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“Математическое моделирование в биомедицине”

Математическое моделирование распространения вирусной инфекции с учётом воспаления

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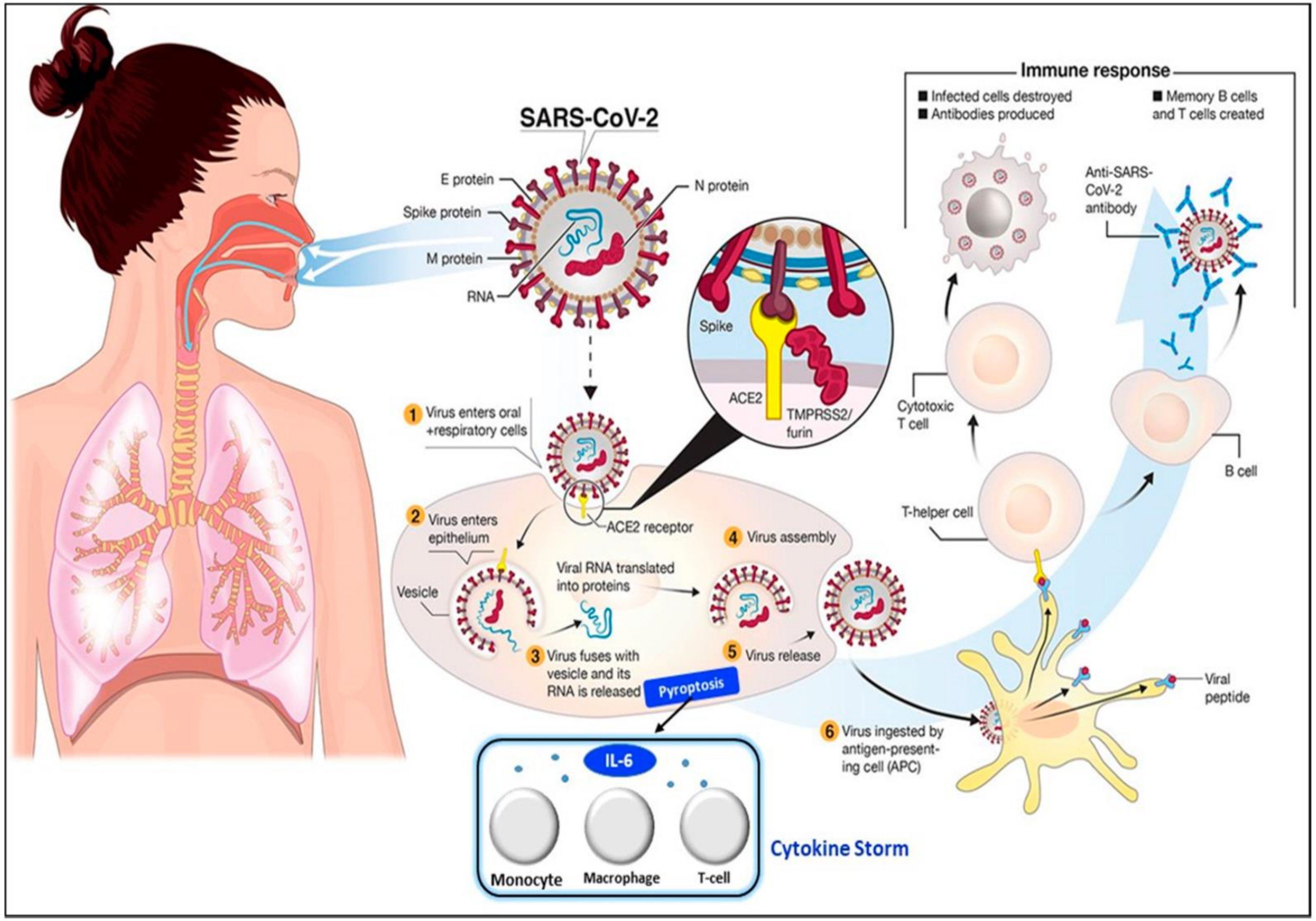
XV конференция «Математические модели и численные методы в биологии и медицине»,
ИВМ РАН, Москва, 1–3 ноября, 2023 г.

