Agent-based and continuum models for spatial dynamics of infection by oncolytic viruses

David Morselli

joint work with Marcello Delitala and Federico Frascoli

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Politecnico di Torino

Swinburne University of Technology

Università di Torino

DISMA Dipartimento di Scienze Matematiche G. L. Lagrange

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Overview

1. Introduction and motivation
2. Modelling framework
3. Infection with standard diffusion
4. Infection with pressure-driven motion

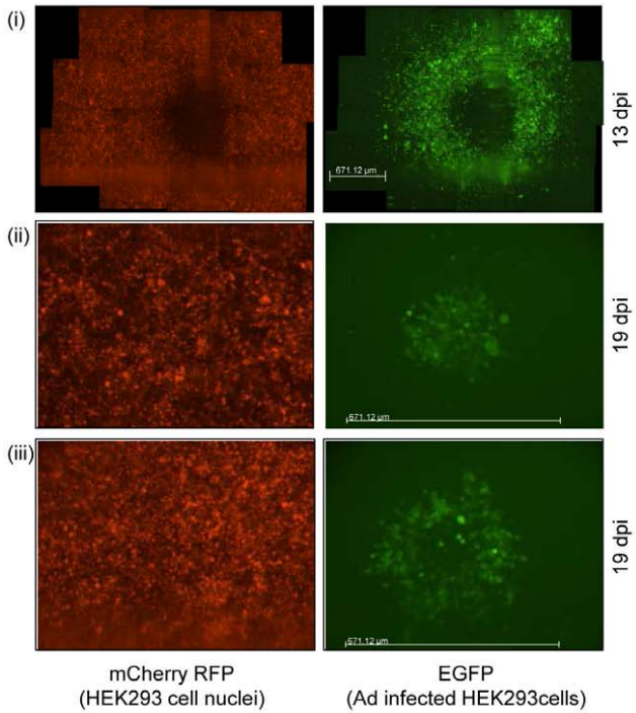
Infection of oncolytic viruses

Oncolytic viruses can infect and destroy cancer cells, while preserving healthy tissues.
Thus, they could minimize side effects of cancer therapies.

PROBLEMS:

- insufficient diffusion of the virus in the cancer, due to stochastic events and physical obstacles (such as extracellular matrix);
- suboptimal features of viral infection (e.g., slow infection rate or fast killing rate);
- inhibition of infection due to hypoxia;
- clearance by the immune system.

We will focus on the first two problems.



D. Wodarz et al., *Complex spatial dynamics of oncolytic viruses in vitro: mathematical and experimental approaches*, 2012.

Which mathematical description is more suitable?

Discrete models

- ✅ track individual cells and allow to consider stochasticity
- ❌ limited in spatial and temporal scales, analytical results are harder

Continuum models

- ✅ track volume fractions, fast to solve numerically and often analytically tractable
- ❌ individual stochastic events cannot be described

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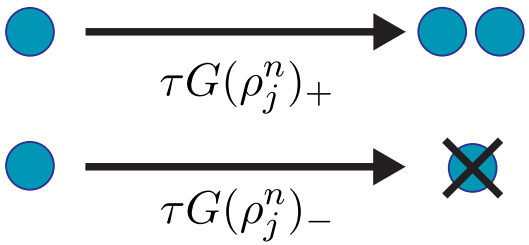
💡 Derive a continuum model as the appropriate limit of an individual based model (large number of cells, small spatial and temporal discretizations). The comparison of the two models allows to:

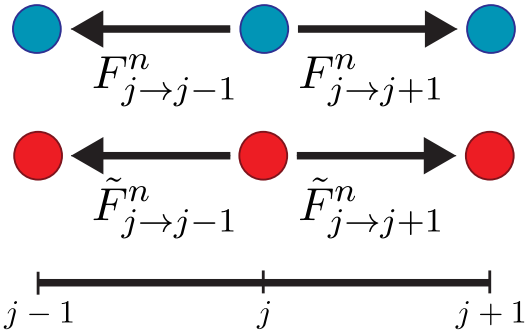
- understand more clearly modelling assumptions for the continuum model;
- gain some theoretical intuition on the behaviour of the individual-based model;
- understand the role of stochasticity;
- gain more robust biological insight.

