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Using Reference Pricing in Tribal Communities (SC, ST, OBC) and Comparison of Health Literacy among Females and Males in East

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Abstract: A one-dimensional framework with a porous membrane is used to study the diffusion dynamics of therapeutic agents from drug-eluting implants using two-layer and multilayer models. Drug transport is studied using langevin dynamics simulations, considering effective diffusion that depends on tortuosity, porosity and the layer's structural characteristics. The two-layer model examines at drug transfer between the stent coating and the artery wall, while the multi-layer model examines at sequential diffusion via additional porous layers. The drug concentration in terms of probability density function transfer from the stent coating to the arterial wall is calculated using stochastic langevin dynamic simulations. mar

Keywords: Diffusion equation, Probability density function, Langevin dynamics, Drug-Eluting Implant, Porous wall

1. Introduction

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Drug-eluting stents are essential for treating coronary artery disease, particularly stenosis, which is defined by blood vessel narrowing. Drug-eluting stents are covered with drugs that are progressively released into the surrounding artery walls, in contrast to bare-metal stents. In order to prevent restenosis (re-narrowing of the artery), drug-eluting stents (DES) combine localized, prolonged drug delivery with mechanical support for blood vessels, revolutionizing the treatment of cardiovascular disorders. Its efficacy is largely dependent on the regulated diffusion of therapeutic drugs into the vascular tissue via the polymeric coating [1]. This drug stops the overgrowth of tissue that can lead to restenosis, which is the re-narrowing of arteries following therapy. Despite the rise in the use of coronary stents, restenosis following angioplasty is still an unsolved issue [2]. Theoretically, nitric oxide (NO) can prevent restenosis by a number of activities. These include reducing platelet aggregation in response to collagen exposure, preventing arterial spasms and inhibiting the growth of smooth muscle cells [3]. Filtration velocity and infinite mass transfer are incorporated into the mass convection-diffusion equation, which is used to describe controlled drug delivery in coronary arteries utilizing stents. A one-dimensional Sturm-Liouville system with discontinuous coefficients is created from the problem [4]. Using mass diffusion, controlled drug delivery through two porous homogenous layers with different characteristics was predicted. Drug concentration profiles were examined over time, and both qualitative and quantitative measurements were added, along with important indicators like emptying time. These indicators aid in assessing the efficacy of cutting-edge medication delivery techniques [5]. Techniques for modeling medication release from vascular stents and its redistribution in arterial tissue were thoroughly examined [6]. Indeed, the structural characteristics of the stent coating have an impact on the drug's diffusion in drug-eluting stents [7]. Drug-eluting coatings with varying porosity offered better control over drug release than coatings with constant porosity, two important factors in this process are porosity and tortuosity [8]. The stent coating's porosity is the existence of void spaces that allow the medicament to travel more easily. It is easier for the medicine to get through these gaps in a covering that is more porous. The complexity of the routes the medication must take within the stent covering, however, is referred to as tortuosity. A more convoluted channel may slow down the diffusion process, which could impact the drug's long-term release. These models used to describe the release behavior of the drug from different regions of the stent, employing the diffusion equation. Factors such as drug diffusivity, cell metabolism, coating thickness, and membrane properties were considered in these models. Few models employed techniques like separation of variables and Fourier series to solve the mathematical equations and obtain solutions for of one-dimensional, two-dimensional and three-dimensional models. These models explained drug diffusivity in the coating and wall, mass flux at interface, permeability of membrane, tortuosity of the medium etc.

Diffusion can be explained in two ways: deterministic and stochastic. Each provides different insights and mathematical tools to characterize the movement of particles or information. Diffusion is described as a bulk process in the deterministic framework, which emphasizes the time-dependent change in particle concentration over individual motion. Particle density driven by concentration gradients is represented smoothly and continuously by the diffusion equation which is governed by Fick's laws. While for stochastic framework, diffusion is represented as a random process that is stimulated by the Brownian motion or other chaotic thermal motion of individual particles. Stochastic differential equations, such as the Langevin equation, which mix random noise and deterministic forces,

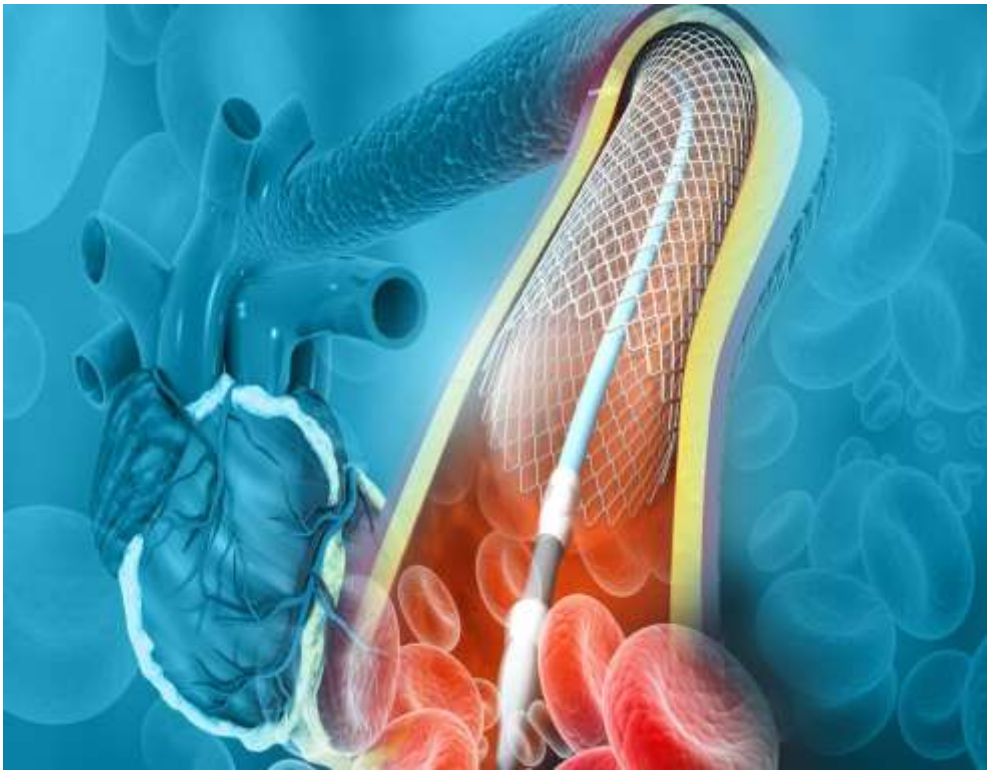
control the motion of these particles. The probabilistic character of molecular trajectories, in which each particle's position changes as a random walk is captured by this method. Since stochastic simulation effectively depicts the microscopic interactions and random thermal fluctuations that control particle motion, it is employed for diffusion, particularly in complex or heterogeneous environments such as drug-eluting stents. A probability density function (PDF) is used to represent the collective behavior of several particles. To tackle this complexity, computer techniques like monte carlo methods and langevin simulations which use the verlet algorithm, have become efficient tools for examining drug diffusion at the molecular level.

