

**RELIABILITY AND SURVIVAL ANALYSIS
IN BIOMECHANISTICS:
APPARENT ANOMALIES, ANALOGIES AND
STATISTICAL PERSPECTIVES**

by

Pranab Kumar Sen
Department of Biostatistics
University of North Carolina

Institute of Statistics
Mimeo Series No. 2136

November 1994

**RELIABILITY AND SURVIVAL ANALYSIS IN BIOMECHANISTICS:
APPARENT ANOMALIES, ANALOGIES
AND STATISTICAL PERSPECTIVES***

Pranab Kumar Sen
University of North Carolina, Chapel Hill, USA

Although reliability and survival analysis share the common objectives of life-time studies, often, they differ in motivations, interpretations and basic approaches. This picture is studied in the context of biomechanistics where a more complex approach is generally needed, and some statistical perspectives are appraised.

1. INTRODUCTION

Any system, whether mechanistic or biologic, has a life span. Replacement of inactive or weak component(s) by new one(s) prolongs the life of a mechanistic system, while in a biologic system, such a replacement may not always be feasible so that proper care may be needed to maintain life quality. Such biologic systems include human beings as well as subhuman primates, plants and a variety of other organisms; even somatic or germ cells belong to this class. Reliability theory has its genesis in mechanistics and operations research and system analysis (ORSA), while survival analysis is most popularly adopted in biologic systems analysis. For both the systems, life time is characterized by a failure (death) of the system, although in many cases, sickness or substandard quality of life may precede a failure. For diverse systems, there is considerable variation in the life and death phenomena, and this may call for diverse statistical modeling and analysis schemes for their studies. In this respect it may be wise to take into account various extraneous factors associated with a system; they may provide useful background information on failure and thereby suggest suitable means of reducing the margin of error for statistical conclusions as are to be drawn from a system-study. The fundamental assumption in this setup is that the length of life or failure time T is a nonnegative random variable (r.v.). As such, the life of a system is characterized by the probability law associated with the r.v. T .

In a purely mechanistic system, generally, there are some controllable factors which can be effectively incorporated in maintaining the quality of life and to prolong its span. In a biologic system, although such factors can be identified and their impacts on the system can be interpreted in a meaningful way, they may not fully control the variation of life spans. For this reason, there is a genuine need to incorporate sound statistical methodology (and theory), probability theory and stochastic processes to study effectively the life table of a system with the primary objective of improving its quality. Yet, these two broad disciplines may often differ drastically in their foundations as well as operational approaches. Due to pioneering efforts of a host of research statisticians, this impasse is being eliminated to a greater extent, and there is ample room for further development of research work in this complex field.

*Dedicated to the memory of Professor Purnendu K. Bose

Biomechanic systems are the hybrid of biologic and mechanistic systems. Thanks to the advent of modern biotechnology and computer-incentive medical technology, mechanistic systems are increasingly adopted in biomedical complexities. But there are major obstacles too:

You may replace the engine of your car whenever you want,
but can you do so, even in desperation, with your heart?

Breast implants, by-pass surgeries and induced pace makers, heart transplants, DNA damage repairs, blood transfusion, bone marrow transplants, kidney transplants etc. are notable examples of such biomechanic systems. Metal imputation of hip-joints, artificial limbs have more visible non-living material component(s) which the living organs may not totally accept as compatible. Thus, biomechanistic systems may inherit some features of mechanistic system, but to a greater extent they possess dominant stochastic factors. This may introduce more complications in modeling a biomechanistic system and formulating appropriate statistical analyses schemes.

In order to fit biomechanistic systems within the complex setup of biologic and mechanistic systems, it may therefore be wiser to characterize the general discrepancies in the biologic and mechanistic systems, and to examine their common features too, so as to formulate suitable stochastic models for biomechanistic systems in the light of these factors. This is the main objective of the current study.

In Section 2, the preliminary notions in reliability theory and survival analysis are presented. Section 3 deals with their apparent anomalies, while the analogies are considered in Section 4. Statistical perspectives are then chalked out in Section 5 with due emphasis on some problems of life interest. There are numerous open problems and some of these are posed briefly in the concluding section.

2. PRELIMINARY NOTIONS

Let $F(t) = P\{T \leq t\}$, $t \in \mathbb{R}^+ = [0, \infty)$ be the distribution function (d.f) of the failure time T . The complementary part of $F(t)$ is known as the survival function (s.f.) in survival analysis and reliability function (r.f.) in reliability theory. Thus, we let

$$S(t) = R(t) = 1 - F(t), t \geq 0 \quad (2.1)$$

If F admits a probability density function (pdf) f almost everywhere (a.e.), then the failure rate or instantaneous force of mortality $h(t)$ is defined as

$$h(t) = -(d/dt)\log S(t) = f(t)/S(t), t \geq 0. \quad (2.2)$$

In reliability theory, $h(t)$ is generally referred to as the hazard rate. Note that $S(t)$ or $R(t)$ is \downarrow in $t \in \mathbb{R}^+$ and $S(0) = 1$, $S(\infty) = 0$. Thus, $h(t)$ is ≥ 0 , $\forall t \geq 0$. The cumulative (or integrated) failure/hazard rate $H(t)$ is defined by

$$H(t) = \int_0^t h(u)du, t \geq 0, \quad (2.3)$$

so that by (2.2) and (2.3),

$$R(t) = S(t) = \exp\{-H(t)\}, t \in \mathbb{R}^+, \quad (2.4)$$

and hence, $H(0) = 0$ and $H(\infty) = \infty$. The above discussion pertains to an equivalence relation in terms of characterization of the probability law for failure times:

$$F(t) \Leftrightarrow \{S(t) \text{ or } R(t)\} \Leftrightarrow \{h(t)\} \Leftrightarrow \{H(t)\}. \quad (2.5)$$

