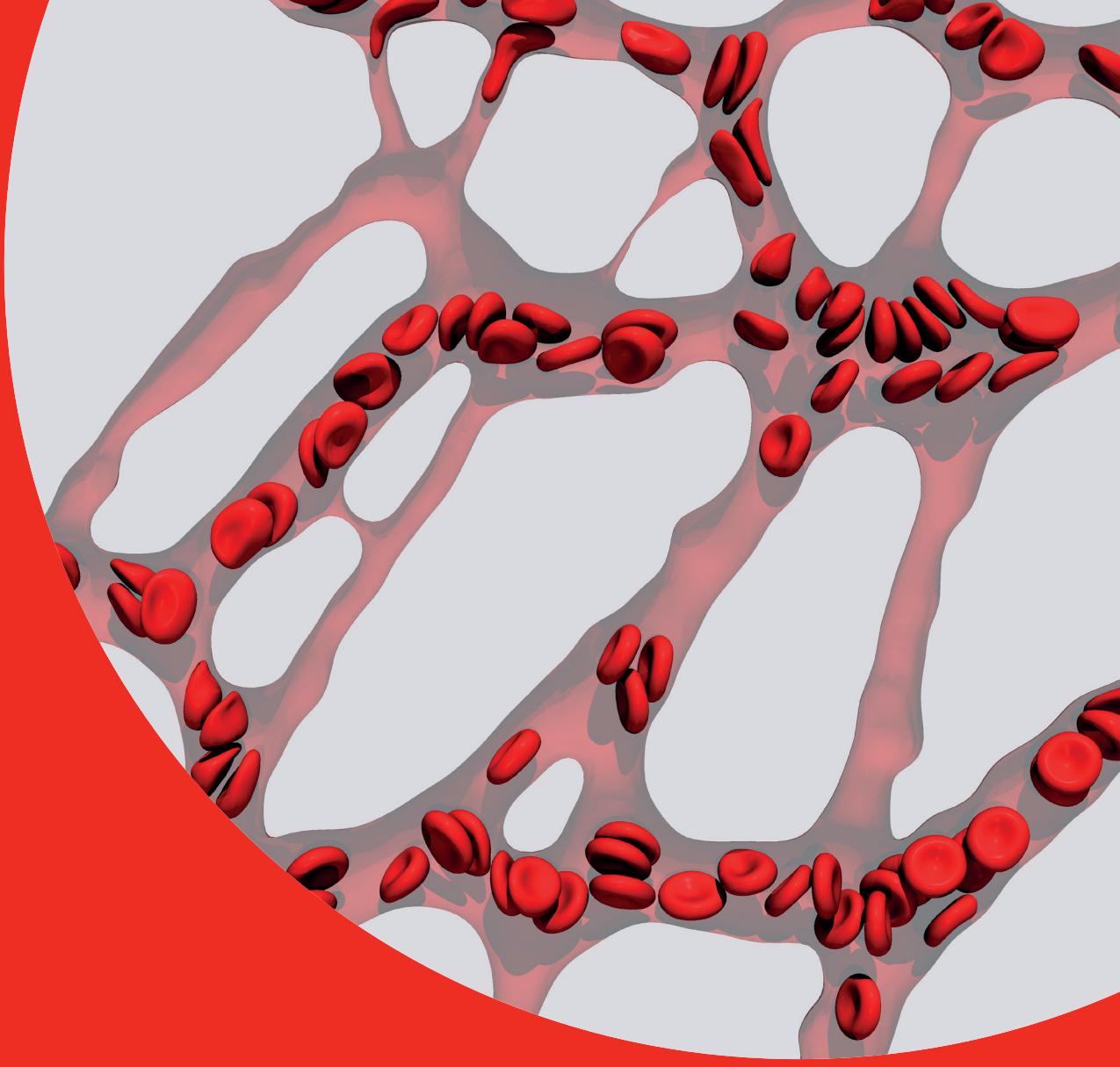

Microrheology and Transport in Complex Biological Media

16–18 May 2022
Online

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Programme

Monday 16 May 2022

13:00 **Introduction**

13:15 **Keynote 1: Imaging-Guided Modelling of Blood Flow and Mass Transport in Real-World Tissues**
Rebecca Shipley, UCL, UK

14:00 **Invited: Blood delivery to the placenta: Interpreting organ scale function from tissue imaging**
Alys Clark, University of Auckland, New Zealand

14:30 **Invited: Simple models of a complex fluid: Characterising rheology and transport in the blood with one-dimensional flows**
Philip Pearce, UCL, UK

15:00 Break

15:20 **Physical and geometric determinants of transport in feto-placental microvascular networks**
Alexander Erlich, Institut de Biologie du Développement de Marseille (IBDM), France, and Institut de Recherche sur les Phénomènes Hors Equilibre (IRPHE), France