Pathophysiology of the SARS-CoV-2 virus

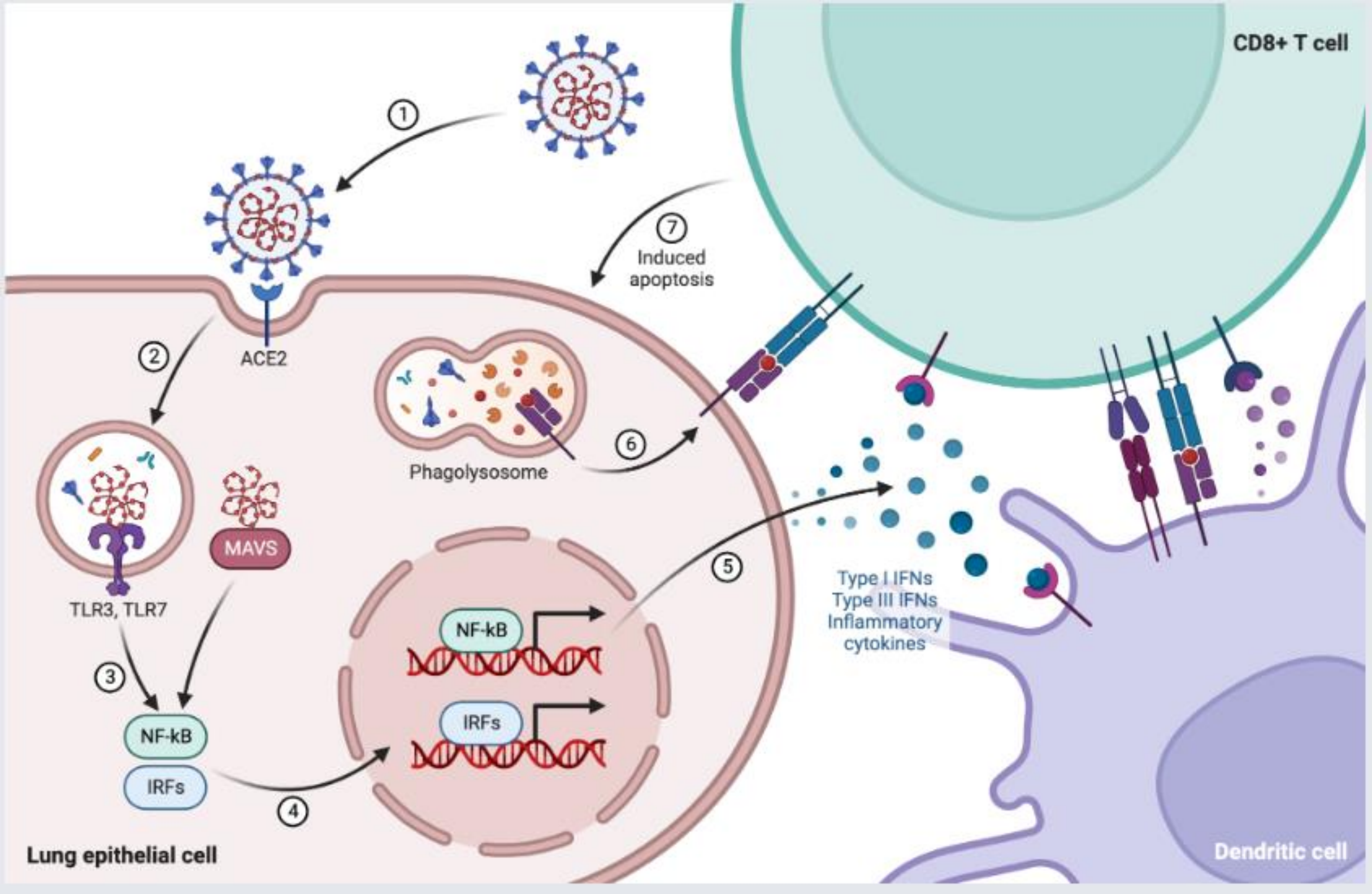


Infection-Mediated Clinical Biomarkers for a COVID-19 Electrical Biosensing Platform

by Reena Sri Selvarajan [1], Subash C. B. Gopinath [2], Noraziah Mohamad Zin [3] and Azrul Azlan Hamzah [1,*]

Sensors **2021**, *21*(11), 3829; https://doi.org/10.3390/s21113829

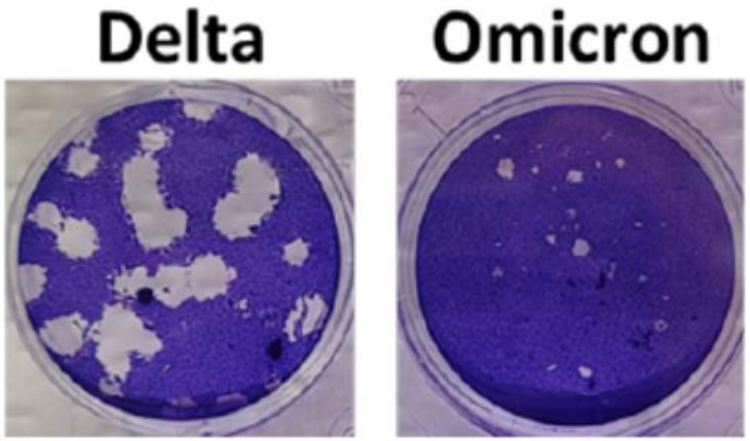
Virus infection - immune response - inflammation

