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Survival Probability of Sickle Cell Patients with Respect to HbF Levels

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Abstract: Sickle Cell Anaemia (SCA) constitutes a factor in the health of mankind. One of the regulating agents concealed in the mortality factors of SCA sufferers is their level or quantity of Foetal Haemoglobin. This study proposes a function which relatively describes the chance of survival of SCA patients in respect to their Foetal Haemoglobin levels. It is observed that survival increases as the level of foetal haeoglobin increases, decreases as age increases and this depicts the real life scenario. These are shown graphically.

Key words: Sickle cell anaemia, survival probability, death modulus, foetal haemoglobin

INTRODUCTION

Sickle Cell Anaemia (SCA) is one of the most common and most studied inherited diseases which are predominant in tropical region where malaria is prevalent. It is also referred to as the great masquerader. Life expectancy of patients with SCA is quite variable. For male SCA patients it is about 42 years, while that of females is about 48 years (Platt *et al.*, 1994). Also, the life-span of normal erythrocytes is about 120 days, while that of erythrocytes of SCA patients is often considerably less than 60 days (King, 1965). Such cells show a greatly shortened life span, since they clump together (often causing vascular obstruction) and are rapidly destroyed (King, 1965).

One of the regulating agents concealed in the mortality factors of SCA sufferers is their Foetal Haemoglobin (HbF) level, although the value of the survival probability for every age depends of course on the general condition of life of individuals in the population. Survival of SCA sufferers is a relevant problem in its own right, because the disease has no definite cure, except management regimes that help patients to cope with their condition. This study proposes a survival function for SCA patients as a function of their HbF level. General survival functions found in the literature are related to the solution of the classical MacKendrick Von Foerster (1926) type model of population dynamics and its variants. No attempt is often made to derive explicit form of the latter and from a previous study by Tchuenche (2002) and the predominance of this genetic defect in tropical regions, we decided to carry out this study, with the objective to derive a function which describes the chance of survival of patients in relation to their age and level of HbF. This function is a crude approximation of reality as survival depends on the general conditions of life of individuals in the population, but robust enough to generate results related to observed trends. It is therefore a patient-dependent parameters function, a critical property which can only be determined clinically and for mathematical convenience and tractability, we account only for the age and on of the most important survival factors, the quantity of HbF (Kotila *et al.*, 2000).

BRIEF HISTORY OF THE DISEASE

Clendennen and Lwanda (2003) reported that when on a journey into the hinterlands west of Lake Malawi (then Nyassa) in 1863, David Livingstone and almost two dozen African companions of varying ethnicity and birth place encountered a strange and, to Livingstone, unprecedented disease. The symptoms appear soon after the men had climbed from the lake shore to a plateau of over 3,000 feet and were exhibited by almost half of the Africans. One case was to prove fatal. Livingstone took notes on the spot, mentioned the problem in letters after a few months and commented for the last time in a book published two years later, but he was never able to satisfy himself concerning the time nature and identity of the disease.

The first indisputable case of SCA in the literature was described in a dental student studying in Chicago between 1904 and 1907 (Herrick, 1910). Coming from the Northern part of the Island Grenada in the Eastern Caribbean, he was first admitted to the Presbyterian

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Hospital, Chicago in late December 1904 and a blood test showed the features characteristic of homozygous sickle cell (SS) disease. Herrick (1904-05) and his intern, Ernest Irons both had an interest in laboratory investigation as Herrick had previously presented a study on the value of blood examination in reaching a diagnosis. Then Irons reported the result of the blood test of the student which he described as containing drawings of the abnormal red cells and the photomicrographs showed irreversibly sickle cells and this left little doubt the diagnosis was a Sickle Cell Disease (SCD).

The second case, Ellen Anthony, aged 25 years, had already been under observation in the wards of the University of Virginia Hospital from 1907 and the strange blood film sent to pathologists at John Hopkins University Hospital was considered an unusual case of pernicious anaemia (Savitt, 1997). The diagnosis became clear with the publication of Herrick's paper in 1910 and within three months, this second case was reported in February 1911 (Washburn, 1911). The third case, a woman aged 21 years, reported from Washington University Medical School in 1915 by Cooke and Meyer, raised suspicions of a genetic basis, as three siblings had died from severe anaemia and blood from both the patient and her asymptotic father showed a sickling deformity of the red cells on incubation (Emmel, 1917). The fourth case was a 21 year old black man in the wards of John Hopkins Hospital (Mason, 1922).

