STOCHASTIC PROCESSES IN PHYSIOLOGY

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1. Introduction

By virtue of their statistical characteristics, living systems and living organisms have in common the very general property of variation. This phenomenon occurs at both inter- and intraorganism levels. Several authors have emphasized the statistical character of the activity of nervous fibers (Pecher [36], [37]), of nerve-muscle junctions (del Castillo and Katz [5]), and of the nervous system (McCullough and Pitts [32], Rosenblatt [38]), to give a small biased sample of the literature.

This paper considers four other physiological systems:

1. Intrarenal system variation in glucose resorption for increasing load of glycemia when the rate of glucosuria is studied.

2. Intravisual system variation in time for the recovery of visual capacity after a controlled dazzling.

3. Intracardiac variation in time of ventricular response on complete arhythmia by auricular fibrillation.

4. Interorganism variation in survival time after application of an acaricide to a population of susceptibles. This is an interesting case of a mortality curve.

The first two situations have in common the morphologically and physiologically proven existence of a great number of anatomical and functional units, the *nephrons* for the kidney and the *retinons* (rods and cones) for the retina.

The fourth situation corresponds to a group of distinct individuals submitted at time zero to the action of an acaricide. On the hypothesis of independent reaction to the specific stimulus in each of the three situations, it is reasonable to set up a simple stochastic model in which the intensity of the process may be guessed from experimental curves giving the mean evolution of the system, or to consider the situation from the point of view of waiting or holding times.

After having shown the adequacy of model to describe, or rather exhibit the phenomena, the important statistical problem should be raised of estimation of the parameters of the stochastic model. This point is hardly considered here.

2. Evolution of the glucosuria when the glycemic load is increased

2.1. *The facts.* In physiological conditions, when the glycemic load is about 1 mg/ml, no glucosuria is observed. If the glycemic load x is increased by in-

gestion of intravenous perfusion of glucose, glucosuria appears at a mean threshold level of 1.2 mg/ml, the so-called Claude Bernard threshold labeled x_B. For an increasing glycemic load, the rate of glucose urinary elimination follows curve 3 of figure 1. The first part x_BM increases with increasing slope tending to the slope of the straight line MF. Figure 1 was constructed from graphs in Govaerts and Muller [20], Govaerts [13], and Smith [40], pp. 93–95.

2.2. *Physiolcgical model.* Microscopical and physiological studies have shown that the mammalian kidney consists of a great number of elementary units,

