Validation of computational predictions of regional lung deposition

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Disclaimer

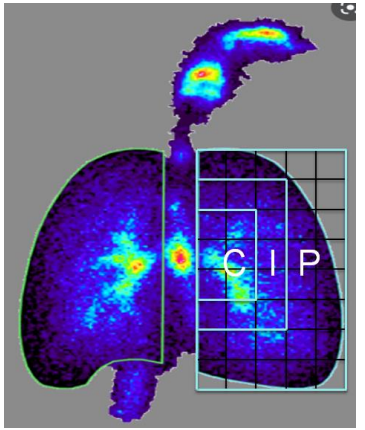
- I am a consultant for Emmace Consulting AB, Lund, Sweden, and I work with many pharmaceutical companies on inhalation science.
- I am also a majority shareholder of Mimetikos AB, owner of the Preludium™ software.

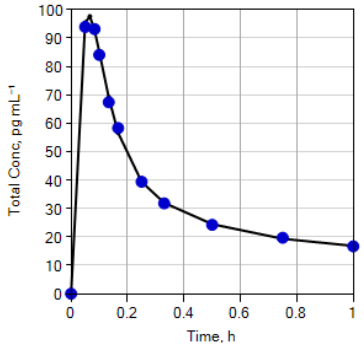
Background

- Computer models of lung deposition are important
  - For predicting and/or understanding clinical studies.
  - For facilitating development of inhalation products.
- Validation of such models is challenging
  - Must be indirect since generational *in vivo* data are lacking.
  - Hence, no direct records to compare with.
  - Hence, either *in vivo* data or *in silico* predictions must be transformed for them to become comparable.
  - This require assumptions.

Validation approaches to be discussed:

- Planar scintigraphy
  - The most common type of *in vivo* data adressing lung deposition.
  - Provides an image where each Region of Interest, RoI (e.g.,central, intermediate and peripheral), contains a mixture of airway generations.
  - Hence, one cannot directly compare, say predicted deposition in generations 1-8 with the activity recorded in the central region of the image.
- Pharmacokinetics (C *vs* t plasma curve, Cmax, AUC, etc)
  - Downstream biomarkers, even more indirect.
  - Based on different regions having different rate and/or extent of absorption.
  - Requires mechanistic model for absorption from lung into system.
  - Which in turn requires validation.





Planar scintigraphy *vs* Generational deposition

- Each RoI captures activity in a mixture of generations
  - Not possible to translate RoI activity to generational deposition (fuzzy → detailed).
  - Possible to translate generational deposition to RoI activity (central, C, intermediate, I and peripheral, P) (detailed → fuzzy).
    - Requires a translation map.
    - Such a map has been published by Schroeter et al*, based on a 2D projection of a 3D mathematical model of a lung.
  - Essentially this downgrades generational deposition to a blurred image.
  - Captured and computed RoI can be directly compared.

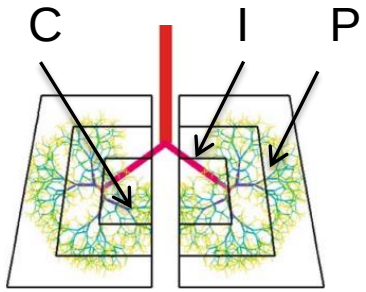


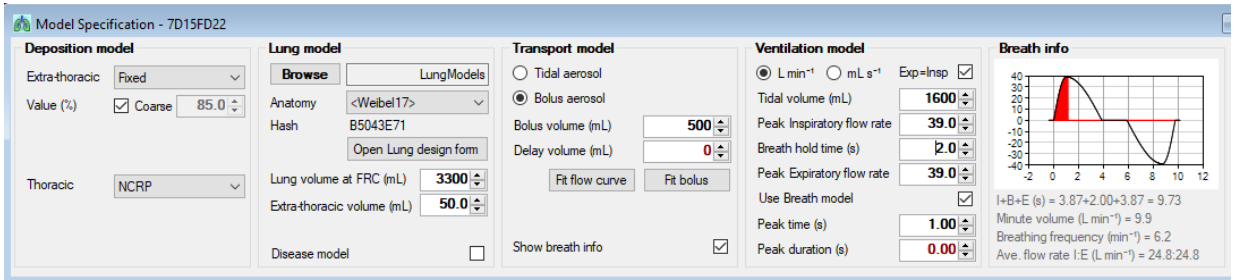
Fig. 4. Planar view of the 3-D airway morphology model (generations 0–12) with overlaid partition.

