Two Dimensional Drug Diffusion Between Nanoparticles and Fractal Tumors

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Abstract. Drug delivery methods based on nanoparticles are some of the most promising medical applications in nanotechnology to treat cancer. It is observed that drug released by nanoparticles to the cancer tumors may be driven by diffusion. A fractal tumor boundary of triangular Von Koch shape is considered here and the diffusion mechanism is studied for different drug concentrations and increased fractality. A high order Finite Elements method based on the Fenics library is incorporated in fine meshes to fully resolve these irregular boundaries. Drug concentration, its transfer rates and entropy production are calculated in an up to forth order fractal iteration boundaries. We observed that diffusion rate diminishes for successive prefractal generations. Also, the entropy production around the system changes greatly as the order of the fractal curve increases. Results indicate with precision where the active sites are, in which most of the diffusion takes place and thus drug arrives to the tumor.

1. Introduction
Nanotechnology and nanoscience have huge potential to bring benefits to many areas of research and applications. Also, are attracting rapidly increasing investments from enterprises and governments all over the world. Recently, nanotechnologies and nanoscience received sufficient experimental, numerical and theoretical attention in nanomaterials, metrology, electronics, optoelectronics, biotechnology and nanomedicine [1]. Nanotechnology in medicine is promising in areas such as the drug delivery targeted at specific sites of the body, molecular imaging, and disease diagnosis.

One important nanotechnology-in-medicine application is the transfer of antibiotics through nanoparticles to tumors. Antibiotics attack the cancer tumors upon released by the nanoparticles through diffusion. Tumors outer boundary is complicated, irregular shaped reminiscent of fractal structures, with a shape made of similar parts [2].

Diffusion of drugs or antibiotics in this particular case is a very common phenomenon. This implies a direct connection to Laplacian, as many important diffusion phenomena obey the steady-state Laplace’s equation. The Laplace equation is a linear equation, however, the complexity of the
problem is due to the geometrical irregularities of the boundaries. Due to this fact, an important number of studies on the distribution of Laplacian fields around geometrically irregular, and fractal objects have been justified [3].

In the past few decades, an important field of interdisciplinary research has been developed based on new geometry concepts, the fractal geometry of nature, pioneered by Mandelbrot [4]. The fractal geometry approximates the naturally discovered disordered morphologies. Some characteristic examples are the terminal part of the respiratory system of mammals, the biological membranes and the porous electrodes or catalysts [5].

2. Formulation

A concentration difference $c_1 - c_2$ is applied across the vertical boundaries of a cell, over a characteristic length $L$, and the cell obeys to zero flux boundary conditions along its horizontal boundaries, Figure 1a. Under these boundary conditions the steady state Laplace equation that satisfies the concentration, $c$, is written as:

$$\nabla^2 c = 0$$

(1)

the normalized entropy production, $P$, on the grounds of non-equilibrium thermodynamics, is expressed as:

$$P = \int \frac{(\nabla c)^2}{c} \, dr$$

(2)

Quantities, $c$ and $P$ can be evaluated, before addressing the role of complex boundaries in the entropy production, in the simple reference case of a two-dimensional box of length $L_x$ and height $L_y$, as shown in Figure 1. The corresponding solution for $c$ is written as:

$$c(y) = \frac{c_2 - c_1}{L_y} y + c_1$$

(3)

with $c_1 = c_1(0)$ and $c_2 = c_2(L_y)$. The normalized entropy production is given by

$$P = \frac{L_y}{L_x} (c_1 - c_2) \ln \frac{c_1}{c_2}$$

(4)

The Laplace equation, Eq. 1, for geometries associated to the first fifth orders, $n$, of the Von Koch curve at the fractal boundary, see Fig. 1a, has been solved using a fourth order Finite Elements method based on Fenics library [6] with about 200k elements. A detail of the finite element mesh is shown in Figure 1b. The continuity of the shapes allowed the application of a linear interpolation of the potential field and a constant value of its gradient on a given element. The entropy production had been computed for various values of concentration, $c_2$. While concentration $c_1$ is kept constant
(c₁=1.0). The values $c₂ = 0.001, 0.007, 0.02, 0.05, 0.5, 0.7, 0.9$ and 0.99 have been used for all the orders of the fractal curve.