Previous models for drug-eluting stents used convection-diffusion equations in one and two dimension to describe drug release, considering factors like diffusivity, concentration and membrane properties. These mathematical models have been solved by variable separation, marker and cell method, laplace transform, Fourier series and langevin dynamics. Developed models using Langevin dynamics have not incorporated the concept of effective diffusivity for drug-eluting stents. To address this, the proposed approach integrates effective diffusivity into the diffusion equation, along with additional parameters like porosity, diffusivity, and permeability, to provide a more accurate and comprehensive understanding of drug release dynamics from stent implants. A stochastic framework for simulating drug molecule mobility is offered by Langevin dynamics, which combines random thermal fluctuations with deterministic forces (such as interactions with the medium). This method depicts how porosity and tortuosity affect drug molecules' effective diffusivity at the microscale. Accuracy in the modeling of particle trajectories is ensured by updating molecule locations over tiny time steps using the verlet algorithm, a very robust and accurate numerical integration technique. Large particle ensembles can be simulated using Monte Carlo methods, which rely on probabilistic sampling (for example, from a normal distribution). A realistic representation of drug diffusion behavior in controlled delivery systems is offered by Langevin simulations [9]. Langevin simulations are effective for modeling diffusion in two-layer [10] and multi-layer systems [11], where each layer has distinct diffusivity. In two-layer systems, particles transition across an interface with continuity in flux but may experience changes in concentration or diffusivity, often incorporating semi-permeable membrane effects. Multi-layer systems extend this to multiple interfaces, modeling sequential diffusion through layers with spatially varying properties. Using the Langevin equation, which accounts for friction and stochastic noise, these simulations handle complex boundary conditions and sharp diffusivity changes, making them ideal for applications like drug-eluting stents and layered porous materials.

The current study uses Langevin dynamics to investigate drug release phenomena in drug-eluting systems in two and multilayer porous media in a one-dimensional model. The Langevin theory is explained mathematically in Section 1. A probability density function (PDF) based on the two-layer theory is developed in Section 2, which also examines the effect of semi-permeable membranes on drug-eluting stents and analyzes the drug mass profile and the associated outcomes. In Section 3, this method is expanded upon by developing a probability density function using multi-layer theory and

investigating the manner in which semi-permeable membranes affect drug diffusion. A thorough analysis of the resulting mass profile is also provided. In addition to providing insights into drug

behavior in two-layer and multi-layer porous media, the findings improve the knowledge of drug release mechanisms, including effective diffusivity in drug-eluting systems.



- Figure 1: Schematic diagram of drug-eluting stent

2. Mathematical Formulation for Langevin Theory

Fick's Second Law is applicable to characterize the diffusion process in a two-layered system, such as a drug-eluting stent, where each layer has a distinct effective diffusion coefficient D_e. The law is taken into consideration with spatially changing diffusivity and regulates the movement of drug molecules due to concentration gradients as,

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial J(x,t)}{\partial x} = \frac{\partial}{\partial x}\left(D_e(x)\frac{\partial P(x,t)}{\partial x}\right) \quad (1)$$

$$D_e = \frac{\phi_e D_w}{\tau}$$

where D_e is the effective diffusivity, ϕ is the porosity, τ is the tortuosity, and D_w is the corresponding free diffusion of the drug in water.

P(x, t) is the probability density function being at position x at time t,

$$J(x,t) = -D_e(x)\frac{\partial P(x,t)}{\partial x}$$ is the probability flux.

$$m\frac{dv}{dt} = -\alpha(x)v + \beta\big(x(t)\big) \qquad (2)$$

In eq.(2) langevin's equation, which characterizes motion under the influence of two effective forces—stochastic thermal noise and friction control the dynamics of a diffusing particle with mass m and velocity v. The resistive force proportional to the particle's velocity is accounted by the friction component (the first term on the right-hand side of the langevin equation), while the random fluctuations brought on by the system's thermal energy are represented by the stochastic noise (the second term). The dynamics of a diffusing particle with mass m and velocity v are governed by langevin's equation, which describes the motion under the influence of two effective forces: friction and stochastic thermal noise. The friction term (the first term on the right-hand side of the Langevin equation) accounts for the resistive force proportional to the particle's velocity, while the stochastic noise (the second term) represents random fluctuations caused by thermal energy in the system.

The friction coefficient $\alpha(x)$ is related to the diffusivity $D(x)$ (as described in Fick's second law) through Einstein's relation:

$$\alpha(x) = \frac{k_B T}{D(x)} \qquad (3)$$

where T is the temperature of the system, and k_B is Boltzmann's constant. The stochastic noise $\beta(x)$ is modeled as a random variable chosen from a Gaussian distribution with the following properties:

- Zero mean: $\langle\beta\big(x(t)\big)\rangle = 0$, indicating no net bias in the fluctuations.
- Delta-function autocorrelation: $\langle\beta(t)\beta(t')\rangle = 2k_B T\alpha\big(x(t)\big)\delta(t-t')$, ensuring the noise is temporally uncorrelated and its magnitude is consistent with thermal fluctuations.

From an ensemble of simulated trajectories, the particle's position's probability density function (PDF), $P(x,t)$, is defined the initial position of the particle is sampled from the initial PDF $P(x,0)$. The statistical behavior of the particle's diffusion under the specified physical parameters can be described by computing the time-dependent PDF $P(x,t)$ by averaging over these trajectories.

