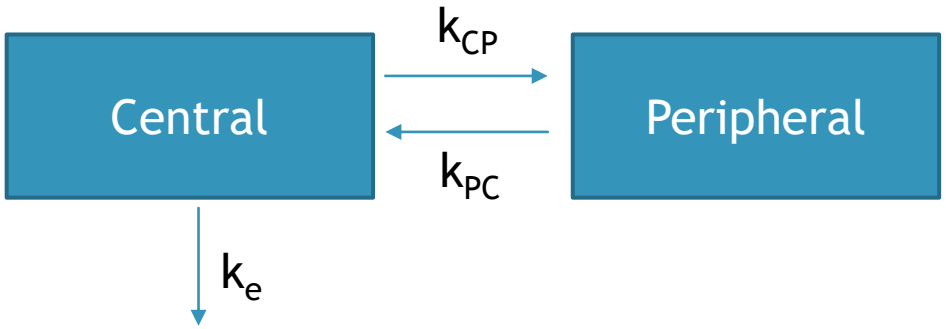
Model building in MoBi

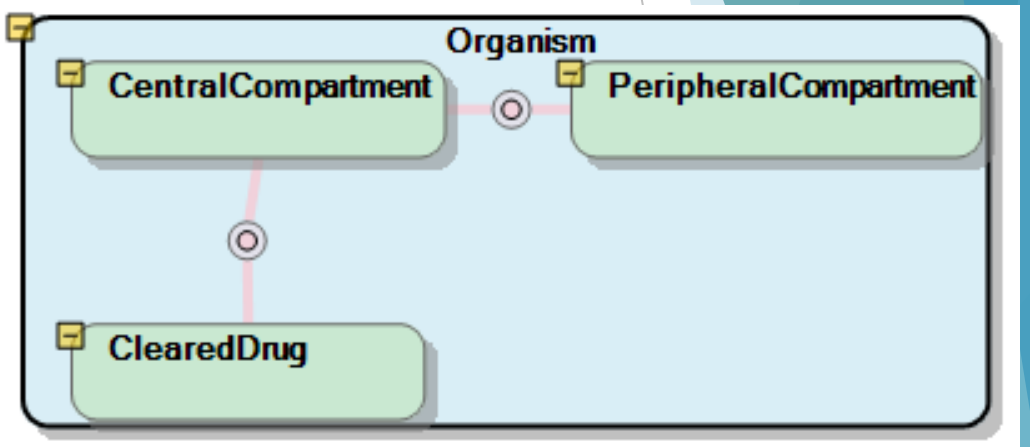
Moriah Pellowe

Two compartment model in MoBi

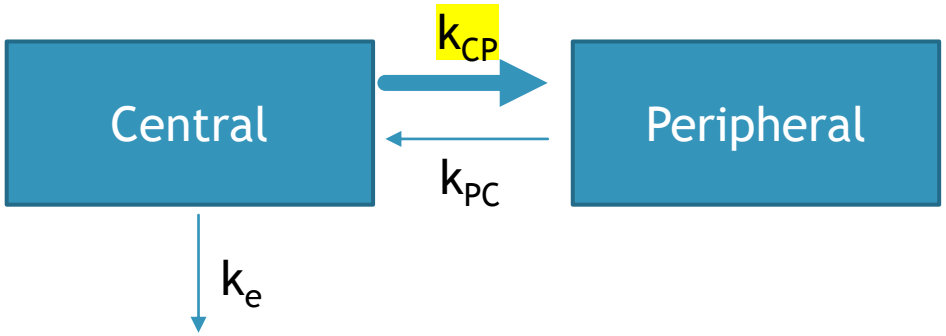
Live demo

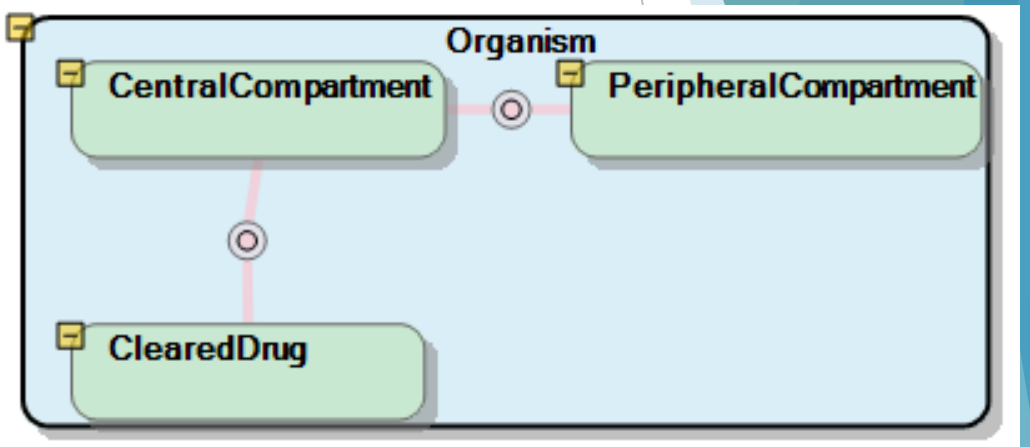
Two compartment model

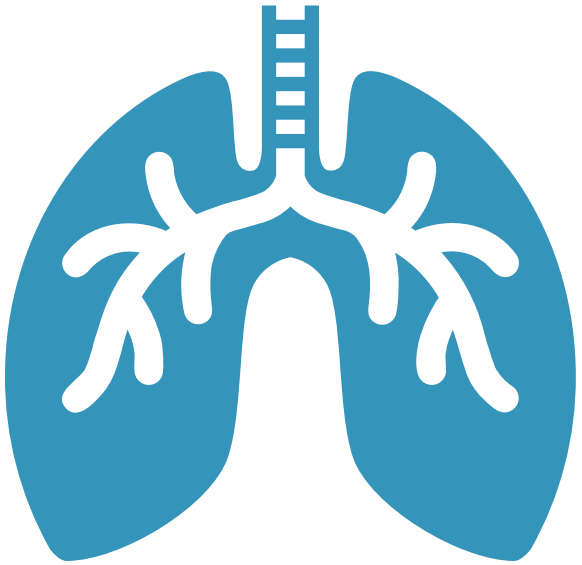




Two compartment model







Inhalation model

Integration of MoBi with ospsuite R toolbox

Disclaimer

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Outline

- **Objective:** Demonstrate integration of MoBi with the ospsuite R toolbox
  - Case study: Mechanistic inhalation model for dry powder inhalation within the Open Systems Pharmacology framework (MoBi)
- Inhalation model - Boger & Wigström (2018) PDE model
  - Lung structure
  - Particle deposition
  - Particle dissolution
  - Mucociliary clearance
- Integration of MoBi and ospsuite R toolbox for particle deposition

Lung structure

- Weibel et al., 1963
- Symmetric branching
- 24 generations
  - Generations 1-16 : tracheobronchial region
  - Generations 17-24: alveolar region
- Three main compartments
  - Epithelial lining fluid (solid and liquid drug)
  - Epithelium
  - Subepithelium

