Curvature effects on a simplified reaction-diffusion model of biodegradation

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Abstract

The biodegradation process of some types of polymers occurs due to many different factors including their morphology, structure and chemical composition. Although this is a complicated process, most of its important stages like the diffusion of monomers and the hydrolysis reactions have been modeled phenomenologically through reaction-diffusion equations, where the properties of the polymers were encompassed [1]. Using a simplified reaction-diffusion model for the biodegradation of polymers [1], in this contribution we study the possible effects of the curvature of the system's geometry in the degradation process, which is characterized by the interaction of the corresponding reaction rate and the diffusion coefficient. To illustrate the problem of diffusion on a curved surface we consider the surface of a cylinder and of the so-called Gaussian bump [2]. We show how the degradation process is affected by the curvature of the system for the simplified model.

Keywords

Biodegradation process, Reaction-Diffusion systems, Diffusion in curved surfaces.

1. Introduction

Many of the biological processes or applications of interest where it is possible to use diffusion and reaction-diffusion processes as models, occur on curved substrates. In [3] was introduced the simplest model for the Brownian motion of a free particle, which takes place on a Riemannian geometry. This can be done basically replacing the Laplacian by the Laplace-Beltrami operator in the diffusion equation which is the appropriate operator that transform properly under manifold transformations. In that work was found that the geodesic mean square distance can be Taylor expanded at short times, and its corresponding coefficients can be expressed in terms of geometric quantities such that the curvature scalar. Although these results are valid for very short times, they show that, in addition to having an anomalous behavior, there are modifications due to the curvature of the space where the diffusion process takes place. The curvature effects have also been studied on a thick surface embedded in three-dimensional space with use of the so-called Riemann normal coordinates. In [4] an effective diffusion coefficient that takes into account the thickness and curvature effects was introduced. It has been shown that the curvature of a system plays an important role in confined diffusion processes for two-dimensional embeddings [5], where authors derive general effective diffusion coefficient to describe the diffusion in a narrow varying channels defined on curved surfaces. In these works it was shown that the effective diffusion coefficients for channels on curved surfaces depend on the particular geometry of the surface and in particular may depend on the curvature thereof [6, 7]. Differential geometry tools have been recently used to explore further mappings on such systems [8]. Reaction-diffusion systems that give rise to pattern formation have also been studied on curved surfaces, for instance instability criteria in pattern formation in this models could be modified by geometry [9]. It has been found that on thick surfaces one can have space-dependent reaction kinetics. A transition from a homogeneous steady state to an inhomogeneous steady state (a pattern) can be obtained by changing the thickness. This may depend on the geometry [10]. Even when the thickness is negligible is possible to find modified dispersion relations reflecting the surface curvature [9]. It has also been seen that position, orientation and size of patterns can be controlled through geometry [11]. Indeed, that are pattern formation models where the curvature plays a central role and even is related with the conformation process of the membrane [12].

An interesting application of reaction-diffusion equations is in the modeling of the degradation process that occurs in certain materials. Biodegradation is a complex process involving several factors ranging from chemical composition to structure and morphology. The important stages of biodegradation have been summarized in a phenomenological model [1], which characterizes the process through reaction rate and diffusivity constants. The main objective in this contribution is to see the effects that different curved geometries can have on the biodegradation process. through on this reaction-diffusion model. We solve a simplified reaction-diffusion system that neglects porosity. For this we chose three different geometries a flat plate, a cylindrical rod and the so-called Gaussian bump [2].

The paper is organized as follows: In section 2 we review the phenomenological model for the biodegradation of certain polymers, reviewing the species involved in the hydrolysis reactions and the effective diffusion. In section 3 we propose the simplified system and solve it numerically with particular choose of initial and boundary conditions. For each of the three geometries a qualitatively similar behavior was found although there are specific changes. For critical times in which the maximum concentration is reached, it is observed that for the cylindrical rod the maximum is reached faster, then the Gauss bump and finally for the flat plate. A summary is presented in section 4.

