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THRESHOLD SECRETORY MECHANISM: A MODEL OF DERIVATIVE ELEMENT IN BIOLOGICAL CONTROL

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A secretory system can be considered a collection of packets of a stored substance, each packet characterized by a threshold to a stimulatory releasing agent. In terms of macroscopic release of the substance, the rate equation contains explicitly and naturally the time derivative of the stimulus intensity. Elaboration of this general model for threshold secretory mechanisms was motivated by insulin secretion data discussed here. Experimental data on the same type of secretory system (pancreas), the hormone secretion as well as electrical characteristics of the secretory cells, lead to a conjecture that the packets might be identified with the whole secretory cells, rather than the granules or vessicles of the stored hormone.

Threshold phenomenon in biophysico-chemical systems may be responsible for a variety of interesting effects in biology. Processes manifesting themselves as threshold excretion, siphon effect or a trigger mechanism are merely representations of different organizational complexity of some form of elemental threshold mechanism such as saturation or allosterism. These elemental mechanisms are the consequence of the Law of Mass Action, but they transgress this law as they exceed this level of organization. From a higher stand point on the hierarchical scale of organization, they are viewed as being governed by another set of simple rules in a degree of abstraction analogous to the Law of Mass Action. This law states that the rate of a reaction v is proportional to the product of concentrations of the constituents c_i, namely, $v = k \prod_i c_i$.

The rule of threshold processes states that the rate of the process v is zero for a constituent concentration c below a threshold concentration θ, and is some function of the concentration $f(c)$ otherwise, viz.,

$$v = \mathscr{H}(c - \theta)f(c, \theta), \tag{1}$$

where $\mathscr{H}$ is the Heaviside unit step function: it is zero for $c < \theta$, unity otherwise. Just as the rate coefficient k of the Law of Mass Action is open to empirical estimation, the threshold θ and the functional form of $f(c)$ may be experimentally determined. On the other hand, the rate coefficient may also be accessible to computational procedures for simpler reaction mechanisms (Eyring, 1965). Similarly so, the threshold θ and the $f(c)$ in (1) may be computed, at least for simple threshold mechanisms (Ličko, 1972).

Once a rule of a threshold process is established, an analysis and synthesis of more complex threshold systems may be attempted. Presently we will utilize the threshold reaction concept in discussing a secretory mechanism. This mechanism possesses an interesting inherent characteristic, namely, the stimulus rate sensitivity whose existence is often assumed for the interpretation and simulation of endocrine data (Cerasi, 1967; Dallman and Yates, 1969; Foster, 1970; Srinivasan *et al.*, 1970).

Model. Consider a product of biochemical processes in an organism which is released only upon an adequate stimulus. Hormones and neurotransmitters usually belong to this group of substances, most of them retained in granular or vessicular form in the secreting cells. We refer subsequently to the unit storage of such a substance as a *packet*, leaving it at present unidentified as anatomical structure. Furthermore, consider the process of release of the material as a threshold reaction: to every packet a certain threshold θ is assigned such that the stimulus effectively acts only upon those packets whose thresholds are below the stimulus level S. In other words, on the basis of this assumption there exists a threshold density function $\xi(\theta, t)\, d\theta$ of equal* packets, representing the number of packets in the threshold interval $(\theta, \theta + d\theta)$, and therefore, the amount of the substance releasable by stimulus level shift from $S = \theta$ to $S + dS = \theta + d\theta$.

Total releasable amount of the substance by a given stimulus level $S(t)$ at any time is

$$X[S(t), t] = \int_0^{S(t)} \xi(\theta, t)\, d\theta. \tag{2}$$

* The assumption of equality of the packets is not a restrictive one, it is used here merely for the convenience of description of the model.

