58	46	77	AS	AA	AA	AA	AA	AA	AS
7.	49	31	11	54	65	35	48	AA	AA	AA	AA	AA	AA	AA
8.	89	64	99	7	44	68	8	AS	AA	SS	AA	AA	AA	AA
9.	76	75	45	63	86	44	70	AS	AS	AA	AA	AS	AA	AS
10.	54	90	16	13	0	8	77	AA	AS	AA	AA	AA	AA	AS
11.	94	50	17	64	6	86	8	AS	AA	AA	AA	AA	AS	AA
12.	92	94	35	68	29	67	30	AS	AS	AA	AA	AA	AA	AA
13.	40	47	79	70	26	78	36	AA	AA	AS	AS	AA	AS	AA
14.	95	42	31	57	44	53	11	AS	AA	AA	AA	AA	AA	AA
15.	16	48	53	35	49	70	57	AA	AA	AA	AA	AA	AS	AA

16.	14	36	5	48	11	10	79	AA	AA	AA	AA	AA	AA	AS
17.	26	20	39	24	5	8	15	AA	AA	AA	AA	AA	AA	AA
18.	19	80	71	40	80	7	89	AA	AS	AS	AA	AS	AA	AS
19.	54	0	34	32	30	88	19	AA	AA	AA	AA	AA	AS	AA
20.	28	76	71	1	43	9	56	AA	AS	AS	AA	AA	AA	AA
21.	66	10	86	25	90	33	27	AA	AA	AS	AA	AS	AA	AA
22.	73	77	69	65	21	77	13	AS	AS	AS	AA	AA	AS	AA
23.	67	87	88	29	87	20	69	AA	AS	AS	AA	AS	AA	AS
24.	8	66	39	49	26	9	88	AA	AA	AA	AA	AA	AA	AS
25.	16	44	54	82	29	35	70	AA	AA	AA	AS	AA	AA	AS
26.	82	35	70	6	63	2	77	AS	AA	AS	AA	AA	AA	AS
27.	59	82	30	64	33	67	93	AA	AS	AA	AA	AA	AA	AS
28.	34	70	5	45	76	23	67	AA	AS	AA	AA	AS	AA	AA
29.	38	82	44	38	10	55	21	AA	AS	AA	AA	AA	AA	AA
30.	61	17	34	43	13	16	8	AA	AA	AA	AA	AA	AA	AA
31.	93	93	31	99	76	23	29	AS	AS	AA	SS	AS	AA	AA
32.	0	23	39	47	47	61	71	AA	AA	AA	AA	AA	AA	AS
33.	61	90	98	31	37	82	12	AA	AS	SS	AA	AA	AS	AA
34.	3	27	32	23	11	23	97	AA	AA	AA	AA	AA	AA	AS
35.	62	92	75	30	85	52	85	AA	AS	AS	AA	AS	AA	AS
36.	35	40	9	23	56	81	19	AA	AA	AA	AA	AA	AS	AA
37.	17	9	8	62	32	56	69	AA	AA	AA	AA	AA	AA	AS
38.	46	6	59	25	18	90	4	AA	AA	AA	AA	AA	AS	AA
39.	25	8	95	20	31	6	12	AA	AA	AS	AA	AA	AA	AA
40.	56	36	70	76	54	0	40	AA	AA	AS	AS	AA	AA	AA

41.	38	80	91	73	44	48	46	AA	AS	AS	AS	AA	AA	AA
42.	14	95	9	28	83	0	43	AA	AS	AA	AA	AS	AA	AA
43.	88	98	29	49	76	75	10	AS	SS	AA	AA	AS	AS	AA
44.	62	82	87	44	78	59	53	AA	AS	AS	AA	AS	AA	AA
45.	65	18	56	57	4	64	48	AA	AA	AA	AA	AA	AA	AA
46.	77	63	67	69	49	44	23	AS	AA	AA	AS	AA	AA	AA
47.	88	81	91	37	61	35	56	AS	AS	AS	AA	AA	AA	AA
48.	38	21	1	91	4	69	91	AA	AA	AA	AS	AA	AS	AS
49.	67	60	70	13	43	9	86	AA	AA	AS	AA	AA	AA	AS
50.	24	45	73	89	80	51	76	AA	AA	AS	AS	AS	AA	AS
51.	33	60	40	0	37	71	23	AA	AA	AA	AA	AA	AS	AA
52.	0	11	64	68	70	50	93	AA	AA	AA	AA	AS	AA	AS
53.	88	7	7	46	99	18	97	AS	AA	AA	AA	SS	AA	SS
54.	78	64	35	34	5	71	86	AS	AA	AA	AA	AA	AS	AS
55.	94	68	47	60	93	98	19	AS	AA	AA	AA	AS	SS	AA
56.	68	57	42	77	1	53	24	AA	AA	AA	AS	AA	AA	AA
57.	39	87	38	75	28	82	31	AA	AS	AA	AS	AA	AS	AA
58.	29	72	68	91	85	26	44	AA	AS	AA	AS	AS	AA	AA
59.	39	5	59	52	51	4	34	AA	AA	AA	AA	AA	AA	AA
60.	49	2	27	86	6	12	78	AA	AA	AA	AS	AA	AA	AS
61.	66	63	25	52	90	72	65	AA	AA	AA	AA	AS	AS	AA
62.	63	16	59	82	93	46	72	AA	AA	AA	AS	AS	AA	AS
63.	94	31	22	97	78	47	75	AS	AA	AA	SS	AS	AA	AS
64.	11	79	19	89	26	88	20	AA	AS	AA	AS	AA	AS	AA
65.	5	47	63	11	28	85	65	AA	AA	AA	AA	AA	AS	AA

