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A Look into Applied Numerical Methods for Drug Delivery Models

I. Abstract

With the advancement of medicine, new drugs, therapeutics, and treatments have been developed, including more advanced drug delivery devices and techniques. These devices incorporate various materials that allow for the controlled release of a specific drug, typically measured as concentration over a time interval. To construct such a device, an adequate mathematical model for drug release must first be designed, which is typically solved using numerical methods. However, since the body is a dynamic and complex system, this task can be quite challenging. In this review, we analyze two papers, each with separate approaches to modeling a controlled drug release system. The first paper, by McGinty and Pontrelli, utilizes a system of partial differential equations (PDEs) that are solved numerically to approximate drug release from a polymer into a tissue with second-order accuracy. The second paper by Heredia *et al.* utilizes polynomial interpolation of a large data set to construct predictive equations for the release of a drug via the polymer poly(lactic-co-glycolic acid). We review both methods, carefully considering how the models implement numerical methods, the preliminary results from both, the effectiveness of each model, and how the two approaches compare.

II. Introduction & Background

Drug delivery is an important research direction in the field of bioengineering. It focuses on developing systems for the delivery of effective therapeutic drugs in humans [1]. There are many types of drugs that produce various effects through different biochemical mechanisms; as such, it is valuable to design systems that best deliver a drug to a local target. It is only by combining specific drugs with the correct routes of administration that it is possible to optimize therapeutic performance and minimize side effects in the body [2].

Conventional dosage forms for drug delivery include solutions, lotions, mixtures, creams, pastes, ointments, powders, suppositories, suspensions, injectables, pills, immediate-release capsules and tablets, and so on to treat various diseases [1]. In recent years, however, newer devices have been developed with much improved therapeutic potential such as oral controlled release systems, fast dispersing dosage forms, liposomes, taste-masking systems, transdermal patches, aerosols, and site-specific delivery systems [1]. These allow the drug to cross the physiological barriers that undermine the delivery efficiency of conventional drug administration and that limit drug candidates to small molecules and lipophilic drugs. Novel drug delivery devices (DDDs) also allow precise delivery to targeted tissue, facilitate interactions with the desired cell type in a complex tissue microenvironment, and mitigate clearance by off-target organs or dangerous immune responses [3]. Furthermore, the DDDs ensure that the drug release process is slow and sustained. Both of these criteria can be achieved through active or passive delivery methods [4]. The classification of the methods often depends on both the material encapsulating the drug and the membranous qualities of target sites on the body.

DDDs with polymer coatings are widely used, since current research has shown that polymers are able to be transferred into an aerosol, are stable against forces generated during aerosolization, are biocompatible, are able to target specific sites or cell populations, and are able to degrade within an acceptable time period [4]. Polymer-formulated DDDs generally contain a durable structure coated with a thin layer of polymer that contains the drug. The polymer layer is in direct contact with the biological tissue. The drug is transported from the polymer coating via dissolution and diffusion to the tissue where it is subject to diffusion and advection in its free phase and may bind to drug binding sites. Polymer coatings are designed to control drug release, while the holistic device structure generally has a different purpose (e.g. to locate the delivery or to act as a scaffold). Examples of such structures include coronary stents, transdermal patches, and therapeutic contact lenses [5]. The DDDs complement the limitations of conventional drug delivery systems including oral and injectable methods. In comparison, the DDDs are less dependent on patient discipline in periodically taking medication. When higher doses of drugs are administered, targeted delivery reduces the impact on the rest of the body [5]. In addition, the release rate can be better controlled such that the correct dose can be delivered over an extended period of time. Overall, the DDDs allow for both a more convenient, painless drug delivery, and a more sustained release profile with reduced side effects.

As drug delivery generally contains two parts, the second part is concerned with the transport of the drug in biological tissue. Both processes can be mathematically modeled, and their efficiency can be predicted. The entire journey of dynamic drug delivery, from the polymeric coating where the drug is encapsulated at the manufacturing stage to the cell receptors where the drug eventually binds, should be considered in the modeling. Most existing models deal with the drug release process alone, while other models consider only the absorption in the tissue. Far fewer models attempt to fully couple a mechanistic description of drug release with tissue absorption. Such models are needed, as the drug delivery starts from the polymer and undergoes a cascade of reactions and kinetics as the drug is first released and then absorbed. The models should effectively simulate the efficiency of a wide range of drug delivery devices that encompass many different applications.