15 :40 **Theoretical model for focused-light-induced cytoplasmic streaming (FLUCS)**
Weida Liao, University of Cambridge, UK

16:00 **Positron imaging for flow characterisation: towards the micro-scale**
Tom Leadbeater, University of Cape Town, South Africa

16:20 **Open Discussion**

Tuesday 17 May 2022

13:00 **Introduction**

13:15 **Keynote 2: Predicting blood cell trafficking in capillary vessel networks in silico: High fidelity modeling and machine learning applications**
Prosenjit Bagchi, Rutgers University, USA

14:00 **Invited: Flows shaping network architecture**
Karen Alim, TU Munich, Germany

14:30 **Invited: Platelet margination and flow dynamics in healthy and diabetic microcirculation**
Gábor Závodszky, University of Amsterdam, The Netherlands

15:00 Break

15:20 **Numerical simulation of cellular blood flow in canonical disordered porous media**
Qi Zhou, University of Edinburgh, UK

15:40 **Liquid flow through nanoporous media: non-linear response and blocking**
Msc Roya Ebrahimi Viand, Freie Universität Berlin, Germany

16:00 **Collective motion in two-dimensional microswimmer suspensions**
Viktor Skultety, University of Edinburgh, UK

16:20 **Panel Discussion**

Wednesday 18 May

09:00 **Introduction**

09:15 **Keynote 3: Spatial distribution of red blood cells in periodic microfluidic networks**
Sylvie Lorthois, IMFT, France

10:00 **Invited: Understanding form and function in vascular tumours**
Helen Byrne, University of Oxford, UK

10:30 **Invited: The role of capillary diameter alterations during health and disease - insights from blood flow modelling**
Franca Schmid, ETH Zurich, Switzerland

11:00 Break

11:20 **Invited: Computational fluid dynamics modeling and simulation of gastric mixing and emptying in the human stomach**
Yohsuke Imai, Kobe University, Japan

11:50 **Microfluidic model of micro-haemodynamics**
Qi Chen, University of Manchester, UK

12:10 **Network effect of vessel compression on the partitioning of red blood cells at bifurcations in vascular networks**
Romain Enjalbert, The University of Edinburgh, UK

12:30 **Open Discussion**

13:00 End

(Invited) Blood delivery to the placenta: Interpreting organ scale function from tissue imaging

Alys Clark

University of Auckland, New Zealand

The placenta provides the growing fetus with nutrients and removes waste from the fetal circulation. Therefore, it plays a critical role in the health of the developing fetus. The blood vessels in the developing placenta and the uterus that feeds it form a complex, and often tortuous, network of blood vessels. Clinically, in pregnancy, the complexities of these systems cannot easily be assessed. The mainstay of clinical imaging in pregnancy, ultrasound, typically measures only the function of the largest blood vessels in the system. However, the resolution of ex vivo imaging is much higher and the detail of the vascular system that can be captured ex vivo (after delivery) is rapidly increasing. Here I will present computational models that aim to understand how complexities observed in ex vivo imaging reflect at the organ scale. I will discuss techniques that we are employing to map ex vivo data to computational models, and trade-offs in modelling that need to be made to predict how the organ will respond to perturbations to the vascular structure of the placenta and uterus.

(Invited) Simple models of a complex fluid: Characterising rheology and transport in the blood with one-dimensional flows

Philip Pearce

UCL, UK

Blood is a complex fluid: its properties emerge from physical interactions at the levels of proteins and cells. It is often essential to account for the dynamics of these constituents for a mechanistic understanding of blood flow. However, in some cases, simple one-dimensional flow models can be applied to extract salient features of the blood from experimental data. In this talk, I'll discuss several applications of this approach, including characterising transport regimes in the placenta from images of vascular networks, and characterising blood rheology in sickle cell disease patients from measurements in a microfluidic device.

Physical and geometric determinants of transport in feto-placental microvascular networks

Alexander Erlich[1,2], Philip Pearce[3], Romina Plitman Mayo[4], Oliver Jensen[5], and Igor Chernyavsky[5]

[1]Institut de Biologie du Développement de Marseille (IBDM), France, [2]Institut de Recherche sur les Phénomènes Hors Equilibre (IRPHE), France, [3]Applied Mathematics, University College London, UK, [4]Department of Biological Regulation, Weizmann Institute of Science, Rehovot, Israel, [5]School of Mathematics, University of Manchester, Manchester, UK

What governs the supply of a human fetus with oxygen from the mother? We address this question with a model of the human feto-placental microvasculature. The physical setup in the human placenta is unique: the maternal and fetal blood supplies are separated by a thin layer of villous tissue (the syncytiotrophoblast), through which oxygen is exchanged by diffusion. Compared to other vasculatures, the capillaries are unusually loopy and bulged. Oxygen transfer from mother to fetus can be estimated using 3D finite-element simulations on realistic geometries. However, owing to the computational expense of such calculations, it is infeasible to perform them on entire feto-placental capillary networks. Instead, we introduce a reduced 1D network model to simulate blood flow and oxygen transfer in feto-placental capillary

networks efficiently. We validate the reduced model against full 3D computational fluid dynamics simulations on three-dimensional feto-placental geometries, obtained by confocal microscopy. The reduced model is used to study how network topology and vessel geometry affect oxygen transfer to the fetus. This reduced 1D flow and transport model of the feto-placental microvasculature may contribute to multiscale models of the placenta and other biological systems.

