Secondary targeting EDXRF system optimized for detection of gold, silver and gadolinium nanoparticles

B Casanelli\textsuperscript{1}, R Saavedra\textsuperscript{1}, M Vásquez\textsuperscript{1} y M Santibáñez\textsuperscript{1,2}

\textsuperscript{1} Departamento de Ciencias Físicas, Universidad de la Frontera, Temuco, Chile.
\textsuperscript{2} Centro de Física e Ingeniería en Medicina (CFIM), Facultad de Ingeniería y Ciencias, Universidad de La Frontera, Temuco, Chile.

E-mail: b.casanelli01@ufromail.cl

Abstract. In this work we seek to increase the amount of X-rays photons capable of excite nanoparticles of Au, Ag and Gd from a common emission spectrum of a mini-tube of X-rays, with the purpose of optimize its detection. For this, we used the secondary target method and we investigated three targets for each element, in order to find which is the one that improves better the detection limit. A 3D model is designed to mount the system in a Cartesian geometry. It was used a CAD (computer-aided design) software to model parts and components which are necessary to locate the mini-tube and the detector. Also, Monte Carlo code (through XMIM-SIM software) was used to simulate the interactions and study the spectrum of each target and sample, and a numerical computer software to correct and interpret the data. Finally we obtained that the best targets for Au and Gd are Y and Zn, respectively, achieving improvements up to 140% in the detection limit. For Ag nanoparticles the results did not show improvements regarding the case without target.

1. Introduction

Energy Dispersive X-ray Fluorescence (EDXRF) is an effective, fast and non-destructive technique to determine trace elements in different types of samples [1–3] based on the stimulated photoelectric absorption (predominant effect for photons with energy lower than 100 keV [4]) and the spontaneous emission, that allow to identify the element through the analysis of the photons emitted when the atom returns to its ground state.

The secondary target method was described and designed in the late last century [5–9]. In this technique the primary radiation from the X-ray tube excite a target which emits a secondary radiation that is used as a source to excite the sample [10]. The intensity of the primary beam is strongly reduced by the process, but the new quasi-monochromatic spectrum can produce a great improvement of the detection limit, as demonstrated by Lindgren and Selin [11], getting an increase in the fluorescent signal and a decrease in the produced background.

Recently, different nanoparticles have been functionalized to act as tumor markers and simultaneously be applied on highly localized treatments. Gold, silver and gadolinium nanoparticles have been the focus on several studies, since they are enhancers of local dose delivery for orthovoltage radiotherapy [12–16] as well as a contrast agent with a better attenuation than the traditional compounds used [12,17]. Several EDXRF systems have been implemented to identify and quantify nanoparticles \textit{in vivo}, reaching different detection limits [18,19]. The most common
problems of studying these nanoparticles agents in vivo are: how to increase the sensitivity of the systems in order to reduce measurement times required, and how to reduce the dose of radiation given to the patient, allowing the study of different nanoparticles of interest. To increase the sensitivity in EDXRF systems is necessary increase the production of fluorescence photons exciting the sample with energies near to the absorption edge of the nanoparticles.

In this work is shown the form of optimize the primary spectrum through secondary targets, and the criteria that allow to choose the best target to excite nanoparticles of Au, Ag and Gd, reducing the background and increasing the characteristic peak of interest.

2. Method

2.1. Selection of elements and targets

The composition of the targets is directly related with the element under study, since its K\textsubscript{α} transition should have the right amount of energy to excite mainly the atom edges of the nanoparticles before the rest of the sample [10]. The emission K\textsubscript{α} had been used as a criterion for choosing the target since is the one with the highest probability to occur.

To select the targets a database was set up and programmed to compare and select the best alternatives for each element and absorption edge. The data was extracted from the National Institute of Standards and Technology (NIST) [20].

After using the algorithm, the results are studied with the purpose of selecting targets acquirable and manageable at normal conditions and discarding, for example, targets made of Xe to observe the transition K\textsubscript{α} of Ag, because its ordinary state is gaseous.

The finally selected targets are presented in table 1.

| Element | Transition | Targets          |
|---------|------------|------------------|
| Gd      | L\textsubscript{α1} and L\textsubscript{β1} | Ni, Cu and Zn    |
| Au      | L\textsubscript{α1} and L\textsubscript{β1} | Sr, Y and Zr     |
| Ag      | K\textsubscript{α1} and K\textsubscript{β1} | Sb, I and Ba     |

2.2. 3D Design

The design and construction of a 3D structure that allows mounting the tube of X-rays, the targets and the detector are necessary for a second stage of the project, in which, already selected the best targets through computer simulations, real tests are made.

The montage, shown in the figure 1-a-b, consist in a fixed part where is possible to put a mini-tube of X-rays (model M237), a changeable part in where is the carousel of targets, and the detector (model XR100SDD). In the design it is satisfied a Cartesian geometry, since this form the X-rays from the target and tube have a low probability of scattering from the sample into the detector, as proven by Standzenieks and Selin [21].

Alternatively, the changeable carousel can be replaced by a specially mount for the mini-tube (figure 1-c), and then realize EDXRF without targets, which serves to compare results.