Drug release models can be classified into empirical and mechanistic models. Empirical drug release models, which are based on the experimental behavior of the system studied, can often greatly mimic the behavior of the actual system, especially when an appropriate number of parameters are included in the model. However, they cannot predict the effect that any changes in the parameters would have on the release rate. On the other hand, mechanistic drug release models are based on the physical mechanisms that influence the release process. Real phenomena such as drug diffusion or dissolution, erosion, swelling, precipitation, and degradation of the polymer are taken into account, so they can be complex to apply [6]. With these models, predictive simulations are possible, but confirmation of the validity of the model against experimental data is still necessary. Since 1961, when Higuchi presented an equation that describes drug release from solid drugs suspended in ointment bases, numerous contributions to empirical and mechanistic models have been made on the drug release processes. Papers have been published to summarize the drug release models for coated formulations and for matrices. Most parameters of the models describe the drug properties and polymer properties [7]. For the drug release part of the delivery, the modeling focused on critical factors such as drug diffusion, dissolution, and solubility in the polymer coating. For the drug transport part, the modeling included factors such as diffusion, convection, and reaction of the drug in the targeted biological tissue. The success of the DDD is

therefore dependent on the correct extent of drug elution, the rate of release, partitioning, accumulation and binding within the tissue [8]. In this respect, mathematical modeling provides a useful tool to understand the combined action of the processes, and consequently to help devise optimisation strategies for targeted drug delivery.

A common numerical method used in drug delivery models has been partial differential equations (PDEs). This allows for the intersection of concrete engineering with the world of chemistry and biology. For example, research has been done regarding drug delivery in catheterized arterial blood flow in patients with atherosclerosis [8]. In this drug delivery system, it must be taken into account that there will be diffusion of the drug within both the plasma and the red blood cells, thus negating a coupled differential equation system. Therefore, this problem is modeled with a PDE that is developed in terms of the drug concentration, blood plasma velocity, hematocrit value and the diffusion coefficient of the drug/fluid [8]. Then, to numerically solve this mode with an atherosclerosis region, a conservative-implicit finite difference scheme is developed [8]. Through this process, it was found that the evolution of the drug concentration varies in magnitude depending on the roles played by the convection and diffusion effects [8]. This is important, as changing certain parameters in the drug delivery system then affects the therapeutic performance and effectiveness of the drug. For the cases where the diffusion coefficient is sufficiently large, the convection effect is not strong enough, and the drug was delivered mostly in the central part of the blood flow region. In particular, the drug was not able to effectively reach the atherosclerosis zone [8]. On the other hand, when the diffusion coefficient is sufficiently small, the convective effect dominates over the diffusion effect, and the drug was delivered effectively over the blood flow region and on the atherosclerosis zone. This example further demonstrates the importance of bioengineering and the plausibility of the use of PDEs for improving drug delivery in the future in terms of both effectiveness and versatility.

The model proposed by McGinty and Pontrelli was a mechanistic model. It was able to account for both processes of drug release and tissue absorption [7]. The modeling can account for both nonlinear saturable reversible binding, which is most common, and special cases such as linear reversible binding and linear irreversible binding. The drug release section of the model focused on the drug coating. It presented a diffusion–dissolution model which included solubility, before demonstrating a number of special cases. The tissue absorption section of the model was then presented, which was modeled around convection, diffusion, and reaction and included a nonlinear saturable reversible binding model. Both sections used a numerical method approach, solving the proposed systems of PDEs. Spatial discretization was adopted, which reduces the PDES into systems of ordinary differential equations (ODEs). Finally, one particular example of a DDD, the drug-eluting stent, was simulated, through which it was demonstrated that the model was able to predict important characteristics such as the correct duration of the release and the time-varying mass of drug in the tissue [7]. The model accounted for the combined effects of diffusion, dissolution and solubility in the polymer coating and can model several different types of binding in the tissue, ranging from nonlinear saturable reversible to linear irreversible binding.

