Blood Plasma Thermograms Dataset Analysis by Means of InterCriteria and Correlation Analyses for the Case of Colorectal Cancer

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Abstract: *The approaches of InterCriteria Analysis and Correlation Analysis are applied to a dataset of calorimetric and statistical parameters obtained from blood plasma proteome thermograms of colorectal cancer patients. The analysis was performed for four individual predefined subsets of calorimetric profiles. Specific interrelations between the studied criteria were identified that were found to differ among the different calorimetric subsets. For three of the subsets the enthalpy of the thermal profiles was in strong consonance with the excess heat capacity of the immunoglobulins assigned thermal transition. For the calorimetric subsets that differed most from the control healthy set a strong interrelation between the excess heat capacities of the main plasma proteins (albumin and immunoglobulins) was additionally evident. Our results demonstrate that these mathematical approaches can complement the analysis of calorimetric datasets generated for a variety of diseases.*

Keywords: *InterCriteria analysis, Correlation analysis, Differential scanning calorimetry, Colorectal cancer.*

Introduction

Differential scanning calorimetry (DSC) was recognized as a useful tool for thermodynamic characterization of the blood plasma proteome in a variety of diseases (see [5-10, 12-15]). The DSC scan (thermogram) allows for the determination of transition temperatures (T_m), excess heat capacities (c_P) of the successive thermally induced transitions and the calorimetric enthalpy of denaturation (ΔH_{cal}, i.e. the integrated area under the heat capacity curve) of the plasma proteome. Applied to colorectal cancer (CRC) it revealed strong modification of the CRC calorimetric profiles compared to the typical one of healthy individuals. Since the

thermograms did not show one characteristic CRC calorimetric profile, they were classified in several groups based on the ratio of the heat capacities of the transitions assigned to albumin (HSA), c_P^{HSA}, and immunoglobulins (*Igs*), c_P^{Igs}, centered at about 62 °C and 70 °C (c_P^{HSA}/c_P^{Igs}); the groups were further divided in subgroups based on the calorimetric enthalpy ΔH_{cal} [13]. The defined calorimetric sets were further characterized by the weighted average center of the thermogram (T_{FM})

$$T_{FM} = \int_{T_1}^{T_2} T c_P^{ex}(T)dT \Big/ \int_{T_1}^{T_2} c_P^{ex}(T)dT , \quad (1)$$

where T_1 and T_2 are the initial and final temperatures of the thermogram, respectively [5].

The recorded thermograms were analyzed by the statistical routine developed by Fish et al. [4] for classification of DSC curves relative to a comparative control reference set that reveals the degree of similarities between the control and CRC thermograms by a similarity metric parameter ρ, which combines two factors: similarities in shape (Pearson's correlation coefficient, r) and in space (spatial distance metric, P):

$$\rho = \left(P^w r^{2-w} \right)^{1/2} , \quad (2)$$

where $0 \leq w \leq 2$. The value for $w = 1.5$ was obtained after empirical optimization. The parameter ρ varies in the [0, 1] range, ρ close to 0 indicating high dissimilarity and ρ close to 1 showing high similarity in shape between the CRC and the control reference thermograms.

In this work, we apply the InterCriteria Analysis (ICrA) approach on a dataset of thermodynamic parameters derived from thermograms of blood plasma proteome of patients diagnosed with CRC recorded by differential scanning calorimetry. The multicriteria decision making method, proposed and elaborated by Atanassov et al. [1, 2] is based on intuitionistic fuzzy sets and index matrices; it allows to uncover the extent of correlation between multiple parameters and easy and straightforward identification of those that are in strong consonance. The analysis yields the coefficients $\mu(c_i,c_j)$, $\nu(c_i,c_j)$ and $\pi(c_i,c_j)$ that correspond to the degree of non-parametric correlation between each pair of criteria in the set. In addition the ICrA approach is complemented by correlation analysis that strengthens the decision making and the selection of strong intercriteria correlations.

