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A VECTOR COMPOSED OF MEDICAL PARAMETERS: DETERMINATION OF THE DISTRIBUTION CLASS

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In the paper, the authors present a method for determining the distribution class to which a selected random vector with medical parameters as components belongs. The method is based on the statistical significance test. The optimal selection problem for the significance level where the probability of the vector identification error is minimal has been solved. In order to tackle the problem, the authors used the prior information on belonging the vector components to the definite distribution class in which the statistical relationship between the medical parameters was taken into account. The developed mathematical model of patient condition should serve as support of decision-making on further treatment tactics.

Keywords: mathematical simulation, distribution class, significance test, power of test

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ОПРЕДЕЛЕНИЕ КЛАССА РАСПРЕДЕЛЕНИЯ ВЕКТОРА МЕДИЦИНСКИХ ПОКАЗАТЕЛЕЙ

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В статье представлен разработанный авторами метод определения класса распределения, к которому принадлежит выбранный случайный вектор с медицинскими показателями в качестве компонент. Метод основан на статистическом критерии значимости. Решается задача об оптимальном выборе уровня значимости, при котором вероятность ошибки идентификации вектора минимальна. Для этого используется априорная информация о принадлежности компонент вектора к определенному классу распределения, в котором учитывается статистическая зависимость между медицинскими показателями. Разработанная математическая модель состояния пациента должна служить поддержкой принятию решения о выборе дальнейшей тактики лечения.

Ключевые слова: математическое моделирование, класс распределения, критерий значимости, мощность критерия

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Introduction

The goal of this study consisted in constructing a probabilistic model for forecasting medical outcomes of diseases for patients who underwent radical prostatectomy. The model should allow to estimate whether recurrence of the tumor is likely. A database composed of several medical indicators was accumulated for this purpose for groups of patientswho did not suffer recurrence of the tumors, and for those who did. These indicators vary from patient to patient within each group, filling a certain domain in the space of indicators with some density different for the two groups. The system of indicators is combined into a vector, which is regarded as the implementation of a random vector with a distribution law derived from the observed data. This random vector generalizes the experimental data and characterizes the group as a whole. The next step is determining (with a sufficient degree of reliability) whether a vector with the indicators of a particular patient is the implementation of one of the two given random vectors, or, in other words, to which of the two groups the patient most likely belongs to.

We solved this problem using the statistical significance test [1]. One of the two distributions is regarded as the null hypothesis, and the other as the alternative hypothesis. If a random vector falls into the so-called acceptance region, the null hypothesis is accepted. Otherwise, the alternative hypothesis is assumed to hold true. Errors in attributing a vector (classifying it as belonging to a certain probability distribution) by this algorithm can be made in two cases: either the true null hypothesis is erroneously rejected (type I error), or, conversely, the false null hypothesis is erroneously accepted (type II error). Any value (between 0 and 1) can be obtained for the probability of type I errors by choosing an acceptance region. However, changing the probability of type I error also leads to a change in the probability of type II error. Extending the acceptance region obviously reduces the probability of type I errors and increases the probability of type II errors.

Thus, it seems a natural step to choose an acceptance region so as to minimize the probability of type II errors for a given level of significance, that is, the probability of type I error [2, 3].

The problem of choosing an optimal acceptance region in the above sense was solved by introducing the Neyman–Pearson criterion [3]. However, this criterion is used as part of a more general interpretation of the significance test by introducing a certain degree of randomization. As a result, the answer to the question whether the null hypothesis is accepted or rejected is probabilistic.

Practically speaking, the total error of vector attribution by the distribution law is most important. This characteristic consists of two sources: type I and type II errors. If the a priori probabilities of the hypotheses about the distribution law are known, then the probability of the total error can be minimized by choosing an optimal significance level. The above optimization problem is solved in this paper.

The second section of the paper describes a probabilistic model within which we constructed an optimized criterion for attributing a random vector by the distribution law. In the third section, we consider a practical application of this criterion to medical research. Finally, the last section discusses the results obtained and potential options for developing the given method.

