Development of a Bolus Injection System for regional deposition studies of nanoparticles in the human respiratory system

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Abstract. This study presents the work carried out in developing a precision bolus injection system in order to understand the regional deposition of nanoparticles (NP) in human lung. A real-time control system has been developed that is capable of storing graphite NP, assessing human breathing pattern and delivering a bolus of the stored NP at a pre-determined instance of the inhalation phase of breathing. This will form the basis for further development of a system to deliver radioactive nanoparticles to enable 3-dimensional lung imaging using techniques such as positron emission tomography (PET). The system may then be used to better understand the actual regional deposition in human lung, which could validate or challenge the current computational lung models such as that published by the International Commission for Radiation Protection (ICRP-1994). A dose related response to inhaled PM can possibly be shown, which can be used to review the current workplace exposure limits (WELs).

1. Introduction
Particulate matter (PM) deposited in human lung are known to cause adverse health effects both in normal subjects and in patients with chronic obstructive pulmonary disease (COPD), asthma and cardiovascular diseases. PM is composed of both fine (micrometer) and ultrafine (or nano-particles, NP) particles and it is hypothesised that the NP may cause greater health hazards than their larger counterparts [1].

The advent of nano-technology means that engineered nano-particles are now being produced in large amounts which might represent a risk to the workforces involved. At present there is no clear idea of how these might have an impact on the health and therefore there are no current Workplace Exposure Limits (WEL) for nano-materials. Also, the amount of exposure in an individual is also associated with rate of respiration i.e., the physical effort, and hence the dose. Hence, the system measuring the impact should take the inhalation patterns and lung volume into consideration.

In this study a method to achieve a controlled delivery of bolus of graphite NP into the lungs, at different instances in the inhalation cycle was developed. The prototype bolus injection system
comprising of an electro-mechanical system and a real-time software control system was used to control the entire operation of bolus delivery.

2. Background
Some of the previous studies are based on the hypothesis that different size fractions of the PM, preferentially deposit in different regions of lung [2]. There is some data available on the mechanism of deposition; however, they mostly deal either with lung models [3], computer simulations [4] or mathematical calculations [2, 5]. The (1994) ICRP model of lung deposition [6], shown below in figure 1, is primarily based on the principles of computational fluid dynamics. The accuracy of such a model has been questioned due to inaccurate assessment of Brownian motions with respect to particle deposition [7, page 26].

![ICRP model for lung deposition of particles (1994)](image)

Hence, to understand the exact method of NP deposition and their distribution within the lung it is necessary to carry out the study in vivo. This involves:
- A mechanism for storage and controlled delivery of recently-generated NP to lung.
- Ability to select different PM size distributions to study preferential deposition.
- Identifying the areas where the NP actually deposited by means of imaging such as Positron Emission Tomography (PET).

This study partially fulfils the 1st and to a lesser extent 2nd requirement and will form the basis for development of 3rd stage which will involve the design of a clinical system for controlled delivery of radioactive labelled NP (such as Technegas) required for PET lung imaging.

3. System Design and Implementation
The first prototype system has been developed with the general assumption that the particles inhaled at the beginning of inhalation has a greater tendency to deposit in distal lung (e.g. alveolar region) and the ones inhaled towards the end of inhalation deposit more proximally (e.g. tracheo-bronchial region).

So, if short pulses of bolus were to be injected at a given point in the inhalation cycles as in figure 2, then cumulative accumulation of particles in a specific region could be achieved.

As shown in the ICRP model (figure 1), there is also the tendency for size dependant regional deposition. This can now be observed by using different size fractions, introduced as short pulses to compare the size dependant deposition at a specified target site. In this way, the need for continuous inhalation of large doses to study regional deposition may be avoided.
3.1. System Requirements
To achieve the above objectives the first prototype system was designed to comply with the following main end-user requirements [8].

1. Breath activation – the system should be able to detect the start of breathing cycle and activate the data acquisition and the control system.
2. Breath Pattern detection – Examine breath pattern histograms and identify the maximum (Vmax) and minimum (Vmin) lung volumes on the basis of a prescribed quantitative method, such as moving averages.
3. Programmable bolus size – Once programmed, the system should determine the parameters necessary to deliver the bolus as in equation (1) below.
4. Deliver a bolus of NP aerosol at a selected point of the inhalation cycle.
5. Programmable site of deposition in the lung as determined by the time of release.

The desired deposited dose \( W \) of a bolus of PM may be written as:

\[
W_{(\text{deposited})} = \Delta w_{(T^0, t, p)} \times D_f \times \Delta t \times n \tag{1}
\]

Where, \( \Delta w_{(T^0, t, p)} \) is the weight of the PM of a chosen size distribution, released during a time window of \( \Delta t \); \( D_f \) is the deposition factor based on inhalation and exhalation concentration, and \( n \) is the chosen number of breath cycles over which the total weight of the bolus is dispensed [9]. The subscripts \( (T^0, t, p) \) denote that \( \Delta w \) is dependent on the temperature, elapsed time of storage of the aerosol and the pressure \( (p) \) at which the aerosol was stored. The whole operation can be represented as shown in figure 2 below.