The second model performed a statistical analysis of nanoprecipitated drug delivery systems based on poly(lactic-co-glycolic acid) (PLGA) [9]. The modeling focused on drug release without much emphasis on tissue absorption. PLGA is one of the most used polymers, with excellent biocompatibility, biodegradability, and allows spatio-temporal control of the release of a drug by altering its chemistry. Although mathematical models offer a good alternative as they allow interpreting and predicting

experimental findings and saving time and money, there is no general model that describes all types of drug release of polymeric drug delivery systems. In their study, Heredia *et al.* performed a statistical comparison of several commonly used mathematical models in order to find one that best describes the drug release profile from PLGA particles synthesized by nanoprecipitation method [9]. For this purpose, 40 datasets extracted from scientific articles published since 2016 were collected. Each set was fitted by zero to fifth order polynomials, Korsmeyer-Peppas, Weibull and the Hyperbolic Tangent Function. Some data sets had few observations that do not allow the application of a statistical test, thus bootstrap resampling technique was performed. Statistical evidence showed that the Hyperbolic Tangent Function model was the one that best fits most of the data. By choosing the right model it would be possible to reduce the number of experiments required and gain an understanding of the physicochemical dynamic of the phenomena, thus facilitating the development of new pharmaceutical products. Mathematical models in general are able to interpret and predict experimental findings and are used as an abstraction of a real system with assumptions and simplifications. These mathematical expressions provide a qualitative and quantitative description of the main phenomena involved in drug release by incorporating more parameters in their equation, related or not to physicochemical properties.

III. Model Descriptions

III.1. Coupled drug release and tissue absorption models.

In developing a model for drug delivery devices, researchers McGinty and Pontrelli consider solid polymer coatings that encapsulate a drug, thus controlling drug release by dissolution. They assume that the encapsulated drug's concentration varies continuously and that the fluid penetrates and fully saturates the polymer instantaneously; if it were not instantaneous, the model would result in a moving boundary, at which there would be a discontinuity in drug concentration [7].

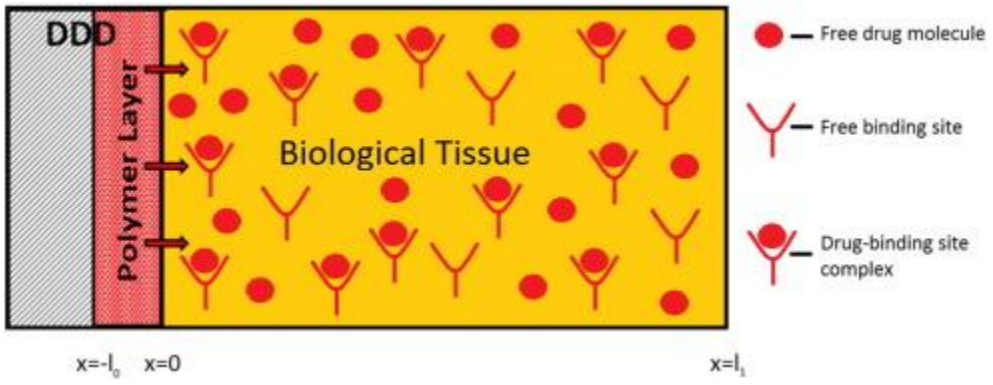

Figure 1. McGinty and Pontrelli's model for drug release. Reprinted from [7].

Through literature review, they determined that the drug dissolution and diffusion through the polymer coating can be described by the equations

$$\frac{\partial b_0}{\partial t} = -\,Da_0^{(\alpha)} b_0^{\alpha}\left(1 - \frac{c_0}{S}\right) \text{ and } \frac{\partial c_0}{\partial t} = D\frac{\partial^2 c_0}{\partial x^2} + Da_0^{(\alpha)} b_0^{\alpha}\left(1 - \frac{c_0}{S}\right),$$

over the domain *(–L,0)*, where b_0 is the concentration of the drug bound to the polymer and c_0 is the concentration of the dissolved drug, both in mol/cm^3. S is the drug solubility (maximum possible

concentration) in mol/cm^3. α is a unitless constant ranging from 0 to 1 that describes the rate of drug dissolution, with a value of 0 being the fastest to reach equilibrium and 1 being the slowest [7]. D and $Da_0^{(\alpha)}$ are dimensionless values defined as