Probabilistic model

We consider three-dimensional random vectors with a distribution A or B: $W^{(A)}$ and $W^{(B)}$ in this model. The first two components of the vector are continuous random variables, and the last component takes only the values 0 or 1. The quantities $m_i^{(A)}$, $\sigma_i^{(A)}$, ($I = 1, 2, 3$) are, respectively, the mathematical expectations and standard deviations of the components of the vector $W^{(A)}$. Notations are similar for $W^{(B)}$.

Let $m_i^{(A)}[n]$ be the conditional expectation $W^{(A)}$, ($i = 1, 2$), when $W^{(A)}_3 = n$. We introduce the same notations for conditional standard deviations and covariance of

continuous components. The distribution of the discrete component is given by the quantity $p_n = P\{W_3 = n\}$.

Conditional and unconditional characteristics of continuous components are related by the formulas

$$m_i = \sum_{n=0,1} m_i[n]\, p_n$$

$$\sigma^2{}_i = \sum_{n=0,1} \left(\left(\sigma_i[n]\right)^2 + \left(m_i[n]\right)^2 \right) p_n - m_i^2$$

$$\mathrm{Cov}_{12} = \sum_{n=0,1} m_1[n]\, m_2[n]\, p_n - m_1 m_2.$$

The problem solved in this paper is to determine most reliably to which of the distributions (*A* or *B*) the given vector *W* belongs. The significance test is used for this purpose.

Let us call the set

$$\widetilde{D} = \bigcup_{n=0,1} D_n \bigcap \left\{ W_i, i = 1,2,3 \middle| W_3 = n \right\},$$

$$D_n = \left\{ W_i, i = 1,2,3 \middle| x_1^{(n)} \le W_1 \le x_2^{(n)} \wedge y_1^{(n)} \le W_2 \le y_2^{(n)} \right\} \quad (1)$$

the acceptance region.

Each of the two values of W_3 has its own range of acceptable values W_1 and W_2. Starting from Eq. (1), we use the symbols $\bigcup$ and $\bigcap$ for the operations of union and intersection on sets, the symbol Λ for conjunction of conditions.

The situation when the vector has the distribution *A* is taken as the null hypothesis H_0. If the vector has the distribution *B*, the alternative hypothesis H_1 is accepted. According to the significance test, if

$$(W_1, W_2) \in \widetilde{D},$$

then hypothesis H_0 is accepted in this and only in this case.

Type I error (erroneously rejecting the null hypothesis) occurs with a probability

$$P_1 = P\left((W_1, W_2) \notin \widetilde{D} \middle| H_0 \right).$$

The probability of type II error (erroneously accepting the null hypothesis) is

$$P_2 = P\left((W_1, W_2) \in \widetilde{D} \middle| H_1 \right).$$

From a practical standpoint, it is preferable to choose the acceptance region so as to obtain the minimum value of P_2 for the given probability P_1, close to zero. Mathematically, the problem is formulated as follows:

$$\min P\left((W_1, W_2, W_3) \in \widetilde{D} \middle| H_1 \right) =$$

$$= \min \sum_{n=0,1} p_n{}^{(B)} P\left((W_1, W_2) \in D_n \middle| H_1 \right) =$$

$$= \sum_{n=0,1} p_n{}^{(B)} \min P\left((W_1, W_2) \in D_n \middle| H_1 \right).$$

Therefore,

$$\left\{ x_1^{[n]}, x_2^{[n]}, y_1^{[n]}, y_2^{[n]} \right\} = \underset{x_1^{[n]}, x_2^{[n]}, y_1^{[n]}, y_2^{[n]}}{\arg\min} P\left((W_1, W_2) \in D_n \middle| H_1 \right), \quad (2)$$

where arg min(*f*) denotes a function yielding the argument values of *f*(*x*) at the minimum point.

