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Development of a bio-mathematical model in rats to describe clearance, retention and translocation of inhaled nano particles throughout the body.

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Abstract. Studies of the translocation of inhaled nanoparticles from rodent lungs to different target organs provide data to model the inhalation and translocation of nanoparticles. A compartmental model was developed based on biological information about the major organs and how they interrelate. This model, which is quantified by a set of differential equations 'describing' the passage of nanoparticles through the body, gives estimates of the particle mass present in each organ. Optimal parameter estimates were found by minimising the model mean squared error. Data from two different studies in rats (one endotracheal instillation and one inhalation exposure) were used to calibrate the model. Most of the nanoparticle mass remained in the lungs. The overall fit of the model to the total measured particle mass in the body was very good for both studies (R^2=0.98-0.99), although different parameter estimates were sometimes required to fit the study-specific data. The model fit to the measured particle mass by organ was very good for the lungs, brain, and spleen (R^2=0.81-0.98) in both studies, but not as good for the liver and kidney (R^2=0.32-0.53). While this model describes the retention and translocation of nanoparticles from the lungs reasonably well, further model evaluation and validation is needed using additional data.

1. Introduction

There is a need to quantify the distribution of internalised particles in the body for hazard and risk assessment. Traditionally, the quantification process is done by mathematical modelling. For micron size particles, the route of exposure is usually via inhalation and the target organ is the lungs. Models have been developed to describe the exposure-dose-response relationship for a range of particles, for example the paper by Tran, Kuempel and Castranova [1]. Nanoparticle (NP), exposure can be via many routes (inhalation, ingestion and dermal) and the target organs can be beyond the portal of entry. We introduce a new mathematical model describing the exposure-dose-response relationship for internalised NP, with the exposure dose part of the model being described here and the extension to include dose-response presented in a later paper.

2. Model Development

The model to be used is an extension to an earlier model describing the retention and clearance of particles in the lungs [1] and [2]. The original model consists of compartments representing the mass

of particles (i) on the alveolar surface; (ii) inside macrophages; (iii) in the interstitial space; (iv) in the lymph nodes; (v) in the olfactory; (vi) in the upper airways region.

