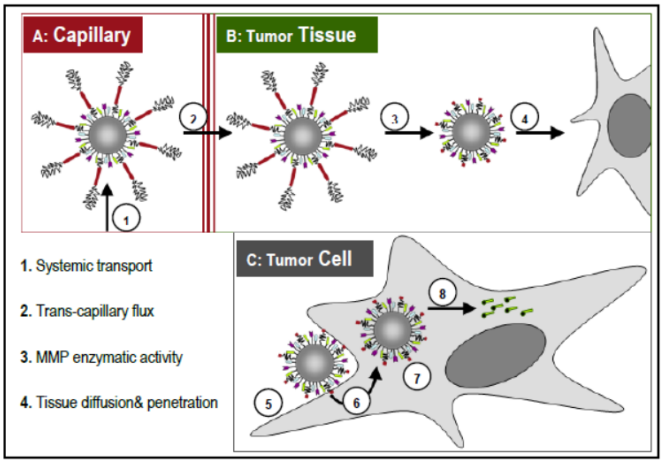
SaveMe – FP7 Integrated Project
(http://fp7-saveme.com/)



An estimated 3.2 million new cancer cases and 1.7 million deaths per year in Europe define cancer as a crucial public health problem especially as these numbers are anticipated to increase. The SaveMe project is addressing major urgent needs for cancer diagnosis and treatment through design and development of novel **modular nanosystem platforms integrating advanced functionalized nano-core particles and active agents.** The modular platform will enable the design of diverse active nanosystems for diagnostic or therapeutic applications.

Role of Ascend Technologies Ltd in the SaveMe project

Ascend Technologies has developed a number of *in-silico* models for the novel nanosystems and has calibrated the models based on the available *in-vitro* and *in-vivo* experiments. The models are used for prediction of toxicity and optimization of pharmacokinetics and tumour penetration features.

1. Physiologically based pharmacokinetics (PBPK)
2. Transport and uptake of nanosystems
3. Tumour growth

Physiologically Based Pharmacokinetics

The Physiologically Based Pharmacokinetic Models (PBPK) are a very important tool for estimating toxicity of chemical compounds on humans when developing new drugs. The main area of interest and research in PBPK is to determine and analyse fate of the drugs or other chemical compounds

administrated into living organism. The PBPK model of drugs and other chemicals in living organisms is very complex and depends on properties of chemical molecules or in this case nanosystems (NS), blood flow, physical and chemical characteristics of tissues and organs, tissue compositions, affinity of tissues to different chemical and physical properties, permeability of various tissue membranes.

In this study a PBPK modeling is used to assess the exposure of non-target tissue systems in patients to the developed NP systems. Results from *in-vitro* experiments are used to derive dose related toxicity to non-targeted tissue systems in humans. The model takes into account the four main physiological processes in the organism: Absorption, Distribution, Metabolism and Extraction (ADME). This study shows that the PBPK model can be used for more accurate calculation of the required therapeutic dose.

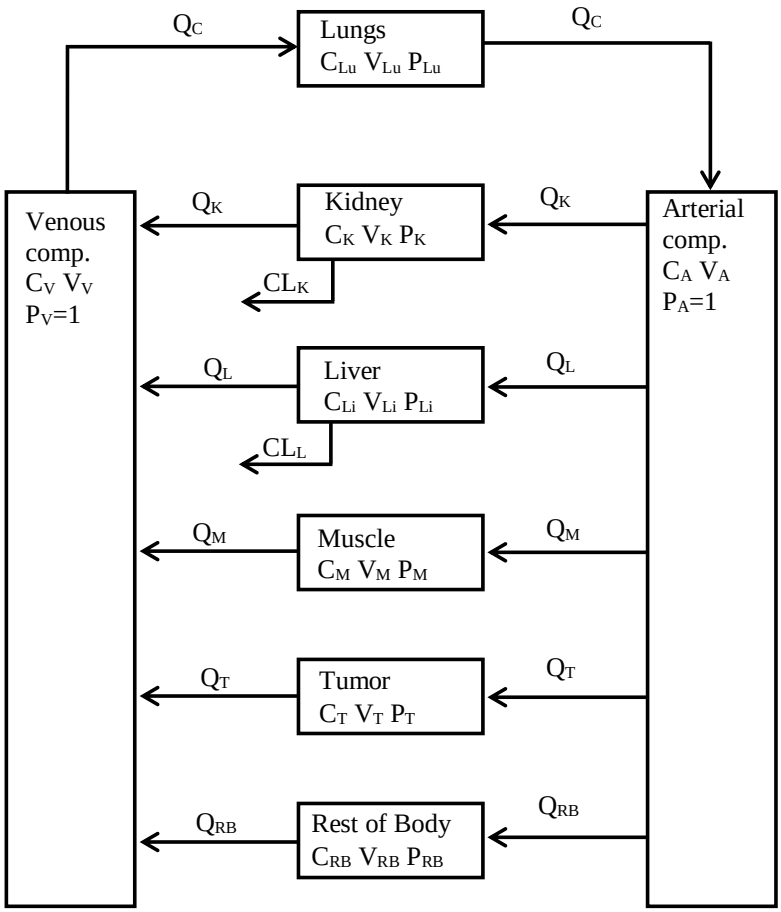
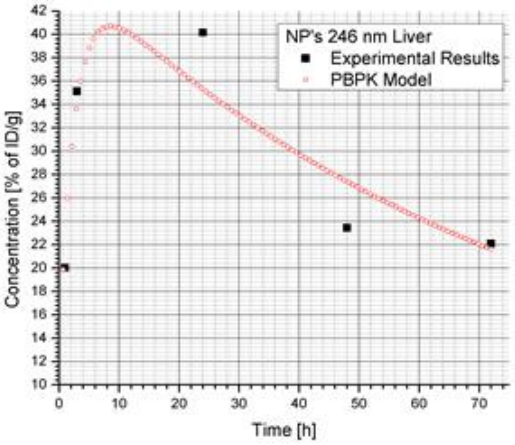
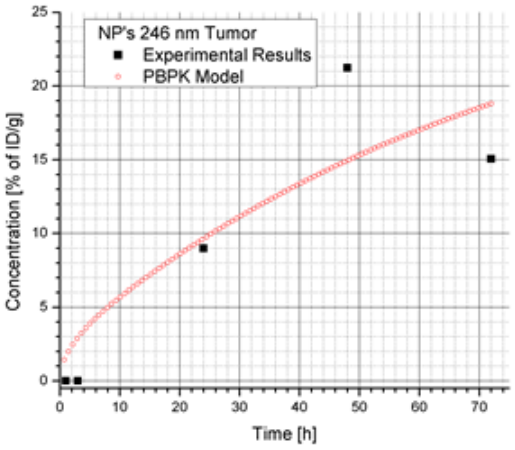