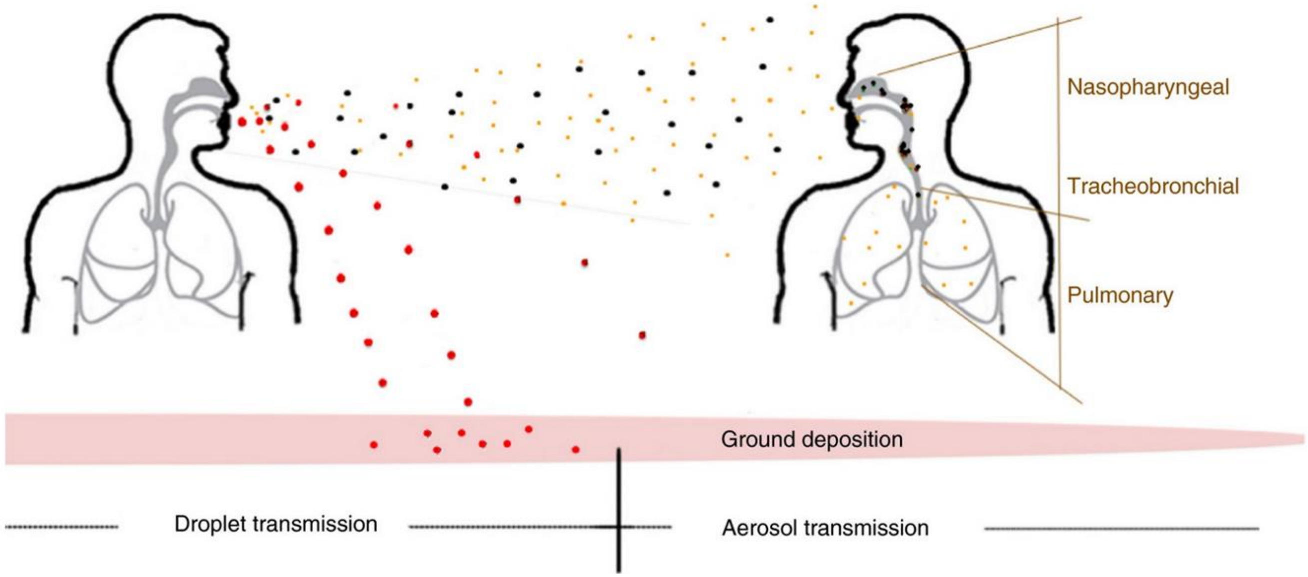


Acute Immune Responses to Coronaviruses

Gillian Dunphy

Infection spreading virulence and infectivity

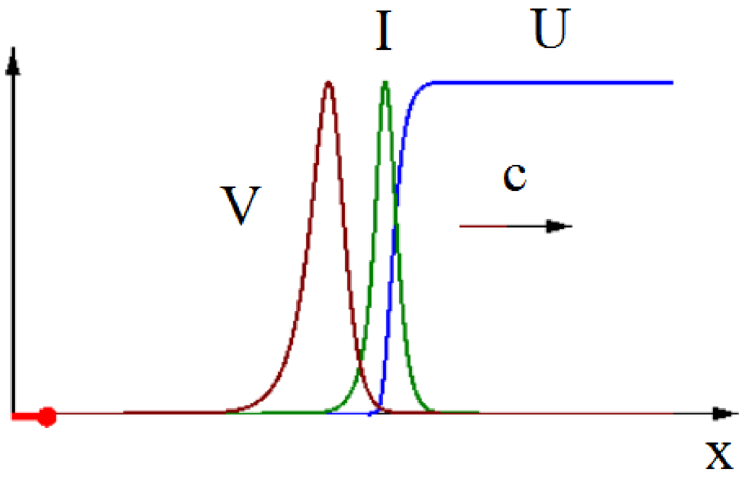




$$\frac{\partial U}{\partial t} = -aUV,$$

$$\frac{\partial I}{\partial t} = aUV - \beta I,$$

$$\frac{\partial V}{\partial t} = D\frac{\partial^2 V}{\partial x^2} + bI_\tau - \sigma V$$



System characteristic	Biological interpretation
wave speed c	virulence (disease severity)
total viral load $\int V\,dx$	infectivity

Model from 3 equations

[Ait+22] L Ait Mahiout et al. "Virus replication and competition in a cell culture: Application to the SARS-CoV-2 variants". en. In: *Appl. Math. Lett.* 133.108217 (Nov. 2022), p. 108217.

$$\frac{\partial U}{\partial t} = -aUV,$$

$$\frac{\partial I}{\partial t} = aUV - \beta I,$$

$$\frac{\partial V}{\partial t} = D\frac{\partial^2 V}{\partial x^2} + bI_\tau - \sigma V$$

$$R_v = abu_0/(\beta\sigma)$$

$$R_v(\omega - 1) = \ln\omega \qquad \omega = u_f/u_0.$$

$$V_x \approx bcu_0/(\beta\sigma). \qquad V_X \equiv \int_{-\infty}^{\infty} v(x)dx = -\frac{c}{a}\ln\omega\ .$$

$$c = \min_{\mu>\mu_0} F(\mu) \equiv \frac{\sqrt{D\mu}}{\sqrt{\mu + \sigma - abu_0 e^{-\mu\tau}/(\mu+\beta)}}\ ,$$

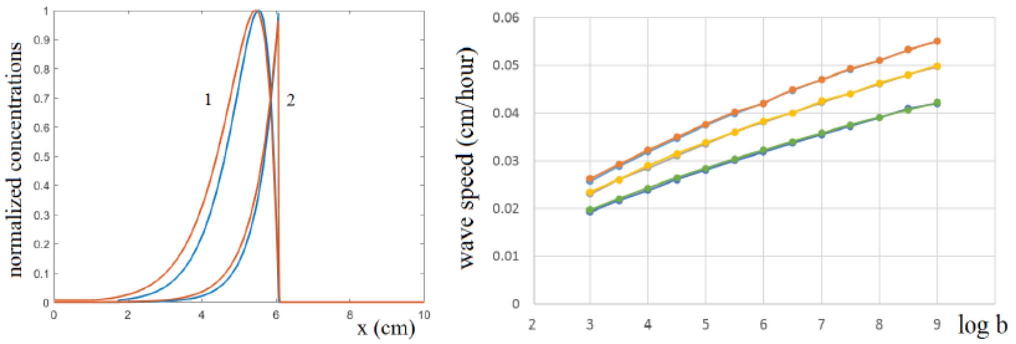


Figure 1: Left: virus concentration (curve 1) and concentration of infected cells (curve 2) in numerical simulations (red) and analytical approximation (blue) for the values of parameters: $a = 0.1$ $(1/(hour \cdot virus)), b = 1000$ $(copies/(hour \cdot cell)), \beta = 0.1$ $(1/hour), \sigma = 0.1$ $(1/hour), D = 10^{-4}$ $(cm^2/hour)$. Analytical and numerical solutions for $v(\xi)$ are normalized by its maximum, $v_{max} = 3672$ $(copies/ml)$. Right: wave speed in numerical simulations and analytical formula (curves coincide) for the values of parameters: $a = 0.1, D = 0.001, \beta = 0, \tau = 2$ $(hour)$ (upper curve), $\tau = 5$ (middle curve) and $\tau = 8$ (lower curve).