Agent-based models

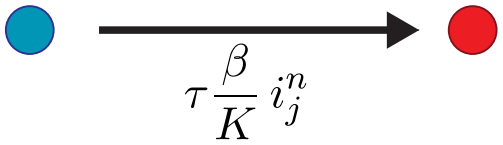
Proliferation of uninfected cells



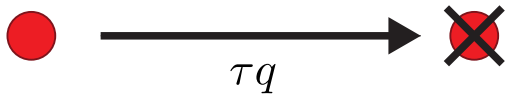
Cells' movement



Infection



Death of infected cells



Pressure: $\rho_j^n := u_j^n + i_j^n$

Growth probability: $G(\rho) = p\left(1 - \frac{\rho}{K}\right)$ (or also $G(\rho) = p$)

Cell's movement:

pressure independent

$$F^n_{j\to j\pm1} := \frac{\theta_u}{2}$$

pressure dependent

$$F^n_{j\to j\pm1} := \theta_u \frac{(\rho_j^n - \rho_{j\pm1}^n)_+}{2K}$$

Formal derivation of continuum model (sketch)

At each time step t_n an uninfected cell at point x_j can reproduce

The "principle of mass balance" gives the equation

$$u_j^{n+1} = (1 + \tau p) u_j^n$$

Formal derivation of continuum model (sketch)

At each time step t_n an uninfected cell at point x_j can reproduce, move

The "principle of mass balance" gives the equation

$$u_j^{n+1} = \frac{\theta_1}{2}(1+\tau p)u_{j-1}^n + \frac{\theta_1}{2}(1+\tau p)u_{j+1}^n + (1-\theta_1)(1+\tau p)u_j^n$$

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which is equivalent to

$$\frac{u_j^{n+1} - u_j^n}{\tau} = \theta_1 \frac{u_{j-1}^n + u_{j+1}^n - 2u_j^n}{2\tau} + p u_j^n - \beta u_j^n i_j^n + \dots$$

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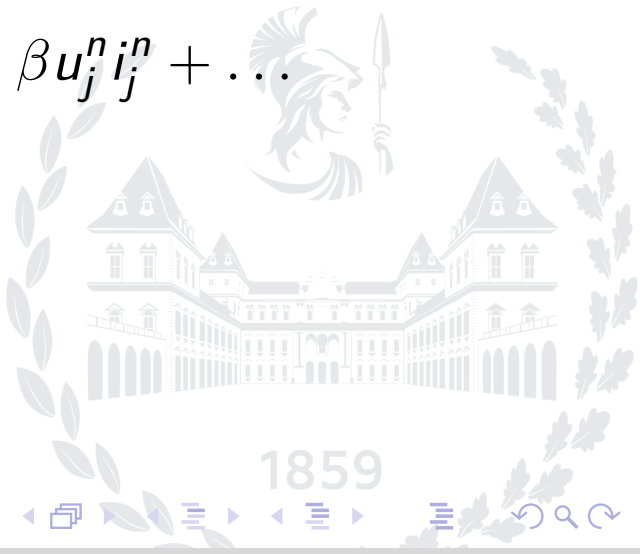

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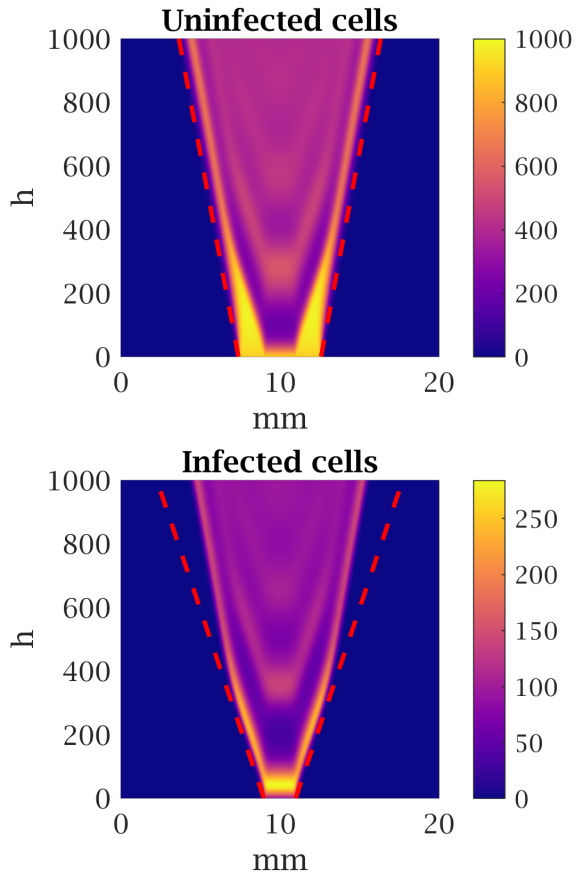
Letting $\tau, \delta \to 0$ in such a way that $\frac{\delta^2}{2\tau} \to D$ we obtain

$$\partial_t u(t,x) = \theta_1 D \partial_{xx}^2 u(t,x) + p u(t,x) - \beta u(t,x) i(t,x)$$

