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A novel cellular automata-partial differential equation model for understanding chlamydial infection and ascension of the female genital tract

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Chlamydia trachomatis is amongst the most common sexually transmitted diseases in the world and when left untreated, may lead to serious sequelae particularly in women such as pelvic inflammatory disease, ectopic pregnancy and infertility. Currently, most mathematical modelling in the literature regarding *Chlamydia* is based on time dependent differential equations. The serious pathology associated with *C. trachomatis* occurs when the chlamydial infection ascends to the upper genital tract. But no modelling study has investigated the important spatial aspects of the disease. In this work, we include spatiotemporal considerations of the progression of chlamydial infection in the genital tract. This novel direction is achieved using cellular automata modelling with probabilistic decision processes. In this presentation, the modelling strategy will be described, as well as its relationship with existing models and the advances in understanding that are achieved with such a model. Such an approach provides valuable insights into disease progression and will lead to experimentally testable predictions and a basis for further investigation in this area.

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1 Introduction

We present a multi-dimensional model of chlamydial infection in the female genital tract, with an aim of describing a number of important aspects of the infection, and eventually providing greater understanding of the spatial progression of *Chlamydia trachomatis* from the lower to upper tract. This application is highly important because chlamydial disease ascension of the female genital tract accounts for a significant proportion of cases of female infertility and other morbidities. The model presented describes the dynamics and organisation of chlamydial particles, as well as healthy and infected epithelial cells (the target cells for *Chlamydia*) over time and in space, using a hybrid cellular automata/partial differential equation (CA/PDE) model. The CA facilitates both deterministic and stochastic modelling strategies as well as the ability to easily combine spatial and temporal changes. The PDE effectively models random motion of the small infectious particles.

2 Model Description

We model cell-particle and cell-cell interactions described in the biological literature by extending the mathematical work of Wilson's ordinary differential equation model [2] in a manner similar to the hybrid CA/PDE model of Mallet and de Pillis [1]. Essentially, the computational domain is a grid representing the mucosal layer of the genital tract. By imposing periodic conditions to the sides of the grid, a pseudo-three dimensional cylindrical representation of the mucosal layer is formed (see Fig. 1). Each grid element represents a biological cell-sized space in which either a healthy or an infected cell resides, possibly along with a number of extracellular *Chlamydia* particles. Computationally these are stored in separate structures.

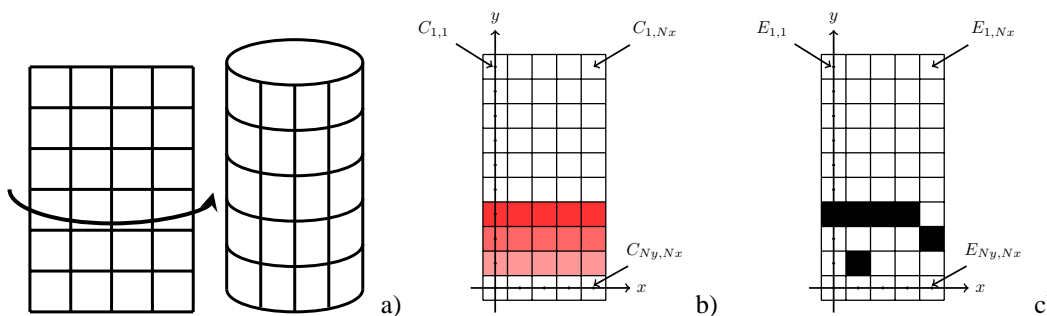


Fig. 1 a) The pseudo-3D cylindrical domain representing the genital tract that is the basis for the cellular automata grids with $N_x \times N_y$ automata elements, for b) Chlamydia particles, $C_{i,j} \in [0, C_{\max}]$ and c) healthy ($E_{i,j} = 0$) and infected ($E_{i,j} = 1$) epithelial cells.

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At each time step, each grid element is investigated and checked for infection status. If the grid location holds an uninfected cell, the cell can become infected with probability $P_{\text{inf}} = 1 - \exp(-k_1 C_{i,j}^2)$, where $C_{i,j}$ is the local level of infectious particles and k_1 is a free shape parameter. Those elements already infected are tracked with a timer which is increased at each time step. Between 48 and 72 hours, the infected cells can lyse with probability $P_{\text{lys}} = 1 - \exp(-k_2 (I_{i,j}^t)^2)$ where $I_{i,j}^t$ is the cell's infection length and k_2 is a free shape parameter. If the cell lyses, a healthy cell from below the mucosal layer moves up to fill the grid element and a quantity, $\Delta C_{i,j} = \exp(I_{i,j}^t \ln(C_{\text{max}})/t_{\text{lys}})$, of new infectious particles is released locally. This reflects the binary reproduction of particles which has occurred inside the infected cell following the initial internalisation of an infectious particle and up to the time $I_{i,j}^t$. Here, C_{max} is the maximum number of particles which would be released at the maximum time to lysis (72 hours), denoted t_{lys} .