66.	46	71	31	28	27	59	10	AA	AS	AA	AA	AA	AA	AA
67.	81	25	20	79	93	50	66	AS	AA	AA	AS	AS	AA	AA
68.	18	10	9	32	46	13	66	AA	AA	AA	AA	AA	AA	AA
69.	5	78	67	94	9	54	74	AA	AS	AA	AS	AA	AA	AS
70.	5	3	8	69	12	39	97	AA	AA	AA	AS	AA	AA	SS
71.	27	9	71	91	76	39	39	AA	AA	AS	AS	AS	AA	AA
72.	94	75	41	96	80	37	86	AS	AS	AA	AS	AS	AA	AS
73.	42	54	69	14	64	42	27	AA	AA	AS	AA	AA	AA	AA
74.	58	37	74	72	85	77	15	AA	AA	AS	AS	AS	AS	AA
75.	87	18	21	26	49	46	84	AS	AA	AA	AA	AA	AA	AS
76.	28	57	16	1	82	71	90	AA	AA	AA	AA	AS	AS	AS
77.	47	86	5	98	55	48	54	AA	AS	AA	SS	AA	AA	AA
78.	81	38	25	41	86	18	24	AS	AA	AA	AA	AS	AA	AA
79.	89	11	84	96	65	95	63	AS	AA	AS	AS	AA	AS	AA
80.	37	13	42	6	29	81	23	AA	AA	AA	AA	AA	AS	AA
81.	20	51	82	90	94	77	46	AA	AA	AS	AS	AS	AS	AA
82.	46	70	41	85	30	71	74	AA	AS	AA	AS	AA	AS	AS
83.	14	69	61	96	86	61	48	AA	AS	AA	AS	AS	AA	AA
84.	70	90	69	80	99	52	65	AS	AS	AS	AS	SS	AA	AA
85.	85	78	46	96	5	69	97	AS	AS	AA	AS	AA	AS	SS
86.	93	15	7	70	11	40	61	AS	AA	AA	AS	AA	AA	AA
87.	2	57	38	73	33	31	47	AA	AA	AA	AS	AA	AA	AA
88.	86	65	23	69	76	66	27	AS	AA	AA	AS	AS	AA	AA
89.	36	95	85	58	91	94	6	AA	AS	AS	AA	AS	AS	AA
90.	74	54	33	64	54	11	15	AS	AA	AA	AA	AA	AA	AA

91.	64	39	37	84	36	69	64	AA	AA	AA	AS	AA	AS	AA
92.	2	89	12	3	57	17	83	AA	AS	AA	AA	AA	AA	AS
93.	86	36	53	88	1	28	43	AS	AA	AA	AS	AA	AA	AA
94.	47	84	35	57	0	20	62	AA	AS	AA	AA	AA	AA	AA
95.	14	14	71	65	3	15	15	AA	AA	AS	AA	AA	AA	AA
96.	28	58	42	2	69	67	33	AA	AA	AA	AA	AS	AA	AA
97.	99	93	31	75	21	58	63	SS	AS	AA	AS	AA	AA	AA
98.	88	52	22	43	88	11	48	AS	AA	AA	AA	AS	AA	AA
99.	30	86	71	38	10	26	35	AA	AS	AS	AA	AA	AA	AA
100.	55	11	77	11	36	47	32	AA	AA	AS	AA	AA	AA	AA
101.	68	30	71	63	20	84	76	AA	AA	AS	AA	AA	AS	AS
102.	8	71	52	92	91	8	8	AA	AS	AA	AS	AS	AA	AA
103.	89	82	40	86	29	74	69	AS	AS	AA	AS	AA	AS	AS
104.	16	88	75	11	98	83	51	AA	AS	AS	AA	SS	AS	AA
105.	90	76	78	70	45	68	38	AS	AS	AS	AS	AA	AS	AA
106.	29	83	83	57	80	65	78	AA	AS	AS	AA	AS	AA	AS
107.	44	56	91	86	21	75	38	AA	AA	AS	AS	AA	AS	AA
108.	86	76	10	28	71	82	29	AS	AS	AA	AA	AS	AS	AA
109.	60	98	90	0	10	22	12	AA	SS	AS	AA	AA	AA	AA
110.	21	87	71	32	39	16	86	AA	AS	AS	AA	AA	AA	AS
111.	37	39	92	42	12	55	11	AA	AA	AS	AA	AA	AA	AA
112.	80	0	41	9	90	20	13	AS	AA	AA	AA	AS	AA	AA
113.	22	90	42	24	38	52	53	AA	AS	AA	AA	AA	AA	AA
114.	96	46	63	22	98	26	65	AS	AA	AA	AA	SS	AA	AA
115.	69	36	19	10	92	83	28	AS	AA	AA	AA	AS	AS	AA

