Modeling of the effects of inerferon on spatial spread of viral infection

Anna Marciniak-Czochra,

and Marek Kimmel

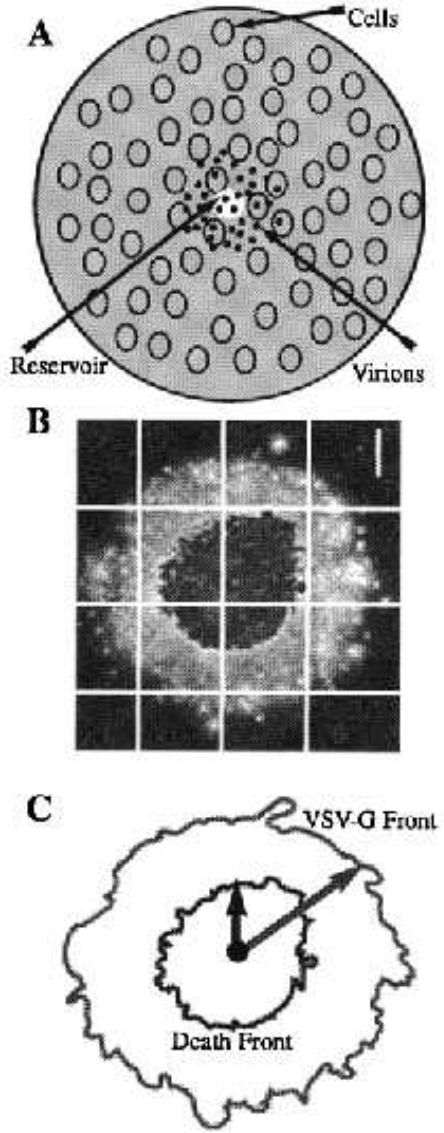
December 2005

Acknowledgment

We thank Prof. Allan Brasier of University of Texas Medical Branch in Galvestone, TX, USA for his input concerning the biological assumptions of our models.

Experiments

We consider a population of cells (tissue culture system) and its response to the infection with the RSV (respiratory syncythial virus).



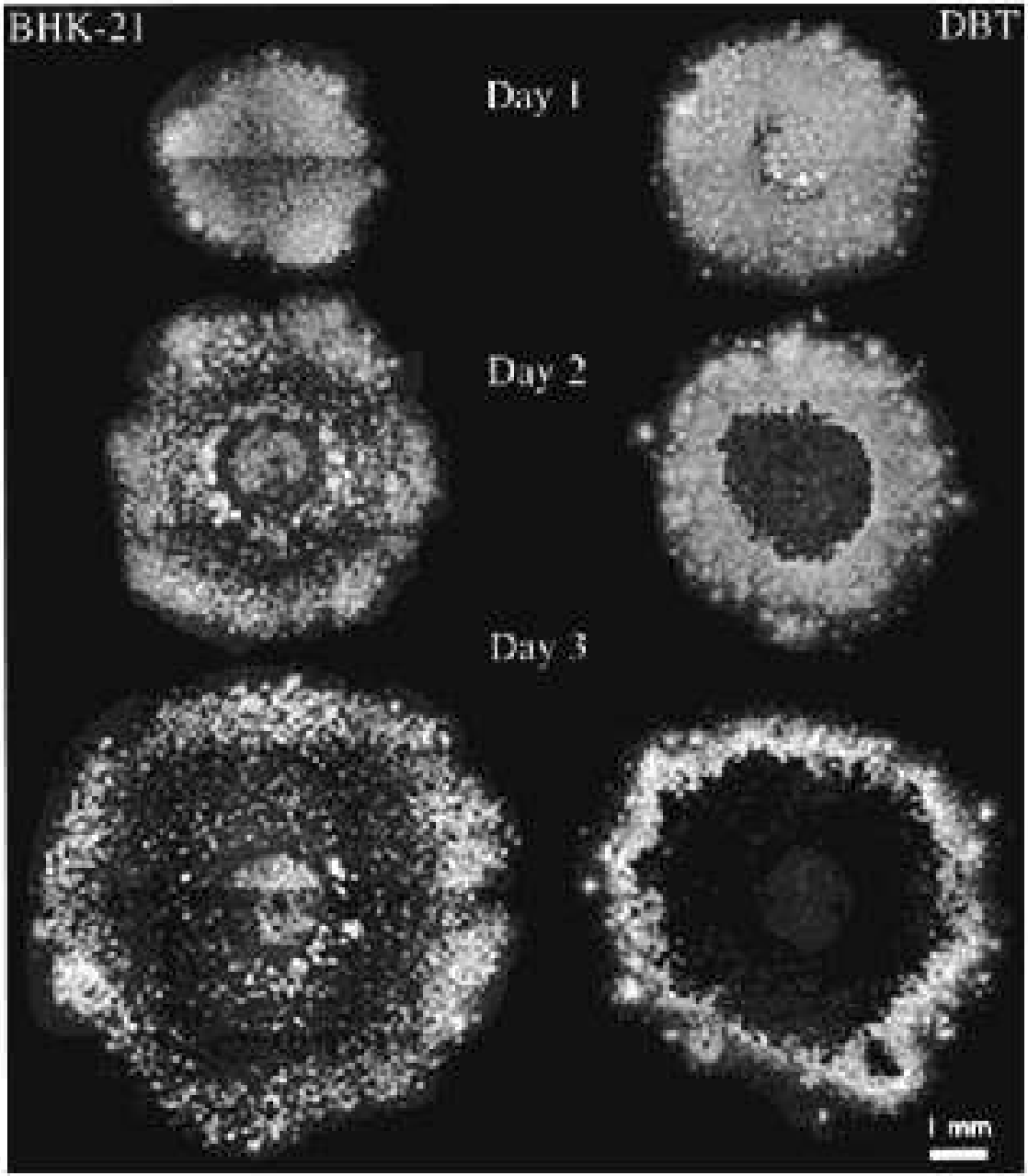
Infection

- The virion must identify and bind to its cellular receptor
- become internalized,
- uncoat,
- synthesize viral proteins,
- replicate its genome,
- assemble progeny virions,
- exit the host cell.

While these events are taking place, intrinsic host defenses activate in order to defeat the virus, which includes, e.g.,

- activation of the interferon system,
- induction of apoptosis,
- and attempted elicitation of immune responses via chemokine and cytokine production.

Spatial spread of infection, Duca et al. (2001)



- A planar cell culture has been infected by placing a small virus reservoir in the center of the culture.
- Following this, a wave of infection was observed in the form of an expanding ring, followed by a spreading area of cell death.

Interpretation of experiments of Duca et al. (2001)

(i) Infected cells are dying with delay with respect to infection.

There is no influence of immune defense of any kind and the ring of infected cells expands indefinitely.

(ii) Infected cells produce a factor such as interferon, which spreads to adjacent uninfected cells and makes them resistant.

The resulting ring of infected cells may stop expanding at the moment at which enough resistant cells are produced.

- Thus, scenarios (i) and (ii) lead to testable predictions. As documented by Duca et al. (2001) both types of behavior are observed, depending on cell type and possibly on the initial virus load.

Aims

- To model spatial spread of RSV infection and interferon activity.

Aims

- To model spatial spread of RSV infection and interferon activity.

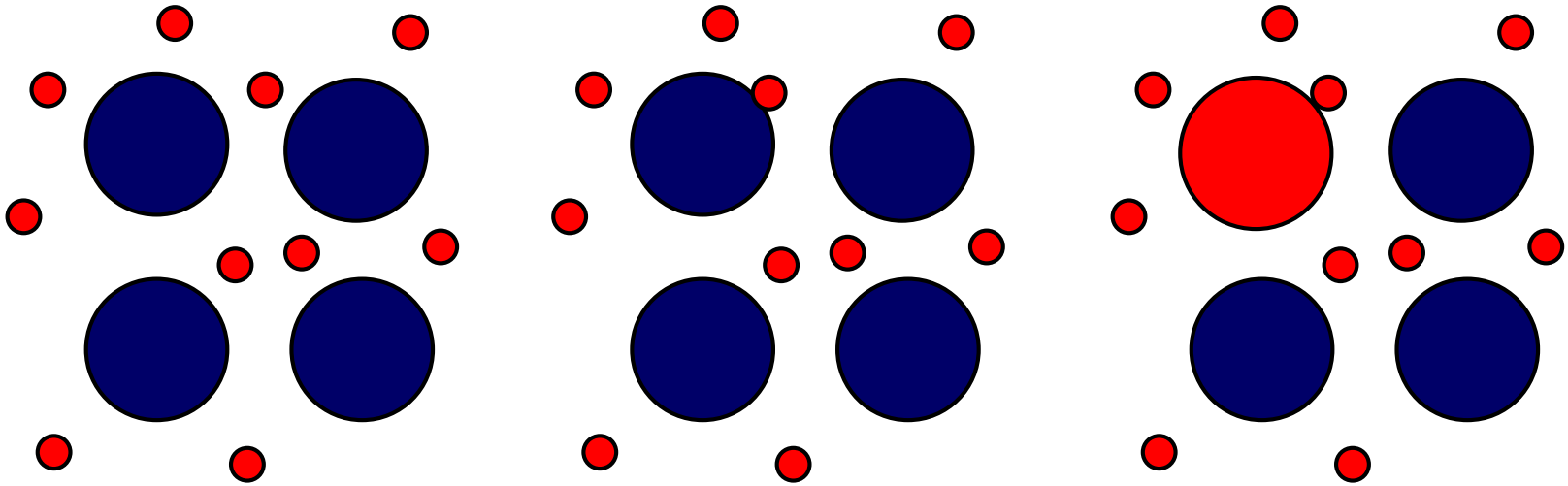
- To study the role of interferon and additional structure in the population of uninfected cells related to their resistance level.
  Resistance level is an individual feature of every cell and manifests itself in the lowered probability of the cell becoming infected.