[1] A. Erlich, P. Pearce, R. Plitman Mayo, O. E. Jensen, I. L. Chernyavsky. Physical and geometric determinants of transport in feto-placental microvascular networks. Science Advances 5(4), eaav6326 https://doi.org/10.1126/sciadv.aav6326 (2019)

[2] A. Erlich, G. A. Nye, P. Brownbill, O. E. Jensen, I. L. Chernyavsky. Quantifying the impact of tissue metabolism on solute transport in feto-placental microvascular networks. Inerface Focus https://doi.org/10.1098/rsfs.2019.0021 (2019)

Theoretical model for focused-light-induced cytoplasmic streaming (FLUCS)

Weida Liao, and Eric Lauga

University of Cambridge, UK

Recent experiments in cell biology have probed the impact of artificially-induced intracellular flows in cell division and in the spatiotemporal organisation of cells and organisms [1]. Using focused light localised in a small region of the cell, a thermo-viscous flow is induced globally inside the cell. This so-called focused-light-induced cytoplasmic streaming perturbs physical transport processes, allowing the investigation of cellular organisation. To enable future use of this method, quantitative models need to be proposed to link the external light forcing to the produced flows. In this work, we present a fully analytical theoretical model of the fluid flow induced by the focused light. We model the effect of the focused light as a small temperature change induced locally in the fluid, which causes a small change in both the density and the viscosity of the fluid [2,3]. In turn, this results in a local compressible fluid flow. We analytically solve for the instantaneous flow field induced by the translation of a heat spot of arbitrary time-dependent amplitude along a scan path of arbitrary length. We show that the leading-order instantaneous flow field results from the thermal expansion of the fluid and is independent of the thermal viscosity coefficient. In particular, this leading-order velocity field is proportional to the thermal expansion coefficient and the size of the temperature perturbation imposed by the heat spot. The far field is typically dominated by a source or sink flow, proportional to the rate of change of the heat-spot amplitude. However, the net displacement of a material point due to a full scan of the heat spot is instead quadratic in the heat-spot amplitude and can be due to both thermal expansion and thermal viscosity changes. The corresponding average velocity of material points (shown in the figure) is a hydrodynamic source dipole in the far field, with direction dependent on the relative importance of thermal expansion and thermal viscosity changes. Our quantitative findings show excellent agreement with recent experimental results [4] and will help design new controlled experiments to establish the physiological role of physical transport processes inside cells, in particular for animal development.

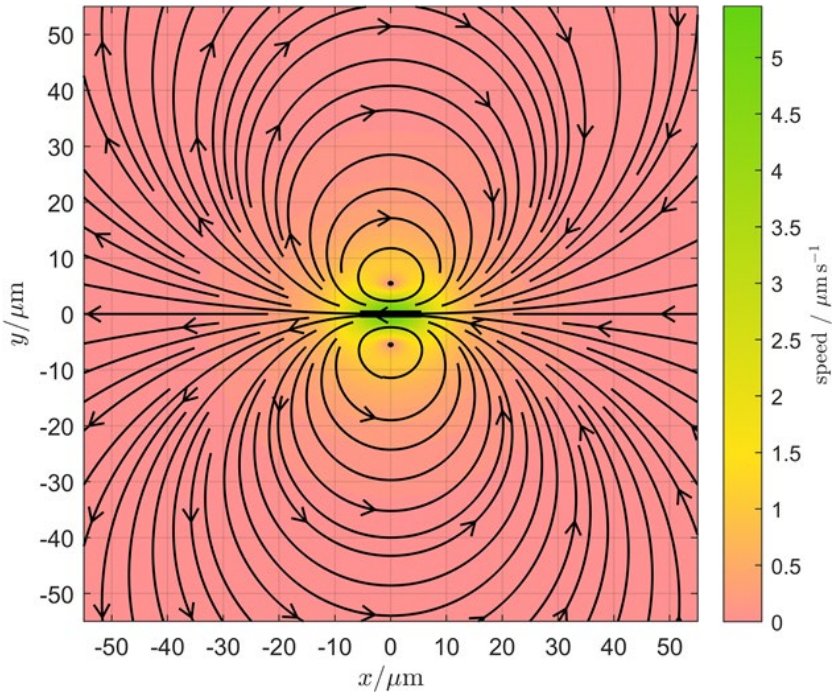

Figure 1: Theoretical average velocity of material points.

