Cancer Informatics

ORIGINAL RESEARCH

Design of an Expert System for Mitigating Trace Element Toxicity in Cancer Risk Management

P.T. Krishna Kumar[1], P.T. Vinod[2], Vir V. Phoha[3], S.S. Iyengar[4] and Puneeth Iyengar[5]

[1]Materials Science Group, Indira Gandhi Centre for Atomic Research, Kalpakkam Tamil Nadu, India. [2]School of Information Technology Engineering, VIT University, Vellore, Tamil Nadu, India. [3]College of Engineering and Science, Louisiana Tech University, Nethken Hall, Ruston, LA, USA. [4]School of Computing and information Science, Florida International University, Miami, FL, USA. [5]UT Southwestern Medical Centre, Dallas, TX, USA.
Corresponding author email: gstptk@gmail.com

Abstract: Cancer risk management involves obliterating excess concentration of cancer causing trace elements by the natural immune system and hence intake of nutritious diet is of paramount importance. Human diet should consist of essential macronutrients that have to be consumed in large quantities and trace elements are to be consumed in very little amount. As some of these trace elements are causative factors for various types of cancer and build up at the expense of macronutrients, cancer risk management of these trace elements should be based on their initial concentration in the blood of each individual and not on their tolerable upper intake level. We propose an information theory based Expert System (ES) for estimating the lowest limit of toxicity association between the trace elements and the macronutrients. Such an estimate would enable the physician to prescribe required medication containing the macronutrients to annul the toxicity of cancer risk trace elements. The lowest limit of toxicity association is achieved by minimizing the correlated information of the concentration correlation matrix using the concept of Mutual Information (MI) and an algorithm based on a Technique of Determinant Inequalities (TDI) developed by the authors. The novelty of our ES is that it provides the lowest limit of toxicity profile for all trace elements in the blood not restricted to a group of compounds having similar structure. We demonstrate the superiority our algorithm over Principal Component Analysis in mitigating trace element toxicity in blood samples.

Keywords: carcinogenic trace elements, high correlation coefficient, cancer screening, expert system, mutual information

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Introduction

Among diseases, cancer has the highest rate of mortality worldwide. Prevention and early diagnosis of cancer are the daunting tasks of the medical fraternity. It is now well established that diet has a significant effect on cancer incidences.[1] For many years food was accepted as the source of all nutrients required to accomplish the physiological functions needed for development, growth, health, and reproduction. For humans, macronutrients like Na, Ca, Mg, K, and Cl are required in large quantity, whereas trace elements (TE) like Cr, Mn, Fe, Co, Cu, Zn and Mo are required in quantities of less than 100 mg per day and are called micronutrients.[2] It has been observed that an imbalance of TEs is one of the significant causative factors for diseases.[3,4] Further, there is a strong association between macronutrients and TEs resulting in the buildup of toxic or carcinogenic metals at the expense of macronutrients, leading to cancer.[5–9]

Deficiency in any trace element leads to undesirable pathological conditions that can be prevented or reversed by adequate supplementation. However, supplementation should be carefully administered given the toxic effects of TEs when taken in excess of the required amount. In order to prevent excess consumption of TE, a Tolerable Upper Intake Level (TUIL), the highest level of nutrient that is likely to pose no risk to the general population, has been prescribed by the U.S. Food and Nutrition Board of the Institute of Medicine[10] for Mn, Fe, Cu, Zn and Se and not for any other elements. The risk of adverse effects also increases with any intake above the TUIL.[11] However, the estimates made for TUILs is based on a risk assessment model with varying uncertainty factors and never considered the initial concentration of TE in each individual.[12] Furthermore, the risk assessment model never considered the complex interaction among nutrients[13] or drug nutrient interactions, and hence requires scientific validation.[11]

The variation in concentration of some of TEs in the blood when compared to their inherent initial concentration is used for cancer screening on an individual by individual basis. The existence of this inherent initial concentration leads to a correlation among the TEs and forms a dynamic balance due to complex interactions among them. The existing chemometric techniques like Multivariate Linear Regressions (MLR), step wise regression, Principal Component Analysis (PCA), Artificial neural networks (ANNs), and Backpropagation neural networks (BpNN) are unable to predict the initial concentration of TEs and hence do not provide satisfactory results for cancer screening.[14,15] Furthermore, supplementation in order to treat a particular disease should consider the toxic levels of all the other TEs[16] that these chemometric techniques fail to account.

