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Macromolecules diffusion through mucosal epithelia: An enhanced mathematical model

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ABSTRACT

Macromolecules therapeutic and curative efficiency are generally subordinated to their ability to diffuse through tissues and mucus. Recently, several mathematical models which describe diffusion profiles of macromolecules in different organic tissues have been developed. Mucosal tissues remain the most difficult to model. In fact, interaction between macromolecules and mucosal epithelia structures are sophisticated as long as both macromolecules and epithelia fibres are not easy to configure. In the last two decades, many interpretations of macromolecules diffusion through epithelia have been proposed, i. e. the elastic continuum, obstruction-scaling and tubular medium models. In this study, we propose a mathematical model which introduces conjointly macromolecules realistic geometrical characteristics and epithelia behaviour in terms of physical obstruction.

KEYWORDS

Macromolecules;
Diffusion;
Mucosal tissues;
Epithelia;
Mathematical models;
Stokes-Einstein model;
Boubaker polynomials expansion scheme (BPES);
Boundary conditions.

INTRODUCTION

Synthetic and natural macromolecules as antibodies, globular proteins, nucleic acids, drugs and flexible linear polymers showed to have some promising potential in applications, such[1-4]. In major of these applications, macromolecules have to be transported through underlying epithelial cells layer and hence diffuse inside the targeted tissues. Modeling this transport process has been described as a very complex task. Lin *et al.*[1] developed a macromolecules one-dimensional transport model in a semi-infinite medium with realistic boundary conditions, yielding accurate profiles of macromolecules concentration versus penetration depth at specific time points. Radomsky *et al.*[2] proposed similarly a particular model for macromolecules crossed epithelial medium: *the mucus-filled capillary tubes network*. This model was supported by appropriate imaging of macromolecules concentration profiles along the tubes along with other results. Des Rieux *et al.*[3] established an in-vitro model of the human epithelium and succeeded to monitor the influence of macromolecules concentration at the apical side, temperature, size and surface properties on diffusion dynamics. Weinstein[4] proposed earlier a mathematical model of proximal tubule epithelium. This model took into account cotransport, and passive permeability properties of some macromolecules. The steady-state transport data yielded by

the modeled epithelium was fitted by a three-parameter pump-leak model of transport so that the uncertainty in extracting individual membrane properties from epithelial has been underscored.

In this paper, the proposed mathematical model introduces the notion of geometrical radius and outlines epithelia behaviour in terms of columnar physical obstruction.

PROBLEM FORMALIZATION

Model main governing parameters and presumptions

In order to model the transport of macromolecules through mucosal epithelia, it is unavoidable to observe separately two major entities: macromolecule (diffusing entity) and epithelia (medium). For the medium, geometry, quantifiable parameters, and defined boundary conditions have to be accurately established (Figure 1). Macromolecules were supposed to be uniformly supplied at a high concentration in the lumen of the epithelial tissue (Figure 1, $x < 0$).