Aims

- To model spatial spread of RSV infection and interferon activity.
- To study the role of interferon and additional structure in the population of uninfected cells related to their resistance level.
  Resistance level is an individual feature of every cell and manifests itself in the lowered probability of the cell becoming infected.
- To design experiments in planar cultures of monolayer epithelial cells to investigate paracrine effects, allowing examination of the effect of NF-κB or IFNγ on viral replication and spread.

Model of viral infection

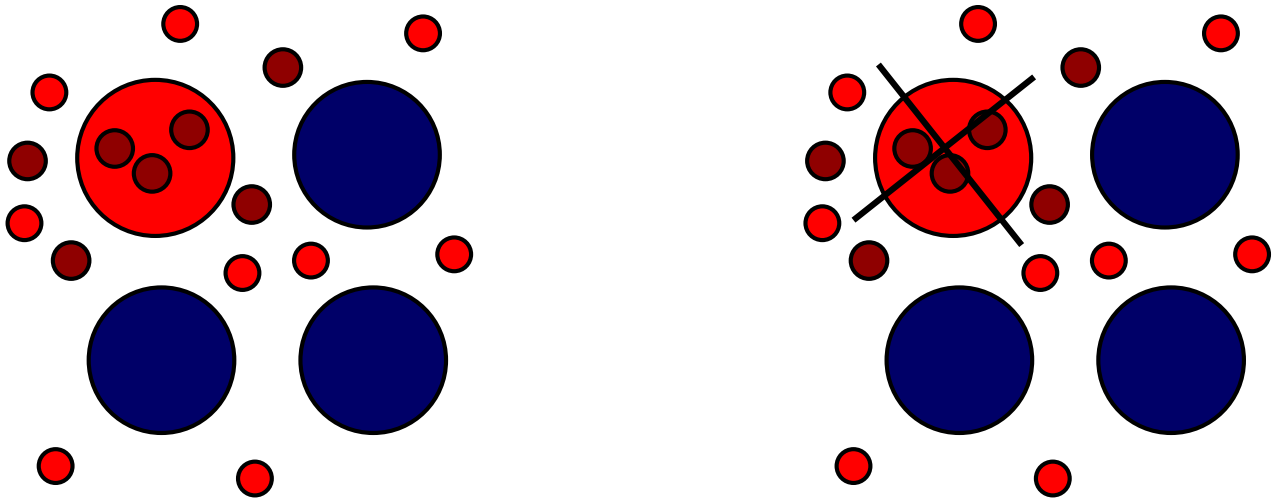
- We consider a population of uninfected cells, denoted by u, spread on the unit-square domain $[0,1] \times [0,1]$.
- In tissue culture, the cells actively divide until the dish is exposed to RSV, whereupon all the cells stop dividing.
- We assume that new target cells are produced everywhere at a rate m.
- Uninfected cells are attacked by extracellular virus, denoted by v_e.
- The infection spreads via diffusion of the extracellular virus.
- The rate of infection is proportional to the concentration of virus and uninfected cells.



Assumptions

We assume that

- Virion binding to a target cell consumes this virion (following Haseltine et al.).
- Infected cells produce new virions (at a rate a_3).
- Uninfected and infected cells die with the rates μ_u and μ_c respectively. The increased value of coefficient μ_c manifests the higher mortality of the cells, which are attacked by virions.
- We distinguish the population of the intracellular virus and denote it by v_i. The intracellular virions burst from the cells at a rate b.



Model

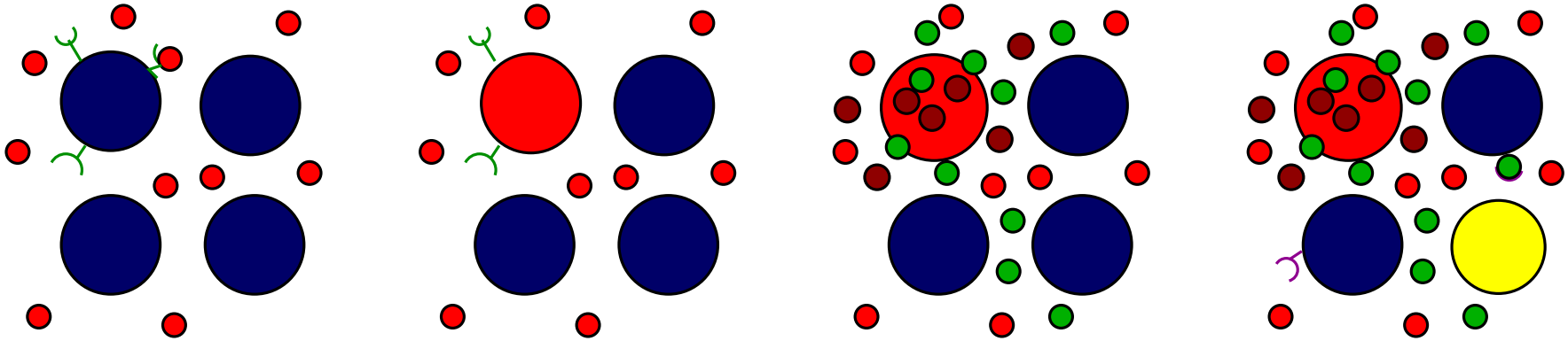
$$
\begin{aligned}
\frac{\partial}{\partial t}u &= m - p_u v_e u - \mu_u u, \\
\frac{\partial}{\partial t}c &= p_u v_e u - \mu_c c, \\
\frac{\partial}{\partial t}v_i &= a_3 c - b v_i, \\
\frac{\partial}{\partial t}v_e &= D_v \Delta v_e + b v_i - p_v v_e u - \mu_v v_e,
\end{aligned}
$$

with zero-flux boundary conditions for v_e.

Initial conditions involve a spike of extracellular virus at the center of the unit square.

Modeling cell-virus-interferon interactions

- Virus activates the signaling pathway, which leads to the synthesis of the interferon (IFN), denoted by i (at a rate a_1).
- Current evidence indicates that the virus shuts off IFN production after 10-15 h of infection. Thereafter the cell makes virions, but not IFN.



Interferon dynamics

- Interferon is released from the cells and spread by diffusion. Then:
  - Interferon interacts with receptors located on the membrane of uninfected cells, which leads to activation of the reactions cascade in the uninfected cells and production of proteins, which protect the cells from the viral infection. This process takes 12-24 hours.
  - Interferon which binds to the cell membrane is internalized and metabolized in the cell (at a rate b_i).
  - Interferon can also induce its own synthesis in the uninfected cells (at a rate a_2) via activation of IFN pathway.

Preliminary model describing spatial spread of infection

$$
\begin{aligned}
\frac{\partial}{\partial t}u &= m - p_u v_e u - \mu_u u - b_u u i, \\
\frac{\partial}{\partial t}c &= p_u v_e u - \mu_c c, \\
\frac{\partial}{\partial t}v_i &= a_3 c - b v_i, \\
\frac{\partial}{\partial t}v_e &= D_v \Delta v_e + b v_i - p_v v_e u - \mu_v v_e, \\
\frac{\partial}{\partial t}i &= D_i \Delta i + a_1 c + a_2 u i - b_i u i - \mu_i i, \\
\frac{\partial}{\partial t}r &= b_u u i - \mu_r r,
\end{aligned}
$$

Question

Shall we consider different coefficients p_u and p_v reflecting the fact that it is more than one virion, which is used up for infection of one cell? And similarly with b_i and b_u... how much interefron does one need for changing the cell from uninfected to resistant?

