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**Book of Abstracts**

## **Nanoparticle-Mediated Targeted Drug Delivery: Models and Experiments**

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Nanoparticles offer a promising medical tool for targeted drug delivery, for example to treat inflamed endothelial cells during the development of atherosclerosis. To inform the design of such therapeutic strategies, we develop a computational model of nanoparticle internalization into endothelial cells, where internalization is driven by receptor-ligand binding and limited by the deformation of the cell membrane and cytoplasm. We specifically consider the case of nanoparticles targeted against ICAM-1 receptors, of relevance for treating atherosclerosis. The model computes the kinetics of the internalization process, the dynamics of binding, and the distribution of stresses exerted between the nanoparticle and the cell membrane. The model predicts the existence of an optimal nanoparticle size for fastest internalization, consistent with experimental observations, as well as the role of bond characteristics, local cell mechanical properties, and external forces in the nanoparticle internalization process. We have initiated *in vitro* experiments aimed at testing the validity of the model predictions. Preliminary experimental results in this regard will be presented.

# Computational Fluid Dynamics Modelling of Stented Coronary Arteries

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## ABSTRACT

Stents are medical implants deployed in a blood vessel in order to prevent blockage of e.g. an artery. It is well established that these medical devices can lower the risk of numerous heart diseases like Stenosis, thrombosis and transient ischemic attacks. However, there are remaining side effects that have to be dealt with. An emerging in-stent restenosis leads to a reduction of the blood flow rate, which causes the reoccurrence of the initial problem under different circumstances. High changes of wall shear stress (WSS) within the stent in symbiosis to areas of low WSS (0-0.4Pa) can provoke accelerated growth of scar tissue [1]. The objective of the present work is comparing the WSS using Computational Fluid Dynamics Simulations (CFD) under different conditions. Thereby, various simulations have been conducted for different geometries and strut thicknesses. The blood was represented by either a Newtonian or Non-Newtonian model.

Numerical results confirm the shear thinning (Non-Newtonian) behaviour of Carreau fluids during the whole cardiac cycle. It is shown that reduction of strut thickness by 50% increases average WSS along stented blood vessel regions up to 50%. This behaviour is helpful especially at vessel regions close to stent struts. The comparison between different stent geometries shows that it is favourable to minimize the area of stent struts. In particular, the area exposed to low WSS (0 to 0.4 Pa) is smaller at stent geometries with minimized strut areas.

Furthermore, it is shown that steady-state solution of average WSS deviates less than 5% in comparison to the transient results. Moreover, this simplification drastically reduces the computational effort, thus the remaining capacity can be used for parameter studies of further optimizations.

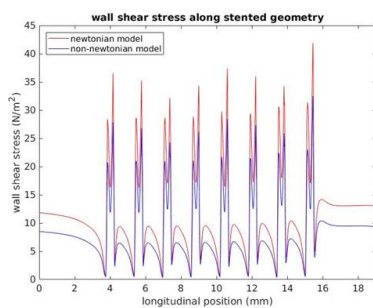


Figure 1: Wall shear stress of different viscosity models along stented geometry.

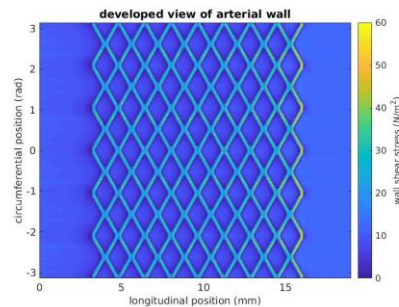


Figure 2: Developed view of arterial wall with deployed stent. Peak of WSS along inlet side.

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## **Are we using the most efficient shelled microbubbles?**

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### **ABSTRACT**

Currently, there is a great deal of interest in using thin-shelled microbubbles as a transportation mechanism for localised drug delivery, particularly for the treatment of various types of cancer. The technique used for such site-specific drug delivery is sonoporation. Sonoporation is the temporary enhancement of the capillary walls using an external ultrasound signal in conjunction with an ultrasound contrast agent (UCA). Despite there being numerous experimental studies on sonoporation, the mathematical modelling of this technique has still not been extensively researched. Presently there exists a very small body of work that models both hemispherical and spherical shelled microbubbles sonoporating due to acoustic microstreaming. Acoustic microstreaming is believed to be one of the mechanisms for sonoporation via shelled microbubbles.

We will present a theoretical model for the sonoporation of a liquid-crystalline shelled microbubble pulsating in direct contact with a capillary wall. This adopts a novel approach to modelling shelled microbubbles since it models the shell specifically as a liquid-crystalline material. Currently, there exists no previous literature pertaining to sonoporation of a liquid-crystalline shelled microbubble. The mathematical expression for the maximum wall shear stress will be presented, illustrating its dependency on the shell's various material parameters. We will discuss the sensitivity analysis which was performed for the wall shear stress considering the shell's thickness, its local density, the elastic constant of the liquid-crystalline material, the interfacial surface tension and the shell's viscoelastic properties. We have discovered that a liquid-crystalline shelled microbubble yields a maximum wall shear stress that is two orders of magnitude greater than the stress generated by commercial shelled microbubbles (such as SonoVue) that are currently in use within the scientific community. In conclusion, we propose that using liquid-crystalline shelled microbubbles may significantly enhance the efficiency of site-specific drug delivery.

# Modelling the Drug Particle Transport during Transarterial Drug Delivery for Liver Cancer: a Feasibility Study

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## ABSTRACT

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Unresectable HCC is currently being treated using local injections of chemo- or radioembolization particles during transarterial liver catheterization. This strategy aims to increase local drug concentrations near the tumorous tissue. Though promising, the optimal treatment conditions are still unknown. As the vasculature feeding the tumor plays a key role, we explored the added value of 3D numerical models to optimize HCC drug delivery.

A patient-specific 3D hepatic arterial geometry was obtained from micro-CT data of a human liver [1] and meshed using 8.9 million volume elements. Computational fluid dynamics (CFD) calculations were performed using Fluent (Ansys, USA) to simulate both the blood flow (continuous shear-thinning fluid phase) and drug particle transport (discrete phase) in the liver. Particle tracking allowed calculating the trajectories of individual drug carriers through the 3D flow field. Baseline boundary conditions included a velocity inlet of 0.155 m/s at the hepatic artery, an outlet flow distribution (Murray's law) and a uniform surface injection of  $10^4$  particles. A sensitivity study was performed to study the impact of relevant parameters (injection velocity, particle size etc.) on the particle distribution.

Results showed that the cross-sectional injection location has a large impact on the particle distribution, as also found in [2]. A good choice of this parameter may allow targeting a specific outlet or tumor. Other parameters having a significant impact on the particle distribution, are the injection plane (proximal/distal catheter position), the particle density (1600-3600 kg/m<sup>3</sup>), and the particle diameter (40-100  $\mu$ m), leading to changes in the outlet-specific number of exiting particles up to  $\pm$  64%, 61%, and 79%, respectively. In contrast, variations of the injection velocity (0.1-0.2 m/s) had only little impact (up to  $\pm$  6%).

This feasibility study indicates the potential of patient-specific computational models to optimize targeted drug delivery for liver cancer [3]. Future work will focus on validating the numerical modelling approach and testing it in a cohort of HCC patients that received transarterial therapy.

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# On the relationship between mechanical deformation and drug transport properties of the arterial wall

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## ABSTRACT

Endovascular devices such as stents and balloons have become the most successful devices to treat advanced atherosclerotic lesions. However, one of the main issues with these interventions is the development of restenosis. The coating of stents and balloons with antiproliferative substances to reduce this effect is now standard, although such drugs can also delay re-endothelialization of the intima. The drug release strategy is therefore a key determinant of drug-eluting devices efficacy.