In this paper, instead of estimating the initial concentration, we propose an information theory based Expert System (ES) for estimating the Lowest Limit of Toxicity Association (LLTA) for cancer screening, supplementation, and mitigation of toxicity of TE. Medical and biomedical intelligent data analysis is a complex field based on statistical methods. Medicinal doctors admit that they are still doing evidential medicine instead of making diagnosis based on hard facts, whereas an ES can guide them in their decision.[17] As carcinogenic toxic TEs build up at the expense of macronutrients, leading to cancer, the ES estimates the LLTA between the macro and micronutrients. The ES is based on minimizing the total toxicity of any particular TE by decreasing its association with the macro and micronutrients in blood samples. The ES considers the dynamic environment of interacting TEs and minimizes the total toxicity using the information theoretic concept of mutual information (MI). MI is a generalized measure of correlation, analogous to a linear correlation coefficient, but is sensitive to non-linear dependencies between TEs. In particular, a vanishing MI implies that the toxicity among the nutrients are independent, but not so with vanishing Pearson coefficient.[18] Thus MI provides a general measure of association between nutrients that is applicable regardless of the shape of their concentration distribution. Furthermore MI, unlike linear or rank order correlation, is insensitive to non-monotonic dependence between macro and micro nutrients.[19] The ES is based on an algorithm maximizing the MI by estimating the bounds for the correlated information between nutrients, using the technique of determinant Inequalities (TDI) developed by the authors.[20] This technique is unlike other ES which are restricted to a group of compounds having similar structure.[21] The advantage of the ES is that for any specific treatment due to toxicity of a particular TE, its LLTA for the rest of the macro and micronutrients are computed so that a complete toxic

fingerprint of the entire TE in the body is available to the physician. Such a fingerprint would enable the physician to prescribe required medication containing the macronutrients to annul the toxicity of cancer risk TE.[22] We demonstrate the superiority of our ES based on MI over the Principal Component Analysis (PCA) in the analysis of a blood sample.

We first formulate the relationship between toxicity and the concentration of the nutrients using covariance information. As the interaction between TEs and macronutrients are stronger in cancer risk groups, we then use the information theoretic concept of MI to depict the strong correlation between them. We then deal with TDI to maximize the MI and the algorithm developed to estimate LLTA. We apply our technique to the analysis of blood samples and discuss the results. The flow chart for cancer screening is depicted in flow chart 1; the flow chart 2 portrays cancer management with macronutrients.

Covariance Information Model for Toxicity

Let C_i ($i = 1, \ldots, N$) be the concentration of each of the N macronutrients, C_j ($j = 1, \ldots, n$) be the concentration of each of the n TE, and let T_i and T_j be respective toxicity. We can write,