Continuum models with standard diffusion

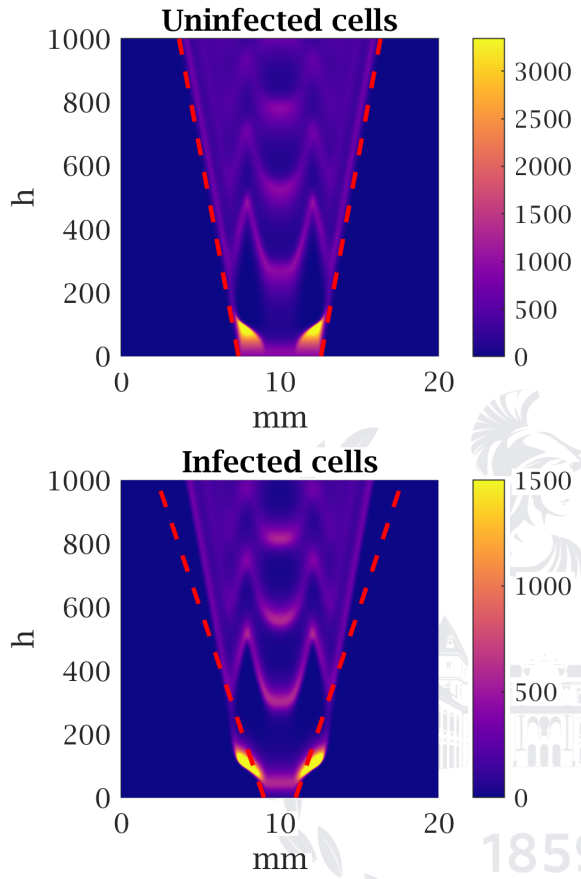
Logistic growth

$$\begin{cases} \partial_t u = D_u \partial^2_{xx} u + pu\left(1 - \frac{u+i}{K}\right) - \beta ui \\ \partial_t i = D_i \partial^2_{xx} i + \beta ui - qi \end{cases}$$

