# Study of the Effect of the Blood Pressure and the Nanoparticle Concentration on the Delivery of the Nanoparticles to the Tumor Tissues by Simulations

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SPECIFIC AND TARGETED DRUG DELIVERY IS A NECCESITY!

# NANOCARRIERS IN DRUG DELIVERY

- Polymer based nanoparticles:
  - Albumin- taxol(Abraxen)[1]
  - PEG-PLA-Taxol[2]
- Liposomes:
  - Doxil[3]
- Carbon nanotubes
  - CNT-amphotericin B[4]

**[1] W. J. Gradishar, S. Tjulandin, N. Davidson, H. Shaw, N. Desai, P. Bhar, M. Hawkins, and J. O'Shaughnessy, "Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer," *J Clin Oncol*, vol. 23, pp. 7794-803, Nov 1 2005.**

**[2] T. Y. Kim, D. W. Kim, J. Y. Chung, S. G. Shin, S. C. Kim, D. S. Heo, N. K. Kim, and Y. J. Bang, "Phase I and pharmacokinetic study of Genexol-PM, a cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies," *Clin Cancer Res*, vol. 10, pp. 3708-16, Jun 1 2004.**

**[3] M. Markman, "Pegylated liposomal doxorubicin in the treatment of cancers of the breast and ovary," *Expert Opin Pharmacother*, vol. 7, pp. 1469-74, Aug 2006.**

**[4] W. Wu, S. Wieckowski, G. Pastorin, M. Benincasa, C. Klumpp, J.-P. Briand, R. Gennaro, M. Prato, and A. Bianco, "Targeted Delivery of Amphotericin B to Cells by Using Functionalized Carbon Nanotubes," *Angewandte Chemie International Edition*, vol. 44, pp. 6358-6362, 2005.**

# FACTORS WHICH MAY INFLUENCE DRUG DELIVERY

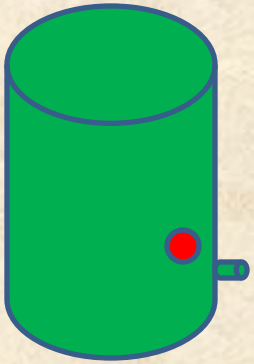
- Blood Pressure in the tumor microvessels
- Size of the Nanoparticle
- Density of Nanoparticles

# UNIQUE PATHOPHYSIOLOGY OF TUMOR TISSUES

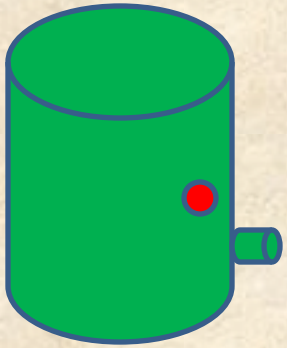
- Tumor microvessels are much “leakier” than those in normal vessels[5]
- Angiogenesis[5]
- Increased expression of the pre –angiogenic factors[5]

**[5] J. M. Brown and A. J. Giaccia, "The Unique Physiology of Solid Tumors: Opportunities (and Problems) for Cancer Therapy," *Cancer Research,* vol. 58, pp. 1408-1416, April 1, 1998.**

# RELATIVE SIZE OF THE NANOPARTICLE



healthy tissue blood vessel



Tumor tissue blood vessel

# FROM THE LITERATURE

- The median diameters of the pores in the liver sinusoids is 106 nm[6].
- The maximum pore size of the tumor vessel is assumed to be the maximum size of the liposome which could penetrate into the tumor tissue (400-600 nm)[6].
- Diameter of a capillary vessel is 4-9 um[7].
- Thickness of the capillary wall is about 0.5 um[7].

**[6] F. Yuan, M. Dellian, D. Fukumura, M. Leunig, D. A. Berk, V. P. Torchilin, and R. K. Jain, "Vascular Permeability in a Human Tumor Xenograft: Molecular Size Dependence and Cutoff Size,"** ***Cancer Research*****, vol. 55, pp. 3752-3756, September 1, 1995 1995.**

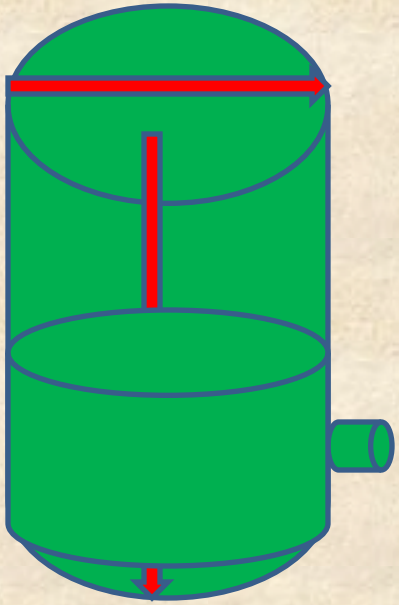
**[7] J. E. Hall and A. C. Guyton,** ***Guyton and Hall textbook of medical physiology*****, 12th ed. Philadelphia, Pa.: Saunders/Elsevier.**

# DIMENSIONS OF THE BLOOD VESSEL IN OUR MODEL

Nanoparticle

Diameter of nanoparticle=100 nm.

