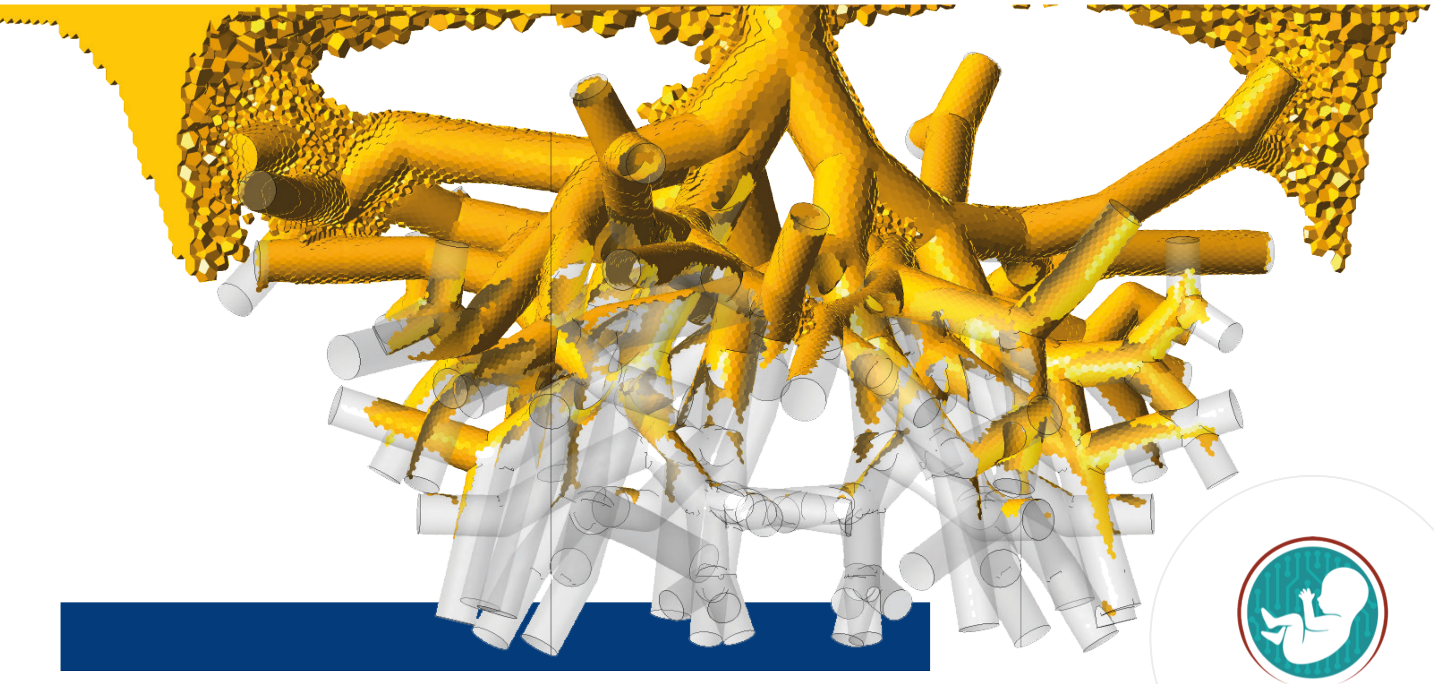

Modelling the placental villus and fluid field

by Francesco Franchini[1], Novella Saccenti[1], Erik Mazzoleni[1], Daniele Cortesi[1], Carla Baldasso[1], Alessandra Manzin[2], Riccardo Ferrero[2]
1. EnginSoft - 2. INRiM - Department of Advanced Materials Metrology and Life Science

How to model the complex geometry of the villus and surrounding fluids

The work presented in this article is part of the LIFESAVER project funded by the European Union and executed by the two main partners, the National Metrology Institute of Italy (INRiM) and EnginSoft.

The LIFESAVER project aims to simulate the structure and function of the placenta at the end of the first trimester (approximately 12 weeks of gestation) to simulate the transport of substances from the mother to the foetus. Little technical information is available in the literature on the structure and function of human placenta at this early stage of development.