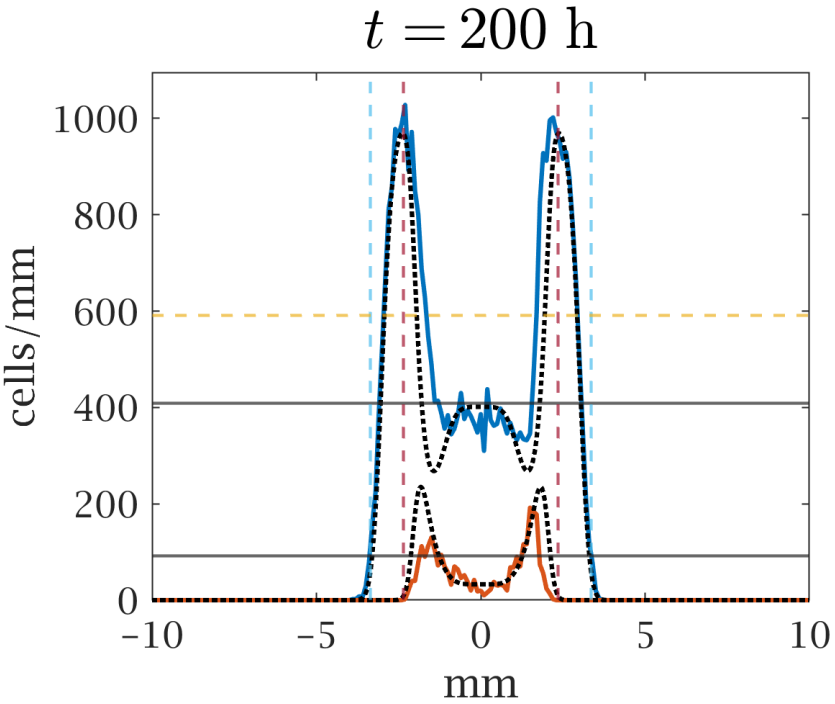


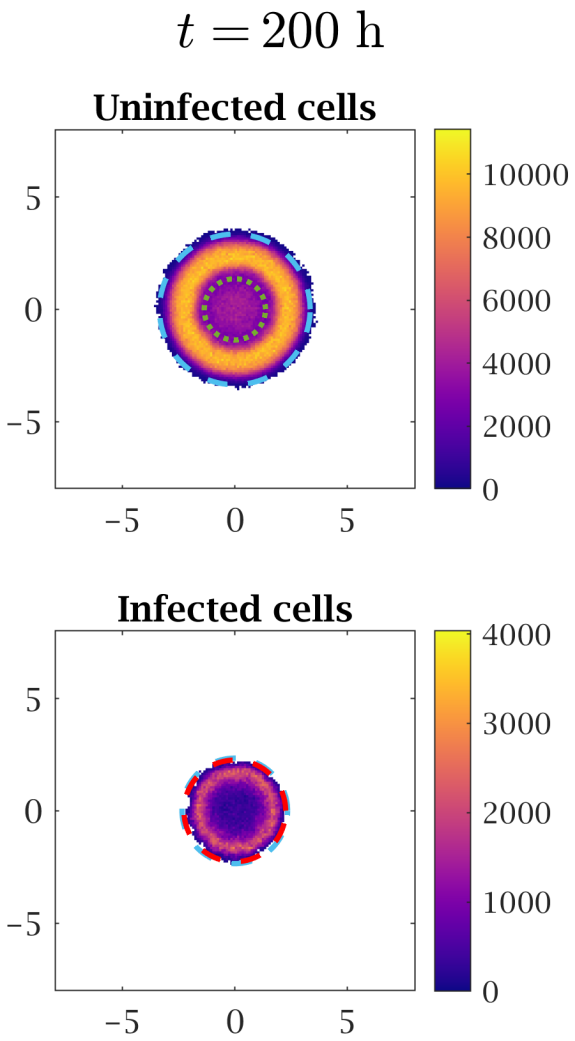
Exponential growth

$$\begin{cases} \partial_t u = D_u \partial^2_{xx} u + pu - \beta ui \\ \partial_t i = D_i \partial^2_{xx} i + \beta ui - qi \end{cases}$$



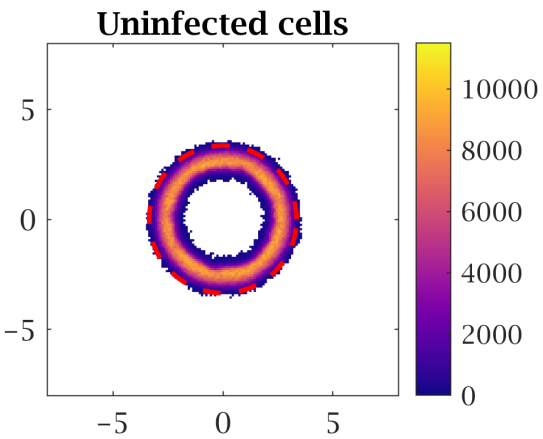
Model with logistic growth and standard diffusion



