A simulation platform for optimising X-ray imaging of Gold Nanoparticles

Rouchota Maritina¹, Loudos George², Papadimitroulas Panagiotis³, Kagadis George¹

¹University of Patras, Rion, Patras, Greece
²Technological Educational Institute of Athens, Ag. Spiridonos 28, Egaleo, Athens, Greece
³Bioemission Technology Solutions, Alexandras 116, Athens, Greece

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Motivation & Purpose

Being able to visualize GNPs through X-Ray/CT imaging will provide:

- A **contrast agent** with better properties than iodine for the visualization of the circulatory system

- The radiolabeling process of the NPs – needed to follow the **targeted radiopharmaceutical root** - may be accurate but it might modify their nature and properties, whereas x-rays do not add to complexity or **modification**

- A big number of animals is needed to test appropriate concentration of GNPs that will provide adequate contrast for each x-ray system
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This project aims to:

- Develop a model to perform x-ray imaging studies on a simulation level
- Validate the model
- Provide a tool to optimize x-ray imaging protocols
- Provide a tool to allow reduction in the number of animals needed for an in vivo x-ray GNPs imaging study
- Confirm results in vivo
Theoretical Calculations on the attenuation of the NP solutions

- Concentrations PW (%) were used together with the solutions’ densities
- Example for iron oxide calculations – 100mg/ml:

\[
\rho \text{ (Fe}_3\text{O}_4 \text{ solution)} = \text{Conc PW } (\text{Fe}_3\text{O}_4 \text{, } \%) \cdot \rho (\text{Fe}_3\text{O}_4) \\
+ [1 - \text{Conc PW } (\text{Fe}_3\text{O}_4 \text{, } %)] \\
\cdot \rho (\text{Water})
\]

\[
(\mu/\rho)_{\text{MIX}} \text{ for all energies from NIST (e.g. for 100mg/ml)}
\]

\[
\mu_{\text{MIX}} = (\mu/\rho)_{\text{MIX}} \cdot \rho (\text{Fe}_3\text{O}_4 \text{ solution})
\]
X-Ray Attenuation – Theoretical Evaluation

Comparison - 100mg substance/ml - Linear Attenuation Coefficient - Iodine, Gold, Fe3O4

Cortical Bone
Soft Tissue
Au Solution - 100mg/ml
Iodine Solution - 100mg/ml
Fe3O4 solution - 100mg/ml

E (MeV)

μ (1/cm)
An example from literature - J. Hainfeld et al (2006)

X-ray image of mouse leg before injection –
tumour and increased vascularity

2 min after tail vein injection of gold NPs
(AuroVist 1.9nm)

2 min after tail vein injection of equal weight iodine contrast agent
(Omnipaque)
The platform
Simulation of the system set up

The CMOS detector of the x-ray system

Simulated in vivo experiment
Simulation of the system set up

Simulation of the NPs solutions

The CMOS detector of the x-ray system

Simulated in vivo experiment
Simulation of the system set up

The CMOS detector of the x-ray system

Simulated in vivo experiment

Simulation of the NPs solutions

Import of the NPs bio kinetics in MOBY

http://dx.doi.org/10.1371/journal.pone.0020594
Simulation of the system set up

Simulation of the NPs solutions

Import of the NPs bio kinetics in MOBY

Run the simulation and export x-ray images

http://dx.doi.org/10.1371/journal.pone.0020594
Simulation of the system set up

• Solutions of different concentrations are placed into identical holes in a PMMA phantom
• Solutions are also injected intravenously in mice
• Irradiations are performed with an x-ray beam of 35 kVp, 0.5 mA for 0.1 sec exposure time
• The solutions and phantom are simulated to match the experimental conditions
• Spectrum and number of primary photons are exported through SpekCalc for any x-ray source
• MOBY computational mouse phantom
Validation of system simulation – Iodine solutions

- Validation of the beam spectrum through HVL measurements
- Validation of the whole system set up through imaging commercial iodine solutions
Validation of system simulation - Iodine Attenuation

GVs wrt Iodine Concentration

Concentration (mgI/ml) vs GVs ± SD
The simulation is based on 2 main points:

- In CT/X-ray the direct visualization of NPs is not possible, **density variations are visible** (LeBrun, 2016)
- The geometry and **size of the NPs do not affect the image** contrast (Nohyun Lee, 2013)
Simulation of NPs solutions – Definition in GATE