It was Mason who noted the similar features of the first four case reports and was the first to use the term Sickle Cell Anaemia. The discovery by Emmel (1917) of the sickle cell phenomenon in the father of the third case suggested a genetic basis for sickle cell disease (Serjeant, 2001). SCA is then an inherited, non-gender linked Mendelian disease that in homozygous state and in the presence of certain adverse conditions can lead to severe haemolytic anaemia, accompanied by painful `crises' due to its abnormal haemoglobin S (HbS). The genetic abnormality is caused by a substitution of valine for glutamic acid at position six in the beta chain of the normal haemoglobin A. HbS changes shape as it deoxygenates and sickling causes red cells to become more fragile, rigid and easy to aggregate (Clendennen, 2003).

MODEL FRAMEWORK

Nearly 50 years of clinical and basic research have established that high HbF concentrations reduce the severity of Sickle Cell Disease (SCD) by preventing the formation of HbS polymers (Steinberg, 1999). The beneficial effects of high Foetal Haemoglobin F concentrations in SCD stimulated studies to determine whether drug treatment could increase the production of HbF in patients with SCA and thus ameliorate their disease clinically. HbF levels are often elevated in sickle cell anaemia patients (they are also referred to as SS individuals) and this feature can be used as an index of clinical severity of the disease (Kotila *et al.*, 2000). Raised HbF has long been observed in SCA patients (Singer *et al.*, 1951) and its widely accepted that persistent high levels of HbF in SS patients is associated with mild clinical and haemotological conditions. In addition, the death rate of SS patients is inversely correlated with haemoglobin concentrations. What is also significant with respect to the longevity of SS patients is that malnutrition and poor living conditions influence the severity of the disease. Indeed, Platt *et al.* (1994) noted that a low level of HbF was associated with an increase risk of death. For the purpose of this study and to keep the model simple but elegant and rigorous enough to mimic reality, HbF concentrations will be taken into consideration in the derivation of the proposed equation of life expectancy of SS patients. This is because higher concentrations of HbF reduce the polymerization of HbS and the number of deformed, dense and damaged erythrocytes. Also, cells with a high HbF content survive longer, attenuating haemolysis (Steinberg, 1999). Odenheimer *et al.* (1984) noted long ago that of all the risk factors identified in the study of SCA, HbF level was the one known to be relatively stable throughout life and patients with high levels have an improved life expectancy. Thus the most straightforward laboratory risk factor is HbF levels.

There is a wide spectrum of clinical severity in this disease as regards life expectancy, frequency of crises, degree of anaemia and extent of involvement (Dean and Schechter, 1978), but it is most unusual that there is a single cause for a disease without any other intervening factors playing a role (Alderson, 1976). Since the most important variable that appears to correlate with protection of patients from manifestation of the disease is the presence of an adequate level of normal haemoglobin (HbA>45%) or elevated levels of HbF, the latter is taken into consideration in our analysis.

THE SURVIVAL FUNCTIONS

Notations:

- $\mu(a)$ is the death rate of individuals aged a.
- g is the quantity of haemoglobin F
- $\pi(0, a, g)$ is the survival function for individuals at age a with an average HbF levels g, say. $(0 \leq \pi(\cdot, \cdot) \leq 1)$.

One of the regulating agents concealed in the mortality of SS patients is HbF, although the value of the survival function $\pi(\cdot,\cdot)$, say, for every age (of life) depends of course on the general condition of life of individuals in the population. This condition forces π to be a patient-dependent parameter function, a critical property which can only be determined clinically.

The function: The general autonomous survivorship function for the classical MacKendrick Von Foerster age structured population dynamics is of the form (Tchuenche, 2003)

$$\pi(0,a) = \exp\{-\int_0^a \mu(\alpha)d\alpha\} \qquad (1)$$

But, this classical model does not describe inherited anomalies. Tchuenche (2002) developed a more appropriate settings for these diseases, taking into account an additional factor g, say, which could represent size, mass, caloric content, HbF levels or any other attribute that characterizes the physiological behavior of individuals in the population under study (Tchuenche, 2005).