Many mathematical models describing drug transport in arteries have been developed. They usually consider an intact vessel and arterial properties such as permeability, porosity, tortuosity and diffusivity dictate the transport of drugs within the respective wall layers. However, most of these models do not take into account the mechanical deformation of the porous arterial wall and the resulting impact on drug transport properties<sup>1</sup>. Therefore, the aim of this study is to analyse the influence of the mechanical expansion of the device on drug transport properties of the artery. In particular, we seek to establish relationships between mechanical force generated through device expansion and alteration in diffusion and convection within the arterial wall, as well as permeability across the endothelium.

We present a 2D numerical model of arterial drug transport following drug-coated balloon (DCB) deployment. To simulate the mechanical expansion, a hyperelastic constitutive model was used to describe arterial wall material properties and a linear elastic model is adopted for the device. The arterial wall is modelled as a multilayer anisotropic porous structure distinguishing intima, media and adventitia. Darcy's law is used to calculate plasma filtration through the tissue and convection-diffusion equations are used to model drug transport through intima, media and adventitia. Endothelium is considered completely denuded and internal and external elastic laminae are treated as semipermeable membranes and the flux across them is described by Kedem-Katchalsky equations<sup>2</sup>. A non-linear saturable reversible binding model describes binding of drug to specific and non-specific sites<sup>3</sup>.

By relating mechanical deformation to changes in key drug transport parameters, we are able to simulate time-varying drug tissue concentrations as a function of deformation. Mechanical deformation of the arterial wall results in modified drug transport properties and tissue drug concentrations, highlighting the importance of coupling solid mechanics with drug transport.

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## **Drug delivery from biomaterial orthopedic implants: a mathematical approach**

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In recent years, the use of orthopedic implants has raised greatly. These implants are used for example to stabilize fractures or to replace joints. Biocompatible metals and metallic alloys are extensively used but, despite biocompatibility, infections occur as pathogens adhere to implant surfaces.

Implant infections are extremely resistant to antibiotics and host defenses. Several strategies have been explored to control infections and other adverse tissue reactions, as inflammations or rejections. Systemic administration of drugs leads to a relatively low drug concentration at the target site and the administration of higher concentrations may only increase the occurrence of side effects as toxicity, renal and liver complications.

Efficient ways of delivering drug through *in situ* orthopedic eluting devices are desirable and this has given rise to several approaches. The mixing of drug and bone cement represents a precursor of local drug delivery in orthopedics. However, in real systems, the drug mainly diffuses through the cracks that are formed during the cement drying process being difficult the control of the drug release rate. Also adding the antibiotic decreases the material's durability, leading to a high incidence of bone cement fractures. Hollow titanium implants perforated with micro holes and loaded with drug and stainless steel hollow tubular reservoirs with encapsulated drug have been proposed to avoid the drawbacks of bone cement.

The coating of metallic prosthesis with polymeric materials, where drug has been dispersed, has generated much interest during the last years. Mathematical models of drug delivery from polymeric coatings of metallic devices can be of great help to manufacturers and clinicians. The behavior of drug release can be simulated for short and long times. Both behaviors have clinical importance: early times - the first 6 hours after surgery – are crucial to prevent pathogens from rapid proliferation; late times act as long time defense.

In this work, we present a mathematical model for drug release from a polymeric coating of a metallic implant and study its effect on a bacterial community, responsible for an infectious process. The mathematical model is composed by a system of three partial differential equations, describing the drug release from the biodegradable polymeric coating that is coupled with an ordinary differential equation for the concentration of bacteria. The mass released from the polymeric coating represents the link between the space-time differential system and the ordinary differential equation. An analytical study of the dependence of the concentration of bacteria on the parameters that characterize the process is presented. Numerical simulations that illustrate the effectiveness of the approach are included.

## Acoustically stimulated microbubbles for bone fracture repair

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**Background and Aims:** 10% of bone fracture cases result in costly and debilitating conditions such as delayed or non-union, where the bone fails to heal properly. The aim of this project is to promote bone repair using gas-filled, lipid-coated microbubbles (MBs) or perfluorocarbon nanodroplets, which carry drugs and release them on exposure to ultrasound. One of the challenges faced is microbubble stability during storage, handling and administration, which significantly affects therapeutic effect *in-vivo*. We tested the hypotheses that firstly MB preparation is non-toxic to human cells and secondly, microbubbles stability is affected by viscosity, temperature and dye-incorporation.

**Method:** To test cytotoxicity, MBs were fabricated using a 9:1 molar ratio of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) to polyoxyethylene(40) stearate (PEG40S) lipids, which were hydrated in PBS and sonicated to form a MB suspension. MG63 osteocarcinoma cells were treated with MBs at a range of concentrations between  $6 \times 10^7$  and  $6 \times 10^5$  MBs/mL. Following 72 hours incubation in 37°C and 5% CO<sub>2</sub>, Alamar Blue® assay was carried out to quantify cell viability. The equivalent concentrations of lipid suspensions (LS) (not sonicated) were tested for the effect of free MB constituents (n=3, 3 repeats). To test stability, media with different viscosity (2-10 times greater than PBS) were prepared by hydrating the lipid films in solutions composed of different proportions of PBS, glycerol and propylene glycol. MBs were then stored at 4°C or incubated in a 37°C, 95% humidity and 5% CO<sub>2</sub> environment, and their stability was measured in terms of mean diameter and concentration over a period of 6 days. Finally, the effect of the incorporation of a lipophilic fluorescent dye, 1,1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate (Dil), was determined as it enables MB tracking *in-vivo* and *in-vitro*. Molar ratios of Dil:MB in the range 1:4000-1:400 were tested.

**Results:** Cytotoxicity tests revealed that increasing MB concentrations reduced cell viability overall, with the highest cell death measured upon incubation with  $3 \times 10^7$  (1:2) MB/mL ( $41,800 \pm 4,100$  vs  $13,700 \pm 4500$ ;  $p < 0.001$ ). Incubation with LS caused a significantly more rapid reduction in cell viability compared to equivalent concentrations of MB suspension. This is evident as 1:5 dilution of LS ( $1.2 \times 10^7$  Lipids/ml), significantly reduced viability compared to  $1.2 \times 10^7$  MBs/ml, ( $p < 0.05$ ). Stability tests revealed that temperature had a significant effect on MBs mean diameter. At 37°C, the diameter increased over two hours from  $4.67 \pm 1.45$  to  $18.24 \pm 11.63$   $\mu\text{m}$ , while concentration decreased from  $2.65 \times 10^8$  to  $4 \times 10^6$  MBs/mL. In contrast, at 4°C, the mean diameter increased from  $3.9 \pm 0.42$  to  $10.72 \pm 0.7$   $\mu\text{m}$  while the concentration decreased from  $2 \times 10^8$  to  $4 \times 10^6$  MBs/mL over six days. An increase in the viscosity (from 1.58 to 15.38 cP) led to smaller MBs, with mean diameter of  $2.92 \pm 2.88$  vs  $3.66 \pm 2.89$   $\mu\text{m}$  (just after production) and  $4.06 \pm 4.49$  to  $6.26 \pm 5.05$   $\mu\text{m}$  (after 1 day). Incorporation of the lipophilic dye, Dil, significantly affected MB size. The average diameter increased, with increasing viscosity, from  $4.99 \pm 3.8$  to  $5.48 \pm 2.99$   $\mu\text{m}$ , after production. Whereas, at day 6 the mean diameter increased from  $13 \pm 11.82$  to  $17.94 \pm 14.74$   $\mu\text{m}$  with increasing Dil:MB ratio.

