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LIPUS Activation of Gold Nanoparticle Anticancer Drug Carriers for Cancer Treatment

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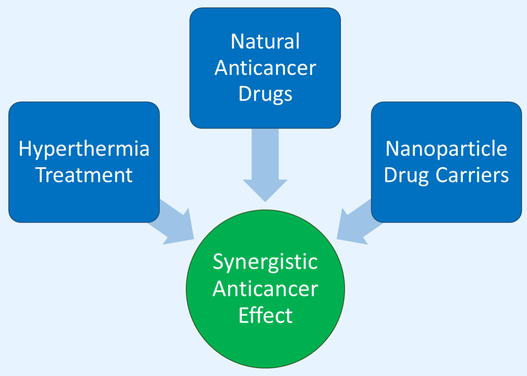
Introduction:

With more than 10 million new cases of cancer predicted every year, there is significant motivation for the development of more efficient and accurate anticancer drugs [1]. When using conventional anticancer drugs healthy cells are often killed along with tumour cells, causing toxicity to the patient. Ultimately, this can limit the achievable dose to tumour cells, as well as patient outcome [1]. To overcome this limitation a number of anticancer drug delivery systems have been proposed, with one attractive method being that of nanoparticle drug delivery. Nanoparticle drug carriers can offer a number of advantages, including: the efficient delivery of lipophilic drugs, protection from aggressive environments, and both targeted and controlled drug delivery [1]. In this work the advantages of nanoparticle drug carriers and natural anticancer drugs, such as curcumin [2], were combined in a drug delivery system. Furthermore, active targeting was achieved by inducing anticancer drug release noninvasively via therapeutic low-intensity pulsed ultrasound (LIPUS) activation; either through mechanical stimulation or bulk heating of a region of interest such as a tumour. Gold nanoparticles (GNPs) were selected as anticancer drug carriers due to their inertness and high surface to volume ratio. Additionally, gold compounds have been shown to inhibit proliferation and cause cell cycle arrest in tumour cells [3]. GNPs in particular have also been shown to play a role in mediating anti-cancer activity, and improving uptake of chemotherapeutic drugs into tumour cells [4]. In order to model anticancer drug release, a numerical COMSOL® based model of LIPUS activated anticancer drug release from GNP drug carriers was developed. Through simulating drug release for a variety of LIPUS and GNP parameters, the mechanisms of action behind ultrasound-nanoparticle interactions can be studied, and an optimized set of LIPUS exposure and GNP parameters can be determined. These parameters can then be applied experimentally to achieve efficient LIPUS induced targeted anticancer drug release from GNP drug carriers in *ex vivo* and *in vivo* tissue models.



Methods:

Proof of Concept:

As a proof of concept experiment, our group successfully induced the release of curcumin from GNP drug carriers embedded in *ex vivo* porcine muscle tissue:

- Samples submerged in 37°C water tank & heated for 5 minutes using our patented LIPUS device with 9 possible power settings:
- GNPs synthesized using room temperature green synthesis method [5]

Total Acoustic Power (W)

DC	H	M	L
H	8.40 ± 0.05	3.66 ± 0.03	1.82 ± 0.01
M	4.12 ± 0.04	1.81 ± 0.02	0.90 ± 0.01
L	3.29 ± 0.01	1.45 ± 0.01	0.71 ± 0.01

Power

- Drug release quantified by comparing fluorescence emission peak (RF-5301 Spectrofluorophotometer, Shimadzu, Kyoto, Japan) before and after LIPUS exposure
- Tissue sample temperature was confirmed to reach the hyperthermia regime (up to ~45°C) at the location of the GNP using thermocouple measurements (Omegaette HH306, Omega Engineering Inc. Stamford, CT)