The quality of the discrete-time numerical integrator has a significant impact on the accuracy of the Langevin dynamics simulation approach for computing $P(x,t)$.To determine the value of α, we employ

the inertial convention [12,13] in conjunction with the effective and reliable approach of Grønbech-Jensen and Farago (G-JF) [14,15]. The G-JF integrator uses the following set of equations when conservative pressures from a potential energy gradient are absent, and is given as,

$$x_{n+1} = x_n + bdtv_n + b\frac{dt^2}{2m}\beta_{n+1}, \quad (4)$$

$$v_{n+1} = av_n + b\frac{\beta_{n+1}}{m}, \quad (5)$$

the coordinate $x_n = x(t_n)$ and velocity $v_n = v(t_n)$ by a single time step from time $t_n = ndt$ to $t_{n+1} = t_n + dt$. β_{n+1} is a Gaussian random number that satisfies the G-JF eq.(3) and eq.(4) above.

$$\langle\beta_n\rangle = 0; \quad \langle\beta_n\beta_l\rangle = 2\alpha k_B T dt\delta_{n,l}, \quad (6)$$

Additionally, the algorithm's damping coefficients are

$$B = \left[1 + \frac{\alpha dt}{2m}\right]^{-1}, \quad (7)$$

$$A = \left[1 - \frac{\alpha dt}{2m}\right]b \quad (8)$$

The integrator needs to be supplemented with a convention for selecting the value of α to be utilized in eqs. (5) and (6) at each time step because the friction changes in space. The Itô-Stratonovich dilemma [16,17] refers to the uncertainty around the proper selection of α. In this case, the recently suggested inertial convention is employed, which gives α the value of the spatial average of α(x)along the inertial trajectory from xn to $\tilde{x}$n+1 = xn+ vn dt,

$$\overline{\alpha} = \frac{\int_{x_n}^{\tilde{x}_{n+1}} \alpha(x)dx}{\tilde{x}_{n+1} - x_n} = \frac{A(\tilde{x}_{n+1}) - A(x_n)}{\tilde{x}_{n+1} - x_n} \quad (9)$$

The primitive function of $\alpha(x)$ is represented by $A(x)$. Even for reasonably large time steps, the inertial convention produces very accurate results, while any plausible convention for choosing α yields the proper PDF at the limit of infinitesimally short time step $dt \to 0$. The inertial trajectory is the leading approximation to the particle's true path for tiny time scales, $dt \ll \frac{m}{\alpha}$. This is the reason for this attribute of the inertial convention.

3. For Two-Layer System

The drug reservoir layer and a rate-controlling layer are two separate layers that work together to release the medicine in two-layer drug-eluting stents. To maximize drug delivery rates and maintain therapeutic efficacy, it is essential to investigate drug diffusion in this system. The stochastic nature of drug

molecule mobility can be captured and examined by using probability density functions (PDFs). The geographical and temporal distribution of drug molecules as they permeate the layers is thoroughly shown by these functions. Understanding important factors like effective diffusivity and the effects of layer characteristics (such as thickness and porosity) on the total release kinetics is important to analyze. PDFs make it possible to accurately model drug behavior using Monte Carlo simulations. This helps to improve the design of controlled drug delivery systems in stents for targeted and long-lasting therapeutic effects.

Assuming in eq.(1) that $0 < D(x) < \infty$ ($-\infty < x < \infty$), the resulting $P(x,t)$ (for $t > 0$) must be a continuous function for any initial condition. The flux $j(x,t) = -D(x)\frac{\partial}{\partial x}P(x,t)$ must also be continuous if no source or sink of probability are present in the system. These properties of the PDF also apply to layered systems where $D_e(x)$ is piecewise constant.

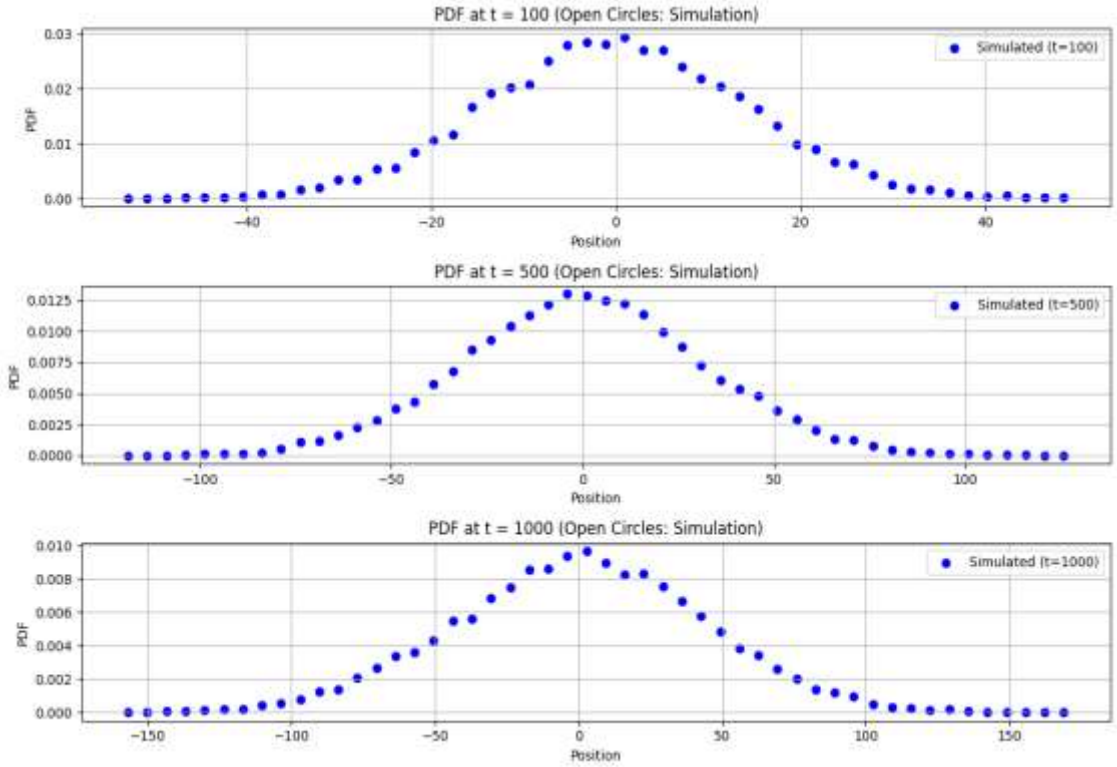
In this study, we consider a one-dimensional, two-layer model for a Diffusive Exchange System (DES). Before deriving that model, we first consider the simplest two-layer system [where $D(x) = D_{e_1}$ for $x < 0$ and $D(x) = D_{e_2}$ for $x > 0$]. As stated above, both the PDF and the flux must be continuous, including at $x = 0$, which sets the boundary conditions at the interface between the layers.

Assuming that a particle is initially located at $x = x_0 > 0$, i.e., $P(x,0) = \delta(x - x_0)$, the normalized (i.e., satisfying $\int_{-\infty}^{\infty} P(x,t)dx = 1$) solution of eq.(1) for $t > 0$ is given by:

$$P(x,t) = \begin{cases} \frac{A}{\sqrt{4\pi D_{e_1} t}} e^{-\frac{(x-x_1)^2}{4D_{e_1}t}}, & \text{if } x < 0, \\ \frac{1}{\sqrt{4\pi D_{e_2} t}} e^{-\frac{(x-x_0)^2}{4D_{e_2}t}} + \frac{B}{\sqrt{4\pi D_{e_2} t}} e^{-\frac{(x+x_0)^2}{4D_{e_2}t}}, & \text{if } x > 0, \end{cases} \quad (10)$$

where, $D_{e_1} = \frac{\phi_1 D_w}{\tau_1}$ and $D_{e_2} = \frac{\phi_2 D_w}{\tau_2}$

$x_1 = x_0\sqrt{\frac{D_1}{D_2}}$, $A = \frac{2}{1+\sqrt{\frac{D_2}{D_1}}}$, and $B = \frac{1-\sqrt{\frac{D_1}{D_2}}}{1+\sqrt{\frac{D_1}{D_2}}}$.



