Mathsys project: Modelling uterus implantation potential to understand recurrent pregnancy loss (RPL).
Supervisors: Burroughs (Mathematics Institute) & Brosens (Medical School)

Background: The uterus is the most dynamic tissue in the human body that undergoes iterative cycles of tissue regeneration and clearance, exhibiting growth rates exceeding most cancers. The uterus lining, called the *endometrium*, makes critical decisions to enable implantation, miscarry or continue with pregnancy. In this project we take a mechanistic tissue level approach to understand endometrium dynamics related to implantation potential.

The project: You will build an ordinary differential equation (ODE) model of the endometrium state. It is known from analysis of uterus biopsy data that the uterus is either primed for implantation and pregnancy or is not receptive to implantation during the 4 day implantation window. The balance between two antagonistic cell types determines which state the uterus is in: *Senescent cells* (sensitive to stress signals) which are pro-clearance and miscarriage, and *stress-resistant (decidual) cells* that are pro-pregnancy. In absence of pregnancy the senescent cells 'win', the uterine lining is destroyed and the cycle recommences, whilst implantation leads to increased progesterone levels that shifts the balance in favour of the stress-resistant cells, and thus allows the implantation to progress to a stable pregnancy. These two cell types differentiate from a common precursor, the hormone progesterone promoting differentiation to the stress-resistant cells. Mathematically this balance, and feedbacks between these cells, see figure, suggests the system is **bistable**. However this is in the context of the monthly cycle driving endometrium renewal so the system is not stationary. Recurrent pregnancy loss (RPL) is a condition where women undergo repeated miscarriage. There is a correlation between women with RPL and a bias of the endometrium towards the senescent cells (pro-clearance).

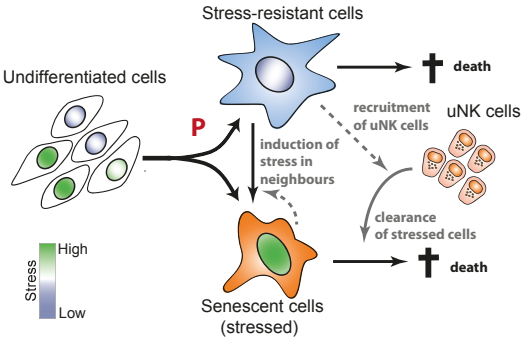

Figure. During the implantation window endometrial stromal cells differentiate into specialized decidual cells or senescent cells. Decidual cells recruit and activate immune cells (uNK) to eliminate their senescent counterparts, whilst senescent cells induce senescence in local decidual cells. Progesterone (P) promotes differentiation to decidual cells.

The project will comprise 3 components. Firstly, you will build an ODE model that incorporates the key biology. Secondly you will analyse this system under a stationarity assumption, ie carry out a standard dynamical systems analysis (determine steady states, stability, analyse bifurcations). Thirdly, you will examine the nonstationary case, ie examine how the bifurcation dynamics occurs as the cycle progresses. Analogies to hysteresis may be useful.

Desirable skills. Experience with dynamical systems methods is essential (bifurcations). Programming, eg in MatLab, will also be needed to simulate the system.

Possibilities of a PhD.
This can extend to a PhD with UHCW as external partner, under supervision of Burroughs (primary) and Brosens (WMS) and Ott (Computer Science). A large project in WMS is collecting biopsies and performing state of the art single cell omics analysis. The PhD would involve fitting the endometrium state model to that omics data to determine model parameters and infer model structure, hence driving development of the endometrium state model (data driven modeling). Bayesian techniques such as Markov chain Monte Carlo (MCMC) algorithms will likely be the best approach, using recently developed Hamiltonian MCMC that work well on ODE fitting to data.