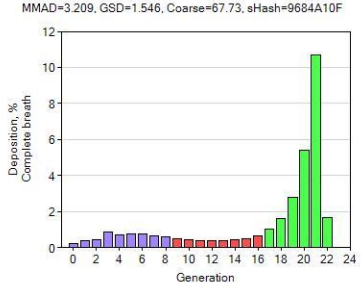
Generation	Region of interest		
	C	I	P
1	100.0	0.0	0.0
2	100.0	0.0	0.0
3	50.0	50.0	0.0
4	50.0	50.0	0.0
5	25.0	75.0	0.0
6	25.0	50.0	25.0
7	25.0	50.0	25.0
8	20.3	54.7	25.0
9	18.8	49.2	32.0
10	19.1	43.8	37.1
11	18.6	39.8	41.6
12	18.0	39.3	42.8
13	17.7	39.6	42.7
14	17.7	38.8	43.4
15	18.0	38.2	43.8
16	18.0	38.3	43.7
17	18.1	38.1	43.7
18	18.1	38.0	43.8
19	18.2	38.0	43.8
20	18.2	38.1	43.8
21	18.2	38.1	43.7
22	18.2	38.1	43.7
23	18.2	38.1	43.7

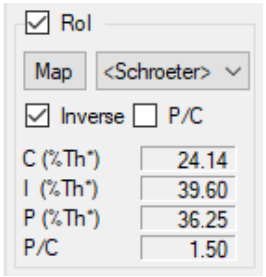
* Schroeter et al 2005: Pharm Res 22(10)1692

Mimetikos Preludium™ software

- 1D typical path semi-mechanistic algorithms for generational deposition by impaction, sedimentation and diffusion.
- Inputs: Particle size distribution (MMAD, GSD, Coarse fraction), lung morphology (e.g., scaled Weibel), aerosol transport (e.g., bolus), ventilation (e.g., unsteady breathing pattern), disease (e.g., bronchoconstriction).
- Output: generational deposition, deposition in RoI (using Schroeter map).







Validation - scintigraphic data*

- Considered all papers from Newman and co-workers 1981-2007 (n=37) as collated by Clark** (largest collection using consistent methodology & RoI definition).
- Retained those with sufficient information and technique to allow reliable *in silico* predictions and where *in vitro* (impactor measurement) and *in vivo* (scint study) conditions were similar (e.g., PIF).
- Culled data comprised14 papers with 18 study legs on 9 DPI*** brands.
  - 11 healthy volunteer and 7 mild-moderate asthmatic legs (8-14 subjects per leg).
- Mouth-throat (MT) deposition, total lung deposition (TLD), and mapped C, I, P fractions were computed in Preludium and compared to corresponding *in vivo* results (average for study leg).

* Olsson & Kassinos 2020, JAMPDD DOI: 10.1089/jamp.2020.1620

** Clark 2012, JAMPDD 2012;25(4):179-187

*** Due to non-biorelevant impactor tests, MT deposition and PSD could not be reliably estimated for pMDIs, hence excluded

Scintigraphic validation – Results MT & TLD

In silico and *in vivo* measures correlate with an almost one-to-one relation over a wide range (R^2>0.90, p<0.0001).