This entity also defines the threshold distribution function up to the stimulus level $S(t)$. Hence, the rate of change of the amount of the releasable material when its packets face the stimulus level $S(t)$ is

$$\dot{X}[S(t), t] = \int_0^{S(t)} \dot{\xi}(\theta, t)\, d\theta + \xi[S(t), t] \frac{dS(t)}{dt}. \tag{3}$$

Mere inspection of (3) reveals a startling result: the rate of change of the releasable amount of the packeted substance depends not only upon the stimulus level $S(t)$ [the first term of the right-hand side of (3)], but also upon *the rate of change* of the stimulus level, $dS(t)/dt$. Moreover, the second term of (3), representing the *derivative element*, is attenuated by the threshold density function $\xi[S(t), t]$, so that the effectiveness of the derivative element is not necessarily uniform over the range of the stimulus level S, nor over the time t.

If we attempt to give a biophysically meaningful interpretation to the mechanism of release of the packeted substance, we must assume that at any threshold level θ, the rate of the release is a function of the number of packets (or the amount of substance stored in them) of the given threshold. Then, according to (1), the rate equation for the release of the substance from the packets of the thresholds between θ and $\theta + d\theta$ is

$$\dot{\xi}(\theta, t)\, d\theta = -\mathscr{H}[S(t) - \theta] f[\xi(\theta, t), S(t), \theta, t]\, d\theta. \tag{4}$$

This equation holds for the entire population of packets with non-negative thresholds, $0 \leqslant \theta < \infty$.

Therefore,

$$\dot{X}[S(t), t] = -\int_0^{S(t)} f[\xi(\theta, t), S(t), \theta, t]\, d\theta + \xi[S(t), t] \frac{dS(t)}{dt}, \tag{5}$$

because $\dot{\xi}(\theta, t)\, d\theta = 0$ for all $\theta > S(t)$.

Equation (4) contains only a loss term, even though this loss term is in its most general form. In any actual situation, *refilling* of the packets must be considered and, possibly, a *redistribution* process must take place to maintain the initial threshold density function. These two processes have been described (Grodsky, 1972) for a particular set of assumptions and functions fitted to the experimental data on insulin release. Here, for the sake of completeness, we merely include a function $G[S(t), t]$ into (3) and (5). Thence,

$$\dot{X}[S(t), t] = -F\{X[S(t), t], S(t), t\} + G[S(t), t] + \xi[S(t), t] \frac{dS(t)}{dt}, \tag{6}$$

with

$$F\{X[S(t), t], S(t), t\} = \int_0^{S(t)} f[\xi(\theta, t), S(t), \theta, t]\, d\theta.$$

However, in general we shall conclude that the processes of refilling and redistribution, $G[S(t), t]$, must be very slow in comparison with the release process, $F\{X[S(t), t], S(t), t\}$ and the effective rate of change of the stimulus intensity, $\xi[S(t), t][dS(t)/dt]$, if the characteristic response pattern of the system is to be observed. We consider such a response pattern as a spike response of the F function to every step of a staircase stimulation, as depicted in Figure 1.

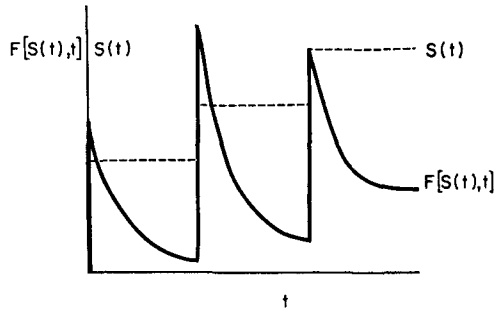

Figure 1. The rate of release $F[S(t), t]$ of a substance stored in packets of differential sensitivity in a staircase stimulation

Each stimulus step can be thought of as a limit ramp function, increasing from the stimulus level S_1 to S_2 in a time interval Δt,

$$S(t) = S_1 + ct \quad \text{for } 0 \leqslant t \leqslant \Delta t \tag{7}$$

and

$$S_2 = S_1 + c\,\Delta t.$$

Taking the limit for Δt approaching zero of the integral of (6), we arrive at

$$X(S_2) - X(S_1) = \int_{S_1}^{S_2} \xi(S, 0)\, dS, \tag{8}$$

since the integrals of the first two terms of right-hand side of (6) vanish in the process of taking the limit for $\Delta t \to 0$, both funtions F and G being bounded.