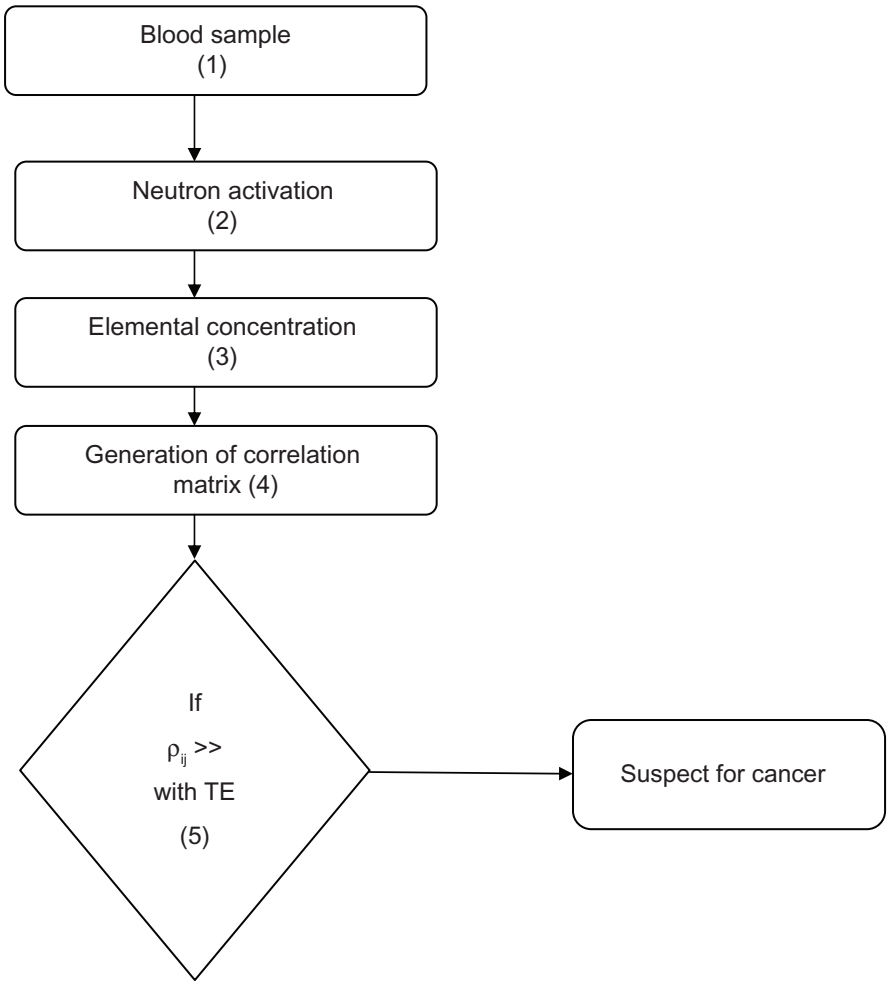
$$T_i = T_i(C_i) \tag{1}$$

Using the first order perturbation theory, we can calculate any change in T_i due to small changes in dC_i of C_i as

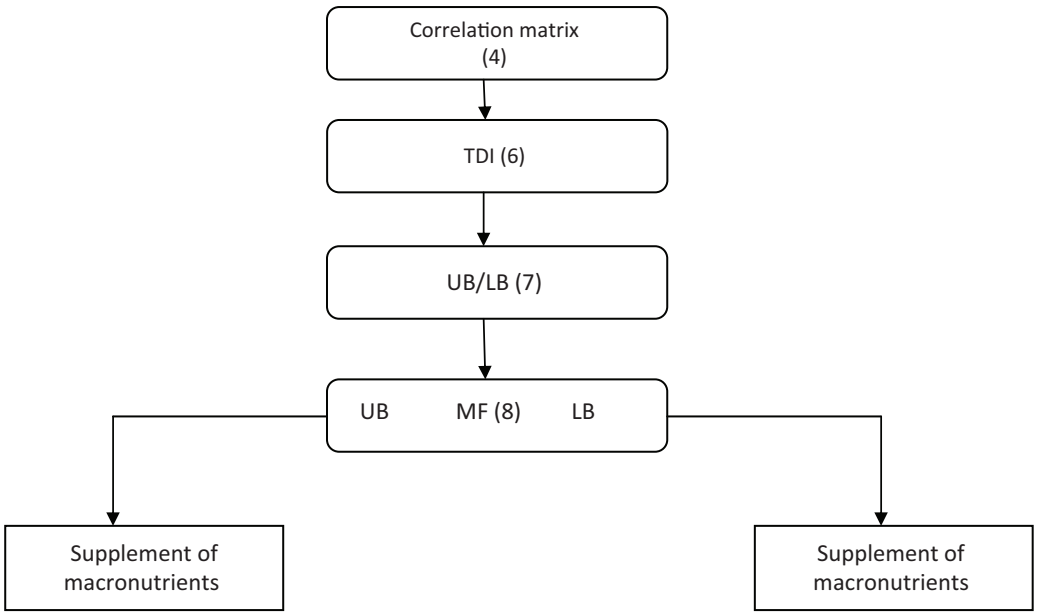
$$dT_i = \sum_i \frac{\partial T_i}{\partial C_i}\, dC_i \tag{2}$$

Using the notation $\delta T = (dT/T)$ and $\delta C = (dC/C)$ the relative variance-covariance in T is usually obtained as $(\delta T_i\ \delta T_j)$ and can be expressed using Eq. (2) as

$$(\delta T_i\ \delta T_j) = B\,(\delta C_i\ \delta C_j)B^{tp} \tag{3}$$



Flow Chart 1. Cancer screening using trace elements.