$D = D_0 / D_1$ and $Da_0^{(\alpha)} = \frac{\beta_0 B^{\alpha-1} Sl_1^2}{D_1}$,

where D_0 is the diffusion coefficient through the porous polymer (cm^2/s), and D_1 is the diffusion coefficient through the tissue (cm^2/s), β_0 is the dissolution rate ([mol/cm^3]$^{-2/3}$), and B is the initial concentration (mol/cm^3) of the drug bound to the polymer. Lastly, it is important to note that the temporal and spatial dimensions of the system are nondimensionalized, so the x presented in the equations is equal to the measured x divided by l_1, which helps scale x values in the system to values more intrinsic to the system. Consequently, the domain $(-l_0, l_1)$ (see Figure 1 above) becomes $(-L, 1)$, where $L = l_0 / l_1$. The temporal dimension is similarly scaled such that $t = D_1 t_{data} / l_1^2$, which scales the values to a predicted diffusion time through the tissue. This scaling is why some values, such as D_1, appear in the final equations above.

The authors assume that the drug (ligand) binds reversibly to free binding sites (receptors) in the tissue to form a complex, described by the chemical reaction: *ligand* + *receptor* ⇌ *complex* with an equilibrium dissociation constant $K_d = k_1^r / k_1^f$ [7]. In the reaction, k_1^r is the rate constant of the reverse/dissociation reaction (s^{-1}), while k_1^f is the rate constant of the forward/association reaction ([mol cm^{-3} s]$^{-1}$). After consulting further literature, McGinty and Pontrelli determined that the diffusion and binding of the drug in the porous tissue can be described with the system consisting of the equations

$\frac{\partial c_1}{\partial t} = \frac{\partial^2 c_1}{\partial x^2} - \frac{v_1 l_1}{D_1}\frac{\partial c_1}{\partial x} - \frac{k_1^f l_1^2 b_{max}}{D_1}\left(c_1\left(1 - \frac{b_1}{b_{max}}\right) - \frac{b_1}{b_{max}/K_d}\right)$ and

$\frac{\partial b_1}{\partial t} = \frac{k_1^f l_1^2 b_{max}}{D_1}\left(c_1\left(1 - \frac{b_1}{b_{max}}\right) - \frac{b_1}{b_{max}/K_d}\right)$, both over the interval (0,1).

In these equations, v_1 is the convection velocity (cm/s) of the drug in the biological tissue and b_{max} is the local density of free binding sites (mol/cm^3). Lastly, c_1 refers to the free concentration of the drug in biological tissue, while b_1 refers to the concentration of the drug bound to a receptor [7].

To complete their system of PDEs, the researchers define several boundary and initial conditions. First, at the interface between the polymer and the tissue (see Figure 1 above) at $x = 0$, a continuity of flux is created, resulting in the boundary condition equation

$-D\frac{\partial c_0}{\partial x} = -\frac{\partial c_1}{\partial x} + \frac{v_1 l_1}{D_1} c_1$ at x = 0.

In addition, the authors acknowledge that a concentration jump between the two layers may occur, resulting in another boundary condition equation at $x = 0$ given by

$-D\frac{\partial c_0}{\partial x} = \frac{Pl_1}{D_1}(c_0 - c_1)$, where P is the overall mass transfer coefficient (cm/s) [7].

For the other two boundaries at $x = -L$ and $x = 0$, the researchers assume Robin-type boundary conditions, which are a combination of Dirichlet (known value of dependent variable) and Neumann (known value of derivative) conditions [7]. At $x = -L$, The resulting boundary conditions are

$-\frac{\partial c_0}{\partial x} = \frac{\gamma_0 l_1}{D_1} c_0$ at $x = -L$ and $-\frac{\partial c_1}{\partial x} + \frac{v_1 l_1}{D_1} c_1 = \frac{\gamma_1 l_1}{D_1}$ at $x = 0$.