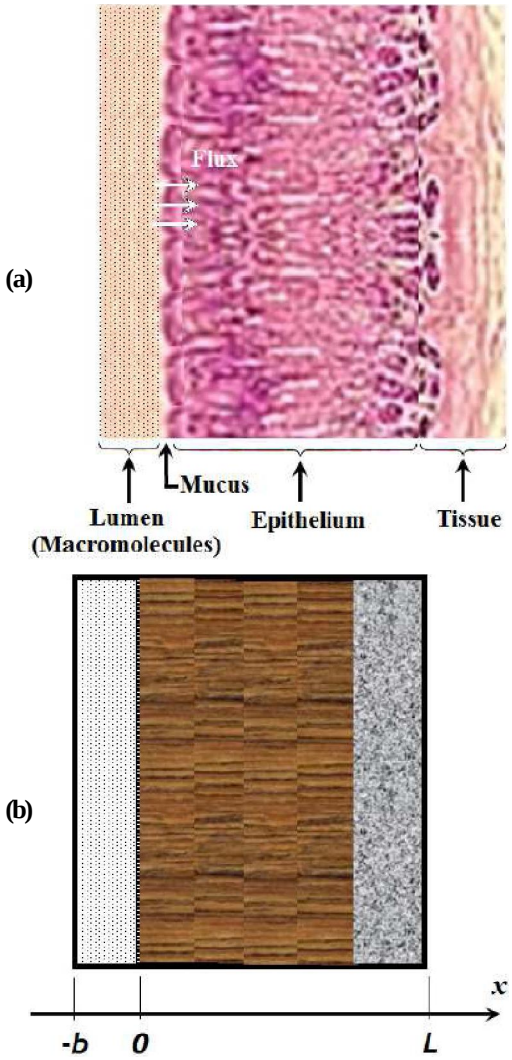

Figure 1 : Real (a) and schematized (b) view of the studied system

In the majority of precedent studies, macromolecule is generally dealt with as a hydrodynamic moving body. It is subjected, according to the approach, either to a hydrodynamic force (or drag) or a confinement to a random path (Brownian motion). The first approach states that the mean diffusion coefficient D_0 of a macromolecule is determined by a hydrodynamic Stokes-Einstein model derived drag action, produced by interactions with its surrounding medium:

$$D_0 = \frac{k_B}{6\pi\mu}\frac{T}{r_H}\left(1+\theta_C\right) \quad (1)$$

where k_B is Boltzmann's constant, T is absolute temperature, μ is medium viscosity, θ_C is a coefficient that depends on macromolecule size and initial solution ionic strength[5] and r_H is the hydrodynamic radius of the diffusing macromolecule.

This approach has been deserving a particular attention since the definition of r_H, the hydrodynamic radius, as the "*radius of a hypothetical hard sphere that diffuses with the same speed as the macromolecule under study*"[6], is rather statistical, with a minor relevance to macromolecule geometry:

$$r_H = \sqrt[3]{\frac{3m}{4\pi\rho N_A}} \quad (2)$$

where *m* is macromolecule's molecular weight, N_A is Avogadro's number ($N_A = 6.023 \times 10^{23}$ mol^{-1}) and ρ is macromolecules mean density.

Moreover, pure occlusion models were usually based on the theory of steric inhibition due to physical contact at the level of fibres, which occupy volume within epithelia. The problem is hence reduced to that of a stochastic random walk of a macromolecule with hydrodynamic radius r_H, through the available fractional volume of straight cylindrical columnar cavities with radius r_f[6-10]. For a given macromolecule, i. e. Lysozyme, a comparative scheme of some commonly defined radii is given in Figure 2.

One of the causes of divergence and contradictoriness between the proposed models[1-9] is

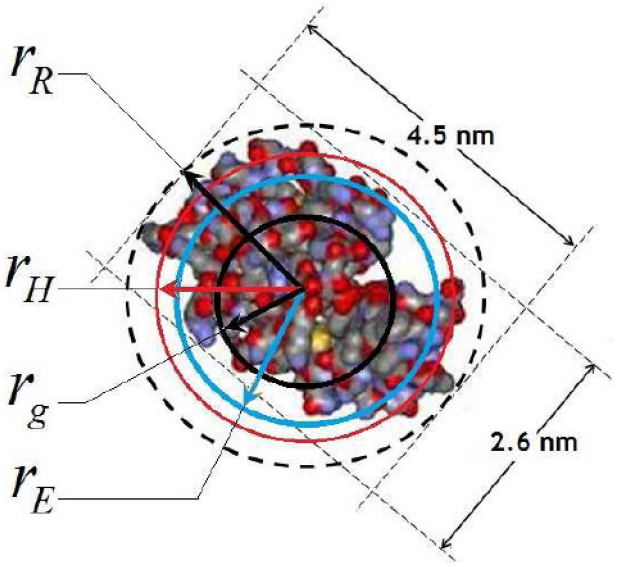

Figure 2 : Macromolecule different radii (case of Lysozyme)

