In silico clinical trials of regional lung deposition: how they could impact real life product development and patient care

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Extended Summary

Over the last decade, we have witnessed an impressive expansion in the application of *in silico* methods for the prediction of regional lung deposition of inhaled drugs. This activity is reflected in the number of papers that have appeared in the scientific literature since the early 2000s. Yet, a critical review of the related literature also reveals a significant stratification in terms of the numerical methods used, and often, in the degree of rigor with which computer experiments are designed and executed. At the same time, different authors seem to have different visions as to what the ultimate role of *in silico* methods should be in the product development cycle, as well as in the patient-care setting. Here, we first take a look at the limitations set by the current simulation technology, as well as the expected advances that are forthcoming. We then use this information in order to outline a vision for the role of *in silico* methods in the near future, where possible offering examples from current simulations. The extent to which *in silico* methods will have an impact on product development and patient care will depend not only on the simulation technology itself, but also on the degree to which the technology is understood and thus trusted by key stakeholders, such as regulators and the industry. In this context, we highlight the importance of achieving a community consensus for a well-designed validation and verification strategy for *in silico* methods that are used for lung deposition predictions.

The ex-cast dose, i.e. the portion of delivered drug that escapes deposition in the mouth-throat region is in general accepted to be a good predictor of total lung deposition. The strong correlation between ex-cast dose and total lung dose offers the basis of *in vitro* methods that rely on model mouth-throats and cascade impactor assemblies for the estimation of total lung deposition. However, it is only under special circumstances that total lung deposition is by itself sufficient to understand and characterize an inhalation product. For example, knowing total lung dose goes a long way in understanding the behaviour of a drug with close to prefect lung bioavailability, especially when targeting systemic circulation. Under such conditions, having a vague sense of where the drug particles land might be considered sufficient. More often than not, though, the site of deposition is of critical importance. This is for example the case of drugs designed to treat topical disease in the lungs and for drugs with limited bioavailability. The development of these drugs has to take into account the competing mechanisms of dissolution and absorption on one hand and clearance on the other. These mechanisms vary significant over the lung structure.

The complexity of the respiratory system, both in terms of structure and tissue lines, becomes a challenge when one tries to predict the behaviour of an inhaled drug. It is also a challenge when one tries to simulate the deposition of drug particles, often meaning that different simulation technologies should be considered for different parts of the lung.

Depending on the inhalation rate, the flow can enter the mouth in a laminar or turbulent state. However, except for exceedingly low inhalation rates that are characteristic of sedentary conditions, the flow quickly transitions to turbulence, even when it enters in a laminar state. This means that appropriate simulation approaches, such Large Eddy Simulations (LES) or Reynolds Averaged Navier-Stokes (RANS) need to be used to simulate the flow and particle deposition that occurs in the extrathoracic airways. Within COST Action MP1404 – "SimInhale", we have carried a large collaborative comparison of the performance of various simulation approaches. Experiments were commissioned[1],[2] to measure and characterize the flowfield in the same geometry and *in vitro* deposition results were used for the assessment of the performance of the simulations methods considered. The SimInhale benchmarking[2] has shown that in general *in silico* methods performed well as predictors of regional deposition, as compared to experiments, but it also raised further questions that call for best practice guidelines, an objective that we plan to address within the SimInhale. These results are likely to have different implications depending on one's underlying objective. For example, when the objective is to use *in silico* methods in support of patient-specific care, one has to worry that accuracy and repeatability are not sacrificed under the pressure to deliver results quickly. The consensus that seems to be emerging is that the limits where acceptable accuracy is lost are yet not well understood and further community-wide benchmarking is needed. The same concerns need to be taken into account in simulations designed to elucidate the role that various patient-controlled factors, such inhaler positioning and handling, have on the amount of drug that is filtered in the oropharyngeal cavity. On the other hand, when the objective is to repeat large number of simulations, for example in the context of *in silico* population studies, questions of simulation efficiency can be addressed by clever design of the simulation campaign. In this later context, the accuracy of simulations results can be maintained more readily. For example, a typical scenario is one where a large number of simulations of drug deposition in the bronchial tree are to be carried for certain population groups,

