A Gaussian Markov random field based model for the porous structure of pharmaceutical film coatings

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26 May 2016

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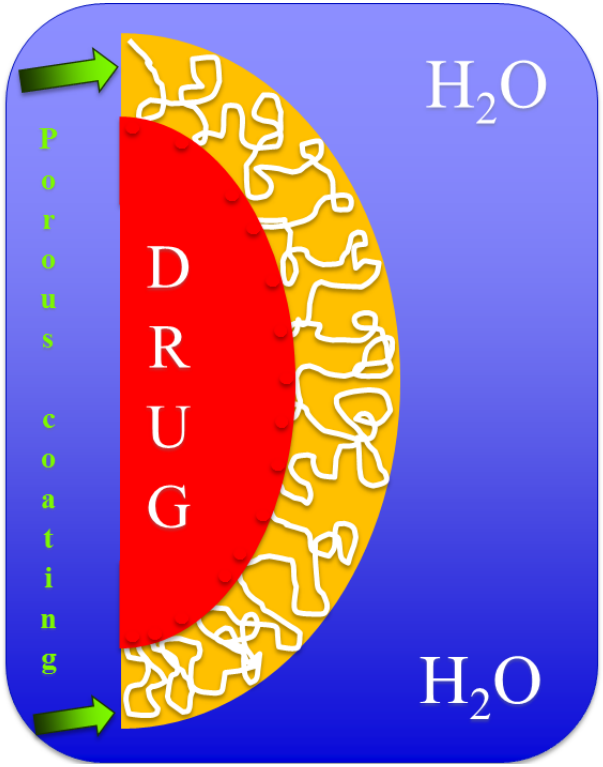
Overview

Working with the microstructure of a **porous coating**, which controls the release of the drug contained in the core of the pill/tablet.

- **Goal**: Understand how the **rate of release** of the drug depends on the coating's microstructure.



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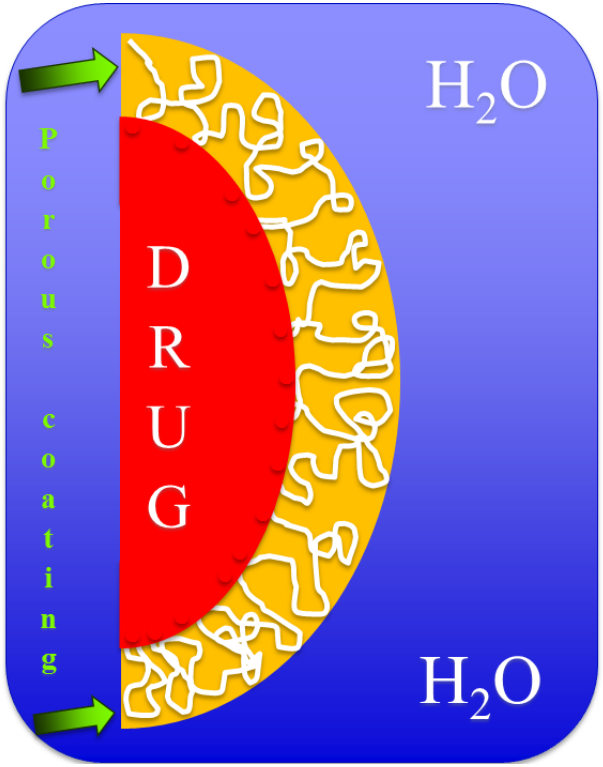
Overview

Working with the microstructure of a **porous coating**, which controls the release of the drug contained in the core of the pill/tablet.

- **Goal**: Understand how the **rate of release** of the drug depends on the coating's microstructure.
- **Method**: Use a **thresholded Gaussian Markov random field model** of the coating's microstructure, from which we can generate microstructures and
  - numerically simulate mass transport through the generated structures,
  - analyze how the transport depends on the microstructure.



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The porous polymer coating

- The tablet coating consists of an ethylcellulose/ hydroxypropylcellulose (EC/HPC) polymer blend.
- The HPC is washed out after intake of the tablet, creating a porous structure.
- We use confocal laser scanning microscopy (CLSM) images of EC/HPC free films.