In survival analysis, there is generally more emphasis on $S(t)$ or $h(t)$ while in reliability theory $R(t)$ and $H(t)$ play a dominant role. Note that by (2.2), (2.3) and (2.4),

$$\begin{aligned} -\log S(t) (= -\log R(t)) &= H(t), \quad t \in \mathbb{R}^+ \text{ is concave/convex} \\ \text{according as } h(t) \text{ is } \uparrow \text{ or } \downarrow \text{ in } t \in \mathbb{R}^+ & \end{aligned} \quad (2.6)$$

Also, for $h(t) \uparrow$ (or \downarrow) we have an increasing (or decreasing) failure rate (IFR or DFR) distribution; if $h(t) = h > 0, \forall t \in \mathbb{R}^+$, we have $S(t) = \exp(-ht), t \geq 0$, so that F is exponential. The reliability specialists have special affections for constant failure rate (CFR) d.f.'s, followed by IFR/DFR systems. The Weibull d.f. deserves special mention in this context; it is defined by

$$S_W(t) = \exp\{-\lambda t^\gamma\}, \quad t \in \mathbb{R}^+, \quad (2.7)$$

where $\lambda > 0$ and $\gamma > 0$ are suitable parameters; $\gamma = 1$ relates to the CFR case. Note that S_W belongs to the DFR/IFR class according as γ (the shape parameter) is < 1 or > 1 . Another notable d.f. is the gamma one for which the pdf is

$$f(t; c, p) = c^p (\Gamma p)^{-1} t^{p-1} \exp(-ct), \quad t \in \mathbb{R}^+, \quad (2.8)$$

where $c > 0$ and $p > 0$ are parameters. Again, for $p=1$, (2.8) is an exponential pdf, while the gamma d.f. belongs to the DFR/IFR class according as p is < 1 or > 1 . In passing we may remark that for the Weibull family, the hazard rate $h_W(t)$ has an upper asymptote (as $t \rightarrow \infty$) 0 or $+\infty$ according as γ is < 1 or > 1 , while for the gamma family, this upper asymptote is a finite positive number. There are some other generalizations of the concept of IFR/DFR class of d.f.'s, extensively studied in reliability theory, and we shall introduce some of them briefly later on.

In reliability theory and survival analysis, it is common to have some concomitant r.v.'s (or covariates) along with the primary variate T . We denote a covariate by Z , and note that, in general, Z may have some nonstochastic and some stochastic components; the nonstochastic component may typically arise from the design of the study. Parallel to (2.1), let $S(t|z)$ be the (conditional) s.f. of T , given $Z = z$. This immediately leads to the conditional hazard function (c.h.f.)

$$h(t|z) = - (d/dt) \log S(t|z), \quad t \in \mathbb{R}^+, \quad z \in Z. \quad (2.9)$$

Note that the IFR/DFR family may not include the location-scale family of d.f.'s, and hence, the conventional linear model approach may not be that convenient for hazard regression. Generalized linear models (GLM) [viz, McCullagh and Nelder (1989)] have often been adopted, and the concepts of Poisson regression as well as logistic regression models have their genesis in this setup. Thanks to the innovative efforts of D.R. Cox (1972), the proportional hazard model (PHM) occupies a focal stand in survival analysis: It may be posed as follows.

$$h(t|z) = h(t|0) \exp \{\beta'z\}, \quad t \in \mathbb{R}^+, \quad z \in Z, \quad (2.10)$$

where the baseline hazard $h(t|0)$ is arbitrary (nonnegative) while the second factor depicting the hazard regression (on the covariate) is of a specified parametric form. Note that

$$\log h(t|z) = \log h(t|0) + \beta'z, \quad z \in Z, \quad t \in \mathbb{R}^+, \quad (2.11)$$

provides a regression model which is termed hazard regression. In this setup, it may not be necessary to assume that $h(t|0)$ is \uparrow or \downarrow in $t \in \mathbb{R}^+$, so that $h(t|0)$ is of nonparametric flavor. For this reason, (2.10) is often regarded as the origin of the modern semi-parametric models (SPM). Moreover, by (2.10),

$$h(t|z)/h(t|0) = \exp \{ \beta'z \}, \quad \forall t \in \mathbb{R}^+, \quad (2.12)$$

which justifies the terminology of proportional hazards. The same proportionality holds for the cumulative hazard rates. In particular, if z can take only two values 0 and 1, we have on letting $c = \exp(\beta)$ (>0) that $h(t|1)/h(t|0) = c > 0, \forall t \in \mathbb{R}^+$, so that $S(t|1) = [S(t|0)]^c, t \geq 0$. In the literature, this is known as the Lehmann (1953) alternative model for the two-sample problem. Thus, PHM has its genesis in the Lehmann model.