2. Simplified reaction-diffusion model of biodegradation

Reaction-diffusion equations have been used to describe various degradation processes [13], for instance the gradual decomposition of polymer microspheres made up different materials used for the controlled drugs release and delivery at certain time periods [14]. Have also been used to model the degradation of various biomaterials as fixation devices in the human body [1] and other biomedical applications [15] such as implants and bioadhesives [16], tissue engineering [17], etc. The development of many of these bioproducts has been based on trial and error approaches, so that mathematical models of degradation are very important for their design and optimization.

Although the biodegradation process of a biodegradable material is a rather complicated process, it has been possible to isolate the most important features of the reactions involved to simplify the modeling using systems of reaction-diffusion equations that are consistent with the known experimental data. In [1] the biodegradation of a biodegradable polymer used for orthopedic purposes is studied. These materials are made from polyglycolic and polylactic acids because of their proven biocompatibility. We base our comparative study on this model in due to its mathematical clearness. The relevant components involved in the process may be considered as follows: Polymer chains that can hydrolyze, crystallize, but not diffuse; monomers which diffuse and are the product of the hydrolysis reactions; water as the medium where diffusion take place. In the hydrolysis reaction water molecules attack the ester bounds of the polymer chain. Thus, biodegradation can be described using the molar concentration of the ester polymer bounds and the molar concentration of monomers present in the system. It is possible to introduce the degree of crystallinity through the Avrami equation, in the present model is not included although an exhaustive study can be found in [18]. On the other hand, as the biodegradation process occurs in a porous material, the diffusion coefficient of monomers depends on the corresponding porosity which in turn depends on the partial concentrations of the constituents.

The reaction-diffusion system that governs the biodegradation process can be written in dimensionless variables, normalized to a characteristic length of the device and the initial ester bound molar concentration, as follows [1]

$$\begin{aligned} \frac{\partial C_m}{\partial t} &= (k + C_m^{1/2})C_e - \alpha D_0 \left[|\nabla C_m|^2 + \nabla C_m \cdot \nabla C_e\right] + D_0 \left[1 + \alpha(1 - C_m - C_e)\right] \nabla^2 C_m, \\ \frac{\partial C_e}{\partial t} &= -(k + C_m^{1/2})C_e, \end{aligned} \tag{1}$$

where $C_e(\mathbf{x}, t)$ and $C_m(\mathbf{x}, t)$ are the molar concentrations of ester bounds and of monomers respectively. From Eqs. (1) the reduction in ester bound concentration C_e is entirely due to the hydrolysis reactions. In the first term the constant k is the reaction rate of the hydrolysis, the power of C_m is known as the dissociation exponent, it is fixed at $1/2$ due to experimental evidence but in general can be considered an adjustable parameter. For the production rate of monomers the same reactions are considered with the corresponding diffusion process with an effective diffusivity depending on C_e and C_m due to the porosity of the system. This dependence imply the two nonlinear terms in the equation for C_m, taken the porosity coefficient α as constant and with a constant diffusion coefficient D_0 for free monomers.

As was shown in [1], the biodegradation process is defined by the competition between the reaction rate and the diffusion coefficient. There are four regions, fast diffusion dominated, slow diffusion dominated, fast hydrolysis reaction with irrelevant diffusion, and a region with k and D_0 not so large where all processes are relevant. We focus on this last region.

Although the effect of porosity is important, it does not affect the evolution of the system qualitatively speaking. The net effect of the two non-linear terms is to reduce the concentration of C_m a little faster. The terms that are coupled to laplacian slightly increase the concentration. Because of this we decided to further simplify the system by neglecting porosity taking $\alpha = 0$ instead of 4.5 as in the original model, so that the effect of the geometry of the device becomes clearer.