The goal of the LIFESAVER project is to create and demonstrate a new, digitally cloned in vitro system to mimic prenatal conditions near the placental interface that can predict the risk of foetal exposure to a drug or chemical.

The focus is on a digital twin of the placenta, specifically the exchange of substances from the maternal to the foetal domain. The article briefly describes the geometries of a villus structure generated by INRiM and how these geometries were used to calculate the velocity and pressure fields and the mean residence time of blood in the domain.

Two different geometries and two different physical models were used to find the best fit, targeting fluid behaviour and residence time predicted from the literature. The blood residence time in the intervillous space (IVS) was derived from the literature and used as a guide to configure the porosity and permeability fields. INRiM created the geometry by following the expected structure of a first trimester human placental villus and then used it as the core of the computational fluid dynamics (CFD) simulations. CFD simulations of blood entry and diffusion within the domain were performed using commercial software.

Background: the LIFESAVER project

Pollution from microplastics, chemicals, and antibiotics has become a serious environmental problem over the past decade, posing a threat to human health, including the unborn. However, little is known about the effects on pregnant women and their foetuses when exposed to these pollutants or drugs. The placenta, which is essential for protecting the foetus by allowing essential nutrients and oxygen to pass through, unfortunately also allows harmful substances to reach the foetus. For example, microplastics have been found on both the maternal and foetal sides of the placenta.

Tests on pregnant women are ethically prohibited and tests on animals are ineffective because their placentas behave differently from human placentas. The LIFESAVER project, led by EnginSoft, will fill this knowledge gap. The project aims to develop a laboratory system that can predict how chemicals cross the placenta. The approach is based on the hybridization of several innovative

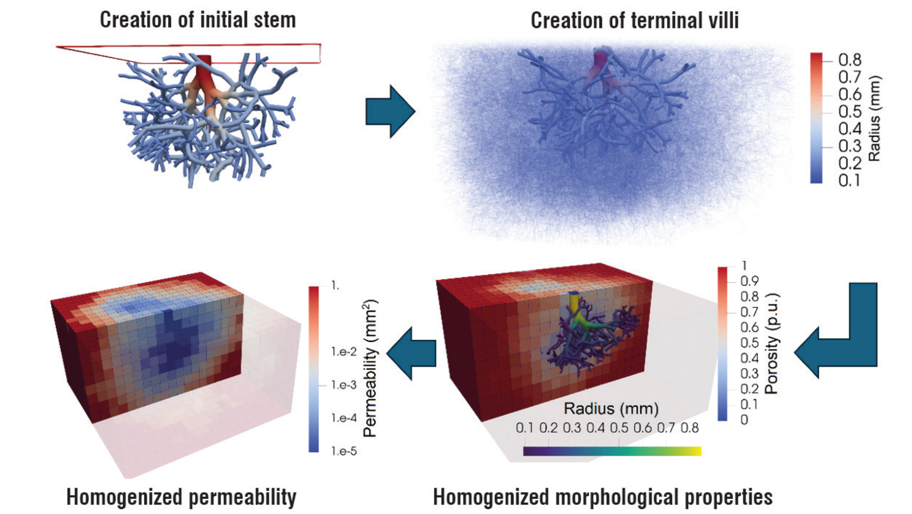

Fig.1. Diagram of the process used to generate the IVS space and determine the homogenous hydraulic properties for simulating porous flow.

technologies, integrating "biodigital twin" systems with perinatal derivatives to enable effective screening of chemicals and pharmaceuticals.

EnginSoft's role is to develop the biodigital twin, which simulates the fluid dynamics of maternal and foetal blood and, thanks to sophisticated machine learning algorithms, is able to predict in silico the diffusion of chemicals across the placenta. The high-fidelity biodigital twin was created in collaboration with INRiM, which provided a detailed model of the villi and the transport kinetics.

Geometry of a villus tree

INRiM generated a 3D structure of the villus and intervillous space (IVS) using the developed fractal algorithm based on the parametric formalism of the Lindenmayer system (L-system), resulting in a complex villus structure with a realistic villus surface-to-volume ratio. Initial parameters for setting up the fractal algorithm, such as initial villus radius, bifurcation strategy, and villus length, were derived from placental structure data collected from literature reviews.