Numerical simulations

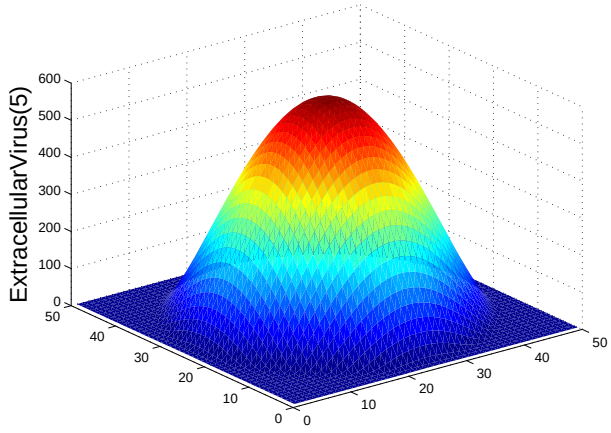
- Parameters used in simulations: $D_v = 0.01$, $D_i = 0.005$, $p_u = p_v = 1.2$, $b_u = b_i = 0.1$, $m = 1$, $a_3 = 5$, $b = 1$, $m_4 = 1$, $\mu_c = 0.01$, $\mu_u = 0.01$, $\mu_r = 0.01$.

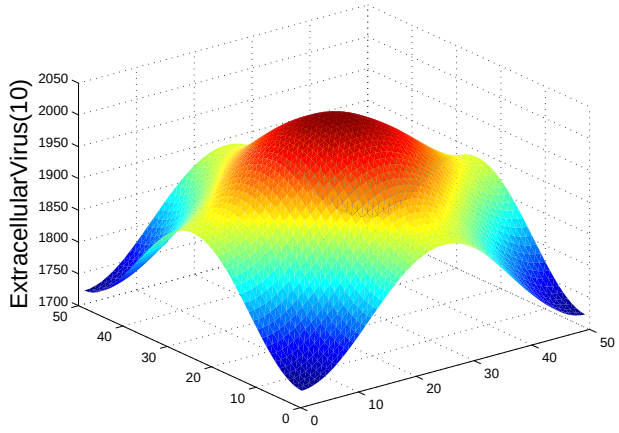
- Initially all the variables are set to zero, exept the concentration of virus, which has a peak of the value 10 in the middle of domain, on the square $[0.4, 0.6] \times [0.4, 0.6]$.

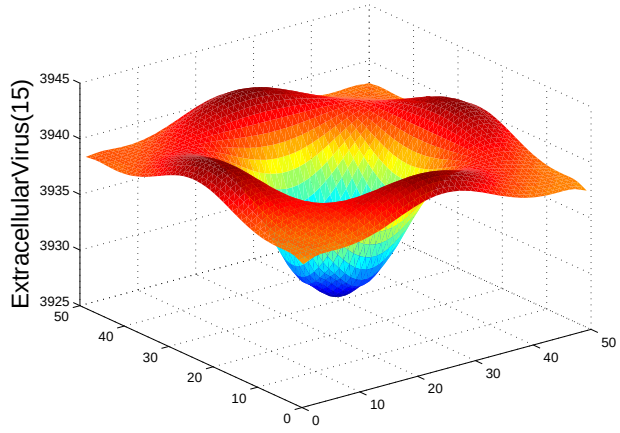
- Dynamics produced by the model is qualitatively consistent with the experiments of Duca et al. (2001).

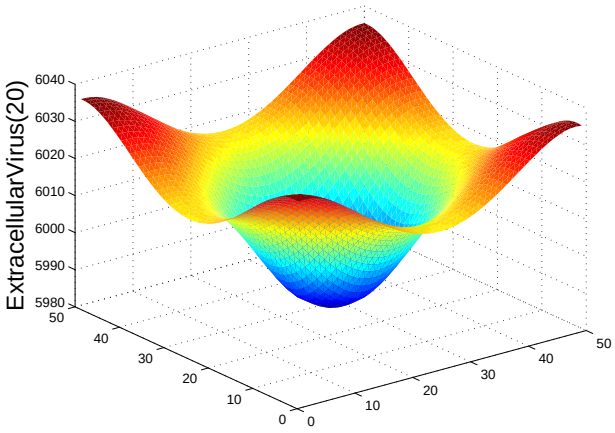
- The behavior is consistently reproduced for a wide range of parameter values.