[1] Mittasch et al., Nat. Cell Biol., 20, 344 (2018).
[2] Weinert and Braun, J. Appl. Phys., 104, 104701 (2008).
[3] Weinert et al., Phys. Rev. Lett., 100, 164501 (2008).
[4] Erben et al., Opt. Express, 29, 30272 (2021).

Positron imaging for flow characterisation: towards the micro-scale

Tom Leadbeater, Steve Peterson, Andy Buffler, Ameerah Camroodien, Robert van der Merwe, and Mike van Heerden

University of Cape Town, South Africa

Positron imaging techniques are a class of hard-field quantitative measurements sensitive to the spatial concentration distribution of a suitably labelled radioactive tracer substance. Conventional Positron Emission Tomography (PET), whilst able to differentiate nano-molar concentration gradients, has relatively low spatial resolution and often measures the steady state or only slowly varying phenomena. For dynamic systems, Positron Emission Particle Tracking (PEPT) allows the tracking of a radioactive flow-following tracer particle entrained within a system of flow, enabling non-invasive study of dynamic systems across scientific disciplines. Typically, PEPT is used to examine conditions of turbulence at speeds up to 10 m/s, with high densities or high mass loading, or systems that are otherwise optically inaccessible.

On the micro-scale, PEPT performance is limited by the achievable activity in radiolabelling a suitable tracer particle, and the fixed geometry of conventional detector systems. In enabling the application of PEPT towards these scales, a hybrid detection system has been developed combining scintillator and semiconductor detector devices in an optimised geometry. A bismuth germanate oxide scintillator array consisting of 1024 detector pixels (4.1 x 4.0 x 30 mm) forms a field of view of 150 x 196 x 101 mm. A pair of pixelated cadmium zinc telluride room temperature semiconductors (9680 pixels of 1.8 x 1.8 x 0.5 mm) form a high spatial resolution region of 62 x 42 x 20 mm placed within the larger field of view. The design

choice maximises absolute efficiency by merit of the scintillators, and enhances spatial resolution through the semiconductors.

Initial results indicate the performance of PEPT in the study of microscale flows within the measurement volume and at low (<1 m/s) flow rate with position uncertainty on the 10s micron scale. Potential applications include characterisation of flows in capillaries and micro-fluidic devices.

(Keynote) Predicting blood cell trafficking in capillary vessel networks in silico: High fidelity modeling and machine learning applications

Prosenjit Bagchi

Rutgers University, USA

The primary function of the circulatory system is to supply oxygen and nutrients to tissues and scavenge cellular waste products. Red blood cells (RBCs), which constitute nearly 45% of the blood volume, serve as the oxygen carrier. The exchange of oxygen and other biochemicals between blood and tissues primarily occurs in the smallest blood vessels, known as capillary vessels. Together with their upstream and downstream vessels known as arterioles and venules, and vascular junctions, capillaries form architecturally complex vascular networks, also referred to as microvascular networks. Prior in vivo studies have shown that the distribution of blood flow and RBCs in a network is both spatially and temporally heterogeneous, although the physical mechanisms underlying this remain under investigation. The knowledge of how RBCs and blood flow are distributed in a microvascular network is of immense pathophysiological importance. Although recent advances in imaging techniques have enabled mapping of many capillary vessels in vivo, direct measurements of spatially and temporally resolved RBC and flow distribution are possible only over relatively small tissue volumes. To overcome this limitation, theoretical models of network blood flow are often used to obtain flow and RBC distribution in large microvascular networks after image acquisition. Such models, however, have limitations as they treat each blood vessel as a 1D segment, and they do not directly predict cell-cell and cell-vessel interactions that can affect cell and flow distribution. Recently, our group has developed a high-fidelity computational model that accurately predicts 3D deformation of each of nearly a thousand red blood cells flowing in physiologically realistic microvascular networks in silico that are comprised of multiple vessels and bifurcations retaining complete 3D geometric details as observed in vivo.

In this talk, first an overview of the computational method will be presented. This will be followed by results on the cellular-scale mechanisms causing network-wide heterogeneous spatial and temporal distributions of RBCs. Next, the influence of reduced RBC deformability on altering such mechanisms will be discussed. In the last part of the talk, we will discuss the applicability machine learning techniques to the prediction blood flow and RBC distributions in microvascular networks over longer times.

(Invited) Flows shaping network architecture

Karen Alim

TU Munich, Germany

Vascular networks constantly reorganize to optimize function. Some veins grow, others shrink and disappear. How can a local adaptation mechanism account for the plethora of vein dynamics observed? Here, we quantify network-wide vein dynamics in the slime mold Physarum polycephalum. We identify that flow shear stress is driving adaptation yet with a time delay. Vein fate, however, depends, beyond shear stress, on the

vein's connections to the network and relative position. Finally, as network architecture constantly changes vein fate is dynamic driving overall network reorganization including avalanches of vein disappearance. Addition of external stimuli on top drives vein adaptation dynamics – imprinting the stimuli location into the network architecture. The memory of the stimulus location within the network architecture is retained during network reorganization and impacts overall network function.

