Computational Study of Drug Release from Drug-Eluting Implants

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Abstract:

Our team sought to model a drug-eluting matrix implant and calculate drug release profiles considering drug diffusion and dissolution from the implant, with the hopes of uncovering how altering certain drug design parameters would affect the drug release from the implant. We utilize Molecular Dynamics (MD) simulations to generate a model of drug crystals of various aspect ratios randomly placed and oriented inside of a simulation region representative of a matrix implant. We develop a version of the finite difference method algorithm to numerically solve the dissolution of the drug crystals and diffusion of the dissolved drug through the implant. By combining the MD-generated implant structures and finite difference method, we determine the drug release profile from implant. We then examine varying the implant design parameters to study the parameters’ influence on the drug release speed. We find that increasing the radius of matrix implant will increase the quantitative amount of drug released. However, when the drug release profiles are normalized by the implant surface area, the drug release profiles obtain a consistent shape for all implant radii studied. Finally, we vary the drug aspect ratio (length over diameter), and we determine that longer aspect ratio drugs result in an increased drug release rate.
Introduction:
Sustained uptake of pharmaceutical compounds is required for the treatment of chronic diseases[1], preventive healthcare[2], and contraception[3]. Repeated oral administration or injection of drugs is essential to the success of the treatment. However, the drug administration process requires the patient’s access, compliance, and diligence.[4,5] Long-lasting, drug-eluting implants provide many advantages compared to traditional drug delivery methods including improved patient compliance[6], increased patient comfort[7], and reduced drug side effects[8]. Furthermore, the implants can also provide localized and site-specific delivery of drugs which improves the drug effectiveness.[9]

Drug-eluting implants were first applied in the 1990s for contraception.[10] Based on the implant design, they can be classified into three types: matrix implants, reservoir implants, and osmotic implants.[11] In this project, we will focus on matrix implants which consist of drug crystals dispersed in a polymer matrix. Drug release from these implants occurs by drug dissolution and subsequent drug diffusion through the polymer matrix and/or the channels created by previously dissolved drugs.[12] Thus, the drug release rate is controlled by factors including 1) the drug solubility, 2) the drug crystal dissolution rate, and 3) the drug diffusivity through the implant.

To ensure the implant performs as expected, it is important to understand the implant's drug release profile over time because the profile indicates the drug release rate at different periods. This information is crucial to avoid unwanted drug side effects and maximize the efficiency of the implants. Matrix implants tend to have a relatively high initial drug release, followed by a decrease in the drug release rate, and then a steady release rate.[13] This initial release can be helpful if the application requires a quick accumulation in the target site. However, it can also be harmful if the loaded drug requires a narrow therapeutic concentration range because the quick initial release may cause acute toxicity to local tissue or the whole body.[11]

The implants’ drug release rate is influenced by 1) the formulation of the drug-embedded implant, 2) the chemical and physical properties of the drug, polymer, and excipients, and 3) the manufacturing process. This work seeks to focus on identifying the influence of the drug/implant design parameters as they are not fully understood. There is a need to map drug design parameters to release rates. However, massive experiments would be required to determine the relationship between design and drug release behavior. As the implants are usually designed to work in vivo from several months to several years, the massive and time-consuming experiments required could slow down the development of new implants. There is a clear demand for a high-throughput approach to understanding the drug release process that can provide guidance on the design of implants.

In this work, we utilize a computational approach to link drug design to the drug release profile from the implant of interest. A computational approach potentially allows for a cheaper, high-throughput analysis compared to experiments where each drug design of interest would need to be painstakingly produced. Furthermore, a computational approach may enable finer control over the drug design parameters than experiments. We first generate a computational model and method to disperse the desired drug crystals in the implant. Then to understand the drug release from the implants, we utilize a method that can simulate the drug crystal dissolution[14] and subsequent diffusion[15] which requires solving their respective differential equations throughout the simulation. We select the finite difference method because it is designed to evaluate derivatives numerically over time even with complicated boundary conditions. Finally, we examine how the implant formulation (implant radius) and drug crystal aspect ratio (length to width) impact the overall drug release profile from the implant.

Project goal:
In this project, we develop a computational approach to generate models of implants with randomly placed drug crystals and simulate the drug release behavior of these implants. More specifically, there are three objectives in this project:

Objective 1: generate a model implant with randomly embedded drug crystals for a given set of drug crystal parameters (drug diameter, aspect ratio, and loading). We determine an appropriate 3D model for drug crystals and a method to randomly distribute and orient the drug crystals in the cylindrical implant.

Objective 2: develop a method to simulate drug release from the structures produced in Objective 1. We use the finite difference method to numerically determine the drug release profile considering drug dissolution and diffusion in the implant.