The above development relates to the case when T has a pdf. It is common to encounter a response variable (Y) which is binary and has a probability law depending on the covariate Z . In a logistic regression mode. we set

$$\begin{aligned} P\{Y = 1|Z = z\} &= 1 - P\{Y = 0|Z = z\} \\ &= \{1 + \exp(-\alpha - \beta'z)\}^{-1}, \quad \forall z \in Z \end{aligned} \quad (2.13)$$

Then the logit of Y defined as

$$\log\{P(Y = 1|Z = z)/P(Y = 0|Z = z)\} \text{ is } \alpha + \beta'z, \quad (2.14)$$

depicting a linear regression on the covariate. If in (2.13) instead of a logistic model we work with a normal d.f., we have the so called normit/probit model, where the linearity in (2.14) is not the case. Some other notions will be introduced in later sections.

3. APPARENT ANOMALIES

The equivalence relations in (2.5) and their extension to the conditional setup [see (2.9)] provide the basic link between various approaches to statistical analyses of life-time data models. Yet these approaches, often, differ considerably in their basic philosophies and/or operational manuals. The functions $F(t), S(t), R(t), H(t)$ in a parametric setup depend on a common set of parameters which are finite dimensional vectors. On the other hand, any attempt to go beyond a strict parametric model encounters a possible incompatibility clause from statistical analysis simplicity point of view. For example, instead of assuming that the d.f F is exponential/Weibull/gamma, suppose that we assume that

$$F \text{ belongs to the IFR/DFR class.} \quad (3.1)$$

Within this broader setup, the parametric structure of F or even $h(\bullet)$ or $H(\bullet)$ is no longer available, and hence, one may have to deal with an infinite dimensional

parameter space, treating the entries $h(\bullet)$, $H(\bullet)$ or $S(\bullet)$ as parametric functions. In a real life problem, given a finite set of observations pertaining to a model, it may be necessary to reduce such parameter-functionals to suitable finite dimensional parameters. The two branches, reliability and survival analysis, often, differ considerably in their approaches to such formulations.

In reliability theory, the major emphasis is on characterizations of life distribution classes and on their statistical interpretations. The concept of "aging" underlies most of these developments. A d.f. F is termed new better (or worse) than used (NB(W)U), if $S(x+y)$ is \leq (or \geq) $S(x)S(y)$ for every $s, y \geq 0$. If $S(\bullet)$ has a finite mean $\mu = \int_{\mathbb{R}^+} S(t)dt$, then F is NB(W)U in expectation if $\int_{\mathbb{R}^+} [S(x+t)/S(x)]dt$ is \leq (or \geq) μ , $\forall x \geq 0$. Similarly, if $x^{-1} \int_0^x h(t)dt$ is \uparrow (or \downarrow) in $x \in \mathbb{R}^+$, then F has increasing (or decreasing) failure rate average (IFRA/DFRA). Finally, F has decreasing mean residual life (DMRL) if the mean residual life at age x

$$\mu(x) = \int_0^\infty \{S(x+t)/S(x)\}dt \text{ is } \downarrow \text{ in } x \in \mathbb{R}^+. \quad (3.2)$$

It is easy to verify that

$$\begin{aligned} \text{IFR} \Rightarrow \text{IFRA} \Rightarrow \text{NBU} \Rightarrow \text{NBUE}, \\ \Rightarrow \quad \text{DMRL} \quad \nearrow \end{aligned} \quad (3.3)$$

and a similar picture holds for the DFR family. Alternative to the IFR/DFR family, often, a mixture model

$$S(t) = \int_{\Theta} S(t;\theta)d\pi(\theta), t \in \mathbb{R}^+ \quad (3.4)$$

is considered and its characterizations are made similarly. From statistical applications point of view the main problems are to provide optimal (nonparametric) estimators of $S(t)$ given a priori that it belongs to a suitable class (viz., IFR/DFR etc.). Also, the mean residual life $\mu(x)$, $x \in \mathbb{R}^+$, is a parameter (function) of good interest, and it may be desirable to estimate $\mu(\bullet)$ under DMRL or similar conditions. We may refer to Hollander and Proschan (1984) for an excellent review of this field.

The survival function $S(\bullet)$ or some of its characterizations remain equally important in survival analysis. Nevertheless, in most applications, the problem is to compare survival on two or more groups (formed by treatment combinations). In this setup, it is common to have a number of covariates, so that we are essentially to deal with conditional survival functions or related hazard functions [see (2.9)]. This generality adds additional complications in statistical modeling and analysis procedure. For example, referred back to the PHM in (2.10), one may be really interested in three regression parameter β , and $h(\bullet|Q)$ may itself be treated as a nuisance parameter (function). A similar situation arises in a progressive censoring scheme (PCS) in survival analysis models [viz., Chatterjee and Sen (1973)] where the underlying $S(\bullet)$ is treated as a nuisance parameter (without necessarily bringing the PHM in the picture). Similarly, the mean residual life is of considerable interest in many problems in survival

analysis, but more important in this content is the study of the impact of suitable treatment in its prolongation [viz., bypass surgery for heart diseases].