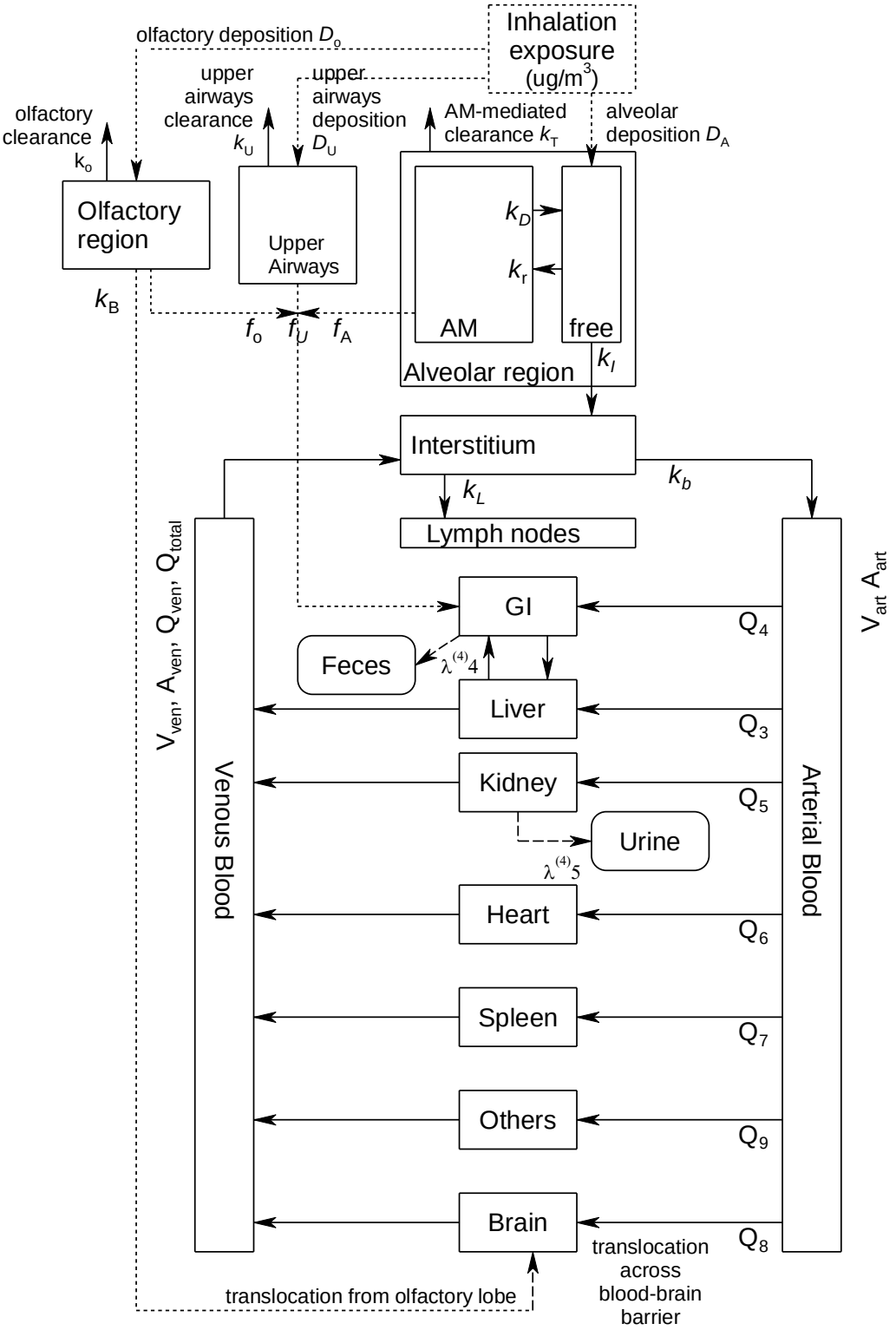

Figure 1: The model describing the kinetics of inhaled nanoparticles.

It is assumed that NP can move into the extra-pulmonary compartments because of their size. The model is therefore extended by adding the translocation route from the interstitium to the venous blood and by adding a model of the circulation of blood around the major organs in the body (Figure 1). The major organs considered here are brain, heart, liver, kidney, spleen, gastrointestinal tract and 'other' which represents other tissue sites not specifically named in the model.

First-order kinetic processes were assumed to dictate the retention and clearance of NP from each of these organ tissues. Each organ was represented by a compartment which contains sub-compartments for the tissue, capillary and sequestration as outlined in Figure 2.

Using a series of differential equations to represent the movement of NP throughout the body the mass of NP in each organ was estimated, given information about the organ characteristics and experimental conditions. The details of the differential equations and the estimates of the parameters obtained through the model calibration will be reported in a later paper.

The model requires information regarding the volume of the organ tissue, the volume of the organ capillary and the blood flow rate to each organ. The required information was collected from a number of papers; [3], [4], [5], [6], [7].

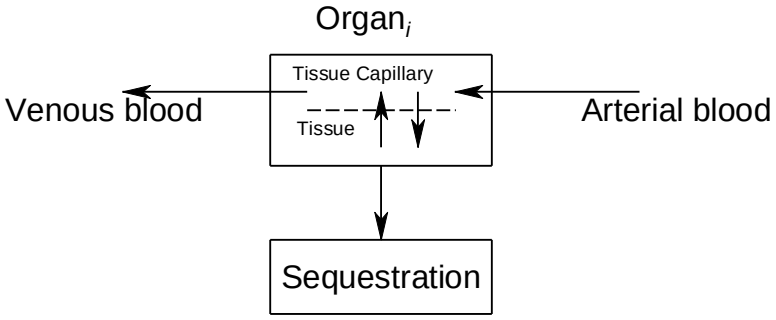

Figure 2: Extra pulmonary organ retention and excretion

3. Methods for Model calibration

The first step was to obtain data with which to compare the results of our model and therefore enable model calibration. The data was extracted by examining plots from papers published on translocation of ultrafine particles and confirmed through communication with the authors of the papers themselves. The model calibration was based on data from two different experiments.

3.1. Data

The first paper from which data was obtained was Semmler *et al.* [8]. This paper was chosen for two reasons: (1) There was data available for the translocation of iridium NPs to a number of organs; lung, brain, spleen, liver and kidney, and (2) The translocation was measured up until 6 months after the initial exposure.