Based on the aforementioned, we proposed the following explicit form of this general function, which describes the chance of survival of sickle cell sufferers. It is well-known that $\pi(\cdot,\cdot)$ decreases with age and increases as g is increased. Thus, for simplicity of discussions and without restriction of the generality of the model, we now define a new survivorship function

$$\pi(0,a,g) = \exp\{-\frac{1}{10^2 \times g}\int_0^a \mu(\alpha)d\alpha\} \qquad (2)$$

where 10^2 is added for technical reasons in order to obtain realistic values of π (the quantity of HbF is generally given in percentage). g is the quantity of the foetal haemoglobin (HbF and for practical purpose, it is fixed (i.e., independent of age). The higher the quantity of HbF, the higher the survival probability. In fact, $\pi(0,a,g)$ decreases as age and death rate increase and increases as g increases. Equation 2 captures the dynamical evolution of survival of patients in respect to their level of HbF as described in the literature. Equation 2, which represents the survivorship function of sickle cell patients, is a non increasing function of age with the following properties (Tchuenche, 2002)

$$\pi(0,a,g) = \begin{cases} 1, & \text{for } a = 0 \text{ (life birth!)} \\ 0, & \text{for } a = \infty \text{ (no one is eternal!)} \end{cases}$$

Without any ambiguity of notations, we write $\pi(0, a, g)$ simply as $\pi(a, g)$ in the graphical representation. Also, for the purpose of simulation, the death rate is written as c. We assume that the disease-related death rate is age dependent only. In general it is not easy to have an absolute form for μ and we often rely on census data only. This heuristic approach forces us to assume further that $\mu(\alpha) = c$, a constant, which represents the average death rate of individuals in the cohort under consideration. This simplification enables us to use MatLab codes in order to obtain the graphical representations below.

INTERPRETATION OF THE RESULTS

In Fig. 1, the death rate is higher than that in 2. We then notice that the surface of the function in 1 is larger
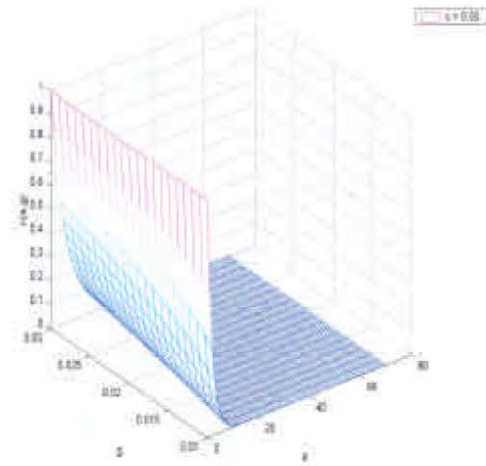

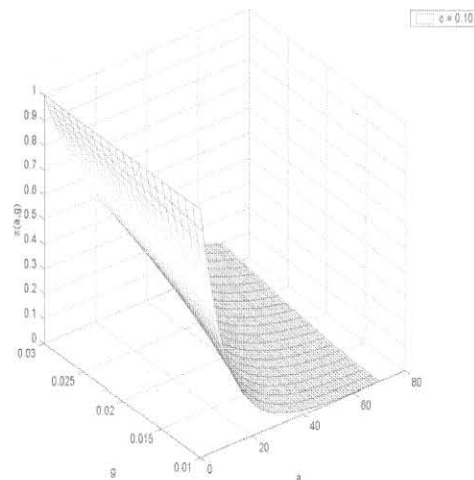Fig. 1: Survival function when $0.01 \le g \le 0.03$ and $\mu: = c = 0.5$

