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The Possibility Distribution for the Controlled Bloodstream Concentrations of Any Physiologically Active Substance

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***Abstract*—**In many ways, biomedical analysis is analogous to possibilistic reasoning. In spite of that, there are hardly any applications of possibility theory in biology or medicine. The aim of this work is to demonstrate the use of possibility theory in an epidemiological study. In the paper, we build the possibility distribution for the controlled bloodstream concentrations of any physiologically active substance through few approximate considerations. This possibility distribution is tested later against the empirical histograms obtained from the panel study of the eight different physiologically active substances in 417 individuals.

***Keywords*—**Possibility distributions, physiologically active substances, bloodstream concentrations.

I. Introduction

THE need for mechanisms that help to treat incomplete and uncertain knowledge explains the grown-up interest in fuzzy systems. Possibility theory seems to be one of the most promising concepts in this field, especially for modeling complex biological or medical processes.

Suppose we have a process $x(t)$, for which we do not have enough information available in order to specify its value x unequivocally for all times t. In possibility theory, learning more about the process $x(t)$ means restricting the range of possible values for x. In fact, possibility distributions hold *negative* information. They do not support but exclude facts [2,4,6,9].

This is exactly how it goes in biomedical studies. Due to the lack of precise mathematical techniques for dealing with systems comprising a very large number of interacting elements or involving a large number of variables, the information about biomedical processes mostly has a negative character: we know *what cannot be* better than *what can be*. (For example, without measurement we do not know what the systolic blood pressure can be for a healthy person; however, we do know that it cannot be higher than 160 mmHg or lower than 90 mmHg.) Biomedical studies, going from approximate data and extracting meaningful information from massive data, lead to a restriction on possible values of a process $x(t)$.

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However, despite this visible analogy between biomedical and possibilistic reasoning, there are not many cited applications of possibility theory in life sciences.

The aim of our work is to demonstrate the use of possibility theory in an actual biomedical (epidemiological) study. In particular, our goal is to obtain the possibility distribution for the bloodstream concentrations of any physiologically active substance.

II. Building the Possibility Distribution Through Approximate Considerations

It is known that the bloodstream concentration of any physiologically active substance (say a hormone, protein, steroid, glucose, triglyceride or uric acid) is controlled by two conflicting processes: *secretion* and *utilization*. The process of secretion is responsible for production of the substance and its release into the blood stream, while the utilization process removes the substance from the blood through consumption or degradation [7].

Though for different substances these processes may be very much different (by their nature), we believe that the following assumptions hold for all of them:

1. If the bloodstream substance is controlled by the secretion-utilization processes, its level can never drop to zero. In other words, zero concentration of the controlled physiologically active substance is *absolutely* impossible.
2. A very high level of the controlled substance is impossible too, but not quite much as zero level. It is so because the precise highest limit for bloodstream concentrations of a given substance does not exist. Therefore, the possibility of high concentrations must vanish only *asymptotically*.
3. For each controlled substance, it must be the level of the *equilibrium* between the secretion and utilization processes, that the concentration of the substance is possible without any restriction. *The further* from the equilibrium in either side, *the less* the concentration is possible.
4. The function representing the distribution of possible bloodstream concentrations for a given controlled substance must be *continuous*.

5. In addition, this possibility distribution function must be *finite* together with its derivatives of at least the first and second orders.

Let the function $\mathrm{Pos}(x)$ be the possibility distribution for the controlled bloodstream concentrations x of a given substance:

$$\mathrm{Pos}(x)\big|_{0\le x<\infty} \in [0,1] \quad . \tag{1}$$

Then the assumption 1 can be written down as follows:

$$\mathrm{Pos}(0) = 0 \quad . \tag{2}$$

From the assumption of *continuity*, it follows that the function $\mathrm{Pos}(x)$ must be defined at every point in the vicinity of zero:

$$0 = \mathrm{Pos}(0) = \mathrm{Pos}(+0) \quad . \tag{3}$$

Hence, near zero the function $\mathrm{Pos}(x)$ takes the form:

$$\mathrm{Pos}(x)\big|_{x\to 0} \sim x^m \tag{4}$$

where m is some positive parameter. It follows then, that according to the assumption of *finiteness*, this parameter must not be less than 1:

$$\left.\frac{d^2\mathrm{Pos}(x)}{dx^2}\right|_{x\to 0} \sim m(m-1)x^{m-2} < \infty \quad . \tag{5}$$

Since the only function that can vanish asymptotically while be finite at zero is the exponential function of a negative argument, the assumption 2 can be expressed mathematically as follows

$$\mathrm{Pos}(x)\big|_{x\to\infty} \sim \exp\left(-\alpha x^s\right) \quad , \tag{6}$$

where α and s are positive parameters. This expression will also satisfy the assumption of finiteness at zero, if the parameter s is not less than 1 when $m = 1$.

