Multiscale modelling of Chlamydia trachomatis infection

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Chlamydia trachomatis is the most common sexually transmitted pathogen of humans, with over 90 million new adult cases occurring worldwide each year. Without treatment, Chlamydial infection can have severe detrimental effects on reproductive health, especially in women. Little is known about the mechanisms by which the infection progresses from the lower to upper genital tract, where the infection becomes problematic and persistent. This motivates development of mathematical models to investigate the dynamics of the infection process. In this talk, we present the results of one of the VPH Exemplar Projects (VPH-EP10), which has been working to develop a dedicated environment for mathematical/computational modelling of sexually transmitted infections (STIs), focusing upon Chlamydia trachomatis as a representative case study.

The project focuses upon the mark-up and simulation of "within-host" models of Chlamydia trachomatis infection from the literature. The models use multiscale approaches to describe the spatial progression of C. trachomatis infection in the female genital tract, coupling a continuum description of extracellular Chlamydial particle motion to cell-scale and tissue-scale models of infection of the genital epithelium. In each of these models, the genital tract is considered cylindrical; Chlamydial infection is studied on the surface of the cylinder. The models are necessarily multiphase, incorporating phase-dependent infection and immune responses through the 28-day menstrual cycle. Chlamydia exists in two forms. The extracellular form is infectious and metabolically inert, whereas the intracellular form replicates via binary fission, but is non-infectious. Both the extracellular and intracellular Chlamydial particles are subjected to innate and adaptive (cell-mediated) immune system responses. It is thought that the cells of the humoral and cell-mediated immune systems undergo a chemotactic migration towards locations of greater concentration of infection due to the cytokines and chemokines produced in response to both free Chlamydial particles and infected epithelial cells. Infection of an epithelial cell occurs when free Chlamydial particles undergo endocytosis by a healthy cell; there is some evidence to suggest that this occurs in a manner dependent upon the menstrual phase. The internalised particles differentiate from the extracellular to intracellular form, replicate, and differentiate back to the extracellular form prior to eventual lysis of the epithelial cell, releasing new Chlamydial particles into the genital tract.

The models considered here deploy a number of approaches. The model of (Wilson, 2004) uses ordinary differential equations to describe how the concentrations of free extracellular chlamydial particles and healthy/infected mucosal epithelial cells evolve over time in the lower genital tract. The models of (Oskouei, 2010) and (Mallet, 2011) effectively extend this model to incorporate spatial information through partial differential equation (PDE) formulations, elucidating the manner in which the infection ascends the tract. The model of (Mallet, 2009) takes a more refined approach

for description of infection in the endocervix, where the nature of intracellular processes becomes more key in determining persistence. This model couples a PDE description of extracellular Chlamydia to a cellular automata model of the epithelium, describing the behaviour of each epithelial cell individually, incorporating explicit cell-scale models of cell infection, lysis and immune responses. For each model, simulations are compared against experimental data for Chlamydia caviae infection in guinea pigs, a bacterial infection highly representative of C. trachomatis infection in humans.

This Exemplar Project demonstrates the application of existing VPH toolkit software to the reproductive system, focusing upon (i) coupling of models at different spatial scales, (ii) demonstrating assosciated interoperability of tools across these scales, and (iii) clear annotation of models to improve their clinical accessibility. Although C. trachomatis is presented as a representative case study, the modelling approach is extensible to other STIs, including gonorrhoea and syphilis. Other STIs will be incorporated into this project in the future; components of models proposed for a wider range of STIs will be easier to code independently in the light of current work, facilitating efficient comparison of models and results across infections.

References

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