Blood vessel



Diameter of blood vessel =8 um.

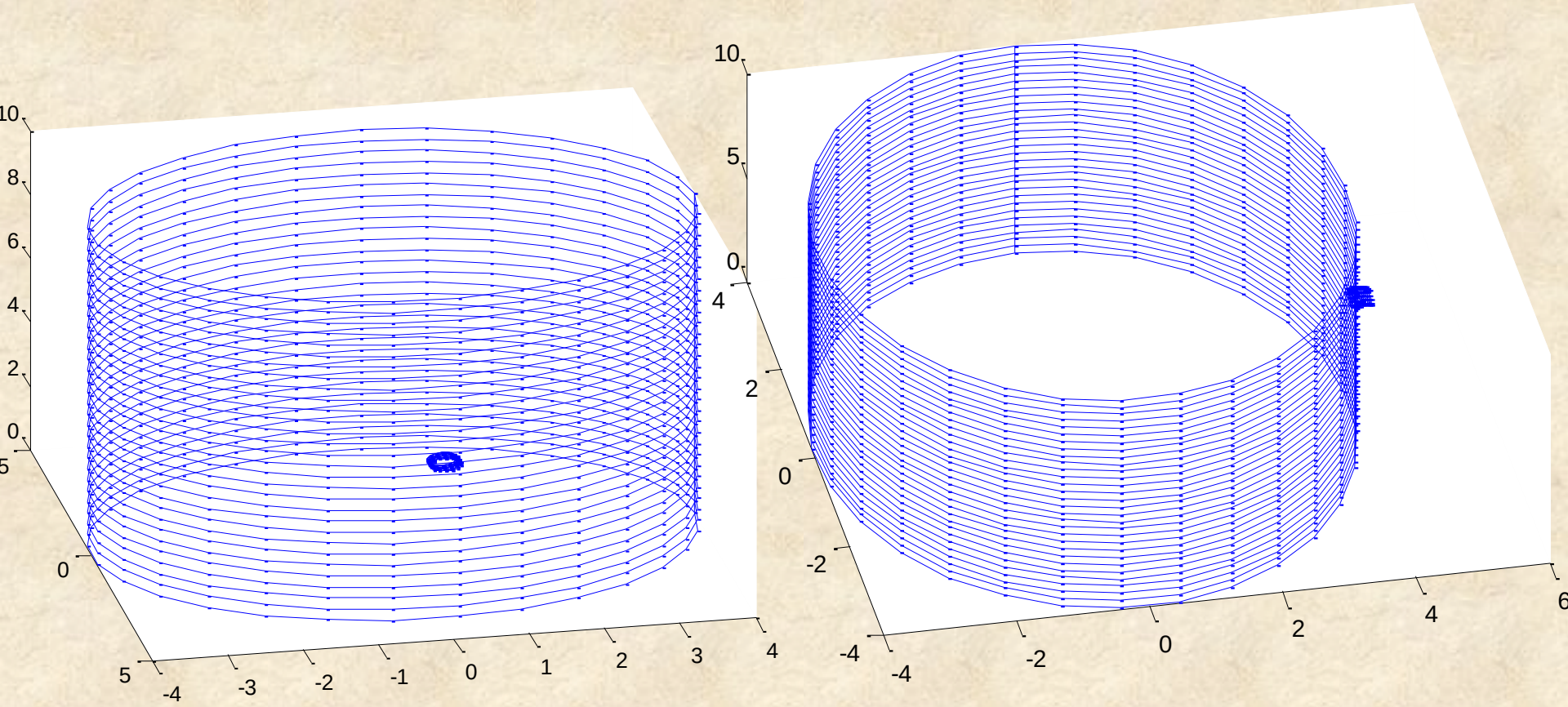
Length of the pore= 0.3 um.

