A Critical Evaluation of Some Problems Associated with Clinical Caries Trials by Computer Simulation: Discussion of Dr. Lu's Presentation

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Before I comment directly on Dr. Lu's interesting paper, I will first exercise a formal discussant's prerogative of talking on any subject he pleases that is remotely related to the presentation of the speaker. Therefore, at this time I wish to spend about two minutes delivering my philosophy on the role of simulation in science.

The value of simulation of a system is related to the extent of our knowledge concerning that system. Unlike what one might think on first musing, the value of simulation is not proportional to the amount of our knowledge, nor, actually, does it bear any monotone relationship, either increasing or decreasing, to that knowledge. Rather, I submit that the utility of the simulation (see Fig. 1) is a sort of inverse Gaussian distribution. In this distribution, the benefits from the simulation are greatest when the knowledge is minimal or maximal and are least when our understanding of the system or process being simulated is moderate.

One of the best examples of simulation where the knowledge is maximal would be the NASA Manned Spacecraft Program. Here, the physical and chemical laws describing the behavior of the rockets, launch vehicles, spacecraft, and lunar rovers are well understood. The simulation can proceed in exquisite detail, with both digital and analog simulation as well as actual physical mock-up devices. The purpose of simulation in this case, and in other systems of which there is extensive knowledge, is either to reduce cost or to minimize risks to humans or animals, or both. Another example of the extremely detailed system would be the computer simulation of wind tunnel experiments. Costs for the use of large aircraft wind tunnels can run as high as $10,000 per minute. By the year 1990, the use of large array processing digital computers for simulation of airflow over air and spacecraft will likely have supplanted the use of wind tunnels in the vast majority of aircraft design experiments.

At the opposite end of the spectrum are simulations concerning systems where there is very little knowledge. This allows the exploration of a variety of "what if" scenarios. The primary purpose of such simulation is qualitative rather than quantitative behavior and an understanding of the interrelations of various parts of the system. Examples would be universes with negative or repulsive gravities, chemical systems having silicon rather than carbon backbones, or complex econometric models of novel socioeconomic environments. Here, classes and types of behavior are of major interest. Questions such as, Can stable, oscillatory solutions exist? Does the system grow indefinitely? Is the behavior stable or chaotic? — represent some of the areas of interest.

The final region, that of moderate information, would be typical of a number of biomedical simulations. Thus, simulations of dental caries, the development of cancer metastases, or the onset of atherosclerosis would be examples of this type. Sufficient experimental data exist that one would not employ simulation in the qualitative style of minimal information systems. Conversely, there is not sufficient detail that one can employ the simulation techniques at the other end of the spectra which mimic the real process in considerable detail.

Having delivered myself of this philosophy of simulation, I would now like to comment on the interesting paper of Dr. Lu. Dr. Lu's detailed discrete simulation of the caries experience of tooth surfaces in two groups over a period from birth to age thirty provides valuable insights into some of the problems and pitfalls of dental caries clinical trials. Their work revealed two interesting findings: First, the net caries increment, representing transitions from sound to incipient caries, plus the transition of incipient lesions to frank caries is a more sensitive measure than the traditional DMFS score. This finding is important, in that it directs dental clinical trials investigators to a measure that is most sensitive to the subtle changes going on during a three-year caries clinical trial. Particularly, it shows that such components of the DMFS as UU merely contribute to the variance while providing no information about the ongoing caries process, whereas a component such as SU measures more the result of treatment than of the disease.

The second major result of Dr. Lu's simulation concerns the influence of examiner error. He has shown that, where the examiner error is unbiased and not too large, there is little effect on the fundamental conclusions of the trial. If, on the other hand, an examiner manifests bias, either consciously or unconsciously, or the magnitude of the error becomes too great, then the findings of the trial can be seriously compromised.

While I am in essential agreement with these conclusions, I wish to comment in more detail on two assumptions of this simulation that affect both results. The first concerns the selection of the gamma distribution as the survival time distribution for the tooth surfaces. Of all the standard parametric survival distributions — including the exponential, log-normal, gamma, Weibull, Gompertzian, or linear-exponential model — the gamma probably exhibits the most desirable behavior. For $r \geqslant 2$, there is positive aging with the gamma distribution — that is, increased risk with increasing time of exposure. I believe a more realistic type of aging behavior for dental caries can be modeled than that provided by the gamma distribution. To illustrate this point, we must introduce the concept of the hazard function from survival distribution theory.