**Conclusion:** MBs are a safe drug delivery method when used below a concentration of  $3 \times 10^7$  MBs/mL according to the results from a 72 hour incubation. Their stability is reduced with increasing storage temperature, however, it is enhanced by increasing the viscosity of the suspension medium. Incorporation of Dil into the lipid shell also decreased stability. To achieve therapeutic efficacy, future studies will focus on improving stability at different temperatures and labelling techniques that do not alter MB properties. Reducing the cytotoxic effect of free lipids will also be explored and drug encapsulation/release will be investigated.



# Release and activity of rifampicin from biodegradable polymer formulations

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## ABSTRACT

Implantation of an indwelling medical device is often required in order to successfully treat a serious medical issue. However, infection of such devices is an ongoing problem, and can occur when microorganisms, predominantly *Staphylococcus* species, adhere to the device surface<sup>1</sup>. Biodegradable polymer drug delivery technology may be of use in some devices as a means of delivering a high local dose of antimicrobial in order to help prevent infection pathogenesis. In this study the broad spectrum antibiotic rifampicin has been formulated with the polymers PLA (Poly(L-Lactide)) and PLGA (Poly(D,L-lactic-co-glycolic acid(65:35))) and the *in vitro* drug release over 1 week analysed. Based on the release data (Fig. 1A), the PLGA:rifampicin formulations of 50:50 and 60:40 were selected for further analysis. A 4 week drug release study showed that over the examined period >95% of the rifampicin load was released from both formulations, however increasing the ratio of polymer to drug significantly changed the percentage release profile (Fig. 1B). Investigation of antimicrobial activity revealed that both formulations were able to produce consistently large zones of inhibition in disk diffusion assays over the 4 weeks examined, indicating successful bacterial inhibition (Fig. 1C). What this preliminary study has revealed is that rifampicin can be readily released from PLA and PLGA, and that release can be controlled by adjusting the ratio of polymer to drug. It has also shown that the antimicrobial activity of the rifampicin can be retained for at least 4 weeks. Therefore biodegradable polymers may represent a promising material for use in implanted medical devices as a means of delivering a high local concentration of antimicrobial to help prevent infection pathogenesis.

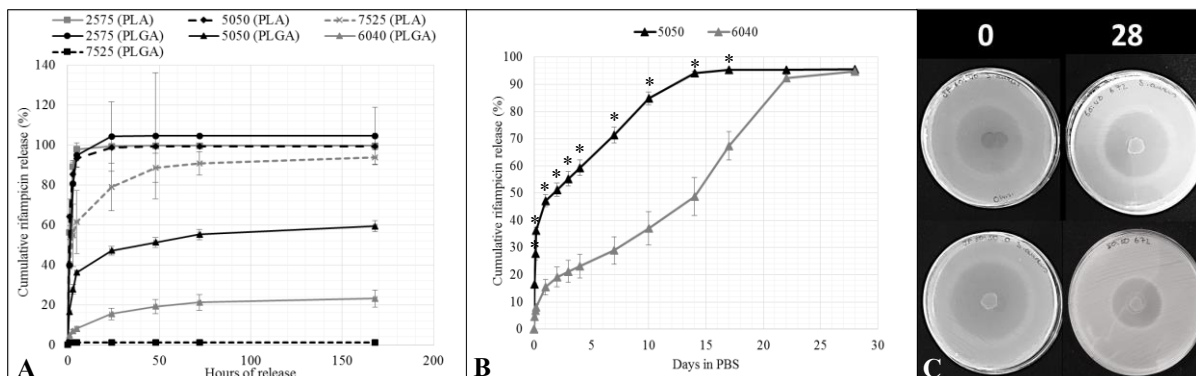


Fig.1: **A** shows the release of rifampicin from a variety of biodegradable polymer formulations into PBS (37°C; 120rpm) over 1 week. **B** shows release of rifampicin from PLGA formulations over 4 weeks under the same conditions (Statistical analysis by one-way Anova and Tukeys post hoc test,  $*p \leq 0.05$ ; for all data  $n=3 \pm SEM$ ). **C** shows zones of inhibition produced by the formulations against *Staphylococcus aureus* after 0 hours/28 days in PBS (top = 60:40; bottom = 50:50 PLGA:rifampicin)

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# Estimating drug release properties of intraocular lens material with rotational symmetric model

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## ABSTRACT

Understanding the way in which drug is released from potential drug carrying material can aid in the development of an effective delivery strategy to a given target area. To this end, numerical models using a finite element approach for modelling interface conditions in the context of diffusive transport are applied to simulate release curves. Due to rotational symmetry, the geometry of the biconvex optical part of an intraocular lens, as well as experiments done on disc shaped material, can be fully taken into account. This is an improvement on previous one dimensional models which presumed only layered systems [1,2]. The interface conditions considered may result in concentration jumps due to drug partitioning and/or mass transfer effects between adjacent material bodies.

When compared to release experiments carried out on intraocular lens material, simulations yield valuable insight into drug-material properties. It is generally assumed that a unique set of model parameter values explain the release properties of a given system. However, for some cases multiple sets of parameters can adequately explain the same experimental data. Insight gained by analysing the model parameter space can be used to make adjustments to experimental conditions that will determine the unique set.

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# Modelling the evolving ductility of biodegradable polymers

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## ABSTRACT

Drug-eluting stents have become desirable due to the reduction in restenosis that they offer following stenting [1]. A biodegradable polymer coating, often PLGA [2], containing drug, coats a stent, and the drug is released as the polymer degrades. To help combat issues relating to delamination and breakages during deployment, it is vital to investigate the failure mechanisms of biodegradable polymers.

A non-linear relationship was seen between the molecular weight,  $M_n$ , and failure strain,  $\epsilon_f$ , for polypropylene [3]. A significant decrease in ductility was previously found for polylactide as degradation proceeded [4] (Fig.1b). Here, we explore the relationship between ductility and molecular weight distributions of degrading PLGA.

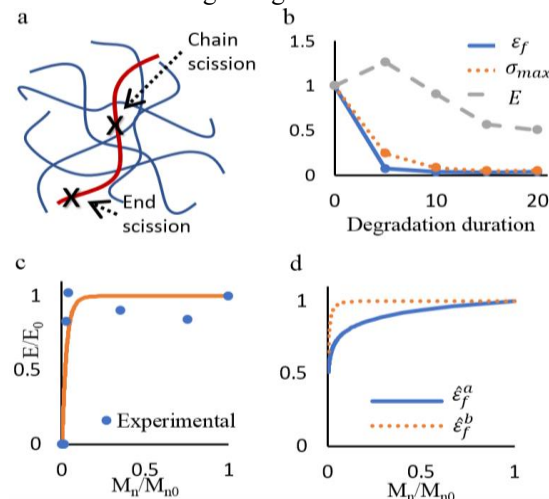


Figure 1: (a) Ensemble of polymer chains undergoing chain scission. (b) Modulus, strength, and ductility of PLA during degradation. Relationship between molecular weight and (c) modulus and (d) ductility.

A microscale model of polymer chain scissions was developed in MATLAB, motivated by Shirazi et al. [5]. Representative polymer chain distributions were generated and subjected to randomly assigned sequences of end-scissions and chain-scissions (Fig. 1a). The evolving distribution of chain length was tracked and failure criteria were then explored based on the ratio of free chain length to fully extended chain length as the chain length decreases with each scission.