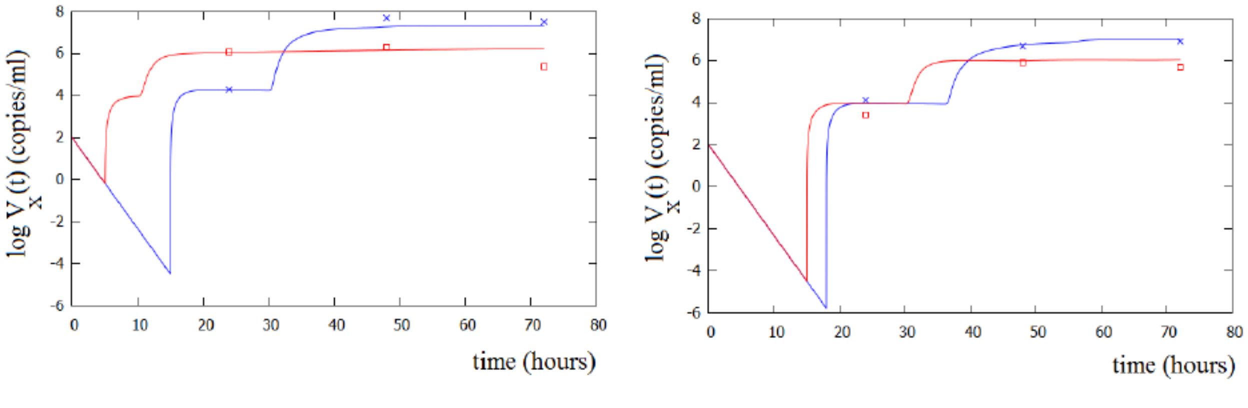


Figure 3: Left: human nasal cells, experimental results from [5] (dots) and numerical simulations with the values of parameters for Delta (blue): $a = 10^{-5}, b = 2 \cdot 10^7, \beta = 0.01, \sigma = 1, \tau = 15$; for Omicron (red): $a = 10^{-4}, b = 10^6, \beta = 0.01, \sigma = 1, \tau = 8$. Right: human lung cells, experimental results from [5] (dots) and numerical simulations with the values of parameters for Delta (blue): $a = 10^{-5}, b = 10^7, \beta = 0.01, \sigma = 1, \tau = 17$; for Omicron (red): $a = 10^{-4}, b = 10^6, \beta = 0.01, \sigma = 2, \tau = 15$. Common parameters: $D = 0.001, L = 10, x_0 = 1, v_0 = 1, U_0 = 1$. Units of parameters are given in Figure 1.

Model of the viral infection with respect to inflammation

$$\frac{\partial U}{\partial t} = k_1(U_0 - U) - k_2 UV,$$

$$\frac{\partial W}{\partial t} = k_2 UV - k_3 SW - \sigma_1 W,$$

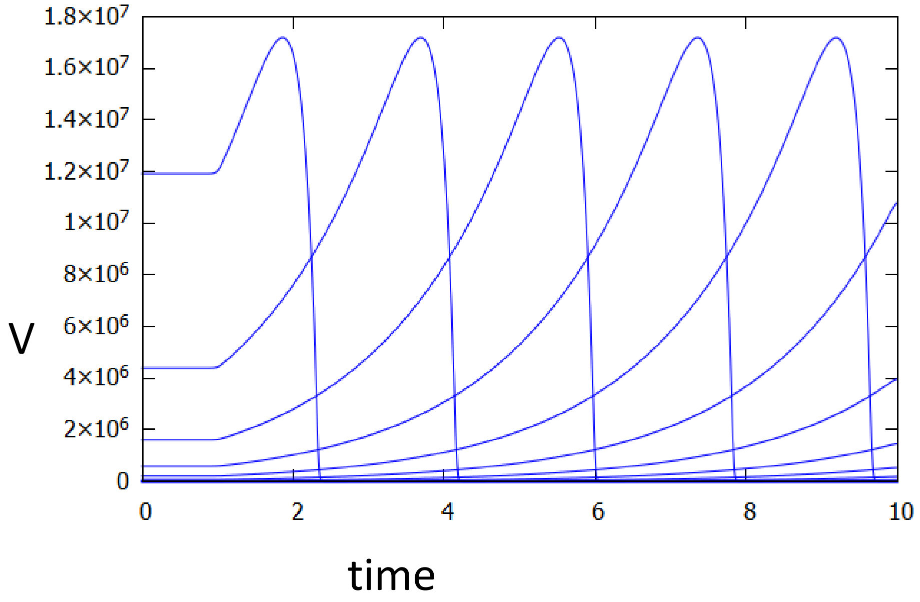
$$\frac{\partial V}{\partial t} = D_1 \frac{\partial^2 V}{\partial x^2} + bW - \sigma_3 V,$$

$$\frac{dS(t)}{dt} = k_6 J(W) - k_7 J(W) S - \sigma_4 S,$$

$$J(W) = \int_{-\infty}^{+\infty} W(x,t)\, dx.$$

- U - uninfected cells
- W - infected cells
- V - virus
- S - inflammatory cytokines

Citation: Mozokhina, A.; Ait Mahiout, L.; Volpert, V. Modeling of Viral Infection with Inflammation. *Mathematics* **2023**, *11*, 4095. https://doi.org/10.3390/math11194095



Case 1: clearance of cytokines = 0

- Swell / edema
- Stationary points: $W = 0,\ V = 0,\ S$ and U are arbitrary.
- Virus replication number: $R_v^{(2)} = \dfrac{k_2 b U_0}{\sigma_3 (k_3 S_0 + \sigma_1)} < 1.$

- Wave
  - total viral load: $\ln X = R_v(X - 1), \quad R_v = \dfrac{k_2 b u_0}{\sigma_3 (\alpha + \sigma_1)},$ $\quad \alpha = k_3 k_6 / k_7. \quad X = u_f / u_0$

$$J(v) = -\frac{c \ln X}{k_2} \approx \frac{c R_v}{k_2}.$$

α – effective cell death due to inflammation

for α -> 0 all formulas are the same as for UIV system

for $\alpha > \frac{k_2 b u_0}{\sigma_3} - \sigma_1$

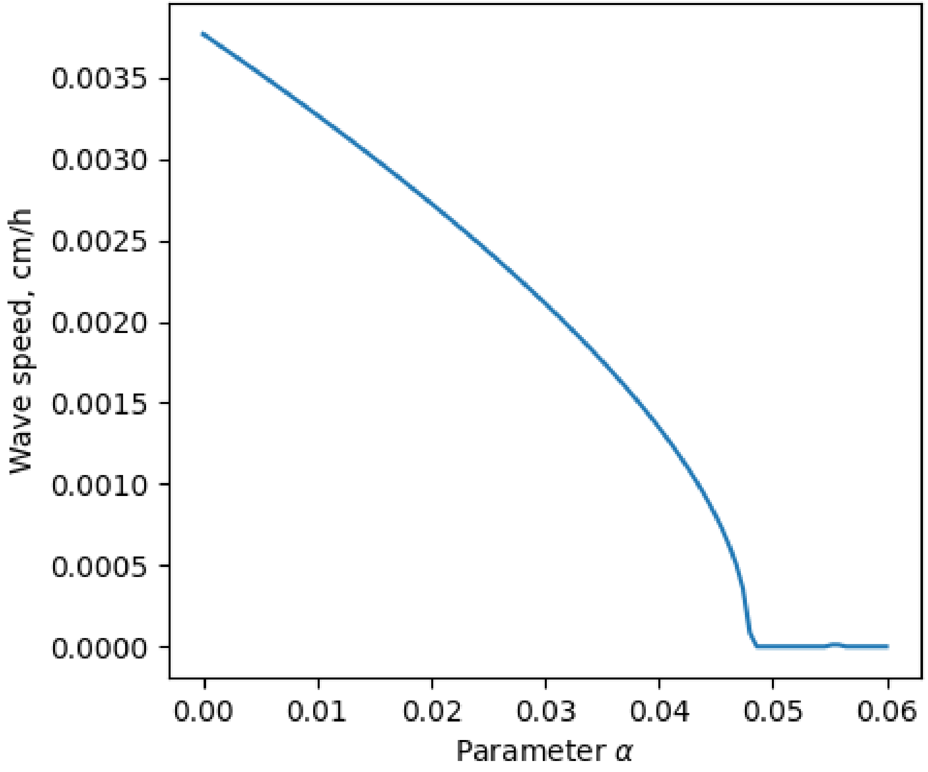
there is no solution of the equation for X