116.	35	15	39	13	74	23	63	AA	AA	AA	AA	AS	AA	AA
117.	5	66	43	47	40	98	33	AA	AA	AA	AA	AA	SS	AA
118.	11	47	93	52	56	55	27	AA	AA	AS	AA	AA	AA	AA
119.	56	80	72	86	54	15	58	AA	AS	AS	AS	AA	AA	AA
120.	74	19	12	57	17	19	67	AS	AA	AA	AA	AA	AA	AA
121.	64	66	39	95	63	26	42	AA	AA	AA	AS	AA	AA	AA
122.	93	93	92	8	33	68	20	AS	AS	AS	AA	AA	AA	AA
123.	46	22	36	81	59	35	59	AA	AA	AA	AS	AA	AA	AA
124.	78	56	17	31	35	92	53	AS	AA	AA	AA	AA	AS	AA
125.	60	78	6	96	61	44	77	AA	AS	AA	AS	AA	AA	AS
126.	31	9	60	14	84	70	34	AA	AA	AA	AA	AS	AS	AA
127.	84	37	79	68	64	67	62	AS	AA	AS	AA	AA	AA	AA
128.	76	49	35	11	43	21	31	AS	AA	AA	AA	AA	AA	AA
129.	29	81	82	39	75	30	42	AA	AS	AS	AA	AS	AA	AA
130.	37	26	21	89	35	83	86	AA	AA	AA	AS	AA	AS	AS
131.	10	79	13	75	48	20	12	AA	AS	AA	AS	AA	AA	AA
132.	20	4	26	75	50	9	15	AA	AA	AA	AS	AA	AA	AA
133.	89	50	71	75	4	25	97	AS	AA	AS	AS	AA	AA	SS
134.	69	29	20	47	46	46	19	AS	AA	AA	AA	AA	AA	AA
135.	63	83	76	94	39	51	51	AA	AS	AS	AS	AA	AA	AA
136.	96	67	62	34	9	43	27	AS	AA	AA	AA	AA	AA	AA
137.	44	66	94	47	18	20	64	AA	AA	AS	AA	AA	AA	AA
138.	86	11	59	21	2	43	33	AS	AA	AA	AA	AA	AA	AA
139.	55	87	69	97	48	48	82	AA	AS	AS	AS	AA	AA	AS
140.	17	88	41	92	1	37	45	AA	AS	AA	AS	AA	AA	AA

141.	4	73	62	68	45	72	82	AA	AS	AA	AA	AA	AS	AS
142.	60	71	84	19	52	98	70	AA	AS	AS	AA	AA	SS	AS
143.	9	53	80	87	43	45	94	AA	AA	AS	AS	AA	AA	AS
144.	8	83	56	82	42	39	45	AA	AS	AA	AS	AA	AA	AA
145.	74	62	68	52	14	76	87	AS	AA	AA	AA	AA	AS	AS
146.	99	3	72	42	40	60	40	SS	AA	AA	AA	AA	AA	AA
147.	21	53	48	29	38	50	51	AA	AA	AA	AA	AA	AA	AA
148.	54	2	10	4	27	35	14	AA	AA	AA	AA	AA	AA	AA
149.	12	59	3	72	3	54	39	AA	AA	AA	AS	AA	AA	AA
150.	66	60	86	86	25	5	85	AA	AA	AS	AS	AA	AA	AS
151.	88	68	25	27	22	39	41	AS	AA	AA	AA	AA	AA	AA
152.	66	17	16	63	49	57	56	AA	AA	AA	AA	AA	AA	AA
153.	29	75	25	96	98	85	55	AA	AS	AA	AS	SS	AS	AS
154.	82	77	87	83	4	15	99	AS	AS	AS	AS	AA	AA	SS
155.	7	45	24	1	16	89	96	AA	AA	AA	AA	AA	AS	AS
156.	38	73	24	4	71	6	85	AA	AS	AA	AA	AS	AA	AS

Result of birth from different mating

Genotype	**No of Birth**						
	1st gen./trial	2nd gen./trial	3rd gen./trial	4th gen./trial	5th gen./trial	6th gen./trial	7th gen./trial
AA	107	98	106	97	110	114	107
AS	47	55	47	55	41	39	43
SS	2	3	3	4	5	3	6

CONCLUSION

From the population size of the gene pool of 3136 alleles with 2640 **A** alleles and 496 **S** alleles.