Figure above: PBPK model with 8 compartments including tumour

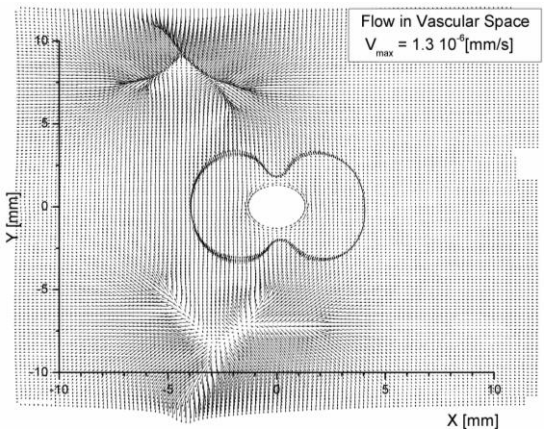


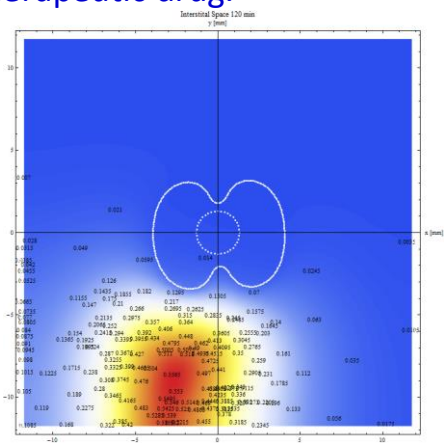


Figures above: (left) nanoparticles' concentrations change in liver in time; (right) nanoparticles' concentration change in tumour in time

Transport and uptake of nanosystems

The model for transport and uptake of nanoparticles (NPs) in tissue is based on the dual porosity (DP) approach. According to the DP approach the tissue is considered to consist of two porous systems representing the interstitial and the vascular space. The flow and the transport DP models consider that there is exchange of fluid and solute through the walls of the blood vessels. An in-house developed meshless techniques has been employed to solve this system. A necrotic core is included in the model. The influence of the NP uptake on tumour growth is modelled through influence on model parameters related to tumour growth. The geometry of the tumour is obtained from the tumour growth model. The model can be used for analysis of the distribution of NP in tissue/tumour and release of therapeutic drug.



