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Simulation of transport and extravasation of nanoparticles in tumors which exhibit enhanced permeability and retention effect

Vishwa Priya Podduturi[a,b], *Isidro B. Magaña*[b], *D. Patrick O'Neal*[a,b], *Pedro A. Derosa*[a,c,d,*]

[a] *Institute for Micromanufacturing, Louisiana Tech University, Ruston, LA 71272, United States*
[b] *Biomedical Engineering, Louisiana Tech University, Ruston, LA 71272, United States*
[c] *Physics, Louisiana Tech University, Ruston, LA 71272, United States*
[d] *Math and Physics, Grambling State University, Grambling, LA 71245, United States*

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ABSTRACT

Determining the factors that influence the delivery of sub-micron particles to tumors and understanding the relative importance of each of these factors is fundamental to the optimization of the particle delivery process. In this paper, a model that combines random walk with the pressure driven movement of nanoparticles in a tumor vasculature is presented. Nanoparticle movement in a cylindrical tube with dimensions similar to the tumor's blood capillary with a single pore is simulated. Nanoparticle velocities are calculated as a pressure driven flow over imposed to Brownian motion. The number and percentage of nanoparticles leaving the blood vessel through a single pore is obtained as a function of pore size, nanoparticle size and concentration, interstitial pressure, and blood pressure. The model presented here is able to determine the importance of these controllable parameters and thus it can be used to understand the process and predict the best conditions for nanoparticle-based treatment. The results indicate that the nanoparticle delivery gradually increases with pore size and decreases with nanoparticle size for tumors with high interstitial fluid pressure (in this work we found this behavior for head and neck carcinoma and for metastatic melanoma with interstitial pressures of 18 mmHg and 19 mmHg, respectively). For tumors with lower interstitial fluid pressure (rectal carcinoma with 15.3 mmHg) however, delivery is observed to have little sensitivity to particle size for almost the entire nanoparticle size range. Though an increase in nanoparticle concentration increases the number of nanoparticles being delivered, the efficiency of the delivery (percentage of nanoparticles delivered) is found to remain closely unaffected.

* *Corresponding author at*: Institute for Micromanufacturing, P.O. Box 10137, 911 Hergot Avenue, Ruston, LA 71272, United States. Tel.: +1 318 257 5139; fax: +1 318 257 5104.
E-mail address: pderosa@latech.edu (P.A. Derosa).
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1. Introduction

Solid tumors represent about 85% of cancers and have been the subject of a large international research effort [1]. The successful outcome of tumor treatments often depends on physicians' experience and available techniques [2–4]. Survival rates have improved over the past few decades with a one-year's survival rate going from 69.9% in 1975 to 81.8% in 2008, and a 10 year survival rate going from 41.9% in 1975 to 60.6% in 1999 [5–7]. Tumors that are surgically accessible are removed. If surgical removal is not feasible, which can be the case for tumors that lie near sensitive tissues, such as head, neck, and brain, or those which have metastasized, often fall within the domain of radiation or chemotherapy [8]. Chemotherapy involves injecting an inherently toxic substance [9] and relies on the high metabolic activity of malignant cells to quickly absorb the chemotherapeutic agent. However, the uptake and retention of traditional chemotherapeutic small/macro-molecules can be hindered by abnormal blood and interstitial fluid pressures (IFP) in the tumors [10] and thus, even less systemically toxic agents (such as Herceptin), developed in recent years [11], can cause significant side effects.

Identified at least thirty years ago, the anatomical and physiological characteristics of tumors underwent much study in the 1980s [12,13] and 1990s [14], but since these characteristics vary with tumor size, type, and location [15,16], quantifying usable metrics to inform drug and nanoparticle (NP) design have been elusive. Although early empirical studies, such as those employing polystyrene spheres or liposomes laden with chemotherapeutics, are representative of a perceived class of sub-micron particles which have identified the particle's size that provides substantial improvement over the weak uptake observed with macromolecules in some tumors [17], these studies are not general in form and do not necessarily apply to other particles or conditions.