3. Curvature effects in effective one-dimensional systems

In this section we study the simplified biodegradation process through reaction-diffusion system in three different geometries. The first system is a plate where the degradation process occurs in the thickness direction, and therefore the monomer concentration only depend on the x coordinate. At the edge concentration of monomers decreases to zero $C_m(x = L) = 0$, while in the other end we impose non-flux boundary condition $\partial_x C_m(x = 0) = 0$. For C_e we ask that in $x = L$ is concentration is maximum. Moreover, at the beginning of the process only ester bounds are present. So, the system reduces to

$$\begin{aligned} \frac{\partial C_m}{\partial t} &= (k + C_m^{1/2})C_e + D_0 \frac{\partial^2 C_m}{\partial x^2}, \\ \frac{\partial C_e}{\partial t} &= -(k + C_m^{1/2})C_e, \end{aligned} \tag{2}$$

Solving numerically the system of equations we can see that the concentration of monomers begins to increase when hydrolysis starts acting, and due to the diffusion they leave the plate causing C_m to have a maximum in time from which it begins to decay until there are no ester bounds with whom to interact. Indeed we can also noted that C_e decreases due to the hydrolysis reactions. Corresponding results can be seen in Fig.1, where we plot both concentration for monomers and ester bounds as function of time and position. This behavior is similar to that of an autocatalytic reaction between two chemicals interacting in a confined region as in [19, 20], where analytical solutions of traveling waves in terms of hyperbolic tangent functions were obtained. It is possible that in this case similar semi-analytical solutions could be obtained.

As we will see, although qualitatively similar the behavior on the studied curved surfaces and that of the plate, specific values may vary. In fact, as it was advanced in [1], in the cylinder it is easier to reach the uniform degradation state than in the plate, due to the larger contact

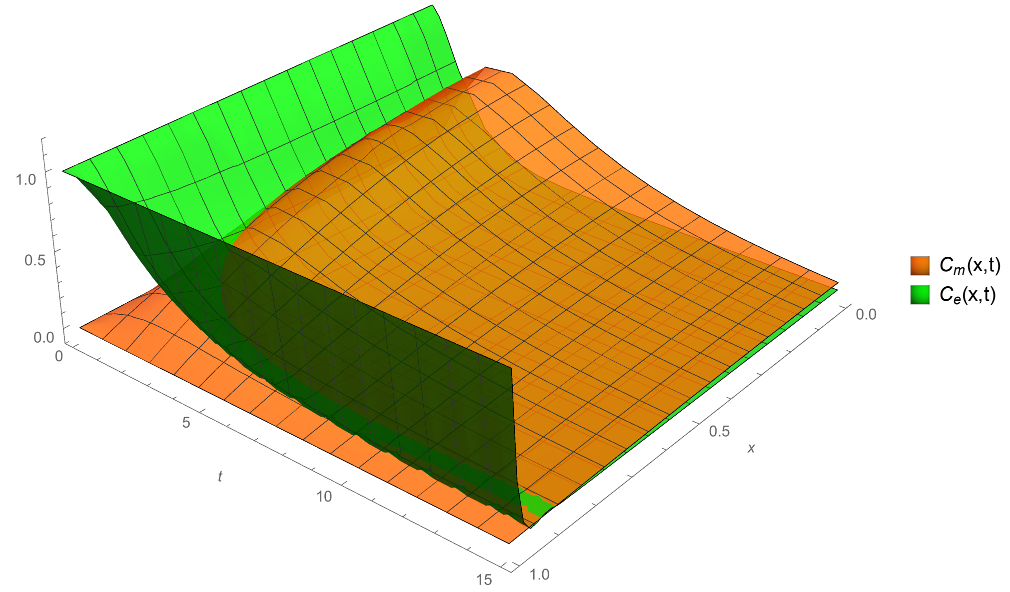

Figure 1: Normalized molar concentration of monomers (orange) and ester bound (green) as function of time and position is shown. Simulations using finite difference method were performed with $k = 0.1$ and $D_0 = 0.1$.

area with water of the former. This was done using the so-called biodegradation map which shows the behavior of the system in terms of the relation between diffusivity D_0 and reaction rate k. As the biodegradation map has not been constructed in the present study, the effect of the geometry can be found for fixed D_0 and k for instance, with the maximum value of C_m^* and the time t_* at which it is reached.