the assumption concerning macromolecule geometry. Figure 2 illustrates this fact: for the given example, r_g, r_R and r_E are defined as gyration, rotational and equivalent radii, respectively. Gyration radius r_g is defined through the relation:

$$\mathbf{r_g} = \sqrt{\frac{\sum_{\text{All atoms}} \mathbf{m_i r_i^2}}{\sum_{\text{All atoms}} \mathbf{m_i}}} \qquad \textbf{(3)}$$

where m_i is the mass of the i^{th} atom in the macromolecule and r_i is the distance from the centre of mass to the i^{th} atom.

Rotational radius r_R is obtained by rotating the macromolecule about the geometric centre while equivalent radius r_E is the radius of a solid sphere with the same mass and specific volume as the considered macromolecule.

In the present model, a different approach has been adopted. Intrinsic geometrical characteristics of the macromolecule have been preferentially taken into account through considering the geometrical radius r_G, which is calculated on the basis of macromolecule real outer parallelepiped dimensions *a*, *b* and c (Figure 3):

$$\mathbf{r_G} = \frac{\sqrt{\mathbf{a^2 + b^2 + c^2}}}{\mathbf{2}} \qquad \textbf{(4)}$$

Values of the geometrical radii for some macromolecules are gathered in TABLE 1 along with other characteristics[11-16].

Governing equations and resolution protocol

According the summarized assumptions of the model, namely:

- ✓ Diffusing macromolecules follow a random walk: at each time unit, a given macromolecule either achieves a *full unit x-oriented motion step* or *not at all*,
- ✓ Fibre spatial distribution is independent of thickness of the layer or macromolecules motion, as per Ogston's geometrical assumption[17],
- ✓ Each unit motion step is related to the mean radius of spaces in fibre system,
- ✓ Each macromolecule has an effective forward motion (*x*-oriented) once the condition $r_G < r_f$ holds,

macromolecules diffusion through mucosal epithelia can hence be described by the diffusion coefficient profile $D_m(x)$ inside mucus ($0 < x < L$). Many studies considered this profile as a characteristic constant of the traversed medium. Accordingly, most of the models shared the simplistic presumption of *"interconnected pores path"* as presented by Deen[18], Anderson *et al.*[19] and Pappenheimer *et al.*[20] in the earliest models. In the actual model, spatial juxtaposing of mucus fibres is taken into account through steric occlusion function g(*x*), which traduces trajectory distortion along diffusion path, in concordance with Ogston's approximation[17]:

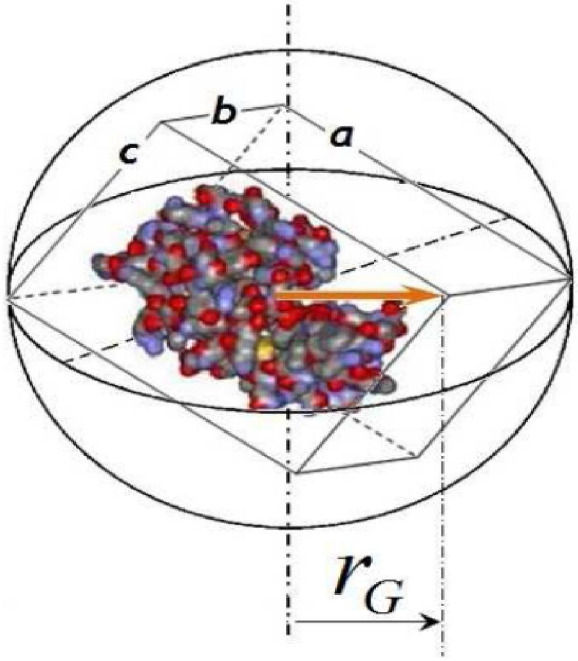

Figure 3 : Geometrical radius r_G definition scheme (case of Lysozyme)