Diameter of the pore= 0.6 um

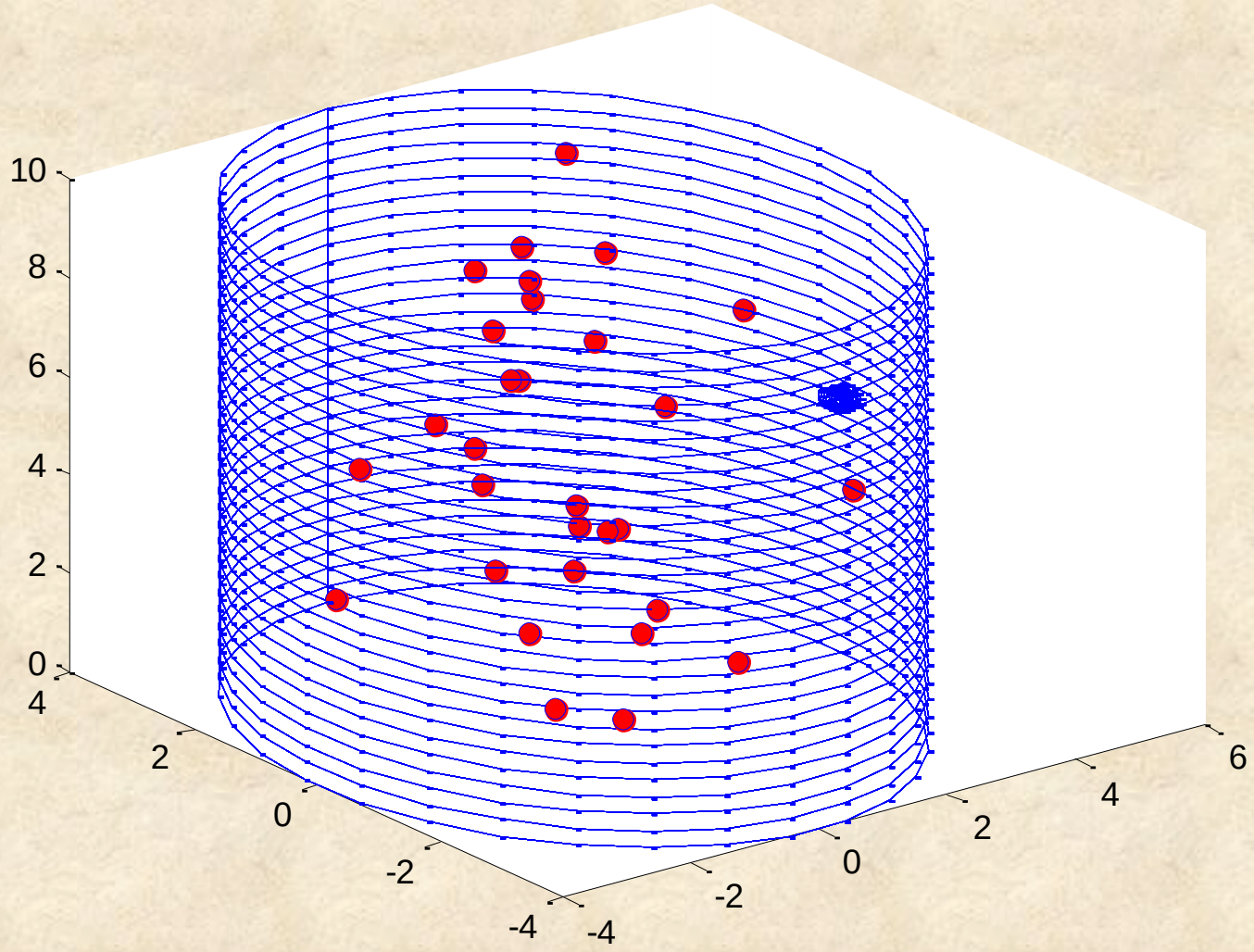
Length of unit blood vessel= 10 um.

Length of the blood vessel= 1 mm

# FIGURE OF THE BLOOD VESSEL WITH SINGLE PORE SIMULATED



# STEP 1



# STEP 2

- For each time step, the nanoparticles are displaced.
- Displacement is due to:
  - Velocity of the flow
  - Random movement due to collisions with other molecules.