The assumption 3 means that the function $\mathrm{Pos}(x)$ reaches its maximum at the level of the equilibrium x_0:

$$\mathrm{Pos}(x_0) = 0 \quad . \tag{7}$$

Besides, this assumption requires that the $\mathrm{Pos}(x)$ must be a monotonic function ascending before the level x_0 and descending afterward:

$$\mathrm{Pos}(x_2) < \mathrm{Pos}(x_1) \quad \text{if} \begin{cases} x_2 < x_1 < x_0 \\ \text{or} \\ x_0 < x_1 < x_2 \end{cases} . \tag{8}$$

Considering the expressions (4)-(8) together and setting the parameters as

$$\begin{aligned} &z = (x_0)^{-1} x \quad , \\ &\alpha = m s^{-1} (x_0)^s \quad , \\ &m = 1 + n \quad , \quad n = 0 \text{ or } n \ge 1, \\ &s = (+0)^n + k \quad , \quad k \ge 0, \end{aligned} \tag{9}$$

we get that the function $\mathrm{Pos}(x)$ should take the form:

$$\mathrm{Pos}(z;n,k) = z^{1+n} \exp\left\{ \frac{1+n}{(+0)^n + k} \left[1 - z^{(+0)^n + k} \right] \right\} \quad . \tag{10}$$

The only parameter of the this function that cannot be equal to zero is the level of the equilibrium x_0. So, the "origin" form of the function (10) will be

$$\mathrm{Pos}(z;0,0) \equiv \mathrm{Pos}(z) = z e^{1-z} \quad . \tag{11}$$

We believe that the function $\mathrm{Pos}(z)$ represents the possibility distribution for the *normally* controlled bloodstream concentrations of any physiologically active substance.

III. Relation between the Possibility and Probability Distributions

Let $p(x)dx$ be the probability that the controlled bloodstream concentration of a given substance is found near the value x, and $p(x)$ be the probability distribution at this value. As to the relation between the possibility distribution $\mathrm{Pos}(x)$ and the corresponding probability distribution $p(x)$, we make the following assumptions:

A. If the concentration x is impossible, it cannot be probable either [10]. The opposite is not true: the concentration x may be not probable, but yet possible.

B. If the concentration x is possible without any restriction, it must be also the most probable.

From the assumptions A and B, it immediately follows:

$$\underset{\mathrm{Pos}(z)=0}{p(z)} = p(0) = p(\infty) = 0 \quad , \tag{12}$$

$$\underset{\mathrm{Pos}(z)=1}{p(z)} = p(1) = p_{max} \quad . \tag{13}$$

These two equalities mean that the probability distribution $p(z)$ must have *approximately the same behavior* as the possibility distribution $\mathrm{Pos}(z)$: the function $p(z)$ must ascend (not necessarily monotonically) throughout the interval $(0;1)$, attain the maximum p_{max} at $z = 1$, and then descend all through the interval $(1;\infty)$.

Let $\beta(z)$ denotes the ratio of the function $p(z)$ to the function $\mathrm{Pos}(z)$:

$$\beta(z) = \frac{p(z)}{\mathrm{Pos}(z)} \quad ; \tag{14}$$

let us estimate the range of the ratio $\beta(z)$ in the intervals $(0;1)$

and $(1;\infty)$.

According to the assumption A, the minimum of the $\beta(z)$ may be zero

$$\min_{z\in(0;1)\vee(1;\infty)} \beta(z) = \widetilde{\beta}_{\min} = \frac{\min\{p(z)\}}{\mathrm{Pos}(z) > 0} \geq 0 \qquad (15)$$

and the maximum of the $\beta(z)$ is finite

$$\max_{z\in(0;1)\vee(1;\infty)} \beta(z) = \widetilde{\beta}_{\max} = \max\left\{\frac{0 \leq p(z) < p_{\max}}{0 < \mathrm{Pos}(z) < 1}\right\} < \infty \quad , \qquad (16)$$

hence, the ratio $\beta(z)$ must have the limited variation.