The emergence of sicklers (**SS**) still stands the chance of average of 3% for seven trials. The implication of this is that there is great possibility for the population of **SS** to increase over time.

Applying Monte Carlos techniques where 156 births were simulated for seven trials. We critically observed that the population of sicklers (**SS**) fluctuates between 2,3,4,5 and later jumped to 6 in the 7^{th} trial which is about 4% of neonates simulated.

The consequence of this is that the population of sicklers is most likely to increase over time in this technological advancement era. Therefore a curative measure is paramount.

Considering the integral equations derived in equation (iv), (v) and (vi). We observed that there will be no birth of sicklers but meanwhile, there will be abundant of **AS** and **SS** in the population that will not likely take celibacy as a way of life. Hence the relative activities between **AS** &**AS**, **AS** & **SS** will no longer be zero.

Though bone marrow transplants is a milestone as a curative measure to SCA. But it is too expensive with an average cost of N8m – N6m which is not affordable for a common Nigerian hence we suggest that a cheaper curative measure should still stands an area of research that must not be neglected.

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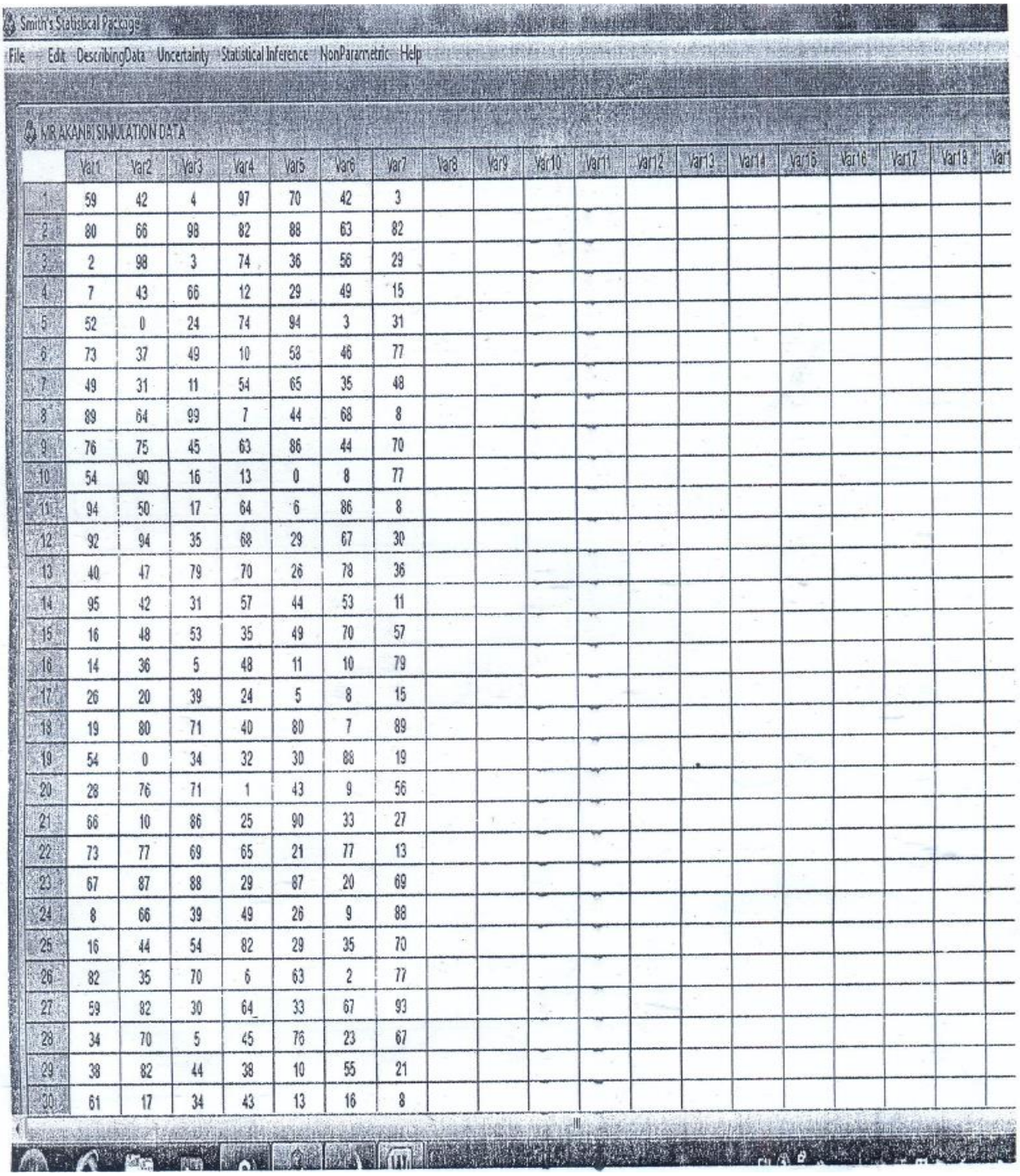
APPENDIX

Random numbers generated by Smith's Statistical Package.