In reliability studies, the concept of total time on test (TTT) has been widely accepted as an operational tool. For $n(\geq 1)$ items in a life testing scheme (simultaneous entry), let $T_{n:0} = 0 < T_{n:1} < \dots < T_{n:n} < T_{n:n+1} = +\infty$, be the ordered failure times, and let $k_n(t) = \max \{k: T_{n:k} \leq t\}$, $t \geq 0$. Then upto a time point $t(>0)$, the total time (life) spent on testing is

$$V_n(t) = \sum_{j \leq k_n(t)} T_{n:j} + (n - k_n(t))t, \quad t > 0,$$

so that $V_n(t)$ is \uparrow in $t \in \mathbb{R}^+$. The genesis of $V_n(\bullet)$ lies in the statistical analysis of exponentially distributed failures [viz., Epstein and Sobel (1955)], where some exact statistical analysis can be carried out. This definition of $V_n(\bullet)$ refers to the without replacement scheme where failed items are not replaced by new ones. In the with replacement scheme, we have $V_n(t) = nt$, $\forall t > 0$, so that TTT does not have any statistical significance. This TTT transformation has been widely used in other situation as well--although sans exponentiality, exact statistical analysis may have to be replaced by asymptotics. Conceptually, the TTT transformation may appear to be quite appropriate but in actual practice it is not so commonly used. The presence of concomitant variables and possible censoring, staggered entry plans and departures from exponentiality generally make the situation quite different. Moreover, comparisons of survival functions adjusted by concomitant variates and censoring have good interpretability, and in a proportional hazard setup, the Cox (1972) partial likelihood approach works out quite conveniently. The TTT transforms are generally non-robust, while the PHM approach has a relatively greater robustness perspective.

Monitoring of reliability studies is common, but it is more in the spirit of quality control, so that statistical tools developed for quality control are more often adopted for reliability monitoring. In survival analysis, censoring is a relatively common phenomenon. It may be due to withdrawal of a subject from an experimental scheme due to lack of compliance, migration or even failure due to causes other than the one under study. Censoring may also be due to termination of a follow-up scheme prior to having responses on all the participating units. This is typically the case with studies relating to a "low mortality" phenomenon--as is generally the situation in clinical trials. Medical ethics often dictate some monitoring schemes in survival analysis. For this reason, the quality control oriented monitoring methodology may often be unsuitable in survival analysis. Sequential procedures are also common to both reliability and survival analysis problems, and yet, they differ considerably in their formulations. The classical sequential analysis may be usually adopted for reliability problems; we may refer to Chapter 13 of Ghosh, Mukhopadhyay and Sen (1995) for some details. In survival analysis, the sequential procedures are more in the spirit of time-sequential ones. the basic difference is that replacement of failed units by new ones in a reliability model is a relatively routine task, while in a biologic model, such a replacement may often be either unpracticable or possible in exceptional situations, but the replaced item may experience a lot of hostility from the host organism and have a quite different life distribution. We may again refer to Ghosh, Mukhopadhyay and Sen (1995, Ch. 12). Survival analysis places good emphasis on suitable measures of "risk" due to some assignable factors, and they may also be quite different from measures of risk in reliability theory which are mostly based on hazard functions. Cost and time

constraints in survival analysis problems are generally different from that in reliability theory.

There is another important issue which divides reliability and survival analysis to a greater extent. In reliability setups, the primary response variables (s) [viz., the system lifetime] is observable. In many survival analysis problems, specially dealing with human subjects, such a failure time recording is either not possible or is too costly to do so; there are generally ethical guidelines to check that nobody is put to any treatment which leads to an increased risk, and if any such phenomenon occurs, these subjects are to be switched to alternative treatment groups for a better chance of living. Therefore, it is quite common to look for other response variables which are closely associated with this primary variable, are comparatively less expensive to observe and yet provide enough statistical modeling and analysis insights. These are known as surrogate endpoints (or variables) in clinical trials and medical studies. A special issue of Statistics in Medicine (1989) is devoted to this interplay of surrogate endpoints in medical studies, their basic statistical foundations and the allied analysis complexities. Such complexities are not only reflected in the analysis schemes but also in the very planning (or design) aspects. There has been some work done in very recent past in this important field, mainly from survival analysis point of view, and there is ample room for interpretations and further modifications from reliability analysis point of view. We may refer to Sen (1994a) for some details; other references are cited there. There are some other differences between the reliability and survival analysis approaches which may depend more specifically on particular problems at hand, and we shall not stress on them here.

4. ANALOGIES

It has been identified that there are some basic differences in reliability and survival analysis methodology and theory. Yet, they share a number of common features too. In both the approaches, the acquired data set relates to failure times along with other information on censoring, if any, and concomitant variables. Therefore, a unified approach may perhaps be formulated by defining the parameters of interest as functionals of $S(\bullet)$ or $R(\bullet)$. Note that the mean residual life, hazard function, median residual life etc. are all such functionals of $S(\bullet)$. The choice of such a functional naturally depends on the specific problem at hand, nature of the response variables and the design of the study. Moreover, such a functional must have good physical interpretations in relation to the general objectives of the study. Within this broad framework it may be advantageous to walk from either avenue. The Cox (1972) PHM is (2.10) is a classical example in this respect. Recalling this hazard formulation, we have a strong reliability flavor, while the arbitrariness of the baseline hazard retains the strong nonparametric aspects of survival analysis. Not only for this model but also for many others, reliability theory and survival analysis both place good emphasis on nonparametrics/semi-parametrics, and thereby are more robust than specific parametric model based analyses. To stress this point further, we consider the case of a binary response (failed or not) where the covariate Z is also binary (exposed or not to a given toxicant). By reference to the logistic regression model in (2.13)- (2.14), we have for this particular problem