2.3. First spectrum simulation

Next stage is know the spectrum emitted from the targets when the primary radiation interact with it. To predict it, Monte Carlo code is used through the software XMI-MSIM [22].
Figure 1. a) 3D design with carousel system. b) Travel of the beam. b-1) Primary radiation is emitted from the mini-tube. b-2) This radiation interacts with the target, and a secondary quasi-monochromatic radiation is scattered. b-3) The secondary spectrum interacts with the sample, and a third beam is produced, in which the background noise is very low and the characteristics X-rays of the element under study can be measured clearly. b-4) The final beam arrives to the detector. c) Alternative montage in which the carousel has been replaced with the mini-tube, and the EDXRF is without targets.

For the simulation was used a tube of 35 keV whit filament of W and window of Be; samples (targets) with thickness of 0.2 cm with purity of 100% and 3 cm of air on it; 3 cm sample-source distance, 3 cm sample-detector distance, 45° between sample and beam, 90° between source and detector; and Solid-State Drive (SDD) detector of Si with thickness of 0.045 cm. After simulate the nine targets, is used numerical computer software to correct the deconvoluted spectra with the SDD Efficiency and adjust it with the Lambert-Beer equation and the mass attenuation coefficient of dry air (obtained from NIST) with the purpose of find the real spectrum that comes from the target.

2.4. Second spectrum simulation
Now the spectrum of each target is loaded as primary radiation and shot on the corresponding samples. The configuration is similar to the previous one, except for the composition of the samples, which are composed of 2.5 cm of water (that simulates the human tissues), 1 cm of 1% nanoparticles solution in water (as reference layer), and 3 cm of dry air.
In the same way is simulated a spectrum without the 1% of nanoparticles in the reference layer, to get the background noise only.

3. Results
After simulating the same process described in the 2.3 and 2.4 subsections for all targets, are compared the intensity, background noise (BN) and the limit of detection (LOD) of the three targets for each element in energy intervals corresponding to transitions under study, obtaining the results shown in the tables 2, 3, and 4. Additionally, the process was simulated without targets, obtaining the results shown in the table 5. LOD improvements are shown in table 6.

For the calculus of LOD, is used the equation

$$\text{LOD} = 3 \sqrt{\frac{B}{H}}$$ (1)

where $B$ is the number of counts in background, and $H$ is the sensitivity [10,23]. To determine $H$ was used the background subtraction method, in which is subtracted the simulation without nanoparticles (background) to the simulation with nanoparticles [14,24], as shown in figure 2.
Figure 2. Spectrum of Zr for analysis of Au (note that graph (a), (b) and (c) has a logarithmic scale on the y-axis). a) The corrected unconvoluted spectrum that is emitted from the target of Zr. b) The obtained spectrum from the sample using the target. c) The obtained spectrum from the sample using the target but without nanoparticles (only background noise). d) The spectrum without background noise ((b) less (c)), in which can be see the transition $L_{\alpha 1}$ (first left large peak) and the transition $L_{\beta 1}$ (second left large peak) of the Au.

Table 2. Results for Gd.

| Target | $I_{\alpha 1}$ | $I_{\beta 1}$ | $I_{\alpha 1}$ LOD | $I_{\beta 1}$ LOD |
|--------|---------------|---------------|---------------------|---------------------|
| Ni     | 2.9308E7      | 1.6560E5      | 4.1655E-5           | 2.9256E6           |
| Cu     | **2.9337E7**  | 1.9433E5      | 4.5080E-5           | 2.0713E7           |
| Zn     | 2.8220E7      | **1.2636E5**  | **3.7789E-5**       | **2.5901E7**       |

Table 3. Results for Au.

| Target | $I_{\alpha 1}$ | $I_{\beta 1}$ | $I_{\alpha 1}$ LOD | $I_{\beta 1}$ LOD |
|--------|---------------|---------------|---------------------|---------------------|
| Sr     | 6.8937E7      | 2.6084E5      | 2.2226E-4           | 7.1574E7           |
| Y      | **7.1377E7**  | **2.0207E5**  | **1.8894E-5**       | **7.6535E7**       |
| Zr     | 5.9723E7      | 2.2063E5      | 2.3594E-5           | 6.5606E7           |

Table 4. Results for Ag.

| Target | $I_{\alpha 1}$ | $I_{\beta 1}$ | $I_{\alpha 1}$ LOD | $I_{\beta 1}$ LOD |
|--------|---------------|---------------|---------------------|---------------------|
| Sb     | **1.2916E7**  | **1.2696E6**  | **2.6171E-4**       | **8.8583E5**       |
| I      | 3.3858E6      | 6.6232E5      | 7.2110E-4           | 3.0458E5           |
| Ba     | 1.4271E6      | **5.7659E5**  | 1.5962E-3           | **1.5080E5**       |
Table 5. Results without targets.