The evolution of the predicted modulus,  $\bar{E}$ , based on the number of chains above a critical  $M_n$ , is compared to experimental data in Fig. 1c; a steep decrease in  $\bar{E}$  is observed for smaller  $M_n$ . Two criteria for  $\epsilon_f$  are presented in Fig. 1d:  $\epsilon_f^a$  is based on  $M_n$  of the ensemble of chains and  $\epsilon_f^b$  is based on the number of chains above a critical length. Both criteria show a substantial decrease in ductility with decreasing  $M_n$ ; however,  $\epsilon_f^a$  shows this decrease earlier.

This computational investigation of  $\epsilon_f$  of an evolving biodegradable polymer and its dependence on  $M_n$  will aid in designing biodegradable drug-eluting medical devices with suitable degradation rates and sufficient mechanical integrity for their purpose. Work is ongoing to include first order kinetics and link this to continuum finite element models.

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# Mathematical modelling to guide experimental protocols for *in vitro* drug testing

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## ABSTRACT

Drug discovery is a long and expensive process, with the development of a single drug taking many years to complete and the cost increasing significantly at each stage of testing. In addition, regulation states that the use of animals in drug testing must be minimised or avoided. Therefore, it is critical that the drug discovery process is as efficient as possible and it is important to develop novel *in vitro* drug testing systems which better reflect the *in vivo* environment so that initial screening tests offer more physiologically accurate results [1,2].

Mathematical models can be used to simulate the environment within *in vitro* drug testing systems which can aid in the design process and set-up of experiments. In this work, we have developed a mathematical model to describe fluid flow and oxygen/drug transport within single and connected Kirkstall QV900 chambers (Fig. 1a). This has allowed us to provide simple but useful relationships that enable prediction of the environment within the chambers when parameters such as input flow rate and inlet concentration are varied for different cell types. We have demonstrated the utility of our model by applying it to two separate studies in collaboration with experimental groups: (i) *in vitro* zonation of primary rat hepatocytes, and (ii) *in vitro* macrophage infection by *Leishmania major*. In this talk, we will discuss our findings and the potential significance of our results.

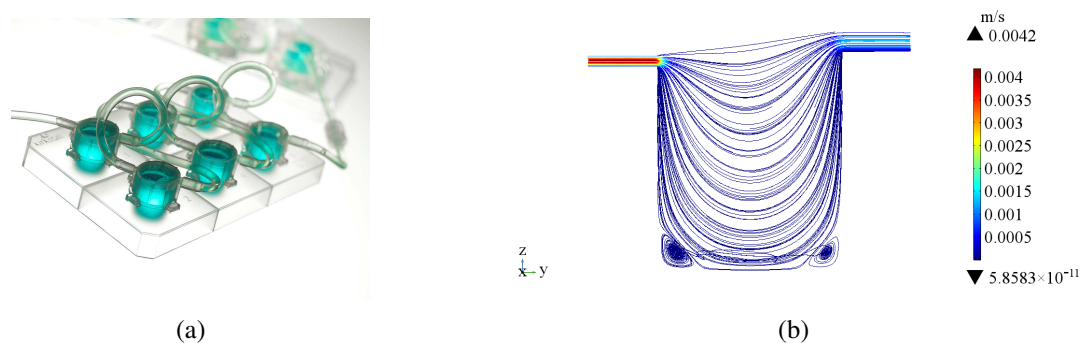


Figure 1: (a) The QV900. [www.kirkstall.org] (b) Example of flow streamlines in a single chamber.

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# A mathematical model for photothermal ablation of spherical tumors

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## ABSTRACT

Photothermal ablation is a promising new technique for treatment of some cancers, where metal nanoparticles are introduced into the tumour and the system is locally heated with a laser to destroy the malignant cells. The aim is to have nanoparticles accumulate within the tumour and not in the surrounding healthy tissue, so that the heat source leads to a differential increase in temperature in the cancer and hence cell death. In this study we consider a mathematical model for nanoparticle delivery to a vascularised spherical tumour, examining the distribution of nanoparticles through the tumour and the surrounding tissue. In this model we consider nanoparticles conjugated with ligands which selectively bind to tumour cell surface receptors and eventually leads to nanoparticle internalization within the cell. We study how the mass of accumulated nanoparticles within the tumour (and the surrounding tissue) is influenced by the degree of tumour vascularity, ligand nanoparticle conjugation and tumour cell capacity for internalized nanoparticles. We suggest an optimal timescale to maximize the efficiency of ablation across a range of physiological cases.

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# Modelling and experiments of drug release from orthopaedic pins: a student's perspective

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## ABSTRACT

In recent times, much interest has been generated in the study of drug release from orthopaedic implants, mainly in the form of drug release experiments in-vitro [1]. From the literature, these experiments examine different designs of prototype orthopaedic implants or reimagining current orthopaedic devices. Some examples include drug filled designs [2, 3], drug releasing coatings [4] and surface structure alterations for releasing drugs [5]. A purely experimental study can be very costly and time consuming and one way to alleviate these costs is to combine experimentation with a theoretical approach. By constructing mathematical models, which are validated against experimental data, one has a way to simulate different scenarios of the experiment, for example, changing the device geometry, without having to rerun experiments.

In this talk, we focus on two prototype fixation pins by Gimeno et al. [2, 3]. We present idealised mathematical models of the in-vitro experiments and some key results will be demonstrated from the mathematical studies. Finally, a discussion will be given on the cooperation between theorists and experimentalists, from the point of view of a PhD student.

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# Surface Acoustic Waves Nebulisation of Liposomes for Pulmonary Drug Delivery

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## ABSTRACT

Pulmonary diseases, such as asthma, are generally treated by the inhalation of aerosols that has the advantage of reducing the off-target (e.g. toxicity) effects associated with systemic delivery in blood. Effective respiratory drug delivery requires a droplet size distribution between 1 and 5  $\mu\text{m}$ . Inhalation of aerosols with wide droplet size distribution, out of this range, results in deposition of drug in not-targeted area of the respiratory tract, introducing undesired side effects on the patient.

To regulate the drug release and to facilitate the uptake from cells, drugs are often encapsulated into protective liposomes. However, a multistep process is required for their formation, often performed at the formulation step, therefore limiting the range of available drugs or their shelf life. Using surface acoustic waves (SAWs), a pulmonary drug delivery platform was produced, which enabled the formation of defined size aerosols and the formation of liposomes in situ.

SAWs are mechanical waves, propagating along the surface of a piezoelectric substrate. They were generated using an interdigital transducer on lithium niobate with an excitation frequency of 9.6 MHz at a power of 1W [1]. Disposable silicon superstrates were etched using photolithography and dry etch processes to create an array of cylindrical through-holes with different diameters and pitches [2].

Superstrates were coupled with the SAW substrate through water-based gel. As the SAW propagates on the superstrate, it enables nebulisation of a lipid solution deposited onto it. The cylindrical cavities restricted the formation of large drops in the aerosol, while at the same time unilamellar liposomes were created.

SAW formed liposomes showed a higher monodispersity compared to the control sample, as well as displayed, a faster production rate.

To test the aerosol's size, dynamic light scattering and laser diffraction methods were used, both showing the size control of the aerosolised particles.

The use of silicon superstrate with cavity size of 100-200  $\mu\text{m}$ , produced an aerosol with a mean droplet size within the optimum range for pulmonary drug delivery, containing the liposomes in which the medicine could be loaded. Additionally, analysis of liposomes with Cryo-TEM showed formation of vesicles with narrow size distribution between 80-100 nm and optimal morphology in order to be used for drug delivery.

Encapsulation of nucleic acids in liposomes through the developed SAW platform was also investigated. In vitro delivery of siRNA and DNA Luciferase were achieved using A549 cell line, lung carcinoma from human. In conclusion, SAW pulmonary drug delivery platform was engineered, in order to combine multiple time consuming steps (formation of liposomes, drug loading, nebulisation) into a unique platform with the aim of specifically delivering the medicament in a targeted area, reducing the drug's side effects.