The data were initially obtained from each paper but the actual data were later provided by the authors. The data obtained from Semmler *et al.* [8] were transformed from the fraction of the initial dose given in the paper to the estimated mass of NPs. The initial lung burden was given in the paper as 11.21μg, but this was later modified to 3.5μg [10]. The authors confirmed that the new lung burden was the more accurate one.

As this study used an endotracheal route of exposure there was no olfactory deposition and therefore a number of the parameters in our model did not need to be estimated (i.e. f_o, k_o and k_B) as there were no particles moving to the other organs from the olfactory region.

The second set of data was obtained from a study by Takenaka *et al.* [9]. This study differed from the first in particle type (silver), route of exposure (whole body inhalation) and length of follow-up (Table 1). We used the same model as for the first paper with changes to some of the parameters. On examining the data it appeared that the inhaled silver NPs were deposited in the nasal and upper airway regions of the respiratory tract, but not in the alveolar region of the lung; for this reason the parameters for the alveolar region were set to be zero in this model.

A program, Mutiple-Path Particle Dosimetry (MPPD) [11], was used to determine the deposition fractions in the olfactory, upper airways and alveolar regions. This program is designed to calculate deposition and clearance of aerosols in rats and humans given information about the particle characteristics, exposure conditions, and breathing patterns. The program is free and can be downloaded from www.thehamner.org/technology-and-development/technology-transfer/index.html

Table 1: The experimental conditions of both of the studies used for model calibration.

	Semmler	Takenaka
Particle Type	Iridium	Silver
Aerosol Concentration	200 μg / m^3	133 μg / m^3
Particle Diameter	15 to 20 nm	17.1 nm (MMD), 1.38 (GSD)
Duration of exposure	1.5 hours	6 hours
Breathing Frequency	45 min^{-1}	Not Given
Inspiratory Fraction	75 – 80 %	Not Given
Breathing Scenario	Endotracheal	Inhalation
Length of Follow-up	6 months	7 days

3.2. Obtaining optimal estimates of the parameters

Using sensible initial parameter estimates a constrained minimisation of the sum of squares was carried out to obtain the best parameter estimates possible, using MATLAB vs 7.0.

A vector of the list of all of the actual data obtained from the papers is denoted as y. The mass of particles estimated by the model to be in each organ, at each time point for which there are actual data is then denoted by x. The parameters to be estimated can be denoted by the vector θ, where $\theta = [\theta_1, \ldots, \theta_n]$. We then carried out a search over many possible estimates of the parameters and choose the vector θ which minimises the mean square error (MSE). Where the MSE is a measure of the amount by which the estimated, y_i, mass of NPs differs from the true mass of NPs, x_i, and is calculated by:

$$\sum_i (x_i - y_i)^2 .$$

The R^2 value was calculated as a measure of how good a fit to the model gave to the actual data. This was calculated by:

$$R^2 = \frac{\left[\sum_i (x_i y_i) - \left(\sum_i x_i \sum_i y_i\right)/n\right]^2}{\left[((\sum_i x^2 - (\sum_i x)^2/n)(\sum_i y^2 - (\sum_i y)^2/n))^{1/2}\right]^2}$$

The mean square error (MSE) is a measure of the amount by which the estimated, y_i, mass of NPs differs from the true mass of NPs, x_i, and is calculated by:

$$\frac{1}{n}\sum_i (x_i - y_i)^2$$

4. Results

4.1. Model for Semmler *et al.*

After calibration the mass of NP estimated by the model was very close to the actual mass but the estimates for the other organs were not. This is because the majority of the deposited particles were in the lung and the minimisation appears to 'concentrate' on minimising this difference.

Fixing the lung parameters and re-running the model gave a better fit for all of the organs, but with a slightly poorer fit for the lung than in the initial run. Adjusting the model, by changing the translocation rate to the lymph nodes slightly, gave a compromise between the two. Transforming the estimated mass to fractions of the initial lung burden enabled the standard errors of the original data to be shown. Figures 3 - 5 show the estimated fraction of NP in each organ from the resulting model and the actual fractions given in the paper, along with their standard errors.

Table 2 shows the R^2 values for each organ. The overall R^2 of 0.99 suggests that the data obtained from the final model is a very good fit to the data. Considering the organs separately however, there is a suggestion that the model does not fit the data very well for both the kidney and the liver.