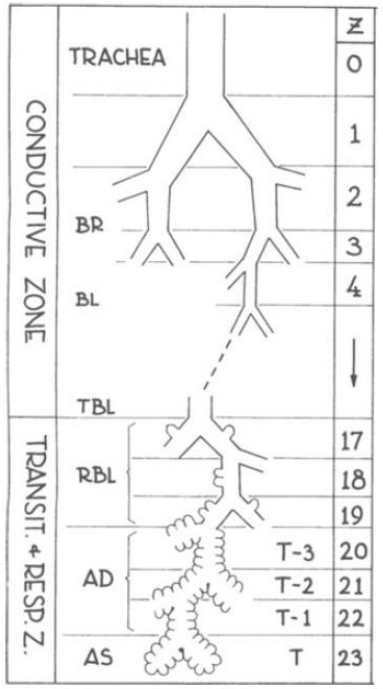


Fig. 82

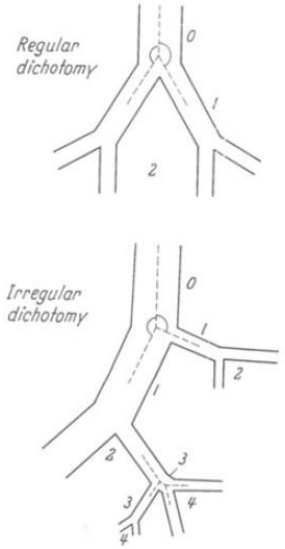
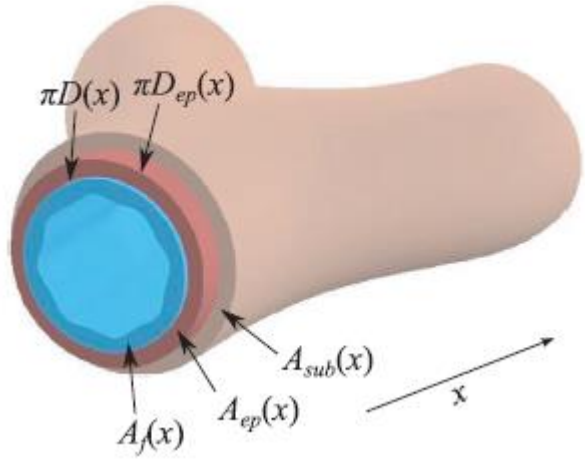


Fig. 83

i	N_i	D_i [cm]	L_i [cm]
1	1	1.539	10.26
2	2	1.043	4.07
3	4	0.71	1.624
4	8	0.479	0.65
5	16	0.385	1.086
6	32	0.299	0.915
7	64	0.239	0.769
8	128	0.197	0.65
9	256	0.159	0.547
10	512	0.132	0.462
11	1024	0.111	0.393
12	2048	0.093	0.333
13	4096	0.081	0.282
14	8192	0.070	0.231
15	16384	0.063	0.197
16	32768	0.056	0.171
17	65536	0.051	0.141
18	131072	0.046	0.121
19	262144	0.043	0.10
20	524288	0.040	0.085
21	1048576	0.038	0.071
22	2097152	0.037	0.060
23	4194304	0.035	0.050
24	8388608	0.035	0.043



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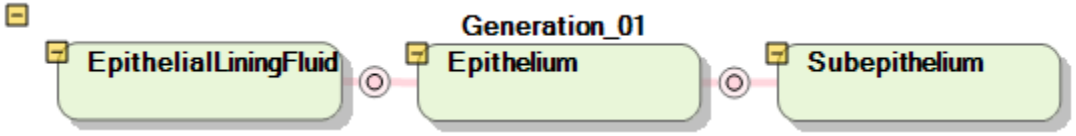
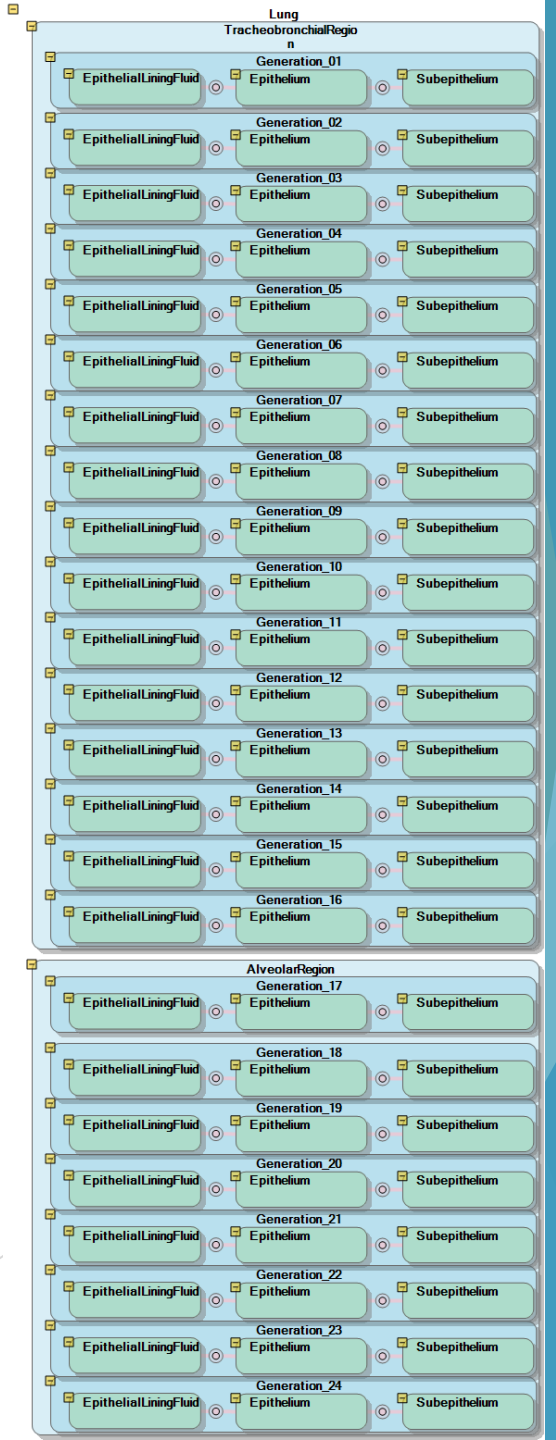