The goal of the study was to establish interdependences between the derived calorimetric parameters that were not inferred so far from the calorimetric data and to discuss their importance for the clinical application of the DSC approach.

InterCriteria analysis

The concept of intercriteria analysis is specifically developed for multicriteria decision making scenarios, where some of the criteria are more cost unfavourable than others, i.e. are more expensive or require more human resource or time to be measured or evaluated. The method's aim is identification of sufficiently high levels of correlation between such criteria and others that are estimated as cheaper, quicker or easier for measurement or evaluation, so that the unfavourable ones are ignored in further decision making.

The developed ICrA approach is based on the apparatus of index matrices (IMs) and intuitionistic fuzzy sets (IFSs) [1-3]. IFSs are extensions of Zadeh's fuzzy sets, which feature a non-membership function in addition to the fuzzy set's membership function. Briefly, the IFS is formally denoted by:

$$A = \{\langle x, \mu_A(x), \nu_A(x)\rangle \mid x \in E\}, \tag{3}$$

where $\mu_A(x)$ defines the membership of an element x to the set A, evaluated in the [0; 1]-interval; $\nu_A(x)$ defines the non-membership of the element x to the set A, where $\mu_A(x) \in [0; 1]$, $\nu_A(x) \in [0; 1]$, and $(\mu_A(x) + \nu_A(x)) \in [0; 1]$. The fact that the sum $\mu_A(x) + \nu_A(x)$ can be strictly smaller than 1 allows for a third degree $\pi_A(x)$, which complements this sum up to 1 and is called index of uncertainty, hesitation margin, etc.

Let us have an index matrix (IM) with elements $a_{i,k}$, $i = 1, ..., m$, $k = 1, ..., n$,

$$M = \begin{array}{c|ccccccc} & O_1 & \dots & O_k & \dots & O_l & \dots & O_n \\ C_1 & a_{C_1,O_1} & \dots & a_{C_1,O_k} & \dots & a_{C_1,O_l} & \dots & a_{C_1,O_n} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots & \ddots & \vdots \\ C_i & a_{C_i,O_1} & \dots & a_{C_i,O_k} & \dots & a_{C_i,O_l} & \dots & a_{C_i,O_n} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots & \ddots & \vdots \\ C_j & a_{C_j,O_1} & \dots & a_{C_j,O_k} & \dots & a_{C_j,O_l} & \dots & a_{C_j,O_n} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots & \ddots & \vdots \\ C_m & a_{C_m,O_1} & \dots & a_{C_m,O_j} & \dots & a_{C_m,O_l} & \dots & a_{C_m,O_n} \end{array},$$

where C_i is a criterion, taking part in the evaluation; O_k is an object, being evaluated; $a_{i,k}$ is the evaluation of the k-th object against the i-th criterion, and it is defined as a real number or another object that is comparable according to relation R with all the rest elements of the index matrix M, so the relation $R(a_{C_iO_k}, a_{C_jO_k})$ holds for each i, j, k. The relation R has dual relation $\overline{R}$, which is true in the cases when relation R is false, and vice versa.

The number of cases when relations $R(a_{C_iO_k}, a_{C_jO_k})$ and $R(a_{C_iO_l}, a_{C_jO_l})$ are simultaneously valid is $S^{\mu}_{i,j}$; the number of cases when relations $R(a_{C_iO_k}, a_{C_jO_k})$ and their dual $\overline{R}(a_{C_iO_l}, a_{C_jO_l})$ are simultaneously valid is $S^{\nu}_{i,j}$. Then

$$0 \le S^{\mu}_{i,j} + S^{\nu}_{i,j} \le \frac{n(n-1)}{2}, \tag{4}$$

since the total number of pairwise comparisons between the object is $n(n-1)/2$.