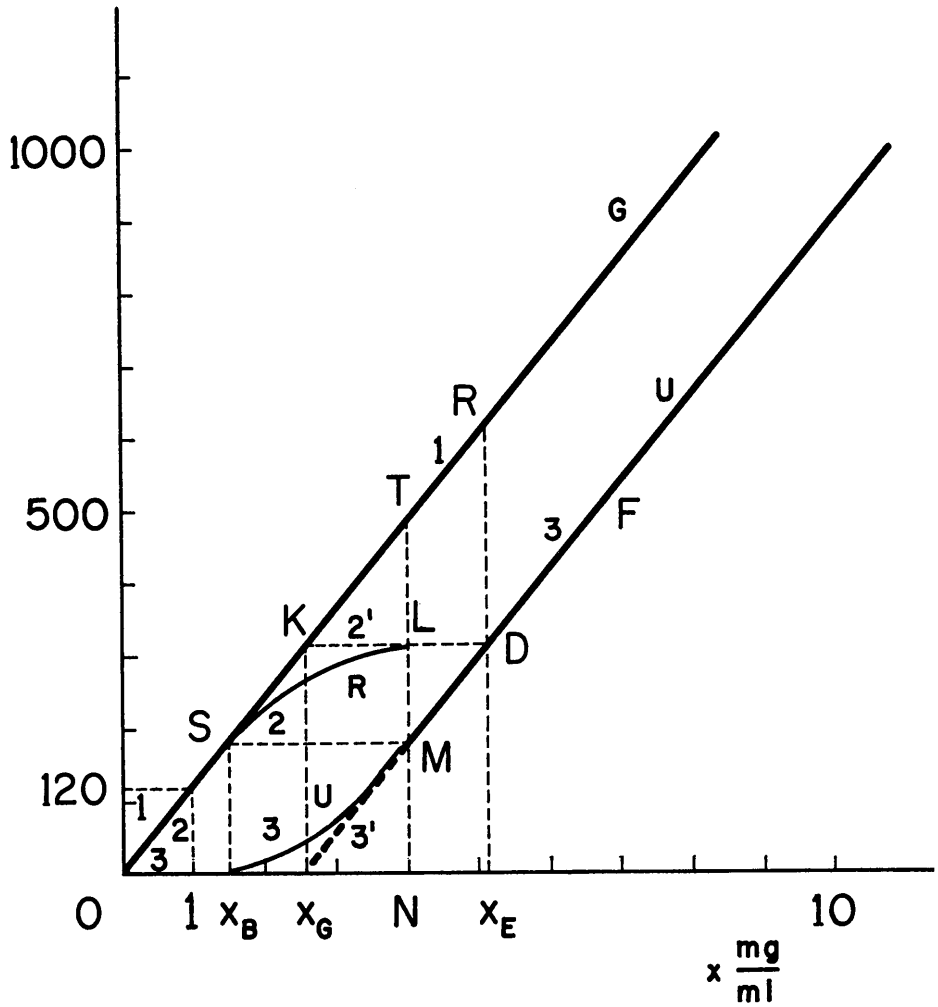

FIGURE 1

Glucose resorption as a function of x, the plasmatic glucose concentration.
Curve 1: $G(x)$, glucose filtration rate in the glomerule, in mg/min,
Curves 2 and 2′: $R(x)$, tubular resorption rate of glucose, in mg/min,
Curves 3 and 3′: $U(x)$ urinary excretion rate of glucose, in mg/min.

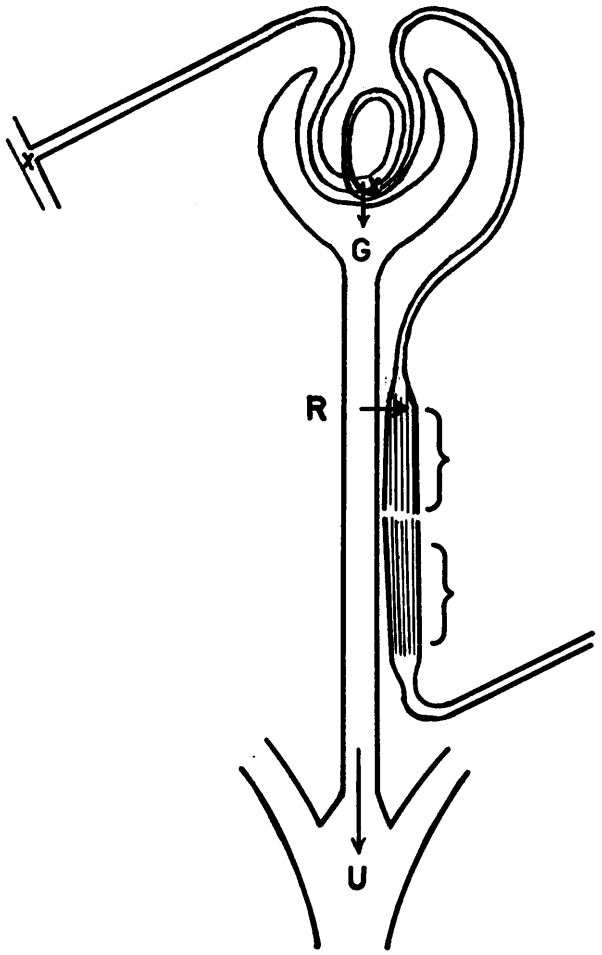

FIGURE 2

Mammalian kidney structure for glucose filtration and resorption.

the nephrons, whose relevant structure for glucose filtration and resorption is sketched in figure 2.