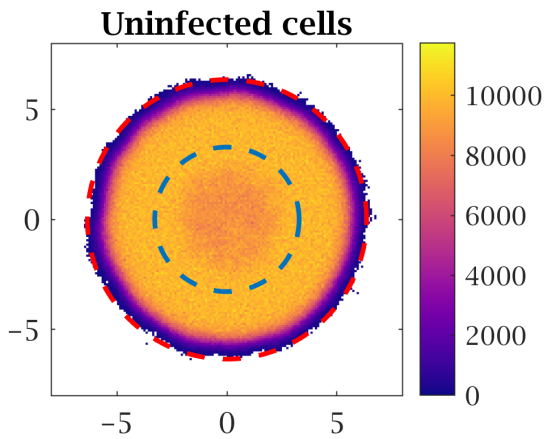


Other phenomena with logistic growth

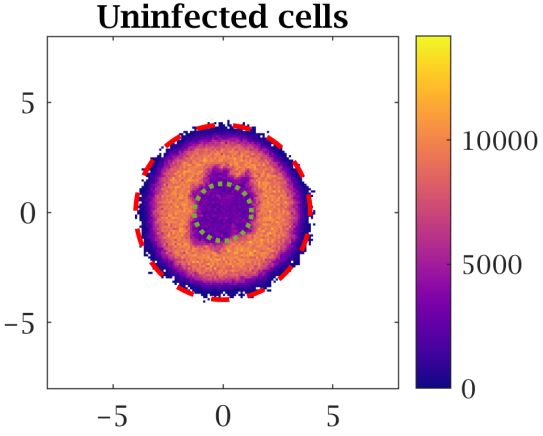
$t = 200$



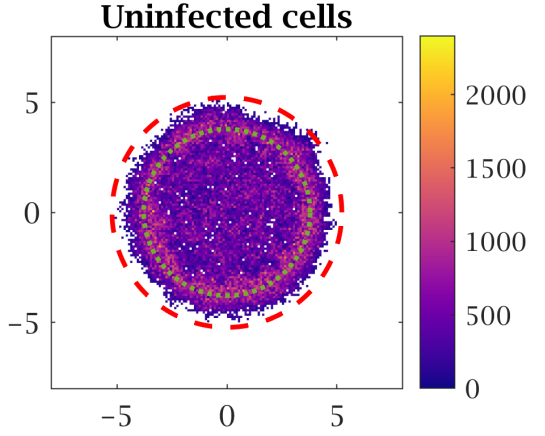
$t = 1000$



$t = 365$



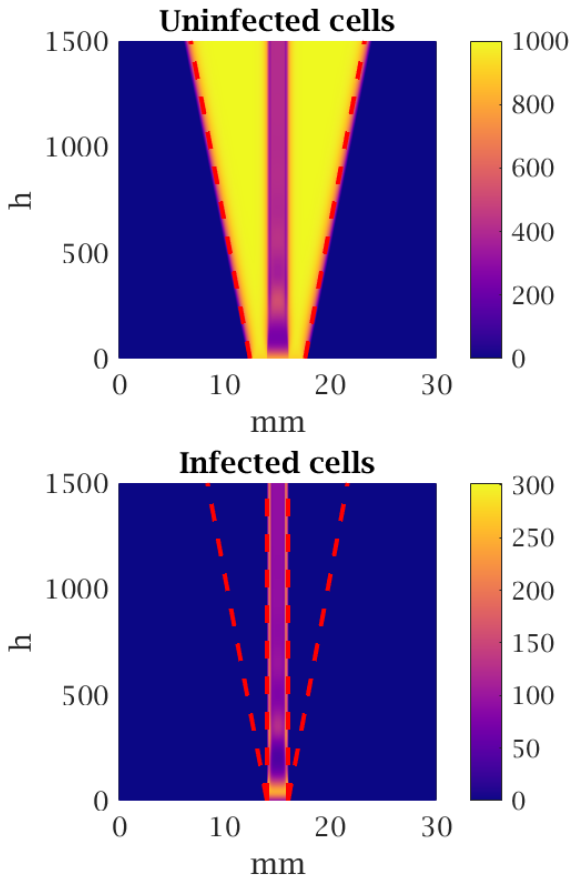
$t = 700$



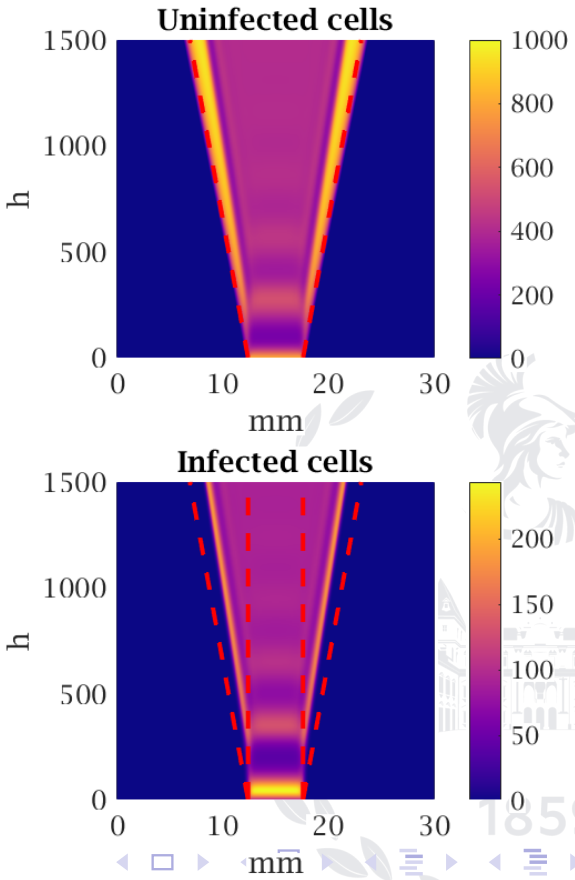
Continuum model with pressure-driven motion

$$\begin{cases} \partial_t u = D_u \partial_x (u \partial_x (u+i)) + pu\left(1 - \frac{u+i}{K}\right) - \beta ui \\ \partial_t i = D_i \partial_x (i \partial_x (u+i)) + \beta ui - qi \end{cases}$$