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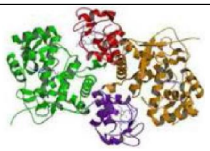
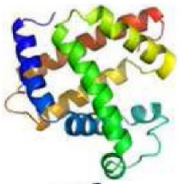
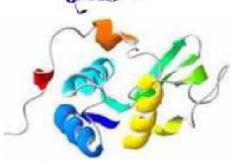
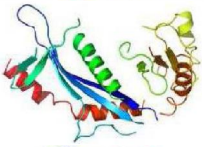
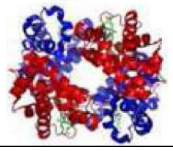
TABLE 1 : Geometrical radius of r some macromolecules along with relevant characteristics.

Macromolecule	Scheme	Dimension (nm)			Hydrodynamic radius r_H* (nm)	Geometrical radius r_G* (nm)	Ref.
		a	b	c			
Cytochrome c		2.5	2.5	3.5	1.87	2.48	[11]
Myoglobin		4.3	3.5	2.3	2.26	3.00	[12]
Carboxypeptidase		5.0	4.2	3.8	2.84	3.77	[13]
Lysozyme		4.5	2.6	3.0	2.24	3.09	[14]
Ribonuclease		3.8	2.8	2.2	1.96	2.60	[15]
Haemoglobin		6.4	5.5	5.0	3.69	4.90	[16]

(*) using formula (2); (**) using formula (4)

$$g(x) = e^{-\sqrt{\phi}\left(\frac{r_G + r_f}{r_f}\right)\left(\frac{x}{L}\right)} \quad (5)$$

where ϕ is the available fractional volume caused by presence of straight cylindrical cavities radius r_f.

Mucosal epithelium is presented as an *L*-thick layer (Figure 1) containing an irregular network of entangled flexible mucin fibres. The pores that exist between the fibres are swollen with fluid. Pappenheimer et al.[20] evoked additional dynamic constraints due to eventual macromolecules-fibres interaction which decreases mobility through the medium. These constraints are not considered in the actual model.

The resolution protocol is based on the Boubaker Polynomials Expansion Scheme (*BPES*). According to the definition[21-40], this scheme is performed by applying the expression:

$$\begin{cases} \hat{D}(x) = \dfrac{D_m(x)}{D_0} = \dfrac{f(x)}{\left(\dfrac{k_B}{6\pi\mu}\dfrac{T}{r_G}(1+\theta_C)\right)} \\ f(x) = \dfrac{1}{2N_0}\displaystyle\sum_{q=1}^{N_0}\xi_q . B_{4q}(\alpha_q \dfrac{x}{L}) \end{cases} \quad (6)$$

where $\hat{D}(x)$ is the dimensionless diffusivity profile, B_{4q} denotes the *4q*-Boubaker polynomials, α_q is 4*q*-Boubaker polynomial minimal root, N_0 is a prefixed integer and $\xi_q|_{q=1,\ldots,N0}$ are unknown real coefficients.

We have here a pre-resolution verification of the boundary conditions expressed by Eq.(7-8) due to the *BPES* properties[23-35,40]:

$$\begin{cases} D_m(x)|_{x=0} = D_0 \\ D_m(x)|_{x=L} = 0 \end{cases} \quad (7)$$

$$\begin{cases} \left.\dfrac{dD_m(x)}{dx}\right|_{x=0} = 0 \\ \left.\dfrac{dD_m(x)}{dx}\right|_{x=L} = d_0 = g'(x)\big|_{x=L} = \\ -\sqrt{\phi}\left(\dfrac{r_G + r_f}{r_f}\right)\dfrac{1}{L}e^{-\sqrt{\phi}\left(\frac{r_G+r_f}{r_f}\right)} \end{cases} \quad (8)$$