This paper considers only the glucose resorption, using the notation

x: plasmatic glucose concentration, in mg/ml

$G(x)$: glucose filtration rate in the glomerule, in mg/min

$R(x)$: tubular resorption rate of glucose, in mg/min

$U(x)$: urinary excretion rate of glucose, in mg/min.

Experimentally, we observe that

$$G(x) = gx, \tag{1}$$

where g ml/min is the glomerule filtration rate which can be determined by

administration of creatinine or sodium thiosulfate. In the absence of secretion, the relation of conservation of the glucose mass at every plasmatic load is written

$$G(x) = R(x) + U(x), \tag{2}$$

which is an analogue of the Kirchhoff law in electricity. For $x < x_B$ we have $U(x) = 0$, so that $G(x) = R(x)$. For $x > x_B$, the observed $U(x)$ follows curve 3 in figure 1 (Govaerts and Muller [20]; Govaerts [13]–[17]; Govaerts and Lambert [18]).

The glomerule filtration rate $G(x)$ is known from creatinine clearance. Thus it is easy to construct this rate, by differencing curve 2 in figure 1, which shows the progressive failure in resorption. The maximal resorption rate is observed in NL, for a load x_M. For increasing glucose plasmatic loads over N, the urinary excretion rate $U(x)$ follows a course MF which is parallel to the filtration curve $G(x)$ with a constant difference.

$$NL = MT = DR = Tmg \text{ mg/min}. \tag{3}$$

The Tmg (Shannon and Fisher [39] and Smith [40]) is the maximal glucose resorption rate, which can be determined experimentally.

2.3. *Stochastic model for glucose resorption by the mammalian kidney.* Two sets of states have to be considered; they are glycemic loads below the Claude Bernard threshold x_B and over this threshold.

2.3.1. $x < x_B$. The kidney is constructed of a great number N of nephrons supposed to act independently and fully resorbing glucose under a glucose plasmatic load x. The organ is said to be in the state S_n when n nephrons are active per unit volume, thus realizing a random spatial process. Let ξ be the intensity of the process expressed in units $(\text{mg/ml})^{-1}$.

Using classical notation, we then have (Feller [8]; Hald [22])

$$P_n'(x) = -\xi P_n(x) + \xi P_{n-1}(x), \tag{4}$$

$$P_0'(x) = -\xi P_0(x). \tag{5}$$

The initial conditions are

$$P_0(0) = 1, \qquad P_n(0) = 0, \qquad n \geqq 1, \tag{6}$$

whence

$$P_0(x) = e^{-\xi x}, \tag{7}$$

$$P_n(x) = e^{-\xi x}\frac{(\xi x)^n}{n!}, \qquad n \geqq 0; x \geqq 0. \tag{8}$$

The mean number of nephrons resorbing per unit volume at load x is

$$\mu(x) = \xi x. \tag{9}$$

The total number of resorbing nephrons in the kidney is $N\xi x$. In man, N is of the order 1×10^6 to 1.3×10^6 in nonpathological renal conditions (Hayman and Johnson [23]). If ρ mg is the average glucose mass resorbed per nephron and unit time, the total rate of resorption at load x is

$$R(x) = N\rho\xi x. \tag{10}$$

Comparing (1) and (10), it is possible to write

$$g = N\rho\xi. \tag{11}$$

This relation establishes a link between the experimental filtration value g ml/min and the quantity $N\rho\xi$, obtained from the Poisson model and characterizing the integral resorption of the filtered substance. In physical units, ρ is expressed in mg/min and ξ in $(\text{mg/ml})^{-1}$. Since N is dimensionless, the product $N\rho\xi$ is expressed in units (mg/min) $\times$ (ml/mg) or ml/min, or in the same physical units as those of the filtration rate g. From (11) another interesting relation holds, namely,

$$Tmg = N\rho, \tag{12}$$

both in units mg/min.