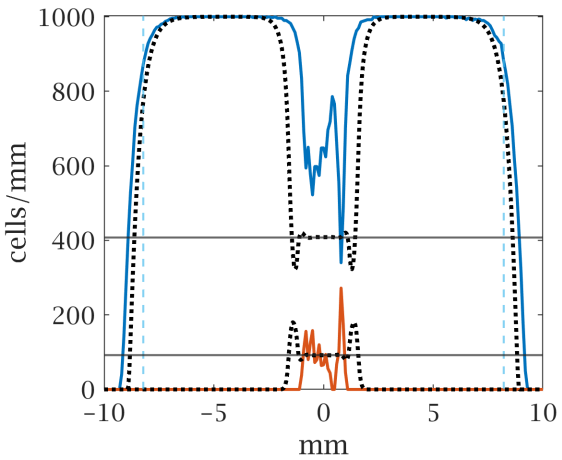
Initial infection localised



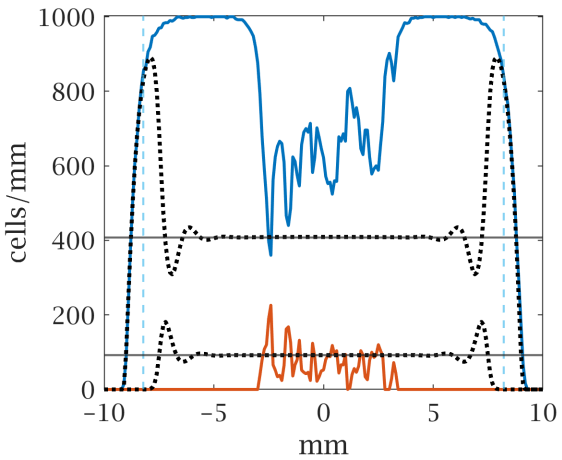
Initial infection spread



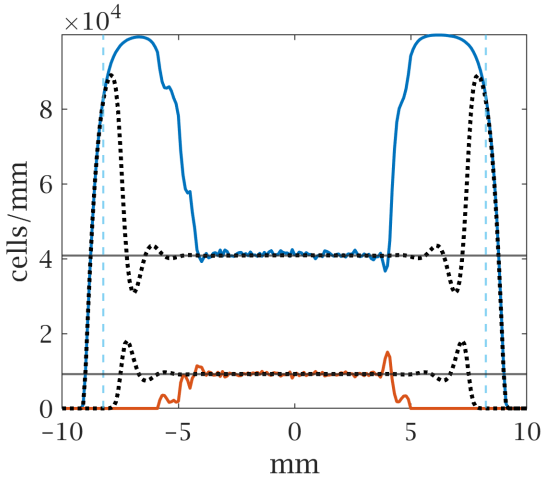
Ineffective infection



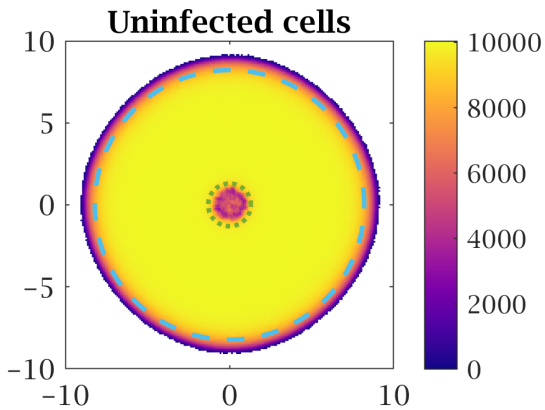