Objective 3: determine the influence of drug diameter, aspect ratio, and loading on the drug release rate from the implant. We consider how the implant design parameters such as cylinder radius affect the drug release profile. We want to observe the sensitivity in the change in the drug release profile to these parameters.
Computational Approach:

Objective 1:
We use the LAMMPS Molecular Dynamics (MD) package\cite{16} to generate a model of the drug-eluting implant and produce a random displacement and orientation of all of the drug crystals throughout the model. We represent each drug crystal as a series of connected spheres with a diameter equal to the drug diameter and the number of connected spheres is equal to the drug aspect ratio. We incorporate a 5% dispersity in the drug diameter by choosing drug diameters from the lognormal distribution with the set drug diameter and set dispersity. We then create a simulation box with a length and width of 2 mm to match the experimental cylindrical implant radius. The simulation box has a height of 0.1 mm which is smaller than the experimental implant height of 40 mm. This choice means our simulation box represents a portion of the cylindrical implant, and the choice balances the computational intensity of modeling a large implant. Also, for our system of interest, our mentor Dr. Lamm determined that the drug primarily is released radially instead of through the cylinder ends, so we will scale our drug release results based on the ratio of the cylindrical slice modeled compared to the experimental length.

To prevent drug overlap when placing the drug crystals, all drug crystals are initially placed with identical orientations in the simulation box as shown in Figure 1a. Then, we perform a sufficiently long MD simulation in the NVT ensemble\cite{17} to ensure the drug crystals obtain a random orientation and position that is not related to their initial starting structure. We only retain drug crystals that are within the implant radius we are modelling. While we do not explicitly represent the polymer in the implant, we note that the space between the drugs is treated as polymer.

Figure 1: Example VMD visualization of the LAMMPS MD simulation that uses a connected series of spheres to represent the drug crystals inside of a cylindrical implant a) before the MD simulation, b) after MD simulation, and c) after simulation but with some crystals hidden. Individual drug crystals can be seen represented as a collection of spheres attached together.

Figure 2: Schematic representing dissolution and diffusion for drug crystals. Differential equations governing the dissolution and diffusion of the drug are provided along with how the FDM numerically solves the equations. The diffusion equation is shown for the FDM in only the x direction for clarity. \( \frac{dC}{dt} = \frac{DC_{i,j,k}}{\Delta t} = D\frac{C_{i-1,j,k} - 2C_{i,j,k} + C_{i+1,j,k}}{\Delta x^2} \). Figure 1b and 1c provide a visualization of a sample implant structure with all drug crystals colored differently to illustrate how the final structure is randomly oriented and positioned.

Objective 2:
We code the Finite Difference Method (FDM) to solve for dissolution of the drug crystals and diffusion of the dissolved drug through the implant.
FDM is commonly used to investigate the dissolution and diffusion of drugs in pharmaceutical studies.[17] Scientists have also used FDM to study the drug release from implants composed of different particle shapes.[18]

The dissolution and diffusion of the drug can be described numerically using differential equations, and we show the Noyes-Whitney dissolution equation[19] and Fick’s law for diffusion[17] used in this study in Figure 2. The FDM numerically solves differential equations by treating the differential as a finite difference (Δ) to progressively solve the equations over time. The FDM obtains the finite difference (in our case of concentration, C) by discretizing the implant into a regularly spaced grid and calculating the finite difference between neighboring grid points. Thus, the change in concentration (Δconcentration) for a short time interval (Δt) is determined by considering the grid point’s neighbors and the grid point’s previous concentration by solving the diffusion and dissolution equations (Figure 2).

Before initiating the FDM simulation, the MD structure from Objective 1 is discretized into grid points with grid points within a drug crystal marked as crystalline drugs. To consider drug crystals as effectively touching despite not actually touching, we mark grid points as connectors if they are between two drug crystals within a distance d̄touching which can be adjusted. The connector grid points do not have crystalline drug, but they are retained to enable drug diffusion through the points. Grid points within the implant that are not marked as crystalline or connectors are set as polymer and removed because for this problem, the dissolved drug cannot diffuse through the polymer matrix. Grid points radially outside of the structure are marked as boundary points and have their concentration constantly set to zero to mimic sink conditions. The grid points neighboring the boundary points within the implant are marked as grid points that can dissolve because the solvent can access those grid points. The FDM proceeds by solving for the crystalline and dissolved drug concentration for each grid point. To speed up the FDM, we only consider grid points that are dissolving or have already fully dissolved because the other grid points will have no change in their concentration. When a crystal in a grid point fully dissolves, its neighboring grid points are marked as able to dissolve since solvent can now access the neighboring grid points. Over the course of the FDM, the amount of released drug between each time step is obtained by determining the amount of drug that diffused out from the implant during the corresponding time point. Figure 3 shows a schematic representing the transformation from a real-world system to an FDM compatible system. In the FDM, the grid point spacing is an important parameter to balance representing the high-resolution of the drug crystals morphology in the structure (small grid point spacing) with the computational intensity of performing the FDM on all of the grid points (larger intensity for more grid points). To reduce the computational intensity of the FDM, one can consider increasing the grid point spacing and investigating smaller implant structures.[18]