The final derivation step consists hence of calculating the set coefficients $\left.\hat{\xi}_q\right|_{q=1,\ldots,N_0}$ **which minimize the functional $\prod_{N0}$:**

$$\begin{cases} \Pi_{N_0} = \left(\sum_{q=1}^{N_0}\hat{\xi}_q W_q - \int_0^L e^{-\sqrt{\phi}\left(\frac{r_G+r_f}{r_f}\right)\left(\frac{x}{L}\right)}dx\right)^2 \\ \text{with : } W_q = \dfrac{1}{2N_0 D_0}\int_0^L \xi_q . B_{4q}(\alpha_q \dfrac{x}{L})dx \end{cases} \quad (9)$$

The final solution is hence:

$$\hat{D}(x) = \frac{D_m(x)}{D_0} = \frac{1}{2N_0}\sum_{q=1}^{N_0}\hat{\xi}_q . B_{4q}(\alpha_q \frac{x}{L}) \quad (10)$$

The specific dimensionless diffusivity $\hat{D}_i$ of a macromolecule (*i*) is thus evaluated as a mean value:

$$\hat{D}_i = \frac{1}{L}\int_0^L \hat{D}(x)dx = \frac{1}{2N_0}\sum_{q=1}^{N_0}\int_0^L \hat{\xi}_q . B_{4q}(\alpha_q \frac{x}{L})dx \quad (11)$$

RESULTS AND DISCUSSION

Calculations have been carried out for the macromolecules presented in TABLE 1. Obtained values of the dimensionless diffusivity have been plotted versus geometrical radius (Figure 4). In this figure, dotted line corresponds to a fragment of the abacus developed by Amsden *et al.*[41] fitted to the range of the actual study.

A primal comparison with the results published by Radomsky *et al.*[2] Saltzman *et al.*[6] and Cu *et al.*[42] led instantaneously to the evoked remark about "*poor estimates for smaller solutes*"[2,6,42] and the non-concordance of the experimental data with predicted results for radii between 2.0 nm and 8.0 nm. The present result shows that this problem is inexistent for the whole range 1nm-10nm. This difference is favourable to the use of the geometrical radius rather than the hydrodynamic one. Moreover, the presumption of constant diffusivity along the epithelial tissue makes the expression of dimensionless diffusivity strictly proportional to inverse radius. Indeed, this dependence explains the sharp decrease of diffusivity for high size macromolecules but raises problems for small values. In the actual model, Eq. (9) and Eq. (11) monitor an additional regulatory r_G-dependence via the coefficients $\left.\hat{\xi}_q\right|_{q=1,\ldots,N_0}$. **This dependence supports the uncontroversial and expected decreasing trend for high radii while giving acuter results for small ones.**

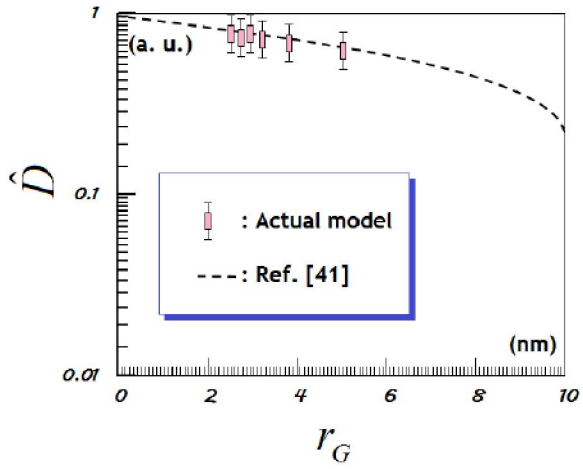


Figure 4 : Dimensionless diffusivity versus geometrical radius r_G

The actual results have been in good agreement with those of Olmsted *et al.*[43], except for the case of biological molecules (so-called virus-like particles). In fact the actual model doesn't discuss the effects of chemical or biological interaction between macromolecules and fibers bodies. Nevertheless, dimensionless diffusivity concordance with other results presents a meaningful support to the adopted presumption concerning cylindrical-pores epithelial tissue modelling against the juxtaposed-rods configuration proposed by Clague *et al.*[44] and Perrins *et al.*[45].