We write the expressions for the probabilities of type I and type II errors:

$$\Phi_1{}^{(C)}(n) = F^{(C)}(x_2^{(n)}, y_2^{(n)})[n] - F^{(C)}(x_1^{(n)}, y_2^{(n)})[n],$$

$$\Phi_2{}^{(C)}(n) = F^{(C)}(x_2^{(n)}, y_1^{(n)})[n] - F^{(C)}(x_1^{(n)}, y_1^{(n)})[n],$$

$$P_1 = 1 - \sum_{n=0,1} p_n{}^{(A)} [\Phi_1{}^{(A)}(n) - \Phi_2{}^{(A)}(n)],$$

$$P_2 = \sum_{n=0,1} p_n{}^{(B)} [\Phi_1{}^{(B)}(n) - \Phi_2{}^{(B)}(n)]. \quad (3)$$

where $F^{(C)}(x,y)[n]$ ($C = A$ or $C = B$) is the conditional function for the distribution of the vector (W_1 and W_2).

Knowing the probability that the vector is attributed erroneously is important for deciding which class, *A* or *B*, this random vector belongs to. This probability can be determined if the a priori probability P_A of a vector belonging to class *A* is known.

Let P_{err} be the probability of erroneous attribution. Then,

$$P_{err} = P_A P_1 + (1 - P_A) P_2. \quad (4)$$

Let $P^{(0)}{}_2(P_1)$ be the probability of type II error, calculated by the optimized algorithm at a significance level P_1. It is natural to set P_1 so that (4) takes the minimum value $P^{(0)}{}_{err}$, i.e.,

$$P_1^{(0)} = \underset{P_1 \in [0,1]}{\arg\min} \left[P_A \cdot P_1 + (1 - P_A) \cdot P_2^{(0)}(P_1) \right];$$

$$P_{err}{}^{(0)} = P_A \cdot P_1^{(0)} + (1 - P_A) \cdot P_2^{(0)}(P_1^{(0)}). \quad (5)$$

Example application of the attribution algorithm to medical data

The above-described algorithm for attributing random vectors was applied to data for urologic oncology patients who underwent tumor removal surgery. Prostate cancer is considered the most commonly diagnosed cancer in men and the second (according to statistical data) cause of death from cancer [12]. The level of prostate-specific antigen p (PSA) in blood serum [5, 6], measured in ng/ml, closely correlates with the volume of the tumor. The tumor's growth rate is characterized by the PSA doubling time [7, 8].

Initially, there were two groups of patients with different outcomes of radical prostatectomy. Each patient was characterized by individual values of preoperative and postoperative factors [9–12]. The array of patients was divided into two groups: tumor recurrence was detected in 33 patients, and no recurrence was observed in 37. Predicting options for further treatment after surgery is an important task, since it affects the final result of radical prostatectomy [9, 13–15].

We selected a total of three factors:

W_1 is the initial PSA, ng/ml;

W_2 is the PSA doubling time, months;

W_3 is the surgical margin of the tumor, i.e., whether any cancer cells are found in the resection line. We assumed that $W_3 = 0$ if these cells were not found, and $W_3 = 1$ otherwise.

Group A included patients who did not have recurrences for a certain period of time, and group B included patients with recurrences. Table 1 shows the number of patients in groups.

The quantities W_1 and W_2 in group B have a noticeable correlation. Table 1 gives the estimates for the correlation coefficients with $W_3 = 0$ and 1.

Table 2 gives the main characteristics of the distributions A and B.

Let us explain how we constructed the two-dimensional conditional (i.e., with a fixed value of W_3) distribution function of the random vector W_1, W_2 required to calculate the probabilities of type I and type II errors

Let

$$x_k, y_k; (k = \overline{1, N}), \tag{6}$$

be conditional samples of continuous components W_1 and W_2, respectively, arranged in ascending order. Next, let the points

$$(x_{i(j)}, y_{k(j)}); (j = \overline{1, N}) \tag{7}$$

represent the experimental data. Let us introduce the notations

$$\begin{aligned}
&\xi_0 = 2x_1 - x_2;\\
&\xi_i = 0.5(x_i + x_{i+1}); (i = \overline{1, N-1});\\
&\xi_N = 2x_N - x_{N-1};\\
&\eta_0 = 2y_1 - y_2;\\
&\eta_i = 0.5(y_i + y_{i+1}), (i = \overline{1, N-1});\\
&\eta_N = 2y_N - y_{N-1}.
\end{aligned} \tag{8}$$

Table 1

Data set and incidence analysis by patient group

Group of patients	Number of patients		Coefficient of correlation for W_1 and W_2		False attributions (number and total error)		
	$W_3 = 0$	$W_3 = 1$	$W_3 = 0$	$W_3 = 1$	$W_3 = 1$	$W_3 = 1$	Relative error
A (no recurrence)	37	3	0.0058	0,0430	12	0	0.30
B (with recurrence)	33	5	–0.2000	–0.3600	6	1	0.18

Notations: W_1 is the initial PSA level, ng/ml; W_2 is the PSA doubling time, months; W_3 is the surgical margin of the tumor; we assumed that $W_3 = 0$ if there were no abnormal cells, and $W_3 = 1$ otherwise.