- Figure 2: The Probability Density function of two-layer system; Results of the Langevin dynamics simulations at t=100,500,1000

From the above graph, at t=100, the drug distribution is narrowly concentrated around the release site, indicating minimal diffusion. By t=500, the probability density function (PDF) broadens, showing increased dispersion of drug molecules due to diffusion. At t=1000, the distribution becomes even wider, demonstrating continued spread as molecules move further from the initial release point. This progression follows Langevin dynamics, where the mean squared displacement (MSD) increases over time due to stochastic thermal forces and damping effects. The widening PDF highlights the balance between drug retention near the stent and effective penetration into arterial tissues for controlled drug delivery.

This solution can be interpreted as follows: For $x > 0$, the PDF represents two diffusion processes associated with (i) the original particle, which has a unity weight and is located at $x = x_0$, and (ii) an image particle of weight B, located at $x = -x_0$. For $x < 0$, the PDF represents diffusion of an image particle of weight $A = 1 - B$, located at $x = x_1$.

Notice that for $D_1 = D_2$, we have $x_1 = x_0$, $A = 1$, and $B = 0$, which reduces Eq. (8) to the well-known Gaussian solution for a particle diffusing in an infinite space with constant diffusivity.

Two interesting limiting cases were considered:

1. $\frac{D_{e_2}}{D_{e_1}} \to \infty$ (i.e., $D_{e_2} = D$ and $D_{e_1} \to 0$): In this case, $B \to 1$, and the solution is equivalent to a system with a reflecting wall at the origin:

$$P(x,t) = \frac{1}{\sqrt{4\pi D_{e_2} t}} e^{-\frac{(x-x_0)^2}{4D_{e_1} t}} + \frac{1}{\sqrt{4\pi D_{e_2} t}} e^{-\frac{(x+x_0)^2}{4D_{e_2} t}} \quad (x > 0), \qquad (11)$$

2. $\frac{D_{e_2}}{D_{e_1}} \to 0$ (i.e., $D_{e_2} = D$ and $D_{e_1} \to \infty$): In this case, $B \to -1$, and the solution becomes:

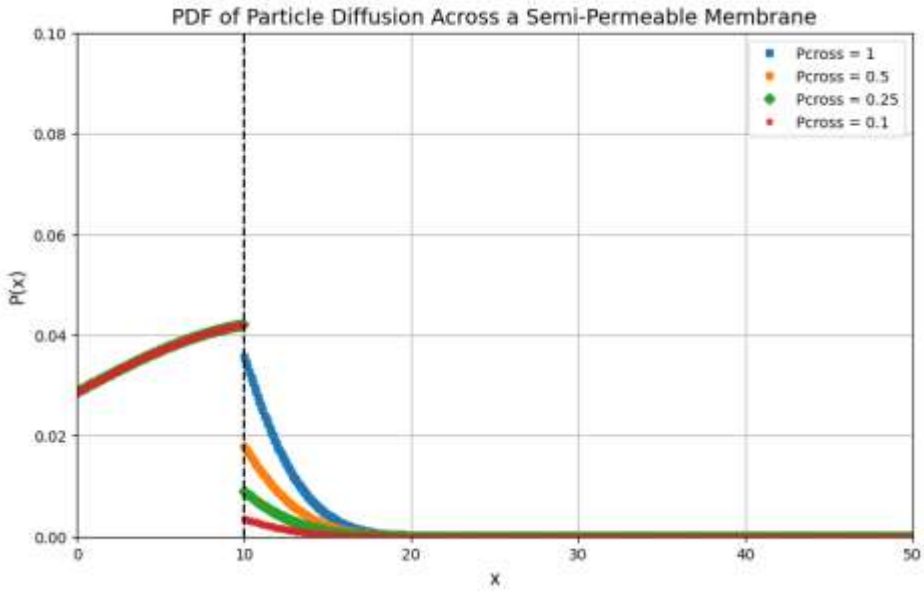
$$P(x,t) = \frac{1}{\sqrt{4\pi D_{e_2} t}} e^{-\frac{(x-x_0)^2}{4D_{e_2} t}} - \frac{1}{\sqrt{4\pi D_{e_2} t}} e^{-\frac{(x+x_0)^2}{4D_{e_2} t}}, \quad x > 0, \qquad (12)$$

These results underscore the importance of the diffusivity ratio $\frac{D_2}{D_1}$ in shaping the diffusion profile across the interface.

3.1 Impact of Semi Permeable Membranes in Drug-Eluting Stents

The modern medical technology known as drug-eluting stents (DES) is intended to deliver drugs to target tissues in a regulated and sustained manner. Drug release is mostly controlled by a semi-permeable barrier, which permits selective diffusion while inhibiting burst release. Reflection at barriers, including tissue interfaces or stent coatings, also influences effective diffusivity by rerouting drug molecules, which in turn affects release efficiency. All of these elements interact to influence DES therapeutic efficacy and direct the development of the drug delivery system.

Langevin simulations for drug-eluting stents can be used to represent the Probability Density Function (PDF) of particle diffusion across a semi-permeable membrane, as shown in the graph. The y-axis displays the probability density function P(x), which indicates the possibility of particle positions at various distances from the membrane, while the x-axis reflects the position x, which most likely indicates the distance across the membrane.



- Figure 3: Pcross for semi permeable membrane in two-layer system; Langevin dynamics simulations for Pcross = 1,0.5,0.25,0.1

By using eq.(11), different values of Pcross, or the likelihood of particles passing through the semi-permeable barrier are represented by the curves. Particles have the maximum probability of crossing the membrane when Pcross = 1. For Pcross=1 (blue curve), particles cross the membrane with the highest probability, indicating no resistance to diffusion. As Pcross decreases, the permeability of the membrane is reduced, and the curves show progressively lower probabilities of particle movement. At Pcross =0.5 (green curve), there is moderate resistance and at Pcross=0.25 (orange curve) and Pcross=0.1 (red curve), diffusion becomes even more restricted, simulating a less permeable membrane. Optimizing drug-eluting stents requires understanding membrane permeability. Higher Pcross indicates faster release, while lower values suggest slower diffusion due to resistance. Langevin simulation models drug diffusion as a stochastic process, combining concentration-driven and random forces. Initially, a strong gradient pushes drugs into the artery wall, with particle movement decreasing in the coating and increasing in the wall over time.

