

On the unphysical hypotheses in pharmacokinetics and oral drug absorption: time to utilize instantaneous rate coefficients instead of rate constants

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Abstract

Objectives: We investigate the unphysical assumptions associated with i) the homogeneity of the well mixed compartments of pharmacokinetics and ii) the diffusion limited model of drug dissolution.

Methods: To this end, we i) tested the homogeneity hypothesis using Monte Carlo simulations for a reaction and a diffusional process that take place in Euclidean and fractal media, ii) re-considered the flip-flop kinetics assuming that the absorption rate for a one-compartment model is governed by an instantaneous rate coefficient and iii) re-considered the extent of drug absorption as a function of dose.

Results: We found that drug diffusional processes and reactions are slowed down in heterogeneous media. By applying power law and Weibull input functions we show that the shape of concentration vs time curves is highly dependent on the time exponent of the input functions. Finally, the shape of the fraction absorbed as a function of dose plots, were found to be dependent on the stoichiometry value and the solubility of drug.

Conclusions: Our results give an insight into the complex picture of in vivo drug dissolution since diffusion-limited and reaction-limited processes seem to operate under in vivo conditions concurrently.

Methods

Diffusional processes and reactions in homogeneous-heterogeneous media

In this work diffusional processes were examined in homogeneous as well as on heterogeneous (fractal) environments. For the homogeneous case, an empty square lattice was used initially where a random walker is placed at a randomly chosen lattice site. Then the walker performs random walks, i.e. moves to one of its four nearest neighbors with equal probability. At each step position of the walker is monitored. When the walker completes a predetermined number of steps process is repeated starting from a new lattice site. For the heterogeneous case, random walks on the famous percolation fractal were studied.

Flip-flop kinetics with time varying absorption rate coefficient

Simulations were performed using a first order absorption and first order elimination in a one-compartment model.

$$\frac{dA_0}{dt} = -k_a \cdot A_0, \quad A_0(0) = F \cdot D$$
$$\frac{dA_1}{dt} = k_a \cdot A_0 - k_{el} \cdot A_1, \quad A_1(0) = 0$$

Time dependent coefficients, k , based on fractal kinetics concepts were proposed:

$$k_{a,Power} = k_1 t^{-h}$$

The absorption rate coefficient resulting from a case where the absorbed drug follows a Weibull distribution is:

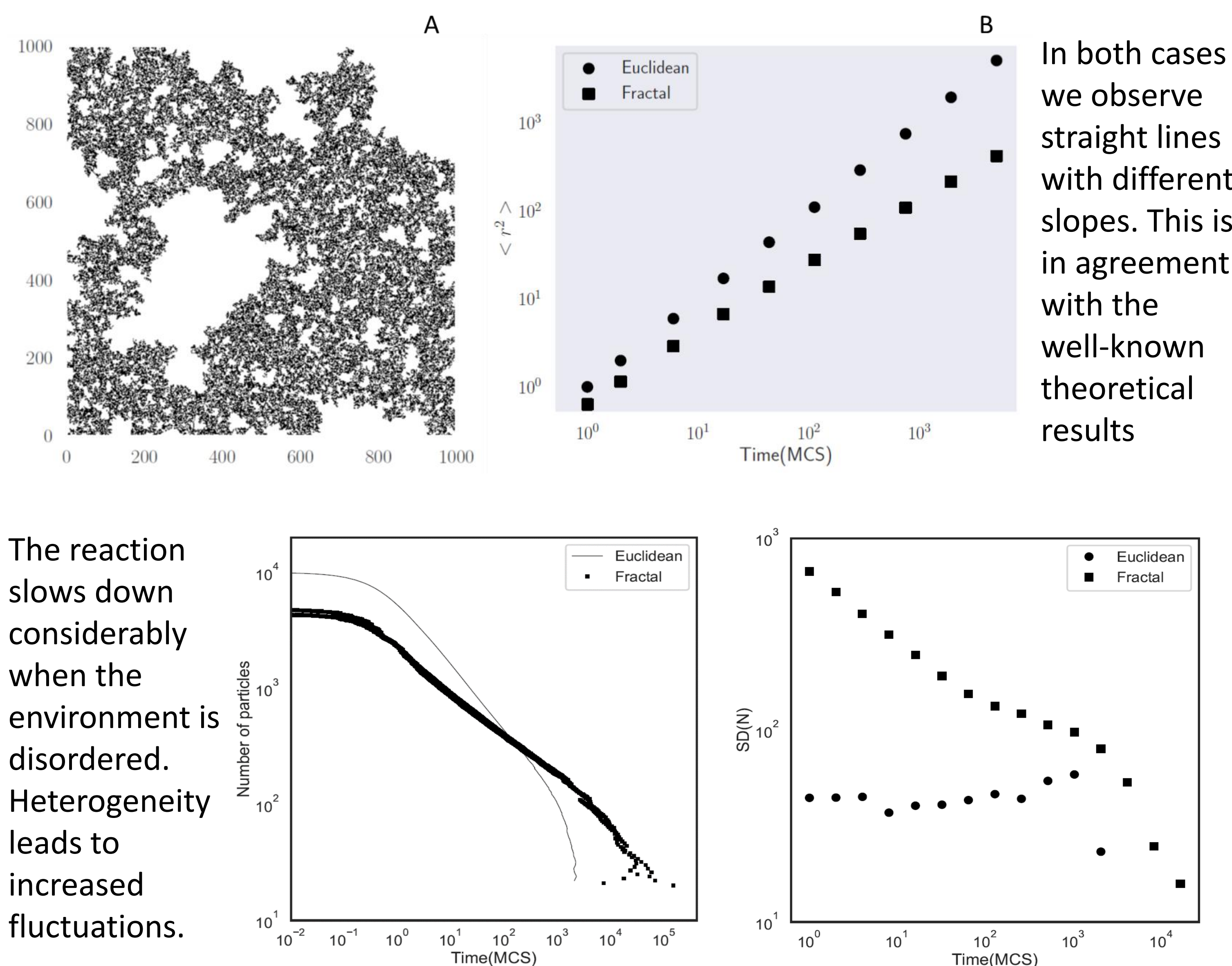
$$k_{a,Weibull} = \frac{\beta}{\alpha} \cdot \left(\frac{t}{\alpha} \right)^{\beta-1}$$