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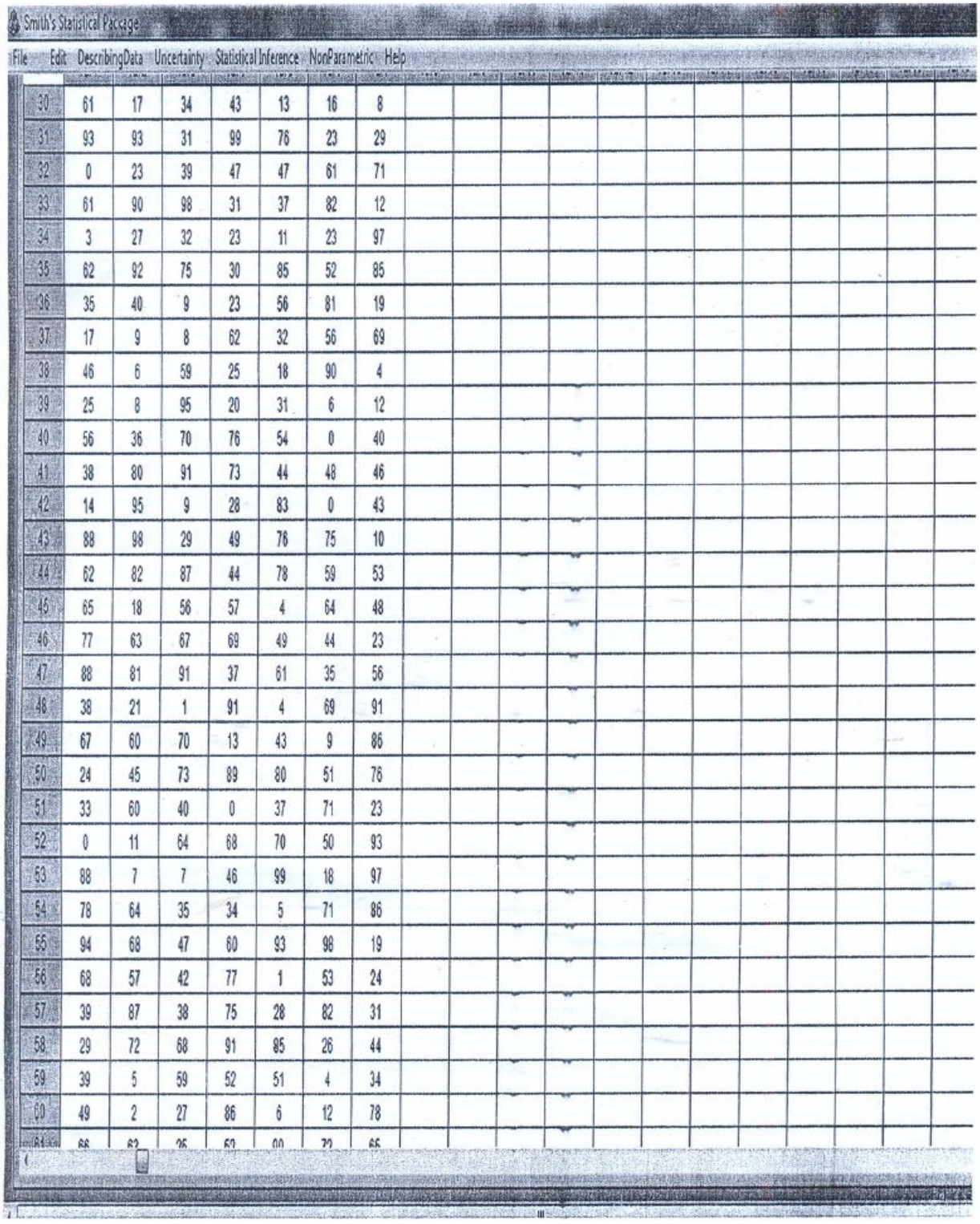