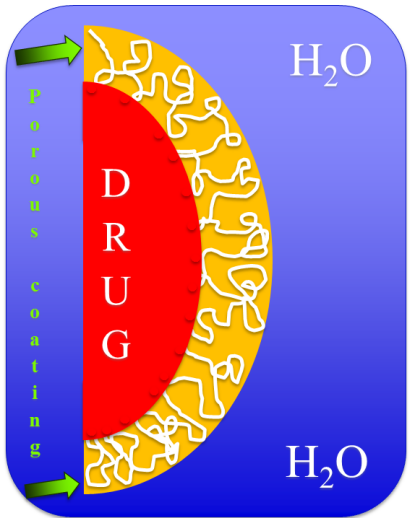

Figure: Illustration of a porous tablet coating.

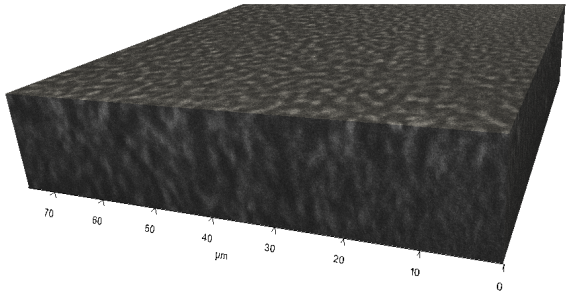

Figure: A set of CLSM images of the EC/HPC material used for the tablet coating, where the bright domains are rich in HPC.

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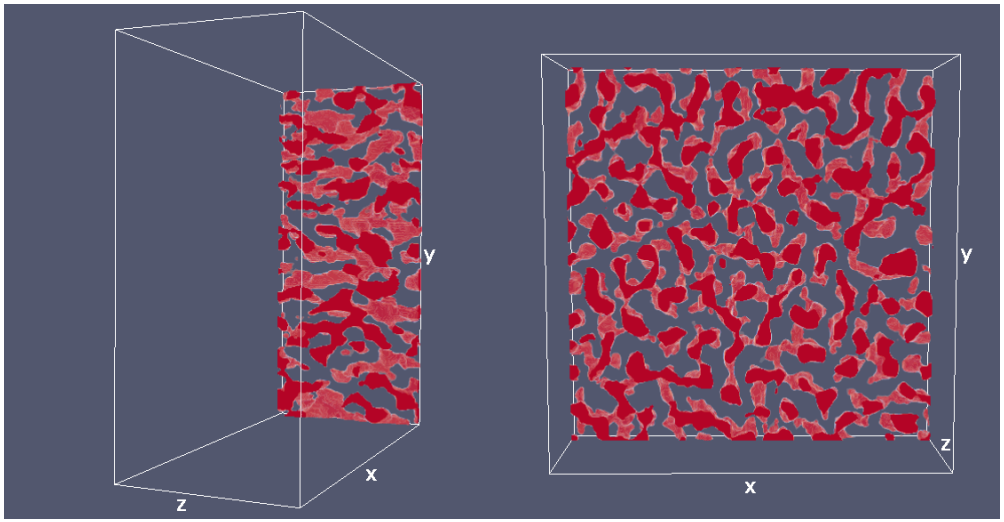
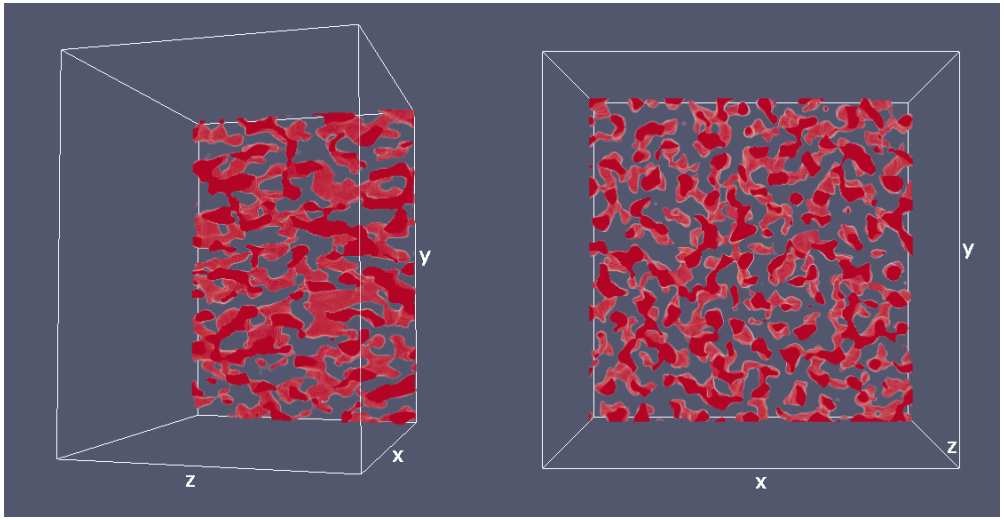
3D sections of the microscopy data:



3D sections of a simulation from the model:



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The model for the pore structure

The **model for the microscopy pore structure** is a thresholded Gaussian Markov random field (GMRF)[1]. I.e. we have

1. a latent GMRF $\mathbf{s} \sim \mathcal{N}(0, Q^{-1})$, and
2. the model for the pore space is the thresholded vector $\mathbf{y}$, where

$$y_i = \mathbb{1}_{[u,\infty)}(s_i)$$

for each pixel i (y_i equals one if there is a pore at pixel i and zero otherwise).

[1] A GMRF is a Gaussian vector with a sparse precision matrix Q (inverse covariance matrix).

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The latent GMRF

We want a different behaviour in the x-,y-plane than in the z-direction, so we need an **anisotropic** model.

We also want a model that is **computationally efficient** to estimate and simulate from.

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The latent GMRF

We want a different behaviour in the x-,y-plane than in the z-direction, so we need an **anisotropic** model.

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$\Rightarrow$ We use a **separable latent GMRF model**

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The latent GMRF

We want a different behaviour in the x-,y-plane than in the z-direction, so we need an **anisotropic** model.

We also want a model that is **computationally efficient** to estimate and simulate from.

$$\Rightarrow \text{We use a } \textbf{separable latent GMRF model}$$

i.e., the precision matrix for the latent GMRF $\mathbf{s} \sim \mathcal{N}(0, Q^{-1})$ is

$$Q = Q_{x,y} \otimes Q_z,$$

where $\otimes$ denotes the Kronecker product.

This means that $Q_{x,y}$ and Q_z are (proportional to) the marginal precision matrices for the x-,y-plane and the z-direction respectively.

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The marginal GMRFs

So we have the precision matrix

$$Q = Q_{x,y} \otimes Q_z.$$

$Q_{x,y}$ and Q_z are the precision matrices of so called

oscillating Matérn (oscM) GMRFs.

These in turn are determined by approximate solutions to an SPDE that defines a Gaussian field called the

oscillating Matérn (oscM) Gaussian random field.

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The oscM Gaussian field

The **oscM Gaussian random field** has range parameter $\kappa > 0$ and oscillation parameter $\theta \in [0, 1)$, and the spectral density

$$f(\mathbf{u}) \propto \left(\kappa^4 + 2\cos(\pi\theta)\kappa^2|\mathbf{u}|^2 + |\mathbf{u}|^4\right)^{-1}.$$

The spectral density of the **regular Matérn field** with smoothness parameter $\nu = 2$ is

$$f(\mathbf{u}) \propto \left(\kappa^4 + 2\kappa^2|\mathbf{u}|^2 + |\mathbf{u}|^4\right)^{-1},$$

so the regular Matérn field is obtained by setting $\theta = 0$.