Since the derived geometry cannot be handled by a full Navier-Stokes CFD approach, the computational complexity was overcome by introducing a simplified model in which part of the domain under study was treated as a porous media with multiple levels of porosity. The structure of the villi is simplified and only the main branches obtained from the first seven bifurcation steps are meshed. In the remaining part of the volume, equivalent homogenized properties are derived from the full villus structure.

In particular, this part of the IVS is divided into a grid of 20x20x20 cells. In each cell, equivalent structural/morphological properties such as equivalent villus diameter, equivalent villus length, and porosity were calculated.

Based on these properties, two porosity models were applied to obtain the corresponding equivalent hydraulic conductivity as input for solving the simplified Darcy equation in the porous domain. The first model is based on the well-known Carman-Kozeny equation, which is best suited for oriented fibre structures.

Therefore, we chose a second model, proposed by Nabovati et al. [1] for randomly oriented fibre structures, which is more appropriate for describing the structure of villi.

INRiM designed two geometric shapes, which EnginSoft used for the CFD simulations. These are: 1) the 3D model of the intervillous space, consisting of the main trunk of the villus branch plus an entrance artery and two exit veins, and 2) the 20x20x20 cell grid of the remaining volume, with equivalent homogenized properties obtained with the Carman-Kozeny and Nabovati models.

The computational model of fluids around the villus

Fluid dynamic simulations can be used to calculate important parameters such as residence time and pressure losses. Ansys software was used for these simulations.

The flow through the porous region is modelled by adding a viscous loss term to the standard fluid flow equations. This term is modelled by Darcy's law, which states that the pressure drop is proportional to velocity and hydraulic conductivity.

Since the physically present volume block is not represented in the model, the simulations report a surface velocity within the porous

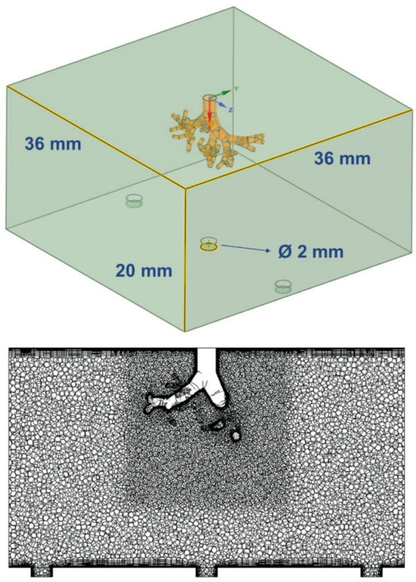

Fig.2. Geometry and meshing for Cases 1 and 2.

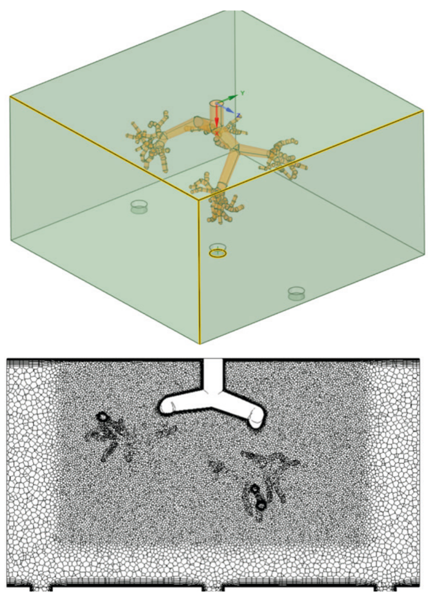

Fig.3. Geometry and meshing of Case 3.

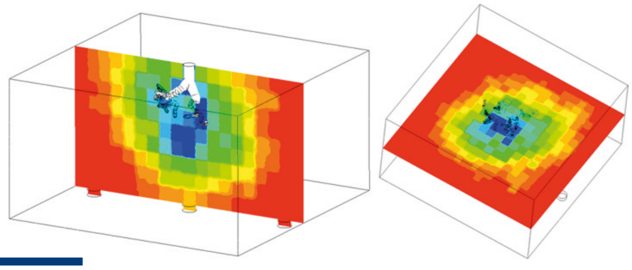

Fig.4. Case 1 porosity field.