# VELOCITY OF THE FLOW

- Velocity of the flow is derived from the Hagen-poiseuille equation[8].

$$v = \frac{P(R^2 - x^2)}{4\eta l}$$

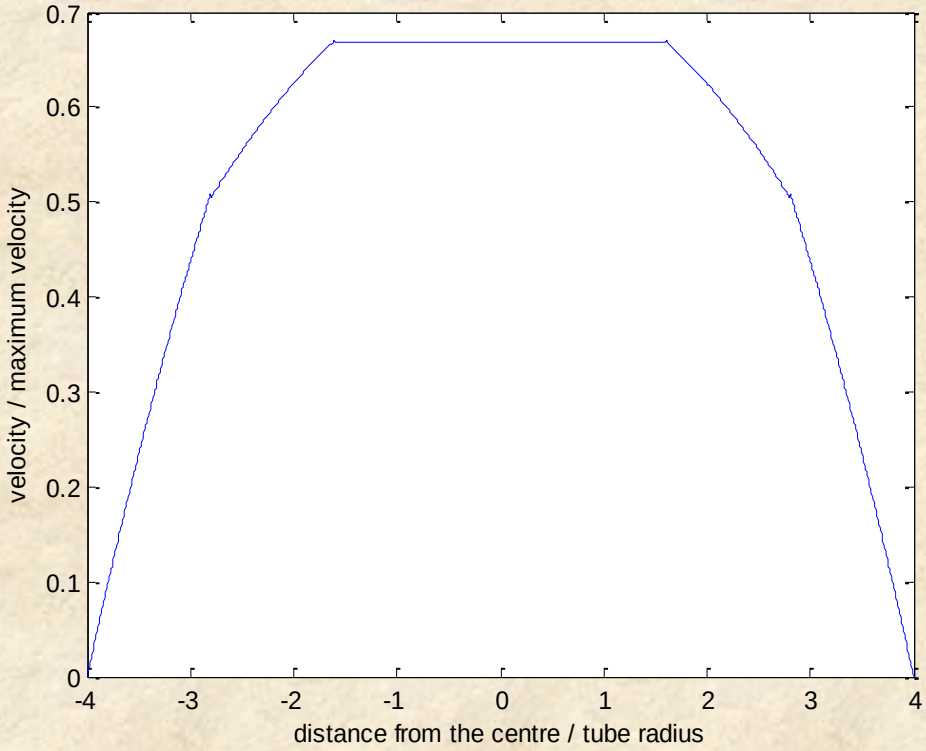
Where:

- ✓ V= velocity of the nanoparticle
- ✓ P= pressure drop across the blood vessel.
- ✓ R= radius of the blood vessel
- ✓ x= distance of the nanoparticles from the centre of the blood vessel
- ✓ η=dynamic viscosity of the blood plasma, $1.1\times10^{-3}\,Pa-Sec$
- ✓ l=length of the blood vessel

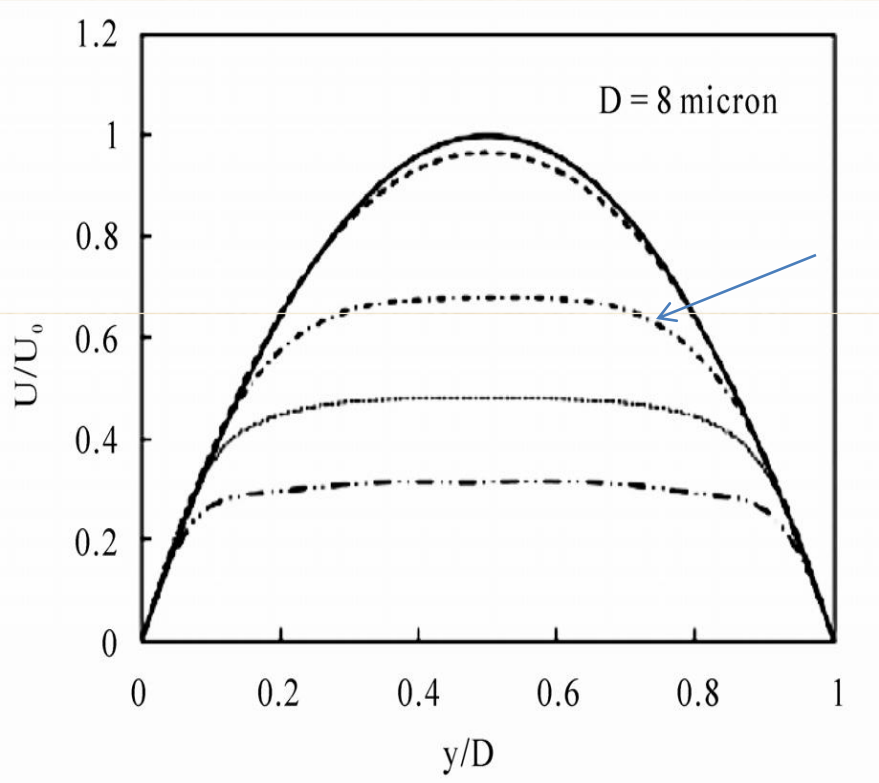
**[8] G. A. Truskey, F. Yuan and D. F. Katz, *Transport Phenomenon in Biological Systems*, 2nd ed. Upper Saddle River, NJ: Prentice Hall, 2008**