In the case of a biodegradable infinite cylinder, Eq. (1) is reduced to a one-dimensional problem due to the symmetry of the system and that degradation occurs from the cylinder surface radially outwards. Thus, the concentrations just depend on r and the system is simply as follows

$$\begin{aligned} \frac{\partial C_m}{\partial t} &= (k + C_m^{1/2})C_e + D_0\frac{\partial^2 C_m}{\partial r^2} + \frac{D_0}{r}\frac{\partial C_m}{\partial r}, \\ \frac{\partial C_e}{\partial t} &= -(k + C_m^{1/2})C_e, \end{aligned} \tag{3}$$

The other system to consider is the so-called Gaussian bump that also reduces to a one-dimensional problem because it is a surface of revolution. Indeed, a point on the surface can be parametrized as $\mathbf{R} = (r\cos\phi, r\sin\phi, h\,\exp\left(-r^2/r_0^2\right))$, where h is the height of the bump and r_0 is the radius of its waist [2]. We choose this surface because mathematically has positive, negative and zero curvature which allows to study transitions at different values of curvature. As is well known the Laplacian on curved surfaces is generalized with the Laplace-Beltrami operator, which in general is $\nabla_{LB}^2 = g^{-1/2}\partial_a\left(g^{1/2}\,g^{ab}\partial_b\right)$, where g is the determinant of the metric g_{ab}. For the Gaussian bump the metric is diagonal $g_{ab} = \text{diag}\{\ell(r), r^2\}$, where $\ell(r) = 1 + (h^2r^2/r_0^4)\exp\left(-r^2/r_0^2\right)$. Determinant is $g = r\sqrt{\ell(r)}$. Therefore, the system can be expressed as

$$\begin{aligned} \frac{\partial C_m}{\partial t} &= (k + C_m^{1/2})C_e + \frac{D_0}{\ell(r)}\frac{\partial^2 C_m}{\partial r^2} + \frac{D_0}{r\,\ell(r)}\left(1 - \frac{r\ell'}{2\ell}\right)\frac{\partial C_m}{\partial r}, \\ \frac{\partial C_e}{\partial t} &= -(k + C_m^{1/2})C_e. \end{aligned} \tag{4}$$

Note that both sets of equations (3) and (4) must be dimensionless so that a characteristic length should be introduced in each case, for the cylinder is the radius of the pin and for the bump is r_0, we also consider a default aspect ratio $h = r_0$. In both cases, the effect of being two-dimensional curved surfaces embedded in three dimensions can be thought to be reflected in the additional terms in the monomers concentration equation. Numerically obtained results are condensed in Fig. 2, where the behavior of concentrations for different geometries is shown. It can be appreciated that the concentrations of ester bounds are very similar in all three cases decreasing in time. This is expected since they do not diffuse.