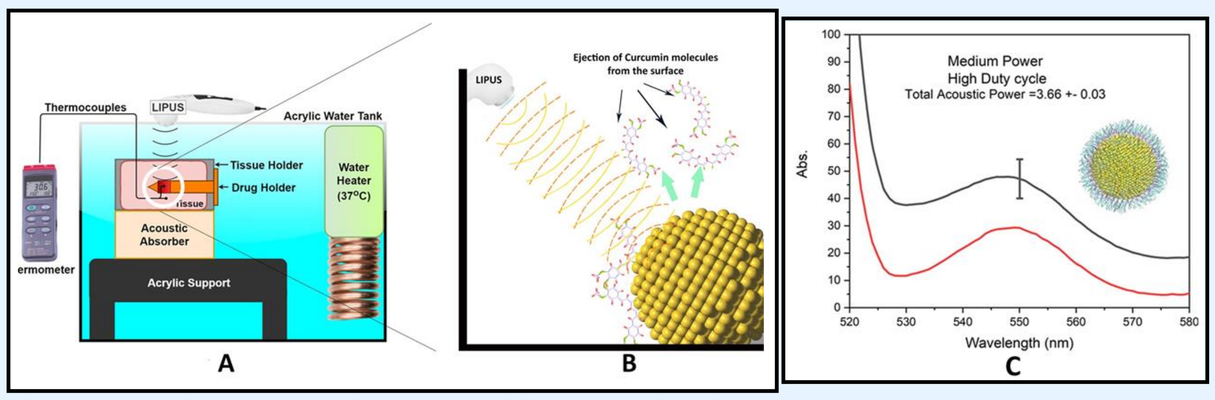


Figure 1: (A) The experimental set up used for LIPUS-induced curcumin release (B) Ejection of curcumin molecules from the surface of GNPs by ultrasound waves (C) An example of result obtained - Percentage increase in fluorescence of curcumin between control (GNPs heated in water bath) and an active sample (GNPs treated with LIPUS) (Red curve is the Control; Black curve is after LIPUS).

Modelling Thermal Interactions:

Currently, no established mathematical model of thermal ultrasound-nanoparticle interactions exists. In order to optimize temperature-induced drug release, a COMSOL based simulation model will be developed to model this drug delivery system.

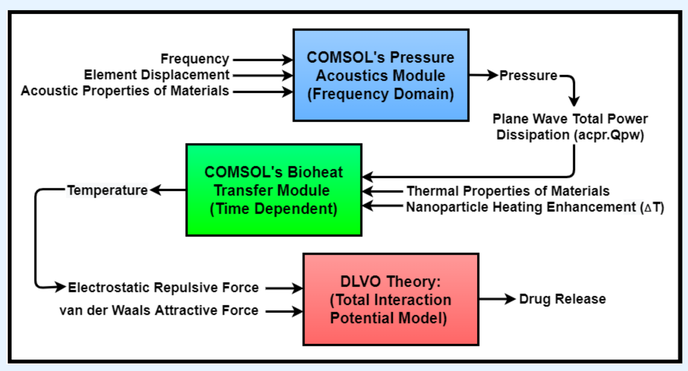


Figure 2: Simulation workflow for modelling temperature-induced drug release. Here COMSOL's acoustics module is used to simulate the LIPUS acoustic field. COMSOL's bioheat transfer module is then used to simulate heat flow in the tissue sample. Lastly, drug release is quantified by comparing temperature dependent electrostatic repulsion and attractive Van der Waals forces with DLVO theory.

Modelling Non-Thermal Interactions:

Liposome non-thermal drug release contributed to shear stress & acoustic streaming induced by ultrasonic radiation force & the collision of nanocarriers. GNP non-thermal drug release is not well documented or understood, however we expect similar non-thermal interactions to be present (an accepted mathematical model of mechanically induced drug release is lacking).

Proposed Method of Study:

- Perform drug release experiment for curcumin for two trials
  - Trial 1 = Heating with water bath for 5 minutes (control)
  - Trial 2 = Heating with LIPUS modality for 5 minutes
- % increase in fluorescence between control & ultrasound samples is then contributed to non-thermal drug release
- Perform multiple trials with variable transducer total acoustic power (TAP) & determine TAP relationship with % drug release

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Results:

Simulating LIPUS Pressure Acoustics & Bioheat Transfer In Ex Vivo Tissue:

The LIPUS device was successfully simulated using COMSOL's frequency domain pressure acoustics module and compared with Field II for validation [6]. COMSOL's pressure and intensity profiles show good agreement with Field II, suggesting accuracy in pressure field modelling. Using COMSOL's BHT module, heat transfer was also simulated showing high agreement with experimental thermocouple measurements.

