Gaussian random field based models for the porous structure of pharmaceutical film coatings

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Keywords

Gaussian random fields, threshold, latent field, oscillating covariance function, Gaussian Markov random fields, stochastic partial differential equations, porous materials, pharmaceutical coatings, permeability.

Introduction

Drug release from oral tablets can be controlled using polymer film coatings, and is determined by the porous structure of the coatings. Our aim is to analyze the transport properties of ethylcellulose/hydroxypropylcellulose (EC/HPC) polymer films using Gaussian random field based models.

Materials and Methods

We use three-dimensional confocal laser scanning microscopy (CLSM) images of phase separated EC/HPC polymer free films. The HPC is water-soluble, in contrast to the EC, and will when it is dissolved leave a porous structure with pores consisting of the space that was previously occupied by HPC (Boissier et al., 2012).

We formulate two kinds of Gaussian random field based models for the pore structure; the first is based on thresholded Gaussian random fields, and the second on latent Gaussian random fields with a binomial likelihood.

Due to the large size of the CLSM images, efficient estimation methods are needed. The stochastic partial differential equation approach by Lindgren et al. (2011) provides a link between our Gaussian random field model and a Gaussian Markov random field (GMRF) which approximates the Gaussian random field. Using the GMRF has the advantage that the precision matrix—i.e. the inverse covariance matrix of the discrete field defined by the pixel locations—is sparse, which allows us to use efficient methods for sparse matrices in the computations.

Furthermore, a stationary model is not appropriate for these polymer films. Inhomogeneities are especially noticeable in the z-direction due to the process of spraying the polymer solution. The stochastic partial differential equation approach makes incorporating non-stationarity in the model straightforward.

Results and Discussion

It is found that Gaussian fields with the oscillating Matérn covariances of Lindgren et al. (2011) fits the data very well. Figure 1 shows a thresholded sample field from this Gaussian field in two dimensions, where the black areas correspond to the pores. Figure 2 shows the empirical covariance functions obtained from 50 samples from the same model, plotted against the empirical covariance function obtained from a homogeneous part of one two-dimensional CLSM image.

The parameters for our homogeneous two-dimensional models, formulated using GMRFs with an oscillating Matérn covariance function, have been estimated using Markov chain Monte Carlo and integrated nested laplace approximations (Rue et al., 2009). To measure goodness-of-fit, we have compared the empirical covariance functions (see Figure 2). We have also looked at a point process induced by the pore centroids, with marks such as area and perimeter of the pores, and compared the point process induced by samples from the model with the point process induced by the data. The Gaussian random field models seem to provide a good fit to the CLSM images of EC/HPC polymer films.

Future work: We will extend the model by adding non-stationarity, which will enable us to formulate three dimensional models. We will also investigate the geometric characteristics further, using for instance the intrinsic volumes. In addition, we will test the model by comparing estimates of permeability obtained using samples from the model, with estimates obtained using microscopy images, and compare these with experimental results.

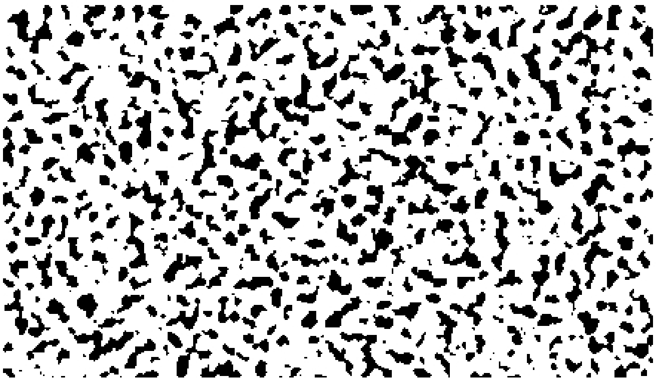

Figure 1. A thresholded sample from the Gaussian random field model with an oscillating covariance function. Black areas correspond to pores.

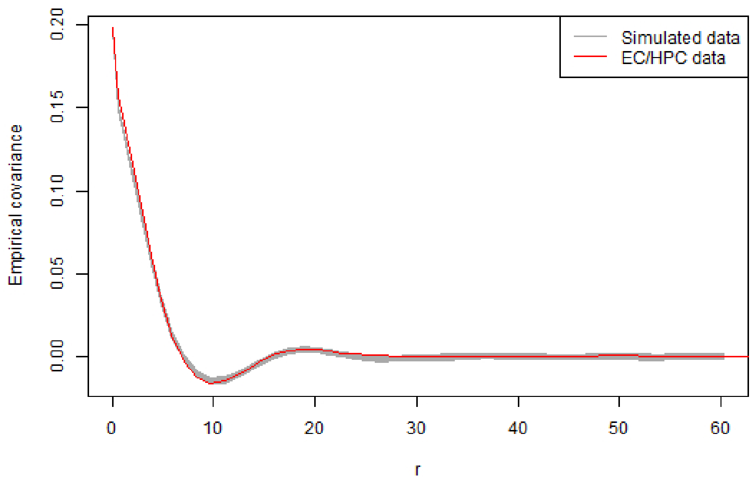

Figure 2. Comparison of empirical covariance functions of 50 samples from the thresholded Gaussian random field model, with the empirical covariance of a homogeneous part of a CLSM image.

References

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