(Invited) Platelet margination and flow dynamics in healthy and diabetic microcirculation

Gábor Závodszky

University of Amsterdam, The Netherlands

Blood is the single most important fluid in the human body. It has an important role in most healthy and pathologic processes. Yet many of its properties are not fully understood, primarily due to its complex cellular nature. The interactions between the individual cells give rise to a series of important phenomena, such as platelet margination, plasma skimming, the Fåhræus–Lindqvist effect, and the formation of a cell free layer.

Such processes are fundamental in understanding the progression of several healthy and pathologic events occurring on the level of the microcirculation. In recent years, the increase in the available computational capacity made the detailed simulation of cellular flows possible, including the deformation and interaction of the cells. In the current talk I will introduce some of the recent results obtained by combining experimental works with simulations, carried out with our open-source cellular simulation HemoCell (www.hemocell.eu). I will focus on the cellular trafficking of the two most numerous components, red blood cells and platelets. The aim will be to investigate the effects of the increased rigidity of diabetic red blood cells on platelet margination, the increase in wall shear stress in real retinal microaneurysms as cells are transported, and the effect of curved and stenosed geometries on high shear rate platelet aggregations. For all these cases the simulations are deployed to complement the information available from microfluidic experiments by providing further detailed insight into the parameters. The combination of *in vitro* and *in silico* information helps to further our understanding on the respective pathologies.

Numerical simulation of cellular blood flow in canonical disordered porous media

Qi Zhou, Miguel Bernabeu[1], and Timm Krüger[1]

University of Edinburgh, UK

Extensive research has been conducted on fluid flows through porous media, ranging from pore-scale, Darcy-scale to field-scale. However, the mechanisms underpinning the flow of blood and the associated transport of solutes in biological tissues/organs such as the highly porous human placenta are still unclear [1]. As the flow passages within these systems become comparable to the size of a red blood cell (RBC, which is 8 μm in diameter), the cellular character of blood introduces non-trivial spatiotemporal heterogeneities in the system that require microscopic interrogation. In this work, we aim to characterise the microscopic blood flow within canonical porous media consisting of disordered pillar arrays.

The porous media geometries, both heterogeneous and highly confined, are constructed by introducing an incremental level of disorder to regular obstacle arrays originally arranged on a square grid following [2]. Based on the lattice Boltzmann and immersed boundary methods [3], we model three-dimensional cellular blood flow through the disordered porous media as a suspension of deformable RBCs in plasma [4]. The simulated porous media have a porosity of 57%-67% and the volume fraction of RBCs (known as haematocrit) within is in the range of 10%–30%.

Our results demonstrate an intricate interplay of structural disorder, rheological property, and time-dependent effects on the localisation of RBCs within the porous media, which is of high-level heterogeneity and characteristic of preferential paths subject to the “channelling effect” [5] together with emerging phenomena such as channel occlusion by cells. We report the effect of incremental disorder on the hydrodynamic resistance of the porous media, which exerts a much stronger influence on the cellular blood flow than its Newtonian counterpart (where only plasma is present). We further elucidate how the RBC dynamics contributes to the network flow distributions under different levels of disorder.

The role of RBCs in the intervillous space of the human placenta (complex porous media) is multifold. On the one hand, RBCs facilitate the transport of gases and other solutes. On the other hand, the RBCs’ localisation can substantially affect the flow patterns in the porous media. To bridge microscopic characterisation and tissue/organ-level modelling, generalised constitutive relationships need to be derived through cross-validation of simulations and experiments.

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Liquid flow through nanoporous media: non-linear response and blocking

Msc Roya Ebrahimi Viand[1] and Felix Höfling[1,2]

[1]Freie Universität Berlin, Germany, [2]Zuse Institute, Germany

Regarding molecular transport, the heterogeneous and crowded environments inside of cells have close analogies to structures found in porous media [1]. In addition to diffusion [2], directed flow is a major transport mechanism in porous media. Such flows can either be generated by molecular pumps (such as molecular motors) or they emerge in response to a gradient of pressure. The pressure-flow relation and how it depends on the structure and geometry of the medium is of central importance for the understanding and control of such flows.

We have employed non-equilibrium molecular dynamics (NEMD) simulations to study the flow of dense liquids through regular bead packings as a model for a nanoporous medium [3]. Upon decreasing the porosity of the medium, which is a measure for the volume fraction accessible to the fluid, we find a significant non-linear response, beyond Darcy's law. The linear permeability varies over two orders of magnitude and vanishes beyond a critical porosity. Our large-scale NEMD simulations further exhibit a substantial increase of temperature inside of the porous medium, which we attribute to energy dissipation in the medium and energy conservation outside of it.