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# A multiscale computational model of nanoparticle-based drug delivery to the microvasculature

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## ABSTRACT

The use of nanoparticles loaded by therapeutic and imaging agents is one of the most promising innovation in the field of the treatment of complex diseases, typically cancer. The advance nano-fabrication technologies can control a large spectrum of design parameters (size, shape, surface properties, ...) which should be properly tuned in order to improve the performance in the treatments. However, identifying the best combination of such parameters using a trial and error approach based on animal experiments is expensive and impractical. For this reason, computational models are emerging as complementary tools to guide the design and optimization of nano-based therapies [3].

We address this need in the particular case of nanoparticles designed to be delivered in the vascular system and interacting with the microvasculature. This is a very challenging flow and transport problem because it combines the intricate shape of microvasculature, which is responsible of the high spatial variability of flow conditions, with a complex cascade of phenomena that determine the interaction of nanoconstructs with the vascular wall. We set up a multiscale approach that combines a mesoscale model for microcirculation with a microscale description of the particle-wall interaction. More precisely, we exploit dimensional model reduction techniques to describe the blood flow and the related transport phenomena as one-dimensional sources embedded within the three-dimensional space and we model how individual particles interact with the wall on the basis of the Lattice Boltzmann method [1, 2]. The computational model is then applied to simulate particle delivery to a representative portion of a tumor, with the aim to compare the accumulation of particles in the microvascular network and the distribution of therapeutic agents in the surrounding tissue for different design parameters.

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# Anisotropic Diffusion Models with Diffusion Tensor Linked to Tissue Fibre Orientation for Drug Eluting Stents Simulations

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## ABSTRACT

We consider the dissolution, transport and binding of sirolimus on an axisymmetric domain representing the polymer coating layer and the anisotropic porous artery wall in the vicinity of a stent strut. We employ a novel numerical method, based on the FEM, considering Darcy flow [1], a non-linear dissolution model for the dynamics in the coating, and a non-linear saturable binding model that includes both specific and non-specific binding in the arterial wall, as proposed by McGinty-2016[2].

The anisotropy in drug transport parameters, and in particular the diffusion tensor, is related to tissue fibres orientation. In a previous work [3] the diffusion tensor in the artery wall was considered orthotropic, with principal directions aligned with longitudinal (larger diffusion eigenvalue) and radial (smaller diffusion eigenvalue) directions, due to the orientation of tissue fibres in the artery wall, particularly plain muscle fibers in fine bundles, arranged in lamellae and disposed circularly around the vessel. However, the presence of the stent causes the compression and realignment of tissue fibres, such that they are parallel to the stent surface in its proximity. Hence, the principal directions of the diffusion tensor must be re-oriented in the vicinity of the stent to properly account for this stent-artery interaction.

In this work, the diffusion tensor is obtained by a similarity transformation, considering the realignment of the principal directions obtained by an algebraic approach. The principal directions of the diffusion tensor are determined by the gradient of a level function which marks the layers of tissue of the artery wall. Two approaches are considered for the estimation of the level function: the signed distance function computed from the inner arterial wall, and the solution of the Laplace equation with homogeneous Dirichlet boundary conditions on the inner arterial wall.

Simulations using the proposed models show that the spatial distribution of sirolimus is greatly influenced by the flow and the arterial wall properties. The effect of the anisotropic diffusion tensor is seen in the sirolimus concentration distribution around the polymer layer, that becomes considerably more uniform around the stent than in the orthotropic model, and in the reduced mass flux, resulting from the realignment of the principal directions of the tensor with the direction of the interface.

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# Development of an *in vitro* artery model to characterize drug delivery from endovascular stents and grafts

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## ABSTRACT

**Background:** Local drug delivery strategies have emerged as a powerful means of improving vascular implant performance. Despite this, the precise mechanisms governing release and uptake of drug within the treated artery are poorly characterised. Crucially, the impact of artery wall composition on drug transport kinetics is unclear [1]. The recent use of *in vitro* models has provided useful insights in this area [2], although the transport of clinically relevant drugs within such systems remains to be fully explored.

**Methodology:** In this study, we developed a simplified *in vitro* artery mimic material comprising low viscosity alginate (3% (w/v) crosslinked with CaCO<sub>3</sub>:D-(+)-glucuronic acid d-lactone solution). We then investigated the effect of gelatin inclusion (2.5% w/v) within this material, on the transport of rapamycin and rifampicin through the model construct, over a 24 hr incubation period (Fig. 1). These drugs are used in endovascular stents and grafts due to their antiproliferative and antibacterial properties respectively.

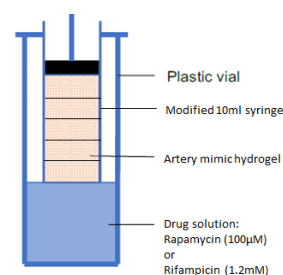


Figure 1 Experimental set up for drug uptake and spatial distribution within artery mimic

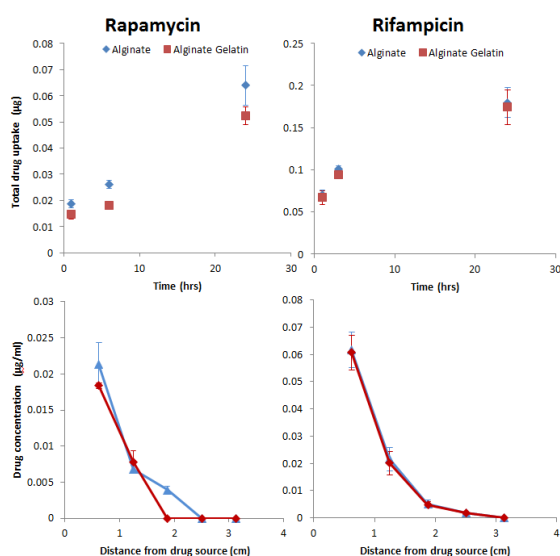


Figure 2 Columns of alginate or alginate:gelatin were incubated in PBS:ethanol (90:10) containing either rapamycin (0.1mM) or rifampicin (1.2mM). Periodically, the column would be removed and sliced into 5 equal gel sections, which were then incubated in methanol overnight to strip out the drug. Drug content was subsequently measured using UV-spectroscopy (rapamycin 278 nm, rifampicin 334 nm). The upper panels show the total drug taken up into the whole gel. The lower panels show the estimated spatial drug concentration through the gel column. Data represent mean  $\pm$  stdev from 3 replicates.

**Results:** The gels produced were of uniform consistency and remained stable following 24 hrs incubation in PBS:ethanol. Our drug transport study revealed that inclusion of gelatin within the artery mimic reduced uptake of rapamycin and lead to an altered distribution within different layers of the material (Fig. 2, left panels). In contrast, rifampicin uptake and distribution were unchanged with gelatin inclusion (Fig. 2 right panels).

**Discussion and Conclusion:** The artery mimic is a useful platform for investigating how different artery wall components impact on drug transport kinetics. Gelatin inclusion provides a simplified model of collagen and increases the biocompatibility of the mimic, permitting future cell seeding. Drug transport characteristics were dependent on the presence of gelatin, an effect which was drug dependent. These findings may have important implications on the future optimization of vascular implant design and the drive towards personalised treatments and devices.

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# Is it necessary to account for non-uniform binding site density when modelling drug-eluting stents?