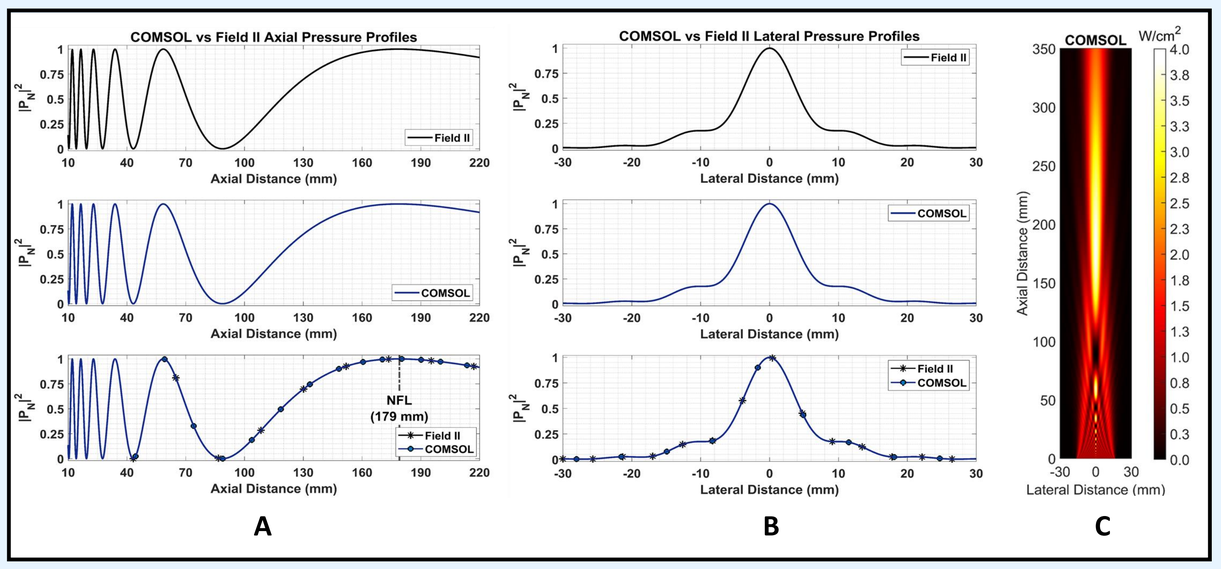

Figure 3: (A) Axial pressure profiles (B) Lateral pressure profiles (C) 2D intensity field.

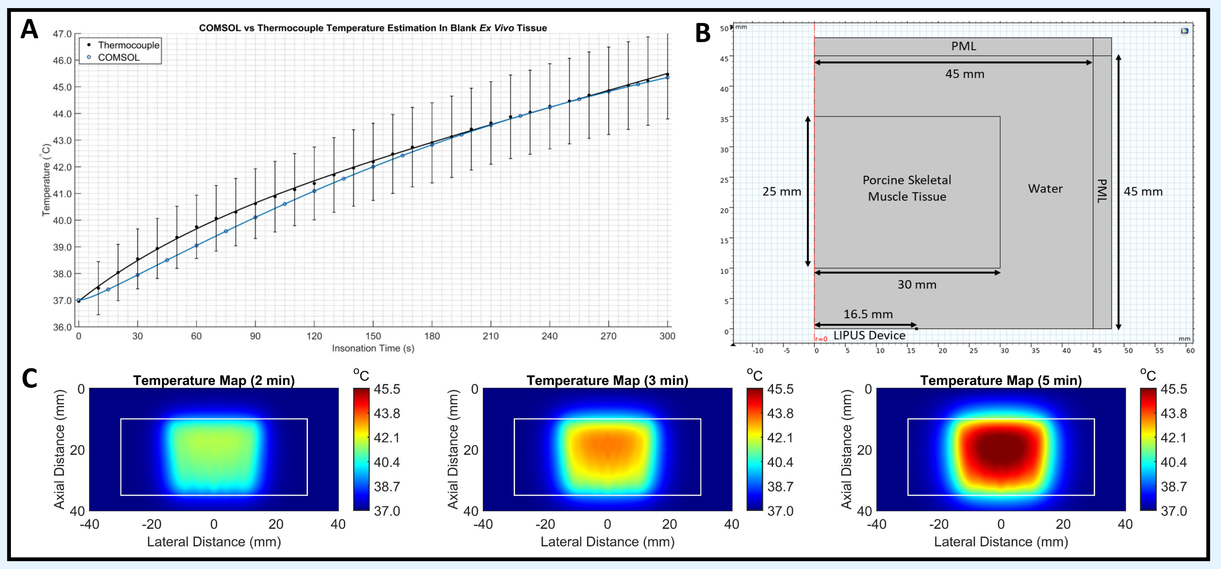

Figure 4: (A) Comparison of experimental thermocouple measurements and COMSOL predicted tissue temperature (B) 2D axisymmetric COMSOL geometry used (C) 2D temperature maps for LIPUS heating of *ex vivo* tissue.

Conclusions:

- **LIPUS-induced curcumin release was achieved from GNP drug carriers in the hyperthermia temperature regime**
- **It is expected that a synergistic anticancer effect will be observed with this drug delivery system, & furthermore, the drug delivery system can be optimized through simulation modelling of ultrasound-GNP interactions**
- **A simulation workflow was developed for temperature induced drug release considering only thermal ultrasound-GNP interactions**
- **An experimental procedure is proposed to determine a relationship between non-thermal ultrasound-GNP interactions and drug release**
- **The LIPUS device in question was simulated on COMSOL and the pressure acoustics and bioheat transfer validated**

Conclusions:

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