Thus, for a step function stimulation, integration of (6) simply involves solving the differential equation given by (6) without the third term. This term is, however, important for setting the new initial condition for X by the step as it is given by (8).

An Example: *Insulin Secretion.* The idea of the threshold distribution of packets came out of the analysis of data on glucose perfused pancreas in vitro (Ličko *et al.*, 1971). Of the three stimulatory patterns, namely, glucose step

function, glucose staircase function and glucose ramp function, the results of the second type of the stimulation were the most puzzling. These results are schematically shown in Figure 1. If the first step of glucose causes depletion of the insulin pancreatic storage, consecutive steps should not bring about any more release of insulin. Thus, we were compelled to consider the stored insulin as only partially available at any given glucose concentration, a "compartmental conglomerate of differential sensitivity to the stimulator". Furthermore, since the response to every step is exponential and independent of glucose concentration S, we assumed

$$f[\xi(\theta, t), S(t), \theta, t] = m\xi(\theta, t), \tag{9}$$

and thus obtained for a step function stimulation

$$F(S, t) = m \int_0^S \xi(\theta, t)\, d\theta = mX(S, t). \tag{10}$$

From the experimental data it was also possible to determine that $G(S, t)$ function derives its form from a first order process:

$$\begin{aligned} G(S, t) &= Y(S, t) \\ \dot{Y}(S, t) &= \alpha[Y(S, \infty) - Y(S, t)], \end{aligned} \tag{11}$$

where $Y(S, \infty)$ is an experimentally determined function

$$Y(S, \infty) = \frac{0.5S^{10}}{8.8 \times 10^{21} + 2.2 \times 10^{15}S^3 + 3.5 \times 10^6 S^7 + S^{10}}, \tag{12}$$

shown in Figure 2. Integrating the second equation of (11), we find

$$G(S, t) = [Y(S, 0) - Y(S, \infty)]\, e^{-\alpha t} + Y(S, \infty). \tag{13}$$

Thus, (6) becomes

$$\dot{X}(S, t) = -mX(S, t) + [Y(S, 0) - Y(S, \infty)]\, e^{-\alpha t} + Y(S, \infty), \tag{14}$$

the third term of (6) being zero for all $t > 0$, as shown above. Integrating (14), we arrive at

$$X(S, t) = \left[X(S, 0) - \frac{mY(S, 0) - \alpha Y(S, \infty)}{m(m - \alpha)}\right] e^{-mt} + \frac{Y(S, 0) - Y(S, \infty)}{m - \alpha} e^{-\alpha t} + \frac{Y(S, \infty)}{m}. \tag{15}$$

The values of the rate coefficients m and α were estimated as 0.62 min^{-1} and 0.034 min^{-1}, respectively.

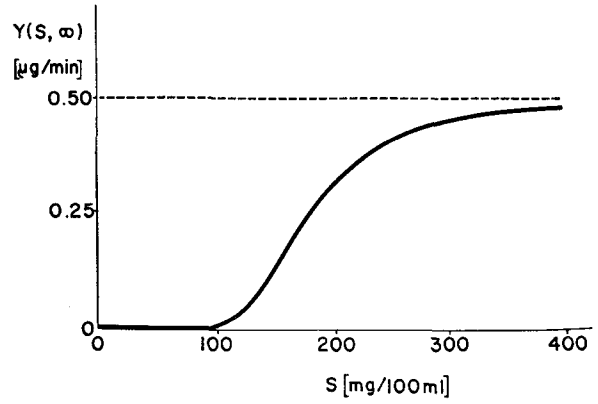

Figure 2. Steady state rate of insulin replenishment into the portion of insulin storage which is releasable by the glucose concentration S. (Data from rat pancreas perfusion by Grodsky, 1972)