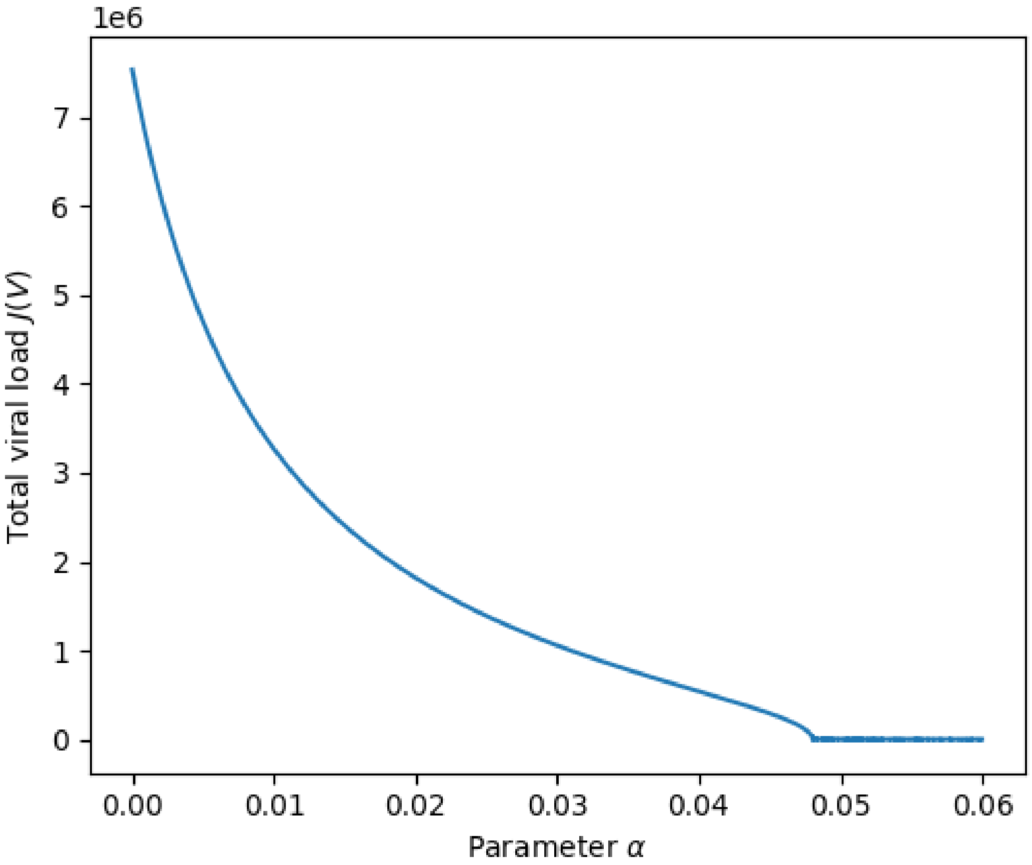
  - wave speed: $c^2 = \min\limits_{\mu > \mu_0} \dfrac{D_1(\mu + \sigma_1 + \alpha)\mu^2}{(\mu + \sigma_3)(\mu + \sigma_1 + \alpha) - b k_2 u_0}.$

Dependence of the total viral load and the wave speed on the effective cell death due to inflammation

for α = 0 – the same as in UIV without inflammation

```
vel=0.0037683636560039402
jv=7513497.885188183
```





inflammation reduces both infectivity and severity of the disease

The values of the wave speed and the total viral load are bounded from above by the values obtained in UIV system

Case 2: clearance of cytokines ≠ 0

- Stationary points: $W = 0,\ V = 0,\ S = 0$ and any U.
- Virus replication number: $R_v^{(1)} = \dfrac{k_2 b U_0}{\sigma_1 \sigma_3} < 1.$ - the same as for UIV system
- Wave
  - Total viral load: $\ln X(\ln X - q) = R_v(X-1)(\ln X - r),\qquad R_v = \dfrac{k_2 b u_0}{\sigma_3(\alpha+\sigma_1)},$

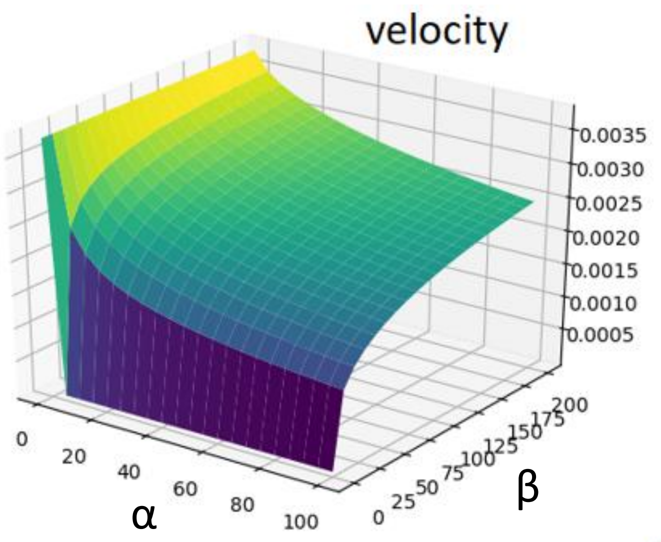
$$q = \frac{bk_2\sigma_1\beta}{\sigma_3 c(\alpha+\sigma_1)},\ r = \frac{bk_2\beta}{\sigma_3 c},\qquad \beta = \sigma_4/k_7.$$