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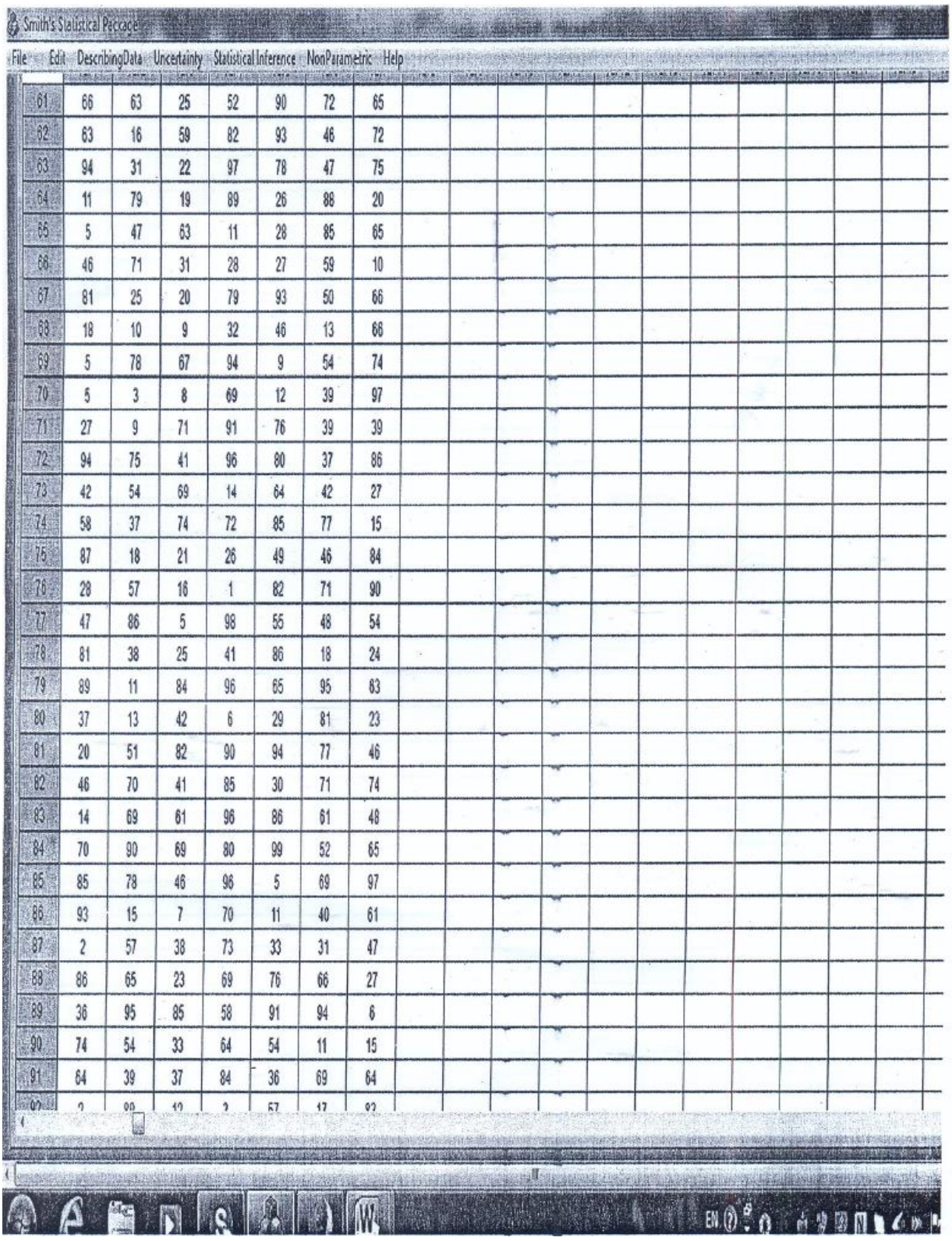