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## ABSTRACT

**Introduction.** Many mathematical models have been developed to try to understand drug release from stents and subsequent redistribution in the arterial wall<sup>1</sup>. Models have highlighted the importance of accounting for specific and non-specific binding<sup>2</sup>, concluding that for sirolimus-eluting stents it is more important to sustain release than to increase dose. Modelling has also been used to explain how differences in the binding properties of paclitaxel and sirolimus lead to different retention, suggesting that the optimal delivery strategy is drug-dependent<sup>3</sup>. However, these conclusions have been made based on the assumption that the density of binding sites is uniform across the arterial wall. This is despite experimental evidence to the contrary, suggesting a variation across the wall thickness, with noticeable differences between and within the media and adventitia<sup>4-5</sup>. Target receptor densities for paclitaxel and sirolimus do not follow the same spatial pattern<sup>5</sup> and when components of disease are present, the picture is further complicated<sup>6</sup>. The aim of this study is therefore to investigate the role of non-uniform binding site density in determining arterial drug distribution following stent-based delivery.

**Methods.** We develop a 2D axisymmetric model of coupled stent drug release and redistribution in the arterial wall, similar to that employed by Bozsak et al.<sup>3</sup>. The novelty in our model is that we allow the density of binding sites to be a function of radial distance. The form of the function is derived from published experimental data, by relating binding site density to the partition coefficient. We simulate a number of cases for different drugs.

**Results and Discussion.** Whilst plots of time-varying normalised mean concentration are similar for the range of cases considered, our results highlight clear differences in spatially-varying concentration of bound drug in the arterial wall. Therefore, by assuming a uniform density of binding sites across the wall, current models may be misguiding the optimal drug delivery strategy. We close with a discussion of limitations in current modelling and experimental approaches in the field.

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# Mathematically modelling the stability of solid dispersions in storage

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## ABSTRACT

Many drugs currently on the market or in development are poorly water-soluble. This presents a serious challenge to the pharmaceutical industry because orally delivered drugs that are poorly soluble tend to pass through the gastrointestinal tract before they can fully dissolve, leading to poor drug bioavailability [1]. One strategy to improve drug solubility is to use a solid dispersion [2]. A solid dispersion typically consists of a hydrophobic drug embedded in a hydrophilic polymer matrix. When the dispersion dissolves in the stomach, drug-polymer interactions maintain the drug at supersaturated levels, thereby accelerating drug dissolution.

Unfortunately, despite extensive research, the dissolution behaviour of solid dispersions is only partially understood [3]. This makes the design of successful solid dispersions a somewhat hit and miss affair. Clearly, the construction of reliable mathematical models that capture the key interactions between the drug, polymer and solvent molecules in a dissolving solid dispersion would greatly assist with their rational design.

In this presentation, we develop mathematical models describing the storage and dissolution of solid dispersions [4]. The models consist of coupled systems of nonlinear partial differential equations. We then analyze in detail a particular problem describing a solid dispersion in storage. The drug-polymer interaction in the dispersion is modelled using Flory-Huggins theory [5], and we use the model to identify regimes in the model parameter space that lead to stable, metastable and unstable storage behaviour (phase separation). We illustrate the various phenomena arising using numerical simulations.

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# Predicting skin permeability from small datasets

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## ABSTRACT

Measurement of the percutaneous absorption of exogenous chemicals has become increasingly important over the last 25 years for a variety of reasons, including pharmaceutical efficacy and, in a number of fields, toxicity. Since the publication of the Flynn data set [1] there has been considerable interest in the development of mathematical models that relate the percutaneous absorption of exogenous chemicals to the physicochemical properties of permeants. This began with the work of El Tayer [2] and has grown into a distinct area of research, mostly based on the use of a range of methods to interrogate the Flynn data set, or variations thereon. However, many QSPR models of skin permeation (reviewed in [3]) have been shown to be significantly limited in their predictive ability, for example being poorly correlated with experimental data which covered the stated range of applicability of these models [4,5]. QSPRs have therefore gained little widespread use or credibility in the broader field of percutaneous absorption. In addition, collation of experimental data is expensive and issues with variability in skin permeation persist. Therefore, rather than adding to existing datasets, and possibly developing a dataset which is skewed or biased, the aim of our study was to consider the nature of the dataset used to construct models. The use of manually modified hyperparameter methods was explored in order to explore the quality of models that could be produced with small datasets. Optimisation methods, including Grid Search, Conjugate Gradient, Random Search, Evolutionary Algorithm and Hyper-prior, were evaluated and applied to previously published data. Data sets were also altered in a structured manner to reduce their size, which retained the range, or 'chemical space' of the key descriptors. The Hyper-prior Smoothbox kernel results in the best models for the majority of data sets, and they exhibited significantly better performance than benchmark QSPR models, which performed poorly. Thus, the design of the data set, and possibly also the approach to validation of the model, is critical in the development of improved models. The size of the data set, if carefully controlled, was not generally a significant factor for these models and models of high statistical quality could be produced from substantially smaller data sets, potentially with significant implications for the use of animals in generation of such data and in costs associated with producing suitable *in vitro* data.

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# Design and Optimization of Polymeric Nanoshuttles for Active Delivery and Diagnosis

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Current medical practice can benefit from the recent advances in nanotechnology. Nanometric engineered materials interact with cells, tissue and organs at a molecular level, they may be used as probes for ultrasensitive molecular sensing and diagnostic imaging or carriers for drug and gene delivery. To this aim, the elaboration of practical guidelines for optimal design of functional nanocarriers for medicine requires a deep understanding of the interaction between the physical-chemistry properties of the nanoparticle surface with the complex protein machinery existing at the cell membrane. Following these guidelines, smart, efficient and safe nanocarriers can be engineered to target specific cells or tissues.

In particular, nanoparticle parameters, such as charge, shape, surface chemistry all can affect the mechanism of cellular uptake and their fine tuning result relevant both to assess the real biological risks coupled with the use of nanomaterial (nanopathology and nanotoxicology) and to engineer carriers able to improve the medical practice. By sapiently modulating those parameters, it is possible to activate mechanisms of cellular uptake different from those commonly used by cells: these open the possibility to activated/modulated the cell membrane crossing. Herein, the design and production of novel degradable polymeric nanocapsules via layer-by-layer technology will be presented along with a detailed characterization of their *in vitro* and *in vivo* performances. Particular attention will be devoted to surface molecular decoration able to guide the nanoparticle throughout the cytosol.

# Determination of the effect of onium hexafluorosilicates on the properties of gels

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## ABSTRACT

An effective method of preventing caries is mineralization and fluoridation of the enamel. Pharmacological studies have shown a higher caries prophylaxis effectiveness of onyx hexafluorosilicates compared to sodium fluoride and sodium monofluorophosphate. When designing the gel composition with cetylpyridinium hexafluorosilicate and octenidine-hexafluorosilicate it is necessary to select the nature and concentration of the gelling agent.

As gel formers, various high-molecular agents were used – sodium alginate, xanthan gum, cellulose derivatives (CEPC, CMC, MCC and NaCMC) and carbomer of polyacrylic acid. Experimental samples were evaluated for organoleptic parameters, rheological properties, thermal stability and colloidal stability and pH values.

Studies have shown that medicinal substances affect the stability of gels. When they are introduced, irrespective of the sequence of the process, the gelling of carbomer and sodium alginate is carried out. For gels based on derivatives of cellulose and xanthan gum there is a significant decrease in viscosity indexes. Gels derived from derivatives of cellulose and xanthan gum remain stable, withstand the colloidal test and thermal stability, indicating the possibility of their use in the production of caries prophylactic agents based on onium hexafluorosilicates.