Flow Chart 2. Cancer management by supplementing macronutrients.

The value of $(\partial T/\partial C)\ C/T$, which is linear under our linear perturbation theory and constant over the chosen statistical ensemble, is called relative sensitivity matrix B, ie, $B = (\partial T/\partial C)\ C/T$. The linearity of the sensitivity data ensures the covariance data are not independent.

In Eq. (3) the product of the concentrations $(\delta C_i\ \delta C_j)$ is the basic definition of the covariance matrix M_C and hence, Eq. (3) can be rewritten as $M_T = B\ M_C\ B^{tp}$ where $M_T = (\delta T_i\ \delta T_j)$ is the relative variance—covariance matrix for T and B^{tp} is the transpose of B.

The correlation coefficient ρ_{ij} between the concentration C_i and C_j is defined as

$$\rho_{ij} = [\text{Cov}\ (C_i, C_j)/\{\text{Var.}\ (C_i)\}^{0.5}\{\text{Var.}\ (C_j)\}^{0.5}] \quad (4)$$

ρ_{ij} vary between +1 and −1 and is a measure of strength of the association between the concentrations of the nutrients. Any decrease in ρ_{ij} from its present value indicates the decrease in the strength of association between the concentrations of the nutrients and hence the toxicities among them, as per Eq. (3). The strength of the association among the nutrients vanishes and the toxicities become independent when $\rho_{ij} = 0$.

Preliminaries on Mutual Information

Let, T_1, T_2 be toxicities of any two nutrients whose corresponding concentrations are C_1 and C_2 respectively in the blood. Let T_0 be the inherent initial toxicity having concentration C_0. According to information theory[23] the uncertainty in T_1 is measured by its entropy $H(T_1)$. The uncertainty in T_1 given the knowledge of T_2 is given by the conditional entropy $H(T_1|T_2)$. The uncertainty of the pair T_1, T_2 is measured by joint entropy $H(T_1,T_2)$.

Mutual Information, $MI(T_1,T_2)$ is defined as the reduction of the uncertainty in T_1 due to knowledge of T_2 (or vice versa) ie,

$$MI(T_1,T_2) = H(T_1) - H(T_1\,|\,T_2) = H(T_2) - H(T_2\,|\,T_1) = H(T_1) + H(T_2) - H(T_1,T_2) \quad (5)$$

$MI(T_1,T_2)$ for two variables is always a non-negative quantity and it is zero only when the toxicities T_1 and T_2 is independent.

When $MI(T_1,T_2) = 0$, then $H(T_1) + H(T_2) = H(T_1,T_2)$—the joint entropy of total toxicity is the sum of the individual entropy of toxicities and is the maximum toxic limit.

When, $MI(T_1,T_2) > 0$, then, $H(T_1,T_2) < H(T_1) + H(T_2)$. Thus, the joint entropy of total toxicity is less than the sum of the individual entropy of toxicities.

Figure 1 depicts pictorially the association and independence of toxicities for $MI(T_1,T_2) > 0$ and $MI(T_1,T_2) = 0$ respectively.

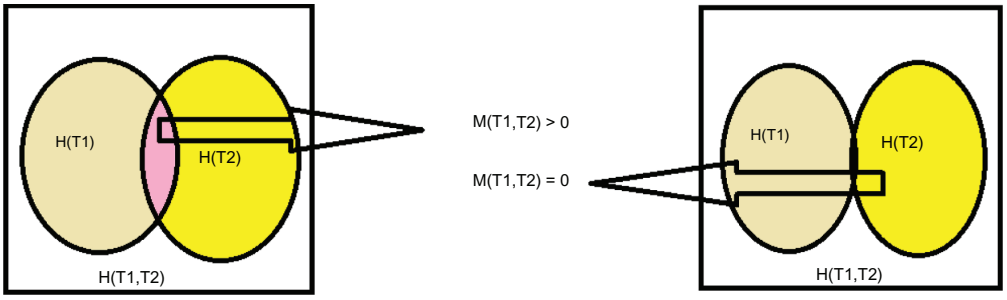


Figure 1. The association and independence of toxicities for $MI(T_1,T_2) > 0$ and $MI(T_1,T_2) = 0$ respectively.