Classical or fractal kinetics in a reaction-limited in vivo model of drug dissolution

In this work we utilize an in vivo reaction limited model of dissolution to study the effect of the stoichiometry value of the dissolution/reaction on the fraction of dose absorbed. Both integer (1.0 and 2.0) and non-integer (0.7, 1.5) stoichiometry (α) values were examined.

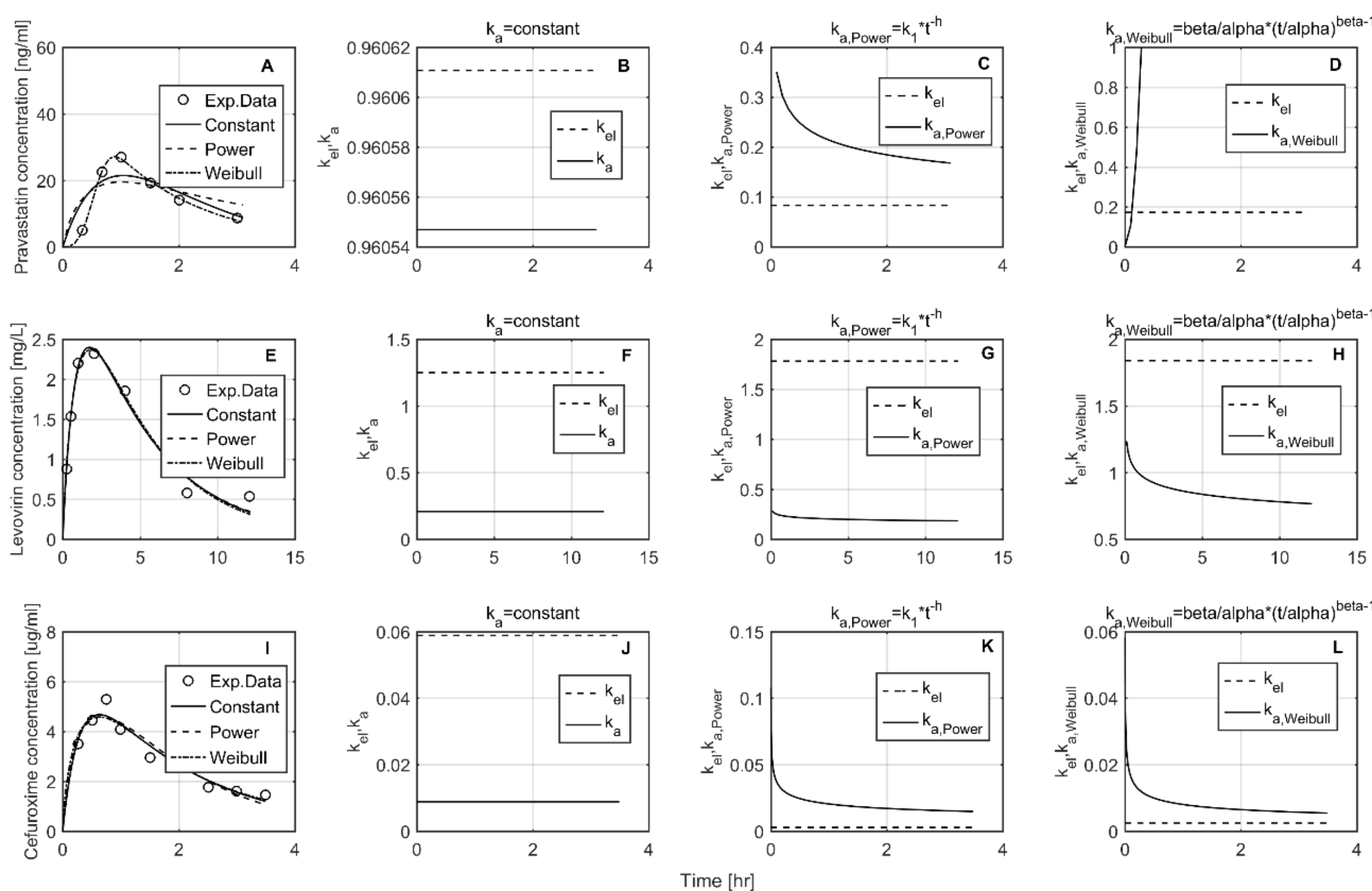
Results

Diffusional processes and reactions in homogenous-heterogeneous media



The reaction slows down considerably when the environment is disordered. Heterogeneity leads to increased fluctuations.