Particle deposition

- Deposition in lung and in extrathoracic region (before trachea)
  - Drug deposited in the extrathoracic region is subject to oral absorption
- Inhale phase, breath hold phase, exhale phase
- Deposition mechanisms
  - Inertial impaction
  - Gravitational sedimentation
  - Diffusion
  - Empirical equations for each mechanism (Yu & Diu, 1982)
- Alternatively, custom deposition

Particle deposition

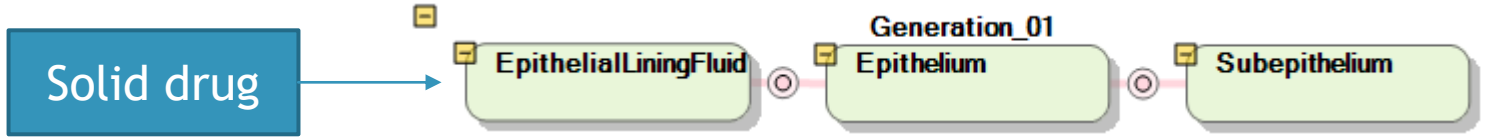
- Deposition is calculated in R and interfaces with MoBi using the R toolbox
- Input :
  - Particle radius mean and SD (normal distribution)
  - Number of particle size bins to consider
  - Drug density
  - (optionally) Breathing parameters
- Output :
  - Proportion of drug in each generation for each particle size
  - Number of particles in a volume of 1 L for each particle size bin
    - Used to calculate the number of particles in each bin

ET	0.104796
1	0.016083
2	0.013948
3	0.012638
4	0.012038
5	0.024138
6	0.027856
7	0.028657
8	0.026391
9	0.026352
10	0.023941
11	0.02129
12	0.019646
13	0.017085
14	0.016138
15	0.017045
16	0.021227
17	0.027639
18	0.044106
19	0.07218
20	0.121111
21	0.204382
22	0.101314
23	0
24	0

Particle dissolution

- Noyes-Whitney dissolution
- Modified PK-Sim particle dissolution for the lung (Willmann et al., 2010)
- Assumptions:
  - Particles do not precipitate
  - Solubility is constant, i.e. no local solubilities
  - Only unbound drug in the ELF
  - Kp_lung = Kp_ELF = 6.5

$$-\frac{\mathrm{d}X_s}{\mathrm{d}t} = \frac{DS}{h}\left(C_s - \frac{X_d}{V}\right)$$



Mucociliary clearance (MCC)

- Maximum MCC rate of 0.36 cm/min
- The MCC rate for generation i is proportional to the ratio of the cross-sectional areas of generation i and generation 1

$$\alpha(x) = -\alpha_0 \frac{A(x)}{A(x_{min})}$$

- The residence time for each generation was calculated based on this MCC rate and the length of the generation
- Assumptions:
  - Only solid drug particles are moving upwards