In the simulation set-up of boundary driven flows, we have implemented non-equilibrium reservoirs at the boundaries by means of a local thermostat that also acts as a pump. Combining with a state-of-the-art NEMD approach based on the adaptive resolution simulation technique [4,5], the required simulation volume can be decreased considerably. This simulation approach is expected to be highly applicable for research on flow in porous as well as biological media.

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[2] M. Spanner, F. Höfling, S. C. Kapfer, K. R. Mecke, G. E. Schröder-Turk and T. Franosch, Phys. Rev. Lett. 116, 060601 (2016)
[3] R. Ebrahimi Viand and F. Höfling, (2022) Manuscript in preparation
[4] R. Ebrahimi Viand, F. Höfling, R. Klein and L. Delle Site, J. Chem. Phys. 153, 101102 (2020)
[5] R. Klein, R. Ebrahimi Viand, F. Höfling and L. Delle Site, Adv. Theory Simul. 4, 2100071 (2021)

Collective motion in two-dimensional microswimmer suspensions

V Škultéty[1], Cesare Nardini[2], Joakim Stenhammar[3], Davide Marenduzzo[1], and A. Morozov[1]

[1]SUPA, School of Physics and Astronomy, The University of Edinburgh, UK, [2]Service de Physique de l'État Condensé, CNRS UMR 3680, France [3]Division of Physical Chemistry, Lund University, Sweden

A collection of microswimmers immersed in an incompressible fluid is characterised by strong orientational interactions due to the long-range nature of the hydrodynamic fields generated by individual organisms. As a result, suspensions of swimmers may exhibit a state often referred to as collective motion or 'bacterial turbulence', which is dominated by jets and vortices comprising many microswimmers. The onset of collective motion can be understood within the mean-field kinetic theory for dipolar swimmers. In 3D, the theory predicts that the instability sets in at the largest scale available to the suspension.

While the main focus of previous theoretical studies was on 3D unconfined suspensions, the majority of collective motion experiments are performed next to solid boundaries. To understand the effect of such

quasi-2D confinement, we develop a modified kinetic theory for a suspension of microswimmers confined to a 2D plane embedded in a 3D fluid. The key feature of the model is the presence of an effective fluid in-plane compressibility. We analyse the stability of the homogeneous and isotropic state, and observe a new type of instability associated with strong density fluctuations, that is absent in bulk 3D systems. The orientational instability present in 3D is found as well, although any instability arising in quasi-2D appears to set in at the smallest accessible scale. Our results are in a qualitative agreement with recent Lattice-Boltzmann simulations.

(Keynote) Spatial distribution of red blood cells in periodic microfluidic networks

Sylvie Lorthois

IMFT, France

The physics of blood flow in small vessel networks is dominated by the interactions between Red Blood Cells (RBCs), plasma and blood vessel walls. The resulting couplings between the microvessel network architecture and the heterogeneous distribution of RBCs at network-scale are still poorly understood. Here, we elucidate how a local effect, such as RBC partitioning at individual bifurcations, interacts with the global structure of the flow field to induce specific preferential locations of RBCs in model microfluidic networks [1]. First, using experimental results, we demonstrate that persistent perturbations to the established hematocrit profile after diverging bifurcations may bias RBC partitioning at the next bifurcations. By performing a sensitivity analysis based upon network models of RBC flow, we show that these perturbations may propagate from bifurcation to bifurcation, leading to an outsized impact of a few crucial upstream bifurcations on the distribution of RBCs at network-scale. Based on measured hematocrit profiles, we further construct a modified RBC partitioning model that accounts for the incomplete relaxation of RBCs at these bifurcations. This model allows us to explain how the flow field results in a single pattern of RBC preferential location in some networks, while it leads to the emergence of two different patterns of RBC preferential location in others. Our findings have important implications in understanding and modeling blood flow in physiological and pathological conditions.

[1] A. Merlo, M. Berg, P. Duru, F. Risso, Y. Davit and S. Lorthois. A few upstream bifurcations drive the spatial distribution of red blood cells in model microfluidic networks. *Soft Matter* 18, 1463–1478 (2022).

(Invited) Understanding form and function in vascular tumours

Helen Byrne

University of Oxford, UK

Over the past twenty-five years we have witnessed an unparalleled increase in understanding of cancer. At the same time, mathematical modelling has emerged as a natural tool for unravelling the complex processes that contribute to the initiation and progression of tumours, for testing hypotheses about experimental and clinical observations, and assisting with the development of new approaches for improving its treatment. In this talk I will reflect on how increased access to experimental data is stimulating the application of new theoretical approaches for studying tumour growth. I will focus on two case studies which illustrate how

mathematical approaches can be used to characterise and quantify tumour vascular networks, and to understand how microstructural features of these networks affect tumour blood flow.