Proposition 1. *Equation (2.17) has a solution* $X \in (0,1)$ *if and only if* $R_v^{(1)} > 1.$

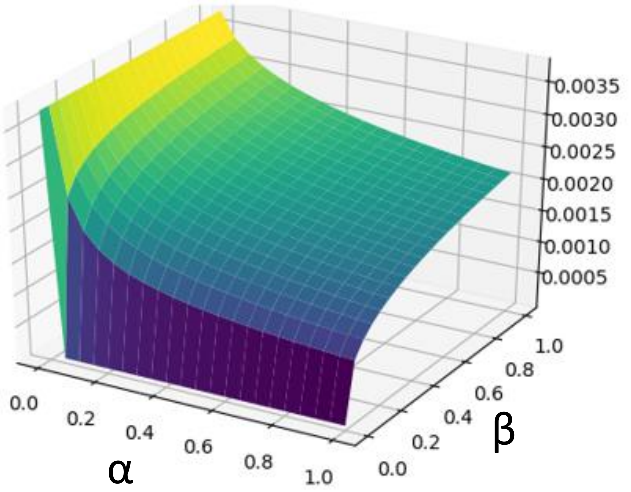
- wave speed: $c^2 = \min\limits_{\mu>\mu_0} \dfrac{D_1[(\mu+\sigma_1)(J(w)+\beta)+\alpha J(w)]\mu^2}{(\mu+\sigma_3)[(\mu+\sigma_1)(J(w)+\beta)+\alpha J(w)] - bk_2u_0(J(w)+\beta)},$

For α -> 0 (β -> 0 or β is fixed): the UIV case
For β -> 0 (α is fixed, ≠0): the previous (sigma4=0) case - all the dynamics depends only on α
For β -> infinity (α is fixed): the UIV case where the R_v inversely depends on alpha

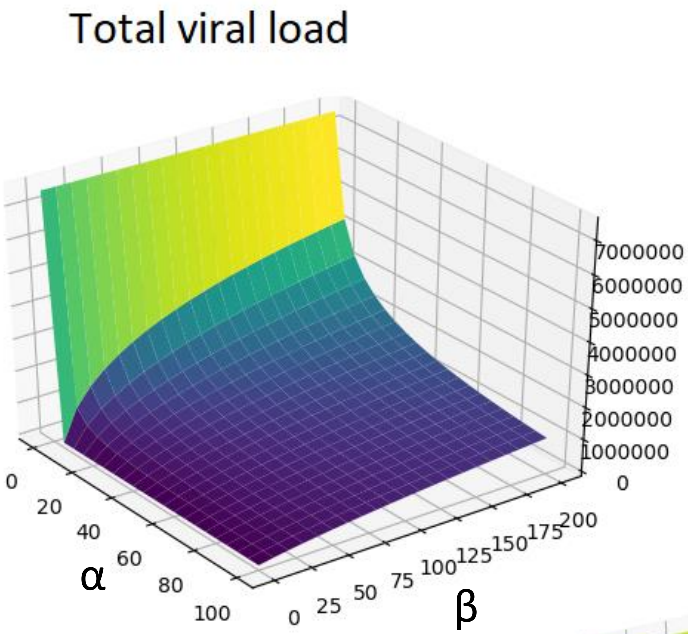
Dependence of the total viral load and the wave speed on the inflammation parameters



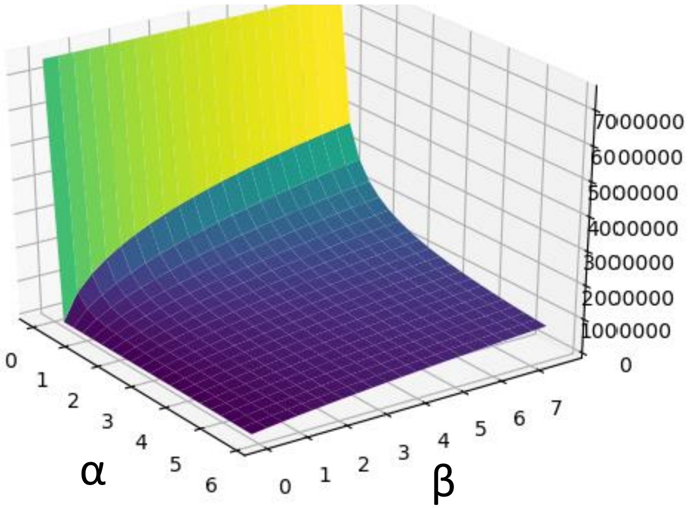

```
alpha_range = np.linspace(1e-12,100,21)
beta_range = np.linspace(1e-12,200,21)
```




```
alpha_range = np.linspace(1e-12,1.0,21)
beta_range = np.linspace(1e-12,1.0,21)
```




```
alpha_range = np.linspace(1e-12,100,21)
beta_range = np.linspace(1e-12,200,21)
```