❖ The simulation is based on 2 main points:
  • In CT/X-ray the direct visualization of NPs is not possible, density variations are visible (LeBrun, 2016)
  • The geometry and size of the NPs do not affect the image contrast (Nohyun Lee, 2013)

❖ Definition of a compound/mixture in GATE:
1. Definition of any non-existing material (e.g. Fe$_3$O$_4$) – its density, number of elements, state, name and chemical composition
2. Name and number of all present elements/materials and their per weight (PW%) concentration in the mixture
3. Name and density of compound/mixture

\[
\rho (Fe_3O_4 \text{ Solution}) = \text{Conc } PW (Fe_3O_4, \%) \times \rho (Fe_3O_4) + [1 - \text{Conc } PW (Fe_3O_4, \%)] \times \rho (\text{Water})
\]

Fe$_3$O$_4$:
- d=5.17 g/cm$^3$; n=2;
- state=Solid
  +el: name=Iron; n=3
  +el: name=Oxygen; n=4

Solution Fe$_3$O$_4$ 50mg/ml:
- d=1.1986 g/cm$^3$; n=2;
  +mat: name=Water; f=0.952
  +mat: name=Fe$_3$O$_4$; f=0.048
Validation of NPs Attenuation

Simulation

Experiment
Validation of NPs Attenuation

Fe$_3$O$_4$ GVs - Experimental vs Simulated Data

Concentration (mg/ml)

GV±SD

Experimental vs Simulated Data

Bone

Soft Tissue

Experimental

Simulated
Import of GNPs bio distribution in MOBY

μg Au/g tissue or % of given dose/tissue

Change tissue properties accordingly

Modified tissues to account for the GNPs

Liver with 20mg GNPs:
  d=1.2106 g/cm³; n=2;  
  +mat: name=Liver; f=0.99174
  +el: name=Gold; f=0.00826

Blood with 10mg GNPs:
  d=1.1749 g/cm³; n=2;  
  +mat: name=Blood; f=0.9937
  +el: name=Gold; f=0.0063

Spleen with 0.15mg GNPs:
  d=1.077 g/cm³; n=2;  
  +mat: name=Spleen; f=0.99905
  +el: name=Gold; f=0.00095
Export of x-ray images
1. Full Accumulation in the liver

- No NPs
- 5mgAu in liver 0.2% PW
- 10mgAu in liver 0.4% PW
- 20mgAu in liver 0.8% PW
- 40mgAu in liver 1.64% PW
1. Full Accumulation in the liver

Detectability of structures can be measured through the Contrast to Noise Ratio of the structure.

\[ CNR = \frac{GV_{str} - GV_{bkg}}{SD_{bkg}} \]
2. Full Accumulation in the bloodstream

- No veins in MOBY mouse phantom – blood only visible in the heart
- Typical mouse blood volume taken into account for PW concentration
Healthy female albino mice of >6 weeks age
About 15 g body mass
Anesthetized via isoflurane
Injected with 100μl of PEGylated nanoshells suspended in 0.9% NaCl via tail vein
Dose injected: 10μgAu/g of mice weight (0.15mgAu/mouse)
Concentrations for 4hrs post administration

Table 6  Bio-distribution of PEG-coated 110/10 nm silica/gold nanoshells among mice organs at 4 h to 28 days after intravenous injection at a dose of 10 μg g⁻¹ animal. Adapted from ref. 81