γ_0 (cm/s) and γ_1 (s/cm) are constants that can be adjusted manually so that the fluxed predicted by these equations match the collected data. Lastly, the authors assume that the drug delivery device, such as a stent, starts with an initial concentration of drug B that is entirely bound to the polymer. This results in the initial conditions $b_0(x,0) = B$, $c_0(x,0) = 0$, $c_1(x,0) = 0$, and $b_1(x,0) = 0$. McGinty and Pontrelli employ their model for the case of a stent, which is a wire mesh that is inserted into the coronary arteries that can release a drug [7].

III.2. Statistical analysis of release kinetics.

PLGA is a biopolymer synthesized by the polymerization of polyglycolic acid and polylactic acid monomers [9]. Drug transport systems made with PLGA nanoparticles tend to show a biphasic behavior in which a sudden initial release dominated by diffusion is followed by a period of slow and continuous release, where polymer degradation/erosion is the most influential mechanism [9]. PLGA is stable, biocompatible, degradable under physiological conditions, non-immunogenic, and non-toxic [9]. Moreover, the selection of characteristics such as molecular weight, inherent viscosity and the glycolic acid:lactic acid ratio can control the duration and behavior of the release profile of a PLGA system [9]. Despite the marked benefit of using PLGA in drug delivery and several FDA approvals, not many products have reached the market due to the difficulty and cost of the development and manufacture of a PLGA DDD [9]. The use of mathematical models can facilitate development of new pharmaceutical products by reducing the number of experiments and the time and cost associated. The study done by Heredia *et al.* statically analyzed the ability of five mathematical models, explained below, and four polynomials to describe and predict the drug release profile from PLGA particles synthesized by a nanoprecipitation method.

1. *Zero-order kinetic model:* $Q_t = k_0 \times t + Q_0$, where Q_t is the percentage of the released drug after time t, k_0 is rate constant for zero-order kinetics, t is time, and Q_0 is the initial percentage of the released drug (usually 0).
   This model assumes a single-phase ideal condition in which the drug release is continuous with a constant rate and is only dependent on time and not dependent on the dissolved concentration in the release medium.
2. *First-order kinetic model:* $Q_t = Q_0 \times e^{k_1 \cdot t}$, linearized as $\ln ln\left(Q_t\right) = \ln\left(Q_0\right) + k_1 \times t$, where Q_t is the percentage of the released drug after time *t*, k_1 is the rate constant for first-order kinetics, t is time, and Q_0 is the initial percentage of the released drug (usually 0).
   This model assumes that the rate of drug release is only dependent on the concentration of drug remaining in the device.
3. *Korsmeyer-Peppas model (also known as Power Law):* a semi-empirical model that states $Q_t = k_{KP} \times t^n$, linearized as $\ln ln\left(Q_t\right) = \ln\left(k_{KP}\right) + n \cdot \ln(t)$, where Q_t is the percentage of released drug after time *t*, k_{KP} is the Korsmeyer-Peppas rate constant nanoparticles incorporating geometric characteristic structures, t is time, and n is the release exponent.

This model is developed specifically for the release of a drug molecule from a polymeric matrix [10]. The exponent *n* encodes information about the drug release mechanism—whether diffusion, swelling, or a combination of both determines the drug release profile. This model is only applicable to the first ~60% of the release process [9-11].

4. *Weibull model:* an empirical model $Q_t = 1 - e^{(\alpha \cdot t)^{\beta}}$, which is linearized to be $\ln\left[-\ln\left(1 - Q_t\right)\right] = \ln(\alpha) + \beta \cdot \ln(t)$, where Q_t is the percentage of the released drug after time t, α is a scale parameter that defines the timescale of the process, *t* is time, and β is the curve shape factor (sigmoidal, parabolic, or exponential)
   Although this empirical model does not have a kinetic nature and its parameters are not physically related to the drug release process, the ability of the logarithmic form of both time and drug release to dampen abrupt changes in drug release rate has allowed the model to be applied to dissolution kinetic properties [10].
5. *Hyperbolic tangent function:* $Q_t = Q_\infty \cdot \tanh\left(\alpha \cdot t^{1/2}\right)$, linearized to be $atanh\left(\frac{Q_t}{Q_\infty}\right) = \alpha \cdot t^{1/2}$, where Q_t is the percentage of the released drug after time *t*, Q_∞ is the total percentage of released drug, α is a constant related to particle size and diffusion constant, and *t* = time.
   Modified from the Korsmeyer-Peppas model, this hyperbolic tangent model is developed by Eltayeb *et al.* for the application of the entire release process [12].

