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Reduction of Systematic Error in Radiopharmaceutical Activity by Entropy Based Mutual Information

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ABSTRACT

The quality of the radiation dose depends upon the gamma count rate of the radionuclide used. Any reduction in error in the count rate is reflected in the reduction in error in the activity and consequently on the quality of dose. All the efforts so far have been directed only to minimize the random errors in count rate by repetition. In the absence of probability distribution for the systematic errors, we propose to minimize these errors by estimating the upper and lower limits by the technique of determinant in equalities developed by us. Using the algorithm we have developed based on the technique of determinant inequalities and the concept of maximization of mutual information (MI); we show how to process element by element of the covariance matrix to minimize the correlated systematic errors in the count rate of ^{113m}In. The element wise processing of covariance matrix is so unique by our technique that it gives experimentalists enough maneuverability to mitigate different factors causing systematic errors in the count rate and consequently the activity of ^{113m}In.

Keywords: Random and Systematic Errors; Covariance Matrix; Limits for Correlated Elements by Determinant Inequalities; Mutual Information; Reduction of Systematic Errors by Maximizing Mutual Information

1. Introduction

Radiopharmaceuticals are used in nuclear medicine to study the functioning of organs and tissues. One of the major objectives of these radiopharmaceuticals in radio therapy is to ensure precise delivery of dose to a tumour. As radiation dose is proportional to the radioactivity, any error in measured activity will affect the dose deposited to the organ. Hence, it is important to estimate the amount of radiation delivered by these radiopharmaceuticals both for optimization of image quality and for radiation protection purposes.

The quality of the dose depends upon the gamma count rate of the radionuclide used [1]. The error in the number of counts at the gamma camera is a measure of the error in dose deposited at the human body tissues, which is a cumulative effect of the errors due to instrumentation and nuclear characteristics of the radiopharmaceuticals. Thus, any reduction in error in the count rate is reflected in the reduction in error in the activity and consequently on the quality of dose. The total error in the count rate estimate should include both the random and the systematic errors. To quantify the errors, covariance matrix has been identified as the error matrix as per international recommendation [2]. The diagonal and off diagonal elements of the covariance matrix represent uncorrelated random and the correlated systematic errors respectively. To our knowledge, so far many attempts have been made only to minimize the random error by repetition as it decreases by $\sqrt{N}$ if a measurement is repeated N times. On the contrary, the systematic error can never be reduced by repetition and is the main cause of correlation [3].

All the attempts made so far on systematic errors of SPECT imaging, either neglected them [4] or randomized them [5]. The only approach suggested to mitigate the systematic errors is to assume a statistical distribution for them like in Linearized Bayesian Update Procedure (LBUP) [6]. Assuming a statistical distribution for the systematic error requires knowledge of the second central moment or the variance. In the case of the systematic errors, the initial estimate is taken as the mean or the first moment of the probability density function. The estimate of the corresponding variance or the second central moment depends strongly on the availability of supplementary knowledge. As variance is seldom available for the systematic errors, their probability density function cannot be assumed and hence, LBUP cannot be applied in principle.

To circumvent the lack of knowledge of variance, we propose in this paper, estimation of limits for the systematic errors. Accordingly, if the upper and lower limit of the systematic error can be estimated and no additional information exists, then one can assume a constant probability

density within these limits [2]. We have developed an algorithm based on the Technique of Determinant Inequalities (TDI) to estimate these limits. These limits are used to maximize the information theoretic concept of Mutual information (MI) to reduce the systematic errors. We demonstrate the utilization of our approach in reducing the systematic errors and consequently the total error in the gamma count rate of ^{113m}In.