i	N_i	D_i [cm]	L_i [cm]
1	1	1.539	10.26
2	2	1.043	4.07
3	4	0.71	1.624
4	8	0.479	0.65
5	16	0.385	1.086
6	32	0.299	0.915
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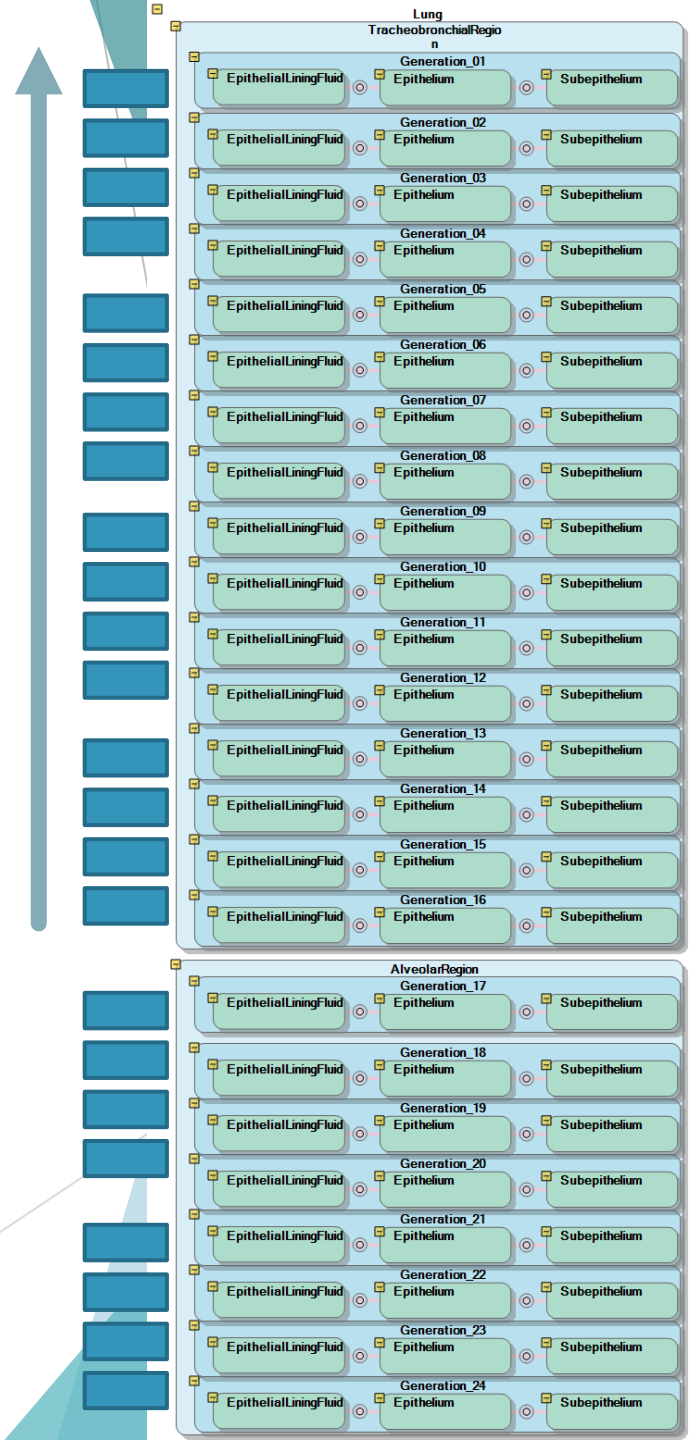
Mucociliary clearance (MCC)

Generation #	Residence time (Boger & Wigström, 2018) [min]	Approximation [min]	Number of slices
1	28.5	30	2
2	24.62	30	2
3	21.2	15	1
4	18.64	15	1
5	48.2	45	3
6	67.34	60	4
7	88.57	90	6
8	110.19	105	7
9	140.35	135	9
10	174.45	180	12
11	209.86	210	14
12	253.31	255	17
13	282.78	285	19
14	310.16	315	21
15	326.56	330	22
16	358.75	360	24
SUM	2463.48	2460	164

Mucociliary clearance (MCC)

- Every 15 minutes, solid drug is moved from one slice to the slice above for the tracheobronchial region



