ELSEVIER

Simulation Practice and Theory 8 (2000) 17–24

SIMULATION PRACTICE AND THEORY

www.elsevier.nl/locate/simpra

Modeling of interstitial fluid pressure in solid tumor

Jani Pusenjak, Damijan Miklavcic *

Faculty of Electrical Engineering, University of Ljubljana, Trzaska 25, 1000 Ljubljana, Slovenia

Received 1 June 1999; received in revised form 17 January 2000

Abstract

Interstitial fluid pressure (IFP) is one of the main obstacles for macromolecular agents uptake and distribution in solid tumors. It has been demonstrated to reduce effectiveness of different macromolecular agents used in *in vivo* anti-tumor therapies, which on the other hand showed very good anti-tumor properties in *in vitro* conditions [L.T. Baxter, R.K. Jain, Microvascular Research 37 (1989) 77–104]. With an appropriate model we demonstrated the correlation between different physiological properties of solid tumor and IFP. The model which we present showed high correlation with results from literature and thus represents a good simulation of physiological processes that govern fluid dynamics in solid tumors. One of the potential uses of presented model is drafting of future experiments which would lead to more effective chemo- or immuno-therapy of solid tumors. This model could also serve as an aid to the interpretation of different experimental results concerning IFP.

Keywords: Interstitial fluid pressure; Solid tumors; Drug delivery; Modeling

1. Introduction

An advance in genetic engineering and drug development technology in the past decades has led to various novel, potentially useful, anti-cancer drugs [9]. Among them are monoclonal antibodies, growth factors, biological response modifiers, etc. In spite of their effectiveness in *in vitro* conditions they did not show adequate effectiveness in *in vivo* conditions. Reasons for such a discrepancy are numerous physiological barriers which cause nonuniform and inadequate distribution of these

* Corresponding author. Fax: +386-1 426 4658.
E-mail address: damijan@svarun.fe.uni-lj.si (D. Miklavcic).

0928-4869/00/$ - see front matter
PII: S0928-4869(00)00003-3

drugs in solid tumors [9]. One of the main barriers for these drugs to penetrate from vessels into tumor interstitium and further to tumor cells is interstitial fluid pressure (IFP) which in solid tumors is elevated [3,8,9,14,15]. In order to understand and control this physiological property of the solid tumor, several mathematical models have been developed [1,16], but we were not able to find any which would consider the solid tumors an input/output system which would include several parameters such as tumor size or tumor cell density. Therefore the aim of the present work was to develop a mathematical model which would adequately describe different physiological properties of solid tumors with respect to IFP and enable various system analyses and parametrizations. Such analyses could help in understanding and controlling IFP in solid tumors, thus improving strategies for drug delivery in solid tumors.

2. Model development

We assumed that our system consists of tumor cells, tumor interstitium and has normal tissue and tumor vasculature as a system boundary. For transvascular transport of fluid we used Eq. (1) based on Starlings' hypothesis of volume flow of fluid

$$J = L_{\mathrm{p}} A_{\mathrm{c}}(p_{\mathrm{v}} - p_{\mathrm{i}} - \sigma_T[\pi_{\mathrm{v}} - \pi_{\mathrm{i}}]), \tag{1}$$

where J is volume flow across a vessel wall (m^3/s), L_{p} the hydraulic conductivity of the vessel wall (m^2 s/kg = m/Pa s), A_{c} the surface area of the vessel wall (m^2), p_{v} the vascular fluid pressure (Pa), p_{i} represents IFP (Pa), σ_T the osmotic reflection coefficient, π_{i} the colloid-osmotic pressure of interstitial fluid (Pa), and π_{v} is the colloid-osmotic pressure of plasma (Pa) [11]. To describe transport of fluid in an interstitial compartment we assumed convection to be the prevailing factor responsible for this transport. We must be aware that transport of fluid due to diffusion also exists but if we assume that interstitial fluid has the same composition in tumor as well as in normal tissue, diffusion fluid transport is negligible. To describe convection of fluid through interstitial space we used Darcy's Law [12]

$$\vec{u} = -\frac{K \cdot A}{\mu} \cdot \nabla \vec{p}, \tag{2}$$

where $\vec{u}$ is the vector of volume flow (m^3/s) in $\nabla \vec{p}$ the divergence of pressure vector (Pa), K the hydraulic conductivity of porous material (d – darcy = m^2) [4], A the surface area of the material through which fluid flows (m^2), and μ is the viscosity of fluid (kg/m s).

The next step was the development of a theoretical mechanical analogy which will represent IFP in a solid tumor (Fig. 1). We considered a reservoir which has one moving surface connected to a spring (enables changes in reservoir volume) and has three connections with surroundings. Two of them represents transvascular transport of fluid from vessels to interstitial space (filtration) and vice versa (reabsorption).