For every i, j, such that $1 \le i \le j \le m$, and for $n \ge 2$ we determine two numbers:

$$\mu_{C_i,C_j} = 2\frac{S^{\mu}_{i,j}}{n(n-1)}, \nu_{C_i,C_j} = 2\frac{S^{\nu}_{i,j}}{n(n-1)}, \tag{5}$$

$$0 \le \mu_{C_i,C_j} + \nu_{C_i,C_j} \le 1 \tag{6}$$

The pair, constructed from these two numbers, plays the role of the intuitionistic fuzzy pair, evaluating the relations between any two criteria C_i and C_j. In this way the IM M that relates evaluated objects with evaluating criteria can be transformed to another index matrix M^* that gives the relations among any pair of criteria

$$M^* = \begin{array}{c|ccc} & C_1 & \dots & C_m \\ \hline C_1 & \langle \mu_{C_1,C_1}, \nu_{C_1,C_1} \rangle & \dots & \langle \mu_{C_1,C_m}, \nu_{C_1,C_m} \rangle \\ \vdots & \vdots & \ddots & \vdots \\ C_m & \langle \mu_{C_m,C_1}, \nu_{C_1,C_m} \rangle & \dots & \langle \mu_{C_m,C_m}, \nu_{C_m,C_m} \rangle \end{array}.$$

Along the main diagonal the pairs are always ⟨1, 0⟩, while the pair $\langle \mu_{C_i,C_j}, \nu_{C_i,C_j} \rangle$ is identical with the pair $\langle \mu_{C_j,C_i}, \nu_{C_j,C_i} \rangle$. Alternatively, it is practical to work with two index matrices M^{μ} and M^{ν}, rather than with the index matrix M^* of IF pairs.

Finally, the algorithm requires the determination of threshold values for both the membership and the non-membership functions, which are needed to evaluate the precision of the ICrA decision making. We call that two criteria are in relation of either 'positive consonance', or 'negative consonance', or 'dissonance', depending on their intercriteria pair's comparison with these two defined threshold values.

Let $\alpha, \beta \in [0; 1]$ be the threshold values, against which we compare the values of μ_{C_i,C_j} and ν_{C_i,C_j}. We call those criteria C_i and C_j are in:

- (α, β)-positive consonance, if $\mu_{C_i,C_j} > \alpha$ and $\nu_{C_i,C_j} < \beta$;
- (α, β)-negative consonance, if $\mu_{C_i,C_j} < \beta$ and $\nu_{C_i,C_j} > \alpha$;
- (α, β)-dissonance, otherwise.

Correlation analysis

The parameters that characterize a certain object or a process may take various values and may be considered instances of random variables. If X and Y are two such variables, the coefficient of correlation $r(X, Y)$ is determined according to the formula:

$$r(X,Y) = \frac{cov(X,Y)}{\sigma(X).\sigma(Y)}, \tag{7}$$

where $cov(X, Y)$ denotes the covariance of X and Y, while $\sigma(X)$ and $\sigma(Y)$ are their standard deviations.

If n observations $x(1), x(2), \dots, x(n)$ and $y(1), y(2), \dots, y(n)$ of X and Y, respectively, have been made, then the covariance and standard deviations are evaluated according to the following formulas:

$$cov(X,Y) = \frac{1}{n-1}\sum_{i=1}^{n}(x(i) - \tilde{x})(y(i) - \tilde{y}) \tag{8}$$

$$\sigma^2(Z) = \frac{1}{n-1}\sum_{i-1}^{n}(z(i)-\tilde{z})^2 \quad (9)$$

where $\tilde{x}, \tilde{y}, \tilde{z}$ are the mean values of *X*, *Y* and *Z*, respectively.

The values of $r(X, Y)$ are in the interval [–1, 1], where the boundary values (±1) are obtained in case of normal distributions and linear dependence between the quantities. If the distributions are not normal, the correlation coefficient can be used only as one of the possible measures for the degree of dependence between *X* and *Y*. Since the type of distribution is usually not known in advance, it is advisable to use also other criteria, which in combination may give a more reliable estimation of the dependence between random quantities.