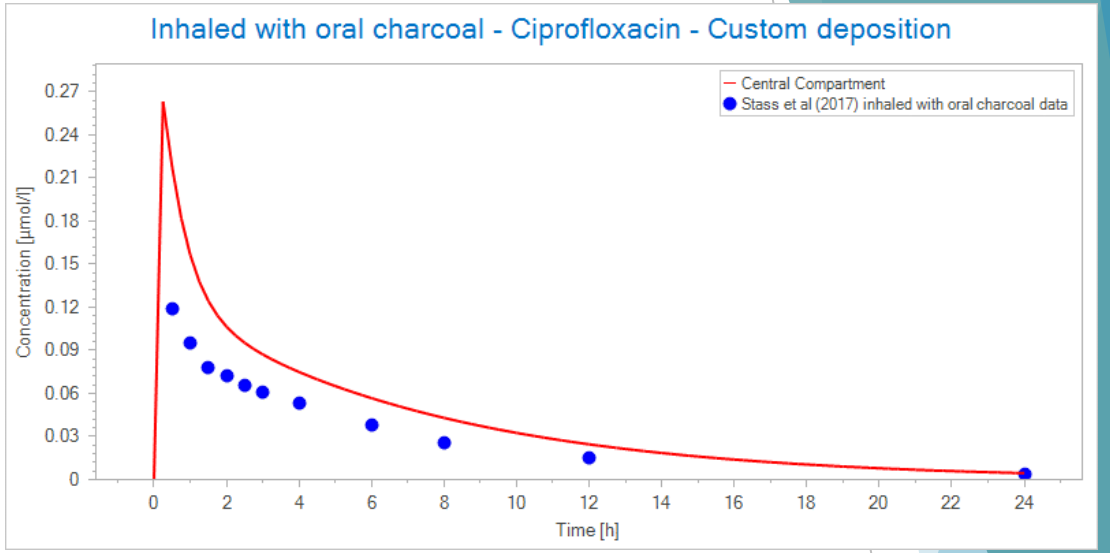
Particle deposition using the R toolbox

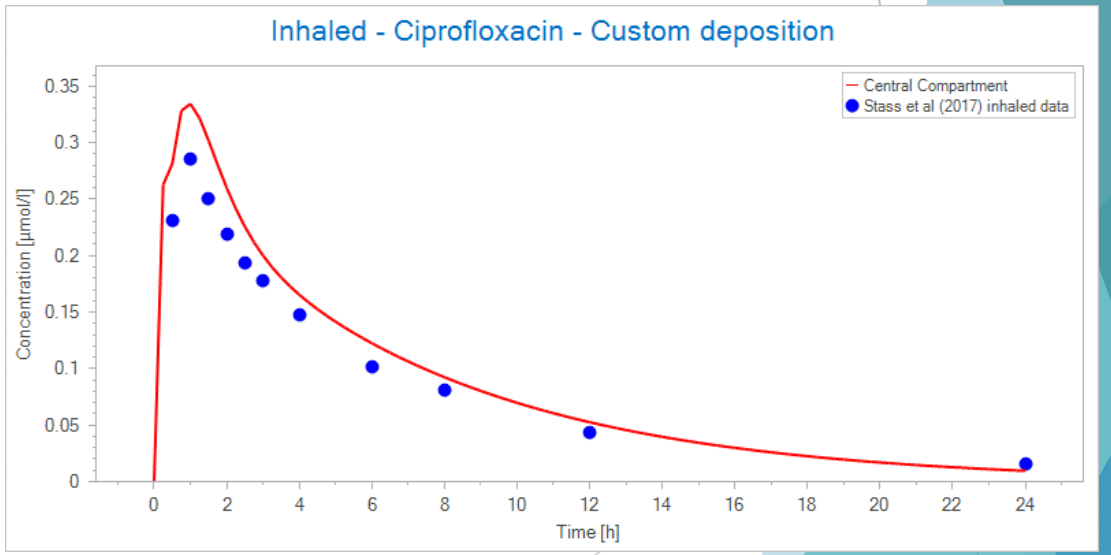
Model structure

- Inhalation model is connected to two-compartment model for evaluation
- Parameters concerning disposition are fit to IV and oral data
- Deposition is either:
  - Calculated using deposition equations OR
  - Manually input based on additional information