The third connection represents the border between tumor tissue and surrounding normal tissue. It was shown by several authors that the value of the IFP throughout

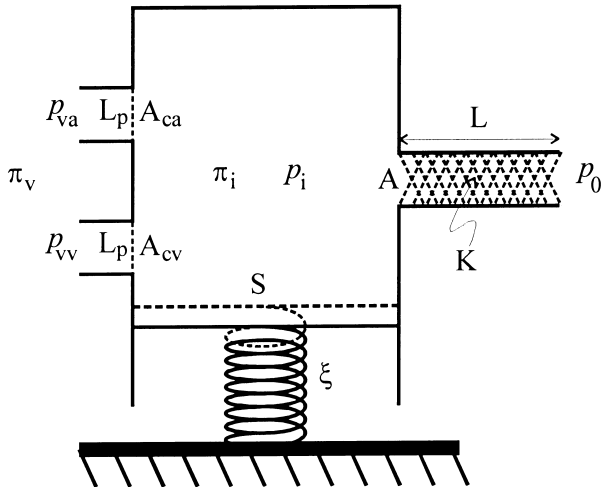

Fig. 1. Mechanical analogy for IFP in solid tumor. Parameters are presented in Table 1.

the tumor is uniform and that it creates a gradient from that inner-tumor value to the value in the normal tissue at the tumor–normal tissue interface [1,2,15]. An idealized shape of that gradient is depicted on the left side of Fig. 2. In general it has a sigmoidal shape which would create a spatial derivative in our model and thus partial differential equation with two independent variables (time and space). To avoid unnecessary complications and problems solving such an equation in the first step we decided to linearize this gradient and thus simplify Darcy's Law in

$$\frac{KA}{\mu}\frac{\mathrm{d}p_i}{\mathrm{d}r} = \frac{KA}{\mu}\frac{p_i - p_0}{L}, \tag{3}$$

where r is the coordinate of spherical coordinate system, p_i the IFP in tumor, p_0 the IFP in surrounding tissue, and L is the length of border where IFP gradient is

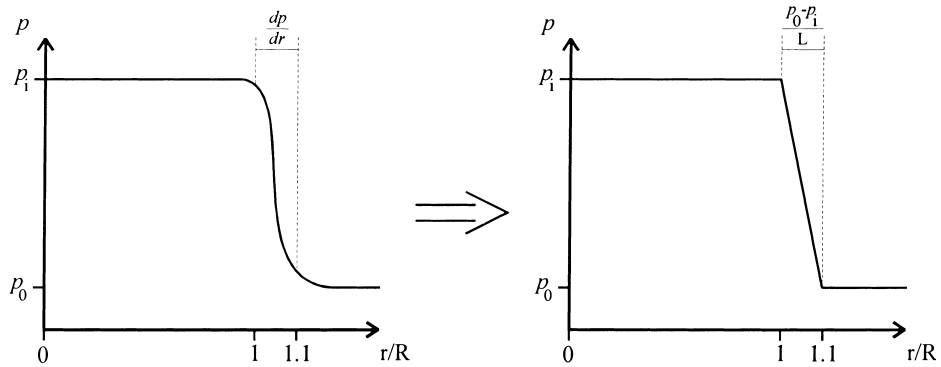

Fig. 2. IFP profile at the tumor–normal tissue interface (left) and its linearization (right).

created. We also assumed that the solid tumor has a shape of perfect sphere with radius R.

The spring and moving surface in our model represent collagen fibers which are one of most important parts of interstitium and have elastic property [7]. We assumed that in collagen fibers, when they are deformed, a tension appears which creates a force and thus a pressure (solid tissue pressure) which is transmitted to the surrounding interstitial structures such as membranes of tumor cells and vessel wall cells. According to Guytons' theory collagen and interstitial gel represent "solid" bodies which transmit solid tissue pressure. Since solid tissue pressure is in equilibrium with the IFP its value is negative with respect to the value of IFP and proportional to the value of IFP [6]. This assumption is valid if the total tissue pressure is equal to surrounding atmospheric pressure with value set to 0 Pa [6]. This gives us relationship between the IFP and collagen fibers extension or compression

$$\frac{\mathrm{d}V}{\mathrm{d}t} = S\frac{\mathrm{d}h_\mathrm{i}}{\mathrm{d}t} = \frac{S}{\xi}\frac{\mathrm{d}F_\mathrm{i}}{\mathrm{d}t} = \frac{S^2}{\xi}\frac{\mathrm{d}p_\mathrm{i}}{\mathrm{d}t}, \tag{4}$$

where h_i is the longitudinal translation of interstitial space that affects IFP (m), S the surface area of the same interstitial space (m^2), ξ the elasticity coefficient of collagen fibers and interstitial space (N/m), F_i the force which is created due to compression or extension of collagen fibers and interstitial space (N), and p_i represents IFP (Pa).