Results and discussions

In this work, we analyze four CRC subgroups – $CRC1_1$, $CRC1_2$, $CRC3_1$ and $CRC3_2$ (as defined in [13]) that contained a large number of cases. Representative thermograms for healthy individuals and for the analyzed calorimetric subgroups are shown in Fig. 1. The main parameters determined from the thermograms are: the excess heat capacities c_P^F, c_P^{HSA} and c_P^{Igs} assigned to fibrinogen, human serum albumun and immunoglobulins, respectively; the c_P^{HSA}/c_P^{Igs} ratio; the calorimetric enthalpy, ΔH_{cal}; the weighted average center of the thermograms, T_{FM} and the statistic parameters (*r*, *P*, and ρ). From these criteria a matrix is generated that was subjected to ICrA and correlation analysis (example presented in Table 1).

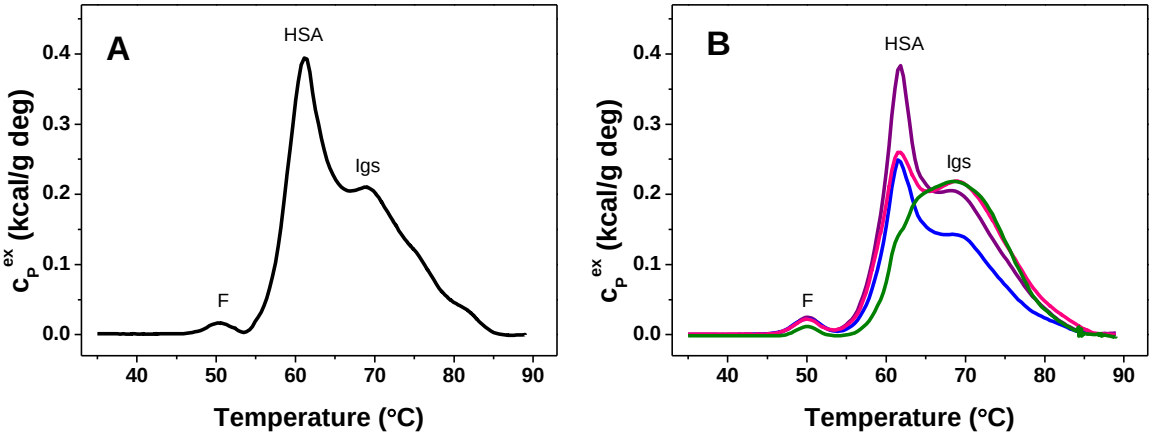

Fig. 1 DSC thermograms of blood plasma proteome representative for the healthy set (A) and the analyzed CRC subgroups (B, $CRC1_1$ – purple, $CRC1_2$ – blue, $CRC3_1$ – pink and $CRC3_2$ – green). For clarity the transitions of the most abundant plasma proteins (fibrinogen, F, albumin, HSA and immunoglobulins, Igs) are labeled.

The c_P^{HSA}/c_P^{Igs} ratio and the total enthalpy of the thermograms from the $CRC1_1$ subgroup are similar to the control values, thus the $CRC1_1$ subgroup deviates the least from the control one. The $CRC1_2$ subgroup has the same c_P^{HSA}/c_P^{Igs} ratio as that of the control, but the enthalpy ΔH and both c_P^{HSA} and c_P^{Igs} values are significantly lower than those of the control. The $CRC3_1$ and $CRC3_2$ subgroups on the average do not differ in enthalpy but have strongly reduced c_P^{HSA}/c_P^{Igs} ratio compared to the healthy set [13].

Table 1. ICrA analysis (μ and ν) matrix containing the investigated calorimetric and statistical parameters for the $CRC3_2$ subgroup