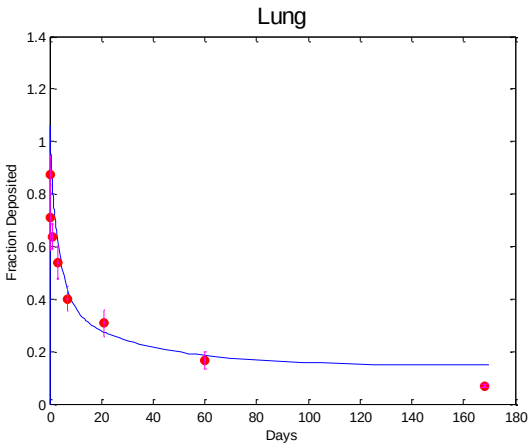

Figure 3: The fraction deposited in the lung estimated by the final model as well as the actual data points and their error bars.

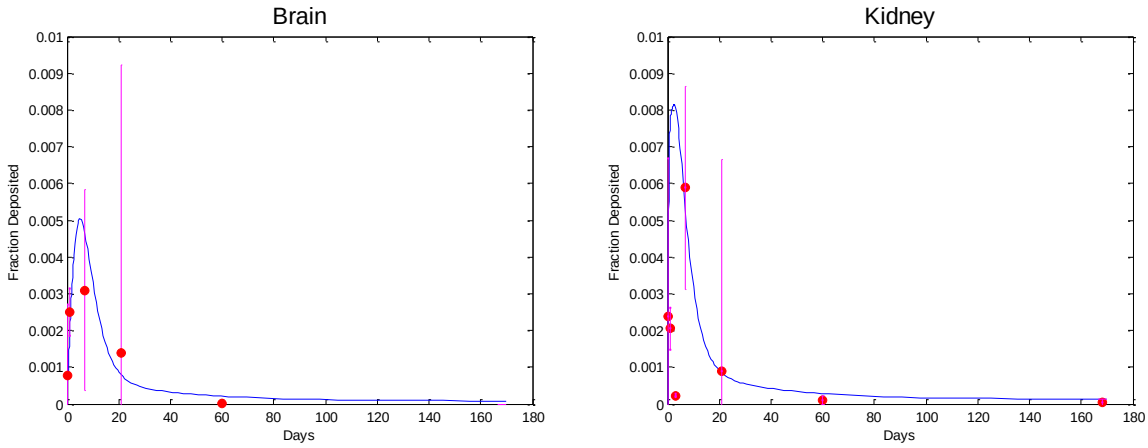

Figure 4: The fraction deposited in the brain, left, and kidney, right, estimated by the final model as well as the actual data points and their error bars.

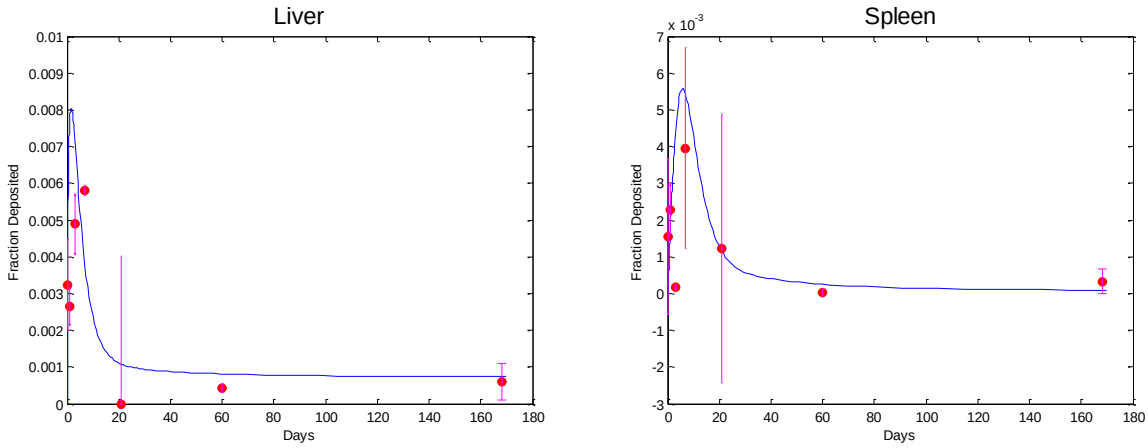

Figure 5: The fraction deposited in the liver, left, and spleen, right, estimated by the final model as well as the actual data points and their error bars.

Table 2: The R^2 and mean square error (MSE) values obtained when comparing the fitted data to the actual data for each organ separately and for the body as a whole.