When $X(S, 0)$ was plotted as a function of glucose concentration, a log-normal distribution (the threshold distribution function) curve resulted (Figure 3), approximated by

$$\frac{X(S, 0)}{X_{\max}} = \frac{1}{\sigma\sqrt{2\pi}} \int_0^S e^{-[(\ln\theta - \ln\theta_0)^2/2\sigma^2]}\, d \ln\theta \doteq \frac{1}{1 + Ce^{-k \ln S}} = \frac{S^k}{C + S^k}, \quad (16)$$

where glucose concentration S is in units of mg/100 ml and the values of the constants $X_{\max}$, k and C are: $X_{\max} = 1.65$ µg of insulin; $k = 3.3$; $C = 1.51 \times 10^7$. Differentiating with respect to S, the following threshold density function was obtained

$$\frac{\xi(\theta, 0)}{X_{\max}} = \frac{kC\theta^{k-1}}{(C + \theta^k)^2}, \quad (17)$$

shown in Figure 3 as the dashed curve.

"*Packets*". The concept of material stored in packets of differential sensitivity need not picture any specific anatomical structure. It would seem plausible to identify the packets with the granules or vessicles. These may differ in their thresholds either by their individual physico-chemical characteristics (e.g., of their membranous envelopes), or, by local microenvironment in the cell (such as non-uniform distribution of enzymes or other important molecules throughout the cell). On the other hand, one can think of whole cells as packets which release their stored material (by exocytosis) only if the stimulus level reached the cellular threshold. Although the experimental data

is not complete yet, it seems that the latter interpretation is more in accord with the current findings.

Mathews and Dean (1970) systematically studied the electrical properties of mice pancreatic cells under the glucose stimulation. They reported a "sigmoidal" electrical action potential curve as a function of the logarithm of glucose concentration (a log-normal distribution). Their experimental data

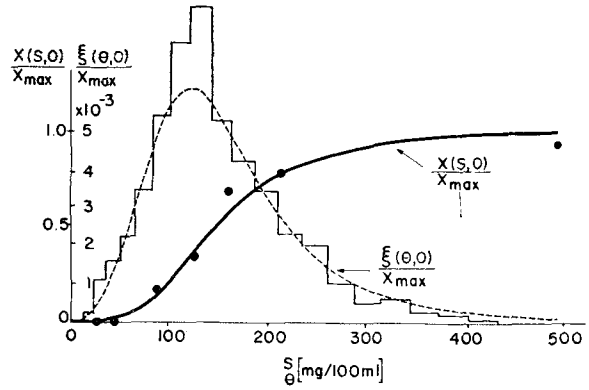

Figure 3. The initial threshold density function $\xi(\theta, 0)$ (dashed line) and the initial threshold distribution function $X(S, 0)$ (full line) for insulin in rat pancreas (data by Grodsky, 1972). Full circles represent relative number of mice pancreatic islet cells found in the state of electrical activity (action potential). The histogram shows the frequency distribution of membrane potential for mice pancreatic islet cells upon the transformation $\theta = 0.09E^{3/2}$. (The mice pancreas data—full circles and the histogram—are from Matthews and Dean, 1970)

is plotted in Figure 3 as full circles, while the smooth curve fits adequately with the insulin secretion data in rat pancreatic perfusates (Grodsky, 1972). Matthews and Dean also reported in the same paper a "normal frequency distribution" of islet cell membrane potentials. As shown in Figure 3, this distribution (histogram) coincides with the threshold density function by employing the following simple transformation

$$\theta = 0.09E^{3/2} \tag{18}$$

where θ is the threshold glucose concentration in millimoles and E is the membrane potential in millivolts.

Inspection of Figure 3 reveals a remarkable coincidence of the results obtained in two different laboratories with two different species and methods. Although

this coincidence is no proof of any relation between the thresholds and membrane potentials, it suggests that it might be more meaningful to relate the notion of a packet to the whole cell rather than to a granule or a vessicle.

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