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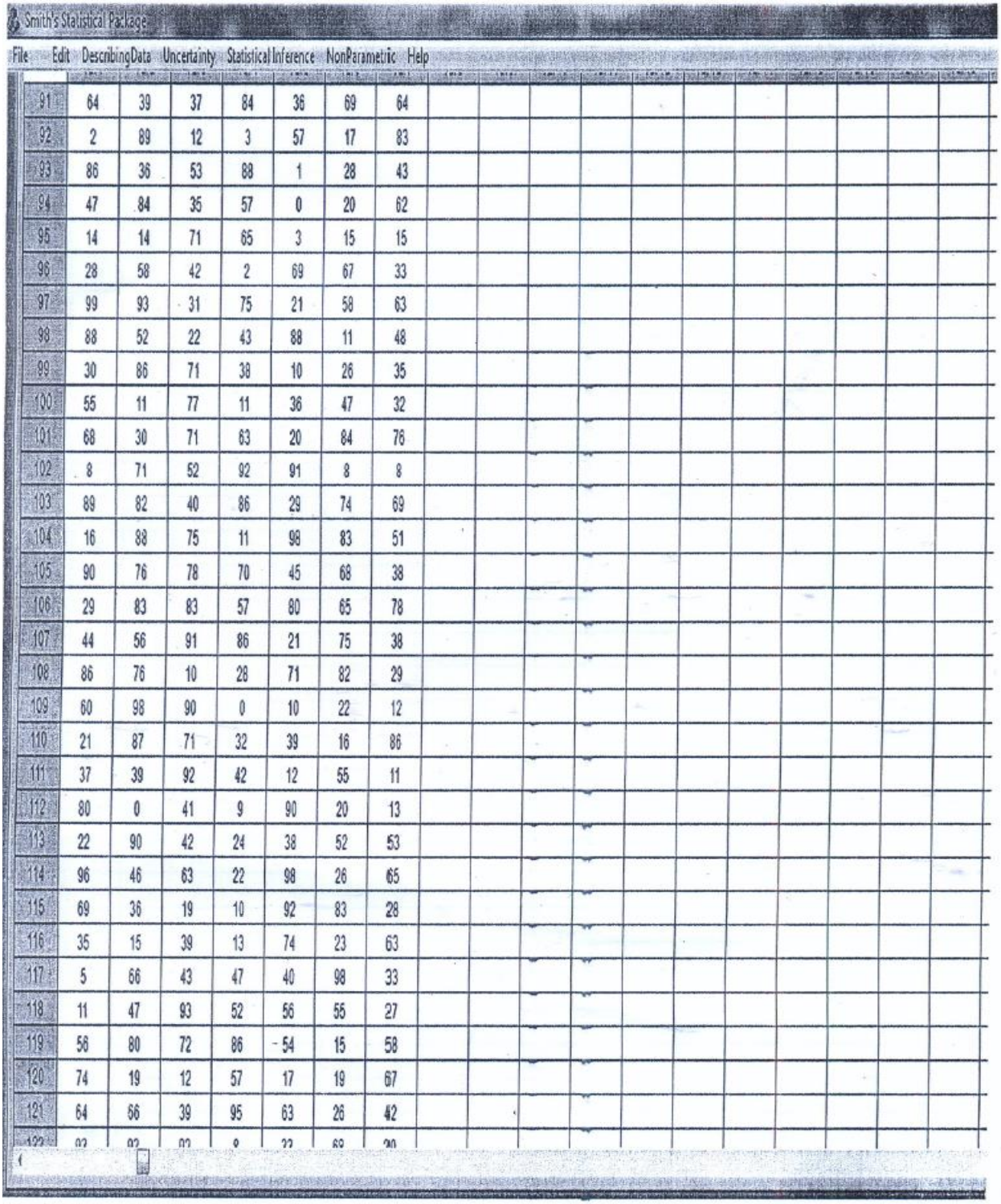

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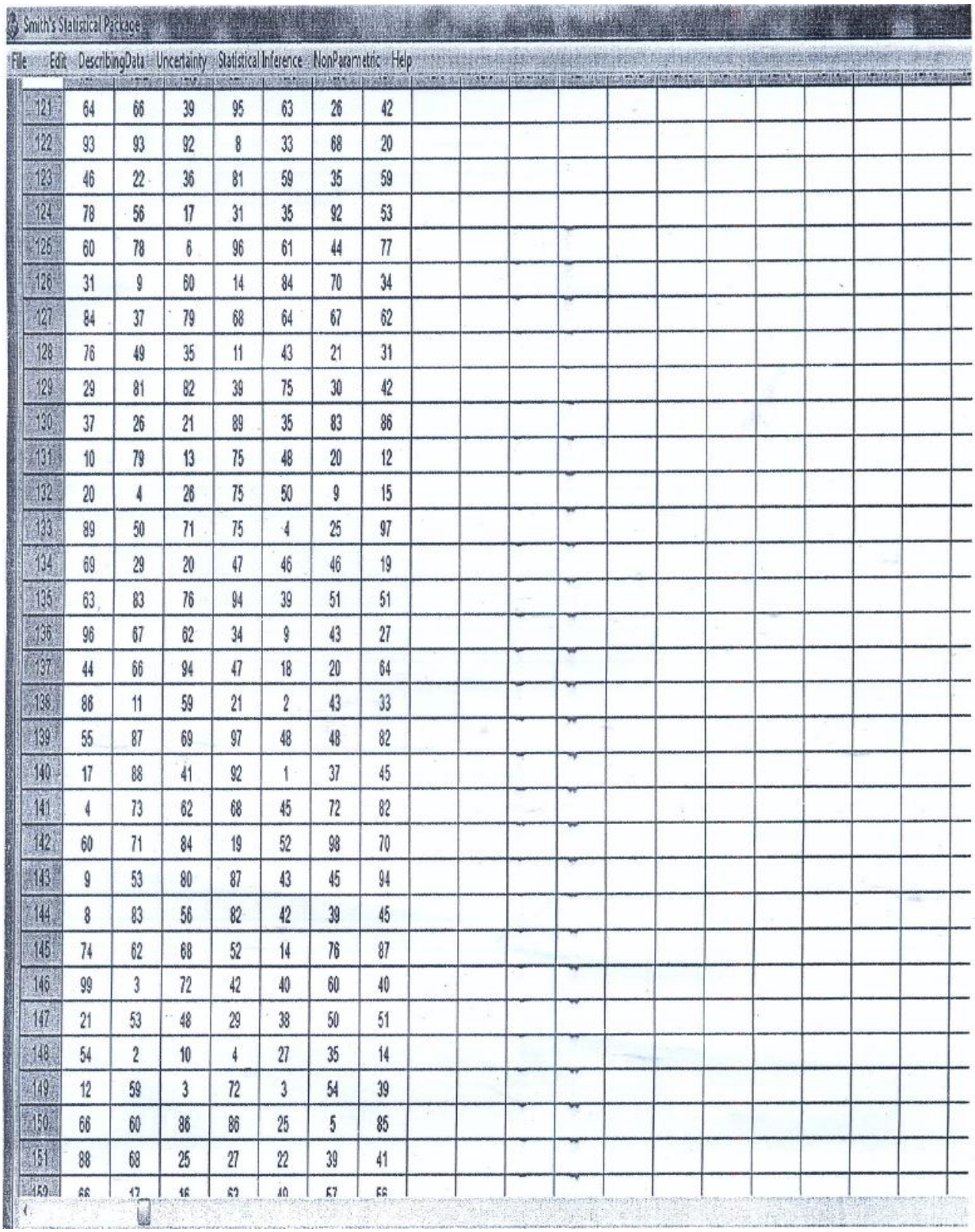