IV. Numerical Methods

IV.1. Finite-difference and spatial discretization methods for solving PDEs.

In their multifaceted model combining equations for drug release, transport, and absorption into tissue, McGinty and Pontrelli employ spatial discretization, standard finite differences, and analytical techniques to solve a system of four governing PDEs. These are intended to model drug release in a polymer matrix (via diffusion-dissolution equations) and drug dynamics and tissue absorption (via drug binding, convection, and transport equations). While each of these individual differential equations is strongly rooted in prior research, their coupling into a single set of equations is novel.

The system of PDEs is coupled through the use of specific initial, interface, and boundary conditions that ensure continuity and smoothness where necessary, as previously described. To recap, the conditions ensure flux continuity (between the polymer and tissue), account for a potential concentration jump across the polymer-tissue interface, and drug loss to blood flow at the boundaries [7]. More specifically, the conditions are specified as derivatives between the two sides of the interface or boundary. In order to simplify calculations, second-order centered finite differences are used to approximate second derivatives in the system, and a direct Taylor series expansion is performed for the interface boundary conditions to reduce the complexity of the systems [7]. Centered finite differences are also derived from a Taylor-series expansion of a given function.

$$\left.\frac{\partial^2 c_0}{\partial x^2}\right|_{x_j} \simeq \frac{c_0^{j-1}-2c_0^j+c_0^{j+1}}{h_0^2} \qquad c_0^{N-1} \approx \tilde{c}_0^N - \frac{h_0 \partial \tilde{c}_0^N}{\partial x} + \frac{h_0^2}{2}\frac{\partial^2 \tilde{c}_0^N}{\partial x^2}$$

$$c_0^{N-2} \approx \tilde{c}_0^N - 2h_0\frac{\partial \tilde{c}_0^N}{\partial x} + 2h_0^2\frac{\partial^2 \tilde{c}_0^N}{\partial x^2}$$

$$\left.\frac{\partial^2 c_1}{\partial x^2}\right|_{x_j} \simeq \frac{c_1^{j-1}-2c_1^j+c_1^{j+1}}{h_1^2} \qquad c_1^1 \approx \tilde{c}_1^0 + h_1\frac{\partial \tilde{c}_1^0}{\partial x} + \frac{h_1^2}{2}\frac{\partial^2 \tilde{c}_1^0}{\partial x^2}$$

$$c_1^2 \approx \tilde{c}_1^0 + 2h_1\frac{\partial \tilde{c}_1^0}{\partial x} + 2h_1^2\frac{\partial^2 \tilde{c}_1^0}{\partial x^2}$$

Centered finite differences (left) and Taylor-series approximations (right).

These simplifications allow the authors to implement spatial discretization; spatial discretization refers to the process of solving for a solution to a given set of PDEs in only a finite, discrete domain of points, rather than an infinite and continuous domain [13]. It operates by determining approximate ODEs at each point in a grid within the domain (i.e. "pointwise"), and solving the resultant system of equations [13]. This methodology can be effective in cases where numerous PDEs must be solved simultaneously, such as here. The resultant system of ODEs can be readily solved using numerous techniques.

$$\frac{dY}{dt} = A(Y)$$

ODE form resulting from spatial discretization of PDEs.

Because the model is likely a stiff system, meaning there are both rapidly- and slowly-changing concentration segments, simply due to the nature of diffusion, adaptive time step models such as adaptive Runge-Kutta are ideal and not computationally intensive [14]. In this case, MATLAB's in-built multi-step ode15s method was used [7,15]. Runge-Kutta methods implement an increment function (ϕ) that is representative of the slope of a given function over a given interval (h), following the form $y_{i+1} = y_i + \phi h$ [14]. The resulting equation is used iteratively across an ODE with a provided initial condition. 4th-order Runge-Kutta is the most popular for its balance of accuracy and low computational complexity [14].

IV.2. Polynomial interpolation.