Grand mean	MT (%DD)	TLD (%DD)
In vivo	67.9	31.4
In silico	62.3	36.9

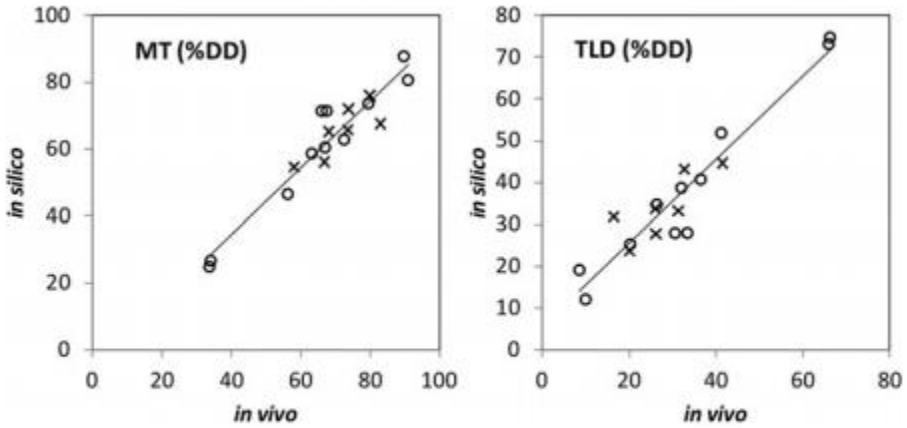


FIG. 1. Unweighted linear regression of *in silico* on *in vivo* results for MT and TLD, % delivered dose. Healthy volunteers (O) and asthmatics (X). MT, mouth–throat; TLD, total lung deposition.

* Olsson & Kassinos 2020, JAMPDD DOI: 10.1089/jamp.2020.1620

Scintigraphic validation – Results C, I, P & P/C

Significant correlation for P/C (R^2=0.39, p<0.01) but *in silico* predicted a somewhat less central deposition than *in vivo*.

C somewhat underpredicted, I somewhat overpredicted ➔ P close, slightly overpredicted.

Grand mean	C	I	P	P/C (range)
In vivo	34	34	33	1.2 (0.6 – 2.0)
In silico	25	40	36	1.5 (0.8 – 2.1)

Note: average ratio ≠ ratio of averages

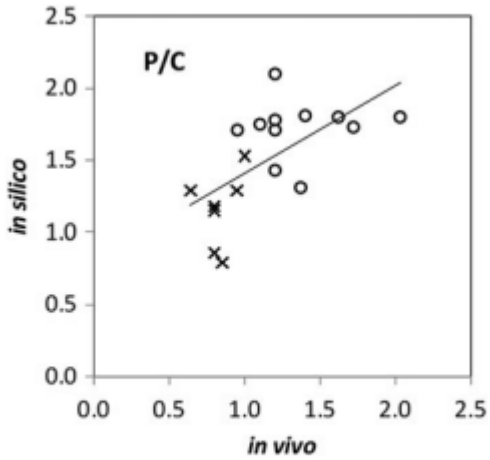


FIG. 3. Unweighted linear regression of *in silico* on *in vivo* results for the *P/C* ratio. Healthy volunteers (O) and asthmatics (X).

Possible *in silico* P/C range = 0.0 – 2.4.
Possible *in silico* I range = 38 – 41 ➔ the Schroeter mapping is misspecified to some degree.

* Olsson & Kassinos 2020, JAMPDD DOI: 10.1089/jamp.2020.1620

Scintigraphic validation – Conclusion & reflection

- Using an unbiased collection of 18 study legs of DPI deposition and one example of a generation to RoI mapping:
- *In silico* predicted mouth-throat and total lung deposition was highly correlated to *in vivo* outcome with virtually no bias over a wide range.
- *In silico* predicted regional lung distribution was correlated to *in vivo* outcome with a bias towards underestimating central deposition.
- The regional bias is due to a misspecification in the Schroeter mapping to RoI, and possibly also in the Weibel morphological lung model used in Preludium.
- However, a direct comparison of computed alveolar/tracheobronchial (A/TB) deposition ratio with the *in silico* P/C results gave a much larger bias (average 4.2 vs 1.5) demonstrating the necessity of making a translation to comparable measures.