# VELOCITY PROFILE

In our model



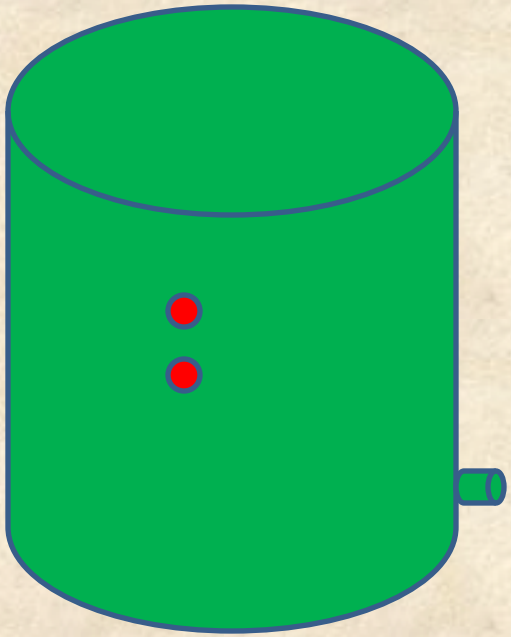

From the literature[9]



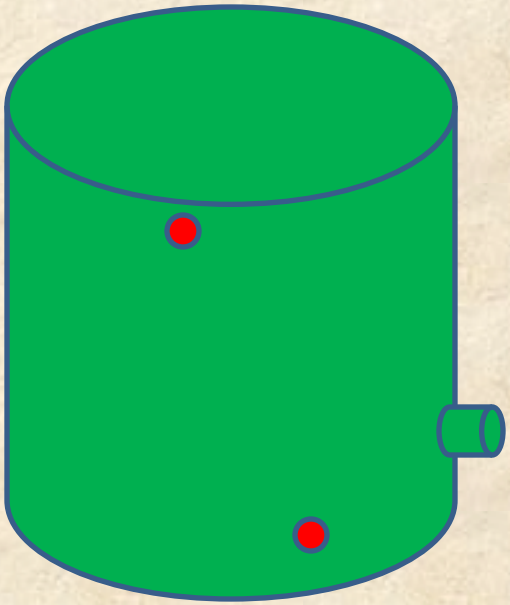

[9] T. Wong, and Z. Xing, "Characterization of Blood Flow in Capillaries by Numerical Simulation," *Journal of Modern Physics*, vol.1, pp. 349-356, September 15, 2010.

# RANDOM MOVEMENT

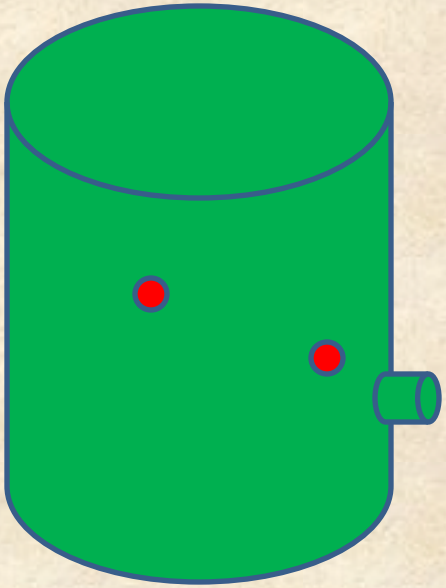
- Monte Carlo Techniques generate random movement.