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The oscM Gaussian field

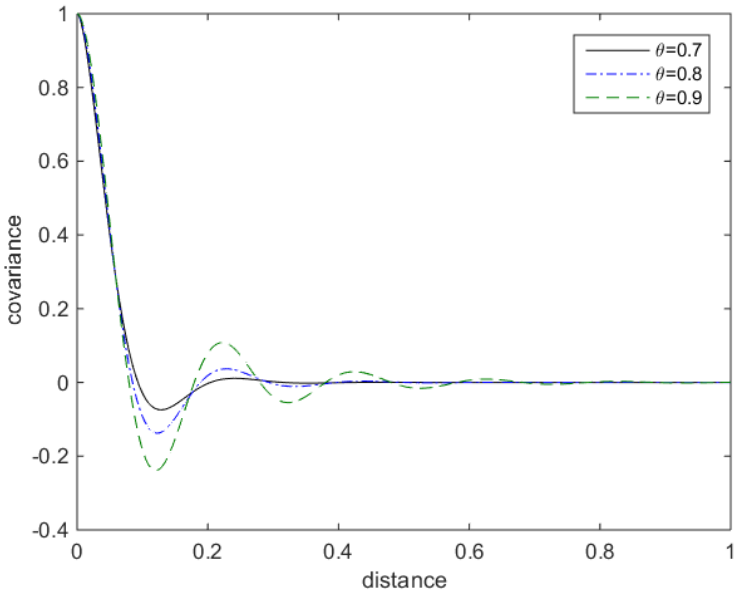
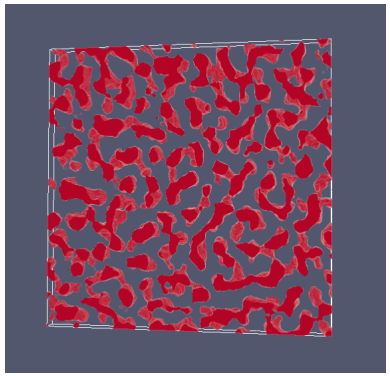
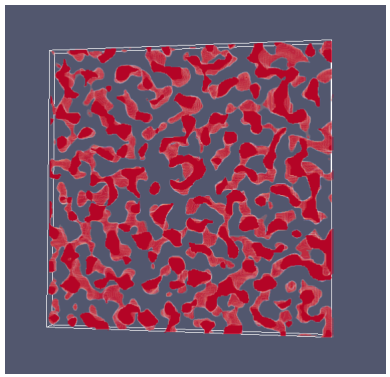


Figure: The oscillating Matérn covariance functions for different values of the oscillation parameter θ.



(a) Pore structure from CLSM image.



(b) Model generated pore-structure.

Figure: Thin 3D slices in the x-,y-plane.

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Model inference

The model is fitted using a **Markov Chain Monte Carlo algorithm**, where we take advantage of the sparsity and Kronecker product structure of the precision matrix of the latent field.

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Assessing the model fit

To assess how well the model fits the data, we use:

1. Empirical covariance.
2. Size distributions (granulometry).
3. Diffusion simulations using Gesualdo.

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Size distributions

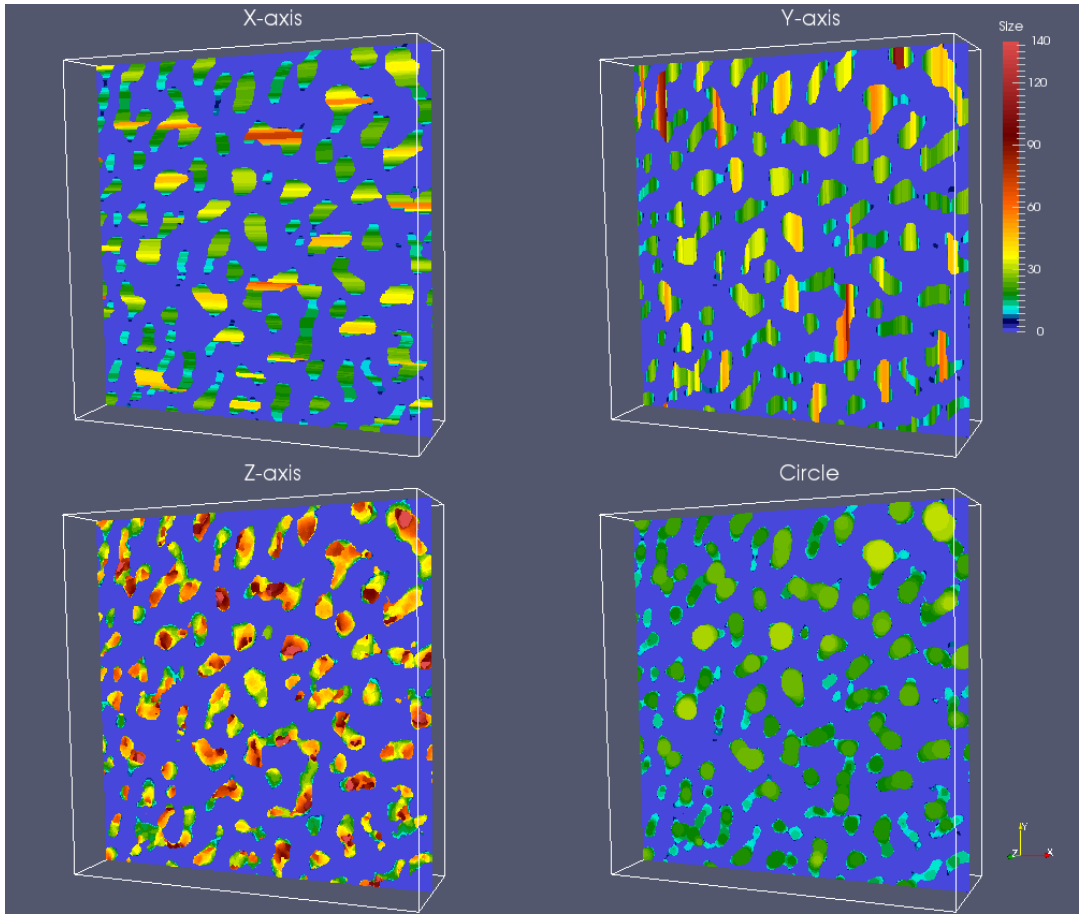

Figure: Size distributions for three lines (aligned with the x-, y- and z-axis) and the sphere, shown for a slice in the x, y-plane.

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Size distributions

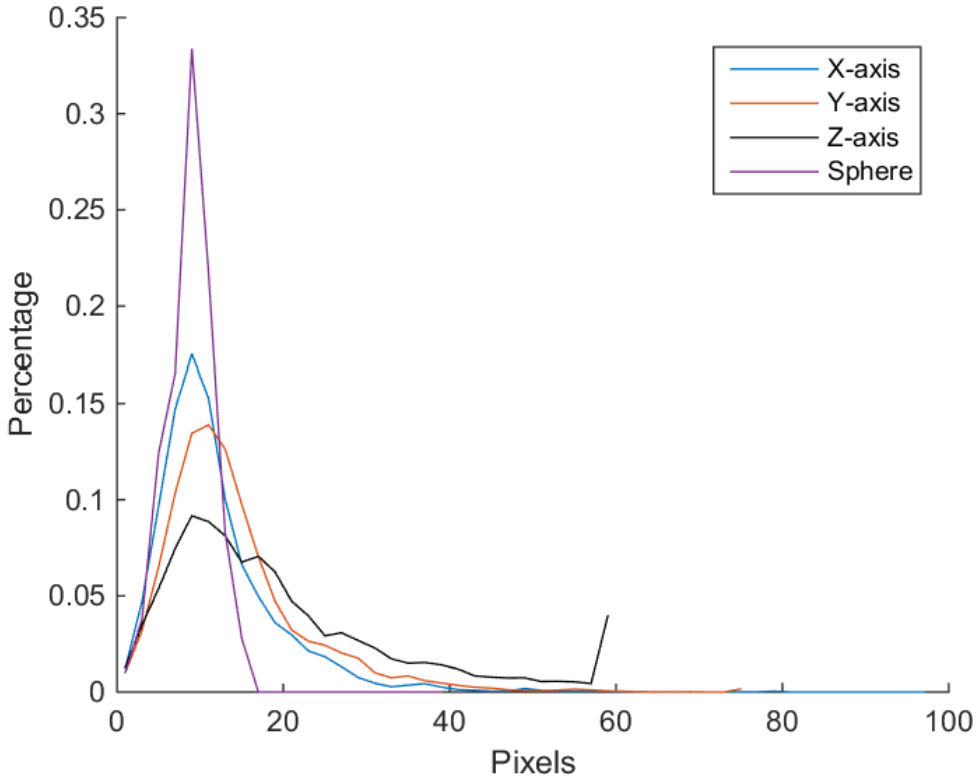

Figure: Size distributions for three lines (aligned with the x-, y- and z-axis) and the sphere.