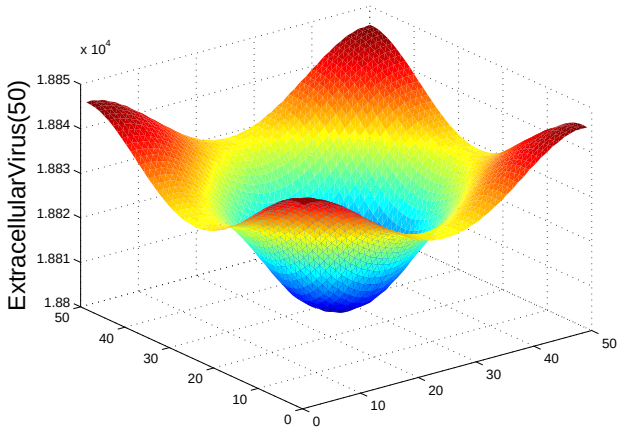
Extracellular Virus

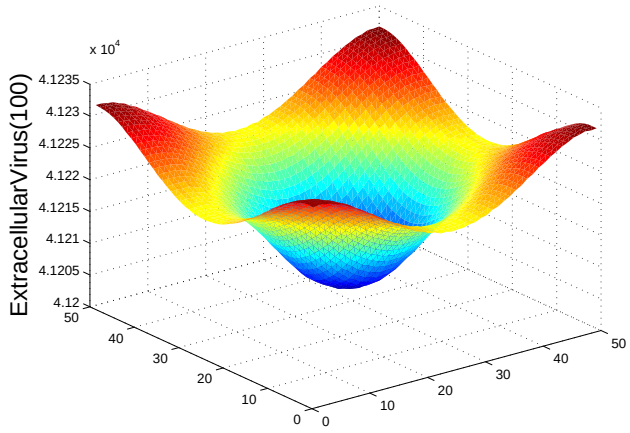




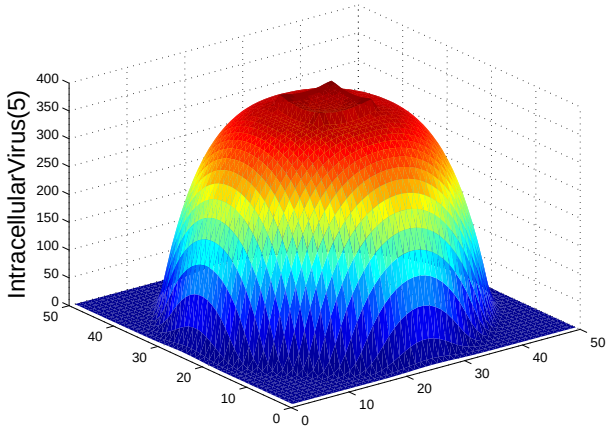


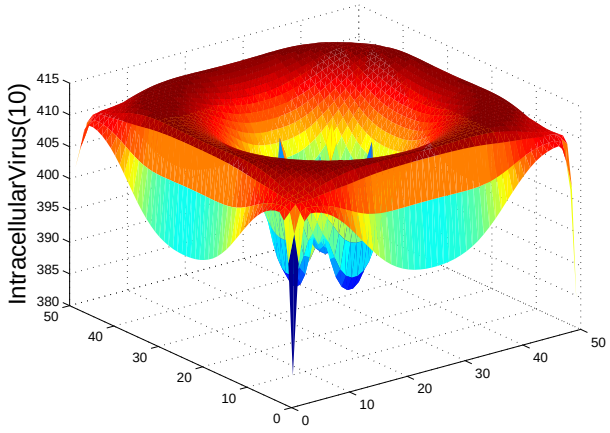


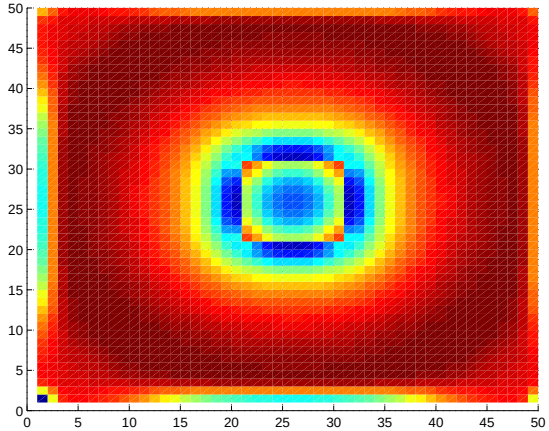


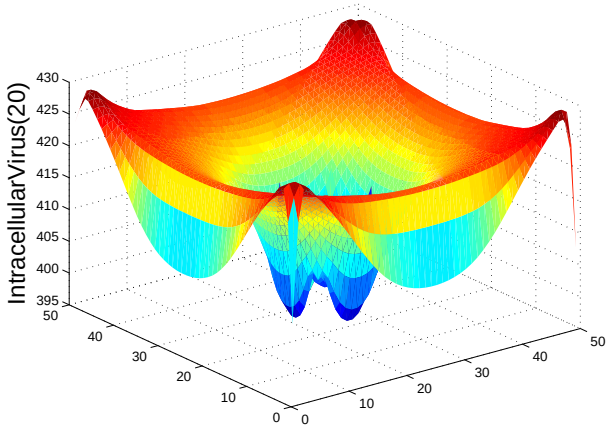


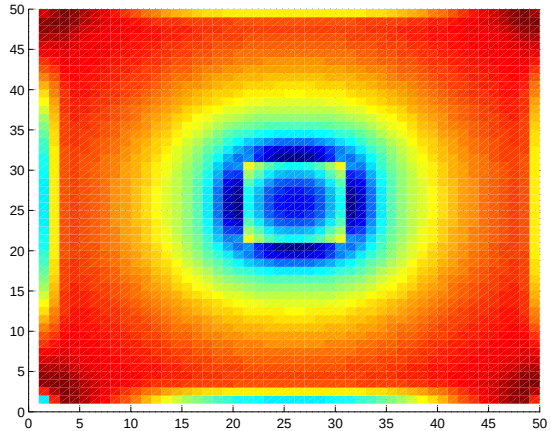
Intracellular Virus

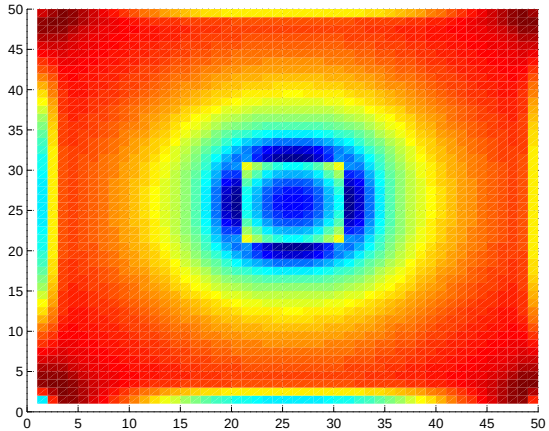




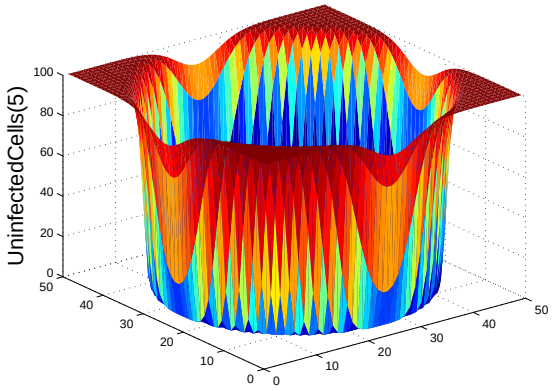


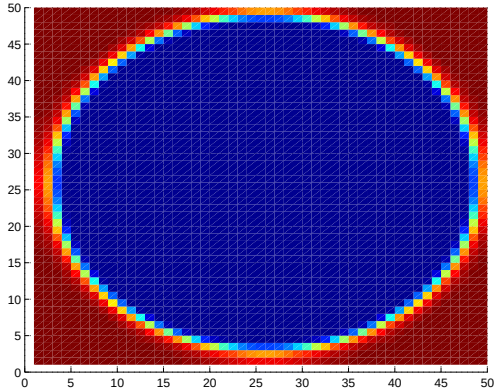


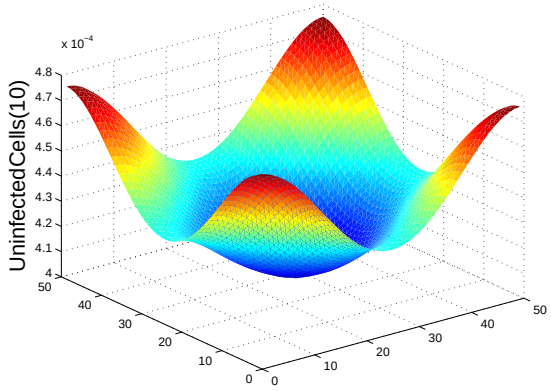


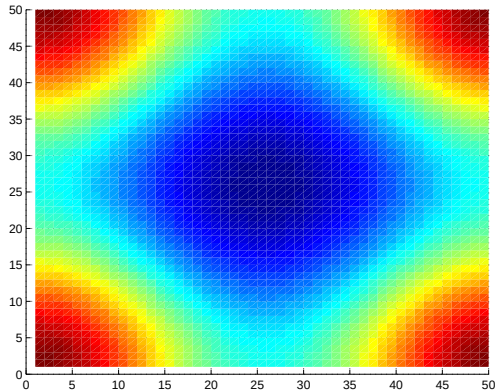


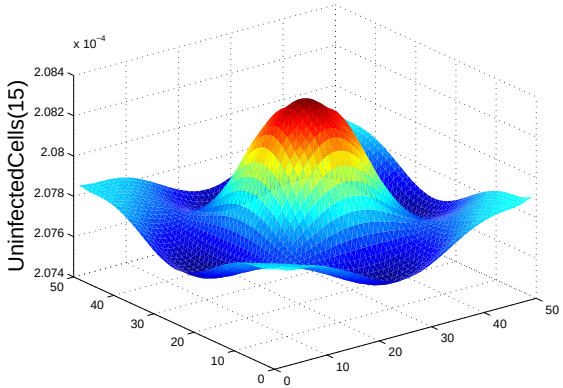
Uninfected cells

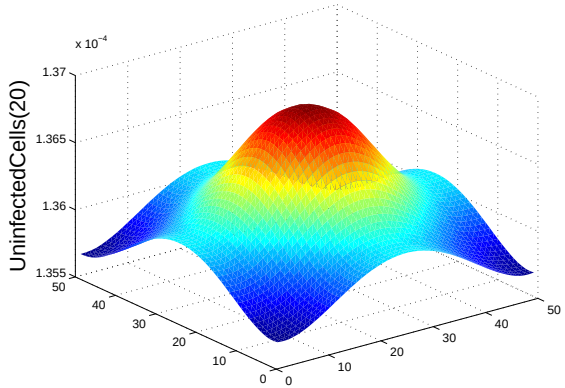


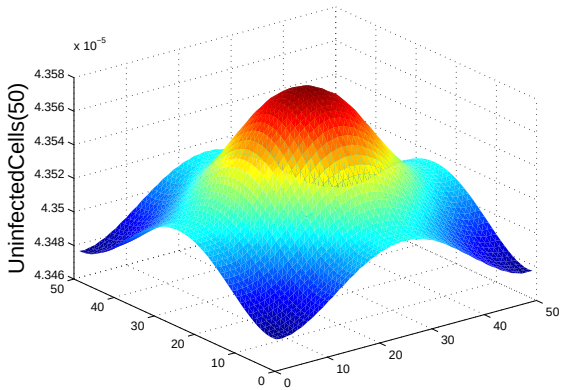


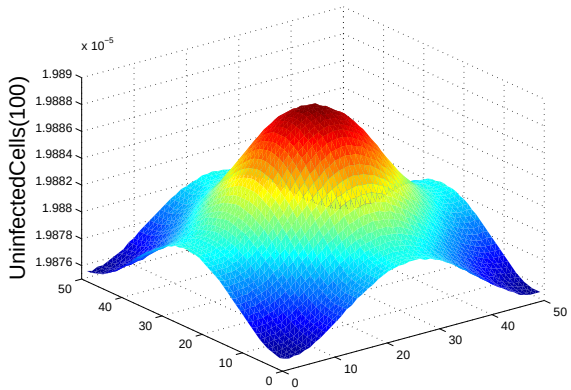




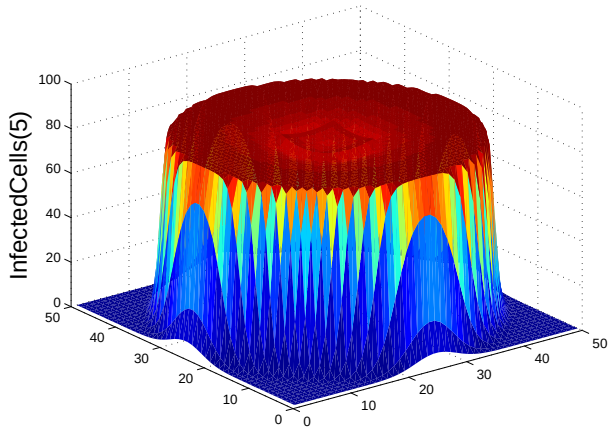


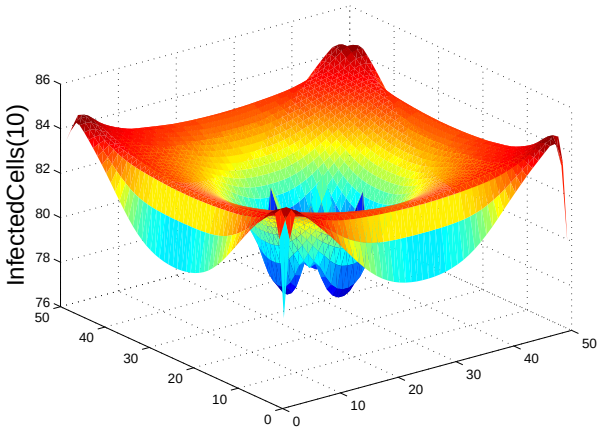


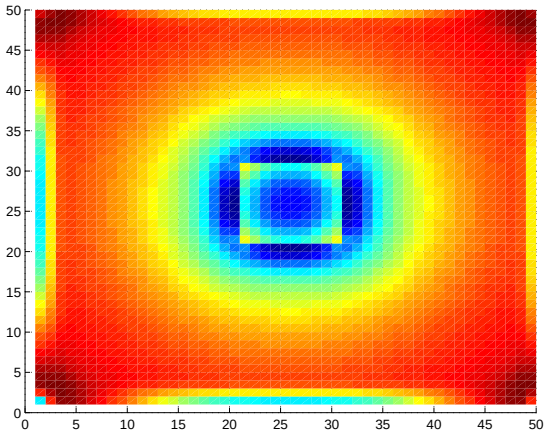


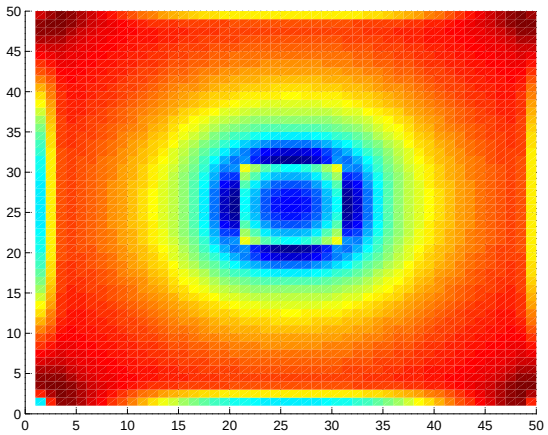


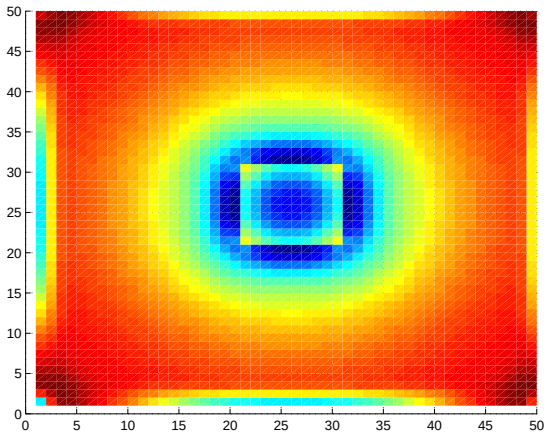
Infected cells