# BOUNDARY CONDITION

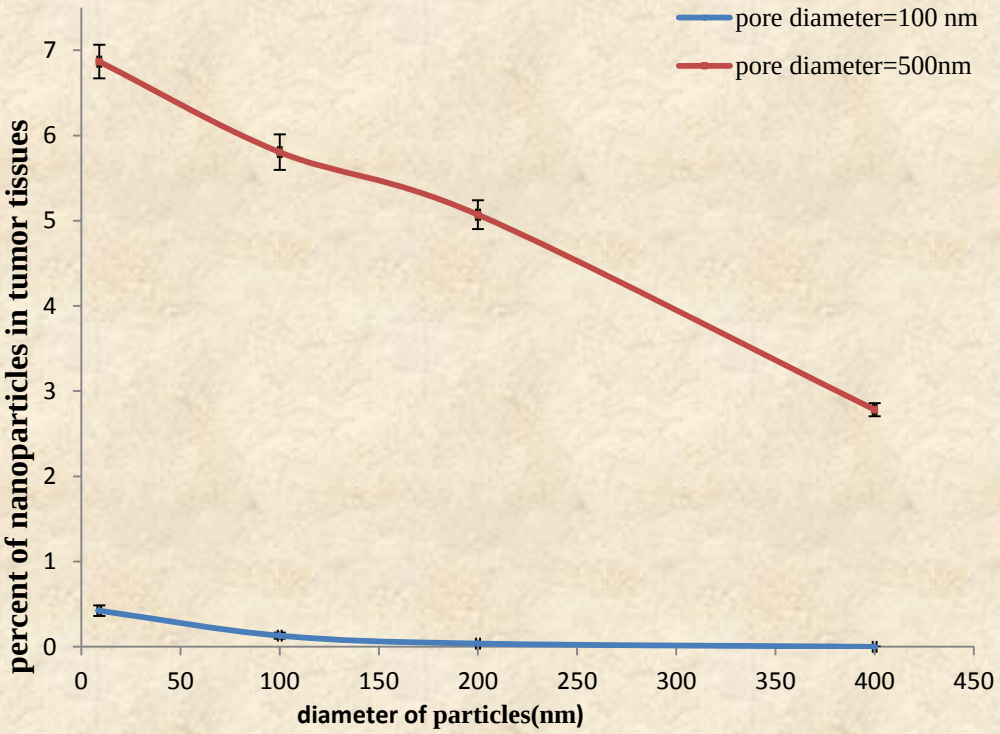


# DENSITY REMAINS CONSTANT

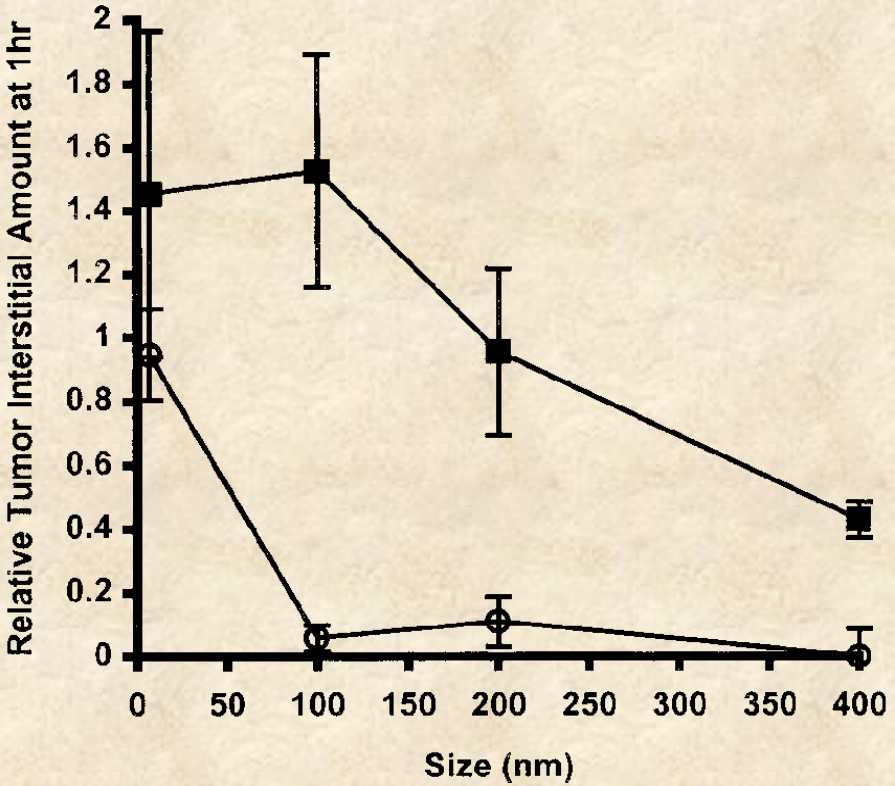