**Figure 3:** Scheme of drug-eluting system in the real world, for the MD simulation, and used in FDM.  

**Objective 3:**

We simulate drug release by combining Objective 1 and Objective 2. As mentioned previously, the FDM is computationally intensive, so we wish to understand how to reduce the FDM computational intensity without affecting the resulting drug release profiles. To do this, we must perform numerous FDM simulations, so we consider a generic drug crystal with a solubility of 0.1 mg/μm³, a dissolution rate of 0.5 μm/s, and a diffusivity of 0.5 μm²/s to achieve a more rapid drug dissolution than the drug of interest that is designed to be slowly dissolving. Using this generic drug, we first examine the impact of the grid spacing (Δs) in the FDM on the drug release curves. The smaller the Δs, the finer the resolution of the drug crystals in the implant and the more grid points the FDM must simulate, increasing the computational intensity. Thus, we seek to understand whether varying Δs quantitatively or qualitatively affects the drug release rate from a structure created in Objective 1. Additionally, we vary the implant radius to examine the impact on the drug release profiles. We are interested in whether a smaller implant radius maintains a similar qualitative drug release profile as a larger implant radius because the smaller implant radius can run in substantially less time to enable faster exploration of the drug design parameters. We also determine that scaling the drug release by the cylindrical surface area enables...
the drug release curves to collapse onto each other for the various implant radius examined. We conclude by investigating the drug of interest using the FDM, and we set the drug constants of solubility to 1 mg/cm³ (given by Dr. Lamm), dissolution rate to 6x10⁻⁴ cm/s [20,21], and diffusivity to 6x10⁻⁶ cm²/s [22] using literature constants of other similar drugs when unknown.

The University of Delaware’s DARWIN supercomputing cluster is used to run our LAMMPS simulation and run our python script that performed the FDM. For the LAMMPS simulations, we utilize 64 CPUs and run for a total of ~10 CPU-hours. For the FDM, we request 4 CPUs. The FDM runs for generic drug solubility, dissolution rate, and diffusivity ran for ~200 CPU-hours, and the FDM runs for the drug of interest were run for ~2 weeks through the end of the class semester (utilizing ~1,350 CPU-hours).

Results and Discussion:

For Objective 1, we demonstrate that we are able to create a drug-embedded implant structure when varying the drug design parameters in Figure 1. The MD approach is able to produce implant structures for the various drug design parameters of drug diameter, aspect ratio, and loading. We also incorporate a dispersity in the drug diameter to mimic the experimental drug crystals which are not monodisperse; the drug aspect ratio is constant for all drug diameters. To ensure the drug crystals are randomly dispersed and oriented, we ensure that the root mean squared displacement during the MD simulation is larger than the drug crystal length, and the orientational order parameter[17] S2 is ~0 indicating negligible orientational ordering.

For Objective 2, we validate the FDM by applying it to a small-scale sample system to understand if the FDM can simulate drug dissolution and diffusion to obtain realistic drug release profile shapes (Appendix Figure A1). In Figure A1a, we show the 2D slice of a 3D connected network of drug crystals (white), and to mimic the experimental system, we only allow the drug to dissolve when there is no crystalline drug in the drug crystal in front of it. Additionally, the dissolved drug can only diffuse through the space that was previously occupied by drug crystals (white area). We determine the drug release through the bottom of this sample system and plot the cumulative drug release (Figure A1b) and instantaneous drug release (Figure A1c). By examining the drug release profile curves, we observe that their shapes match with the expected drug release shape with an initial period of rapid drug release followed by a more consistent, slower drug release. Thus, this sample system indicates to us that our FDM is performing as expected, so we can confidently apply the FDM to the structures produced in Objective 1.

For Objective 3, we combine both Objective 1 and Objective 2 to simulate the drug release from the computational models of the drug crystals embedded in the implant. In Figure 4, we examine how adjusting the FDM grid spacing (∆s) and implant radius (R) influences the drug release profile. For this case, we consider a generic drug (solubility (0.1 mg/µm³), dissolution rate (0.5 µm/s), and diffusivity constants (0.5 µm²/s)) to enable the FDM to finish in ~1-2 days on the DARWIN supercomputer. In Figure 4a, when we increase ∆s, we obtain a larger amount of drug released which is due to the larger grid spacing resulting in an effective enlargement of the drug crystals. Larger grid spacing also increases the variability between each structure due to the larger change in the structure after the grid point assignment. However, the qualitative drug release shapes are similar for ∆s = 1 µm and ∆s = 2 µm indicating that for a sufficiently fine grid resolution, the