$$\log\{P(Y = 1|Z = 1)/P(Y = 0|Z = 1)\} - \log\{P(Y = 1|Z = 0)/P(Y = 0|z = 0)\} = \beta \quad (4.1)$$

so that β reduces to the conventional log-odd ratio. In this case, one could have started with a bivariate distribution of the underlying traits and linked β with a convenient measure of association of this underlying distribution. But such a measure of association may depend highly on the form of the underlying d.f.; on the other hand, β has largely a nonparametric flavor. The proportional odd ratio model in survival analysis has its genesis in this setup. If in (2.13), Y refers to a response (or not) during a time-interval $(0, t)$, say, then it is understood that the parameters α and β are possibly time-dependent. Thus, we may write

$$P(Y_t = 1|Z = z) = 1 - P(Y_t = 0|Z = z) = \{1 + e^{-\alpha(t) - [\beta(t)]'z}\}^{-1}, \quad (4.2)$$

for $t \geq 0$, and taking into account the fact that if $Y_t = 1$ for some $t > 0$, then $Y_{t'} = 1$ $\forall t' \geq t$, we need to set a restraint that $\alpha(t) + [\beta(t)]'Z$ is \uparrow in t . Thus, under (4.2), analogous to (2.14), we have a time-dependent logit model:

$$\log\{P(Y_t = 1|Z = z)/P(Y_t = 0|Z = z)\} = \alpha(t) + [\beta(t)]'Z, \quad (4.3)$$

and statistical conclusion to be made on $\alpha(t)$, $\beta(t)$ should then take into account the isotonic nature of this logit (in t). In a survival analysis problem, often, the covariate Z is time-dependent (i.e., $Z = Z(t)$, may vary with $t \geq 0$). In such a case, (2.10) extends to

$$h(t|Z(t) = z(t)) = h(t|0) \exp\{\beta'z(t)\}, \quad t > 0. \quad (4.4)$$

But there are some situations where even this time-dependent covariate PHM may not be appropriate. An example of this type has been cited in Sen (1994b): The blockage of the upper aorta (to the brain) due to aging and fatty deposits within the arterial channel. Surgery and medication are alternative procedures to reduce the blockage, and for various reasons, the two hazard functions are not proportional. This raises the lack of robustness of the Cox PHM. One possibility is to extend further (4.4) wherein the coefficients (β) are allowed to vary with time, i.e.,

$$h(t|Z(t) = z(t)) = h(t|0) \exp\{[\beta(t)]' [z(t)]\}, \quad (4.5)$$

which retains the flavor of the Cox (1972) partial likelihood principle to a certain extent, and yet, eliminates the need for the PHM. For some details, we may refer to Murphy and Sen (1991) and Sen (1994b). We can conclude this section with the remark that both reliability and survival analysis are atuned to modeling lifetime data in a way that from observational studies, (partial/conditional) likelihood functions can be constructed in such a manner that statistical conclusions can be drawn in a valid and efficient way. The method of sieves [Grenander (1981)], discretized likelihood and other tools can be used to draw statistical conclusions. Since mostly in lifetime data, we have the occurrence of some characteristic events (viz., failure) overtime, it is also natural to formulate suitable counting processes approach to such models. Indeed, the recent monograph by Andersen et al. (1993) provides a detailed account of such recent developments covering a larger domain of reliability and survival analysis models. There is ample room for further developments in this sector.

5. STATISTICAL PERSPECTIVES

Biomechanistic systems combine the complexities of the usual mechanistic systems with the biologic ones. From a biomedical/biomathematical/bioengineering modeling point of view, it may be quite tempting to import the general principles underlying a mechanistic system, but in view of the dominant biologic part (leading to a variety of uncontrolled stochastics), such principles are to be appraised in the light of statistical principles. Thus, statistical perspectives occupy a focal stand in biomechanistic systems, for modeling as well as drawing conclusions. Both reliability and survival analysis tools are very useful in this context, but a deeper integration of them may generally be necessary to accomplish the task adequately.

We illustrate this with a couple of examples:

(I) Heart By-pass Surgery Model. Deposition of LIPIDS or fatty substance within the arterial channel is a normal aging process; nevertheless, this system (call it biomechanistic or not) has an unnatural growth if the cholesterol level in the blood is high. There are other factors, such as, smoking, lack of physical exercise, consumption of red-meat or other fatty foods, occupational stress and others, which also have good impact on the acceleration of this arteriosclerosis process. By-pass surgery is a remedial factor to eliminate some of the arterial congestions. The extent of this surgery (i.e., single, double or triple) depends on the existing condition, and the aftermath and recuperation process is also very much dependent on it. The living style after the surgery is also more regulated and generally quite different from the pre-surgery phase. Repetition of the surgery is possible after a while, but that depends on the state of the patient, and the life styles at different phases are not that comparable (in an exchangeable sense.) Socio-economic and cultural backgrounds are also pertinent in this content.