With such assumptions and simplifications we can derive the final equation for the mathematical model of IFP in solid tumor from the balance equation i.e., the change of mass that flows into the system is equal to the sum of the change of the mass that flows out of the system and the change of mass that remains in the system. When we are dealing with fluids which are incompressible we can write

$$\frac{\mathrm{d}V_\mathrm{in}}{\mathrm{d}t} = \frac{\mathrm{d}V_\mathrm{out}}{\mathrm{d}t} + \frac{\mathrm{d}V_+}{\mathrm{d}t}. \tag{5}$$

The three parts of the Eq. (5) (from left to right) represent Starlings' equation, Darcy's equation and Eq. (4), respectively.

The final equation of IFP in tumor is therefore given by

$$\frac{\mathrm{d}p_\mathrm{i}}{\mathrm{d}t} + A' \cdot p_\mathrm{i} = B \cdot p_\mathrm{va} - C \cdot \Delta p - D \cdot \Delta\pi + E \cdot p_0. \tag{6}$$

Equivalence expressions of the parameters A', B, C, D and E are presented in Table 1.

We also introduced some new parameters and variables: $K_0 = (K \cdot A)/\mu$, $A_\mathrm{c} = A_\mathrm{ca} + A_\mathrm{cv}$, $\Delta\pi = \pi_\mathrm{v} - \pi_\mathrm{i}$, and $\Delta p = p_\mathrm{va} - p_\mathrm{vv}$.

The value of the parameters which are used in our model are presented in Table 2.

3. Results

To verify our model we performed a simulation using Matlab® v4.2c.1 with the Simulink® vl.3 toolbox. Depicted in Fig. 3 is the result of a simulation using values

Table 1
Expressions of the parameters of the model of IFP in solid tumors

Parameter	izraz
A'	$[(L_pA_c + K_0/L)\xi]/S^2$
B	$L_pA_c \cdot \xi/S^2$
C	$L_pA_{cv} \cdot \xi/S^2$
D	$\sigma_T \cdot B$
E	$K_0 \cdot \xi/L \cdot S^2$

Table 2
Base values and units of parameters of solid tumor IFP model

Parameter	Base value	Unit
p_i	Output var.	Pa
p_{va}	Input var.	Pa
p_{vv}	Input var.	Pa
p_0	Input var.	Pa
π_i	1064[a]–1995[b]	Pa
π_v	2660[b]–3724[a]	Pa
L[a,c]	0.0004[d]	m
L_p[a]	2.1×10^{-11} [e]	m^2 s/kg = m/Pa s
	0.36×10^{-11} [f]	
K_0[a]	6.23×10^{-18} [e]	m^4/Pa s
	1.29×10^{-18} [f]	
A	2.01×10^{-4} [d]	m^2
A_{ca}[g]	$0.5\,A_c$	m^2
A_{cv}[g]	$0.5\,A_c$	m^2
A_c[a]	5.36×10^{-3} [e]	m^2
	1.88×10^{-3} [f]	
S[g]	0.029	m^2
ξ[g]	2.467×10^8	N/m
σ_T[a]	0.82[e]	
	0.91[f]	

[a] Ref. [6].
[b] Ref. [12].
[c] Ref. [11].
[d] R = tumor radius (in our case 0.004 m).
[e] Value for tumor tissue.
[f] Value for normal tissue.
[g] Assumption due to insufficient data in literature.

of parameters A', B, C, D, and E for tumor tissue shown in Table 3 and values of the input variables shown in Table 4.

As we can see there are two values which can evaluate the accuracy of our model: the time constant and the stationary state of the output signal. We add a sinusoid signal to one of the input signals t.i. to the value of the blood pressure in the arterial-side vessels p_{va} (Table 4), but it has almost no effect due to a negligible time constant of that signal with respect to the time constant of the system (IFP in solid tumors). The value of the time constant of the model of IFP can be calculated as $1/A' = 27.4$ s and

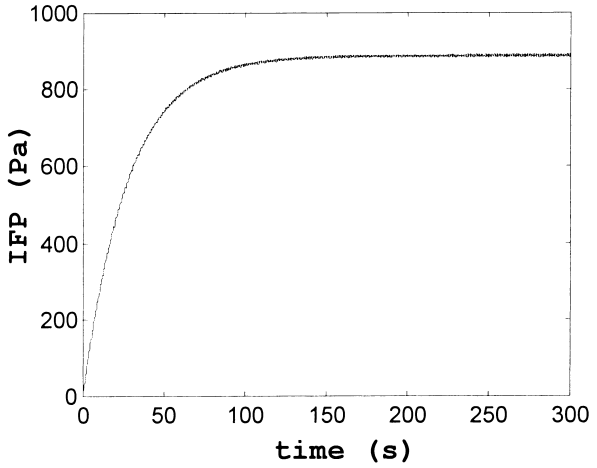

Fig. 3. Time course of IFP as a result of simulation, using values of input variables and parameters shown in Tables 3 and 4.