Several authors have shown that Tmg varies little for one individual (see, for example, Verbanck [41]). As N also is constant, there is a strong argument for the practical constancy of ρ mg/(nephron $\times$ min).

The proportion of elementary volumes in which no nephron is acting is given by (7). For a load x increasing from 0 to the Claude Bernard threshold x_B, we find that $P_0(x)$, the probability of the state S_0 of the kidney in which no nephron is acting, decreases exponentially from 1 to $\exp(-\xi x_B)$. Conversely, the probability of a state different from S_0, that is, of finding an elementary volume where at least one nephron is acting, increases from 0 to $1 - \exp(-\xi x_B)$.

2.3.2. $x > x_B$. Govaerts [13], [14] introduced the concept of "weak" and "strong" nephrons as well as the unequal functional capacity of resorption of the nephrons reflected in the shape of the glucose excretion curve by the kidney. Here we are looking for a probabilistic interpretation of this state of affairs.

When the glucose plasmatic load is increased over x_B, there is a progressive failure in the capacity of resorption of the *system of nephrons*. We now introduce the excess of load over the threshold $u = x - x_B$, that is, for $u > 0$, and imagine that the probability of finding an elementary area in which a nephron fails to resorb follows the well-known law of exponential holding times (Feller [8], [9]). The operational time here is the excess of load $u = x - x_B$.

In analogy with the exposition of Feller ([8], p. 424), for loads greater than x_B, the probability that a nephron still resorbing at load u fails to resorb within the next load increase du is, up to terms of higher order,

$$\frac{dF(u)}{1 - F(u)} \tag{13}$$

provided that $F'(u)$ exists.

Let us consider the particular case of exponential holding excess loads,

$$F(u) = 1 - e^{-\eta u}, \qquad \eta > 0, \tag{14}$$

where η is in units $(\text{mg/ml})^{-1}$. The probability (13) becomes

$$\frac{\eta e^{-\eta u}\, du}{e^{-\eta u}} = \eta\, du. \tag{15}$$

If then, a nephron holds an excess load $u = x - x_B$, the probability that the holding excess load will fail to be resorbed within the next interval du, is $\eta\, du + o(du)$ and independent of what has happened for lower excess loads. Although not writing in terms of holding times, Fortet ([10], pp. 83–84) describes an analogous case in terms of conditional probability.

We are assuming, as a first approximation, that ρ is the same in this glucosuric set of states as in the aglucosuric set. The glucose mass resorbed per unit time at excess load u is

$$R(u) = N\rho(1 - e^{-\eta u}). \tag{16}$$

The total mass resorbed at load $x > x_B$ is the sum of two terms,

$$R(x) = N\rho\xi x_B + N\rho[1 - e^{-\eta(x - x_B)}]. \tag{17}$$

According to (17), the rate of urinary excretion of glucose over the Claude Bernard threshold may be written as

$$\begin{aligned} U(x - x_B) &= N\rho\xi x - N\rho\xi x_B - N\rho[1 - e^{-\eta(x - x_B)}] \\ &= N\rho[\xi(x - x_B) - 1 + e^{-\eta(x - x_B)}]. \end{aligned} \tag{18}$$

When $x \to x_B$ with decreasing values, $U(x - x_B) \to 0$, as is to be expected.

2.3.3. *Probabilistic interpretation of the Claude Bernard threshold x_B.* The Claude Bernard threshold x_B is the transition point from a set of states of nephrons fully resorbing at any glucose load $x < x_B$ (according to a Poisson process) to a set of states when the nephrons resorb an excess load $u = x - x_B$ according to an exponential holding excess load process, which is (Feller [9], p. 412) the zero term in a Poisson distribution in u, that is, the holding excess load up to the occurrence of the first failure to resorb.