<table>
<thead>
<tr>
<th>Time</th>
<th>Concentration of Au (μg g⁻¹ organ)</th>
<th>Blood</th>
<th>Liver</th>
<th>Kidney</th>
<th>Spleen</th>
<th>Lung</th>
<th>Muscle</th>
<th>Brain</th>
<th>Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>0.0009</td>
<td>0.0007</td>
<td>0.0011</td>
<td>0.0174</td>
<td>0.0071</td>
<td>0.0230</td>
<td>0.0011</td>
<td>0.0049</td>
</tr>
<tr>
<td>4 h</td>
<td></td>
<td>313.7</td>
<td>103.8</td>
<td>52.22</td>
<td>952.2</td>
<td>88.58</td>
<td>3.796</td>
<td>7.187</td>
<td>9.531</td>
</tr>
<tr>
<td>1 day</td>
<td></td>
<td>29.17</td>
<td>311.8</td>
<td>27.61</td>
<td>1890</td>
<td>12.71</td>
<td>1.060</td>
<td>0.547</td>
<td>5.912</td>
</tr>
<tr>
<td>7 days</td>
<td></td>
<td>0.0187</td>
<td>313.4</td>
<td>21.49</td>
<td>2863</td>
<td>6.066</td>
<td>1.916</td>
<td>0.0684</td>
<td>7.319</td>
</tr>
<tr>
<td>14 days</td>
<td></td>
<td>0.0290</td>
<td>324.5</td>
<td>19.30</td>
<td>2039</td>
<td>3.738</td>
<td>0.779</td>
<td>0.0310</td>
<td>5.365</td>
</tr>
<tr>
<td>21 days</td>
<td></td>
<td>0.0430</td>
<td>252.0</td>
<td>23.53</td>
<td>1738</td>
<td>4.748</td>
<td>1.593</td>
<td>0.1243</td>
<td>8.333</td>
</tr>
<tr>
<td>28 days</td>
<td></td>
<td>0.0567</td>
<td>227.2</td>
<td>24.70</td>
<td>1703</td>
<td>3.781</td>
<td>1.023</td>
<td>0.0293</td>
<td>6.875</td>
</tr>
</tbody>
</table>

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No NPs

Heart: 0.0314% PW
Liver: 0.104% PW
Spleen: 0.095% PW
all other organs < 0.01% PW
Healthy female albino mice of >6 weeks age
About 15 g body mass
Anesthetised via isoflurane
Injected with 100μl of PEGylated nanoshells suspended in 0.9% NaCl via tail vein
Dose injected: 10μgAu/g of mice weight (0.15mgAu/mouse)
Concentrations for 7 days post administration


No NPs

Liver: 0.03% PW
Spleen: 0.286% PW
all other organs < 0.01% PW

Liver: 0.03% PW
Spleen: 0.286% PW
all other organs < 0.01% PW

PW Au concentration (%)

CNR (%)

0 0.05 0.1 0.15 0.2 0.25 0.3 0.35

0 1 2 3 4 5 6 7 8

Liver: 0.03% PW
Spleen: 0.286% PW
all other organs < 0.01% PW

PW Au concentration (%)

CNR (%)
Balb/C mice injected subcutaneously with EMT-6 syngeneic mammary carcinoma cells
Injected with 1.9nm GNPs (Nanoprobes) – concentration of
Dosage: 1.35gAu/kg (appr. 27mg Au for 20g mouse) – in 0.01ml/g mouse

Table 1. Biodistribution of gold 5 min post i.v. injection of 1.35 g Au/kg.

<table>
<thead>
<tr>
<th></th>
<th>% injected dose/g</th>
<th>Tumour-to-tissue ratio</th>
<th>Tumour periphery-to-tissue ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour</td>
<td>4.9 ± 0.6</td>
<td>1.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Tumour periphery</td>
<td>8.9 ± 3.2</td>
<td>0.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.4 ± 0.1</td>
<td>3.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Liver</td>
<td>2.8 ± 0.1</td>
<td>1.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Kidney</td>
<td>132.0 ± 2.7</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Blood</td>
<td>18.6 ± 3.7</td>
<td>0.3</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Liver: 0.076% PW
Kidney: 3.57% PW
Heart: 0.5% PW
all other organs < 0.01% PW
A simulation platform for x-ray imaging studies with NPs has been developed and validated.

Both phantom and in vivo imaging studies performed.

Possibility of other NPs solutions as well (e.g. magnetic NPs).

Gives the possibility to optimize imaging protocols and thus reduce the number of animals needed for an in vivo x-ray imaging study with NPs.
Overview and Next Steps

❖ A simulation platform for x-ray imaging studies with NPs has been developed and validated
❖ Both phantom and in vivo imaging studies performed
❖ Possibility of other NPs solutions (e.g. magnetic NPs)
❖ Possibility to optimize imaging protocols and reduce the number of animals needed for in vivo NPs imaging study

NEXT STEP:

❖ Expand the platform to simulate tomographic x-ray imaging too (Computed Tomography) and validate it through Hus
❖ Use it to explore advanced imaging techniques (e.g. Dual Energy)