When conducting their analysis, Heredia *et al.* employed several numerical methods to fit against each of the 40 datasets, including zero-order, first-order, Korsmeyer-Peppas, Weibull, and 2nd-5th order polynomial interpolations, as previously described [9]. Although the data processing and analytical steps were applied to all methods, only polynomial interpolation will be discussed here.

As the polynomials were tested for their ability to effectively characterize the diffusive properties of various PLGA-based nanoparticle and drug combinations, the primary dependent variable was Q_t, the percentage of the released drug after time t. Thus, the form of the 2nd-order polynomial was $Q_t = a + bt + ct^2$, 3rd-order was $Q_t = a + bt + ct^2 + dt^3$, and so forth. The coefficients of each polynomial were determined through a simple linear regression method by calculating the sum of squares of the fit. The accuracy and effectiveness of the polynomial interpolated fits were also evaluated with the regression model using the the regression coefficient R^2, the corrected regression coefficient R^2_a, the sum of squares of residual *SSR*, sum of squares of the error *SSE*, sum square of total variation *SST*, the *T*-statistic, and the *F*-statistic. It is worth noting the importance of the last two statistics as they indicate

the statistical significance of the model and ultimately whether or not the model was rejected. Additionally, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were calculated for each interpolation and dataset, a metric that is particularly important for polynomial regression as it measures the accuracy of the model with regards to its complexity (number of parameters) [16].

The complete results of each interpolation with each dataset are summarized in Table 4 of the paper. Heredia *et al.* note that the values for AIC-BIC and R^2–R^2_a were the same for all datasets. Regarding the accuracy and effectiveness of the interpolations, 9 datasets did not fit any polynomial model, 11 datasets rejected the 2nd-order polynomial, 23 rejected the 3rd-order polynomial, 27 rejected the 4th-order polynomial, and 25 rejected the 5th-order polynomial [9]. The least rejected and most accurate model was found to be the 2nd-degree equation with 38% of the datasets fitting it, then followed by the 3rd, 5th, and 4th-degree polynomials. However, the R^2–R^2_a values among the unrejected models tended to increase as the degree of the polynomial increased, suggesting that added complexity potentially provided a better exact fit over a better generalized fit (see Figure 2 below).

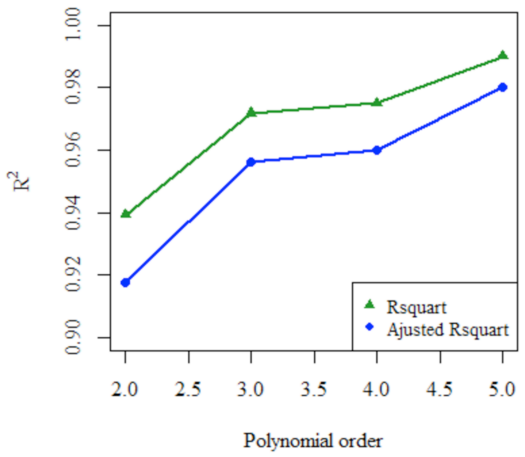

Figure 2. R^2 values for the polynomial interpolations. Reprinted from [9].

After considering the statistical results of each polynomial interpolation, Heredia *et al.* rejected all polynomial models. Although the R^2 and R^2_a values for the models were relatively high (>0.9) and suggested a good fit, the values improved with increasing polynomial order. When fitting a polynomial interpolation, fewer terms—and thus lower order—are preferred as increased complexity can result in overfitting. In particular, if there are n data points and the order of the polynomial is n-1, then the model will pass through all data points and have zero error, a case in which the polynomial will not be suitable for interpolative estimations. This was further validated by the values from the AIC-BIC statistics, where the values were more positive relative to the other mathematical models. As the AIC-BIC test determines the goodness of the fit while penalizing increased complexity, the results indicate the ineffectiveness of the interpolations to accurately predict future values.

V. Discussion

V.1. Discussion of finite-difference and spatial discretization methods for solving PDEs.