(II) Inhalation Toxicology Model. The bronchiole in human lungs branch out to millions of alveoli (cells) where inhaled (oxygen-rich) air interacts with (CO₂ and H₂O rich) blood and purifies the same; the oxygen-rich blood goes back to the heart for circulation in the body, and the impure air is breathed out. This is apparently a simple biomechanistic system. However, in actual practice, the phenomenon is highly complex [cf. Sen (1993)]. The main complications arise due to two factors: (a) What is inhaled through the nose (and mouth) may contain good amount of toxic elements, and (b) in the alveoli, the simple biochemical action may lead to molecular level of penetration. The air we breath in may contain dust, sulphur, mercury and carbon particles, CO and other toxic gases. These are mainly due to (active or passive) smoking, industrial exhausts and emissions, automobile exhausts, environmental smoking and a thousand and one other causes. Many of these factors have been identified as carcinogen. Although, the human body system has a mechanism of absorbing some of these toxicants at the entrance (nostrils) or in the larynx and getting rid of them through the formation of mucus and spitting them out, the finer particles and gases make their way through the bronchus all the way to the alveoli. The alveoli form the confrontation ground with the blood and somatic cells. The gaseous exchange there ignites biochemical reactions with the toxicants, and the aftermath may lead to carcinogenic activity, formation of lung tumor and finally to the initiation of lung cancer. And yet, the picture varies from person to person, and even under controllable conditions, the outcome variables are highly stochastic.

The congestion in the upper aorta problem referred to in the preceding section is another typical biomechanistic model. Many of the human organs are in pair (viz., lungs, kidneys, feet, hands, ears, eyes). Most of the bones have lateral symmetric positions (i.e., left and right), so are the joints (e.g., hip-bone joints, knee caps, pelvic and public joints, torsals, etc.). The ligaments are also laterally symmetrically placed. yet the functioning of the components within each pair may not be exchangeable in a statistical sense. Right handed people have comparatively weaker control on left hand and vice versa. The optic nerves in the two eyes have different duties and very rarely the two eyes have identical functioning capabilities. Those who have eye glasses can check that the powers are generally non-identical. One of the ears has a different role then the other. So also the two lungs are not identical in their functional role. The kidneys may have comparable functional role in the human renal system, and yet, there are some variation either due to chance factors or to some genetic ones. The two ovaries in the female reproductive system are supposed to functionally similar, but may develop differential role at some stage. For example, the incidence of ovarian cancer often invades one of the ovaries leaving the other one relatively strong. A similar phenomenon is observed with breast cancer incidence in females. Can we use the "system in parallel." setup in reliability theory to describe such biomechanistic systems? Can the growth of a (lung) tumor be regarded as a biomechanistic phenomenon?

The examples cited above and the discussion made thereafter clearly point out the significance of statistical perspectives in biomechanistics. In this respect the first and foremost task is to assess fully the biological, biochemical or ecological perspectives before formulating the statistical ones. In this respect, the picture is grossly different from a conventional ORSA model where physical interpretations for the influencing factors are far easier to incorporate. In many biological systems, ecological perspectives may dominate over cause-effect diagnostics, so that conventional regression models may not be that appropriate. The etiology of a disease related to the biomechanic system may not be precisely known. Moreover, the response variable may not be instantaneously observable. Thus, there may be serious identifiability problems, and scope for significant measurement errors and misclassifications. As an illustration, consider the heart by-pass surgery model. Although we have some ideas about the factors affecting arteriosclerosis, there may not be a comparable control group against which other groups may be statistically compared. Moreover, the growth of the LIPIDS inside the arterial channel may not have a precise bio-mathematical model. There are so many factors affecting it that there may be generally some synergic activity, and a proper statistical assessment of such effects is essential for a valid and efficient analysis of the system. Also, it may not be possible to keep a track of the growth of the LIPIDS inside the arterial channel on a monitoring basis, and even so, there is considerable scope for imprecise measurements (leading to some measurement errors), and misclassification of states is also quite possible. There has been a spur of activities on probabilistic models for tomography--and this has indeed a good scope for modeling in biomechanistics. Finally, the state of the response variable may be highly nonstationary. For example, while it is quite likely to be left out as insignificant at an early stage of development, once it is in an advanced stage, often, the developments are too fast to control, and by-pass surgeries are therefore essential. Yet, there is a general feeling that a significant percentage of the people undergoing by-pass surgery may not really need it and alternative methods may work out even better. In the inhalation toxicology model introduced earlier, the etiology for the formation of a lung tumor is not very precisely known. The symptoms for a lung tumor show up only when the tumor has gained its secure ground, and, once in that stage, growth process may be very

explosive. It may not be possible to establish a one-to-one relation with the degree of smoking or other occupational inhalation problems and formation of lung tumors. Yet, the impacts of such factors are very apparent from various studies and it may be a natural hypothesis that such factors are carcinogens. A simple biologic model mainly relating to cause and effect type relation may not at all be appropriate, while a simple reliability model is far from being adoptable. A comparable approach combining the flexibilities of both reliability and survival analysis is therefore a better alternative. For example, one may think of a logistic regression model, but then one has to allow measurement errors as well as misclassification of states. This has prompted some researchers to adopt some (continuous time parameter) Markov chains for biomechanistic systems. Nevertheless, there is no guarantee that the transition probabilities (from one state to another) are time-homogeneous (or stationary). Hence, if on the contrary, such a simplistic stationarity is assumed, the resulting statistical analysis may not be robust at all, and may even be grossly biased and inefficient.