Selection of gel formulation among cellulose derivatives was carried out in view of their effect on the antimicrobial activity of gels. The antimicrobial action of cetylpyridinium hexafluorosilicate and octenidine-hexafluorosilicate gels was investigated in an effective caries-prophylactic concentration of 1.66 and 3.0 mg / ml, respectively. A certain influence of the gelling agent on the strength of the antimicrobial action of onyx hexafluorosilicates has been experimentally determined. A higher antimicrobial activity in relation to *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and yeast-like fungi *Candida albicans* showed hydroxyethyl cellulose based gels.

Thus, for the development of caries prophylactic gel with cetylpyridinium hexafluorosilicate and octenidine hexafluorosilicate as a gel formulation was selected hydroxyethylcellulose.

# Mathematical modelling of variable porosity coatings and dual drug release

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## ABSTRACT

The topic of controlled drug release has received much attention in recent years, for example in the design of tablets and in local drug delivery devices such as stents, transdermal patches and orthopaedic implants. In recent years, we have developed a series of models for such devices to describe drug release from a polymeric platform and transport in surrounding biological tissues. These works have culminated in the development of a mathematical model that demonstrates agreement with in-vivo drug release and tissue uptake data, for the case of a drug-eluting stent [1].

If, on the one hand, these fully coupled models are indeed necessary to understand the spatio-temporal drug concentration in the surrounding environment, on the other hand it is clear that device manufacturers cannot intervene on the underlying biology. What they can control, however, are the properties of the polymeric platform to ensure the desired drug release profile is achieved. Indeed, the release profile is known to be a key predictor of device performance. Therefore, in the present work we focus instead primarily on the properties of the drug-containing coating.

We consider two particular aspects of the drug coating design. Firstly, the delivery of two therapeutic agents, what we refer to as dual drug delivery. Depending on the particular application in question, it may be desirable for the drugs to be released at similar rates, or perhaps one of the drugs released rapidly with the other being eluted over a longer period of time. In the case of drug-eluting stents, for example, devices which release an anti-proliferative and a ‘pro-healing’ drug have been proposed, whilst a combination of the two has also been suggested. Secondly, motivated by today’s advances in micro and nanotechnology, we propose variable porosity multi-layer coatings as an additional means of controlling the dual drug delivery.

In this talk we present our mathematical model of dual drug delivery from a durable polymer coated device. We demonstrate how the release rate of each drug may in principle be controlled by varying the underlying microstructure of polymer coating or by changing the initial loading configuration of the two drugs [2]. Our results show the role of the relevant material parameters used to tailor the release curves to a given application.

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# Non-linear acoustic emissions from microbubbles flowing in a capillary exposed to focused ultrasound

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## ABSTRACT

**Rationale:** Microbubble ( $\mu\text{b}$ ) suspensions introduced to the vasculature, for exposure to focused ultrasound (FUS) as a minimally invasive and targeted drug delivery modality, continues to attract widespread research interest. Monitoring of the acoustic emissions generated by cavitating  $\mu\text{bs}$  is critical for evaluating efficacy of delivery and avoidance of collateral damage, particularly for applications such as reversible blood-brain barrier disruption [1, 2], and may be complicit in delivery mechanisms. Yet the bubble-based mechanisms for signal generation remain poorly understood, preventing optimisation of the technique both in terms of therapy and safe administration.

**Methods:**  $\mu\text{bs}$  flowing through a 200  $\mu\text{m}$  cellulose capillary, exposed to FUS of frequency  $f_0 = 690$  kHz at varying peak-negative pressure (PNP) amplitudes, are observed via synchronised dual high-speed imaging from orthogonal perspectives, at circa 100,000 frames per second (fps) and shadowgraphically, at up to 10 million fps [3]. In parallel, the acoustic emissions generated by the resolved cavitation activity are collected by a broadband needle hydrophone, with complex calibration over a representative bandwidth, for detector deconvolution.

**Results:** At all PNPs, imaging at 100,000 fps indicates that within several cycles of FUS inception, individual microbubbles have coalesced under the action of secondary radiative forces, to form a cavitation cloud. Subsequent translation is determined by the primary radiation force of the FUS exposure. Shadowgraphic imaging at 10 million fps reveals that the clouds emit periodic shock waves at  $f_0$  for intermediate PNPs, transitioning to  $f_0/2$  at higher PNP, corresponding to features within the acoustic hydrophone data, and subsequent spectral representation.

**Conclusions:** Nonlinear components of the acoustic emissions from  $\mu\text{b}$ -seeded cavitation in a capillary are dominated by periodic shock waves, including harmonics of  $f_0$  and subharmonic components, at  $f_0/2$ . Peak-positive pressure amplitudes of component shock waves, evaluated after filtering for  $f_0$  and deconvolving the detector impulse response, are in the kPa regime, increasing with the PNP of the acoustic driving.

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# Modeling drug delivery in a sirolimus-eluting stent: investigation of physico-chemical properties of coating, drug, and arterial tissue

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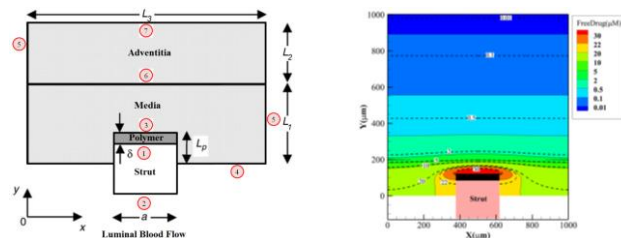
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## ABSTRACT

Drug-eluting stents (DES) have become the standard of care for coronary artery disease, yet further innovation is hampered by cost and experimental techniques. Computational modeling enables determination of the spatio-temporal variation of drug concentration in the arterial wall that cannot be achieved in animal models or human trials. We developed and verified a finite volume solver to study drug delivery in different layers of a porous tissue and polymer coating [1,2]. To extend the realism of existing computational models we here consider under-explored modeling components, including top coat permeability, drug metabolism in adventitia, and inhomogeneity of porosities at tissue layer's borders. Drug was assumed to be loaded in solid state in a porous reservoir separated from the tissue by a top coat, using Sirolimus-like values. Drug transport was modelled as a convection-diffusion-reaction process across the media and adventitia layers, treated as porous media. Further realism was achieved by considering drug dissolution and phase change in the polymer coating, binding and unbinding reactions of free drug in arterial tissue, and drug consumption by vasa vasorum and binding by extracellular matrix cells (ECM) and specific receptors (SR). Numerical analysis shows that neglecting adventitia and drug metabolism overestimates free drug concentration in the tissue (Figure 1) which is perceived as lower if the concentration discontinuity and realistic (instead of universal) porosity at tissue layer borders are considered. These effects are less pronounced for bound drug where binding site density and avidity are determinant factors. And while adventitial forces dictate media uptake they did not alter drug release or pharmacokinetics within polymer coatings, which were dominated rather by diffusion and top coat permeability. Thus, drug kinetics and dynamics in arterial tissue are strongly coupled. Physical design and characteristics of polymer matrices affect release, and biochemical and heterogenic physical properties of arterial tissue and the physico-chemical characteristics of depleted drug play a critical role in dynamics.

**Figure 1. Left:** Schematics of the computational domain with enumerated boundaries, **Right:** Free drug distribution inside tissue at 24h with (solid line) and without (dash line) drug metabolism.