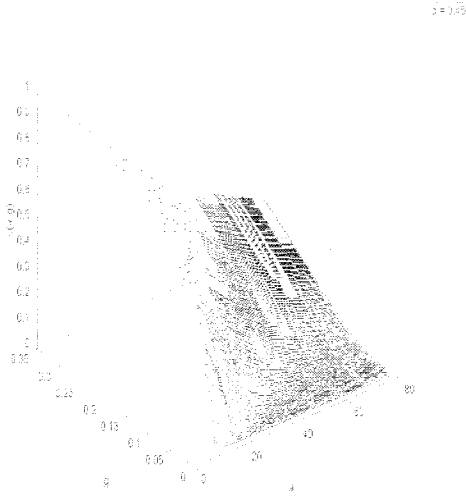Fig. 2: Survival function when $0.01 \le g \le 0.03$ and $\mu = c = 0.1$

Fig. 3: Survival function when $0.05 \le g \le 0.35$ and $\mu = c = 0.45$
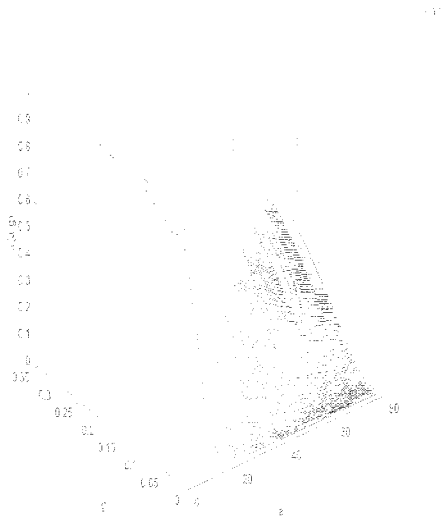

Fig. 4: Survival function when $0.05 \le g \le 0.35$ and $\mu = c = 0.25$

than that in 2, which implies an increasing death toll. Survival is high when the level of foetal haemoglobin is also high. Indeed survival decreases as the level of HbF is decreased. Figure 3-5 are similar to 1 and 2, but viewed in different angles, but with different values of HbF level and the vital rate μ. Here, we notice that survival is high at early ages if HbF level is also high, but reduces drastically as age increases and HbF is also decreased by natural phenomenon. These observations are strikingly related to real life situations and the
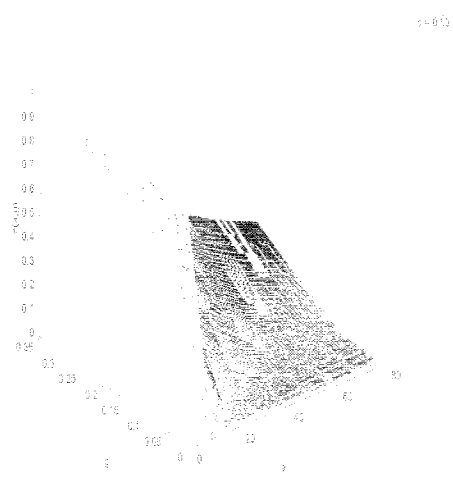

Fig. 5: Survival function when $0.0 \le g \le 0.35$ and $\mu = 0.6$

proposed function can be used to monitor or predict the chance of survival of SCA patients, other conditions being stable. We hope to include in the nearest future other clinical as well as social factors that are paramount in the health status of patients suffering from SCA.

CONCLUSIONS

The need to study new applications of current treatments and to devise new treatment strategies directed at disrupting multiple facets of the pathophysiology of SCA remains paramount (Steinberg, 1999). The quantity of HbF and other factors that partially or totally dominate the symptoms are to be given prominence. In this study, we have proposed a survivorship function which to a greater extent captures the dynamics of life expectancy of sickle cell patients if HbF is considered the most important factor, while other variables which influence their survival are without loss of reality in good conditions. It is also implicitly assumed that their social status is above average. Due to scarcity of well recorded clinical data on the above subject matter, we validated this function based on what is known about HbF and its relation to survival. This equation is being used to monitor in-patients and the data collected will provide a basic tenet for a more detail study and investigation into survival of SCA patients. Also as future direction, we shall introduce a new level of complexity into this function, since HbF alone cannot account fully for longevity of SCA patients.

Monitoring the life expectancy of patients based on HbF as well as their social life (better living conditions, good nutrition) may create a new index of chance of survival. Though it is hard to predict what will happen to

an individual in the nearest future, which is an ultimate goal in its own merit, an attempt to introduce the above social status into dynamical evolution equations may prove useful.

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