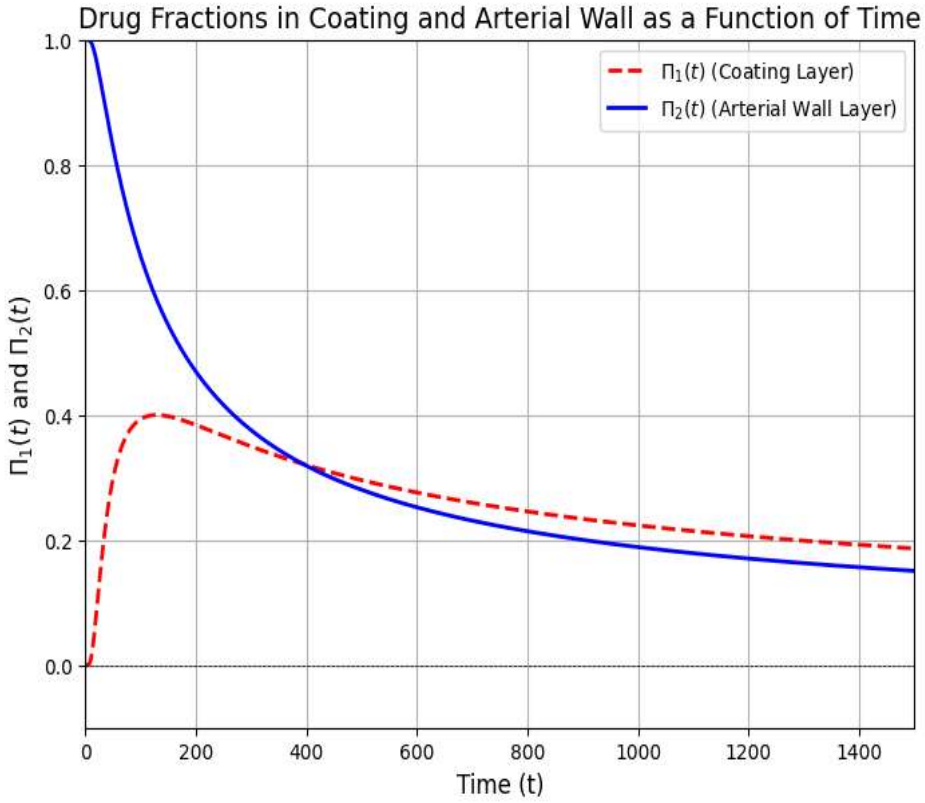
3.2 Mass Profile in Layered Drug Eluting Stent Systems

Drug distribution and release from two drug-eluting stents (DES) are controlled by the mass profile of the stent. Usually, the outer layer regulates diffusion for prolonged release, while the inner layer contains the drug reservoir. Layer thickness, porosity, and membrane permeability are some of the variables that affect the mass profile. To ensure therapeutic efficacy and optimize medication delivery, it is imperative

to comprehend this profile. Probability density functions (PDFs) are one type of mathematical model that is used to anticipate release patterns and simulate mass release.

$$\Pi_1(t) = \int_{-L_1}^{0} P(x,t)\,dx, \qquad (13)$$

$$\Pi_2(t) = \int_{0}^{L_2} P(x,t)\,dx. \qquad (14)$$



- Figure 4: Mass Profile for two-layer system

A drug-eluting stent's coating and arterial wall layers' drug fractions are plotted over time to show how the drug is moved from the coating layer into the artery wall. The blue solid line, which represents the drug fraction in the artery wall, starts at zero and rises as the drug passes through the coating and into the tissue. the other hand, the red dashed line shows the initial high drug percentage in the coating layer, which gradually drops as the drug diffuses into the artery wall.

This graph was explained using the Langevin simulation approach. At first, a significant concentration gradient pushes the drug molecules in the coating layer into the artery wall. By combining deterministic forces (produced by the concentration gradient) and random thermal fluctuations, the Langevin simulation accurately depicts the random movement of drug particles inside the coating and artery wall layers. Over time, the fraction in the coating layer decreases and the fraction in the artery wall increases as a result of the drug particles' random walk, which is influenced by these factors.

Table 1: Parameter values used in the simulation

Parameter	Physical value
L_1	5×10^{-6} m
L_2	10^{-4} m
D_{e_1}	$5 \times 10^{-11} \frac{\text{m}^2}{\text{s}}$
D_{e_2}	$7 \times 10^{-15} \frac{\text{m}^2}{\text{s}}$
D_m	10^{-9} s
$k_B T$	4.3×10^{-21} J
m	1.5×10^{-24} kg
τ_1	2.5×10^{6} s
τ_2	1.4×10^{6} s
τ_m	3.5×10^{-18} s
ϕ_1	0.6×10^{-18} s
ϕ_2	0.6×10^{-18} s

4. Multi-layer System

The movement of materials across a composite medium with several layers, accelerated by concentration gradients, is known as multi-layer diffusion. The diffusion in each layer of a one-dimensional model is controlled by the time-dependent diffusion equation. A plate with finite thickness that extends indefinitely in the other two spatial dimensions is used to model each slab. In this situation, dispersion mostly takes place perpendicular to the slabs. The concentration profile throughout each

layer is described by a one-dimensional mathematical model that was created to present this process. Continuity conditions, which demand that the concentration flux and concentration values be constant across boundaries, guarantee mass conservation at the interfaces between layers. Analyzing diffusion in layered systems, such as membranes, coatings, and biological tissues, requires the use of this approach.

The diffusing substance's concentration in the i-th layer, represented as $c_i(x,t)$, changes over time in accordance with the diffusion equation:

$$\frac{\partial c_i}{\partial t} = D_i \frac{\partial^2 c_i}{\partial x^2}, \qquad (15)$$

where D_i is the diffusion coefficient of the i-th layer

Mass continuity must be assured at the boundary between layers that are adjacent.

Throughout the interface, the concentration flux remains constant. at $x = L_i$:

$$J_i = -D_i \frac{\partial c_i}{\partial x} = -D_{i+1} \frac{\partial c_{i+1}}{\partial x} = J_{i+1}, \qquad (16)$$

where J_i and J_{i+1} are the diffusion fluxes in layers i and $i+1$, respectively.

