

1 Flow and Transport in the Placenta

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Abstract

The Study Group was asked to develop a mathematical model of flow and nutrient delivery within the placenta. Such a model could be used to relate the physical properties of the placenta (such as the morphology and deformability of fetal blood vessels, pressure and flow characteristics of the maternal and fetal circulations) to oxygen delivery, in the overall context of intrauterine growth deficiency.

A simple compartmental model was developed to describe the effect of blood jetting out of a maternal spiral artery on a single deformable villous tree (a group of fetal blood vessels). The permeability of the tree was lumped into a single variable that depends on transverse expansion (as neighbouring branches of the tree are moved apart by the flow) and streamwise compression. Accounting also for elastic restoring forces and the tree's inertia, the problem reduced to that of a forced, damped nonlinear oscillator. Simple estimates of nutrient delivery to the fetus may be obtained from this model. The model highlights a number of important and interesting areas for future work.

1.1 Introduction

This problem is concerned with blood flow and nutrient delivery in the placenta. We were given information about healthy and diseased placentas, and presented with MRI results [3] indicating different flow patterns in normal and abnormal placentas. We were challenged to develop mathematical models that relate placental blood flows to the exchange of oxygen, nutrients and waste products between the fetus and mother.

In a normal, human placenta [1] the fetal and maternal blood systems are separate, but in intimate contact. The fetal arteries branch and subdivide into root-like structures called villi, which bathe in pools of maternal blood called cotyledons. A placenta may contain between 10 and 200 cotyledons, each associated with one or more fetal villous trees (also known as placentones) and at least one maternal artery that spurts fresh blood into the cotyledon. A full-term placenta may contain 100 maternal arteries and between 50 and 200 maternal veins. The fetal villi are not completely rigid, being pushed by the vigorous squirting of blood from the maternal arteries (like seaweed in tide-pools, or trees blowing in the wind). Maternal blood, stripped of its oxygen and nutrients and loaded with fetal waste products, drains away through veins that are usually located in or near the walls (septa) that partition each cotyledon. The development of the villous tree is usually immature near the centre, so that the villi are more loosely packed there, providing a large region near the spurting maternal artery where maternal blood can move more freely.

MRI observations are used to assess perfusion (the flow per unit volume or mass of tissue) and flow characteristics of blood flow in the placenta. Inadequate perfusion is associated with a wide class of pathological conditions, including pre-eclampsia (PE),

that cause intra-uterine growth restriction (IUGR). MRI can therefore be used to screen for these conditions at an early stage in pregnancy.

Following delivery, a normal, healthy placenta usually weighs about 0.5kg, is about 220mm in diameter and 25mm thick after delivery (45mm thick *in vivo*). The villous mass may reach 0.27kg, and the villi have surface area reaching 12m².

Radioangiographic studies indicate that the jets of maternal blood that spurt from the maternal spiral arteries lead to rapid filling of the centres of the villous trees, followed by a slower spreading of maternal blood out through the villous tree [4, 5]. There is considerable blurring of inflow/outflow regions. There is also significant recirculation of maternal venous blood.

IUGR is a disorder associated with a wide range of pathological conditions, including PE, in which normal placental function is compromised. Of interest is the effect on oxygen transport of the detailed structure of the placenta. Factors which may contribute to impaired placental function include (i) villi stiffness (which may be controlled by excessive fibrin deposits), density and branching structure, (ii) the flow rate, pressure and pulsatility of the maternal blood and (iii) the volume and flow rate of the fetal blood.

1.2 Parameter values and estimates

Before developing our model, we characterise the maternal blood flow within each cotyledon and the dominant mechanisms for oxygen transport to (and carbon dioxide removal from) the fetal villi.

We assume the following values for the viscosity ν , total maternal blood flow rate Q , maternal artery diameter L and oxygen (or carbon dioxide) diffusivity D :

$$\nu \sim 10^{-6} \text{m}^2 \text{s}^{-1}, \quad Q \sim 600 \text{ml min}^{-1}, \quad L \sim 1 \text{mm}, \quad D \sim 10^{-8} \text{m}^2 \text{s}^{-1}.$$

Using these values and assuming there are 100 maternal arteries, we obtain the following estimates for the Reynolds number Re , the Prandtl number Pr and the Péclet number, Pe , for the flow near the opening of a typical maternal artery:

$$Re \sim 100, \quad Pr \sim 100, \quad Pe \sim 10^4.$$

As a result, we conclude that O₂ (and CO₂) transport in the blood is dominated by advection. The Reynolds number corresponds to inertia-dominated flow that probably remains laminar.