Many of these biomechanistic systems relate to highly skewed tolerance distributions. For example, for the By-pass Surgery Model (treated earlier), if as a measure of the arterial congestion one takes the proportion of area (U) in an arterial cross section covered by the LIPIDS, one has $0 \leq U \leq 1$, with probability one. The normal aging process leads to a positively skewed distribution of U on $[0,1]$, while under arteriosclerosis, this distribution is likely to be even more skewed to the right. If we take a Box-Cox type of transformation $g(U)$ (where $g(y) = \log y$ or y^λ , for some $\lambda > 0$), for the transformed variable, we may expect a comparatively less skewed distribution. Nevertheless, the arteriosclerosis case may not relate to the normal aging case by change of location/scale parameters alone therefore, a more general class of alternatives may have to be incorporated in such a study. In reliability analysis, the exponential to Weibull to IFR/DFR family of distributions provide a reasonable alternative, and a Pareto type distribution allows a comparatively 'heavy tail' alternative which may be appropriate in some situations. From this perspective, for statistical modeling and analysis of biomechanistic systems, semi-parametrics may have substantially more scope than parametrics. Although semi-parametrics may not compare very favorably with nonparametrics with respect to robustness aspects, in terms of applicability to real data sets, often, they need comparatively smaller sample sizes.

In many biomechanistic schemes the basic objective may relate to an assessment of bioequivalence of alternative treatment protocols (viz., surgery vs. medication in the ascending aorta congestion model). Such bioequivalence relations are generally not related to biochemical or dosimetric equations, and stochastic variability of responses must have to be taken into account in defining such a relation. Recall that in biological assays, the concept of relative potency relates to this bioequivalence. But in a statistical sense, one needs to justify that the regularity assumptions relating to a "dilution assay" are true. Very recently, researchers are formulating more general interpretations of this bioequivalence concept, and statistical perspectives are fundamental in this assessment too.

As has been mentioned earlier, there are generally cost and time constraints in the study of biomechanistic systems, and often, prior to studying on human beings, a parallel model is formulated for some subhuman primates. For example, in order to study the carcinogenicity of artificial sweeteners (as a substitute for sugar), an experiment was planned for monkeys who were under study for a shorter time period but with

“excessively high dose” of this material. It was observed that the incidence of bladder cancer among these monkeys was significantly higher than in the control group. Based on this study it was intended to draw a conclusion for human population that artificial sweeteners are carcinogen, and hence, should be avoided. This scenario is a combination of accelerated life testing (ALT) and extrapolation from one species to another. ALT’s have been introduced in many statistical analysis. In reliability studies involving industrial setups or physical/chemical experimentations, the ALT work out quite well. On the other hand, for biological systems, the picture may be quite different. As in the ‘artificial sweetener’ example, there are generally two important factors: Total duration of exposure to the risk (T, say) and the dose level of the toxicant (D, say). In a normal case, usually T is very large and D is small, although the total effective dose level TD (E, say) may or may not be small. The process of growth of a carcinogen cell may depend on both T and D in a complex manner, and not on E alone. Thus, the effect of an ‘excessively high dose’ level with a small “exposure period” may be quite different from a normal dose level and long exposure period. A very similar picture holds for the inhalation toxicology model described earlier. Thus, there has to be enough justifications for the adoption of an ALT model in biomechanistic systems. The extrapolation problem is also very important in biomechanistics. Although guineapigs, rats, cats, dogs, monkeys and human beings all belong to the mammalian group of animals, there is a gradation of their body mechanisms and brain structures. Therefore, it may not be very wise to assume that the tolerance distributions for different species are comparable in a parametric sense (i.e., they differ only in associated parameters but have the same functional form). Moreover, the level of normal exposure for human being may be quite different from that of others. Without having considerable biological evidence of such bioequivalence relations, it may not be safe therefore to use extrapolation models from one species to another. This brings us to an important issue: What is the scope for generalized linear models in biomechanistics? The Poisson regression or the logistic regression models in an inter-species validity content may not be that appropriate, the proportional hazards models are also equally vulnerable. Nonparametrics may fare better in this context. But without some interspecies link functions, such models may not be that informative from a finite sample stand point. Finally, study of a biomechanistic model may often lead to destructive sampling inspection plans, and hence, surrogate end point models are sometimes used to draw conclusions. Again, in order to qualify for a surrogate endpoint, a response variable has to satisfy certain conditions. Sans these safeguards, the validity and scope for surrogate biomechanistic models in practice may be open to question.

6. CONCLUDING REMARKS

Statistical methodology and modeling are being increasingly used in biomechanistics. Still, there are numerous issues relating to valid and efficient use of statistical principles in this context.

(i) First and foremost, biomechanic models generally relate to studies where there may not be sufficient control over the experimental setups. This may lead to increased level of variability and thereby reduce the level of precision of the conclusions as are to be drawn from the study.

(ii) In a conventional case, generally, a treatment is to be compared with a control group, and there may be more than one such treatment group. In

biomechanistic models, there may be a "control group" in a true sense, so that conventional two (or multi-) sample models may not be that appropriate here.

(iii) Often, with appropriate transformation of variables (and statistics), in a conventional model, the response variable (in the continuous case) is assumed to satisfy the regularity conditions of the classical linear model. As has been explained earlier, in biomechanic models, neither the normality nor the linearity of the deterministic part can be usually taken for granted, and hence, there is a greater need to lay more emphasis on robustness of statistical models/analysis schemes for possible departures from the model based regularity assumptions.

(iv) In view of (i) - (iii), there may be a genuine need to develop more adoptive designs for biomechanic models and related statistical analysis.

(v) Misclassification of states of responses and measurement errors for primary/concomitant variates are more likely to occur in biomechanic models than in conventional reliability studies. These are needed to be taken into considerations in the model building as well as in statistical analysis.