	R^2	MSE
Brain	0.81	0.0000055
Kidney	0.43	0.000031
Liver	0.32	0.000038
Spleen	0.85	0.0000075
Lung	0.98	0.34
Overall	0.99	0.067

4.2. Model for Takenaka e*t al.*

There were a few differences in how we classified the compartments to match the data supplied by Takenaka *et al.* [9]. The lymph nodes were no longer included in the total lung as data were available to enable a direct comparison to these compartments separately. The brain compartment was adjusted

so that the nasal (or olfactory) compartment was no longer included in the brain as data were also available for these separate compartments. Figures 6 to 9 illustrate the mass of nanoparticles estimated to be in each organ, by our model, and the actual mass measured in the study.

Table 3 illustrates the MSE values for the overall model and for each organ individually. For a number of the organs the R^2 value could not be calculated as there were only two data points. The overall model was again a good fit to the data with an overall, $R^2 = 0.98$. Of the 2 organs for which there were more than two data points one was a good fit to the data, lung with $R^2 = 0.98$, and one did not fit as well, liver with $R^2 = 0.53$.

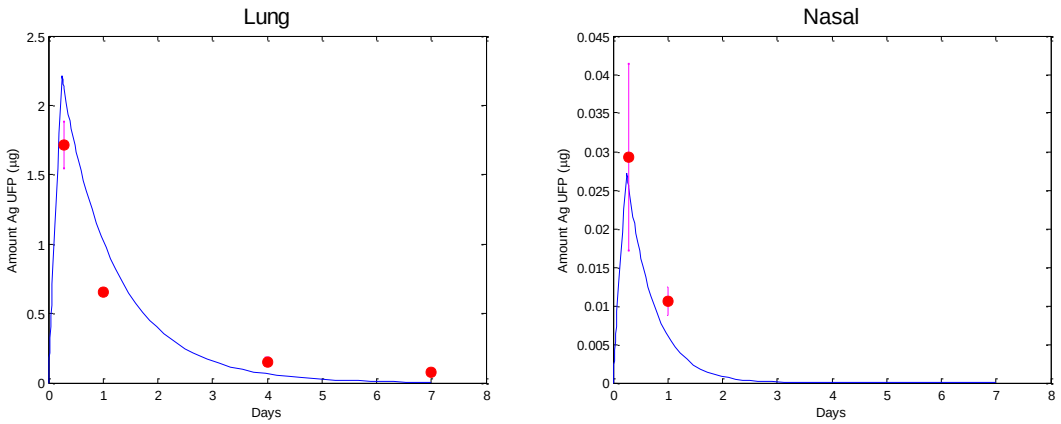

Figure 6: The mass deposited obtained using the parameter estimates for the lung, left, and nasal, right. The points are the actual data obtained from Takenaka *et al.*

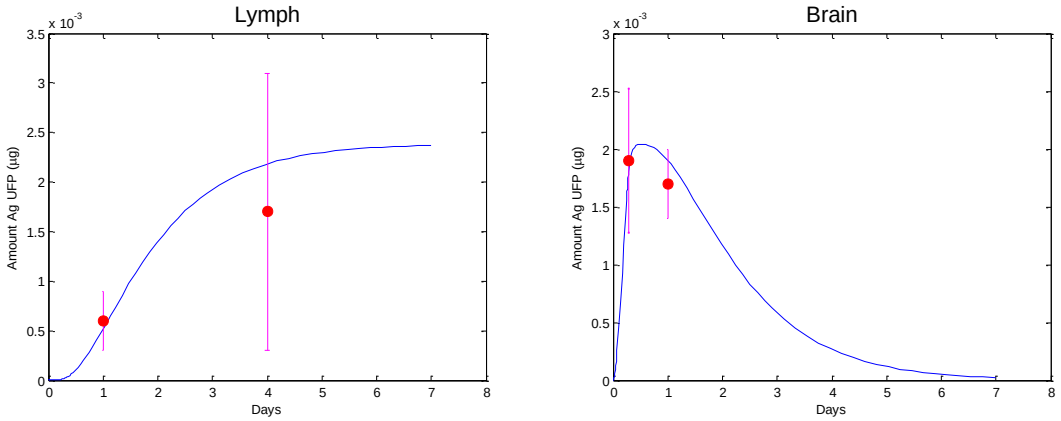

Figure 7: The mass deposited obtained using the parameter estimates for the lymph nodes, left, and brain, right. The points are the actual data obtained from Takenaka *et al.*