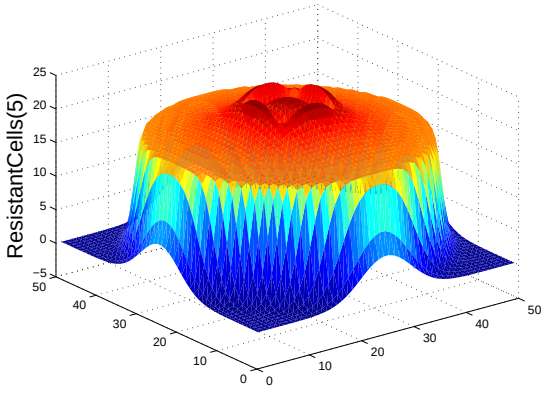


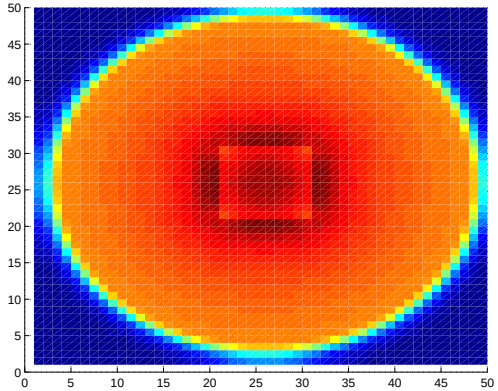


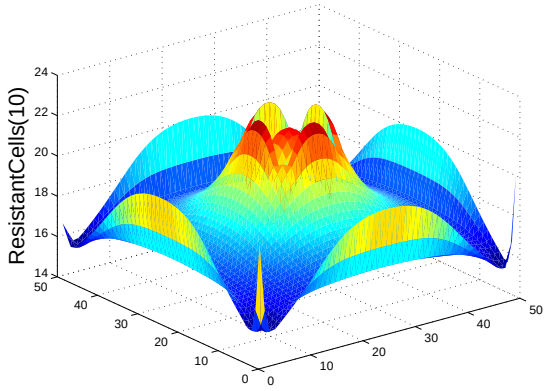


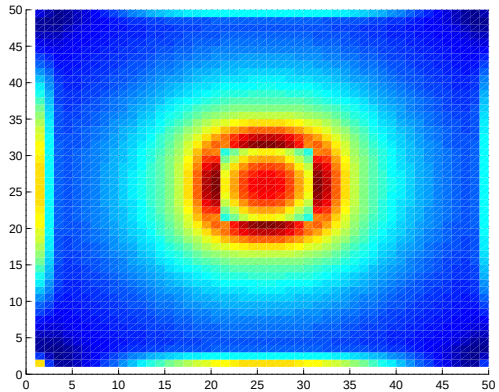


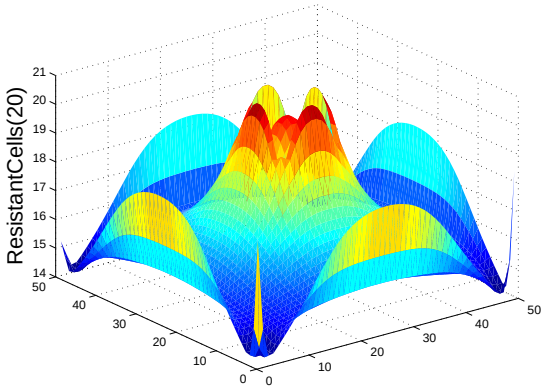
Resistant cells

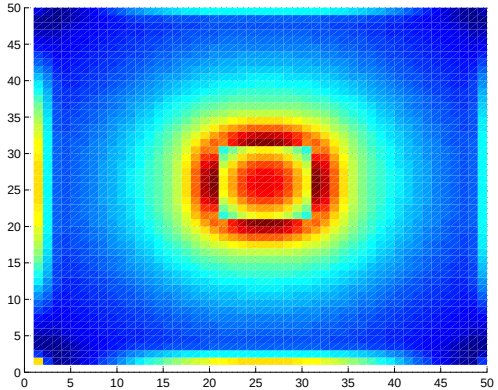


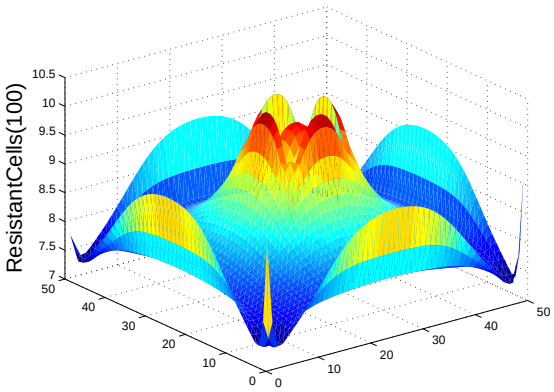


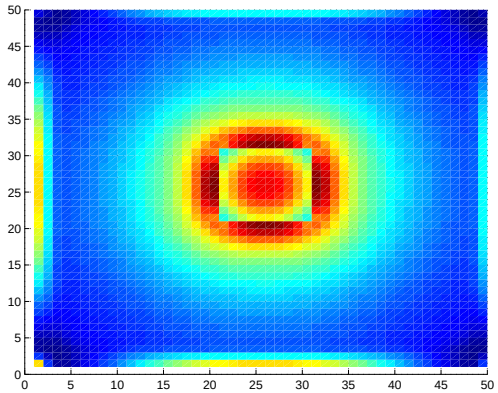




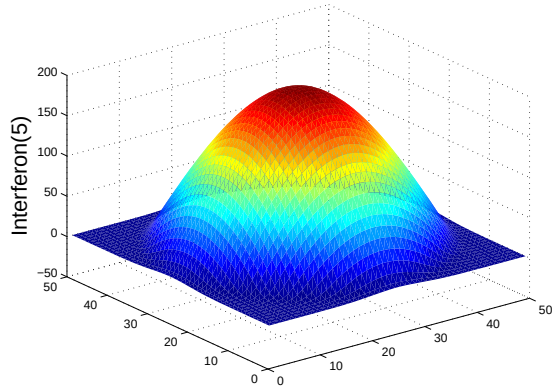


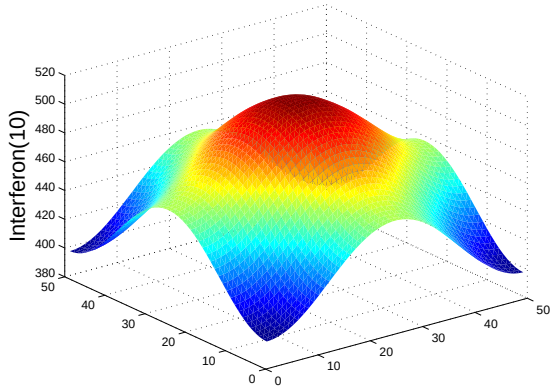


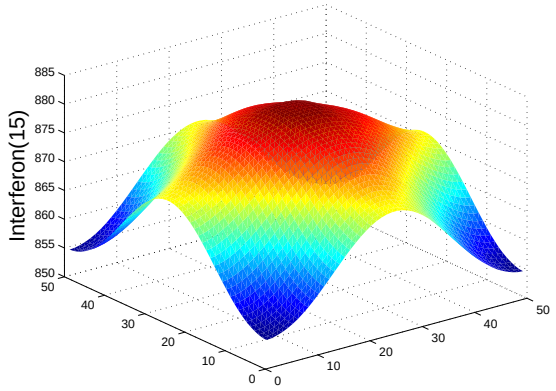


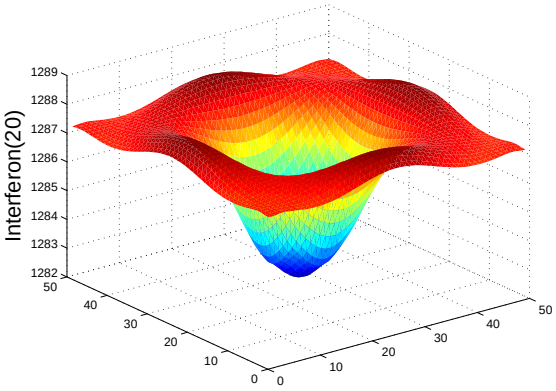


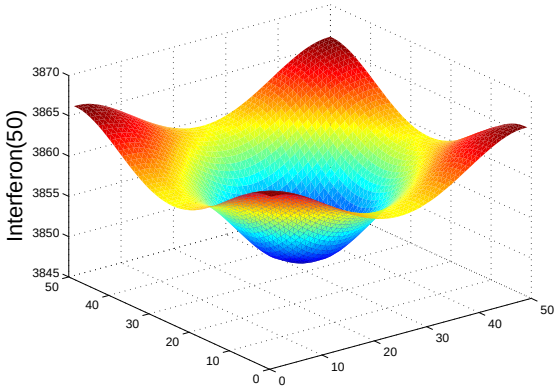
Interferon

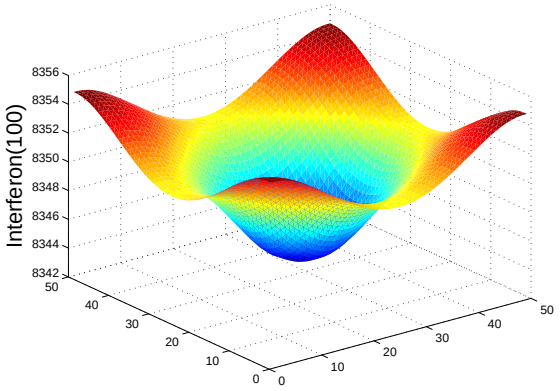

Interferon(5)
200
150
100
50
0
−50
50
40
30
20
10
0
0
10
20
30
40
50


Interferon(10)
520
500
480
460
440
420
400
380
50
40
30
20
10
0
0
10
20
30
40
50


Interferon(15)
885
880
875
870
865
860
855
850
50
40
30
20
10
0
0
10
20
30
40
50


Interferon(20)
1289
1288
1287
1286
1285
1284
1283
1282
50
40
30
20
10
0
0
10
20
30
40
50


Interferon(50)
3870
3865
3860
3855
3850
3845
50
40