Note. The correlation coefficients W_1 and W_2 were found by the formula $R_{XY} = \dfrac{\mathrm{cov}_{XY}}{\sigma_X \sigma_Y}$.

Table 2

Conditional distributions of continuous components of random vector W_1, W_2

W_3	$p_n^{(A)}$	$p_n^{(B)}$	$m_i^{(A)}$	$m_i^{(B)}$	$\sigma_i^{(A)}$	$\sigma_i^{(A)}$
0	0.925	0.868	12.2; 2200	17.4; 998	10.6; 2410	11.0; 2000
1	0.075	0.132	8.33; 1000	30.9; 265	1.48; 558	20.7; 152
Total value	–	–	11.9; 2110	19.2; 901	10.3; 2350	13.5; 1870

Notations: p_n are the distributions of the discrete component; m_i is the mathematical expectation; σ_i is the standard deviation; the superscripts correspond to the data belonging to patient groups *A* and *B*. Two values correspond to the components W_1 and W_2.

To construct the distribution function, let us divide the rectangle

$$[\xi_0, \xi_N; \eta_0, \eta_N] \tag{9}$$

into N^2 rectangles of the form

$$[\xi_{i-1}, \xi_i; \eta_{k-1}, \eta_k]; \left(i = \overline{1,N}; k = \overline{1,N}\right). \tag{10}$$

Next, let us select from all the rectangles those containing the experimental points (7) and combine them into a set S_e:

$$\left[\xi_{i(j)-1}, \xi_{i(j)}; \eta_{k(j)-1}, \eta_{k(j)}\right]; (j = \overline{1,N});$$

$$S_e = \bigcap_{i=1}^{N} \left[\xi_{i(j)-1}, \xi_{i(j)}; \eta_{k(j)-1}, \eta_{k(j)}\right].$$

We assume that the random vector W_1, W_2 is evenly distributed inside each of the N rectangles, and the probability of the random vector falling into each of the rectangles is the same and equal to $1/N$. This probability is equal to zero for all other rectangles. The distribution density then has the form

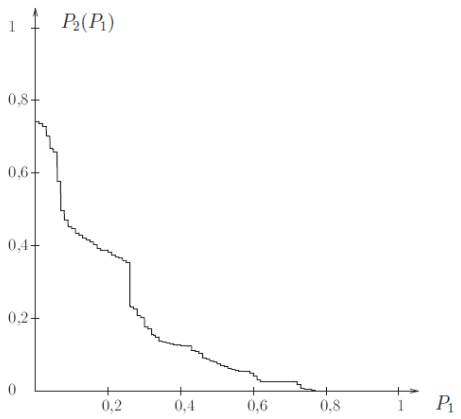

Fig. 1. Probability of type II error as function of probability of type I error

$$\rho(x,y) = \begin{cases} \dfrac{1}{N \cdot \Delta\xi_i \cdot \Delta\eta_k}, \\ \text{if } (x,y) \in \\ \in [\xi_{i-1}, \xi_i; \eta_{k-1}, \eta_k] \subset S_e; \\ 0, \\ \text{if } (x,y) \notin S_e, \end{cases} \tag{12}$$

where $\Delta\xi_i = \xi_i - \xi_{i-1}$; $\Delta\eta_k = \eta_k - \eta_{k-1}$.