While McGinty and Pontrelli's model for drug release, transport, and tissue absorption has numerous advantages, several potential limitations should be considered upon further investigation. In their conclusion, the authors enumerate multiple benefits of their approach; for one, the synthesis (coupling) of multiple PDEs into one all-encompassing framework may be preferable to implementing multiple standalone models [7]. Increased model detail typically corresponds to improved accuracy [14]. However, the inherent complexity of biological systems almost always requires the use of approximations and assumptions, as previously discussed for this case. As a result, truncation error—error due to numerical approximation—is an important factor to assess. In this model for drug delivery, compounded numerical truncation could be a potential problem; errors that result from finite difference approximations, Taylor series approximations, and the spatial discretization process, for example, can accumulate [14]. Furthermore, finite-difference approximations are reliant on a step-size parameter to decrease error. As the authors note, it is difficult to determine the accuracy of more complex models as they require many parameters that make experimental testing difficult [7].

In addition, increasingly complex models are difficult to solve via analytical means; while computational approaches are growing more accurate, extra care should be taken when solving a system of numerous PDEs. For this case in particular, the MATLAB function ode15s is not always accurate, though it does work well for stiff systems [15]. As such, alternative solution approaches may be required for different applications.

V.2. Discussion of polynomial interpolation.

The primary objective of this study was to identify a numerical method that can accurately describe the drug release profile of a drug from a PLGA encapsulated vesicle. However, the drawbacks of polynomial interpolation prevent it from serving as a reliable method to accurately predict the release kinetics of the delivery vector. Extrapolation, the process of using a polynomial interpolation to predict values outside the range of the dataset, can lead to extremely inaccurate results and should typically be avoided [14]. For instance, if the actual data varies significantly from the interpolated curve outside of the normal range, then an extrapolated value will diverge significantly as well. This would have implications when predicting Q_t at longer times t, as many of the datasets will likely contain recorded values for earlier times, thus making long-term predictions more inaccurate. Furthermore, higher order polynomials exhibit increased sensitivity to round off error, causing the model to have oscillatory behavior and inaccuracy [14]. High-order polynomials should generally be avoided to prevent oscillations and maintain the accuracy and precision required for drug delivery. One potential approach to overcoming these problems is to utilize spline interpolation as an alternative to a normal polynomial. Interpolations such as cubic splines are lower-order, piecewise polynomials that are only applied to a subset of the data and are then connected with continuity and smoothness conditions. This enables the model to consider abrupt changes in the data and be resistant to high-order oscillations as well as round off error due to low order [14].

In addition to numerical problems, the use of simplistic models such as polynomial interpolation often cannot account for many of the biological and chemical processes involved with *in vivo* drug delivery. Heredia *et al.* suggest that the drug properties and the chemical environment need to be taken into consideration, as these can affect the degradation rate and diffusibility of the drug. This leads to many

fundamental assumptions for the model, to the extent that the model may be overly theoretical and more qualitative than robustly quantitative.

VI. Conclusions

The need to control the administration of drugs has prompted much research within the field of drug delivery. Naturally, this has led to the development of many mathematical models to accurately characterize the release kinetics of a drug from a delivery vector, enabling researchers to fine-tune its properties to suit their specific needs. However, identifying the optimal mathematical approach to quantify and predict drug release remains a challenging and unsolved task.

The review discusses two potential approaches for analyzing the characteristics of controlled drug release. McGinty and Pontrelli propose the use of a system of PDEs-turned-ODEs to evaluate such kinetics, while Heredia *et al.* utilize several different numerical methods, particularly polynomial interpolation, to do so. The results from McGinty and Pontrelli demonstrate that their model can approximate *in vivo* data with reasonable accuracy, can be applied to a wide variety of drug delivery devices, and is completely unified. However, since they utilize finite difference, their accuracy is limited by their step size. The results from Heredia *et al.* reveal the wide variation between the accuracy of the different mathematical models, with polynomial interpolation serving as an inadequate predictive scheme for controlled drug release, primarily due to potential round-off error and oscillations. Thus, an alternative approach could be employed to predict release profiles while minimizing the complexity of the model.

Although an optimal numerical method for describing drug delivery systems has yet to be established, this review presents a brief look into ongoing research within this field. Ultimately, the further development of advanced mathematical models and methods and a better understanding of drug delivery kinetics can create new therapeutic avenues for clinical applications.

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