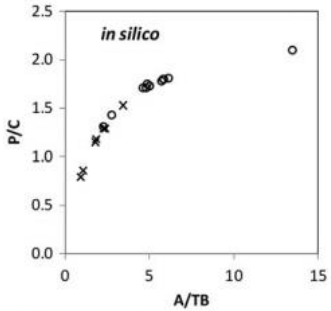
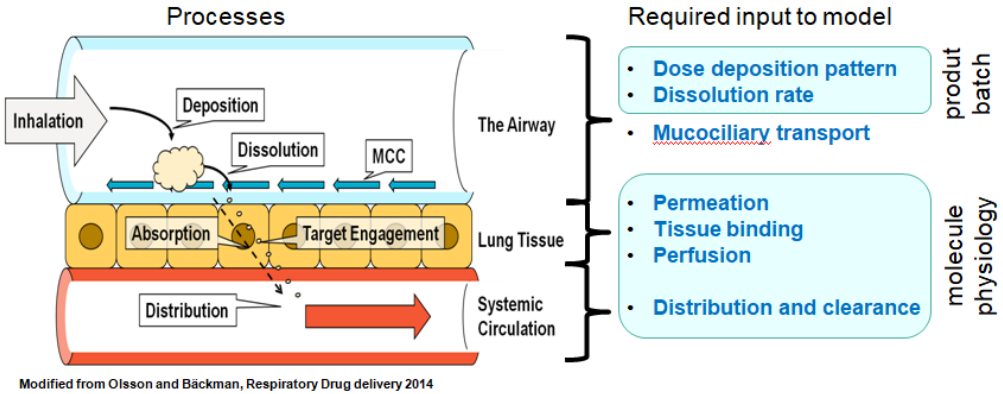


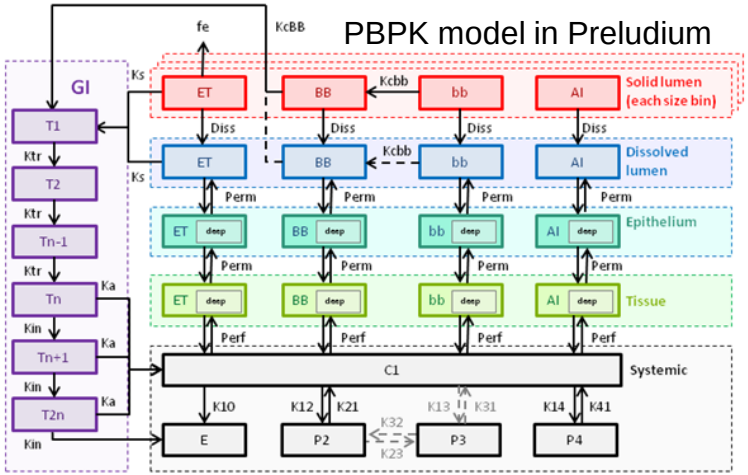
FIG. 4. Relationship between the *in silico* ratios *P/C* and *A/TB*. Healthy volunteers (O) and asthmatics (X).

Validation – PK example

- Systemic PK is downstream lung deposition
- Requires mechanistic modeling of pulmonary processes and a systemic model
- Significantly more input parameters and assumptions than for just deposition
- Case study: Fluticasone proprionate via Advair® Diskus®



Modified from Olsson and Bäckman, Respiratory Drug delivery 2014



- Pulmonary processes by mechanistic simulation
- Rest-of-body processes by empirical (compartmental) modeling

Validation – Fluticasone proprionate *in vitro* data

- Three strengths of Advair Diskus 100/50, 250/50 and 500/50 (FP/SX).
- Concurrent *in vivo** and *in vitro*** data (same batches similar age).
- Very similar Particle Size Distribution (PSD).
- Marked differences in dissolution rate.