For $x < x_B$, in the aglucosuric set of states, the intensity of the Poisson process or the conditional probability of finding any nephron active in resorption is asymptotically

$$p_n(x)\, dx = \xi\, dx, \tag{19}$$

with x in mg/ml and ξ in $(\text{mg/ml})^{-1}$. For $x > x_B$, in the glucosuric set of states, an excess of load $u = x - x_B$ is introduced. In this set of states the probability that a nephron, holding an excess load $u = x - x_B$, will fail to resorb within the next increment du is asymptotically equal to $\eta\, dx$ and independent of what happened for lower excess loads.

2.3.4. *Mean threshold of P. Govaerts.* Govaerts [13], [14] introduced the concept of mean threshold (*seuil moyen*), here labeled x_G. This concept corresponds to a physiological model of resorption of a system of nephrons which would fully resorb for $x < x_G$ and which would all stop the resorption of glucose abruptly for $x = x_G$. On this hypothesis the curve of rate of glucosuria should follow the

segment $0x_G$ and then the straight line 3′ ($x_GMD\cdots$) in figure 1. Conversely, since the filtration curve 1 is the same, the rate of glucose resorption would follow the segments $0K$ and KLD. This model is nonstochastic. It is, however, possible to imagine a stochastic model by putting a Poisson process with intensity ξ for $x < x_G$ and, for $x = x_G$, putting a fixed and no longer random holding load at x_G.

From figure 1, it is easily seen that

$$Tmg = gx_G. \tag{20}$$

From (11) and (12) we write

$$N\rho = x_G N\rho\xi. \tag{21}$$

Thus ξ in ml/mg equals the inverse of x_G in mg/ml.

This relation shows that it is possible to estimate the parameter ξ of the random process of resorption in aglucosuric conditions from experimental measurements in the zone MF. From this very necessary experimental procedure, it is clear that x_G will be estimated by extrapolation of a regression curve from plots of $[x_i, U(x_i)]$ and will thus be subject to a rather high error of estimation.

Using figure 1 and a property of the exponential we may write

$$x_G = x_B + \frac{1}{\eta}. \tag{22}$$

If, then, x_B and x_G can be estimated with sufficient precision, it should be possible to estimate the two parameters ξ and η involved in the stochastic model of glucose resorption in the mammalian kidneys following this model. We could also test the statistical null hypothesis H_0: $\xi = \eta$ and the biologically equivalent null hypothesis in the sense of Neyman [35], say $\mathfrak{H}_0$: the functional state of the mammalian kidney in the glucose resorption is described by one parameter ξ involved in two distinct processes, namely, a Poisson process below the Claude Bernard threshold x_B and a holding excess glucose load above x_B.

Relation (18) gives the equation of the transitory state of the kidney from x_B to the point where the capacity of glucose resorption is exhausted. This point x_E corresponds to the maximum absolute threshold where, for the load x_E, practically all the N nephrons are active in resorbing glucose. According to its very definition it is not easy to fix x_E experimentally, since theoretically it is related to the value $+\infty$ for $u = x - x_B$. Indirect experimental evidence for the exponential holding excess load model could be given in relating $x_E - x_B$ to $1/\eta$. If, owing to an extensive set of accurate experimental data, the biometrician has to look for a more elaborate model (see McKendrick [33], Eggenberger-Pólya [7], Neyman [34], Consael [4]), the proposed model will in any case be useful because it provides a "fil d'Ariane" to the physiologist.

2.3.5. *Two examples.* Smith ([39], p. 88; see also his figure 17, p. 87) stated that the dog is unique in that glomerular activity defined as above is quite uniform throughout the kidneys, all nephrons saturating at the same value of plasma glucose concentration. This is confirmed by Verbanck [41] who deduces the iden-

tity of the Claude Bernard threshold x_B and the Govaert mean threshold x_G, "when these values are determined by experiments where hyperglycemia is slowly induced."

In our stochastic model this corresponds to the unique Poisson process with constant intensity ξ for $0 < x < x_B$ and to the value $\eta \approx \infty$ for the second phase of exponential holding excess load.

"In man, the glucose titration curve has considerable splay, . . ." (Smith [40], p. 88). This corresponds to the second phase of exponential holding excess load characterized by η and following the Poisson phase with intensity ξ. In this case the difference $x_G - x_B = 1/\eta$ is different from zero.