The concentration values at the boundary

$$c_i(L_i, t) = c_{i+1}(L_i, t), \qquad (17)$$

The effective diffusivity $D_e(x)$ of a multi-layer system with Nlayers is piecewise constant, which is described as

$$D_e(x) = D_{i(e)} \quad \text{in the } i\text{-th layer,} \quad \text{where } x \in [x_{i-1}, x_i].$$

The total probability over the entire domain defines as,

$$\int_{-\infty}^{\infty} P(x,t)\, dx = 1, \qquad (18)$$

Probability density function (PDF) $P(x,t)$ for N layers defined as,

$$P(x,t) = \begin{cases} \sum_{m=1}^{M} A_m^{(1)} \frac{1}{\sqrt{4\pi D_{e_1} t}} e^{-\frac{(x - x_m^{(1)})^2}{4 D_{e_1} t}}, & x < x_1, \\ \sum_{m=1}^{M} A_m^{(i)} \frac{1}{\sqrt{4\pi D_{e_i} t}} e^{-\frac{(x - x_m^{(i)})^2}{4 D_{e_i} t}}, & x \in [x_{i-1}, x_i], \\ \sum_{m=1}^{M} A_m^{(N)} \frac{1}{\sqrt{4\pi D_{e_N} t}} e^{-\frac{(x - x_m^{(N)})^2}{4 D_{e_N} t}}, & x > x_{N-1}, \end{cases} \qquad (19)$$

In this case, $A_m^{(i)}$-Boundary conditions determine the weight coefficients for the m-th particle/image particle in the i-th layer. $x_m^{(i)}$- Original and image particle locations in the i-th

layer, D_{e_i}- the i-th layer's effective diffusion coefficient and x_{i-1}, x_i: The i-th layer's boundaries. Boundary Conditions at Interfaces, at each interface $x = x_i$ between the i-th and $(i + 1)$-th layer: where, continuity of the PDF.

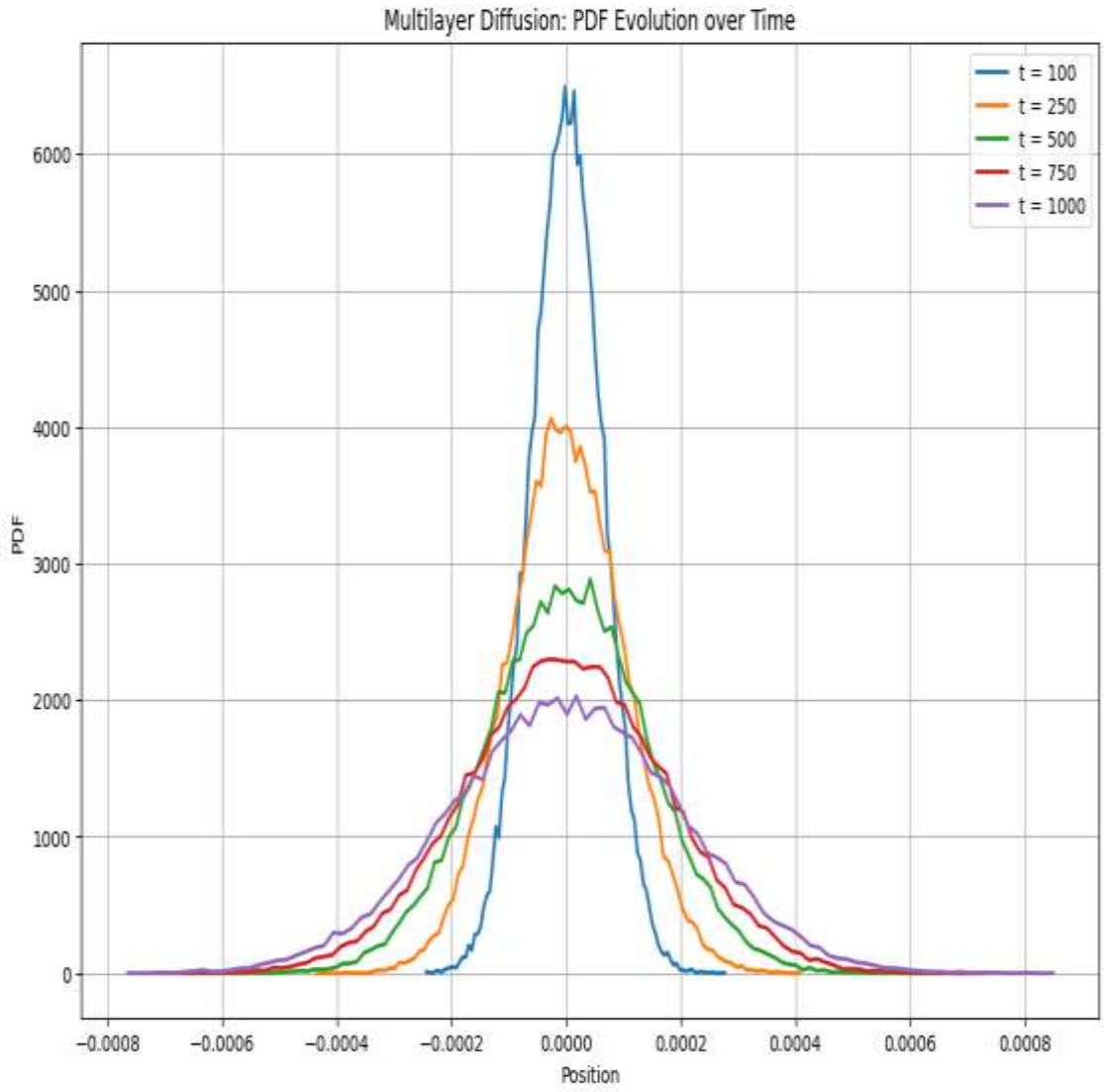
$$P_i(x_i, t) = P_{i+1}(x_i, t), \qquad (20)$$

Continuity of the Flux.

$$D_i \frac{\partial P_i(x,t)}{\partial x}|_{x=x_i} = D_{i+1} \frac{\partial P_{i+1}(x,t)}{\partial x}|_{x=x_i}, \qquad (21)$$

The PDF and probability flux transitions between layers are guaranteed to be uniform under these circumstances.

By using eq.(19) graph shows in fig.(5) illustrates the way the probability density function (PDF) of drug molecules changes over time in a multi-layered drug delivery device, most likely a drug-eluting stent. The place in the system is shown by the x-axis, and the possibility of discovering a therapeutic molecule there is shown by the y-axis. At a given time point (t = 100, 250, 500, 750, and 1000), each curve on the graph represents the PDF. The curves get wider with time, which indicates that the drug molecules are moving farther away from where they were first released. A drop in drug concentration at the release point is indicated by the concurrent decrease in peak height of each curve. The diffusion pattern appears to be rather normal based on the bell-shaped curves. Including the rate of drug release and the spatial distribution of the drug over time, this graph offers important insights into the drug release kinetics inside the multi-layered system.