$MI(T_1,T_2)$ for a Gaussian distribution is expressed as:[23]

$$MI(T_1,T_2) = \text{Constant. Log.}|\text{ Det. } \rho\ | = \text{Constant. Log. G} \quad (6)$$

where G = | Det. ρ | is the absolute value of the determinant of the correlation matrix ρ. Thus, $MI(T_1,T_2)$ is a measure of statistical correlation of toxicities between the nutrients T_1 and T_2—which depends on the absolute value of the determinant of the correlation matrix ρ—and $MI(T_1,T_2)$ is maximum when G is made maximum. For example, when, $\rho = \begin{pmatrix} 1 & \rho_{12} \\ \rho_{21} & 1 \end{pmatrix}$ where ρ_{12} is the correlation coefficient between C_1 and C_2, and G = | Det. ρ | = | $(1 - \rho^2_{12})$ |.

Here G can be maximized by finding the upper and lower bounds of ρ_{12}. Thus, by maximizing G from knowledge of the bounds for the correlated elements of ρ, the strength of the association between the nutrients is minimized. Minimization of the strength of the association leads minimization of total toxicities between the nutrients as previously mentioned and depicted in Figure 1 in the case where $MI(T_1,T_2) > 0$. Thus, an index of minimization of total toxicities between two correlated nutrients is the maximization of MI or G by the estimation of upper and lower bounds for the correlated elements of the correlation matrix ρ. The particular bound value of ρ_{ij} yields the maximum G results in LLTA. Hence, our technique gives a scientific validation for the estimation of T_0 (or the LLTA having concentration C_0) and thus forms the basis for screening, supplementation, and mitigation of toxicity of TE. The algorithm developed by us to determine the upper and lower bounds of the correlated elements for the correlation matrix is done using a Technique of Determinant Inequalities (TDI) is described below.

Technique of Determinant Inequalities

Information theory is endowed with a multitude of powerful theorems for computing bounds on the optimum representation and transmission of information bearing channels. Here, we develop the technique of determinant inequalities to estimate the upper and lower bounds for the constant inherent initial toxicity T_0, which has concentration C_0 in the blood samples and causes correlation or bias. A rigorous estimate of bounds is provided by the upper and lower bounds, U and L respectively, such that $U \geq C_0 \geq L$. This constant bias appears in one or several elements of the determinant G. Let us suppose the sign of the determinant G can be determined. Then G can be considered as a polynomial in C_0 ie, G = G(C_0) and the roots of the determinant function G(C_0) = 0 enable us to estimate the permissible values of C_0; hence the upper and lower bounds can be determined. Thus to determine the bounds on C_0, two conditions must be met—the sign of the determinant G has to be known and the roots of the polynomial G(C_0) = 0 should be determined.

The determinant G is positive when $\rho_{ij} = 0$. In this case, only the uncorrelated diagonal elements of ρ exist. Similarly the determinant G is zero when ρ_{ij} is either +1 or −1. Such a determinant is called a Gram determinant, or Gramian, and its positivity is expressed as an inequality

$$G \geq 0 \quad (7)$$

The upper and lower bounds are determined by solving the polynomial equation G (C_0) = 0. For the

purpose of illustration, let us consider a (3×3) correlation matrix with elements of ρ as follows.

$$\begin{pmatrix} 1 & \rho_{12} & \rho_{13} \\ \rho_{21} & 1 & \rho_{23} \\ \rho_{31} & \rho_{32} & 1 \end{pmatrix}$$

Then G = Det. ρ ≥ 0 requires that $1-\rho_{23}^2-\rho_{12}^2+2\rho_{12}\rho_{13}\rho_{23}-\rho_{13}^2 \geq 0$

From the above equation, it is clear that ρ_{12} must lie between two roots of the quadratic equation, which constitute the upper, and lower bounds of ρ_{12}. The upper bound is $\rho_{13}\rho_{23}+[(1-\rho_{13}^2)(1-\rho_{23}^2)]^{0.5}$ and the lower bound is $\rho_{13}\rho_{23}-[(1-\rho_{13}^2)(1-\rho_{23}^2)]^{0.5}$

Algorithm

The algorithm[24] based on TDI is as follows. Let us designate,

G_i: Determinant with ith row and column deleted,
G_{ij}: Determinant with ith and jth row and column deleted, (Note that when G has only two rows and columns then G_{12}= 1)
g_{ii}: Determinant with $\rho_{ii} = 0$,
g_{ij}: Determinant with $\rho_{ij} = 0$, and row j and column i deleted.