The splay in the tubular resorption in the human kidney is well shown in Smith ([40], figure 18, p. 92) and its glucosuric rate counterpart (figure 19, p. 95) is given, following Govaerts, et al. [19]. In his comments on this graph, where L is our x_G, Smith writes that x_G is the "threshold value of the plasma glucose concentration . . . at which the renal tubules are nominally just saturated. This value neglects the splay in the excretion curve which may be large if there is a wide dispersion in glomerular activity." The stochastic model throws some light on this point. If the exponential holding excess load process holds, the value $x_G - x_B$ corresponds to a fraction $1 - 1/e = 0.63$ of tubules failing in glucose resorption and a fraction $1/e = 0.37$ of tubules not yet failed in resorbing glucose. Moreover, according to Govaerts ([13] p. 50), with a slight modification the mean threshold $x_G - x_B$ is the excess load of glycemia for which the reabsorbing power of all the nephrons would be saturated if this power were equal to the statistical mean of the actual capacities of the nephrons. This is indeed true in an exponential model where the frequency function in excess load $u = x - x_B$ is

$$\frac{dF(u)}{du} = \eta e^{-\eta u} \tag{23}$$

and the expected or mean value of u is

$$E(u) = \frac{1}{\eta} = x_G - x_B. \tag{24}$$

3. Adaptometric curves

The adaptometer of Goldmann-Weekers [11] allows one to register successive plots of the curve of recovery of light sensibility after a fixed dazzling of five minutes duration.

3.1. *Experimental curves.* Let $I(t)$ be the threshold light intensity necessary to see the test object at the time t of the recovery phase. The adaptometer plots t against $\log_{10} I(t)$, which results in two portions, giving rod and cone response respectively [1], [6], [24], [25], [26]. The transition point between the two parts is classically labeled α.

3.2. *Biometric reduction of the adaptometric curves.* By replotting the experimental points in the coordinate system [$\log t$, $\log \log I(t)$], we obtain two straight

lines of clearly different slopes [12], [29], which are indexes of the functional state of the rods and the cones, respectively.

3.3. *Stochastic model of recovery of luminous sensitivity after controlled dazzling.* After five minutes t_0 of strong illumination the retinons recover gradually. We say that the retina is in state S_n, for $n = 0, 1, 2, \cdots$, if n retinons per elementary unit area have recovered their biochemical integrity and functional capacity.

We have shown [30] that it is possible to set up, as a first approximation, a Poisson model for the recovery of luminous sensitivity of the human retina by putting as intensity of the process