The survival function, S(t), is defined as the probability that an individual (in this case a surface) survives longer than time t, *i.e.*,

$$S(t) = P \text{ (an individual surviving longer than t)} = P(T > t).$$

By definition, the cumulative distribution function, F(t), is the probability that an individual fails before time t, *i.e.*,

$$F(t) = P(T \leqslant t).$$

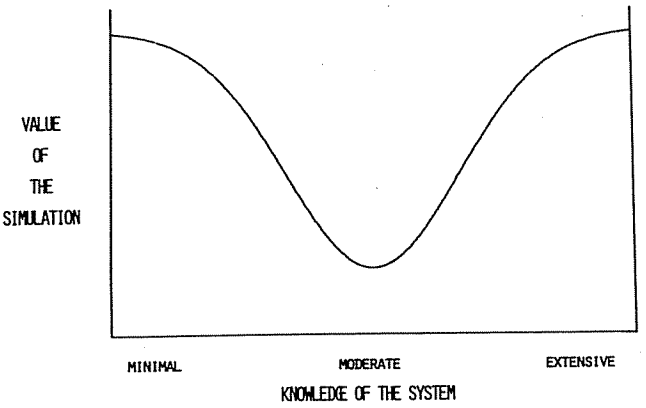

Fig. 1 – Simulation utility.

These two distributions are complementary, *i.e.*,

$$S(t) = 1 - F(t).$$

Like any other continuous random variable, the survival time T has a probability density function f(t) which measures the failure rate at time t and is the derivative of the cumulative distribution function, *i.e.*,

$$f(t) = F'(t).$$

The final (and frequently the most informative) function relating to survival distributions is the hazard function, h(t). The hazard function gives the conditional probability of failing in the interval t, t + dt, given that an individual has survived to the beginning of the interval. It can be shown (E. Lee, **Statistical Methods for Survival Data Analysis.** Lifetime Learning Pubs., Belmont, California, 1980) that

$$h(t) = \frac{f(t)}{S(t)}.$$

From the defining equation, we can derive the following expression interrelating the density, hazard, and survival functions:

$$f(t) = \frac{dF}{dt} = \frac{d}{dt}[1 - S(t)] = -S'(t).$$

Substituting this result in the definition equation of the hazard function above yields.

$$h(t) = \frac{-S'(t)}{S(t)} = \frac{-d(\ln S)}{dt}.$$

Integrating this equation from 0 to t, using the initial condition that S(0) = 1, yields

$$S(t) = \exp\left[-\int_0^t h(x)dx\right].$$

Let us now examine these expressions for the exponential and gamma distributions. For the exponential distribution, the survival function is

$$S(t) = e^{-\alpha t}.$$

Then the density is

$$f(t) = -S'(t) = \alpha e^{-\alpha t}.$$

Finally

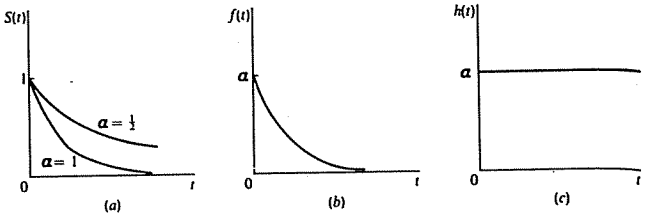

Fig. 2 – The Exponential Distribution: (*a*) Survivorship Function, (*b*) Probability Density Function, (*c*) Hazard Function.

$$h(t) = \frac{f(t)}{S(t)} = \frac{\alpha e^{-\alpha t}}{e^{-\alpha t}} = \alpha.$$

These functions are plotted in Fig. 2 (adapted from Lee, 1980, p. 158). Note that, for the exponential distribution, the hazard function is constant – that is, the conditional probability of failure (dying or developing caries) in any interval is constant. Thus, it is sometimes said that the process has no memory. Radioactive decay is a good example of exponential survival, an atom having the same likelihood of decay in any interval, independent of its age.

Turning to the gamma distribution employed in Dr. Lu's paper, we have the density as

$$f(t) = \frac{\alpha}{(r-1)!}(\alpha t)^{r-1} e^{-\alpha t}.$$

The corresponding survival function and hazard function are more complicated expressions, and there is no particular value in presenting them here. If the reader is interested, he can see Lee, 1980.

The gamma distribution is characterized by two parameters, r and α. When $0<r<1$, there is negative aging, and the hazard rate decreases monotonically from infinity to α as time increases from 0 to infinity. When $r>1$, there is positive aging, and the hazard rate increases monotonically from 0 to α as time increases. Finally, when r = 1, the hazard rate equals α, a constant, as in the exponential. Fig. 3 illustrates the gamma hazard for $\alpha = 1$ and r = 1, 2, and 4 (adapted from Lee, 1980, p. 175).

We see that a gamma distribution with $r>1$ results in increasing risk with increased exposure. In the actual clinical caries situation, at least two types of hazard function are encountered, neither of which has the form of a gamma distribution with $r \geqslant 1$.