# RESULTS COMPARED TO THE EXPERIMENTAL DATA

Nanoparticle Delivery into Tumor Tissues as a Function of their Size



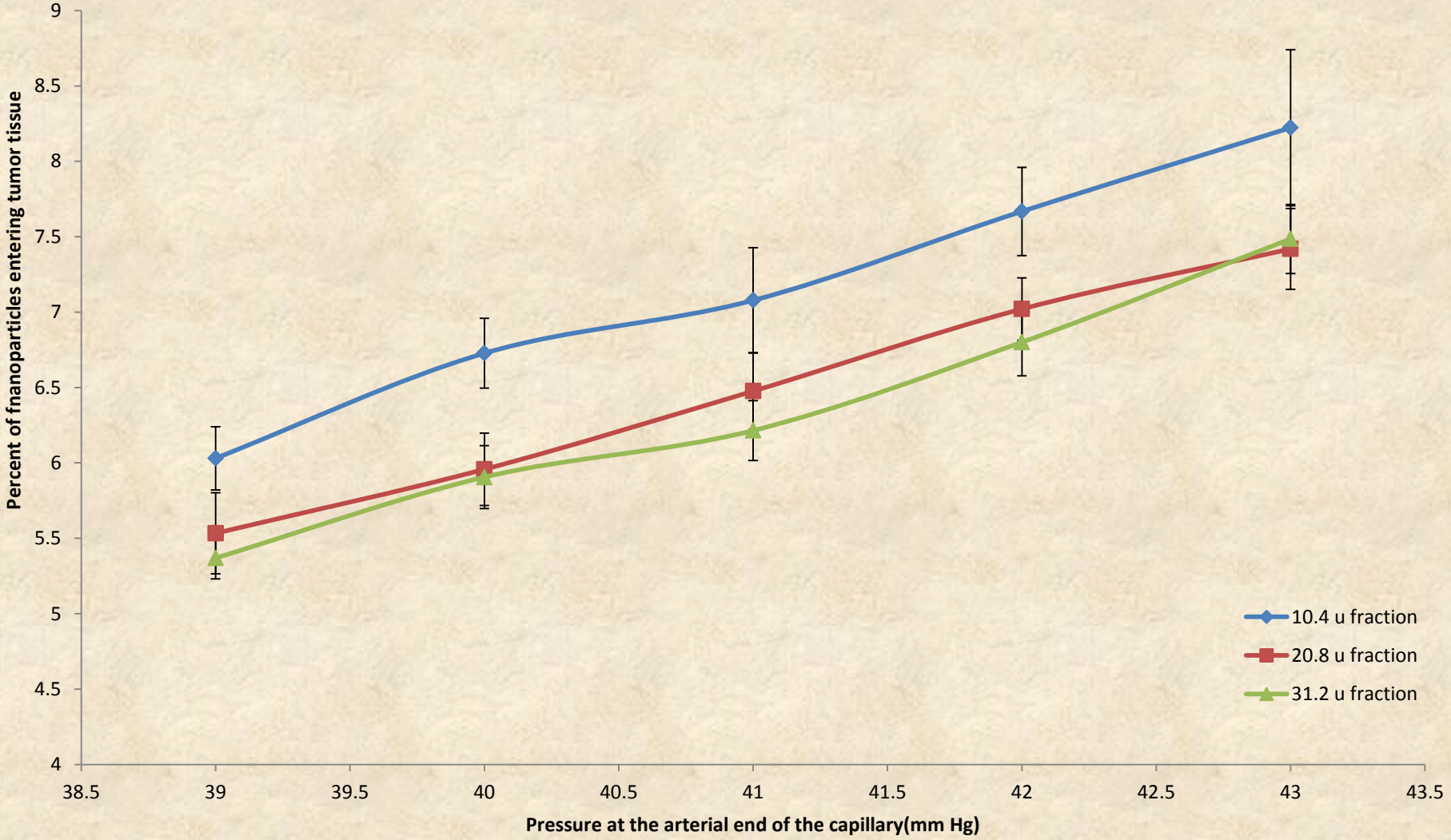

Experimental Data[10]