(vi) Many of the biomechanic models have (explicit or implicit) carcinogenic activity. While the developing branch of Tomography casts a good deal of light on such carcinogens in respect to image processing and tumor development, there remains a greater task to make this branch of statistical sciences usable at the clinical/biological level. Indiscriminate use of statistical packages may lead to disastrous results.

(vii) Mutagenesis or genetic toxicology is very relevant to the study of biomechanistic models with potential carcinogens. This branch is under active development, and it is our hope that more interactions will develop in near future.

(viii) The general objectives of a study of a biomechanistic system are to be laid down as clearly as possible. If the ultimate goal is to assess the risk due to some identifiable factors on the system, then a proper measure of this risk with genuine biological as well as statistical interpretations need to be formulated, and this may also depend on the model.

(ix) The failure rate/survival analysis models and the hazard-regression type of models are to be judged comparatively with respect to their appropriateness in the given situation, and then a proper approach is to be adopted.

(x) In order to draw statistical conclusions with adequate precision, often, a large number of replication of experimentation (under comparable conditions) may be needed. This may run contrary to practical limitations set by time and cost constraints, and there may be other ethical constraints too. Nevertheless, there may be a number of experimentations with similar objectives but possibly under somewhat different experimental setups. In such a case, pooling of statistical information may be advocated to reduce the sampling fluctuations to a further extent. In statistics literature, this is referred to as meta-analysis [viz., Hedges and Oklin (1985)]. The success of meta analysis depends to a certain extent on a concordance of response patterns across the set of experimentations, and if such component studies relate different species/type of subjects or to heterogenesis plans, then pooling of data may not be very advisable.

There are many other (biological/biochemical/genetic) factors which are important in biomechanistics. The advent of modern computers has revolutionized the entire domain of science, technology, medicine and every walk of life. We cannot overlook the impact of computers in biomechanistics. Computer-incentive resampling methods (viz., bootstrap and jackknife procedures) are invading every corner of statistical science, and the prospects look good for biomechanistics too. Although standard resampling plans may not apply to such nonstandard situations, there is ample room for developing more general methodology with biomechanistics in mind.

REFERENCES

- Andersen, P.K., Borgan, O., Gill, R.D. and Keiding, N. (1993). Statistical Models based on Counting Processes. Springer-Verlag, New York.
- Barlow, R.E. and Proschan, F. (1975). Statistical Theory of Reliability and Life Testing: Probability Models. Holt, Rinehart and winston, New York.
- Chatterjee, S.K. and Sen, P.K. (1973). Nonparametric testing under progressive censoring. Calcutta Statist. Assoc. Bull. (1973).
- Cox, D.R. (1972). Regression models and life tables (with discussion). J. Roy. Statist. Soc. B34, 187-220.
- Epstein, B. and Sobel, M. (1955). Sequential life tests in the exponential case. Ann. Math. Statist. 26, 82-93.
- Ghosh, M., Mukhopadhyay, N. and Sen, P.K. (1995). Sequential Estimation. J. Wiley, New York.
- Grenender, U. (1981). Abstract Inference. J. Wiley, New York.
- Hedges, L.V. and Olkin, I. (1985). Statistical Methods for Meta-Analysis. Academic Press, Orlando.
- Hollander, M. and Proschan, F. (1984). Nonparametric concepts and methods in reliability. In Handbook of Staistics, volume 4: Nonparametric Methods (eds: P.R. Krishnaiah and P.k. Sen), North Holland, Amsterdam, pp. 613-655.
- Lehmann, E.L. (1953). The power of rank tests. Ann. Math. Statist. 24, 23-43.
- Mantel, N. and Haenszel, W. (1959). Statistical aspects of the analysis of data from retrospective studies of diseases. J. Nat. Cancer Instit. 22, 719-748.
- McCulluagh, P. and Nelder, J.A. (1989). Generalized Linear Models, 2nd ed. Chapman-Hall, New York.
- Murphy, S. A. and Sen, P.K. (1991). Cox regression model with time-dependent covariates. Stoch. Proc. Appl. 39, 153-180.
- Sen, P.K. (1987). Combination of statistical tests for multivariate hypotheses against

restricted alternatives. In Advances in Multivariate Statistical Analysis (eds. S. Dasgupta and J. K. Ghosh) Ind. Statist. Inst., Calcutta, pp. 377-402.

Sen, P.K. (1993a). Statistical perspectives in clinical and health sciences: The roadway to modern applied statistics. J. Appl. Statist. Sc. 1, 1-50.

Sen, P.K. (1993b). Inhalation toxicology: Awareness, identifiability, statistical perspectives and risk assessment. Keynote address, P.C. Mahalanobis Birth Centenary Internat. Envir. Confer., ISI, Calcutta [to appear in Sankhya, Ser. B. 57 (1995), pt. 2].

Sen, P.K. (1994a). Incomplete multiresponse designs and surrogate endpoints in clinical trials. J. Statist. Plan. Infer. 40. Page #??'s

Sen, P.K. (1994b). Some change-point problems in survival analysis: Relevance of nonparametrics in applications. J. Appl. Statist. Sc. 1, Page #??'s

Sen, P.K. (1994c). Statistical analysis of some reliability models: Parametrics, semi-parametrics and nonparametrics. J. Statist. Plan. Infer. 40, in press.