μ	c_p^{HSA}	c_p^{Igs}	c_p^{HSA} / c_p^{Igs}	c_P^{F}	c_P^{F} / c_p^{HSA}	T_{FM}	ΔH_{cal}	r	P	ρ
c_p^{HSA}	1.00	0.71	0.62	0.38	0.33	0.43	0.81	0.67	0.43	0.48
c_p^{Igs}	0.71	1.00	0.38	0.43	0.43	0.19	0.81	0.57	0.38	0.43
c_p^{HSA} /c_p^{Igs}	0.62	0.38	1.00	0.38	0.48	0.52	0.57	0.57	0.57	0.52
c_P^{F}	0.38	0.43	0.38	1.00	0.76	0.52	0.33	0.67	0.19	0.24
c_P^{F} / c_p^{HSA}	0.33	0.43	0.48	0.76	1.00	0.67	0.33	0.62	0.38	0.33
T_{FM}	0.43	0.19	0.52	0.52	0.67	1.00	0.29	0.52	0.43	0.38
ΔH_{cal}	0.81	0.81	0.57	0.33	0.33	0.29	1.00	0.67	0.57	0.62
r	0.67	0.57	0.57	0.67	0.62	0.52	0.67	1.00	0.29	0.38
P	0.43	0.38	0.57	0.19	0.38	0.43	0.57	0.29	1.00	0.81
ρ	0.48	0.43	0.52	0.24	0.33	0.38	0.62	0.38	0.81	1.00

ν	c_p^{HSA}	c_p^{Igs}	c_p^{HSA} / c_p^{Igs}	c_P^{F}	c_P^{F} / c_p^{HSA}	T_{FM}	ΔH_{cal}	r	P	ρ
c_p^{HSA}	0.00	0.24	0.33	0.38	0.62	0.52	0.14	0.24	0.48	0.38
c_p^{Igs}	0.24	0.00	0.62	0.38	0.57	0.81	0.19	0.38	0.57	0.48
c_p^{HSA} /c_p^{Igs}	0.33	0.62	0.00	0.43	0.52	0.48	0.43	0.38	0.38	0.38
c_P^{F}	0.38	0.38	0.43	0.00	0.05	0.29	0.48	0.19	0.57	0.57
c_P^{F} / c_p^{HSA}	0.62	0.57	0.52	0.05	0.00	0.33	0.67	0.33	0.57	0.57
T_{FM}	0.52	0.81	0.48	0.29	0.33	0.00	0.71	0.43	0.52	0.52
ΔH_{cal}	0.14	0.19	0.43	0.48	0.67	0.71	0.00	0.29	0.38	0.29
r	0.24	0.38	0.38	0.19	0.33	0.43	0.29	0.00	0.62	0.48
P	0.48	0.57	0.38	0.57	0.57	0.52	0.38	0.62	0.00	0.05
ρ	0.38	0.48	0.38	0.57	0.57	0.52	0.29	0.48	0.05	0.00

The ICrA analysis revealed weak interrelations between the studied criteria for the $CRC1_1$ group with the exception of the very strong positive consonance between P and ρ (0.94, Table 2). This trend is preserved for all other studied CRC subgroups (although slightly weaker for $CRC3_1$ and $CRC3_2$) and is further confirmed by the very high correlation coefficient ($corr(\rho, P) \geq 0.97$, Table 2) demonstrating that the change in ρ is due to larger distance deviation of CRC from the healthy thermograms rather than to a change in the thermograms shape.

T_{FM} of the $CRC1_1$ subgroup was found to relate weakly to the ratio of the excess heat capacities of fibrinogen (c_P^F) and albumin (c_P^{HSA}) assigned transitions (μ = 0.29), while for the $CRC1_2$ subgroup T_{FM} depended only on c_P^F (μ = 0.27). Insignificant correlation coefficients were found for those criteria (–0.35 and –0.39, respectively).

ΔH_{cal} was in strong positive consonance with c_p^{Igs} only for the $CRC1_2$ subgroup (μ = 0.82, $corr$ = 0.91), while for the $CRC1_1$ this value was on the border of significance (μ = 0.69, $corr$ = 0.68).

New interrelations appear for the $CRC3_1$ and $CRC3_2$ subgroups – ΔH_{cal} was in consonance with both c_P^{HSA} and c_P^{Igs} that was stronger for $CRC3_2$ subgroup. For $CRC3_1$ the positive consonance ($\mu(_{\Delta H}, c_P^{HSA})$ = 0.76) was accompanied by a low correlation coefficient

($corr(_{\Delta H}, c_P^{HSA})$ = 0.60). No such interrelations were observed for the $CRC1_1$ and $CRC1_2$ subgroups possibly due to the high uncertainty in these groups ($\pi \geq 0.16$, Table 2).