2. Generation of Covariance Matrices from the Neutron Activation Analysis of ^{113m}In

^{113m}In is a diagnostic nuclear medicine agent for internal radiotherapy and is also used as a tracer in experimental studies [7]. In our laboratory, ^{113m}In is produced by neutron activation analysis in a standard neutron field of ^{252}Cf, by the reaction ^{113}In (n, n') ^{113m}In. ^{113}In foils with thickness 2.0 cm were irradiated for about 15 hours at a distance of 6 cm from the ^{252}Cf source. The californium ^{252}Cf is a needle type source, containing about 500 μg of ^{252}Cf encapsulated in a stainless steel cylinder having 5 mm diameter and 17 mm height. Induced gamma activities due to ^{113m}In were measured by a Ge (Li) detector having intrinsic efficiency ε and let the gamma count rate be C. The induced activity A of ^{113m}In depends upon its neutron absorption cross-section Σ, its atom density N and the induced neutron flux density φ of the ^{252}Cf. If m is the tissue mass, so that (A/m) is the activeity per unit mass, the absorbed dose rate D = k (A/m) E, where k is a constant whose value depends on the units used for other factors in the equation and E is the average energy released per transformation. Since, E is a constant for each radionuclide, k and E can be combined into a single constant Ω, hence, D = Ω (A/m). For a particular tissue mass and specific γ radiation, D = Δ A, where Δ = (Ω/m). Thus,

$$D\alpha\ A\alpha\quad C \tag{1}$$

Thus, as activity A and count rate C are proportional, any reduction in the error of the count rate will lead to the reduction in error in the activity as per law of error propagation [8]. In the gamma count rate measurements of ^{113m}In, several measurement systematic errors like back scattering from the room walls, geometrical factors are introduced during its formation and attenuation of the gamma ray and gamma ray intensity are introduced during its decay, requiring corrections. Applying the correction factors f to the count rate,

$$C = A\varepsilon\prod f\,(se) = N\Sigma\varphi\varepsilon\prod f\,(se),\ \text{since } A = N\sum\varphi$$

Here, $f(se)$ is the correction factor for each of the (se) systematic errors. For generality, the above equation is rewritten for any element i as

$$C_i = N_i\Sigma_i\varphi\varepsilon_i\prod f_i(se) \tag{2}$$

In Equation (2), both Σ and φ are unknown. An unknown cross-section is often determined by means of reaction rate ratio measurement relative to a well-known cross-section. The principle behind such relative measurements is the parallel irradiation of two different foils in the same neutron field of ^{252}Cf and subsequently counting their induced activities. Hence, by ratio measurement, unknown neutron flux density φ is eliminated,

$$R_{ij} = C_i/C_j$$
$$= \left[N_i/N_j\right]\left[\sum_i/\sum_j\right]\left[\varepsilon_i/\varepsilon_j\right]\left[\prod f_i(se)\right]/\left[\prod f_j(se)\right]$$

In our analysis, we consider formation of ^{113m}In by two sets of ratio measurement, *i.e.* ^{113}In (n, n') relative to ^{27}Al (n, α) and ^{115}In (n, n') respectively in the standard neutron field of ^{252}Cf.

Differentiating Equation (2) and writing dC/C = δC, one can obtain

$$\delta C_i = \delta N_i + \delta\sum_i + \delta\varepsilon_i + \sum\delta f_i(se) \tag{3}$$

The relative covariance M_C between the count rate C_i and C_j with its various components as in Equation (2) with their respective correlation coefficient ρ_{ij} is obtained as follows,

$$M_C = <\delta C_i\delta C_j> = \rho_{ij}(N)<\delta N_i\delta N_j> + \rho_{ij}\left(\sum\right)<\delta\sum\nolimits_i\delta\sum\nolimits_j> + \rho_{ij}(\varepsilon)<\delta\varepsilon_i\delta\varepsilon_j> + \rho_{ij}(f)<\delta f_i(se)\delta f_j(se)>$$

The Determinant of M_C is designated as G. *i.e.* G = Det. M_C.

The complete list of all the error contributions with their magnitude and the correlation coefficients depicted in curly braces are given is **Table 1**. The two ^{113}In foils used for the relative measurements have same correction factors for mass N and hence the errors are fully correlated $\{P\}$. The correction for geometrical factor $f(gf)$ is the same for all measurements and so the corresponding errors show full correlation {Q}. ^{113m}In is the product nucleus in both the sets of relative measurement and hence the correction factors for half lives $f(hl)$ of ^{113m}In are fully correlated {R}. Similarly since ^{113m}In is a γ emitter, the correction factors for gamma ray attenuation $f(ga)$ and intensity $f(gi)$ are fully correlated $\{S, T\}$. The sources of back scattering are the room walls and the correction factors $f(bs)$ are fully correlated $\{U\}$. The details of constructing the covariance matrix given the various correlation coefficients for the above activation measurement is described in detail in [8].