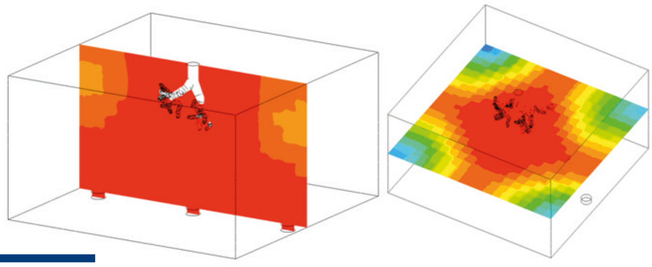

Fig.5. Case 2 porosity field.

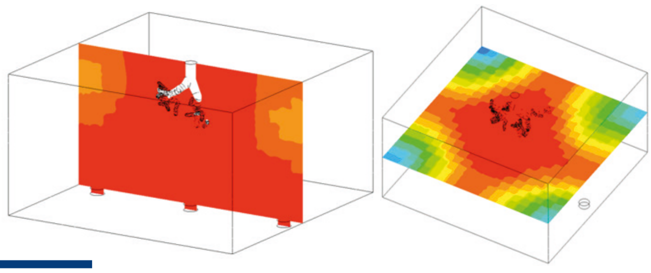

Fig.6. Case 3 porosity field.

medium based on the volume flow rate to ensure continuity of the velocity vectors across the interface of the porous medium.

In Case 1, the CFD simulation results highlight the presence of extensive areas of stagnant flow. This provided experimental evidence for the need to include a region of less restricted flow in front of the inlet artery, as suggested in previous work. To this end, INRiM modified the fractal algorithm used to generate the villus structure to include this feature. A flow rate of 0.0628ml/min was used as input.

In Case 2, the villus geometry is a modified version of the first geometry (Case 1), obtained by preserving the original first branches and including a rearrangement of the others to limit the presence of possible stagnant areas. A flow rate of 0.0619ml/min was set at the inlet.

In Case 3, a completely revised villus geometry was developed, fine-tuning the parameters of the fractal algorithm to achieve a more homogeneous villus structure and reconfigure the first two bifurcations to allow more space for flow to develop before the inlet. A flow rate of 0.0606ml/min was set at the inlet.
INRiM provided the porosity and permeability domains that EnginSoft used for each case, as explained in Figs 4–9.

The fluid domain is a 36x36x20mm^3 volume, characterized by a villus structure at the top, a central circular inlet and two lateral circular outlets at the bottom, each 2mm in diameter. The boundary conditions and fluid properties were taken from the literature and from

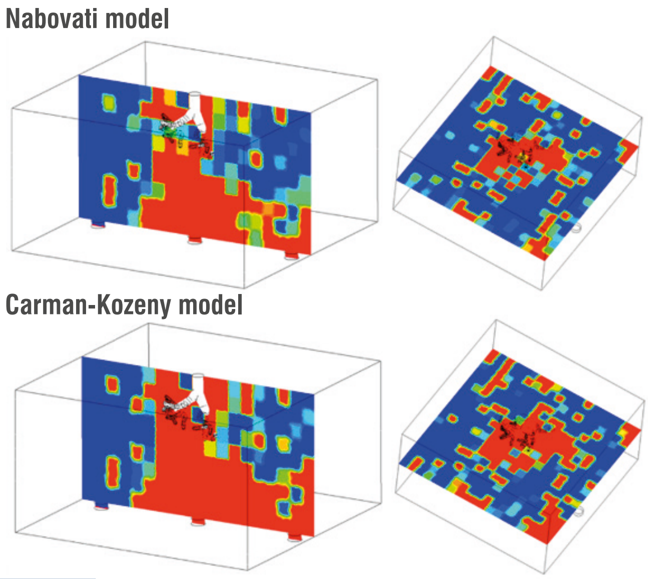

Fig.7. Case 1 permeability field.