CONCLUSION

Macromolecules diffusion through mucosal epithelia has been modeled and results have been compared to some results presented in the related literature. A major motivation of this work was the divergence of the earlier proposed models and the consistency of their assumptions. Adoption of a newly defined macromolecule ra-

dius along with conserving the most adopted epithelial medium conception yielded macromolecules diffusivity values closer to those existing in the recent literature.

The mucosal epithelia have long been identified as critical barriers in macromolecules diffusion toward membrane tissues. Indeed many studies and models have been proposed out for better understanding of factors that affect diffusion dynamics of macromolecules through this barrier. as mucus have been proposed for. In the matter of globular and chain-like macromolecules, models presented two major trends: macromolecule geometry versus hydrodynamic properties.

In this work we have tried to give a mathematical model which better explains observed data for a given dimension range. Further improvement of the significance and performance of the model appears to be possible. Among the governing factors to be studied are the contribution of active transport, environment pH, macromolecule-ligand specific binding effects, possible ionic interactions and temperature-dependent epithelial tissue permeability.

REFERENCES

[1] C.C.Lin, L.A.Segel; Mathematics Applied to Deterministic Problems in the Natural Sciences, in: G.H.Golub, (Ed); 'Classics in Applied Mathematics', Macmillan Publishing Co., New York, NY, 609 **(1995)**.

[2] M.L.Radomsky, K.J.Whaley, R.A.Cone, W.M.Saltzman; Biomaterials, **11**, 619-624 **(1990)**.

[3] A.Des Rieux, Eva G.E.Ragnarsson, E.Gullberg, V.Préat, Y.-J.Schneider, P.Artursson; Eur.J.Pharm. Sciences, **25(4-5)**, 455-465 **(2005)**.

[4] A.M.Weinstein; Mathematical Biosciences, **76(1)**, 87-115 **(1985)**.

[5] J.R.Anderson, F.A.Morales; J.Phys.Chem., **82**, 608-611 **(1978)**.

[6] W.M.Saltzman, M.L.Radomsky, K.J.Whaley, R.A.Cone; Biophys.J., **66**, 508-515 **(1994)**.

[7] L.A.Sellers, A.Allen, E.R.Morris, S.B.Ross-Murphy; Biorheology, **24**, 615-623 **(1987)**.

[8] A.W.Larhed, P.Artursson, E.Bjork; Pharm.Res., **15**, 66-71 **(1998)**.

[9] A.E.Bell, L.A.Sellers, A.Allen, W.J.Cunliffe, E.R.Morris, S.B.Ross-Murphy; Gastroenterology, **88**, 269-280 **(1985)**.

[10] J.R.Pappenheimer, E.M.Renkin, L.M.Borrero; Am.J.Physiol., **167**, 13-46 **(1951)**.

[11] R.Dickerson, I.Geiss; The Structure and Action of Proteins. Benjamin, California, **(1969)**.

[12] J.C.Kendrew, G.Bodo, H.M.Dintzis, W.G.Parrish, H.Wycoff, D.C.Phillips; Nature, **181**, 662-666 **(1958)**.

[13] W.Lipscomb, W.Proc.Robert, A.Welch; Found.Conf. Chem.Res., **15**, 134-139 **(1971)**.

[14] C.C.F.Blake, D.F.Loenig, G.A.Mair, A.C.T.North, D.C.Phillips, V.R.Sarma; Nature, **206**, 757-759 **(1965)**.

[15] G.Kartha, J.Bellowand, D.Harker; Nature, **213**, 862-865 **(1967)**.

[16] M.F.Perutz, M.G.Rossmann, A.F.Cullis, H.Muirhead, G.Will, A.C.T.North, Nature, **185**, 416-422 **(1960)**.

[17] A.Ogston, B.Preson, J.Wells; Proc.R.Soc.Lond., **333**, 297-316 **(1973)**.

[18] W.M.Deen; AIChE J., **33**, **(1987)**.