3. Reduction of Systematic Error by Entropy Based Mutual Information

The fundamental property of systematic error is that they vary between a lower limit L and an upper limit U. If a probability distribution of the error over these limits is

Table 1. Errors and their magnitudes and their correlation in ^{113}In activation measurement.

		Ratio I		Ratio II	
Description of Error Quantities	Symbols of Errors	^{113}In (n,n') %	^{27}Al (n,α) %	^{113}In (n,n') %	^{115}In (n,n') %
Efficiency	ε	2.08	1.06	2.08	2.23
Mass Determination	N	0.1 {P}	0.1	0.1 {P}	0.1
Geometrical Factor	f (gf)	2.0 {Q}	2.0 {Q}	2.0 {Q}	2.0 {Q}
Half Life	f (hl)	0.11 {R}	0.13	0.14 {R}	0.01
Gamma Ray Attenuation	f (ga)	1 {S}	0.5	1 {S}	1
Gamma Ray Intensity	f (gi)	1 {T}	0.1	1 {T}	1
Back Scattering	f (bs)	1 {U}	0.7 {U}	1 {U}	1 {U}
Irradiation and Cooling Time	f (ic)	0.35	0.08	0.35	0.13
Cross-Section	Σ	4.77	2.77	4.77	4.08

{P} represents fully correlated with ρ = 1.0, as Indium foils are used in the two measurements; {Q} represents fully correlated with ρ = 1.0 as the correction factor is the same for the same geometry of foils and {R,S,T} represents fully correlated with ρ = 1.0, as ^{113m}In is the end product in the two measurements; {U} represents fully correlated with ρ = 1.0 as the source of back scattering is from the room walls.

known, then it can be used to describe the error. However, in most of the cases, such a distribution is not known, and it seems reasonable to choose a maximally uncertain density function. The appropriate measure of uncertainty for a distribution is a positive quantity called entropy H, given by,

$$H = \int a(x)\log\left(a(x)\right)dx$$

The larger the entropy, the greater the uncertainty and hence we should choose a density function $a(x)$ that maximizes the entropy subject to the following constraints, $a(x) \geq 0$ for all values of x

$$L \leq x \leq U$$

$\int a(x)dx = 1$ between the Upper and lower limits.

When data on known standards are available, then, the standard techniques for estimating the end points of a uniform distribution can be used to estimate the limits L and U. But, where no such standards are available, the value of end points should be estimated using the knowledge of the measurement process. Further, in our case, systematic error in cross-section dominates over the statistical and hence conventional central limit theorem fails [9] making it necessary to use information theory approach [10]. A novel property of entropy principle is that it remains valid even if one of the sources of errors is highly correlated and dominant [10]. Further, entropy principle does not make assumptions about the distribution of data thereby belonging to the non-parametric family of statistics. According to information theory, MI is a measure of statistical correlation between the variables, A and C [11]. We show below, how in maximizing the MI, the systematic errors are reduced.

The MI between A and C is expressed as [12]

$$MI(A; C) = H(C) + H(A) - H(C, A)$$

or

$$H(C, A) = H(C) + H(A) - MI(A; C)$$

where $H(C)$ and $H(A)$ are the entropies or the uncertainty of C and A respectively and $H(C, A)$ is the joint entropy of C and A.

1) When, $MI(A; C) = 0$, then, $H(C, A) = H(C) + H(A)$, *i.e.* joint entropy or uncertainty is the sum of individual uncertainty of C and A.

2) When, $MI(A; C) > 0$, then $H(C, A) < H(C) + H(A)$ *i.e.* joint entropy or uncertainty is less than the sum of individual uncertainty of C and A. Thus, maximizing, MI implies, minimizing the total uncertainty in both C and A.

When, C is having Gaussian distribution, MI is given by [12],

$$MI(A; C) = \log(\text{Det. } M_C) = \log(G) \quad (4)$$

MI thus depends on the determinant of the covariance matrix M_C and is always positive and maximizing MI is equivalent maximizing the determinant of the covariance matrix M_C.