While sensing and imaging technologies, that are capable of quantitatively characterizing the scale of NP's, have enabled the development of the first round of nanomedical technologies at an experimental or prototype level, an examination of the literature and interaction with various companies currently involved in clinical trials, suggest that the variability in the quality control of the manufacture, storage, and experimental protocols make comparisons difficult [18].

Some of the nanomaterials currently found in the market for cancer therapies are nanocarrier-based drugs. A few examples are: Zinostatin, Stimalmer, Oncaspar, Ontak, Zevalin, Bexxar, Myocet, and Abraxane. These carriers include protein conjugates, immunoconjugates, and liposomes [19]. Additional types of nanomaterials, such as Auroshells and Combidex, are currently undergoing clinical trials. These particles are gold nanoshells and iron oxide NPs, respectively [20]. Gold nanoshells and nanorods have unique optical properties that allow for non-invasive, real-time monitoring of NP concentration in the blood [21–23]. However, whatever type of NP is chosen, of key importance in NP-based cancer treatment is the exploitation of the natural differences between cancerous and healthy tissue for the selective delivery to tumor cells in order to reduce damage to healthy cells. Indeed, some tumors present a unique physiology that distinguishes them from healthy tissue, in particular, they are characterized by an abnormal vasculature and the lack of functioning lymphatic vessels [12]. Studies have demonstrated that the vasculature of some tumors is quantifiably different from normal tissue in the lack of a complete basement membrane, abnormally large interendothelial junctions, permeability, and size [1,12] and these differences are commonly exploited for passive delivery via the enhanced permeability and retention effect (EPR). For example, the average pore cutoff size in tumors is much larger (380–780 nm dia. [14]) than for normal blood vessels (10–20 nm dia. [24]) and thus larger NPs will be selectively absorbed in tumors over healthy tissue. However, some other characteristics of tumor tissue, such as higher IFP than normal tissue [25], lead to a less efficient delivery. Thus, a careful study of all these factors is important in order to take better advantage of those properties resulting in an increased delivery while minimizing the effect of those that would make the delivery less effective.

Mathematical modeling of tumor and tumor vasculature have been proposed and implemented to address different goals. With their model established in 1988 [26], Jain et al. studied the effect of antiangiogenic agents on the tumor IFP [27]. The IFP of various tumors was calculated based on the transport properties of the capillary wall and interstitium and a decrease in the IFP of the tumors after antiangionic treatment was reported. The decrease in IFP occurs because the capillary walls are less permeable than before the treatment. From the point of view of the NP-based treatment, this imposes a trade-off between a more efficient delivery due to a larger pressure gradient from the capillary to the tumor, but through a less permeable wall. The fluid flow through the leaky vasculature of the tumor was also studied using modeling [28]. In that model, the flow along the capillaries, across the capillary walls, and through the interstitium were described by Poiseuille's [24], Starling's [29], and Darcy's laws [30], respectively. However, in their study the authors treated blood as a Newtonian fluid.

Frieboes et al., used a mathematical model to understand some of the variables that may help to explain tumor growth and invasion [31]. Soltani and Chen [10] developed a numerical model to study the fluid flow in the tumor interstitium where the tumor tissue was assumed to be spherical and the fluid flow was governed by conservation of mass and momentum. They studied the fluid velocity and interstitial fluid pressure as a function of the tumor size. Chang et al., developed a network model to study the delivery of colloidal drugs [8] where the tumor interstitium was represented by a 2-D square network while the movement of colloidal particles in the interstitium was simulated by the Brownian dynamic simulation method. Drug delivery for different drug concentrations and different interstitial pressures was studied in that work.

Models to predict NP transport and uptake in tumor tissue have also been discussed in the literature. Goodman et al. [32] developed a mathematical model of NP transport in a non-uniform porous spheroid representing a tumor. NP diffusion into spheroids and particle binding and dissociation at the cell