1.3 The model

After extensive discussion, approaches involving rigid and deformable porous media (mixture theory) were discarded and attention concentrated on modelling the behaviour of a typical villous tree as the blood spurting out of the maternal vein deforms and perfuses it. This villous tree was likened to the staves of a barrel, opening (or billowing outwards) and closing under the influence of the pulsatile, maternal arterial jet. The villi are assumed to return, at least partially, to their undeformed state between pulses of arterial blood.

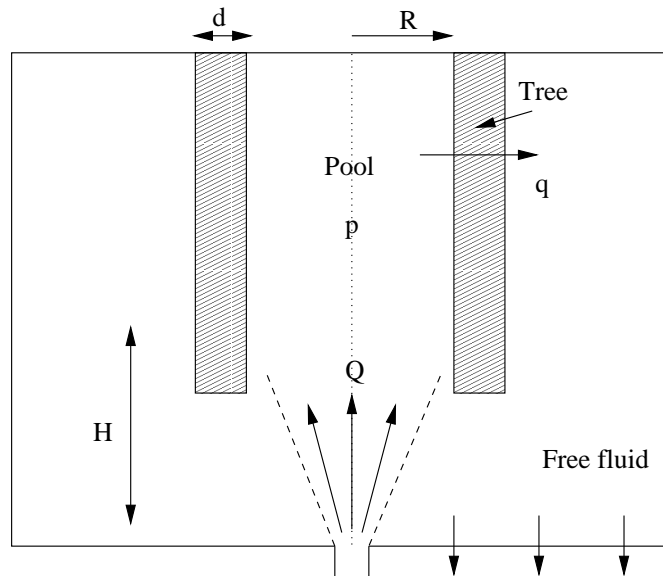


Figure 1: Schematic of model problem.

1.3.1 Governing equations

We consider an axisymmetric cotyledon (figure 1), containing one villous tree which is perfused by one maternal artery. Maternal arterial blood spurting into the cotyledon deforms the villous tree, forming a central pool of free blood. We assume a time-dependent volume flux $Q(t)$ of maternal blood, delivered at pressure p_a (all pressures are measured relative to the pressure in the maternal veins that collect blood when it drains from the placenta). We assume that the jet spurts upwards into the tree and that the momentum of the incoming jet is completely converted into a pressure p of relatively slow moving fluid within the pool. We take this pressure to be positive in the pool, and zero in the surrounding free fluid. Unsteady flow coupled with Bernoulli's equation gives

$$p_a + \frac{\rho}{2} \left(\frac{Q}{A} \right)^2 = p + \rho H Q_t \quad (1.1)$$

where ρ is the density of blood, A the cross-sectional area of the maternal artery, H the length over which the jet decelerates and the subscript t denotes a time derivative.

Fluid then passes through the villous tree which we assume provides the primary viscous resistance to flow. We suppose further that movement of blood in the free fluid-filled space beyond the tree and into the maternal venous circulation occurs with negligible pressure loss. The pressure drop across the tree is therefore p , and Darcy's law gives

$$Rkp = q\mu, \quad (1.2)$$

where q is the total volume flux across the tree, μ is the dynamic viscosity of blood, and k is the permeability of the villous tree (k has units of length squared). We estimate the area presented to the flow to be RL , where $R(t)$ is the radius of the central pool and L its length, assumed constant (to the present level of approximation, we assume that all $O(1)$ constants such as π are unity).

Kinematics requires that the incoming flux Q is balanced by movement of fluid through the tree and expansion of the tree and the central pool. Thus we have

$$Q = q + RR_tL. \quad (1.3)$$

As the tree is deformed by the flow, its permeability is likely to vary significantly. We consider two primary mechanisms that may cause it to change. First, expansion of the villous tree is likely to increase pore spacings, resulting in an increase in permeability. Second, compression is likely to cause consolidation of the tree's internal structure, reducing both pore spacing and permeability. We therefore write

$$k = k_0(1 - \alpha p + \beta(R - R_0)) \quad (1.4)$$

where R_0 is a reference radius and α and β are positive parameters. A more detailed pore-scale analysis could be used to estimate α and β , or more strongly nonlinear dependence of k on p and R . For the present, we assume variations in permeability are small enough that they can be estimated using linear approximations.