The occlusal surface of the first molar would represent the first type of surface hazard. This surface has high infant mortality, representing great risk shortly after eruption which declines with increasing exposure. This is illustrated in Fig. 4. The second class of surfaces might be typified by the distal surface of the first molar. This surface has very low risk until the second molar erupts. Then the hazard increases to a peak and declines with subsequent maturation. This behavior is shown in Fig. 5.

The above remarks apply to permanent surfaces only. For deciduous surfaces, a monotone increasing hazard function may be meaningful. Hazard functions with the properties seen in Figs. 4 and 5 could either be estimated empirically from caries epidemiological data or modeled to have those characteristics. With such a hazard function(s), $\hat{h}(t)$, the simulation could then proceed with survival functions

$$S(t) = \exp\left[-\int_0^t \hat{h}(x)dx\right]$$

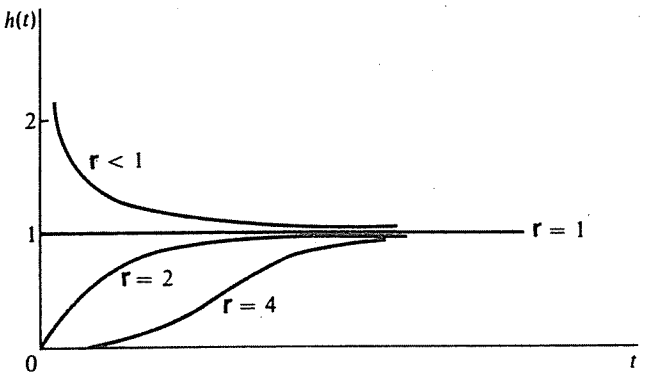

Fig. 3 – Gamma Hazard Functions with $a = 1$.

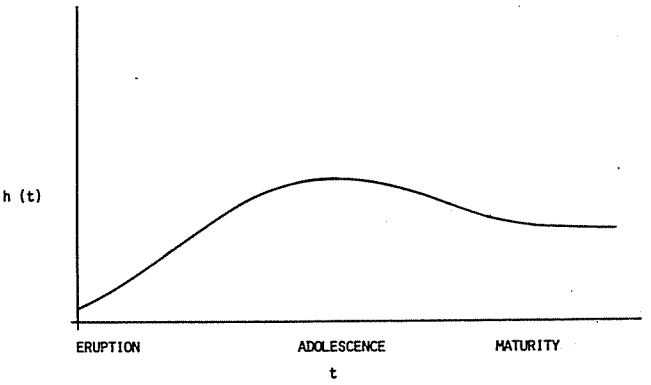

Fig. 5 – Hazard Function for a first molar distal surface.

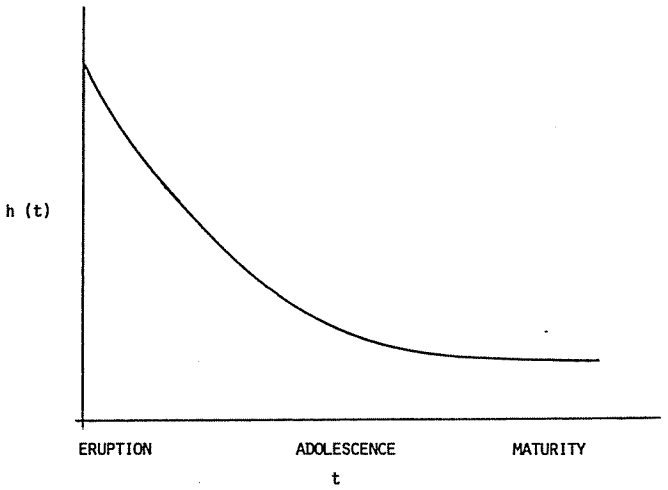

Fig. 4 – Hazard Function for a first molar occlusal surface.

and $$f(t) = \hat{h}(t) \exp\left[-\int_0^t \hat{h}(x)dx\right].$$

I would also like to comment on the assumptions in the simulation relating to the diagnostician's error rate. The assumption is that the error rate is essentially independent of the true state of the surface. Therefore, there is a 95% probability of classifying the state correctly and a 5% chance of erring on either side of the correct classification (as seen from Table 1 in Dr. Lu's paper). Unfortunately, the probability of misclassification does depend upon the true state of the surface. Few diagnosticians would miss a frank caries lesion with overt cavitation. Likewise, a very sound surface that would not catch an explorer would have a high probability of being classified as sound. On the other hand, incipient caries lesions where there is mineral loss would be subject to a much larger error rate. It would be interesting to see the simulation repeated with the examiner error matrix modified to reflect these variations depending upon the true state, and I hope that Dr. Lu will do this for us.