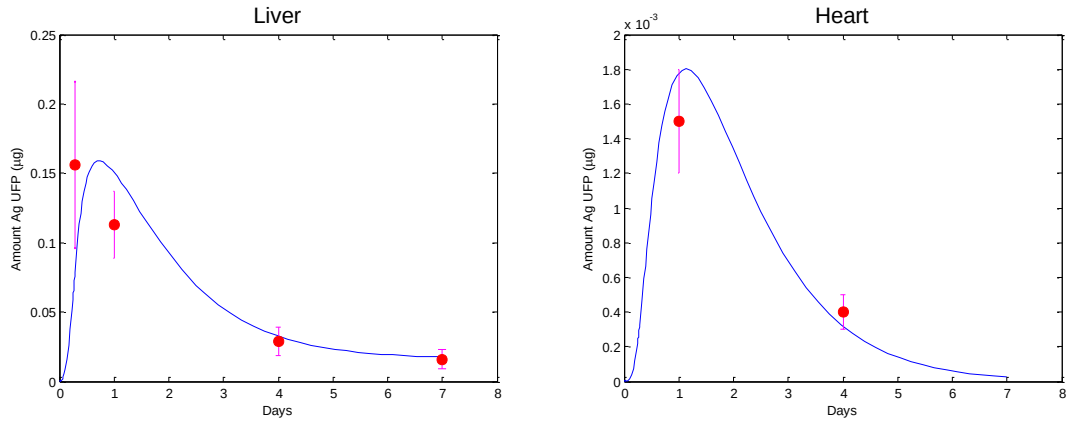

Figure 8: The mass deposited obtained using the parameter estimates for the liver, left, and heart, right. The points are the actual data obtained from Takenaka *et al.*

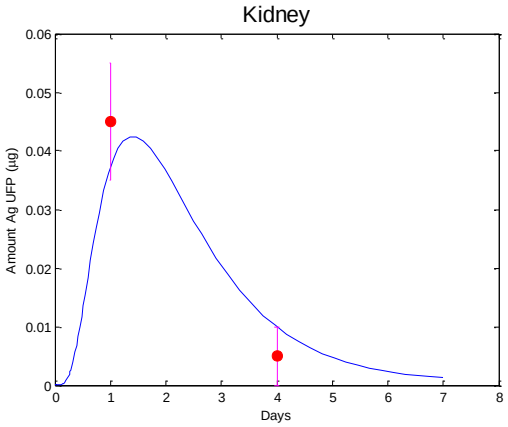

Figure 9: The mass deposited obtained using the parameter estimates in for the kidney. The points are the actual data obtained from Takenaka *et al.*

Table 3: The R^2 and mean square error (MSE) values obtained when comparing the fitted data to the actual data for each organ separately and for the body as a whole.

	R^2	MSE
Brain		0.000020
Nasal Olfactory		0.000040
Lymph		0.00000012
Kidney		0.000042
Liver	0.53	0.0017
Heart		0.000000042
Lung	0.98	0.073
Overall	0.98	0.017

5. Discussion

In this paper, we have described a biologically-based model of nanoparticle clearance from the lungs and translocation to the major organs of the body over time. Model calibration showed that the optimal parameter estimates may be dependent on the route of exposure and the physical-chemical characteristics of the particles.

The parameters associated with the compartments through which the NPs were introduced to the body (olfactory, alveolar and upper airways) are dependent on the method of exposure; olfactory deposition was eliminated when endotracheal instillation was used, while exposure through inhalation eliminated any alveolar deposition. The initial differences in the exposure methods resulted in quite different optimal parameter estimates, despite the fact that the measured mass of NPs in certain organs was quite similar.

It was hoped that the data from the second experiment could have been used to validate the model built using the first data set. However, due to the differences in the experimental conditions, particularly the exposure methods, this was not possible. The next step would ideally be to validate the model using data from further experiments. The main limitation for doing this is that there are rarely two experiments in the published literature with the same conditions. Some attempt is being made to validate the model, however, and will be reported in a later paper.

As noted earlier the mathematical detail of the model and the resulting parameter estimates will be reported at a later date along with an extension of the model to include dose-response estimation.

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