(a) reference

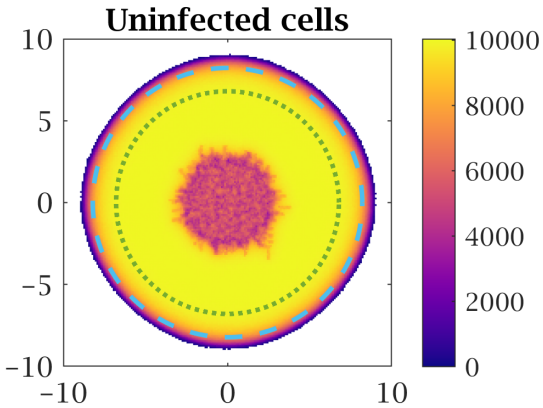


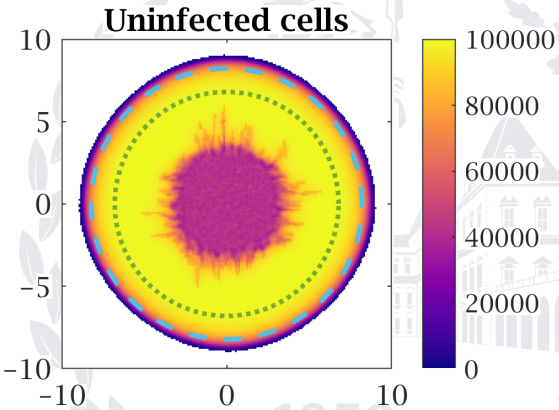
(b) $R_i = R_u$



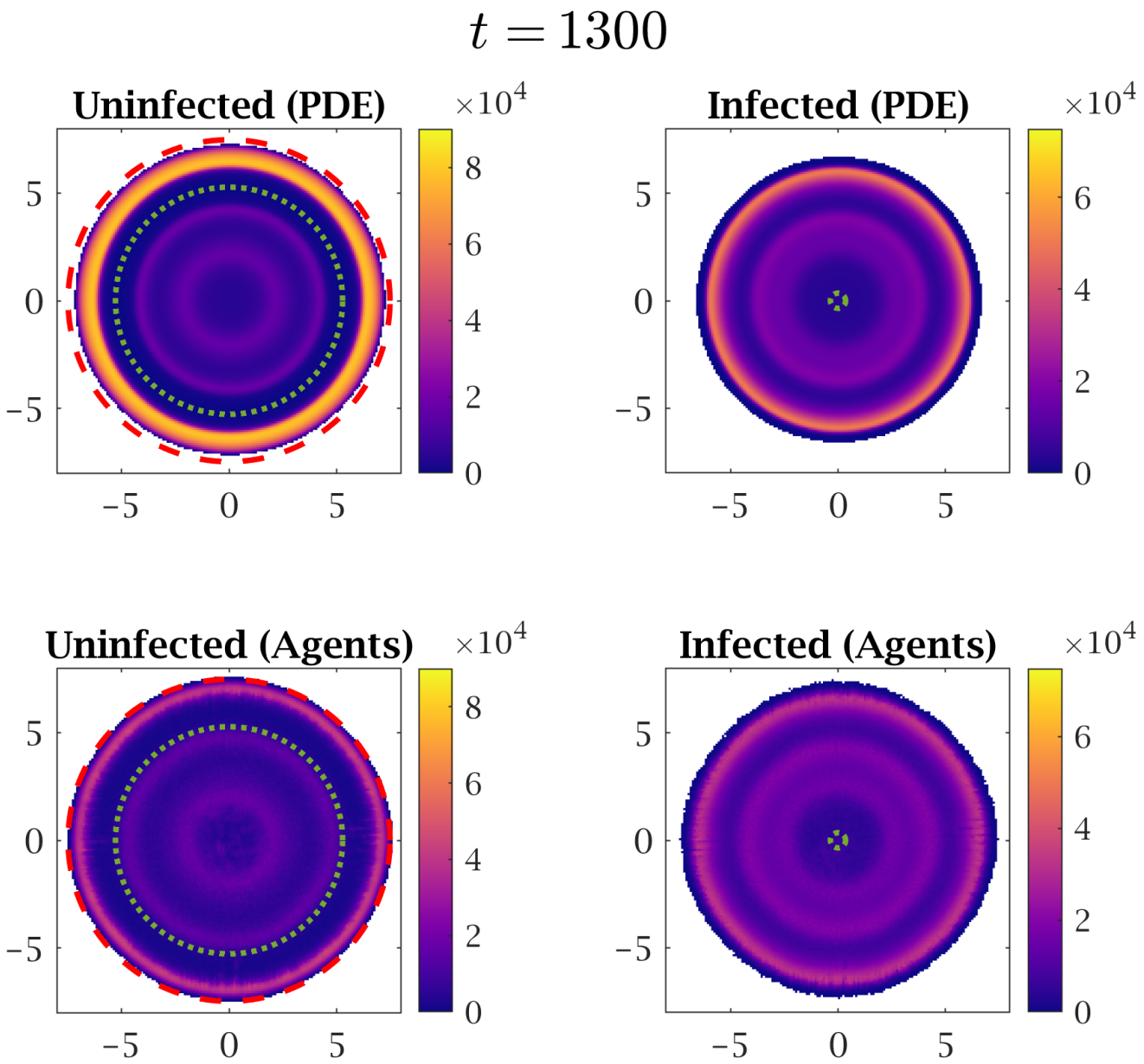
(c) $R_i = R_u$, $K = 10^5$ cells/mm (or cells/mm^2)