- Figure 5: The Probability Density function of multi-layer system; Results of the Langevin dynamics simulations at t=100,250,500,750,1000

The limiting instances can be expanded to take into consideration the effective diffusivity $D_{i(e)}$ in each layer of a multi-layer system with N layers. Let's consider the two multi-layer system scenarios-

Case 1:

$$\frac{D_{(i+1)(e)}}{D_i(e)} \to \infty$$

This indicates a highly reflective interface between layers i and i+1, where the diffusivity in the i-th layer D_i approaches zero in relation to the (i+1)-th layer

$$\left(\frac{D_{(i+1)(e)}}{D_i(e)}\right)$$

.

The reflection takes place at the interface $x = x_i$, essentially acting as a reflecting wall.

In this instance, the PDF P(x,t) can be written as a superposition of the contributions from the original particle and its reflected "image particle."

For $x > x_i$(the area outside the reflecting wall):

$$P(x,t) = \frac{1}{\sqrt{4\pi D_{(i+1)(e)}t}} e^{-\frac{(x-x_0)^2}{4D_{(i+1)(e)}t}} + \frac{1}{\sqrt{4\pi D_{(i+1)(e)}t}} e^{-\frac{(x+x_0)^2}{4D_{(i+1)(e)}t}}, \qquad (22)$$

Case 2:

$$\frac{D_{(i+1)(e)}}{D_i(e)} \to 0$$

This is consistent with a highly absorptive interface in which the (i+1)-th layer $D_{(i+1)(e)} \to D$ has a significantly lower diffusivity and the i-th layer $D_i(e) \to \infty$ functions as a barrier.

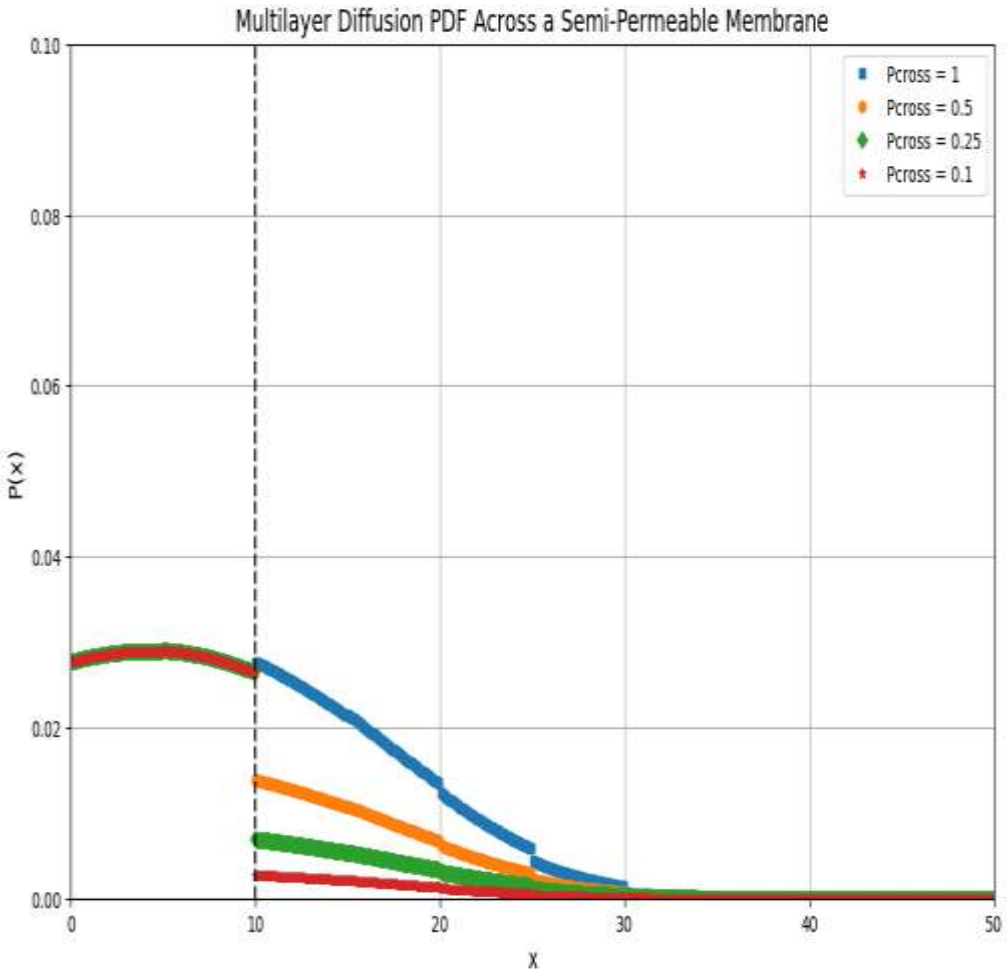
In this instance, the PDF P(x,t) is the difference between the contributions of the original particle and its "negative" image particle.

For $x > xi$ (beyond the interface):

$$P(x,t) = \frac{1}{\sqrt{4\pi D_{(i+1)(e)}t}} e^{-\frac{(x-x_0)^2}{4D_{(i+1)(e)}t}} - \frac{1}{\sqrt{4\pi D_{(i+1)(e)}t}} e^{-\frac{(x+x_0)^2}{4D_{(i+1)(e)}t}}, \qquad (23)$$

4.1 Impact of Semi-Permeable Membrane in Drug-Eluting Stents for multilayer

Multi-layered drug-eluting stents (DES) use semi-permeable membranes that function as selective barriers to affect drug release. These membranes have the ability to modify diffusion rates by partially reflecting drug molecules at layer interfaces. Drug retention, controlled release, and overall therapeutic efficacy are all impacted by this reflection effect, which is dependent on membrane porosity, material characteristics, and drug-membrane interactions.



- Figure 6: Pcross for semi permeable membrane in multi-layer system; Langevin dynamics simulations for Pcross = 1,0.5,0.25,0.1

Fig.(6) describes the impact of membrane permeability on drug diffusion in a multi-layered drug-eluting stent. Using eq. (22), the y-axis displays the probability density function (PDF) of drug molecules at that point, and the x-axis displays the distance from the stent surface. Pcross, which ranges from 1 to 0.1, is the membrane permeability that each curve represents. The PDF curve shifts when Pcross decreases in the direction of the stent surface, indicating a less permeable membrane. This change indicates that a less permeable membrane limits the diffusion of the medicine, causing the concentration of the drug to be higher near the stent and decrease farther away. Drug concentration generally decreases as one gets farther away from the stent surface, as predicted by the diffusion

process. In order to precisely regulate drug delivery and possibly improve therapeutic results, this graph illustrates the manner in which regulating membrane permeability might affect drug release kinetics from a multi-layered stent.