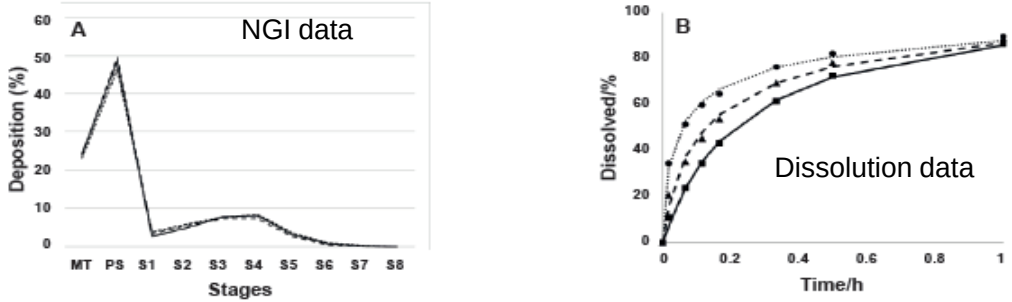


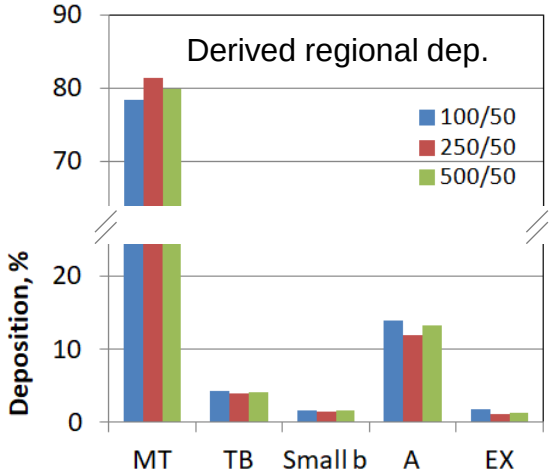
Figure 1. (A) NGI stage deposition (% emitted dose) and (B) actual (data points) and fitted (lines) dissolution profiles of FP from Advair Diskus 100/50 (FP/SX; circles, dotted); 250/50 (triangles, dashed) and 500/50 (squares, solid). Table1 shows the parameters derived from these data. MT and PS are the USP inlet throat and preseparator, respectively. Dissolved amount is expressed as % of total FP mass added to bath.

* Haughie et al 2020, JAMPDD 33(1)34 (part of ANDA submission for Wixela® Inhub®)

** Bäckman & Olsson 2020, Respiratory Drug Delivery 2020. Volume 1, 113-122

Validation – Fluticasone proprionate *in silico*

- NGI + HV morphometry & maneuver ➔ Total and regional lung deposition.*
- Dissolution curves (dissolution bath, solubility) ➔ VMD_{app}, GSD_{app}.
- Very similar predicted deposition.
- Marked difference in dissolution parameters.



Derived dissolution parameters

Product	VMD_{app}	GSD_{app}
100/50	2.76	3.39
250/50	4.10	2.38
500/50	5.08	1.85

All other model parameters from literature

* Bäckman & Olsson 2020, Respiratory Drug Delivery 2020. Volume 1, 113-122

Validation – FP *in silico vs in vivo* PK results

- Similarity in lung deposition manifested in near constant dose-normalized AUCt.
- Difference in dissolution kinetics manifested in trending Cmax and curve shape (Cmax/AUCt).
- Excellent agreement between observed and simulated PK.
- Successful validation of *in silico* model.