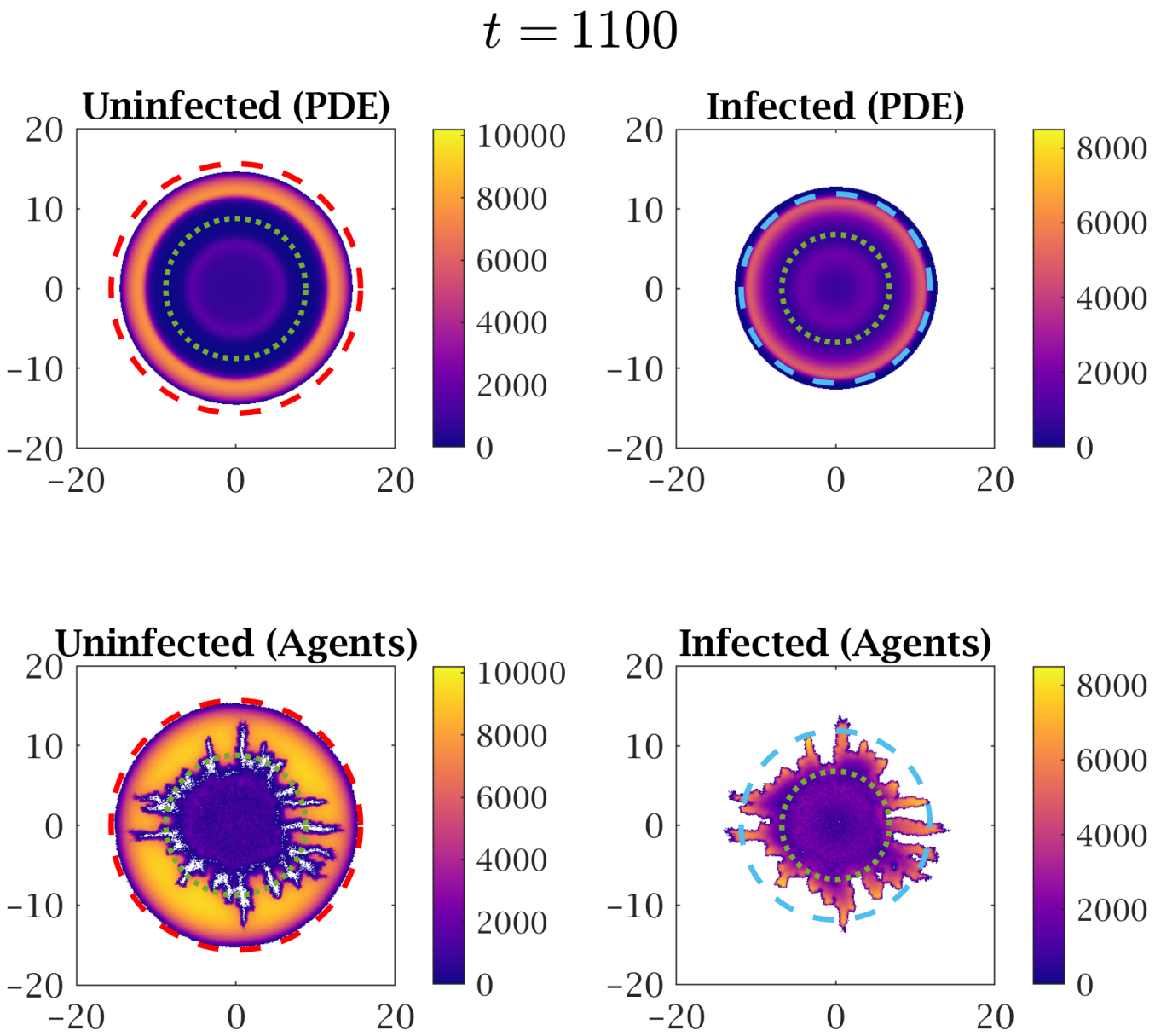




Successful infection



Partial failure



Conclusions and further perspectives

- Numerical simulations show good agreement between agent-based simulations with a sufficently large cell number and the numerical and analytical results for the continuum model.
- Stochasticity may give rise to asymmetric or disperse patterns in the discrete model that cannot be described by the continuum model.
- The model is able to qualitatively reproduce *in vitro* experiments.

Further works could include:

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Thank you for your attention!