Thus, we can conclude that the possibility distribution $\mathrm{Pos}(z)$ *can predict* with fair certainty *the trend* for the probability distribution $p(z)$:

$$p(z)\big|_{z\in(0;1)\vee(1;\infty)} \sim \hat{\beta}\,\mathrm{Pos}(z) \quad , \qquad (17)$$

where

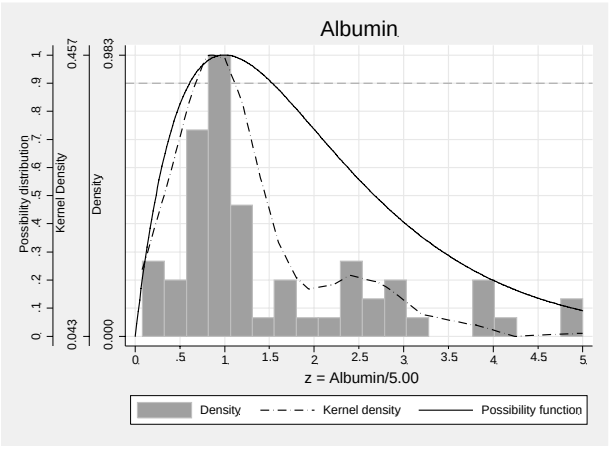
$$\hat{\beta} = \mathrm{const} \in \left[\widetilde{\beta}_{\min}; \widetilde{\beta}_{\max}\right] \quad . \qquad (18)$$

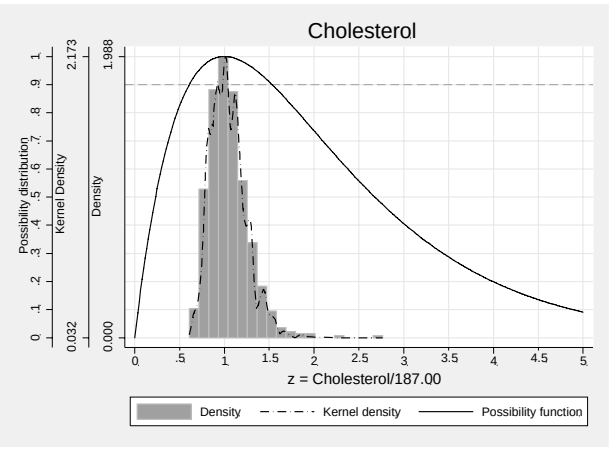
IV. Tests for Association between *P*(*Z*) and Pos(*Z*): Example of a Real-Life Study

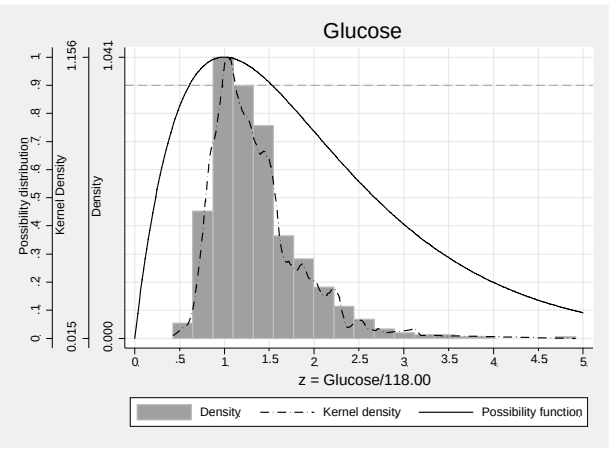
To empirically proof these conclusions, we will use the data obtained from the panel study of the bloodstream concentrations of the different physiologically active substances in diabetic patients done by Prof. S. Weitzman of the Ben-Gurion University of the Negev and his colleagues [1].

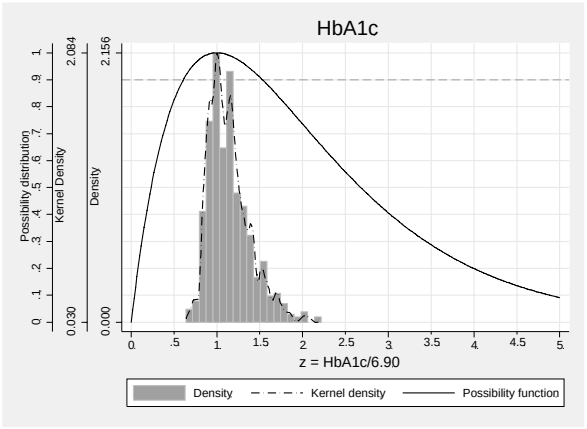
These data were collected in 1997-2003 years. Participants (417 people) were adult patients with diabetes mellitus as well as healthy individuals. During the observation period, in different time, each participant completed several tests for the levels of *albumin*, *cholesterol*, *glucose*, *hemoglobin HbA1c*, low- and high-density lipoproteins (*LDL* and *HDL*), *triglyceride* and *uric acid*.