Following these CA actions, the chlamydial particles move randomly around the domain and this is modelled by solving (numerically, with a centred space, implicit time, finite difference method) a simple 2D-diffusion equation, $C_t = D\nabla^2 C$, with periodic side boundaries, zero-flux upper boundary (cervical mucus plug), and a prescribed zero particle level at the lower boundary (reflecting unfavourable conditions for particles). For compatibility with the integer-based CA, the finite difference mesh is placed over the centres of the CA elements, and the PDE solutions at each mesh point are rounded post-solution, to the nearest integer to provide the $C_{i,j}$ values for the next time step.

3 Results and Discussion

Using this hybrid model, we have successfully modelled multiple lysis events and spatial progression of infection with periods of infectious particle internalisation evident between the peaks in the *Chlamydia* particle levels (see Fig. 2a). In the cell population timecourses, the number of infected cells decreases (reflecting lysis) and the number of healthy cells increases (resulting from replacement by healthy cells). The ascension of infection due to random motion of *Chlamydia* particles was also modelled via the diffusion equation for infectious particles. We were also able to demonstrate the spatial variation in particle levels as a result of the random movement and the internalisation leading to cell infection (see Fig. 2b).

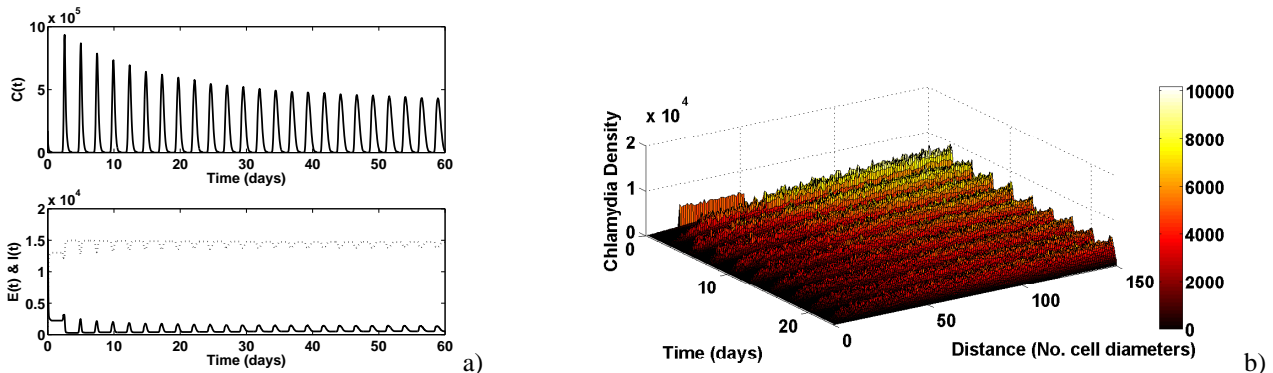


Fig. 2 a) Total number of *Chlamydia* particles (over entire domain) (top) and cell counts (bottom, solid line: healthy, broken line: infected) over ≈ 52 days. b) Change over time in the level of *Chlamydia* particles at different ‘depths’ of the genital tract.

The model described herein, which has successfully modelled some elements of the chlamydial infection process, forms the basis for a comprehensive model of infection in the female genital tract, currently under development. Further development of the model is allowing for consideration of the region above the cervical mucus plug and for describing ascension of infection to the upper tract. Other features such as the menstrual cycle, fluid flow, the host immune response, and improving biological realism of CA rules will also be incorporated as important developments of the model. This model will then be utilised to investigate numerous scenarios, such as the influence of infection at different times of the menstrual cycle, initial bacterial load, and the effectiveness of differential levels of partial host immunity on the overall ascension of infection. Future models will be calibrated with experimental data from animal models (such as the guinea pig) and will pose predictions that can be tested in such models. Experimental results will then drive future modelling work, in an iterative process, to elucidate important insights into what causes the serious pathology associated with chlamydial infection in women and what vaccine (and other) strategies will be most effective in reducing disease burden.

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References

- [1] D. G. Mallet and L. G. de Pillis, *J. Theor. Biol.*, **239**, 334–35 (2006).
- [2] D. P. Wilson, *ANZIAM J.*, **45(E)**, C201–C214 (2004).