Finally, a force balance applied to the tree gives

$$MR_{tt} + E(R - R_0) = pRL. \quad (1.5)$$

Here E is a constant representing the effective spring stiffness of the tree. We assume the tree exhibits a linearly elastic response to deformation from the reference radius R_0 . M represents the inertia of the tree, and includes the added mass of fluid in the free space that must be accelerated when the tree moves. We neglect internal viscous damping within the tree.

1.3.2 Model simplification

Eliminating q between equations (1.2) and (1.3), and substituting for k from (1.4), we find that

$$p[1 - \alpha p + \beta(R - R_0)] = \frac{\mu}{k_0} \left(\frac{Q}{R} - LR_t \right). \quad (1.6)$$

Assuming $\alpha p \ll 1$ and $\beta(R - R_0) \ll 1$, we can approximate this as

$$p = \frac{\mu}{k_0} \left(\frac{Q}{R} - LR_t \right) \left[1 + \frac{\alpha\mu}{k_0} \left(\frac{Q}{R} - LR_t \right) - \beta(R - R_0) \right]. \quad (1.7)$$

Substituting for p in (1.5) we deduce that the motion of $R(t)$, the radius of the central pool, may be described by a forced, damped oscillator:

$$MR_{tt} + E(R - R_0) = RL \frac{\mu}{k_0} \left(\frac{Q}{R} - LR_t \right) \left[1 + \frac{\alpha\mu}{k_0} \left(\frac{Q}{R} - LR_t \right) - \beta(R - R_0) \right]. \quad (1.8)$$

For prescribed functions $Q(t)$, known parameter values, and appropriate initial conditions, we may solve (1.8) to determine $R(t)$. The total volume flux across the tree $q(t)$ and the pressure $p(t)$ may be determined using equations (1.3) and (1.7). It remains to consider how the maternal blood flow into the cotyledon and the subsequent motion of the villous tree affect oxygen transport to the fetus.

1.3.3 Oxygen transport to the fetus

Exchange of gases such as O_2 and CO_2 occurs when blood flows through the villous tree. Denoting by C the O_2 concentration in the maternal blood, we assume that along a streamline

$$C_t = -\Gamma C \quad (1.9)$$

for some mass-transfer parameter Γ . This term captures gas absorption and release both from the fetal circulation, and from the 3–4 μm -thick epithelial layer coating the villous tree. The transit time through the layer, which is assumed to be of approximately constant thickness d , is RLd/q (assuming $R(t)$ and $q(t)$ do not vary rapidly during the transit). The amount of dissolved oxygen delivered to the tree by a volume δV of fluid is

$$\delta V C_0 (1 - e^{-\Gamma RLd/q}). \quad (1.10)$$

Thus over one period T of maternal, arterial blood flow, the net O_2 delivery is given by

$$\int_0^T RLqC_0 (1 - e^{-\Gamma RLd/q}) dt. \quad (1.11)$$

1.3.4 Model nondimensionalisation

We define the following dimensionless parameters:

$$\mathcal{Q} = \frac{Q_0 T}{R_0^2 L}, \quad \mathcal{A} = \frac{\alpha \mu R_0 L}{k_0 T}, \quad \mathcal{B} = \beta R_0, \quad \mathcal{D} = \frac{T R_0 L^2 \mu}{M k_0}, \quad \mathcal{E} = \frac{E T^2}{M}. \quad (1.12)$$

Here Q_0 is the mean arterial flux. \mathcal{Q} measures the ratio of delivered volume in one maternal spurt to the volume of the central pool when in its reference configuration, and will be of the order of 10^{-1} to 10^{-2} . \mathcal{A} is a parameter (assumed small) estimating the change in permeability due to consolidation. \mathcal{B} is a parameter (assumed small) estimating the change in permeability due to expansion of the villous tree. \mathcal{D} measures the damping in the system which arises from frictional resistance due to flow in the porous medium. \mathcal{E} relates the pulse period T to the natural frequency of oscillation of the tree $(M/E)^{1/2}$. If \mathcal{E} is close to unity there is the possibility of a resonant interaction. Writing

$$R = R_0(1 + \widehat{R}), \quad t = T\widehat{t}, \quad (1.13)$$

and $Q = Q_0 \widehat{Q}(\widehat{t})$, (1.8) becomes

$$\widehat{R}_{\widehat{t}\widehat{t}} + \mathcal{E} \widehat{R} = \mathcal{D} \left(\mathcal{Q} \widehat{Q} - (1 + \widehat{R}) \widehat{R}_{\widehat{t}} \right) \left[1 + \mathcal{A} \left(\mathcal{Q} \frac{\widehat{Q}}{1 + \widehat{R}} - \widehat{R}_{\widehat{t}} \right) - \mathcal{B} \widehat{R} \right]. \quad (1.14)$$

The above equation forms a closed problem provided the flux Q is imposed. If maternal pressure is imposed, (1.1) must be used to determine the flux and the system is higher order in time.