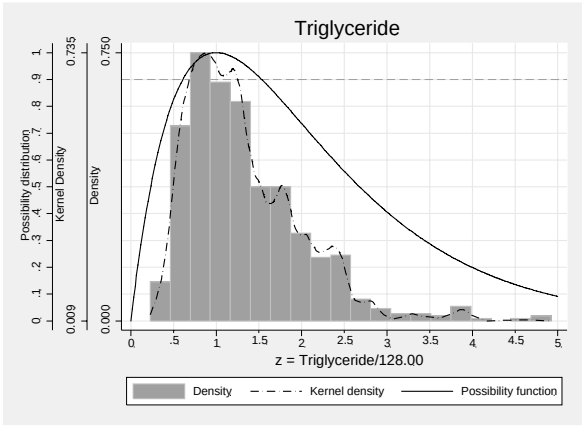
The Fig. 1 shows the empirical histograms for the tested levels along with the kernel density and the possibility function $\mathrm{Pos}(z)$.

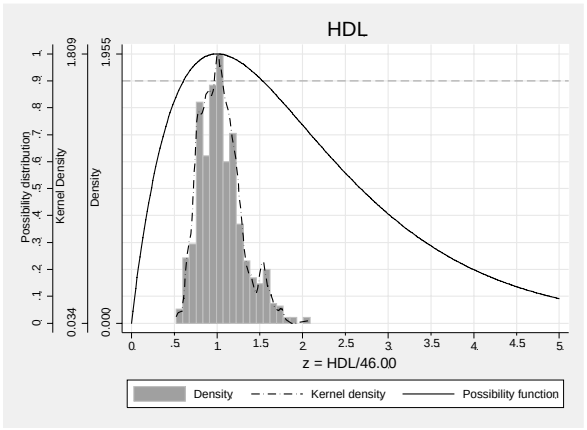


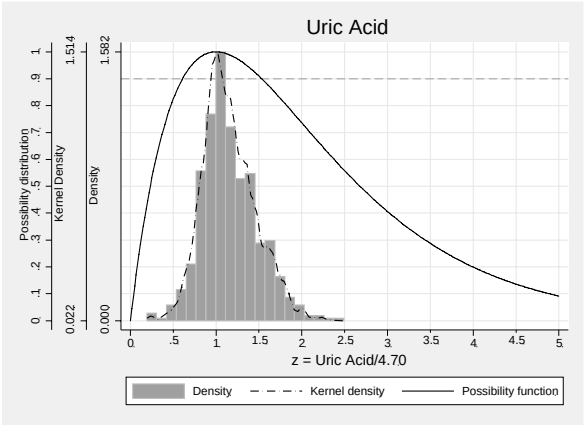












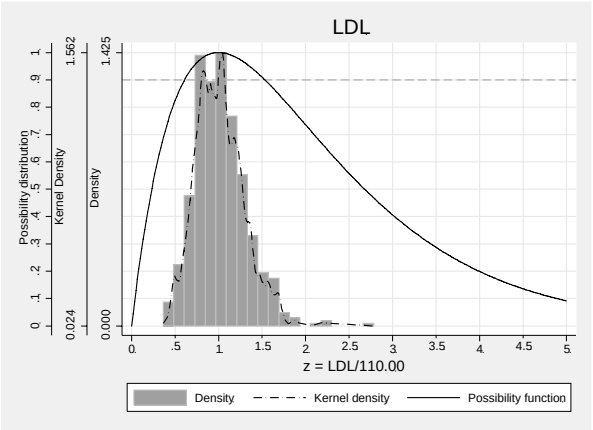


Fig. 1 The empirical histograms for the tested bloodstream levels of the different physiologically active substances

To test association between the empirical distribution $p(z)$ for the given substance and the function $\mathrm{Pos}(z)$, we computed Pearson's correlation coefficient between the corresponding kernel density (used as an approximation of the $p(z)$) and the $\mathrm{Pos}(z)$, and also estimated the linear regression model of the kernel density on the $\mathrm{Pos}(z)$; the results of these tests are presented in the Tables I and II.

TABLE I
CORRELATION BETWEEN
THE KERNEL DENSITY AND THE POSSIBILITY FUNCTION POS(z).