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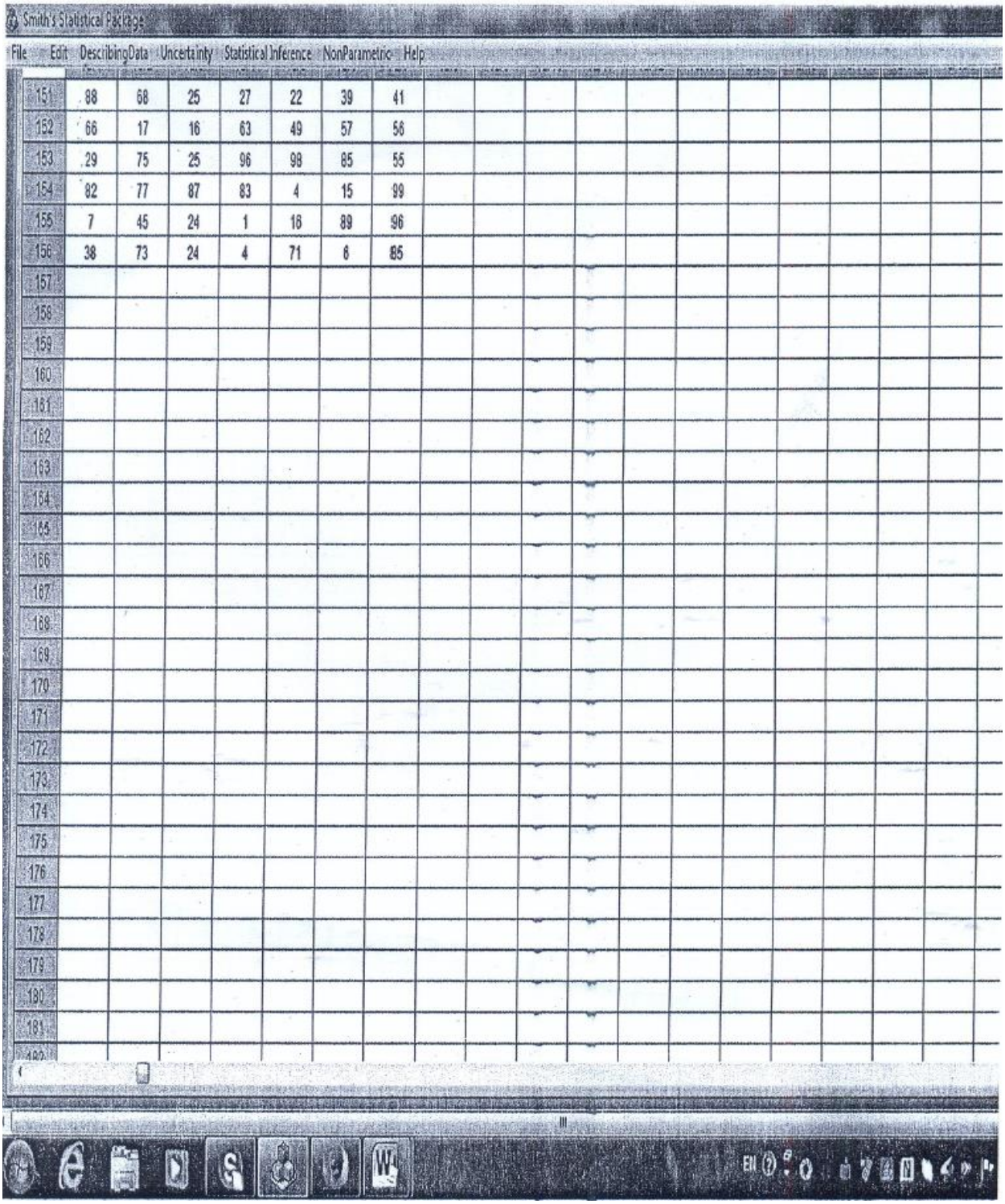
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