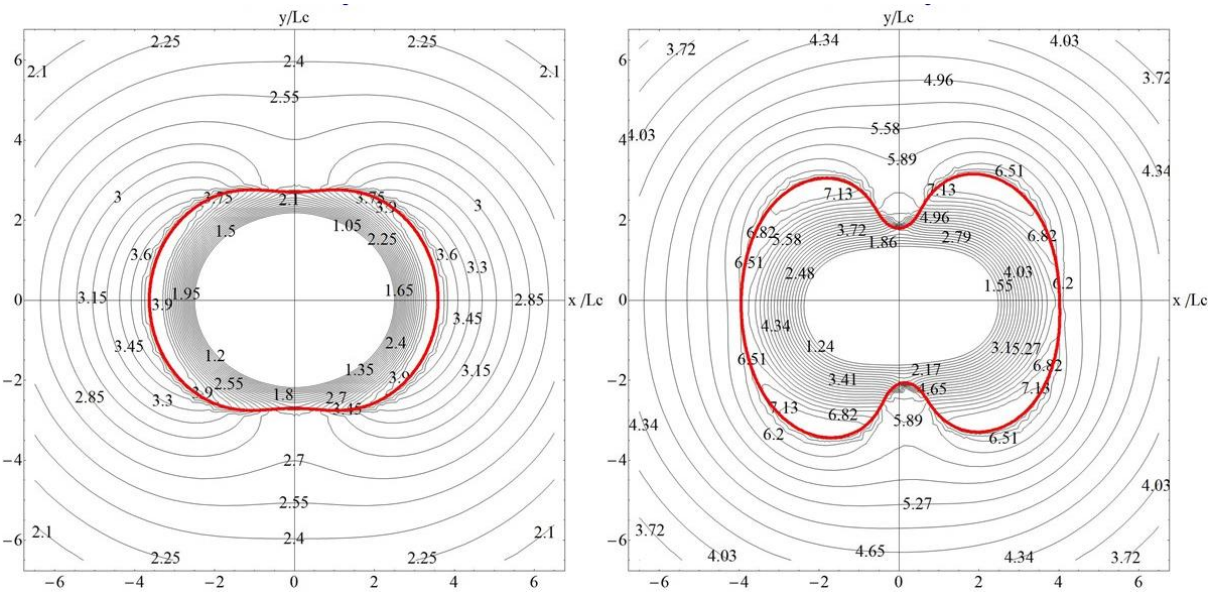


Figures above: (left) blood flow in vascular space; (right) drug delivery through a single blood vessel in vicinity of tumour

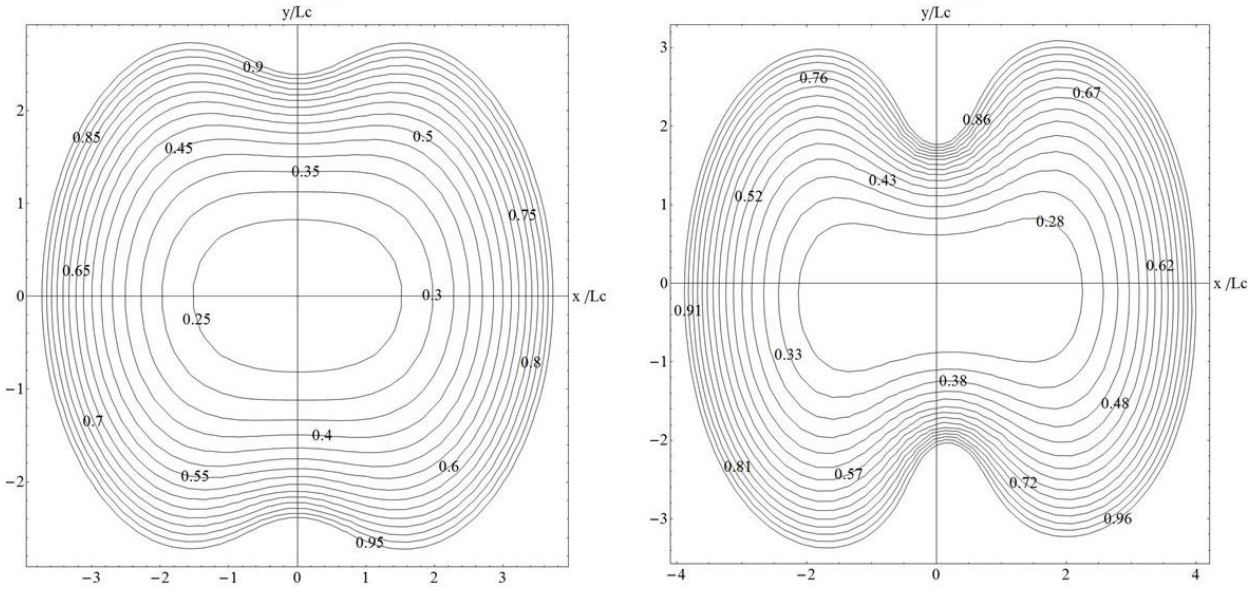
Tumour Growth

The tumour growth is described with a single phase tumour growth model with a sharp interface. The model includes the presence of necrotic core (NC) viable tumour tissue (VTT) and surrounding healthy tissue (HT). The problem can be described as a non-linear moving boundary problem. The numerical implementation has been based on the boundary integral formulation (BIF). The main field variables in the model for tumour growth are cell-to-cell pressure and concentration of nutrients. Three parameters in the model control the tumour growth: the relative strength of cell apoptosis and mitosis, relative strength of cell mitosis to the relaxation mechanisms and extent of vascularization. It has been assumed that tumour growth is much slower process than all other related processes and therefore quasi-steady state governing equations are considered. The time evolution of the system is obtained through moving of the tumour – healthy tissue interface.

The model can be used to simulate and predict different growth regimes, change in the shape and size of tumour, distribution of the nutrient concentration inside the tumour and cell to cell pressure.



Figures above: (left) pressure field after 19 days; (right) pressure field after 31 days



Figures above: (left) distribution of nutrients after 19 days; (right) distribution of nutrients after 31 days