e.g. asthmatics or COPD patients. The aim of such an *in silico* population study could for example be to correlate function and structural metrics of the lung to deposition patterns and ultimately to therapeutic outcomes. In this scenario, one can take advantage of the large number of bronchial tree geometries that are available in chest-CT databases of major hospitals and diagnostic centers. Most of the available chest CT-scans exclude the extrathoracic airways. In a few cases that the extrathoracic airways are available in the CT database itself or from accompanying MRI scans. Even then, however, the mouth is usually shut and the position of the oropharyngeal structures is not representative of an inhalation manoeuvre. In this context, therefore, the best solution would be to avoid the simulation of flow and deposition in patient-specific mouth-throats and to seek to create a library of representative *in silico* mouth-throat models that can then be used in large populations studies. To be able to pull off this proposition, one has to show that estimates of regional deposition in the bronchial tree can be obtained with reasonable accuracy when such *in silico* model mouth-throats are used. We have tackled this very question in a collaboration under MP1404 – "SimInhale", and as will be shown, the results are quite promising.

Yet another perspective emerges in the context of *in silico* estimates of regional deposition in the entire lung. When large sections of the lung that extend to the small airways or even the ascinar regions are considered, the sheer size of the computations involved precludes applying the same methods as described above, at least for the foreseeable future. Fortunately, the low Reynolds numbers that prevail in the deep lung allow one to devise clever shortcuts in order to be able to predict the flowfield and particle deposition with acceptable accuracy and low cost. While 1D methods have been used for many years, here we will present a new model of the deep lung that is based on 3D-CFD but it is computationally efficient[3]. We show that the model predictions are aligned with the global predictions of 1D models such as the NCRP, but the model can also provide a much more detailed view of deposition per bronchial or acinar generation. Furthermore, the model can easily be customized to represent non-standard lung configurations, such as one encounters in a number of chronic lung conditions. Another advantage of the new model is that makes possible the simulation of complete inhalation cycles including different breath-hold manoeuvres.

Thus, a picture emerges where one can imagine hybrid models that rely on *in silic*o models of the mouth-throat, patient-derived upper bronchial trees and efficient deep lung models that allow the simulation of the flow and deposition over the entire lung using 3D CFD. While challenges are still present, this scenario is within reach in the short to medium term. Of course, one could envision several additional refinements to the basic technology we have outlined, but these can be realized as secondary steps once the basic simulation setup is realized.

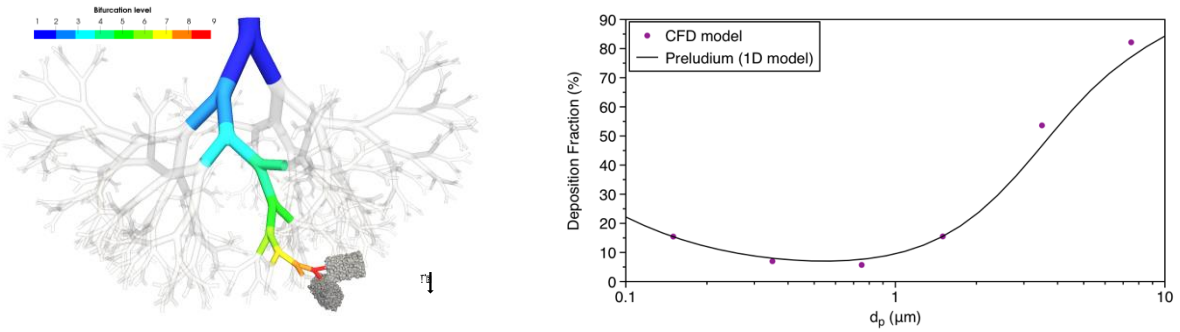

Figure 1 - Example of a new generation 3D CFD-based deep lung model [3].

References

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