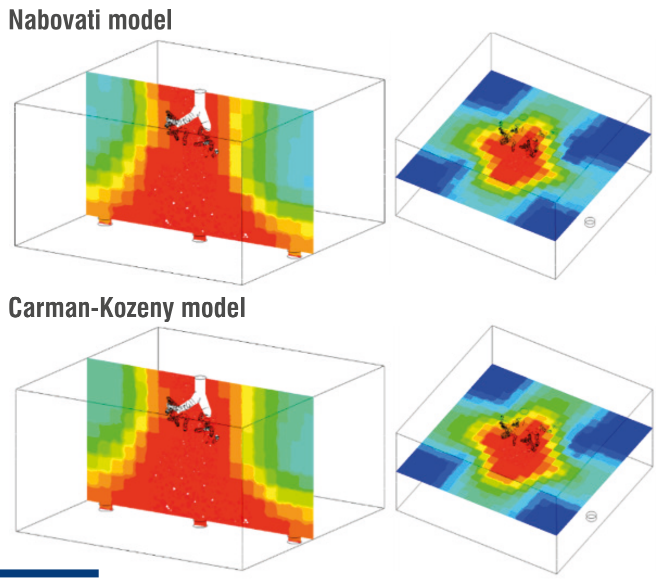

Fig.8. Case 2 permeability field.

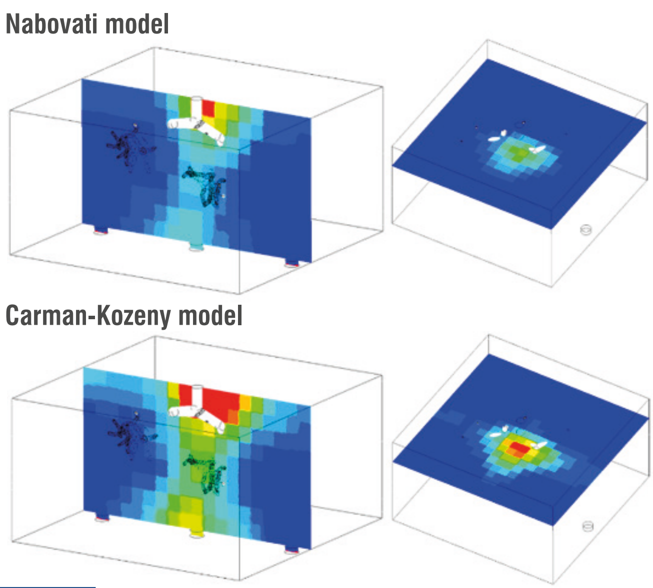

Fig.9. Case 3 permeability field.

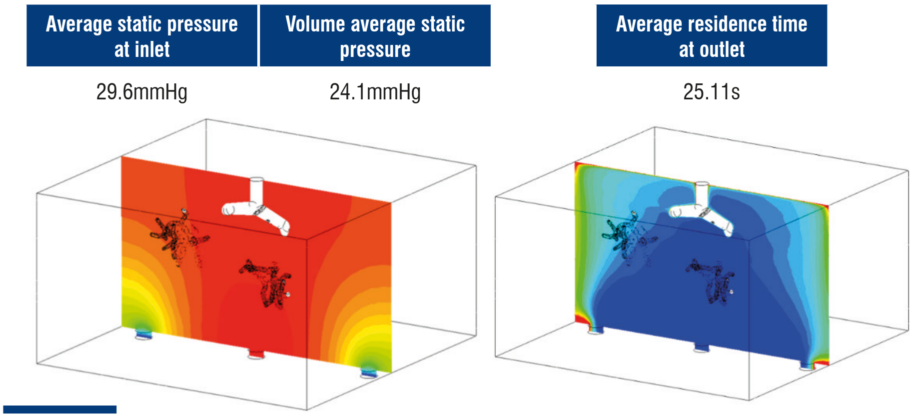

Fig.10. Case 3 - Nabovati pressure field and residence time.