Table 3
Values of parameters of IFP model used in simulation

Parameter	Value
A'	3.646×10^{-2}
B	3.203×10^{-2}
C	1.601×10^{-2}
D	2.626×10^{-2}
E	4.432×10^{-3}

Table 4
Values of input variables obtained from literature for solid tumor

Input	Value (Pa)	Reference
p_{va}	$1702 + 665 \sin(6.24 \text{ rad} \cdot t)$	[10]
Δp	239	[10]
$\Delta \Pi$	665	[1]
p_0	−200	[7]

correlates well with values reported by other authors who measured IFP in solid tumors and other tissues [5,14]. The value of the stationary state is 886 Pa (6.7 mm Hg) which also correlates well with values measured by other authors in solid tumors [13–15].

4. Conclusions

Results of the simulation demonstrate that our model is in good analogy with realistic conditions and IFP in solid tumors. However when interpreting the results

obtained with simulation of our model, one must bear in mind the assumptions and simplifications made when the model was developed. There are also many other parametrizations and verifications of the model needed to prove its full usefulness, but with a lack of experimental data of some parameters and properties used in our model, verification is at the time incomplete. We believe that our model represents first step of a theoretical framework which would enable insight into the properties of solid tumor which are responsible for hindered effectiveness of macromolecular anti-tumor agents. As an upgrade of this model we see development of the model without linearization of the gradient which exists at the tumor–normal tissue interface (Eq. (3)).

With the results of a valid model we could theoretically develop new experimental protocols which could lead to some solutions in anti-cancer treatments.

Acknowledgements

This study was supported by the Ministry of Science and Technology of the Republic of Slovenia.

References

[1] L.T. Baxter, R.K. Jain, Transport of fluid and macromolecules in tumors I. Role of interstitial pressure and convection, Microvascular Research 37 (1989) 77–104.
[2] Y. Boucher, L.T. Baxter, Interstitial pressure gradients in tissue-isolated and subcutaneous tumors: implications for therapy, Cancer Research 50 (1990) 4478–4484.
[3] Y. Boucher, R.K. Jain, Microvascular pressure is the principal driving force for interstitial hypertension in solid tumors: Implications for vascular collapse, Cancer Research 52 (1992) 5110–5114.
[4] R.E. Collins, Flow of Fluids through Porous Materials, Chapman&Hall, London, 1961.
[5] H.O. Fadnes, R.K. Reed, K. Aukland, Interstitial fluid pressure in rats measured with a modified wick technique, Microvascular Research 14 (1977) 27–36.
[6] A.C. Guyton, H.J. Granger, A.E. Taylor, Interstitial fluid pressure, Physiological Reviews 51 (1971) 527–563.
[7] A.C. Guyton, J.E. Hall, Textbook of Medical Physiology – ninth edition. Unit IV – The Circulation & Unit V – The Kidneys and Body Fluids, W.B. Saunders, Philadelphia, PA, 1996, pp. 184–197, 297–312.
[8] R.K. Jain, Barriers to drug delivery in solid tumors, Scientific American, July 1994, pp. 42–49.
[9] R.K. Jain, Delivery of novel therapeutic agents in tumors: physiological barriers and strategies, Journal of the National Cancer Institute 81 (8) (1989) 570–576.
[10] R.K. Jain, Determinants of tumor blood flow: A review, Cancer Research 48 (1988) 2641–2658.
[11] R.K. Jain, Transport of molecules across tumor vasculature, Cancer and Metastasis Reviews 6 (1987) 559–593.
[12] R.K. Jain, Transport of molecules in the tumor interstitium: A review, Cancer Research 47 (1987) 3039–3051.
[13] I. Tufto, E.K. Rofstad, Interstitial fluid pressure fraction of necrotic tumor tissue and tumor cell density in human melanoma xenografts, Acta Oncologica 37 (1998) 291–297.
[14] I. Tufto, E.K. Rofstad, Interstitial fluid pressure in human melanoma xenografts, Acta Oncologica 34 (1995) 361–365.

[15] H. Wiig, et al., Interstitial fluid pressure in DMBA-induced rat mamary tumours, Scandinavian Journal of Clinical and Laboratory Investigation 42 (1982) 159–164.
[16] R.A. Zlotecky, et al., Pharmacologic modification of tumor blood flow and interstitial fluid pressure in a human tumor xenograft: Network analysis and mechanistic interpretation, Microvascular Research 50 (1995) 429–443.