Kernel density for:	Correlation coefficient with Pos(z) in the interval:	
	$0 \le z \le 1$	$1 < z < \infty$
Albumin	0.983*	0.874*
Cholesterol	0.963*	0.717*
Glucose	0.828*	0.888*
HbA1c	0.891*	0.857*
HDL	0.955*	0.850*
LDL	0.930*	0.788*
Triglyceride	0.980*	0.901*
Uric Acid	0.660*	0.920*

Note: * indicates that the significance is less than 0.00005.

TABLE II
LINEAR REGRESSION OF
THE KERNEL DENSITY ON THE POSSIBILITY FUNCTION POS(z).

Kernel density for:	Regression coefficient on Pos(z) in the interval:	
	$0 \le z \le 1$	$1 < z < \infty$
Albumin	0.452*	0.313*
Cholesterol	1.649*	1.407*
Glucose	0.779*	0.830*
HbA1c	1.549*	1.303*
HDL	1.418*	1.153*
LDL	1.198*	0.989*
Triglyceride	0.679*	0.533*
Uric Acid	1.027*	1.008*

Note: * indicates that the significance is less than 0.00005.

It can be readily seen from these tables that all the empirical probability densities of the tested physiologically active substances demonstrate remarkable association with the possibility function (11).

As it follows from the Table II, the kernel density for a given substance can be predicted based on the possibility distribution $\mathrm{Pos}(z)$. For example, for albumin, the predicted kernel density $\hat{\rho}(z)$ is:

$$\hat{\rho}(z) = \begin{cases} (0.452 \pm 0.004) \cdot \mathrm{Pos}(z), & 0 \le z \le 1 \\ (0.452 \pm 0.004) \cdot \mathrm{Pos}(z), & 1 < z < \infty \end{cases} . \quad (19)$$

This finding supports the supposition made before about *probabilities through possibilities* prediction.

V. NORMAL VALUES FOR PHYSIOLOGICALLY ACTIVE SUBSTANCES

A fuzzy set $\aleph$ with the membership function $\mu_{\aleph}(x)$ such that $\mu_{\aleph}(x_0) = 1$ for $x = x_0$ can be viewed as an elastic constraint on the realization of a variable x.

Under such an interpretation of a fuzzy set, $\mu_{\aleph}(x)$ can be regarded as a possibility distribution $\mathrm{Pos}(x)$, which restricts a possibilistic variable x [3-5].

Thus, $\mu_{\aleph}(x')$ shows the possibility degree of the event $x = x'$, and the other way around: the possibility function $\mathrm{Pos}(x')$ shows the degree of membership in the fuzzy set $\aleph$ for the value $x = x'$.

Accordingly, considering the expression (11) as the membership function $\mu_{normal}(x)$ for the normally controlled bloodstream concentrations *z*, we can obtain the normal range for any physiologically active substance.

Indeed, let the concentration z' be normal if the membership function $\mu_{normal}(z') \ge 0.9$, then, solving the equation

$$ze^{1-z} = 0.9 \quad , \quad (20)$$

we will get the following low and upper bounds for the normal range:

$$z_{normal} \in [0.6; 1.5] \quad . \quad (21)$$

The Table III presents the comparison between the normal values defined according to U.S. National Institutes of Health and American Heart Association on large populations of healthy individuals [8] and the bounds defined by the expression (21).

TABLE III
NORMAL RANGE COMPARISON

Substance and its units of measurement	Empirical normal values	Low and upper bounds of the interval that Pos(z)=0.9
Albumin (g/dL)	3.4 ÷ 5.4	3.03 ÷ 7.68
Cholesterol (mg/dL)	High level: > 240	113.14 ÷ 287.05
Glucose (mg/dL)	70 ÷ 126	71.39 ÷ 181.13
HbA1c (%)	High level: > 10.2	4.17 ÷ 10.59
HDL (mg/dL)	High level: 60	27.83 ÷ 70.61
LDL (mg/dL)	High level: 160-189	66.55 ÷ 168.85
Triglyceride (mg/dL)	High level: 200-499	77.44 ÷ 196.48
Uric Acid (mg/dL)	3.0 ÷7.0	2.84 ÷ 7.21

As it can be easily seen from this table, there is a great deal of similarity between the empirically defined normal values and the solutions of the equation $\mathrm{Pos}(z) = 0.9$.

This speaks in favor of the assumption that the function $\mathrm{Pos}(z)$ can represent the possibility distribution for the normally controlled bloodstream concentrations of any physiologically active substance.

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