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# Modelling the effect of flow on ATP/ADP concentration at the endothelial cell surface

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## ABSTRACT

The adenine nucleotides ATP and ADP regulate many aspects of vascular endothelial cell (EC) biology including intracellular calcium concentration, focal adhesion activation, cytoskeletal organization, and cellular motility. *In vivo*, ECs are constantly under flow, and the concentration of ATP/ADP on the EC surface is determined by the combined effects of nucleotide convective and diffusive transport as well as hydrolysis by ectonucleotidases on the EC surface. In addition, experiments have demonstrated that flow induces ATP release from the cells. Previously computational models have incorporated the above effects and thus described ATP and ADP concentration at the EC surface; however, it remains unclear what physical processes are responsible for nucleotide regulation. While some EC responses to flow have been shown to be directly driven by shear stress, others appear to also involve a non-negligible contribution of transport. In the present work, we develop a mathematical model and perform numerical simulations to investigate the relative contributions of shear stress and transport to nucleotide concentration at the EC surface. Because *in vitro* experiments are performed by using confluent cells in some cases and subconfluent cells in other cases, we also investigate the effect of cell density on the results. The outcomes of the simulations demonstrate a complex interplay between shear stress and transport such that transport has a significant contribution at certain shear stress values but not at others. The effect of transport on nucleotide concentration increases with cell density. The present findings enhance our understanding of the mechanisms that govern the regulation of adenine molecules at the EC surface under flow. The next phase of the work will focus on the role of intracellular and extracellular ATP on the regulation of EC shape and migration.

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## Exposure models in biomedical applications

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### ABSTRACT

The materials that comprise medical products contain substances that can be transferred to patients during use. Limited patient exposure to these substances may be desirable, such as in drug delivery applications, but more generally, there is concern for adverse health effects if a potentially toxic chemical is released in sufficient quantities. Historically, the likelihood for adverse health effects to occur due to the release of potentially toxic substances from a medical product has been evaluated primarily through animal testing. However, toxicological risk assessment approaches are increasingly being used, potentially obviating the need for extensive animal testing to assess the potential for adverse effects in patients following the release of chemical compounds. A critical component of these approaches is exposure assessment, yet exposure data are often unavailable, *i.e.* the amount of the chemical compounds that are released from the product and are taken up by the patient. To address this data gap, mass transport / transfer models represent a promising means to establish clinically relevant exposure estimates. However, the use of exposure models to support toxicological risk evaluations and regulatory decision making is virtually non-existent, largely due to challenges associated parameter specification and validation.

This presentation will provide an overview of exposure models and their use in biological risk evaluation of medical products, and include: 1) potential benefits and historical/current use in regulatory applications; 2) types of models spanning multiple length scales that can help inform toxicological risk assessments; 3) challenges associated with use in regulatory decision making; and 4) strategies to use physics-based models to improve biological risk evaluation in the near term.

# Towards personalised drug delivery from stents

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## ABSTRACT

Coronary Heart Disease (CHD) is one of the leading causes of mortality and morbidity worldwide and will remain so for the foreseeable future. The underlying mechanism of CHD is the formation of atherosclerotic plaque, resulting in the thickening of the arteries and a restricted supply of blood to the heart, which can lead to a heart attack. The most common treatments are heart bypass and percutaneous coronary intervention (PCI) with a drug-eluting stent (DES), the latter being the preferred option.

The inception of DES's revolutionised the treatment of CHD, however despite this success there are still situations in which the stent performs poorly, such as in patients with multi-vessel disease and/or with pre-existing morbidities such as diabetes [3, 1]. Recent evidence suggests that the variability in the performance of DES from patient to patient may be dependent on the nature and severity of the plaque within the diseased tissue[2]. This dependency arises because a therapeutic dosage must be distributed and maintained within the arterial wall for the DES to have the desired impact. Drug distribution is often quantified for healthy arteries but there are limited studies on the distributions achieved through the varying plaque levels which can be found within a diseased vessel. In this work we present the foundations of an approach that aims to address the varying levels of disease and complicated geometry that is typical of a diseased vessel.

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# Features of treatment of enterobiasis in accordance with the guidelines by Médecins Sans Frontières

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## ABSTRACT

Helminthiasis is ranked second after tuberculosis. Of the 150 worm species present in the world, about 30 are met in Ukraine. At the same time, an absolute majority is involved in enterobiasis (approximately 75 % of cases among helminthiasis of digestive system) [1].

Enterobiasis (pinworms) refers to nematode infections. The causative agent of the disease is *Enterobius vermicularis*. It is distributed worldwide, including both countries with an unfavorable epidemiological profile and low-level of medical care and developed countries with high-level healthcare. Transmission of pinworms includes faecal-oral and auto-infection routes.

In order to review and extend the clinical protocol for the treatment of enterobiasis in Ukraine, the current practical experience and evidence-based medicine of specialists from other countries of the world are analyzed, in particular, by example of Médecins Sans Frontières.

According to Clinical guidelines by Médecins Sans Frontières [2], enterobiasis is diagnosed by the following clinical features: anal pruritus, more intense at night, vulvovaginitis in women (rarely). Diagnosis includes collection and further detection under the microscope of pinworm eggs from the anal area (scotch tape method).

The recommended pharmacotherapeutic scheme provides the usage of albendazole (PO as a single dose children over 6<sup>th</sup> months and adults 400 mg (200 mg in children over 6 months but < 10 kg) or mebendazole (PO as a single dose children over 6 months and adults 100 mg (50 mg in children over 6 months but < 10 kg). A second dose is recommended after 2 to 4 weeks. This treatment regimen conforms to the general principles of treatment of the enterobiasis recommended by WHO.

For comparison, clinical protocol of enterobiasis treatment includes list and scope of medical services of a mandatory range (patients with enterobiasis need to carry out pathogenetic therapy: strengthening, desensitizing, immunocorrective. Along with this, specific therapy is conducted) and list and volume of medical services of the additional assortment (ultrasound examination if necessary).

Nevertheless, when developing a national clinical protocol for the treatment of enterobiasis in Ukraine, it is advisable to present an extended treatment regimen supplemented with schemes for pathogenetic, desensitizing and symptomatic treatment.

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## **Some aspects of the design of an anti-stress medicated chewing gum**

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### **ABSTRACT**

Stress - a set of nonspecific reactions that arise in the body under the influence of extreme effects. Despite the fact that the pioneer of this term was Hans Selye back in the 1920s, this problem received close attention only in the last decade. According to the Statistic Brain Research Institute, more than 70% of Americans regularly experience the physiological or psychological effects of stress. And 48% admit that a stressful state has a negative effect on their personal or professional life. According to WHO forecasts, by 2020, depression will come first in the world among all diseases, overtaking today's leaders - infectious and cardiovascular diseases. In this regard, it is urgent to develop new anti-stress drugs and improve existing ones.

Stress is classified by duration (acute and chronic), by influence on the body (destructive and constructive), by the object of influence (physiological or psychological).

After the analysis of published data, glycine and an organic magnesium salt were chosen as promising active pharmaceutical ingredients. Glycine is a neurotransmitter, with a proven stress-protective, anti-stress and nootropic effect. Therapy with magnesium preparations restores the balance of the autonomic nervous system. The use of magnesium in the daily diet increases and harmonizes the production of endogenous melatonin. The inclusion of precisely the organic salts of magnesium is based on their high bioavailability.

Traditionally, the most popular dosage forms for therapy and prevention of stress are tablets, tinctures and capsules. Also, in the world pharmaceutical market, anti-stress chewing gums are presented, however, they are just a dietary supplement. They mainly include L-theanine, a derivative of green tea leaves.

As a result of the analysis of literature data, as well as marketing analysis of the pharmaceutical market in Ukraine, active pharmaceutical ingredients (glycine and magnesium citrate) were chosen to create a new medicinal preparation of sedative action in the form of medicated chewing gum. Also, pharmacotechnological studies of active pharmacological ingredients were conducted.

All things consider, given the frequency and prevalence of stress conditions, the creation of a drug for their treatment is an urgent task for pharmacy and medicine.