$$p_n(t) = \frac{\lambda\, dt}{t} = \lambda\, dLnt. \tag{25}$$

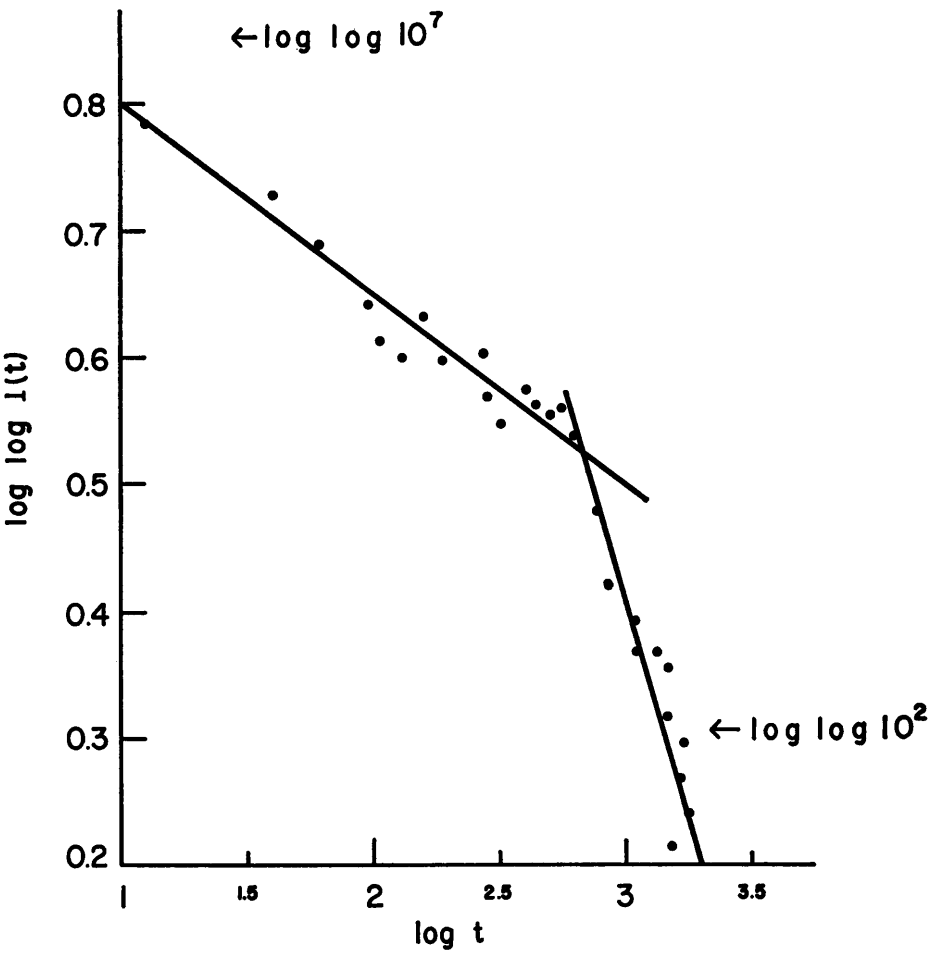

FIGURE 3

Threshold light intensity necessary at time t to perceive the test object.

This gives the mean value

$$\mu(t) = \lambda Ln \frac{t}{t_0}. \tag{26}$$

This mean value provides a good fit of the experimental curves giving $\log \log I(t)$ as a function of $\log t$. The slope λ is clearly different for the system of rods and of cones and in these coordinates the transformed point α appears quite evident (figure 3). In this case, the chronological time t is replaced by an operational time Lnt/t_0, a function of the period t_0 of strong illumination of the retina.

4. Mortality curve of acares submitted to an acaricide action

The evolution of the mortality curve of acares subjected to an acaricide action [31] may be described by a Poisson model with intensity

$$p_n(t)\, dt = \xi t\, dt = \xi\, d\left(\frac{t^2}{2}\right) \tag{27}$$

or, more generally,

$$p_n(t) = \xi t^n\, dt = \xi\, d\left(\frac{t^{n+1}}{n+1}\right). \tag{28}$$

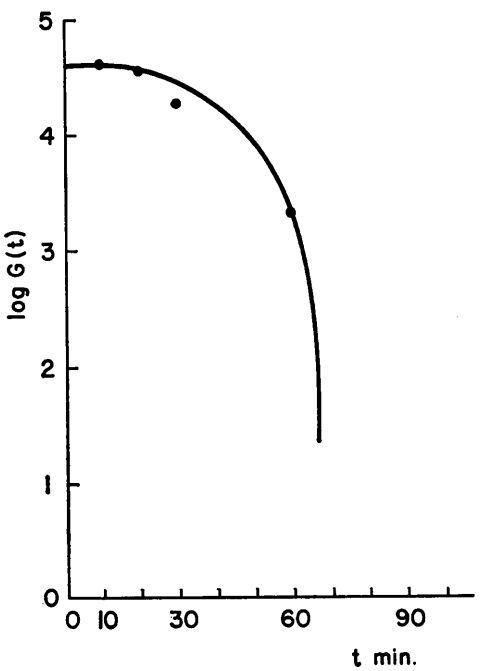

FIGURE 4

Experimental survival curve.

In this case the operational time scale has to be adjusted after the estimation of n. This kind of model has also been considered by Arley [2].

