# Numerical Methods for the Estimation of Effective Diffusion Coefficients and other Parameters of Controlled Drug Delivery Systems

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I miss you...

Haryani Muhd Mahali

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# Abstract

In this thesis we develop various numerical tools for estimating unknown parameters that characterise the diffusion property of a polymeric drug device in controlled drug delivery. Two types of fluid systems are considered in this work: the rotating fluid system and the flow-through fluid system. Based on the consideration of effects from the initial burst and boundary layer phenomena, three mathematical models are developed for the parameter estimation problem. They are the basic model (BM), initial burst model (IB) and boundary layer model (BL). The latter two models can also be combined to form the initial burst and boundary layer model (IB+BL). In these models, up to four unknown parameters need to be determined. These are the diffusion coefficient in the initial burst phase, diffusion coefficient after the initial burst, width of the boundary layer and the time of the initial burst.

We first develop analytical solutions for the diffusion process of a drug from a spherical device to a finite external volume. In these solutions, we assume that the container of the system is spherical and concentric with the spherical device. The formula for the ratio of the mass released in a given time interval and the total mass released in infinite time is also derived for both BM and IB models. We then propose an optimisation approach to the estimation of the parameters based on a nonlinear least-squares method and the developed analytical solutions.

A new observer approach method is developed for the parameter estimation problems. In this approach, we construct estimators for the unknown effective diffusion coefficients characterising the diffusion process of a drug release device using a combination of state observers from the area of adaptive control and the developed drug

diffusion models. We show that the constructed systems are asymptotically stable and the estimators converge to the exact diffusion coefficients. An algorithm is proposed to recursively compute the estimators using a given time series of a release profile of a device. The numerical results show that this approach is much faster than the conventional least squares method when applied to the test problems.

We then present a full numerical approach to the estimation of effective diffusion coefficients of drug diffusion from a device into a container in a flow-through fluid system. Compared to the rotating fluid system considered earlier, this system has a source and a sink condition due to a fluid flowing through the system at a constant rate. In this approach we first formulate the drug delivery problem as an initial boundary value problem containing the diffusion equation. We then propose a continuous nonlinear least-squares problem containing the system as a constraint to estimate the unknown parameters. The nonlinear optimisation problem is discretised by applying a finite volume scheme in space and an implicit time stepping scheme to the equation system, yielding a finite-dimensional nonlinear least-squares problem.

Finally, we extend the full numerical technique to three dimensions for estimating effective diffusion coefficients of drug release devices in both rotating and flow-through fluid systems. The 3-dimensional full numerical technique is crucial for solving the parameter estimation problems in their real 3D geometries.

Extensive numerical experiments have been performed using experimental data from various polymeric devices for all the methods developed in this research to demonstrate their performance. All the numerical results show that our methods are efficient and accurate and thus they provide useful tools for solving real-world problems in optimum design of drug delivery devices.