![Figure 4: Simulated drug release from drug implant structures created in Objective 1 with drug diameter of 10 µm, AR of 1, and drug loading of 30%w. We use a generic set of constants for drug solubility, dissolution rate, and diffusivity to enable these exploratory simulations to finish in ~2 days of running, so the axes are in simulation units. a) shows varying the FDM grid spacing (∆s) for implants with implant radius (R) of 1000 µm which is the experimental implant radius. b) illustrates drug release when R is adjusted. Error bars are the standard deviation of 3 different structures.](image-url)
drug release of the same implant structure generated with different $\Delta s$ possesses similar release curves. The smaller the $\Delta s$, the more computationally intensive the FDM is. In Figure 4b, we examine how the implant radius affects the drug release profile shape. This step will determine if we can simulate implants with smaller radii to obtain similar trends as implants with larger radii at a reduced computational intensity. We scale the drug release value by the ratio of the implant surface area to the experimental radius size ($R = 1000 \mu m$) to obtain similar quantitative drug release values for comparison. We note that changing $R$ does not impact the drug release profile shape with all three radii obtaining similar qualitative shapes. The smaller radii structures possess larger variability because the structures are smaller with a greater dependence on slight variations in the structure compared to the larger implants. Overall, Figure 4b demonstrates that a smaller implant radius can be considered while still providing a similar qualitative release profile at a significantly lower computational intensity.

Then, we varied the drug crystal aspect ratio (AR) for the drug of interest in Figure 5. The two most striking features of the figure are that the drug release profiles appear drastically different from those presented in Figure 4 and there is a quantitative difference in the drug release depending on the drug crystal AR. As we mention in the Methods, the drug we simulate in Figure 4 is a generic, fast-dissolving drug that allows us to quickly simulate the drug release profile to ensure the release curve possesses the expected shape. The drug of interest is designed to be a slowly dissolving, long-lasting drug to provide continual drug release over the long lifetime of the implant. Thus, the reason for the drastically different drug release profile shape in Figure 5 is because the total simulated time is half an hour in real-time. We expect that we would need to simulate close to 10-15 days of drug release to obtain a similar drug release profile shape as that in Figure 4. Instead, we focus on the fact that Figure 5 demonstrates that there is a notable difference in drug release when the drug crystal aspect ratio is changed. We expect that over time, the observed differences will maintain or potentially grow larger indicating that the drug crystal AR significantly influences the drug release from the implant.

Conclusions:

In this work, we develop a method to generate implants containing randomly distributed drug crystals with different parameters (e.g., drug crystal diameter, drug crystal aspect ratio, drug loading ratio). We then adapt the finite difference method to simulate drug release from the generated implants. Combining the two methods, we find the FDM grid spacing and the implant radius quantitatively affect the amount of drug released while maintaining a similar profile shape. When we consider the drug of interest, we observe that a longer drug aspect ratio increases the rate of drug released in the early stages of drug release from the implant. Combining the implant structure generation and FDM code can generate the drug release profile from different drug designs which can help pre-select potential drug design parameters to study further for implants. However, the process is computationally intensive for the drug of interest because the drug is slow-dissolving which requires long FDM simulations. The approach currently developed can serve to provide a qualitative understanding of how the drug design parameters impact the drug release profile from these implants by considering a generic drug with faster dissolution properties. This would show qualitatively which drug design parameters most or least significantly affect the drug release. A qualitative approach could be especially helpful for an industrial application as it would quantify which drug parameters must be finely controlled during production and which can have variability without changing the desired drug release profile. To enable quantitative comparisons with experimental results, future work will need to accelerate the FDM code speed. Suggestions include converting the code from Python to C programming language and enabling or improving the ability for the code to run on multiple CPUs or GPUs at once.
Data and Code availability


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- C. Heil (Conceptualization, methodology, Obj. 1 – MD, Obj. 2 – FDM, Obj. 3 – MD + FDM, software optimization, writing – original draft, editing)
- T. Huber (Software optimization, writing – original draft)
- B. Wang (Conceptualization, writing – original draft, editing)
- M. Lamm (Problem conceptualization, guidance)
- Jayaraman (Computational resources, Editing – Original draft report, Final report)
- S. Chandrasekaran (Computational resources, Editing – Final report)
References:


Appendix:

Figure A1: Drug release evaluation on a sample structure to evaluate the FDM performance. a) provides a 2D image of the 3D structure we consider. To mimic the experimental system of interest, the white crystalline drug cannot diffuse through the black area, and drug crystals can only begin to dissolve when one of its neighbors is finished dissolving. b) and c) do not provide numerical values as we utilize a generic set of constants for the drug solubility, dissolution rate, and diffusivity, so axis values are removed to prevent confusion.