1.4 Further Developments

A number of approaches are now possible, to further the modelling of the villi. We simply outline two of them here — much remains to be done in analysing this model.

We estimate the permeability k_0 by noting that highly permeable formations in groundwater flow have a permeability of the order of one darcy, which is 10^{-12}m^2 . The villous tree may be yet more permeable, so we use here $k_0 \approx 10^{-10}\text{m}^2$. Then $\mathcal{D} \approx 10^4$ is a large damping term (giving overdamped oscillations), and the dominant balance in equation (1.14) is then (dropping the hats)

$$(1 + R)R_t + \frac{\mathcal{E}}{\mathcal{D}}R = \mathcal{Q}Q(t). \quad (1.15)$$

Numerical solutions to this equation tend towards a stable oscillation at the forcing frequency in Q , for a variety of parameter values and initial conditions, with an amplitude of the order of $2\mathcal{Q}\mathcal{D}/\mathcal{E}$.

Another approach to equation (1.14) is to begin by considering the limit $\mathcal{A} = 0$, $\mathcal{B} = 0$. Then we obtain the forced damped oscillator equation,

$$\widehat{R}_{\widehat{t}\widehat{t}} + \mathcal{D}(1 + \widehat{R})\widehat{R}_{\widehat{t}} + \mathcal{E}\widehat{R} = \mathcal{D}\mathcal{Q}\widehat{Q}, \quad (1.16)$$

where the damping depends on the radius. We simply note here that forced damped oscillators have many possible long-term solution behaviours, including periodic and chaotic oscillations.

1.5 Conclusions

We have developed a simple compartmental model that can be used to estimate oxygen delivery via the placenta to the developing fetus. In the model attention focussed on the way in which the deformation and movement of a fetal villous tree contained within a single cotyledon are related to the maternal blood flowing into the region from the maternal spiral artery. The permeability of the villous tree was lumped into a single variable that depends on transverse expansion (as neighbouring branches of the tree are moved apart by the flow) and streamwise compression. Accounting also for elastic restoring forces and the tree's inertia, the problem reduced to that of a forced, damped nonlinear oscillator for the average radius of the villous tree.

It now remains to construct numerical model solutions which show how physical variables such as the motion of the villous tree and oxygen delivery to the fetus depend on the model parameters. There are a several natural parameters that may be of particular interest when assessing the effect of pathology on placental function. They include the flexibility of the villous tree as embodied by the effective spring constant of the tree, E (see equation (1.5)): this parameter may increase due to fibrin deposits which stiffen the villous tree. The volume flux of maternal blood into each cotyledon is another key variable – in certain disorders, inadequate remodelling of the maternal arteries may reduce maternal blood flow to the fetus. Finally, changes in the surface area of the villous tree play an important role in gas exchange between the maternal and fetal blood supplies.

Additionally, this preliminary investigation highlights a number of areas in which significant further work is required. These include characterisation of the permeability of a highly deformable porous medium, and deformation of a tree-like structure in response to flow. These are challenging and interesting topics for modelling.

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References

- [1] Polin, R.A. and Fox, W.W. (1992) *Fetal and neonatal physiology*. Saunders, Philadelphia.
- [2] Mayhew, T.M. and Jairam, I.C. (2000) Stereological comparison of 3D spatial relationships involving villi and intervillous pores in human placentas from control and diabetic pregnancies. *J. Anat.* **197**, 263–274.
- [3] Moore, R.J., Strachan, B.K., Tyler, D.J., Duncan, K.R., Baker, P.N., Worthington, B.S., Johnson, I.R. & Gowland, P.A. (2000) *In utero* perfusing fraction maps in normal and growth-restricted pregnancy measured using IVIM echo-planar MRI. *Placenta* **21**, 726–732.
- [4] Borell, U., *et al* (1958) Eine arteriographische Studie des Plazentar-Kreislaufs. *Geburtshilfe Frauenheilkd* **18**, 1.
- [5] Ramsey, E.M. (1963) Serial and cineradioangiographic visualization of maternal circulation in the primate (hemochorial) placenta, *Am. J. Obstet. Gynecol* **86**, 213.