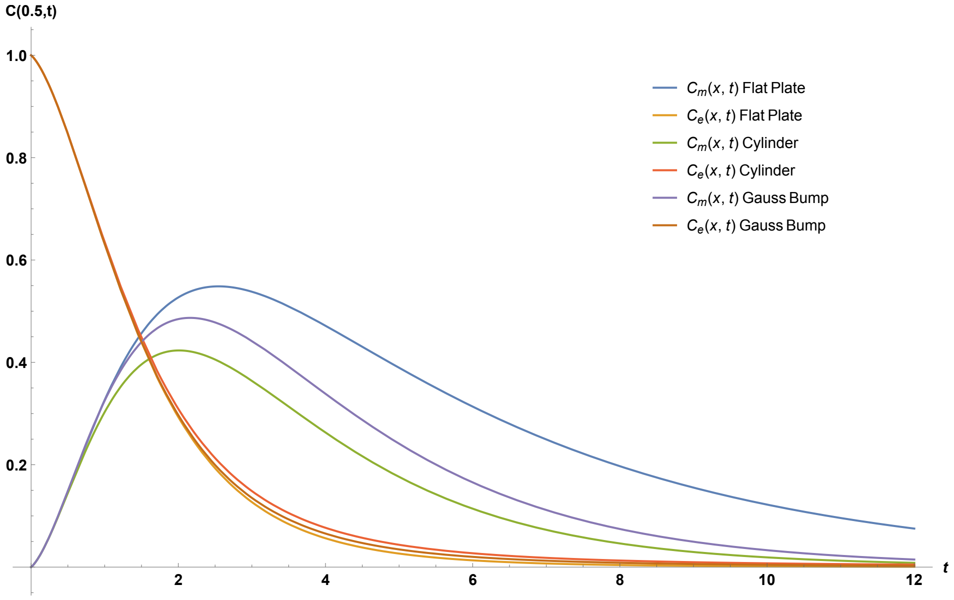

Figure 2: Numerically calculated monomer and ester bound concentrations as function of time for three different geometries. Simulations using finite difference method were carried out for parameter values $k = 0.1$ and $D_0 = 0.1$. Concentrations were evaluated at the center of the domain, for the flat plate at $x = 0.5$, and for cylinder and bump at $r = 0.5$.

However, although qualitatively similar the behavior of monomer concentrations are different for each geometry. For short times both the bump and the plate are quite similar, whereas for long times the bump approaches asymptotically to the cylinder behavior. Furthermore, for each case the maximum concentration has a different value and is reached at different critical times. Approximately, for the flat plate $C^*_{m_{FP}}(t_{*_{FP}} = 2.5475) = 0.548554$, for the Gaussian bump the maximum concentration is $C^*_{m_{GB}}(t_{*_{GB}} = 2.161) = 0.486963$, and for the cylinder case is $C^*_{m_{Cyl}}(t_{*_{Cyl}} = 2.01) = 0.423299$. We note that both the maximum concentration and the corresponding time increase from the cylinder to the bump and finally to the plate. This is evidently due to the fact that diffusion processes are different for each geometry. For instance, the last term of the equation for C_m in both Eqs. (3) and (4) for the cylindrical and Gaussian cases, can be interpreted as a drift term. Nonetheless, the drift velocity is different in each case, and is particularly a different function of r.

On the other hand, it is worth mentioning that this analysis was done for certain fixed reaction and diffusion parameters, and the concentrations were presented at just one point of the domain. A more exhaustive analysis will be necessary, making explicit the dependence on the curvature of the surfaces and considering all their parameters (for example for the bump the aspect ratio can be considered as parameter and take it different from one) to see the effect of the competition between reaction, diffusion and curvature on these systems.

4. Summary and conclusions

It has been seen that the geometry of the system plays an important role in diffusion processes on curved surfaces, surfaces with thickness, confined diffusion, etc. Also, reaction-diffusion processes have recently been studied in curved manifolds giving interesting effects like modifying the properties of Turing patterns, for the appropriate boundary conditions. In this work we study the influence of curvature on the biodegradation process in a simplified reaction-diffusion system for a phenomenological model introduced in [1]. More precisely, we study a simplified system that neglects the porosity of the medium. Although porosity is a very important effect involving concentration-dependent diffusivity, for certain particular parameter values, the behavior of the system does not change qualitatively.

This simplified biodegradation model was studied on three different geometries a plane, a cylinder and a surface of revolution known as the Gaussian bump. The latter two can be reduced to one-dimensional problems in the radial coordinate, so the curvature effect can be summarized in an extra drift term. In all three cases the reaction involved begins to increase the concentration of monomers (product of the degradation of the material) which reaches a maximum at a certain critical time, after which start to decrease due to monomers diffuse out of the system. The value of the maximum concentration and the corresponding critical time are modified according to the curvature of the system. The first maximum is reached in the cylinder, then in the bump and the last is the plate. This is due to the fact that for the cylinder the drag term has a greater effect on the concentration than in the other cases.

Although the influence of curvature in these processes is clear, the simulation was performed for certain fixed parameters, so a thorough analysis is necessary. For example, it would be interesting to know how the magnitude and sign of the curvature influences the degradation process. It would also be interesting to see the behavior under confinement since pattern formation is induced in this case, specifically the instability conditions could be modified by geometry. This could be addressed elsewhere.

Acknowledgments

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