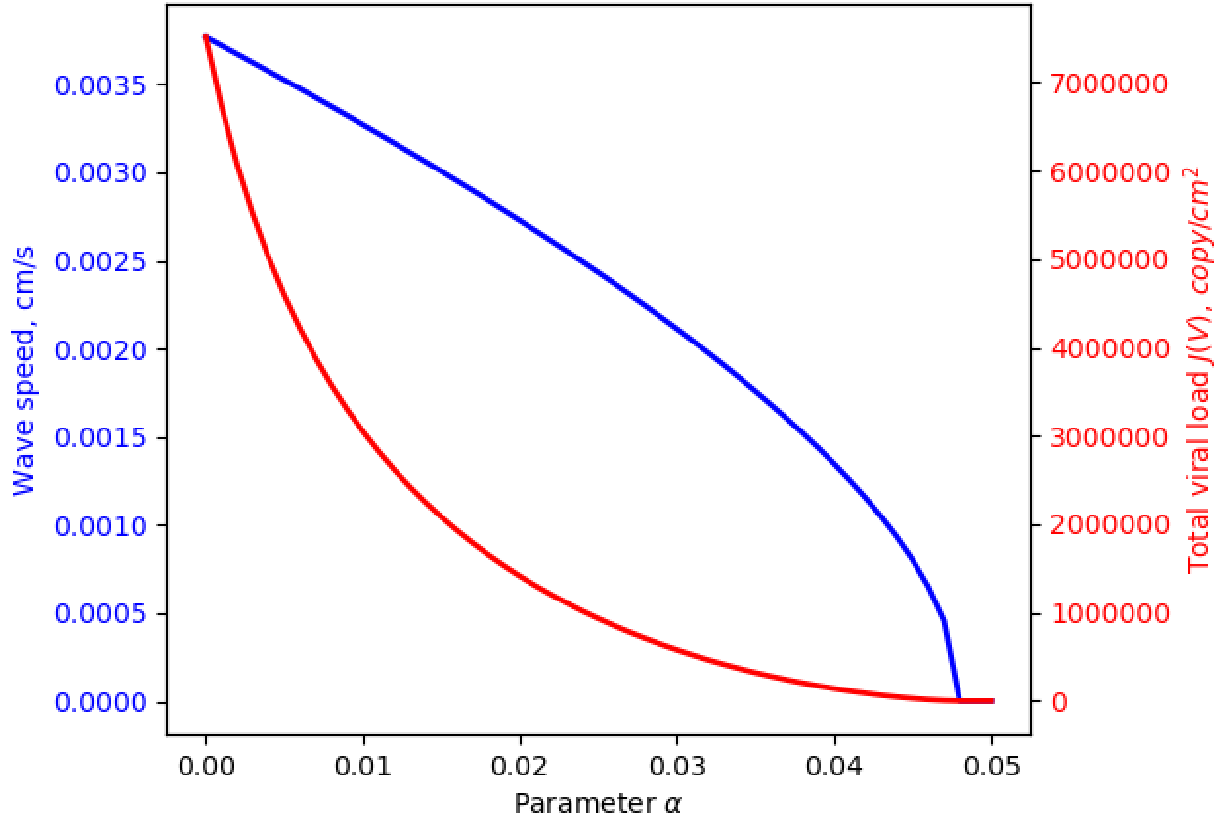

```
alpha_range = np.linspace(1e-12,5.8,21)
beta_range = np.linspace(1e-12,7.6,21)
```

Dependence of the wave speed and total viral load on the effective cell death induced by inflammation (α)

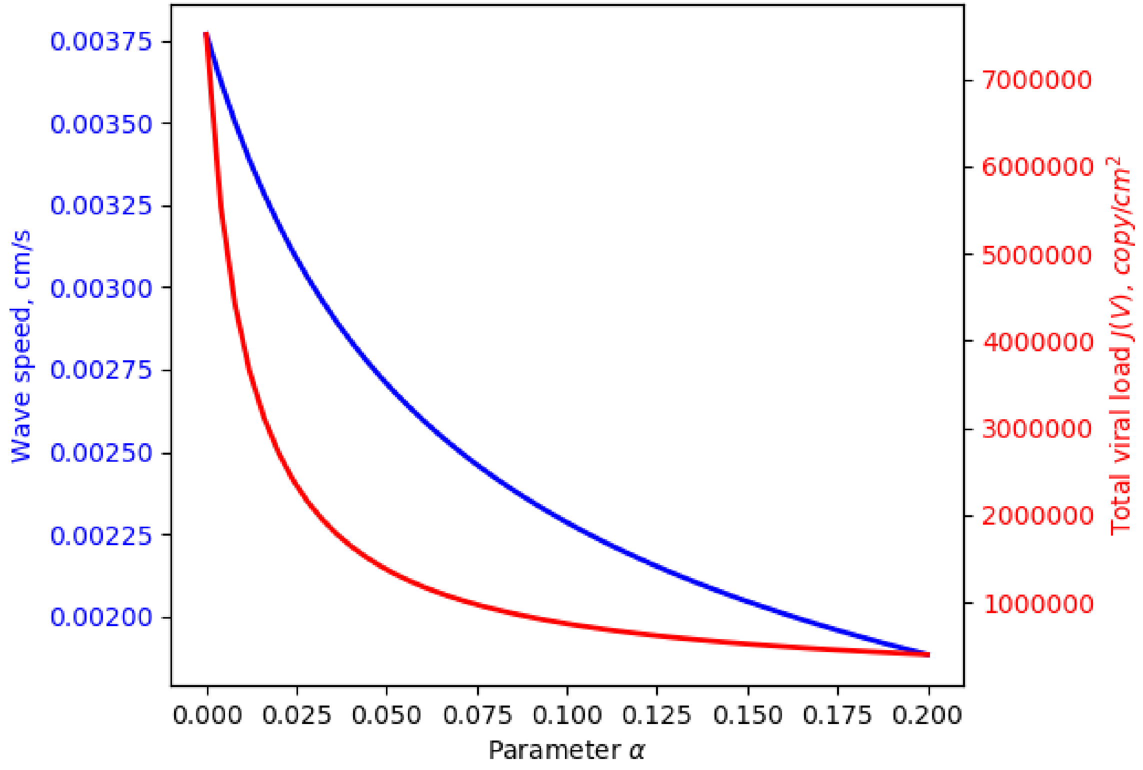
For α -> 0 (β -> 0 or β is fixed): the UIV case:

```
vel=0.0037683636560039402
jv=7513497.885188183
```