Flip-flop kinetics with time varying absorption rate coefficient

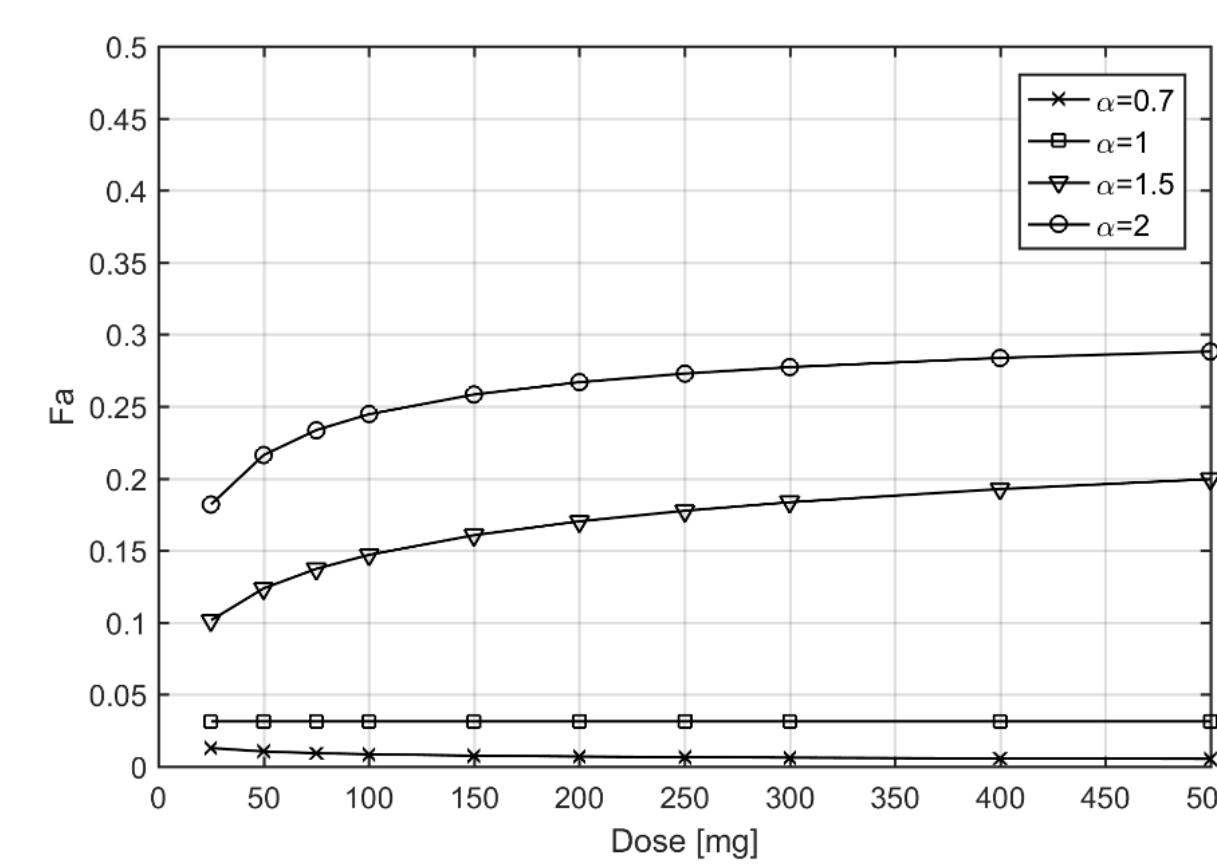
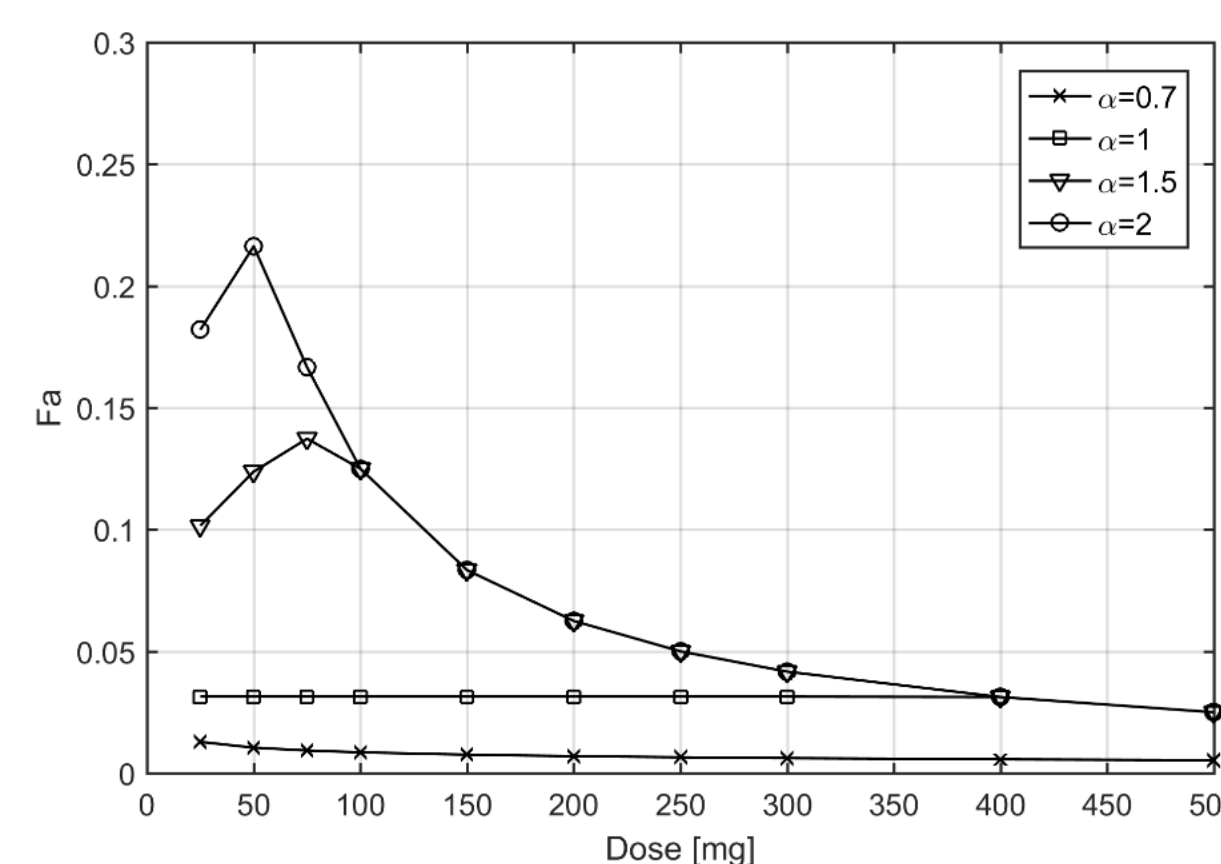


Time varying absorption coefficient may result in better fits (A) and indicate that the prevalence of k_e and k_a is time dependent

Classical or fractal kinetics in a reaction-limited in vivo model of drug dissolution

The graphs exhibit ascending and descending limbs for the higher stoichiometries

For the highly soluble drug a continuous increase of fraction absorbed is observed when the higher stoichiometries are used



Conclusions

Our work revealed that the processes are slowed down in heterogeneous media. Along the same lines fitting of PK data further underlined that the rate limiting process (absorption vs elimination) is time dependent and as such identification of flip-flop behavior can be misinterpreted. Finally, the profile of the fraction of dose absorbed as a function of dose is affected by the solubility of drug and the stoichiometry of the dissolution/reaction