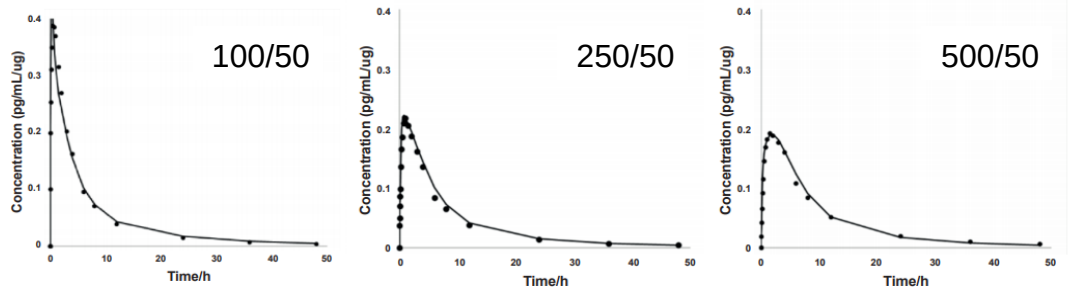


Figure 2. Simulated (solid lines) and observed (markers) dose-normalized plasma concentration versus time for FP following dosing from Advair Diskus (A) 100/50; (B) 250/50; and (C) 500/50 (FP/SX). Simulated and observed concentrations were normalized by division by the total delivered dose in each study.

Product	Observed*			Simulated**		
	AUCt#	Cmax#	Cmax/ AUCt	AUCt#	Cmax#	Cmax/ AUCt
100/50	2.03	0.40	0.19	2.10	0.41	0.19
250/50	1.65	0.23	0.14	1.80	0.21	0.12
500/50	1.95	0.19	0.10	1.95	0.18	0.09

Dose normalized by nominal dose

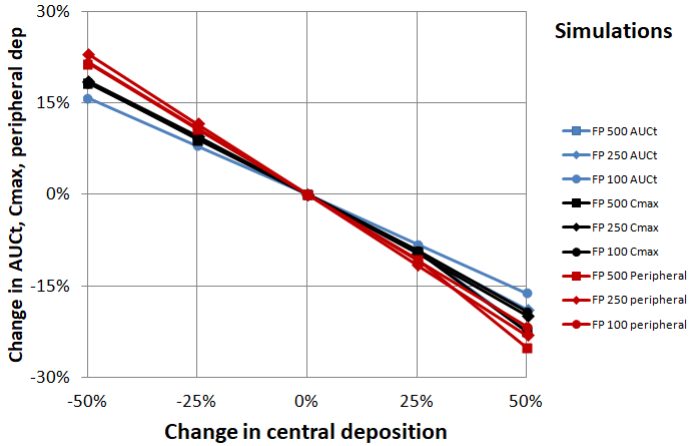
Product	Simulated/Observed**		
	AUCt	Cmax	Cmax/ AUCt
100/50	1.04	1.04	1.00
250/50	1.09	0.92	0.85
500/50	1.00	0.94	0.94

* Haughie et al 2020, JAMPDD 33(1)34

** Bäckman & Olsson 2020, Respiratory Drug Delivery 2020. Volume 1, 113-122

Validation – sensitivity of FP PK to regional deposition

- The simulated central deposition was changed by up to ±50%, adding or subtracting to/from the peripheral deposition.
- The resulting changes in AUCt, Cmax, and peripheral deposition show:
  - Changes are pronounced and proportional to changes in central deposition
  - Changes in AUCt and Cmax closely follow changes in peripheral deposition
- Interpretation
  - Changes in Cmax mainly due to more rapid absorption from periphery
  - Changes in AUCt mainly due to loss by mucociliary clearence from central but not from peripheral deposition



- The successful validation of the PK model indicates that the deposition and dissolution models are valid

Conclusions

- Scintigraphy
  - The validity of mapping generational deposition to 2D scintigraphic RoI was demonstrated.
  - The 2005 Schroeter map can probably be improved with novel space-filling algorithms based on new high-resolution CT data on central airway morphometry.
  - Direct comparison of generational deposition to scintigraphis RoI is an invalid approach.
- PK
  - For a low solubility compound dissolution may be rate-limiting for absorption from the lung.
  - This was successfully modeled for three strengths of Advair Diskus using appropriate parameterization (VMD_{app} & GSD_{app}).
  - Sensitivity analysis demonstrated a pronounced influence of regional distribution on PK output indicating validity of the deposition and dissolution models.