# Ultrasound-mediated drug delivery to tumours and brain

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**Web page https://www.ntnu.edu/physics/biophysmedtech/drugdel**

## Background: Ultrasound mediated delivery of drugs and nanoparticles in tumour tissue

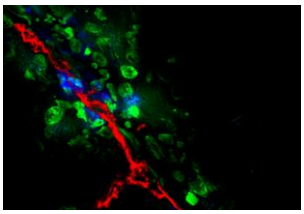

*Figure 1Nanoparticles (blue) do not travel far from the blood vessels (red).The encapsulated drug is taken up by cells (green) close to blood vessels*

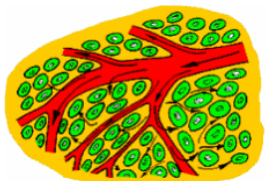

*Figure 2The delivery of nanoparticles/drugs depends on 1) The blood vessel network 2) Transport across the capillary wall 3) Penetration through the ECM. 4) Cellular uptake*

Chemotherapy given alone or combined with radiotherapy or surgery is a common cancer therapy. A prerequisite for successful chemotherapy is that the drugs reach all cancer cells, and toxicity towards healthy tissue is limited. However, upon systemic injection of drugs, it is typically found that less than 1 % accumulates in tumors. Toxic effects on healthy tissue restrict the doses that can be applied and severely limit clinical outcome. A promising strategy for enhancing the accumulation of drugs to tumors, is to encapsulate drugs into nanoparticle carriers (NPs), and take advantage of the enhanced permeability and retention effect (EPR), permitting NPs to cross the leaky tumour capillary walls, but not capillaries in normal tissue. Although the NPs might extravasate across the capillary wall rather easily, the NPs do not to travel far away from the blood vessels and only a small population of cancer cells located close to the blood vessels will be exposed to the cytotoxic drugs as shown in Figure 1. The delivery of free dugs or drugs encapsulated into drugs and NPs depends on the vasculature, the transport across the capillary wall, through the extracellular matrix (ECM), and if the final target is intracellularly, the NPs/drugs have to cross the cell membrane (Figure 2) . In order to improve the distribution of NPs/drugs, the delivery should be combined with a treatment facilitating the delivery.

Ultrasound (US) focused toward the tumour or brain has been reported to improve drug delivery by different mechanical mechanisms such as acoustic radiation force or acoustic streaming and cavitation. Ultrasound in combination with gas filled microbubbles causes cavitation. Cavitation is the oscillation microbubbles in the acoustic field. Such oscillations can be stable and generate mechanical shear stress on the capillary wall thereby increasing the vascular permeability or the microbubbles can collapse in a violent process generating jet streams and shock waves that increase the vascular permeability, improve the transport through the ECM and increase the cellular uptake of NP. The overall aim of our project is to study to what extent US and microbubbles can improve the delivery of distribution of NPs/drugs in tumour tissue and across the BBB, and to understand the underlying mechanism.

## Potential projects for the fall 2023 – spring 2024:

1. **Distribution of drugs in tumor tissue exposed to ultrasound and microbubbles**
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   We have previously imaged the distribution of fluorescently labelled NPs in tumor tissue and compared the distance the NPs move from the vascular wall after ultrasound and microbubble exposure. Now we want to perform similar experiments using a small drug/fluorescent molecule. The background for studying the effect of ultrasound and microbubbles on uptake and distribution of small drugs is that at St.Olavs Hospital, we have two clinical studies treating cancer patients

with standard chemotherapy in combination with focused ultrasound and microbubbles. We need to understand how ultrasound and microbubbles improve the distribution of small drugs in tumor tissue. Tumors with different degrees of vascularization and different amounts of collagen will be compared.

## 2. Multicllular spheroids as a model for drug delivery studies

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Multicellular spheroids constist of cells hold together by ECM and can be a good model to study transport of drugs and nanoparticles. Currenty a masterstudent are establishing and characterizing spheroids from various cancer cell line, and studying the infiltration of NPs. Next we want to study the effect of ultrasound on penetreation of NPs into spheroids.

## 3. Simulation of transport of nanoparticles in tissue

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We are using various models to simulate the transport and distribution of nanoparticles in tissue. Various ultrasound parameters (frequency, pulse length, pules repetition frequency), properties of nanoparticles (size, charge, shape) and properties of the tissue (stiffness, permeability) can be modelled and give new insight in how the various parameters influences the transport of nanoparticles in tissue.

## 4 Simulation of biomolecule adsorption and the effect of nanoparticle coating

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The blood circulation time of the nanoparticles is substantially reduced by protein adsorption. This can be avoided by coating the nanoparticle with surfactants, for instance, polyethylene glycol. The effectiveness of the coating will depend on the type of surfactant used and its characteristics (e.g. length). We will perform atomistic simulations (e.g. molecular dynamics) to investigate and understand the interactions between coated nanoparticles and biomolecules such as proteins on an atomistic scale. We aim to investigate how the interactions change, depending on the characteristics of the surfactant and nanoparticle, how this influences the transport, and to understand how more efficient coatings can be made. This is a theoretical project involving computer simulations and modeling.