As an illustration, let us consider a simple case of just two count rates,

$$\text{Det. } M_C = \begin{pmatrix} c_{11} & c_{12} \\ c_{21} & c_{22} \end{pmatrix}$$

The elements of the covariance matrix can be written as the variances of C_1 and C_2

$c_{11} = \sigma_1^2, c_{22} = \sigma_2^2, c_{12} = c_{21} = \sigma_1\sigma_2\rho_{12}$ where ρ_{12} is the correlation coefficient between C_1 and C_2.

$$G = \text{Det. } M_C = \sigma_1^2\sigma_2^2\left(1-\rho_{12}^2\right) \quad (5)$$

From Equation (5), the maximum value of G is σ_1^2 σ_2^2 when $\rho_{12} = 0$ and minimum value of G is 0, when $\rho_{12} = \pm 1$.

Thus, G depends upon, ρ_{12} in addition to σ_1^2 and σ_2^2. As mentioned earlier, MI quantifies the amount of correlation between the variables A and C and G can be maximized by minimizing ρ_{12}. Minimization of ρ_{12} by estimating its limits leads to minimization of correlated systematic errors. Hence, an index of minimization correlated systematic errors is the maximization of MI by the estimation of upper and lower limits for the correlated elements of M. The technique of determinant Inequalities (TDI) to obtain these upper and lower limits [13] and the algorithm [14] based on TDI is described elsewhere and would not be repeated here. The total error (TE) in the count rate, is given by the sum of Uncorrelated Statistical Error (UCSTE) and the Correlated Systematic Error (CSYE).

$$(\text{TE}) = \left[(\text{UCSTE}) + (\text{CSYE})^2\right]^{0.5} \quad (6)$$

where $\text{UCSTE} = \left[\left\{\sigma_1^2\right\} + \left\{\sigma_2^2\right\}\right]$ and

$$\text{CSYE} = \left[\rho_{12}\right]\left[\sigma_1\sigma_2\right] \quad (7)$$

Hence lesser the value of ρ_{12}, the lesser is the CSYE and consequently decreases the TE in the count rates.

4. Robustness of the Analysis

According to Hadamard's inequality [11],

$$G = \det M \le \prod M_{ij} \quad (8)$$

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 positive value is zero, when ρ_{ij} is either +1 or –1. Since, MI cannot be negative, the value of either the upper or the lower limit of ρ_{ij} which maximizes G is the robust value which maximizes the MI.

5. Results

The complete covariance matrix M_C generated with the contributions due to uncorrelated and correlated errors mentioned in **Table 1** is depicted in **Table 2**. As we have to minimize the correlated systematic error, we focused our attention on the correlated non-diagonal elements in the Matrix M_C. The values of the upper and lower limits for these elements are determined by TDI and are tabulated in **Table 3** along with the corresponding values of G.

6. Discussion

Systematic errors pervade in all types of physical measurements and affected by errors due to instrumentation, environment and personnel. The best investment is therefore to spend the maximum possible effort on identification and minimization of systematic errors. According to **Table 3**, the maximum value of G is 465303 for the ideal case of $\rho_{ij} = 0$. Only the values of lower limit of matrix M_C yield the second largest value of 424657 as compared to both the upper limits and the existing element values of matrix M_C. Further, it is apparent that the value of correlation coefficient is also less for the these lower limits and consequently, the corresponding correlated systematic errors is also less according to Equation (7). Since the systematic error is reduced by the lower limits, the total error in count rate is also reduces according to Equation (6). As activity and dose are proportional to the count rate as per Equation (1), any reduction in error in the count rate is reflected in the reduced errors of dose and activity. From **Table 3**, it is evident that in using our TDI, element wise processing to minimize the systematic error is feasible by using the concept of MI where the entire structure of the covariance matrix is taken and not by the

Table 2. Covariance Matrix M_C for the ^{113}In Activation Measurement.

$$\begin{pmatrix} 34.22 & 4.7 & 7.03 & 5.0 \\ 4.7 & 13.57 & 4.7 & 4.7 \\ 7.03 & 4.7 & 34.23 & 5.0 \\ 5.0 & 4.7 & 5.0 & 28.64 \end{pmatrix}$$

Table 3. Upper and lower limits of the non-diagonal elements of the Matrix M_C of Table 2 and the corresponding values of G where G = Det. M_C.