Using the above method, all concentration and entropy production distributions are estimated with a very good precision for the six geometries and for all values of $c₂$.

![Figure 2](image1.png)

**Figure 2.** Drug concentration for: a) $n=1$ and $c₂=0.05$, b) $n=4$ and $c₂=0.05$, c) $n=1$ and $c₂=0.5$, and d) $n=4$ and $c₂=0.5$

3. Results and conclusion

Drug concentration for some indicative cases of $n=1$ and $n=4$ for the order of the fractal curve and $c₂=0.05$ and 0.5 regarding the concentration gradient are presented in Figure 2. Both fields are shown with 10 iso-concentration increment levels between 1 and 0.05. In the case of lower diffusion rate of $c₂=0.5$, only five contour levels are shown graphically. As it is expected, diffusion is purely two-dimensional as drug approaches near the fractal boundary and it penetrates inside the openings formed by the curve.

![Figure 3](image2.png)

**Figure 3.** Mass transfer for $c₂=0.5$ and for: a) $n=1$ and b) $n=4$. The mass flux lines at the centre of the low boundary are also presented.
Mass transfer has been presented in Figure 3, for \( n=1 \) and \( n=4 \) geometry and concentration \( c_2=0.5 \). When the geometry is like a plate the mass transfer has the same value throughout the height. If there are fractal irregularities drug can penetrate easier from the peaks, as Figure 3 shown. Thus, leads to the conclusion that for higher order fractal geometries, mass flow is bigger for the most of the area and the absorption of the drug is bigger.

In this paper the entropy production has been measured, associated with the first fifth fractal geometries. When the surface is a plate the entropy production is the same along the surface. Although, when the surface is irregular the entropy production is higher. Thus the first geometry \( (n=0) \) has a low and almost the same entropy production throughout the surface. When the geometry is higher, the irregularity is higher. Figure 4b shows that \( n=4 \) and \( n=5 \) have a big distribution due to the fractal boundaries. The last two fractal geometries owns a big number of peaks, as shown in Figure 3, that’s why the entropy production has many ups and downs.

![Figure 4](image)

**Figure 4.** Entropy production \( P \), with different concentration and at \( y \) coordinates, a) shows medium entropy production for \( n=0 \) and b) shows \( x \) direction at point \( x=1.0 \). The red line is for \( n=0 \), blue is for \( n=1 \), yellow is for \( n=2 \), magenta is for \( n=3 \) and green is for \( n=4 \).

When diffusion rate \( (c_1-c_2) \) diminishes, entropy production \( (P) \) increases. Figure 4a, shows entropy production in the first geometry with different concentration \( c = 0.1, 0.3, 0.5, 0.95, 0.98, 0.993, 0.999 \). With very small concentration entropy production is almost zero. Although, for bigger concentrations entropy production values have a significant augmentation.

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5. References

[1] Schroder M 1991 Fractals, Chaos, Power Laws Freeman W H and Co New York
[2] Baish W and Rakesh J K 2000 Fractals and Cancer Cancer Res 60 3683
[3] Karamanos K, Mistakidis S I, Massart T J and Mistakidis I S 2015 Entropy production of entirely diffusional Laplacian transfer and the possible role of fragmentation of the boundaries Fractals 23 1550026
[4] Mandelbrot, B 1982 The fractal geometry of nature Freeman W H and Co San Fransisco
[5] Sapos player B 1997 Universality et Fractales Flammarion Paris
[6] Logg A, Mardal K E and Wells G N 2011 The FEniCS Book Springer