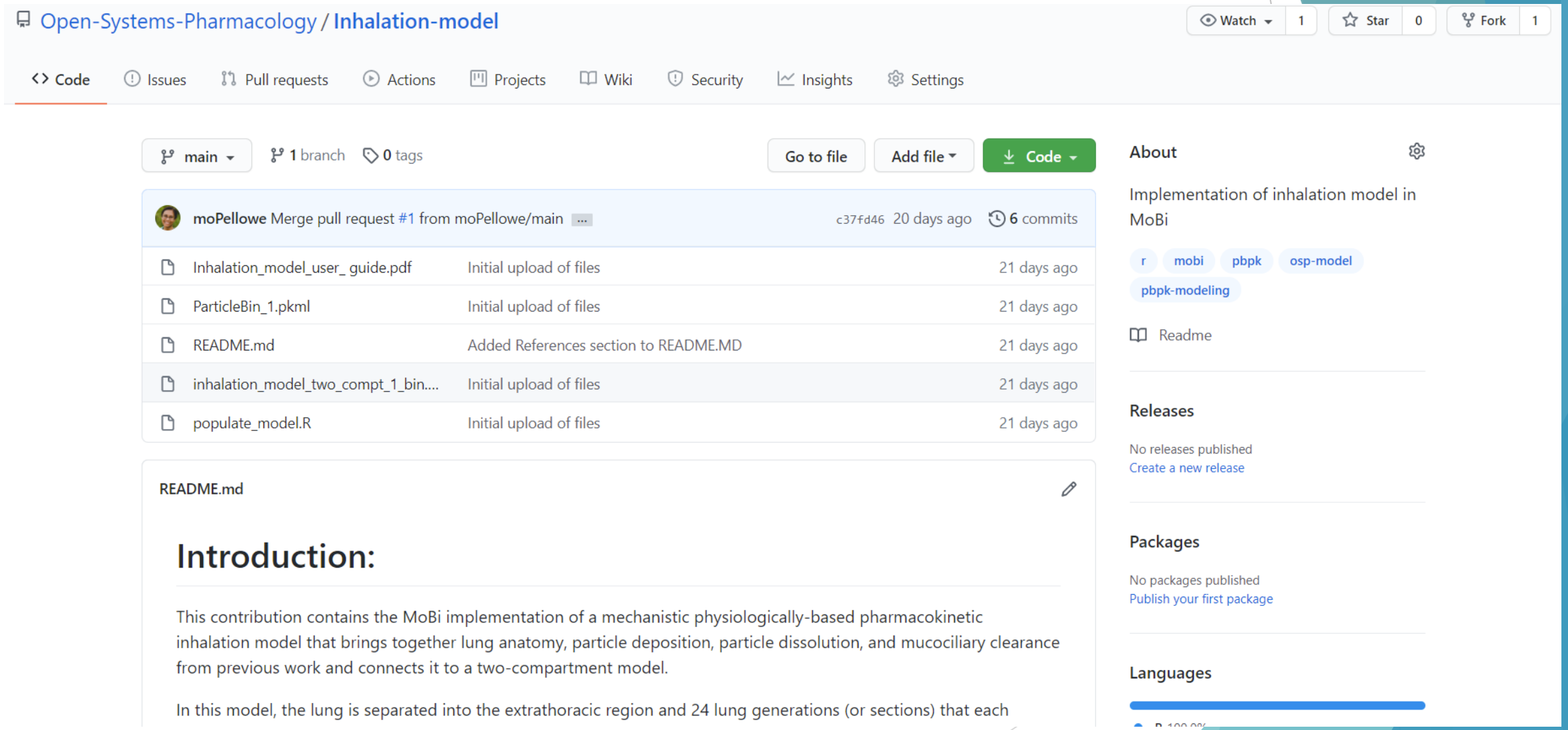
Ciprofloxacin

- Solubility: 38.4e-3 mg/L
- Well-described by the model
- Custom deposition based on additional information (Stass et al., 2017)
  - ET :
    0% (with oral charcoal),
    39.4% (without oral charcoal)
  - Lung : 38.1%
- Lung deposition may be overestimated





Inhalation model on GitHub



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