30
20
10
0
0
10
20
30
40
50


Interferon(100)
8356
8354
8352
8350
8348
8346
8344
8342
50
40
30
20
10
0
0
10
20
30
40
50

Questions arising in modeling

- Do the infected cells die faster than uninfected?
- How new virions burst from the cells? Does it take place all the time or maybe only during the destruction of the cell? This two situations correspond to the different models!

More data on viral replication

- First round of viral RNA transcription is completed about 12 h after viral infection.
- First viral burst occurs about 18 h after infection.
- Number of active viruses increase in the medium until 30 h, saturating at a concentration of 10,000,000 viruses/ml. These cultures are typically 10 ml.
- Cells survive until about 48 h in culture, so there are about 2.5 rounds of viral replication.

Modeling syntesis of the virions

Continuous synthesis:

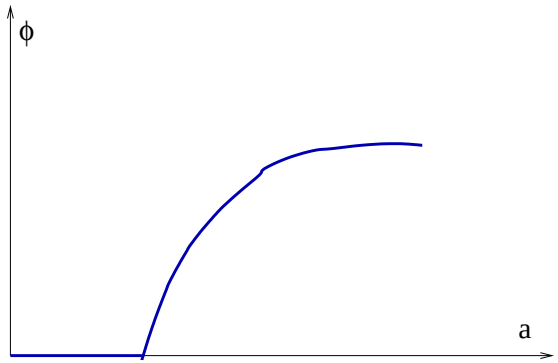
$$\frac{\partial}{\partial t} v_e = D_v \Delta v_e + b v_i - p_v v_e u - \mu_v v_e,$$