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Size distributions

Microscopy data pore structure:

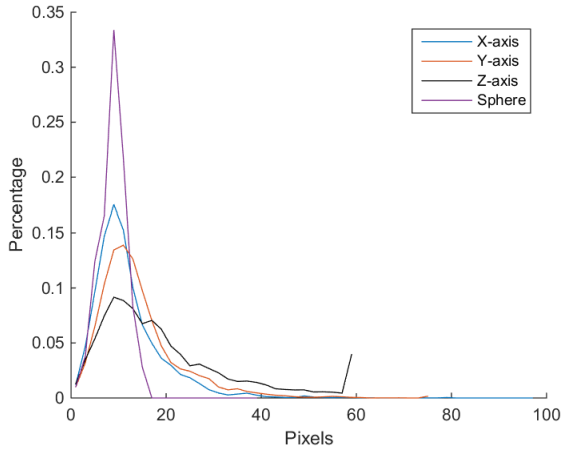

Figure: Size distributions for three lines (aligned with the x-, y- and z-axis) and the sphere.

Three model generated pore structures:

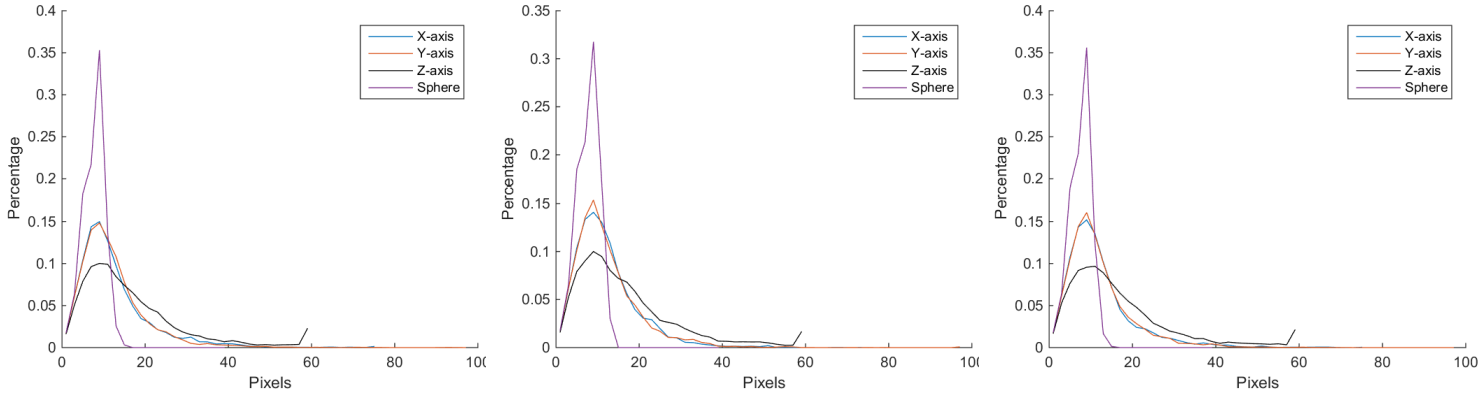

Figure: Size distributions for three lines (aligned with the x-, y- and z-axis) and the sphere.

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To assess how well the model fits the data, we use:

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2. Size distributions (granulometry).
3. **Diffusion simulations using Gesualdo**.