However, a model in terms of holding time may also be considered.

According to (13) the asymptotic probability that an acare still surviving at time t will die within the next interval dt, is

$$\frac{dF(t)}{1 - F(t)}. \tag{29}$$

Experimentally (figure 4) the survival curves from α suggest putting

$$G(t) = ce^{-t^2/2\tau^2} \tag{30}$$

with $c = 1$, where t and τ are expressed in the same time units.

The mortality curve $F(t)$ is

$$F(t) = 1 - G(t) = 1 - e^{-t^2/2\tau^2}, \tag{31}$$

to which corresponds the unimodal frequency function, defined for $t > 0$,

$$\varphi(t) = \frac{t}{\tau^2} e^{-t^2/2\tau^2}. \tag{32}$$

Owing to (31) and (32), equation (29) may be written as

$$\frac{te^{-t^2/2\tau^2}dt}{\tau^2 G(t)} = \frac{t\,dt}{\tau^2}. \tag{33}$$

Thus the asymptotic probability (29) to (33) increases linearly with the time t but is constant in the operational time $(t/\tau)^2$. This is the simplest extension of relation (15). The parameter τ may be regarded as an index of sensitivity of the organisms to the toxic agent.

5. Ventricular activity in case of complete arhythmia by auricular fibrillation

Macrez [27] has given an analysis of the frequency curve of the interval RR of the ECG between two successive ventricular beats in case of complete arhythmia by auricular fibrillation. This interval is a random variable whose frequency curve is unimodal and positively skew. The author uses a concept of "*imminence*" closely related to (13) and (29). Two histograms of about 1000 intervals RR have been fitted by a frequency function of the type (32). This corresponds to a linear relation such as (33) in the initial portion of the distribution. The operational time is $u = t - t_0$, where t_0 (the refractory period of the ventricle) is about 0.40 sec, corresponding to a rate of 150 beats/min. A parameter r corresponding to $1/\tau$ of (33) is regarded as an index of *ventricular receptivity* and is to be added to the classical characteristics of heart activity. The cases of complete ventricular arhythmia by auricular fibrillation, when the imminence increases linearly with $u = t - t_0$, could be regarded as typical, thus giving an objective basis for classification and modalistics of regularization.

The author remarks also that the observed distribution of the RR intervals

may be realized by a ventricle submitted to random impulses which would give a contraction after having received a fixed number of impulses (five impulses in this case).

This example shows the interest of the registration of intraindividual variation of response with time. Its analysis may help to give a deep insight into the determinism of physiological phenomena, which is the aim of the biometrical analysis [3], [28].

6. Conclusions

This paper is intended to show the interest of a probabilistic approach in the biometrical analysis of some physiological phenomena. In such widely different fields as nervous, renal, visual, cardiac, and toxicological physiology, the concept of *random phenomena* appears to be fundamental and a few simple probabilistic models may describe these phenomena in terms of independent units working randomly in space or time. One important feature of these models is the introduction of parameters with physiological meaning which may give indexes of physiological state or activity.

However, it may happen that the phenomena may be represented by two or perhaps more probabilistic models. The first case is the well-known contagious process, discussed, for example, in [8], where the *biologically different schemes* of Eggenberger and Pólya [7] on the one hand and of Greenwood and Yule [21] on the other lead to the *same probability distribution.*

A second example is given with the acare mortality curve where the observed survival curve may be seen as generated by a Poisson process with intensity given by (27) or in relation with the optics of holding times with an imminence of death proportional to t, or constant in operational time $(t/\tau)^2$.

A third example refers to the ventricular response interval RR whose distribution corresponds to a similar concept of imminence or to a Gamma distribution with parameter $n = 5$ [27].

Finally, due to the fact that the argument of the exponentials is dimensionless, the simple models introduced in this paper contain dimensionless variables which allow a juxtaposition of experimental results obtained in different conditions, provided that the statistical problem of estimation of the relevant parameter has been solved previously.

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