In accordance with Eq. (12), the conditional distribution function is an inhomogeneous piecewise bilinear function:

$$F(x,y) = a_{i,k} + b_{i,k}(x - \xi_{i-1}) + c_{i,k}(y - \eta_{k-1}) + \\ + d_{i,k}(x - \xi_{i-1})(y - \eta_{k-1}), \tag{13}$$
$$\text{if } (x,y) \in [\xi_{i-1}, \xi_i; \eta_{k-1}, \eta_k],$$

where the parameters are obtained from continuity condition $F(x,y)$ and the boundary conditions

$$F(\xi_0, y) = F(x, \eta_0) = 0$$

using recurrence relations

$$b_{i,k} = b_{i,k-1} + d_{i,k-1}\Delta\eta_{k-1},$$
$$c_{i,k} = c_{i-1,k} + d_{i-1,k}\Delta\xi_{i-1},$$
$$a_{i,k} = a_{i-1,k-1} + b_{i-1,k-1}\Delta\xi_{i-1} + \\ + c_{i-1,k-1}\Delta\eta_{k-1} + d_{i-1,k-1}\Delta\xi_{i-1}\Delta\eta_{k-1},$$
$$d_{i,k} = \begin{cases} \dfrac{1}{N \cdot \Delta\xi_i \cdot \Delta\eta_k}, \\ \text{if } [\xi_{i-1}, \xi_i; \eta_{k-1}, \eta_k] \subset S_e; \\ 0, \\ \text{if } [\xi_{i-1}, \xi_i; \eta_{k-1}, \eta_k] \notin S_e, \end{cases} \tag{14}$$

with $a_{1,k} = a_{i,1} = b_{1,k} = c_{i,1} = 0$.

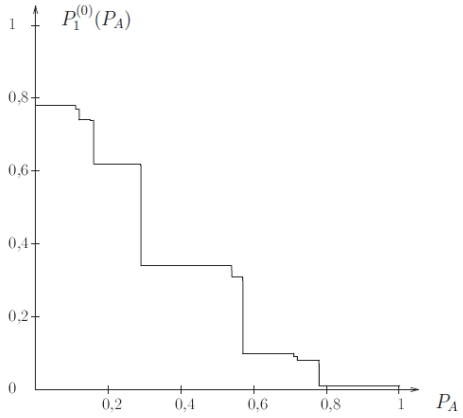

Fig. 2. Optimal significance level as function of a priori probability

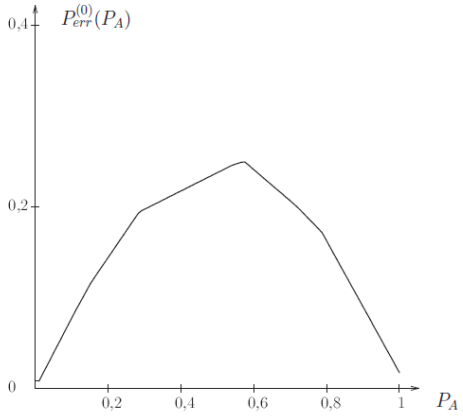

Fig. 3. Minimized attribution error

Fig. 1 shows the dependence of probability of type II error with the optimal acceptance region (1) chosen by Eq. (2). Fig. 2 shows the dependence for the optimal significance level for the given a priori data on whether a patient belongs to group *A*, and Fig. 3 shows the probability for the total error of patient attribution (see Eq. (5).

We applied the attribution algorithm to groups *A* and *B*. Table 1 (right columns) gives the number of errors in determining the group to which the patient belongs. We assumed that a priori probability is $P_A = 0.5$, since the number of patients in both groups is approximately the same. We should also note that the attribution error is close to the maximum value of 0.25 in this case, which can be seen from Fig. 3. The data in Table 1 (false attributions) indicate that the actual total attribution error is close to this estimate.

Conclusion

Example application of the proposed significance test confirms that it can be used in practice, in particular in medicine for predicting complications. Evidently, the probability of error in determining the class to which the given object belongs decreases with increasing number of patients with a known diagnosis.

We should note that the algorithm constructed in this paper is optimal only in the class of significance tests with a connected acceptance region (see Eq. (1)). However, if the distribution has a more complex shape, for example, with a multimodal distribution density, choosing a disconnected acceptance region could produce a more powerful test.

Including a greater number of continuous variables in the test would increase the reliability of the algorithm. However, expanding the number of variables would also make finding the optimal acceptance region more difficult.

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