4.2 Mass Profile in Multi-Layered Drug Eluting Stent Systems

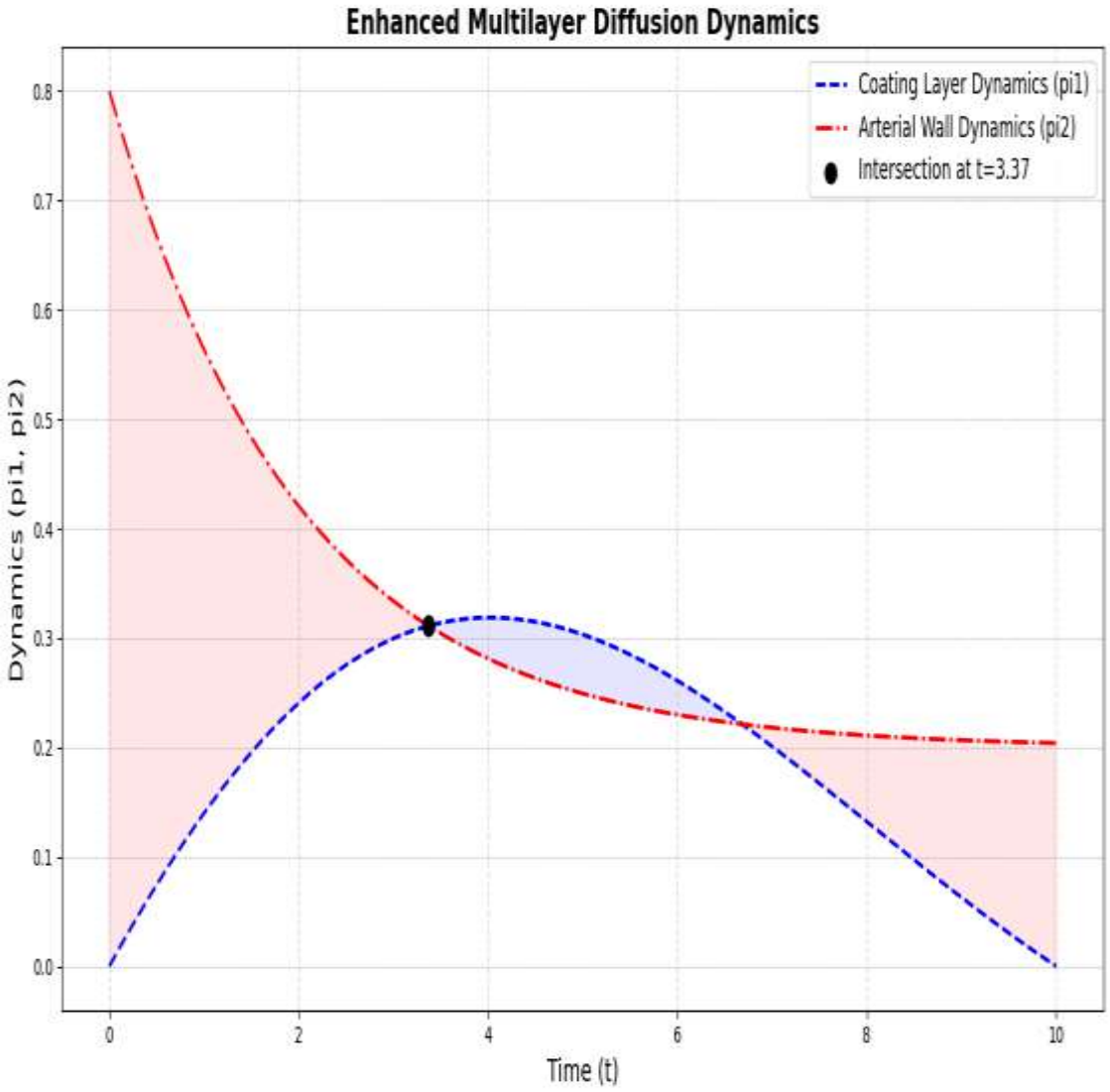
For a drug-eluting stent with multiple layers, the drug fractions $\Pi_1(t)$ and $\Pi_2(t)$ in the artery wall (layer 2) and coating layers (layer 1), respectively. The cumulative fraction of medication that is still present in each coating layer at time t in a multi-layer stent is denoted as $\Pi_1(t)$. This would include integrating the probability density function (PDF) over each coating layer's total thickness.

$$\Pi_1(t) = \sum_i \int_0^{l_i} P_i(x,t)\, dx, \qquad (24)$$

The fraction of drug present in the artery wall at time t after diffusing from the coating layers is denoted by $\Pi_2(t)$. To do this, the PDF would need to be integrated throughout the artery wall's thickness.

$$\Pi_2(t) = \int_0^{l_2} P_2(x,t)\, dx, \qquad (25)$$

By using eq.(24) and eq.(25), the dynamic interaction between drug uptake by the artery wall and drug release from the stent coating is depicted in the fig.7. The y-axis shows normalized dynamics, which most likely reflect the rate of drug uptake $\Pi_2(t)$ by the artery wall and the rate of drug release $\Pi_1(t)$ from the coating layer, while the x-axis shows time. Over time, a decreasing drug release rate is indicated by the coating layer dynamics curve's decreasing tendency. On the other hand, the arterial wall dynamics curve first rises, indicating a rising rate of drug uptake, and then it may plateau or fall, indicating that the drug has beensaturated or redistributed within the tissue. When the drug release rate from the coating layer equals the drug uptake rate by the artery wall, a critical juncture is indicated by the intersection point of these curves, which occurs at t=3.37. The dynamic interaction between drug release and tissue uptake, which is essential for maximizing therapeutic efficacy and reducing side effects, is highlighted in this graph, which offers insightful information about the temporal characteristics of drug delivery from a mass-based stent.



- Figure 7: Mass profile for multi-layer

CONCLUSION

In this study, we employed Langevin dynamics simulations, incorporating Monte Carlo methods and the Verlet algorithm, to model drug diffusion in a two-layer and multi-layer drug-eluting stent (DES) system. By capturing the stochastic nature of molecular motion and interactions within complex tissue structures, our simulations provide valuable insights into the drug release mechanism. The results highlight the influence of random fluctuations on diffusion pathways, aiding in the optimization of drug release profiles. Furthermore, the effective diffusivity obtained from our simulations offers a predictive framework for controlled drug delivery, ensuring sustained therapeutic efficacy. This approach enhances our understanding of drug transport in DES and can be instrumental in designing more efficient stent coatings for improved clinical outcomes.

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