(Invited) The role of capillary diameter alterations during health and disease -insights from blood flow modelling

Franca Schmid[1,2], R Epp[1], B Weber[2] and P Jenny[1]

[1] Institute of Fluid Dynamics, ETH Zurich, Switzerland, [2] Institute of Pharmacology and Toxicology, University of Zurich, Switzerland

Capillaries are the most frequent vessel type of the brain vasculature. As such, the highly interconnected capillary bed is the key location to ensure a robust blood and oxygen supply during baseline and neuronal activation. Nonetheless, despite its relevance, our knowledge of structural and functional properties of the capillary bed remains limited. Our key goals are 1) to improve our understanding of the role of capillaries for the up-regulation of flow and 2) to identify factors contributing to the robustness of capillary perfusion. To attain these goals we perform bi-phasic blood flow simulations in realistic microvascular networks. Throughout our investigations a specific focus is on the impact of red blood cells (RBCs).

During baseline the flow field of the cortical capillary bed is characterized by a large heterogeneity in flow velocities and RBCs densities (1). Based on *in silico* and *in vivo* investigations we show that the presence of RBCs reduces this heterogeneity at the scale of individual divergent bifurcations (2). This is also relevant for single capillary dilations, where the precise response depends on the relative bulk flow velocity difference at the upstream divergent bifurcation. At bifurcations with a low relative velocity difference the number of RBCs increases more in the dilated branch than at bifurcations with a high relative velocity difference. On average a capillary dilation of 10% leads to a flow increase of 23% (per 100 µm) and an increase in the number of RBCs of 20% in the dilated capillary. As such, single capillary dilation has the potential to locally increase the flow rate and redistribute RBCs. Moreover, diameter adaptations at the level of capillaries prove to be indispensable for a very fine-tuned up-regulation of flow (3). Nonetheless, to increase the total inflow by ~25% in a microvascular network embedded in a tissue volume of 1 mm^3 all capillaries need to dilate by 10%. Consequently, active capillary dilation might be relevant for a localized redistribution of flow and RBCs, but is likely not the driving force to induce an overall increase in perfusion.

As evidence increases that disturbances at capillary level are relevant for pathologies like Alzheimer's disease and stroke, we study flow changes in response to single capillary occlusion (4). Comparable to single capillary dilations, the effects of a microstroke are most pronounced in the direct vicinity of the microstroke capillary (MSC) and the severity is governed by the local vascular topology. The largest changes are observed for a MSC with a convergent bifurcation upstream and a divergent downstream (*2-in-2-out*). Here, the flow rate drops by 70% in the directly adjacent vessels and is still reduced by 20% in generation ±3 from the MSC. Significantly, smaller changes are observed for a MSC with a divergent bifurcation upstream and a convergent bifurcation downstream (*1-in-1-out*). Interestingly, MSCs of type *2-in-2-out* are considerably less frequent than MSCs of type *1-in-1-out*. Moreover, they supply a significantly smaller tissue volume with oxygen and nutrients. Therewith, our results suggest that the perfusion of the capillary bed is inherently robust to single capillary occlusions. Moreover, we hypothesize that the different topological configurations might fulfil distinct structural and functional tasks.

Taken together, our investigations provide evidence that capillary alterations impact perfusion characteristics on the local and the global scale, during baseline and activation as well as during health and disease.

[1] Schmid F, Tsai PS, Kleinfeld D, Jenny P, Weber B. Depth-dependent flow and pressure characteristics in cortical microvascular networks. PLOS Computational Biology. 2017;13(2):e1005392.
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[3] Epp R, Schmid F, Weber B, Jenny P. Predicting vessel diameter changes to up-regulate biphasic blood flow during activation in realistic microvascular networks. Frontiers in Physiology. 2020;11:566303.
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(Invited) Computational fluid dynamics modeling and simulation of gastric mixing and emptying in the human stomach

Yohsuke Imai

Kobe University, Japan

The stomach is the digestive organ between the esophagus and the duodenum. The stomach is subdivided into the fundus, corpus, and antrum, and the antrum is connected to the duodenum by the pylorus. The primary roles of the stomach are storage, mixing, and emptying of gastric contents. Gastrointestinal motor functions, including the peristaltic and tonic contractions of the stomach, and the opening and closure of the pylorus, modulate gastric mixing and emptying. Proper coordination of the gastric motor functions is essential for health, but pyloric opening and closure may be impaired by functional disorders or surgical procedures. In addition, the amplitude and frequency of peristaltic contractions may be altered in functional dyspepsia patients. It is thus important to understand how impaired gastric motor functions affect the transport of gastric contents. We have developed a computational fluid dynamics (CFD) model of gastric flow (Imai et al., Am. J. Physiol. Gastrointest. Liver Physiol., 2013; Berry et al., Am. J. Physiol. Gastrointest. Liver Physiol., 2016; Miyagawa et al., Am. J. Physiol. Gastrointest. Liver Physiol., 2016; Ishida et al., J. Roy. Soc. Interface, 2019; Wang et al., Physiol. Rep., 2021). We used an anatomically-realistic geometry of the human stomach. Gastric wall motions are prescribed based on previous experimental data, and are given as moving boundary conditions. Gastric contents are modeled by incompressible Newtonian fluids. The lattice Boltzmann method with an interpolated bounce-back scheme is used for graphics processing unit (GPU) computing of gastric flow. Using this model, we have investigated how the gastric wall motions promote gastric mixing and emptying. In this workshop, we will present our recent results, particularly focusing on the coordination between the antral contractions and the pyloric opening and closure (Ishida et al., J. Roy. Soc. Interface, 2019), and the amplitude and frequency of peristaltic contractions (Ebara et al., submitted).