![Figure 2. Specified lung target (% of Vmax(avg) – Vmin(avg)) and bolus delivery period (Δt)](image)

3.2. System Description
The system block diagram is shown in Figure 3 below. An external particle generator (GFG1000, PALAS - not shown) generates the graphite NP and is let into the system via the pump, which fills the chambers \( C_2 \) and \( C_3 \). The system is ready to deliver the NP once the chambers reach specified pressures. This pressure is maintained at the same level throughout the operation. Storing the PM under pressure would enable the release of a higher concentration of aerosol within a short time window \( (\Delta t) \), for a given bolus size. This improves target resolution as it allows for a finer control of the site of delivery in the lungs.
The data acquisition and control system measures the breathing flow rate using the mass flow meters (MFM) and also calculates the lung volume and average tidal volume. A bolus of aerosol is injected during inhalation at the required lung volume by opening valve $S_3$ for a fixed amount of time specified by the user.

3.3. The software

The control system was initially implemented using National Instruments LabVIEW software (ver.8.0). However, significant jitter in the release valve timing was found due to non-deterministic execution delay, affecting the trigger point at which the bolus was released. Hence the control system was redesigned employing a Real-time Compact Reconfigurable I/O embedded controller (cRIO-9004, National Instruments) that runs the LabVIEW code in real time. The graphical user interface is shown in the figure 4. As shown, the controls on the front panel are used for controlling different operations and are self explanatory.
The block level architectural diagram and the code for the main program are shown in figure 5 and 6 respectively. The cRIO runs the actual control software in real-time and the PC resident software simply acts as a host which provides graphical user interface and display. With this approach, the problem of uncertainty of time (jitter) was resolved.
3.4. Hardware Modifications
It was found that the results using the original mouthpiece led to some errors in the lung volume calculations by the software (constant drifting). This can be seen from figure 8(a) in which the experiment was carried out after attaching the mouthpiece to a sinusoidal air pump. The problem of drifting was found to be due to flow disturbances introduced during the exhalation phase. It was corrected by introducing laminar flow using an additional smoothing filter on the mouthpiece as shown in figure 7 below.

![Figure 7. Modified mouthpiece assembly with Filter](image)

Figure 8(b) shows the current response of the flow system after the above modification.
In addition to the above modifications, it was found out that if the system were to be used without any imposed breath pattern, then the changes in each breath cycle makes the volume integrator base line to continue shifting upwards or downwards depending on the lung volume calculations. For this reason it was decided to add a facility in the software that automatically resets the integrator for each cycle to enable constant base-line to be maintained as shown in figure 9 below.

![Figure 9](image)

Figure 9. Illustration of integrator reset function

4. Discussion of results
The modified system with real time hardware was successfully demonstrated as seen from figure 4, 8(b) and 9. With regard to the properties of PM passing through the system it was observed that the PM size distribution increased with storage time, due to likely causes such as agglomeration and
aggregation. This can be seen by comparing figure 10(a) and (b) below. Figure 10(a) shows the size distribution when the generated aerosol is free flowing through the system without being stored. In contrast, figure 10(b) represents typical distribution graph when the aerosol is stored at 1.3PSI for 1min 30sec. It is evident from the graphs that there were:

- Increase in the mean particle size of PM during storage.
- Reduction in peak values of particle numbers and mass. (This may be attributed to deposition or settling within the storage chambers.)

The Mass Summation curve can be used to see whether a particular mass distribution remains within a required limit of the maximum size distribution. For example in figure 10 (a), over 98% of particles are still within a maximum of 100nm range, whereas in figure 10(b) this has been reduced to about 92%.

Further experimentation revealed that in this particular arrangement, introducing agitation within the storage chamber and the shearing forces at the valve openings, there is a possibility to influence the PM size distribution. The effect of agitation was observed by installing a miniature fan inside chamber C3. The effect of switching the fan ON, on the particle distribution can be observed by comparing the figure 10(b) and (c). There is an observable reduction in peak particle size distribution and particle mass distribution. It should be mentioned that only one type of PM (graphite) was used, and further experimentation with other type of agitations is required to validate this result, as the fan may itself introduce complications.

Figure 10. Variation of particle size distribution with pressure and elapsed time
5. Conclusion
A prototype system for delivery of controlled bolus of PM has been designed. The main control functionalities according to original design specifications have been demonstrated.

Some of the factors affecting the changes in PM size distribution have been observed and the possibility of maintaining the size distribution by impeding the process of particle growth was also observed for one type of NP (graphite), under specified conditions.

From this first experimental model, a number of parameters for re-designing the system towards a clinical prototype have been established.

6. Further Work
Further experimentation is needed to quantify the effect of introducing a disturbance into the storage chamber and increasing shear forces at the point of discharge. This has to be repeated for different aerosols in order to justify that it is possible to break at least in part, the aggregated/agglomerated NP to smaller sizes in order to maintain a required size distribution.

The system would then have to be tested with radioactive labelled NP in a precise manner in safe conditions before assessing the regional deposition in human lung. Techniques for selecting a particular particle size range may also be incorporated. The new design is likely to consist of a much smaller and easily interchangeable discharge cell to enable the use of different aerosols. This work is in progress.

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