| Element | Transition | Intensity (counts/channel) | LOQ | LOD |
|---------|------------|---------------------------|-----|-----|
| Au      | $L_{\alpha1}$: 4.09E8 | 3.99E7 4.63E-5 | 7.10E7 | 6.94E-5 |
| Ag      | $K_{\alpha1}$: 1.50E8 | 9.66E6 6.22E-5 | 1.59E7 | 9.36E-4 |
| Gd      | $L_{\alpha1}$: 1.38E8 | 1.79E7 9.16E-5 | 2.06E7 | 1.14E-4 |

Table 6. Detection limit improvements.

| Element | Transition | Target | Intensity (counts/channel) | Improvement (%) |
|---------|------------|--------|---------------------------|-----------------|
| Au      | $L_{\alpha1}$ | Y    | 4.63E-5 1.89E-5 | 144.98          |
| L$_{\beta1}$ | 6.94E-5 3.07E-5 | 126.06          |
| Ag      | $K_{\alpha1}$ | Sb    | 9.36E-4 4.89E-3 | -80.86          |
| Gd      | $L_{\alpha1}$ | Zn    | 9.16E-5 3.78E-5 | 142.33          |
| L$_{\beta1}$ | 1.14E-4 5.81E-5 | 96.21          |

As expected, the intensity of the primary beam was reduced, as shown in figure 3.

Figure 3. Spectra for Au with and without Y target (log scale on the y-axis).
4. Conclusions
It was possible to design an EDXRF system consisting of a X-rays mini-tube, an SDD detector and a carousel of secondary targets, in a Cartesian geometry which optimizes the signal-to-noise ratio. Likewise, a secondary targeting method was optimized, re-obtaining results shown in the literature about the background reduction and the LOD improvement. Also, we detected some uncertainty in the simulated background, which can introduce errors in the background subtraction method, as suggested by Wu et. al. [24]. Finally, and based on the results exposed in tables 2-6, we conclude that the best targets for Gd and Au are Zn and Y, respectively, in which the LOD can be improved up to 140%, while for Ag the LOD has been worsened approximately between a 40% and 80%. Therefore, in this work, no target for Ag present improvements regarding the case without targets. However, future studies incorporating administered dose criteria could improve these results.

5. Acknowledgments
This project is financed by CONICYT through the project FONDECYT N°11150673 and by the Direction of Investigation of the Universidad de La Frontera DI 16-2016.

6. References
[1] Geraki K, Farquharson M J and Bradley D A 2002 Physics in Medicine and Biology 47 2327
[2] Longoni A, Fiorini C, Leutenegger P, Sciuti S, Fronerotta G, Strüder L and Lechner P 1998 Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment 409 407 – 409
[3] Khuder A, Bakir M, Karjou J and Sawan M 2007 Journal of Radioanalytical and Nuclear Chemistry 273 435–442
[4] Sethi A 2006 X-Rays: Interaction with Matter (John Wiley & Sons, Inc.)
[5] Standzenieks P and Selin E 1979 Nuclear Instruments and Methods 165 63 – 65
[6] Spatz R and Lieser K H 1979 X-Ray Spectrometry 8 110–113
[7] Cristensen L, H, Rasmussen S E, Pind N and Henrikson K 1980 Analytica Chimica Acta 116 7–17
[8] Porter D E 1973 X-Ray Spectrometry 2 85–89
[9] Rao D V, Cesareo R and Gigante G E 1993 X-Ray Spectrometry 22 406–409
[10] Lindgren E S 2006 Energy Dispersive, X-Ray Fluorescence Analysis (John Wiley & Sons, Ltd)
[11] Ida H and Kawai J 2005 Spectrochimica Acta Part B: Atomic Spectroscopy 60 89 – 93
[12] Hainfeld J F, Smilowitz H M, O’Connor M J, Dilmanian F A and Slatkin D N 2013 Nanomedicine 8 1601–1609
[13] Hainfeld J F, Slatkin D N and Smilowitz H M 2004 Physics in Medicine and Biology 49 N309–N315
[14] Mattea F, Vedelago J, Malano F, Gomez C, Strumia M C and Valente M 2017 Radiation Physics and Chemistry 130 442–450
[15] Ngwa W, Kumar R, Sridhar S, Korideck H, Zygnanski P, Cormack R A, Berbeco R and Makrigiorgos G M 2014 Nanomedicine 9 1063–1082
[16] Zhang D G, Feygelman V, Moros E G, Latifi K and Zhang G G 2014 PLoS ONE 9 e109389
[17] Hainfeld J F, Slatkin D N, Focella T M and Smilowitz H M 2006 The British Journal of Radiology 79 248–253
[18] Figueroa R, Santibañez M, Malano F and Valente M 2015 Radiation Physics and Chemistry 117 198–202
[19] Santibañez M, Vásquez M, Figueroa R and Valente M 2016 Radiation Physics and Chemistry 122 28–34
[20] NIST National institute of standards and technology URL https://www.nist.gov
[21] Standzenieks P and Selin E 1979 Nuclear Instruments and Methods 165 63–65
[22] Schoonjans T Xmi-msim URL https://github.com/tschoonj/xmimsim
[23] Gilfrich J V and Birk L S 1984 Analytical Chemistry 56 77–79
[24] Wu D, Li Y, Wong M D and Liu H 2013 Medical Physics 40 051901