Microfluidic model of micro-haemodynamics

Qi Chen[1, 2], Naval Singh[1, 2], Kerstin Schirrmann[1, 2], Igor Chernyavsky[3, 4], and Anne Juel[1, 2]

[1]Manchester Centre for Nonlinear Dynamics, University of Manchester, UK, [2]Department of Physics and Astronomy, University of Manchester, UK, [3]Department of Mathematics, University of Manchester, UK
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The human placenta is an essential organ for the developing fetus, which relies on well-orchestrated haemodynamics to deliver its multiple functions [1]. The geometrical complexity of the placenta and lack of appropriate animal models mean that biomimetic laboratory models offer a powerful tool to investigate haemodynamics and haemorheology in the human placenta and other complex biological tissues [2, 3]. The placental microstructure is effectively a porous medium where the particulate nature of red blood cells (RBCs) is important. However, particle transport and its influence on permeability remain unexplored.

We use droplet and capsule suspensions in planar microfluidic porous media to explore the transport of deformable particles, with the aim of characterising rheology in this setting. Droplets are the simplest RBC analogues but they lack the shear elasticity of the real RBC. In addition, undesired coalescence and breakup limit their use in experiments. A better biomimetic model of RBC is provided by polydimethylsiloxane (PDMS) capsules of adjustable diameter and wall thickness, which are microfabricated using a 3D nested glass capillary device. Their elastic modulus can be varied by an order of magnitude by adjusting the chemistry and the capsules can further be deflated by osmosis to match the area to volume ratio of real RBCs. We test the aptitude of these objects to mimic the motion and large deformations of single red blood cells and of suspensions of RBCs in straight capillaries and arrays of contractions and expansions. Planar porous media of controlled geometry, porosity and different levels of disorder are then constructed by positioning cylindrical pillars in different spatial arrangements within a Hele-Shaw channel. Suspension flows are characterised in terms of the dynamic capsule distribution, flow resistance and permeability as functions of haematocrit (concentration of capsules), capsule geometry, disorder of the medium and capillary number, which provides a measure of the importance of viscous shear forces relative to elastic forces.

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Network effect of vessel compression on the partitioning of red blood cells at bifurcations in vascular networks

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The tumour microenvironment is reported to have numerous abnormalities in vessel structure[1]. These abnormalities have been correlated to a deteriorated patient prognosis as well as tumour tissue hypoxia[2]. Tumour tissue hypoxia in tumours is undesirable as it develops more aggressive tumour phenotypes and is a barrier to treatment efficiency[2]. Vessel compression is one specific phenotype within tumours and causes the abnormal partitioning of red blood cells at a single vascular bifurcation[3]. In this work we show how

vessel compression leads to haematocrit heterogeneity in a vascular network. Due to red blood cells' role in the transport of oxygen in blood, this work provides a mechanism leading to tumour tissue hypoxia.

We model the blood flow though the vessel network using Poiseuille's law, an empirical relation for blood viscosity, and the Pries model for the partitioning of red blood cells at bifurcations. This is a previously developed and validated model[4]. To replicate the effect of a compression on the abnormal partitioning of red blood cells at a bifurcation, we adapt a term in the Pries model through data generated from fully resolved particulate blood flow simulations in HemeLB[5] (https://github.com/hemelb-codes/hemelb).

We investigate how the abnormal partitioning due to a compression at a bifurcation propagates at a network level. Our results show that in a vascular network where a region of the vessels are treated as being compressed, the compressed vessels have a reduced average haematocrit compared to a control simulation with no compressed vessels. Furthermore, the compressed vessels have a wider distribution of haematocrit. We find that the changed haematocrit in the compressed vessels is the consequence not only of the increased resistance to flow in the compressed part of the network, but also the direct effect of the compression on the abnormal partitioning of red blood cells.

In this work, we show a direct biophysical link between vascular compression in networks and haematocrit heterogeneity. This link could be a reason that tumour tissue is hypoxic. Due to the importance of tissue hypoxia in patient prognosis, an improved understanding of the mechanisms leading to tissue hypoxia is important to develop improved therapeutic approaches.

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