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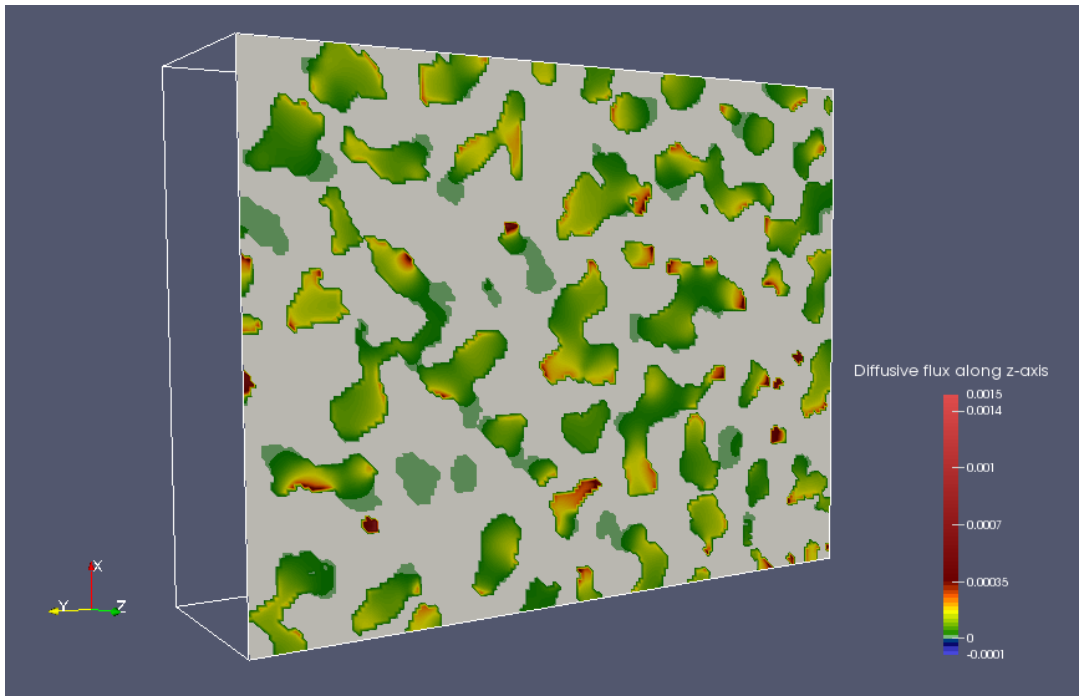
Diffusion simulations

Diffusive flux in the direction of the mass transport (z-axis) through a model generated pore structure.

The **diffusive flux** gives the **amount of substance transported** through a plane perpendicular to the direction of interest (in the figure/video the z-axis), per unit area and second, i.e. $\frac{\mathbf{mol}}{\mathbf{s \cdot m^2}}$.



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Diffusion simulations

Histogram of values of the diffusive flux in each direction (x-,y- and z-direction). The driving force behind the mass transport is a concentration difference along the z-axis, so the diffusive flux is larger in this direction.