[19] J.L.Anderson, J.A.Quinn; Biophys.J., **14**, 130-150 **(1974)**.

[20] J.R.Pappenheimer, E.M.Renkin, L.M.Borrero; Am.J.Physiol., **167**, 13-46 **(1951)**.

[21] J.Ghanouchi, H.Labiadh, K.Boubaker; International Journal of Heat and Technology, **26**, 49-53 **(2008)**.

[22] S.Slama, J.Bessrour, K.Boubaker, M.Bouhafs; Eur. Phys.J.Appl.Phys., **44**, 317-322 **(2008)**.

[23] S.Slama, M.Bouhafs, K.B.Ben Mahmoud; International Journal of Heat and Technology, **26(2)**, 141-146 **(2008)**.

[24] S.Lazzez, K.B.Ben Mahmoud, S.Abroug, F.Saadallah, M.Amlouk; Current Applied Physics, **9(5)**, 1129-1133 **(2009)**.

[25] T.Ghrib, K.Boubaker, M.Bouhafs; Modern Physics Letters B, **22**, 2893-2907 **(2008)**.

[26] K.Boubaker; F.E.Journal of a Math., **31**, 299-320 **(2008)**.

[27] B.K.Ben Mahmoud; Cryogenics, **49(5)**, 217-220 **(2009)**.

[28] S.Fridjine, K.B.Ben Mahmoud, M.Amlouk, M.Bouhafs; Journal of Alloys and Compounds, **479(1-2)**, 457-461 **(2009)**.

[29] C.Khélia, K.Boubaker, T.Ben Nasrallah, M.Amlouk, S.Belgacem; Journal of Alloys and Compounds, **477(1-2)**, 461-467 **(2009)**.

[30] K.B.Ben Mahmoud, M.Amlouk; Materials Letters, **63(12)**, 991-994 **(2009)**.

[31] M.Dada, O.B.Awojoyogbe, K.Boubaker; Current Applied Physics, **9(3)**, 622-624 **(2009)**.

[32] S.Tabatabaei, T.Zhao, O.Awojoyogbe, F.Moses; Int.J.Heat Mass Transfer, **45**, 1247-1255 **(2009)**.

[33] A.Belhadj, J.Bessrour, M.Bouhafs, L.Barrallier; J.of Thermal Analysis and Calorimetry, **97**, 911-920 **(2009)**.
[34] A.Belhadj, O.Onyango, N.Rozibaeva; J.Thermophys. Heat Transf., **23**, 639-642 **(2009)**.
[35] P.Barry, A.Hennessy; Journal of Integer Sequences, **13**, 1-34 **(2010)**.
[36] M.Agida, A.S.Kumar; El.Journal of Theoretical Physics, **7**, 319-326 **(2010)**.
[37] A.Yildirim, S.T.Mohyud-Din, D.H.Zhang; Computers and Mathematics with Applications, **59**, 2473-2477 **(2010)**.
[38] A.S.Kumar; Journal of the Franklin Institute, **347**, 1755-1761 **(2010)**.
[39] S.Fridjine, M.Amlouk; Modern Phys.Lett.B, **23**, 2179-2182 **(2009)**.
[40] A.Milgram; J.of Theoretical Biology, **271**, 157-158 **(2011)**.
[41] B.Amsden; Macromolecules, **32**, 874-879 **(1999)**.
[42] Y.Cu, W.M.Saltzman; Advanced Drug Delivery Reviews, **61**, 101-114 **(2009)**.
[43] S.S.Olmsted, J.L.Padgett, A.I.Yudin, K.J.Whaley, T.R.Moench, R.A.Cone; Biophys.J., **81**, 1930-1937 **(2001)**.
[44] D.Clague, R.Phillips; Phys.Fluids, **8**, 1720-1731 **(1996)**.
[45] W.Perrins, D.McKenzie, R.McPhedran; Proc.R. Soc.Lond., **369**, 207-225 **(1979)**.