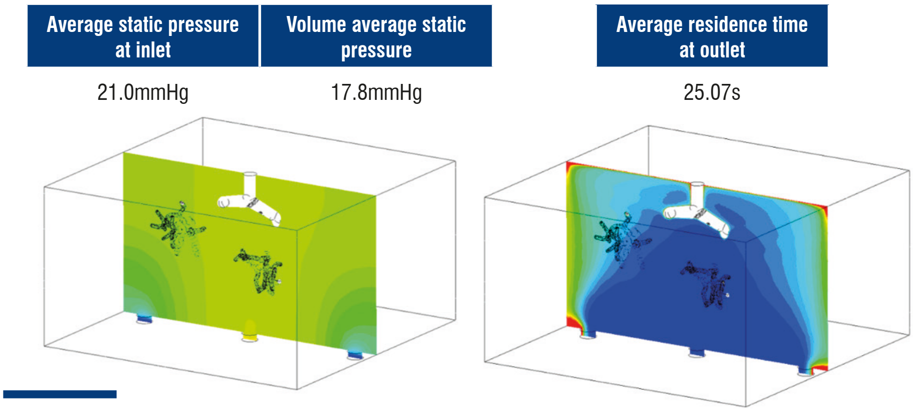

Fig.11. Case 3 - Carman-Kozeny pressure field and residence time.

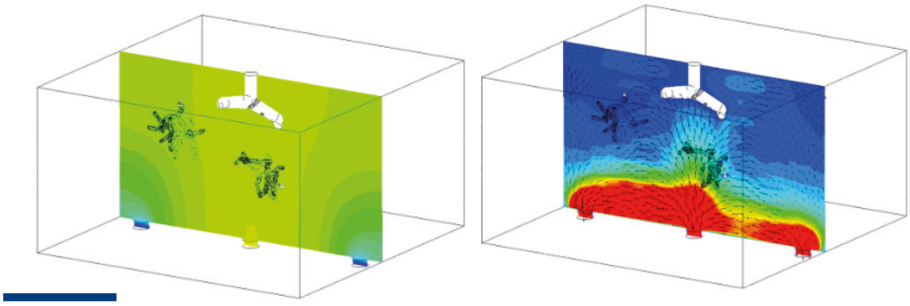

Fig.12. Pressure and velocity distributions for Case 3, using the Carman-Kozeny model.

research conducted by other LIFESAVER partners, with the viscosity of maternal blood modelled using the Carreau fluid equation and a density of 1055kg/m^3.
The outlet pressure was set at 5mmHg, while the inlet flow rate was calculated by implementing an optimization algorithm to obtain an average residence time of 25 seconds. The mesh generated consists of approximately 1–2 million polyhedral elements, depending on the geometry, with a minimum orthogonal quality of 0.1.

The Nabovati and Carman-Kozeny models were applied to each of the three cases and the best case was selected by analysing the velocity, pressure, and residence time fields and comparing the two models.

Conclusions

The modelling of the intervillous space in the first placental trimester was conducted to obtain a digital representation of the local fluid dynamics. INRiM and EnginSoft worked together to achieve this goal: INRiM developed two villus geometries using fractal algorithms and associating the correspondent permeability and porosity fields; EnginSoft performed the CFD simulations of the three cases (geometry 1 + porosity and permeability field 1; rearrangement of geometry 1 + porosity and permeability field 2; geometry 2 + porosity and permeability field 3).

In Case 1, a heterogeneous permeability map with values close to 1 or 0 and a low porosity in the centre of the fluid domain caused flow blockage and an increase in inlet pressure. Stagnation zones were found above the villus structure with residence times exceeding 1,000 seconds.

In Case 2, a more linear permeability map, with high values at the centre and decreasing values towards the corners, allowed continuous flow with low pressure gradients. The stagnation zones were limited to the corners where the residence time was around 100 seconds.

Case 3 is characterized by a permeability map with low values throughout the domain, resulting in higher pressure levels but no significant stagnation zones due to a more uniform porosity distribution. The difference between the Nabovati and Carman-Kozeny models was evident in the pressure distribution and residence time in this case.

In conclusion, Case 3 with the Carman-Kozeny model proved to be the most efficient, demonstrating a shorter fluid residence time without flow blockage and a pressure distribution within the IVS consistent with the data collected in the literature.

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[1] I. L. Chernyavsky, O. E. Jensen, and L. Leach, "A Mathematical Model of Intervillous Blood Flow in the Human Placentone", *Placenta* 31, 44–52 (2010).

For more information:
Novella Saccenti – EnginSoft
n.saccenti@enginsoft.com