According to Eq. (7), G ≥ 0 and hence G_i and G_{ij} are also Gram determinants of lower order. Thus G ≥ 0, $G_i > 0$, $G_{ij} > 0$ and we can establish the following Inequalities:

$$\rho_{ij} + (g_{ii}/G_i) \geq 0,$$

$$(g_+ - \rho_{ij})\,(\rho_{ij} - g_-) \geq 0$$

where $g_\pm = \{(-1)^{i+j}\, g_{ij} \pm (G_iG_j)^{0.5}\}/G_{ij}$.

Thus for the uncorrelated component, the lower bound is $\rho_{ii} \geq -g_{ii}/G_i$, while for the correlated component the upper and lower bounds are

$$g_+ \geq \rho_{ij} \geq g_- \qquad (8)$$

According to Hadamard's inequality, G = Det. $\rho \leq \prod \rho_{ij}$.

The equality is achieved if and only if $\rho_{ij} = 0$. The maximum value of the determinant is the product of the diagonal elements and the least value is zero, when ρ_{ij} is either +1 or −1. Since, the MI cannot be negative, the value of either the upper or the lower bound of ρ_{ij} which maximizes the determinant G is the robust value which maximizes the MI.

Results

Blood samples from 100 patients, consisting of 58 women and 42 men from ages ranging between 20 and 80, were collected in this study. Extreme precaution was taken in the collection of these samples in order to prevent contamination from the exogenous Trace Element (TE). For each of the blood samples, multi-element concentrations were estimated using Neutron Activation Analysis (NAA). NAA is an attractive technique for rapid multi-element analysis of biological samples.[25] The multi-element data, which is the concentration of the macronutrients and the TE for the above 100 patients, was reduced to correlation matrix using the standard chemometric procedures.[26]

The concentration correlation matrix for eleven elements in blood plasma is depicted in Table 1. Among these eleven, we focused our attention on the TE Cr, intake of which increases breast cancer mortality.[16] In Table 2, the lower bound values of ρ_{ij} for ten elements which have correlation with Cr are obtained using Eq. (8) and are compared with the existing values in Table 1. It is observed that only the lower bound values yield the maximum value of G. The values of ρ obtained by the PCA are also tabulated in Table 2 for comparison.

The estimation of lower bounds for ρ as depicted in Table 2 is also very low compared to the existing value of elements. As lower values of ρ leads to decreased toxicities between the macro and the TE, these lower bound values represent the LLTA. Further, MI as represented by the value of G is 0.07 for lower bound values as compared to 0.01 for the existing elements.

Cancer Screening and Management

The flow chart for cancer screening is depicted in flow chart 1. The sequence of screening is depicted serially from 1 to 5 as follows: (1) We collect the blood sample of the patients; (2) We subject these blood samples to NAA; (3) The NAA enables us to determine the elemental concentration of both the macronutrients and the TE; (4) Using these concentration values, we generate the correlation matrix using chemometric techniques; and (5) As TE builds up at the expense

Table 1. Correlation matrix (ρ) between the concentrations of trace elements in blood plasma.

Element	Na	Ca	Mg	K	Cr	Mn	Fe	Co	Cu	Zn	Mo
Na	1.0	–0.05	–0.09	–0.11	–0.07	0.05	0.11	–0.29	0.06	–0.01	–0.17
Ca		1.0	0.63	0.17	–0.03	0.89	0.28	0.11	0.01	0.63	0.03
Mg			1.0	0.16	0.19	0.50	0.30	0.23	–0.19	0.46	0.08
K				1.0	0.06	0.12	0.08	0.08	–0.07	0.15	–0.08
Cr					1.0	–0.05	0.12	0.10	–0.08	0.01	0.08
Mn						1.0	0.27	0.14	0.07	0.52	0.01
Fe							1.0	0.20	–0.39	0.65	–0.09
Co								1.0	–0.23	0.34	0.41
Cu									1.0	–0.28	–0.10
Zn										1.0	0.11
Mo											1.0

of macronutrients, we examine critically the value of correlation coefficient of cancer causing TE with the macronutrients.