Burst during cell's explosion

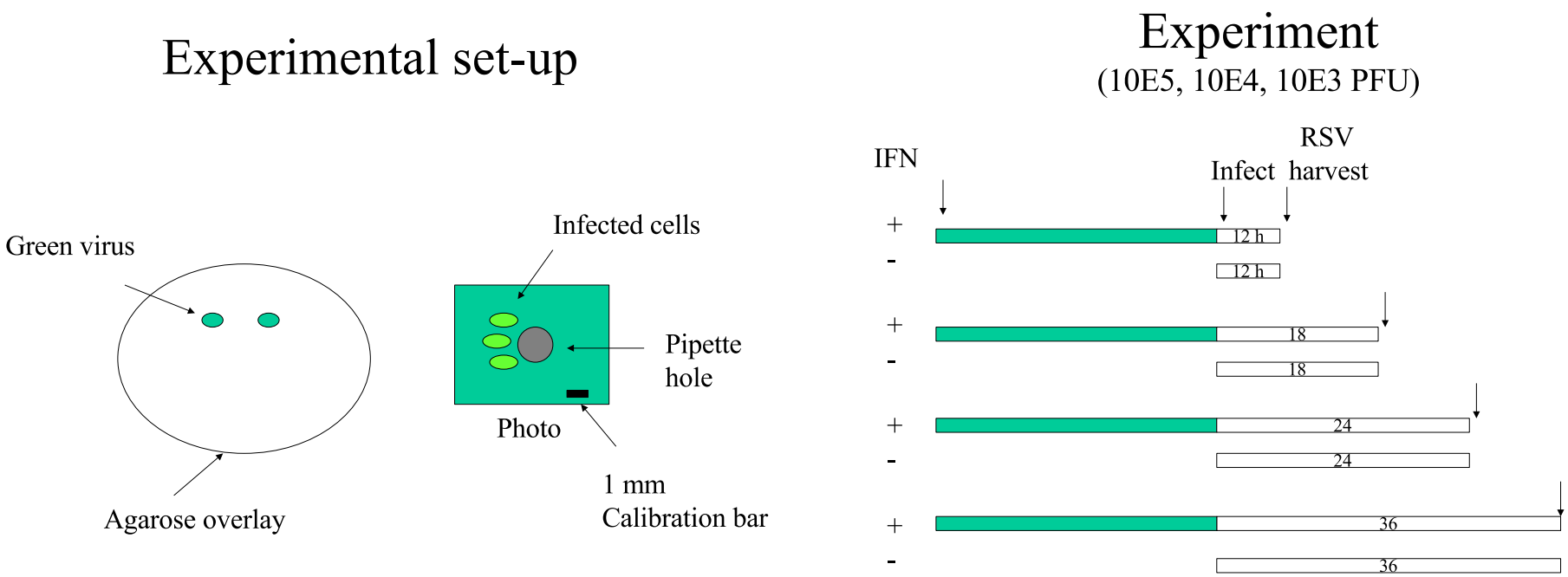
$$\frac{\partial}{\partial t} v_e = D_v \Delta v_e + (b v_e u)(t - \tau) - p_v v_e u - \mu_v v_e,$$

Synthesis after a delay, but then continuous

$$\frac{\partial}{\partial t} v_e = D_v \Delta v_e + (b v_e u) * \phi - p_v v_e u - \mu_v v_e,$$

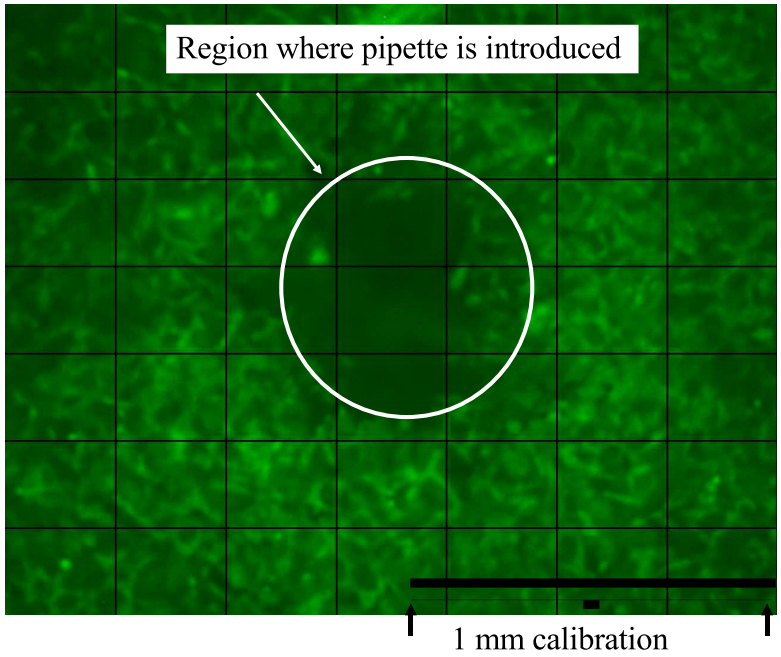


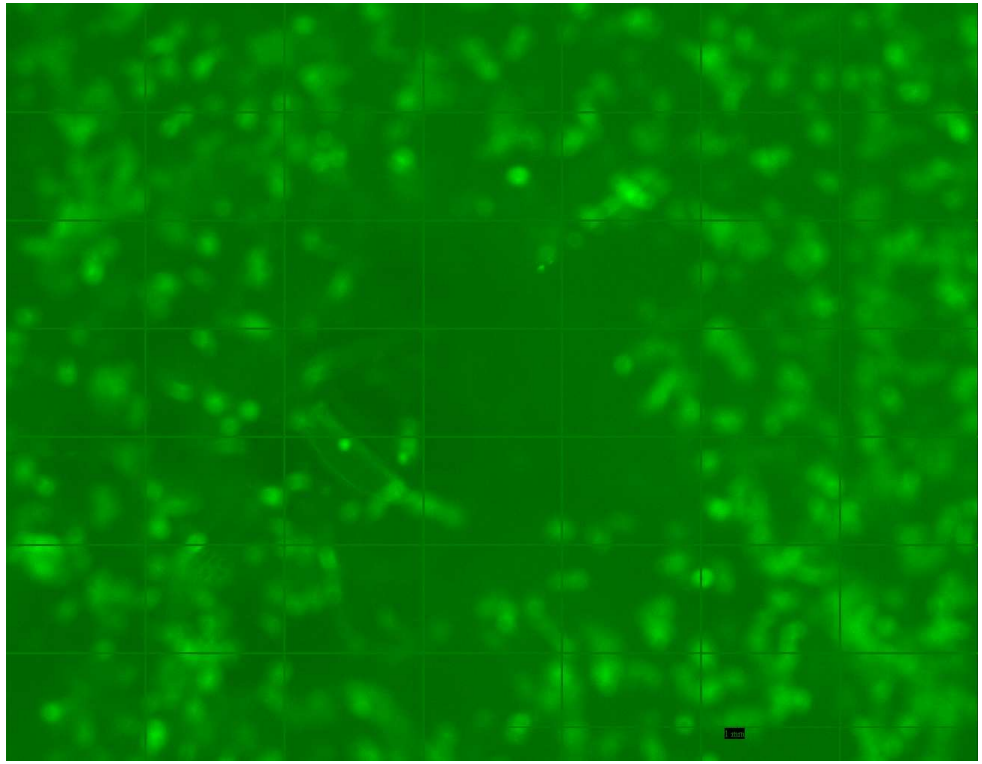
New experiments



- IFN pretreated for 36 h (shorter times had no effect).
- Exposure times for all photographs the same at 5000 msec.

New experiments





Hypotheses:

- Interferon pretreatment changes the initial resistance of the cells and makes it more difficult for virions to invade the cells.
- It has been recently found that resistant cells express the Toll-like receptor, which is important in IFN activation. This pathway amplifies IFN expression in the affected cells once they become infected or exposed to double stranded RNA.

Infection-age structure

- Since intracellular processes in every cell depend on the infection-age of this cell we introduce additional variable a describing this structure.
- We assume that the density of infected cells depends on time and infection-age $c(t, a)$, $a \in [0, \infty]$.
- $\mu_c(a)$ - infection-age specific mortality rate of the infected cells.
- $a_1(a)$ - infection-age specific rate of the interferon production.
- $a_3(a)$ - infection-age specific rate of virions production.

Structured equation

$$\frac{\partial}{\partial t}c(a,t) + \frac{\partial}{\partial a}(g(a,t)c(a,t)) = f_1(c,a,t), \quad (1)$$

$$g(0,t)c(0,t) = f_2(c,a,t) \quad (2)$$

- Coupling with the vector of variables described by ODEs subsystem.
- How to find f_2?