No.	Value of M_{ij} of matrix M_C of **Table 2**	Lower limit of Mij of matrix M_C	Upper limit of Mij of matrix M_C	Value of G with Mij as in **Table 2**	Value of G with Upper limits of M_{ij}	Value of G with Lower limits of M_{ij}	Value of G by Haddamard Inequality with $\rho_{ij} = 0$
1	$M_{12} = 4.7$	–1.3	8.11				
2	$M_{13} = 7.03$	–3.61	11.47				
3	$M_{14} = 5.0$	–2.86	11.41	370401	236656	424657	465303
4	$M_{23} = 4.7$	–1.3	8.11				
5	$M_{24} = 4.7$	–3.17	8.25				
6	$M_{34} = 5.0$	–2.87	11.42				

Principal Component Analysis (PCA) and Factor analysis methods where the covariance matrix is only decorrelated and factored into dominant eigen values. The element wise processing of covariance matrix is a boon to experimentalists as it gives them enough maneuverability to improve the different factors causing systematic errors by way of improving either the quality of measurement or the associated instrumentation. Hence in our case, upper and lower limits have been given for all the correlated elements as an aid for the experimentalists to venture and such flexibility exists only by method of MI and not by PCA and other methods.

REFERENCES

[1] L. Carole, C. Claude, E. Paul, F. Nuno, B. Bernard and T. Regine, "Optimization of Injected Dose Based on Noise Equivalent Count Rates for 2- and 3-Dimensional Whole-Body PET," *Journal of Nuclear Medicine*, Vol. 43, No. 9, 2002, pp. 1268-1278.

[2] K. Weise and W. Woger, "A Bayesian Theory of Measurement Uncertainty," *Measurement Science and Technology*, Vol. 4, No. 1, 1993, pp. 1-11. doi:10.1088/0957-0233/4/1/001

[3] D. L. Smith, "Probability, Statistics and Data Uncertainties in Nuclear Science and Technology," American Nuclear Society, Inc., La Grange Park, Illinois, 1991.

[4] H. J. Kim, B. Zeeberg and R. C. Reba, "Evaluation of Reconstruction Algorithms in SPECT Neuroimaging II: Computation of Deterministic and Statistical Error Components," *Physics in Medicine and Biology*, Vol. 38, No. 7, 1993, pp. 881-895.

[5] D. J. Kadarmas, E. V. R. Di Bella, R. H. Huesman and G. T. Gullberg, "Analytical Propagation of Errors in Dynamic SPECT: Estimators, Degrading Factors, Bias and Noise," *Physics in Medicine and Biology*, Vol. 44, No. 8, 1999, p. 1997.

[6] P. Talou, *et al*., "Covariance Matrices for ENDF/B-VII^{235}, ^{238}U and ^{239}Pu Evaluated Files in the Fast Energy Range," *Proceedings of the International Conference on Nuclear Data for Science and Technology*, 22-27 April 2007, Nice, France.

[7] M. Neves, A. Kling and A. Oliveira, "Radionuclides Used for Therapy and Suggestion for New Candidates," *Journal of Radioanalytical and Nuclear Chemistry*, Vol. 266, No. 3, 2005, pp. 377-384. doi:10.1007/s10967-005-0920-5

[8] D. L. Smith, "Covariance Matrices and Applications to the Field of Nuclear Data," ANL/NDM-62, 1981.

[9] P. Meyer, "Introductory Probability and Statistical Applications," Addison-Wesley, Reading, MA, 1970.

[10] F. H. Frohner, "Evaluation of Data with Systematic Errors," *Nuclear Science and Engineering*, Vol. 145, No. 8, 2003, pp. 342-353.

[11] G. Deco and D. Obradovic, "An Information—Theoretic Approach to Neural Computing," Springer, New York, 1996.

[12] T. Cover and J. Thomas, "Elements of Information Theory," Wiley, New York, 1991.

[13] P. T. K. Kumar, "Estimation of Bounds for Monte Carlo Uncertainty Analysis," *Annals of Nuclear Energy*, Vol. 17, No. 9, 1990, pp. 483-486. doi:10.1016/0306-4549(90)90002-U

[14] P. T. Krishna Kumar, "Algorithm for Evaluation of Bounds for Covariance Based Uncertainty Analysis," *Annals of Nuclear Energy*, Vol. 18, No. 8, 1991, pp. 479-481. doi:10.1016/0306-4549(91)90091-B