beta = 0



beta = 0.1



effective cell death decreases both the severity and infectivity of the disease

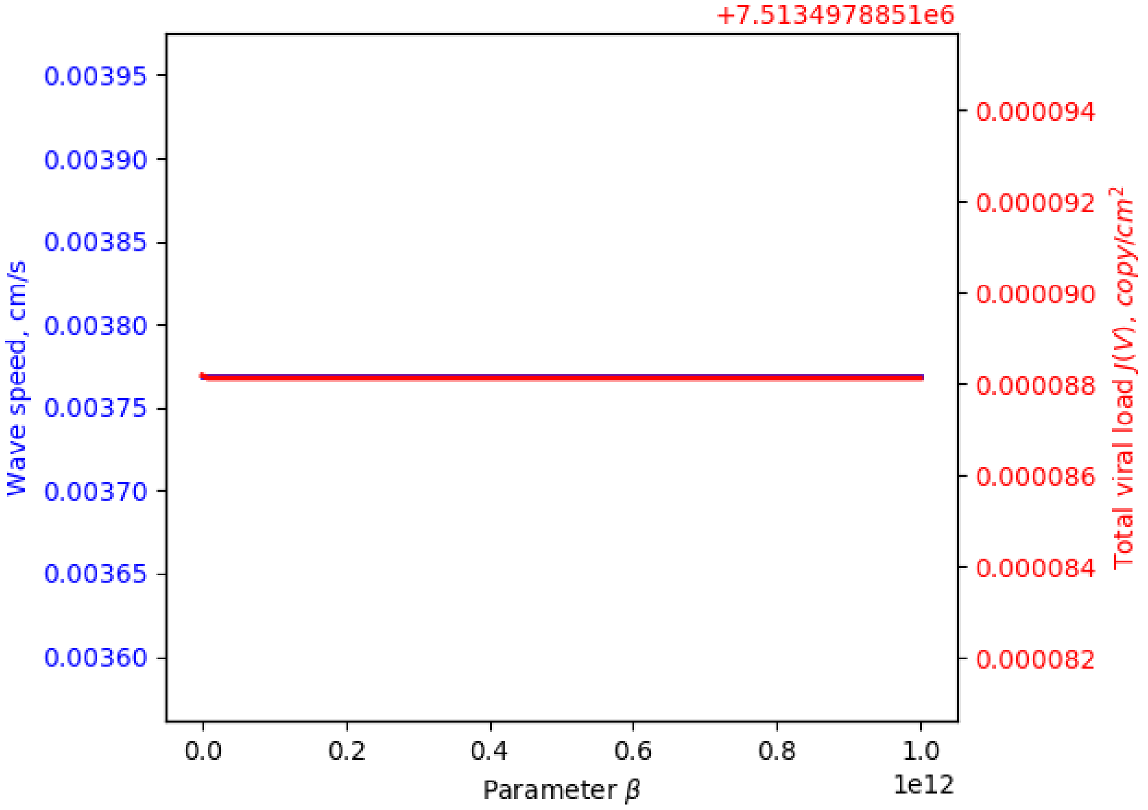
The values of the wave speed and the total viral load are bounded from above by the values obtained in UIV system

Dependence of the wave speed and total viral load on the effective cytokine clearance (β)

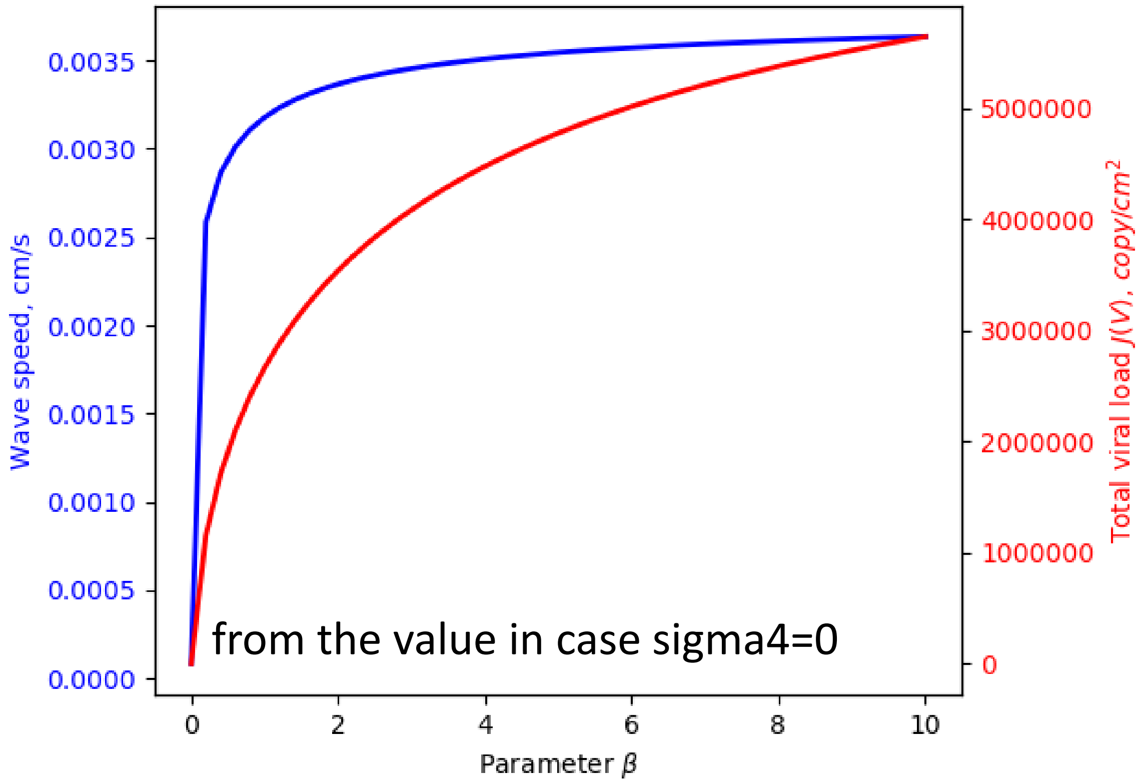
For β -> 0 (α is fixed): the previous (sigma4=0) case - all the dynamics depends only on α
For β -> infinity (α is fixed): the UIV case where the R_v inversely depends on alpha

vel=0.003768363656003940 2
jv=7513497.885188183

alpha = 0



alpha = 0.1



Effective cytokine clearance increases both the wave speed and total viral load from the value of the no-clearance case but not higher that the value of UIV case

Conclusions

- The inflammation decreases both the total viral load and the wave speed
- In the swell (edema) presence, the total viral load and the wave speed are reduced by inflammation (effective cell death induced by inflammation)
- The increased clearance results in the increasing of the total viral load and the wave speed up to values which they have in the case without inflammation (in the infinity)

The results show that the swell can be a positive mechanism for revealing the virus infection. The last conclusion requires further investigations

Thank you for attention!