Table 2. Comparison of the calculated values of $\mu(_{Ci,Cj})$, $\nu(_{Ci,Cj})$, $\pi(_{Ci,Cj})$ and $corr(_{Ci,Cj})$ for the CRC sets of thermodynamic parameters where $_{Ci/Cj}$ criteria are the calorimetric enthalpy, ΔH, or the excess heat capacity of the successive thermal transitions located at 62 °C (c_p^{HSA}) and 70 °C (c_p^{Igs})

criteria/groups	$CRC1_1$	$CRC1_2$	$CRC3_1$	$CRC3_2$
$\mu(c_p^{HSA} c_p^{Igs})$	0.59	0.60	0.77	0.71
$\nu(c_p^{HSA} c_p^{Igs})$	0.26	0.24	0.14	0.24
$\pi(c_p^{HSA} c_p^{Igs})$	0.16	0.17	0.09	0.05
$corr(c_p^{HSA} c_p^{Igs})$	0.53	0.50	0.85	0.45
$\mu(_{\Delta H} c_p^{Igs})$	0.69	0.82	0.80	0.81
$\nu(_{\Delta H} c_p^{Igs})$	0.20	0.07	0.14	0.19
$\pi(_{\Delta H} c_p^{Igs})$	0.11	0.11	0.07	0.00
$corr(_{\Delta H} c_p^{Igs})$	0.68	0.91	0.63	0.69
$\mu(_{\Delta H} c_p^{HSA})$	0.67	0.62	0.76	0.81
$\nu(_{\Delta H} c_p^{HSA})$	0.26	0.29	0.20	0.14
$\pi(_{\Delta H} c_p^{HSA})$	0.06	0.09	0.04	0.05
$corr(_{\Delta H} c_p^{HSA})$	0.73	0.42	0.60	0.73
$\mu(\rho P)$	0.91	0.95	0.88	0.81
$\nu(\rho P)$	0.01	0.01	0.03	0.05
$\pi(\rho P)$	0.08	0.05	0.09	0.14
$corr(\rho P)$	0.99	0.99	0.98	0.97

A consonance between c_p^{HSA} and c_p^{Igs} was also evident for $CRC3_1$ and $CRC3_2$ subgroups ($\mu(c_P^{HSA}, c_P^{Igs})$ above 0.7, although $corr(c_P^{HSA}, c_P^{Igs})$ was below 0.65, Table 2). These findings prove that as expected the enthalpy change depends on the concentrations of the major plasma proteins but also that there is interplay between their levels, a fact that requires further investigation. Only for $CRC1_2$ subgroup ΔH_{cal} was in weak consonance with c_p^{Igs} / c_p^{HSA} ratio (μ = 0.26, $corr$ = –0.72).

Finally, a strong consonance was found between T_{FM} and c_p^{Igs} (μ = 0.19, $corr$ = –0.69) only for the $CRC3_2$ subgroup (that differed most from the healthy set).

Conclusion

The presented results demonstrate that distinct interrelations exist between the calorimetry derived parameters for the analyzed CRC calorimetric subgroups. Both the ICrA approach and the correlation analysis are shown to be helpful for the in-depth analysis of calorimetric datasets obtained from plasma thermograms. They appear to complement each other since in 8 cases ICrA surpasses the correlation analysis but the opposite was also true for the same number of cases. We believe that in future these two approaches can well be applied to data obtained for other diseases with the aim to identify disease specific correlations. Along with other newly developed numerical approaches [9], they can help to interpret the changes occurring in the highly complex calorimetric profile of the blood plasma proteome in malignant conditions.

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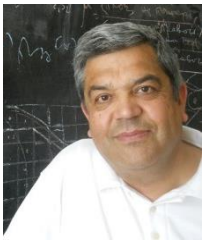

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