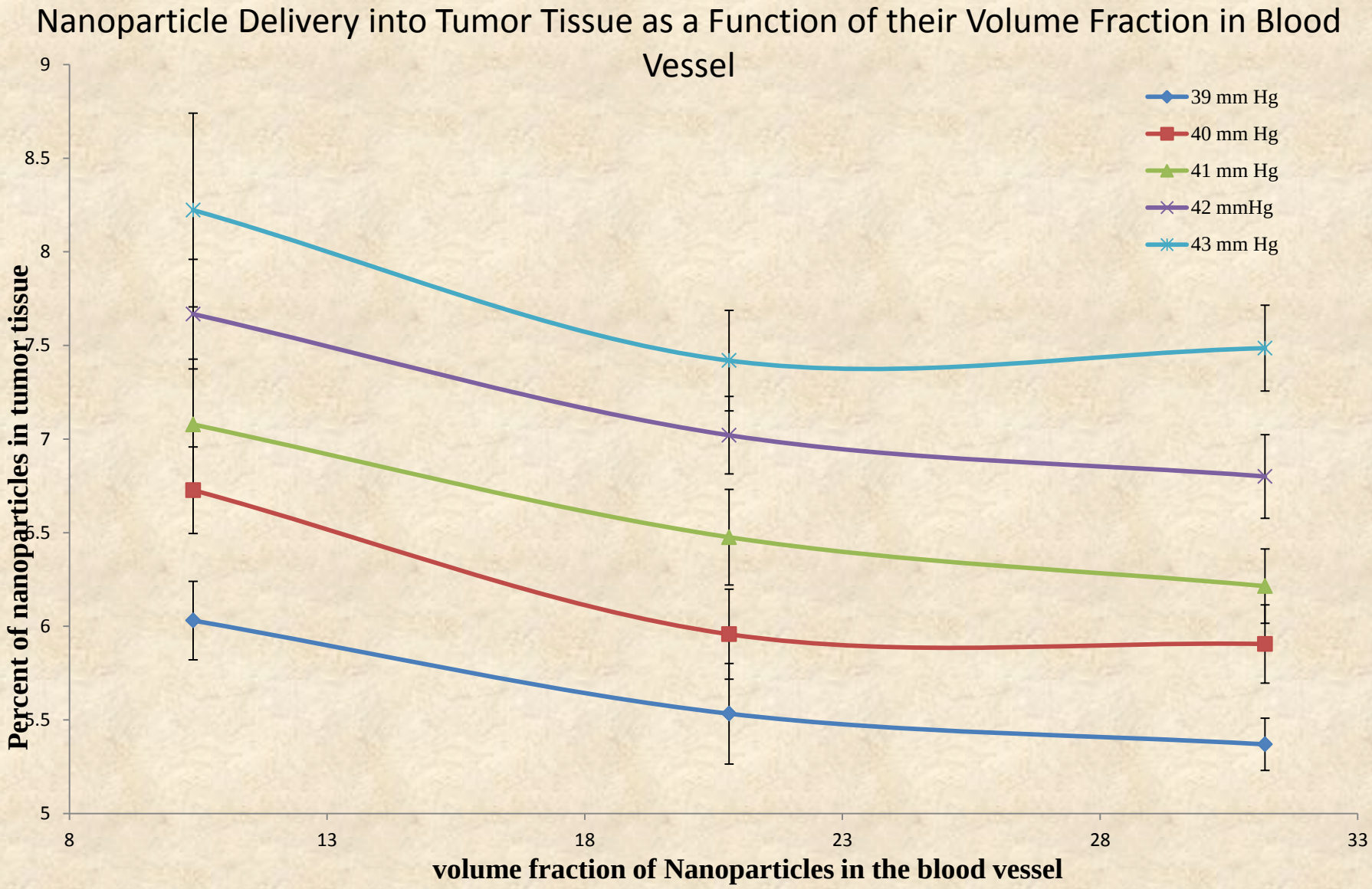

**[10] G. Kong, R. D. Braun, and M. W. Dewhirst, "Hyperthermia Enables Tumor-specific Nanoparticle Delivery: Effect of Particle Size," *Cancer Research*, vol. 60, pp. 4440-4445, August 8, 2000.**

# RESULTS

Nanoparticle Delivery into Tumor Tissue as a function of Blood pressure



# RESULTS


Nanoparticle Delivery into Tumor Tissue as a Function of their Volume Fraction in Blood Vessel
39 mm Hg
40 mm Hg
41 mm Hg
42 mmHg
43 mm Hg
Percent of nanoparticles in tumor tissue
9
8.5
8
7.5
7
6.5
6
5.5
5
8
13
18
23
28
33
volume fraction of Nanoparticles in the blood vessel

# CONCLUSIONS

- Delivery of nanoparticles to the tumor tissue increases with the increased blood pressure.
- Delivery of nanoparticles to the tumor tissue decreases with the increased concentration of nanoparticles in drug but the trend is not steady.

# ACKNOWLEDGEMENT


- We acknowledge the financial support of this research by “Louisiana Alliance for Simulation-Guided Materials Applications- LA-SIGMA”, Federal Award Number: EPS-1003897


LA-SiGMA

Louisiana Alliance for Simulation-Guided Materials Applications