Infection-age structured model

$$
\begin{aligned}
\frac{\partial}{\partial t}u &= m(u) - p_u v_e u - \mu_u u - b_u u i, \\
\frac{\partial}{\partial t}c(t,a) + \frac{\partial}{\partial a}c(t,a) &= -\mu_c(a)u(t)c(t,a), \\
\frac{\partial}{\partial t}v_e &= D_v \Delta v_e + \int_0^\infty a_3(a)c(t,a)da - \mu_v v_e + p_v v_e u, \\
\frac{\partial}{\partial t}i &= D_i \Delta i + \int_0^\infty a_1(a)c(t,a)da + a_2 u - b_i u i, \mu_i i \\
\frac{\partial}{\partial t}r &= b_u u i - \mu_r r,
\end{aligned}
$$

Initial conditions:

$u(0) = u_0,\ r(0) = 0,\ i(0) = 0,\ v_i(0) = 0,$

$v_e(0) = v_0,\ c(0,a) = c_0(a).$

Boundary condition

The change of the total concentration of cells is equal to the difference between influx of the cells from proliferation and outflux of the cells due to their death,

$$\frac{d}{dt}(u + \int_0^\infty c(t,a)da + r) = m(u) - \mu_u u - \int_0^\infty \mu_c(a)c(t,a)da - \mu_r r. \quad (*)$$

Integrating the equation for u over a we obtain,

$$\int_0^\infty \frac{\partial}{\partial t}c(t,a)da + \int_0^\infty \frac{\partial}{\partial a}c(t,a)da = -\int_0^\infty \mu_c(a)c(t,a)da.$$

Hence,

$$\int_0^\infty \frac{\partial}{\partial t}c(t,a)da = c(t,0) - \int_0^\infty \mu_c(a)c(t,a)da.$$

Summing side by side the equations for u, $\int_0^\infty c(t,a)da$ and r and comparing with $(*)$ we conclude that

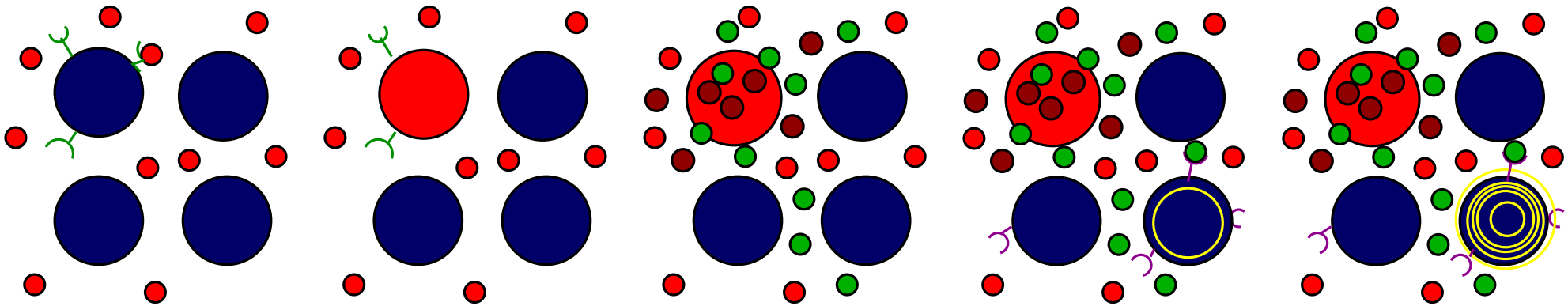
$$c(t,0) = p_v v_e(t) u(t)$$

Properties of the model without diffusion

- Local existence and uniqueness.
- Global existence (nonnegativity of variables + *apriori* estimates for the total number of the cells and the total number of virions).
- Continuous dependence of the solution on the initial conditions in the weak* topology (using results of Diekmann and Getto).
- Equilibria (trivial, disease-free and endemic).

Changing resistance of the cells?

- Now, we want to focus on the role of interferon and consider additional structure in the population of uninfected cells related to their resistance level.
- We assume that together with the production of protective proteins, the level of cell's resistance increases. This manifests itself in the decrease of the probability of infection (decrease of the infection rate).
- We assume that the rate of infection is proportional to the concentration of virons and uninfected cells but also on the concentration of the protective proteins on the cell membrane ("resistance level").
- Considering "resistance level" of cells leads to a structured model.



Modeling the structure in well-mixed (spatially homogeneous) medium

- We assume that resistant cells have resistance level and denote it by $x \in [0, 1]$.

$u(x,t)$	uninfected cells
$c(t)$	infected cells
$v(t)$	virions
$i(t)$	interferon.

- $p(x)$ denotes now a probability that a cell with resistance x is infected by a virion.

- The resistance of a cell changes proportionally to the amount of interferon acting on this cell. Such individual nonlinear change of the resistance is described using function $g(u, x, t)$.

$$\frac{dx}{dt} = g(u, x, t)$$

.

Structured equation

$$\frac{\partial}{\partial t}u(x,t) + \frac{\partial}{\partial x}(g(u,x,t)u(x,t)) = f_1(u,x,t), \quad (3)$$

$$g(0,t)u(0,t) = f_2(u,x,t) \quad (4)$$

- Coupling with the vector of variables described by ODEs subsystem.
- Shall we consider cells proliferation?
- How to find f_2?

New variable

$w(t)$	**target cells (wild-type cells),**
$u(x,t)$	**resistant cells (cells, which are already under influence of interferon)**
$c(t)$	infected cells
$v(t)$	virions
$i(t)$	interferon

- Target cells (wild-type cells) are the cells which are not infected neither influenced by INF.

- Resistant cells are the cells in which interferon already activated production of protective proteins and synthesis of new interferon.

Assumptions

- All uninfected cells, i.e. target and resistant cells, can be infected (with different probabilities).
- Interferon acts on target cells changing them into resistant cells but already with some resistance.
- Interferon acts also on resistant cells changing their resistance.

Nonlinear structure

$$g(x,t) = G(x,i) \tag{5}$$

Model

$$\frac{\partial}{\partial t}u(x,t) + \frac{\partial}{\partial x}(g(x,t)u(x,t)) = -p(x)v(t)u(x,t) - \mu_u u(x,t), \quad (6)$$

$$g(0,t)u(0,t) = \alpha i(t)w(t) \quad (7)$$

$$\frac{d}{dt}w(t) = m(u) - p_w v(t)w(t) - \mu_w w(t) - \alpha i(t)w(t), \quad (8)$$

$$\frac{d}{dt}c(t) = (\int_0^1 p(s)u(s,t)ds + p_w w(t))v(t) - \mu_c c(t), \quad (9)$$

$$\frac{d}{dt}i(t) = a_1 c(t) + a_2 \int_0^1 u(s,t)ds - (b_1 \int_0^1 u(s,t)ds + b_w w(t))i(t) - \mu_i i, \quad (10)$$

$$\frac{d}{dt}v(t) = a_3 c(t) - (\int_0^1 p(s)u(s,t)ds + p_w w(t))v(t) - \mu_v v, \quad (11)$$

with initial conditions $[u(0,x), w(0), c(0), i(0), v(0)] = [0, w_0, c_0, i_0, v_0]$

General form of the model

$$\frac{\partial}{\partial t}u(x,t) + \frac{\partial}{\partial x}(g(x,t)u(x,t)) = -f_1(u(x,t), V(t), x), \quad (12)$$

$$g(0,t)u(0,t) = f_2(u(x,t), V(t)) \quad (13)$$

$$\frac{d}{dt}V(t) = f_3(V(t), \int_0^1 u(s,t)ds) \quad (14)$$

with $g(x,t) = f_4(x, V(t), \int_0^1 u(s,t)ds)$ where u is a scalar function, $u : [0,1] \times [0,\infty) \to \mathbb{R}$ and V is a vector of functions, $V = [w, c, i, v]$, $V : [0,\infty) \to \mathbb{R}^4$.

Spatial process

- We consider now a spatial two-dimensional structure of this process, denoted by $\Omega = [0,1] \times [0,1]$, and introduce a dependence of all the variables on the spatial variable.

- Spatial variable: x, $x \in \Omega$. The resistance level is now denoted by r , $r \in [0,1]$.

- We consider: $u(x,r,t)$, $w(x,t)$, $c(x,t)$, $i(x,t)$, $v(x,t)$.

- Additionaly, we assume that both virus and interferon diffuse with diffusion coefficients d_v and d_i, respectively. We assume zero-flux boundary conditions on the boundary of Ω, $\partial\Omega$.

Spatial model with structure

$$\frac{\partial}{\partial t}u(x,r,t) + \frac{\partial}{\partial r}(g(x,r,t)u(x,r,t)) = -f_1(u(x,r,t),V(x,t),r), \quad (15)$$

$$g(x,0,t)u(x,0,t) = f_2(u(x,r,t),V(x,t)) \quad (16)$$

$$\frac{\partial}{\partial t}V(x,t) = D\Delta_x V(x,t) + f_3(u(V(x,t),\int_0^1 u(x,s,t)ds)$$

where Δ_x denotes a Laplacian operator on Ω and D is a diagonal matrix of diffusion coefficients of the form,

$$D = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & d_i & 0 \\ 0 & 0 & 0 & d_v \end{pmatrix}. \quad (17)$$

For v and i we assume zero-flux boundary conditions.

Further aims

- To study the asymptotic behavior of the spatial model (stationary fronts of infection?)
- To study the properties of the structured model without and with diffusion.

Further modeling tasks

- Estimation of parameters and incorporation of signaling pathways.
- Incorporation of the dynamics at the within-cell level.
- Simulation of the process with cellular automata.