Cancer management by supplementation is depicted in flow chart 2. We start our analysis with the correlation matrix. These correlation matrix are the input data to our technique of Determinant Inequalities (TDI). Upper Bound (UB) and Lower Bound (LB) values for each of correlation coefficients are generated by TDI. The values of either the (UB) or the (LB) which gives the highest value of Mutual Information (MI) is used for supplementation of macronutrients.

Discussion

The variation in concentration of TEs in the blood from inherent initial concentrations is an indication of malignancies and is used for cancer screening and diagnosis in individuals. All existing chemometric techniques like MLR, PCA, ANNs, and BpNN do not provide initial inherent concentration C_0 and hence their concentration estimation does not provide satisfactory results for cancer screening. Furthermore, the above techniques are suitable only for weekly correlated systems and unsuitable for processing the complex and strong correlations between macronutrients and TEs.

As carcinogenic toxic TEs build up at the expense of macronutrients, we have proposed an Expert System (ES) for cancer screening which involves minimizing the strength of the association between macronutrients and TEs using MI. MI is maximum for a higher value of G, leading to least association of toxicities. Hence, our technique gives a scientific validation for the estimation of T_0 or the LLTA having concentration C_0. It therefore forms the basis for screening, supplementation, and mitigation of toxicity of TEs.

Furthermore, from Table 2, the lower bound values are all much lower compared to PCA. As PCA values are higher, they do not lead to decreased association between the macronutrient and the TEs and accordingly cannot be used to predict LLTA. Thus, selective mitigation of toxicity of a specific TE is possible by decreasing its association with the other macro and micronutrients, using an algorithm based on MI. Even though we have chosen Cr for selective mitigation, our algorithm enables us to obtain the bounds for each of the TEs so that their association with the other elements can be selectively decreased by maximization of MI. Such TE-wise mitigation of toxicity is possible only by MI and not by either PCA or Independent Component Analysis (ICA).

Table 2. Comparison of ρ_{ij} for Cr obtained by the technique of determinant inequalities and the principal component analysis (PCA).

No.	Element	Existing value ρ_{ij} from Table 1	LLTA	PCA values
1	Na	–0.07	–0.88	–0.06
2	Ca	–0.03	–0.33	0.94
3	Mg	0.19	–0.67	0.67
4	K	0.06	–0.90	0.15
5	Mn	–0.05	–0.43	0.93
6	Fe	0.12	–0.61	0.34
7	Co	0.1	–0.65	0.14
8	Cu	–0.08	–0.93	–0.09
9	Zn	0.01	–0.46	0.66
10	Mo	0.08	–0.82	0.03
		G = 0.01	G = 0.07	

Note: LLTA is obtained using Eq. (8). G = | Det. ρ |.
Abbreviation: LLTA, Lowest Limit of Toxicity Association.

As regards supplementation, a careful analysis of Table 2 would reveal that the lower bound values are all anti-correlated compared to existing values, which in only some cases are anti-correlated. As mentioned earlier, when macronutrients are consumed by humans in large quantities, because of their anti-correlation with TEs, they reduce the toxicity of TE. Thus, in the above case, the patient who consumes Mg, Fe and Zn in large quantities would not be at risk of breast cancer due to Cr toxicity. The LLTA value gives a scientific proof for supplementation of Mg, Fe, and Zn to boost the immune system against cancer.

Most expert systems provide prediction of toxicity only for a restricted group of compounds based on Quantitative Structure Activity Relationships (QSAR) and never provide toxicity profile for all of the elements present in a sample. Unlike those based on QSAR, our Expert System is not restricted to specific compounds but rather provides the LLTA for all TEs that are in association with any of micro and macronutrients.

Author Contributions

Conceived and designed the experiments: PTK, PTV. Analysed the data PTK, PTV, SSI, PI. Wrote the first draft of the manuscript PTK, PTV. Agree with the manuscript results and conclusions: PTK, PTV, VP, SSI, PI. Jointly developed the structure and arguments for the paper: PTK, PTV, VP, SSI, PI. Made critical revisions and approved final revision: PTK, PTV, VP, SSI, PI. All authors reviewed and approved of the final manuscript.

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