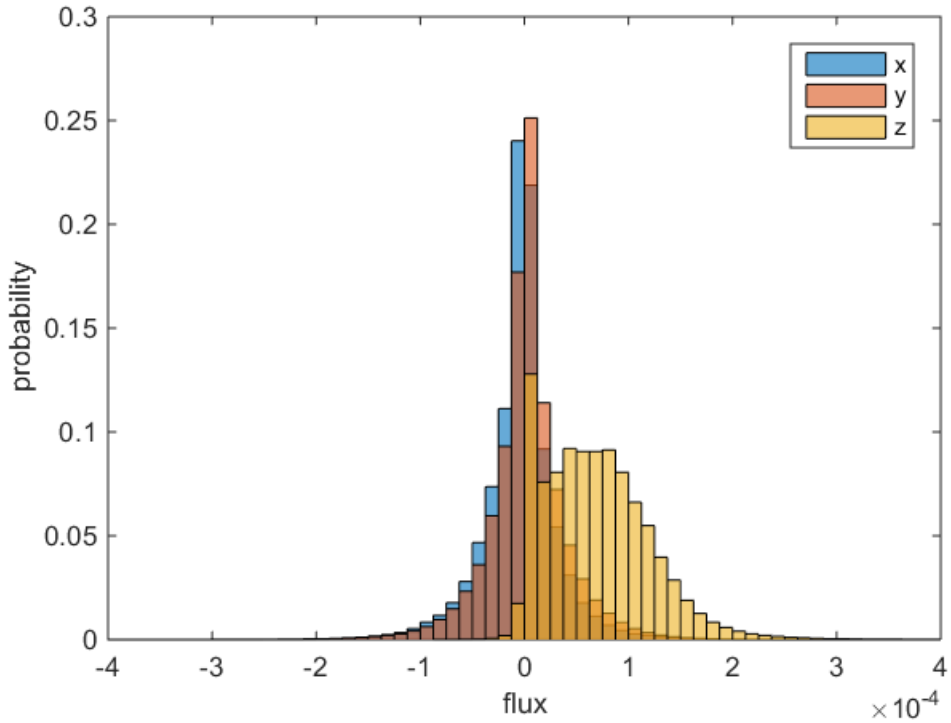

Figure: Histogram of values of the diffusive flux.

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Diffusion simulations

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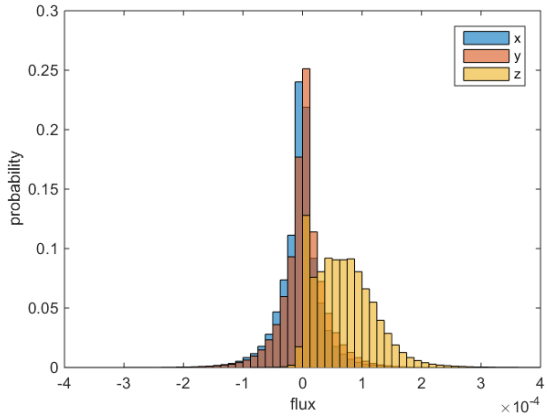

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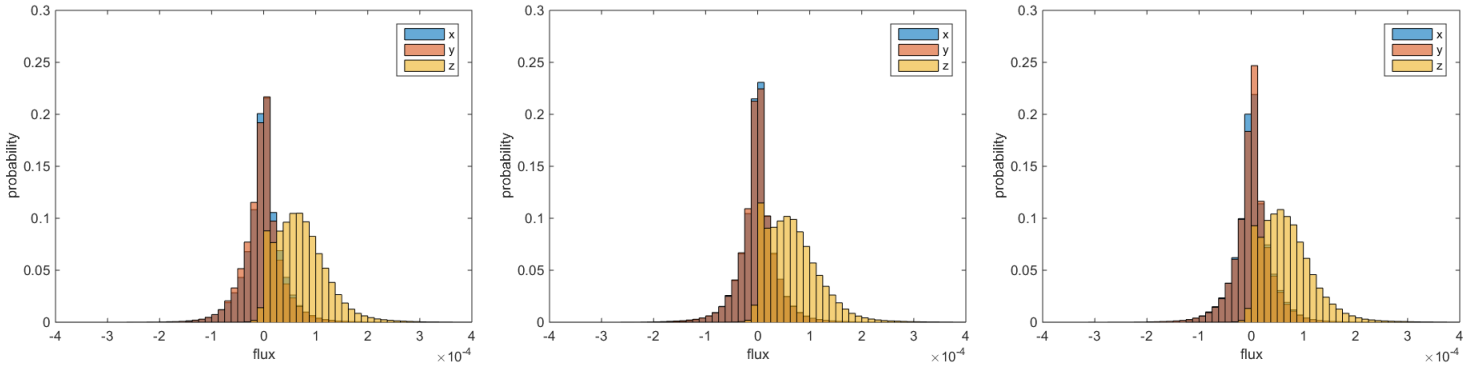

Figure: Histogram of values of the diffusive flux.

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Mass transport analysis using the model

Main goal: understand how the pore structure affects the mass transport (diffusion).

Now that we have a model that seems to fit the microscopy data, we can **go beyond the data** and investigate how the pores' sizes and shapes affect the mass transport by changing the model parameters.

- Does having different sizes of pores in different parts of the pore structure affect the mass transport? Or is it just the porosity and tortuosity that matters?
- What effect does the anisotropy in the microscopy data have on the mass transport?

Can we find **simple measures** that can predict the mass transport? In which cases is this possible?

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Conclusions

- We have found a model that fits stationary parts of the microscopy data well.
- Next step is to analyze the mass transport by simulating diffusion through model generated structures.
- After that we will apply the model to microscopy data from coated tablets (right now we are looking at free films).

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Thank you for your attention!

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